

**NEW SYNTHESIS METHODS EXPLOITING
HYPERCOORDINATION COMPOUNDS OF PHOSPHORUS
AND SILICON**

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Abstract

Introduction: This thesis begins with an overview of the hypercoordinate chemistry of phosphorus and silicon, chemistry in which these elements form more than their usual 3 and 4 bonds. The knowledge collected here is essential to understand the reactivity manifolds discussed in the later Chapters, and can often be surprising to chemists who rarely deviate from studies of carbon compounds.

Chapter 1 epitomises this assertion, as it describes studies that resulted in a new mechanistic proposal for a previously reported phosphorus-catalysed Staudinger Ligation reaction. The proposal expounds the hidden role of *in situ* generated silyl ester species as enhanced reductants and acylating agents, and overturns the originally proposed phosphorus-mediated mechanism.

Chapter 2 involves an in-depth study of the silyl ester species discovered in Chapter 1. First, their application in amidation chemistry is demonstrated through scope (26 examples, 33%–quant. yield) and the synthesis of API molecules (1 step synthesis of flutamide, 3-step formal synthesis of *ent*-lacosamide). A mechanistic study into their base-catalysed formation and reactivity in the context of amidation follows. Kinetic studies provide evidence for a rate-limiting dehydrogenation from a hypercoordinate species, first order in carboxylic acid, amine and silane.

Chapter 3 develops the amidation reaction described in Chapter 2 into a direct reductive amination procedure between carboxylic acids and amines. By utilising our conditions and knowledge of the amidation procedure, we were able to incorporate an iridium-catalysed, silane-mediated reduction of the *in situ* generated amides to give a one-pot method to form

secondary and tertiary amines (28 examples, 15-89% yield). Efforts towards exemplification to the synthesis of Maraviroc are presented.

Chapter 4 also uses silyl esters productively. In this case, the silyl esters of stronger carboxylic acids, such as trifluoroacetic acid, are shown to undergo silane-mediated reduction to aldehyde-level oxidation state species, which undergo reductive amination reactions *in situ*. This discovery was utilised to develop a highly practical trifluoroethylation reaction of primary and secondary amines, allowing previously difficult-to-access, non-basic, highly-functionalised tertiary amine cores to be synthesised in a single step (40 compounds, 34-83% yield).

Chapter 5 returns to a phosphorus theme, and provides evidence that the silyl ester species identified in Chapter 1 are also candidates to explain an enhanced phosphine oxide reduction described in a previously reported catalytic Wittig reaction. Our results are used to develop a highly active silane-mediated reduction system for the reduction of phosphine oxides.

Chapter 6 focuses entirely on the hypercoordination chemistry of phosphorus. Specifically, a novel catalytic system is demonstrated to reproduce Mitsunobu chemistry. The system requires no redox additives, as it operates entirely in a P(V) manifold, producing water as the only by-product. This 'ideal' condensation reaction, the conversion of alcohols to esters, has been demonstrated to operate with inversion of stereochemistry at carbon, making it the first truly *P*-catalytic Mitsunobu reaction.

Acknowledgements

“If I have seen further it is by standing on the shoulders of giants...”

Isaac Newton, borrowed from Bernard of Chartres

This work would not have been possible without Nottingham University Chemistry Department, which funded this PhD, and the help and support of the staff and students in it.

The Chemistry would not have been discovered without a license to roam and the freedom to explore, enabled by Dr. Ross Denton, whose trust I hope I have repaid. It would not have been focused and meaningful without the same; a collection of experiments is not Science without context, direction and the motivation to answer every question honestly.

Finally, it would not have been undertaken without me, the culmination of several decades of interactions with an inestimable number of mentors, friends and family, and the influence of scientists worldwide whom I have never met. It would be an affront to psychology to assume I could disentangle these contributions meaningfully.

And so, of course, I am sourly tempted to try.

For the most part, it will suffice to say that anyone whose company I have sought or experienced has contributed to this work. However, I reserve special mention of my parents, whose influence in both nurturing curiosity and doubting everything as a matter of course has only come to be appreciated as I see how easy it is to be misled, and my Grandad, who asked me only to keep my integrity and make no compromises in my pursuit of Science.

Contents

Introduction – An Introduction to the Relevant Fundamental Chemistry of Silicon and Phosphorus (*p1-45*)

Chapter 1 – Mechanistic Study Into The Catalytic Staudinger Ligation (*p46-66*)

Chapter 1 Experimental Section (*p67-76*)

Chapter 2 – Silyl Esters In Acylation Chemistry: Scope And Mechanism (*p77-134*)

Chapter 2 Experimental Section (*p135-180*)

Chapter 3 – Reductive Amination Reactions Of Carboxylic Acids (*p181-211*)

Chapter 3 Experimental Section (*p212-238*)

Chapter 4 – A Trifluoroethylation Reaction Of Amines Using TFA (*p239-270*)

Chapter 4 Experimental Section (*p271-317*)

Chapter 5 – Phosphine Oxide Reductions Using Activated Silanes (*p318-338*)

Chapter 5 Experimental Section (*p339-342*)

Chapter 6 – A Fully Catalytic Mitsunobu Reaction (*p343-434*)

Chapter 6 Experimental Section (*p435-503*)

Final Summary (*p504*)

Table of Abbreviations

AcOH	acetic acid
API	active pharmaceutical ingredient
app.	apparent
BIBS	di- <i>tert</i> -butylisobutylsilyl
Bn	benzyl
BOC	<i>tert</i> -butoxycarbamate
br.	broad signal
CBz	carboxybenzyl
CCR5	C-C chemokine receptor type 5
COD	cyclooctadiene
COE	cyclooctene
dr	diastereomeric ratio
DAIB	(diacetoxyiodo)benzene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DEAP	4-(<i>N,N</i> -diethylamino)pyridine
DIAD	diisopropyl azodicarboxylate
DIBAL-	
H	diisobutylaluminium hydride
DIPEA	<i>N,N</i> -diisopropylethylamine
DMAP	4-(<i>N,N</i> -dimethylamino)pyridine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
DS	Dean Stark conditions
ee	enantiomeric excess
er	enantiomeric ratio
EtOAc	ethyl acetate
Fe(pc)	iron phthalocyanine
GC-MS	gas chromatography mass spectrometry
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
hERG	human Ether-a-go-go-Related Gene
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
iPrO	isopropoxide/isopropyl
KIE	kinetic isotope effect
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
LUMO	lowest unoccupied molecular orbital
MeCN	acetonitrile
MO	molecular orbital
MS	molecular sieves

NHC	<i>N</i> -heterocyclic carbene
NMM	<i>N</i> -methylmorpholine
NMR	nuclear magnetic resonance
Nu	nucleophile
OTf	triflate, trifluoromethanesulfonate
pic	2-picoline
PKIE	primary kinetic isotope effect
PMHS	polymethylhydrosiloxane
POCOP	1,3-bis((diphenylphosphino)oxy)benzene
PPTS	pyridinium <i>p</i> -toluenesulfonate
Py	pyridine
RDS	rate-determining step
rt	room temperature
SI	supporting information
SKIE	secondary kinetic isotope effect
SSSA	silica-supported sulfuric acid
TBAI	<i>tert</i> -butyl ammonium iodide
TBS	<i>tert</i> -butyldimethylsilyl
tBuDMSi	<i>tert</i> -butyldimethylsilyl
TCAA	trichloroacetic acid
TCE	1,1,2,2-tetrachloroethane
TEA	triethylamine
TFA	trifluoroacetic acid
TFE	trifluoroethyl(ation)
TfOH	triflic acid, trifluoromethanesulfonic acid
THF	tetrahydrofuran
TMDS	1,1,3,3-tetramethyldisiloxane
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
TMSOTf	trimethylsilyltriflate
tol	toluene
TsOH	tosic acid, <i>p</i> -toluenesulfonic acid
VSEPR	valence shell electron pair repulsion

Introduction

An Introduction to the Relevant Fundamental Chemistry of Silicon and Phosphorus

This theory-based introduction introduces some of the concepts, terminology and mechanisms that will be exploited in the chemistry of the later chapters. More focused analyses of the synthesis literature will be given as the relevant topics arise.

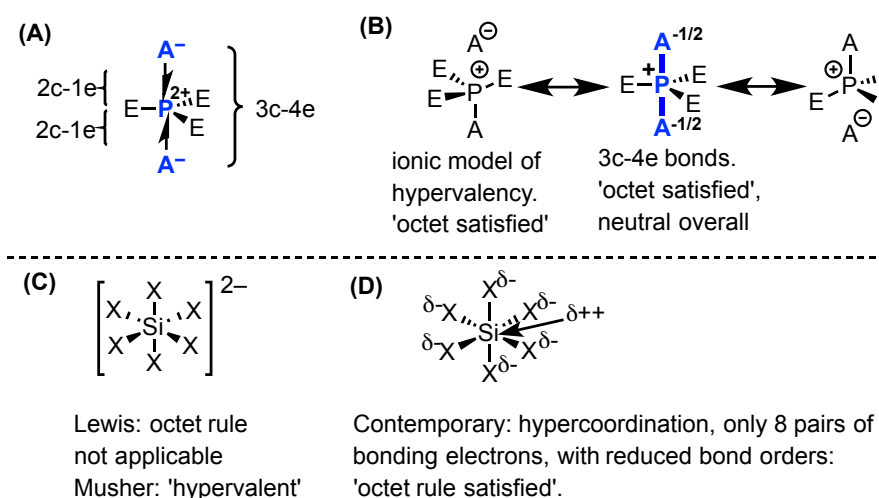
Fundamental Hypercoordination Chemistry of Phosphorus and Silicon

Hypervalency¹ is often defined as the ability of a main group atom to expand its traditional octet of outer shell electrons. Whilst this is visually appealing and aids VSEPR descriptions of such compounds, chemically this is formal convention. More robust definitions put emphasis on the strict observation of an electronic octet (within the valence shell of the central atom), and instead use the concept of ionisation or the two-centre-one-electron (2c-1e) bond. A brief history of the term hypervalency is available;² the consensus in chemistry currently rejects the historically proposed involvement of d-orbitals in the hypervalent chemistry of main group elements like phosphorus on energetic grounds. Whilst *d-functions* are required for accurate (“computational”) calculations of bonding in these species, the involvement of *d-orbitals* is all but non-existent.³ The most commonly encountered hypervalent molecules have at least one pair of collinear 2c-1e bonds leading to the more common description of three-centre-four-electron (3c-4e) bonds, which is a reworking of the 2c-1e model, explicitly counting the electron density remaining at the ligands (Figure 1A).

Much controversy over the definition and use of the term hypervalency has led some to turn to the term *hypercoordination* as an alternative.⁴ Certainly, Smith has sought to clarify the use of terms relating to the subject, noting that to apply the term *hexavalent* to *six-coordinate* silicon structures is to suggest that the silicon centre is Si(VI); what is presumably meant is *hexacovalent*.⁵ Hypercoordination, however, is an attractive term, because it demands that the (modern) octet rule (s^2p^6) at the central atom remains satisfied, and thus drives understanding of hypercoordination chemistry, in which *additional electrons must be stabilised by the ligands rather than the central atom*. Jensen

describes this interaction as $n-\sigma^*$, where n is a non-bonding pair of electrons on the donor and σ^* are antibonding orbitals of an acceptor orbitals. This is akin to partially displacing an existing ligand. In a 3c-4e bond, the opposing ligand reciprocates, resulting in two bonds of intermediate strength (containing $\sim 1e$).⁶ The expelled electrons have some residency in non-bonding orbitals at the ligands themselves. It is for this reason that hypercoordinate compounds typically contain electronegative ligands. This understanding is fundamental to explaining the chemistry of these molecules and this principle is utilised extensively in the design of an organophosphorus P(V) Mitsunobu catalyst in Chapter 6.

Figure 1. Hypervalency vs. Hypercoordination chemistry. (A) 2c-1e electron bonds are often found in pairs (as 3c-4e bonds). (B) Modern consensus enforces the octet rule, describing Musher's hypervalent species as *hypercoordinate*; (C) Lewis did not intend for his octet formalisation to apply to Musher's 'hypervalent species'. (D) A modern 'electron dispersion' view.

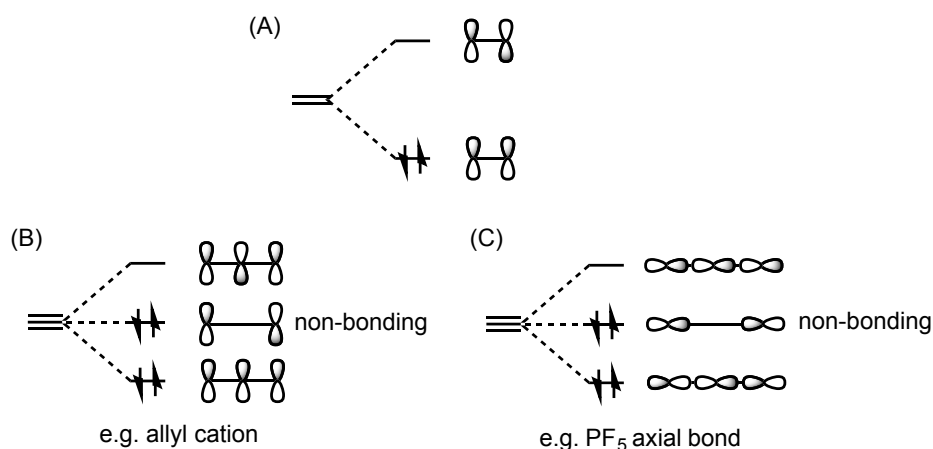


Despite this, there are dissenters; Gillespie and Robinson,⁷ for example, argue that the Lewis octet rule must remain distinct from modern, altered definitions. Thus they claim (as did Lewis) that species such as SF_6 *do violate the Lewis' octet rule*, in contrast to the assertions of contemporary chemists that the rule is technically unbroken if 3c-4e bonds or ionic (dipolar)⁸ formulations are considered. Such period 3 and 4 elements should, they argue, be said to conform to a duodecet (12 electron) rule, using the analogy of reactivity: SF_6 is the analogously unreactive counterpart of CF_4 , despite the polar bonds, and clearly

contains 6 electron pairs around sulfur. The authors go further, suggesting that hypervalency is not a useful concept, arguing that there is fundamentally no difference between the bonding in hypervalent and ‘normal’ bonding in molecules. Whilst there is perhaps a case to be made in terms of understanding intuitive fundamental reactivity of the central atom, that the authors select fluorinated species as their examples goes some way to undermining the argument that hypervalent third row bonding is *identical* to second row bonding with respect to the *ligands*; examination of the molecular orbital theory highlights distinct differences (Figure 2).⁸

Figure 2. Frontier molecular orbital depictions for: (A) a typical π -bond; (B) an allyl anion, with an occupied non-bonding MO, which explains its nucleophilic character at the terminal carbon atoms; (C) an analogous 3c-4e bond, highlighting the localisation of the electrons in the HOMO at the ligands, which have some nucleophilic character.

(Note that the non-bonding molecular orbital symmetry accounts for the apparent phase discrepancy between the π -system (centre) and the σ -system (right).)



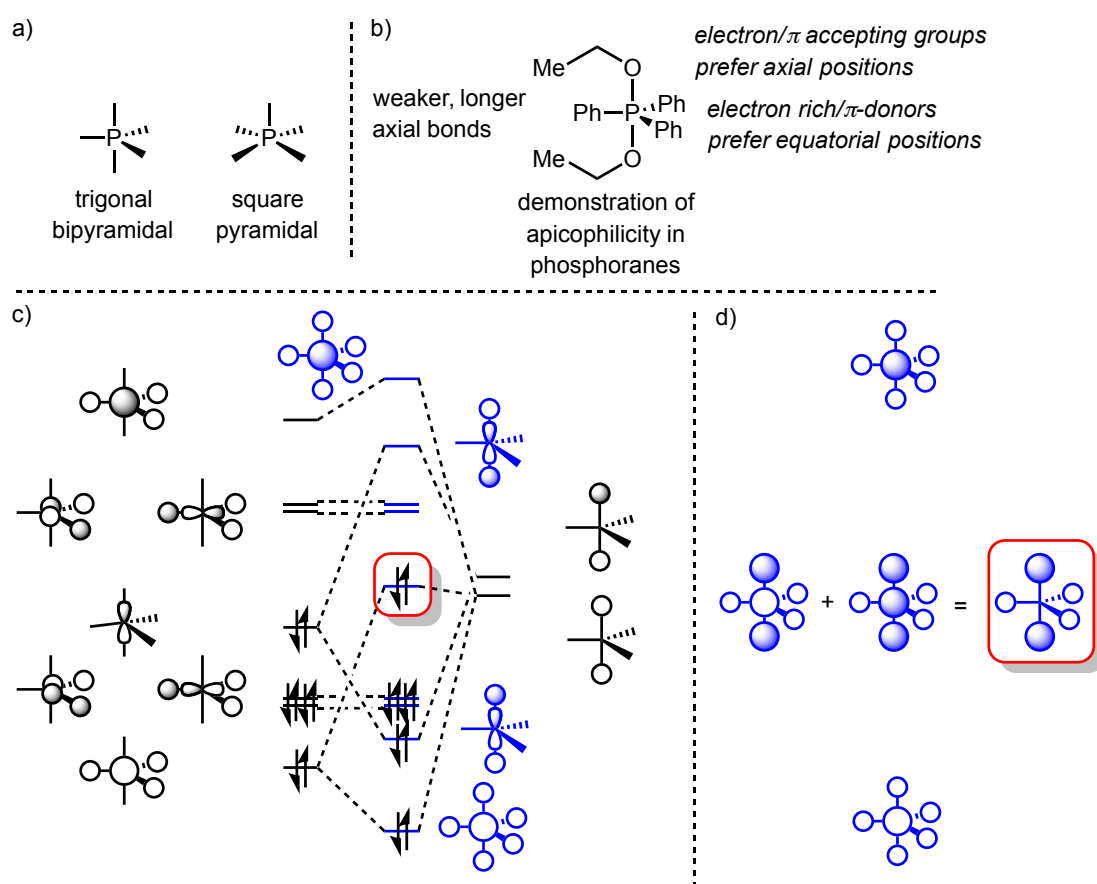
By way of clarification, in this work we take a modern, non-controversial approach, ignoring the pedantic technicalities of historical theory. For while it is, we believe, technically the case that phosphorus(V) breaks the traditionally described octet of *Lewis*, it retains, chemically (and relevantly) speaking, an electronic octet of 8. The concept of apicophilicity⁹ (*vide infra*) very clearly demonstrates the need for a differing view of axial and equatorial bond chemistry, and so the 3c-4e bond model will be utilised; this model

accounts for the fluorinated species endorsed in the dissenting argument above. It is important to note, however, that we deem such an interpretation an extension of the ionic model of hypercoordination; in other words, we would not describe pentavalent phosphorus as *hypervalent*: a resonance of 4-coordination forms (4 electron pairs) with a fifth ionic interaction, on average, provides the same message as a 3c-4e bond, which is that the ligands hold the additional electron density (i.e. as depicted in Figure 1B).⁸ That phosphorus forms *pentacoordinate* species is unquestionable, however, so we will persevere with the 3c-4e system. As always, a sensible practitioner shuns tradition and formality in favour of an intuitive working model.

Some of the most commonly encountered organic hypercoordination molecules centre around phosphorus, which is known to form many *neutral* stable pentavalent hypercoordination molecules in a P(V) oxidation state.¹⁰ These species are all trigonal bipyramidal, with the exception of some spirocyclic species and various degrees of distortion from trigonal bipyramidal to a square based pyramidal geometry (Figure 3A).¹¹ As stated, the requirement for a stable hypercoordination complex is the ability of the ligands to host the additional electrons. Phosphoranes, with five distinct bonds, are clearly members of the hypercoordination family. The theory of 3c-4e bonds is undoubtedly applicable to these molecules, which is easily demonstrated using the concept of apicophilicity. Apicophilic ligands are groups that tolerate electron density and prefer occupying the collinear axial positions of a trigonal bipyramidal pentacoordinated phosphorus(V) molecule, whilst electropositive ligands/ π -donors prefer equatorial positions.¹¹ This arrangement allows the excess electrons of this 3c-4e bond (two are bonding, two are non-bonding/antibonding) to localise at the axial ligands, keeping the (modern) electron octet intact (Lewis would argue that the traditional octet is violated).⁷ It should be noted that sterics also play a role;

Quin suggests that the order of apicophilicity of ligands is in the order: $F > H > CF_3 > PhO > Cl > MeS > MeO > Me_2N > Me > Ph$. Hydrogen sticks out as an electronic anomaly, and any truth to Quin's order must be a sterics-based assertion. The axial bonds are noticeably longer with respect to the equatorial bonds, but all bonds are somewhat elongated in the pentavalent state (Figure 3B).

Figure 3. (A) Geometry of hypercoordination P(V) compounds. (B) The basic rules of ligand orientation in such species and apicophilicity. (C) Full MO diagram of PH_5 , as described by Hoffmann and co-workers. (D) A breakdown of the origin of the occupied non-bonding orbitals with large electron density in the axial positions.



The molecular MO diagram for PH_5 , as derived by Hoffmann and others, is shown in (Figure 3C).¹² The diagram is composed of a planar AX_3 fragment interacting with a linear H-H fragment. The two H-H fragment MOs (bonding/antibonding) have roughly the same energy, as when separated they approach a non-bonding distance. More importantly, whilst the upper H-H antibonding fragment has π -symmetry, and can interact with the P_z

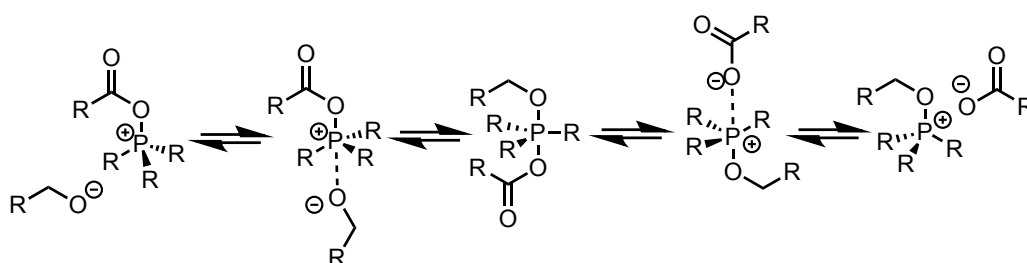
orbital present in the planar AX_3 fragment, the lower bonding axial fragment is left as an essentially non-bonding species in the final MO (boxed). Although it has the correct symmetry to interact in both a bonding and anti-bonding manner with the trigonal σ -orbital fragments (Figure 3D), it is the mutually non-bonding fragments that average to give an MO with electron density at the ligands only. The slightly exaggerated result (boxed on the right), shows that the resulting MO has a greater coefficient for the axial ligands. Although this shows the 3c-4e bond to be a simplification, it very clearly reproduces the overall effect, and demonstrates that the equatorial ligands can also be nucleophilic.

Compounds of silicon can also form hypercoordination complexes, but due to silicon's position in group 14, a pentacoordinate species has an overall charge of -1 (it is still $Si(IV)$), explaining the lower general stability of such compounds.¹⁰ However, due to silicon's low electronegativity, it is Lewis acidic, and thus readily forms ate complexes – adducts in which a Lewis base coordinates to a central Lewis acid, formally increasing its coordination number. The resulting species are thus readily reactive, and a lot of fundamental silicon chemistry in organic synthesis is underpinned by these ate complexes. Thus whilst long-lived pentacoordinate silicate species have been observed in solution phase, isolation is problematic, although possible. Hydrolysis is thought to occur *via* a hexacoordinate species. As such, many of the characterised penta- and hexa-coordinate species of silicon are neutral species in which a ligand has an additional Lewis basic donor, usually an apical tertiary amine, which leads to a pyramidalisation. In line with the ionic theory of hypercoordination, the large majority of pentacoordinate species have multiple electronegative ligands, usually oxygen or fluorine.¹⁰ We consider pentacoordinate silicon species in much of the work to be presented, but understandably suffer from an inability to

observe or isolate such species; in solution, such species tend to be fleeting adducts with limited kinetic (entropic) stability.

Hypercoordination Chemistry of Phosphorus in Synthesis

The balance between the ionic and 3c-4e bond models of hypercoordination are demonstrable through consideration of the Mitsunobu reaction, which shows the extremes of these representations. The key species in a Mitsunobu reaction is the alkoxyphosphonium carboxylate (Scheme 1, *far right*).



Scheme 1. Demonstration of the equilibrium between different phosphonium salts in the Mitsunobu reaction via a pentacoordinate phosphorane species.

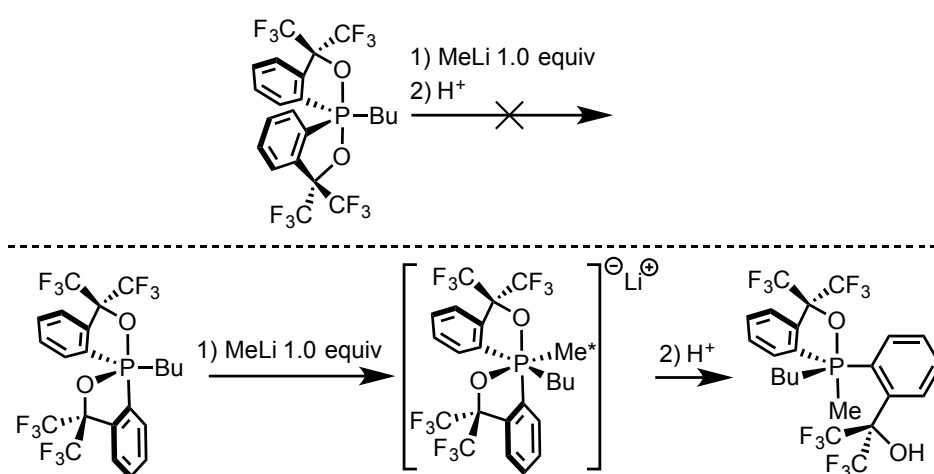
Such a species consists of an X^- ligand – in this case alkoxide – coordinated to form an $X-PR_3^+$ group. This species has a counterion, another X^- group – in this case, carboxylate. Such ligands can often exchange, and do so *via* a pentacoordinate phosphorane species; when the X groups are not the same, this species (*central*) may be described as a mixed (alkoxy/acyloxy) phosphorane (Scheme 1).

In the Mitsunobu reaction, all the permutations of tetra/penta coordinate phosphorus species may exist, although certain configurations are more stable, depending on the usual factors of sterics and electronics, and also the conditions (e.g. solvent). When the electronegative X ligands are halides in R_3PCl_2 structures, the phosphonium salts are favoured in chloroform for most structures (except when the P centre has electron deficient aryl R groups);^{13,14} increasingly apolar solvents, and gas phase species favour the

phosphorane, as would be expected for salt-like species.^{15,16} The salts are named as such, as they are often isolable as crystalline solids, composed of anion and cation parts.

Gilheany has shown that the intermediates in these X-ligand substitutions are the expected trigonal bipyramidal species with a diaxial dichlorophosphorane arrangement (interconverting with inversion). Calculations suggest that this is a distinct intermediate for small equatorial R groups, differing from the charged species that make up an S_N2 reaction at carbon, which is at the apex of the energy profile – a true transition state.¹⁵ Larger equatorial groups increase the energy of the pentavalent state, which tends towards a true stationary (transition) point.

Spirocyclic species can also overturn the generally observed rules of tetra/pentavalent species: thus spirocyclic phosphoranes exist in chloroform where analogous acyclic species would be phosphonium salts. The 3c-4e configuration ensures that the most electronegative ligands occupy axial positions in the trigonal bipyramidal geometry as far as possible. It is possible to synthesise antiapicophilic compounds, which show different reactivity. A particularly striking example is the reaction of the two coordination-isomers of a phosphorane with an organolithium nucleophile (Scheme 2).¹⁷



Scheme 2. Akiba's demonstration of the differing reactivity of antiapicophilic compounds, relative to their stable axial dioxy-state.¹⁷

The isomer with an equatorial oxygenated ligand undergoes reaction with methyllithium, facilitated by the lowering lying σ^*_{PO} (18.7 kcal/mol lower than σ^*_{PC}).¹⁷ The diaxial dioxyposphorane is unreactive; attack into an axial antibonding orbital is geometrically impossible. This principle is of interest in Chapter 6 when considering our own work with dioxyposphoranes. Work into the synthesis and reactivity of apicophilic compounds has seen high interest recently, with Akiba and colleagues very active in this field.^{17–29}

Some phosphonium salts have the counterion integrated into the molecule, on the atom connected to phosphorus. Such compounds are classified in their own reactive group and are often referred to as ylides. They underpin a large branch of phosphorus chemistry. Such compounds are frequently depicted as having P=X double bonds, which remains in conflict with the previous descriptions of hypercoordination. As such, although *technically* the charged ylide form should probably be depicted, it is often convenient to show these species with double bonds; the strength of phosphine oxide bonds is notorious and clearly depicted in the double bond form.³⁰ However, the key reactivity of these species is often more easily visualised from the charged ylide forms. These depictions are discussed further in Chapters 1 and 4, which explore phosphine oxide and iminophosphorane reductions.

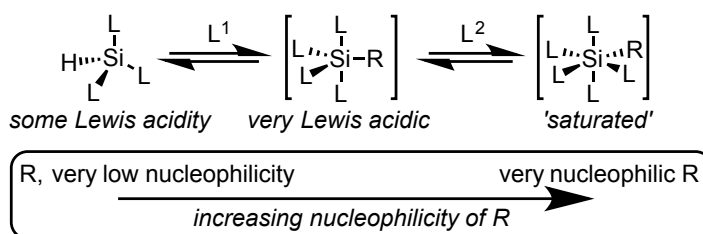
Hypercoordination Chemistry of Silicon in Synthesis

The hypercoordination chemistry of silicon differs from phosphorus(V) compounds in one key respect; the tetracoordinate phosphorus(V) species have a formal positive charge at phosphorus, whilst tetravalent silicon compounds are neutral in their standard form. It is only the Lewis acidity of these silicon compounds, driven by the increased atom (coordination sphere) size and low electronegativity, that promotes apparent *octet expansion*.

As such, the greater the electronegativity of the ligands on silicon, in general, the more Lewis acidic the Si atom becomes. Indeed, it requires rather stabilised systems to allow isolation and characterisation of silicate complexes, generally hexacoordinate forms.¹⁰ A steric component also applies to the generation of more crowded silicon centres.³¹

An initially counterintuitive result is that adding a fifth (anionic) ligand to tetravalent silicon can *increase* its Lewis-acidity, despite the formal negative charge of the complex. This is difficult to reconcile in terms of hypervalency – there are now 10 electron pairs around silicon. However, the 3c-4e concept unmasks this apparent anomaly, by clearly positioning the additional negative charge on the ligands rather than at the heteroatom centre. The silicon atom now instead feels the increasing sphere of electronegative groups withdrawing electron density, thus increasing the effective positive charge at silicon. Any R groups present become increasingly nucleophilic (Figure 4).³²

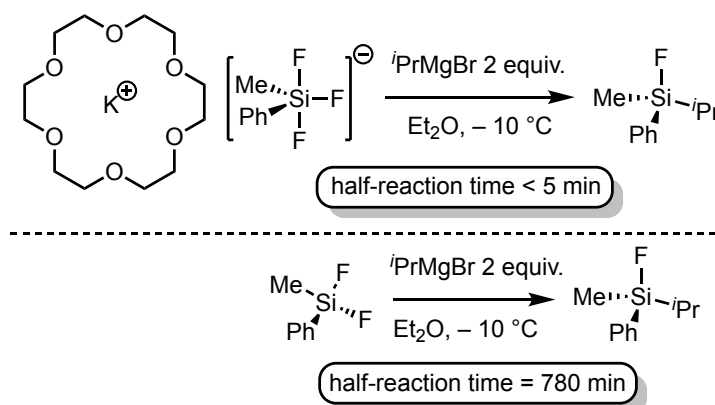
Figure 4. The differing reactivity of increasingly coordinated silicon species.³²



L^1 often anionic ligand but can be neutral Lewis basic. L^2 often neutral donor

This principle was demonstrated by Corriu and co-workers in an elegant experiment in which a pentacoordinate silicate complex showed higher reactivity towards Grignard reagents than did the tetravalent species (Scheme 3).³³ Presumably, as with the phosphorus system above, the low-lying σ^*_{SiF} hypercoordinate equatorial orbital facilitates a rapid reaction by decreasing the kinetic barrier to substitution (relative to a 'normal' bond). Note that the cleavage of Si-F bonds – often thought to be 'strong' by organic chemists (~135

kcal/mol)³⁴ – can be rationalised by the formation of metal fluoride salts that can act as the driving force. It may be useful to think of the Si–F bond as increasing in ionic character as the incoming nucleophile arrives; electrostatic attraction may compensate for the loss in covalency.

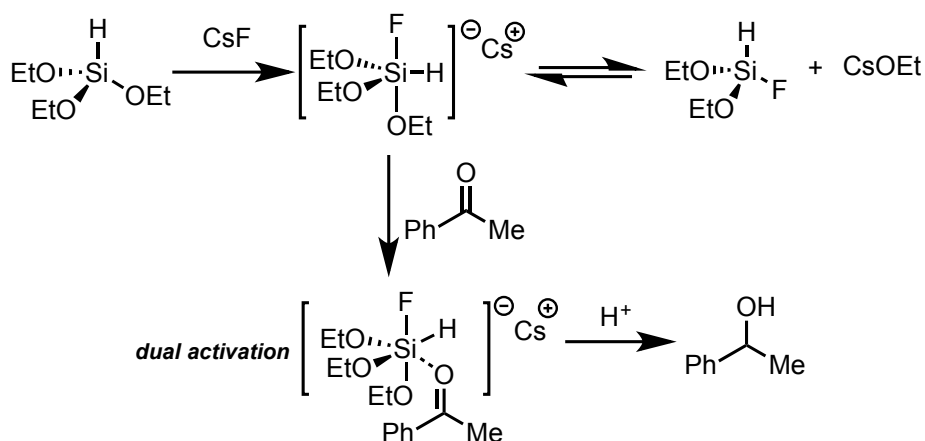


Scheme 3. Corriu's demonstration of the increased reactivity to Grignard reagents of pentacoordinate silicon complexes over analogous tetravalent species.³³

Thus, hypercoordination may act as a template in reducing kinetic barriers. It is important to consider the system as a whole when considering Lewis acidity and substitution. So whilst it is intuitive to say that electronegative ligands withdraw electron density and increase the Lewis-acidity of the silane, it is equally, if not more important, to say that the species resulting from attack is *stabilised by those same electronegative ligands, and that incoming nucleophiles may also be stabilised*. In the case of Grignard addition to a pentavalent silicate species, the incoming carbon-based negative charge can be delocalised across multiple ligands by attacking silicon; moving from pentacoordinate to hexacoordinate means spreading the total charge across six-ligands (3 x 3c-4e bonds). Now it becomes a question of ejecting F^- or C^- , which is a more intuitive question.

As well as an electrophilic Lewis-acidity, the silicate complex can release *nucleophiles* by acting as a scaffold on which a dual-activation can occur. The Lewis acidic silicon is activated by an incoming nucleophile as an ate complex, which transfers the reactivity to a

different ligand, that now acts as a nucleophile. This chemistry is exploited in a variety of complex and stereospecific protocols. A simple exemplification is Corriu's fluoride accelerated reduction of ketones with triethoxysilane, in which the fluoride ligand increases the Lewis acidity at silicon such that both ketone coordination and hydride character is stronger (Scheme 4).³⁵ This principle is key to the chemistry explored in Chapters 1-4.



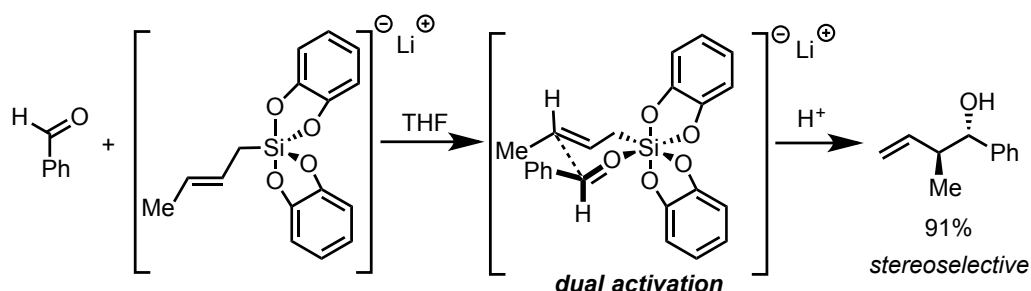
Scheme 4. Corriu's fluoride promoted silane-mediated reduction of ketones.³⁵

A similar mechanism can be drawn for an asymmetric version of this activation reduction reaction, reported by Hosomi and co-workers. An asymmetric ligand – the dianion of prolinol – was utilised to make the activated pentacoordinate silylate complex chiral. The incoming carbonyl group reacted as above, *via* dual activation, but giving enriched ees of alcohol (89% yield, 52% ee for acetophenone).³⁶

Silyl hydrides are often found to occupy equatorial sites, and leave with retention of stereochemistry,³⁷ a result borne from the preference of incoming activating nucleophiles to do so opposite a ligand able to stabilise the negative charge; hydride is a poor acceptor. Conversely, and accordingly, electronegative/stabilised ligands leave with inversion at silicon.³⁸ In the hexacoordinate state, loss of hydride is beneficial in terms of stabilising the resulting pentavalent state; better acceptors *remain behind* to stabilise the charge, whilst the hydride is transferred to a hydride acceptor. If one of the donors is neutral, then this leaves a

stable neutral system. One intriguing example of the nucleophilic activation of silanes is the reaction of phenyllithium with triphenylsilane to form tetraphenylsilane, which is reported to produce LiH as the byproduct.³⁹ Presumably here, the lower 'basicity' (or solubility) of lithium hydride relative to aryl-lithium explains this unusual product.

Sakurai pioneered the field of stereoselective allylsilane chemistry, which utilises the concept of dual-activation to enhance reactivity, and provide a scaffold on which asymmetric processes can occur.³¹ That the product is formed essentially stereoselectively (*anti*/*syn* ratio is identical to the *E*/*Z* alkene ratio) is evidence of the enhanced reactivity afforded through the dual-activation mechanism, in which both the electrophile and nucleophile are activated; i.e. there is essentially no background reaction (Scheme 5).



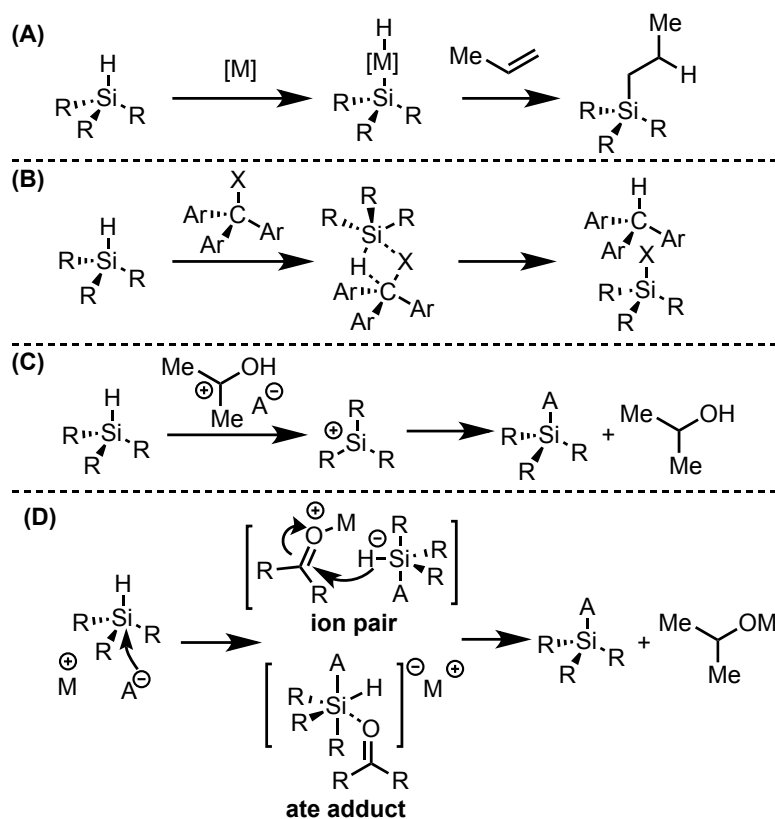
Scheme 5. Sakurai's demonstration of dual activation applied to the stereoselective allyl addition to aldehydes.³¹

A similar approach was applied by Sakurai to reductions of carbonyl functionality.^{40–42} It should be noted that most of the chemistry in this field is based around silanes with 3 or 4 electronegative (Cl, F, O) ligands (i.e. requires hypercoordination which requires electron accepting ligands). Reviews are available.^{32,43} Finally, no exposition of hypercoordination silicon chemistry would be complete without mention of the important work of Denmark, whose contributions include the Pd-catalysed cross-coupling of alkenylsilanols activated by fluoride or alkoxide additives,^{44–46} and asymmetric aldol reactions utilising silyl enol ethers as latent nucleophiles.^{47–50} The principles of dual activation and, particularly, nucleophilic activation of silanes are prominent in the work of Chapters 1–4.

Reagent Class: Hydrosilanes / Hydridosilanes

Due to the lower (Pauling) electronegativity of silicon (1.90) relative to carbon (2.55), and indeed hydrogen (2.20),⁵¹ Si–H and Si–C bonds are polarized away from silicon. This gives them nucleophilic character. Therefore, hydrosilanes are commonly encountered reducing agents.

There are arguably four manifolds of reactivity in which a hydride is transferred. First, the insertion of a transition metal provides a formal R_3Si^+ group capable of activating Lewis bases and a hydridic M–H moiety with reducing power.^{52,53} For alkenes, the Chalk-Harrod mechanism describes an initial anti-Markovnikov addition of M–H across the π -system, followed by a reductive elimination to form a new Si–C bond. However, a more robust account of experimental evidence suggests that insertion of an alkene into the Si–M bond ($Si-M-H + C=C \rightarrow Si-\underline{C}-\underline{C}-M-H$) followed by a hydride reductive elimination occurs in many cases.^{54–56} We make use of this manifold in Chapter 3 in the iridium-catalysed, silane mediated reduction of amides. A concerted mechanism may operate in many cases for ketones; metal-carbon bonds have also been proposed for metals such as rhodium.⁵⁷ Oxygen activation by a metal complex, hydride delivery, and then silylation of the resulting alkoxide is a further alternative. Either way, the transformation is characterised by the initial generation of $[Si]-M-H$ followed by addition across a double bond. This reaction type is generally termed hydrosilylation (Scheme 6A). A second, less commonly invoked mechanism (Scheme 6B) involves a direct σ -bond metathesis, which has been invoked to explain levels of retention in the reduction of triarylmethylhalides.⁵⁸ Third, an external strong acid or Lewis acid can generate a reactive electrophile, to which hydride transfer from the silane can occur, allegedly *via* a silicenium cation – the anion of the strong acid can become silylated in the process (Scheme 6C).



Scheme 6. Potential mechanisms for reduction reactions of hydrosilanes. (A) Metal insertion into Si-H bond and hydrosilylation. (B) Metathesis reaction. (C) Electrophile activation and hydride migration *via* a silicenium cation. (D) Nucleophilic activation *via* a pentacoordinate silicate species.

A final and important method involves the activation of the hydrosilane as an ate complex by a nucleophile (Scheme 6D). The *anion*, such as fluoride, of an AX compound attacks silicon to form an $[\text{R}_4\text{SiX}]^-\text{A}^+$ type adduct, increasing the hydridic nature of the hydrogen on silicon, which reduces the target compound, *which normally must be coordinated to silicon too*.^{59,60} The M^+ is then associated with the reduced compound. This last method is an alteration in focus of the previous mechanism, and is arguably most sensible chemically. Mechanism C is often drawn without this preactivation (e.g. in the case of the TFA/silane reducing system), apparently ignoring the Lewis acidity of silicon.

The AlCl_3 -catalysed triethylsilane-mediated reduction of alkyl halides is prone to rearrangements/Friedel-Crafts side-reactions, clearly indicating the presence of cationic behaviour on the carbon species.⁶¹ Whether a halide atom attacks the hydrosilane before/at

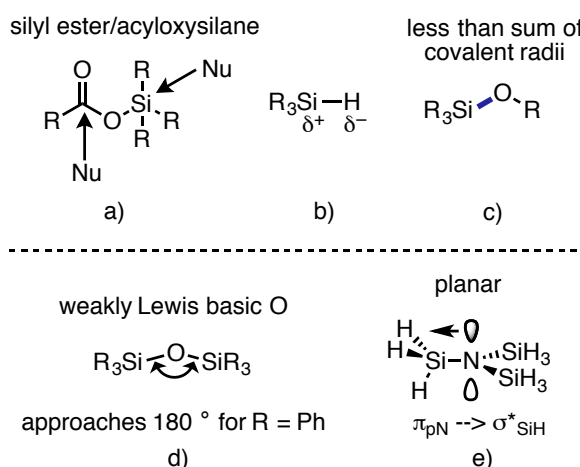
the same time as hydride transfer to the cation is uncertain, but the example in mechanism B suggests it might do.

The exact detail of the final mechanism is complicated by the extensive variety of chemistry available to hypercoordination silicon complexes. As discussed in the case of Corriu's CsF promoted reduction of ketones above, the final mechanism probably involves some extent of electrophile binding to the silicon centre – the dual activation manifold. This author advocates that, if in doubt, established penta- or hexacoordinate silicon species are preferred over elusive trivalent silicenium cations, which have been a controversial topic within silicon chemistry.⁶² In other words, non-activated silanes *do not* act as hydride donors unless extreme electrophiles are present (e.g. full carbocations).⁶³ The most successful systems are those in which the counterion of the activator is associated with the electrophile (as in mechanism D). This mechanism – nucleophilic activation – plays a large role in our investigations in Chapters 1-4. In Chapter 3, it is invoked in our trifluoroethylation procedure, which involves a reduction step. More generally, if the reduced species is a proton, then H₂ release occurs; this is the underlying process in all of the presented work relating to dehydrogenatively formed silyl esters.

Reagent Class: Acyloxysilanes / Silyl Esters and the Si–O bond

Silyl esters, also known as acyloxysilanes, are a relatively rarely encountered functional group in chemistry. They can be thought of as having two electrophilic centres (Figure 5A),⁶⁴ although attack at silicon is more common than attack at the carbonyl centre. Even less common are silyl esters with Si–H bonds, which are hydridic as discussed above (Figure 5B). These species are not well represented in the literature, and a large section of Chapter 2 explores their reactivity.

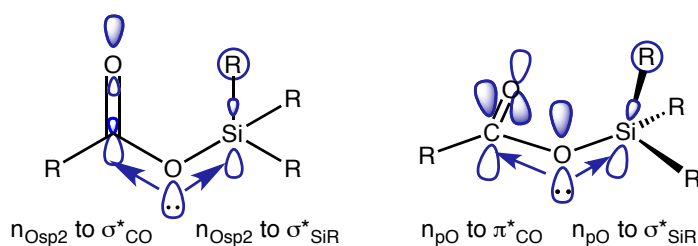
Figure 5. (A) Dual reactivity of silyl esters. (B) polarisation of silicon-hydrogen bonds. (C) Back-bonding in a Si–O bond leads to a short bond. (D) Siloxanes are *very* weakly Lewis basic at oxygen due to secondary orbital effects. (E) Significant secondary orbital effects leads to planarisation at nitrogen.



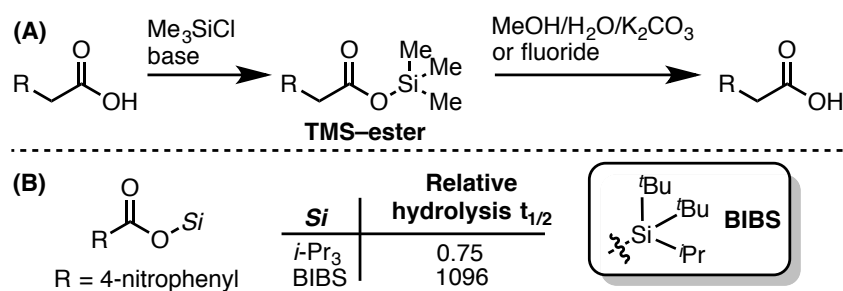
Silicon-oxygen bonds tend to be much shorter than the sum of the covalent radii (1.63-1.67 Å, rather than 1.83 Å),⁶⁵ unlike their carbon ether counterparts (Figure 5C),⁶⁶ reflected in the bond enthalpies (C–O 358 kJ mol⁻¹; Si–O 444 kJ mol⁻¹).⁶⁷ Indeed, siloxane ethers have much wider bond angles (Si–O–Si), indicating partial O–Si double bond character (Figure 5D).⁶⁷ The same applies to N–Si bonds, with trisilylamine being planar; trimethylamine is not (Figure 5E). This results in a much-decreased Lewis basicity of oxygen and nitrogen atoms connected to silicon,^{67,68} and a much-increased acidity of silanol relative to methanol.⁶⁷

Despite these bond length contractions, the O–Si bond is still longer than the corresponding O–C bond and, with the increased Si–R bond lengths factored in, it could be argued that the carbonyl carbon of a silyl ester is less sterically encumbered than a regular ester. In addition, with the oxygen able to delocalize residual negative charge into silicon–R-group antibonding orbitals (Figure 6), the siloxy moiety should be a better leaving group than the corresponding alkoxy one.

Figure 6. Some secondary molecular orbital interactions in silyl esters.



Whilst silyl ethers are commonly encountered as protecting groups for alcohols, silyl esters have received relatively little recent attention in the arena of organic synthesis. Perhaps most familiar of the few exceptions are the use as a protected carboxylic acid,^{69,70} which are readily unmasked by hydrolysis under relatively mild conditions, or with fluoride (Scheme 7).

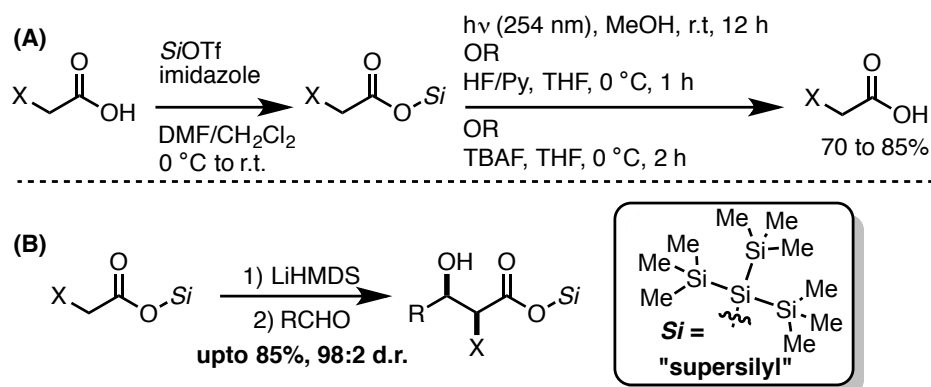


Scheme 7. (A) Synthesis of silyl esters from chlorosilanes, deprotection with fluoride or methanol; (B) Relative rates of hydrolysis of silyl esters are dictated by sterics.

Silyl esters are said to be stable in the absence of moisture,⁷¹ and the kinetic stability of the ester with respect to hydrolysis is generally improved by increasing steric bulk around silicon,^{72,73} for example the BIBS ester,⁷⁴ as cleavage occurs via attack at silicon.⁷¹ Despite this, early experiments in which ¹⁸O labeled water was used is consistent with hydrolysis of the multisilylester tetraacetoxysilane occurring *at the carbonyl group*.⁷⁵

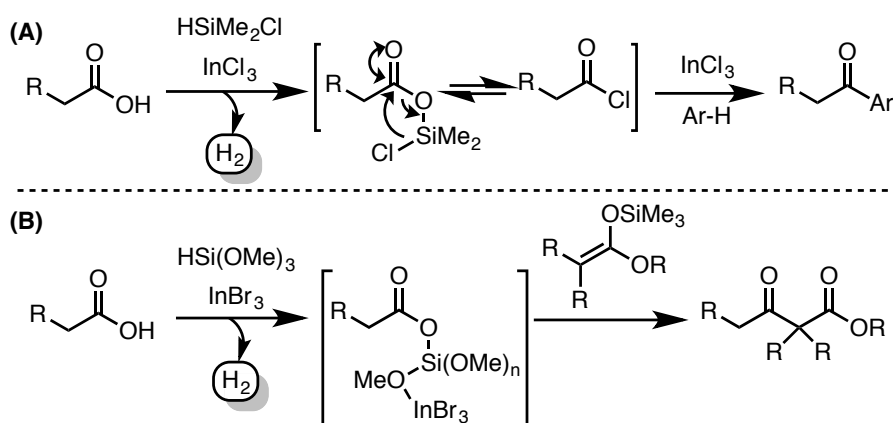
More sterically bulky analogues, such as the recently described super-silyl ester (Scheme 8), allow somewhat harsher conditions to be used in the presence of the silyl ester. The ester is stable to LiHMDS and Grignard reagents, and enolates can be formed with BuLi. Treatment with MeLi resulted in methylation at silicon; however, the ester was stable to

DIBAL-H reduction. The super-silyl group has been applied usefully in synthesis by the group of Yamamoto, and can be removed by fluoride or UV irradiation.⁷⁶⁻⁷⁸



Scheme 8. (A) Yamamoto's supersilyl ester synthesis and deprotection. (B) Application of supersilyl esters in synthesis.⁷⁸

Silyl esters have been used like regular esters in titanium carbene transformations to form silyl enol ethers,⁷⁹ and have also been converted into their disilyl ketene acetals,⁸⁰ which are useful enolate equivalents. Notwithstanding the foregoing examples, use of silyl esters as reactive species *in their own right* appears uncommon, with the exception of some recent work by Baba, who has reported them as intermediates in a cross-Claisen condensation and a Friedel-Crafts acylation (Scheme 9).^{81,82} *In both cases, the silyl ester functions as an activated carboxylic acid.*



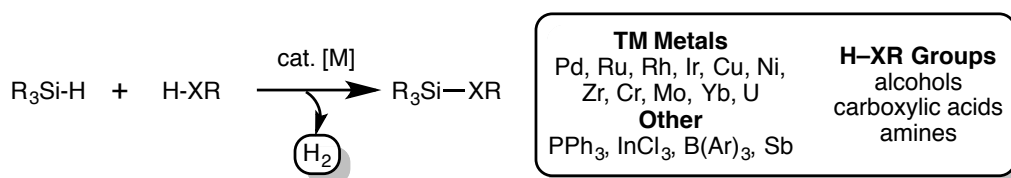
Scheme 9. (A) Baba's Friedel-Crafts acylation using a silyl ester electrophile.⁸² (B) Baba's cross-Claisen reaction via a silyl ester.⁸¹

In the first case, Baba was able to show that the active electrophilic species was likely the acid chloride, which was probably generated intramolecularly from the silyl ester intermediate. Note that the carboxylic acid initially displaces hydride over chloride. In the second case, it is thought that the methoxy groups on the silane coordinate to indium tribromide, increasing the electrophilicity at the carbonyl carbon by withdrawing electron density from the C–OSi bond, presumably specifically reducing the additional $\pi\text{O}_{\text{LP}} \rightarrow \pi^*_{\text{C=O}}$ interaction. Both reactions involve the initial dehydrogenative silanation of the carboxylic acid O–H with a Si–H bond.

Silyl esters are generally considered to be electrophilic at silicon,^{71,83} particularly for oxygen based nucleophiles, with carbonyl attack reportedly favoured for carbon nucleophiles and increasing bulk around silicon.⁶⁴ In contrast to this report, carboxylic acids have been esterified from orthosilicates, in which the alkoxide residues on silicon are apparently transferred to the acyloxy group.⁸⁴ This may result from initial carboxylate attack at silicon, and intramolecular transfer (*vide infra*). In Baba's work, the chloride migration is also purportedly intramolecular.

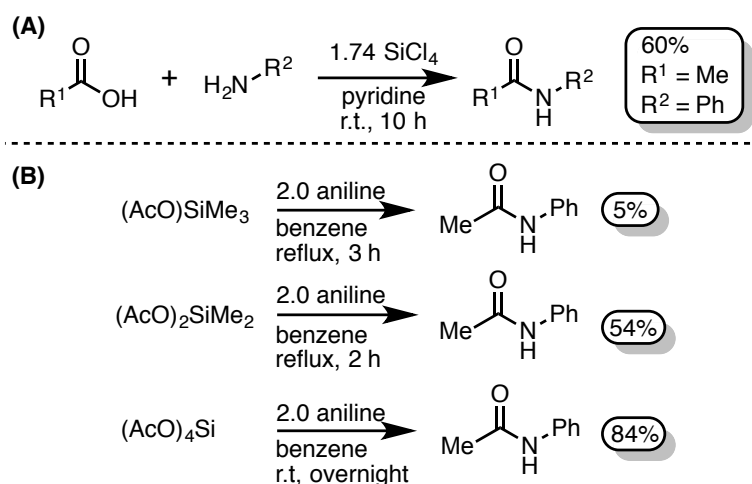
Silyl Esters as Activated Carboxylic Acids for Amidation

In Chapter 2, we explore the use of acyloxysilanes as activated carboxylic acids, specifically for amide coupling reactions. This reaction, which releases only hydrogen, offers a clean method of carboxyl activation, without the release of HCl or other acids. This negates the need for stoichiometric base additives, which are a common component in many stoichiometrically activated amide-coupling reactions. There have been many recent developments in Si–H activation for reaction with RX–H bonds (X = O,N) using catalysts, often transition metals, to form Si–XR bonds (Scheme 10).^{85–96}



Scheme 10. General scheme for metal catalysed dehydrogenative silanation of X-H groups with Si-H bonds⁸⁵⁻⁹⁶

Acyloxysilanes themselves have been investigated in the past as an activated carboxylic acid species in amidation reactions, but were typically accessed from chlorosilanes, particularly tetrachlorosilane. The approach seems to have been researched by Russian chemists prior to 1960,⁷⁵ and independently rediscovered in the West by Chan.^{97,98} The (rediscovered) method reported by Chan (Scheme 11) was concluded to be of little utility in synthesis for several reasons. Aliphatic amines, for example, were poor substrates, probably due to deactivation by the HCl salts present. However, the oligomeric siloxane by-products were described as being much more readily removed than the acylureas that are sometimes observed as by-products with *N,N*-dicyclohexylcarbodiimide (DCC) coupling.

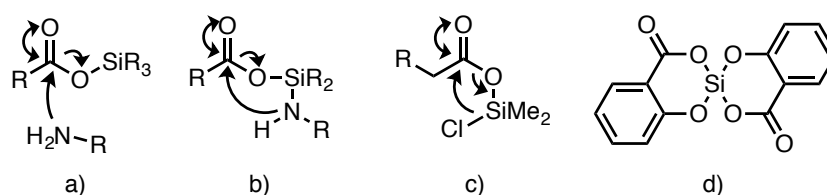


Scheme 11. (A) Chan and Wong's amidation reaction using tetrachlorosilane as a dehydrating agent. (B) Chan and Wong's demonstration of the varying reactivity of different silyl esters.⁹⁷

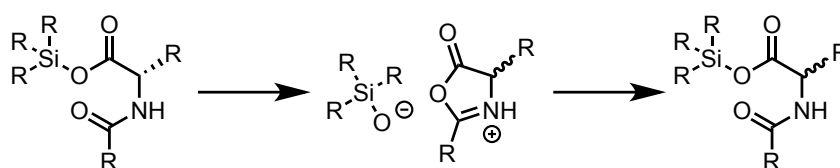
The highly reactive and dehydrating nature of SiCl₄ also led to some poor functional group tolerance. For example, esters were deprotected *in situ*, leading to polymeric peptides. This affinity of ester oxygen atoms for silicon has been utilised more recently in an intriguing halosilation methodology, opening lactones.⁹⁹

Further work by Chan led to the conclusion that the silyl esters could be preformed, and that the reactivity of the silyl ester depended the substitution number at silicon (Scheme 11B).⁹⁸ For example, increasing the number of acyloxy groups at silicon gave significantly better conversions and under milder conditions. It is uncertain whether the steric environment around silicon is to blame for the lack of reactivity at carbon for the monoacyloxysilanes. Electronic changes, or the change in reactive valency at silicon could be the root of the differential reactivity. The authors do not speculate further, except to favour an intramolecular amine delivery mechanism (Figure 7b), based on the lack of reactivity from species (d).

Figure 7. (A) Intermolecular amidation; (B) Intramolecular amidation; (C) Baba's proposed intramolecular chloride transfer;⁸² (D) A silyl ester that is resistant to amidation.

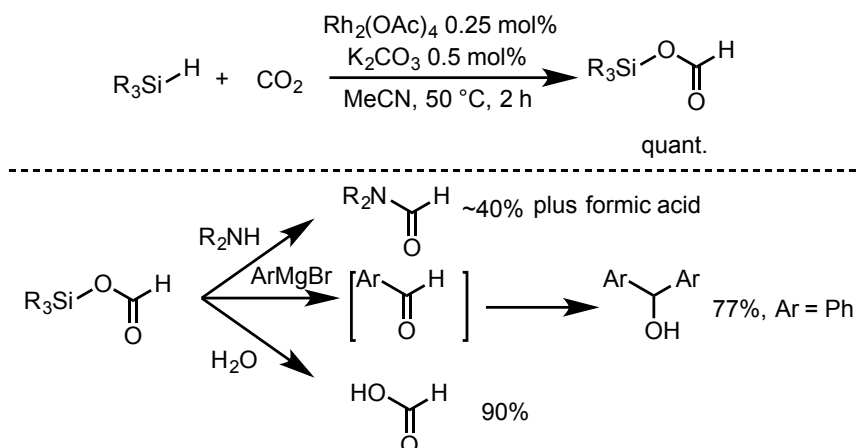


Perhaps the most damning verdict of the methodology is that optically active acetyl-protected amines were racemised, with the activated silyl ester being trapped intramolecularly as the oxazolone, which was found to be optically inactive (Scheme 12).



Scheme 12. Chan's observation of racemisation of amino acids, which restricts use of the amidation reaction for peptide synthesis.⁹⁸

In 2013, the group of Mizuno described a rhodium-catalysed silylation of CO₂ to generate silyl formate species from a range of monohydridosilanes. These silyl esters were formed at 50 °C in acetonitrile, and then acted as electrophiles with amines to form formamides, Grignards to form aldehydes/alcohols, and water to form formic acid (Scheme 13).¹⁰⁰



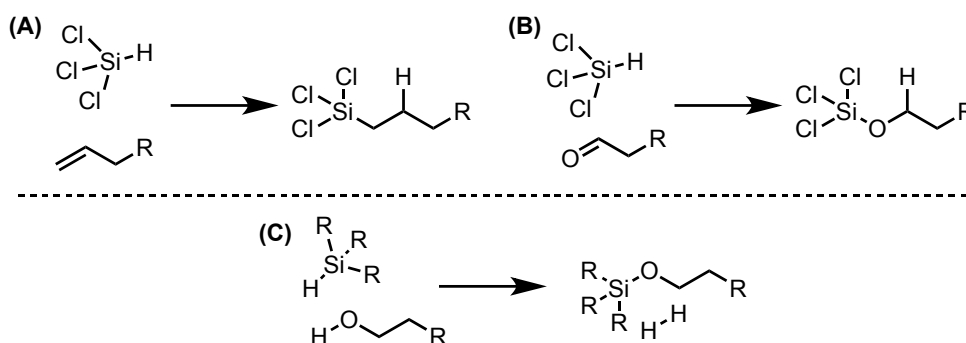
Scheme 13. Mizuno's formation silyl formates and reactions with nucleophiles.¹⁰⁰

In Chapters 1 and 2, we investigate the mechanism of a third method of silyl ester generation; an under-explored base-catalysed dehydrogenative process. This method retains the clean activation that transition metals offer, but without the use of metals, and avoids the issues of acid release that chlorosilanes suffer from.

Base-Catalysed Silane Activation

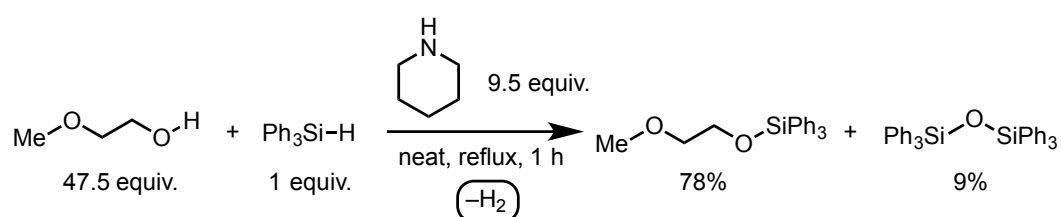
The activation of hydrosilanes with base remains mysteriously unappreciated in the organic synthesis literature. Recalling the extensive list of metal catalysts that have been recently reported to generate new O–Si and N–Si bonds from O–H/N–H and H–Si bonds, it is perhaps *surprising* to these chemists that a simple amine can perform the task in many cases, certainly for alcohols and carboxylic acids.

Hydrosilylation is a well-known process, which is essentially an addition across an unsaturated system; a reduction. This typically needs a metal catalyst to activate the Si–H bond, or increase the polarity of the unsaturated bond. But it is also possible, in the absence of unsaturation, to reduce a *proton* with hydride, releasing hydrogen; a process that can be termed dehydrogenation (Scheme 14).



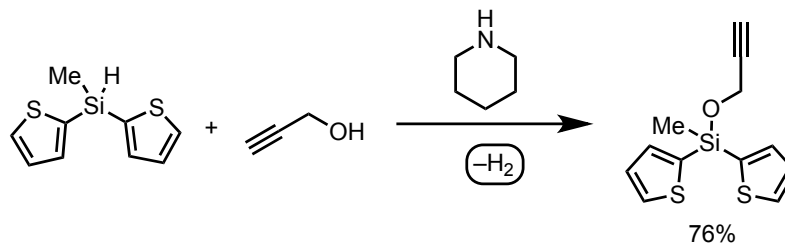
Scheme 14. (A) Hydrosilylation across an alkene; B) Hydrosilylation across a carbonyl group; (C) Hydrosilylation across an O–H bond, leading to dehydrogenation.

In the latter case (Scheme 14C), the reaction is slow, but can be enhanced by the addition of a base. This ‘loosens’ the O–H bond enough to allow interaction by the heteroatom at the Lewis-acidic silicon centre. The additional electron density from this heteroatom is dispersed through to the Si–H bond, increasing its hydridic nature. In the previous cases (A and B), the δ^+ centre is a carbon atom, and so reduction occurs. In this case, the δ^+ centre is a proton, and thus dehydrogenation follows. This theory is not widely appreciated in the literature, but experimental evidence is reviewed by Lukevics and co-workers, who contributed to much of the current understanding.¹⁰¹ Early evidence was reported only in European patents and Russian journals in the 1960s, but the most pertinent early example describes the piperidine-catalysed dehydrogenative silyl ether formation from alcohols and triphenylsilane (Ph_3SiH).¹⁰² The method reported good to moderate yields with simple alcohols and silanols, but suggested that chlorosilanes remained the preferred method for synthesis of triaryl silyl ethers¹⁰³ and siloxanes.¹⁰⁴ No further studies were attempted in this limited communication (Scheme 15).



Scheme 15. Gilman's piperidine catalysed dehydrogenative silyl ether formation.¹⁰²

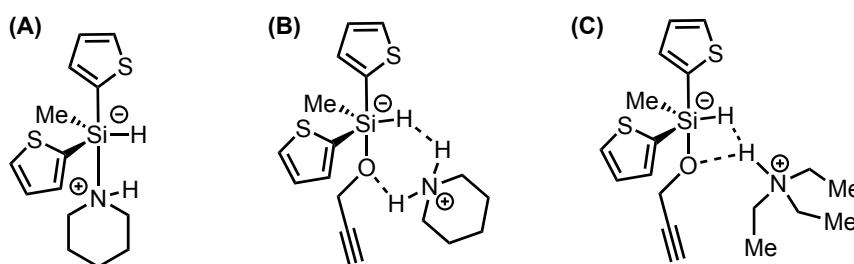
The remainder of this review consists of work (published in Russian) by Lukevics and colleagues. Alcohols react in the presence of piperidines with heteroaryl hydrosilanes releasing hydrogen (Scheme 16).



Scheme 16. Lukevics' piperidine catalysed dehydrogenative silyl ether formation. The conditions are unknown, but the reaction proceeds at 33 °C in polar solvents with 10 mol% piperidine.¹⁰¹

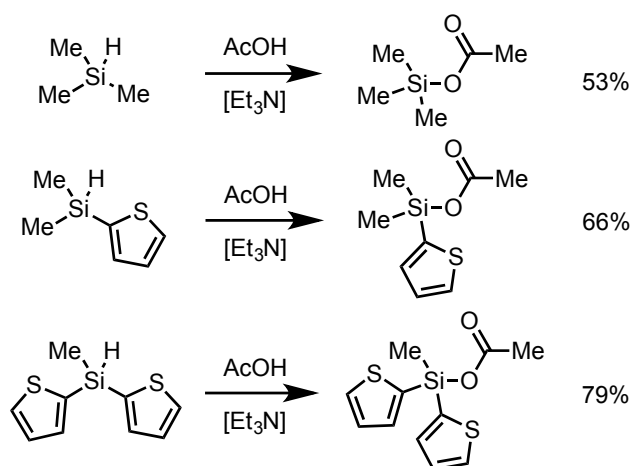
The rate of the reaction is improved in polar solvents, and especially enhanced with piperidine as base. There is no reaction for pyridine or *N,N*-diethylaniline under these conditions, but the reaction rate increases slowly, but expectedly, with increasing basicity; substituted piperidines of varying p*K*_aH (increases by 5 times over p*K*_aH values of 8.11 to 9.94). Triethylamine also conforms to the rate pattern. However, piperidine is ~ 17 times faster than triethylamine, despite only having a modestly increased p*K*_aH (11.22 vs 10.76 for Et₃N). Although it is tempting to suggest a nucleophilic catalysis (Figure 8A), an alternative suggestion involves a concerted mechanism involving a six-membered ring, unavailable for tertiary bases (Figure 8B). Sterics around nitrogen may also play a role.

Figure 8. Potential hydride activation mechanisms; (A) Nucleophilic catalysis; (B) concerted deprotonation/hydride transfer possible for privileged secondary amines; (C) Proton loosening and hydride transfer.



The rate is also faster for more acidic alcohols. Phenols are particularly effective, and appear to react faster with increasing acidity up to a point; *p*-chlorophenol, however, is faster than

p-nitrophenol (perhaps a balance between acidity and nucleophilicity). Sterically hindered systems are predictably slower, out-weighing electronic effects in amino alcohols. Oximes are also viable substrates, notably reacting without reduction of either N–O or N=C bonds. Carboxylic acids undergo a base-catalysed silyl ester formation in the presence of piperidine. Silyl ester formation yields increase with increasing numbers of aryl ligands in place of methyl groups, indicating electronic requirements at silicon (Scheme 17).



Scheme 17. Lukevics' demonstration of differing reactivity towards silyl ester formation with changing silicon electronics.¹⁰¹

Amidation is not reported by Lukevics; triethylamine is the only base reported with carboxylic acids. Interestingly, the rate of silyl ester formation is slower for stronger acids, unlike the alcohol series mentioned above. There may be a balance between acidity to form a sufficient anion, and the nucleophilicity of that anion. Alternatively, more acidic acids may inactivate a nucleophilic base (although this seems an unlikely mechanism for hindered silanes.)

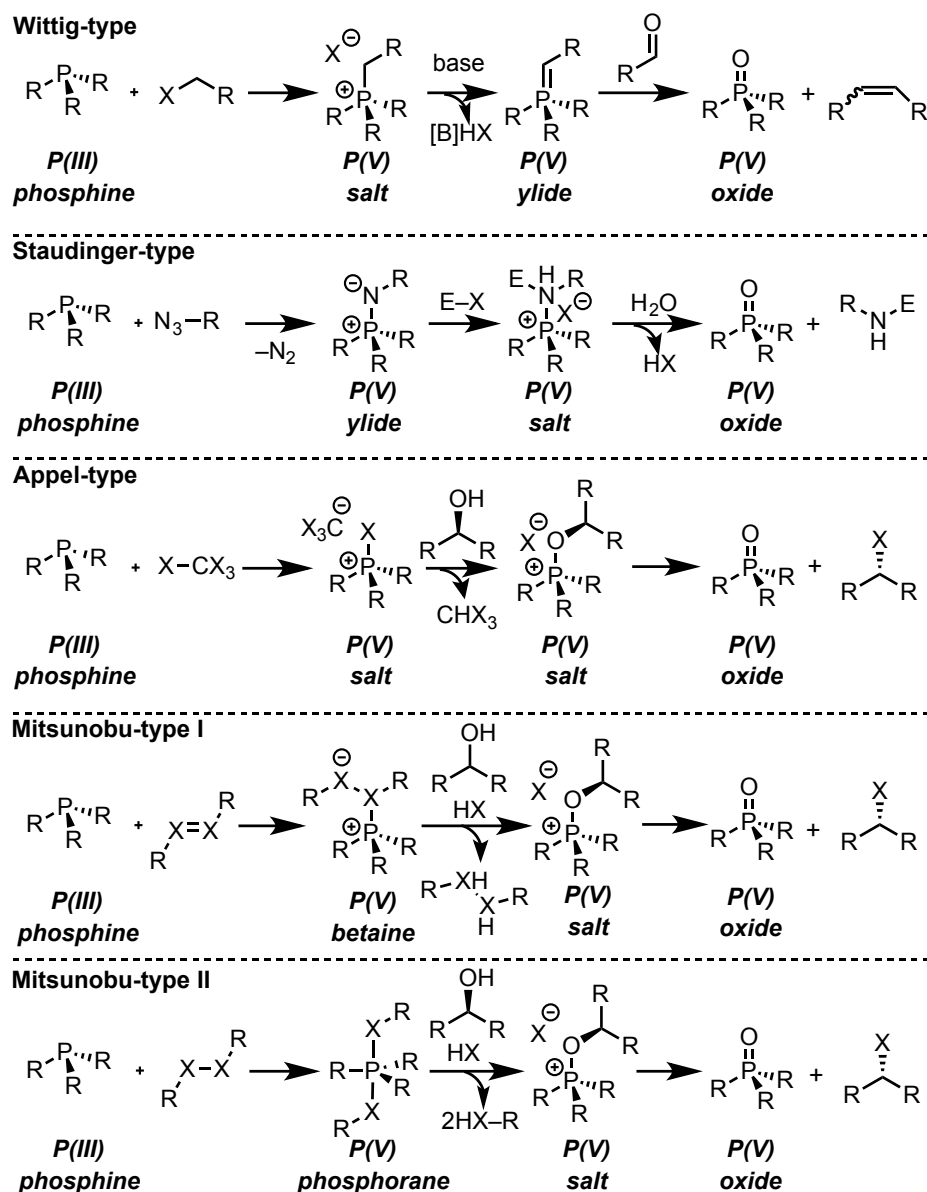
In general, silanes with more electron-withdrawing groups are better substrates for dehydrogenation reactions, consistent with a rate-limiting step involving complexation at silicon. That an isotope effect is observed for ethanol [$k(\text{SiH})/k(\text{SiD}) = 1.65$ and $k(\text{OH})/k(\text{OD}) = 1.35$] may suggest a somewhat concerted mechanism, in which

complexation and hydrogen-loss occur essentially simultaneously. Carboxylic acids may be an exception if full ion pair formation occurs, which may be required to generate enough nucleophilicity at the nucleophilic oxygen atom. The authors are in concordance about the mechanism, indicating they favour N–H partial hydrogen abstraction from OH, or full abstraction for the more acidic substrates.

No silyl ester formation has been studied in the context of amidation from phenylsilane, as we do in Chapters 1-3. However, there are related *observations* in a number of reports. In 2014, Beller and co-workers reported a direct reductive alkylation of carboxylic acids and amines using a platinum catalyst and phenylsilane ‘as the hydride source’. They acknowledge the presence of amides in the reaction mixture, but do not contemplate silyl ester mediated amidation.¹⁰⁵ This reaction will be described in more detail in *Chapter 2*. The group of Cantat have published several times in the area, in both cases forming amides from CO₂ and amines. These reactions, and others, are reflected on at the end of Chapter 4, and the role of silyl esters considered;^{106,107} Cantat explicitly notes the potential role of a silyl formate in one case,¹⁰⁸ but seems less sure in another.¹⁰⁶

Introduction to the Redox Chemistry of Phosphorus

In Chapter 6, we turn to phosphorus as our atom with hypercoordination tendencies. Classical reactions of phosphorus represent fundamental transformations in organic chemistry. The most familiar all follow a general deoxygenation pathway: oxidative activation of P(III) as a reactive P(V) species, followed by a thermodynamic collapse to give a stable phosphine oxide and a deoxygenated product (Scheme 18).

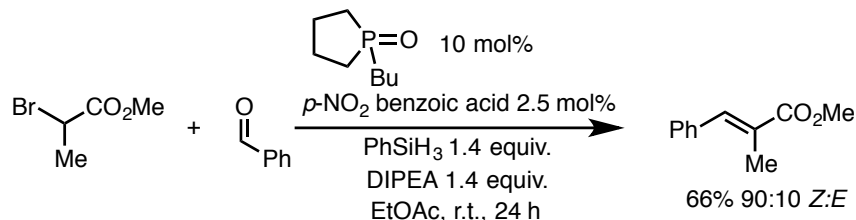


Scheme 18. The basic reactivity and intermediates observed in classical phosphorus-mediated synthesis transformations.

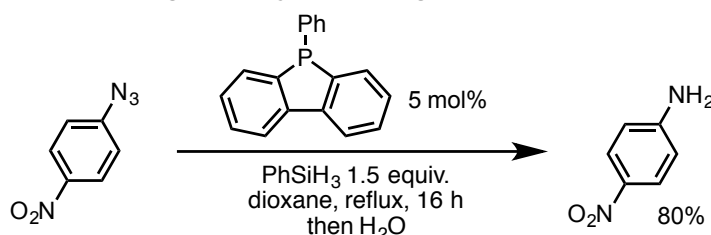
Although incredibly powerful, these reactions often suffer from the need to activate the phosphorus(III) precursor with toxic additives, and the stoichiometric phosphine oxide by-product, which can interfere with purification, and is a relatively high molecular weight form of waste, certainly for triarylphosphine oxides. As such, in the last decade, attention has turned to developing catalytic versions of these reactions. There are two main approaches: The redox neutral cycle,^{109–117} in which the product P(V) species is dehydrated to regenerate the active phosphorus(V) species again; and the P(III)-P(V) redox cycle, in

which the product P(V) is reduced to P(III), which is then reactivated as P(V). Some pertinent examples are given in Scheme 19.

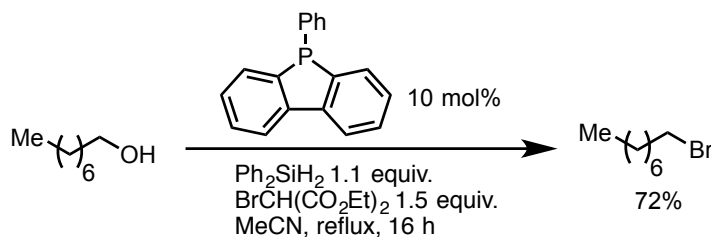
O'Brien's Organocatalytic Wittig Reaction



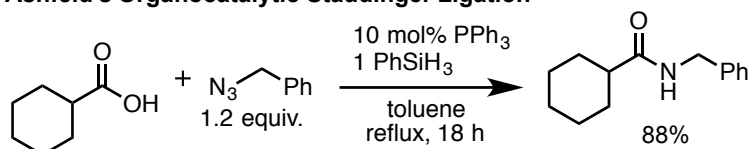
van Delft's Organocatalytic Staudinger Reaction



van Delft's Organocatalytic Appel Reaction



Ashfeld's Organocatalytic Staudinger Ligation



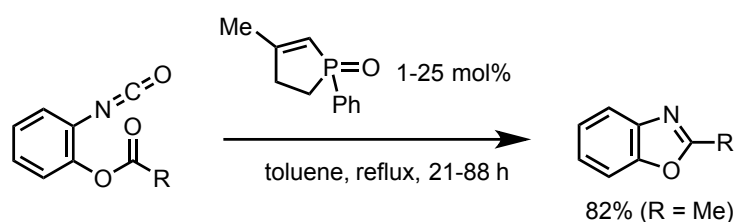
Scheme 19. A selection of representative redox-cycle phosphorus-mediated reactions using silanes to regenerate P(III) from P(V).^{110,112,115,116}

In each case, the silane, either diphenylsilane or phenylsilane, is described as a terminal reductant, and its role is only to reduce the phosphine oxide back to the phosphine, so that the normal P(III)-P(V) chemistry can occur. What appears to have been overlooked in these cases is that reactions that would normally require excess silane are proceeding in relatively low amounts, under less forcing conditions and over shorter times. We explore this observation in the case of O'Brien's catalytic Wittig reaction¹¹⁵ (Chapter 4) and

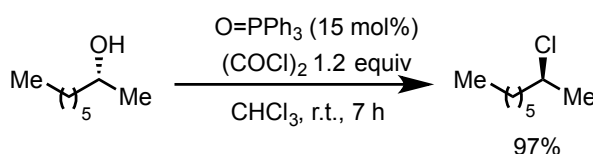
Ashfeld's Staudinger ligation¹¹⁶ (Chapter 1), concluding that *in situ*-activated silanes are generated under the reaction conditions and explain the unexpected activity in both cases.

The redox-neutral approach has been explored by ourselves, but the recent interest in this approach began with Marsden and colleagues, who synthesised phenanthridines and benzoxazoles from the relevant isocyanate substituted aryl precursor (Scheme 20),¹¹⁸ inspired by work performed in the 1960s.¹¹⁹

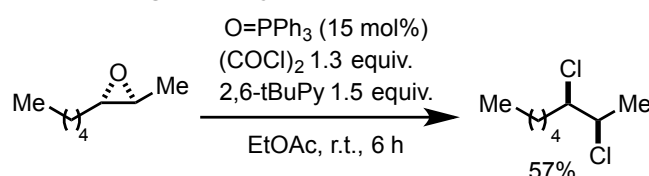
Marsden's Organocatalytic Aza-Wittig Synthesis of Heterocycles



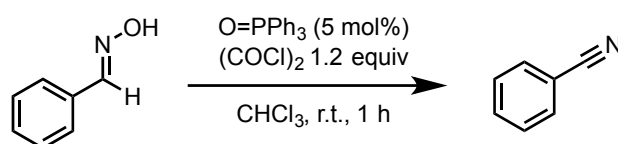
Denton's Organocatalytic Appel Reaction



Denton's Organocatalytic Dichlorination of Epoxides



Denton's Organocatalytic Dehydration of Oximes



Scheme 20. A selection of representative redox-neutral organocatalytic phosphorus-mediated reactions.^{118,120–122}

We have demonstrated the concept using oxalyl chloride to reactivate the phosphorus component in a number of processes.^{121–124} Xu and co-workers have also utilised this approach.¹²⁵ With the exception of the Marsden approach, every example given here, in both the redox-neutral and redox-cycle manifolds, relies on an additional reagent to

turnover the phosphorus species; oxalyl chloride in the former, and a silane in the latter. In this respect, it is arguable that the two approaches are two variants of the same general strategy; dehydration of a substoichiometric phosphorus(V) species using an orthogonal chemical desiccant. Marsden narrowly escapes this classification by building his activation moiety into the substrate, the isocyanate. None of the above procedures releases the true, theoretical-ideal by-product – water – and none of the procedures tackles one of the most important phosphorus reactions; the Mitsunobu reaction. We investigate a redox-neutral, organocatalytic phosphorus-mediated Mitsunobu reaction that releases water as the only by-product in Chapter 6.

References

- 1 J. I. Musher, *Angew. Chem. Int. Ed.*, 1969, **8**, 54–68.
- 2 W. B. Jensen, *J. Chem. Educ.*, 2006, **83**, 1751.
- 3 E. Magnusson, *J. Am. Chem. Soc.*, 1990, **112**, 7940–7951.
- 4 P. von Ragué van Schleyer, *Chem. Eng. News*, 1984, **62**, 4.
- 5 D. W. Smith, *J. Chem. Educ.*, 2005, **82**, 1202.
- 6 W. B. Jensen, *Chem. Rev.*, 1978, **78**, 1–22.
- 7 R. J. Gillespie and E. A. Robinson, *Inorg. Chem.*, 1995, **34**, 978–979.
- 8 C. A. Ramsden, *Chem. Soc. Rev.*, 1994, **23**, 111–118.
- 9 E. L. Muetterties, *Acc. Chem. Res.*, 1970, **3**, 266–273.
- 10 R. R. Holmes, *Chem. Rev.*, 1996, **96**, 927–950.
- 11 L. D. Quin, *A Guide to Organophosphorus Chemistry*, John Wiley & Sons, 2000.
- 12 R. Hoffmann, J. M. Howell and E. L. Muetterties, *J. Am. Chem. Soc.*, 1972, **94**, 3047–3058.
- 13 S. M. Godfrey, C. A. McAuliffe, Robin G. Pritchard, R. G. Pritchard, J. M. Sheffield

- and G. M. Thompson, *J. Chem. Soc. Dalt. Trans.*, 1997, 4823–4828.
- 14 S. M. Godfrey, C. A. McAuliffe, I. Mushtaq, R. G. Pritchard and J. M. Sheffield, *J. Chem. Soc. Dalt. Trans.*, 1998, 3815–3818.
- 15 E. V Jennings, K. Nikitin, Y. Ortin and D. G. Gilheany, *J. Am. Chem. Soc.*, 2014, **136**, 16217–16226.
- 16 S. M. Godfrey, C. A. McAuliffe, R. G. Pritchard and J. M. Sheffield, *Chem. Commun.*, 1996, 2521–2522.
- 17 S. Matsukawa, S. Kojima, K. Kajiyama, Y. Yamamoto, K. Akiba, S. Re and S. Nagase, *J. Am. Chem. Soc.*, 2002, **124**, 13154–13170.
- 18 S. Kojima, M. Nakamoto and K. Akiba, *European J. Org. Chem.*, 2008, **2008**, 1715–1722.
- 19 K. Kajiyama, M. Yoshimune, S. Kojima and K. Akiba, *European J. Org. Chem.*, 2006, **2006**, 2739–2746.
- 20 S. Kojima, K. Kajiyama, M. Nakamoto, S. Matsukawa and K. Akiba, *European J. Org. Chem.*, 2006, **2006**, 218–234.
- 21 K. Kajiyama, M. Yoshimune, M. Nakamoto, S. Matsukawa, S. Kojima and K. Akiba, *Org. Lett.*, 2001, **3**, 1873–1875.
- 22 X.-D. Jiang, S. Matsukawa, K.-I. Kakuda, Y. Fukuzaki, W.-L. Zhao, L.-S. Li, H.-B. Shen, S. Kojima and Y. Yamamoto, *Dalton Trans.*, 2010, **39**, 9823–9829.
- 23 S. A. Bone, S. Trippett and P. J. Whittle, *J. Chem. Soc. Perkin Trans. 1*, 1977, 437.
- 24 M. Nakamoto, S. Kojima, S. Matsukawa, Y. Yamamoto and K. Akiba, *J. Organomet. Chem.*, 2002, **643–644**, 441–452.
- 25 X.-D. Jiang, S. Matsukawa and Y. Yamamoto, *Dalton Trans.*, 2008, 3678–3687.
- 26 X.-D. Jiang, S. Matsukawa, H. Yamamichi, K. Kakuda, S. Kojima and Y. Yamamoto, *European J. Org. Chem.*, 2008, **2008**, 1392–1405.
- 27 K.-Y. Akiba, K. Kajiyama, M. Yoshimune, M. Nakamoto and S. Kojima, *Phosphorus. Sulfur. Silicon Relat. Elem.*, 1999, **144**, 561–564.

- 28 K. C. Kumara Swamy and N. Satish Kumar, *Acc. Chem. Res.*, 2006, **39**, 324–333.
- 29 P. Kommana, N. Satish Kumar, J. J. Vittal, E. G. Jayasree, E. D. Jemmis and K. C. Kumara Swamy, *Org. Lett.*, 2004, **6**, 145–148.
- 30 D. G. Gilheany, *Chem. Rev.*, 1994, **94**, 1339–1374.
- 31 H. Sakurai, *Synlett*, 1989, **1989**, 1–8.
- 32 S. Rendler and M. Oestreich, *Synthesis*, 2005, **2005**, 1727–1747.
- 33 R. J. P. Corriu, C. Guerin, B. J. L. Henner and W. W. C. Wong Chi Man, *Organometallics*, 1988, **7**, 237–238.
- 34 T. Cottrell, *The Strengths of Chemical Bonds*, London Butterworths, 2D ed., 1961.
- 35 J. Boyer, R. J. P. Corriu, R. Perz and C. Reye, *Tetrahedron*, 1981, **37**, 2165–2171.
- 36 S. Kohra, H. Hayashida, Y. Tominaga and A. Hosomi, *Tetrahedron Lett.*, 1988, **29**, 89–92.
- 37 L. H. Sommer and W. D. Korte, *J. Am. Chem. Soc.*, 1967, **89**, 5802–5806.
- 38 C. Breliere, F. Carre, R. J. P. Corriu, M. Poirier and G. Royo, *Organometallics*, 1986, **5**, 388–390.
- 39 W. H. Nebergall, *J. Am. Chem. Soc.*, 1950, **72**, 4702–4704.
- 40 M. Kira, K. Sato and H. Sakurai, *Chem. Lett.*, 1987, 2243–2246.
- 41 M. Kira, K. Sato and H. Sakurai, *J. Am. Chem. Soc.*, 1988, **110**, 4599–4602.
- 42 M. Kira, K. Sato and H. Sakurai, *J. Org. Chem.*, 1987, **52**, 948–949.
- 43 S. E. Denmark and G. L. Beutner, *Angew. Chem. Int. Ed.*, 2008, **47**, 1560–638.
- 44 S. E. Denmark, R. F. Sweis and D. Wehrli, *J. Am. Chem. Soc.*, 2004, **126**, 4865–4875.
- 45 S. E. Denmark and J. D. Baird, *Chem. Eur. J.*, 2006, **12**, 4954–4963.
- 46 S. E. Denmark and R. F. Sweis, *Acc. Chem. Res.*, 2002, **35**, 835–846.
- 47 S. E. Denmark, D. M. Coe, N. E. Pratt and B. D. Griedel, *J. Org. Chem.*, 1994, **59**,

6161–6163.

- 48 S. E. Denmark and B. D. Griedel, *J. Org. Chem.*, 1994, **59**, 5136–5138.
- 49 S. E. Denmark and R. A. Stavenger, *Acc. Chem. Res.*, 2000, **33**, 432–440.
- 50 S. E. Denmark and J. Fu, *Chem. Rev.*, 2003, **103**, 2763–2794.
- 51 J. E. Huheey, *Inorganic chemistry: principles of structure and reactivity*, Harper & Row, 1983.
- 52 H. Nishiyama, S.-B. Park and K. Itoh, *Tetrahedron: Asymmetry*, 1992, **3**, 1029–1034.
- 53 B. H. Lipshutz, K. Noson, W. Chrisman and A. Lower, *J. Am. Chem. Soc.*, 2003, **125**, 8779–8789.
- 54 S. H. Bergens, P. Noheda, J. Whelan and B. Bosnich, *J. Am. Chem. Soc.*, 1992, **114**, 2128–2135.
- 55 S. B. Duckett and R. N. Perutz, *Organometallics*, 1992, **11**, 90–98.
- 56 M. Brookhart and B. E. Grant, *J. Am. Chem. Soc.*, 1993, **115**, 2151–2156.
- 57 K. Riener, M. P. Högerl, P. Gigler and F. E. Kühn, *ACS Catal.*, 2012, **2**, 613–621.
- 58 A. H. Jackson, P. Johnston, G. W. Kenner, R. W. H. Berry, P. Brocklehurst, G. H. Cheeseman, E. K. Nunn, E. H. M. Wright, E. Thomas, R. W. Hay, P. P. Williams, A. C. M. Finch, K. D. Berlin, G. P. Sturm, P. G. Nield, J. D. Austin and C. Eaborn, *J. Chem. Soc.*, 1964, 2262–2280.
- 59 C. Cheng and M. Brookhart, *J. Am. Chem. Soc.*, 2012, **134**, 11304–11307.
- 60 S. Park and M. Brookhart, *J. Am. Chem. Soc.*, 2012, **134**, 640–653.
- 61 M. P. Doyle, C. C. McOske and C. T. West, *J. Org. Chem.*, 1976, **41**, 1393–1396.
- 62 C. Eaborn, *J. Organomet. Chem.*, 1991, **405**, 173–177.
- 63 H. Mayr, N. Basso and G. Hagen, *J. Am. Chem. Soc.*, 1992, **114**, 3060–3066.
- 64 P. F. Hudrlik and R. Feasley, *Tetrahedron Lett.*, 1972, **13**, 1781–1784.
- 65 M. G. Voronkov, V. P. Mileshekevich and Y. A. Yuzhelevskii, *The siloxane bond*:

physical properties and chemical transformations, New York, 1978.

- 66 F. H. Allen and A. J. Kirby, *J. Am. Chem. Soc.*, 1984, **106**, 6197–6200.
- 67 E. Wiberg and N. Wiberg, *Inorganic Chemistry*, Academic Press, 2001.
- 68 I. Fleming, *Molecular Orbitals and Organic Chemical Reactions*, Wiley, Reference., 2009, vol. 2009.
- 69 E. J. Corey and C. U. Kim, *J. Org. Chem.*, 1973, **38**, 1233–1234.
- 70 A. M. Castano and A. M. Echavarren, *Tetrahedron*, 1992, **48**, 3377–3384.
- 71 M. C. Kung, M. V Rioski, M. N. Missaghi and H. H. Kung, *Chem. Commun.*, 2014, **50**, 3262–3276.
- 72 H. Yoshimura, K. Eto, K. Takahashi, J. Ishihara and S. Hatakeyama, *Chem. Pharm. Bull.*, 2012, **60**, 1334–1339.
- 73 A. Iwasaki, Y. Kondo and K. Maruoka, *J. Am. Chem. Soc.*, 2000, **122**, 10238–10239.
- 74 H. Liang, L. Hu and E. J. Corey, *Org. Lett.*, 2011, **13**, 4120–4123.
- 75 Y. K. Yur'ev and Z. V Belyakova, *Russ. Chem. Rev.*, 1960, **29**, 383.
- 76 S. Oda and H. Yamamoto, *Org. Lett.*, 2013, **15**, 6030–6033.
- 77 J. Tan, M. Akakura and H. Yamamoto, *Angew. Chem. Int. Ed.*, 2013, **52**, 7198–7202.
- 78 S. Oda and H. Yamamoto, *Angew. Chem. Int. Ed.*, 2013, **52**, 8165–8168.
- 79 T. Takeda, T. Fukada and A. Tsubouchi, *Tetrahedron Lett.*, 2014, **55**, 1434–1436.
- 80 P. F. Hudrlik, R. R. Roberts, D. Ma and A. M. Hudrlik, *Tetrahedron Lett.*, 1997, **38**, 4029–4032.
- 81 Y. Nishimoto, A. Okita, M. Yasuda and A. Baba, *Angew. Chem. Int. Ed.*, 2011, **50**, 8623–8625.
- 82 S. A. Babu, M. Yasuda and A. Baba, *Org. Lett.*, 2007, **9**, 405–408.
- 83 D. R. Deardorff, S. Shambayati, R. G. Linde and M. M. Dunn, *J. Org. Chem.*, 1988, **53**, 189–191.

- 84 G. Sumrell and G. E. Ham, *J. Am. Chem. Soc.*, 1956, **78**, 5573–5575.
- 85 D. J. Parks, J. M. Blackwell and W. E. Piers, *J. Org. Chem.*, 2000, **65**, 3090–3098.
- 86 J. M. Blackwell, K. L. Foster, V. H. Beck and W. E. Piers, 1999, 4887–4892.
- 87 G. Liu, H. Zhao and T. Thiemann, *Synth. Commun.*, 2007, **37**, 2717–2727.
- 88 M. Chauhan, B. P. S. Chauhan and P. Boudjouk, *Org. Lett.*, 2000, **2**, 1027–1029.
- 89 Y. Ojima, K. Yamaguchi and N. Mizuno, *Adv. Synth. Catal.*, 2009, **351**, 1405–1411.
- 90 H. Q. Liu and J. F. Harrod, *Can. J. Chem.*, 1992, **70**, 107–110.
- 91 V. Volkis, C. Averbuj and M. S. Eisen, *J. Organomet. Chem.*, 2007, **692**, 1940–1950.
- 92 W. Xie, H. Hu and C. Cui, *Angew. Chem. Int. Ed.*, 2012, **51**, 11141–11144.
- 93 C. D. F. Königs, M. F. Müller, N. Aiguabella, H. F. T. Klare and M. Oestreich, *Chem. Commun.*, 2013, **49**, 1506–1508.
- 94 E. Matarasso-Tchiroukhine, *J. Chem. Soc. Chem. Commun.*, 1990, 681–682.
- 95 U. Schubert and C. Lorenz, *Inorg. Chem.*, 1997, **36**, 1258–1259.
- 96 T. Hayashi, C. Hayashi and Y. Uozumi, *Tetrahedron: Asymmetry*, 1995, **6**, 2503–2506.
- 97 T.-H. Chan and L. T. L. Wong, *J. Org. Chem.*, 1969, **34**, 2766–2767.
- 98 T.-H. Chan and L. T. L. Wong, *J. Org. Chem.*, 1971, **36**, 850–853.
- 99 A. Iwata, J. Ohshita, H. Tang, A. Kunai, Y. Yamamoto and C. Matui, *J. Org. Chem.*, 2002, **67**, 3927–3929.
- 100 S. Itagaki, K. Yamaguchi and N. Mizuno, *J. Mol. Catal. A Chem.*, 2013, **366**, 347–352.
- 101 E. Lukevics and M. Dzintara, *J. Organomet. Chem.*, 1984, **271**, 307–317.
- 102 H. Gilman, G. E. Dunn, H. Hartzfeld and A. G. Smith, *J. Am. Chem. Soc.*, 1955, **77**, 1287–1288.
- 103 H. Gilman and G. N. R. Smart, *J. Org. Chem.*, 1954, **19**, 441–450.

- 104 H. Gilman, H. N. Benedict and H. Hartzfeld, *J. Org. Chem.*, 1954, **19**, 419–427.
- 105 I. Sorribes, K. Junge and M. Beller, *J. Am. Chem. Soc.*, 2014, **136**, 14314–14319.
- 106 O. Jacquet, X. Frogneux, C. Das Neves Gomes and T. Cantat, *Chem. Sci.*, 2013, **4**, 2127–2131.
- 107 O. Jacquet, C. Das Neves Gomes, M. Ephritikhine and T. Cantat, *J. Am. Chem. Soc.*, 2012, **134**, 2934–2937.
- 108 C. Das Neves Gomes, O. Jacquet, C. Villiers, P. Thuéry, M. Ephritikhine and T. Cantat, *Angew. Chem.*, 2012, **124**, 191–194.
- 109 H. A. van Kalker, C. te Grotenhuis, F. S. Haasjes, C. R. A. Hommersom, F. P. J. T. Rutjes and F. L. van Delft, *European J. Org. Chem.*, 2013, **2013**, 7059–7066.
- 110 H. A. van Kalker, S. H. A. M. Leenders, C. R. A. Hommersom, F. P. J. T. Rutjes and F. L. van Delft, *Chem. Eur. J.*, 2011, **17**, 11290–11295.
- 111 H. A. van Kalker, F. L. van Delft and F. P. J. T. Rutjes, *ChemSusChem*, 2013, **6**, 1615–1624.
- 112 H. A. van Kalker, J. J. Bruins, F. P. J. T. Rutjes and F. L. van Delft, *Adv. Synth. Catal.*, 2012, **354**, 1417–1421.
- 113 D. C. Lenstra, F. P. J. T. Rutjes and J. Mecinović, *Chem. Commun.*, 2014, **50**, 5763–5766.
- 114 C. J. O'Brien, J. L. Tellez, Z. S. Nixon, L. J. Kang, A. L. Carter, S. R. Kunkel, K. C. Przeworski and G. A. Chass, *Angew. Chem. Int. Ed.*, 2009, **48**, 6836–6839.
- 115 C. J. O'Brien, F. Lavigne, E. E. Coyle, A. J. Holohan and B. J. Doonan, *Chem. Eur. J.*, 2013, **19**, 5854–5858.
- 116 A. D. Kosal, E. E. Wilson and B. L. Ashfeld, *Angew. Chem. Int. Ed.*, 2012, **51**, 12036–12040.
- 117 A. D. Kosal, E. E. Wilson and B. L. Ashfeld, *Chem. Eur. J.*, 2012, **18**, 14444–14453.
- 118 S. P. Marsden, A. E. McGonagle and B. McKeever-Abbas, *Org. Lett.*, 2008, **10**, 2589–2591.

- 119 T. W. Campbell and J. J. Monagle, *J. Am. Chem. Soc.*, 1962, **84**, 1493–1493.
- 120 R. M. Denton, J. An, B. Adeniran, A. J. Blake, W. Lewis and A. M. Poulton, *J. Org. Chem.*, 2011, **76**, 6749–6767.
- 121 R. M. Denton, X. Tang and A. Przeslak, *Org. Lett.*, 2010, **12**, 4678–4681.
- 122 R. M. Denton, J. An, P. Lindovska and W. Lewis, *Tetrahedron*, 2012, **68**, 2899–2905.
- 123 R. M. Denton, J. An and B. Adeniran, *Chem. Commun.*, 2010, **46**, 3025–3027.
- 124 R. M. Denton, J. An and B. Adeniran, *Chem. Commun.*, 2010, **46**, 3025–3027.
- 125 T.-Y. Yu, Y. Wang and P.-F. Xu, *Chem. Eur. J.*, 2014, **20**, 98–101.

Chapter 1

Mechanistic Study Into The Catalytic Staudinger Ligation

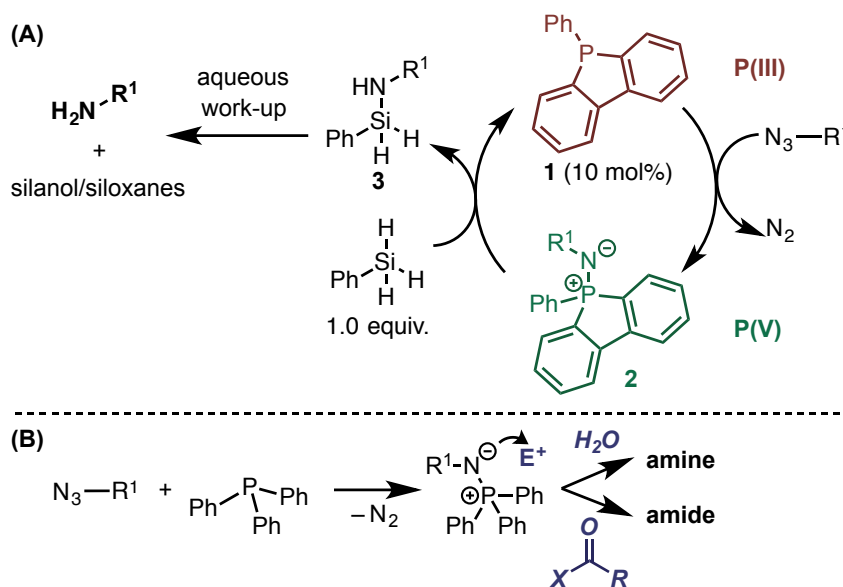
Contributing authors: Keith G. Andrews, Ross M. Denton

Phenylsilane is shown to be a non-innocent terminal reductant in a phosphorus-catalysed Staudinger ligation reaction. Whilst the reaction was originally thought to involve a P(V)-P(III) redox cycle hinging on phosphine oxide reduction and phosphorus-mediated amidation via an aminophosphonium carboxylate species, spectroscopic data demonstrate that these species are destroyed within minutes by the silane. The by-products of the reduction – silyl esters and acyloxysilanamines – are shown to be capable amidation precursors themselves. We therefore provide a revised mechanism for the process, in which amidation is silicon-mediated. The conclusions have deeper implications for the many other phosphorus-catalysed reactions using phenylsilane as a terminal reductant.

A More Critical Role for Silicon in the Catalytic Staudinger Amidation: Silanes as Non-Innocent Reductants, K. G. Andrews, R. M. Denton, *Chem. Commun.*, 2017, [DOI: 10.1039/C7CC03076B](https://doi.org/10.1039/C7CC03076B)

Introduction

In 2012, the group of van Delft published a Staudinger reaction that was substoichiometric in phosphorus.¹ Like most of the contemporary work into making classical phosphorus-mediated reactions substoichiometric ('catalytic') in phosphorus, a hydrosilane was used to turnover the P(V) intermediate and regenerate the active phosphine(III) catalyst. The desired amine product is released on work-up. This reaction therefore belongs to the P(III)–P(V) redox cycle class of organocatalytic phosphorus reactions (Scheme 1A).

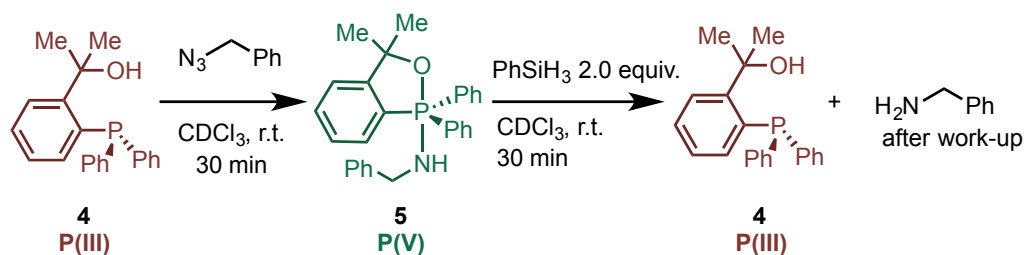


Scheme 1. (A) van Delft's organocatalytic Staudinger reaction.¹ (B) Reactions of iminophosphoranes with electrophiles.

In the classical Staudinger reaction,² water (or other electrophiles)^{3,4} are used to hydrolyse the intermediate ylide (iminophosphorane) (Scheme 1B). van Delft and co-workers reduce this iminophosphorane **2** directly with phenylsilane, resulting in the formation of silylamine products **3** and regeneration of the phosphine **1** (Scheme 1A). (*Note that the authors depict a single silylamine product, **3**, the formal product, in their manuscript, but their ¹H-NMR evidence suggests other species are formed, presumably multisilylamines from the reaction of a silylamine with an iminophosphorane.*)

The strategy relies on the reduction of the iminophosphorane before quenching, because it is substantially easier to reduce than the phosphine oxide. Despite this, because phenylsilane alone is not particularly Lewis acidic, and because the reduction involves attack by the iminophosphorane at silicon, the reaction requires reflux in dioxane to proceed at a reasonable rate. At the end of the reaction, the resulting silylamine **3** is hydrolysed to give silanols/siloxanes and the desired amine product.

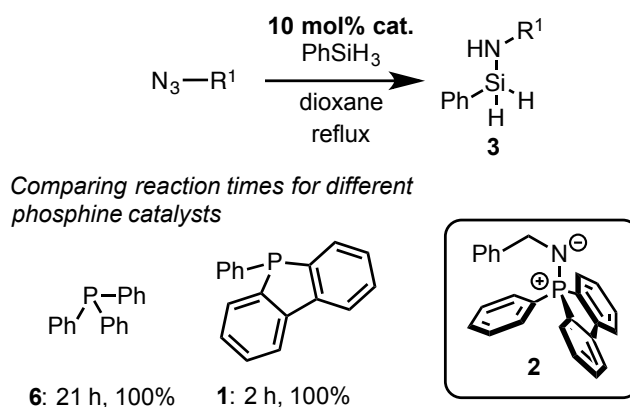
We have utilised a similar redox approach in our own lab, with a catalyst (**4**) that operates at room temperature, using a pendant hydroxyl group to form a phosphorane (**5**) and so increase the rate of reduction, potentially *via* the iminophosphorane (unpublished work, Scheme 2).⁵



Scheme 2. Unpublished work within the group depicting the principle behind a room temperature organocatalytic Staudinger reaction.

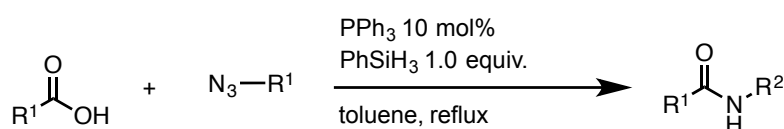
It is important to note that in order to increase the ease of reduction of these iminophosphorane intermediates, catalyst modulation (away from triphenylphosphine) is required. The iminophosphorane of benzyl azide and triphenylphosphine (**6**) is reasonably robust with respect to reduction by phenylsilane. So whilst van Delft's benzophosphole catalyst **1**, at 10 mol% loading, performed the catalysis in 2 h at reflux, triphenylphosphine required 21 h. van Delft's catalyst (**1**) uses geometry to manipulate the reactivity at the phosphorus centre (Scheme 3).¹ The locked benzophosphole ring presumably reduces hindrance around the P–N bond, facilitating attack at silicon and hydride transfer. Altered electron effects resulting from the different orientation of the aryl π -systems are also

possible (Scheme 3, box), perhaps reducing the amount of donation from the ylide (**2**) *N*-electrons to P-R antibonding orbitals.



Scheme 3. van Delft's evidence that benzophosphole catalyst **1** is superior to triphenylphosphine.¹ Boxed: Side view of the benzophosphole catalyst in the iminophosphorane form.

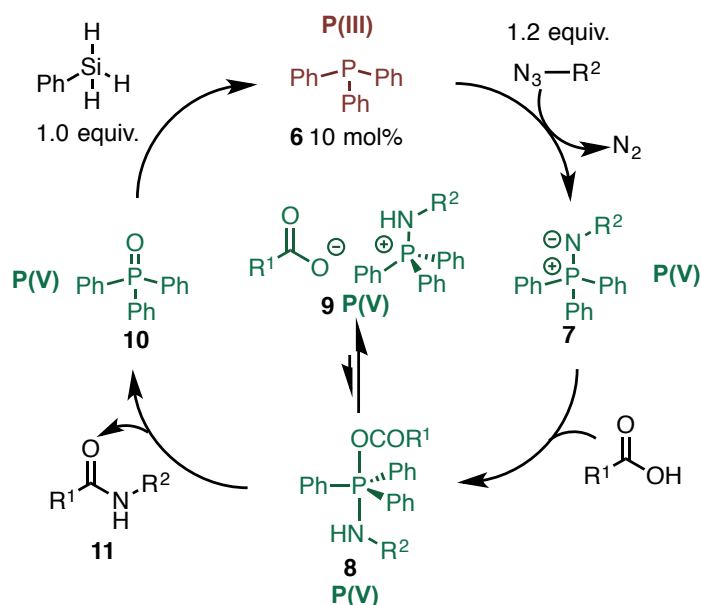
Another paper from 2012, this time from the group of Ashfeld, described a Staudinger ligation reaction, substoichiometric in phosphorus, in which the desired product is an amide derived from an azide. The reaction proceeds in toluene, at temperatures between 60-110 °C, is sometimes left for extended times (e.g. 46 h), and the catalyst is triphenylphosphine (**6**), again at 10 mol% loading (Scheme 4).⁶



Scheme 4. Ashfeld's *P*-catalytic Staudinger ligation reaction.⁶

Like van Delft's catalytic Staudinger reaction, the reaction is based on a stoichiometric reaction; amidation from aminophosphonium carboxylates (**9**) was reported by Garcia and colleagues in 1983.⁷ Again, like van Delft's reaction, Ashfeld and co-workers' method utilises phenylsilane to achieve turnover from P(V) to P(III). This time, however, the authors proposed that turnover of the catalyst occurs *via* reduction of *the corresponding phosphine oxide* (**10**). This was necessary, because the triphenylphosphine oxide *must* be formed if amidation is mediated by phosphorus, which was the case in the original Garcia

reaction, and was assumed to be the case by the authors here. The proposed mechanism of the reaction is shown in Scheme 5.



Scheme 5. Ashfeld's proposed mechanism for the Staudinger ligation reaction, proceeding via reduction of the phosphine oxide.

From our point of view, given the above discussion concerning the work of van Delft and ourselves, the mechanism appeared to suggest that under the new reaction conditions, selective reduction of the robust phosphine oxide **10** occurred in the presence of several more sensitive species, namely the iminophosphorane **7**, phosphorane **8**, and phosphonium salt **9**. Our own interest in catalytic phosphorus-mediated reactions^{8–13} encouraged us to investigate this apparent anomaly further, and provided a starting point for the following studies.

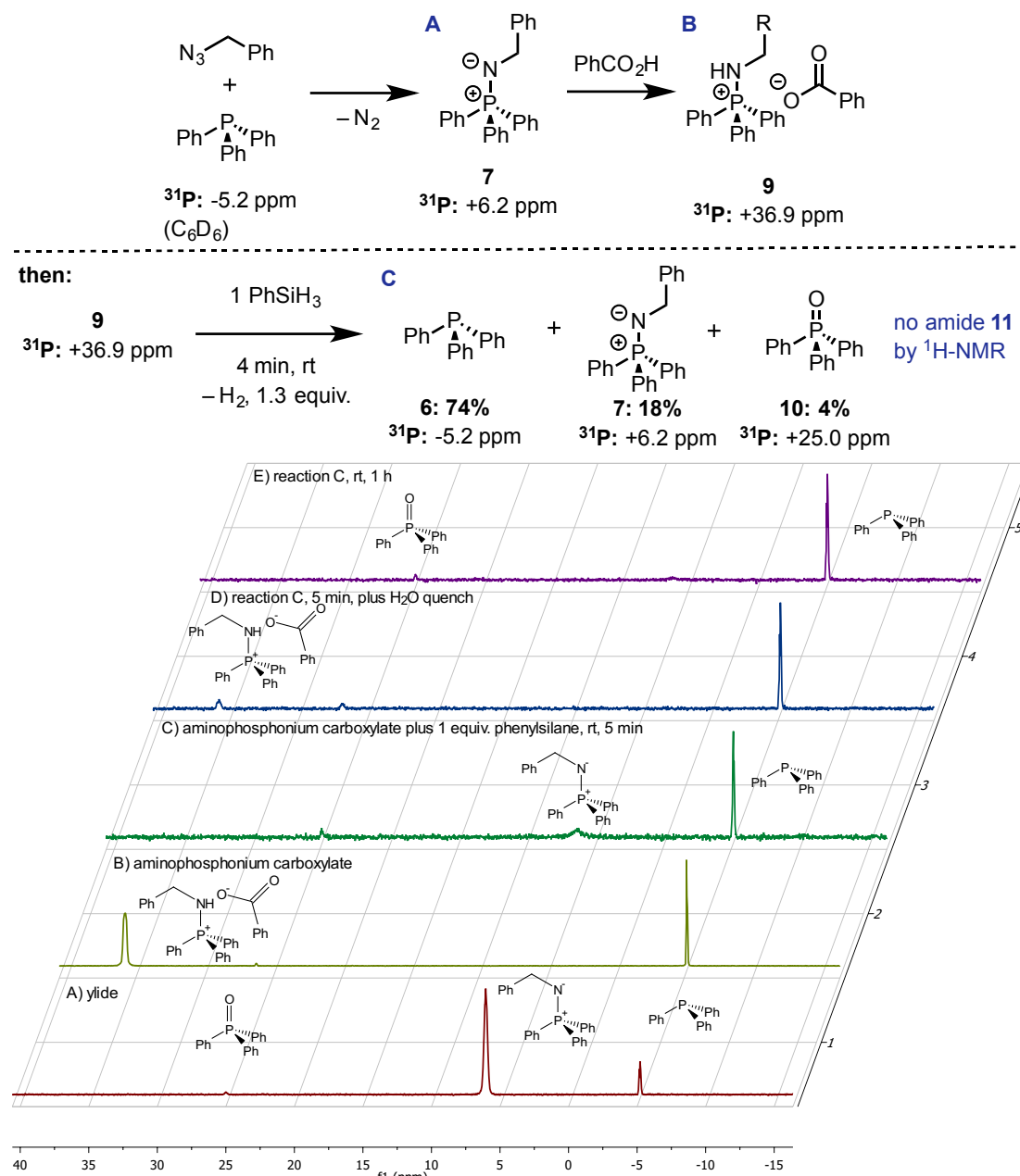
Results and Discussion

Mechanistic Investigation into the Traceless Organocatalytic Staudinger Ligation Reaction

We began by probing the stability of the proposed intermediates in the Staudinger ligation, to confirm whether or not reduction would occur faster or slower than amidation. The

aminophosphonium carboxylate species **9**, proposed to be the species that evolves to the amide, was generated by preforming the iminophosphorane **7** and adding benzoic acid.

Figure 1. Top: Deconstruction of the Staudinger reaction. Bottom: Relevant ^{31}P -NMR plots. (A slight excess of phosphine is used, explaining the signal in B)



Phosphorous conversions were acquired by direct integration of the ^{31}P -NMR signals, and corroborated by comparison to ^1H -NMR signals, taking into account the excess phosphine.

Upon adding phenylsilane (1.00 equivalent), just over one equivalent of hydrogen was evolved within 4 minutes at room temperature, and ^{31}P -NMR analysis indicated a near

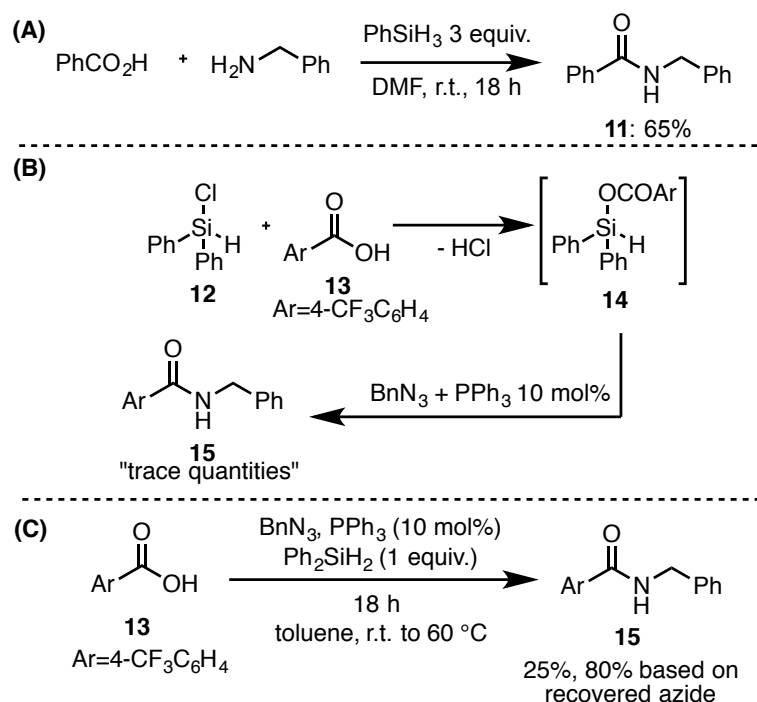
complete reduction of this species to triphenylphosphine **6**. This extensive reduction was surprising, given that van Delft required 21 h for the corresponding reduction (at 10 mol% loading) in the absence of carboxylic acid. Further, some iminophosphorane **7** was regenerated, there was no amide **11**, and only trace phosphine oxide **10** was present at this point (Figure 1).

From these observations, several important corollaries emerge: *first*, we must explain the evolution of hydrogen; *second*, the regeneration of the iminophosphorane **7** deserves interrogation; *third*, the rapid reduction of the aminophosponium carboxylate **9**, which would require extended heating in the absence of carboxylic acid, must be explained; and *finally*, the proposed amidation precursor is no longer a viable contender, so an explanation of amidation is required.

Ashfeld and co-workers had briefly considered in their publication the role of an *in situ* generated silyl ester.⁶ This was necessary given that Ruan and co-workers had reported that 3 equivalents of phenylsilane could mediate the amidation of carboxylic acids and amines at room temperature in DMF in a non-phosphorus related reaction (Scheme 6A).¹⁴ However, the authors dismissed this possibility on the basis of the control experiment depicted below, which uses a derivative of diphenylsilane as the reductant (Scheme 6B).

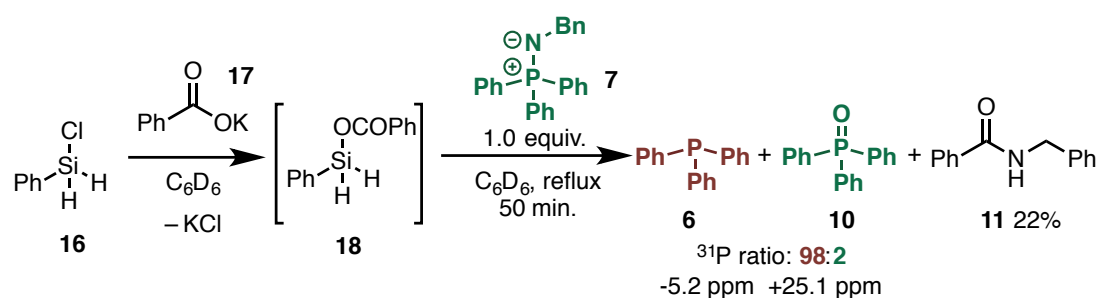
The role of a silyl ester (e.g. **14**) intrigued us because it seemed to account for all of the corollaries above. *First*, such a silyl ester would ostensibly be formed along with the loss of one equivalent of hydrogen; *second*, forming the silyl ester would also regenerate the iminophosphorane **7** by ‘acquiring’ the benzoic acid; *third*, the augmented silane (silyl ester) would be a stronger Lewis acid than the parent silane, and thus be an enhanced

reductant, explaining the rate enhancement; and *finally* the silyl ester, as an activated carboxylic acid, would represent a viable amidation precursor.



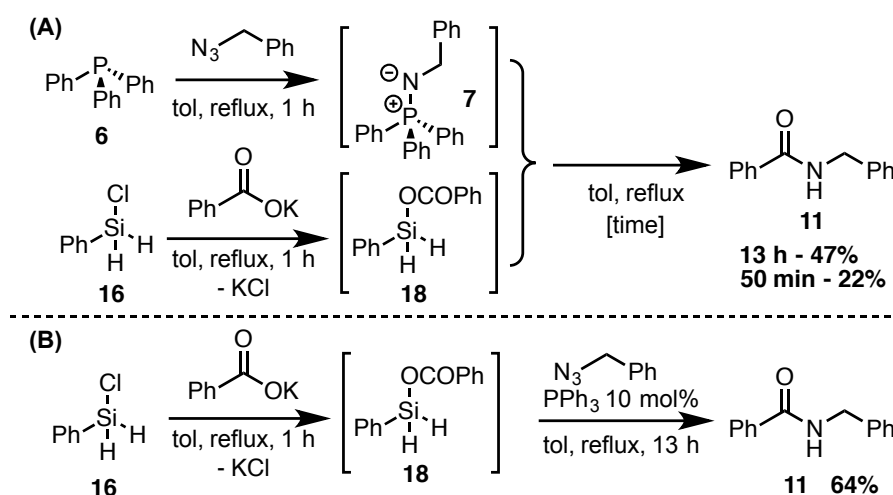
Scheme 6. (A) Ruan's phenylsilane-mediated amidation reaction.¹⁴ (B) Ashfeld's control experiment to rule out the participation of silyl esters 14. c) Ashfeld's low-yielding amidation reaction utilising diphenylsilane.⁶

We considered that a more precise control experiment would involve the presence of a silyl ester derived from phenylsilane, given that Ashfeld and co-workers reported diphenylsilane to be an inferior silane in mediating the reaction (Scheme 6C). Thus we generated the appropriate monosilyl ester **18** from chlorophenylsilane **16** and potassium benzoate **17**, and substituted this reagent in place of the phenylsilane and carboxylic acid in the ligation reaction in a stoichiometric experiment (Scheme 7).



Scheme 7. A control experiment to probe the plausibility of silyl esters in the organocatalytic Staudinger reaction.

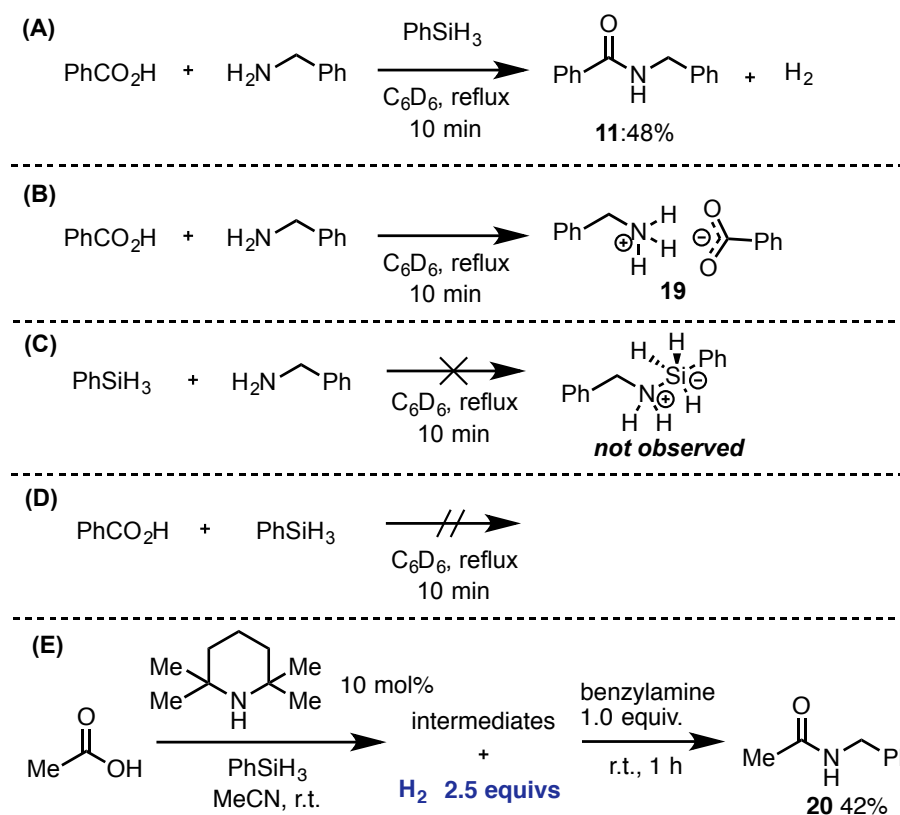
In this instance, 22% of the amide product **11** was formed after 50 minutes at reflux in C_6D_6 . The mass balance of iminophosphorane **7** was presumed present as various silanamine species (not depicted), which was corroborated at this point by the formation of benzylamine upon hydrolysis. This could not be released from an iminophosphorane, as ^{31}P -NMR indicated only phosphine was present. Encouraged, we ran the reaction over a longer time period, both with stoichiometric and substoichiometric phosphine **6**. In both cases the reaction gave substantial levels of amide **11**, with higher levels of amide observed in the catalytic manifold (Scheme 8).



Scheme 8. Deconstruction experiments: (A) Stoichiometric preformed iminophosphorane reacts with a preformed silyl ester to give amide. (B) Preformed silyl ester **18 reacts with substoichiometric phosphine and 1 equivalent of azide to give amide.**

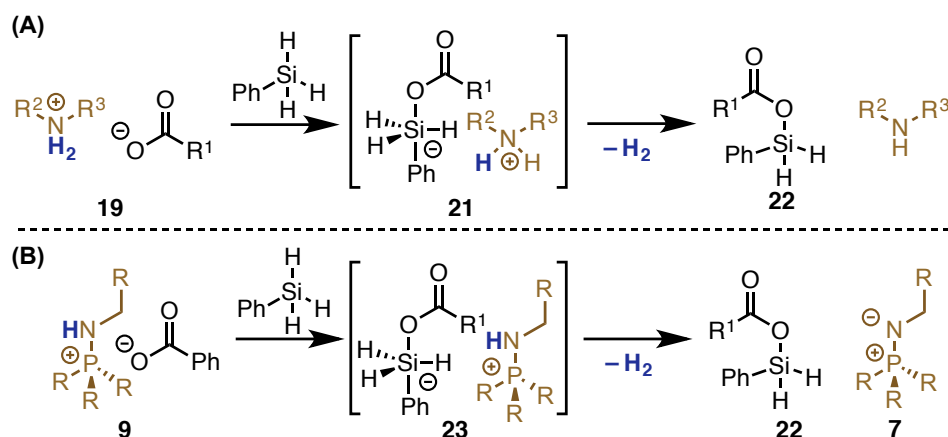
Next, we revisited the work of Ruan and group, who have demonstrated amidation in the presence of phenylsilane.¹⁴ The authors did not offer a mechanistic insight, so we probed the reaction. As detailed in the primary introduction, amidation from silyl esters is well documented. We sought to probe the requirements for the dehydrogenative reaction using benzylamine, benzoic acid and phenylsilane, combining them in all permutations. The dehydrogenative reaction requires all three components (A), whilst the absence of one of the reagents led to no reaction (C-D), except ammonium carboxylate **19** formation. But it

is catalytic in base (E), suggesting that ammonium carboxylate species are required for reaction with phenylsilane (Scheme 9).



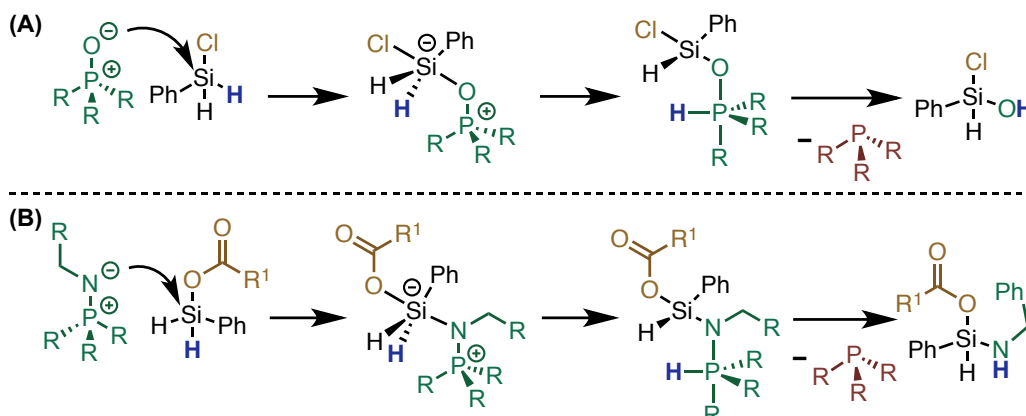
Scheme 9. A-D) Deconstruction of the dehydrogenation reaction of acids and amines in the presence of phenylsilane. e) Silyl ester formation is catalytic in base.

Given that the reaction appears to be catalytic in base, we offer a simple depiction of a possible reaction pathway in Scheme 10A, and highlight the analogous scenario that can occur in the case of an aminophosphonium carboxylate **19**.



Scheme 10. (A) Proposed formal mechanism for the dehydrogenative silyl ester formation from carboxylic acids and phenylsilane in the presence of catalytic base. b) Analogous reaction in the presence of the basic iminophosphorane, *via* the aminophosphonium carboxylate.

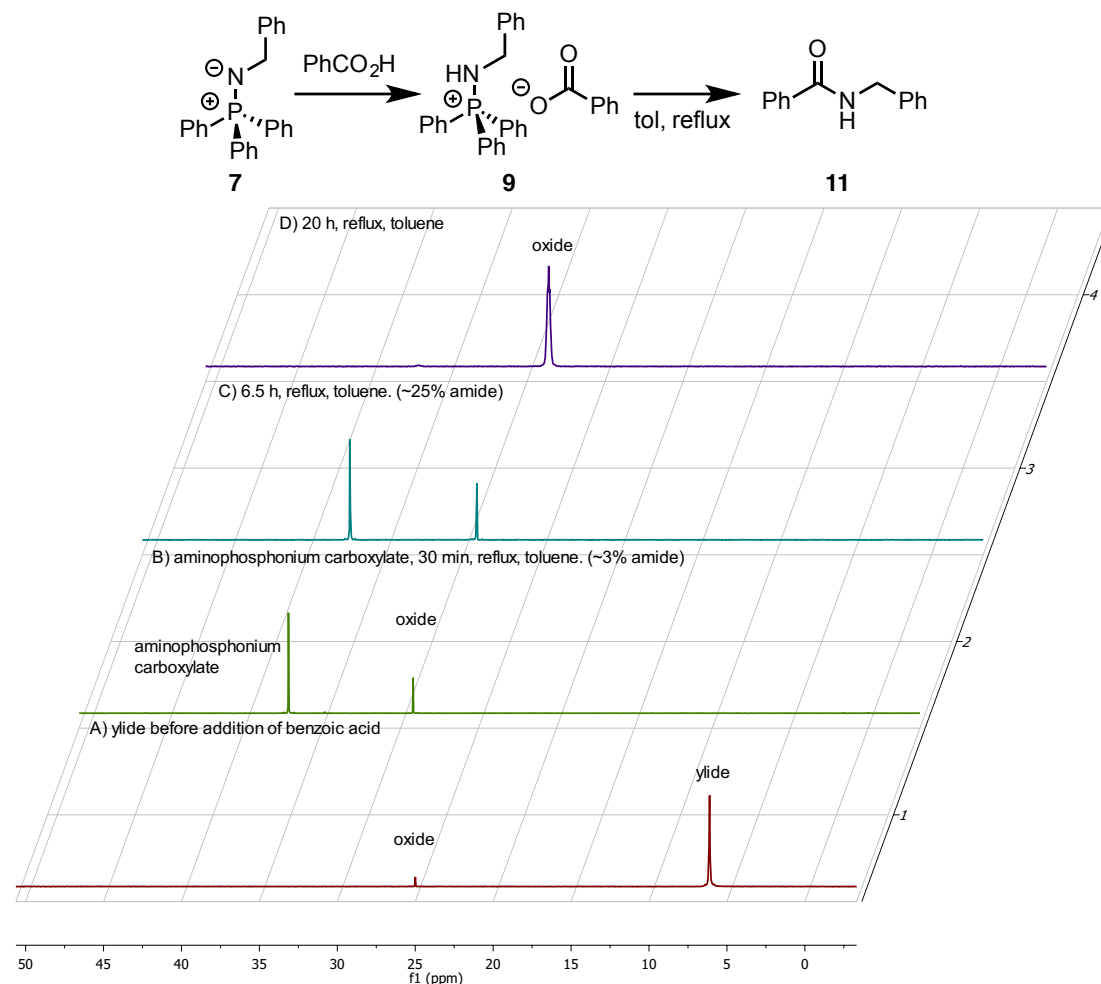
Given that hydrogen evolution appears contingent on the presence of an acidic O–H bond and the presence of a base, we considered the catalytic Staudinger reaction once more. The iminophosphorane **7** can clearly play the role of the base, activating the carboxylic acid as a carboxylate ion, which can attack silicon. This putative ammonium/silicate species **23** evolves hydrogen, reforming the ylide **7** and a silyl ester species, e.g. **22**. The ylide **7** is known to be reduced by phenylsilane to a silylamine,¹ and silyl esters are known to be more Lewis acidic than phenylsilane.¹⁵ Thus, it follows that ylide attack at silicon followed by P–N bond reduction and reductive elimination should occur, by analogy to the mechanism proposed for P=O bond reduction by chlorosilanes (or phenylsilane)¹⁶ (Scheme 11).



Scheme 11. (A) Proposed mechanism for the reduction of phosphine oxides by chlorosilanes. (B) Analogous mechanism for the reduction of iminophosphoranes by silyl esters.

Next, we revisited the thermal amidation from the proposed intermediate **9** (Figure 2), to check that thermal amidation wasn't faster than reduction.

Figure 2. Thermal amidation from aminophosphonium carboxylate **9** is slow

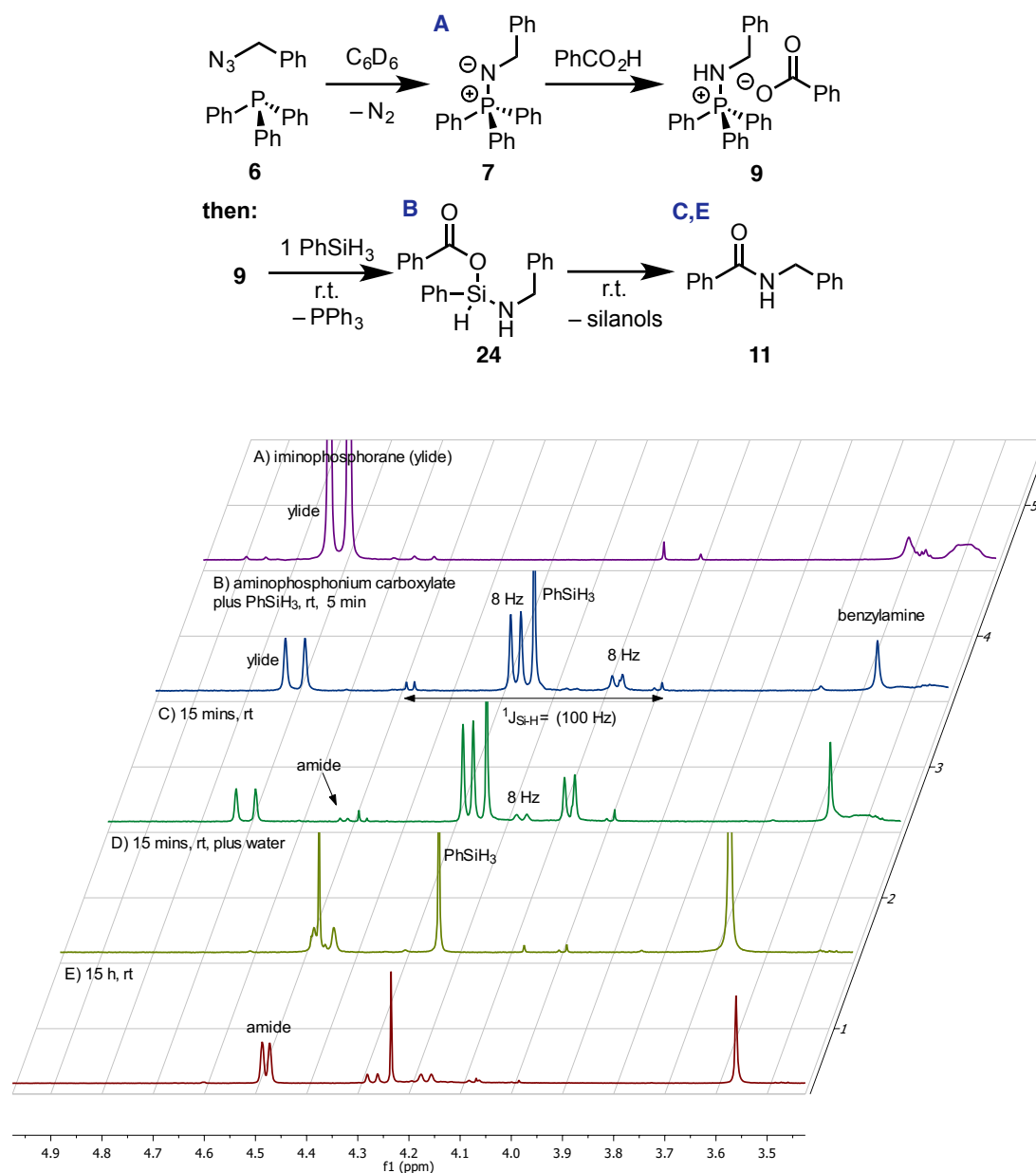


Evident from this brief study is that the thermal reaction is slow, taking in the region of 20 h to go to completion, much too slow to account for the levels of amidation seen when phenylsilane is present. No additional intermediates are visible, highlighting the equilibrium position at the phosphonium carboxylate **9** (i.e., no phosphorane **8** is visible, *vide supra*, Scheme 1).

Finally, we endeavoured to identify any of our proposed intermediates in the reaction mixture. Returning to the full reaction, our hypothesis suggests that silylamines, in

particular mixed acyloxysilylamines (**24**), should be formed by iminophosphorane reduction, and it is from these that amidation occurs (Figure 3).

Figure 3. ^1H -NMR plots (C_6D_6) of the deconstructed Staudinger ligation reaction. a) Preformed iminophosphorane. b) Aminophosphonium carboxylate plus phenylsilane (1 equiv., 15 min). c) Reaction B after 15 min. d) Reaction C, quenched with 1 equiv. water. E) Reaction B after 15 h, r.t.



It is clear, however, that the presence of multiple Si-H bonds and the presence of carboxylic acid could lead to multiple exchange reactions and additional substitutions leading to an undefined set of silicon centred species. Indeed, following the deconstructed reaction by

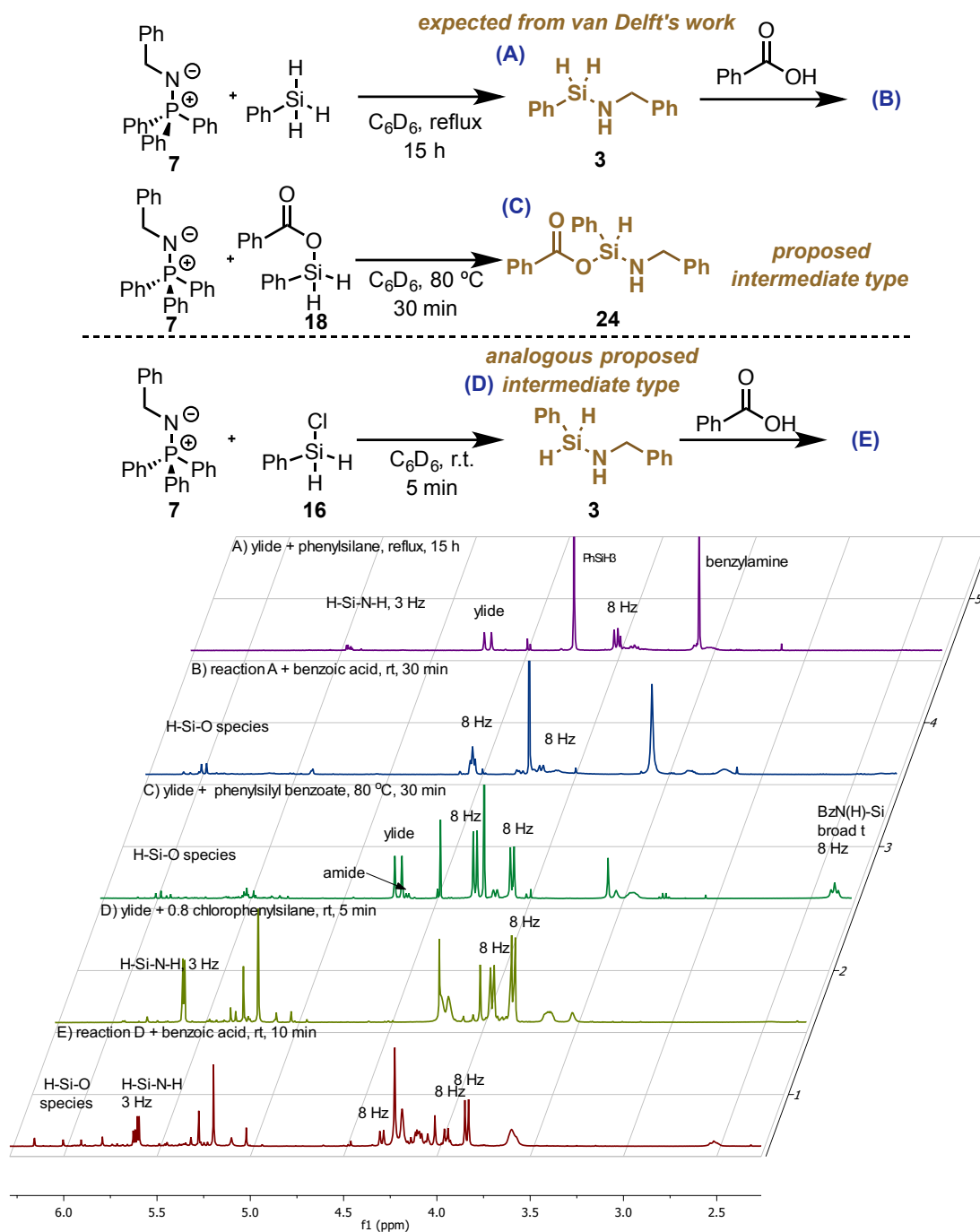
^1H -NMR spectroscopy (Figure 3), indicated that when phenylsilane is added to iminophosphorane **7** ($d, J = 15\text{ Hz}$) (trace A), multiple new species with 8 Hz doublets are formed (B). Amide **11** is observed within 15 minutes at room temperature (C), clearly not consistent with thermal amidation, which requires elevated temperatures and extended reaction times. The 8 Hz species are hydrolysed to benzylamine upon the addition of water (D) – the remaining ylide **7** appears to reform aminophosphonium carboxylate **9** initially when water is added, consistent with the release of carboxylic acid, which again would be expected from the rapid hydrolysis of silyl esters. When reaction C containing the 8 Hz doublets was allowed to stir for 15 h at rt, most of the 8 Hz species were depleted whilst amide **11** became the major benzyl-containing product (E). These spectra all support our hypothesis.

The chemical scheme above is clearly generalised; there are multiple species formed after the addition of phenylsilane, not just one discrete species (e.g. **24**), but the behaviour of these species is what might be expected from the acyloxysilylamine (**24**) depicted. Given our argument rests on the idea that the generated silyl ester species are more reactive than the parent silane, it is not surprising that these species should react divergently once formed. Thus, we tentatively propose that the two major species with 8 Hz doublets are not species **24**, but rather the products of the reaction with **24** with further ylide or further carboxylic acid (derived from aminophosphonium carboxylate **9**).

A further set of orthogonal experiments was performed to corroborate that the species giving 8 Hz doublets are silylamines, beginning with the reduction of iminophosphorane (**7**) with phenylsilane as reported by van Delft and co-workers (Figure 4A). The first point to notice in trace A, is that even after 15 h of heating, ylide still remains, showing the difference in reactivity between phenylsilane and a silyl ester. The reaction of

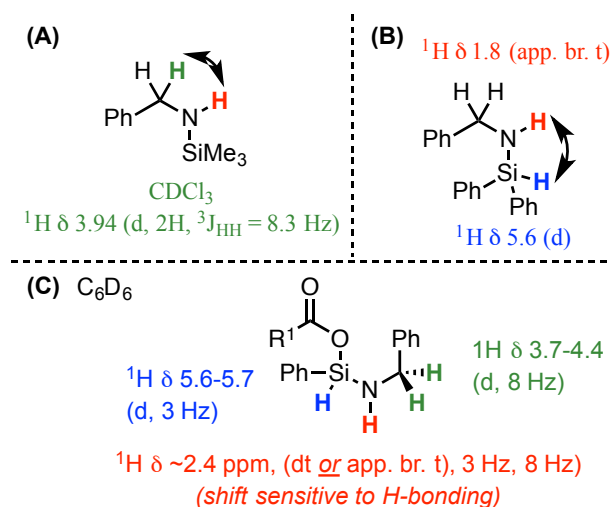
iminophosphorane (**7**) with phenylsilane is reported by van Delft to give a silylamine (**3**): clearly there are several species (Figure 4A), but the major species at 4.1 ppm appears to be the depicted species **3**.

Figure 4. ^1H -NMR traces for; a) iminophosphorane and phenylsilane, b) a plus benzoic acid, c) iminophosphorane plus phenylsilyl benzoate, d) iminophosphorane plus chlorophenylsilane, e) d plus benzoic acid.

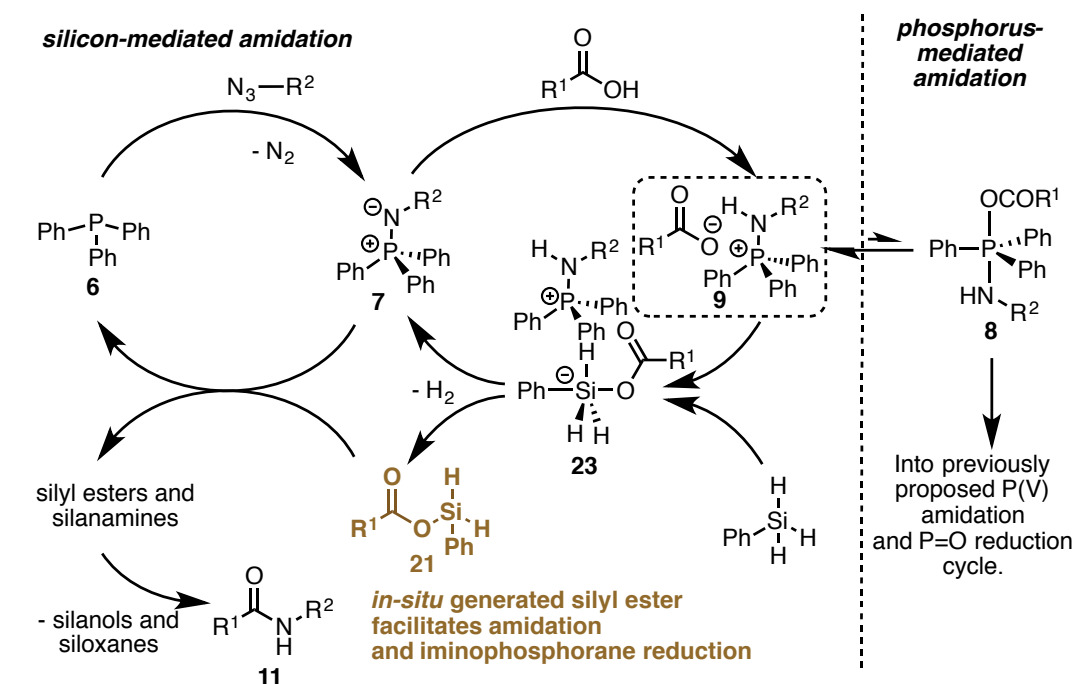


Addition of benzoic acid causes various reactions of these intermediates instantly (B). Two further independent reactions generate the 8 Hz doublet intermediates. The reaction of the iminophosphorane **7** with preformed phenylsilyl benzoate **18** is shown in trace C; we assign the 8 Hz doublets as variously substituted silylamines. Note that the lack of suitable Si-H signals in trace C confirms that the intermediates go on to react further. Amide **11** is formed within half an hour at 80 °C. Chlorophenylsilane **16**, a more reactive silane, forms several reduced species within minutes at room temperature when mixed with iminophosphorane **7**, reducing most of the ylide (P–N) bond (trace D). A significant 3 Hz doublet is observed in the H–Si–N range at ~5.6 ppm, likely the expected silylamine **3**. (Note that in the presence of acids, the nitrogen containing species are prone to shift changes making comparisons difficult). Addition of benzoic acid to this mixture again caused rapid development, including a decrease in the silylamine signal at 5.6 ppm (trace E), demonstrating that a carboxylic acid may react with a silylamine. Finally, the coupling constants observed are consistent across the experiments, and with similar compounds from the literature (Figure 5).

Figure 5. Comparison of: literature ^1H -NMR shifts (a, b) with observed shifts, c).



Thus, we propose a plausible mechanistic pathway that explains all the observations and avoids a phosphine oxide reduction pathway (Scheme 12).



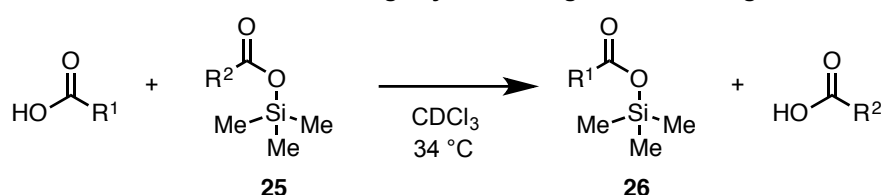
Scheme 12. Proposed revised mechanism for Ashfeld's Staudinger ligation reaction.

Beginning at the top left, phosphine **6** and the azide undergo the typical reaction, releasing nitrogen to form ylide **7**, which is instantly protonated by the excess carboxylic acid present to form aminophosphonium carboxylate **9**. This species, far from existing for long enough to form proposed amidation precursor **8** and undergo amidation to release phosphine oxide, reacts rapidly with phenylsilane in a dehydrogenative reaction to form a silyl ester (e.g. **21**), potentially via a species such as **23**. This species may react with further ammonium carboxylate **9** to form multisilyl esters (likely), or with a molecule of ylide **7** to form various silyl esters and silanamines and regenerate the triphenylphosphine **6**, bypassing the oxide, to re-enter the catalytic cycle. Amidation then occurs from the mixture of activated acids and amines, mediated by silicon. Protonolysis of silylamines to form free amine may also occur, which can react directly with silyl esters to give amide.

Silyl Esters and Amine Exchange in the Literature

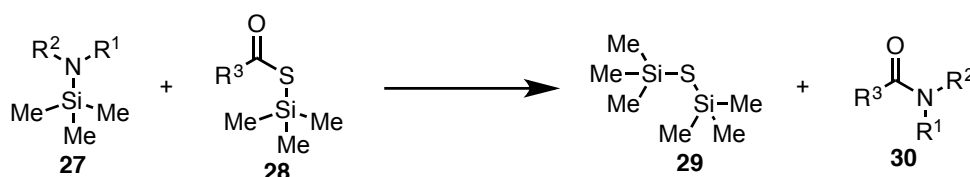
We have left the details of amidation in the above scheme rather vague. This is due to the complexity of the medium, and the fact that amidation could plausibly happen in many different ways. In particular, exchange of ligands at silicon is relatively easy due to the low activation barrier to pentacoordinate silicon formation, from which ligands may be ejected. In Scheme 13, some literature examples of exchange at silicon are depicted.

(A) Kozuka: Rates measured for exchange by monitoring $^1\text{H-NMR}$ Me signal

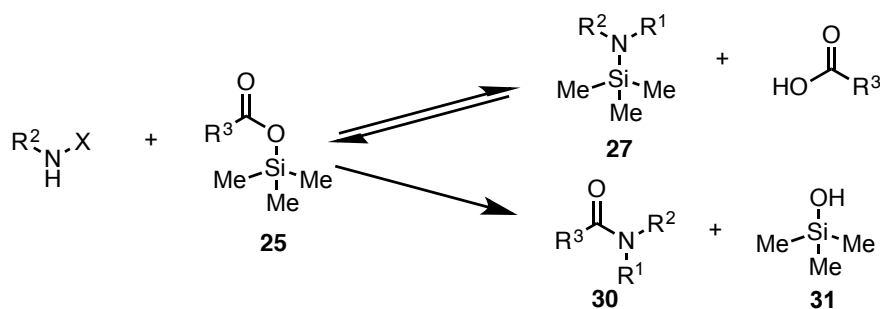


base-catalysis accelerates rate of exchange ($> \times 700$ for acetoxy to chloroacetoxy)

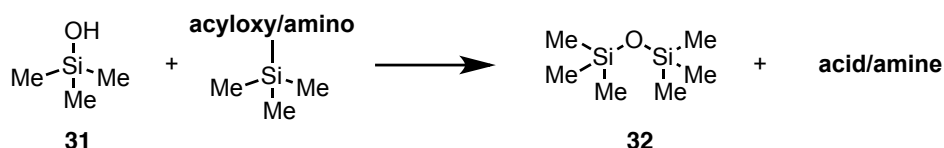
(B) Rühlmann: Bimolecular exchange reactions of thioesters and silanamines



(C) Rühlmann: Amidation and exchange reactions of silyl esters and silanamines



(D) Rühlmann: Silanol or water degradation of sensitive amino/acyloxysilanes

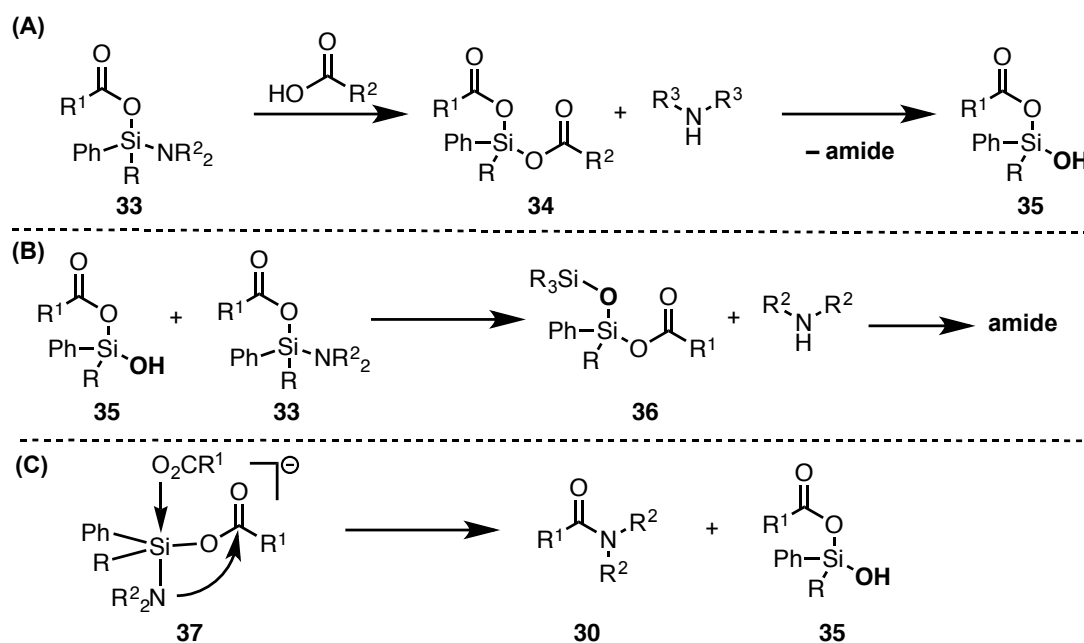


Scheme 13. Examples of silanamine/silyl ester exchange in the literature^{17–20}

Kozuka measured rates of exchange of carboxylic acids at silicon, and determined that the process was limited by proton transfer, and accordingly measured a large acceleration by

base-catalysis when 20 mol% pyridine was included (Scheme 13A).¹⁷ Electron deficient (more acidic) acids were found to displace less acidic acids more easily. In the present case, then, acids might be expected to displace amine with relative ease via proton transfer. Pola et al reported similar results.²¹

Rühlmann has published extensively in the area, and has shown that silylamines **26** can directly amidate thioesters **27** to give the amide products **29** (Scheme 13B).²⁰ Meanwhile, amines are able to enter an equilibrium with silyl esters, but are trapped as amides with the formation of silanol **30** (Scheme 13C). Silanol **30** can also displace carboxylic acids and amines from silicon centres to form robust siloxane linkages **31** (Scheme 13D). They can also form siloxanes with loss of water, which itself is capable of hydrolysis of acyloxysilanes and silanamines.¹⁹ Amidation may therefore occur in a number of ways (Scheme 14).



Scheme 14. Some of the potential pathways to amidation from a mixed acyloxysilane species.

The most likely of these involves displacement of amine by carboxylic acid, silanol or water from a species such as **33**, followed by amidation on a silyl ester, such as **34** (Scheme 14A). Each molecule of amide is generated alongside a silanol **35** that might displace a

subsequent amine molecule from a species like **33**, to generate further amine (Scheme 14B). Alternatively, amidation might be possible directly from a mixed acyloxysilanamine species like **33**, perhaps via activation as shown in species **37** (Scheme 14C). Needless to say, many of the possible routes probably occur under the raised temperature of the reaction mixture, and this part of the pathway is relatively uncontroversial. It may be the case, however, that the reduced yields observed by Ashfeld in the presence of 2 equivalents of phenylsilane (instead of 1) are because of acid and amine sequestration at silicon, leaving fewer molecules to mediate the necessary exchange reactions to give free amine.

Summary

We have conclusively shown that aminophosphonium carboxylates of the type proposed to undergo amidation in the catalytic Staudinger ligation are unstable with respect to reduction to the phosphine and various silylated amines and carboxylate groups in the presence of phenylsilane. Instead it is these silyl-based species that are responsible for amidation. The discovery that augmented hydrosilanes appear to be enhanced reductants of P(V) species this chemistry will be explored in Chapter 4. The nature of the activation of hydrosilanes using bases and acids sparked an interest in the Ruan's phenylsilane reaction, the subject of Chapter 2.

References

- 1 H. a. van Kalker, J. J. Bruins, F. P. J. T. Rutjes and F. L. van Delft, *Adv. Synth. Catal.*, 2012, **354**, 1417–1421.
- 2 Y. G. Gololobov, I. N. Zhmurova and L. F. Kasukhin, *Tetrahedron*, 1981, **37**, 437–472.
- 3 B. L. Nilsson, L. L. Kiessling and R. T. Raines, *Org. Lett.*, 2000, **2**, 1939–1941.
- 4 E. Saxon and C. R. Bertozzi, *Science*, 2000, **287**, 2007–2010.

- 5 C. G. Chapman, University of Nottingham, 2015.
- 6 A. D. Kosal, E. E. Wilson and B. L. Ashfeld, *Angew. Chem. Int. Ed.*, 2012, **51**, 12036–12040.
- 7 J. Garcia, F. Urpí and J. Vilarrasa, *Tetrahedron Lett.*, 1984, **25**, 4841–4844.
- 8 R. M. Denton, J. An and B. Adeniran, *Chem. Commun.*, 2010, **46**, 3025–3027.
- 9 J. An, X. Tang, J. Moore, W. Lewis and R. M. Denton, *Tetrahedron*, 2013, **69**, 8769–8776.
- 10 R. M. Denton, J. An, P. Lindovska and W. Lewis, *Tetrahedron*, 2012, **68**, 2899–2905.
- 11 R. M. Denton, J. An, B. Adeniran, A. J. Blake, W. Lewis and A. M. Poulton, *J. Org. Chem.*, 2011, **76**, 6749–6767.
- 12 R. M. Denton, X. Tang and A. Przeslak, *Org. Lett.*, 2010, **12**, 4678–4681.
- 13 R. M. Denton, J. An and B. Adeniran, *Chem. Commun.*, 2010, **46**, 3025–3027.
- 14 Z. Ruan, R. M. Lawrence and C. B. Cooper, *Tetrahedron Lett.*, 2006, **47**, 7649–7651.
- 15 R. J. P. Corriu, G. Royo and A. Saxce, De, *J. Chem. Soc. Chem. Commun.*, 1980, 892–894.
- 16 E. H. Krenske, *J. Org. Chem.*, 2012, **77**, 3969–3977.
- 17 S. Kozuka, T. Kitamura, N. Kobayashi and K. Ogino, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 1950–1952.
- 18 S. Kozuka and T. Kitamura, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 3384–3386.
- 19 K. Rühlmann, *J. für Prakt. Chemie*, 1962, **16**, 172–181.
- 20 K. Rühlmann, U. Kaufmann and D. Knopf, *J. für Prakt. Chemie*, 1962, **18**, 131–140.
- 21 J. Pola, A. El Attar and V. Chvalovský, *Collect. Czechoslov. Chem. Commun.*, 1976, **41**, 1772–1776.

Chapter 1

Experimental Section

Contents

1. General Information.....	68
2. Supplementary Experiments	70
Hydrogen evolution measurements	70
Catalytic base procedure indicating dehydrocoupling reaction of carboxylic acid and phenylsilane (Scheme 9)	70
A base-catalyst is required for the generation of silyl esters (Scheme 9)	71
Generation and Characterisation of Iminophosphorane 7 and Silyl Ester 18.....	71
2.2 Deconstructed Staudinger Ligation NMR Experiments	72
Amide formation <i>via</i> independent preformation of iminophosphorane (7) and silyl ester (18) (Scheme 7 and 8)	72
Phenylsilane rapidly reduces the aminophosphonium carboxylate (Figure 1)	74
Additional Experiments	74
Thermal amidation (Figure 2)	74
Formation of mixed acyloxysilylamines (Figure 3)	75
Orthogonal formation of mixed silanamines and acyloxysilanamines (Figure 4)	75
3. Experimental References	76

1. General Information

Glassware was dried in an oven overnight before use. All reactions were carried out under an argon balloon atmosphere unless specified. All solvents and reagents were used as supplied unless otherwise stated. Acetonitrile was distilled over calcium hydride onto 4 Å molecular sieves activated by flame-drying the glass vessel under vacuum/argon cycles for 20 min. The distilled solvent was stored under argon for 24 h on the sieves before (dry, purged) cannula transfer to new, activated sieves, twice, to give suitably dry solvent for the kinetic experiments. Diethyl ether, THF and toluene were acquired from a dry solvent still/tower and stored over sodium wire under argon. Chloroform was distilled from phosphorus pentoxide (3% wt) and stored over 4 Å molecular sieves. Anhydrous DMF was purchased and used fresh. DMSO was distilled under reduced pressure and stored over 4 Å sieves. Pyridine was distilled from calcium hydride and stored over 4 Å sieves. Ethyl acetate was distilled from potassium carbonate and stored over 4 Å sieves. Acetone was dried sufficiently by stirring for 48 h with magnesium sulfate and then filtering and degassing under argon. Thin layer chromatography was carried out on Poligram SIL G/UV254 silica-aluminium plates and plates were visualized using ultra-violet light (254 nm) or KMnO_4 solution. For flash column chromatography, fluorochem silica gel 60, 35–70 mesh was used. NMR data were collected at 400 MHz for ^1H ; 101 MHz for ^{13}C ; 377 MHz for ^{19}F ; 162 MHz for ^{31}P and; 79 MHz for ^{29}Si . Data were manipulated directly from the spectrometer or via a networked PC with appropriate software. Reference values for residual solvent were taken as $\delta=7.26$ (CDCl_3) for ^1H NMR; $\delta=77.00$ (CDCl_3) for ^{13}C NMR; $\delta=7.16$ (C_6D_6) for ^1H NMR; $\delta=128.06$ (C_6D_6) for ^{13}C NMR; $\delta=4.79$ (D_2O) for ^1H NMR. ^{19}F -NMR shifts were referenced to CFCl_3 at 0.0 ppm. ^{31}P -NMR shifts are reported relative to phosphoric acid at 0.0 ppm. ^{29}Si -NMR shifts are proton decoupled and reported

relative to tetramethylsilane at 0.0 ppm. NMR-yields were calculated relative to one equivalent of 1,1,2,2-tetrachloroethane as an internal standard; ^1H NMR (400 MHz, CDCl_3) δ 5.95 (s, 2H). Multiplicities for coupled signals are designated using the following abbreviations: s=singlet, d=doublet, t=triplet, q=quartet, quin=quintet, sex=sextet, br=broad signal and ap=apparent. The coupling constants are reported in Hertz. Where appropriate, COSY, HMQC and HMBC experiments were performed to aid assignment. Carbon shifts reported *per* environment: (2C) = two overlapped distinct environments. High-resolution mass spectrometry data were quoted to four decimal places (0.1 mDa) with error limits for acceptance of ± 5.0 ppm (defined as calcd/found mass 10^{-6}). Mass spectra were acquired on a VG micromass 70E, VG autospec or micromass LCTOF. Infrared spectra were recorded on a Perkin-Elmer 1600 FTIR instrument as dilute chloroform solutions. Melting points were recorded on a Stuart manual melting point apparatus. GCMS and HPLC data were obtained thus:

GCMS – machine specifications: Instrument Parameters: Electron Ionisation --- Acquisition mass range 50-500Da --- MS Ion Source conditions: Temperature: 150 °C Ionisation energy: 70eV --- Mass Calibration by PFTBA --- Chromatography conditions: GC column: J&W DB-5MS 30m x 0.25mm x 25um --- Column temperature programme: 40 °C to 260 °C @ 30 °C min⁻¹ --- Carrier gas: Helium --- Inlet temperature: 180 °C --- Transfer line temperature: 150 °C --- Instrument: Mass Spectrometer: JEOL AccuTOF GCX (JEOL Ltd., Tokyo, Japan) --- Gas Chromatograph: Agilent 7890B (Agilent Technologies Inc, Wilmington, USA). (data given includes: rt = retention time.)

Enantiopurities were determined by Reach Separations (BioCity Nottingham, Pennyfoot Street, Nottingham NG1 1GF).

2. Supplementary Experiments

Hydrogen evolution measurements

Rudimentary hydrogen gas volume measuring experiments were performed by connecting a stirring sealed flask containing the reagents to an upturned water-filled measuring cylinder in a reservoir containing water, which was displaced upon gas evolution. The volume of gas collected was read off the cylinder. The tube connecting the flask to the cylinder was packed with calcium chloride to hinder the passage of water vapour back up the tube. The volume of 1 mole of hydrogen was approximated as 23 dm³. The identity of the gas was confirmed as hydrogen by observing the characteristic combustion of a lit splint in the presence of the gas and the resulting water condensation on the walls of the vessel.

Catalytic base procedure indicating dehydrocoupling reaction of carboxylic acid and phenylsilane (Scheme 9)

MeCN-D₃ was filtered through magnesium sulfate into a dry flask under argon and acetic acid (9.1 µL, 0.16 mmol) and 2,2,6,6-tetramethylpiperidine (2.2 µL, 0.016 mmol) were added and the reaction mixture was stirred at room temperature. Phenylsilane (19.7 µL, 0.160 mmol) was then added and the flask sealed immediately with an adaptor as described above. The volume of displaced water was measured over 21 h, with 3.7 cm³ gas approximately equivalent to 1 equivalent of hydrogen. One equivalent of hydrogen was released within 30 min, with two equivalents released after 6 h. After 21 hr, 2.5 equivalents had been collected. Benzylamine (17.5 µL, 0.160 mmol) was then added and the reaction stirred at r.t. for 1 h. ¹H-NMR showed 42% yield of *N*-benzylacetamide **20** relative to TCE as internal standard.

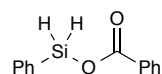
A base-catalyst is required for the generation of silyl esters (Scheme 9)

Benzoic acid, benzylamine and phenylsilane (0.38 mmol scale) were combined stoichiometrically in all permutations in C₆D₆ (0.63 mL) and refluxed for 10 minutes. After this time, the solutions were transferred to a dry NMR tube and the ¹H-NMR spectrum recorded. For **a**, 48% amide was observed (relative to amine). For **b**, only the ammonium carboxylate salt was observed. For **c**, no species were observed at all, and both phenylsilane and benzylamine remained unreacted. For **d**, no new species were observed either.

Generation and Characterisation of Iminophosphorane 7 and Silyl Ester 18

The following reactions were conducted in oven-dried 5 mL flasks under an argon balloon, and fitted with a water condenser when heating is used.

Phenylsilyl benzoate (18)

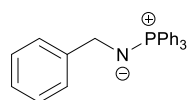


Chloro(phenyl)silane (21.3 µL, 0.160 mmol) was added to a refluxing suspension/solution of potassium benzoate (25.6 mg, 0.160 mmol) in C₆D₆ (0.5 mL) for 30-60 min. The solution, containing solid potassium chloride, was used without further manipulation (filtration leads to hydrolysis of the sensitive silyl ester species). The major species was assigned as phenylsilylbenzoate with the following signals selected from the NMR spectra:

¹H NMR (400MHz, C₆D₆) δ ppm 8.07 - 8.03 (m, 2H), 7.73 - 7.67 (m, 2H), 7.13 - 7.04 (m, 4H), 6.99 - 6.94 (m, 2H), 5.36 (SiH₂, s, 2H); ¹³C NMR (101 MHz, C₆D₆) 167.3, 135.8, 133.4, 131.3, 130.7, 130.6, 130.5, 128.6, 128.5; ²⁹Si NMR (79 MHz, C₆D₆) δ -19.9.

1,3-Diphenyldisiloxane, formed from the reaction of adventitious water, was also present, typically up to 15%.

***N*-benzyl-1,1,1-triphenyl- λ^5 -phosphanimine (iminophosphorane/ylide)³**
(7)



Commercial benzyl azide (Alfa-Aesar, 94%) (12.5 μ L, 0.100 mmol) was added to a solution of triphenylphosphine (0.100 mmol, 26.2 mg) in C_6D_6 (0.5 mL) and the reaction refluxed for 1 h. The ^{31}P -NMR spectrum of the solution indicated a 1:87:11 ratio (by integration) of phosphine oxide(25.0 ppm): iminophosphorane(6.0 ppm):phosphine(-5.2 ppm). The solution was used in further transformations without further manipulation.

^1H NMR (400 MHz, C_6D_6) δ 7.90 - 7.81 (m, 2H), 7.81 - 7.68 (m, 6H), 7.43 - 7.36 (m, 1H), 7.36 - 7.29 (m, 2H), 7.08 - 7.00 (m, 9H), 4.71 (d, J = 15.2 Hz, 2H); ^{31}P NMR (162 MHz, C_6D_6) δ 6.0.

2.2 Deconstructed Staudinger Ligation NMR Experiments

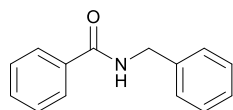
Amide formation *via* independent preformation of iminophosphorane (7) and silyl ester (18) (Scheme 7 and 8)

Stoichiometric (a): The iminophosphorane (ylide) was preformed by stirring benzyl azide (22.0 μ L, 0.176 mmol) in toluene (0.5 mL) at reflux for 1 h in the presence of triphenylphosphine (40.0 mg, 0.153 mmol). Phenylsilylbenzoate **18** was preformed as described above, in toluene (0.5 mL), with 0.153 mmol of each component. The solution of iminophosphorane was then added to the silyl ester and the reaction stirred at toluene

reflux for 13 h. After this time, the reaction was cooled, quenched with methanol and concentrated *in vacuo*. The yield of amide was determined to be 47% amide by ^1H -NMR by comparison to tetrachloroethane as an internal standard. When the reaction was run for 50 min, 22% amide was observed by ^1H -NMR, and ^{31}P -NMR showed 98% phosphine and 2% phosphine oxide.

Catalytic (b): The silyl ester **18** (0.153 mmol) was preformed as described above, in toluene (1.0 mL). Triphenylphosphine (4.0 mg, 10 mol%) was added, and allowed to dissolve before adding the benzyl azide (22.0 mL, 0.176 mmol). The reaction stirred at reflux for 13 h. After this time, the reaction was cooled, quenched with methanol and concentrated *in vacuo*. The yield of amide was determined to be 64% amide by comparison to 1,1,2,2-tetrachloroethane as an internal standard.

***N*-benzylbenzamide¹ (11)**



The amide product was isolated and characterised as follows; the solvent was concentrated and the residue taken up in ethyl acetate, washed once with each aqueous HCl (1 M), saturated aqueous sodium carbonate and brine. The organics were dried over magnesium sulfate, concentrated, and purified by flash column chromatography (8-20% EtOAc in petrol) to give a white solid, consistent with literature data.

^1H NMR (400 MHz, CDCl_3) δ 7.85 - 7.73 (m, 2H), 7.53 - 7.46 (m, 1H), 7.46 - 7.39 (m, 2H), 7.37 - 7.27 (m, 5H), 6.69 - 6.29 (m, 1H), 4.64 (d, J = 5.7 Hz, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 167.3, 138.2, 134.3, 131.5, 128.7, 128.6, 127.9, 127.6, 126.9, 44.1; HRMS (ESI⁺): Exact mass calcd for $\text{C}_{14}\text{H}_{13}\text{NNaO}$ [$\text{M}+\text{Na}$], 234.0889. Found 234.0893, σ =

0.0087; IR (cm^{-1}) (CDCl_3) 3452, 3011, 1658, 1519, 1487; **Mp** 101-102 °C (lit.² 100-101 °C).

Phenylsilane rapidly reduces the aminophosphonium carboxylate (Figure 1)

The iminophosphorane (**7**) of benzyl azide and triphenylphosphine was formed as described above (^{31}P -NMR, δ 6.2 ppm). Added was benzoic acid (1 equivalent) and the solution in C_6D_6 was cooled to room temperature once the benzoic acid had dissolved. At this point, ^{31}P NMR showed the aminophosphonium carboxylate complex **9** (^{31}P -NMR, δ 36.9 ppm). Addition of phenylsilane (1 equivalent) at room temperature was accompanied by 1.3 equivalents of hydrogen gas evolution within 4 min, measured as described above. At this point, ^{31}P -NMR showed oxide:iminophosphorane:phosphine (7:18:74) (δ 25.0 : 6.8 : -5.2 ppm). No amide or the known monobenzoxyisyl ester was observed. After standing at room temperature for several days in the NMR tube, the ^1H -NMR of the sample showed 53% amide **11** and 47% benzylamine.

Additional Experiments

In all cases, the components were prepared as above (0.38 mmol scale), and combined as detailed in the main text in oven-dried flasks (5 mL) in C_6D_6 (0.63 mL) under an argon atmosphere.

Thermal amidation (Figure 2)

Preformed ylide **7** and benzoic acid were combined stoichiometrically (0.38 mmol scale) in toluene (0.63 mL) and the reaction refluxed over 20 h, taking aliquots for NMR at 4 stages and mixing with enough C_6D_6 for solvent locking. The spectra are shown in figure 13 in the main text, and demonstrate the formation of amide and phosphine oxide over 20 h.

Formation of mixed acyloxysilylamines (Figure 3)

Preformed iminophosphorane **7** and benzoic acid were combined stoichiometrically (0.38 mmol scale) in C_6D_6 (0.63 mL) in an NMR tube, and a ^1H -NMR recorded. Phenylsilane (1 equiv) was added and another NMR recorded immediately. Further NMRs were recorded at 15 mins and 15 h. The spectra are shown in **Figure 3** in the main text, and demonstrate for formation of several species whose ^1H -NMR signal is a doublet of 8 Hz. This is consistent with previously reported silylamine species.

Orthogonal formation of mixed silanamines and acyloxysilanamines (Figure 4)

(A) Preformed iminophosphorane **7** and phenylsilane were combined stoichiometrically (0.38 mmol scale) in C_6D_6 (0.63 mL) in a 5 mL flask and heated at reflux for 15 h. After this time, a ^1H -NMR spectrum was recorded. Some iminophosphorane remained, and some benzylamine was also present. A species with 8 Hz (silanamine) was also visible at ~4 ppm. These data are in agreement with the catalytic Staudinger reduction reaction described by Rutjes and co-workers.³ Added to this mixture was benzoic acid, and the reaction stirred at rt for 30 min. Another NMR spectrum was recorded, which showed two new 8 Hz doublets had formed with higher shifts, likely mixed species of type **24**. (B)

(C) Preformed iminophosphorane **7** and preformed silyl ester **8** were combined stoichiometrically (0.38 mmol scale) in C_6D_6 (0.63 mL) in an NMR tube, and a ^1H -NMR recorded after 30 min at 80 °C. Several 8 Hz doublets are visible.

(D) Preformed iminophosphorane **7** and chlorophenylsilane were combined stoichiometrically (0.38 mmol scale) in C_6D_6 (0.63 mL) in an NMR tube, and a ^1H -NMR recorded. This time the silyl hydrides are visible as 3 Hz doublets. Benzoic acid was added at room temperature and an NMR recorded after 10 min (E) generating further species.

All the 8 Hz species formed are various benzylaminosilicon species. Note that, in the reaction mixture, the ammonium carboxylate salt **9** may react with the acyloxysilamine species (e.g. of type **24**) rather than with a silyl ester, which will expend the final hydride and generate a range of species of type **24**.

3. Experimental References

- 1 A. D. Kosal, E. E. Wilson and B. L. Ashfeld, *Angew. Chem. Int. Ed.*, 2012, **51**, 12036–12040.
- 2 Y. Kawagoe, K. Moriyama and H. Togo, *Tetrahedron*, 2013, **69**, 3971–3977.
- 3 H. a. van Kalker, J. J. Bruins, F. P. J. T. Rutjes and F. L. van Delft, *Adv. Synth. Catal.*, 2012, **354**, 1417–1421.

Chapter 2

Silyl Esters in Acylation Chemistry: Scope and Mechanism

Contributing authors; Keith G. Andrews, Declan M. Summers, Ross M. Denton

Silyl esters are formed in a base-catalysed dehydrogenative reaction between silanes and carboxylic acids. Whilst many substituted hydridosilanes have been studied in this context, phenylsilane, a reagent currently in vogue in organic synthesis chemistry, has been little explored. In this Chapter, we explore the reactivity of phenylsilane in the presence of carboxylate species, and the reactivity of the resultant silyl ester species. Kinetic experiments reveal a pentacoordinate transition state to dehydrogenation with a remarkably low activation energy. Indeed, the reaction is shown to be desolvation-limited unless the base is in excess. The scope and utility of the silyl esters in amidation chemistry is reported.

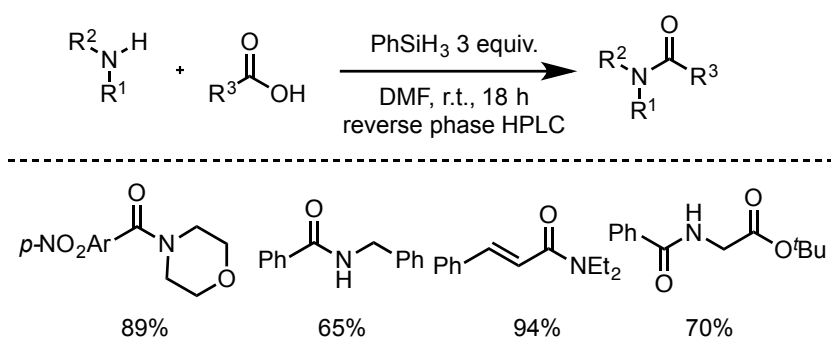
Introduction

The formation of amides from amines and carboxylic acids represents yet another chemical transformation in which the sole by-product *could* be water, but where it very rarely is. Contributing to the kinetic barrier to direct amidation is the formation of ammonium salts, which hinder solubility and reduce the effective concentration of nucleophilic amine. Remarkably, the direct amidation reaction is also slowed by water itself; Whiting has shown that removal of water by a Dean-Stark apparatus from refluxing toluene allows an uncatalysed direct amide reaction to occur for some substrates.¹ It seems that residual water inhibits the amidation process (water may increase the extent of proton transfer by solvating the new ion pairs, deactivating further amine).

With the exception of these often-ignored direct amidation procedures,¹⁻⁵ amide formation strategies generally involve the activation of the carboxylic acid as an activated ester,^{6,7} or *via* different reactive intermediates that can allow interesting orthogonalities.⁸⁻¹⁶ The so-called coupling reagents¹⁷ make up a large bulk of the most popular, reliable reagents,¹⁸⁻²¹ but there are countless other approaches, including stoichiometric boron reagents.²²⁻²⁷ Efforts towards catalytic amide formation are currently popular, with approaches utilising boronic acids²⁸⁻³² and various metals.³³⁻³⁶ Whether it is a lack of generality, convenience, functional group tolerance or simply education on the part of practising chemists, there remains a market for new amidation reactions.^{37,38} There is no doubt that convenience is at the forefront of many practising chemists' minds. The recent drive to identify more atom economical processes is negated by a lag in uptake with respect to implementation.

Although under no illusions that Ruan's phenylsilane mediated amidation is likely to become the amidation method of choice, we were keen to study its mechanism, relating both

to the catalytic Staudinger ligation, discussed in Chapter 1, and for its conceptual approach. In its favour the reaction; i) requires a single liquid reagent, ii) which is relatively cheap (compared to popular coupling reagents; e.g. 6 x cheaper per mol than HATU), iii) produces hydrogen and silanols/siloxanes as by-products instead of stoichiometric acid requiring the addition of base, and iv) appears to have a reasonable scope. In its original format, the reaction utilises dimethylformamide and HPLC purification (Scheme 1).



Scheme 1. Ruan's amidation protocol, mediated by phenylsilane.

Interestingly, these are both often considered beneficial to a practising pharmaceutical chemist who desires ready solubility of polar functionality and the ability to subject the reaction mixture to direct automated purification. With almost nothing known about the reaction, it was deemed worthy of interest in terms of potential extensions and novel discoveries. A particularly desirable goal would be to integrate the reaction with the many existing silane-mediated catalytic amide reduction reactions. This would allow a one-pot reductive amination reaction from carboxylic acids and amines.

Results and Discussion

Development of Ruan's phenylsilane-mediated amidation reaction

We began by confirming the utility of phenylsilane as a coupling reagent, and probing its reaction with different acids at room temperature (Table 1).

Table 1. Initial exploration of conditions under which the amidation reaction operates

1: R = Me
2: R = Cy
3: R = Ph

5: R = Me
6: R = Cy
7: R = Ph

Entry	Time /h	Solvent	Amine equiv.	Acid equiv. (R)	Silane (equiv.)	Yield (%)
1	0.5	EtOAc	1.0	1.0 (Me)	PhSiH ₃ (2.0)	86
2	3.5	EtOAc	1.0	2.0 (Me)	PhSiH ₃ (1.4)	91
3	15	(neat)	1.0	2.0 (Me)	PhSiH ₃ (2.0)	100
4	8	MeCN	1.0	2.0 (Me)	PhSiH ₃ (2.0)	100
5	14	EtOAc	1.0	1.0 (Cy)	PhSiH ₃ (2.0)	54
6	60	EtOAc	1.0	1.0 (Cy)	PhSiH ₃ (4.0)	54
7	6	MeCN	1.0	1.0 (Cy)	PhSiH ₃ (2.0)	47
8	6	MeCN	2.0	1.0 (Cy)	PhSiH ₃ (2.0)	29
9	6	MeCN	1.0	2.0 (Cy)	PhSiH ₃ (2.0)	84
10	4	MeCN	1.0	1.0 (Cy)	PhSiH ₃ (1.3)	53
11	3.5	MeCN	1.0	1.0 (Ph)	PhSiH ₃ (2.0)	34
12	3.5	EtOAc	1.0	2.0 (Ph)	PhSiH ₃ (2.0)	50
13	5.5	EtOAc	1.0	2.0 (Ph)	PhSiH ₃ (2.0)	48

^aYields were calculated via ¹H NMR using tetrachloroethane as an internal standard.

There seemed to be three distinct regimes of reactivity. Only one equivalent of acetic acid **1** was required to give 86% yield of amide **5** (entry 1), with up to quantitative conversions observed for two equivalents of acid (entries 2-4). Both ethyl acetate and acetonitrile were viable solvents. For cyclohexanecarboxylic acid **2**, however, when using one equivalent of acid, the reaction appeared to be capped at 50% conversion (entries 5-8), irrespective of the equivalents of phenylsilane. However, increasing the acid equivalents to two gave higher conversions again (entry 9). Unfortunately, this did not translate to aromatic acids (benzoic acid **3**), which gave higher levels of salt precipitation and appeared to be capped below 50% yield irrespective of the equivalents of acid employed (entries 11-13). As phenylsilane can theoretically accommodate three ligands, we wondered if varying levels of substitution at

silicon was the root of the conversion differences. This mystery was not solved at the time, but later results suggested that the rate of amidation and the rate of silylamine formation might be to blame.

In order to improve the conversion per silane molecule, and aid solubility, we increased the temperature, which we anticipated might overcome the apparent barriers that discriminated between acetic, cyclohexane and benzoic acids. This was met with success, and we carried out a brief optimisation with the previously difficult benzoic acid on the solvent and stoichiometry. Now, the conversion was much higher, without requiring two equivalents of carboxylic acid, providing evidence that the rates/extents of silyl ester formation and trapping of these intermediates could be responsible, and that energy (temperature) barriers to various pathways may play a role. As solvent, toluene seemed to offer a balanced set of properties. It has a wide temperature range for increased solubility of ammonium salts, is a sensible solvent for studying reactions in, and offered compatibility with several existing amide reduction methodologies. Some key results are shown in Table 2. A brief optimisation (Table 2) showed that a 50% excess of carboxylic acid and phenylsilane gave the highest conversion (entry 5). Good yields are still obtainable with 1.0 equivalent of both acid and amine (entry 1). Only 2% amide was formed in the absence of phenylsilane (entry 4), and the reaction failed to proceed at room temperature due to the precipitation of the substrates as a salt (entry 7). It was possible, however, to limit the silane to 0.66 equivalents (entry 9), which equates to just over half an equivalent with respect to acid, and still obtain high conversions (94%). This result indicated that multiple acids could be activated with a single silane molecule. The reaction also proceeded in ethyl acetate, THF and acetonitrile, although the conversions were generally lower. In ethyl acetate, the corresponding

acetamide was sometimes observed in low amounts, making this solvent undesirable for reactions carried out at elevated temperatures.

Table 2. Optimisation of the amidation reaction at higher temperature

Ph-C(=O)OH (3) + NCCPh (4) $\xrightarrow[\text{[solvent] [temperature] [time]}]{\text{PhSiH}_3 \text{ [equiv.]}}$ Ph-C(=O)NCCPh (7)

Entry	Time /h	Temp °C	Solvent	Amine equiv.	Acid equiv.	Silane (equiv.)	Yield (%)
1	15	reflux	toluene	1.0	1.0	PhSiH ₃ (1.0)	75
2	15	reflux	toluene	1.0	1.0	PhSiH ₃ (1.5)	78
3	15	reflux	toluene	1.2	1.0	PhSiH ₃ (1.0)	83
4	15	reflux	toluene	1.2	1.0	–	2
5	13	reflux	toluene	1.0	1.5	PhSiH ₃ (1.5)	100
6	13	reflux	toluene	1.0	1.2	PhSiH₃ (1.2)	93
7	13	20	toluene	1.0	1.2	PhSiH ₃ (1.2)	0
8	13	reflux	acetonitrile	1.0	1.2	PhSiH ₃ (1.2)	66
9	13	reflux	toluene	1.0	1.2	PhSiH ₃ (0.66)	94
10	13	reflux	toluene	1.0	1.2	PhSiH ₃ (0.33)	52
11	4	85	toluene	1.0	1.2	PhSiH ₃ (1.2)	63
12	13	reflux	toluene	1.0	1.2	Ph ₂ SiH ₂ (2.0)	52
13 ^b	13	reflux	toluene	1.0	1.2	PhSiH ₃ (1.2)	87

^aYields were calculated via ¹H NMR using tetrachloroethane as an internal standard. ^bReaction performed in Winchester grade toluene in undried glassware under air atmosphere.

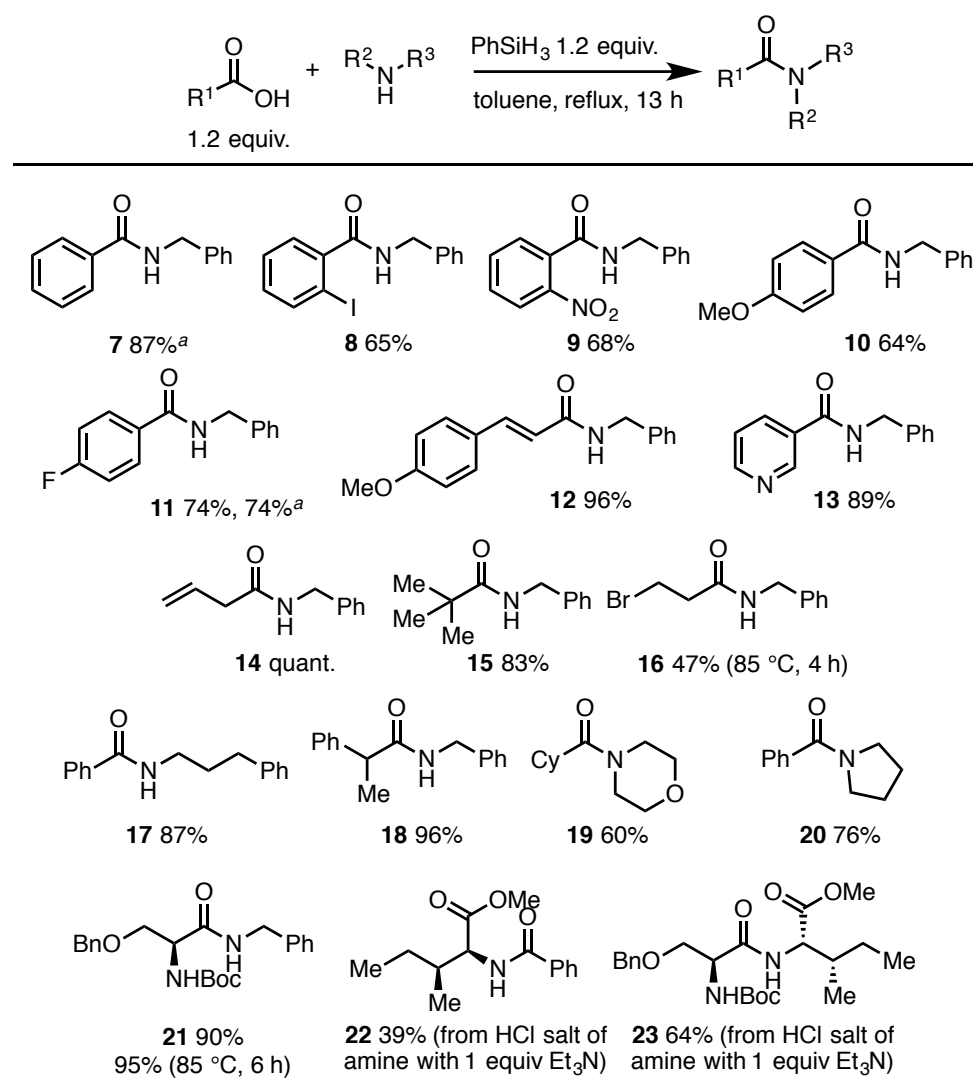
Diphenylsilane was an inferior amidating agent (entry 12), presumably due to increased sterics around the silicon atom; electronics may also play a role. Finally, we ascertained that the reaction did not require meticulously dry conditions (entry 13). We elected to continue with entry 6, which provided a compromise between yield, excesses of components and manoeuvrability for less reactive substrates.

Scope of the amidation reaction

A summary of the initial scope explored is given in Figure 1. Aromatic acids featuring both electron withdrawing and donating groups coupled reasonably well (7-11). Halogens (8)

and nitro groups (**9**), even in a potentially interfering ortho position, gave good yields. Cinnamic acid derivatives were particularly reactive substrates (**12**), though aliphatic acids (**14**, **15**, **18**, **21**) gave some of the most consistently excellent yields.

Figure 1. Initial scope table for the amidation reaction



Reactions carried out with 0.5 mmol amine, 0.6 mmol acid and 0.6 mmol phenylsilane in toluene (1.5 mL).

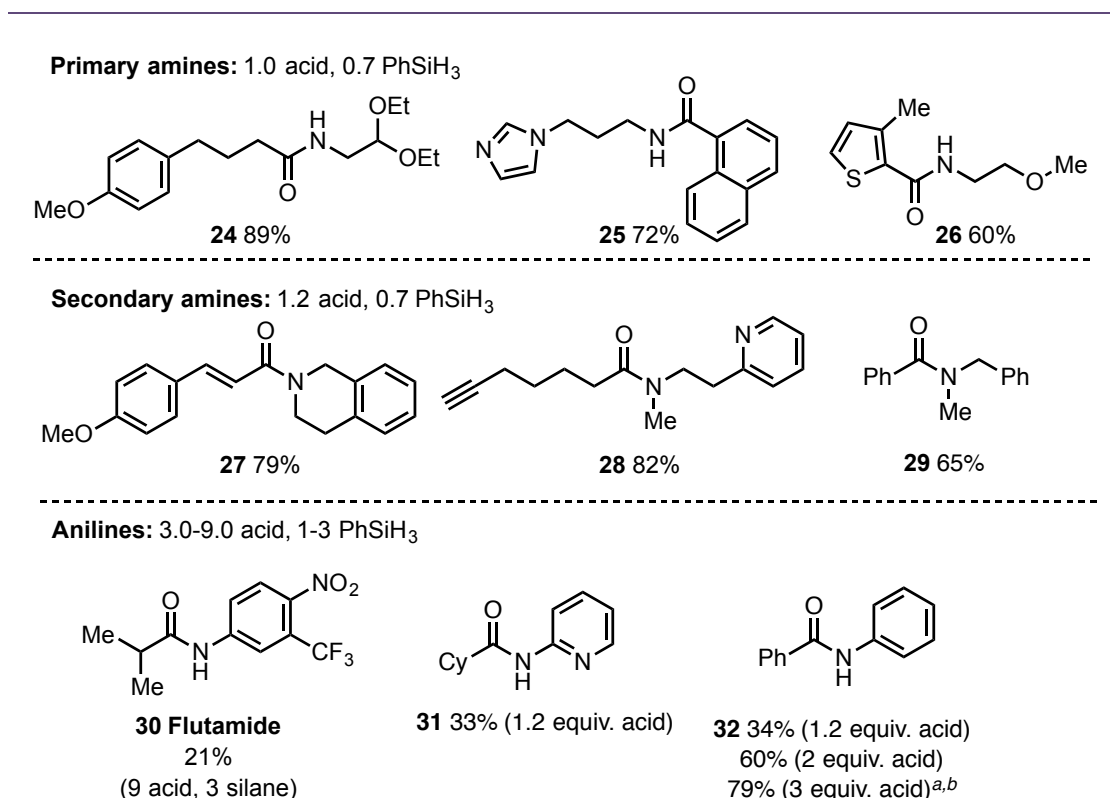
Yields are isolated yields following chromatographic purification. ^aNo chromatography – see SI for full details.

The pyridyl nitrogen of nicotinic acid did not interfere with coupling (**13**), and this basic product could be purified simply *via* acid-base extraction, due to the absence of other acid/base additives. Secondary amines were both slower and lower yielding than primary amines, but morpholine (**19**) and pyrrolidine (**20**) gave good yields. Importantly, *N*-

protected amino acids coupled (**21-23**) and no racemization was visible by inspection of the $^1\text{H}/^{13}\text{C}$ NMR spectra of the crude reaction mixtures for substrates with more than one stereogenic centre (**22,23**). The result was later confirmed by optical rotation measurements (*vide infra*).

We also demonstrated that reduced silane loadings could be used (Figure 2).

Figure 2. Tailored conditions for primary, secondary and aromatic amines.



Reactions carried out with 0.5 mmol amine, 0.6 mmol acid and 0.6 mmol phenylsilane in toluene (1.5 mL) except where stated. Yields are isolated yields following chromatographic purification. ^aNo chromatography – see SI for full details. ^b92% of the remaining acid starting material was reclaimed pure via work up.

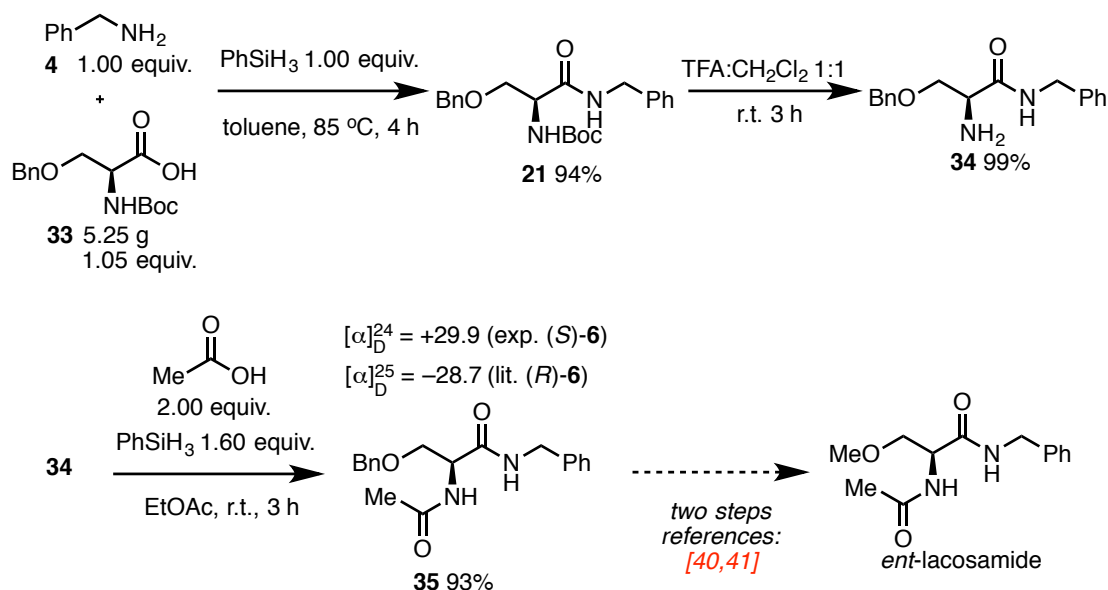
Under these conditions, 0.7 equivalents of phenylsilane could be employed with 1.0 equivalent of carboxylic acid for primary amine substrates (**24-26**). Acetals **24**, imidazoles **25** and thiophenes **26** were tested successfully here. Secondary amines gave improved conversions when 1.2 equivalents of acid were employed, but substoichiometric silane was still viable (**27-29**); terminal alkynes **28** were tolerated. Anilines proved more difficult to

couple, and required three equivalents of acid along with 1.2 equivalents of phenylsilane for useful conversions to be obtained (**32**). API flutamide **30** was synthesised in low yield in the presence of 9 equivalents of carboxylic acid and three equivalents of silane. The main obstruction to successful reactivity was the solubility of highly polar acids and amines. Likewise, amine HCl salts were variable substrates – sometimes (as in the case of entry 23 in Figure 1) they provided good yields of amide in the presence of 1 equivalent of triethylamine, however, some HCl salts suffered from solubility problems.

Exemplification of the reaction in the synthesis of an API

In order to facilitate the purification process a work-up protocol was developed in which the reaction was quenched with a small quantity of silica gel, which sequestered large amounts of the remaining silane (Si-H) species, and the amide was subsequently eluted from the silica gel. We applied this approach in a multigram formal synthesis of the active pharmaceutical ingredient Lacosamide (87% over three steps, Scheme 2). The sequence starts with an efficient amide coupling between BOC and benzyl protected serine and benzylamine. A focused optimisation suggested that a slight (5%) excess of acid was beneficial and the amide was formed in 94% conversion. Following the above described silica gel quench, the amide was recovered in sufficient purity to continue. After the BOC-deprotection, a second amidation reaction was performed, between **34** and acetic acid, and made use of our previous work with acetic acid at room temperature. Polar solvents like EtOAc and MeCN seem to result in the precipitation of an insoluble silicon based material with prolonged reaction times, often benefiting separation of silicon polymers. (Adding methanol to the reaction mixture may also quench silicon hydrides and result in precipitation, but if this process occurs too rapidly, product may become trapped inside the polymeric gels formed). The amide was again purified using the silica gel quench and elution, avoiding dedicated

chromatography. Optical rotation measurement of **35** confirmed no loss of stereochemical information.



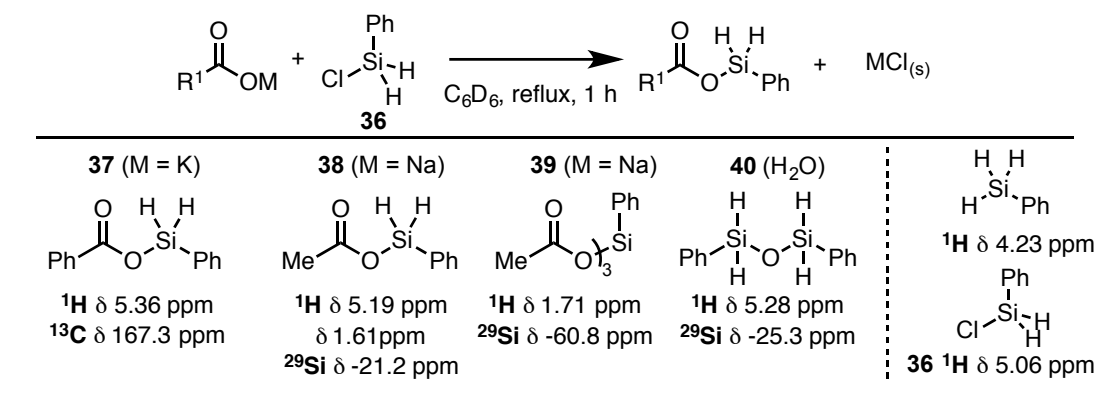
Scheme 2. Formal synthesis of API ent-lacosamide using the phenylsilane-mediated amidation reaction.^{39,40}

With a reasonable scope and practicability demonstrated, we decided to explore the mechanism in more detail, hoping to unmask clues of the fundamental reactivity of the species responsible for this chemistry.

Mechanistic Studies Part I: Qualitative

In order to establish that silyl esters were viable intermediates in the Ruan amidation reaction, and thus our own system, we independently prepared silyl esters **37** and **38** from the chlorosilane **36** or (trichloro)phenylsilane and metals salts of acetic or benzoic acid in toluene or deuterated benzene. Although the acid salts were sparingly soluble, they reacted at reflux over 30-60 min to give the inorganic salt precipitate and the corresponding silyl ester. Filtration is not recommended due to the sensitive nature of the species. The silyl ester species are most suitably prepared in the ‘drier’ apolar solvents. (Deuterated acetonitrile must be exceedingly well handled to allow efficient synthesis of the silyl esters, which are easily quenched – one molecule of water may end up destroying two silyl esters. Even in

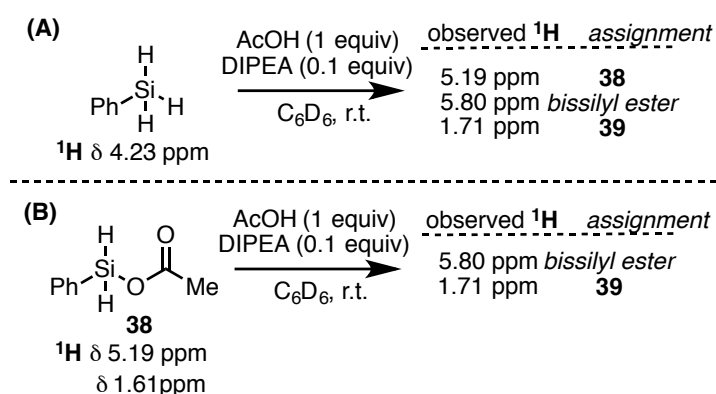
benzene and toluene, ~10% siloxane was normally observed along with the silyl ester in these experiments. These silane species are even more reactive than normal due to the lack of steric hindrance around silicon.) Due to their sensitivity, characterisation was performed in solution. It was possible to observe the monosilyl ester by GC-MS, but normal mass spec destroyed the species (the low molecular weights did not help either). If the reaction is left over longer times (e.g. 4 h), multiple species may be observed. For instance, when potassium benzoate was heated with chlorophenylsilane in benzene, after 4 h, a small amount of phenylsilane was observed (δ 4.23 ppm), along with multiple silyl esters. This suggests some exchange reactions, and the possibility of ‘disproportionation.’ Some of the synthesised species are shown in (Scheme 3).



Scheme 3. Synthesis and characterisation of a selection of silyl esters.

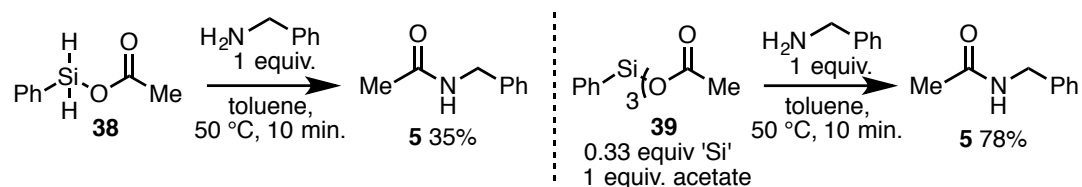
There appears to be a reliable trend between the ¹H NMR shift of the Si–H atoms and the type/extent of substitution. So silyl benzoate **37** (δ 5.36 ppm) gives a slightly decreased shielding compared to the mono-acetate **38** (δ 5.19 ppm), which is more deshielded than the parent chloride **36** (δ 5.06 ppm). Phenylsilane is lowest at δ 4.23 ppm. With characterisation data in hand, we attempted to form and observe these species in the reaction mixture. In the presence of a substoichiometric amount of DIPEA and one equivalent of acetic acid and phenylsilane in deuterated benzene, species consistent with the authentic silyl esters **38** and **39** were observed to form slowly and in small amounts at room

temperature *via* ^1H -NMR spectroscopy (Scheme 4A). We next treated preformed silyl ester **38** with an additional equivalent of acetic acid and DIPEA (Scheme 4B) and the trissilyl ester **39** was observed to form *via* ^1H -NMR spectroscopy. In each case no acetic anhydride, a potential acylating agent, was detected. We supposed the new species in both cases with signal at 5.80 ppm might be the bissilyl ester. Accurate assignment of the trissilyl ester species was also difficult, due to the overlapping of peaks in the proton methyl region.



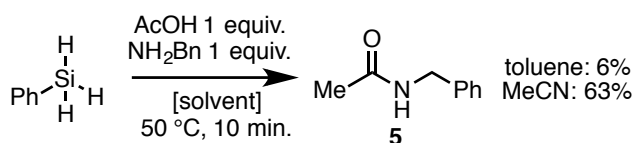
Scheme 4. Observation of independently isolated species in the base-catalysed silyl ester formation reaction.

These results demonstrate that several different silyl esters are plausible intermediates in the silane-mediated amidation. We next probed the reactivity of these species. When benzylamine was added separately to silyl esters **38** and **39**, amide **5** was observed to form. The preformed monosilyl ester **38** underwent relatively slow amidation relative to the trissilyl ester **39** under identical conditions (Scheme 5), in agreement with relative reactivities observed in previous studies utilising non-hydrido silyl esters.^{41,42}



Scheme 5. Tris-silyl esters are more reactive than mono silyl esters.

A direct comparison of the amidation reactions of independently generated silyl esters and the direct amidation process was then made (Scheme 6).

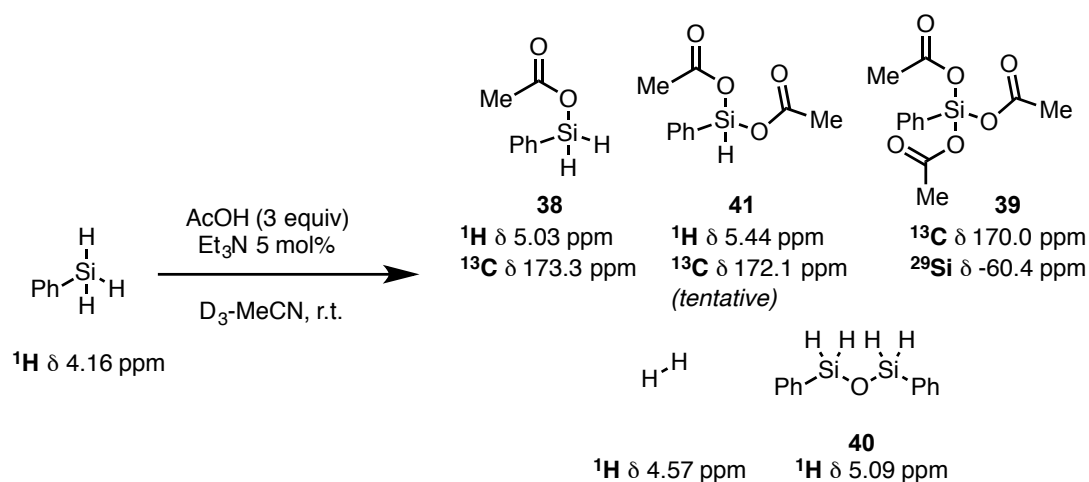


Scheme 6. Comparison of MeCN and toluene as amidation solvents.

When the modified amidation was carried out in toluene a 6% yield of amide was obtained; however, changing the solvent to acetonitrile resulted in 63% conversion. Taken alongside the rates of amidation observed in Scheme 5, these data suggest that formation and reaction of the ammonium carboxylate ion pair with phenylsilane is the rate-limiting step in a non-polar solvent and that the amidation step is relatively rapid. When phenylsilane-mediated amidation reactions were monitored *via* $^1\text{H-NMR}$ spectroscopy, multiple minor silyl species were present (multiple Si-H environments) in addition to phenylsilane, which was consumed more slowly. This indicates that the proposed silyl ester intermediates react rapidly once formed. They also suggest that amidation is faster than silyl ester formation. Indeed, when following the formation of silyl esters in acetonitrile using *catalytic* base (no amidation possible), the reaction was faster than in toluene, and many intermediates were visible, as well as hydrogen gas at 4.57 ppm⁴³ (in benzene, 4.47 ppm).⁴⁴ Some of these species are assigned by analogy to the independently prepared species in benzene (Scheme 7). The additional silyl hydride signals visible are presumably a result of further reaction of the initial formed silyl esters with adventitious water.

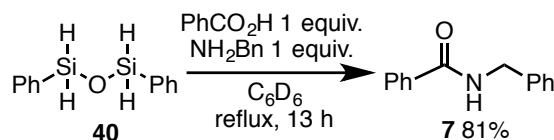
In the experiment in Scheme 7, the intermediates were longer lived with respect to phenylsilane consumption, suggesting that the previous attempts at following the reaction were thwarted by consumption of the intermediates to *amide* rather than specifically to higher silyl esters. Amidation, therefore, may trap many monosilyl esters as amide before multisilyl esters have formed, although as the reaction progresses, the situation may become more complex. Indeed, the species assigned as being more substituted in Scheme 7 appeared

as the reaction progressed, whilst the less substituted initial species were consumed. The integration of the total remaining Si–H signals confirmed that trisubstituted species e.g. trissilyl ester **39** had been formed; the ^{13}C -NMR and ^{29}Si -NMR spectra after extended standing also indicated a majority of this species. There is a clear, downwards trend in the carbonyl ^{13}C -NMR shift as the silane becomes more substituted. Once more, after extended standing, no acetic anhydride was detected by proton or carbon NMR analysis.



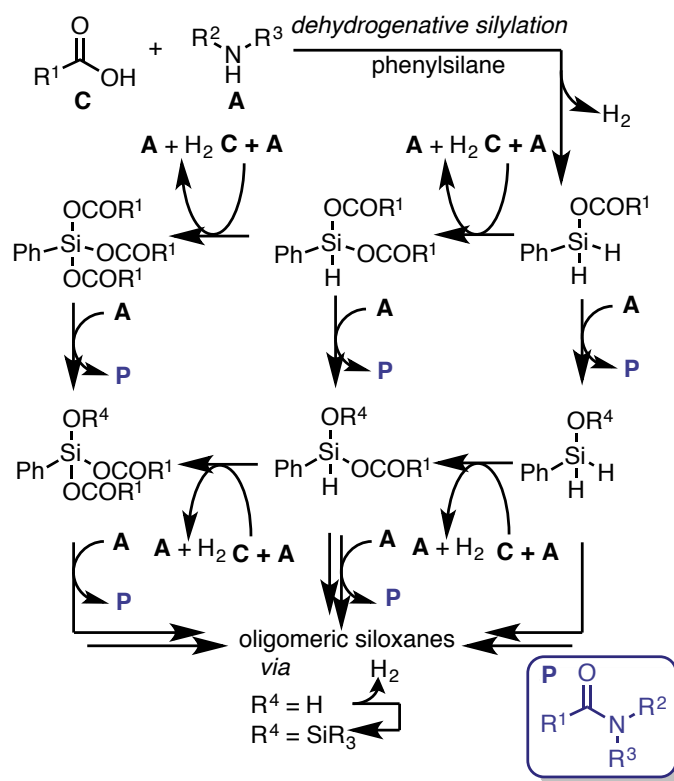
Scheme 7. Some silyl ester species assigned in acetonitrile.

Finally, given that the formal by-product of the amidation reaction is a silanol, which can undergo base-catalysed dehydrocoupling to form a siloxane under the reaction conditions,⁴⁵ we prepared hydridosiloxane **40** by controlled hydrolysis of chlorophenylsilane, and were able to demonstrate that this species could also act as an amidating agent (Scheme 8).



Scheme 8. Hydridosiloxanes are also suitable acylating agents.

Drawing upon these experiments we are now able to depict a qualitative summary of the possible pathways leading to amidation (Scheme 9). We have independently demonstrated that the pivotal acid/amine salt equilibrium is drained *via* irreversible dehydrogenative silylation, to afford a silyl ester.



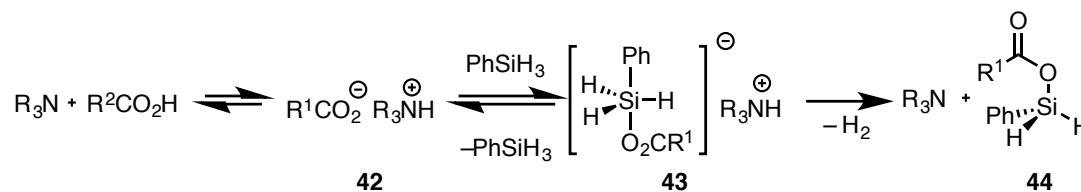
Scheme 9. A depiction of the many possible amidation pathways and precursors making use of the many silicon hydrides available on phenylsilane.

Based on the observation of multiple Si-H species in the presence of base (Scheme 7), we believe that further dehydrogenative esterification of the initially formed monosilyl esters can take place to generate bis- and trissilyl esters. However, the rate of amidation to **P** appears to be highly competitive and monosilyl esters may act as the primary acylating agent in stoichiometric reactions. Amidation of the silyl esters will generate silanols and subsequently hydridosiloxanes products, which we have also demonstrated to be able to mediate amidation. In cases with lower phenylsilane loadings, these species become important sources of additional amidation. Thus, we propose that amidation can occur *via* a number of silyl ester species. *The traffic on a given pathway is variable and likely dependent upon the acidity, nucleophilicity and basicity of the substrates.* Temperature and solvent choice may also impinge on the feasibility of amidation from differing intermediates. The relative reactivity of mono and bis silyl esters is intriguing, but difficult to study. Whilst

mono silyl esters are more Lewis acidic at silicon, the pentacoordinate intermediate formed by attack of a second carboxylate group will have a lower electron density at hydride, potentially slowing dehydrogenation. In order to study questions such as this, we extended our study to quantitative kinetics to better understand the system.

Mechanistic Studies Part II: Quantitative

Based on the information presented above, we sketched a working hypothesis of the mechanism for the formation of silyl esters. The drastic qualitative rate difference between amide formation in toluene and acetonitrile led us to believe that ion pair formation might be important. Further, the lack of any reaction between the silane and amine itself (in the absence of acid) indicated that carboxylate might be the species that initiates attack at silicon (Scheme 10).



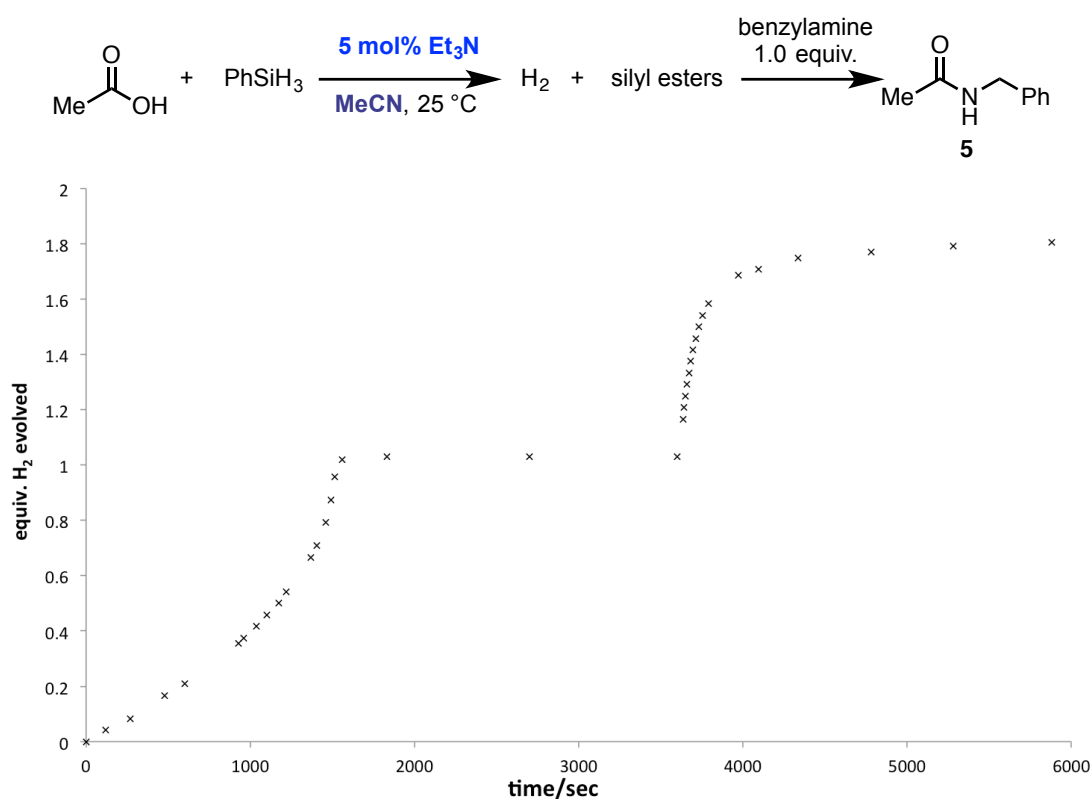
Scheme 10. Working hypothesis of the dehydrogenative silyl ester formation in the presence of catalytic base.

In a series of kinetic experiments, we set out to probe this hypothesis. We elected to study the kinetics of dehydrogenation by measuring the rate of hydrogen evolution by the displacement of water from an upturned measuring cylinder (early results of low resolution proved promising, and a graduated burette was adopted to improve the resolution later on). This, we determined, would allow us to investigate the rate of reactions in the mixture under controlled conditions.

The rate of hydrogenation in toluene was slow at room temperature, and we anticipated solvation problems for more complex systems. Thus, we opted to study the reaction primarily in acetonitrile, which gave an appreciable, but manageable, rate of hydrogen

evolution at 25 °C (oil bath to maintain the temperature). A range of acids and bases were fully solvated at this temperature. An important first experiment in which 5 mol% triethylamine was used as a base catalyst for dehydrogenative silyl ester formation from acetic acid and phenylsilane indicated that the reaction rate *increased* as carboxylic acid was consumed (in acetonitrile at 25 °C, Figure 3).

Figure 3. Chart of hydrogen produced against time for a reaction in which silyl esters are preformed and then reacted with amine.



The rate of hydrogen formation increases until one equivalent of hydrogen has been released, consistent with full consumption of acid. Although we initially interpreted this result as meaning the formed silyl esters were more reactive than phenylsilane, the data below suggests another explanation (*vide infra*). At 3600 s, one equivalent of benzylamine was added, which released another ~0.8 equivalents of hydrogen, much more rapidly than the initial dehydrogenative reaction (although similar to the end of the initial reaction; i.e. at

~1500 s). ¹H-NMR analysis of the final reaction mixture showed 69-74% benzylacetamide was formed (range of repeated runs). Several experiments were performed for comparison (Table 3).

Table 3. Initial rates data for silyl ester and amidation phases of the reaction, performed in MeCN with acetic acid and phenylsilane.

entry	amine	conditions	initial relative rates		conv.	amid. time
			silyl ester	amidation	amide %	t / s
1	Et ₃ N	5 mol% amine, 1 silane	1.0	12	73	2280
2	Et ₃ N	20 mol% amine , 1 silane	17	20	65	1667
3	Et ₃ N	5 mol% amine, 0.67 silane	0.9	4.5	70	2100
4	Et ₃ N	200 mol% amine, 3 silane	350	57	31	1560
5	NMM	20 mol% amine, 1 silane	6.1	6.1	90	5880

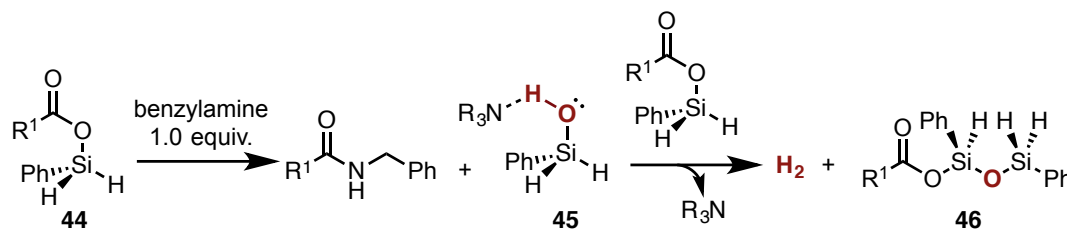
NNM = N-methylmorpholine. Rates quoted relative to silyl ester formation rate of entry 1. The comparisons of yield of amide, whilst instructive in many ways, cannot be taken at face value, because they were left for different time periods (right-most column).

When the loading of base was increased to 20 mol% Et₃N (cf; entries 1 and 2), the initial rate of hydrogen release was faster. When the silane loading was reduced to 0.67 equivalents (cf; entries 1 and 3), the rate of hydrogen generation dropped for both silyl ester formation and amidation stages, but the yield was similar. When the triethylamine and silane were in excess, the rates were much faster (cf. entries 1 and 4). In this case, the reaction was left about the same time as entry 2, but the yield of amide was much decreased (31%). Finally, when the less basic *N*-methyl morpholine (NMM, p*K*_aH = 7.4, H₂O) was used as a base (20

mol%), the initial rate was between a third and a half of the rate compared to when Et₃N was used at the same loading (cf. entries **2** and **5**). When benzylamine was added, however, the yield of amide was the highest yet. Whilst in this case, these early results are not directly comparable themselves (in terms of amide yield) due to the different times of amidation (Table 3), they demonstrate a result that was to become more apparent in future studies. Specifically, higher loadings of more basic amines seem to lower the yield of amide formed. Most instructive in the present case are entries **1** and **4**, which are largely comparable, and in which the yield of amide is 40% lower when 40 times more tertiary amine is present.

We next considered why the second equivalent of hydrogen is released during amidation. Theoretically, it is possible to draw the reaction of a silyl ester and amine to product amide and a silanol, and no hydrogen would be released. Indeed, in the experiments above, it was clear that, although accompanied by dehydrogenation, amidation does not seem to be the cause of the release of hydrogen itself (typically, more hydrogen is released than amidation occurs).

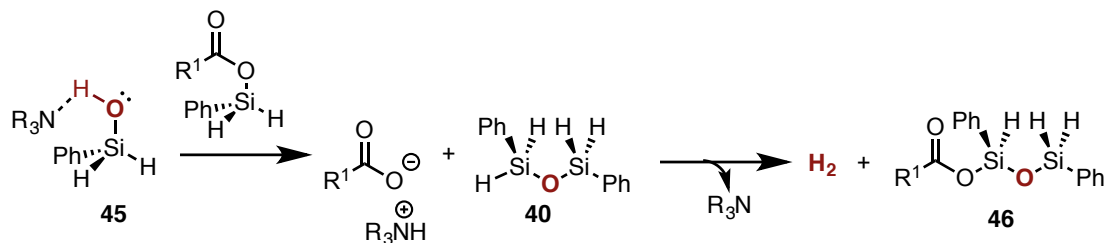
We considered the nature of the by-product silanol. Silanols are more acidic than the analogous alcohols (no consistent data available, but predicted at the upper end of p*K*_a ~7-12),⁴⁶ and can thus easily partake in dehydrocoupling reactions (Scheme 11).



Scheme 11. The production of hydrogen during the amidation phase of the reaction may be due to dehydrogenative siloxane formation from the silanol.

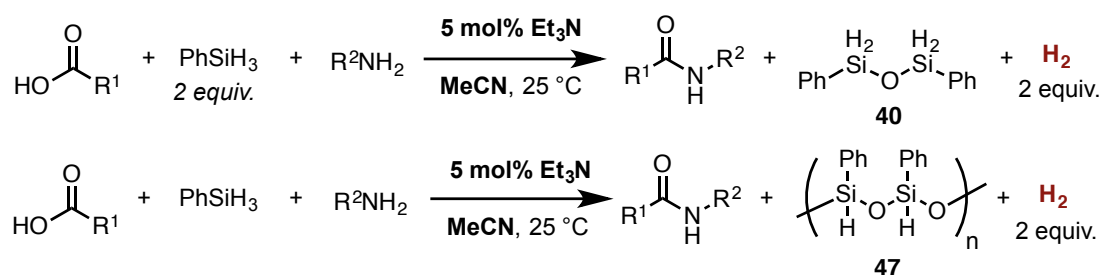
Alcohols are known to react dehydrogenatively with hydridosilanes in the presence of base, and silanols might be expected to react similarly as well.⁴⁷ This would explain the hydrogen

formed in the second stage of the reaction. But a silanol such as **45** can react with a silyl ester in two ways; either dehydrogenatively (as shown in Scheme 11), or by displacing carboxylate (Scheme 12).⁴⁸



Scheme 12. The production of hydrogen during the amidation phase of the reaction may be due to displacement of carboxylate followed by dehydrogenative silyl ester formation.

In both cases, a siloxane (such as **46** or **40**) would be formed. In the latter case, displacement of carboxylate is viable as the product contains a robust Si–O–Si linkage. The rapid exchange of acyloxysilanes by other carboxylic acids has also been documented.⁴⁹ Stronger bases (and higher loadings of bases) may therefore lead to a more substantial deprotonation of silanols (or acids). This would explain the enhanced rate of hydrogen formation in the two reactions in Table 3, which differ only in the identity of the tertiary amine catalyst used. This suggests that, in this case, the reaction of silanol with silane is limited by initial (partial) deprotonation rather than loss of hydrogen (which would be slower from a stronger ammonium acid.) Further, if the extent of siloxide character is higher, a higher proportion of carboxylate ejection may occur. A formal overall reaction scheme for the amidation reaction is suggested in Scheme 13.

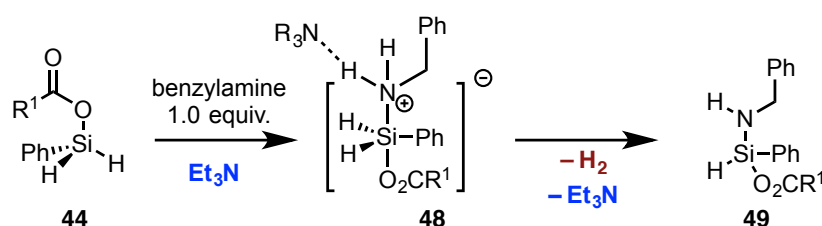


Scheme 13. Formal full equation for the amidation reaction with 1 and 2 equivalents of silane.

As shown, if two equivalents of silane are included, siloxane **40** can act as the oxygen storage molecule (the water surrogate). However, if only one equivalent is included, each silicon group can formally store a whole oxygen atom by forming a polymeric species, such as **47**. Any silyl esters formed from **40** will be less sterically hindered than a silyl ester that resides on a polymeric silicon species such as **47**. Additionally, subsequently forming silyl esters on polymeric siloxanes may also be slower.

We can now begin to propose some explanations for the above observations. First is the proposal that the (substoichiometric) hydrogen formation during amidation is formed from further reaction of the silanol, and is not necessarily concomitant with amidation itself. Second is the proposal that these silanols react with silyl esters in two ways; dehydrogenatively or by displacing carboxylate. Finally, we might suppose that when a single equivalent of silane is present, carboxylate species ejected by amine-catalysed silanol attack at silicon take longer to reform silyl esters by dehydrogenation with the remaining hydride species on polymers such as **47**. Such silyl esters may also be less competent acylating agents. We therefore observe lower extents of amidation when excess basic amines are present to catalyse the reaction of silanol by-product before the initial silyl esters have time to react with nucleophilic amine. The fact that amidation is decreased in proportion to the strength and stoichiometry of the base is further reason to suspect that silyl ester destruction may be occurring. However, it seems that the yield of amide should recover over time if sufficient silane remains, although it may be a case that the decreasing concentrations of both amine and acid make the rates prohibitively slow. Another possibility is amine coordination at silicon on silyl esters to generate electron rich ate complexes that may be less electrophilic at carbon.

Perhaps the most likely reason for decreased amidation in the presence of strong bases is the potential formation of silylamines, which reduce the rate of amide formation by sequestering amine at silicon. Displacement of carboxylate at silicon is known⁴⁹ – tertiary amines may facilitate silylamine formation by deprotonation of amine/silane adducts (e.g. **48**).⁵⁰ Again, carboxylate ejection and loss of hydrogen could both occur. This latter pathway is depicted in Scheme 14.

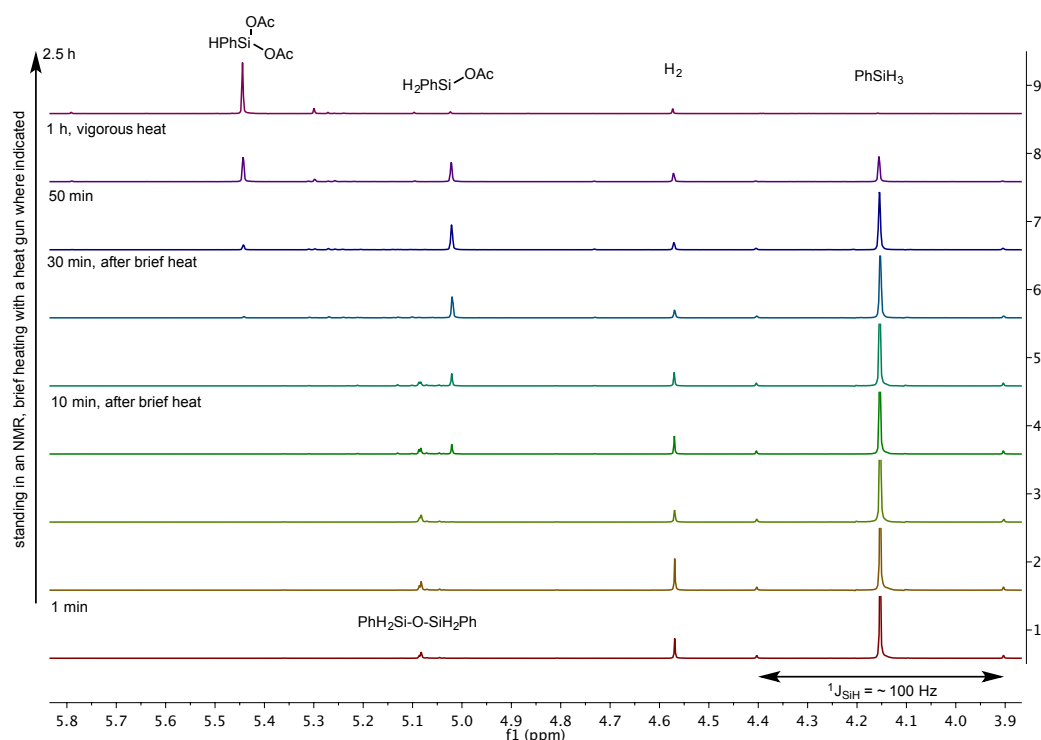


Scheme 14. Hypothesised possible tertiary amine assisted dehydrogenative silylamine formation to give species less able to release amide.

We have previously observed that amines (e.g. benzylamine) do not react with phenylsilane alone at reflux in benzene. However, the increased reactivity of silyl esters may allow such an attack to occur. A basic amine may also catalyse this pathway. Such a manifold may explain why Ashfeld (see Chapter 1) reported a reduced yield of amide when multiple equivalents of silane were used. If silylamines form on different silicon atoms, they must undergo displacement before they can react with silyl esters. The extent with which mixed acyloxysilylamines can undergo internal amide formation is unknown, but higher loadings of silane could sequester all amine and acid, leaving no species available to displace the amine. Despite these unknowns, further work in the group has since made excellent use of *N*-methylmorpholine to pre-generate silyl esters for amidation reactions, but continued attempts to perform the reaction in the presence of tertiary amines has proven to be slow work.

Returning to the question of why the rate of hydrogen formation *increases* as carboxylic acid is consumed (Figure 3, initial phase), we considered the possibility of the monosilyl ester reacting faster than phenylsilane. However, a qualitative experiment in which three equivalents of acetic acid was mixed with 5 mol% Et₃N and 1 equivalent of PhSiH₃ in MeCN seemed to show that the monosilyl ester existed alone until heating was applied (Figure 4).

Figure 4. Formation of bissilyl esters does not immediately follow monosilyl ester formation.



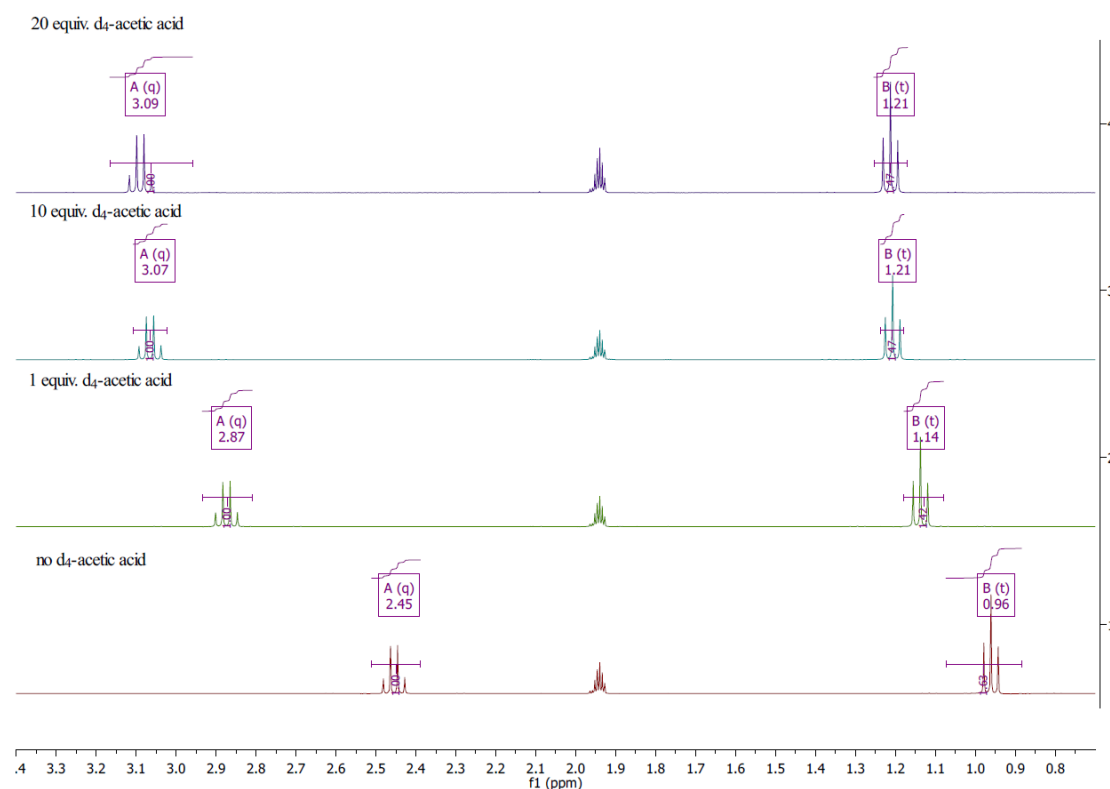
(The excess acetic acid made it hard to see the Me signal in any of the silyl esters, and so the trisilyl ester could not be verified or ruled out. Note that the temperature, time and concentration of components affects the rates of silyl ester formation – the experiments discussed in the preceding section were not followed as rigorously in terms of timing). The reaction was run at room temperature, except the brief heats to reflux.

The ¹H-NMR stack (deuterated acetonitrile) shows that hydrogen is formed rapidly (δ 4.57 ppm), and that the disiloxane **40** is present early on – this later disappears. After a brief heat (the NMR tube is brought to a brief reflux with cautious heat-gun heating), the monosilyl ester is visible in trace 4. The species we assign as the bis-silyl ester isn't visible until a further

brief spell of heating is applied in trace 6, and doesn't really begin to form in larger amounts until the phenylsilane is almost depleted (trace 8).

We next speculated on the role of ion pairs in the reaction medium, as initially hypothesised. The result suggested a (protic) solvation inhibition, and hinted at the importance of a (free) Lewis basic nucleophile to activate silicon. A ^1H -NMR titration experiment (Figure 5) demonstrated a clear chemical shift effect of triethylamine in acetonitrile when increasing (0–20) equivalents of acetic acid were added; the highest concentration reproduces the 5 mol% amine loading used in the catalytic experiments above.

Figure 5. Hydrogen bonding: The effect of the concentration of d_4 -acetic acid on the ^1H -NMR shifts of triethylamine



The acidity equilibrium constants in MeCN for acetic acid ($\text{p}K_{\text{a}} = 21.57$) and protonated triethylamine ($\text{p}K_{\text{a}} = 18.82$) indicate that the equilibrium lies on the side of the neutral species (acid and amine), with only ~ 1 in 1000 existing as the full ion pair. Nonetheless, the titration study above demonstrates that a single equivalent of acid gives the largest shift Δ to

the Et₃N values, as compared to increasing equivalents of acid in acetonitrile, indicating that a solvation/H-bonding network is formed, irrespective of the extent of proton transfer. The tendency for such H-bonding networks to form in relatively weakly-coordinating solvents, and due to the rapidity of proton transfer, the equilibrium position is largely unimportant. Because the acid:amine pair move, on average, together as one, collision with silicon via oxygen is likely to be sufficient to induce full deprotonation, and the success of attack may be viable at various different extents of proton transfer. As long as an acid:amine H-bonding pair is *sufficiently desolvated to expose an oxygen atom*, coordination of carboxylate at silicon may be viable. To probe the theory that desolvation is required to generate a competent nucleophile for silicon, we performed a solvent screen (*vide infra*).

Higher Resolution Measurements

We now elected to study the kinetics of dehydrogenation by measuring the rate of hydrogen evolution via the displacement of water from a graduated burette ($\pm 0.05\text{ cm}^3$) rather than the cruder resolution available using a measuring cylinder as used above. The data obtained using this method were first confirmed to be reproducible, and gave data lines of excellent resolution. At a 1 mmol scale ($24\text{ cm}^3\text{ H}_2$) in 2 mL of solvent, the rate was such that volumes (0.1 cm^3 resolution) and times (~ 1 second resolution) could be easily measured manually. Even with this superficially simple set-up, the resolution was such that if a continuous measurement of a constant reaction rate was made over longer periods, the slight variation ($\pm 0.5\text{ }^\circ\text{C}$) in the temperature of the oil bath was ascertainable in the data plots! In order to adhere to the pseudo-first order conditions (constant concentrations of all reagents), the initial rates were recorded for analysis. This method also reduces the likelihood that higher order silyl esters were forming, and contributing to differing rates of dehydrogenation. As shown in Figure 4 above, this approximation appears valid for acetic acid in MeCN.

Solvent Effects

The results in Table 4 show the initial rates of dehydrogenation in a variety of solvents for a standard set of conditions (relative to the rate in MeCN). As before, the rates were measured

by the rate of hydrogen collection. Analysis of the rates based solely on dielectric constant indicated a correlation, but not a definitive one; adding H-bonding acceptor ability to the analysis brought the anomalous points into line.

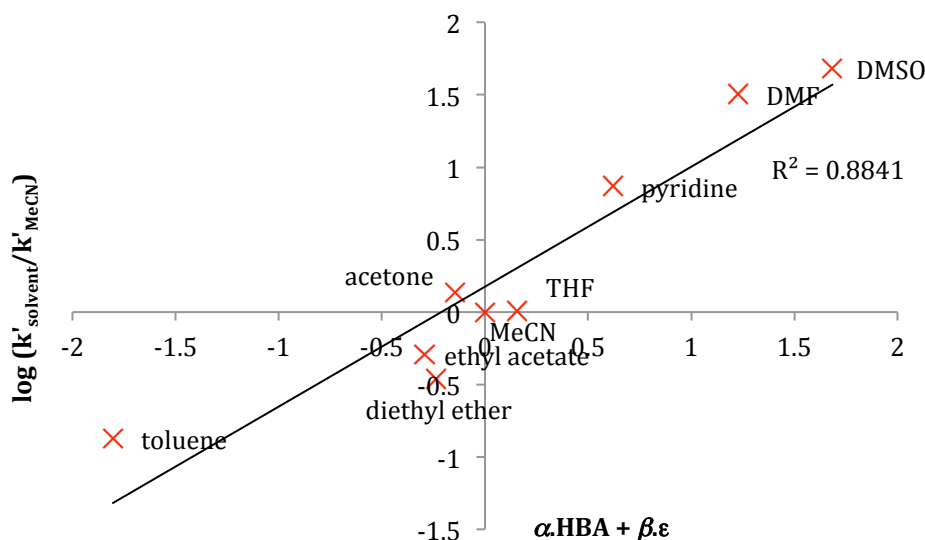
Table 4. Effect of varying solvent on the initial rate of hydrogen evolution.

$\text{Me}-\text{C}(=\text{O})-\text{OH} + \text{PhSiH}_3 \xrightarrow[\text{[solvent], 25 } ^\circ\text{C}]{\text{5 mol\% 2,2,6,6-TMP}} \text{H}_2$			
H-bond			
Solvent	initial rate relative to MeCN	acceptor ability	dielectric constant
MeCN	1.00	0.4	37.5
THF	1.02 ± 0.06	0.55	7.58
CHCl ₃	n.r.	0.1	4.81
DMF	32.1 ± 1.6	0.69	36.7
toluene	0.13 ± 0.03	0.11	2.38
Et ₂ O	0.34 ± 0.03	0.47	4.33
EtOAc	0.51 ± 0.03	0.45	6.02
DMSO	48.4 ± 2.5	0.76	46.7
Acetone	1.36 ± 0.10	0.43	20.7
pyridine	7.44 ± 0.34	0.64	12.4
AcOH	n.r.	0.45	6.15

Results are calculated from the average of three runs. Error calculated using standard error propagation methods, using the confidence interval at 95% in place of the standard deviation. n.r. indicates the rate was too slow to measure in this regime. Values for H-bond acceptors (Kamlet-Taft values)⁵¹⁻⁵³ and dielectric constants taken from widely available tables.⁵⁴ **Experimental details:** 5 mol% 2,2,6,6-TMP in [solvent] 2.00 mL, AcOH 1.0 mmol, PhSiH₃ 1.0 mmol, 25 °C. Hydrogen evolution volume measured as a function of time and the rate determined from the initial straight line portion of the graph at <5% reaction completion to approximate pseudo-first order conditions.

Figure 6 is a LFER plot, which allows the identification of correlations between the rate of a reaction and specific properties of the solvent it is in. Because the graph is plotted as a linear equation, the effects of different properties can be separated, and analysed simultaneously.

Figure 6. LFER plot showing the correlation between H-acceptor ability/dielectric constant of the solvent and the initial rate of dehydrogenation



Plotted using a linear free energy equation of the form $\log(k'_{\text{solvent}}/k'_{\text{MeCN}}) = \alpha.HBA + \beta.\epsilon$: (ϵ = dielectric for the solvent; HBA = hydrogen-bonding accepting constant):

$$\log(k'_{\text{solvent}}/k'_{\text{MeCN}}) = \alpha.HBA + \beta.\epsilon$$

Solved values: $\alpha = 4.27$, $\beta = 1.07$

The prefactors (weighting) of each property, α and β , are solved by minimising the absolute residual values (relative to a linear fit) iteratively, and indicate the extent to which each property is contributing to the difference in rate. Plotting the log of the relative initial rates (MeCN as standard) of the reaction against H-bond acceptor ability and dielectric terms (at 20 °C)⁵⁴ gives a straight line if there is a correlation between the rate differences and the solvent properties in the linear free energy equation.

For the data given in Table 4, the LFER plot, Figure 6, confirmed a positive correlation ($R^2 = 0.88$) between both parameters and the rate of reaction. The solved prefactor values

($\alpha = 4.27$ and $\beta = 1.07$) suggested that the H-acceptor term was dominant. (The parameters were first normalised in terms of range, and offset to give a {0,0} point on the graph for MeCN) to allow direct comparison of the magnitudes between α and β). These results support the theory that the initial step, and the rate-limiting step, *in the presence of excess acid*, is the desolvation of the active Lewis-base (or of discrete ion pairs). In polar solvents, the excess acid, and therefore also the ammonium carboxylate species, are solvated by the solvent. In non-polar solvents, the excess acid diminishes the nucleophilicity of the active Lewis base by solvation (H-bonding). This analysis predicts that performing the reaction in neat acetic acid (a strong H-bond donor) would severely inhibit the rate, despite having an excess of a key reagent. This was subsequently shown to be the case (Table 4 (above), bottom entry). (*Note that a 20-fold excess of protic additives like methanol and phenol react rapidly with phenylsilane in acetonitrile in the presence of base. According to Lukevics,⁴⁵ these substrates only require a 'loosening' of the proton rather than complete ammonium alkoxide formation.*)

We next investigated the effect of the identity of the acid on the rate of hydrogen formation (Table 5). Beginning with acetic acid and increasing carbon atoms through the alkyl series (methyl, ethyl, isopropyl, *tert*-butyl) led to an increased rate of hydrogen production, whilst chloroacetic acid had a slower rate relative to acetic acid (Figure 7 and Table 5).

In general, higher pK_a values (less acidic) gave higher rates of hydrogen production. Higher pK_a values mean a lower extent of deprotonation in the presence of base, but also a higher electronic nucleophilicity. Lukevics has recorded a Hammett analysis σ_p value of -0.68 (with the typical 4-substituted benzoic acids), indicating an enhanced rate of silyl ester formation (for tri(2-thienyl)silane in the presence of piperidine) for electron rich acids,⁴⁵ in agreement

to the results above. These results, however, cannot be explained only in terms of electronics. The increase in rate is *not* linear with increasing pK_a . In contrast to the electronic nucleophilicities, which increase with pK_a due to the +I inductive alkyl effect with increasing carbon substitution, the steric factor operates against this trend.

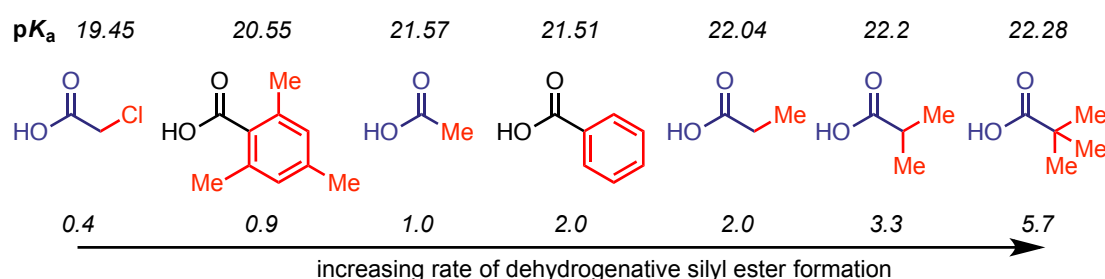
Table 5. Effect of the identity of the acid on the initial rate of dehydrogenation when the acid is in a 20-fold excess in MeCN at 25 °C with 2,2,6,6-TMP and phenylsilane.

$\text{R}-\text{C}(=\text{O})\text{OH} + \text{PhSiH}_3 \xrightarrow[\text{MeCN, 25 } ^\circ\text{C}]{5 \text{ mol\% 2,2,6,6-TMP}} \text{H}_2$			
Acid	(initial) rate relative to AcOH	pK_a (MeCN)	pK_a (ref)
acetic	1.00	21.57	⁵⁵
benzoic	1.99 ± 0.10	21.51	⁵⁶
pivalic	5.68 ± 0.34	22.28	⁵⁵
isobutyric	3.29 ± 0.31	22.2	⁵⁵
chloroacetic	0.43 ± 0.05	19.45	⁵⁵
propanoic	2.00 ± 0.10	22.04	⁵⁵
mesitoic	0.85 ± 0.06	20.55	⁵⁶

Results are calculated from the average of three runs, and quoted to 3 sig fig. Error calculated using standard error propagation methods, using the confidence interval at 95% in place of the standard deviation. Only relative rates are quoted due to the unknown nature of the rate equation in this domain. **Experiment**

Details: 5 mol% Et_3N as stock solution in MeCN (2.00 mL), [acid] 1.0 mmol, PhSiH_3 1.0 mmol, 25 °C. Hydrogen evolution measured as a function of time, with a 1:1 [H]:silyl ester ratio assumed, as demonstrated previously.

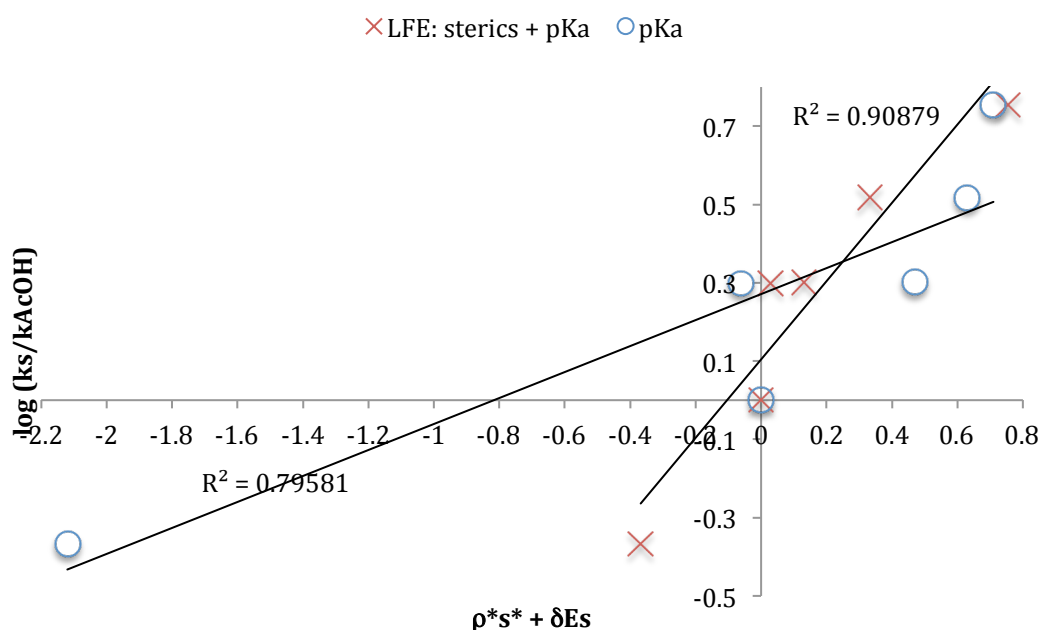
Figure 7. Pictorial display of carboxylic acid R groups, their pK_a s and dehydrogenative rates in acetonitrile.



The most hindered alkyl acid, pivalic, should have a competing steric effect to attack at silicon. Benzoic acid, also, sticks out relative to acetic acid, also suggesting there is a steric component. This *inverse* steric effect – the bulkier species are faster to react – also points to the importance of desolvation kinetics. Extended hydrogen bonding networks would be disrupted by increased steric hindrance, which would prevent close contact of ion pairs and reduce solvation by additional acid molecules, generating free (albeit perhaps only partially deprotonated) carboxylate nucleophiles.

To probe this theory, a linear free energy relationship generated by plotting Charton steric (E_s)^{57,58} and pK_a values in MeCN^{55,56} (instead of inductive constants) against the relative rates (with acetic acid as standard, and iteratively solving the coefficients δ and ρ to minimise the absolute residuals) gave a better fit when the steric parameter was included ($R^2 = 0.91$, red crosses).

Figure 8. Chart showing correlation between $\log(\text{rate relative to AcOH})$ and Charton and acidity constants after solving for ρ and δ . The fit against just the pK_a values is much poorer.



Both the steric coefficient and the pK_a coefficients were positive, indicating a faster reaction with higher pK_a and greater steric hindrance.

An even better demonstration of the steric desolvation effect was observed in a study of the effects of amines on hydrogen production (Table 6).

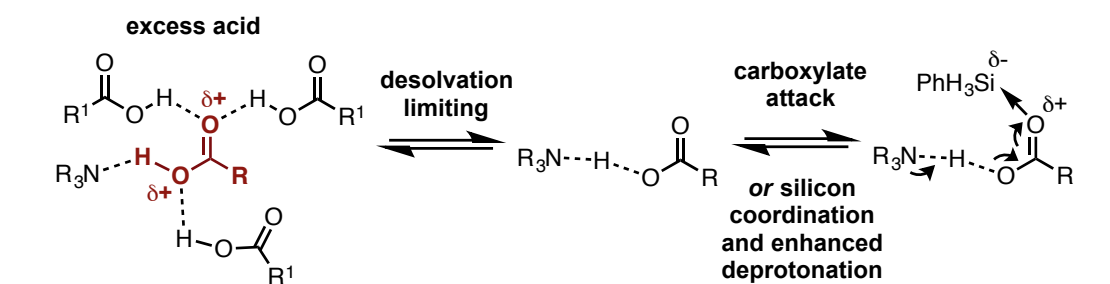
Table 6. Effect of the identity of the amine on the initial rate of dehydrogenation in the presence of a 20-fold excess of acetic acid in MeCN at 25 °C with acetic acid and phenylsilane.

$\text{Me}-\overset{\text{O}}{\parallel}{\text{C}}-\text{OH} + \text{PhSiH}_3 \xrightarrow[\text{MeCN, 25 } ^\circ\text{C}]{5 \text{ mol\% [base]}} \text{H}_2$			
Entry	Amine	initial k' (s^{-1})	rate relative to Et_3N
1	<i>N</i> -methylmorpholine	18.0 ± 0.3	1.39
2	morpholine	13.2 ± 0.8	1.02
3	<i>tert</i> -butylamine	10.6 ± 0.2	0.82
4	Et_3N	12.9 ± 0.4	1.00
5	DiPEA	23.2 ± 1.5	1.79
6	2,2,6,6-TMP	12.6 ± 0.6	0.97
7	DBU	19.7 ± 1.4	1.52
8	imidazole	n.r.	n.r.
9	4- <i>tert</i> -butylpyridine	n.r.	n.r.

Values are the average of three concordant runs. Error calculated using standard error propagation methods, using the confidence interval at 95% in place of the standard deviation. $k' = k[\text{acid}]^a[\text{silane}]^b$. Due to the unknown order in acid in this regime, only k' is reported. Rate = $k'[\text{base}]^c$. n.r. = no rate – i.e. rate too slow to be measured under these conditions. **Experiment Details:** 5 mol% [base] in MeCN (2.00 mL), AcOH 1.0 mmol, PhSiH_3 1.0 mmol, 25 °C. Hydrogen evolution measured as a function of time. Note that acid and silane are in a 20 fold excess.

The variation in initial rate when the base R group(s) are varied (in the presence of excess acid) is significantly less important than altering the R group on the acid. For example, although the pK_a s of DBU and Et_3N are markedly different in MeCN (DBU 24.34; Et_3N 18.82), the rates of dehydrogenation with acetic acid are highly similar (Table 6, entries 7 and 4), in dramatic contrast to the large effects seen when varying acids of similar pK_a s.

DiPEA, on the other hand, of intermediate basicity, has a faster rate (entry **5**), again indicating an inverse steric component to the reactivity (higher sterics = faster reactivity). Because sterically hindered bases (e.g. TMP) are still effective catalysts (and are, in fact, better catalysts), attack of silicon by the carboxylate group (whose steric hindrance lies further from the Lewis basic site) seems assured (over amine attack – there seems no reason to think that a faster elimination of hydrogen to release steric strain from an ate complex is likely given the longer bonds and small steric hindrance of H in the ate complex); the amine acts only as a Brønsted base. Thus, it is concluded that excess acid inhibits the reaction by solvating the ammonium carboxylate pairs, and that desolvation to give a free ammonium carboxylate pair allows the reaction to proceed.



Scheme 15. Depiction of ammonium carboxylate solvation by excess acid and attack of silicon by (partial) carboxylate (not amine).

As the reaction proceeds, the decreasing concentration of acid allows the activation rate to increase (recall the increasing rate as acid is consuming in Figure 3). The more hindered acids and bases are less easily solvated (reduced H-bonding), and thus react faster with the silicon centre. Note that the solvation effects seem to override the rate of dehydrogenation, even for sterically hindered carboxylic acids. This indicates a facile coordination of carboxylate and silane when they do meet: low temperature studies also indicate that this is the case. In fact, the reaction between phenylsilane and the carboxylate has a remarkably low activation energy, proceeding quickly even at $-40\text{ }^\circ\text{C}$ (*vide infra*).

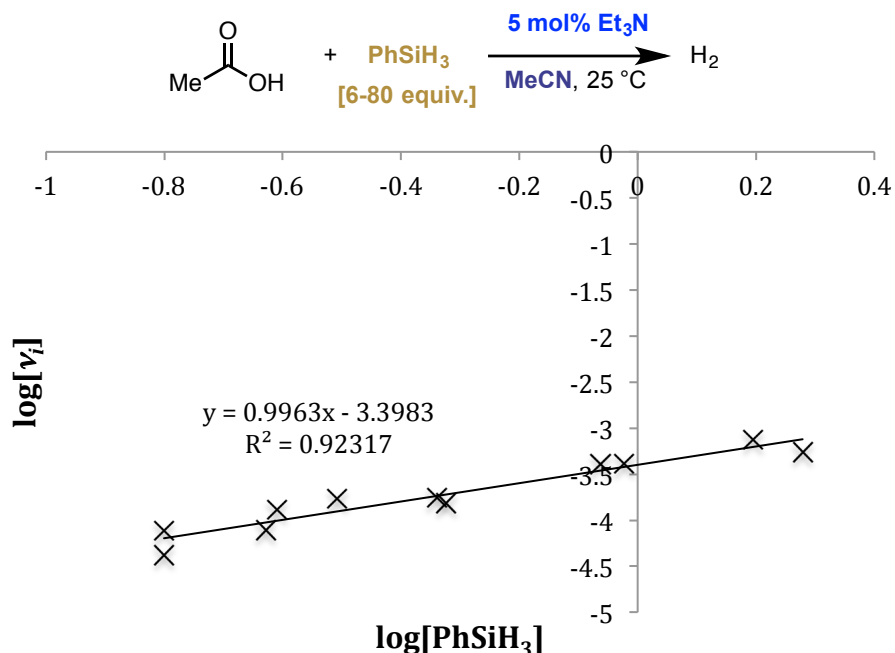
A separate experiment using sodium acetate as the base also led to hydrogen formation (although with a slow rate), demonstrating that the amine is not required. Sodium acetate would be completely solvated by acetic acid in MeCN, and is therefore expected to be slower to desolvate and react. Jencks has described desolvation limited reactions in the case of amines and acids.^{59,60}

Reaction Component Orders

With strong evidence in favour of desolvation, acid:amine pair formation, and carboxylate attack at silicon, we sought to corroborate or refute our proposed pentavalent silicate intermediate. The rate equation order of each component in the dehydrogenation reaction was obtained using the isolation approach. By engineering conditions in which the concentrations of all but one component are approximated to be unchanging, initial rate data can be harvested from the straight lines at the beginning of each reaction, and the rates compared against changing concentration of a specific component to ascertain the order of the component in isolation (pseudo first order conditions).

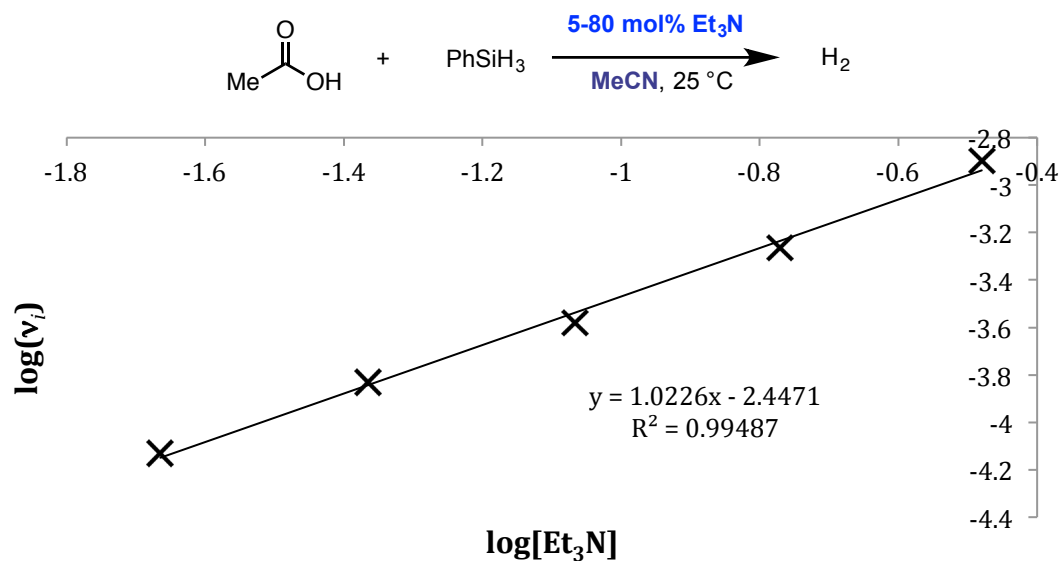
Thus, in the presence of excess acid (unchanging concentration approximation), and 5 mol% triethylamine (constant concentration as acts as a catalyst; Schowen has used catalytic methoxide in a similar scenario),⁶¹ the initial rate of the reaction was shown to follow first order kinetics in phenylsilane when a log/log plot was generated from initial rate data collected at different silane concentrations. Similarly, the initial rate data confirmed the reaction to be first order in amine when excess acid and silane were used, and the concentration of amine varied (Figure 9 and Figure 10).

Figure 9. A plot of $\log(v_i)$ against $\log[\text{PhSiH}_3]$ for a range of concentrations gave a gradient of 1 indicating the dehydrogenation reaction is first order in phenylsilane in an excess of acetic acid and 5 mol% catalytic (not-consumed) Et_3N in MeCN at 25 °C.



Standard least squares regression gives a gradient of 1.00 with an associated error of ± 0.10 . The confidence limits at 95% are ± 0.22 for the gradient. The R^2 value is 0.92317.

Figure 10. A plot of $\log(v_i)$ against $\log[\text{Et}_3\text{N}]$ for a range of concentrations gave a gradient of 1 indicating the dehydrogenation reaction is 1st order in triethylamine in an excess of phenylsilane and acetic acid in MeCN at 25 °C.



Standard least squares regression gives a gradient of 1.02 with an associated error of ± 0.04 . The confidence limits at 95% are ± 0.08 for the gradient. The R^2 value is 0.99487.

Method

Plotting a log/log plot of the form:

$$\log v = \log k + s \log [S]$$

where v is the initial rate, k is a constant and $[S]$ is the concentration of silane (or base) gave a straight line

where the gradient is S . This log/log plot derives from the first order rate equation:

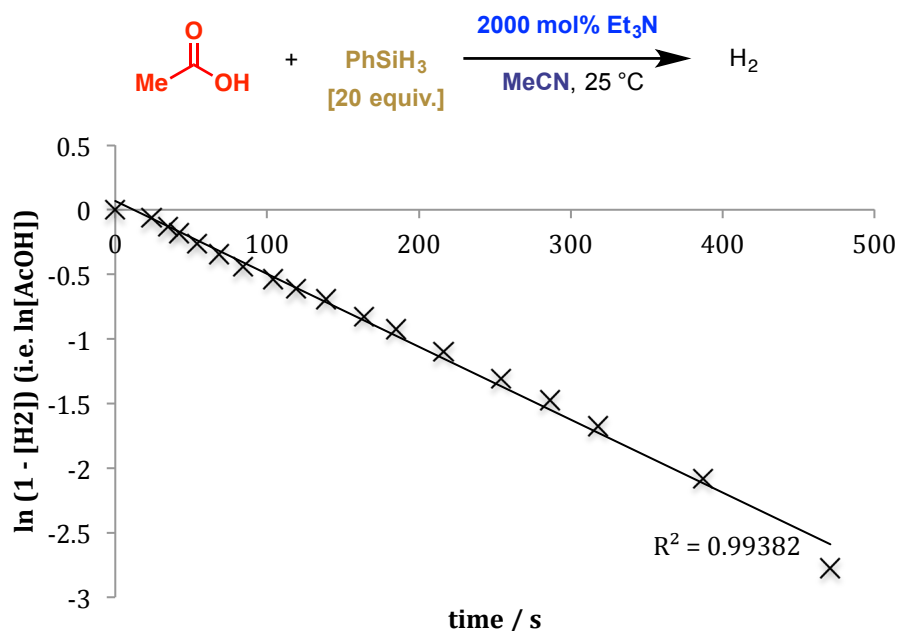
$$\text{rate} = k[S]^s$$

where $k = k'$, assuming constant concentration of all reagents.

Thus the gradient of the line gives the order of the reaction with respect to S .

With the order in silane and base confirmed, all that remained was the order in acid. For this, we measured a single reaction through to completion. Because silicates (i.e. pentacoordinate anions of silicon) can be more Lewis acidic than the parent tetravalent silane species, it was important to rule out/confirm the participation of an additional molecule of acid in the dehydrogenation step. In an excess of Et_3N and phenylsilane, the reaction rate was measured to 93% completion as a function of hydrogen evolution. The reaction was performed at -35°C in order to make the rate measurement manageable; at room temperature, the rate was too fast to record reliable data. In the event, a plot of $\ln[\text{AcOH}]$ (with AcOH mmol calculated as $\text{AcOH}_{\text{initial}} - \text{mmol H}_2 \text{ evolved}$) against time produced a straight line, indicating first order kinetics in acid. This also confirmed that desolvation was no longer being measured. (Figure 11: *plots of the data assuming zero and second order kinetics gave less good fits as determined by least squares regression analysis.*)

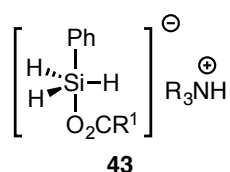
Figure 11. A plot of $\ln[\text{AcOH}]$ against time (s) gave a straight line (measured up to 93% conversion) indicating first order kinetics with respect to concentration of acetic acid in MeCN at $-35\text{ }^{\circ}\text{C}$ in an excess of phenylsilane and triethylamine.



The slight variation in linearity is a result of small temperature fluctuations whilst trying to maintain $-35\text{ }^{\circ}\text{C}$.

This stoichiometry result (1:1:1) clearly needs to be subject to the caveat that the reaction *can* operate under single stoichiometries. It is plausible that, in an excess of acid, a second acid molecule is deprotonated instead of the ammonium counterion. However, the fact that the counterion is both more acidic (in MeCN), and more likely to be in close proximity (as an ion pair), we feel justified in concluding that the proposed pentavalent intermediate ammonium silicate is the likely species from which hydrogen evolution occurs. (*The lifetime of the intermediate is uncertain, and the species may be a transition state rather than full intermediate.*)

Figure 12. Proposed intermediate/transition species responsible for the evolution of hydrogen.



Effect of the Silane

We next examined the nature of the silane in these reactions. The initial dehydrogenation rates of phenylsilane, diphenylsilane and triphenylsilane at 40 °C in MeCN were recorded as above. Diphenylsilane was ~ 14-15 times slower to react than phenylsilane, whilst triphenylsilane was too slow to measure over 45 min (Table 7).

Table 7. Effect of the silane identity on the initial rate dehydrogenation at 40 °C in MeCN with acetic acid and Et₃N.

$\text{Me}-\overset{\text{O}}{\parallel}{\text{C}}-\text{OH} + [\text{silane}] \xrightarrow[\text{MeCN, 40 } ^\circ\text{C}]{5 \text{ mol\% Et}_3\text{N}} \text{H}_2$			
<i>silane</i>	$v_i \cdot 10^4 [\text{H}_2]$ (mmol.mL ⁻¹ s ⁻¹)	$k' \text{ (s}^{-1}\text{)}$	rate relative to PhSiH ₃
PhSiH₃	9.49 ± 0.33	41.4 ± 1.4	1.00
Ph₂SiH₂	0.63 ± 0.05	2.8 ± 0.2	0.07
Ph₃SiH	< 0.03	< 0.2	–

Data is the average of three runs, error calculated as confidence interval at 95%.

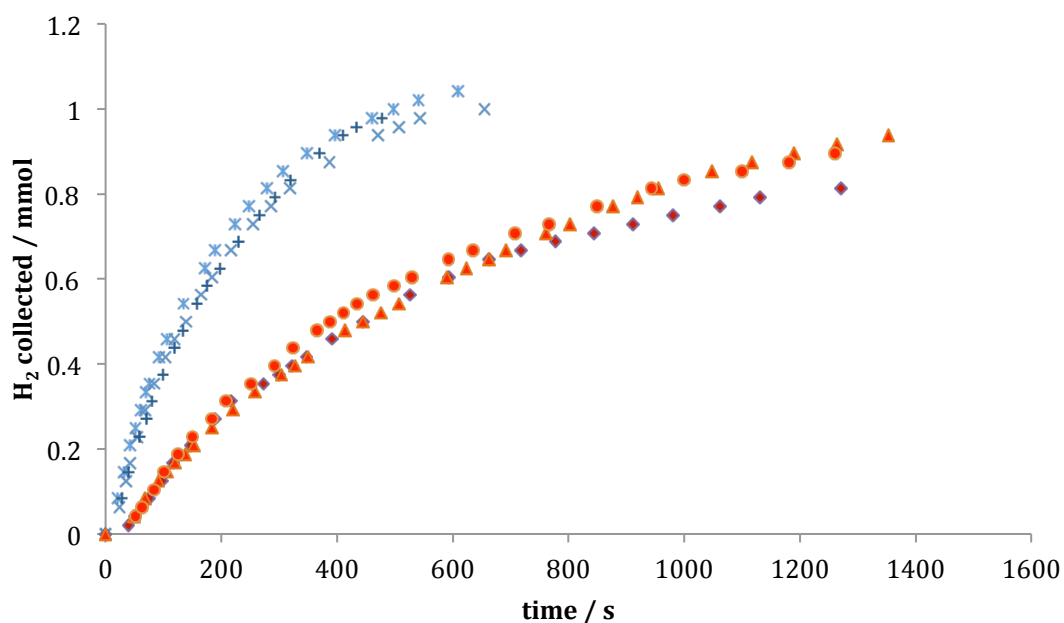
*Rate constant $k' = k[\text{acid}]^a[\text{silane}]$ which are assumed to be at constant concentration. Overall rate equation assumed to be $d[\text{H}_2]/dt = k[\text{base}][\text{silane}][\text{acid}]^a$, where a is unknown in this regime, but base and silane are first order. **Experimental details:** 5 mol% Et₃N (0.05 mmol) as stock solution in MeCN (2.00 mL), acetic acid 1.0 mmol, [silane] 1.0 mmol, 40 °C.*

Although a simple steric analysis at silane may explain the reduced dehydrogenative rate of the higher phenylsilanes – acetate can attack opposite a phenyl substituent (i.e. between three H groups) in phenylsilane, minimising steric clashes – replacing hydrides with phenyl groups also means that phenyl groups would have to occupy equatorial positions, as the incoming acetate is a more apicophilic ligand. The collision statistics are also reduced, as there are fewer hydrides per silane. These results are in line with our attempts of limited success in using silanes other than phenylsilane in the base-catalysed amidation reaction.

Kinetic Isotope Studies

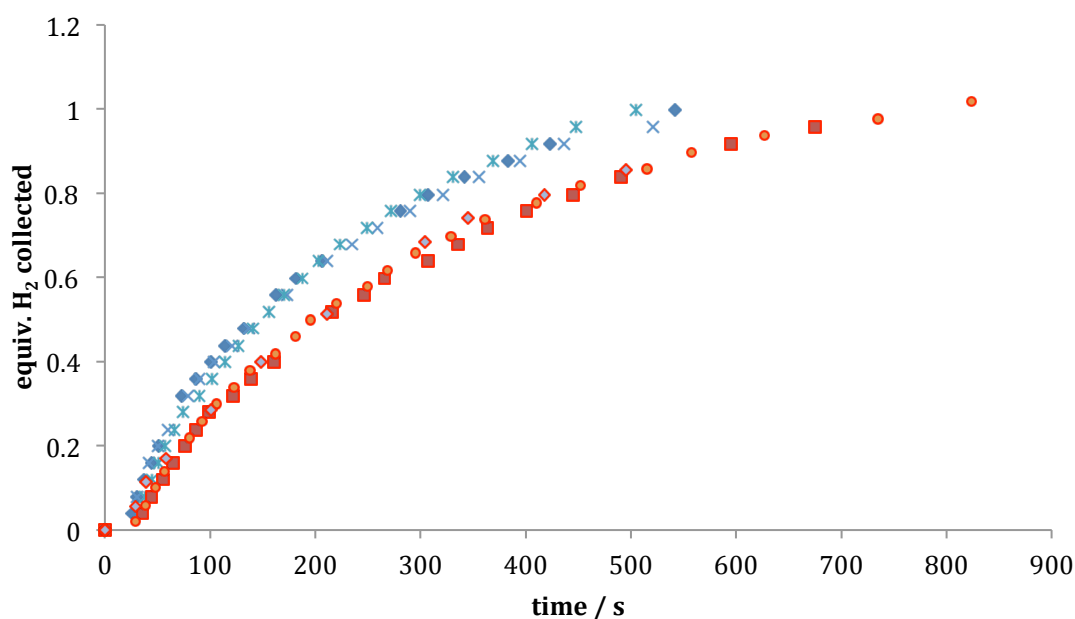
To probe the steps involving proton transfer, we decided to perform a kinetic isotope effect experiment. In the presence of excess silane and base in MeCN at $-35\text{ }^{\circ}\text{C}$ (previously demonstrated to be free from desolvation effects), the rate of hydrogen production with acetic acid was compared with that of d_4 -acetic acid. A primary kinetic isotope effect of $k_{\text{H}}/k_{\text{D}} = 2.75 \pm 0.39$ demonstrated a proton bond breaking step in the rate determining step. This experiment assumes that any secondary effects (concerning the acidity of the carboxylic acid) from the deuterated beta carbon are negligible compared to the error, and that the result is primarily a reflection of the O–D bond breaking step. ($\text{p}K_{\text{a}}$ values for acetic acid and d_4 -acetic acid have been compared in water and found to be 4.63 and 4.65,⁶² or 4.76 and 4.77⁶³ respectively, much too small to affect the KIE significantly). The result is visualised in Figure 13 (acetic acid is the top trace).

Figure 13. Visualisation of the kinetic isotope effect measured when AcOH and d_4 -AcOD were reacted in MeCN in the presence of a 20-fold excess of Et_3N and PhSiH_3 at $-35\text{ }^{\circ}\text{C}$.



We next sought to check whether a kinetic isotope effect would be observed with deuterated phenylsilane. Deuterated phenylsilane (PhSiD_3) was synthesised using deuterated lithium aluminium hydride (sodium borohydride proved ineffective) and trichlorophenylsilane by refluxing for 16 h in ether. The resulting mixture was highly pyrophoric, and attempts to distil the desired silane, which formed quantitatively by ^1H -NMR analysis, was made difficult by acidic species that co-distilled and gave a highly unstable acidic solution of phenylsilane. Eventually, rapid filtration through alumina silicate in a pentane solution under nitrogen provided neutral, deuterated phenylsilane for use in the kinetic experiments. (Removal of the last traces of pentane/ether to obtain pure phenylsilane was also difficult, and these traces were taken into account in the resulting experiments.)

Figure 14. Visualisation of the putative kinetic isotope effect measured when PhSiH_3 or PhSiD_3 were reacted in MeCN in the presence of a 20-fold excess of Et_3N and acetic acid at -35°C .



In the event, a small kinetic isotope was measured, $k_{\text{H}}/k_{\text{D}} = 1.28 (+0.21, -0.18)$. Although the graph is pictorially striking and the reproducibility reasonable, the error margins (*confidence interval at 95% based on the spread of the three runs for each system*

calculated, and propagated to give the maximum errors) are at the very limit of confirming an effect. We turned to the literature for comparison of similar systems.

Summary of KIEs recorded in the above section

At 238 K; $k_{\text{OH}}/k_{\text{OD}} = 2.75 \pm 0.39$

At 238 K; $k_{\text{SiH}}/k_{\text{SiD}} = 1.28 (+0.21, -0.18)$

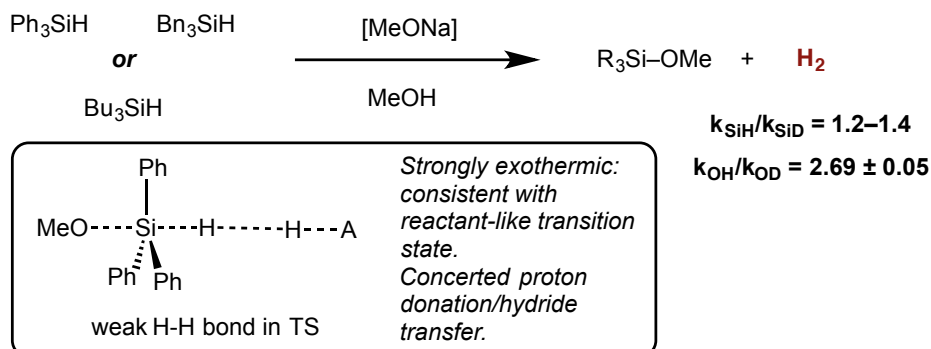
Analysis of Similar Kinetic Isotope Effects

Schowen and associates have investigated the methoxide catalysed alcoholysis of various hydridosilanes (R_3SiH ; $\text{R}=\text{alkyl}$) with methanol, and found kinetic isotope effects in the region of $k_{\text{Si-H}}/k_{\text{Si-D}} = 1.2\text{--}1.4$. They also determined the kinetic isotope effect for MeOH and MeOD, and recorded a value of $k_{\text{OH}}/k_{\text{OD}} = 2.69 \pm 0.05$. Their analysis suggests a pentacoordinate silicate transition state in which the silyl hydride bond is still relatively strong, and the incipient H–H bond relatively weak (Scheme 16A). They note, in their discussion, the difficulty in concluding anything about the system from the KIE, due to the fact that theoretical values for KIEs of hydride transfer are complicated by non-linearity in the TS.⁶¹ This is, at least in part, due to the contribution of various bending and stretching modes, which alter the energy gap between the zero-point energy and the transition state thus determining the different barriers to reaction for Si–H and Si–D bonds. Nonetheless, both their KIE values are in excellent agreement with the data recorded here, and involve a similar system (an oxygen donor and a protic acceptor).

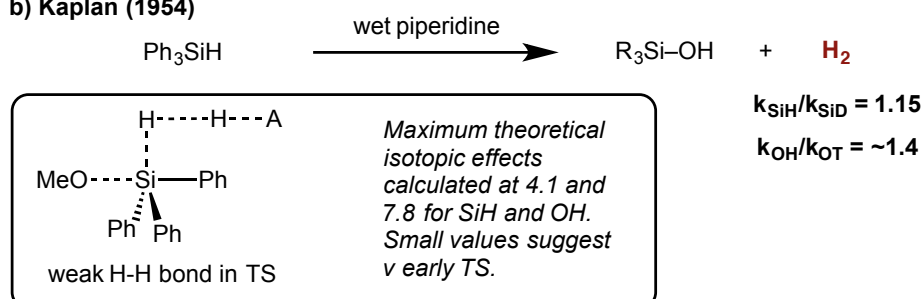
Kaplan and Wilzbach have examined the dehydrogenation of triphenylsilane in wet piperidine, and determined a KIE of $k_{\text{Si-H}}/k_{\text{Si-D}} = 1.15$ (Scheme 16B).⁶⁴ Eaborn and Jenkins reveal a range of $k_{\text{OH}}/k_{\text{OD}}$ values for the alcoholic solvolysis of hydridosilanes depending on the nature of the organosilicon compound, with values between **2.3 and 5.0**.

They expound a bent $R_4Si-H-HA$ transition state, and suggest that a reversible attack at silicon is followed by a rate determining loss of hydrogen (Scheme 16C).⁶⁵

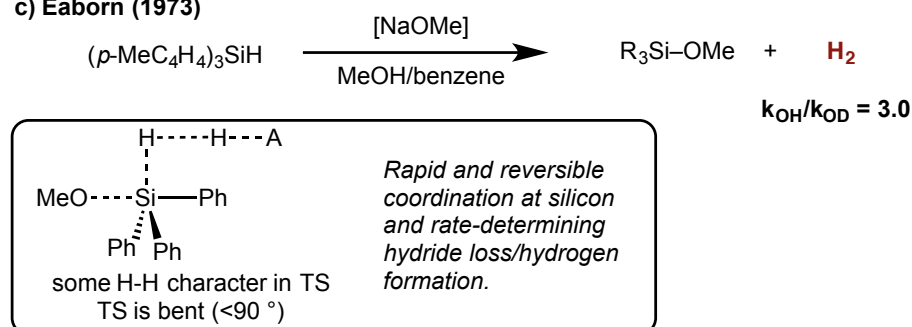
a) Schowen (1971)



b) Kaplan (1954)



c) Eaborn (1973)



Scheme 16. Literature recorded kinetic isotope effects and mechanism investigations

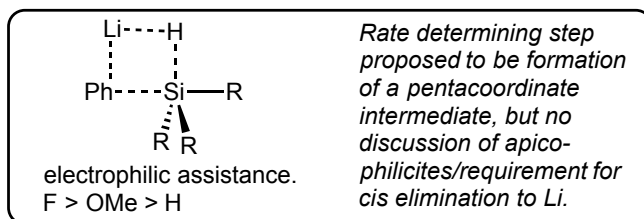
Corriu has measured a primary kinetic isotope effect of $k_{Si-H}/k_{Si-D} = 1.3$ for the substitution of H or D at a silicon centre ($R^1R^2R^3Si-X$; $R^{1,2,3} = Ph, Et, naphthyl$; $X = H$ or D) by $PhLi$ in ether. In this case, the authors suggest that attack of silicon is rate limiting, because F, OMe and H all had similar magnitudes of substitution with the organometallic reagents. However, the reactions proceed with retention of configuration (i.e.

electrophilically assisted elimination of the leaving group from the equatorial position, with an axial nucleophile), and in this case, ionic and apicophilicity effects complicate the analysis (Scheme 17D).⁶⁶

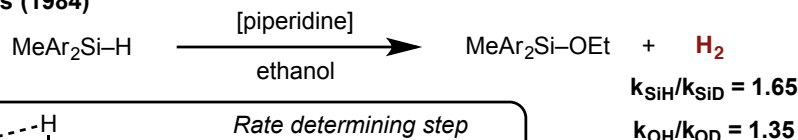
d) Corriu (1973)



$$k_{\text{SiH}}/k_{\text{SiD}} = 1.3$$

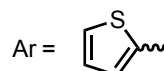
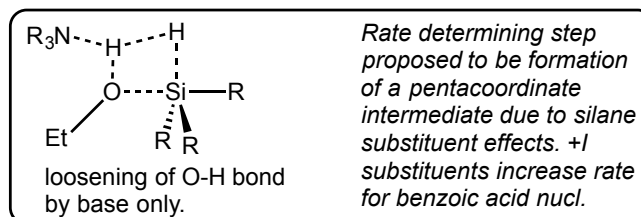


e) Lukevics (1984)

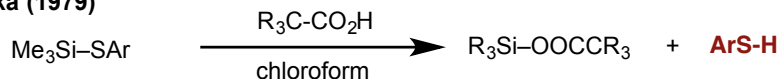


$$k_{\text{SiH}}/k_{\text{SiD}} = 1.65$$

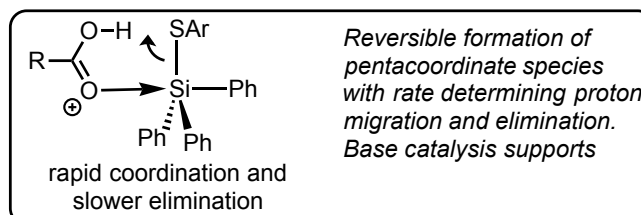
$$k_{\text{OH}}/k_{\text{OD}} = 1.35$$



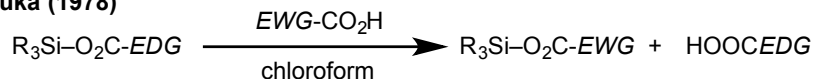
f) Kozuka (1979)



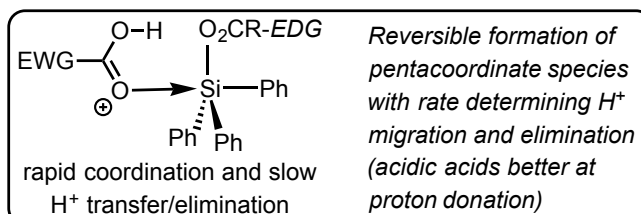
$$k_{\text{OH}}/k_{\text{OD}} = 3.0$$



g) Kozuka (1978)



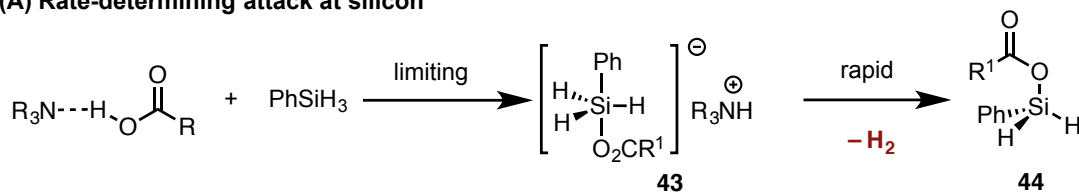
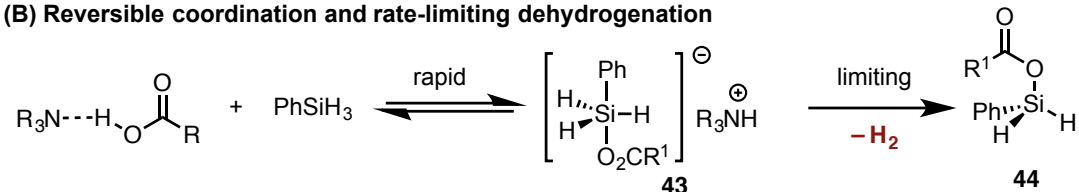
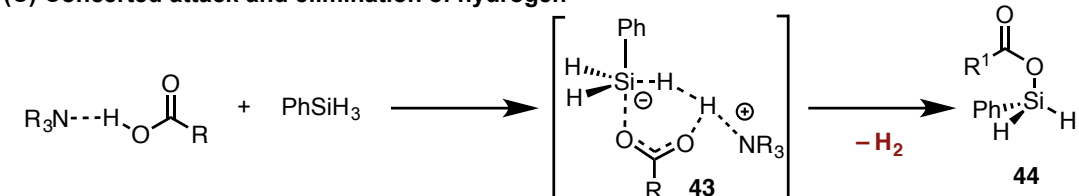
$$k_{\text{OH}}/k_{\text{OD}} = 3.0$$



Scheme 17. Literature isotope effects and mechanistic studies: continued.

More recently, Lukevics reported values of $k_{\text{(SiH)}}/k_{\text{(SiD)}} = 1.65$ and $k_{\text{(OH)}}/k_{\text{(OD)}} = 1.35$ for the reaction of methyl-di-2-thienylsilane with ethanol in the presence of piperidine. Electron-withdrawing groups at silicon enhance the rate, interpreted by Lukevics to mean a rate-determining attack at silicon. Further, benzoic acids were faster to react with donating *para*-substitution (Scheme 17E).⁴⁵ Kozuka and Kitamura have investigated the displacement of thiophenols from arylthiotrimethylsilanes (ArS)Me₃Si with carboxylic acids, and observed both a base catalysis and a KIE for the reaction. The KIE for the acid OH/D was $k_{\text{(OH)}}/k_{\text{(OD)}} = 3.0$. In this reaction, the proton transfer to sulfur and elimination of thiophenol was proposed to be the rate-determining step, following reversible attack of the carboxylic acid at silicon (Scheme 17F).⁶⁷ The same group reported the acyloxy exchange of acyloxytrimethylsilanes with different carboxylic acids and found that *more acidic carboxylic acids displace less acidic acids*. As the authors suggest, this can only be consistent with a rapid and reversible attack at silicon followed by a rate-limiting proton transfer, as the nucleophile is poorer and less basic. In accordance, a KIE was measured of $k_{\text{(OH)}}/k_{\text{(OD)}} = 1.7$ for several acids (slower deuteride transfer in the RDS, Scheme 17G).⁴⁹

With the foregoing in mind, and with reassurance that the experimental values recorded here are in good agreement with the related existing literature, we can begin an analysis of the KIE results. Three possible mechanisms are considered (for systems in which desolvation is not rate-limiting; Scheme 18).

(A) Rate-determining attack at silicon**(B) Reversible coordination and rate-limiting dehydrogenation****(C) Concerted attack and elimination of hydrogen**

Scheme 18. Possible dehydrogenation mechanistic details

If attack at silicon were rate determining (mechanism A), the hydridic KIE would have to be a secondary KIE, in which the changing hybridisation of silicon contributed to the energy barrier. Because there are three deuterium atoms present, such a KIE would be enhanced relative to single deuteride substitution. The extent of proton transfer to generate a nucleophilic carboxylate species would account for the protic KIE, although clearly a separate/initial deprotonation step cannot be occurring. If loss of hydrogen were rate determining (mechanism B), the hydridic KIE would be primary, and depend on the strength of the Si–D bond at the transition state, as well as the deviation from linearity of the forming D–H bond in the TS. The protic KIE would again be primary and falls exactly into the expected range. The final option, C, the concerted mechanism, would be difficult to interrogate, due to the competing effects, but could conceivably produce KIEs in the range observed.

The experiment with excess base at low temperature (–35 °C) was repeated with trifluoroacetic acid in place of acetic acid to probe the difference in the initial rate of

hydrogen evolution. This stronger acid produced hydrogen 20 times more slowly than acetic acid. Whilst this could mean that attack at silicon is limiting (trifluoroacetate is less nucleophilic), the presence of a more electron withdrawing carboxylate group at silicon could reduce the hydridic power of the hydrogens on silicon.

In light of the literature analyses, and given that steric hindrance is minimal at PhSiH_3 , we propose that the rate-determining step is loss of hydrogen from a small population of transiently existent species such as **43** (mechanism B), the mechanism our data is most consistent with. The extent to which this step is concerted is unknown; the average rate would depend on the statistics of organisation when the carboxylate attacks (the protonated counterion needs to be correctly orientated). Kozuka's work with carboxylic acids seems to show that attack at silicon can be rapid and reversible (even for more hindered species). Schowen, Kaplan and Eaborn all favour this mechanism too. Although we have no Hammett analysis to work with, the different reactivity of the variously substituted silanes (mono-, bi- and tri-phenyl) suggests that sterics at silicon become important very quickly (although whether this limits approach or simply reduces the instances of successful collisions by restricting the required transition state is unknown).

Corriu has demonstrated, on the basis of X-ray evidence, that hydride ligands show a remarkable proclivity to occupy the equatorial position in ate complexes, and that this explains the observed retention of stereochemistry when substituting for hydride at silicon.⁶⁸ We, therefore, draw loss of hydride from the equatorial position, although we have no evidence for this. Attempts to model the transition state, using ammonia, acetic acid and phenylsilane (DFT/B3LYP/6-31G+) did not yield conclusive results, due to competing loss of the carboxylate ligand.

Mechanistic Summary

Silyl esters form along with one equivalent of hydrogen in a base-catalysed reaction with phenylsilane. Amidation occurs via facile attack of the amine on the silyl ester, and probably a rate determining loss of siloxide/silanol (proton transfer would aid this loss). The second equivalent of hydrogen released during the amidation stage is likely due to dehydrogenative siloxane formation; additional silyl ester formation from displaced carboxylate may also contribute. Silylamine formation by carboxylate displacement or dehydrogenation is also possible (evidence for this is circumstantial only). All of these processes may be accelerated by the presence of additional basic nitrogen atoms, which leads to a decrease in rate (and possibly magnitude) of amide, but faster dehydrogenation reactions. This decrease in amidation efficiency is proposed to be due to destruction of unhindered silyl esters in favour of less reactive species, or sequestering of amine molecules as silylamines.

The kinetic experiments performed supported our working hypothesis. The reaction is limited first by the desolvation of ion pairs, which must be desolvated from excess acid in order to react. As a result, more hindered acids and amines react faster when the acid is in excess, because they are more poorly solvated. The H-bonded amine/acid pair then attacks silicon, either through a full carboxylate anion, or a partially deprotonated species, and hydrogen is released from the ammonium counterion, likely via a 6-membered transition state with an equatorial hydrogen and axial carboxylate, although these may be reversed.

The reaction is first order in all three components and, when acid is not in excess, the rate-determining step is probably the release of hydrogen from the pentavalent silicate species, as determined from a KIE for the acid ($k_{\text{OH}}/k_{\text{OD}} = 2.8$), and a putative effect for the silane ($k_{\text{SiH}}/k_{\text{SiD}} = 1.3$). The rate of the reaction is still relatively fast at $-35\text{ }^{\circ}\text{C}$ in MeCN, highlighting the low activation energy associated with attack at silicon and the resulting

hydride loss. Hindered silanes are much slower to release hydrogen, but it is unclear what the reason for this is; conflicting literature data cannot decide between rate-limiting attack at silicon, and proton transfer to lose hydrogen.

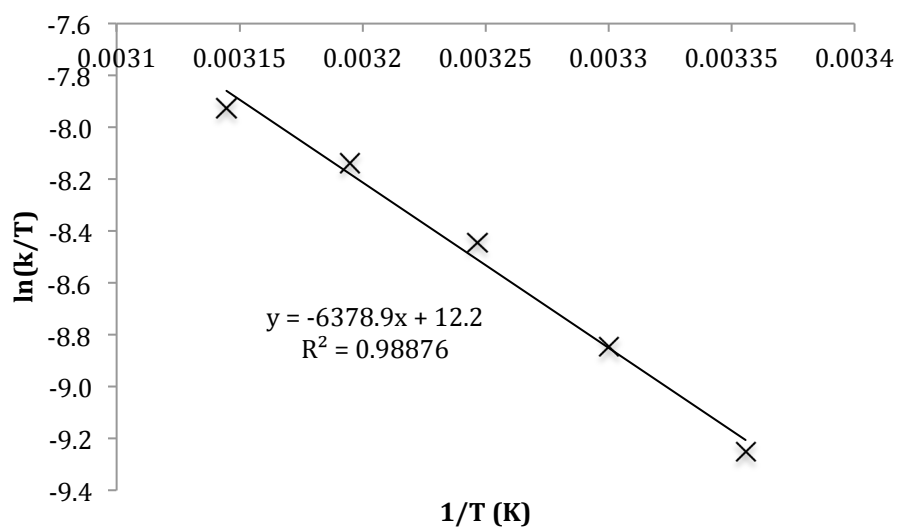
Potential for Studying Desolvation Kinetics – Role of the substrate

Because the reaction appears to be desolvation limited in the presence of excess acid, we speculated that studying the effect of temperature on the initial rate in the presence of excess acid might allow access to activation parameters of desolvation from H-bonded complexes. The assumptions that must hold for this to be valid include: irreversible dehydrogenation, and; a very low energy barrier to ammonium silicate formation and dehydrogenation. The first assumption is almost assured, whilst the second assumption seems to arise from the observation of desolvation as the RDS in our initial experiments and the fact the reaction remains rapid at low temperature when in excess base.

We measured the initial rates of hydrogen release at five temperatures (25–45 °C) in MeCN with 20-fold excesses of acid and silane and generated an Eyring plot (Figure 15). The plot gave a reasonable straight line. We made the assumption that the rate equation was as shown, which arises from the 1:1:1 stoichiometry discovered previously:

$$v = k[\text{amine}][\text{acid}][\text{silane}]$$

Figure 15. Eyring Plot for initial rate data collected at 25, 30, 35, 40, and 45 °C for acetic acid and phenylsilane (20-fold excesses) with a 5 mol% loading of triethylamine in acetonitrile.



A plot of $\ln(k_T/T)$ against $1/T$ gives a straight line. The slope gives $-\Delta H/R$ and the intercept gives $\ln(k/h) + \Delta S/R$. Thus an estimate of the enthalpy of activation and entropy of activation can be made. The error parameters given below are an estimate of the error calculated using S , the standard error, from a linear regression. For ΔG , standard error propagation rules were subsequently employed.

Eyring analysis is reserved for simple bimolecular reactions. Thus, making the assumption that desolvation involves the simple, rate-limiting dissociation of an ion pair from the surface of an H-bonded aggregate (contestable), and using a second order rate equation dependent on [ammonium carboxylate] (assumed to be equal to concentration of amine) and [silane], the activation parameters extracted from the Eyring data are (calculated at 298 K in MeCN):

$$\Delta H_{\text{act}} = 53.0 \pm 3.3 \text{ kJ/mol} = +12.7 \pm 0.8 \text{ kcal/mol}$$

$$\Delta S_{\text{act}} = 114.5 \pm 12.0 \text{ J/mol.K} = +27.4 \pm 2.9 \text{ cal/mol.K}$$

$$\Delta G_{\text{act}} = 18.9 \pm 4.8 \text{ kJ/mol} = +4.5 \pm 1.2 \text{ kcal/mol}$$

The Arrhenius equation solved in the linear form gives the following:

$$\ln(k) = \ln(A) - (E_A/R)(1/T)$$

$$E_{\text{act}} = +55.6 \text{ kJ/mol} = +13.3 \text{ kcal/mol}$$

giving a difference of 2.6 kJ/mol between E_{act} and ΔH_{act} , which is equal to $\sim RT$, the expected difference between the two values at 298 K.

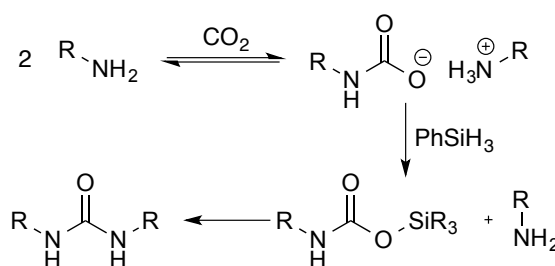
The values of the apparent activation parameters are consistent with a desolvation model, namely that the reaction is disfavoured (endothermic, and so driven by the irreversible loss of hydrogen), and involves a large positive entropic term (i.e. indicating a dissociative mechanism), expected for a desolvation step in which the solvent and substrate molecules are released from an ordered solvation sphere. The barrier to the reaction is appropriately low for an appreciable rate at room temperature. The figures are in the region expected for overcoming H-bonding strengths.⁵⁹ Examining the effect of the dehydrogenation rate on amine and acid identity (Table 5 and Table 6), this tool may prove useful in acid/base pair screening in reaction design in different solvents. Although these values, if valid, have no known comparable figures in the literature, the qualitative result is perhaps useful as a tool to analyse the nature of this system; namely, that, even at dilute excesses of acid, the amine/acid ion pairs are preferentially solvated by these acid molecules rather than MeCN, and that desolvation from the excess substrate (acid) is non-trivial and rate-limiting. Thus it would be expected that adding the carboxylic acid dropwise to an otherwise comparable solution of amine would give an increased rate of reaction despite the much-decreased availability of acid.

In summary, initial rate data for the dehydrogenation reaction in a regime of solvation limitation over 5 temperatures have been used to generate an Eyring plot. It remains uncertain to what extent the assumptions made here are valid, but extraction of the activation parameters gives figures consistent with the reaction they describe. Namely, the process of desolvation is unfavourable, but viable at room temperature, with a large positive entropic contribution (dissociative process).

Silane activation in the literature and novel acylation reactions

The conclusions of the above study are clear: phenylsilane reacts rapidly with protic oxygen-based nucleophiles in the presence of catalytic base, even at $-35\text{ }^{\circ}\text{C}$ in MeCN. Metal additives can themselves catalyse the formation of silyl esters.

In light of the recent interest in utilising CO_2 as a C_1 building block, especially by Cantat, Dyson and others,^{69–82} we were inspired to consider the following hypothesis: could phenylsilane activate an ammonium carbamate (formed from the equilibrium of amines with CO_2) and thus mediate an acylation to form a urea? We decided that utilising two equivalents of amine might result in the trapping of any silyl carbamate as a urea (Scheme 19).



Scheme 19. Hypothesised dehydrogenation reaction of an ammonium carbamate with phenylsilane and subsequent acylation to give a urea.

To probe the hypothesis, two equivalents of benzylamine were combined with CO_2 , with and without phenylsilane as acylation mediator and with and without DBU as a strong CO_2 absorber (Table 8).

In the absence of phenylsilane, no urea was observed (entries 1–2). The best yield (88% isolated yield of urea **50**) was obtained when substoichiometric DBU was present as an additive (entry 4). These results are unoptimised, and simply follow from the mechanistic analysis above, demonstrating a simple synthesis of ureas using CO_2 as the carbon source. It

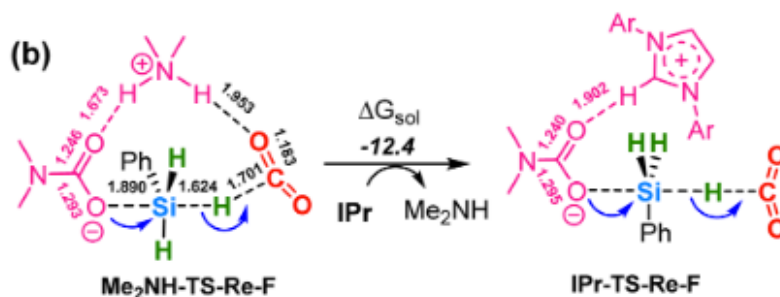
is anticipated that the above instruction will aid the rational development of further base-catalysed phenylsilane mediated acylation and reduction reactions.

Table 8. Phenylsilane-mediated urea synthesis from CO₂ and amine.

$\text{Bn-CH}_2\text{-NH}_2 + \text{CO}_2 \xrightarrow[\text{THF, 70 } ^\circ\text{C, 20 min}]{\text{DBU 0.4 equiv. PhSiH}_3 \text{ 1 equiv.}} \text{Bn-CH}_2\text{-NH-C(=O)-NH-CH}_2\text{-Bn}$ 50			
entry	PhSiH ₃	DBU	result
1	–	–	ammonium carboxylate
2	–	1 equiv.	ammonium carboxylate
3	1 equiv.	–	<10% urea
4	1 equiv.	1 equiv.	88% urea 50 isol.

Reaction performed on 0.25 mmol scale in a dried vial. To the amine (0.5 mmol) in THF (0.6 mL) was added the reactants as shown in the table, and the reaction heated to 70 °C. Three portions of (excess) solid CO₂ were added to each vial over 10 min and a CO₂ atmosphere maintained with a CO₂ balloon. After 20 min, the reactions were concentrated and the product distribution calculated by ¹H-NMR in d⁶-DMSO.

It should be noted that even in mainstream mechanistic studies, silyl esters are infrequently appreciated. The following example from a recent computational study⁷⁷ into the NH-carbene-catalysed formylation of amines with CO₂ and phenylsilane as reductant draws the following two transition states, which compare the supposed role of the NHC vs. a typical amine substrate. (*Do not view the scheme as a reaction – it is showing the energy decrease on switching states*).



Scheme 20 (reproduced)⁷⁷ – Li's suggestion that an NHC-catalysed transition state is lower than the amine-catalysed process. Both omit to consider that intramolecular hydrogen loss is more likely than collision with a third species and direct reduction.⁷⁷

Note that both transition states involve the statistically unlikely collision of three molecules (or two if you accept the ate complex as a single species), and that hydride transfer to CO_2 is preferred by the authors over dehydrogenation from the acidic counterion (essentially unimolecular). This is typical of the lack of appreciation of dehydrogenative processes of silanes in the presence of Lewis basic/Lewis acidic counterion. Another investigation into Fu's borane promoted reductive amination⁸³ suffers from the same lack of rigour.⁸⁴

Mechanism of Amidation

Throughout the discussion so far, the reason silyl esters undergo such efficient amidation has remained unmentioned. Given that the leaving group – a silanol of some description – may be approximately as acidic as a phenol group,⁴⁶ it seems strange that such a fast amidation reaction occurs. Whilst oxygen lone-pair donation into various Si–R antibonding orbitals explains the higher acidity of silanol over methanol, it does not explain why methyl esters are relatively robust in the presence of amines, whilst silyl esters may undergo efficient amidation at ambient temperature. As briefly discussed in the main introduction, it is possible that decreased oxygen resonance into the ester carbonyl due to increased donation towards silicon makes for a more electrophilic centre. Additionally, the increased distance of silicon from the π^* of the carbonyl (relative to carbon in esters) leads to lower steric hindrance.

These facts present an intriguing possibility, suggested by Eaborn in a study of Si–O and O–C bond cleavage of silyl esters.⁴⁸ Based on relative rate data comparing hindered silyl esters and acyl chloride, the authors suggest that, whilst formation of the tetrahedral intermediate is rate limiting in the case of acyl chlorides (and chloride is then easily dispelled), in the case of silyl esters, attack at the carbonyl is rapid and reversible, and that loss of siloxide is rate-

determining. This is consistent with the general picture of the reactivity of silicon, in which kinetic barriers seem to be low, and so thermodynamic products are formed easily. In this case, the formation of amide is irreversible under the reaction conditions. The difference in reactivity between an acetoxysilyl ester and the trifluoroacetoxysilyl ester was estimated to be ~500 in favour of the fluorinated ester.⁴⁸

Conclusions

We have developed an improved phenylsilane-mediated amidation reaction based on Ruan's reaction of a similar nature. Our modified reaction conditions expand the scope and efficiency of the reaction and the procedure benefits from an improved purification protocol. The reaction can now operate at substoichiometric silane loadings, and is amenable to reductive conditions.

We have also interrogated the mechanism of the amidation, confirming that silyl esters are formed *in situ* and are precursors to amide formation. A variety of acylating agents are likely productive intermediates in the amidation pathway, but monosilyl esters are most likely the key species in the reaction. Further, the mechanism of the base-catalysed dehydrogenation reaction has been studied and the dehydrogenation step found to involve one molecule each of acid, base and silane in acetonitrile. A potential approach to measuring desolvation thermodynamics was proposed, and it remains to be seen whether this approach (or similar) can allow meaningful or useful parameters to be extracted. Finally, the mechanistic insight should allow the further rational design of acylation reactions, supported by the demonstration of the application of this knowledge to a novel urea synthesis.

References

- 1 H. Charville, D. A. Jackson, G. Hodges, A. Whiting and M. R. Wilson, *Eur. J. Org. Chem.*, 2011, **2011**, 5981–5990.
- 2 J. Cossy and C. Pale-Grosdemange, *Tetrahedron Lett.*, 1989, **30**, 2771–2774.
- 3 L. Gooßen, D. Ohlmann and P. Lange, *Synthesis*, 2008, **2009**, 160–164.
- 4 F. L. Dunlap, *J. Am. Chem. Soc.*, 1902, **24**, 758–763.
- 5 J. A. Mitchell and E. E. Reid, *J. Am. Chem. Soc.*, 1931, **53**, 1879–1883.
- 6 E. Baumann, *Berichte der Dtsch. Chem. Gesellschaft*, 1886, **19**, 3218–3222.
- 7 C. Schotten, *Berichte der Dtsch. Chem. Gesellschaft*, 1884, **17**, 2544–2547.
- 8 B. Shen, D. M. Makley and J. N. Johnston, *Nature*, 2010, **465**, 1027–1032.
- 9 J. W. Bode and S. S. Sohn, *J. Am. Chem. Soc.*, 2007, **129**, 13798–13799.
- 10 P.-C. Chiang, Y. Kim and J. W. Bode, *Chem. Commun.*, 2009, 4566–4568.
- 11 H. U. Vora and T. Rovis, *J. Am. Chem. Soc.*, 2007, **129**, 13796–13797.
- 12 C. Gunanathan, Y. Ben-David and D. Milstein, *Science*, 2007, **317**, 790–792.
- 13 L. U. Nordstrøm, H. Vogt and R. Madsen, *J. Am. Chem. Soc.*, 2008, **130**, 17672–17673.
- 14 A. J. A. Watson, A. C. Maxwell and J. M. J. Williams, *Org. Lett.*, 2009, **11**, 2667–2670.
- 15 N. A. Owston, A. J. Parker and J. M. J. Williams, *Org. Lett.*, 2007, **9**, 3599–3601.
- 16 N. A. Owston, A. J. Parker and J. M. J. Williams, *Org. Lett.*, 2007, **9**, 73–75.
- 17 E. Valeur and M. Bradley, *Chem. Soc. Rev.*, 2009, **38**, 606–631.
- 18 J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, 1955, **77**, 1067–1068.
- 19 J. M. Humphrey and A. R. Chamberlin, *Chem. Rev.*, 1997, **97**, 2243–2266.
- 20 C. A. G. N. Montalbetti and V. Falque, *Tetrahedron*, 2005, **61**, 10827–10852.
- 21 Z. J. Kamiński, *Biopolymers*, 2000, **55**, 140–164.

- 22 R. M. Lanigan, P. Starkov and T. D. Sheppard, *J. Org. Chem.*, 2013, **78**, 4512–4523.
- 23 P. Nelson and A. Pelter, *J. Chem. Soc.*, 1965, **0**, 5142–5144.
- 24 J. Tani, T. Oine and I. Inoue, *Synthesis*, 1975, **1975**, 714–715.
- 25 D. B. Collum, S.-C. Chen and B. Ganem, *J. Org. Chem.*, 1978, **43**, 4393–4394.
- 26 P. Starkov and T. D. Sheppard, *Org. Biomol. Chem.*, 2011, **9**, 1320–1323.
- 27 R. M. Lanigan and T. D. Sheppard, *Eur. J. Org. Chem.*, 2013, **2013**, 7453–7465.
- 28 K. Ishihara, S. Ohara and H. Yamamoto, *J. Org. Chem.*, 1996, **61**, 4196–4197.
- 29 R. M. Al-Zoubi, O. Marion and D. G. Hall, *Angew. Chem. Int. Ed.*, 2008, **47**, 2876–2879.
- 30 N. Gernigon, R. M. Al-Zoubi and D. G. Hall, *J. Org. Chem.*, 2012, **77**, 8386–8400.
- 31 K. Arnold, A. S. Batsanov, B. Davies and A. Whiting, *Green Chem.*, 2008, **10**, 124–134.
- 32 K. Arnold, B. Davies, D. Hérault and A. Whiting, *Angew. Chem. Int. Ed.*, 2008, **47**, 2673–2676.
- 33 W.-J. Yoo and C.-J. Li, *J. Am. Chem. Soc.*, 2006, **128**, 13064–13065.
- 34 S. Seo and T. J. Marks, *Org. Lett.*, 2008, **10**, 317–319.
- 35 K. Ekoue-Kovi and C. Wolf, *Chem. Eur. J.*, 2008, **14**, 6302–6315.
- 36 Y. Suto, N. Yamagiwa and Y. Torisawa, *Tetrahedron Lett.*, 2008, **49**, 5732–5735.
- 37 D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer, Jr., R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks and T. Y. Zhang, *Green Chem.*, 2007, **9**, 411–420.
- 38 J. S. Carey, D. Laffan, C. Thomson and M. T. Williams, *Org. Biomol. Chem.*, 2006, **4**, 2337–2347.
- 39 WO2011039781 (A1), 2011, 68.
- 40 P. Morieux, C. Salomé, K. D. Park, J. P. Stables and H. Kohn, *J. Med. Chem.*, 2010,

- 53, 5716–5726.
- 41 T.-H. Chan and L. T. L. Wong, *J. Org. Chem.*, 1969, **34**, 2766–2767.
 - 42 T.-H. Chan and L. T. L. Wong, *J. Org. Chem.*, 1971, **36**, 850–853.
 - 43 E. F. van der Eide, M. L. Helm, E. D. Walter and R. M. Bullock, *Inorg. Chem.*, 2013, **52**, 1591–1603.
 - 44 B. Liu, T. Roisnel, J.-F. Carpentier and Y. Sarazin, *Chem. - A Eur. J.*, 2013, **19**, 2784–2802.
 - 45 E. Lukevics and M. Dzintara, *J. Organomet. Chem.*, 1984, **271**, 307–317.
 - 46 C. Eaborn and W. A. Stańczyk, *J. Chem. Soc., Perkin Trans. 2*, 1984, 2099–2103.
 - 47 K. Rühlmann, U. Kaufmann and D. Knopf, *J. für Prakt. Chemie*, 1962, **18**, 131–140.
 - 48 G. A. Ayoko and C. Eaborn, *J. Chem. Soc. Perkin Trans. 2*, 1986, 1357–1361.
 - 49 S. Kozuka, T. Kitamura, N. Kobayashi and K. Ogino, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 1950–1952.
 - 50 D. P. Graddon and B. A. Rana, *J. Organomet. Chem.*, 1977, **136**, 315–321.
 - 51 M. H. Abraham, P. L. Grellier, M. J. Kamlet, R. M. Doherty, R. W. Taft and J.-L. M. Abboud, *Rev. Port. Quim.*, 1989, **31**, 85–92.
 - 52 M. J. Kamlet and R. W. Taft, *J. Am. Chem. Soc.*, 1976, **98**, 377–383.
 - 53 R. W. Taft and M. J. Kamlet, *J. Am. Chem. Soc.*, 1976, **98**, 2886–2894.
 - 54 A. A. Maryott and E. R. Smith, *Table of Dielectric Constants of Pure Liquids*, National Bureau of Standards, 1951.
 - 55 H. Bartnicka, I. Bojanowska and M. Kalinowski, *Aust. J. Chem.*, 1991, **44**, 1077.
 - 56 F. Eckert, I. Leito, I. Kaljurand, A. Kütt, A. Klamt and M. Diedenhofen, *J. Comput. Chem.*, 2009, **30**, 799–810.
 - 57 M. Charton, *J. Org. Chem.*, 1976, **41**, 2217–2220.
 - 58 M. Charton, *J. Am. Chem. Soc.*, 1975, **97**, 1552–1556.

- 59 W. P. Jencks, 1987, pp. 155–167.
- 60 J. P. Richard and W. P. Jencks, *J. Am. Chem. Soc.*, 1984, **106**, 1373–1383.
- 61 K. O'Donnell, R. Bacon, K. L. Chellappa, R. L. Schowen and J. K. Lee, *J. Am. Chem. Soc.*, 1972, **94**, 2500–2505.
- 62 R. McConnell, W. Godwin, B. Stanley and M. S. Green, *J. Ark. Acad. Sci.*, 1997, **51**, 135–140.
- 63 R. A. Robinson, M. Paabo and R. G. Bates, *J. Res. Natl. Bur. Stand. - A. Phys. Chem.*, 1969, **73A**, 299–308.
- 64 L. Kaplan and K. E. Wilzbach, *J. Am. Chem. Soc.*, 1955, **77**, 1297–1302.
- 65 C. Eaborn and I. D. Jenkins, *J. Organomet. Chem.*, 1974, **69**, 185–192.
- 66 R. J. P. Corriu and B. J. L. Henner, *J. Chem. Soc. Chem. Commun.*, 1973, 116.
- 67 S. Kozuka and T. Kitamura, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 3384–3386.
- 68 C. Breliere, F. Carre, R. J. P. Corriu, M. Poirier and G. Royo, *Organometallics*, 1986, **5**, 388–390.
- 69 L. Zhu, L.-S. Wang, B. Li, W. Li and B. Fu, *Catal. Sci. Technol.*, 2016, **6**, 6172–6176.
- 70 H. Lv, Q. Xing, C. Yue, Z. Lei and F. Li, *Chem. Commun.*, 2016, **52**, 6545–6548.
- 71 C. P. Yap, H. T. Poh and W. Y. Fan, *RSC Adv.*, 2016, **6**, 5903–5906.
- 72 O. Jacquet, C. Das Neves Gomes, M. Ephritikhine and T. Cantat, *J. Am. Chem. Soc.*, 2012, **134**, 2934–2937.
- 73 A. Tlili, X. Frogneux, E. Blondiaux and T. Cantat, *Angew. Chem. Int. Ed.*, 2014, **53**, 2543–2545.
- 74 C. Das Neves Gomes, O. Jacquet, C. Villiers, P. Thuéry, M. Ephritikhine and T. Cantat, *Angew. Chem.*, 2012, **124**, 191–194.
- 75 X. Frogneux, E. Blondiaux, P. Thuéry and T. Cantat, *ACS Catal.*, 2015, 3983–3987.
- 76 S. Savourey, G. Lefèvre, J.-C. Berthet and T. Cantat, *Chem. Commun.*, 2014, **50**, 14033–14036.

- 77 Q. Zhou and Y. Li, *J. Am. Chem. Soc.*, 2015, **137**, 10182–10189.
- 78 K. Motokura, D. Kashiwame, A. Miyaji and T. Baba, *Org. Lett.*, 2012, **14**, 2642–2645.
- 79 M. Aresta and E. Quaranta, *Tetrahedron*, 1991, **47**, 9489–9502.
- 80 F. J. Fernández-Alvarez, M. Iglesias, L. A. Oro and V. Polo, *ChemCatChem*, 2013, **5**, 3481–3494.
- 81 F. D. Bobbink, S. Das and P. J. Dyson, *Nat. Protoc.*, 2017, **12**, 417–428.
- 82 C. Maeda, Y. Miyazaki and T. Ema, *Catal. Sci. Technol.*, 2014, **4**, 1482–1497.
- 83 M.-C. Fu, R. Shang, W.-M. Cheng and Y. Fu, *Angew. Chem. Int. Ed.*, 2015, **54**, 9042–9046.
- 84 Q. Zhang, M.-C. Fu, H.-Z. Yu and Y. Fu, *J. Org. Chem.*, 2016, **81**, 6235–6243.

Chapter 2

Experimental Section

Contents

1. General Information.....	137
2. Experimental Details	137
2.1 Initial optimisation of amidation reaction (Table 1)	137
2.2 Full table of optimisation with increased temperature (Table 2).....	137
2.3 General procedure for the silane mediated amidation of acids and amines (Figure 1)	138
2.4. General procedure for the mild acetylation of amines	140
2.5 Characterisation of amide products in Figure 1	141
2.6 Gram-scale formal synthesis of <i>ent</i> -lacosamide.....	154
2.7 Phenylsilane-mediated urea synthesis using CO ₂ (Table 8)	157
3. Mechanistic Experiments – Qualitative	158
3.1 Hydrogen evolution measurements.....	158
3.2 Amidation Competition Experiment: Primary vs. Secondary Amine	158
3.3 Representative <i>in situ</i> silyl ester formation.....	159
3.4 Comparison of reactivity of preformed acetoxysilyl esters (Schemes 5-6)	161
3.5 Evidence of the formation of silyl esters from phenylsilane (Scheme 4)	162
3.6 Silyl esters in Acetonitrile (Scheme 7)	163
3.61 Formation from the chlorosilane	163
3.62 Base-catalysed silyl ester observation in acetonitrile:	164

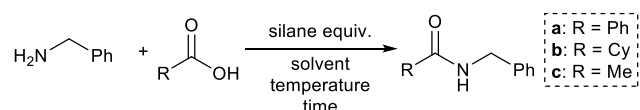
4. Kinetic Experiments – Quantitative.....	164
4.1 Set-up.....	164
4.11 Example Data	167
4.12 Analysis.....	168
4.2 Initial Results.....	169
4.21 Table 3	169
4.22 Figure 4: NMR titration study.....	169
4.3 Experiments performed in an excess of acid.....	170
4.31 Varying the acid: acetic, benzoic, pivalic, isobutyric, chloroacetic, propanoic, mesitoic (Table 5).....	170
4.32 Varying the amine: 2,2,6,6-tetramethylpiperidine, <i>N</i> -methyl morpholine, tertiary butylamine, triethylamine, diisopropylamine, morpholine, DBU (Table 6)	170
4.33 Varying the solvent: acetonitrile, THF, chloroform, DMF, toluene, diethyl ether, ethyl acetate, DMSO, acetone, pyridine (Table 4)	170
4.34 Sodium acetate catalyses the dehydrogenative reaction	172
4.35 Varying the silane: PhSiH ₃ and Ph ₂ SiH ₂ and Ph ₃ SiH compared (Table 7)	172
4.36 Kinetic isotope effect between H ₃ CCO ₂ H and D ₃ CCO ₂ D at low temperature (Figure 11).....	172
4.37 Synthesis of deuterated phenylsilane	173
4.38 Kinetic isotope effect of deuterated silane at low temperature (Figure 12)	174
4.4 Orders of the Components in the rate equation	174
4.41 Order of the dehydrogenative silylation reaction in base. (Figure 9)	174
4.42 Order of the dehydrogenative reaction in phenylsilane (Figure 9)	176
4.43 Reaction is first order in acid when base is in excess (Figure 11).....	177
4.44 Trifluoroacetic acid in excess of base at low temp.....	177
5. References	178

1. General Information

Refer to Chapter 1 Experimental Section

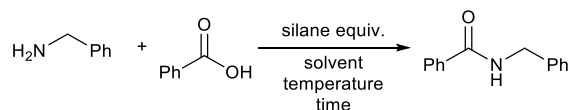
2. Experimental Details

2.1 Initial optimisation of amidation reaction (Table 1)



Reactions performed on a 0.16 mmol scale in 0.5 mL solvent, with the equivalents outlined in the table. In all cases, the amine was added last to a stirring solution of the acid and silane at room temperature. Yields were calculated *via* ^1H NMR using 1,1,2,2-tetrachloroethane as an internal standard. Times are not representative of reaction length, but are the NMR-yield of product at the time stated.

2.2 Full table of optimisation with increased temperature (Table 2)



Yields were calculated *via* ^1H -NMR using 1,1,2,2-tetrachloroethane as an internal standard. Reactions performed on a 0.16 mmol scale in 0.5 mL solvent, with the equivalents outlined in the table. In all cases, the amine was added last to a stirring solution of the acid and silane at the indicated temperature. Reaction performed in Winchester grade toluene in undried glassware under air atmosphere. Parts of this table appear in the supporting information for a recent publication by our group.¹ Times are not representative of reaction length, but are the NMR-yield of product at the time stated.

2.3 General procedure for the silane mediated amidation of acids and amines (Figure 1)

A one-neck 10 mL round-bottomed flask was charged with acid (0.6 mmol) and fitted with a water condenser and an argon balloon. Toluene (1.5 mL) was added and the solution heated to reflux (submerging up to the solvent level in an oil bath at 116 °C) with stirring before adding phenylsilane (0.6 mmol) and finally the amine (0.5 mmol). Liquid reagents were added rapidly via syringe through the top of the flask by partial removal of the condenser. The reaction mixture was stirred at reflux for 13 h. (*see below for purification methods*)

Notes on the reaction protocol: The order of addition of reagents is unimportant, so solid acids and amines can be conveniently combined initially. However, it appears preferable for the acid and amine to be in solution before the addition of silane. Therefore, heating to dissolve the acid/amine/salts before silane addition is advised. More basic amines result in rapid hydrogen evolution, which has on occasion caused bubbles to rise up the condenser shortly after addition. Larger scale reactions may require a cautious addition of silane (e.g. over a period of several minutes, depending on scale) to the acid and amine or addition of silane at a lower temperature (as for scale up).

For HCl salts of amines, triethylamine (1 equiv., 0.5 mmol) was added along with the amine. Aliphatic primary amines and aliphatic acids generally react much faster; 2-6 h at 85 °C is often sufficient. For less reactive amines, it is possible to increase the yield dramatically by using increased equivalents of acid. This acid can be reclaimed pure *via* a base extraction of the organic layer in the work-up. Diphenylsilane (Ph_2SiH_2) can be used instead of

phenylsilane in many cases, although the conversion is lower. A minimum of two equivalents of diphenylsilane should be used with toluene reflux for 13 h.

Purification (for 0.5 mmol scale reactions)

Method A: The reaction was quenched with ethanol (2 mL) while hot and stirred for a further minute at reflux before allowing to cool. The reaction was then concentrated *in vacuo*, taken up in EtOAc (20 mL) and washed successively with 20 mL of each 1 M aqueous HCl solution, saturated aqueous sodium carbonate and brine. For products containing basic centres, the acid wash was omitted. The organics were dried over magnesium sulfate and concentrated. The residues were purified by flash column chromatography beginning with a two column-volume petrol wash and then a gradient elution with EtOAc as stated.

Method B: The reaction was quenched with silica (0.5 g/0.5 mmol) and concentrated to dryness *in vacuo*. The resulting silica was dry-loaded onto a short column and purified by flash column chromatography as above. Sometimes, if the carboxylic acid starting material co-elutes with the desired amide, it is necessary to wash an EtOAc solution of the product with a sodium carbonate solution to yield the clean amide after chromatography.

Method C: The reaction was quenched with silica (0.5 g/0.5 mmol) and concentrated to dryness. The dry silica was washed with a little petrol before releasing the amide with CH₂Cl₂/MeOH or EtOAc. The resulting material was worked-up as for Method A (omitting chromatography) to give amide that were judged to be pure by ¹H-NMR, without full chromatography.

Method D: *For reactions that afford high conversions and in which the product has a basic centre.* The reaction was concentrated and taken up in ethyl acetate (20 mL). The

organics were extracted with HCl (3 x 20 mL of 1 M aqueous solution) and the combined aqueous layers basified to ~pH 10 with sodium carbonate. The aqueous was then extracted with dichloromethane (3 x 20 mL) and the combined organics dried (MgSO_4) and concentrated *in vacuo*.

Notes on purification: We have found that the silicon-based by-products from the reaction display signs of oligomerization by proton and carbon NMR. To aid purification, it is recommended that the reaction is quenched to cap free Si valences which may otherwise form further silanols during the work-up and interfere with chromatography. Such EtO-capped oligomers elute early with 5-8% EtOAc in petrol by chromatography, but it is preferable to trap the free Si valences (presumably) covalently with silica by adding silica to the hot reaction. It is sometimes beneficial to wash the silica with petrol before releasing the product with a minimum volume of a polar eluent. This method has been observed to remove 70 to >95% of the silicon by-product.

2.4. General procedure for the mild acetylation of amines

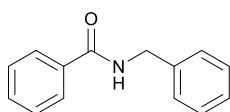
Acetic acid (2 equiv., 1 mmol) was dissolved in acetonitrile or ethyl acetate (0.4 mL) with the amine (0.5 mmol) at room temperature. Added was phenylsilane (2 equivalents, 1 mmol) and the reaction stirred for 2 h or as required. The reaction often becomes heterogeneous towards completion.

Notes: The solution can be heated if a salt precipitates on initial mixing, although often this dissolves during the progress of the reaction. In ethyl acetate, a solid often precipitates after this time. The product can be purified as above. If the amine is a liquid, the reaction can often be started neat, adding co-solvent to aid stirring/completion of the reaction if precipitation occurs.

2.5 Characterisation of amide products in Figure 1

All isolated yields are quoted with respect to the limiting reagent (amine). The amide products were synthesised following the general procedure outlined above unless stated otherwise.

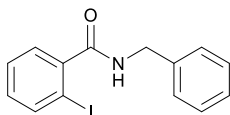
***N*-benzylbenzamide² (7)**



Purified by method C to give a white solid (92 mg, 87%).

¹H NMR (400 MHz, CDCl₃) δ 7.85 - 7.73 (m, 2H), 7.53 - 7.46 (m, 1H), 7.46 - 7.39 (m, 2H), 7.37 - 7.27 (m, 5H), 6.69 - 6.29 (m, 1H), 4.64 (d, *J* = 5.7 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 167.3, 138.2, 134.3, 131.5, 128.7, 128.6, 127.9, 127.6, 126.9, 44.1; HRMS (ESI⁺): Exact mass calcd for C₁₄H₁₃NNaO [M+Na], 234.0889. Found 234.0893, σ = 0.0087; IR (cm⁻¹) (CDCl₃) 3452, 3011, 1658, 1519, 1487; Mp 101-102 °C (lit.³ 100-101 °C).

***N*-benzyl-2-iodobenzamide⁴ (8)**

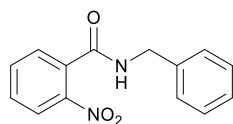


Purified by method A (0-30% EtOAc in petrol) to give a white solid (109 mg, 65%).

¹H NMR (400 MHz, CDCl₃) δ 7.85 (dd, *J* = 0.7, 7.9 Hz, 1H), 7.47 - 7.27 (m, 7H), 7.09 (ddd, *J* = 2.0, 7.2, 7.9 Hz, 1H), 6.08 (br. s., 1H), 4.63 (d, *J* = 5.7 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 169.1, 142.0, 139.9, 137.5, 131.1, 128.7, 128.3, 128.1 (2C), 127.7, 92.4, 44.2; ¹³C NMR (101 MHz, MeOD) δ ppm 172.5, 144.1, 140.8, 139.6, 132.0, 129.5, 129.2,

129.0, 128.9, 128.3, 93.2, 44.7; **HRMS** (ESI+): Exact mass calcd for $C_{14}H_{12}INNaO$ $[M+Na]$, 359.9856. Found 359.9845, $\sigma = 0.0085$; **IR** (cm^{-1}) ($CDCl_3$) 3432, 3011, 1664, 1514, 1462; **Mp** 124-125 °C (lit.⁵ 124-125 °C).

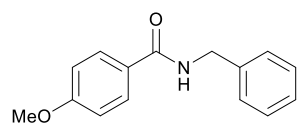
***N*-benzyl-2-nitrobenzamide⁶ (9)**



Purified by method A (0-100% EtOAc in petrol) to give a white solid (87 mg, 68%).

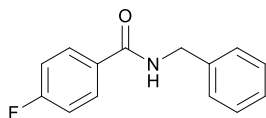
¹H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, $J = 1.0, 8.2$ Hz, 1H), 7.65 - 7.58 (m, 1H), 7.56 - 7.50 (m, 1H), 7.46 (dd, $J = 1.3, 7.5$ Hz, 1H), 7.38 - 7.25 (m, 5H), 6.36 (br. s., 1H), 4.57 (d, $J = 5.7$ Hz, 2H); **¹³C NMR** (101 MHz, $CDCl_3$) δ 166.3, 146.3, 137.4, 133.6, 132.7, 130.4, 128.7, 128.6, 128.0, 127.7, 124.5, 44.2; **HRMS** (ESI+): Exact mass calcd for $C_{14}H_{12}N_2NaO_3$ $[M+Na]$, 279.0740. Found 279.0738, $\sigma = 0.0064$; **IR** (cm^{-1}) ($CDCl_3$) 3433, 3010, 1672, 1534, 1350; **Mp** 123-124 °C (lit.⁶ 121-122 °C).

***N*-benzyl-4-methoxybenzamide² (10)**



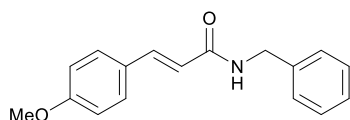
Purified by method A (0-30% EtOAc in petrol) to give a white solid (77 mg, 64 %).

¹H NMR (400 MHz, $CDCl_3$) δ 7.81 - 7.71 (m, 2H), 7.40 - 7.26 (m, 5H), 6.96 - 6.82 (m, 2H), 6.48 (br. s., 1H), 4.61 (d, $J = 5.6$ Hz, 2H), 3.83 (s, 3H); **¹³C NMR** (101 MHz, $CDCl_3$) δ 166.9, 162.2, 138.4, 128.8, 128.7, 127.8, 127.5, 126.6, 113.7, 55.4, 44.0; **HRMS** (ESI+): Exact mass calcd for $C_{15}H_{16}NO_2$ $[M+H]$, 242.1176. Found 242.1171, $\sigma = 0.0078$; **IR** (cm^{-1}) ($CDCl_3$) 3456, 3011, 1653, 1607, 1498; **Mp** 130-131 °C (lit.² 130-131 °C).

***N*-benzyl-4-fluorobenzamide⁷ (11)**

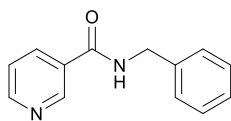
Purified by method A (0-30% EtOAc in petrol) to give a white solid (85 mg, 74%). A second example was purified by method C to give a white solid (85 mg, 74%).

¹H NMR (400 MHz, CDCl₃) δ 7.88 - 7.72 (m, 2H), 7.41 - 7.27 (m, 5H), 7.13 - 7.02 (m, 2H), 6.51 (br. s., 1H), 4.61 (d, *J* = 5.7 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 166.3, 164.7 (d, *J* = 253.2 Hz, ArCF), 138.0, 130.5 (d, *J* = 3.1 Hz, F-ArC-C(O)), 129.3 (d, *J* = 8.4 Hz, F-ArCH), 128.8, 127.9, 127.7, 115.6 (d, *J* = 22.0 Hz, F-ArCH), 44.2; ¹⁹F NMR (377 MHz, CDCl₃) δ -108.1; HRMS (ESI⁺): Exact mass calcd for C₁₄H₁₂FNNaO [M+Na], 252.0795. Found 252.0782, σ = 0.0055; IR (cm⁻¹) (CDCl₃) 3453, 3111, 1660, 1605, 1497; **Mp** 143-144 °C (lit.⁸ 143-144 °C).

***(E)*-N-benzyl-3-(4-methoxyphenyl)acrylamide⁹ (12)**

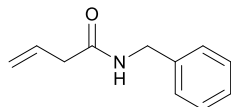
Purified by method A (0-70% EtOAc in petrol) to give a white solid (128 mg, 96%).

¹H NMR (400 MHz, CDCl₃) δ 7.62 (d, *J* = 15.6 Hz, 1H), 7.44 - 7.38 (m, 2H), 7.35 - 7.24 (m, 5H), 6.89 - 6.80 (m, 2H), 6.33 (d, *J* = 15.6 Hz, 1H), 6.30 (br. s, 1H), 4.54 (d, *J* = 5.5 Hz, 2H), 3.81 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 166.3, 160.9, 141.1, 138.2, 129.4, 128.7, 127.8, 127.5, 127.4, 117.9, 114.2, 55.3, 43.8; HRMS (ESI⁺): Exact mass calcd for C₁₇H₁₇NNaO₂ [M+Na], 290.1151. Found 290.1150, σ = 0.0018; IR (cm⁻¹) (CDCl₃) 3442, 3011, 1665, 1626, 1605, 1577, 1254, 1274; **Mp** 142-143 °C (lit.¹⁰ 143-145 °C).

***N*-benzylnicotinamide¹¹ (13)**

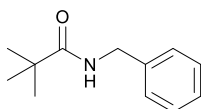
Purified by method D to give a white solid (94 mg, 89%).

¹H NMR (400 MHz, CDCl₃) δ 8.95 (m, 1H), 8.66 (m, 1H), 8.13 (m, 1H), 7.40 - 7.25 (m, 6H), 6.89 (br. s., 1H), 4.64 (d, *J* = 5.6 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 165.5, 152.1, 147.8, 137.7, 135.2, 130.1, 128.8, 127.9, 127.7, 123.5, 44.1; HRMS (ESI⁺): Exact mass calcd for C₁₃H₁₂N₂NaO [M+Na], 235.0842. Found 235.0845, σ = 0.0025; IR (cm⁻¹) (CDCl₃) 3449, 3011, 1666, 1592, 1519, 1455; **Mp** 76-78 °C (lit.¹² 74 °C).

***N*-benzylbut-3-enamide¹³ (14)**

Purified by method A (0-30% EtOAc in petrol) to give a white solid (88 mg, quant.).

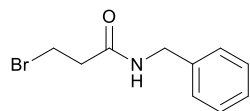
¹H NMR (400 MHz, CDCl₃) δ 7.41 - 7.21 (m, 5H), 6.04 (br. s., 1H), 6.02 - 5.91 (m, 1H), 5.29 - 5.18 (m, 2H), 4.45 (d, *J* = 5.7 Hz, 2H), 3.13 - 2.99 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 170.4, 138.1, 131.2, 128.7, 127.7, 127.5, 119.9, 43.6, 41.5; HRMS (ESI⁺): Exact mass calcd for C₁₁H₁₃NNaO [M+Na], 198.0889. Found 198.0912, σ = 0.0119; IR (cm⁻¹) (CDCl₃) 3442, 3011, 1668, 1639, 1518; **Mp** 33 °C (lit.¹⁴ 48.5-49 °C).

***N*-benzylpivalamide² (15)**

Purified by method A (0-15% EtOAc in petrol) to give a white solid (79 mg, 83%).

¹H NMR (400 MHz, CDCl₃) δ 7.38 - 7.21 (m, 5H), 5.95 (br. s., 1H), 4.43 (d, *J* = 5.6 Hz, 2H), 1.23 (s, 9H); **¹³C NMR** (101 MHz, CDCl₃) δ 178.3, 138.6, 128.7, 127.6, 127.4, 43.5, 38.7, 27.6; **HRMS** (ESI⁺): Exact mass calcd for C₁₂H₁₇NNaO [M+Na], 214.1202. Found 214.1206, *σ* = 0.0013; **IR** (cm⁻¹) (CDCl₃) 3465, 3011, 2967, 1652, 1513; **Mp** 80-81 °C (lit.¹⁵ 80-81 °C).

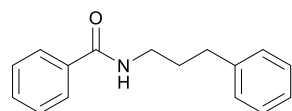
***N*-benzyl-3-bromopropanamide¹⁶ (16)**



Reaction run for 4 h at 85 °C. Purified by method A (0-20% EtOAc in petrol) to give a white solid (57 mg, 47%).

¹H NMR (400 MHz, CDCl₃) δ 7.42 - 7.26 (m, 5H), 6.00 (br. s., 1H), 4.46 (d, *J* = 5.6 Hz, 2H), 3.65 (t, *J* = 6.6 Hz, 2H), 2.78 (t, *J* = 6.6 Hz, 2H); **¹³C NMR** (101 MHz, CDCl₃) δ 169.5, 137.8, 128.7, 127.8, 127.6, 43.8, 39.7, 27.4; **HRMS** (ESI⁺): Exact mass calcd for C₁₀H₁₂BrNNaO⁺ [M+Na], 263.9994. Found 263.9995, *σ* = 0.0078; **IR** (cm⁻¹) (CDCl₃) 3444, 3010, 1675, 1518; **Mp** 98-99 °C (lit.¹⁷ 102-103 °C).

***N*-(3-phenylpropyl)benzamide¹⁸ (17)**

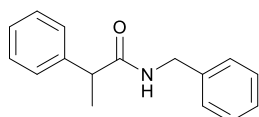


Purified by method A (0-30% EtOAc in petrol) to give a white solid (104 mg, 87%).

¹H NMR (400 MHz, CDCl₃) δ 7.77 - 7.63 (m, 2H), 7.54 - 7.45 (m, 1H), 7.45 - 7.36 (m, 2H), 7.35 - 7.26 (m, 2H), 7.26 - 7.15 (m, 3H), 6.23 (br. s., 1H), 3.51 (td, *J* = 6.0, 7.2 Hz,

2H), 2.74 (t, $J=7.2$ Hz, 2H), 1.98 (tt, $J=7.2, 7.2$ Hz, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 167.4, 141.4, 134.6, 131.3, 128.5, 128.4, 128.4, 126.8, 126.0, 39.8, 33.5, 31.1; **HRMS** (ESI+): Exact mass calcd for $\text{C}_{16}\text{H}_{17}\text{NNaO}$ $[\text{M}+\text{Na}]$, 262.1202. Found 262.1202, $\sigma = 0.0065$; **IR** (cm^{-1}) (CDCl_3) 3454, 3011, 1657, 1522, 1487; **Mp** 60-61 °C (lit.¹⁹ 60 °C).

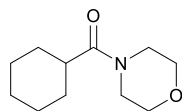
($\pm$)-*N*-benzyl-2-phenylpropanamide²⁰ (18)



Purified by method A (0-30% EtOAc in petrol) to give a white solid (115 mg, 96%).

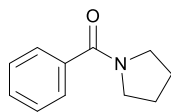
^1H NMR (400 MHz, CDCl_3) δ 7.39 - 7.21 (m, 8H), 7.19 - 7.11 (m, 2H), 5.68 (br. s., 1H), 4.48 - 4.32 (m, 2H), 3.61 (q, $J=7.2$ Hz, 1H), 1.57 (d, $J=7.2$ Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 174.0, 141.3, 138.3, 128.9, 128.6, 127.6, 127.4, 127.3, 127.3, 47.1, 43.5, 18.5; **HRMS** (ESI+): Exact mass calcd for $\text{C}_{16}\text{H}_{18}\text{NO}$ $[\text{M}+\text{H}]$, 240.1383. Found 240.1383, $\sigma = 0.0098$; **IR** (cm^{-1}) (CDCl_3) 3436, 3011, 1668, 1513, 1454; **Mp** 77-78 °C (lit.²¹ 78 °C).

cyclohexyl(morpholino)methanone^{22,23} (19)



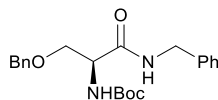
Purified by method A (0-20% EtOAc in petrol) to give a white solid (59 mg, 60%).

^1H NMR (400 MHz, CDCl_3) δ 3.75 - 3.37 (m, 8H), 2.42 (tt, $J=3.4, 11.5$ Hz, 1H), 1.89 - 1.44 (m, 7H), 1.34 - 1.18 (m, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 174.7, 67.0, 66.9, 45.9, 41.9, 40.2, 29.3, 25.8, 25.8; **HRMS** (ESI+): Exact mass calcd for $\text{C}_{11}\text{H}_{19}\text{NNaO}_2$ $[\text{M}+\text{Na}]$, 220.1308. Found 220.1311, $\sigma = 0.0018$; **IR** (cm^{-1}) (CDCl_3) 3010, 2934, 2858, 1627, 1450, 1436, 1115.

phenyl(pyrrolidin-1-yl)methanone²² (20)

Purified by method A (0-25% EtOAc in petrol) to give a white solid (67 mg, 76%).

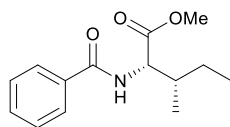
¹H NMR (400 MHz, CDCl₃) δ 7.53 - 7.45 (m, 2H), 7.42 - 7.33 (m, 3H), 3.63 (t, *J* = 6.8 Hz, 2H), 3.40 (t, *J* = 6.8 Hz, 2H), 1.99 - 1.90 (m, 2H), 1.90 - 1.80 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 169.7, 137.2, 129.7, 128.2, 127.0, 49.5, 46.1, 26.3, 24.4; HRMS (ESI⁺): Exact mass calcd for C₁₁H₁₃NNaO [M+Na], 198.0889. Found 198.0906, σ = 0.0084; IR (cm⁻¹) (CDCl₃) 3001, 1615, 1577, 1432.

***tert*-butyl (*S*)-(1-(benzylamino)-3-(benzyloxy)-1-oxopropan-2-yl)carbamate²⁴ (21)**

Reaction run at 85 °C for 6 h. Purified by method A (0-25% EtOAc in petrol) to give a white solid (183 mg, 95%).

¹H NMR (400 MHz, CDCl₃) δ 7.40 - 7.15 (m, 10H), 6.75 (br. s., 1H), 5.42 (br. s., 1H), 4.61 - 4.41 (m, 4H), 4.32 (br. s., 1H), 3.96 (dd, *J* = 3.7, 9.1 Hz, 1H), 3.61 (dd, *J* = 6.4, 9.1 Hz, 1H), 1.43 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 170.2, 155.5, 137.9, 137.3, 128.6, 128.5, 127.9, 127.8, 127.5, 127.4, 80.3, 73.5, 70.0, 54.1, 43.5, 28.2; HRMS (ESI⁺): Exact mass calcd for C₂₂H₂₈N₂NaO₄ [M+Na], 407.1941. Found 407.1950, σ = 0.0102; IR (cm⁻¹) (CDCl₃) 3431, 3011, 2983, 1713, 1676, 1524, 1487, 1455; Mp 81-82 °C.

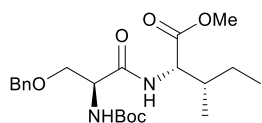
methyl benzoyl-*L*-isoleucinate²⁵ (22)



Purified by method A (0-20% EtOAc in petrol) to give a white solid (48 mg, 39%).

^1H NMR (400 MHz, CDCl_3) δ 7.84 - 7.77 (m, 2H), 7.55 - 7.48 (m, 1H), 7.48 - 7.40 (m, 2H), 6.66 (d, J = 7.9 Hz, 1H), 4.83 (dd, J = 5.0, 8.5 Hz, 1H), 3.77 (s, 3H), 2.09 - 1.93 (m, 1H), 1.60 - 1.46 (m, 1H), 1.33 - 1.18 (m, 1H), 1.01 - 0.90 (m, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ 172.6, 167.1, 134.1, 131.7, 128.6, 127.0, 56.7, 52.2, 38.3, 25.4, 15.5, 11.6; HRMS (ESI+): Exact mass calcd for $\text{C}_{22}\text{H}_{28}\text{N}_2\text{NaO}_4$ [$\text{M}+\text{Na}$], 407.1941. Found 407.1950, σ = 0.0102; IR (cm^{-1}) (CDCl_3) 3438, 3009, 2969, 1736, 1662, 1516, 1486; Mp 88-89 °C.

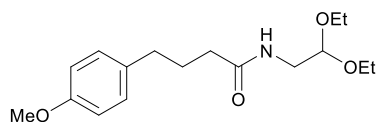
methyl O-benzyl-N-(tert-butoxycarbonyl)-L-seryl-L-isoleucinate²⁶ (23)



Purified by method A (0-30% EtOAc in petrol) to give a white solid (140 mg, 64%).

^1H NMR (400 MHz, CDCl_3) δ 7.39 - 7.26 (m, 5H), 7.11 (br. s., 1H), 5.42 (br. s., 1H), 4.59 - 4.52 (m, 3H), 4.31 (br. s., 1H), 3.93 (dd, J = 3.8, 9.2 Hz, 1H), 3.70 (s, 3H), 3.58 (dd, J = 6.9, 9.1 Hz, 1H), 1.92 - 1.81 (m, 1H), 1.45 (s, 9H), 1.40 - 1.30 (m, 1H), 1.14 - 1.01 (m, 1H), 0.92 - 0.82 (m, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ 172.0, 170.3, 155.5, 137.4, 128.4, 127.9, 127.9, 80.3, 73.6, 69.9, 56.7, 53.7, 52.0, 37.8, 28.3, 25.0, 15.5, 11.5; HRMS (ESI+): Exact mass calcd for $\text{C}_{22}\text{H}_{35}\text{N}_2\text{O}_6$ [$\text{M}+\text{H}$], 423.2490. Found 423.2492, σ = 0.0016; IR (cm^{-1}) (CDCl_3) 3426, 3010, 2972, 1737, 1713, 1679, 1488, 1488, 1368, 1164; Mp 66-68 °C.

N-(2,2-diethoxyethyl)-4-(4-methoxyphenyl)butanamide (24)

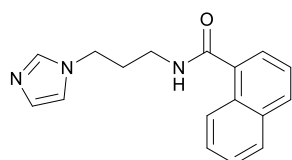


Amidation: Carboxylic acid (1.0 equiv), amine (1.0 equiv, 0.5 mmol), PhSiH₃ (0.7 equiv).

Purified by method B using Et₃N treated silica (30-60% EtOAc/petrol) to give a pale yellow oil (138 mg, 89%).

¹H NMR (400 MHz, CDCl₃) δ 7.14 – 7.04 (m, 2H), 6.87 – 6.78 (m, 2H), 5.62 (br. t, *J* = 5.8 Hz, 1H), 4.49 (t, *J* = 5.2 Hz, 1H), 3.78 (s, 3H), 3.70 (dq, *J* = 9.5, 7.1 Hz, 2H), 3.54 (dq, *J* = 9.5, 7.1 Hz, 2H), 3.39 (dd, *J* = 5.8, 5.2 Hz, 2H), 2.59 (t, *J* = 7.5 Hz, 2H), 2.17 (t, *J* = 7.9 Hz, 2H), 1.94 (tt, *J* = 7.9, 7.5 Hz, 2H), 1.21 (t, *J* = 7.1 Hz, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 172.8, 157.8, 133.5, 129.3, 113.8, 100.7, 62.8, 55.2, 41.8, 35.7, 34.2, 27.3, 15.3; HRMS (ESI⁺): Exact mass calcd for C₁₇H₂₈NO₄ [M+H], 310.2013. Found 310.2012, σ = 0.0015; AT-IR (cm⁻¹) (neat) 3305, 2975, 2930, 1645, 1583, 1544, 1511, 1243.

***N*-(3-(1*H*-imidazol-1-yl)propyl)-1-naphthamide²⁷ (25)**



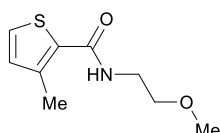
Amidation: Carboxylic acid (1.0 equiv), amine (1.0 equiv, 0.5 mmol), PhSiH₃ (0.7 equiv).

Purified by Method A (0–6% MeOH in dichloromethane), to give a viscous, pale yellow oil (100 mg, 72%).

¹H NMR (400 MHz, CDCl₃) δ 8.31 – 8.16 (m, 1H), 7.93 – 7.82 (m, 2H), 7.58 – 7.48 (m, 3H), 7.45 – 7.38 (m, 2H), 6.98 (s, 1H), 6.94 (s, 1H), 6.60 (t, *J* = 6.2 Hz, 1H), 4.04 (t, *J* = 6.9 Hz, 2H), 3.48 (td, *J* = 6.6, 6.2 Hz, 2H), 2.11 (tt, *J* = 6.9, 6.6 Hz, 2H); ¹³C NMR (101

MHz, CDCl₃) δ 170.0, 137.0, 134.1, 133.6, 130.7, 130.0, 129.6, 128.3, 127.2, 126.5, 125.2, 124.9, 124.6, 118.8, 44.6, 37.2, 31.3; **HRMS** (ESI⁺): Exact mass calcd for C₁₇H₁₈N₃O [M+H], 280.1444. Found 280.1465, σ = 0.0051; **AT-IR** (cm⁻¹) (neat) 3233, 3109, 3047, 2929, 2872, 1636, 1538, 1506, 1256.

***N*-(2-methoxyethyl)-3-methylthiophene-2-carboxamide (26)**

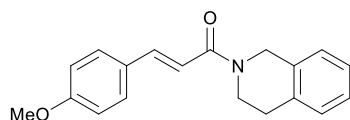


Amidation: Carboxylic acid (1.2 equiv), amine (1.0 equiv), PhSiH₃ (1.0 equiv).

Purified by work-up, then column (pentane /EtOAc (20-40%) to give a pale yellow oil (59 mg, 60%).

¹H NMR (400 MHz, CDCl₃) δ 7.26 (d, J = 5.0 Hz, 1H), 6.88 (d, J = 5.0 Hz, 1H), 6.21 (s, 1H), 3.64 – 3.58 (m, 2H), 3.56 – 3.52 (m, 2H), 3.38 (s, 3H), 2.51 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 163.1, 140.7, 131.9, 131.2, 126.5, 58.8, 39.5, 15.7; **HRMS** (ESI⁺): Exact mass calcd for C₉H₁₄NO₂S [M+H], 200.0740. Found 200.0745, σ = 0.0093; **AT-IR** (cm⁻¹) (neat) 3318, 2927, 2892, 2830, 1629, 1541, 1510, 1454, 1282, 1115, 1091.

***(E)*-1-(3,4-dihydroisoquinolin-2(1*H*)-yl)-3-(4-methoxyphenyl)prop-2-en-1-one (27)**



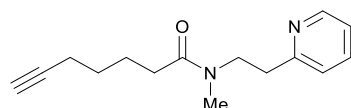
Amidation: Carboxylic acid (1.2 equiv), amine (1.0 equiv, 0.5 mmol), PhSiH₃ (0.7 equiv).

Purified by method B (20-40% EtOAc/petrol), and the product fractions purified further

using the work-up from method A to remove traces of starting material and give an off-white solid (116 mg, 79%). NMR data complicated by rotamers.

¹H NMR (400 MHz, CDCl₃) δ 7.69 (d, *J* = 15.3 Hz, 1H), 7.55 – 7.45 (m, 2H), 7.25 – 7.09 (m, 4H), 6.94 – 6.88 (m, 2H), 6.83 (d, *J* = 15.3 Hz, 1H), 4.83 (s, 2H), 3.99 – 3.85 (m, 2H), 3.84 (s, 3H), 2.94 (s, 2H); **¹³C NMR** (101 MHz, CDCl₃) δ 166.2 (br, C=O), 160.8 (MeOAr), 142.5 (C=C), 135.2 (br, Ar, 0.5C), 134.2 (br, Ar 0.5C), 133.7 (br, Ar 0.5C), 132.7 (br, Ar 0.5C), 129.3 (MeOAr), 128.9-125.9 (br m, 4C), 128.0, 115.0 (br, C=CH), 114.2 (MeOAr), 55.3 (OMe), 47.5 (br. CH₂, 0.5C), 44.8 (br. CH₂, 0.5C), 43.5 (br. CH₂, 0.5C), 40.1 (br. CH₂, 0.5C), 29.7 (br. CH₂, 0.5C), 28.6 (br. CH₂, 0.5C); **HRMS** (ESI⁺): Exact mass calcd for C₁₉H₂₀NO₂ [M+H], 294.1489. Found 294.1506, σ = 0.0038; **AT-IR** (cm⁻¹) 2998, 2956, 2910, 2871, 2840, 1643, 1598, 1510, 1454, 1429, 1245, 1176; **Mp** 123-125 °C.

***N*-methyl-*N*-(2-(pyridin-2-yl)ethyl)hept-6-ynamide (28)**



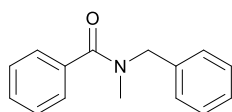
Amidation: Carboxylic acid (1.2 equiv), amine (1.0 equiv, 0.5 mmol), PhSiH₃ (0.7 equiv).

Purified by method B (EtOAc/pentane (20-100%), then 1-3% MeOH in EtOAc). The column product was dissolved in EtOAc and washed a saturated sodium carbonate solution to remove traces of carboxylic acid and give a pale yellow oil (100 mg, 82%). NMR data complicated by rotamers.

¹H NMR (400 MHz, CDCl₃) δ 8.58 – 8.48 (m, 1H), 7.60 (m, 1H), 7.23 – 7.07 (m, 2H), 3.76 – 3.66 (m, 2H), 3.04 – 2.97 (m, 2H), 2.92 (s, 0.5H), 2.90 (s, 0.5H), 2.28 (t, *J* = 7.4 Hz, 1H), 2.22 – 2.05 (m, 3H), 1.92 (2xt, *J* = 2.6 Hz, 1H), 1.75 – 1.43 (m, 4H); **¹³C NMR** (101

MHz, CDCl₃) (all pairs of signals from rotamers except final shift) δ 172.6, 172.5, 159.3, 158.2, 149.6, 149.2, 136.6, 136.4, 123.6, 123.5, 121.8, 121.4, 84.2, 84.2, 68.4, 68.4, 49.6, 48.2, 37.0, 36.1, 35.9, 33.3, 32.9, 32.0, 28.1, 28.1, 24.3, 24.0, 18.2; **HRMS** (ESI⁺): Exact mass calcd for C₁₅H₂₁N₂O [M+H], 245.1648. Found 245.1659, σ = 0.0153; **AT-IR** (cm⁻¹) (neat) 2932, 2865, 1634, 1591, 1474, 1434, 1474.

***N*-benzyl-*N*-methylbenzamide²⁸ (29)**

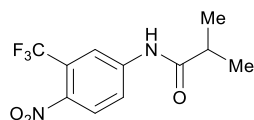


Two equivalents of acid used. Purified by method A (0-20% EtOAc in petrol) to give a white solid (68 mg, 60%). Benzoic acid was recovered from the work-up as a white solid (95% of unconverted acid).

As 1:1 mixture of rotamers

¹H NMR (400 MHz, CDCl₃) δ 7.51 - 7.27 (m, 9H), 7.18 (br. s., 1H), 4.77 (br. s., 1H), 4.52 (br. s., 1H), 3.03 (br. s., 2H), 2.87 (br. s., 1H); **¹³C NMR** (101 MHz, CDCl₃) δ 172.2, 171.6, 137.0, 136.5, 136.2, 129.5, 128.5, 128.1, 127.5, 126.9, 126.7, 55.1, 50.7, 36.9, 33.1; **HRMS** (ESI⁺): Exact mass calcd for C₁₅H₁₅NNaO [M+Na], 248.1046. Found 248.1038, σ = 0.0033; **IR** (cm⁻¹) (CDCl₃) 3011, 1625, 1499, 1403, 1359.

***N*-(4-nitro-3-(trifluoromethyl)phenyl)isobutyramide (Flutamide)²⁹ (30)**

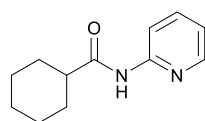


Amidation: Carboxylic acid (9 equiv), amine (1.0 equiv, 0.5 mmol), PhSiH₃ (3 equiv).

Purified by silica quench, base-wash work-up to remove excess acid, column (pentane /EtOAc (10-20%)), to give a pale yellow solid (29.6 mg, 21%).

¹H NMR (400 MHz, CDCl₃) δ 8.04 – 7.94 (m, 3H), 7.73 (s, 1H), 2.58 (hept, *J* = 6.9 Hz, 1H), 1.28 (d, *J* = 6.9 Hz, 6H); **¹³C NMR** (101 MHz, CDCl₃) δ 176.0, 142.7, 142.4, 127.1, 125.3 (q, *J* = 34.3 Hz), 122.0, 121.7 (q, *J* = 273.6 Hz), 118.2 (q, *J* = 5.8 Hz), 36.8, 19.3; **¹⁹F NMR** (376 MHz, CDCl₃) δ -60.11 (s, 3H); **HRMS** (ESI+): Exact mass calcd for C₁₁H₁₁F₃N₂NaO₃ [M+Na], 299.0613. Found 299.0610, σ = 0.0887; **AT-IR** (cm⁻¹) 3357, 3127, 3055, 2984, 2943, 1714, 1610, 1539, 1505, 1342, 1313; **Mp** 111-112 °C (lit.²⁹ 111.5-112 °C).

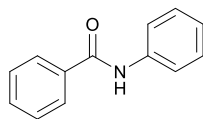
***N*-(pyridin-2-yl)cyclohexanecarboxamide²³ (31)**



Purified by method A (chromatography solvent system: CH₂Cl₂ with 0.1% Et₃N) to give a white solid (34 mg, 33%).

¹H NMR (400 MHz, CDCl₃) δ 8.44 (br. s., 1H), 8.24 (m, 2H), 7.70 (m, 1H), 7.02 (m, 1H), 2.25 (tt, *J* = 3.5, 11.7 Hz, 1H), 2.03 - 1.89 (m, 2H), 1.88 - 1.74 (m, 2H), 1.74 - 1.61 (m, 1H), 1.61 - 1.44 (m, 2H), 1.36 - 1.19 (m, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 174.9, 151.7, 147.3, 138.5, 119.5, 114.2, 46.4, 29.4, 25.6, 25.6; **HRMS** (ESI+): Exact mass calcd for C₁₂H₁₆N₂NaO [M+Na], 227.1155. Found 227.1153, σ = 0.0021; **IR** (cm⁻¹) (CDCl₃) 3419, 3011, 2936, 2858, 1693, 1596, 1577, 1513, 1433, 1300; **Mp** 89-90 °C (lit.³⁰ 89-90 °C).

***N*-phenylbenzamide³¹ (32)**

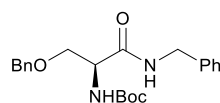


Purified by method A (0-15% EtOAc in petrol) to give a white solid. One equivalent of acid gave 33 mg, 34%. Two equivalents of acid gave 59 mg, 60%. An example using three equivalents of acid was purified by method C, providing 78 mg, 79%. For this example, the unreacted carboxylic acid starting material was recovered by extracting the ethyl acetate organic layer with saturated sodium bicarbonate solution (3 x 10 mL). The aqueous layer was acidified to > pH 3 with aqueous HCl (3 M) and extracted with dichloromethane (3 x 20 mL), dried over magnesium sulfate, and concentrated to give a white solid (124 mg, 92% of unreacted). The purified amide gave the following data:

¹H NMR (400 MHz, CDCl₃) δ 7.93 (br. s., 1H), 7.89 - 7.81 (m, 2H), 7.71 - 7.59 (m, 2H), 7.58 - 7.50 (m, 1H), 7.50 - 7.42 (m, 2H), 7.41 - 7.32 (m, 2H), 7.19 - 7.11 (m, 1H); **¹³C NMR** (101 MHz, CDCl₃) δ 165.8, 137.9, 135.0, 131.8, 129.1, 128.7, 127.0, 124.5, 120.2; **HRMS** (ESI⁺): Exact mass calcd for C₁₃H₁₁NNaO [M+Na], 220.0733. Found 220.0732, σ = 0.0267; **IR** (cm⁻¹) (CDCl₃) 3437, 3011, 1677, 1600, 1524, 1437; **Mp** 162-163 °C (lit.³² 162-163 °C).

2.6 Gram-scale formal synthesis of *ent*-lacosamide

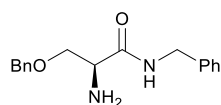
***tert*-butyl (*S*)-(1-(benzylamino)-3-(benzyloxy)-1-oxopropan-2-yl)carbamate²⁴ (21)**



To a 500 mL flask charged with O-benzyl-N-(tert-butoxycarbonyl)-L-serine (5.25 g, 17.8 mmol) and fitted with a water condenser was added toluene (53 mL) and the solution heated to 85 °C under argon. To the resulting solution was added benzylamine (1.85 mL, 16.9 mmol) followed by phenylsilane (2.09 mL, 16.9 mmol) and the reaction mixture was stirred for 4 h. After this time, the reaction was quenched with silica gel (17 g) and stirred for 10 minutes whilst hot. The quenched reaction mixture was then concentrated to dryness and the residue poured onto a thin bed of silica in a fritted sinter funnel. The silica pad was washed with petrol (20 mL) and then the product released with 80:20 CH₂Cl₂:MeOH. The resulting liquid was concentrated, taken up in ethyl acetate, washed with 1 M aqueous HCl, saturated sodium bicarbonate and brine and the organics dried over MgSO₄ to give a crude white solid (6.74 g). The product was estimated to be 91% pure by mass by ¹H-NMR, equating to 94% yield (assuming that the average molecule of phenylsilane was converted to “PhSi(=O)OH”).

21 was characterised above.

(S)-2-amino-N-benzyl-3-(benzyloxy)propanamide³³ (34)

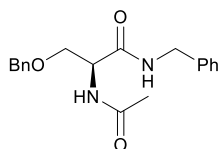


The crude material from the previous step (**21**) was dissolved in dichloromethane (30 mL) before trifluoroacetic acid (30 mL) was added. The reaction was stirred at room temperature for 3 h in a vented flask and then concentrated *in vacuo*. The residue was taken up in dichloromethane, washed with saturated sodium carbonate solution, dried over MgSO₄ and concentrated to dryness to give a viscous orange oil (5.137 g). Assuming that no silicon by-product had been removed since the previous step, the yield was estimated at

99%. The amine was loaded onto 15 g silica, washed with 30 mL 90:10 petrol:ethyl acetate and flushed with 80:20:0.1 CH₂Cl₂:MeOH:Et₃N, which increased the purity of the amine to 93% molar purity by ¹H-NMR relative to silane by-product.

¹H NMR (400 MHz, CDCl₃) δ 7.78 (br. s., 1 H), 7.60 - 6.83 (m, 10 H), 4.60 - 4.51 (m, 2 H), 4.50 - 4.39 (m, 2 H), 3.84 - 3.70 (m, 2 H), 3.69 - 3.60 (m, 1 H), 1.90 (br. s., 2 H); ¹³C NMR (101 MHz, CDCl₃) δ 172.4, 138.3, 137.8, 128.6, 128.4, 127.8, 127.7, 127.6, 127.3, 73.3, 72.3, 55.0, 43.1; HRMS (ESI+): Exact mass calcd for C₁₇H₂₁N₂O₂ [M+H], 285.1598. Found 285.1589, σ = 0.0190.

(S)-2-acetamido-N-benzyl-3-(benzyloxy)propanamide³⁴ (35)

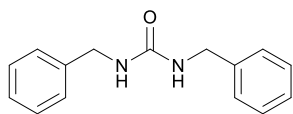


The majority of the crude amine **34** from the previous step (4.64 g, 93% molar purity, 15.2 mmol) was dissolved in ethyl acetate (50 mL) and acetic acid (1.74 mL, 30.4 mmol) followed by phenylsilane (3.22 mL, 24.3 mmol) were added. The reaction mixture was stirred at room temperature for 3 h. After this time, a white precipitate had formed. Silica was added (15 g) and the reaction heated briefly to reflux. The quenched reaction mixture was concentrated to dryness *in vacuo* and the residue loaded onto a bed of silica in a large sintered funnel. The silica pad was washed with 20:80 EtOAc:petrol (100 mL) and 50:50 EtOAc:petrol (100 mL) before elution of the amide with 100% EtOAc. The solution was concentrated *in vacuo* and taken up in ethyl acetate, washed with saturated sodium carbonate solution to remove traces of acid, dried over MgSO₄ and concentrated to *in vacuo* to give a white solid (4.60 g, 93%).

¹H NMR (400 MHz, CDCl₃) δ 7.37 - 7.15 (m, 10H), 6.87 (br. s., 1H), 6.53 (d, *J* = 6.7 Hz, 1H), 4.61 (td, *J* = 4.2, 7.2 Hz, 1H), 4.58 - 4.37 (m, 4H), 3.88 (dd, *J* = 4.2, 9.2 Hz, 1H), 3.53 (dd, *J* = 7.5, 9.2 Hz, 1H), 1.99 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 170.2, 169.9, 137.7, 137.2, 135.6, 128.7, 128.5, 128.0, 127.8, 127.5, 127.5, 73.5, 69.5, 52.5, 43.6, 23.1; **HRMS** (ESI+): Exact mass calcd for C₁₉H₂₂N₂NaO₃ [M+Na], 349.1523. Found 349.1520, σ = 0.0151; **IR** (cm⁻¹) (CDCl₃) 3419, 3009, 1665, 1398, 1455, 1371, 1242, 1103; **Mp** 146-148 °C (lit.³¹ 145-146 °C); [α]²⁴_D = +29.9 (*c* 0.7, CHCl₃) (lit. (*ent*)-**17** [α]²⁵_D = -28.7 (*c* 0.7, CHCl₃)).³¹

2.7 Phenylsilane-mediated urea synthesis using CO₂ (Table 8)

1,3-dibenzylurea³⁵ (**50**)



Benzylamine (218 μ L, 2.00 mmol) was dissolved in dry THF (1 mL) with DBU (15 μ L, 0.1 mmol, 10 mol%) and phenylsilane (123 μ L, 1 mmol) in a 10 mL round-bottomed flask fitted with a condenser, itself fitted with a suba seal and an empty balloon. The reaction was heated to reflux (oil bath, 70 °C) and an excess of CO₂ was added as dry ice pellets, 1 small pellet/5 min, over 20 min, by dropping the pellets down the condenser and replacing the balloon. Doing so caused rapid gas evolution; the pressure in the balloon was controlled manually (the reaction gave similar results without using the balloon). After ~20 min, a white solid precipitated, and the reaction was cooled, diluted with ether and stirred to break up the solid. The solid was filtered and washed with ether (and dichloromethane to remove residual silane material if necessary), to give the title compound as a white solid (210 mg, 88%).

^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 7.38 – 7.16 (m, 11H), 6.45 (t, $J = 6.1$ Hz, 2H), 4.23 (d, $J = 6.0$ Hz, 4H); **^{13}C NMR** (101 MHz, $\text{DMSO}-d_6$) δ 158.1, 140.9, 128.2, 127.0, 126.5, 43.0; **HRMS** (ESI+): Exact mass calcd for $\text{C}_{15}\text{H}_{17}\text{N}_2\text{O}$ $[\text{M}+\text{H}]$, 241.1335. Found 241.1327, $\sigma = 0.0111$; **AT-IR**: (neat) 3317, 3030, 2916, 2872, 1625, 1606, 1567 cm^{-1} ; **Mp** 175-176 $^\circ\text{C}$ (lit.³⁵ 172-173 $^\circ\text{C}$).

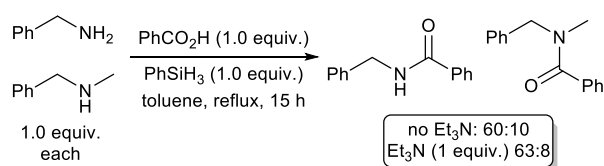
The experiment was repeated exactly with the reagent combinations given in Table 8 to give the results as shown in Table 8.

3. Mechanistic Experiments – Qualitative

3.1 Hydrogen evolution measurements

Rudimentary hydrogen gas volume measuring experiments were performed by connecting a stirring sealed flask containing the reagents to an upturned water-filled measuring cylinder in a reservoir containing water, which was displaced upon gas evolution. The volume of gas collected was read off the cylinder. The tube connecting the flask to the cylinder was packed with calcium chloride to hinder the passage of water vapour back up the tube. The volume of 1 mole of hydrogen was approximated as 23 dm^3 . The identity of the gas was confirmed as hydrogen by observing the characteristic combustion of a lit splint in the presence of the gas and the resulting water condensation on the walls of the vessel. For the more-rigorous kinetic experiments, see dedicated section later.

3.2 Amidation Competition Experiment: Primary vs. Secondary Amine

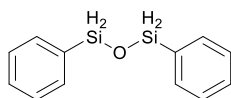


Benzoic acid (61.1 mg, 0.500 mmol) was dissolved in toluene (1.5 mL) and the reaction heated to reflux (oil bath at 116 °C). Added was benzylamine (54.6 μ L, 0.500 mmol), methylbenzylamine (64.5 μ L, 0.500 mmol) and finally phenylsilane (61.7 μ L, 0.500 mmol) and the reaction stirred for 15 h. The reaction was concentrated and the conversion to amide deduced by comparison to 1,1,2,2-tetrachloroethane as an internal standard in chloroform. In order to ensure that the more basic methylbenzylamine was not limited by preferential salt formation, the reaction was run exactly as before, but with the initial addition of one equivalent of triethylamine (69.8 μ L, 0.500 mmol) to benzoic acid, before the addition of the remaining components. The result was the same, showing a ~6:1 ratio in favour of the primary amine as depicted in the scheme above.

3.3 Representative *in situ* silyl ester formation

Phenylsilyl benzoate (37) – SEE CHAPTER 1, COMPOUND 18

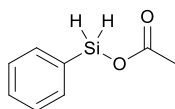
1,3-diphenyldisiloxane³⁶ (40)



Chloro(phenyl)silane (0.160 mmol, 21.3 μ L) was added to C₆D₆ (0.4 mL) and stirred overnight at room temperature in the presence of 2 drops (an excess) of water. The resulting solution was filtered by gravity through magnesium sulfate to remove water/HCl. ¹H-NMR spectroscopy showed the disiloxane to be the major species (91% of the Si-H ¹H-NMR signals present are the disiloxane). This solution was used without further purification in further reactions.

^1H NMR (400MHz, C_6D_6) δ 7.53 - 7.47 (m, 4H), 7.15 - 7.08 (m, 6H), 5.28 (s, 4H); ^{13}C NMR (101 MHz, C_6D_6) δ 134.4, 134.0, 130.8, 128.4; ^{29}Si NMR (79 MHz, C_6D_6) δ -25.3.

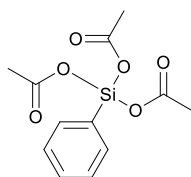
Phenylsilyl acetate (38)



Chloro(phenyl)silane (21.3 μL , 0.160 mmol) was added to a refluxing suspension/solution of sodium acetate (13.1 mg, 0.160 mmol) in C_6D_6 (0.5 mL) and heated with stirring for 30 min. The solution was used without further manipulation.

^1H NMR (400MHz, C_6D_6) δ 7.69 - 7.64 (m, 2H), 7.20 - 7.10 (m, 3H), 5.19 (SiH₂, s, 2H), 1.61 (s, 3H); ^{13}C NMR (101 MHz, C_6D_6) δ 171.7, 135.8, 131.3, 130.8, 128.4, 21.5; ^{29}Si NMR (79 MHz, C_6D_6) δ -21.2.

Phenyltriacetoxysilane³⁷ (39)



Trichloro(phenyl)silane (25.6 μL , 0.160 mmol) was added to a C_6D_6 (0.5 mL) suspension of anhydrous sodium acetate (39.4 mg, 0.480 mmol) and the reaction stirred at reflux for 3.5 h. The reaction was cooled and filtered through cotton wool and used without further purification. The major species in solution was adjudged to be phenyltriacetoxysilane. A small amount of acetic acid was present, as was an unidentified species.)

¹H NMR (400MHz, C₆D₆) δ 8.08 - 7.99 (m, 2 H), 7.20 - 7.17 (m, 3 H), 1.71 (s, 9 H); ¹³C NMR (101 MHz, C₆D₆) δ 168.8, 135.3, 132.4, 132.0, 128.4, 21.9; ²⁹Si NMR (79 MHz, C₆D₆) δ -60.8.

3.4 Comparison of reactivity of preformed acetoxysilyl esters (Schemes 5-6)

From phenyltriacetoxysilane (39): To a toluene solution (1.5 mL) containing phenyltriacetoxysilane (0.160 mmol) prepared as described above was added benzylamine (52.4 μL, 0.480 mmol) and the reaction stirred at 50 °C for 10 min. The reaction was quenched with methanol (2 mL) and concentrated. The conversion to *N*-benzylacetamide was calculated relative to tetrachloroethane as internal standard by inspection of the ¹H-NMR spectrum and quoted as a conversion with respect to amine.

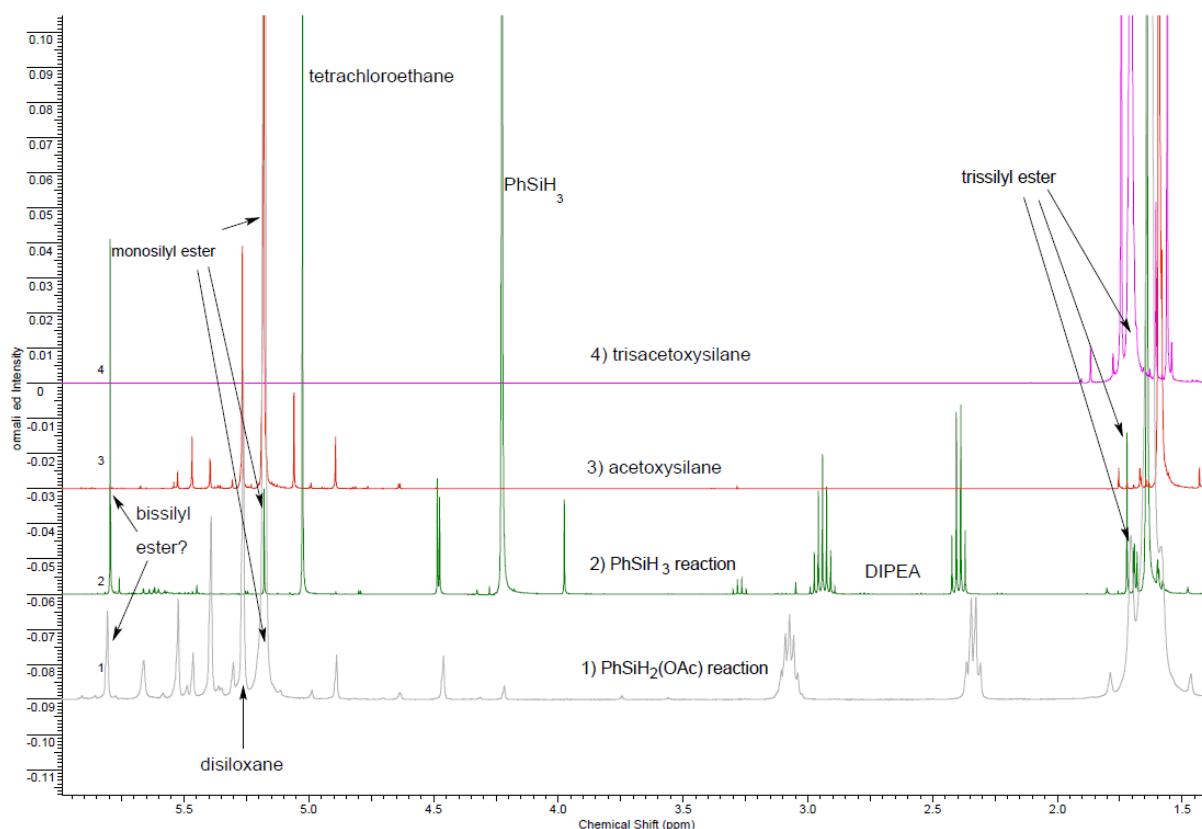
From phenylsilyl acetate (38): To a toluene solution (0.5 mL) containing phenylsilyl acetate (0.160 mmol) prepared as described above was added benzylamine (17.5 μL, 0.160 mmol) and the reaction stirred at 50 °C for 10 min. The reaction was processed in the same way as for phenyltriacetoxysilane.

From phenylsilane: Phenylsilane (19.7 μL, 0.160 mmol) was added to the appropriate solvent (0.5 mL) containing acetic acid (9.2 μL, 0.16 mmol) and the temperature raised to 50 °C before adding the benzylamine (1 equiv.). The reaction was processed in the same way as for phenyltriacetoxysilane.

3.5 Evidence of the formation of silyl esters from phenylsilane (Scheme 4)

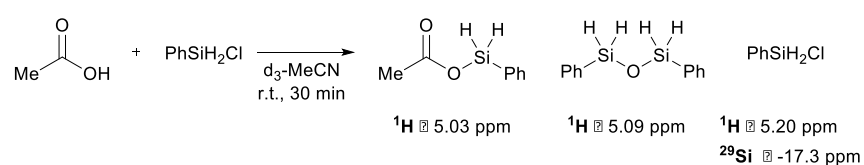
In a vented NMR tube was combined phenylsilane (39.4 μL , 0.320 mmol) or phenylsilyl acetate (0.320 mmol), formed as described above, in C_6D_6 (0.5 mL) with acetic acid (0.32 mmol) and added was *N,N*-diisopropylethylamine (2.3 μL). Each solution was shaken and the ^1H and ^{13}C NMR spectra recorded after 10 mins and 1 h. Selected signals are shown in the scheme above. The observed signals were minor with respect to the starting silane/acetyl signals. Minor signals other than those tentatively assigned above were present; in the case of the reaction of **38**, the presence of disiloxane **40** led to the formation of further derivatives.

Overlaid ^1H -NMR (400 MHz, C_6D_6), spectra: *From bottom up* (1) reaction B (1 h); (2) reaction A (1 h); (3) phenylsilyl acetate, (4) phenyltriacetoxysilane. (*many of the signals are $^1J_{\text{Si-H}}$ satellites*). The presence of proton donor (acetic acid) leads to minor shift variations.



3.6 Silyl esters in Acetonitrile (Scheme 7)

3.6.1 Formation from the chlorosilane



Chloro(phenyl)silane (16.6 μL , 0.125 mmol) was added to a suspension of sodium acetate (10.3 mg, 0.125 mmol) in $\text{D}_3\text{-MeCN}$ (0.5 mL) for 30 min at rt. The solution was characterised as follows; summary in the scheme above. Signals extracted from the mixture:

Phenylsilyl acetate: ${}^1\text{H}$ NMR (400 MHz, $\text{D}_3\text{-MeCN}$) δ 7.77 – 7.69 (m, 2H), 7.54 – 7.45 (m, 3H), 5.03 (s, 2H), 2.09 (s, 3H); ${}^{13}\text{C}$ NMR (101 MHz, $\text{D}_3\text{-MeCN}$) δ 173.3, 136.0, 132.2, 131.8, 129.2, 22.4.

3.62 Base-catalysed silyl ester observation in acetonitrile (Figure 4):

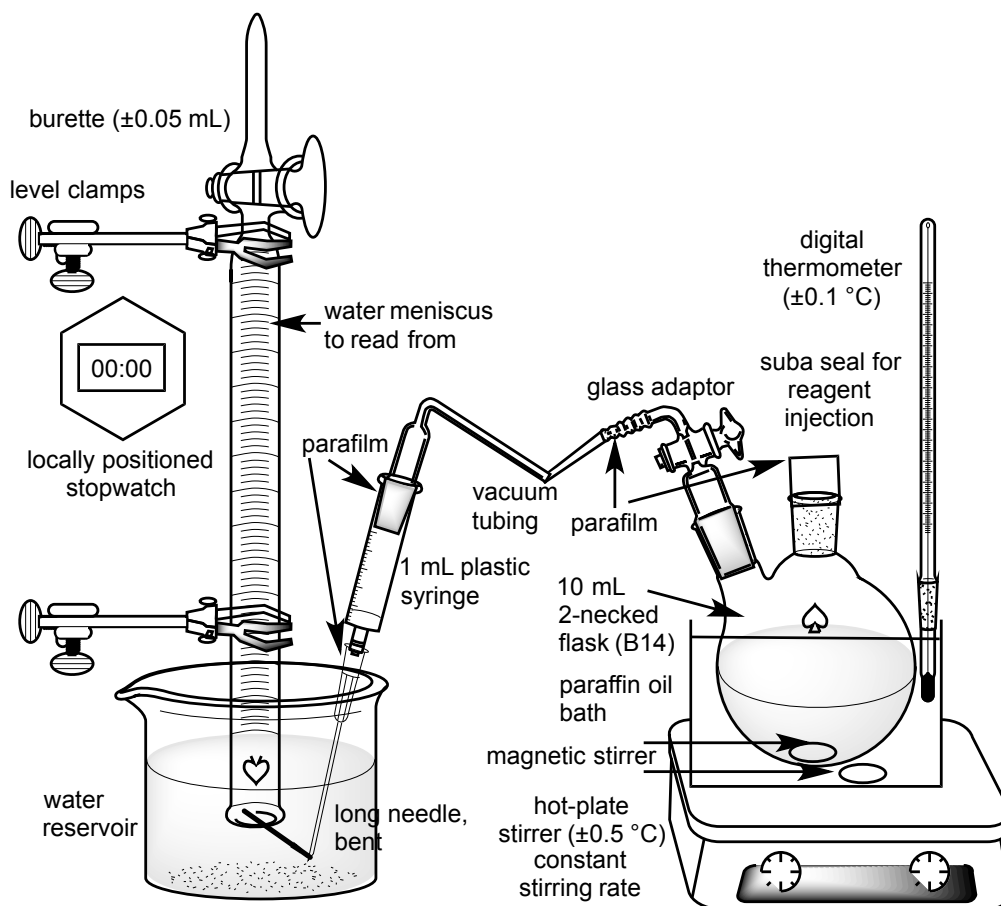
In a vented NMR tube was combined phenylsilane (12.3 μL , 0.100 mmol) and acetic acid in $\text{D}_3\text{-MeCN}$ (0.5 mL) with acetic acid (17.2 μL , 0.300 mmol) and added was catalytic triethylamine (1 μL , ~5 mol%). The reaction was observed by NMR spectroscopy after 5 min, and again as specified. Brief heating to develop the reaction was applied using a heat gun, bring the mixture briefly to reflux and cooling again. The monosilyl ester was assigned by comparison to the above at 5.02 ppm. Dissolved hydrogen gas is visible at 4.57 ppm. The disiloxane is initially visible at 5.08 ppm, but reacts divergently over time. The bisilyl ester appears not to form until heating is applied (tentatively assigned at 5.44 ppm). Over time, a white precipitate, believed to be insoluble siloxane oligomers, was observed in at the bottom of the NMR tube.

4. Kinetic Experiments – Quantitative

Dry solvents used as detailed in the general information. For groups of experiments requiring a constant (e.g. 5 mol% level) of base, a stock solution was generated so that 2.000 mL of this solution contained exactly the requisite mmol of base. For experiments that resulted in significant volume changes, the amount of solvent was corrected to give a constant volume. In experiments where the percentage volume change was small, the solvent level was not altered, however where the concentration was required in further calculations, the true concentration was used.

4.1 Set-up

A sketch of the basic set-up is provided below.



Above a large water reservoir at room temperature was suspended a graduated burette (50.0 cm^3 , $\pm 0.05 \text{ cm}^3$), filled with water. Whilst closed, the Teflon tap demonstrated an insignificant gas leakage (i.e. insignificant water level alteration) to affect measurements over the time period of an experiment, even when containing mostly hydrogen. (Although it is appreciated the set-up utilised in these experiments is not state-of-the-art, the reproducibility of the results was excellent, and similar results could be obtained by using a simple measuring cylinder with only 0.5 cm^3 resolution.) A two-necked 10 mL round-bottomed flask containing a small magnetic stirrer bar was flame-dried, sealed with suba seals, and purged with argon, and left standing under an argon balloon. Once at ambient temperature, solvent was added (typically $2 \times 1.000 \text{ mL}$, via microsyringe) and the flask left to reach the desired temperature in an oil bath ($\pm 0.5 \text{ }^\circ\text{C}$) or a suitably large dry ice/acetone bath ($\sim 2 \text{ L}$ volume), which was large enough to manually maintain a temperature of -35

± 1 °C by attentive addition of dry ice pellets. The time taken for the temperature of the internal mixture to reach the desired temperature was measured once using an internal probe (~20 min), and this delay was allowed for each subsequent experiment.

Typically, the required quantity of carboxylic acid was added, followed by either the silane or base. Note that the dryness of the solvent/reagents could be ascertained by mixing the silane and base (in the absence of acid), which led to the base-catalysed reaction of water with silane. In the presence of acid, however, the water reaction is thought to be shut down, as the base preferentially interacts with the more acidic (and in large excess) carboxylic acid rather than any residual water.

An argon flushed rubber vacuum tubing fitted with: at one end, an adapted 1 mL syringe with a long needle bent to sit at the bottom of the burette in the reservoir and, at the other end: a B14 ground-glass joint with hose connection (both ends sealed air-tight with parafilm) was then connected to one of the necks of the flask. The adaptor was sealed to the flask with parafilm, as was the remaining suba seal. At this point, the argon balloon was removed, which stemmed the tide of bubbles (but which presumably left the internal pressure just below that required to release gas bubbles). After recording the burette level, the final reagent (silane or base) was then injected through the remaining suba seal, and the timer started immediately. The top of the suba seal was then quickly re-sealed with an additional piece of parafilm (important!). The needle to the burette was positioned so that bubbles rose directly up to the top of the burette, and did not get stuck on the side. When required, a gentle tapping of the burette was sufficient to restore a flat meniscus/remove partial bubbles.

Measurements were made by hand, recording the time in whole seconds for various burette levels (0.1 mL) from a stopwatch positioned directly next to the burette. Many dense measurements were made in the initial section of the experiment to acquire initial rate data. Due to a slight (systematic) lag in the data at the beginning (pressure build up for bubble release and also bubble transit time), the zero point and often first reading was not included in analyses. Note that the average conditions used in the experiments were initially screened to give a rate of bubble evolution that was accurately measurable by hand. A minimum of three concordant results were recorded for each experiment.

Data were processed in Microsoft Excel, using Stat Plus to calculate various parameters, gradients and errors etc.

4.11 Example Data

Experiment: 1.00 mmol PhSiH_3 added to 1.00 mmol propanoic acid and 0.05 mmol Et_3N in 2.00 mL dry acetonitrile (as stock solution) at 25 °C. Initial rate measured as the gradient of a straight line generated when plotting concentration of hydrogen collected against time (in seconds) between 0.01 and 0.05 equivalents of hydrogen release (pseudo first order conditions) using a minimum of 5 points, after discarding the first two/three points which are prone to hydrogen pressure/transit lag.

Three concordant results were recorded: concordant results are defined in terms of relative gradients, as small variances in the initial lag time displace absolute values slightly.

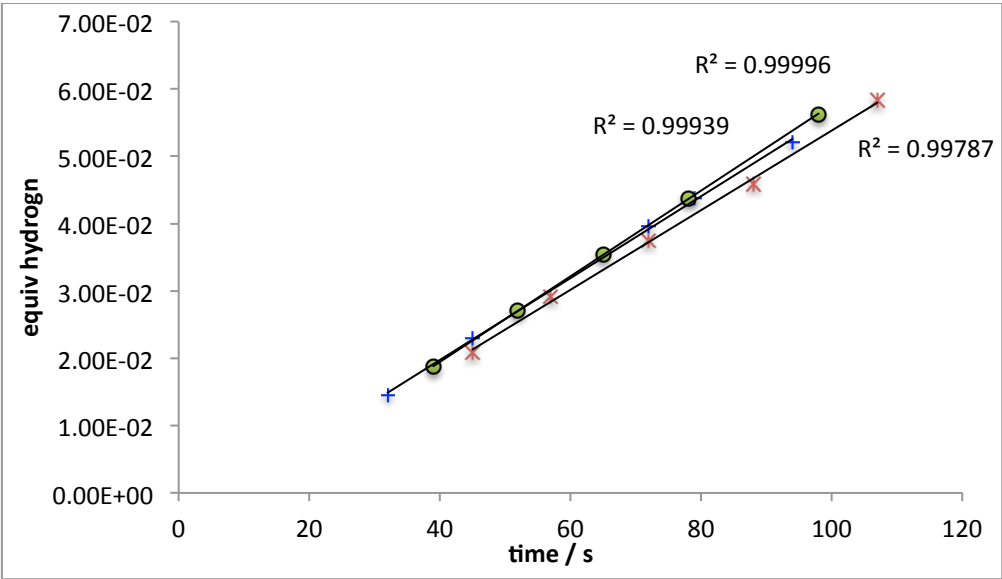
Raw data obtained as described above:

Run 1			Run 2			Run 3		
burette			burette			burette	time /	
cm ³	time / s	Equiv. H ₂	cm ³	time / s	Equiv. H ₂	cm ³	s	Equiv. H ₂
48.75	0	0.00E+00	46.6	0	0.00E+00	48.75	0	0.00E+00
48.5	25	1.04E-02	46.4	21	8.33E-03	48.5	24	1.04E-02
48.4	32	1.46E-02	46.1	45	2.08E-02	48.3	39	1.88E-02
48.2	45	2.29E-02	45.9	57	2.92E-02	48.1	52	2.71E-02
47.8	72	3.96E-02	45.7	72	3.75E-02	47.9	65	3.54E-02
47.7	79	4.37E-02	45.5	88	4.58E-02	47.7	78	4.37E-02
47.5	94	5.21E-02	45.2	107	5.83E-02	47.4	98	5.63E-02

4.12 Analysis

	Run1	Run2	Run3	Average	Error (±)
H ₂ equiv/s (x 10 ⁴)	6.01	5.83	6.26	6.03	0.24

Graphical representation of data used showing agreement of 3 data runs:



Error calculated as the confidence interval at 95% using:

$$\text{Error} = \sigma [0.95(n-1)] / \text{sqrt}(n)$$

where σ = standard deviation and n = number of data points used (3 in the above).

These rates, in terms of equivalents of hydrogen per second, were then converted to the ratio relative to a standard set of conditions for comparison with data obtained when varying parameters.

4.2 Initial Results

4.21 Table 3

MeCN (2.00 mL) containing phenylsilane (equivalents given in table, 1 equiv = 123 μL = 1 mmol) and acetic acid (1 mmol, 57.2 μL) were equilibrated in the equipment described above (basic set-up), and added was the relevant base as shown in the table (5 mol% = 0.05 mmol). The final concentrations are not directly comparable as the solvent volume was not adjusted to take into account differing base volumes. However these changes are miniscule compared to the bulk solvent. The rate of hydrogen evolved was measure as the rate of water volume displace as described above against time. After the times described, benzylamine (1 mmol, 109.2 μL) was injected to the closed system, and the rate of hydrogen displaced measured against time again. After hydrogen evolution had ceased, the reaction mixture was concentrated, 1,1,2,2-tetrachloroethane (52.8 μL) added, and a ^1H -NMR spectrum recorded. The conversion to amide was determined by comparison to the integral of the internal standard.

4.22 Figure 4: NMR titration study

Dry triethylamine (2 μL , 5 mol%) was placed in a dry NMR tube, and $\text{d}_3\text{-MeCN}$ (0.55 mL) was added to ensure the amine was fully in solution. A ^1H -NMR spectrum was recorded.

Added sequentially to the tube, recording an NMR spectrum in between each addition, was d4-acetic acid. The volumes added such that the amine:acid were equimolar, then a 10 fold excess of acetic acid, and then a 20 fold excess. A large deshielding effect was observed on the chemical shift as acid was added, indicating significant hydrogen bonding.

4.3 Experiments performed in an excess of acid

4.31 Varying the acid: acetic, benzoic, pivalic, isobutyric, chloroacetic, propanoic, mesitoic (Table 5)

Details: 5 mol% Et₃N as stock solution in MeCN (2.00 mL), added [acid] 1.0 mmol, and PhSiH₃ 1.0 mmol, 25 °C. Hydrogen evolution measured as a function of time; initial rates compared.

4.32 Varying the amine: 2,2,6,6-tetramethylpiperidine, N-methyl morpholine, tertiary butylamine, triethylamine, diisopropylamine, morpholine, DBU (Table 6)

Details: 5 mol% [base] in MeCN (2.00 mL), AcOH 1.0 mmol, PhSiH₃ 1.0 mmol, 25 °C. Hydrogen evolution measured as a function of time. Note that acid and silane are in a 20-fold excess. Initial rates recorded.

4.33 Varying the solvent: acetonitrile, THF, chloroform, DMF, toluene, diethyl ether, ethyl acetate, DMSO, acetone, pyridine (Table 4)

Details: 5 mol% 2,2,6,6-TMP in [solvent] 2.00 mL, AcOH 1.0 mmol, PhSiH₃ 1.0 mmol, 25 °C. Hydrogen evolution measured as a function of time to gain initial rates.

Using a linear free energy equation of the form: (ϵ = dielectric for the solvent; HBA = hydrogen-bonding accepting constant)

$$\log(k'_{\text{solvent}}/k'_{\text{MeCN}}) = \alpha \cdot \text{HBA} + \beta \cdot \epsilon$$

and minimising the |differences| to iteratively solve for prefactors α and β resulted in a good fit, demonstrating a positive correlation between both the dielectric constant and the hydrogen bond-accepting ability of the solvent in promoting the reaction.

Solved values: $\alpha = 4.27$, $\beta = 1.07$

Because the dielectric constants for each solvent were scaled to operate over the same magnitude of range as the HBA values, α and β can be roughly compared. The majority of the weighting on the right hand side of the equation comes from the α .HBA term, indicating that HBA ability is a better predictor of rate in a given solvent.

Scaled values used: Calculated by scaling the dielectric values into the same range as that covered by the H-bond accepting terms.

Solvent	original values		normalised values	
	H-bond accept	dielectric	H bond	dielec
MeCN	0.4	37.5	0	0
THF	0.55	7.58	0.15	-0.4488
CHCl ₃	0.1	4.81	-0.3	-0.49035
DMF	0.69	36.7	0.29	-0.012
toluene	0.11	2.38	-0.29	-0.5268
Et ₂ O	0.47	4.33	0.07	-0.49755
EtOAc	0.45	6.02	0.05	-0.4722
DMSO	0.76	46.7	0.36	0.138
Acetone	0.43	20.7	0.03	-0.252
pyridine	0.64	12.4	0.24	-0.3765
		Range	0.66	0.6648

4.34 Sodium acetate catalyses the dehydrogenative reaction

Details: At 25 °C in MeCN 2.00 mL, with 1.00 mmol AcOH, 1.00 mmol PhSiH₃ and 0.05 mmol NaOAc. Measured hydrogen evolution as a function of time.

Results: Reaction did proceed, at 0.1 times the rate of Et₃N under otherwise identical conditions. Reaction rate was linear (as expected in excess acid/silane), and slowed down only towards completion.

4.35 Varying the silane: PhSiH₃ and Ph₂SiH₂ and Ph₃SiH compared (Table 7)

Details: 5 mol% Et₃N (0.05 mmol) as stock solution in MeCN (2.00 mL), acetic acid 1.0 mmol, [silane] 1.0 mmol, 40 °C oil bath. Hydrogen evolution measured as a function of time, and the initial rate determined from the gradient of the straight line obtained at the start of the reaction. The reaction is pseudo first order, with acid and silane assumed constant (1 mmol, 20 fold excess), the reaction limited by base (0.05 mmol). Thus the experiment determines differences in reactivity of different silanes.

4.36 Kinetic isotope effect between H₃CCO₂H and D₃CCO₂D at low temperature (Figure 11)

Details: At –35 °C, 0.2 mmol [AcOH or d⁴-AcOD] was reacted in MeCN (2.00 mL), 550 uL Et₃N (~4.0 mmol = ~20 equiv) and 500 uL PhSiH₃ (~4.0 mmol = ~20 equiv) and hydrogen evolution measured as a function of time.

Results: Comparison of both the initial rate and the relative rates as a function of conversion showed a clear kinetic isotope effect. **The value of $k_H/k_D = 2.75 \pm 0.39$.**

Visualisation of the kinetic isotope effect (three runs for each AcOH and d₄AcOD) is shown below. The slower reaction is the deuterated acid. *Error in the kinetic isotope effect given as the largest ratio using the confidence intervals at 95% for the two sets of data.*

4.37 Synthesis of deuterated phenylsilane

To deuterated lithium aluminium hydride (LiAlD_4 , 62.44 mmol, 2.4 g) in dry ether (200 mL) under argon at 0 °C in a 500 mL flask fitted with a large condenser was added cautiously (dropwise) trichloro(phenyl)silane (5.0 mL, 31.22 mmol). The reaction was warmed to room temperature, and then refluxed for 24 h. After this time, ^1H -NMR of the highly reactive mixture showed full conversion to the deuterated silane. Careful filtration under argon removed the solids, which were cautiously quenched. The solution was concentrated carefully at ambient temperature to remove most of the ether, and immediately returned to an atmosphere of argon. Ideally, the mixture is refiltered to remove further solids that precipitate.

A short path distillation was attempted at ~atmospheric pressure under argon, and the fraction boiling at 120 °C was collected. This solution was acidic and decomposed upon standing. To remove the acidic components, the material must be passed rapidly through a short pad of alumina as a pentane solution, using pressure to force the solution through. WARNING! This creates a highly pyrophoric alumina waste product, which spontaneously ignites the remaining pentane upon quenching, made more dangerous by its dispersion on the alumina particles. This must be attempted only in an empty fumehood with a large aqueous quenching pot, by slow addition of the alumina to the water. Ideally the alumina is dried of pentane before attempting.

The filtrate pentane solution was then very carefully concentrated *in vacuo* to give the desired deuterated-phenylsilane with small amounts of pentane remaining. These traces were very hard to remove without losing phenylsilane to evaporation on the scale attempted here. Eventually, deuterated-phenylsilane (1.5 g, 13.5 mmol >94% pure) was obtained for use in the kinetic experiments; ^1H NMR (400 MHz, C_6D_6) δ 7.42 – 7.36 (m,

1H), 7.14 – 7.03 (m, 2H); ^{13}C NMR (101 MHz, C_6D_6) δ 136.1, 130.1, 128.4. (final signal hidden beneath the solvent peak); ^2H NMR (61 MHz, C_6H_6) δ 4.23 (s, 1H) (referenced to trace $\text{C}_6\text{H}_5\text{D}$ in the solvent).

To ensure the small loss in phenylsilane purity was not interfering with the kinetic experiments, a solution of phenylsilane in pentane was filtered through alumina and concentrated to the same purity as the deuterated silane for use in the experiments below, and showed no measurable difference to the initial rate values obtained.

4.38 Kinetic isotope effect of deuterated silane at low temperature (Figure 12)

Details: At $-35\text{ }^\circ\text{C}$, 0.1 mmol AcOH was reacted in MeCN (1.00 mL), 260 μL Et_3N (~ 4.0 mmol = ~ 20 equiv) and 250 μL PhSiH_3 or PhSiD_3 (~ 2.0 mmol = ~ 20 equiv) and hydrogen evolution measured as a function of time.

Results: Comparison of both the initial rate and the relative rates as a function of conversion showed a kinetic isotope effect. **The value of $k_{\text{H}}/k_{\text{D}} = 1.28 (+0.21, -0.18)$.** Value is the average of three runs for each AcOH and d_4AcOD . The slower reaction is the deuterated acid. *Error in the kinetic isotope effect given as the largest ratios using the confidence intervals at 95% for the two sets of data.*

4.4 Orders of the Components in the rate equation

4.41 Order of the dehydrogenative silylation reaction in base. (Figure 9)

Details: For 5 concentrations of Et_3N , the full rate of hydrogen evolution to completion was measured. The rate remained linear for the entire measurement indicating that our pseudo first order conditions were valid; thus acetic acid (10 mmol) and phenylsilane (2 mmol) in MeCN (2.00 mL) were at a sufficient excess to maintain the first order approximation. The equivalents of base were varied as follows: 0.05, 0.10, 0.20, 0.40, 0.80 mmol Et_3N . The

initial rates were extracted from the rate data to give 5 rates as a function of base concentration. Because Et_3N is not consumed during the reaction, and so remains at constant concentration, the range designated as an ‘initial rate’ could be extended allowing more precise data measurement.

Results: Plotting a log/log plot of the form:

$$\log v = \log k + b \log[B]$$

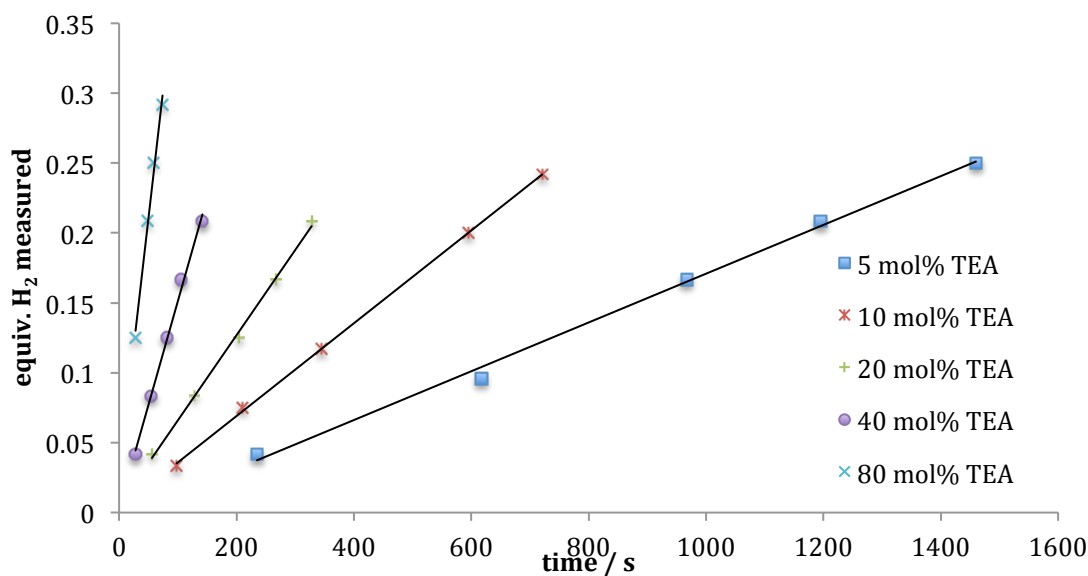
where v is the rate, k is a constant and $[B]$ is the concentration of base gave a straight line where the gradient is b . This log/log plot derives from the first order rate equation:

$$\text{rate} = k[B]^b$$

where $k = k'$, assuming constant concentration of all reagents in excess.

Thus the gradient of the line gives the order of the reaction. In the event, the gradient obtained was 1.0, revealing that the reaction is first order in base under these conditions.

The main graph is shown in Figure 10.



Standard least squares regression gives a gradient of 1.02 with an associated error of ± 0.04 . The (error) confidence limits at 95% are ± 0.08 for the gradient. The R^2 value is 0.99487.

4.42 Order of the dehydrogenative reaction in phenylsilane (Figure 9)

Details: The concentration of phenylsilane was varied and the rate measured as a function of the concentration. MeCN (variable), AcOH (1 mmol), and Et₃N (0.05 mmol) were used. As base is the limiting reagent, and is not consumed, the reaction is under pseudo first order conditions with a 20-fold excess of acetic acid and a constant concentration of base. The silane is present in 6-80 fold excesses, and so is assumed to be in constant concentration over the initial period of the reaction. The initial rates were obtained for 11 concentrations of silane. *Note that this method was preferred over simply taking one concentration and following the rate against concentration over time because the exact nature of the silane species, and the potential differing reactivity of any such formed species are unknown.*

Results: Plotting a log/log plot of the form:

$$\log v = \log k + s \log [S]$$

where v is the rate, k is a constant and $[S]$ is the concentration of base gave a straight line where the gradient is s . This log/log plot derives from the first order rate equation:

$$\text{rate} = k[S]^s$$

where $k = k'$, assuming constant concentration of all reagents.

Thus the gradient of the line gives the order of the reaction. In the event, the gradient obtained was 1.0, revealing that the reaction is first order in silane.

Standard least squares regression gives a gradient of 1.00 with an associated error of ± 0.10 .

The confidence limits at 95% are ± 0.22 for the gradient. The R^2 value is 0.92317.

4.43 Reaction is first order in acid when base is in excess (Figure 11)

Details: At $-35\text{ }^{\circ}\text{C}$ in a dry ice/acetone bath, manually controlled, 0.2 mmol AcOH was reacted in MeCN (2.00 mL), with 550 μL Et₃N ($\sim 4.0\text{ mmol} = \sim 20\text{ equiv}$) and 500 μL PhSiH₃ ($\sim 4.0\text{ mmol} = \sim 20\text{ equiv}$) and hydrogen evolution measured as a function of time.

Results: Using the first order integrated rate equation, a plot of $\ln(1 - d[\text{H}_2])$ (i.e. log of the rate of acid concentration change) against time shows a straight line with gradient = k' up to approx. 90% conversion. *(At this point, the line deviates slightly from linearity: this deviation indicates a rate slightly faster than that which would be expected at that concentration of remaining acid. This is thought to be due to in situ hydrolysis now competing, and thus replenishing the acid and so enhancing the rate of hydrogen evolution. Small temperature fluctuations whilst trying to maintain $-35\text{ }^{\circ}\text{C}$ are also possible.)* Three further repeats confirmed the result. Attempts to plot the data as 2nd order/zero order provided far inferior fits.

4.44 Trifluoroacetic acid in excess of base at low temp

Details: At $-35\text{ }^{\circ}\text{C}$ in a dry ice/acetone bath, manually controlled, 0.2 mmol CF₃COOH was added to MeCN (2.00 mL), 550 μL Et₃N ($\sim 4.0\text{ mmol} = \sim 20\text{ equiv}$) and 500 μL PhSiH₃ ($\sim 4.0\text{ mmol} = \sim 20\text{ equiv}$) and hydrogen evolution measured as a function of time.

Results: The rate of the reaction with trifluoroacetic acid, whilst in the presence of 20-fold excess base (acid limiting conditions), is ~ 20 times slower than acetic acid.

5. References

- 1 K. G. Andrews, D. M. Summers, L. J. Donnelly and R. M. Denton, *Chem. Commun.*, 2016, **52**, 1855–1858.
- 2 A. D. Kosal, E. E. Wilson and B. L. Ashfeld, *Angew. Chem. Int. Ed.*, 2012, **51**, 12036–12040.
- 3 Y. Kawagoe, K. Moriyama and H. Togo, *Tetrahedron*, 2013, **69**, 3971–3977.
- 4 B. Yao, C. Jaccoud, Q. Wang and J. Zhu, *Chem. Eur. J.*, 2012, **18**, 5864–5868.
- 5 M. O. Kitching, T. E. Hurst and V. Snieckus, *Angew. Chem. Int. Ed.*, 2012, **51**, 2925–2929.
- 6 P. Zhichkin, E. Kesicki, J. Treiberg, L. Bourdon, M. Ronsheim, H. C. Ooi, S. White, A. Judkins and D. Fairfax, *Org. Lett.*, 2007, **9**, 1415–1418.
- 7 S. Das, B. Join, K. Junge and M. Beller, *Chem. Commun.*, 2012, **48**, 2683–2685.
- 8 C. Mamat, A. Flemming, M. Köckerling, J. Steinbach and F. Wuest, *Synthesis*, 2009, **2009**, 3311–3321.
- 9 B. Zhang, P. Feng, Y. Cui and N. Jiao, *Chem. Commun.*, 2012, **48**, 7280–7282.
- 10 V. N. Britsun, A. N. Esipenko and M. O. Lozinskii, *Chem. Heterocycl. Compd.*, 2006, **42**, 396–402.
- 11 A. Orliac, D. Gomez Pardo, A. Bombrun and J. Cossy, *Org. Lett.*, 2013, **15**, 902–905.
- 12 X. Cui, Y. Zhang, F. Shi and Y. Deng, *Chem. Eur. J.*, 2011, **17**, 1021–1028.

- 13 G. A. Molander, T. Barcellos and K. M. Traister, *Org. Lett.*, 2013, **15**, 3342–3345.
- 14 C. M. Marson, U. Grabowska, A. Fallah, T. Walsgrove, D. S. Eggleston and P. W. Baures, *J. Org. Chem.*, 1994, **59**, 291–296.
- 15 P. Starkov and T. D. Sheppard, *Org. Biomol. Chem.*, 2011, **9**, 1320–1323.
- 16 L. Pasquinucci, O. Prezzavento, A. Marrazzo, E. Amata, S. Ronsisvalle, Z. Georgoussi, D.-D. Furla, G. M. Scoto, C. Parenti, G. Aricò and G. Ronsisvalle, *Bioorg. Med. Chem.*, 2010, **18**, 4975–4982.
- 17 S. Kushner, R. I. Cassell, J. Morton and J. H. Williams, *J. Org. Chem.*, 1951, **16**, 1283–1288.
- 18 W. A. Nack, G. He, S.-Y. Zhang, C. Lu and G. Chen, *Org. Lett.*, 2013, **15**, 3440–3443.
- 19 K. Kindler, B. Hedemann and E. Schärfe, *Justus Liebigs Ann. Chem.*, 1948, **560**, 215–221.
- 20 T. Maki, K. Ishihara and H. Yamamoto, *Org. Lett.*, 2006, **8**, 1431–1434.
- 21 I. Shiina and Y. Kawakita, *Tetrahedron*, 2004, **60**, 4729–4733.
- 22 D. Glynn, D. Bernier and S. Woodward, *Tetrahedron Lett.*, 2008, **49**, 5687–5688.
- 23 O. Itsenko, T. Kihlberg and B. Långström, *J. Org. Chem.*, 2004, **69**, 4356–4360.
- 24 S. Fuse, N. Tanabe and T. Takahashi, *Chem. Commun.*, 2011, **47**, 12661–12663.
- 25 D. T. S. Rijkers, H. P. H. M. Adams, H. C. Hemker and G. I. Tesser, *Tetrahedron*, 1995, **51**, 11235–11250.
- 26 A. Mahindra, K. Nooney, S. Uraon, K. K. Sharma and R. Jain, *RSC Adv.*, 2013, **3**,

16810–16816.

- 27 Us. Pat., DE3406416 (A1), 1984.
- 28 C. Li, E. A. Pace, M.-C. Liang, E. Lobkovsky, T. D. Gilmore and J. A. Porco, *J. Am. Chem. Soc.*, 2001, **123**, 11308–11309.
- 29 B. P. Bandgar and S. S. Sawant, *Synth. Commun.*, 2006, **36**, 859–864.
- 30 M. E. Rogers, R. A. Glennon, J. D. Smith, M. R. Boots, N. Nanavati, J. E. Maconaughey, D. Aub, S. Thomas, R. G. Bass and G. Mbagwu, *J. Med. Chem.*, 1981, **24**, 1284–1287.
- 31 S. Iwahana, H. Iida and E. Yashima, *Chem. Eur. J.*, 2011, **17**, 8009–8013.
- 32 A. Correa and C. Bolm, *Angew. Chem. Int. Ed.*, 2007, **46**, 8862–8865.
- 33 P. Strazzolini, N. Misuri and P. Polese, *Tetrahedron Lett.*, 2005, **46**, 2075–2078.
- 34 P. Morieux, C. Salomé, K. D. Park, J. P. Stables and H. Kohn, *J. Med. Chem.*, 2010, **53**, 5716–5726.
- 35 K. Thalluri, S. R. Manne, D. Dev and B. Mandal, *J. Org. Chem.*, 2014, **79**, 3765–3775.
- 36 J. Moineau, M. Granier and G. F. Lanneau, *Langmuir*, 2004, **20**, 3202–3207.
- 37 Y. Nakaido and T. Takiguchi, *J. Org. Chem.*, 1961, **26**, 4144–4145.

Chapter 3

Reductive Amination Reactions Using Carboxylic Acids

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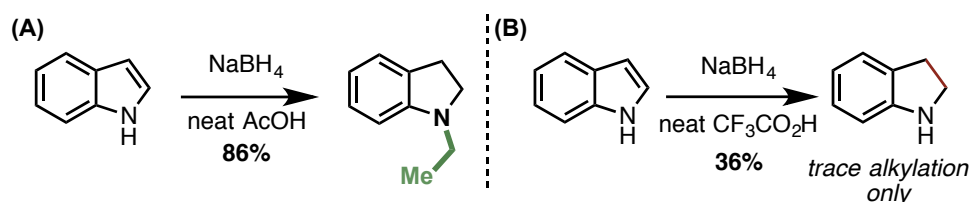
Reductive amination reactions of amines represent an essential tool in organic chemistry, and most practicing chemists associate the reaction with aldehydes and ketones. In this Chapter, we sought to challenge this status quo by expanding the term to include carboxylic acids, an altogether more challenging transformation that, at the outset of our work, represented a novel inception. The importance of this fundamental transformation is underscored by the fact that there are now no fewer than five reports, including our own, that use carboxylic acids in reductive amination reactions. Although all with their merits and limitations, it is the one-pot two-step approach described in this chapter that offers the unique possibility of tailoring conditions for substrates with variable, reducible extraneous functionality.

Catalytic reductive N-alkylation of amines using carboxylic acids: K. G. Andrews, D. M. Summers, L. J. Donnelly and R. M. Denton, *Chem. Commun.*, 2016, **52**, 1855–8.

Introduction

Reductive amination reactions using carboxylic acids

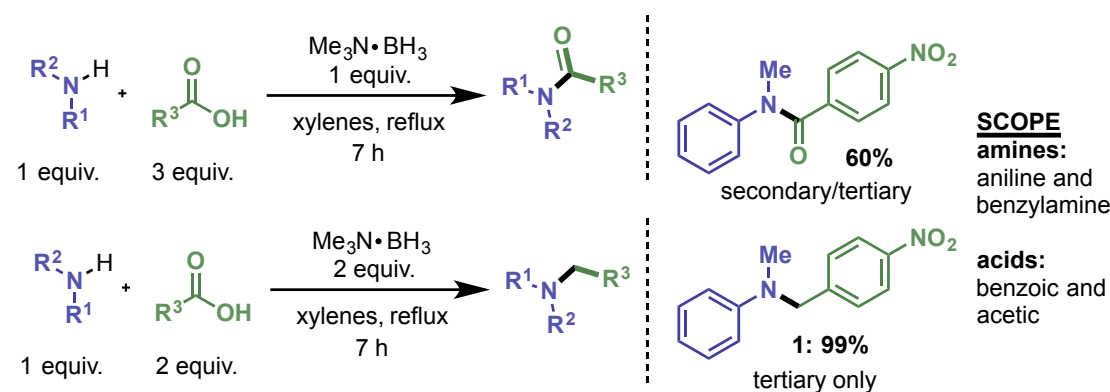
A direct reductive amination procedure using carboxylic acids and amines would constitute a powerful method. A wide range of carboxylic acids are available, and are significantly easier to store and handle than many aldehydes. Reducing carboxylic acids to aldehydes is non-trivial and is often performed by reduction to the alcohol and reoxidation, or by partial reduction of a Weinreb amide^{1,2} or thioester.³ There are very few reported attempts to perform reductive aminations directly on carboxylic acids. An early such attempt by Gribble required neat carboxylic acids as the solvent, and sometimes thermal-activation. The reduction was achieved using sodium borohydride, and was limited in scope. (Scheme 1).⁴



Scheme 1. Examples of reactions reported by Gribble, including a reductive amination of indole with acetic acid (A), and the failed attempt with trifluoroacetic acid (B).⁴

Soon afterwards, Liberatore and co-workers published their related studies.⁵ They measured three equivalents of hydrogen to be rapidly evolved upon mixing carboxylic acids and sodium borohydride, and a slower fourth equivalent, assigning the active species as sodium triacetoxyborohydride; related reactions rose to prominence following this work.^{6,7} Interestingly, this reagent is used in the classic reductive amination reaction, using *aldehydes*. It is worth noting at this point the similarity between the reaction of phenylsilane and carboxylic acids, and that of borohydride and carboxylic acids.

The only work of real note involving reductive aminations from carboxylic acids was published in 1983 by Trapani and co-workers. Primary and secondary amines react with carboxylic acids in the presence of trimethylamine-borane to give the amide if the reaction is performed with amine:borane:acid 1:1:3, whilst the amine is produced if the ratio is 1:2:2 (Scheme 2).⁸



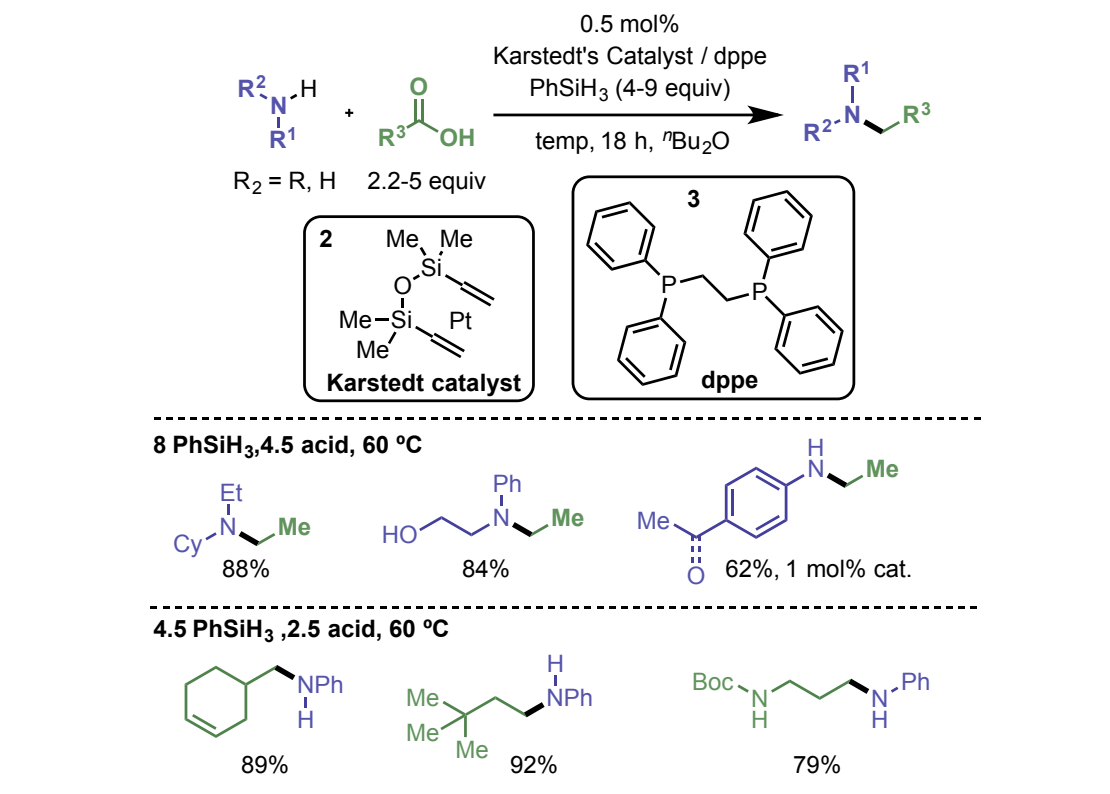
Scheme 2. Trapani's reductive alkylation of secondary amines (bottom). Reducing the tris(methylamine)borane loading gives amidation (top)⁸

Overalkylation prevents efficient synthesis of secondary amines using the amination method, but tertiary amines are accessed in good yields. The scope was not explored in depth, but a nitroaryl group (Scheme 2; **1**) survives unreduced. Although a boron activated acylating agent may form *in situ*, thermal amidation is also a possibility here, as the reaction runs at reflux in xylenes (bp ~ 140 °C). Formation and reduction of an amide is likely; borane is a known mediator of amide reductions. Cole-Hamilton and co-workers added an interesting but non-preparative report in 2007.⁹

A new generation of reductive amination reactions

As we explored the work to be presented here, a strongly related work was published by the group of Beller.¹⁰ Using phenylsilane (“as a terminal reductant”) in the presence of the commercially available Karstedt catalyst (**2**, [Pt(CH₂=CHSiMe₂)₂O]), the work describes the *N*-alkylation of amines with carboxylic acids. The reaction uses mild conditions

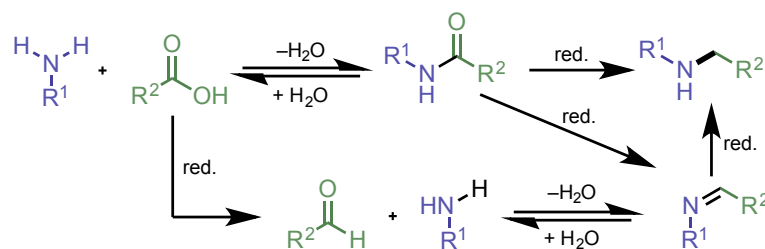
(although requires a Schlenk tube), tolerates a range of aliphatic, fluorinated and aromatic carboxylic acids and shows high selectivity for monoalkylation in the presence of a suitable ligand, dppe (**3**; bis(diphenylphosphino)ethane). Alcohols, esters, alkenes, ethers, BOC and CBz groups are tolerated, but ketones and amides are reduced (Scheme 3).¹⁰



Scheme 3. Beller's direct *N*-alkylation reaction between amines and carboxylic acids.¹⁰

Carboxylic acids have a limitation in this reaction manifold; they can only give rise to amines containing a methylene group alpha to nitrogen where the carbonyl existed; in reductive amination, use of a ketone allows mono α -substitution. In our own experience with phenylsilane-mediated amide couplings, anilines are relatively less reactive. So the high activity of anilines shown in the reaction by Beller suggests that the mechanism of the current reaction is likely aldehyde dominated, as proposed by the authors. Despite identifying amide products in the reaction mixture, Beller and co-workers did not mention the possibility of a (Pt catalyst-independent) phenylsilane-mediated amidation pathway at this time. Amides are shown to be reduced under the reaction conditions. Alcohols are also

identified (at room temperature), and the reaction relies on the trapping of aldehyde intermediates with amines to ensure product selectivity, as the alcohols represent a non-productive pathway. This explains the requirement for such large stoichiometries of sacrificial acid (2.2–5.0) and silane (4–9 equiv.). The authors' proposed mechanism is shown in Scheme 4.



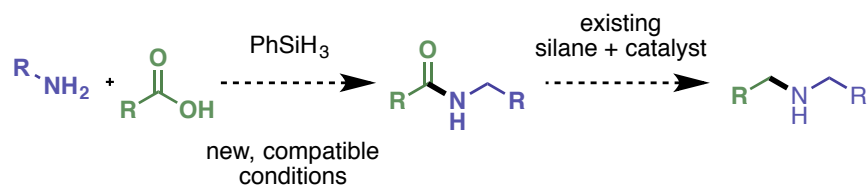
Scheme 4. Beller's proposed mechanism for the *N*-alkylation of amines using carboxylic acids.¹⁰

The mild conditions are beneficial in terms of suppressing the reduction of other functional groups, such as alkenes. It is evident that some substrate dependent condition tuning (equivalents, temperature) was required, reducing the off-the-shelf applicability of the method. The range of amines exemplified was limited, with no cyclic amines reported; whether this was due to the requirement for intricate reaction tuning is uncertain. Achieving the balance between reduction of the acid, imine formation from the aldehyde and subsequent reduction may have been difficult, with competing amidation and slow reduction a possible problem.

Since Beller's work in late 2014, along with the work we present in this chapter,¹¹ several other amination protocols have appeared, notably Fu and co-workers' report using the Piers borane,¹² another addition from Beller using hydrogen as the terminal reductant (which requires autoclave conditions),¹³ and Minakawa and co-workers' ruthenium-catalysed protocol.¹⁴ With the exception of Beller's initial report, these protocols are neither broad in their scope of viable amines (largely anilines), nor functional group tolerance. Fu and co-

workers have also used computational studies to try and understand their amination reaction;¹⁵ this report also omits mention of the base-catalysed silyl ester formation studied in depth in chapter 2 of this Thesis.

The reduction of imines/iminium ions – the (likely) prominent mechanism in the Beller reaction – represents one method of reductive amination. A second involves the reduction of *in situ* generated amides. At the time our work was completed, such combined methods of amidation and reduction did not exist to the best of our knowledge. However, a large number of silane-mediated reductions of amides had been recently reported. Whilst many amide coupling reactions leave reaction mixtures unsuitable for subsequent silane-mediated reactions, including those containing excesses of amines, acids, salts and reducible solvents, our modified Ruan amidation was developed specifically with subsequent reduction in mind. Our proposed one-pot reaction scheme is shown in Scheme 5.



Scheme 5. Proposed manifold for a novel reductive amination reaction between carboxylic acids and amines.

Importantly, due to its two-step nature, we expected over-alkylation would not occur. At the time of inception, this general manifold represented a novel protocol, although Beller published soon afterwards.¹⁰ Our two-phase amidation/reduction protocol, however, remains unique in its strategy at this point in time.

Silane-mediated amide reduction methodologies

Silane-mediated amide reduction methodologies are dependent on activation of the amide group, which is relatively inert with respect to borohydride or aluminohydride reduction,

compared to aldehydes, ketones and esters. This is indicative of the relative electrophilicity of the carbonyl centre with respect to hydride transfer. Amides, however, tend to be more Lewis basic through oxygen, due to nitrogen lone pair resonance. This means they are more susceptible to alkylative-activation at oxygen. Tertiary amides are not only more Lewis basic and easier to activate, they also produce a charged imidate species upon alkylation that is more easily reduced. Thus Lewis acids tend to be utilised for the goal of amide activation (Figure 1).

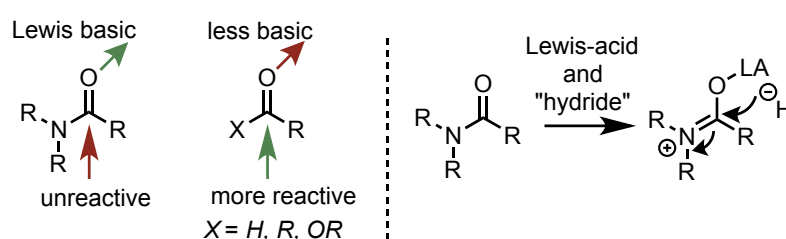
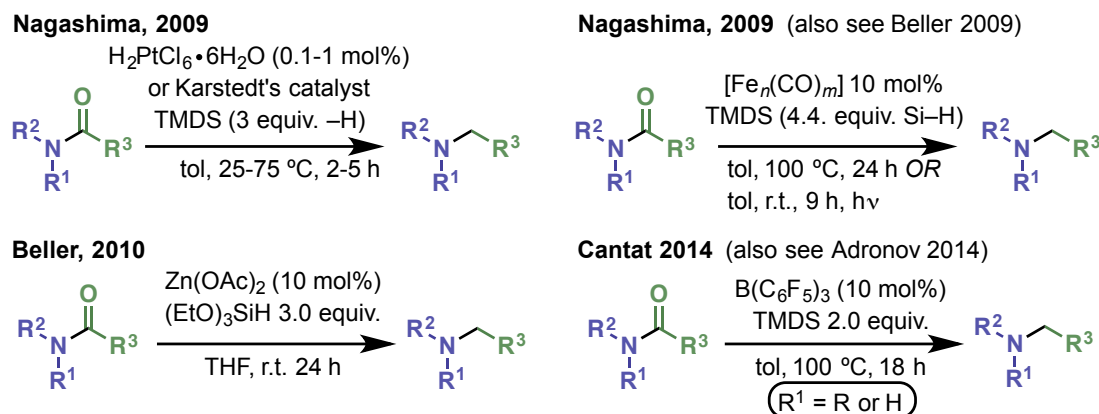


Figure 1. An approach to amide reduction involving Lewis acid activation

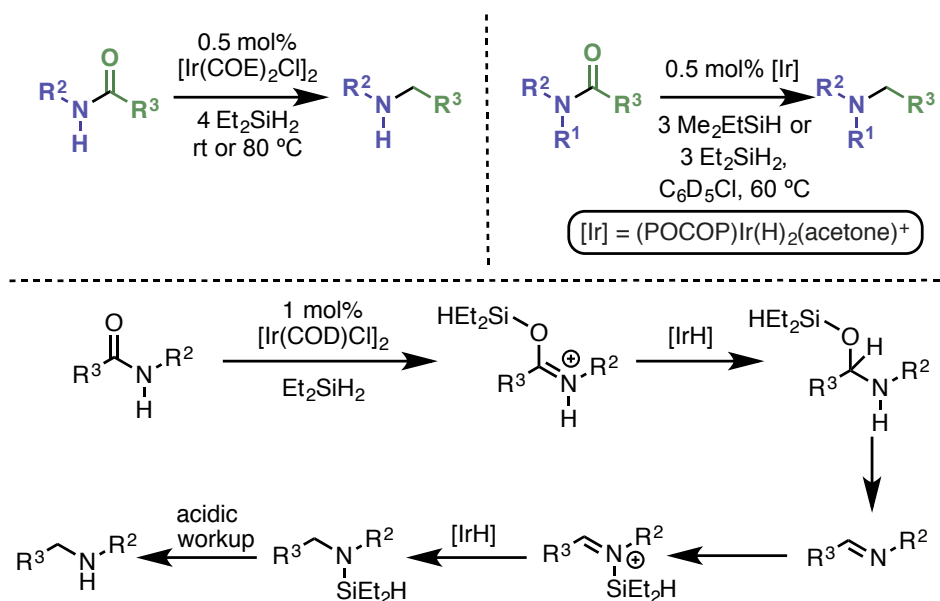
Typically, the Lewis-acid and reductant components are simply a silane, which is separated into H^- and $^+\text{SiR}_3$ groups by a metal catalyst. An early example was reported by Buchwald and co-workers, utilising stoichiometric $(^i\text{PrO})_4\text{Ti}$ and diphenylsilane.¹⁶ In this case, the reduction proceeds *via* the enamine, and yields aldehyde as the product. The group of Nagashima has been busy in this area utilising ruthenium complexes,^{17–20} and gives a excellent overview of the wider area up to 2009;²¹ titanium,²² rhodium,^{23,24} and molybdenum catalysts have all been utilised.²⁵ Subsequently, there have been many more procedures reported; a short review is available.²⁶ Nagashima's iron carbonyl catalyst can operate under thermal or photo-assisted conditions but showed limited functional group tolerance.²⁷ Beller and colleagues published shortly afterward with a very similar iron catalysed reaction, showing slightly wider tolerance.²⁸ A boronic acid catalyst showed excellent activity in conjunction with phenylsilane in reducing primary, secondary and tertiary amides using

phenylsilane.²⁹ Cantat and group used $B(C_6F_5)_3$ and TMDS as silane for secondary and tertiary benzamides using TMDS as the reductant, but aliphatic analogues were not exemplified.³⁰ Contemporarily, Adronov and co-workers demonstrated good activity with $B(C_6F_5)_3$ and TMDS, showing a similar scope.³¹ A representative selection of silane-mediated amide reduction methods is shown in Scheme 6.



Scheme 6. A representative selection of recently reported silane-mediated amide reduction methodologies.^{21,27,30,32}

Since we began working in this area, there have been tens of new reports of new amide reduction methodologies each year (a selection from 2015-16, published after our work was well underway.)³³⁻⁴³ At the time, however, the most compatible procedures were considered to be Beller's zinc catalysed methodology (Scheme 6, above), or that of Brookhart and co-workers (Scheme 7 below).^{44,45} Beller's zinc methodology (first reported with $ZnCl_2$ by Calas in the 1960s)⁴⁶ was briefly examined (and has since been explored more widely within our group, with the benefit of the additional work presented in chapter 2 to guide its progress).^{32,47} At the time, however, initial results suggested Brookhart's methodology would be suitable. The reaction utilises $[Ir(COE)_2Cl]_2$ or $(POCOP)Ir(H)_2(acetone)^+$ and Et_2SiH_2 or Me_2EtSiH in solvents similar to toluene, and suggests selectivity between secondary and tertiary amides, so we began exploring the possibility of combining this reaction with our new amidation conditions (Chapter 2).



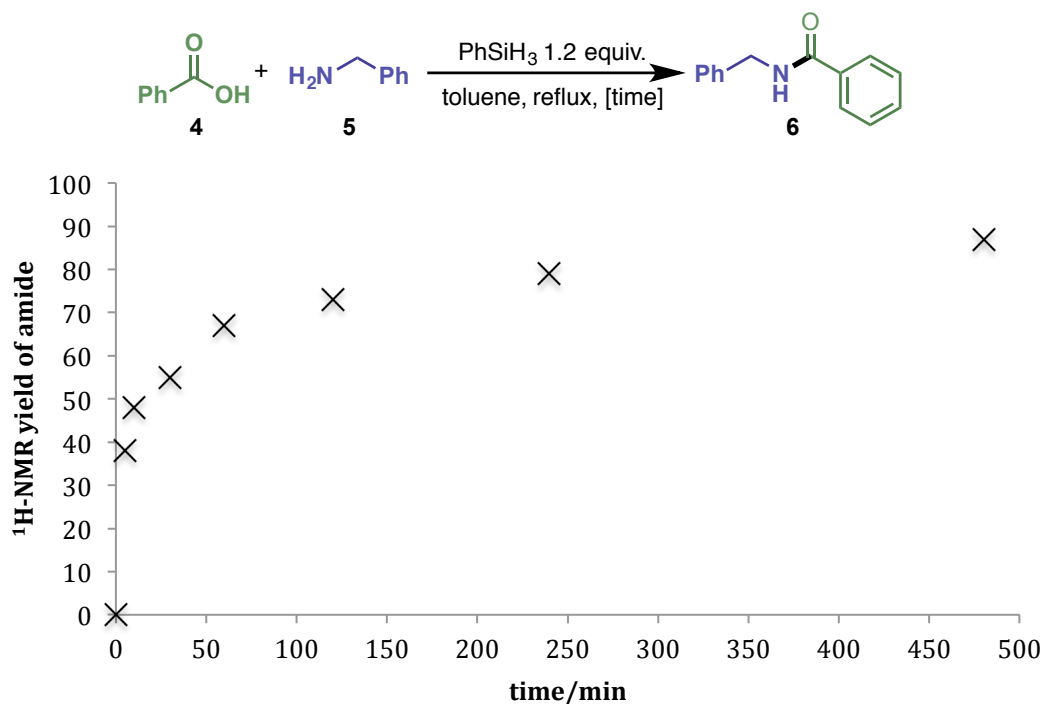
Scheme 7. Brookhart's recently reported amide reduction methodologies, with proposed mechanistic outline.^{44,45}

Results and Discussion

Development of a One-Pot Reductive Amination Reaction

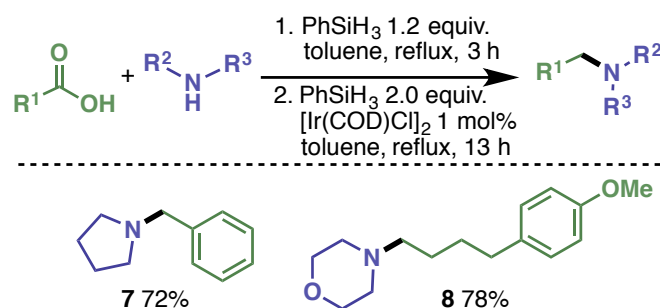
The proposed reaction involves the silane-mediated *in situ* formation of amide, followed by reduction. This would ensure primary amines were not susceptible to double alkylation. To identify the ideal reaction time before the catalyst was to be added, we monitored the amidation reaction of benzoic acid **4** and benzylamine **5** to give amide **6** by ^1H -NMR spectroscopy (Figure 2). The reaction rate began to plateau after about three hours, so we began by allowing a 3 h amidation period. To this reaction was added 1 mol% $[\text{Ir}(\text{COD})\text{Cl}]_2$ and further phenylsilane (2 equivalents), and the reaction allowed to heat for 13 h.

Figure 2. Conversion to amide with respect to time under the developed amidation conditions



^aEach reaction carried out individually (to prevent destruction of sensitive species) with benzoic acid (0.19 mmol), benzylamine (0.16 mmol) and phenylsilane (0.19 mmol) in toluene (0.5 mL) at reflux. The reaction was quenched with ethanol (2 mL) after the specified time and concentrated and the yield of amide was determined by $^1\text{H-NMR}$ relative to tetrachloroethane as internal standard.

We began with secondary amines, which would give more readily reducible (more Lewis-basic) tertiary amides. This approach proved successful, with tertiary amines **7** and **8** formed in good yield (Scheme 8).

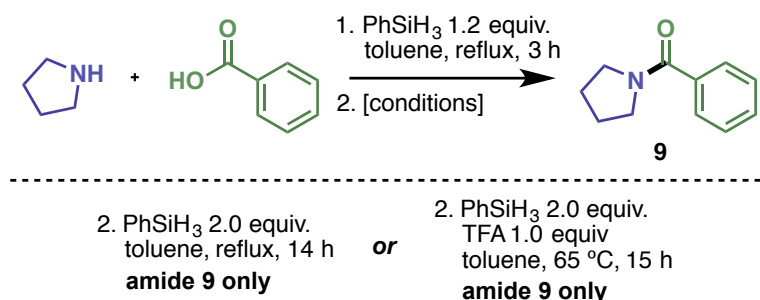


Scheme 8. Proof-of-principle of a one-pot reductive amination reaction of secondary amines and carboxylic acids.

Note that our reductive procedure differs from the original Brookhart procedure in two ways. Firstly, we use $[\text{Ir}(\text{COD})\text{Cl}]_2$ instead of $[\text{Ir}(\text{COE})_2\text{Cl}]_2$, although this alteration is not

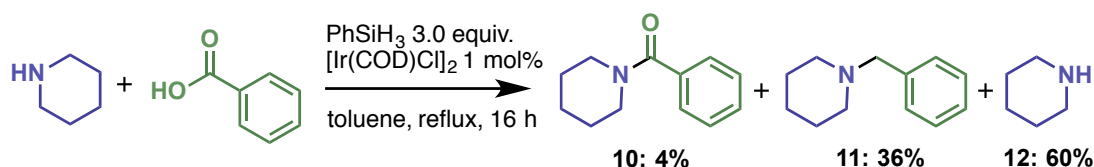
expected to have much of an effect. Indeed, Brookhart and co-workers demonstrated that this catalyst was active under their own conditions. However the use of phenylsilane, significantly cheaper and easier to handle than the originally-used, volatile, diethylsilane, is novel to this reaction. Indeed, Brookhart's procedure was exemplified for secondary amides, whilst this procedure concerns tertiary amides.

Next, we demonstrated the requirement for a catalyst. In the absence of iridium, only amide was formed when further phenylsilane was added after 3 h. Likewise, in the presence of a strong Lewis acid, trifluoroacetic acid (TFA), shown to play a potentially privileged role in silane-based reactions (see section 3.7 and Chapter 4), no reduction was observed (Scheme 9).



Scheme 9. In the absence of catalyst, reduction is not observed. Acidic conditions (TFA, 1 equiv.) do not aid reduction either.

A further experiment suggested that adding the catalyst from the start of the reaction was not conducive to an efficient reaction (Scheme 10).



Scheme 10. The reaction was not efficient in a single step in which the catalyst was present from the start of the reaction.

Next, the reaction times and the equivalents of acid were explored briefly in an optimisation process using tetrahydroisoquinoline (less volatile than the previous amines examined) and

benzoic acid. The process included a brief amidation optimisation process, as secondary amines had been shown to be poorer substrates under the originally optimised amidation conditions (Table 1).

Table 1. Initial optimisation experiments of the amination reaction to ascertain regimes worthy of further exploration

Entry	amidation phase			reduction phase			Amide 13 (%)	Amine 14 (%)
	Acid Eq.	PhSiH ₃ Eq.	time/h	cat %	PhSiH ₃ Eq.	time/h		
1	2.0	1.0	15	-	-	-	80	n/a
2	1.5	1.0	3	-	-	-	92	n/a
3	1.5	1.2	3	1%	2.0	3.0	0	76
4	1.2	0.7	15	-	-	-	75	n/a
5	1.0	0.7	15	-	-	-	84	n/a
6	1.0	0.7	15	1%	1.0	3.0	50	50

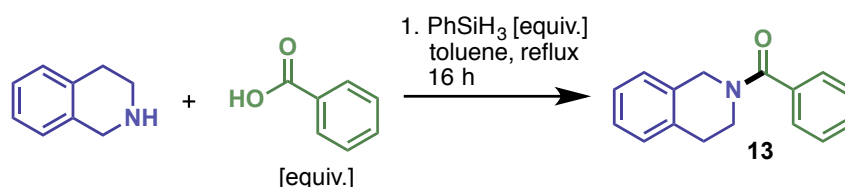
^aEach reaction carried out with 1 equiv. amine (0.16 mmol) in toluene (0.35 mL) at reflux. The reaction was concentrated and the product ratio was determined by ¹H-NMR relative to 1,1,2,2-tetrachloroethane as internal standard.

The ratio of silane to acid required balancing for efficient amidation (entries 4 and 5). Entry 3 indicates that the reduction time can be lowered to 3 h, whilst entry 6 suggests that 1.0 equivalent of reductive silane is insufficient, although this may be due to partial consumption for remaining amidation in this case.

At this point, the project was explored further within the group; some of the following results are adapted from the report of Declan Summers' Masters Research Project, which was undertaken under the supervision of this author.⁴⁸ We first explored in more detail the conversion to amide under varying ratios of silane and amide. The results were in good

agreement with the previous data, and suggested that entry 6 was the optimum ratio of acid:phenylsilane for the initial amidation of secondary amines (Table 2).

Table 2. Focused amidation step optimisation.



Entry	Acid Eq.	PhSiH ₃	Amide %
1	1.0	0.7	79
2	1.2	0.7	78
3	1.5	0.7	87
4	1.0	1.0	87
5	1.2	1.0	88
6	1.5	1.0	95

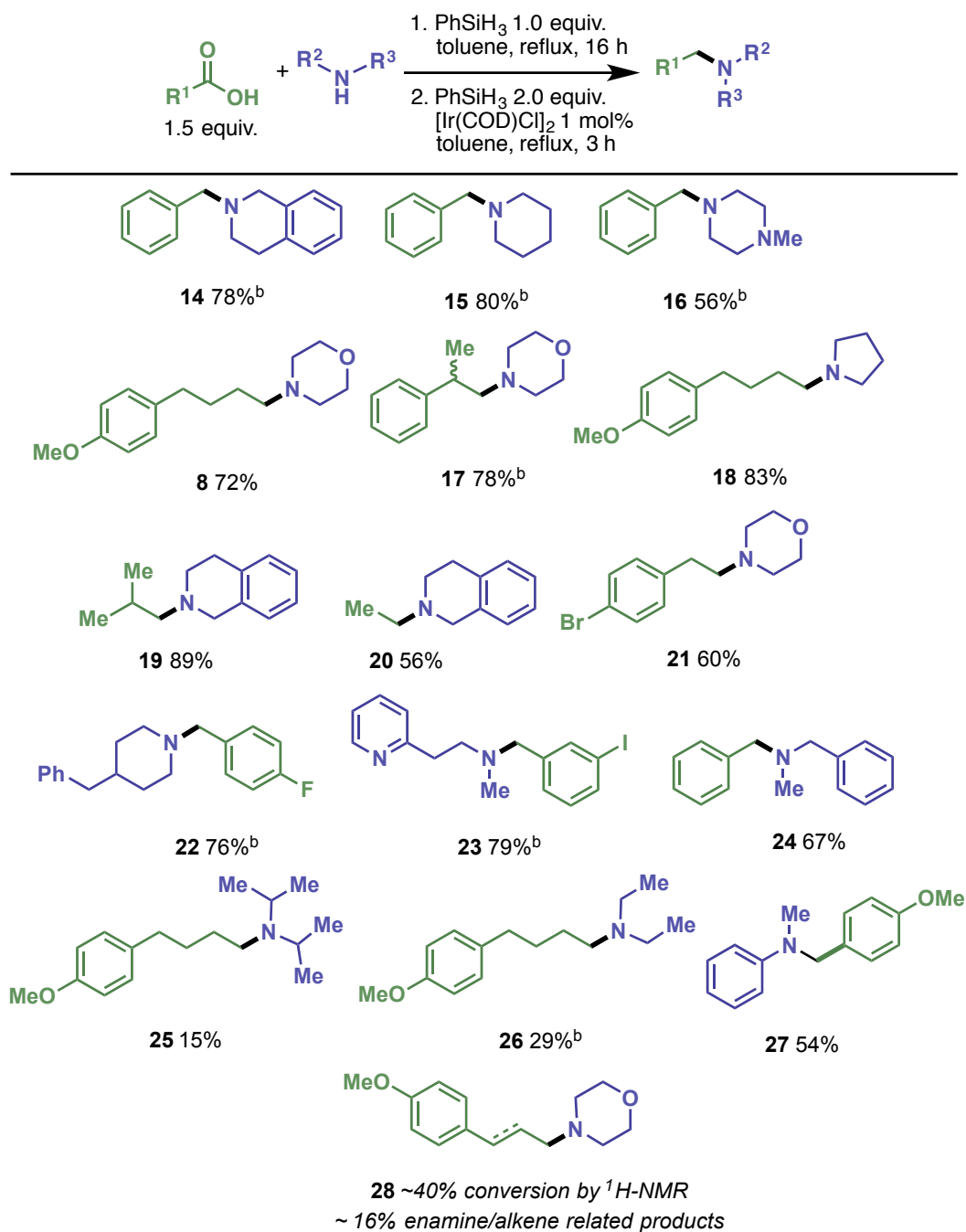
^aData taken from D. Summers' Masters project report. All reactions were carried out on a 0.16 mmol scale with respect to 1,2,3,4-tetrahydroisoquinoline with 0.2 mL of toluene as reaction solvent. After 16 h, the reaction was concentrated and conversion to the amide was measured by ¹H-NMR spectroscopy using 0.08 mmol of 1,1,2,2-tetrachloroethane as an internal standard.

These amidation conditions were combined with the previously optimised reduction conditions; 1 mol% [Ir(COD)Cl]₂, phenylsilane (2.0 equiv.) over 3 h at reflux to give the final conditions. These conditions were used to explore the scope of tertiary reductive aminations (Figure 3) (Andrews, Summers, Donnelly).¹¹

The reaction proceeds with both aromatic (**14-16**) and aliphatic (**17-22**, **25-26**) acids, with cyclic amines, both basic (e.g. **15**) and deactivated systems (**16-18**). Of interest are the pharmaceutically relevant small amines, such as morpholine. Likewise, low molecular weight aliphatic acids (**20-21**) are excellent substrates for capping amines; the related aldehydes are potentially less desirable to handle due to volatility (and odour). In the case of

25 and **26**, the steric hindrance is believed to retard both the amidation and reduction steps, although we have shown that amidation is yield limiting in these cases.

Figure 3. Scope of the reductive alkylation reaction of secondary amines and carboxylic acids

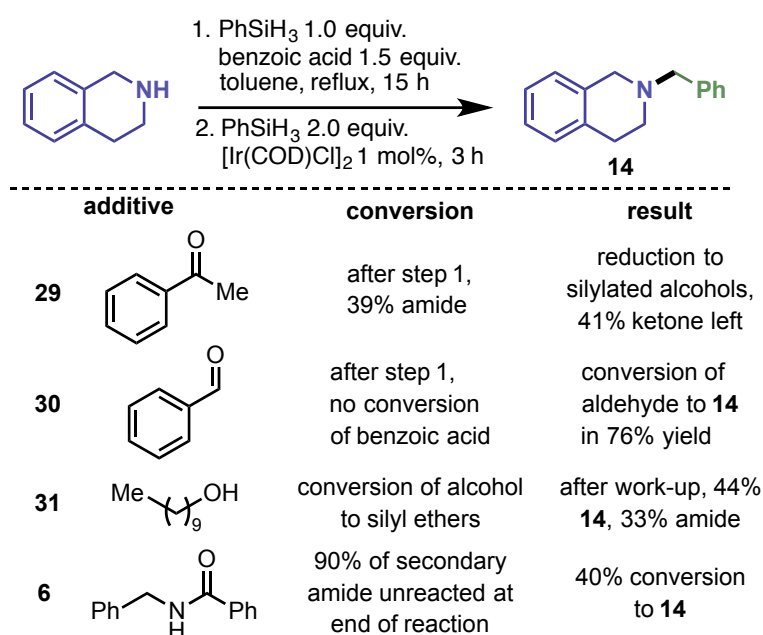


^aAll reactions were carried out on a 0.5 mmol scale with respect to starting amine, reactions were carried out in 0.6 mL of solvent. Reactions purified via an acid/base work up. ^bReaction further purified via flash column chromatography. (compounds **15**, **16**, **17**, **18**, **20**, **25**, **26** synthesised by D. Summers).

Trans-cinnamic acid was tested to probe the tolerance of alkene functionality, however some reduction of the alkene was observed (**28**). It is uncertain at this point whether reduction of the conjugated iminium is the cause,³⁰ or whether reduction of the alkene in the product/starting acid with iridium hydride species is to blame, although non-conjugated alkenes were not tolerated either. Methylaniline underwent alkylation in a moderate yield to give amine **27**. Unfortunately, a range of reducible groups such as nitriles, nitro groups, esters, and alkenes were poorly tolerated.

Some additives were included in the standard reaction to observe their behaviour (Scheme 11). Perhaps unsurprisingly, ketone **29** was largely reduced under the conditions. Aldehyde **30** underwent reductive amination and decanol (**31**) was silylated under the reaction conditions with only 44% of the desired amine recovered. Secondary amide **6** largely survived reduction, but again only 40% of the desired amine was formed.

Scheme 11. An equivalent of various additives were included in the standard alkylation to probe their tolerance to the reaction conditions

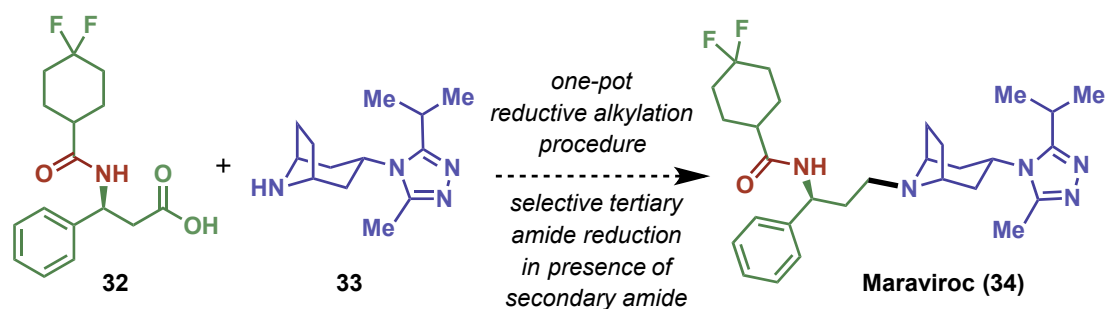


^aall reactions were carried out on a 0.5 mmol scale with respect to amine with 0.6 mL of toluene as reaction solvent. Reactions carried out by L. Donnelly.

To conclude this section; it is clear that the amination procedure holds promise, and that for many substrates the reaction works well. A benefit over classical reductive amination with aldehydes in terms of purification is that excess acid is easily removed from the reaction mixture by base-washing. Unreacted amine may be problematic (true of the aldehyde protocol too), but most of the starting amine will at least reach the amide, which is easier to separate. Functional group tolerance is clearly the most problematic aspect of the reaction, but some more interesting scope is discussed later (*vide infra*).

Attempts to exemplify the synthesis of API Maraviroc

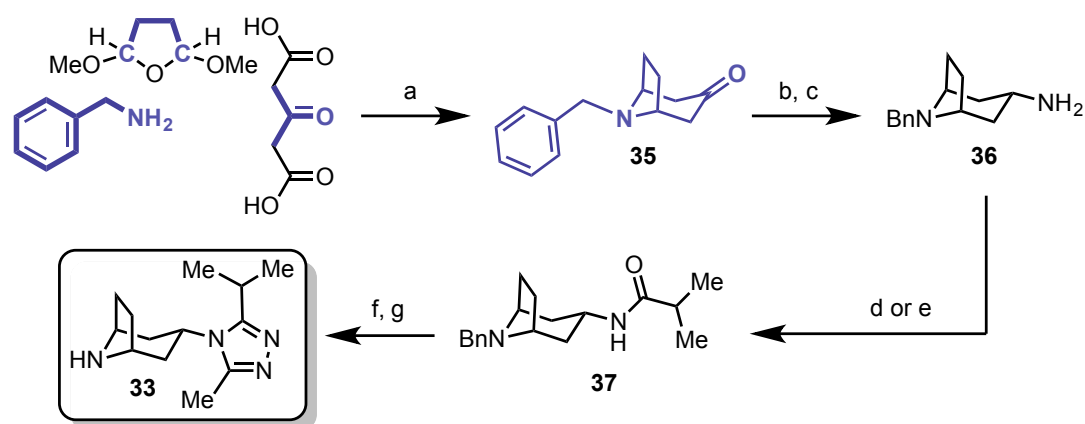
Maraviroc **10**, a drug used in HIV-1 therapy, is a cell-entry inhibitor that targets the CCR5 receptor.^{49,50} We decided to incorporate our new synthesis method into the synthesis of this pharmaceutically relevant material in order to probe its applicability. We hoped to exemplify the bond formation shown in Scheme 12, which requires the reductive alkylation of a hindered secondary amine **8** with an aliphatic carboxylic acid **9**, in the presence of a secondary amide and a triazole unit.



Scheme 12. Proposed bond disconnection using the new reductive amination procedure to synthesis Maraviroc.

Thus the proposed coupling is ambitious in terms of exemplification. The disconnection would allow a late stage incorporation of a library of left-hand-side groups with, for example, variation at the phenyl group. Typically, this coupling requires oxidation state manipulation, from ester to alcohol and then aldehyde, in the presence of the secondary amide, or

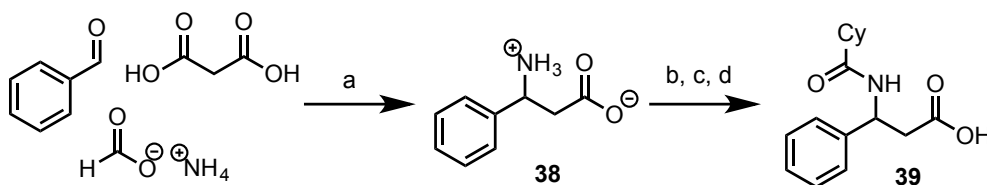
protected amine, followed by a reductive amination. We hoped to couple the acid directly, and secure a selective reduction of the tertiary amide. The amine fragments were synthesised by D. Summers within the group according to the procedure in Scheme 13. Amine/carbonyl chemistry assembles the tropanone ring of **35**, which is converted to the oxime and reduced with sodium giving high selectivity to the equatorial primary amine **36**. This amine is converted to amide **37** before a dehydration reaction, trapping with acetic hydrazide and dehydrative cyclisation occur to give the triazole; the benzyl group is finally removed to give amine **33**.



Scheme 13. Synthetic route to amine fragment **33**

(a) (i) $\text{HCl}_{(\text{aq})}$, r.t., 24 h, (ii) $\text{NaOAc}_{(\text{aq})}$, 50 °C, 3 h, 47%; (b) $\text{NH}_2\text{OH}\cdot\text{HCl}$, Py., EtOH, 85 °C, 16 h, 94%; (c) Na-Metal, EtOH, 120 °C, 16 h, 90%; (d) isobutyric acid, PhSiH_3 , toluene, 110 °C, 16 h, 35%; (e) isobutyric acid chloride, K_2CO_3 , dichloromethane/ H_2O , r.t., 4 h, 84%; (f) (i) PCl_3 , CH_2Cl_2 , r.t., 2 h. (ii) AcNHNH_2 , tert-amyl alcohol, dichloromethane, r.t., 16 h. (iii) AcOH , EtOAc, 80 °C, 4 h, 30%; (g) Pd/C 10%. H_2 , MeOH. r.t., 4 d, 70%.

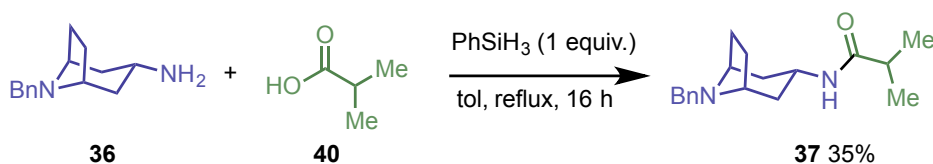
In the case of the second fragment, the difluoromethylene group was omitted and the synthesis was made racemic to give a suitable model acid **39** (Scheme 14). The sequence again starts with basic amine/carbonyl chemistry to yield the β -amino acid **38**, which is protected as its ethyl ester and amidated, and finally deprotected to give acid **39**, a model fragment for **32**.



Scheme 14. Synthetic route to amine fragment 33

(a) EtOH, reflux, 16 h. (b) SOCl₂, EtOH, r.t., 16 h. (c) Cyclohexane carbonyl chloride, K₂CO₃, dichloromethane/H₂O, r.t., 16 h. 9% over 3 steps; (d) LiOH, THF/H₂O, r.t., 3 h. 68%.

A full discussion of the synthesis of these fragments is given in the primary source.⁴⁸ Of note was the low-yielding attempted phenylsilane-mediated amidation step in the triazole fragment, step d, to give **13** (Scheme 15).

Scheme 15. Attempted phenylsilane mediated amidation of isobutyric acid and tropanone-derived amine **36**.

This was a surprising result, as aliphatic acids (e.g. acetic acid) tend to couple easily with primary amines, and so a series of experiments were performed to explore the reason for the low conversion to amide. As the acid had previously been shown to give high conversions (with a secondary amine) we explored the role of tertiary amine present in **36** (Table 3). Entries 1–3 (Table 3) once again showed the importance of acid to silane ratio. In terms of the current study, what is more interesting is the apparently inhibitive effect of additional equivalents of amine. Addition of triethylamine to the reaction resulted in an approximately one third decrease in conversion to amide (entry 4). Additional cyclohexylamine had a similar effect (entry 6). Interestingly, comparing entry 1 to 3 suggests that this might be a more general effect, which is dependent on the ratio of acid, amine and silane.

Table 3. Investigation into the role of acid:amine stoichiometry on the yield of amide

Entry	Acid Eq.	Amine Eq.	TEA Eq.	PhSiH ₃	Amide 42 (%)
1	2.0	1.0	-	2.0	73
2	1.0	1.0	-	1.5	63
3	2.0	1.0	-	1.5	97
4	2.0	1.0	1.0	1.5	61
5	1.0	1.0	-	0.75	60
6	1.0	2.0	-	0.75	45
7	1.0	1.0	1.0	0.75	45

^aAll reactions were carried out by D. Summers on a 0.16 mmol scale with respect to cyclohexylamine with 0.2 mL of toluene as reaction solvent. After 16 h, the reaction was concentrated and conversion to the amide was measured by ¹H-NMR spectroscopy using 0.08 mmol of 1,1,2,2-tetrachloroethane as an internal standard.

We next conducted a study examining whether there was a correlation between conversion to amide and basicity of additional amines present (Table 4).

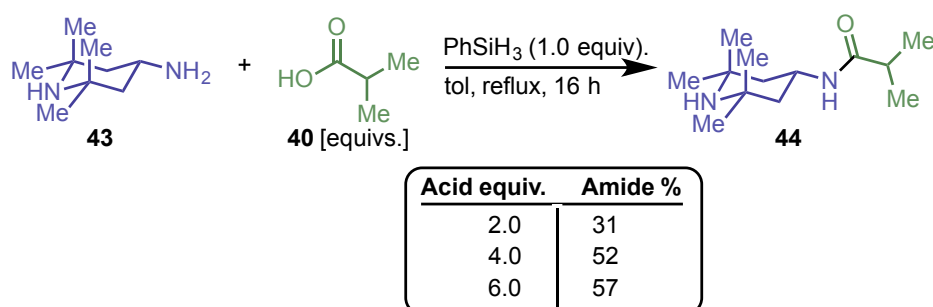
Table 4. The effect of amine additive basicity on yield of amide

Entry	amine	pK _a H	Amide %
1	2,2,6,6-tetramethylpiperidine	11.1	52
2	TEA	9.0	61
3	pyridine	5.2	68
4	pyrazine	0.6	62

^aAll reactions were carried out by D. Summers on a 0.16 mmol scale with respect to cyclohexylamine with 0.2 mL of toluene as reaction solvent. After 16 h, the reaction was concentrated and conversion to the amide was measured by ¹H-NMR spectroscopy using 0.08 mmol of 1,1,2,2-tetrachloroethane as an internal standard.

With the exception of pyrazine (entry 4), the bases in entries 1-3 showed a reasonable trend of increasing yield as basicity decreased. Under the same conditions minus the extra base

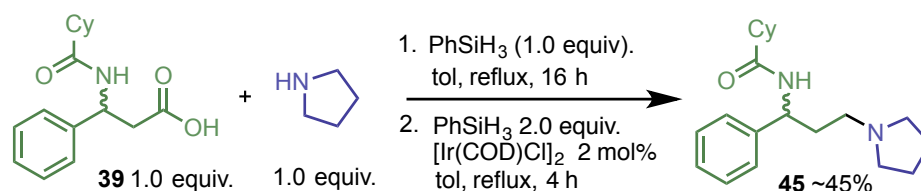
(*vide supra*, entry 3, Table 3), 97% amide was formed. Although the pyrazine result remains unexplained, there is otherwise a possible correlation between pK_aH of the amine additive, and conversion to amide. Such a correlation was also noted in Chapter 2. It was possible to increase the conversion to amide by increasing the equivalents of acid (Scheme 16), although the above experiments do not rule out thermal amidation, which tends to be faster for aliphatic acids.



Scheme 16. The additional of excess acid reverses the negative effect of addition basic nitrogen atoms.

The inhibitive effect of too much amine led to the mechanistic work already presented in Chapter 2, which suggested that the role of reasonably acidic by-product silanols might destroy silyl esters in the presence of strong base. Such an effect would be increased for reactions in which amidation was slow. Excess base would accelerate the reaction of silanols with silyl esters, destroying key reactive intermediates. Alternatively, the amines may be sequestered as silanamines, also potentially catalysed by the presence of stronger bases. As previously mentioned, preforming the silyl esters should help to improve the competition in favour of amidation – later results within the group have confirmed this. This concludes the presentation of supporting data from Declan Summers' Master's Report.⁴⁸

With the required fragments in hand, it was now possible for us to explore the key-coupling step in the synthesis of Maraviroc **34**. We began by exploring the selectivity of the amide reduction step with pyrrolidine as a surrogate amine (Scheme 17).



Scheme 17. Attempt at selective amine formation in the presence of a secondary amide in a trial coupling of Maraviroc-like fragments

Preliminary results suggest an un-optimised ~45% conversion to the desired secondary amide/tertiary amine **43** using pyrrolidine as amine. The hindered amine **33** in Maraviroc was less reactive; it was suggested that future studies might be based around the preformation of silyl esters before reactive amine addition. Indeed, such an approach has subsequently been developed in the group by Tom Tongue, and is now operating well to give a selective reduction of tertiary amides in the presence of secondary species. Synthesis of Maraviroc remains difficult, however, due to low-yielding amidation in the key-coupling step.

Summary of Part I

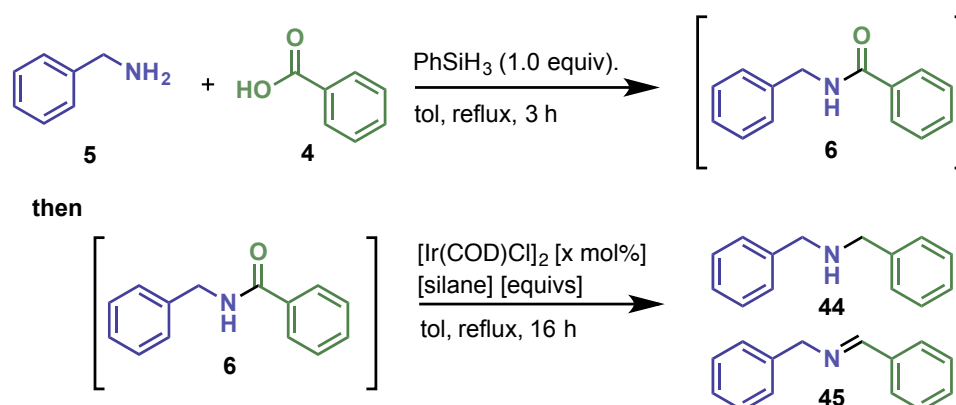
We have developed a direct reductive alkylation of secondary amines with carboxylic acids. The reaction operates as a one-pot procedure, amidation followed by reduction, and uses a commonly used iridium catalyst and phenylsilane as coupling agent and hydride source. In its present form, we believe this to be the first example of this approach. The procedure requires far fewer equivalents of silane and acid compared to the related existing methodology reported by Beller, although the yields are slightly lower. The reaction is particularly successful for low molecular weight acids and amines, including cyclic, pharmaceutically relevant amines such as morpholine, which were not exemplified in Beller's report. In our attempts to exemplify the synthesis of Maraviroc, we revealed several further clues about the amidation reaction manifold, which have been discussed in Chapter 2.

Additionally, we have begun to explore the key step, and have currently demonstrated a synthetically useful tolerance of secondary amides during the synthesis of tertiary amines, something that Beller's protocol does not offer.

The Reductive Alkylation of Primary Amines

Whilst the approach to tertiary amines proceeded smoothly using phenylsilane as reductant in the presence of iridium, secondary amines were not amenable to this approach. Thus an extensive optimisation process was undertaken using benzoic acid and benzylamine, using Brookhart's originally reported reagent, diethylsilane (Table 5).⁴⁵

Table 5. Initial attempts at the reductive amination reaction between carboxylic acids and primary amines



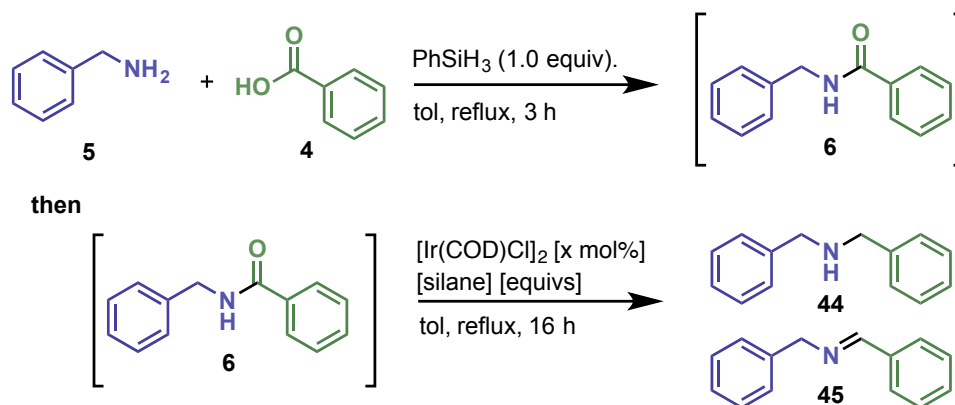
Entry	Cat mol%	Reductive Silane	Eq.	Temp °C	6 %	45 %	44 %
1	1	Et ₂ SiH ₂	4	RT	59	12	30
2	1	Et ₂ SiH ₂	4	80	–	44	66
3	1	PhSiH ₃	2	80	major		
4	2	Et ₂ SiH ₂	4	80	–	20	80
5	2	PhSiH ₃	2	80	70		30
6	2	Et ₂ SiH ₂	5	RT		major	
7	4	PhSiH ₃	2	110-80	75	5	20
8	1	Et ₂ SiH ₂ (2) PhSiH ₃ (2)		110	–	66	33

^aAll reactions were carried out on a 0.16 mmol scale with respect to amine with 0.35 mL of toluene as reaction solvent. After the required time, the reaction was quenched with methanol, concentrated and conversion to the amide was measured by ¹H-NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard.

At room temperature, the reduction step was incomplete (entry 1). At 80 °C, no amide remained, but reduction of the imine was incomplete (entry 2). Brookhart and co-workers were able to isolate imine as the major product by lowering the catalyst loading, time and temperature, indicating that reduction of amide to imine is rapid, whilst reduction of imine to amine is slower. This is because the imine needs to be activated by silylation before reduction can take place, and is apparently less Lewis-basic than the amide, potentially due to the difference between the affinity of oxygen and nitrogen for silicon. Likewise, this is likely to be why phenylsilane is a poorer silane in this chemistry (entry 3, 5, 7); this silyl group is more amenable to various substitution reactions, making it a poorer activation group (i.e. the silylimines formed may be decomposed before reduction can occur, or PhSiH_3 may be less stable when activated by iridium). Entry 6, in which the reaction was allowed to cool after catalyst addition, showed that temperature was required to reduce the imine. Note that diethylsilylamines are the product under strictly anhydrous conditions;⁴⁵ a methanol quench is used to cleave these in the above reactions. The most successful conditions were entry 4, which were taken forward to further optimisation (Table 6).

At 80 °C, it was difficult to ensure 100% imine reduction (entries 2-5), so the reaction temperature was increased to 110 °C. At these temperatures, it was possible to bring the time down to two hours, and the equivalents of diethylsilane down to 3 equivalents (entry 10). The amidation time could also be brought down to two hours and still achieve a reasonable conversion (entries 9-10), although clearly the amount of amide present at this time is lower (recall Figure 2). The catalyst loading needed to be 3 mol% to ensure complete imine reduction. The amidation phenylsilane equivalents were successfully brought down to 0.75 (entry 10).

Table 6. Focused optimisation of the reductive amination reaction

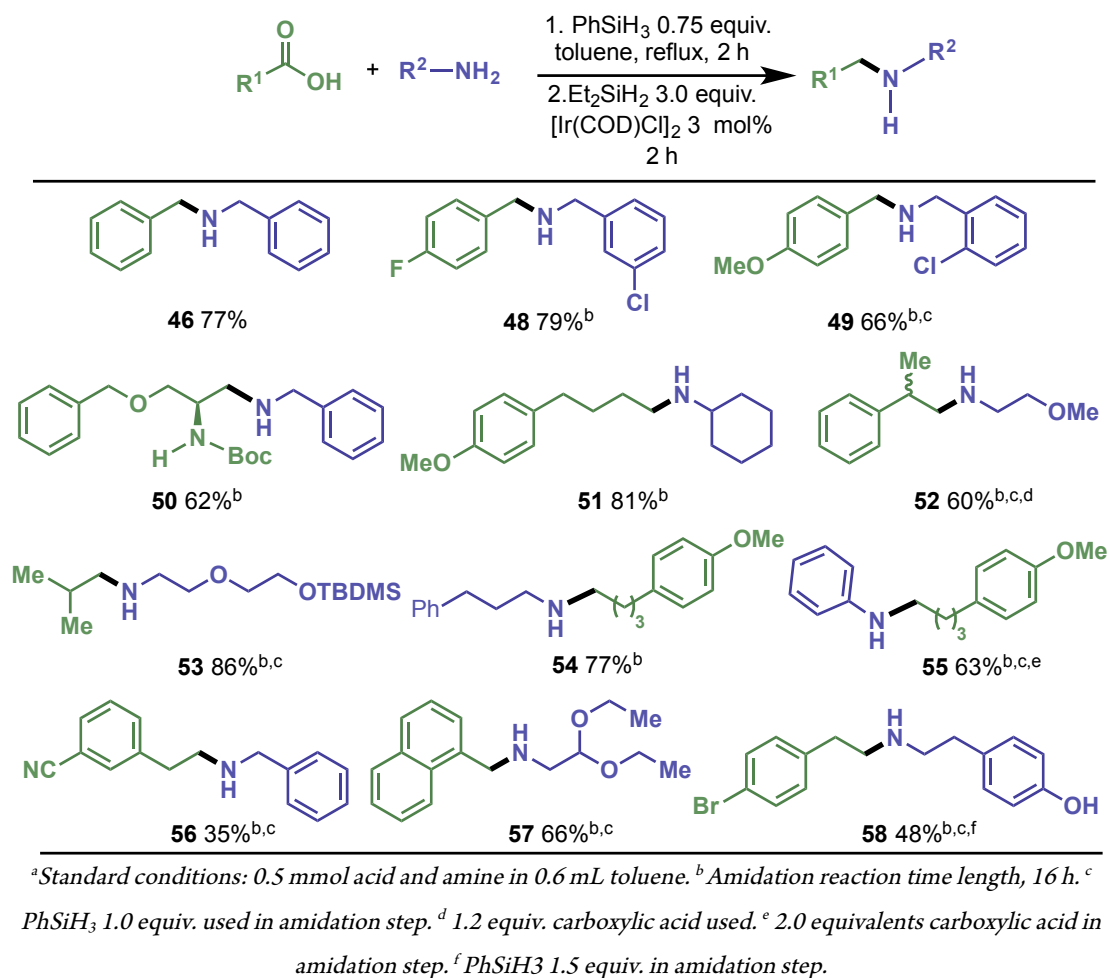


Entry	amid. time/h	cat. mol%	Et_2Si H_2 eq.	time /h	temp / $^\circ\text{C}$	45 %	44 %
1	3	2.0	4.0	16	110	25	75
2	3	3.0	4.0	16	80	<5	>95
3	3	4.0	4.0	16	80	<5	>95
4	3	3.0	5.0	16	80	<5	>95
5	3	2.5	5.0	16	80	10	90
6	3	3.0	4.0	1	110	10	90
7	3	3.0	4.0	3	110	<5	>95
8	3	3.0	4.0	2	110	-	64 isol
9	2	3.0	4.0	2	110	-	70 isol
10 ^b	2	3.0	3.0	2	110	-	77 isol

^aAll reactions were carried out on a 0.16 mmol scale with respect to amine with 0.35 mL of toluene as reaction solvent. After the required time, the reaction was concentrated and conversion to the amide was measured by ¹H-NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. ^b0.75 equiv. PhSiH_3 used in amidation step.

With this data in hand, we proceeded to explore the scope of the reductive alkylation of primary amines with carboxylic acids (Figure 4). The procedure works well with (moderately) electron poor and electron rich aromatic acids (**46-49**), and tolerates aryl-halides (**48-49**). Aliphatic acids are similarly as effective (**51-56**), even with hindering alpha substitution (**52**). Less basic amines are also tolerated (**52**). Of high interest is the tolerance of BOC-protected amines, allowing the preparation of differentially protected amines (**50**), and of differentially substituted 1,2-diamines directly from amino acids.

Figure 4. Scope of the reductive amination reaction between carboxylic acids and primary amines



It was necessary to increase the amidation reaction time in a number of cases to ensure sufficient amide formation. Non-conjugated alkenyl and alkynyl carboxylic acids substrates were tested, but significant reduction of the pi-system was observed in both cases. TBS groups (**53**) and acetals (**57**) both survived the conditions. Nitro and ester groups were once again not tolerated. Nitriles were poor substrates in the amination reaction (only 35% of amine **56** was isolated). The problem arises in the reduction step, as nitriles are tolerated in the amidation reaction. Phenol **58** likely becomes silylated during the reaction, but a basic work-up allows the free phenol to be recovered.

Whilst the scope here is of more interest than that demonstrated in the synthesis of tertiary amines, there are still clearly limitations. Nonetheless, the approach to synthesising amines represents a new tool for synthesis chemists, and reveals a new manifold that will no doubt become better developed as more selective catalyst conditions are discovered. The scope for trapping partially reduced intermediates with nucleophiles is exemplified in a recent disclosure from the Dixon group.⁵¹

Chapter Summary

Primary and secondary amines undergo a reductive amination reaction with carboxylic acids, first in the presence of phenylsilane as an acylating agent, with a second reductive step with an iridium catalyst and further silane as a hydride source. The reaction represents the first two-step, one-pot amidation/reduction sequence of its type. Compared to contemporaneously published efforts using silanes and a catalyst to perform this transformation, the reaction is not exceptional in its tolerance to other reductively labile groups, but does not require Schlenk conditions or suffer from over-alkylation due to its two-step nature. This approach reduces the equivalents of acid and silane required for good conversions to product, as no sacrificial reagents are required to make up for competing processes.

Perhaps more importantly, the novel approach to the reaction means that the protocol will be easily amendable to cheaper silanes and catalysts for the reduction step, which may be mixed and matched for different substrates. This should allow the tolerance of many reducible functional groups, and therefore expand the scope of the protocol. The benefits of using carboxylic acids over aldehydes for these transformations include the large range of acids commercially available, as well as their easier handling and storage requirements.

References

- 1 S. Nahm and S. M. Weinreb, *Tetrahedron Lett.*, 1981, **22**, 3815–3818.
- 2 Y.-H. Wang, J.-L. Ye, A.-E. Wang and P.-Q. Huang, *Org. Biomol. Chem.*, 2012, **10**, 6504–6511.
- 3 T. Fukuyama, S. C. Lin and L. Li, *J. Am. Chem. Soc.*, 1990, **112**, 7050–7051.
- 4 G. W. Gribble, P. D. Lord, J. Skotnicki, S. E. Dietz, J. T. Eaton and J. Johnson, *J. Am. Chem. Soc.*, 1974, **96**, 7812–7814.
- 5 P. Marchini, G. Liso, A. Reho, F. Liberatore and F. Micheletti Moracci, *J. Org. Chem.*, 1975, **40**, 3453–3456.
- 6 G. W. Gribble and D. C. Ferguson, *J. Chem. Soc. Chem. Commun.*, 1975, 535–536.
- 7 G. W. Gribble, *Org. Process Res. Dev.*, 2006, **10**, 1062–1075.
- 8 G. Trapani, A. Reho and A. Latrofa, *Synthesis*, 1983, **1983**, 1013–1014.
- 9 A. A. Núñez Magro, G. R. Eastham and D. J. Cole-Hamilton, *Chem. Commun.*, 2007, 3154–3156.
- 10 I. Sorribes, K. Junge and M. Beller, *J. Am. Chem. Soc.*, 2014, **136**, 14314–14319.
- 11 K. G. Andrews, D. M. Summers, L. J. Donnelly and R. M. Denton, *Chem. Commun.*, 2016, **52**, 1855–1858.
- 12 M.-C. Fu, R. Shang, W.-M. Cheng and Y. Fu, *Angew. Chem. Int. Ed.*, 2015, **54**, 9042–9046.
- 13 I. Sorribes, J. R. Cabrero-Antonino, C. Vicent, K. Junge and M. Beller, *J. Am. Chem.*

- Soc.*, 2015, **137**, 13580–13587.
- 14 M. Minakawa, M. Okubo and M. Kawatsura, *Tetrahedron Lett.*, 2016, **57**, 4187–4190.
- 15 Q. Zhang, M.-C. Fu, H.-Z. Yu and Y. Fu, *J. Org. Chem.*, 2016, **81**, 6235–6243.
- 16 S. Bower, K. A. Kreutzer and S. L. Buchwald, *Angew. Chem. Int. Ed.*, 1996, **35**, 1515–1516.
- 17 H. Sasakuma, Y. Motoyama and H. Nagashima, *Chem. Commun.*, 2007, 4916–4918.
- 18 S. Hanada, T. Ishida, Y. Motoyama and H. Nagashima, *J. Org. Chem.*, 2007, **72**, 7551–7559.
- 19 Y. Motoyama, K. Mitsui, T. Ishida and H. Nagashima, *J. Am. Chem. Soc.*, 2005, **127**, 13150–13151.
- 20 K. Matsubara, T. Iura, T. Maki and H. Nagashima, *J. Org. Chem.*, 2002, **67**, 4985–4988.
- 21 S. Hanada, E. Tsutsumi, Y. Motoyama and H. Nagashima, *J. Am. Chem. Soc.*, 2009, **131**, 15032–15040.
- 22 K. Selvakumar, K. Rangareddy and J. F. Harrod, *Can. J. Chem.*, 2004, **82**, 1244–1248.
- 23 R. Kuwano, M. Takahashi and Y. Ito, *Tetrahedron Lett.*, 1998, **39**, 1017–1020.
- 24 T. Ohta, M. Kamiya, M. Nobutomo, K. Kusui and I. Furukawa, *Bull. Chem. Soc. Jpn.*, 2005, **78**, 1856–1861.
- 25 A. C. Fernandes and C. C. Romão, *J. Mol. Catal. A Chem.*, 2007, **272**, 60–63.

- 26 D. Addis, S. Das, K. Junge and M. Beller, *Angew. Chem. Int. Ed.*, 2011, **50**, 6004–6011.
- 27 Y. Sunada, H. Kawakami, T. Imaoka, Y. Motoyama and H. Nagashima, *Angew. Chem. Int. Ed.*, 2009, **48**, 9511–9514.
- 28 S. Zhou, K. Junge, D. Addis, S. Das and M. Beller, *Angew. Chem. Int. Ed.*, 2009, **48**, 9507–9510.
- 29 Y. Li, J. A. Molina de La Torre, K. Grabow, U. Bentrup, K. Junge, S. Zhou, A. Brückner and M. Beller, *Angew. Chem. Int. Ed.*, 2013, **52**, 11577–11580.
- 30 E. Blondiaux and T. Cantat, *Chem. Commun.*, 2014, **50**, 9349–9352.
- 31 R. C. Chadwick, V. Kardelis, P. Lim and A. Adronov, *J. Org. Chem.*, 2014, **79**, 7728–7733.
- 32 S. Das, D. Addis, S. Zhou, K. Junge and M. Beller, *J. Am. Chem. Soc.*, 2010, **132**, 1770–1771.
- 33 A. Volkov, F. Tinnis, T. Slagbrand, P. Trillo and H. Adolfsson, *Chem. Soc. Rev.*, 2016, **45**, 6685–6697.
- 34 N. Nakatani, J. Hasegawa, Y. Sunada and H. Nagashima, *Dalton Trans.*, 2015, **44**, 19344–19356.
- 35 S. Das, Y. Li, C. Bornschein, S. Pisiewicz, K. Kiersch, D. Michalik, F. Gallou, K. Junge and M. Beller, *Angew. Chem. Int. Ed.*, 2015, **54**, 12389–12393.
- 36 S. Das, Y. Li, L.-Q. Lu, K. Junge and M. Beller, *Chem. Eur. J.*, 2016, **22**, 7050–7053.
- 37 X. Cui, Y. Li, C. Topf, K. Junge and M. Beller, *Angew. Chem. Int. Ed.*, 2015, **54**,

- 10596–10599.
- 38 Y. Ogiwara, T. Uchiyama and N. Sakai, *Angew. Chem. Int. Ed.*, 2016, **55**, 1864–1867.
- 39 T. V. Q. Nguyen, W.-J. Yoo and S. Kobayashi, *Adv. Synth. Catal.*, 2016, **358**, 452–458.
- 40 F. Tinnis, A. Volkov, T. Slagbrand and H. Adolfsson, *Angew. Chem. Int. Ed.*, 2016, **55**, 4562–4566.
- 41 F. D. Bobbink, S. Das and P. J. Dyson, *Nat. Protoc.*, 2017, **12**, 417–428.
- 42 P.-Q. Huang, Q.-W. Lang and Y.-R. Wang, *J. Org. Chem.*, 2016, **81**, 4235–4243.
- 43 Q.-W. Lang, X.-N. Hu and P.-Q. Huang, *Sci. China Chem.*, 2016, **59**, 1638–1644.
- 44 S. Park and M. Brookhart, *J. Am. Chem. Soc.*, 2012, **134**, 640–53.
- 45 C. Cheng and M. Brookhart, *J. Am. Chem. Soc.*, 2012, **134**, 11304–11307.
- 46 R. Calas, *Pure Appl. Chem.*, 1966, **13**, 61–80.
- 47 S. Das, D. Addis, K. Junge and M. Beller, *Chem. - A Eur. J.*, 2011, **17**, 12186–12192.
- 48 D. Summers, University of Nottingham, 2015.
- 49 S. J. Haycock-Lewandowski, A. Wilder and J. Åhman, *Org. Process Res. Dev.*, 2008, **12**, 1094–1103.
- 50 M. Roche, H. Salimi, R. Duncan, B. L. Wilkinson, K. Chikere, M. S. Moore, N. E. Webb, H. Zappi, J. Sterjovski, J. K. Flynn, A. Ellett, L. R. Gray, B. Lee, B. Jubbs, M. Westby, P. A. Ramsland, S. R. Lewin, R. J. Payne, M. J. Churchill and P. R. Gorry, *Retrovirology*, 2013, **10**, 43–62.

- 51 Á. L. Fuentes de Arriba, E. Lenci, M. Sonawane, O. Formery and D. J. Dixon, *Angew. Chem. Int. Ed.*, 2017, **56**, 3655–3659.

Chapter 3

Experimental Section

Contents

1. General Information.....	213
2. Experimental Details	213
2.01 Amide formation as a function of time (Figure 2).....	213
2.02. Initial general procedure for the one pot (amidation/reduction) reductive amination of carboxylic acids and secondary amines (Scheme 8)	213
2.03 Reductive Alkylation of Secondary Amines with carboxylic acids (Table 1)	215
2.04 One-pot procedure experiment (Scheme 10).....	215
2.05 General procedure for secondary amine amidation test reactions (Table 2)	216
3. Alkylation of Secondary Amines with Carboxylic Acids	216
3.01 General Procedure (Figure 3).....	216
3.02 Scale-up reaction protocol: Gram scale synthesis of 23 (Figure 3)	218
3.03 Additional functional group tolerance experiments (Scheme 11).....	219
3.04 Data and specific experimental details for tertiary amines (8,14-27)	219
3.05 Maraviroc Details (Schemes 12-17, Tables 3-4)	226
4. Reductive alkylation of primary amines with carboxylic acids	226
4.01 Optimisation details (Table 5, 6).....	226
4.02 General procedure for the reductive alkylation of primary amines with carboxylic acids (Figure 4)	227
4.03 Reductive alkylation under non-inert conditions (Figure 4)	228
4.04 Data and specific experimental details for secondary amines 46, 48-58	229
5. References	237

1. General Information

See Chapter 1.

2. Experimental Details

2.01 Amide formation as a function of time (Figure 2)

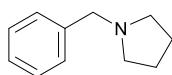
Benzoic acid (19.5 mg, 0.190 mmol) was dissolved in toluene (0.5 mL) and the reaction heated to reflux (oil bath at 116 °C). Added was benzylamine (17.5 μ L, 0.160 mmol) and phenylsilane (23.7 μ L, 0.190 mmol) and the reaction stirred for the allotted time before quenching with ethanol (2 mL) and cooling rapidly to room temperature. The reaction was concentrated and the conversion to amide deduced by comparison to 1,1,2,2-tetrachloroethane as an internal standard in chloroform.

Entry	Time (min)	Amide NMR yield (%)
1	5	38
2	10	48
3	30	55
4	60	67
5	120	73
6	240	79
7	480	87

2.02. Initial general procedure for the one pot (amidation/reduction) reductive amination of carboxylic acids and secondary amines (Scheme 8)

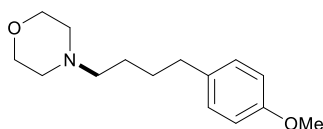
A flask fitted with a water condenser and an argon balloon was charged with acid (0.6 mmol). Toluene (1.5 mL) was added and the solution heated to reflux with stirring before adding phenylsilane (0.6 mmol) and finally the amine (0.5 mmol). After 3 h, $[\text{Ir}(\text{COD})\text{Cl}]_2$ (5 μmol , 1 mol%) was added along with phenylsilane (1 mmol) and the reaction refluxed over 13 h. After this time, the reaction was cooled concentrated and taken up in ethyl acetate (15 mL). The organics were extracted with HCl (3 x 20 mL of a 1M aqueous solution) and the combined aqueous fractions basified to > pH10 *via* portion-wise addition of solid sodium carbonate. The aqueous was extracted with dichloromethane (3 x 20 mL), the combined organics dried (MgSO_4) and concentrated *in vacuo* to give the amine.

1-benzylpyrrolidine¹ (7)



Purified by method D to give a pale yellow oil (59 mg, 73%). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.56 - 7.13 (m, 5H), 3.62 (s, 2H), 2.61 - 2.38 (m, 4H), 1.87 - 1.67 (m, 4H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 139.3, 128.9, 128.2, 126.8, 60.7, 54.1, 23.4; **HRMS** (ESI⁺): Exact mass calcd for $\text{C}_{11}\text{H}_{16}\text{N}_1$ $[\text{M}+\text{H}]$, 162.1277. Found 162.1269, $\sigma = 0.0065$; **IR** (cm^{-1}) (CDCl_3) 2968, 2798, 1454, 1131.

4-(4-(4-methoxyphenyl)butyl)morpholine (8)



Purification 2: Product was isolated as a yellow oil (81 mg, 71%). $^1\text{H NMR}$ (270 MHz, CDCl_3): 7.14 - 7.01 (m, 2H), 6.90 - 6.74 (m, 2 H), 3.78 (s, 3H), 3.69 (m, 4H), 2.55 (t, $J = 7.4$ Hz, 2H), 2.47 - 2.37 (m, 4H), 2.38 - 2.30 (m 2H) 1.69 - 1.44 (m, 4 H); $^{13}\text{C NMR}$ (68

MHz, CDCl₃): 157.7, 134.5, 129.2, 113.7, 67.0, 59.0, 55.2, 53.8, 34.9, 29.5, 26.1; **IR** (CDCl₃) ν (cm⁻¹): 3010, 2938, 1612, 1513, 1466, 1245, 1178, 1116, 1036; **HRMS** (ESI⁺): Exact mass calculated for C₁₅H₂₃NO₂ [M+H] 250.1762. Found: 250.1824.

2.03 Reductive Alkylation of Secondary Amines with carboxylic acids (Table 1)

Optimisation: Data given in the main text. A flask fitted with a water condenser and an argon balloon was charged with acid (0.16 mmol = 1 equiv.). Toluene (0.35 mL) was added and the solution heated to reflux with stirring before adding phenylsilane (various equiv.) and finally the amine (0.16 mmol). After the stated time, [Ir(COD)Cl]₂ (various mol%) was added along with phenylsilane (various equiv.) by temporary removal of the condenser and addition, and the reaction refluxed again for the stated time. After this time, the reaction was cooled concentrated and the conversion calculated by comparison to an added internal standard (tetrachloroethane) by ¹H-NMR in chloroform.

2.04 One-pot procedure experiment (Scheme 10)

Benzoic acid (23.4 mg, 0.19 mmol) was suspended in toluene (0.2 mL) and the solution was heated to reflux (110 °C) before phenylsilane (59 μ L, 0.48 mmol) and piperidine (15.8 μ L, 0.16 mmol, 1 equiv.) were added; upon the addition of amine, gas evolved rigorously from the reaction mixture. After 2 min, [Ir(COD)Cl]₂ (1 mg, 5 μ mol, 1 mol%) was added. The reaction was stirred at reflux for 16 h before concentration and ¹H-NMR analysis using 1,1,2,2-tetrachloroethane as internal standard. Piperidine was the major amine containing product indicating that a one pot procedure was unlikely to be viable as the amidation pathway was being shut down.

2.05 General procedure for secondary amine amidation test reactions (Table 2)

Benzoic acid (various equiv.) was suspended in toluene (0.2 mL) and the solution was heated to reflux (110 °C) before phenylsilane (various equiv.) and 1,2,3,4-tetrahydroisoquinoline (0.16 mmol) were added; upon the addition of amine, gas evolved rigorously from the reaction mixture. The reaction was stirred at reflux for 15 h. After this time the reaction was cooled to room temperature and the solvent removed *in vacuo*. 1,1,2,2-tetrachloroethane (0.08 mmol) was then added to the reaction and the conversion of starting material to amide was deduced by integrating the product to the 1,1,2,2-tetrachloroethane internal standard peak in the ¹H-NMR spectrum, which characteristically appears as a singlet at 5.95 ppm in CDCl₃.

3. Alkylation of Secondary Amines with Carboxylic Acids

3.01 General Procedure (Figure 3)

An oven-dried 10 mL round-bottom flask fitted with a water condenser and an argon balloon was charged with carboxylic acid (0.75 mmol). Anhydrous toluene (0.6 mL) and phenylsilane (0.50 mmol) were added and the flask incubated in an oil bath at 111-115 °C to dissolve the acid (if required/possible). On a small scale, the amine (0.50 mmol) was then added carefully by temporary removal of the condenser, generally accompanied by the vigorous release of hydrogen gas. *Note that at smaller scales, the amine can be added to the (almost) refluxing solution; for larger scale reactions a large volume of hydrogen is released, and it is preferable to remove the reaction from the heat and add the amine portionwise at a lower temperature.* After 15 h at reflux, [Ir(COD)Cl]₂ (5.0 μmol, 1 mol%)

and then further phenylsilane (1.00 mmol) were added by temporary removal of the condenser, and the reaction mixture was stirred at reflux for 3 h.

After this time toluene was removed *in vacuo* and the residue was dissolved in ethyl acetate (7.5 mL). The organic layer was extracted with 3 M aq. hydrochloric acid (3 x 5.0 mL) and the combined acid washings were basified (pH ~ 9) with 6 M aq. sodium hydroxide with ice-bath cooling. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic layer dried over magnesium sulfate and concentrated *in vacuo* to give the crude product. (If the product contains sensitive or acidic or basic groups, the reaction should be worked-up omitting the acid/base washes as necessary.)

Purification 1: The crude product was dry loaded onto silica and purified by Flash column chromatography (pentane/ethyl acetate) to give the product. **Purification 2:** Excess amine was removed *in vacuo* and no further purification was required. **Purification 3:** For amines with poor aqueous solubility (i.e. poor extraction efficiency into aqueous acid), the general work-up was modified as follows: The concentrated reaction mixture was dissolved in ethyl acetate (7.5 mL). The solution was washed with 1 M aq NaOH (2 x 10 mL). The organic layer was retained and purified by flash column chromatography after drying over MgSO₄.

Reaction Notes: The reaction is best performed from the free base. The amine and acid can be combined first, before adding the silane last to initiate the reaction. The room temperature combination of acid and amine in toluene sometimes this leads to a salting out of the ammonium carboxylate which may hinder the reaction efficiency, however successful reactions have been performed in this way. In an amidation test reaction (0.16 mmol), the conversion to product dropped from 93% to 87% when the reaction was performed under

an air atmosphere (open condenser), in undried glassware and in Winchester-grade toluene (see section 2.2 in this document). In these cases it may be helpful to increase the silane loading by ~0.1 equivalents to consume the excess moisture. Hindered amides can benefit from increasing the reduction time to 4 h.

Chromatography notes: (Basic) amines may streak during chromatography. Two mitigating strategies used here are: a) running the column with 0.1-1% Et₃N in all eluent, and: b) pretreating the silica (column and/or dry-loading) with triethylamine prior to chromatography. For the latter, the following protocol was used: Silica was slurried in ethyl acetate and added was ~2 mL triethylamine/8 g silica and the slurry stirred for 15 min. The silica was filtered and washed with ethyl acetate and then petrol or pentane. The silica was then slurried as per normal in the column solvent.

3.02 Scale-up reaction protocol: Gram scale synthesis of 23 (Figure 3)

An oven-dried 25 mL round-bottom flask fitted with a water condenser and an argon balloon was charged with carboxylic acid (1.86 g, 7.50 mmol). Anhydrous toluene (6.0 mL) and phenylsilane (620 µL, 5.00 mmol) were added and the flask incubated in an oil bath at 111-115 °C to dissolve the acid, which appeared to be only partially soluble. The reaction was removed from the heat and allowed to cool partially. **CAUTION:** To the reaction was added portionwise (to maintain a manageable level of hydrogen gas evolution) *via* microsyringe by temporary partial removal of the condenser the amine (692 µL, 5.00 mmol). Adding the amine caused the undissolved acid to dissolve as well as copious vigorous hydrogen gas evolution. Upon completion of addition, the reaction was returned to the heat and visually monitored for 5 minutes; the subsequent hydrogen evolution remained steady and controlled. After 15 h at reflux, the reaction was removed from the

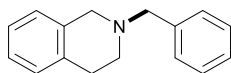
heat temporarily and $[\text{Ir}(\text{COD})\text{Cl}]_2$ (50 μmol , 1.0 mol%) and then further phenylsilane (1.24 mL, 10.0 mmol) added by temporary removal of the condenser. The reaction mixture was stirred at reflux for 3 h further. The reaction was then cooled and quenched with 1 M NaOH, leading to further hydrogen evolution. The reaction was diluted with dichloromethane and the organic layer separated. The aqueous layer was acidified and re-extracted into dichloromethane to recover the unreacted carboxylic acid. (In this case, some silanol was present in the mixture. Dissolving this mixture in ethyl acetate and extracting the carboxylic acid with sodium carbonate instead of hydroxide before acidification and re-extraction with dichloromethane yielded pure carboxylic acid, as judged by ^1H -NMR and ^{13}C -NMR (0.55 equivalents, 0.68 g)). To obtain the amine, the initial organic layer was extracted with 3 x 1 M HCl solution, the combined aqueous layers basified to $\sim$ pH 10 cautiously with 6 M NaOH with cooling in an ice bath and the desired amine extracted into dichloromethane (x3), washed with brine, dried over magnesium sulfate and concentrated. The crude mixture was purified further by chromatography (see example **3e** below) to remove a bright yellow impurity and yield the amine as a pale yellow oil (1.4 g, 79%).

3.03 Additional functional group tolerance experiments (Scheme 11)

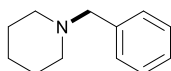
All reactions performed as per the general reaction, and analysed by ^1H -NMR with 1,1,2,2-tetrachloroethane as internal standard.

3.04 Data and specific experimental details for tertiary amines (8,14-27)

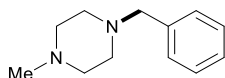
All compounds synthesized using the general procedure for tertiary amine production (above) unless stated otherwise.

2-benzyl-1,2,3,4-tetrahydroisoquinoline (14)²

Purification 1. Product was isolated as a pale yellow oil (87 mg, 78% yield). **¹H NMR** (400 MHz, CDCl₃): 7.42 – 7.38 (m, 2H), 7.37 – 7.31 (m, 2H), 7.31 – 7.26 (m, 1H), 7.15 – 7.07 (m, 3H), 7.01 – 6.96 (m, 1H), 3.70 (s, 2H), 3.64 (s, 2H), 2.91 (t, *J* = 5.9 Hz, 2H), 2.76 (t, *J* = 5.9 Hz, 2H); **¹³C NMR** (101 MHz, CDCl₃): 137.1, 134.3, 129.1, 128.6, 128.7, 128.3, 127.2, 126.6, 126.1, 125.6, 62.7, 56.0, 50.5, 29.0; **HRMS** (ESI+): Exact mass calculated for C₁₆H₁₇N [M+H] 224.1395. Found; 224.1398.

1-benzylpiperidine (15)³

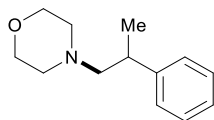
Purification 1. Product was isolated as a pale yellow oil (70 mg, 80%). **¹H NMR** (270 MHz, CDCl₃): 7.40-7.10 (m, 5H), 3.48 (s, 2H), 2.37 (m, 4H), 1.68 – 1.49 (m, 4H), 1.68 – 1.49 (m, 2H); **¹³C NMR** (68 MHz, CDCl₃): 138.4, 129.3, 128.1, 126.8, 63.9, 54.4, 25.9, 24.3; **HRMS** (ESI+): Exact mass calculated for C₁₂H₁₇N [M+H] 176.1395. Found: 176.1474.

1-benzyl-4-methylpiperazine (16)¹

Purification 1. Product was isolated as a pale yellow oil (54 mg, 56%). **¹H NMR** (270 MHz, CDCl₃): 7.36 – 7.21 (m, 5H), 3.50 (s, 2H), 2.48 (br. s, 8H), 2.29 (s, 3H); **¹³C**

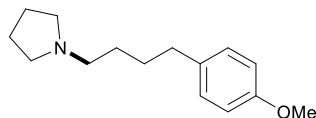
NMR (68 MHz, CDCl_3): 138.0, 129.2, 128.2, 127.0, 62.9, 54.9, 52.8, 45.8; **HRMS** (ESI+): Exact mass calculated for $\text{C}_{12}\text{H}_{18}\text{N}_2$ $[\text{M}+\text{H}]$ 191.1504. Found 191.1517.

4-(2-phenylpropyl)morpholine (17)⁴



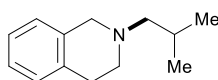
Purification 1: Product was isolated as a pale yellow oil (80 mg, 78%). **¹H NMR** (270 MHz, CDCl_3): 7.39 - 7.09 (m, 5 H), 3.80 - 3.52 (m, 4 H), 3.03 - 2.82 (m, 1 H), 2.55 - 2.24 (m, 6 H), 1.26 (d, $J = 6.9$ Hz, 3 H); **¹³C NMR** (101 MHz, CDCl_3): 134.2, 128.4, 127.2, 126.2, 67.0, 66.5, 54.0, 37.0, 20.0; **HRMS** (ESI+): Exact mass calculated for $\text{C}_{13}\text{H}_{19}\text{NO}$ $[\text{M}+\text{H}]$ 206.1500. Found: 206.1537.

1-(4-(4-methoxyphenyl)butyl)pyrrolidine (18)



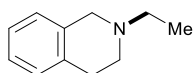
Purification 2: Product was isolated as a yellow oil (89 mg, 83%). **¹H NMR** (270 MHz, CDCl_3): 7.15 - 6.99 (m, 2 H), 6.88 - 6.74 (m, 2 H), 3.78 (s, 3 H), 2.55 (t, $J = 7.2$ Hz, 2 H), 2.51 - 2.40 (m, 6 H), 1.77 (m, 4 H), 1.68 - 1.49 (m, 4 H); **¹³C NMR** (68 MHz, CDCl_3): 157.6, 134.6, 129.2, 113.6, 56.5, 55.2, 54.2, 34.9, 29.8, 28.7, 23.4; **IR** (CDCl_3) ν (cm^{-1}): 3011, 2937, 2801, 2424, 1612, 1513, 1465, 1300, 1246, 1178, 1121, 1036; **HRMS** (ESI+): Exact mass calculated for $\text{C}_{15}\text{H}_{23}\text{NO}$ $[\text{M}+\text{H}]$ 234.1813. Found: 234.1814.

2-isobutyl-1,2,3,4-tetrahydroisoquinoline (19)⁵



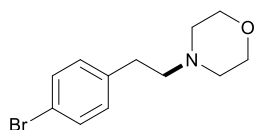
Purification 2: Product was isolated as a pale yellow oil (83 mg, 89%). **¹H NMR** (400 MHz, CDCl₃): 7.16 – 7.07 (m, 3H), 7.05 – 6.99 (m, 1H), 3.59 (s, 2H), 2.90 (t, *J* = 5.9 Hz, 2H), 2.69 (t, *J* = 5.9 Hz, 2H), 2.26 (d, *J* = 7.4 Hz, 2H), 1.92 (dh, *J* = 7.4, 6.7 Hz, 1H), 0.95 (d, *J* = 6.7 Hz, 6H); **¹³C NMR** (101 MHz, CDCl₃): 135.3, 134.6, 128.6, 126.6, 125.9, 125.5, 66.8, 56.7, 51.1, 29.2, 25.7, 21.0; **HRMS** (ESI⁺): Exact mass calculated for C₁₃H₁₉N [M+H] 190.1590. Found 190.1595; σ = 0.0036.

2-ethyl-1,2,3,4-tetrahydroisoquinoline (20)⁶



Purification 2: Product was isolated as a pale yellow oil (46 mg, 56%). **¹H NMR** (270 MHz, CDCl₃): 7.21 - 6.93 (m, 4 H), 3.65 (s, 2 H), 2.93 (t, *J* = 5.9 Hz, 2 H), 2.76 (t, *J* = 5.9 Hz, 2 H), 2.61 (q, *J* = 7.2 Hz, 2 H), 1.20 (t, *J* = 7.2 Hz, 3 H); **¹³C NMR** (68MHz, CDCl₃): 134.5, 134.2, 128.6, 126.6, 126.1, 125.6, 55.6, 52.1, 50.6, 29.0, 12.3; **HRMS** (ESI⁺): Exact mass calculated for C₁₁H₁₅N [M+H] 162.1237. Found 162.1249.

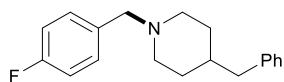
4-(4-bromophenethyl)morpholine (21)⁷



Amidation: Between 2-(4-bromophenyl)acetic acid and morpholine. 16 h, 1.50 equiv. phenylsilane instead of 1.0 equiv. Purification: The crude reaction solution was quenched with HCl in methanol (0.5 mL) and 1 M aq. HCl (0.5 mL), and stirred for 1 h to break-up the enamine by-product. The solution was diluted in ethyl acetate (7.5 mL) and subjected to the general work up. The crude product was then distilled *in vacuo* at 50 °C for 2 h to remove the final traces of morpholine. Product isolated as yellow oil (80 mg, 60%). **¹H**

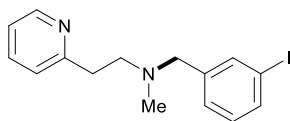
NMR (300 MHz, CDCl₃) δ 7.48 – 7.32 (m, 2H), 7.15 – 7.04 (m, 2H), 3.75 – 3.70 (m, 4H), 2.80 – 2.70 (m, 2H), 2.61 – 2.46 (m, 6H); **¹³C NMR** (75 MHz, CDCl₃) δ 139.1, 131.4, 130.4, 119.8, 66.9, 60.4, 53.6, 32.7; **HRMS** (ESI+): Exact mass calcd for C₁₂H₁₇BrNO [M+H], 270.0488. Found 270.0474, σ = 0.0518.

4-benzyl-1-(4-fluorobenzyl)piperidine (22)⁸



Purification 3: Product isolated as an off-white waxy solid (108 mg, 76%). **¹H NMR** (400 MHz, CDCl₃) δ 7.26 (s, 4H), 7.23 – 7.17 (m, 1H), 7.17 – 7.13 (m, 2H), 7.04 – 6.96 (m, 2H), 3.45 (s, 2H), 2.87 – 2.83 (m, 2H), 2.55 (d, J = 7.0 Hz, 2H), 1.90 (td, J = 11.7, 2.5 Hz, 2H), 1.68 – 1.57 (m, 2H), 1.40 – 1.24 (m, 2H); **¹³C NMR** (101 MHz, CDCl₃) δ 161.9 (d, J = 244.6 Hz), 140.7, 134.3 (d, J = 3.2 Hz), 130.5 (d, J = 7.7 Hz), 129.1, 128.1, 125.7, 114.8 (d, J = 20.9 Hz), 62.6, 53.7, 43.2, 37.9, 32.2; **¹⁹F NMR** (377 MHz, CDCl₃) δ -116.2 – -116.3 (m); **HRMS** (ESI+): Exact mass calcd for C₁₉H₂₃FN [M+H], 284.1809. Found 284.1819, σ = 0.0019.

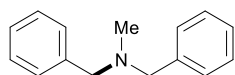
***N*-(3-iodobenzyl)-*N*-methyl-2-(pyridin-2-yl)ethan-1-amine (23)**



Purification 1; flash column chromatography with pentane/EtOAc/ Et₃N (0-70% gradient EtOAc, with 0.5 mol% Et₃N throughout on Et₃N pre-treated silica). Product isolated as a pale yellow oil (139 mg, 79%). **¹H NMR** (400 MHz, CDCl₃) δ 8.54 – 8.50 (m, 1H), 7.64 – 7.57 (m, 2H), 7.57 – 7.53 (m, 1H), 7.23 – 7.18 (m, 1H), 7.17 – 7.14 (m, 1H), 7.14 – 7.09 (m, 1H), 7.00 (t, J = 7.7 Hz, 1H), 3.48 (s, 2H), 3.04 – 2.94 (m, 2H), 2.84 –

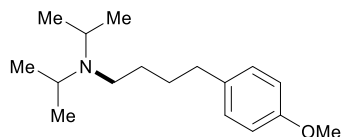
2.76 (m, 2H), 2.27 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) 160.4, 149.2, 141.8, 137.7, 136.2, 136.0, 129.9, 128.0, 123.2, 121.2, 94.3, 61.5, 57.2, 42.1, 36.2; **AT-IR** (neat) ν (cm^{-1}): 3053, 3007, 2943, 2790, 1590, 1565, 1472, 1434, 1048, 994; **HRMS** (ESI+): Exact mass calcd for $\text{C}_{15}\text{H}_{18}\text{IN}_2$ $[\text{M}+\text{H}]$, 353.0509. Found 353.0516, $\sigma = 0.0001$.

***N*-benzyl-*N*-methyl-1-phenylmethanamine (24)⁹**



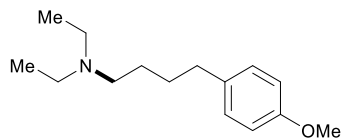
Purification 2: Product isolated as light yellow oil (71 mg, 67%). ^1H NMR (300 MHz, CDCl_3) δ 7.48 – 7.19 (m, 10H), 3.54 (s, 4H), 2.20 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 139.3, 128.9, 128.2, 126.9, 61.8, 42.2; **HRMS** (ESI+): Exact mass calcd for $\text{C}_{15}\text{H}_{18}\text{N}$ $[\text{M}+\text{H}]$, 212.1434. Found 212.1454, $\sigma = 0.0322$.

***N,N*-diisopropyl-4-(4-methoxyphenyl)butan-1-amine (25)**

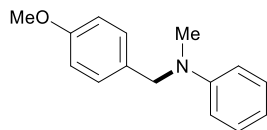


Note, stopping the reaction after the amidation phase indicated 15% amide; the low yield is thus due to hindrance in the amidation step as opposed to reduction.

Purification 2: Product was isolated as a yellow oil (20 mg, 15%). ^1H NMR (270 MHz, CDCl_3): 7.15 - 7.00 (m, 2 H), 6.90 - 6.76 (m, 2 H), 3.78 (s, 3 H), 3.03 (br. s., 2 H), 2.56 (t, $J = 7.5$ Hz, 2 H), 2.42 (t, $J = 6.5$ Hz, 2 H), 1.68 - 1.36 (m, 4 H), 1.02 (d, $J = 6.3$ Hz, 12 H); ^{13}C NMR (68 MHz, CDCl_3): 157.6, 134.9, 129.2, 113.6, 55.2, 48.7, 45.3, 34.9, 30.7, 29.5, 20.4; **IR** (CDCl_3) ν (cm^{-1}): 2937, 2801, 1612, 1513, 1465, 1245, 1178, 1121, 1036, 829; **HRMS** (ESI+): Exact mass calculated for $\text{C}_{17}\text{H}_{29}\text{NO}$ $[\text{M}+\text{H}]$ 264.2383. Found 264.2332.

***N,N*-diethyl-4-(4-methoxyphenyl)butan-1-amine (26)**

Purification 2: Product was isolated as a pale yellow oil. (32 mg, 27%). **¹H NMR** (270 MHz, CDCl₃): 7.18 - 7.02 (m, 2 H), 6.90 - 6.67 (m, 2 H), 3.78 (s, 3 H), 2.70 - 2.32 (m, 8 H), 1.73 - 1.39 (m, 4 H), 1.01 (t, *J* = 7.2 Hz, 6 H); **¹³C NMR** (68 MHz, CDCl₃): 157.6, 134.6, 129.2, 113.6, 55.2, 52.7, 46.8, 34.9, 30.9, 26.4, 11.5; **IR** (CDCl₃) ν (cm⁻¹): 3011, 2937, 1612, 1512, 1466, 1384, 1300, 1245, 1178, 1036; **HRMS** (ESI⁺): Exact mass calculated for C₁₅H₂₅NO [M+H] 236.1970. Found: 236.2046.

***N*-(4-methoxybenzyl)-*N*-methylaniline¹⁰ (27)**

Amidation stage performed with two or three equivalents of carboxylic acid (which increases the conversion of the amidation step for lower reactivity amines such as anilines). The reaction was diluted with ethyl acetate, washed with 1 M aqueous NaOH solution and brine and purified by flash column chromatography (5% EtOAc/pentane) to give a pale yellow oil (62 mg, 54% for 3 equivalents carboxylic acid: 45 mg, 40% for 2 equivalents of carboxylic acid.) **¹H NMR** (400 MHz, CDCl₃) δ 7.25 – 7.19 (m, 2H), 7.18 – 7.13 (m, 2H), 6.88 – 6.83 (m, 2H), 6.77 (d, *J* = 8.3 Hz, 2H), 6.72 (t, *J* = 7.3 Hz, 1H), 4.47 (s, 2H), 3.79 (s, 3H), 2.99 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 158.6, 149.8, 130.9, 129.1, 127.9, 116.5, 113.9, 112.5, 56.0, 55.3, 38.3; **HRMS** (ESI⁺): Exact mass calcd for C₁₅H₁₈NO [M+H], 228.1383. Found 228.1381, σ = 0.0108.

3.05 Maraviroc Details (Schemes 12-17, Tables 3-4)

For full synthetic details, see Declan Summers' Masters Report

The fragment coupling attempt (**Scheme 17**) was made using the typical amination of secondary amines procedure, with a 16 h reflux period and a 4 h reduction period. After this time, ¹H-NMR analysis suggested that ~ 45% of the monoamide **43** was present, although the product was not isolated. The amidation ran reasonably well to incorporate new multiplets at ~3.4 ppm from the pyrrolidine. Partial reduction led to the enamine, with a d and dt alkene signals at ~6.5 ppm. These signals disappeared as the reaction proceeded. The retention of original secondary amide multiplet at 5.4 ppm indicated the original amide was untouched.

4. Reductive alkylation of primary amines with carboxylic acids

4.01 Optimisation details (Table 5, 6)

Procedure: A flask fitted with a water condenser and an argon balloon was charged with acid (0.16 mmol = 1 equiv.). Toluene (0.35 mL) was added and the solution heated to reflux with stirring before adding phenylsilane (various equiv.) and finally the amine (0.16 mmol) – hydrogen gas evolution was observed. After the stated time, [Ir(COD)Cl]₂ (various mol%) was added along with phenylsilane (various equiv.) by temporary removal of the condenser and addition, and the reaction refluxed again for the stated time. After this time, the reaction was quenched with methanol, cooled, concentrated and the conversion calculated by comparison to an added internal standard (1,1,2,2-tetrachloroethane) by ¹H-NMR in chloroform.

4.02 General procedure for the reductive alkylation of primary amines with carboxylic acids (Figure 4)

An oven-dried 10 mL round-bottom flask fitted with a water condenser and an argon balloon was charged with carboxylic acid (0.50 mmol). Anhydrous toluene (0.6 mL) and phenylsilane (0.38 or 0.50 mmol) were added and the flask incubated in an oil bath at 111-115 °C to dissolve the acid (if required/possible). On a small scale, the amine (0.5 mmol) was then added carefully by microsyringe by temporary removal of the condenser, generally accompanied by the vigorous release of hydrogen gas. *Note that at smaller scales, the amine can be added to the (almost) refluxing solution; for larger scale reactions a large volume of hydrogen is released, and it is preferable to remove the reaction from the heat and add the amine portionwise at a lower temperature.* After 2 or 13-15 h, the reaction was removed from the heat and allowed to cool slightly. Then $[\text{Ir}(\text{COD})\text{Cl}]_2$ (15 μmol , 3.0 mol%) was added along with diethylsilane (1.5 mmol) (volatile, cool reaction before adding). After 5 min, the reaction was returned to the heat and the reaction refluxed over 2-3 h. After this time, the reaction was purified in one of the following ways.

Purification 1: Reaction quenched with methanol and stirred to give a precipitate (silicon based), which was filtered off before further purification.

Purification 2: The residue was dissolved in a minimum of diethyl ether and added dropwise to a solution of HCl (1.0 M) in diethyl ether to give a precipitate, the HCl salt of the amine. Amine-HCl salt filtered. The solid was partitioned between 3 M NaOH and dichloromethane and the organics separated. The aqueous was extracted two further times, the organics combined, dried over magnesium sulfate, filtered and concentrated to give the amine.

Purification 3: The residue was dry loaded onto silica and purified by flash column chromatography.

Purification 4: The hot reaction was quenched with silica and gas evolution allowed to complete before being concentrated (i.e. an instant dry load) and purified directly by flash column chromatography.

Purification 5: The reaction was cooled, concentrated and taken up in ethyl acetate. The organics were extracted with 3 x HCl (1M aqueous solution) and the combined aqueous fractions basified to > pH10 by careful addition of sodium hydroxide (6 M, aqueous) with ice-bath cooling. The aqueous layer was extracted with dichloromethane (four portions), the combined organics dried (MgSO₄) and concentrated *in vacuo*.

Notes: The reaction is best performed from the free base. The amine and acid can be combined first, before adding the silane last to initiate the reaction. The room temperature combination of acid and amine in toluene sometimes this leads to a salting out of the ammonium carboxylate which may hinder the reaction efficiency, however successful reactions have been performed in this way.

4.03 Reductive alkylation under non-inert conditions (Figure 4)

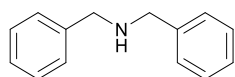
The full reduction reaction with dibenzylamine (**46**) has been performed in *undried glassware, Winchester-grade toluene* and *open to air* (no argon balloon). On a 0.16 mmol scale, the reaction (1.0 PhSiH₃, amidation 15 h, reduction 2 h) gave a conversion to the desired amine of 60%. At 0.50 mmol scale (1.0 PhSiH₃, amidation 15 h, reduction 3 h), the conversion was 82%. These conversions compare well with the isolated yield under controlled conditions (2 h amidation, 2 h reduction) of 77%.

In non-controlled cases it may be helpful to increase the silane loading by ~0.1 equivalents to consume the excess moisture. Additionally, it is recommended that such reactions are performed over the longer reaction times (particularly the amidation step).

4.04 Data and specific experimental details for secondary amines 46, 48-58

Amines prepared according to the general method above. Reaction times, varying equivalents and purification details shown below if required.

Dibenzylamine (46)¹¹



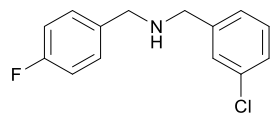
Amidation: Between benzoic acid and benzylamine. 2 h, 0.75 equiv. phenylsilane.

Purification: 4, eluting with 10% EtOAc in petrol. Product isolated as pale yellow oil (76 mg, 77%). ¹H NMR (400 MHz, CDCl₃) δ 7.45 - 7.23 (m, 10 H), 3.86 (s, 4 H), 1.93 (br. s.,

1 H); ¹³C NMR (101 MHz, CDCl₃) δ 140.3, 128.3, 128.1, 126.9, 53.1; HRMS (ESI⁺):

Exact mass calcd for C₁₄H₁₆N [M+H], 198.1277. Found 198.1286, σ = 0.0059.

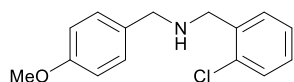
N-(3-chlorobenzyl)-1-(4-fluorophenyl)methanamine (48)



Amidation: Between 4-fluorobenzoic acid and (3-chlorophenyl)methanamine. 13 h, 0.75 equiv. phenylsilane. Purification steps: 1, 2 and 3 (dry-loaded onto silica pretreated with triethylamine. Eluted with 5-20% EtOAc in pentane). Product isolated as pale yellow oil (98 mg, 79%). ¹H NMR (400 MHz, CDCl₃) δ 7.41 - 7.19 (m, 6H), 7.10 - 6.95 (m, 2H),

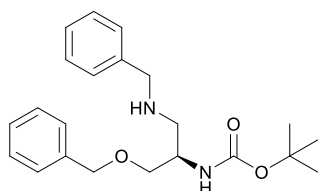
3.78 (s, 2H), 3.77 (s, 2H), 1.60 (s, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 161.9 (d, J = 244.7 Hz), 142.3, 135.8 (d, J = 3.1 Hz), 134.2, 129.6, 129.6 (d, J = 7.8 Hz), 128.1, 127.1, 126.2, 115.1 (d, J = 20.8 Hz), 52.5, 52.3; **AT-IR** (neat) ν (cm^{-1}): 3306, 3064, 2827, 1600, 1574, 1508, 1219, 773; **HRMS** (ESI+): Exact mass calcd for $\text{C}_{14}\text{H}_{14}\text{ClFN}$ $[\text{M}+\text{H}]$, 250.0793. Found 250.0805, σ = 0.0375.

***N*-(2-chlorobenzyl)-1-(4-methoxyphenyl)methanamine (49)¹²**



Amidation: Between 4-methoxybenzoic acid and (2-chlorophenyl)methanamine. 13 h, 1.00 equiv. phenylsilane. Purification: 5 and then 3, eluting with 2-12% EtOAc in pentane, using triethylamine treated silica for the dry load and column. Product isolated as pale yellow oil (87 mg, 66%). ^1H NMR (400 MHz, CDCl_3) δ 7.44 – 7.34 (m, 2H), 7.31 – 7.14 (m, 4H), 6.91 – 6.86 (m, 2H), 3.90 (s, 2H), 3.81 (s, 3H), 3.76 (s, 2H), 1.82 (s, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 158.6, 137.6, 133.7, 132.2, 130.2, 129.5, 129.3, 128.2, 126.7, 113.7, 55.2, 52.5, 50.6; **HRMS** (ESI+): Exact mass calcd for $\text{C}_{15}\text{H}_{16}\text{ClNNaO}$ $[\text{M}+\text{Na}]$, 284.0813. Found 284.0801, σ = 0.0330.

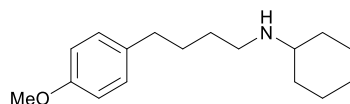
***tert*-butyl (R)-(1-(benzylamino)-3-(benzyloxy)propan-2-yl)carbamate (50)**



Amidation: Between *O*-benzyl-*N*-(*tert*-butoxycarbonyl)-L-serine and benzylamine. 13 h, 0.75 equiv. phenylsilane. Purification: 1, concentration, and then 3, eluting with 2-20%

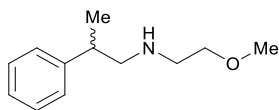
EtOAc in petrol, using triethylamine treated silica for the dry load and column. Product isolated as pale yellow oil (114 mg, 62%). **¹H NMR** (400 MHz, CDCl₃) δ 7.57 – 7.00 (m, 10H), 5.11 (s, 1H), 4.58 – 4.43 (m, 3H), 3.87 (s, 1H), 3.84 – 3.73 (m, 2H), 3.67 – 3.45 (m, 2H), 2.93 – 2.71 (m, 2H), 1.45 (s, 9H); **¹³C NMR** (101 MHz, CDCl₃) 155.7, 140.2, 138.0, 128.4, 128.3, 128.0, 127.6, 127.6, 126.9, 79.6, 73.2, 70.6, 53.7, 50.1, 49.7, 28.4; **AT-IR** (neat) ν (cm⁻¹): 3313, 3030, 2974, 2930, 2867, 1696 (C=O), 1495, 1454, 1365, 1165, 734; **HRMS** (ESI+): Exact mass calcd for C₂₂H₃₁N₂O₃ [M+H], 371.2329. Found 371.2327, σ = 0.0015.

***N*-(4-(4-methoxyphenyl)butyl)cyclohexanamine (51)¹³**



Amidation: Between 4-(4-methoxyphenyl)butanoic acid and cyclohexanamine. 13 h, 0.75 equiv. phenylsilane. Purification: 1, concentrated filtrate, dry loaded onto silica, loaded onto an equally short silica bed, washed with pentane (50 mL), then 4:96 EtOAc:pentane, and then finally the product was eluted cleanly with EtOAc/2% Et₃N and concentrated to give the amine. Product isolated as pale yellow oil (106 mg, 81%). **¹H NMR** (400 MHz, CDCl₃) δ 7.13 – 7.01 (m, 2H), 6.85 – 6.75 (m, 2H), 3.76 (s, 3H), 2.65 – 2.58 (m, 2H), 2.55 (t, *J* = 7.5 Hz, 2H), 2.37 (tt, *J* = 10.5, 3.7 Hz, 1H), 1.93 – 1.79 (m, 2H), 1.76 – 1.66 (m, 2H), 1.66 – 1.54 (m, 3H), 1.54 – 1.43 (m, 2H), 1.32 – 0.94 (m, 5H); **¹³C NMR** (101 MHz, CDCl₃) 157.6, 134.5, 129.1, 113.6, 56.8, 55.1, 46.8, 34.8, 33.6, 30.0, 29.5, 26.1, 25.0; **HRMS** (ESI+): Exact mass calcd for C₁₇H₂₇NO [M+H], 262.2165. Found 262.2170, σ = 0.0005.

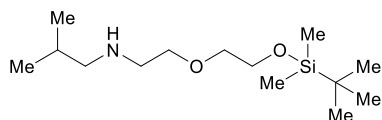
***N*-(2-methoxyethyl)-2-phenylpropan-1-amine (52)**



Amidation: Between 2-phenylpropanoic acid (1.20 equivalents) and 2-methoxyethan-1-amine. 13 h, 1.00 equiv. phenylsilane. Purification: 5, then 3 with 0-100% EtOAc in pentane, before eluting with 10% MeOH in EtOAc (+2 % Et₃N) using triethylamine treated silica for the dry load and column. Product isolated as pale yellow oil (57 mg, 60%).

¹H NMR (400 MHz, CDCl₃) δ 7.34 – 7.27 (m, 2H), 7.24 – 7.17 (m, 3H), 3.43 (t, *J* = 5.3 Hz, 2H), 3.30 (s, 3H), 2.94 (ddq, *J* = 7.0 Hz, 7.0 Hz, 7.0 Hz, 1H), 2.85 – 2.68 (m, 4H), 1.54 (s, 1H), 1.26 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 145.3, 128.4, 127.1, 126.2, 71.8, 58.6, 57.1, 49.1, 39.9, 19.9; **AT-IR** (neat) *ν* (cm⁻¹): 3330, 3028, 2928, 2877, 2821, 1666, 1452, 1115, 910; **HRMS** (ESI⁺): Exact mass calcd for C₁₂H₂₀NO [M+H], 194.1539. Found 194.1561, *σ* = 0.0042.

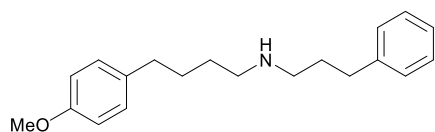
***N*-(2-(2-((*tert*-butyldimethylsilyl)oxy)ethoxy)ethyl)-2-methylpropan-1-amine (53)**



Amidation: Between isobutyric acid and 2-(2-((*tert*-butyldimethylsilyl)oxy)ethoxy)ethan-1-amine. 16 h, 1.00 equiv. phenylsilane. Purification: Reaction quenched with methanol, concentrated, dissolved in dichloromethane, washed with saturated sodium bicarbonate solution, dried over MgSO₄ and concentrated. The crude residue was then purified by flash column chromatography with pentane/EtOAc/MeOH (0-100% gradient EtOAc, then 5% MeOH in EtOAc). Product isolated as a pale yellow oil (119 mg, 86%). ¹H NMR (400 MHz, CDCl₃) δ 3.75 (t, *J* = 5.2 Hz, 2H), 3.60 (t, *J* = 5.2 Hz, 2H), 3.52 (t, *J* = 5.3 Hz, 2H),

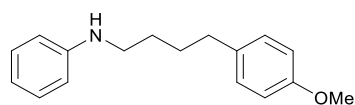
2.78 (t, $J = 5.3$ Hz, 2H), 2.44 (d, $J = 6.9$ Hz, 2H), 2.14 (br. s, 1H) 1.76 (dh, $J = 6.9, 6.7$ Hz, 1H), 0.90 (d, $J = 6.7$ Hz, 6H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (101 MHz, CDCl_3) 72.5, 70.5, 62.7, 58.0, 49.5, 28.3, 25.9, 20.7, 18.4, -5.3; **AT-IR** (neat) ν (cm^{-1}): 2954, 2929, 2857, 1674, 1463, 1252, 1102, 832; **HRMS** (ESI+): Exact mass calcd for $\text{C}_{14}\text{H}_{34}\text{NO}_2\text{Si}$ $[\text{M}+\text{H}]$, 276.2353. Found 276.2352, $\sigma = 0.0062$.

4-(4-methoxyphenyl)-N-(3-phenylpropyl)butan-1-amine (54)



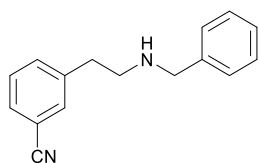
Amidation: Between 4-(4-methoxyphenyl)butanoic acid and 3-phenylpropan-1-amine 13 h, 0.75 equiv. phenylsilane. Purification: Petrol/EtOAc 0-100%, then flush with 20% MeOH in EtOAc. Product eluted partially as a (silicate?) salt, which was removed by dissolving in EtOAc and washing with sodium bicarbonate. (Column would benefit from inclusion of triethylamine.) Product isolated as pale yellow oil (115 mg, 77%). ^1H NMR (400 MHz, CDCl_3) δ 7.33 – 7.25 (m, 2H), 7.22 – 7.15 (m, 3H), 7.12 – 7.07 (m, 2H), 6.87 – 6.79 (m, 2H), 3.79 (s, 3H), 2.69 – 2.60 (m, 6H), 2.57 (t, $J = 7.5$ Hz, 2H), 1.89 – 1.77 (m, 2H), 1.66 – 1.47 (m, 4H), 1.27 (s, 1H); ^{13}C NMR (101 MHz, CDCl_3) 157.6, 142.0, 134.5, 129.2, 128.3, 128.3, 125.7, 113.6, 55.2, 49.7, 49.4, 34.8, 33.6, 31.5, 29.5, 29.4; **AT-IR** (neat) ν (cm^{-1}): 3026, 3002, 2930, 1611, 1510, 1454, 1243, 1177, 1031, 819; **HRMS** (ESI+): Exact mass calcd for $\text{C}_{20}\text{H}_{28}\text{NO}$ $[\text{M}+\text{H}]$, 298.2165. Found 298.2163, $\sigma = 0.0173$.

N-(4-(4-methoxyphenyl)butyl)aniline (55)¹⁴



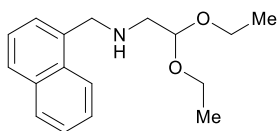
Amidation: Between 4-(4-methoxyphenyl)butanoic acid (2.00 equiv.) and aniline. 16 h, 1.00 equiv. phenylsilane. Purification: Purified by method 2 and then by flash column chromatography with pentane/EtOAc (0-40% gradient). Product isolated as a very pale yellow oil (81 mg, 63%). **¹H NMR** (400 MHz, CDCl₃) δ 7.22 – 7.15 (m, 2H), 7.15 – 7.07 (m, 2H), 6.89 – 6.82 (m, 2H), 6.74 – 6.68 (m, 1H), 6.64 – 6.58 (m, 2H), 3.81 (d, *J* = 1.1 Hz, 4H), 3.14 (t, *J* = 7.0 Hz, 2H), 2.62 (t, *J* = 7.2 Hz, 2H), 1.80 – 1.57 (m, 4H). **¹³C NMR** (101 MHz, CDCl₃) 157.7, 148.3, 134.2, 129.2, 129.2, 117.2, 113.7, 112.7, 55.2, 43.9, 34.7, 29.1, 29.0; **HRMS** (ESI⁺): Exact mass calcd for C₁₇H₂₂NO [M+H], 256.1696. Found 256.1683, σ = 0.0041.

3-(2-(benzylamino)ethyl)benzonitrile (56)



Amidation: Between 2-(3-cyanophenyl)acetic acid and benzylamine. 16 h, 1.00 equiv. phenylsilane. Purification: Purified by method 5 and then by flash column chromatography with pentane/EtOAc/ Et₃N (0-30% gradient EtOAc, with 0.5 mol% Et₃N throughout). Product isolated as a very pale yellow oil (39 mg, 35%). **¹H NMR** (400 MHz, CDCl₃) δ 7.52 – 7.47 (m, 2H), 7.46 – 7.42 (m, 1H), 7.41 – 7.22 (m, 6H), 3.81 (s, 2H), 2.94 – 2.88 (m, 2H), 2.88 – 2.82 (m, 2H); **¹³C NMR** (101 MHz, CDCl₃) 141.5, 139.8, 133.3, 132.2, 129.9, 129.2, 128.5, 128.1, 127.1, 118.9, 112.4, 53.7, 49.8, 35.9; **AT-IR** (neat) ν (cm⁻¹): 3062, 3029, 2926, 2228 (-CN), 1643, 1451, 735; **HRMS** (ESI⁺): Exact mass calcd for C₁₆H₁₇N₂ [M+H], 237.1386. Found 237.1389, σ = 0.0269;

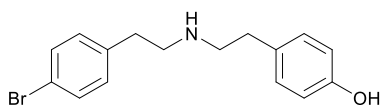
2,2-diethoxy-*N*-(naphthalen-1-ylmethyl)ethan-1-amine (57)¹⁵



Amidation: Between 1-naphthoic acid and 2,2-diethoxyethan-1-amine. 16 h, 1.00 equiv. phenylsilane. Purification: Reaction quenched with methanol, concentrated, dissolved in dichloromethane, washed with 1.0 M sodium hydroxide solution, dried over MgSO_4 and concentrated. The residue was dry loaded onto silica, and purified by flash column chromatography with pentane/EtOAc (0-100% gradient, with 0.5 mol% Et_3N throughout on Et_3N pre-treated silica). Product isolated as a yellow oil (90 mg, 66%).

^1H NMR (400 MHz, CDCl_3) δ 8.17 – 8.09 (m, 1H), 7.91 – 7.82 (m, 1H), 7.81 – 7.73 (m, 1H), 7.58 – 7.37 (m, 4H), 4.65 (t, J = 5.6 Hz, 1H), 4.27 (s, 2H), 3.74 – 3.63 (m, 2H), 3.57 – 3.45 (m, 2H), 2.87 (d, J = 5.6 Hz, 2H), 1.70 (s, 1H), 1.19 (t, J = 7.1 Hz, 6H); ^{13}C NMR ((101 MHz, CDCl_3) δ 135.8, 133.9, 131.8, 128.7, 127.7, 126.0, 126.0, 125.6, 125.4, 123.6, 102.1, 62.3, 52.0, 51.5, 15.4 HRMS (ESI+): Exact mass calcd for $\text{C}_{17}\text{H}_{24}\text{NO}_2$ $[\text{M}+\text{H}]$, 274.1802. Found 274.1807, σ = 0.0009.

4-(2-((4-bromophenethyl)amino)ethyl)phenol (58)

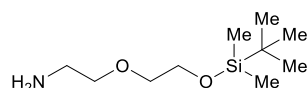


Amidation: Between 2-(4-bromophenyl)acetic acid and 4-(2-aminoethyl)phenol (tyramine). 16 h, 1.50 equiv. phenylsilane. Purification: Quenched with HCl in methanol, stirred for 1 h, concentrated, HCl precipitated by adding a solution of the crude residue slowly to HCl (1.0 M in ether). The salt was partitioned between sodium bicarbonate solution/water (just enough to neutralise the salt) and dichloromethane, and the organic layer dried and concentrated. The residue was dry loaded onto silica, and purified by flash

column chromatography with pentane/EtOAc (0-100% gradient). Product isolated as an off-white solid (77 mg, 48%). **¹H NMR** (400 MHz, Methanol-*d*₄) δ 7.41 – 7.37 (m, 2H), 7.09 – 7.05 (m, 2H), 6.99 – 6.94 (m, 2H), 6.71 – 6.67 (m, 2H), 2.85 – 2.65 (m, 8H); **¹³C NMR** ((101 MHz, Methanol-*d*₄) δ 157.0, 140.1, 132.6, 131.6, 131.4, 130.6, 121.0, 116.3, 51.9, 51.5, 35.8, 35.6; **AT-IR** (neat) ν (cm⁻¹): 3273, 2918, 2850, 1513, 1448, 1271, 1256, 1105, 815, 733; **HRMS** (ESI+): Exact mass calcd for C₁₆H₁₉BrNO [M+H], 320.0645. Found 320.0630, σ = 0.0832.

Substrates synthesised:

2-(2-((*tert*-butyldimethylsilyl)oxy)ethoxy)ethan-1-amine¹⁶



2-(2-Aminoethoxy)ethan-1-ol (5.30 mmol, 557 mg) was dissolved in dichloromethane (10 mL) with imidazole (1.08 g, 15.9 mmol) at room temperature before adding *tert*-butylchlorodimethylsilane (10.6 mmol, 1.61 g) and stirring for 20 h. The reaction was quenched with water, solid sodium chloride was added and the organic layer separated and washed with brine, dried and concentrated. The crude was purified by flash column chromatography (pentane/ether) to give the desired as a clear oil (1.13 g, 97%). **¹H NMR** 400 MHz, CDCl₃) δ 3.80 – 3.69 (m, 2H), 3.57 – 3.43 (m, 4H), 2.86 – 2.81 (m, 2H), 1.60 (s, 2H), 0.90 – 0.86 (m, 9H), 0.07 – 0.03 (m, 6H); **¹³C NMR** (101 MHz, CDCl₃) δ 73.4, 72.4, 62.7, 41.9, 25.9, 18.3, -5.3; **HRMS** (ESI+): Exact mass calcd for C₁₀H₂₆NO₂Si [M+H], 220.1727. Found 220.1737, σ = 0.0050.

5. References

- 1 M. H. S. A. Hamid, C. L. Allen, G. W. Lamb, A. C. Maxwell, H. C. Maytum, A. J. A. Watson and J. M. J. Williams, *J. Am. Chem. Soc.*, 2009, **131**, 1766–1774.
- 2 R. Kawahara, K. Fujita and R. Yamaguchi, *Adv. Synth. Catal.*, 2011, **353**, 1161–1168.
- 3 S. Lu, C. Li, J. Wang, Y. Pan, X. Cao and H. Gu, *Chem. Commun.*, 2014, **50**, 11110–11113.
- 4 V. K. Srivastava and P. Eilbracht, *Catal. Commun.*, 2009, **10**, 1791–1795.
- 5 C. Perrio-Huard, C. Aubert and M.-C. Lasne, *J. Chem. Soc. Perkin Trans. 1*, 2000, 311–316.
- 6 L. Huang and J. Zhao, *Chem. Commun.*, 2013, **49**, 3751–3753.
- 7 Y.-Y. Ku, T. Grieme, Y.-M. Pu, A. V. Bhatia and S. A. King, *Tetrahedron Lett.*, 2005, **46**, 1471–1474.
- 8 J.-P. Tremblay-Morin, S. Raeppele and F. Gaudette, *Tetrahedron Lett.*, 2004, **45**, 3471–3474.
- 9 J. Zheng, C. Darcel and J.-B. Sortais, *Chem. Commun.*, 2014, **50**, 14229–32.
- 10 O. S. Nayal, V. Bhatt, S. Sharma and N. Kumar, *J. Org. Chem.*, 2015, **80**, 5912–8.
- 11 D. B. Bagal, R. A. Watile, M. V. Khedkar, K. P. Dhake and B. M. Bhanage, *Catal. Sci. Technol.*, 2012, **2**, 354–358.
- 12 H.-R. Wang, M. Wu, H. Yu, S. Long, A. Stevens, D. W. Engers, H. Sackin, J. S.

- Daniels, E. S. Dawson, C. R. Hopkins, C. W. Lindsley, M. Li and O. B. McManus, *ACS Chem. Biol.*, 2011, **6**, 845–856.
- 13 J. Matsuo, A. Kawana, Y. Fukuda and T. Mukaiyama, *Chem. Lett.*, 2001, **30**, 712–713.
- 14 M. Oki and K. Mutai, *Bull. Chem. Soc. Jpn.*, 1965, **38**, 387–392.
- 15 A. Piergentili, F. Del Bello, F. Gentili, M. Giannella, W. Quaglia, C. Vesprini, R. J. Thomas and G. M. Robertson, *Tetrahedron*, 2007, **63**, 12912–12916.
- 16 S. Bevers, S. Schutte and L. W. McLaughlin, *J. Am. Chem. Soc.*, 2000, **122**, 5905–5915.

Chapter 4

A Trifluoroethylation Reaction Of Amines Using TFA

Contributing authors: Keith G. Andrews, Radmila Faizova, Jack Saunders, Paige Rist, Ross M. Denton

Tertiary amines tend to be highly basic, a property that often dominates the determination of characteristics that define the behaviour of pharmaceutical, agricultural and materials chemical products. Moderating and tuning the basicity of amines is therefore highly desirable. One method of doing this is to incorporate local fluorine atoms, which lower the energy, and therefore basicity, of nitrogen lone pairs. However, methods of synthesising complex, non-basic amines are underdeveloped in terms of tolerating extraneous functionality, and often require highly reactive, undesirable alkylating agents. In this Chapter, we demonstrate the applicability of an amine trifluoroethylation reaction using trifluoroacetic acid (TFA) as the fluorine source, and phenylsilane as the mediator and reductant. The reaction is proposed to operate through the in situ reduction of silyl esters to give aldehyde level intermediates, which undergo a reductive amination reaction. The chemoselectivity of the reduction makes the reaction highly tolerant of other functional groups.

Introduction

Amine Basicity

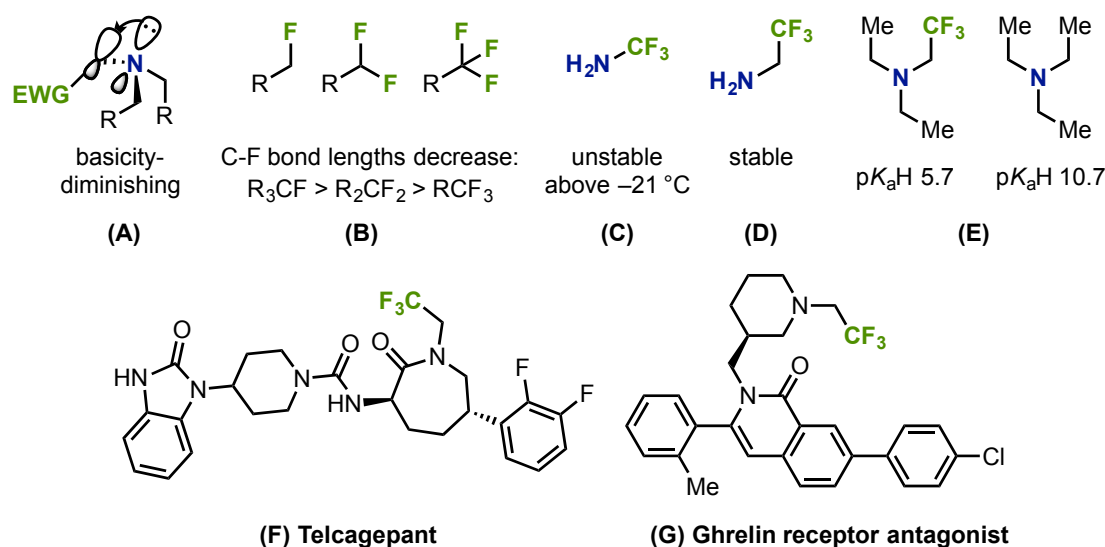
Amines are the archetypal basic moiety in organic molecules. Positioned between oxygen and carbon in the periodic table, nitrogen forms bonds with larger dipoles than typical hydrocarbons, but with more basic lone pairs than those found on oxygen. This gives nitrogen chemistry a unique set of variable behaviours, and the chemistry of a given nitrogen atom can be definitive in altering a molecule's physico-chemical properties.

Lone pairs are the highest energy electrons around an atom. This drives their tendency to partially delocalise into the surrounding sigma framework (and pi, when available). Further, negative inductive effects ($-I$) may lower the energy of the lone pair, reducing its availability (Bent's rule would say the N-X bonds take more *p*-character when X is more electron-withdrawing, and so the lone pair would acquire more *s*-character, making it less directional and lower in energy). Typically, the more electron-withdrawing an R group around nitrogen, the less basic the lone pair. And so the groups surrounding a nitrogen atom may influence the properties of a molecule quite strongly (Figure 1A).

Fluorine, on the other hand, if on carbon, often influences surrounding atoms' chemistry more than its own.^{1,2} Fluorine not only seeks to retain its lone pairs of electrons, it is also a powerful electron sink due to its high electronegativity. In C-F bonds, this results in a high dipole moment, on a par with C-Cl bonds (due to a balance of bond length and polarisation). Surprisingly for a polar bond, the C-F bonds are very stable. The high charge disparity between F and C leads to a large additional ionic contribution to the bond, strengthening it. These properties make the C-F bond the strongest of any carbon single

bond, and correspondingly unreactive. For species of the type $H_{4-x}CF_x$, the length of the C-F bond decreases as the number of fluorine atoms on the carbon centre increases (Figure 1B), and so multifluorocarbon groups, like trifluoromethyl, are especially stable.

Figure 1. Some chemical properties of fluorine and nitrogen.



It is unsurprising, then, that fluorinated alkyl groups adjacent to nitrogen atoms make for useful, stable and strong moderators of nitrogen lone pairs in molecules. However, the first species one might draw with this information, trifluoromethylamine (Figure 1C), is unstable and decomposes at $-21\text{ }^{\circ}\text{C}$.³ The fluorinated carbon atom must be one position further away for a stable amine; this leads us to the trifluoroethyl group (Figure 1D). This group is one of the smallest, most atom efficient modifiers of an amine's basicity available to chemists. For instance, 5 log units are lost from the pK_aH in ethylamine when the ethyl group is exchanged for a trifluoroethyl group (10.7 to 5.7; Figure 1E).⁴

The utility in altering the basicity of nitrogen atoms is far-ranging. In medicinal chemistry, membrane permeability⁵⁻⁷ and pharmacokinetic properties^{2,8} are vastly tunable. Additionally, basic amines are prone to oxidation, which leads to toxic metabolites (especially for anilines).⁹ Toxic hERG activity is also correlated with basicity.¹⁰⁻¹² The importance of the

role of fluorine atoms in medicinal chemistry candidates in general has also been reviewed,^{8,13} with conformation, intrinsic potency, metabolic stability and bioisosteres important.¹⁴ Telcagepant, a calcitonin gene-related peptide receptor antagonist investigated for acute migraine treatment, is shown in Figure 1F, along with a ghrelin-receptor antagonist in Figure 1G.^{15–19} Thus, with such an important emphasis on controlling basicity in amines, and such a powerful way to achieve that goal, it is surprising that the existing methods of trifluoroethylating amines are insufficient.

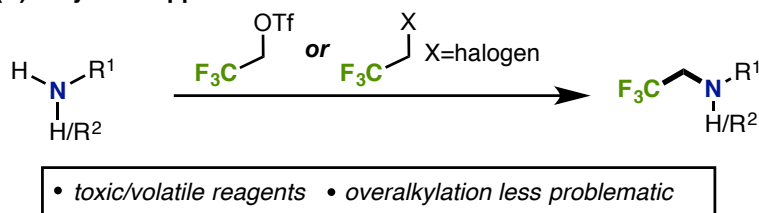
Methods of Synthesising Trifluoroethylamines

A significantly investigated means of synthesising trifluoroethylamines involves the nucleophilic attack of an amine with an alkyl halide or pseudohalide. However, these reagents are often extremely volatile, and are potent alkylating agents; the combination of toxicity and risk of exposure makes them highly undesirable reagents. Their high reactivity also makes synthesis, storage and handling difficult, although because they are deactivating groups, over-alkylation is curbed somewhat (Scheme 1A).

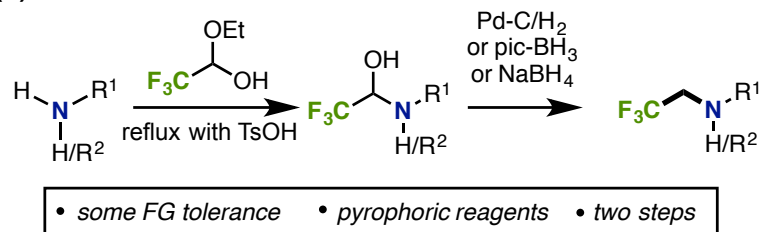
Reductive amination (Scheme 1B) with sodium borohydride or Pd-C/H₂ is another preferred route, but the aldehyde is a gas at –18 °C and is prone to polymerisation.²⁰ Various acetals are sometimes used, but the tendency of the CF₃ carbonyls to form the hemiaminal (rather than the imine) can make reaction with unreactive amines more difficult.²⁰ Formation of the amide with trifluoroacetic anhydride, and subsequent reduction of the amide (Scheme 1C) is another commonly employed route, but is available only when other reducible functionality is absent, as borane²¹ or lithium aluminium hydride²² are often required to reduce the amide. More recent approaches using catalytic metals or boranes are applicable to anilines and require Schlenk techniques (discussed in Chapter 3).^{23,24} The

direct use of trifluoroethylamine as a nucleophile is possible (Scheme 1D),²⁵ but the amine is volatile (36 °C) and expensive (£3900/mol: accessed 03-2017). Hartwig has recently developed a metal-catalysed coupling to form fluoroalkylated anilines.²⁶ Although powerful, such an approach inherently requires the synthesis of the fluorinated alkylamine to begin with. A range of other esoteric approaches have been developed.^{27–33}

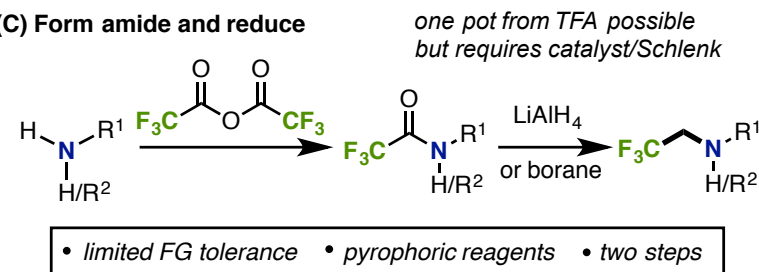
(A) Alkylative approach



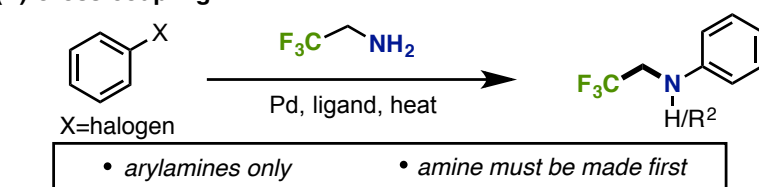
(B) Reductive amination



(C) Form amide and reduce



(D) Cross-coupling



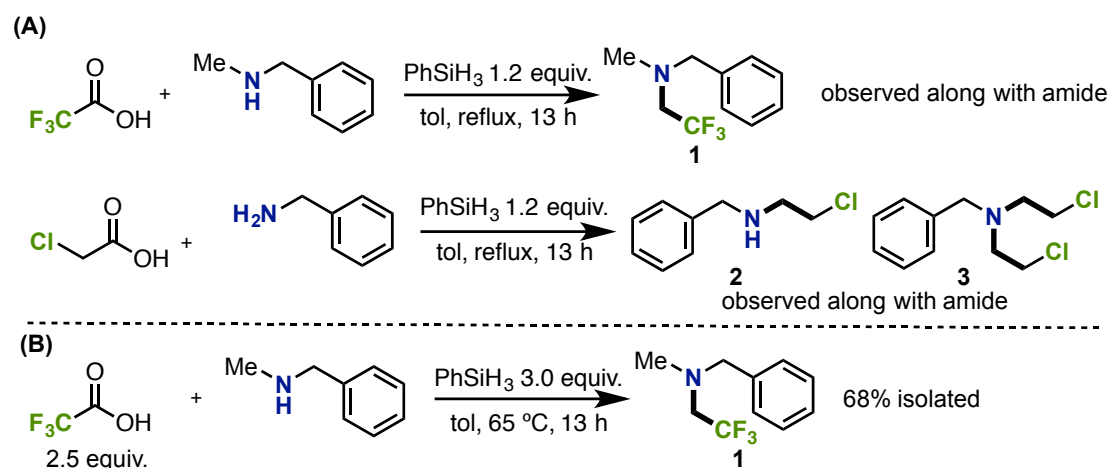
Scheme 1. Existing methods of trifluoroethylating amines

Examples of trifluoroethylamines-containing therapeutics are relatively rare (some mentioned in Figure 1),^{19,25,34–38} but Hartwig points out²⁶ that the low-representation in therapeutic molecules is likely contributed to by synthesis limitations. The reaction we

present below solves many of these issues, and opens ease of synthesis to a wide range of molecules.

Reaction Discovery

As hinted at in the introduction, the discovery of the reaction was fortuitous. Attempts to trifluoroamidate *N*-methyl-benzylamine led to the discovery of the *in situ* reduction of the carboxamide group. Chloroacetic acid also gave reduced products, in lower conversions (Scheme 2A). After augmenting the conditions a little, it was found that amine **1** could be isolated as the major product from the reaction with TFA (Scheme 2B).



Scheme 2. (A) Initial discovery of the trifluoroethylation reaction whilst trying to amidate, and; (B) subsequent proof of concept of good conversion.

At this point, the project was explored further within the group; (see Rada Faizova's Masters Research Project for details, which was undertaken under the supervision of this author).³⁹ We began by first optimising the proof-of-concept reaction previously discovered using trifluoroacetic acid, phenylsilane and *N*-methylbenzylamine. Although MeCN and EtOAc proved useful solvents, we focused on THF and toluene as drier media. THF gave reasonable solvating power, whilst the higher boiling temperature of toluene offered room for more forcing conditions if required. Pyridine appeared to inhibit the reduction entirely;

as did DMSO, which may have been reduced, as deduced by the odour of the reaction. This unconfirmed result (based on smell alone) may constitute new reactivity, as PhSiH_3 alone does not reduce sulfoxides.⁴⁰

Silanes other than PhSiH_3 were briefly investigated, but were not viable reagents. Diphenylsilane gave only 30% of the desired product after 20 h under the optimised reaction conditions, whilst triethoxysilane and PMHS (polymethylhydrosiloxane) were both ineffective reagents to mediate the trifluoroethylation reaction. These results are all consistent with previous data in the context of amidation; reactive silyl esters need to be formed and phenylsilane is the most suitable reagent for the job, having three available hydrides, and little steric hindrance.

The initial optimisation experiments reduced the reaction time down to a few hours, and identified 1.75 equiv TFA and 2.00 equiv phenylsilane as a key ratio of reagents. A more precise set of experiments was conducted to confirm these results (Table 1). The first three entries highlight the importance of the ratio of acid to silane. This ratio was later interpreted in terms of residual acidity; excess acid is required for the reaction to work. An excess of silane tends may lead to more silyl esters and a reduction in the concentration of free acid. Higher conversions to amine required in the range of 2 equivalents of acid and silane. Entries 4 and 5 introduced the amine as the HCl salt, and reduced the required level of TFA. That a better conversion to amine was observed over entry 2 suggests that the identity of the excess acid can be varied, and is not limited to carboxylic acids (although HCl salts of amines often encounter solubility issues). Entry 6 highlights further the importance of acid/silane ratio: decreasing the acid to 1.5 equivalents gave a significant conversion loss. Whilst running the reaction without precaution against moisture gave a comparable result (entry 8), it was, nonetheless, slightly less efficient than the controlled conditions (entry 7).

Table 1. Optimisation of the trifluoroethylation reaction.

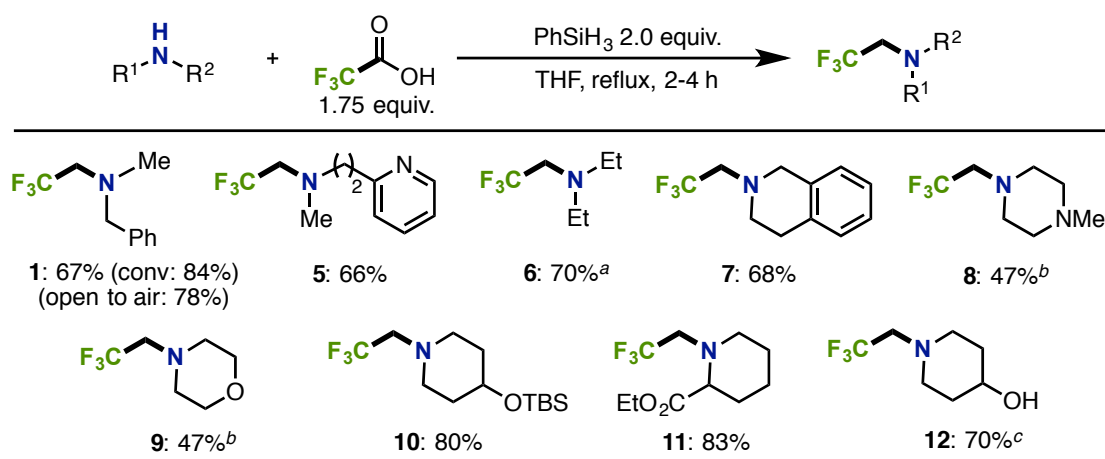
	solv	time /h	TFA equiv	PhSiH ₃ equiv.	additives/ conditions	amide %	amine %
1	tol	16	1.00	1.00	-	18	42
2	tol	16	1.00	2.00	-	43	39
3	tol	4	2.00	2.00	-	9	85
4	tol	4	1.00	2.00	amine.HCl	17	52
5	tol	4	1.00	2.00	amine.HCl + 1 drop Et ₃ N	31	50
6	THF	4	1.50	2.00	-	22	71
7	THF	4	1.75	2.00	-	8	84
8	THF	4	1.75	2.00	open to air/undried solvent	8	78
9	THF	3	1.75	2.00	-	6	80
10	THF	3	1.00	2.00	-	54	0

Finally, in THF, the ratio of acid/silane was shown to be even more important than in toluene (entry 10). Entry 7 was taken as our optimised conditions.

Scope of the Trifluoroethylation Reaction

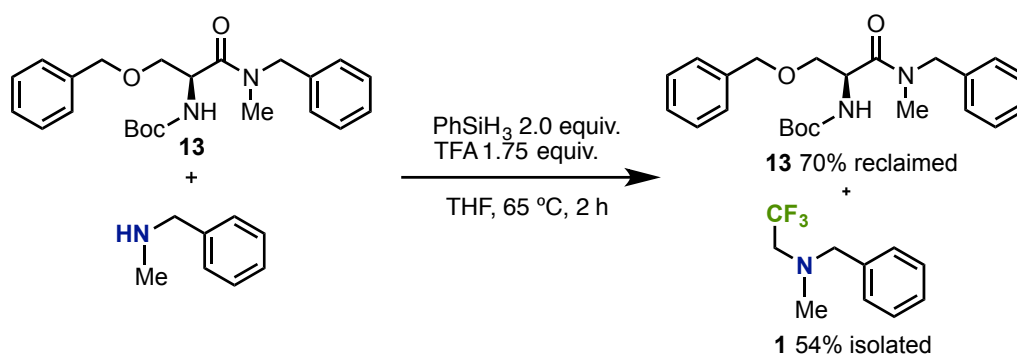
Early scope work was carried out in conjunction with R. Faizova to generate the following examples (Figure 2). Conversions were generally 70-90% for cyclic and acyclic, basic and deactivated amines, with losses during isolation due to volatility and solubility. Of interest was rarely reported compound **6**, the trifluoroethylated analogue of triethylamine, which may find use as a less basic hindered amine. The pK_a of the HCl salt of the amine was determined by potentiometric titration of 0.001 M NaOH into a solution of **30c** and found to be 5.2, comparable to related amines.^{41,42} Secondary alcohol **12** was quenched with aqueous sodium hydroxide to cleave *O*-silylated species before further purification.

Figure 2. Scope of the trifluoroethylation reaction



Reactions were performed on a 0.5 mmol scale in 0.6 mL of THF. Products were purified by an acid-base work-up; ^aIsolated by precipitation with 1M HCl in Et₂O. ^bproduct is volatile; ^cThe reaction was quenched with 1 M NaOH to desilylate the hydroxyl group. Compounds 6,7,8,9 synthesised by R. Faizova.

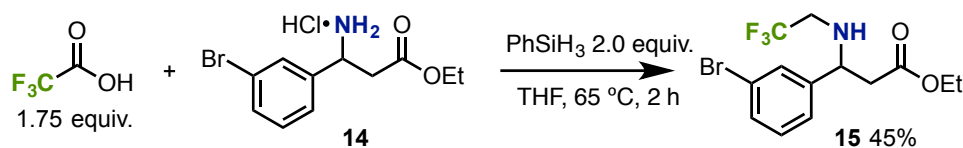
Functional groups tolerated included alcohols (**12**), TBS-ethers (**10**), amines/pyridines (**5,8**), esters (**11**), nitriles (MeCN) and ethers (**9**). Esters, ethers and nitriles were also shown to be tolerated in the solvent study; ethyl acetate, diethyl ether/THF and acetonitrile are all viable solvents. Tertiary amides and *N*-BOC protected amines were also tolerated as an external additive (Scheme 3, Faizova) (*the merits of inter and intra-functional group screening have been discussed.*)⁴³



Scheme 3. Tolerance of Boc groups to the reaction conditions.

Despite many attempts to trifluoroethylate primary amines, the reactions mainly produced mixtures of products. Typically trifluoroacetamides were recovered, or over-alkylated

species. One exception was the HCl salt of this primary amine, part of a β -amino acid, which gave a reasonable conversion to the desired amine (Scheme 4).

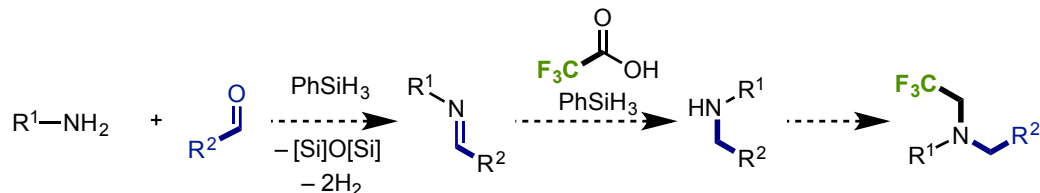


Scheme 4. A rare and low yielding example of a primary amine trifluoroethylation reaction.

Primary amines were investigated again at a later date (*vide infra*) but without success. This concludes the work performed in conjunction with R. Faizova.

Alkylation–Trifluoroethylation of Primary Amines

Having failed to adapt the reaction to primary amines (which we now believe to be inherently limited by the mechanism), we set about incorporating an initial alkylation step into the reaction (Scheme 5).



Scheme 5. Proposed reaction manifold for an alkylation-trifluoroethylation of primary amines.

The conditions lent themselves to a reductive amination with a primary amine and aldehyde, followed by *in situ* trifluoroethylation for the following reasons:

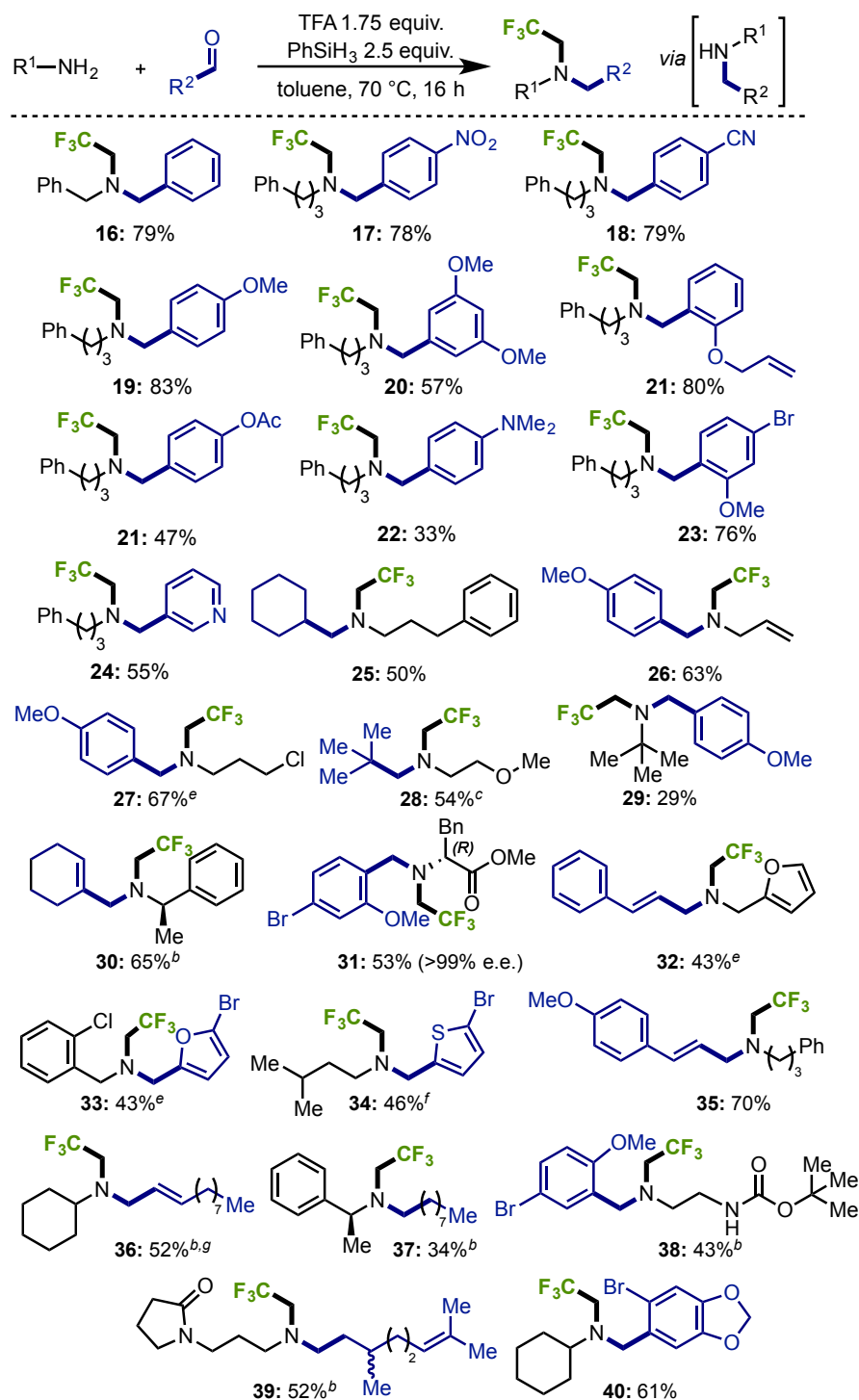
- the acidic conditions would promote imine formation.⁴² This step should typically be rapid enough to outcompete other reactions;
- the hydrosilane can consume the water produced, and drive the equilibrium to imine;

- c) PhSiH_3 and TFA have previously been used in the reduction of ketones. Although the acidity would be lower here, ketimines are generally more susceptible to activation and reduction due to their increased Lewis basicity;
- d) The resulting secondary amines should undergo our trifluoroethylation reaction *in situ*.
- e) The reduced basicity of the tertiary amines due to the induction from the trifluoroethyl group should enhance the separation of the desired product relative to other products formed.

The reaction was tried by first mixing a primary amine and aldehyde, adding 0.5 equivalents of phenylsilane, and heating for 10 min to drive imine formation and consume any water. Then 1.75 equiv TFA and 2.00 phenylsilane were added and the reaction refluxed, with the hope that a reduction and typical trifluoroethylation reaction would follow. In the event, the reaction proved successful, and we optimised the reaction and surveyed the reaction scope. The scope that follows represents the effective testing of two reactions; the new three-component coupling, *and* the standard trifluoroethylation of secondary amine, which is part of the process. Although the reaction could be performed in THF, toluene was utilised in order to increase the temperature for less reactive amines/aldehydes. The scope of the reaction proved to be very wide, tolerating many reducible functional groups, and allowing significantly-functionalised, non-basic tertiary amine cores to be generated (Figure 3).

Most pleasing was the tolerance of a range of reducible functionality; alkenes (Figure 3; **21**, **26**, **30**, **32**, **35**, **36**, **39**), esters (**21**, **31**), nitro (**17**), nitrile (**18**), amides (**39**), and aryl halides (**23**, **31**, **33**, **34**, **38**, **40**) were retained during the reaction. Acid sensitive functional groups such as BOC-protected amines (**38**) and furans (**32**, **33**) are also tolerated. The stereointegrity of amino acid derivative **31** was preserved.

Figure 3. Scope table for the three-component alkylation-trifluoroethylation of primary amines

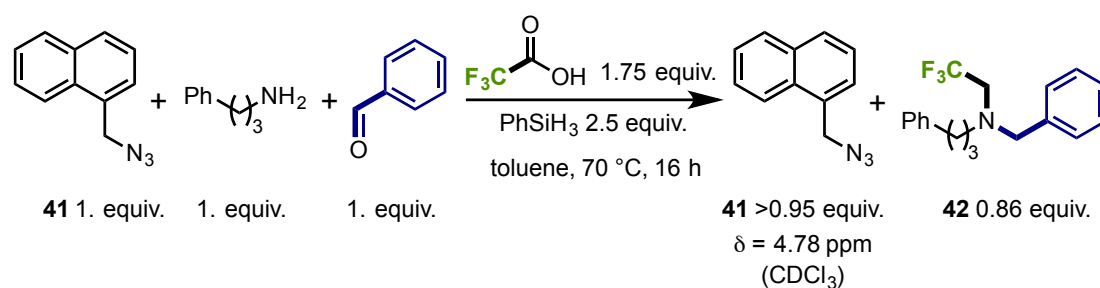


^a Typically, amine (0.50 mmol) and aldehyde (0.50 mmol), toluene (0.5 mL) and PhSiH₃ (0.25 mmol) were stirred for 10 min at 70 °C. TFA (0.875 mmol) and further PhSiH₃ (2.0 mmol) were added and the reaction heated at 70 °C for 16 h. Slight timing/temperature modifications are described in the experimental section for:

^b Method B (alkyl aldehydes), ^c Method C/D (hindered aldehydes), ^d 5.00 mmol scale from HCl salt of amine,

^e trifluoroacetic acid (1.50 mmol) used. ^f trifluoroacetic acid (1.00 mmol) used, ^g as mixture of 93:7 trans:cis alkenes.

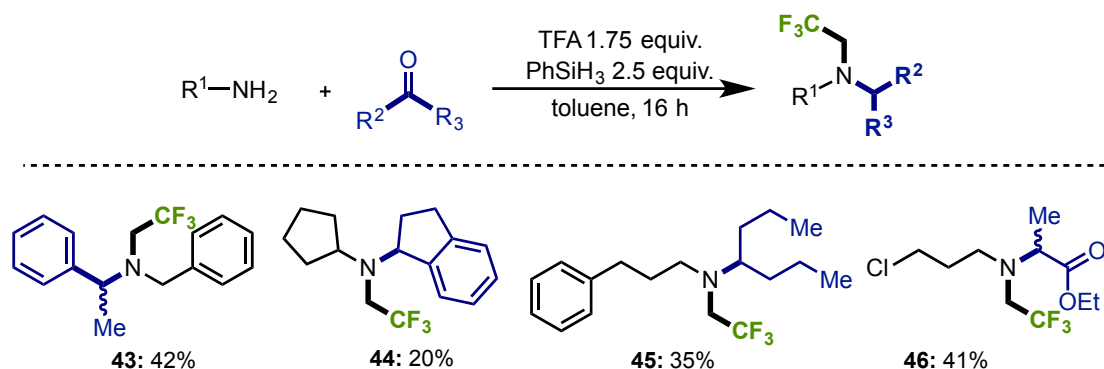
Phenolic acetate **31** suffered from some transamidation/deacetylation. Moderately basic amines (e.g. **22**, **24**) tend to give lower conversions, but still work. Alkyl chloride **27** was prepared at gram-scale (5.00 mmol) from the HCl salt of the amine. Typically, an initial imine-forming period was followed by the standard reaction, with minor timing/temperature adjustments beneficial (+10-20% conversion) for difficult substrates. Hindered imines, for example, required higher temperatures. Slight excesses of trifluoroacetic acid were used for substrates containing coordinating heteroarenes (**32-34**). Stabilised aldehydes (benzaldehydes, enals) performed better than alkyl aldehydes. Alkyl aldehydes are more reactive with respect to forming aminals or returning to the aldehyde, and so primary amine off-pathway reactions (amidation, trifluoroethylation of the primary amine, over-alkylation) were more frequent. More hindered alkyl aldehydes (**25**, **28**, **39**) performed better. Azides, such as **41**, were also tolerated when introduced as an additive, and did not interfere with the formation of product **42** (Scheme 6).



Scheme 6. Demonstration of azide tolerance under the reaction conditions.

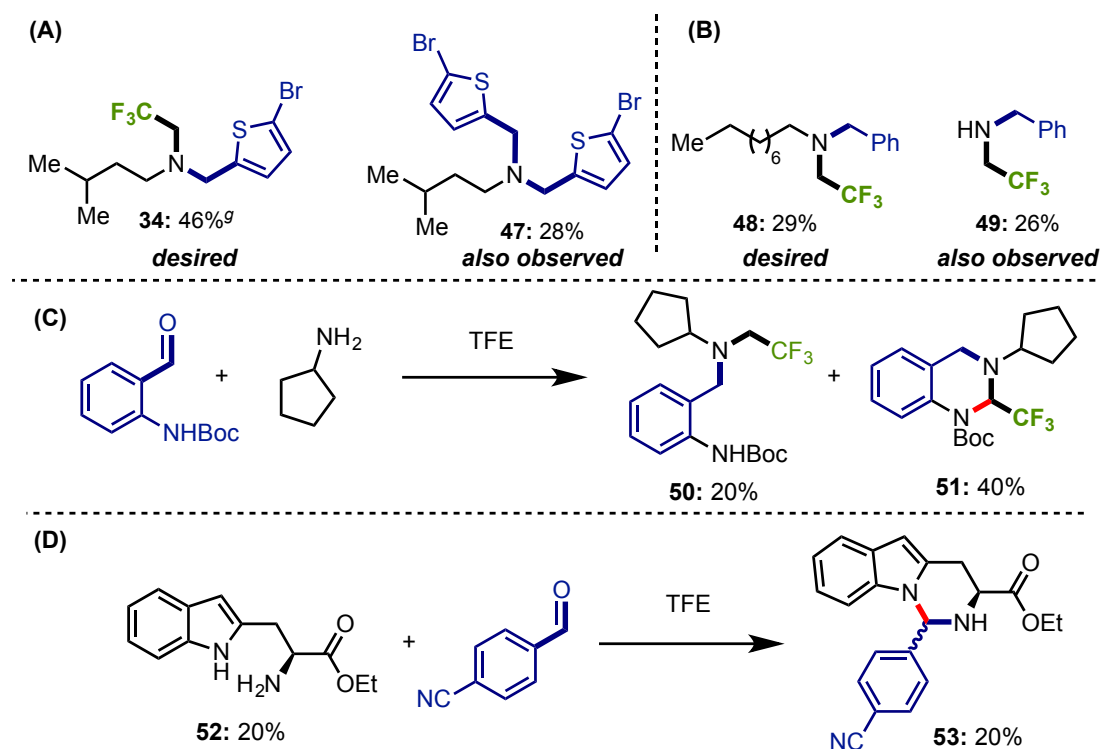
The procedure was also amenable to ketones (Figure 4; **43–46**), although the yields were lower. Amine **46** is an interesting trifluoroethylated amino acid derivative synthesised from ethyl pyruvate.

Figure 4. Scope of the alkylative trifluoroethylation reaction with ketones



Some of the competing reactions observed during the reaction are shown in Figure 5. Over-alkylation (Figure 5A) is a common problem (e.g. to form species such as **47**), rectified, at least in part, by a better imine formation and reduction.

Figure 5. Competing reactions; (A) over alkylation; (B) under alkylation; (C) Internal trapping of partially reduced intermediates during trifluoroethylation; and (D) internal trapping of imine or imidate intermediates before trifluoroethylation.



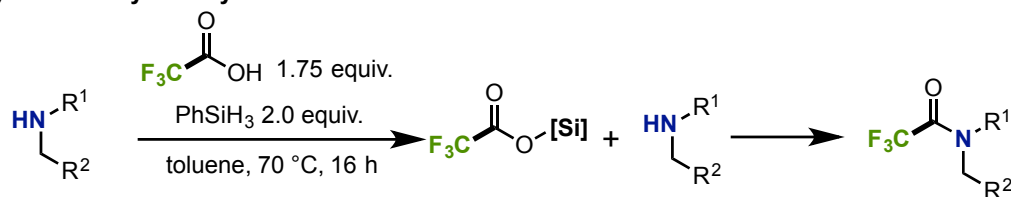
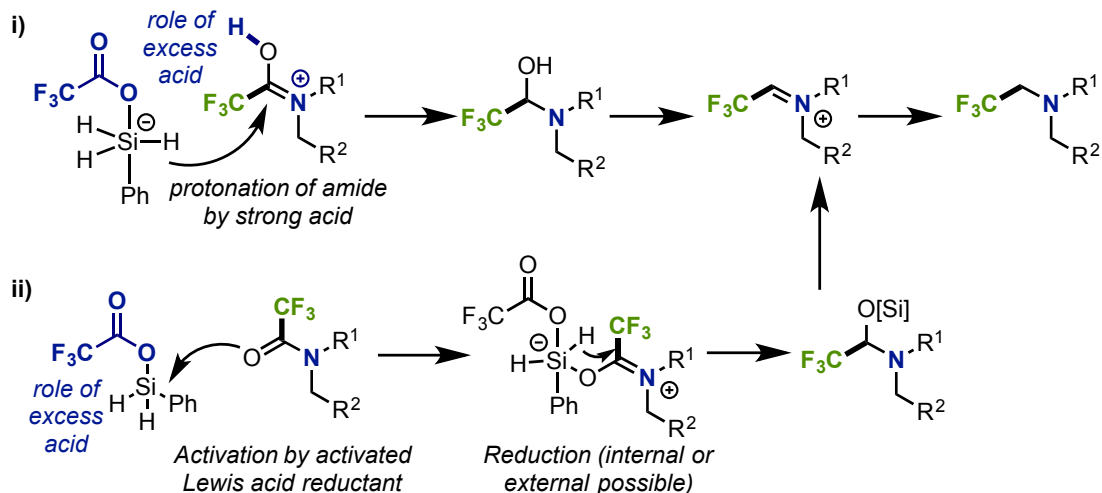
Over-alkylation leads to an excess of free primary amine (relative to aldehyde), and this primary amine can sometimes undergo a small amount of trifluoroethylation (e.g. to **49**) or amidation to the trifluoroacetamide (Figure 5B). Both the initial imine (Figure 5D) and a partially reduced CF₃ imidate (Figure 5C) are susceptible to intramolecular trapping (i.e. as species such as **53** and **51**). Low levels of amidation of the secondary amine is also seen for many substrates. The order of the reaction steps (alkylation, then trifluoroethylation) is supported both by our observation that primary amines are poor substrates, and also that trifluoroethylated amines are slow to form both carbinolamines and imines.⁴²

Mechanism of the Trifluoroethylation Reaction

The mechanism of this intriguing and unexpected reaction remains beyond our full understanding at this point in time. The first pathway we sought to rule out is discussed first.

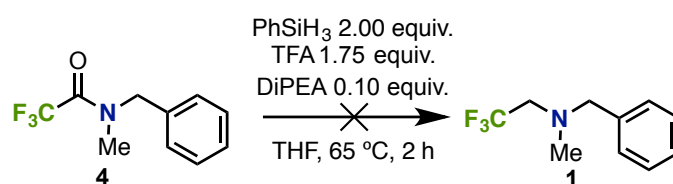
1) Reduction of an in situ generated amide (discredited)

Our initial hypothesis was that the reaction proceeded as for our amidation reaction, and that the amide was subsequently reduced. We supposed that either the presence of a strong acid could protonate the amide (Scheme 7B-i), or that an *in situ* generated silyl ester would act as an activating agent (Scheme 7B-ii), on account of its increased Lewis acidity. In both cases, the activated amide would be susceptible to reduction (Scheme 7).

(A) Base-catalysed silyl ester formation and amidation**(B) Acid or Lewis-acid activation of amide and subsequent reduction**

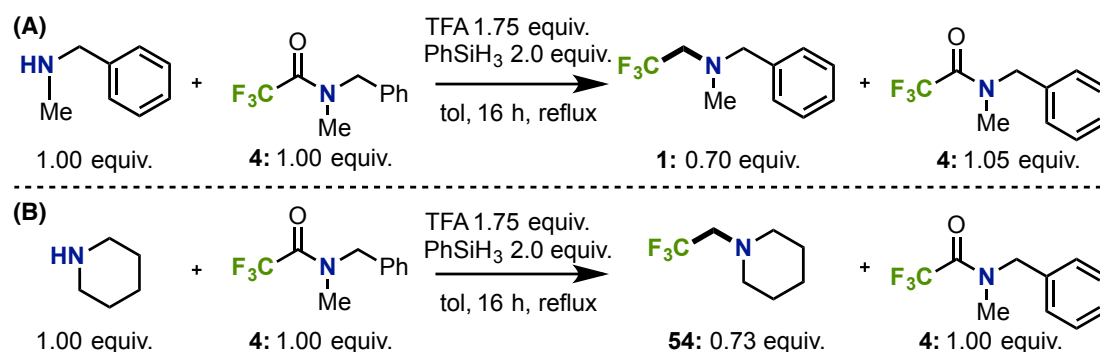
Scheme 7. Hypothesis 1: (A) *In situ* generation of the amide via the silyl ester followed by; (B) Reduction via i) protonation of the amide and reduction or ii) Activation by a Lewis acidic silyl ester and reduction.

We were excited that if this pathway were occurring we might be able to develop a metal-free reduction of amides, catalysed instead by trifluoroacetic acid. Needless to say, this motivated us to explore this possibility thoroughly. However, every experiment gave a clear result; amides are not reduced under the reaction conditions. First, we attempted the reaction with a tertiary base additive in place of the amine to see if an external amide would be reduced. We ran the standard reaction, with 10 mol% DiPEA in place of the secondary amine and 1 equivalent of amide **4**. Whilst the typical hydrogen formation (silyl ester formation) took place, the amide was untouched after 2 h at reflux (Scheme 8).



Scheme 8. Amide not reduced under conditions in which an activated reductant might be formed.

Next, we replicated the reaction conditions more completely, this time performing the desired transformation in the presence of 1 equivalent of an amide additive. In both the case of a different amide (**4**, in B), and the same amide that would be formed (**4**, in A), being present, no reduction was observed (Scheme 9), but product amine was generated.



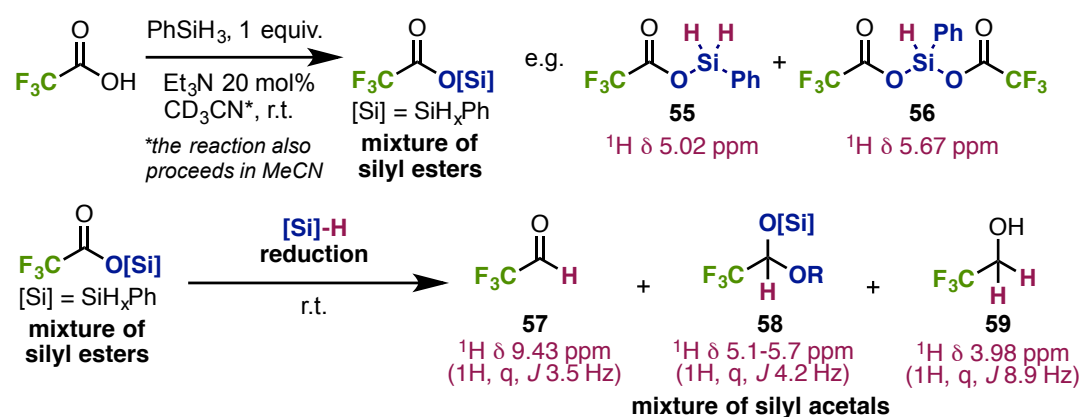
Scheme 9. Amides are not reduced under the reaction conditions. (additional evidence: tolerance of basic amide **39** in Figure 3 and **13** in Scheme 4)

Later, once we had finished investigating the scope tables shown above, it became clear that activated reducing agents could not be responsible, nor could any Lewis basic advantage be operative; a trifluoroacetamide is a poor Lewis base, and therefore any reducing agent that could reduce this amide would be unlikely to tolerate the extensive range of functional groups tested, including esters, carbamates and more basic tertiary amides. We put this hypothesis aside, convinced it was not operative.

2) Reduction of the trifluoroacetic acid to trifluoroacetaldehyde and subsequent reductive amination

This hypothesis was put forward as the next most likely route. The electron poor trifluoroacetic acid could easily be more susceptible to reduction than a regular carboxylic acid, and thus privileged behaviour might be observed in proportion to the pK_a of the acid. The reduction of the acid to aldehyde could be selective over other functional groups *via* the intermediacy of a silyl ester, because the required hydride transfer could be intramolecular.

Furthermore, no further difficult reductions would be required, as the following reductions would be of imines or iminiums. Reduction of carboxylic acids is known with silanes, although only under metal-catalysed conditions. We sought therefore to accumulate evidence of any aldehyde formation. Experiments of the type shown below were attempted. In this experiment, a tertiary amine is used, which is able to catalyse the formation of silyl esters without the ability to undergo amination or amidation. We monitored the reaction mixture by ^1H -NMR (Scheme 10).

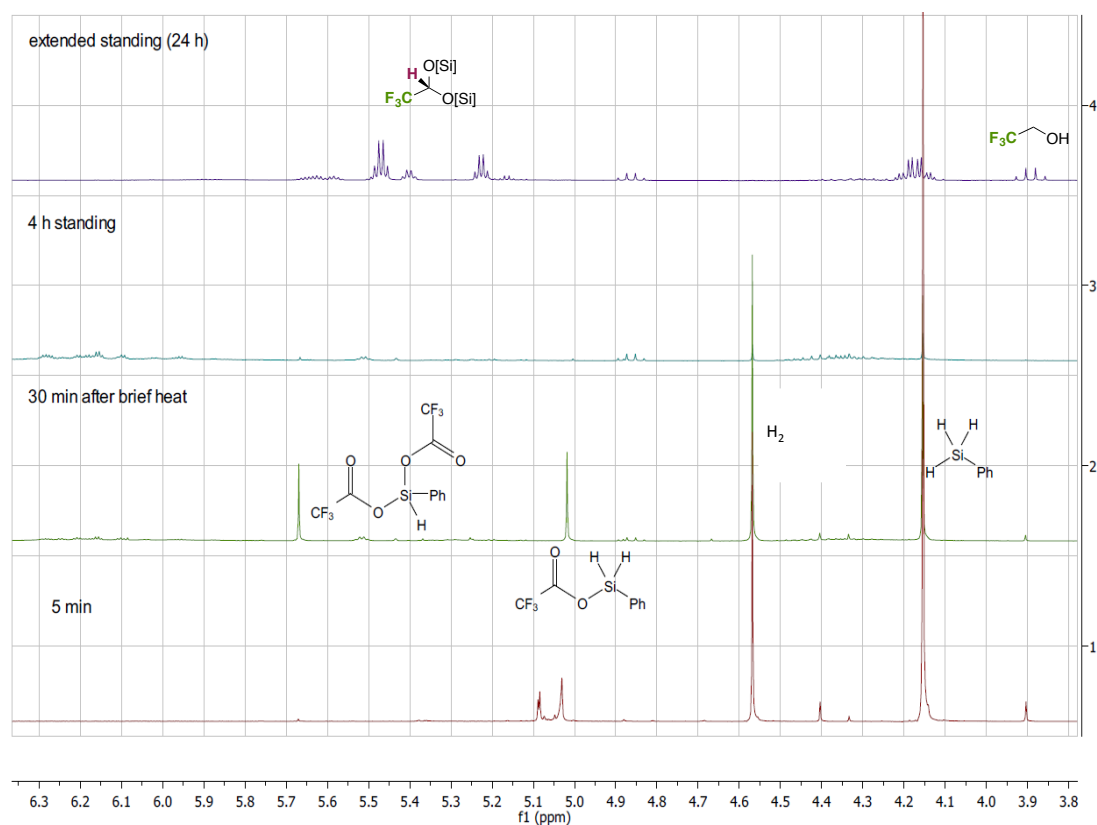


Scheme 10. Attempts to observe the aldehyde under conditions in which amine/amide etc cannot form ($R = \text{Si}$ or H)

However, the reaction mixture proved difficult to interpret. Initially, silyl esters were observed, assigned by analogy to the species synthesised from the chlorosilanes in Chapter 2. After 30 min and a brief period of heating (the NMR tube was brought cautiously to reflux and cooled again), the Si–H signals of the mono and bis-silyl esters were visible (Figure 6, below). But these species reacted divergently. After 4 h, nearly all of the silane hydride signals were diluted amongst many unidentifiable species, with weak signals visible between 4 and 7 ppm. However, (somewhat fortuitously) the same sample was analysed again after standing for 24 h, despite the lack of promise after 4 h. Now, distinct quartets were visible, drawing attention because of the possibility that new hydrogen atoms adjacent to a CF_3 group would appear as a quartet. After careful analysis, and consulting the literature, these signals were assigned as silylated acetals – partially reduced products of trifluoroacetoxysilyl

esters, at the aldehyde oxidation state ($^3J_{HF} = 4.2$ Hz).⁴⁴ Further, trifluoroethanol was identified at 3.98 ppm ($^3J_{HF} = 8.9$ Hz). Additionally, a very small amount of trifluoroacetaldehyde was visible (9.43 ppm; q, $^3J_{FH} = 3.5$ Hz).

Figure 6. ^1H -NMR evidence of silyl esters and reduced forms (acetals) and trifluoroethanol

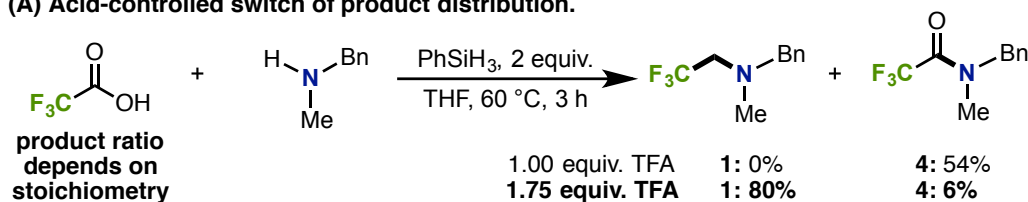


Given that reduced species were observed, it seemed likely that they represent a possible pathway. Whether they constitute the main pathway is still uncertain, due to the immense difficulty in observing these reactive intermediates, which as well as being too short lived to examine under the reaction conditions, also exist on a variety of siloxane polymers, preventing identification of any discrete species.

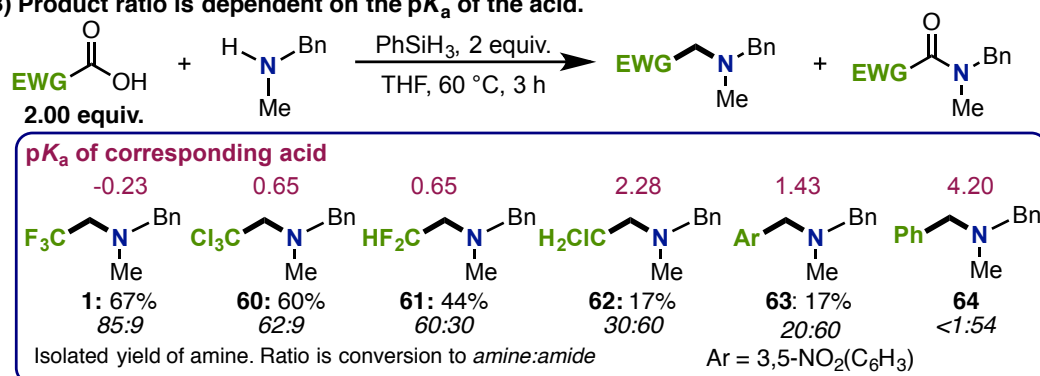
We next considered why the desired trifluoroethylamine was observed only in the presence of excess strong acid. Firstly, we repeated some experiments from the optimisation process and observed that in the presence of 1 equivalent of TFA only amide was formed in

moderate yield (54%). However, in the presence of 1.75 equivalents of TFA, 80% amine was observed, along with 6% amide (Scheme 11A).

(A) Acid-controlled switch of product distribution.



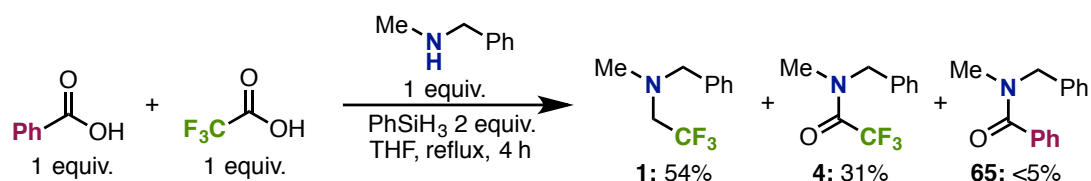
(B) Product ratio is dependent on the pK_a of the acid.



Scheme 11. (A) Amine is only observed with excess acid; (B) Amine is only observed if acid is sufficiently acidic.

If 1.50 equivalents TFA were utilised, the ratio of amine to amide was 71:22, an intermediate level. Clearly, then, the amount of acid present acts as a switch; excess acid is required to give amine product, otherwise amide prevails. The second set of experiments (Scheme 11B) show what happens when the pK_a of the acid is increased towards a typical acid (benzoic acid). Trichloro-, difluoro- and chloro-acetic acids, along with dinitrobenzoic acid, all give intermediate ratios of amine to amide. On this evidence, any α -fluoro- or chloro- acid should give a reasonable yield of alkylated product, allowing bespoke alkylation reactions and difluoroethylations.

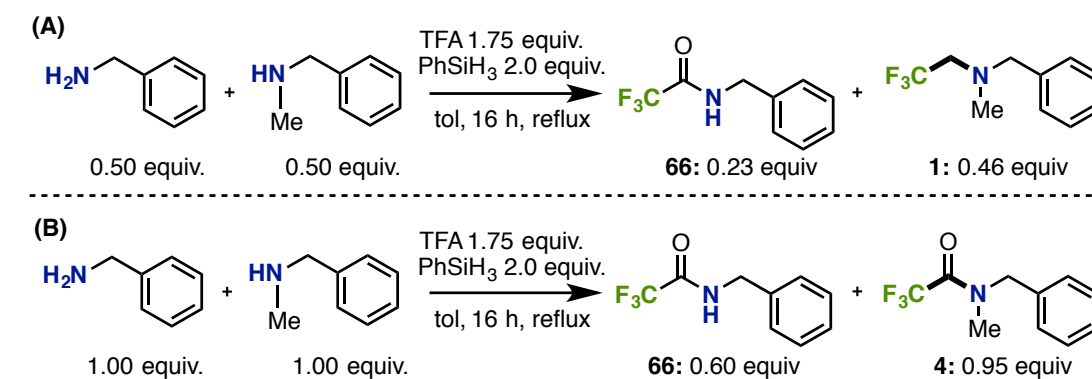
Next, a competition experiment was performed that demonstrated that it was the nature of the acid that led to *in situ* reduction, and hence amination. Benzoic acid and trifluoroacetic acids were combined (one equivalent each) and subjected to the trifluoroethylation experiment (Scheme 12).



Scheme 12. Competition between trifluoroacetic acid and benzoic acid: only acidic acids are reduced to give amine under the reaction conditions.

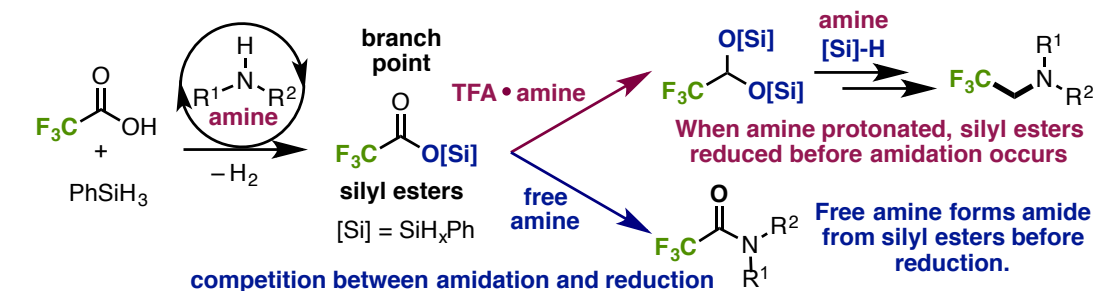
Only the amine of trifluoroacetic acid is seen; benzoic acid does not undergo reductive amination under the same conditions. It is noted that the ratio of amine to amide was intermediate between highly acidic (1.75 equivalents of TFA) and less acidic (1.00 equivalents TFA) conditions, demonstrating once more the role of excess acid as a switch. Additionally, the trifluoroacetic acid far outcompetes the benzoic acid in terms of conversion. This is likely due to the increased electrophilicity towards nucleophilic attack, and the fact that acidic acids have been shown to displace less acidic acids from silyl esters under acidic conditions (see Chapter 2).⁴⁵ Further, it demonstrates it is only the highly electrophilic acid that is reduced under the reaction conditions. In other words, TFA does not necessarily act as a Brønsted acid to activate the silyl esters for reduction (although it might do), as no benzaldehyde-derived products were observed; the major benzoic acid-derived product here was the amide. Trifluoroacetic acid is likely privileged towards reduction due to its high electrophilicity.

Next we competed two amines under the reaction conditions, 1 primary and 1 secondary. Firstly, at half an equivalent each, benzylamine and *N*-methylbenzylamine were subjected to the trifluoroethylation reaction. The secondary amine underwent smooth trifluoroethylation to **1** in 92% conversion (0.46 equivalents). The primary amide, however, only underwent *amidation* to **66**, at a moderate 46% conversion. It would appear, therefore, that secondary amines have an inherent structural privilege to form the trifluoroethylamine (Scheme 13A).



Scheme 13. Competition reactions between primary and secondary amines highlight the fast reaction of the secondary amine, and its tendency to form the amine over the amide, even in the same reaction pot.

The second competition experiment (Scheme 13B), in which a whole equivalent of each amine was utilised, again demonstrated that it is excess acid that primarily controls the amine:amide switch. With no excess acid, both amines formed amide only, with the secondary amine (95% amide **4**) again outcompeting the primary amine (60% amide **66**) (Scheme 13B). With the foregoing experiments in mind, the following reaction mechanism seems to fit the evidence best. Firstly, a mixture of silyl ester species is generated via the typical base-catalysed dehydrogenation reaction (Scheme 14).

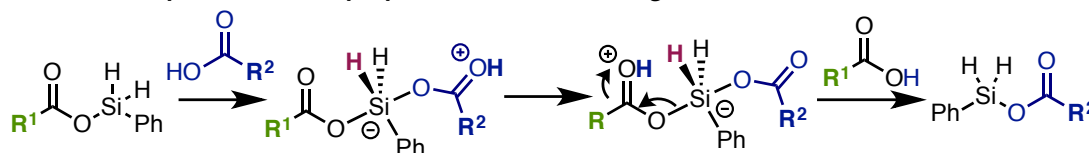


Scheme 14. Proposed reaction mechanism for the trifluoroethylation process

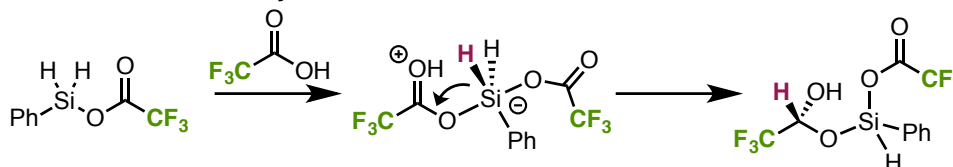
These silyl esters would ordinarily act as acylating agents to form amide. Indeed, in the absence of excess acid, they react with the amine to form amide (bottom pathway). However, due to the presence of the excess strong acid under the trifluoroethylation conditions, we suppose that the amine is protonated, and therefore slow to acylate. In this case, the reduction of the highly electrophilic trifluoromethyl silyl ester species to the

aldehyde oxidation level is competitive. We have not investigated whether this reduction is inter or intramolecular, but an intramolecular hydride transfer upon complexation with an external activator seems highly plausible. Recalling Kozuka's proposed mechanism for carboxylic acid exchange at acyloxysilanes (Scheme 15A) in which proton transfer is limiting (Chapter 2),⁴⁵ we might suppose that a similar process can occur here, with one minor difference; after coordination of the incoming carboxylic acid, instead of carboxylate ejection, a 1,3-hydride transfer would lead to the reduced acid product (Scheme 15B). The similarities with proposed mechanisms for the selective borane reduction of carboxylic acids should be noted.

(A) Kozuka's proposed exchange of carboxylic acids at acyloxysilanes:
proton transfer proposed to be rate-limiting



(B) Potential mechanism for reduction of the silyl ester intermediate:
coordination and hydride transfer rather than substitution

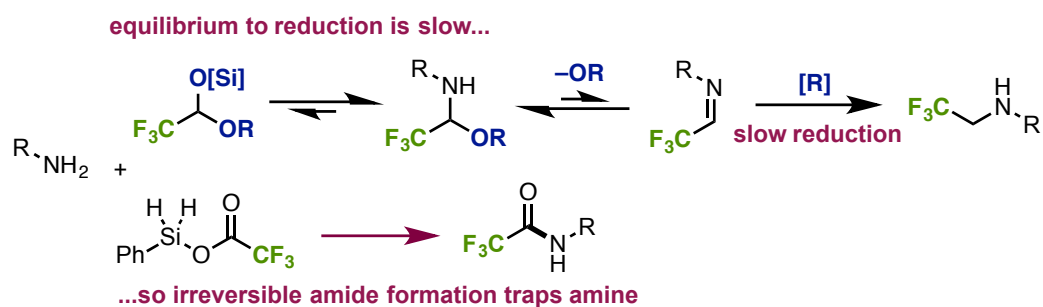


Scheme 15. (A) Kozuka's carboxylic acid exchange mechanism. b) Analogous reaction, putatively leading to intramolecular hydride transfer and reduction in the present case.

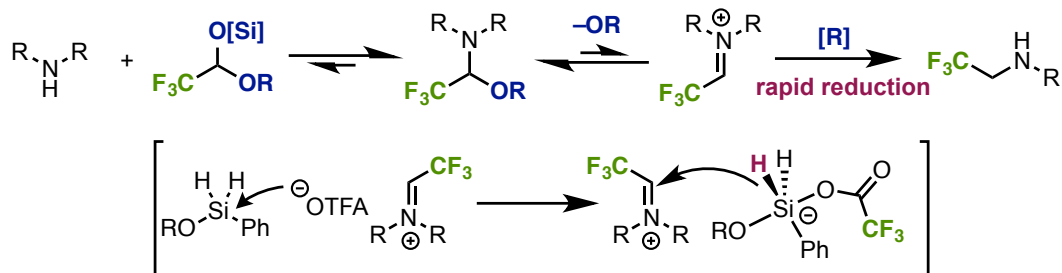
This pathway offers a more detailed explanation for the additional molecule of acid required. In this depiction, the extra acid attacks an existing silyl ester (base-catalysed, as demonstrated by Kozuka), generating a species that undergoes a redox exchange (carbonyl is reduced, silane is oxidised). Whatever the mechanism of reduction (which would be difficult to demonstrate), the reaction of the resulting silyl acetals is easier to speculate upon. The amine may then deprotonate the newly formed hemiacetal, eliminate siloxide and trifluoroacetaldehyde, which it immediately traps as the hemiaminal. Alternatively, an acid-

promoted reaction may give the aldehyde and silanol. Regardless, acetal species of trifluoroacetaldehyde are known to undergo reductive amination reactions, as shown by Mimura.²⁰ Trifluoromethyl carbonyl species are known to preferentially exist in an acetal form, whether it be the hydrate in water, the hemiacetal in alcohols, or the hemiaminal (or aminal) in the presence of an amine. It is this tendency that allows a suggestion of an explanation for the different reactivity of primary and secondary amines. Primary amines would form neutral imine species upon hydrolysis of trifluoroacetaldehyde (or derivatives), whilst secondary amines would form highly electrophilic iminium ions (Scheme 16).

(A) Primary amines form neutral intermediates and may be slow to be reduced



(B) Secondary amines form charged intermediates which are easily reduced



Scheme 16. Primary (A) and secondary (B) amines have an inherent structural difference that leads to differing reactivity.

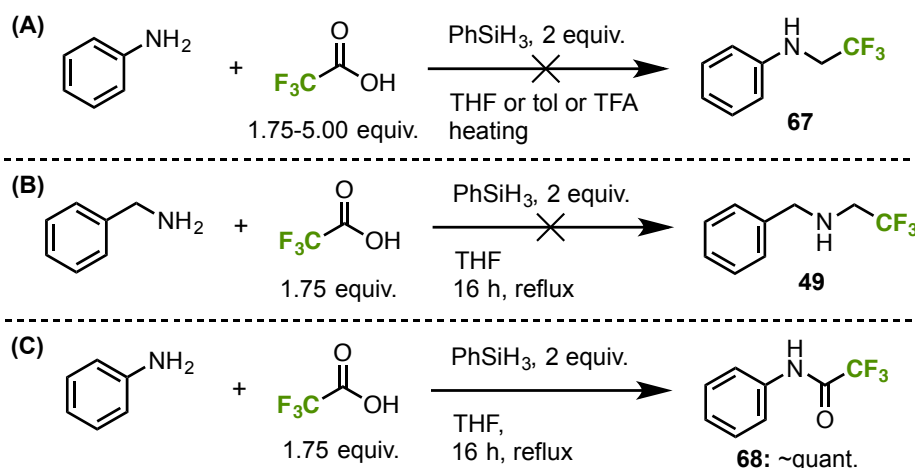
Not only are the iminium ions formed in the case of the secondary amines more electrophilic with respect to reduction, they also have a counterion. As shown in Scheme 16B, the counterion, perhaps a trifluoroacetate or siloxide anion, can activate a silane molecule for reduction. This process might thus be considered a form of dual activation, in which both the nucleophile and electrophile are activated.

In conclusion, as far as the mechanism is concerned, the exact details are unknown. However, we have ruled out amide reduction, and demonstrated that partially reduced intermediates are formed under similar reaction conditions. These intermediates are known to undergo reductive amination reactions. We have also provided details of several competition experiments and stoichiometry and pK_a studies that support our hypothesis. Firstly, we have proposed that the excess acid plays a role in preventing amine attack of silyl esters until reduction has occurred. The excess acid may also play a role in promoting the reduction of existing silyl esters to the acetal oxidation level. Secondary amines have been proposed to undergo a facile reduction as compared to primary amines due to the formation of highly reducible iminium cations instead of neutral imines, as even in a competition experiment, primary amines formed only amide.

Anilines and Primary Amines

We were keen to expand the scope of the reaction to anilines; a brief summary of further studies within the group are given here.⁴⁶ Attempts to trifluoroethylate *N*-methylaniline under the standard conditions did not give conversions exceeding 40%. Aniline did not produce more than trace quantities of the desired secondary amine under a number of different conditions; neither did benzylamine (Scheme 17).

We reasoned that aniline was insufficiently nucleophilic to form the required imine for reduction, or perhaps favoured amidation due to its decreased basicity; aniline reacted under the standard amidation conditions to give an unexpectedly high conversion to amide (c.f. Chapter 2: aniline reacts only to ~ 30% conversion with 1 equivalent of less acidic acids, e.g. benzoic acid).

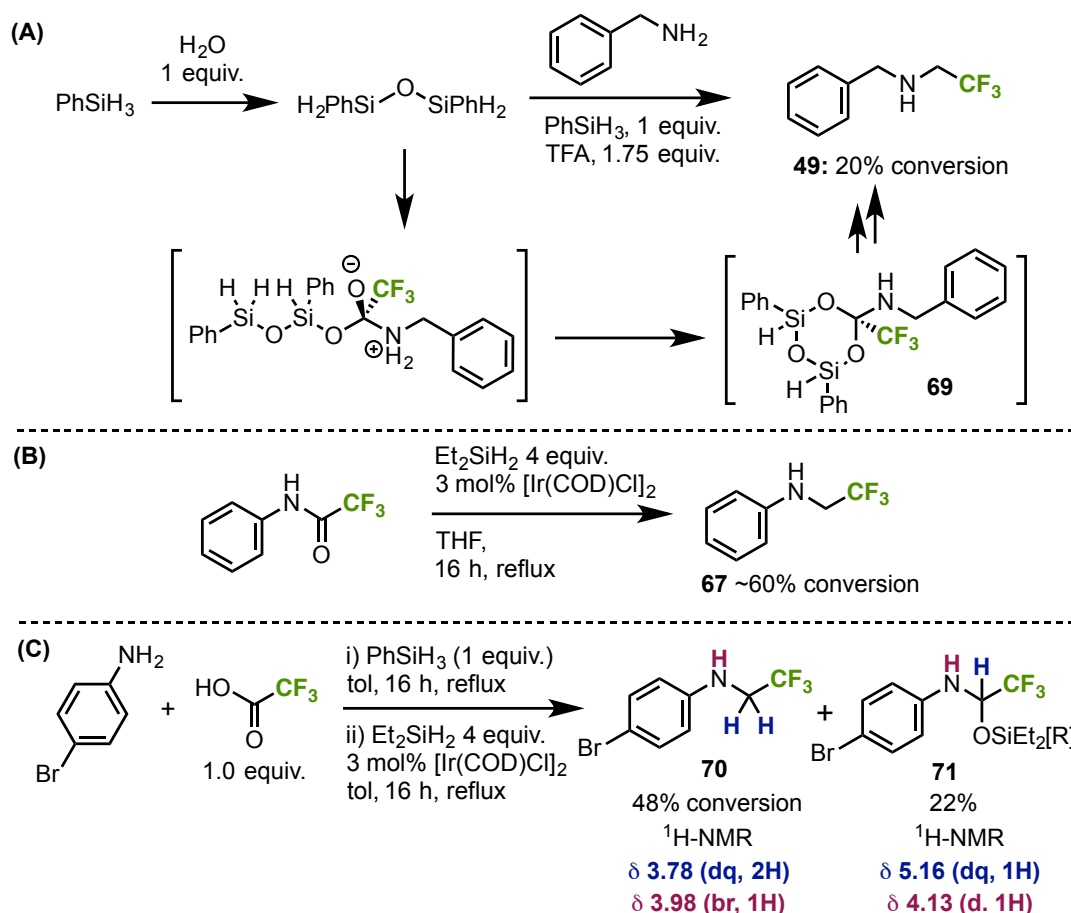


Scheme 17. Neither aniline nor benzylamine gave any desired amine when subjected to the trifluoroethylation conditions (and variants)

We therefore attempted to use 1,3-diphenyldisiloxane (the disiloxane of phenylsilane) as the silane component, hoping that it would provide a way of enhancing the silylation of the acetal or tetrahedral intermediates by bringing a second silane centre into close proximity. Although the reaction failed for aniline, it succeeded in generating 20% of the trifluoroethylated amine when benzylamine was used as the amine Scheme 18 shows the thought process behind the reaction design.

As depicted, we initially thought that the tetrahedral intermediate of amine attack at a silyl ester might play a role in the reaction mechanism. In this case, we hoped we might trap this intermediate to generate bis-silylated intermediate **69**, which would then begin eliminating silanol to form imines or carboximides that might be susceptible to reduction. Tetramethyldisiloxane was briefly investigated as a cyclic silane in this capacity, but failed to demonstrate the desired activity. It may well be worth re-examining, as Nagashima has exemplified related reactivity. The reduction of trifluoroacetanilide using the Brookhart conditions did provide the desired trifluoroethylaniline (Scheme 18B). The two-step-one-pot amidation/reduction procedure gave moderate conversions (Scheme 18C), but

required significant reaction times, and was prone to becoming stuck at the silylated hemiaminal.



(it is uncertain what the final group on the silane of species **70** is: it is plausibly the silanol, as the silyl hydride species cannot be identified in the proton NMR.)

Scheme 18. A) Attempt at trapping a putative tetrahedral intermediate did give a higher conversion than starting from phenylsilane; B) Reduction of trifluoroacetanilide using the Brookhart reduction conditions; C) One-pot synthesis of trifluoroethylaniline leading to acetal species.

Chapter Conclusions

We have developed a novel trifluoroethylation reaction of secondary amines, arising from an intriguing *in situ* reduction pathway. The reaction uses trifluoroacetic acid as a convenient trifluoroethyl source, and phenylsilane as the mediator of the chemistry, and terminal reductant. The reaction was exemplified primarily through an additional reaction – an alkylative trifluoroethylation of primary amines – in which an amine and aldehyde are combined to give a secondary amine *in situ*, before the trifluoroethylation reaction proceeds.

This reaction showed unprecedented scope and tolerance of many reducible functional groups, far exceeding the current scope of any other reductive syntheses. This protocol offers several distinct advantages over existing methodologies, notably practical ease and step efficiency, functional group tolerance, safety and robustness, even in the presence of air and moisture. The generation of tertiary trifluoroethylated amine cores represents a novel method to access highly functionalised species that may prove useful in drug design due to the significantly decreased basicity of the amine centre.

References

- 1 T. Liang, C. N. Neumann and T. Ritter, *Angew. Chem. Int. Ed.*, 2013, **52**, 8214–8264.
- 2 D. O'Hagan, *Chem. Soc. Rev.*, 2008, **37**, 308–319.
- 3 G. Klöter, W. Lutz, K. Seppelt and W. Sundermeyer, *Angew. Chem. Int. Ed.*, 1977, **16**, 707–708.
- 4 M. Morgenthaler, E. Schweizer, A. Hoffmann-Röder, F. Benini, R. E. Martin, G. Jaeschke, B. Wagner, H. Fischer, S. Bendels, D. Zimmerli, J. Schneider, F. Diederich, M. Kansy and K. Müller, *ChemMedChem*, 2007, **2**, 1100–1115.
- 5 A. Avdeef, *Absorption and Drug Development*, John Wiley & Sons, Inc., Hoboken, NJ, USA, 2003.
- 6 A. Avdeef, *Curr. Top. Med. Chem.*, 2001, **1**, 277–351.
- 7 M. B. van Niel, I. Collins, M. S. Beer, H. B. Broughton, S. K. Cheng, S. C. Goodacre, A. Heald, K. L. Locker, A. M. MacLeod, D. Morrison, C. R. Moyes, D. O'Connor, A. Pike, M. Rowley, M. G. Russell, B. Sohal, J. A. Stanton, S. Thomas, H. Verrier, A. P.

- Watt and J. L. Castro, *J. Med. Chem.*, 1999, **42**, 2087–2104.
- 8 E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly and N. A. Meanwell, *J. Med. Chem.*, 2015, **58**, 8315–8359.
- 9 Z. Rappoport, *The Chemistry of Anilines, Part 1*, John Wiley & Sons, 1st edn., 2007.
- 10 D. Alberati, D. Hainzl, S. Jolidon, E. A. Krafft, A. Kurt, A. Maier, E. Pinard, A. W. Thomas and D. Zimmerli, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 4311–4315.
- 11 B. Fermini and A. A. Fossa, *Nat. Rev. Drug Discov.*, 2003, **2**, 439–447.
- 12 C. Jamieson, E. M. Moir, Z. Rankovic and G. Wishart, *J. Med. Chem.*, 2006, **49**, 5029–5046.
- 13 W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359–4369.
- 14 J. T. Palmer, C. Bryant, D.-X. Wang, D. E. Davis, E. L. Setti, R. M. Rydzewski, S. Venkatraman, Z.-Q. Tian, L. C. Burrill, R. V Mendonca, E. Springman, J. McCarter, T. Chung, H. Cheung, J. W. Janc, M. McGrath, J. R. Somoza, P. Enriquez, Z. W. Yu, R. M. Strickley, L. Liu, M. C. Venuti, M. D. Percival, J.-P. Falgoutyret, P. Prasit, R. Oballa, D. Riendeau, R. N. Young, G. Wesolowski, S. B. Rodan, C. Johnson, D. B. Kimmel and G. Rodan, *J. Med. Chem.*, 2005, **48**, 7520–7534.
- 15 R. Vorberg, N. Trapp, D. Zimmerli, B. Wagner, H. Fischer, N. A. Kratochwil, M. Kansy, E. M. Carreira and K. Müller, *ChemMedChem*, 2016, **11**, 2216–2239.
- 16 Q. A. Huchet, B. Kuhn, B. Wagner, N. A. Kratochwil, H. Fischer, M. Kansy, D. Zimmerli, E. M. Carreira and K. Müller, *J. Med. Chem.*, 2015, **58**, 9041–9060.
- 17 F. Xu, M. Zacuto, N. Yoshikawa, R. Desmond, S. Hoerrner, T. Itoh, M. Journet, G. R.

- Humphrey, C. Cowden, N. Strotman and P. Devine, *J. Org. Chem.*, 2010, **75**, 7829–7841.
- 18 J. L. Adams, J. C. Boehm, T. F. Gallagher, S. Kassis, E. F. Webb, R. Hall, M. Sorenson, R. Garigipati, D. E. Griswold and J. C. Lee, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 2867–2870.
- 19 A. van Oeveren, M. Motamedi, N. S. Mani, K. B. Marschke, F. J. López, W. T. Schrader, A. Negro-Vilar and L. Zhi, *J. Med. Chem.*, 2006, **49**, 6143–6146.
- 20 H. Mimura, K. Kawada, T. Yamashita, T. Sakamoto and Y. Kikugawa, *J. Fluor. Chem.*, 2010, **131**, 477–486.
- 21 J. C. Wong, G. Tang, X. Wu, C. Liang, Z. Zhang, L. Guo, Z. Peng, W. Zhang, X. Lin, Z. Wang, J. Mei, J. Chen, S. Pan, N. Zhang, Y. Liu, M. Zhou, L. Feng, W. Zhao, S. Li, C. Zhang, M. Zhang, Y. Rong, T.-G. Jin, X. Zhang, S. Ren, Y. Ji, R. Zhao, J. She, Y. Ren, C. Xu, D. Chen, J. Cai, S. Shan, D. Pan, Z. Ning, X. Lu, T. Chen, Y. He and L. Chen, *J. Med. Chem.*, 2012, **55**, 8903–8925.
- 22 H. Y. Kim, J. A. Wiles, Q. Wang, G. C. G. Pais, E. Lucien, A. Hashimoto, D. M. Nelson, J. A. Thanassi, S. D. Podos, M. Deshpande, M. J. Pucci and B. J. Bradbury, *J. Med. Chem.*, 2011, **54**, 3268–3282.
- 23 I. Sorribes, K. Junge and M. Beller, *J. Am. Chem. Soc.*, 2014, **136**, 14314–14319.
- 24 M.-C. Fu, R. Shang, W.-M. Cheng and Y. Fu, *Angew. Chem. Int. Ed.*, 2015, **54**, 9042–9046.
- 25 N. Zhang, S. Ayral-Kaloustian, T. Nguyen, J. Afragola, R. Hernandez, J. Lucas, J. Gibbons and C. Beyer, *J. Med. Chem.*, 2007, **50**, 319–327.

- 26 A. T. Brusoe and J. F. Hartwig, *J. Am. Chem. Soc.*, 2015, **137**, 8460–8468.
- 27 T. Umemoto and Y. Gotoh, *J. Fluor. Chem.*, 1985, **28**, 235–239.
- 28 T. Umemoto and Y. Gotoh, *J. Fluor. Chem.*, 1986, **31**, 231–236.
- 29 V. Montanari and G. Resnati, *Tetrahedron Lett.*, 1994, **35**, 8015–8018.
- 30 D. D. DesMarteau and V. Montanari, *Chem. Commun.*, 1998, 2241–2242.
- 31 T. Umemoto and Y. Gotoh, *Bull. Chem. Soc. Jpn.*, 1991, **64**, 2008–2010.
- 32 J. Zhang, G. R. Martin and D. D. DesMarteau, *Chem. Commun.*, 2003, 2334–2335.
- 33 T. Umemoto and Y. Gotoh, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 3823–3825.
- 34 F. R. Freemon, M. S. H. Al-Marashi and J. C. M. Lee, *J. Clin. Pharmacol.*, 1977, **17**, 398–401.
- 35 J. R. Schultz, H. Tu, A. Luk, J. J. Repa, J. C. Medina, L. Li, S. Schwendner, S. Wang, M. Thoolen, D. J. Mangelsdorf, K. D. Lustig and B. Shan, *Genes Dev.*, 2000, **14**, 2831–2838.
- 36 B. P. Fauber, G. de Leon Boenig, B. Burton, C. Eidenschenk, C. Everett, A. Gobbi, S. G. Hymowitz, A. R. Johnson, M. Liimatta, P. Lockey, M. Norman, W. Ouyang, O. René and H. Wong, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 6604–6609.
- 37 A. Santamaria, R. Neef, U. Eberspächer, K. Eis, M. Husemann, D. Mumberg, S. Prechtel, V. Schulze, G. Siemeister, L. Wortmann, F. A. Barr and E. A. Nigg, *Mol. Biol. Cell*, 2007, **18**, 4024–4036.
- 38 B. M. Nilsson, *J. Med. Chem.*, 2006, **49**, 4023–4034.
- 39 Radmila Faizova, University of Nottingham, 2015.

- 40 S. C. A. Sousa and A. C. Fernandes, *Tetrahedron Lett.*, 2009, **50**, 6872–6876.
- 41 C. Brown, H. C., Braude, E. A., Nachod, *Determination of organic structures by physical methods*, Academic Press, New York, 1955.
- 42 J. Hine and F. A. Via, *J. Am. Chem. Soc.*, 1972, **94**, 190–194.
- 43 K. D. Collins and F. Glorius, *Nat. Chem.*, 2013, **5**, 597–601.
- 44 JP2016084310 (A), 2016.
- 45 S. Kozuka, T. Kitamura, N. Kobayashi and K. Ogino, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 1950–1952.
- 46 P. Rist, University of Nottingham, 2016.

Chapter 4

Experimental Section

Contents

1.0 General information.....	273
2.0 General procedures and characterisation data	273
Initial procedure for the trifluoroethylation of <i>N</i> -methyl-1-phenylmethanamine	273
2.1 Trifluoroethylation of secondary amines with trifluoroacetic acid	274
2.10 General Procedure	274
2.11 Practical and scale-up notes	275
2.12 Characterisation data for compounds 1 and 5-12	276
2.13 Alkylation of secondary amines using other acidic acids (compounds 60-64), Figure 2.....	282
2.2 Alkylative-trifluoroethylation of primary amines with aldehydes/ketones and trifluoroacetic acid.....	285
2.20 General Procedure	285
2.21 Characterisation data: compounds 10-35.....	287
2.22 Full data: compounds 43-46 (ketones)	306
3.0 Supporting Experiments	309
3.01 – Figure S1: Optimization Table	310
3.02 – Azide tolerance (Scheme 6)	311
3.03 – Figure S2: Competition Experiments (Scheme 13).....	311

3.04 – Figure S3: Resubjection of amide to the reaction conditions (Scheme 9).....	312
3.05 – Attempts to observe trifluoroacetaldehyde (Scheme 10, Figure 6).....	313
3.06 – Carboxylic acid competition experiment (Scheme 12).....	314
3.07 – HPLC - Enantiopurities	315
3.1 – Anilines and primary amines (Scheme 17)	315
3.10 Attempted Trifluoroethylation of aniline	315
3.11 Attempted Trifluoroethylation of benzylamine	315
3.12 Successful trifluoroacetamidation of aniline.....	315
3.13 Iridium catalysed reduction of trifluoroacetanilide: Scheme 18B	316
3.14 Iridium catalysed trifluoroethylation of 4-bromoaniline: Scheme 18C	316
6.0 References	316

1.0 General information

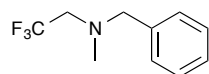
see Chapter 1 Experimental Section

2.0 General procedures and characterisation data

Initial procedure for the trifluoroethylation of *N*-methyl-1-phenylmethanamine

A flask fitted with a water condenser and an argon balloon was charged with trifluoroacetic acid (2.50 equivalents, 1.25 mmol). Toluene (1.5 mL) was added and the solution heated to 65 °C with stirring before adding phenylsilane (3.0 equivalents, 1.5 mmol) and finally the amine (0.5 mmol). After 13 h, the reaction was concentrated *in vacuo* and the residue taken up in ethyl acetate (15 mL). The organics were extracted with HCl (3 x 20 mL of a 1M aqueous solution) and the combined aqueous fractions basified to > pH10 with solid sodium carbonate. The aqueous was extracted with dichloromethane (3 x 20 mL), the combined organics dried (MgSO₄) and concentrated *in vacuo* to give the amine.

***N*-benzyl-2,2,2-trifluoro-*N*-methylethan-1-amine¹ (1)**



Purified by method D and cautiously dried to give a volatile, pale yellow oil (61 mg, 68%).

¹H NMR (400 MHz, CDCl₃) δ 7.49 - 7.27 (m, 5H), 3.74 (s, 2H), 3.06 (q, *J* = 9.5 Hz, 2H), 2.46 (s, 3H); ¹³C NMR (101MHz, CDCl₃) δ 138.1, 128.8, 128.4, 127.4, 125.9 (q, *J* = 282.8 Hz) 62.1, 56.8 (q, *J* = 30.1 Hz), 42.8; ¹⁹F NMR (377 MHz, CDCl₃) δ -68.77 (t, *J* =

9.6 Hz); **HRMS** (EI+, via GC/MS): Exact mass calcd for C₁₀H₁₂N₁CF₃ [M+H], 203.0922. Found 203.0927, $\sigma = 0.0025$; **IR** (cm⁻¹) (CDCl₃) 2964, 2797, 1455, 1318, 1272, 1148, 1095.

2.1 Trifluoroethylation of secondary amines with trifluoroacetic acid

2.10 General Procedure

See 2.11 for notes

To an oven-dried 10 mL round-bottomed flask^{(see [note a](#))} fitted with a water condenser under an argon atmosphere (balloon) was added THF (0.5 mL) and the amine (0.50 mmol) as the free base.^(note b for HCl salt variation) The reaction flask was submerged up to the solvent level in an oil bath at 70 °C and added immediately by microsyringe *via* partial, *brief*, removal of the condenser was phenylsilane (123 μ L, 1.00 mmol) followed by trifluoroacetic acid (67.0 μ L, 0.875 mmol). (**NOTE: rapid and copious H₂ gas evolution**).^c The reaction was then stirred at reflux for 2-4 h. The reaction was allowed to cool and was concentrated.^d The crude reaction was diluted with ether and either:

Purification A) washed with a saturated aqueous sodium bicarbonate solution,^e the organics dried over magnesium sulfate, and the solution concentrated to about 2 mL volume.^f This material was then purified by flash column chromatography, dry loading the oil and eluting with ethyl acetate/pentane (ratios specified below).^g

OR

Purification B) extracted x3 into aqueous HCl (3 M). The combined aqueous layers were basified to $\approx$ pH 10 with an aqueous NaOH solution (6 M) and extracted with

dichloromethane x3. The combined organics were dried over magnesium sulfate and concentrated to dryness to give the amine as the free base directly. The material could optionally be precipitated as the HCl salt by the addition of HCl in ether (1 M) and filtration.

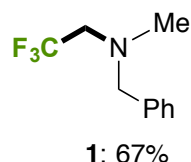
2.11 Practical and scale-up notes

- a) The reaction retains a high level of performance in non-dried glassware, Winchester grade THF and open to air (see [optimization table](#)).
- b) A limited range of amine HCl salts have been trialled. For instance, the HCl salt of methylbenzylamine was used in the presence of triethylamine (0.50 mmol, 1 equiv) and resulted in an 83% conversion to the desired amine. A white precipitate was present through-out the reaction, which did not seem to interfere. See also **compound 27**.
- c) **Scale-Up:** Reactions should be conducted in a flask at least 20 times the solvent volume, particularly on scale, due to the vigorous hydrogen gas evolution. For reactions above 2.0 mmol, the phenylsilane should be added last, at room temperature, and the flask gradually warmed to temperature. These reactions should NOT be performed in a sealed vessel. The largest reaction performed here was at 5.0 mmol scale.
- d) At this point, the conversion was optionally determined by analysing the ^1H -NMR spectrum in the presence of an internal standard (1,1,2,2-tetrachloroethane: $(\text{CDCl}_3)_s$, 2H, $\delta = 5.94$).

- e) If the product is not base-sensitive, the majority of the silane waste can be removed in the work-up stage by washing the ether layer thoroughly with a 1 M sodium hydroxide solution.
- f) At this point, leaving the crude material in its fully concentrated form often leads to the precipitation of silicon-based solid material, which can trap product material and reduce recovery of the product, so it is beneficial to leave the crude material dissolved in dichloromethane or to column the crude material immediately. (Low molecular weight amines often become relatively volatile as the trifluoroethylated product.)
- g) Silicon-waste precipitation sometimes hinders using the eluent dissolution loading technique for chromatography. Note that, unless a second more basic amine was present in the molecule, it was never necessary to add additional base (e.g. Et₃N) to the column eluent. Elution of product was typically achieved using a manually regulated gradient (x-y%) of the more polar solvent, increasing in even intervals of the lowest significant figure (e.g. 3-6% = 3,4,5,6%: 10-40% = 10,20,30,40%).

2.12 Characterisation data for compounds 1 and 5-12

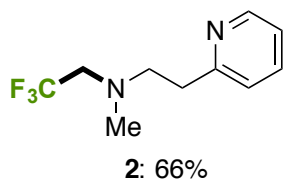
N-benzyl-2,2,2-trifluoro-*N*-methylethan-1-amine (1)¹



Title compound prepared using the general trifluoroethylation method. Purification using method B (acid/base work-up and salt precipitation) to give a clear oil (68 mg, 67%).

¹H NMR (400 MHz, CDCl₃) δ 7.45 – 7.27 (m, 5H), 3.74 (s, 2H), 3.06 (q, *J* = 9.6 Hz, 2H), 2.46 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 138.1, 128.8, 128.4, 127.4, 125.8 (q, *J* = 281.4 Hz), 62.1, 56.8 (q, *J* = 30.3 Hz), 42.8; **¹⁹F NMR** (376 MHz, CDCl₃) δ – 68.77 (t, *J* = 9.6 Hz); **IR** (cm⁻¹) (CDCl₃) 2964, 2797, 1455, 1318, 1272, 1148, 1095; **HRMS** (ESI⁺): Exact mass calcd for C₁₀H₁₂NF₃ [M+H], 204.095. Found 204.0996, σ = 0.0035.

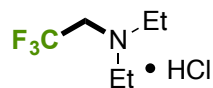
2,2,2-trifluoro-*N*-methyl-*N*-(2-(pyridin-2-yl)ethyl)ethan-1-amine (2)



Title compound prepared using the general trifluoroethylation method. Purification A (chromatography, 25-65% EtOAc in pentane with 0.5% Et₃N) to give a pungent, pale yellow oil (72 mg, 66%).

¹H NMR (400 MHz, CDCl₃) δ 8.52 (ddd, *J* = 4.9, 1.8, 1.1 Hz, 1H), 7.58 (ddd, *J* = 7.8, 7.6, 1.8 Hz, 1H), 7.17 (d, *J* = 7.8 Hz, 1H), 7.11 (ddd, *J* = 7.6, 4.9, 1.1 Hz, 1H), 3.05 (q, *J* = 9.6 Hz, 2H), 3.00 – 2.92 (m, 4H), 2.50 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 159.7, 149.3, 136.3, 125.7 (q, *J* = 281.0 Hz), 123.3, 121.3, 57.8, 57.5 (q, *J* = 30.4 Hz), 43.0, 36.3; **¹⁹F NMR** (376 MHz, CDCl₃) δ -69.60 (t, *J* = 9.6 Hz); **IR** (cm⁻¹) (CDCl₃) 2961, 2256, 1593, 1476, 1320, 1147, 1101; **HRMS** (ESI⁺): Exact mass calcd for C₁₀H₁₃F₃N₂Na [M+Na], 241.0923. Found 241.0936, σ = 0.0063.

***N,N*-diethyl-2,2,2-trifluoroethan-1-amine hydrochloride (6)²**

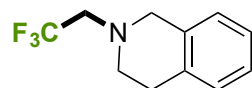


3: 70%^a

Title compound prepared on 5.0 mmol scale using the general trifluoroethylation method. The product was distilled with the solvent to give a solution in THF, and the amine was then precipitated as the HCl salt by the addition of HCl in ether, 1 M to give a white solid (677 mg, 70%).

¹H NMR (270 MHz, D₂O) δ 4.12 (q, J = 8.9 Hz, 2H), 3.38 (q, J = 7.1 Hz, 4H), 1.31 (t, J = 7.1 Hz, 6H); ¹³C NMR (126 MHz, D₂O) δ 119.5 (q, J = 284.5 Hz), 51.3 (q, J = 34.3 Hz), 49.8, 7.8; ¹⁹F NMR (376 MHz, D₂O) -66.11 (t, J = 8.9 Hz); IR (cm⁻¹) (CDCl₃) 2979, 1264, 1191, 1144, 1027; HRMS (ESI+): Exact mass calcd for C₆H₁₂NF₃ [M+H], 156.0922. Found 156.0955 σ < 0.05.

2-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinoline (7)¹



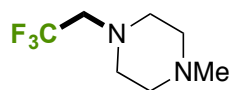
4: 68%

Title compound prepared using the general trifluoroethylation method. Purification B (acid/base work-up as described above) to give a pale yellow oil (73 mg, 68%).

¹H NMR (270 MHz, CDCl₃) δ 7.23 - 7.06 (m, 3H) 7.02 (d, J = 5.1 Hz, 1H) 3.89 (s, 2H) 3.16 (q, J = 9.6 Hz, 2H) 3.08 - 2.81 (m, 4H); ¹³C NMR (68 MHz, CDCl₃) δ 133.9, 133.7, 128.8, 126.5, 126.3, 125.8, 125.5 (q, J = 280.1 Hz), 57.9 (q, J = 30.6 Hz), 55.9, 51.4, 28.6; ¹⁹F NMR (376 MHz, CDCl₃) δ -69.18 (t, J = 9.6 Hz); IR (cm⁻¹) (CDCl₃) 3009, 2928,

2809, 1603, 1319, 1272, 1147, 1100; **HRMS** (ESI+): Exact mass calcd for $C_{11}H_{13}F_3N$ [M+H], 216.095. Found 216.105, $\sigma = 0.0420$.

1-methyl-4-(2,2,2-trifluoroethyl)piperazine (8)

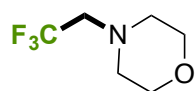


5: 47%

Title compound prepared using the general trifluoroethylation method. Purification B (acid/base work-up as described above) to give a pale yellow oil (43 mg, 47%).

^1H NMR (270 MHz, $CDCl_3$) δ 2.96 (q, $J = 9.6$ Hz, 2H), 2.72 (t, $J = 4.8$ Hz, 4H), 2.55-2.44 (m, 4H), 2.31 (s, 3H); **^{13}C NMR** (68 MHz, $CDCl_3$) δ 125.3 (q, $J = 279.3$ Hz), 58.4 (q, $J = 30.3$ Hz), 54.9, 53.4, 45.9; **^{19}F NMR** (376 MHz, $CDCl_3$) -69.11 (t, $J = 9.6$ Hz); **IR** (cm^{-1}) ($CDCl_3$) 2927, 2855, 1239, 1137, 1026; **HRMS** (ESI+): Exact mass calcd for $C_7H_{13}F_3N_2$ [M+H], 183.1064. Found 183.1111, $\sigma = 0.0055$.

4-(2,2,2-trifluoroethyl)morpholine (9)³



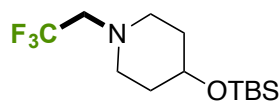
6: 43%

Title compound prepared using the general trifluoroethylation method. Purification B (acid/base work-up as described above) to give a pale yellow oil (40 mg, 47%).

^1H NMR (400 MHz, $CDCl_3$) δ 3.76 – 3.68 (m, 4H), 2.95 (q, $J = 9.6$ Hz, 2H), 2.69 – 2.63 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 125.5 (q, $J = 283.9$ Hz) 66.9, 59.2 (q, $J = 30.1$ Hz), 54.0; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -69.09 (t, $J = 9.6$ Hz); **IR** (cm^{-1}) ($CDCl_3$)

3689, 3619, 3006, 2976, 1601, 1391, 1240, 1046, 909; **HRMS** (ESI⁺): Exact mass calcd for C₆H₁₁F₃NO [M+H], 170.0787. Found 170.0791, σ = 0.0128.

4-((tert-butyldimethylsilyl)oxy)-1-(2,2,2-trifluoroethyl)piperidine (10)

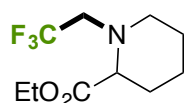


7: 80%

Title compound prepared using general trifluoroethylation method A. Purification using method A (chromatography, 3-6% EtOAc in pentane) to give a clear oil (119 mg, 80%).

¹H NMR (400 MHz, CDCl₃) δ 3.78 – 3.67 (m, 1H), 2.94 (q, J = 9.7 Hz, 2H), 2.88 – 2.75 (m, 2H), 2.57 – 2.41 (m, 2H), 1.85 – 1.69 (m, 2H), 1.68 – 1.50 (m, 2H), 0.88 (s, 9H), 0.04 (s, 6H); **¹³C NMR** (101 MHz, CDCl₃) δ 125.6 (q, J = 280.3 Hz), 66.7, 58.5 (q, J = 30.2 Hz), 51.0, 34.5, 25.8, 18.1, -4.7; **¹⁹F NMR** (376 MHz, CDCl₃) δ -69.13 (t, J = 9.7 Hz); **IR** (cm⁻¹) (neat) 2952, 2930, 2888, 2857, 1697, 1471, 1315, 1272, 1254, 1141, 1095, 1075, 1056; **HRMS** (ESI⁺): Exact mass calcd for C₁₃H₂₇F₃NOSi [M+H], 298.1809. Found 298.1822, σ = 0.0060.

ethyl 1-(2,2,2-trifluoroethyl)piperidine-2-carboxylate (11)



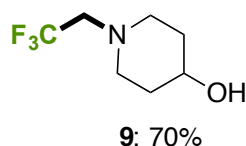
8: 83%

Title compound prepared using general trifluoroethylation method. Purification A: (chromatography, 3-6% EtOAc in pentane) to give a clear oil (100 mg, 83%).

¹H NMR (400 MHz, CDCl₃) δ 4.28 – 4.09 (m, 2H), 3.53 (app. t, J = 4.8 Hz, 1H), 3.25 – 3.04 (m, 3H), 2.71 (app. dt, J = 11.2, 4.5 Hz, 1H), 2.04 – 1.93 (m, 1H), 1.90 – 1.77 (m,

1H), 1.66 – 1.47 (m, 3H), 1.36 – 1.22 (m, 4H); ^{13}C NMR (101 MHz, CDCl_3) δ 173.0, 125.7 (q, $J = 280.0$ Hz), 62.8, 60.5, 57.1 (q, $J = 30.8$ Hz), 50.4, 28.9, 25.5, 20.9, 14.3; ^{19}F NMR (376 MHz, CDCl_3) δ -71.11 (t, $J = 9.7$ Hz); IR (cm^{-1}) (neat) 2940, 2859, 1929, 1272, 1197, 1176, 1135, 1112, 1094, 1065, 1024; HRMS (ESI+): Exact mass calcd for $\text{C}_{10}\text{H}_{16}\text{F}_3\text{NNaO}_2$ [M+Na], 262.1025. Found 262.1041, $\sigma = 0.0014$.

1-(2,2,2-trifluoroethyl)piperidin-4-ol (12)⁴



Title compound prepared using the general trifluoroethylation method A but with 2.5 equivalents of phenylsilane (1.25 mmol). A modified work-up procedure was used: after 4 h, the reaction was cautiously quenched whilst still hot with 1 M aqueous NaOH solution (gas released!) and allowed to stir, cooling to ambient temperature, over 1 h (to cleave any O-silylated species). The reaction was diluted with ether and the organic layer separated and dried with magnesium sulfate. (The majority of the desired alcohol was extracted from the hydroxide solution using this method, leaving most of the silane waste in the aqueous layer. Attempts to neutralise/acidify the aqueous layer and extract further product led to the extraction of undesired silane waste material.) The resulting oil was purified further by chromatography using a gradient of 20-70% EtOAc in pentane (10 % step rate) to give a clear oil (64 mg, 70%) that formed a low-melting waxy solid on standing.

^1H NMR (400 MHz, CDCl_3) δ 3.70 (tt, $J = 8.6, 4.1$ Hz, 1H), 2.96 (q, $J = 9.7$ Hz, 2H), 2.92 – 2.85 (m, 2H), 2.48 (ddd, $J = 12.1, 9.7, 3.1$ Hz, 2H), 1.92 – 1.84 (m, 2H), 1.75 (br. s, 1H), 1.59 (dddd, $J = 12.9, 9.7, 8.6, 3.8$ Hz, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 125.5 (q, $J =$

280.4 Hz), 67.1, 58.2 (q, $J = 30.6$ Hz), 51.4, 34.3; ^{19}F NMR (376 MHz, CDCl_3) δ -69.07 (t, $J = 9.7$ Hz); IR (cm^{-1}) (neat) 3330, 2926, 1595, 1430, 1270, 1130, 1091, 1066, 1024, 997; HRMS (ESI+): Exact mass calcd for $\text{C}_7\text{H}_{13}\text{F}_3\text{NO}$ $[\text{M}+\text{H}]$, 184.0944. Found 184.0946, $\sigma = 0.0007$.

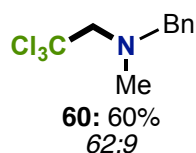
2.13 Alkylation of secondary amines using other acidic acids (compounds 60-64),

Figure 2

The general trifluoroethylation method used above is applicable to other acidic acids by substituting trifluoroacetic acid for another acid; trichloroacetic acid, difluoroacetic acid, dinitrobenzoic acid and chloroacetic acid have all been used successfully, with yields depending on acidity. Lower acidity acids tend to give more amide product; higher acidities give more amine. Other *alpha*-fluorinated carboxylic acids should be amenable to this protocol. For lower acidities, increasing excesses of acid (typically to two equivalents) may improve the yield slightly.

Conversions shown as a ratio of amine to amide.

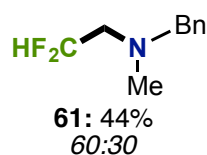
N-benzyl-2,2,2-trichloro-*N*-methylethan-1-amine (60)^s



Title compound prepared using general trifluoroethylation method A, but with 2 equivalents of trichloroacetic acid instead of trifluoroacetic acid. Purified by flash column chromatography (3-6% EtOAc/pentane); isolated as a clear oil (72 mg, 60%).

¹H NMR (400 MHz, CDCl₃) δ 7.42 (d, *J* = 7.0 Hz, 2H), 7.39 – 7.33 (m, 2H), 7.32 – 7.26 (m, 1H), 4.00 (s, 2H), 3.55 (s, 2H), 2.55 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 138.8, 128.6, 128.3, 127.2, 101.3, 75.4, 63.1, 43.2; **IR** (cm⁻¹) (neat) 2904, 2847, 2797, 1495, 1454, 1348, 1021, 982, 781, 735, 696; **HRMS** (ESI⁺): Exact mass calcd for C₁₀H₁₃Cl₃N [M+H], 252.0108. Found 252.0095, σ = 0.0252.

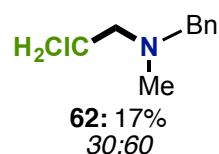
***N*-benzyl-2,2-difluoro-*N*-methylethan-1-amine (61)⁶**



Title compound prepared using general trifluoroethylation method A but using two equivalents of difluoroacetic acid in place of the trifluoroacetic acid. Purification using standard work-up and chromatography (8-15% EtOAc in pentane) to give a clear oil (41 mg, 44%).

¹H NMR (400 MHz, CDCl₃) δ 7.40 – 7.24 (m, 5H), 5.84 (tt, *J* = 56.1, 4.4 Hz, 1H), 3.64 (s, 2H), 2.79 (td, *J* = 14.9, 4.4 Hz, 2H), 2.38 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 138.2, 128.9, 128.4, 127.3, 116.1 (t, *J* = 241.1 Hz), 62.8, 58.6 (t, *J* = 24.9 Hz), 43.3; **¹⁹F NMR** (282 MHz, CDCl₃) δ -118.73 (dt, *J* = 56.1, 14.9 Hz); **IR** (cm⁻¹) (neat) 3064, 3029, 2853, 1495, 1408, 1122, 1043, 1025; **HRMS** (ESI⁺): Exact mass calcd for C₁₀H₁₄F₂N [M+H], 186.108. Found 186.1086, σ = 0.0015.

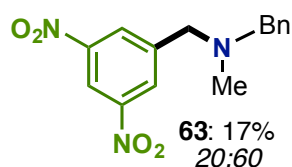
***N*-benzyl-2-chloro-*N*-methylethan-1-amine (62)⁷**



CAUTION! Compound shares motif with extremely cytotoxic nitrogen mustard compounds. Title compound prepared using general trifluoroethylation method A, but with 2 equivalents of chloroacetic acid instead of trifluoroacetic acid. Purification using standard work-up and chromatography (10-20% EtOAc in pentane) to give a clear oil (16 mg, 17%).

^1H NMR (400 MHz, CDCl_3) δ 7.44 – 7.30 (m, 5H), 3.65 – 3.57 (m, 4H), 2.80 (t, J = 7.0 Hz, 2H), 2.32 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 138.43, 128.94, 128.31, 127.18, 62.25, 58.56, 42.31, 41.61; IR (cm^{-1}) (neat) 2794, 1454, 1123, 1043, 1025, 739, 698; HRMS (ESI+): Exact mass calcd for $\text{C}_{10}\text{H}_{14}\text{NCl}$ [$\text{M}+\text{H}$], 184.0815. Found 184.0913, σ = 0.0078.

***N*-benzyl-1-(3,5-dinitrophenyl)-*N*-methylethanamine (63)**



Title compound prepared using general trifluoroethylation method A, but with 2 equivalents of 3,5-dinitrobenzoic acid instead of trifluoroacetic acid. Purified by flash column chromatography (30-70% CH_2Cl_2 /pentane); isolated as a clear oil (25 mg, 17%).

^1H NMR (400 MHz, CDCl_3) δ 8.92 (t, J = 2.2 Hz, 1H), 8.57 (d, J = 2.2 Hz, 2H), 7.43 – 7.31 (m, 4H), 7.30 – 7.27 (m, 1H), 3.70 (s, 2H), 3.64 (s, 2H), 2.27 (s, 3H); ^{13}C NMR (68 MHz, CDCl_3) δ 148.5, 144.8, 138.1, 128.9, 128.9, 127.5, 126.9, 117.5, 62.2, 60.0, 42.6; IR (cm^{-1}) (CDCl_3) 3011, 2932, 1543, 1345, 909; HRMS (ESI+): Exact mass calcd for $\text{C}_{15}\text{H}_{16}\text{N}_3\text{O}_4$ [$\text{M}+\text{H}$], 302.1135. Found 302.1143, σ = 0.0006.

2.2 Alkylative-trifluoroethylation of primary amines with aldehydes/ketones and trifluoroacetic acid

2.20 General Procedure

*****the above [notes](#) (2.11) also apply to these methods*****

(It is possible to run this reaction in THF if solubility is an issue. Toluene was used for dryness and its higher boiling point.)

Alkylative-trifluoroethylation Method A (typical, unhindered, aryl aldehydes):

To an oven-dried 10 mL round-bottomed flask fitted with a water condenser under an argon atmosphere (balloon) was added the amine (0.50 mmol) and aldehyde (0.50 mmol) (which sometimes precipitated immediately as the imine). Toluene was added (0.5 mL), followed by phenylsilane (31 μ L, 0.25 mmol). The reaction was stirred at **70 °C for 10 min**. Then trifluoroacetic acid (67.0 μ L, 0.875 mmol) and further PhSiH₃ (123 μ L, 1.00 mmol) were added and the reaction heated at **70 °C for 16 h**.

Alkylative-trifluoroethylation Method B (typical, unhindered, alkyl aldehydes):

To an oven-dried 10 mL round-bottomed flask fitted with a water condenser under an argon atmosphere (balloon) was added the amine (0.50 mmol) and aldehyde (0.50 mmol) (which sometimes precipitated immediately as the imine). Toluene was added (0.5 mL), followed by phenylsilane (31 μ L, 0.25 mmol). The reaction was stirred at **25 °C for 30-**

45 min. Then trifluoroacetic acid (67.0 μL , 0.875 mmol) and further PhSiH_3 (123 μL , 1.00 mmol) were added and the reaction heated at **110 °C for 4 h.**

Alkylative-trifluoroethylation Method C (hindered aldehydes):

To an oven-dried 10 mL round-bottomed flask fitted with a water condenser under an argon atmosphere (balloon) was added the amine (0.50 mmol) and aldehyde (0.50 mmol). Toluene was added (0.5 mL), followed by phenylsilane (31 μL , 0.25 mmol). The reaction was stirred at **70 °C for 30 min.** Then trifluoroacetic acid (67.0 μL , 0.875 mmol) and further PhSiH_3 (123 μL , 1.00 mmol) were added and the reaction heated at **70 °C for 16 h.**

Alkylative-trifluoroethylation Method D (hindered aldehydes/less reactive amines):

To an oven-dried 10 mL round-bottomed flask fitted with a water condenser under an argon atmosphere (balloon) was added the amine (0.50 mmol) and aldehyde (0.50 mmol) (which sometimes precipitated immediately as the imine). Toluene was added (0.5 mL), followed by phenylsilane (31 μL , 0.25 mmol). The reaction was stirred at **70 °C for 30 min.** Then trifluoroacetic acid (67.0 μL , 0.875 mmol) and further PhSiH_3 (123 μL , 1.00 mmol) were added and the reaction heated at **110 °C for 16 h.**

Alkylative-trifluoroethylation Method E (ketones):

To an oven-dried 10 mL round-bottomed flask fitted with a water condenser under an argon atmosphere (balloon) was added the amine (0.50 mmol), ketone (0.50 mmol), toluene (0.5 mL) **and trifluoroacetic acid (7 μL , 0.05 mmol)** to encourage imine formation. **After 30 min at 70 °C,** phenylsilane (31 μL , 0.25 mmol) was added and the

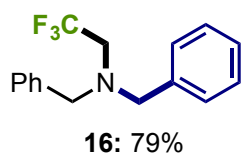
reaction stirred at **25 °C for 10 min.** Then trifluoroacetic acid (**63.2 μ L, 0.825 mmol**) and further PhSiH_3 (123 μ L, 1.00 mmol) were added and the reaction heated at **110 °C for 4 h.**

Purification of alkylated-trifluoroethylated primary amines: For all methods, the reaction was allowed to cool, concentrated under reduced pressure, and the conversion determined using ^1H -NMR spectroscopy (relative to internal standard, 1,1,2,2-tetrachloroethane). The crude reaction was diluted with ether and washed with a saturated aqueous sodium bicarbonate solution, the organics dried over magnesium sulfate, and the solution concentrated to about 2 mL volume. The crude material was typically purified by flash column chromatography by dry loading the oil onto a minimum amount of silica, loading onto a silica column, and eluting from the column with ethyl acetate/pentane (ratios specified below).

2.21 Characterisation data: compounds 10-35

as depicted, the bold blue fragment with emboldened N-C bond is the aldehyde fragment and the non-bold black bond is the original amine moiety.

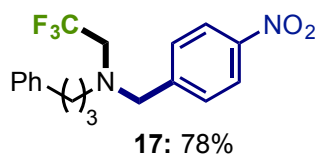
N,N-dibenzyl-2,2,2-trifluoroethan-1-amine (16)⁸



Title compound prepared using general alkylative-trifluoroethylation method A. Purified using standard work-up and flash column chromatography (0-10% Et_2O in pentane); isolated as a clear oil (110 mg, 79%).

¹H NMR (400 MHz, CDCl₃) δ 7.43 – 7.26 (m, 10H), 3.83 (s, 4H), 3.13 (q, *J* = 9.5 Hz, 1H); **¹³C NMR** (101 MHz, CDCl₃) δ 138.3, 128.8, 128.4, 127.3, 126.1 (q, *J* = 282.7 Hz), 58.2, 52.9 (q, *J* = 30.1 Hz). **¹⁹F NMR** (376 MHz, CDCl₃) δ -67.85 (t, *J* = 9.6 Hz); **IR** (cm⁻¹) (neat) 3064, 3030, 2840, 1602, 1496, 1307, 1178, 1134, 1084. **HRMS** (ESI+): Exact mass calcd for C₁₆H₁₇F₃N [M+H], 280.1308. Found 280.1315, σ = 0.0023.

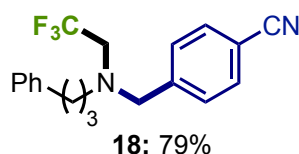
***N*-(4-nitrobenzyl)-3-phenyl-*N*-(2,2,2-trifluoroethyl)propan-1-amine (17)**



Title compound prepared using general alkylative-trifluoroethylation method A. Purified using standard work-up and flash column chromatography (2-8% EtOAc in pentane); isolated as a clear oil (137 mg, 78%).

¹H NMR (400 MHz, CDCl₃) 8.21 – 8.15 (m, 2H), 7.54 – 7.47 (m, 2H), 7.29 – 7.22 (m, 2H), 7.21 – 7.14 (m, 1H), 7.14 – 7.07 (m, 2H), 3.89 (s, 2H), 3.13 (q, *J* = 9.4 Hz, 2H), 2.66 (t, *J* = 7.3 Hz, 2H), 2.63 – 2.55 (m, 2H), 1.81 (m, 2H); **¹³C NMR** (101 MHz, CDCl₃) δ 147.3, 146.6, 141.6, 129.1, 128.4, 128.2, 125.9, 125.7 (q, *J* = 281.5 Hz), 123.6, 58.8, 54.5 (q, *J* = 30.6 Hz), 54.0, 33.0, 29.1; **¹⁹F NMR** (376 MHz, CDCl₃) δ -69.30 (t, *J* = 9.4 Hz); **IR** (cm⁻¹) (neat) 3027, 2940, 2855, 1603, 1519, 1344, 1269, 1136, 1090; **HR-GC-EIMS**: rt = 16.44 min. Exact mass calcd for C₁₈H₁₉N₂O₂F₃, 352.13931. Found 352.13767, (mass difference: -4.67 ppm).

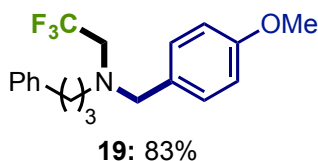
4-(((3-phenylpropyl)(2,2,2-trifluoroethyl)amino)methyl)benzonitrile (18)



Title compound prepared using general alkylative-trifluoroethylation method A. Purified using standard work-up and flash column chromatography (2-10% EtOAc in pentane); isolated as a clear oil (131 mg, 79%).

^1H NMR (400 MHz, CDCl_3) 7.64 – 7.59 (m, 2H), 7.48 – 7.42 (m, 2H), 7.30 – 7.24 (m, 2H), 7.22 – 7.16 (m, 1H), 7.14 – 7.09 (m, 2H), 3.84 (s, 2H), 3.12 (q, $J = 9.4$ Hz, 2H), 2.65 (t, $J = 7.2$ Hz, 2H), 2.62 – 2.56 (m, 2H), 1.88 – 1.73 (m, 2H); **^{13}C NMR** (101 MHz, CDCl_3) δ 144.5, 141.6, 132.2, 129.1, 128.3, 128.2, 125.9, 125.7 (q, $J = 281.4$ Hz), 118.8, 111.1, 59.0, 54.4 (q, $J = 30.3$ Hz), 53.9, 33.0, 29.1; **^{19}F NMR** (376 MHz, CDCl_3) δ -69.28 (t, $J = 9.4$ Hz); **IR** (cm^{-1}) (neat) 2935, 2849, 2228 (CN), 1608, 1269, 1135, 1090; **HR-GC-EIMS**: rt = 15.05 min. Exact mass calcd for $\text{C}_{19}\text{H}_{19}\text{N}_2\text{F}_3$, 332.14948. Found 332.14814, (mass difference: -4.04 ppm).

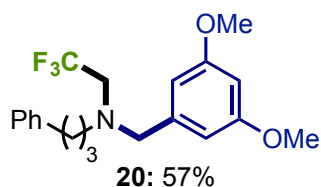
***N*-(4-methoxybenzyl)-3-phenyl-*N*-(2,2,2-trifluoroethyl)propan-1-amine**
(19)



Title compound prepared using general alkylative-trifluoroethylation method A. Purified using standard work-up and flash column chromatography (5% EtOAc in pentane); isolated as a clear oil (141 mg, 83%).

^1H NMR (400 MHz, CDCl_3) δ 7.26 (m, 4H), 7.21 – 7.11 (m, 3H), 6.90 – 6.84 (m, 2H), 3.82 (s, 3H), 3.73 (s, 2H), 3.07 (q, J = 9.6 Hz, 2H), 2.66 (t, J = 7.0 Hz, 2H), 2.63 – 2.57 (m, 2H), 1.80 (m, 2H); **^{13}C NMR** (101 MHz, CDCl_3) δ 158.8, 142.2, 130.5, 130.0, 128.4, 128.3, 126.0 (q, J = 281.8 Hz), 125.7, 113.7, 58.4, 55.2, 53.8 (q, J = 30.3 Hz), 53.6, 33.1, 29.3; **^{19}F NMR** (376 MHz, CDCl_3) δ 69.03 (t, J = 9.6 Hz); **IR** (cm^{-1}) (neat) 3062, 2937, 2836, 1612, 1511, 1269, 1245, 1132, 1090, 1076. **HRMS** (ESI+): Exact mass calcd for $\text{C}_{19}\text{H}_{23}\text{F}_3\text{NO}$ $[\text{M}+\text{H}]$, 338.1726. Found 338.1726, σ = 0.0025.

***N*-(3,5-dimethoxybenzyl)-3-phenyl-*N*-(2,2,2-trifluoroethyl)propan-1-amine (20)**

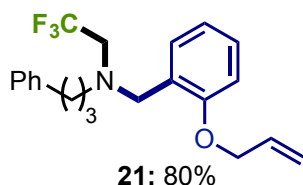


Title compound prepared using general alkylative-trifluoroethylation method A. Purified using standard work-up and flash column chromatography (6-11% EtOAc in pentane); isolated as a clear oil (105 mg, 57%).

^1H NMR (400 MHz, CDCl_3) δ 7.31 – 7.25 (m, 2H), 7.22 – 7.13 (m, 3H), 6.54 (d, J = 2.3 Hz, 2H), 6.40 (t, J = 2.3 Hz, 1H), 3.80 (s, 6H), 3.75 (s, 2H), 3.11 (q, J = 9.5 Hz, 2H), 2.70 (t, J = 7.1 Hz, 2H), 2.64 (t, J = 7.3 Hz, 2H), 1.82 (tt, J = 7.3, 7.1 Hz, 2H); **^{13}C NMR** (101 MHz, CDCl_3) δ 160.8, 142.1, 141.2, 128.3 (2C), 126.0 (q, J = 281.6 Hz), 125.7, 106.4, 99.2, 59.3, 55.2, 54.1 (q, J = 31.4 Hz), 53.9, 33.2, 29.4; **^{19}F NMR** (376 MHz, CDCl_3) δ -68.97 (t, J = 9.5 Hz); **IR** (cm^{-1}) (neat) 2939, 2839, 1596, 1456, 1269, 1204, 1135, 1091, 1056;

HRMS (ESI⁺): Exact mass calcd for C₂₀H₂₅F₃NO₂ [M+H], 368.1832. Found 368.1830, σ = 0.0006.

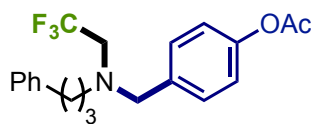
***N*-(2-(allyloxy)benzyl)-3-phenyl-*N*-(2,2,2-trifluoroethyl)propan-1-amine**
(21)



Title compound prepared using general alkylative-trifluoroethylation method A. Purified using standard work-up and flash column chromatography (3-5% EtOAc in pentane); isolated as a clear oil (145 mg, 80%).

¹H NMR (400 MHz, CDCl₃) δ 7.41 (dd, J = 7.5, 1.7 Hz, 1H), 7.32 – 7.12 (m, 6H), 6.97 (t, J = 7.5 Hz, 1H), 6.88 (d, J = 8.2 Hz, 1H), 6.07 (ddt, J = 17.3, 10.5, 5.2 Hz, 1H), 5.42 (ddt, J = 17.3, 1.7, 1.7 Hz, 1H), 5.29 (ddt, J = 10.5, 1.7, 1.3 Hz, 1H), 4.56 (ddd, J = 5.2, 1.7, 1.3 Hz, 2H), 3.91 (s, 2H), 3.16 (q, J = 9.6 Hz, 2H), 2.71 (t, J = 7.1 Hz, 2H), 2.63 (t, J = 7.6 Hz, 2H), 1.83 (tt, J = 7.6, 7.1 Hz, 2H); **¹³C NMR** (101 MHz, CDCl₃) δ 156.7, 142.3, 133.4, 130.4, 128.4, 128.3, 128.1, 127.0, 126.0 (q, J = 282.2, 281.2 Hz), 125.7, 120.6, 117.3, 111.7, 68.9, 54.6 (q, J = 30.2 Hz), 54.2, 52.8, 33.2, 29.5; **¹⁹F NMR** (376 MHz, CDCl₃) δ -69.47 (t, J = 9.6 Hz); **IR** (cm⁻¹) (neat) 3027, 2933, 2861, 1601, 1588, 1492, 1453, 1270, 1133, 1090; **HRMS** (ESI⁺): Exact mass calcd for C₂₁H₂₄F₃NNaO [M+Na], 386.1702. Found 386.1702, σ = 0.0050.

4-(((3-phenylpropyl)(2,2,2-trifluoroethyl)amino)methyl)phenyl acetate
(21)

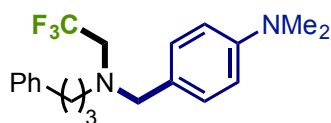


21: 47%

Title compound prepared using general alkylative-trifluoroethylation method A. Purified using standard work-up and flash column chromatography (6-12% EtOAc in pentane); isolated as a clear oil (85 mg, 47%).

^1H NMR (400 MHz, CDCl_3) δ 7.37 – 7.31 (m, 2H), 7.30 – 7.23 (m, 2H), 7.21 – 7.10 (m, 3H), 7.08 – 7.01 (m, 2H), 3.78 (s, 2H), 3.09 (q, J = 9.5 Hz, 2H), 2.67 (t, J = 7.1 Hz, 2H), 2.60 (t, J = 7.6 Hz, 2H), 2.31 (s, 3H), 1.80 (tt, J = 7.6, 7.1 Hz, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 169.5, 149.8, 142.0, 136.2, 129.6, 128.3, 125.9 (q, J = 281.9 Hz), 125.8, 121.4, 58.5, 54.0 (q, J = 30.2 Hz), 53.7, 33.1, 29.3, 21.1; ^{19}F NMR (376 MHz, CDCl_3) δ -69.05 (t, J = 9.5 Hz); IR (cm^{-1}) (neat) 2936, 2850, 1761, 1506, 1369, 1269, 1213, 1191, 1134, 1089, 1077; HRMS (ESI+): Exact mass calcd for $\text{C}_{20}\text{H}_{22}\text{F}_3\text{NNaO}_2$ [$\text{M}+\text{Na}$], 388.1495. Found 388.1503, σ = 0.0003.

N,N-dimethyl-4-(((3-phenylpropyl)(2,2,2-trifluoroethyl)amino)methyl)aniline (22)



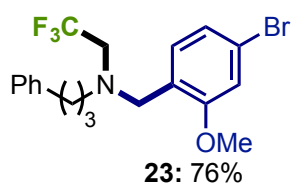
22: 33%

Title compound prepared using general alkylative-trifluoroethylation method A with the following modifications: Initially, the amine and aldehyde were stirred in toluene for 10 min at 110 °C. The trifluoroacetic acid and phenylsilane were then added at 25 °C and the

reaction heated for 4 h at reflux. Purified using standard work-up and flash column chromatography (5-9% EtOAc in pentane); isolated as a clear oil (57 mg, 33%).

^1H NMR (400 MHz, CDCl_3) δ 7.30 – 7.22 (m, 2H), 7.21 – 7.11 (m, 5H), 6.77 – 6.66 (m, 2H), 3.69 (s, 2H), 3.06 (q, J = 9.6 Hz, 2H), 2.95 (s, 6H), 2.66 (t, J = 7.0 Hz, 2H), 2.61 (t, J = 7.7 Hz, 2H), 1.80 (tt, J = 7.7, 7.0 Hz, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 150.0, 142.3, 129.8, 128.4, 128.3, 126.1 (q, J = 283.2 Hz), 126.1, 125.7, 112.5, 58.4, 53.6 (q, J = 30.0 Hz), 53.6, 40.7, 33.2, 29.4; ^{19}F NMR (376 MHz, CDCl_3) δ -68.92 (t, J = 9.6 Hz); IR (cm^{-1}) (neat) 2935, 2852, 2805, 1614, 1521, 1269, 1131, 1089, 1075; HRMS (ESI+): Exact mass calcd for $\text{C}_{20}\text{H}_{26}\text{F}_3\text{N}_2$ $[\text{M}+\text{H}]$, 351.2043. Found 351.2047, σ = 0.0008.

***N*-(5-bromo-2-methoxybenzyl)-3-phenyl-*N*-(2,2,2-trifluoroethyl)propan-1-amine (23)**

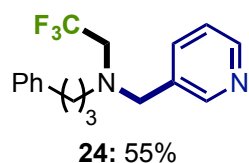


Title compound prepared using general alkylative-trifluoroethylation method A. Purified using standard work-up and flash column chromatography (3-7% EtOAc in pentane); isolated as a clear oil (159 mg, 76%).

^1H NMR (400 MHz, CDCl_3) δ 7.52 (d, J = 2.6 Hz, 1H), 7.34 (dd, J = 8.7, 2.6 Hz, 1H), 7.31 – 7.24 (m, 2H), 7.22 – 7.12 (m, 3H), 6.74 (d, J = 8.7 Hz, 1H), 3.81 (s, 2H), 3.79 (s, 3H), 3.14 (q, J = 9.5 Hz, 2H), 2.68 (t, J = 7.2 Hz, 2H), 2.65 – 2.59 (m, 2H), 1.88 – 1.74 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 156.7, 142.1, 132.5, 130.7, 128.3 (2C), 125.9 (q, J = 281.5 Hz), 125.7, 112.9, 112.0, 55.5, 54.6 (q, J = 30.5 Hz), 54.1, 52.5, 33.1, 29.3; ^{19}F NMR

(376 MHz, CDCl₃) δ -69.41 (t, J = 9.5 Hz); **IR** (cm⁻¹) (neat) 2939, 1486, 1269, 1249, 1134, 1090, 1030; **HRMS** (ESI⁺): Exact mass calcd for C₁₉H₂₂BrF₃NO [M+H], 416.0831. Found 416.0831, σ = 0.0086.

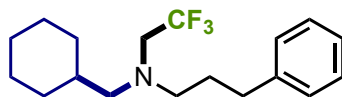
3-phenyl-*N*-(pyridin-3-ylmethyl)-*N*-(2,2,2-trifluoroethyl)propan-1-amine
(24)



Title compound prepared using general alkylative-trifluoroethylation method A but with 2.75 equiv. TFA. Purified using standard work-up and flash column chromatography (20-30% EtOAc in pentane with 1% Et₃N throughout); isolated as a clear oil (85 mg, 55%).

¹H NMR (400 MHz, CDCl₃) δ 8.59 – 8.46 (m, 2H), 7.74 – 7.61 (m, 1H), 7.29 – 7.21 (m, 3H), 7.19 – 7.13 (m, 1H), 7.13 – 7.06 (m, 2H), 3.79 (s, 2H), 3.09 (q, J = 9.4 Hz, 2H), 2.65 (t, J = 7.1 Hz, 2H), 2.57 (t, J = 7.8 Hz, 2H), 1.79 (tt, J = 7.8, 7.1 Hz, 2H); **¹³C NMR** (101 MHz, CDCl₃) δ 150.0, 148.9, 141.8, 136.4, 134.1, 128.3, 128.3, 125.8, 125.8 (q, J = 281.7, 280.8 Hz), 123.4, 56.6, 54.2 (q, J = 30.4 Hz), 53.8, 33.0, 29.2; **¹⁹F NMR** (376 MHz, CDCl₃) δ -69.28 (t, J = 9.4 Hz); **IR** (cm⁻¹) (neat) 3028, 2940, 2858, 1577, 1425, 1269, 1136, 1077; **HRMS** (ESI⁺): Exact mass calcd for C₁₇H₁₉F₃N₂Na [M+Na], 331.1393. Found 331.1407, σ = 0.0766.

***N*-(cyclohexylmethyl)-3-phenyl-*N*-(2,2,2-trifluoroethyl)propan-1-amine**
(25)

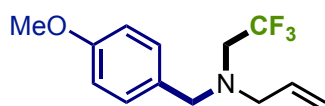


25: 50%

Title compound prepared using general alkylative-trifluoroethylation method A. Purified using standard work-up and flash column chromatography (3-6% EtOAc in pentane); isolated as a clear oil (79 mg, 50%).

^1H NMR (400 MHz, CDCl_3) δ 7.33 – 7.25 (m, 2H), 7.23 – 7.16 (m, 3H), 3.01 (q, J = 9.6 Hz, 2H), 2.68 – 2.57 (m, 4H), 2.37 (d, J = 7.1 Hz, 2H), 1.86 – 1.62 (m, 7H), 1.38 (t, J = 10.8, 7.1, 3.4 Hz, 1H), 1.30 – 1.09 (m, 3H), 0.93 – 0.76 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 142.3, 128.4, 128.3, 126.0 (q, J = 281.0 Hz), 125.7, 62.5, 55.8 (q, J = 30.1 Hz), 55.1, 36.4, 33.2, 31.4, 29.5, 26.8, 26.1; ^{19}F NMR (376 MHz, CDCl_3) δ -69.79 (t, J = 9.6 Hz); IR (cm^{-1}) (neat) 2922, 2851, 1451, 1270, 1135, 1093; HRMS (ESI+): Exact mass calcd for $\text{C}_{18}\text{H}_{27}\text{F}_3\text{N}$ [$\text{M}+\text{H}$], 314.2090. Found 314.2094, σ = 0.0028.

***N*-(4-methoxybenzyl)-*N*-(2,2,2-trifluoroethyl)prop-2-en-1-amine (26)**



26: 63%

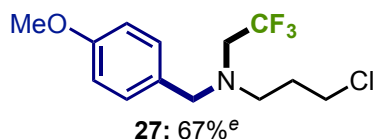
Title compound prepared using general alkylative-trifluoroethylation method A. Purified using standard work-up and flash column chromatography (1-2% EtOAc in pentane); isolated as a clear oil (82 mg, 63%).

^1H NMR (400 MHz, CDCl_3) δ 7.31 – 7.21 (m, 2H), 6.93 – 6.82 (m, 2H), 5.84 (ddt, J = 16.8, 10.2, 6.5 Hz, 1H), 5.25 – 5.15 (m, 2H), 3.81 (s, 3H), 3.74 (s, 2H), 3.24 (d, J = 6.5 Hz, 2H), 3.08 (q, J = 9.6 Hz, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 158.9, 134.9, 130.3, 130.0,

126.0 (q, $J = 281.4$ Hz), 118.3, 113.7, 57.8, 56.8, 55.2, 52.8 (q, $J = 30.2$ Hz); ^{19}F NMR (376 MHz, CDCl_3) δ -68.95 (t, $J = 9.6$ Hz); IR (cm^{-1}) (neat) 3005, 2937, 2906, 2837, 1612, 1511, 1244, 1136, 1074; HR-GC-EIMS: rt = 11.25 min. Exact mass calcd for $\text{C}_{13}\text{H}_{16}\text{NOF}_3$, 259.11785. Found 259.11854, (mass difference: 2.65 ppm).

3-chloro-*N*-(4-methoxybenzyl)-*N*-(2,2,2-trifluoroethyl)propan-1-amine

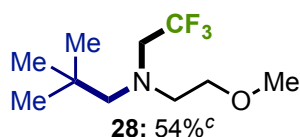
(27)



Title compound prepared using general alkylative-trifluoroethylation method A using the HCl salt of the amine. (No additional base was added in this case, but should be added for highly crystalline/poorly soluble salts (e.g. triethylamine, 1 equiv.)). Purified using standard work-up and flash column chromatography (1.0-2.5% EtOAc in pentane); isolated as a clear oil (70 mg, 47%). The reaction was also performed on a 5.00 mmol scale ([see scale up safety notes](#)), providing the title compound as a clear oil (970 mg, 67%).

^1H NMR (400 MHz, CDCl_3) 7.24 – 7.19 (m, 2H), 6.90 – 6.83 (m, 2H), 3.81 (s, 3H), 3.73 (s, 2H), 3.56 (t, $J = 6.6$ Hz, 2H), 3.07 (q, $J = 9.5$ Hz, 2H), 2.79 (t, $J = 6.6$ Hz, 2H), 1.91 (tt, $J = 6.6, 6.6$ Hz, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 158.9, 130.1, 129.9, 125.9 (q, $J = 281.8$ Hz), 113.8, 58.5, 55.2, 54.0 (q, $J = 30.3$ Hz), 51.3, 42.5, 30.8; ^{19}F NMR (376 MHz, CDCl_3) δ -69.13 (t, $J = 9.5$ Hz); IR (cm^{-1}) (neat) 2960, 2838, 1612, 1586, 1511, 1268, 1244, 1136, 1084, 1034, 974, 812; HR-GC-EIMS: rt = 12.24 min. Exact mass calcd for $\text{C}_{13}\text{H}_{17}\text{NOF}_3\text{Cl}$, 295.09453. Found 295.09467, (mass difference: 0.50 ppm).

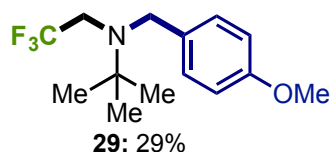
***N*-(2-methoxyethyl)-2,2-dimethyl-*N*-(2,2,2-trifluoroethyl)propan-1-amine**
(28)



Title compound prepared using general alkylative-trifluoroethylation method C. Purified using standard work-up and flash column chromatography (0-1% EtOAc in pentane); isolated as a clear oil (61 mg, 54%). Compound is volatile.

¹H NMR (400 MHz, CDCl₃) δ 3.49 (t, *J* = 6.2 Hz, 2H), 3.34 (s, 3H), 3.20 (q, *J* = 9.5 Hz, 2H), 2.87 (t, *J* = 6.2 Hz, 2H), 2.44 (s, 2H), 0.88 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 126.0 (q, *J* = 282.9 Hz), 71.5, 68.8, 58.8, 57.8 (q, *J* = 29.7 Hz), 56.1, 33.3, 27.8; ¹⁹F NMR (282 MHz, CDCl₃) δ -74.04 (t, *J* = 9.5 Hz); IR (cm⁻¹) (neat) 2954, 2870, 1272, 1135, 1093; HR-GC-EIMS: *rt* = 9.34 min. Exact mass calcd for C₁₀H₂₀NOF₃, 227.1492. Found 227.1489, (mass difference: -0.94 ppm).

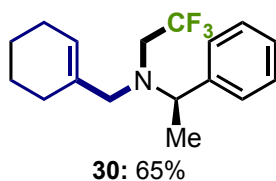
***N*-(4-methoxybenzyl)-2-methyl-*N*-(2,2,2-trifluoroethyl)propan-2-amine**
(29)



Title compound prepared using general alkylative-trifluoroethylation method A. Purified using standard work-up and flash column chromatography (3-7% EtOAc in pentane); isolated as a clear oil (40 mg, 29%).

¹H NMR (400 MHz, CDCl₃) δ 7.33 – 7.23 (m, 2H), 6.88 – 6.78 (m, 2H), 3.86 (s, 2H), 3.80 (s, 3H), 3.18 (q, *J* = 9.5 Hz, 2H), 1.12 (s, 9H); **¹³C NMR** (101 MHz, CDCl₃) δ 158.2, 134.0, 128.4, 126.0 (q, *J* = 280.5 Hz), 113.4, 55.6, 55.2, 54.9, 51.9 (q, *J* = 31.1 Hz), 27.5; **¹⁹F NMR** (376 MHz, CDCl₃) δ -69.90 (t, *J* = 9.5 Hz); **IR** (cm⁻¹) (neat) 2971, 1511, 1242, 1129, 1047; **HRMS** (ESI⁺): Exact mass calcd for C₁₄H₂₁F₃NO [M+H], 276.1570. Found 276.1580, σ = 0.0084.

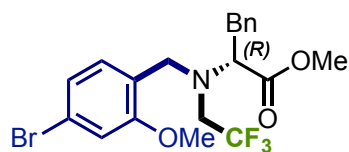
(*R*)-*N*-(cyclohex-1-en-1-ylmethyl)-2,2,2-trifluoro-*N*-(1-phenylethyl)ethan-1-amine (30)



Title compound prepared using general alkylative-trifluoroethylation method B. Purified using standard work-up and flash column chromatography (2-10% EtOAc in pentane); isolated as a clear oil (97 mg, 65%).

¹H NMR (400 MHz, CDCl₃) 7.35 – 7.27 (m, 4H), 7.24 – 7.19 (m, 1H), 5.58 – 5.50 (m, 1H), 4.03 (q, *J* = 6.9 Hz, 1H), 3.12 – 2.84 (m, 4H), 2.08 – 1.92 (m, 3H), 1.90 – 1.78 (m, 1H), 1.61 – 1.47 (m, 4H), 1.35 (d, *J* = 6.9 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 142.4, 135.8, 128.1, 127.9, 126.9, 126.1 (q, *J* = 280.3 Hz), 125.4, 58.1, 58.0, 50.2 (q, *J* = 30.8 Hz), 26.3, 25.3, 22.7, 22.6, 14.6; **¹⁹F NMR** (282 MHz, CDCl₃) δ -69.56 (t, *J* = 9.5 Hz); **IR** (cm⁻¹) (neat) 2929, 2837, 1494, 1449, 1269, 1135, 1097 **HRMS** (ESI⁺): Exact mass calcd for C₁₇H₂₃F₃N [M+H], 298.1777. Found 298.1763, σ = 0.0581; [α]_D²⁶ +22.2° (c 1.0, EtOH).

methyl *N*-(4-bromo-2-methoxybenzyl)-*N*-(2,2,2-trifluoroethyl)-*D*-phenylalaninate (31)

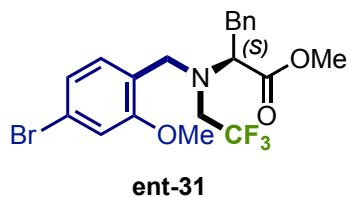


31: 53% (>99% e.e.)

Title compound prepared using general alkylative-trifluoroethylation method A using enantiopure *D*-phenylalanine methyl ester. Purified using standard work-up and flash column chromatography (10-15% EtOAc in pentane); isolated as a clear oil (121 mg, 53%). The ee of the material was determined by HPLC to be >99% by comparison to the (*S*-) enantiomer (see [HPLC data](#)).

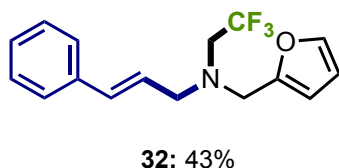
¹H NMR (400 MHz, CDCl₃) δ 7.36 – 7.17 (m, 5H), 7.13 – 7.06 (m, 2H), 6.69 (d, *J* = 8.5 Hz, 1H), 4.01 (d, *J* = 15.3 Hz, 1H), 3.86 (d, *J* = 15.3 Hz, 1H), 3.75 (s, 3H), 3.69 (dd, *J* = 7.8, 7.0 Hz, 1H), 3.65 (s, 3H), 3.53 – 3.31 (m, 2H), 3.09 (dd, *J* = 13.9, 7.8 Hz, 1H), 2.94 (dd, *J* = 13.9, 7.0 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 173.0, 156.6, 137.4, 132.4, 130.9, 128.9, 128.5, 128.4, 126.6, 125.4 (q, *J* = 279.8 Hz), 112.9, 111.8, 65.0, 55.4, 52.1 (q, *J* = 31.6 Hz), 51.5, 51.2, 36.6; ¹⁹F NMR (376 MHz, CDCl₃) δ -70.72 (t, *J* = 9.3 Hz); IR (cm⁻¹) (neat) 2952, 1732, 1487, 1271, 1244, 1138, 1091, 1029; HRMS (ESI⁺): Exact mass calcd for C₂₀H₂₁BrF₃NNaO₃ [M+Na], 482.0549. Found 482.0550, σ = 0.0059; [α]_D²⁶ +5.2° (c 1.0, EtOH).

methyl *N*-(4-bromo-2-methoxybenzyl)-*N*-(2,2,2-trifluoroethyl)-*L*-phenylalaninate (*ent*-31)



Title compound prepared using general alkylative-trifluoroethylation method A. Purified using standard work-up and flash column chromatography (10-15% EtOAc in pentane); isolated as a clear oil (104 mg, 45%). The ee of the material was determined by HPLC to be >99% by comparison to the (*R*-) enantiomer (see [HPLC data](#)). Identical data to the other enantiomer, except: $[\alpha]_D^{26} -5.2^\circ$ (*c* 1.0, EtOH).

(*E*)-*N*-(furan-2-ylmethyl)-3-phenyl-*N*-(2,2,2-trifluoroethyl)prop-2-en-1-amine (32)

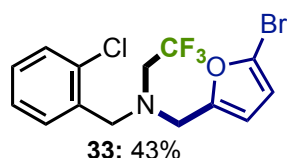


Title compound prepared using general alkylative-trifluoroethylation method A, but using 3 equivalents of trifluoroacetic acid. Purified using standard work-up and flash column chromatography (1-2% EtOAc in pentane); isolated as a clear oil (64 mg, 43%).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.45 – 7.15 (m, 6H), 6.56 (d, $J = 15.8$ Hz, 1H), 6.36 (dd, $J = 3.2, 1.9$ Hz, 1H), 6.23 (dt, $J = 15.8, 6.7$ Hz, 1H), 6.26 – 6.24 (m, 1H) 3.90 (s, 2H), 3.46 (d, $J = 6.7$ Hz, 2H), 3.17 (q, $J = 9.5$ Hz, 2H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 151.5, 142.5, 136.7, 133.5, 128.6, 127.7, 126.4 (2C), 125.8 (q, $J = 280.3$ Hz), 110.1, 109.3, 57.0, 52.7 (q, $J = 30.8$ Hz), 50.3; $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ -69.63 (t, $J = 9.5$ Hz); **IR** (cm^{-1}) (neat) 3028, 2932, 2839, 1599, 1497, 1269, 1138, 1068; **HR-GC-EIMS**: *rt* = 12.49 min.

Exact mass calcd for $C_{16}H_{16}NOF_3$, 295.11785. Found 295.11764, (mass difference: -0.70 ppm).

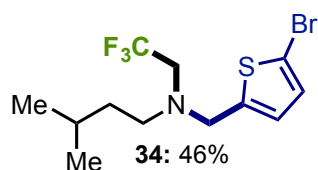
***N*-((5-bromofuran-2-yl)methyl)-*N*-(2-chlorobenzyl)-2,2,2-trifluoroethan-1-amine (33)**



Title compound prepared using general alkylative-trifluoroethylation method A, but using 3 equivalents of trifluoroacetic acid. Purified using standard work-up and flash column chromatography (3-6% CH_2Cl_2 in pentane); isolated as a clear oil (83 mg, 43%).

^1H NMR (400 MHz, $CDCl_3$) 7.57 (dd, $J = 7.7, 1.8$ Hz, 1H), 7.35 (dd, $J = 7.7, 1.4$ Hz, 1H), 7.32 – 7.23 (m, 1H), 7.21 (td, $J = 7.7, 1.8$ Hz, 1H), 6.25 (d, $J = 3.3$ Hz, 1H), 6.21 (d, $J = 3.3$ Hz, 1H), 3.97 (s, 2H), 3.81 (s, 2H), 3.22 (q, $J = 9.4$ Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.4, 135.6, 133.9, 130.2, 129.5, 128.5, 126.9, 124.3 (q, $J = 281.0$ Hz), 112.1, 111.8, 55.3, 53.7 (q, $J = 31.0$ Hz), 50.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -69.42 (t, $J = 9.4$ Hz); IR (cm^{-1}) (neat) 3067, 2923, 1501, 1443, 1269, 1139, 1077; **HR-GC-EIMS**: rt = 12.95 min. Exact mass calcd for $C_{14}H_{12}NOF_3ClBr$, 380.97374. Found 380.97266, (mass difference: 2.65 ppm).

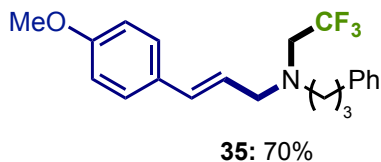
***N*-((5-bromothiophen-2-yl)methyl)-3-methyl-*N*-(2,2,2-trifluoroethyl)butan-1-amine (34)**



Title compound prepared using general alkylative-trifluoroethylation method A, but using 2 equivalents of trifluoroacetic acid. Purified using standard work-up and flash column chromatography (0-4% CH₂Cl₂ in pentane); isolated as a clear oil (79 mg, 46%).

¹H NMR (400 MHz, CDCl₃) δ 6.89 (d, *J* = 3.7 Hz, 1H), 6.68 (d, *J* = 3.7 Hz, 1H), 3.92 (s, 2H), 3.09 (q, *J* = 9.5 Hz, 2H), 2.71 – 2.62 (m, 2H), 1.61 (dh, *J* = 6.9, 6.6 Hz, 1H), 1.43 – 1.33 (m, 2H), 0.88 (d, *J* = 6.6 Hz, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 143.8, 129.2, 126.2, 125.8 (q, *J* = 281.8 Hz), 111.6, 53.6, 53.4 (q, *J* = 30.5 Hz), 52.2, 36.3, 25.8, 22.6; ¹⁹F NMR (376 MHz, CDCl₃) δ -69.06 (t, *J* = 9.5 Hz); IR (cm⁻¹) (neat) 2957, 2929, 2870, 1467, 1268, 1139, 1076; HR-GC-EIMS: rt = 11.85 min. Exact mass calcd for C₁₂H₁₇NF₃SBr, 343.0212. Found 343.0203, (mass difference: -2.42 ppm).

(*E*)-3-(4-methoxyphenyl)-*N*-(3-phenylpropyl)-*N*-(2,2,2-trifluoroethyl)prop-2-en-1-amine (35)

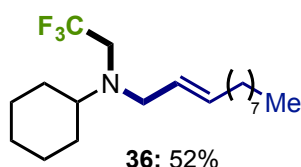


Title compound prepared using general alkylative-trifluoroethylation method A. Purified using standard work-up and flash column chromatography (3-6% EtOAc in pentane); isolated as a clear oil (127 mg, 70%).

¹H NMR (400 MHz, CDCl₃) δ 7.35 – 7.24 (m, 4H), 7.20 (m, 3H), 6.91 – 6.85 (m, 2H), 6.47 (d, *J* = 15.9 Hz, 1H), 6.08 (dt, *J* = 15.9, 6.8 Hz, 1H), 3.83 (s, 3H), 3.41 (d, *J* = 6.8 Hz, 2H), 3.10 (q, *J* = 9.6 Hz, 2H), 2.72 (t, *J* = 7.2 Hz, 2H), 2.67 (t, *J* = 7.7 Hz, 2H), 1.83 (tt, *J* = 7.7, 7.2 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 159.2, 142.1, 132.7, 129.6, 128.4, 128.3, 127.5, 125.9 (q, *J* = 280.7 Hz), 125.8, 124.0, 114.0, 57.4, 55.3, 54.2, 53.9 (q, *J* = 30.4 Hz),

33.1, 29.3; **¹⁹F NMR** (376 MHz, CDCl₃) δ -69.69 (t, J = 9.6 Hz); **IR** (cm⁻¹) (neat) 2936, 2837, 1607, 1510, 1269, 1300, 1133, 1091, 1033; **HRMS** (ESI⁺): Exact mass calcd for C₂₁H₂₄F₃NNaO [M+Na], 386.1702. Found 386.1702, σ = 0.0185.

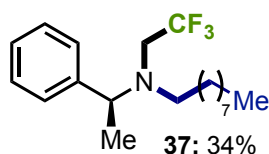
(*E*)-*N*-(2,2,2-trifluoroethyl)-*N*-(undec-2-en-1-yl)cyclohexanamine (36)



Title compound prepared using general alkylative-trifluoroethylation method B. Purified using standard work-up and flash column chromatography (1-2% EtOAc in pentane); isolated as a clear oil (87 mg, 52%) as a 7:93 ratio of cis:trans isomers, as determined from integration of the pair of allylamine methylene doublets. Attempts to reduce isomerisation by altering the times and temperatures of each part of the protocol proved unsuccessful.

¹H NMR (400 MHz, CDCl₃) δ 5.60 – 5.48 (dt, J = 15.3, 6.8 Hz, 1H), 5.46 – 5.36 (dt, J = 15.3, 6.4 Hz, 1H), 3.30 (d, J = 6.7 Hz, 0.14H, NCH₂CH=CH - cis), 3.21 (d, J = 6.4 Hz, 1.86H, NCH₂CH=CH - trans), 3.00 (q, J = 9.5 Hz, 2H), 2.56 (tt, J = 11.3, 3.2 Hz, 1H), 2.02 (dt, J = 7.0, 6.8 Hz, 2H), 1.84 – 1.73 (m, 4H), 1.66 – 1.58 (m, 1H), 1.42 – 0.98 (m, 17H), 0.88 (t, J = 6.8 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) (*trans only*) δ 133.9, 127.8, 126.0 (q, J = 279.7 Hz), 60.4, 54.2, 50.6 (q, J = 30.8 Hz), 32.3, 31.9, 29.5, 29.5, 29.3, 29.3, 29.1, 26.1, 26.0 (d, J = 1.3 Hz), 22.7, 14.1; **¹⁹F NMR** (376 MHz, CDCl₃) δ -71.23 (t, J = 9.5 Hz); **IR** (cm⁻¹) (neat) 2925, 2854, 1452, 1272, 1135, 1094, 1067; **HR-GC-EIMS**: rt = 13.09 min. Exact mass calcd for C₁₉H₃₄NF₃, 333.2638. Found 333.2640, (mass difference: 0.69 ppm).

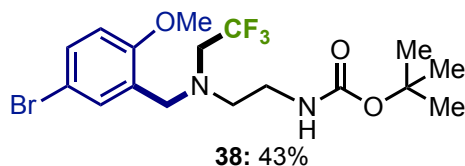
(*S*)-*N*-(1-phenylethyl)-*N*-(2,2,2-trifluoroethyl)nonan-1-amine (37)



Title compound prepared using general alkylative-trifluoroethylation method B. Purified using standard work-up and flash column chromatography (0.5-2% EtOAc in pentane); isolated as a clear oil (55 mg, 34%).

^1H NMR (400 MHz, CDCl_3) δ 7.43 – 7.32 (m, 4H), 7.32 – 7.25 (m, 1H), 4.04 (q, J = 6.8 Hz, 1H), 3.16 (dq, J = 15.5, 9.5 Hz, 1H), 3.02 (dq, J = 15.5, 9.5 Hz, 1H), 2.61 (dt, J = 13.2, 7.2 Hz, 1H), 2.51 (dt, J = 13.2, 7.4 Hz, 1H), 1.52 – 1.43 (m, 2H), 1.41 (d, J = 6.8 Hz, 3H), 1.37 – 1.16 (m, 12H), 0.92 (t, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 143.0, 128.1, 127.7, 127.0, 126.0 (q, J = 279.9 Hz), 59.7, 51.7 (q, J = 31.2 Hz), 51.0, 31.9, 29.6, 29.4, 29.3, 28.0, 26.8, 22.7, 15.9, 14.1; ^{19}F NMR (376 MHz, CDCl_3) δ -70.20 (t, J = 9.5 Hz); IR (cm^{-1}) (neat) 2925, 2855, 1270, 1137, 1095; **HR-GC-EIMS**: r_t = 12.78. Exact mass calcd for $\text{C}_{19}\text{H}_{30}\text{NF}_3$ [$\text{M}+\text{H}$], 329.2325. Found 329.2315, (mass difference: -2.88 ppm); $[\alpha]_{\text{D}}^{26} +15.6^\circ$ (c 1.0, EtOH).

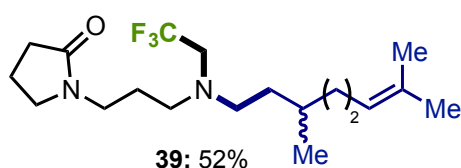
***tert*-butyl (6-((5-bromo-2-methoxybenzyl)(2,2,2-trifluoroethyl)amino)hexyl)carbamate (38)**



Title compound prepared using general alkylative-trifluoroethylation method B. Purified using standard work-up and flash column chromatography (2-10% EtOAc in pentane); isolated as a clear oil (107 mg, 43%).

¹H NMR (400 MHz, CDCl₃) δ 7.50 (d, *J* = 2.6 Hz, 1H), 7.31 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.72 (d, *J* = 8.7 Hz, 1H), 4.50 (br. s, 1H, NH), 3.78 (s, 3H), 3.76 (s, 2H), 3.10 (q, *J* = 9.6 Hz, 2H), 3.12 – 3.01 (m, 2H), 2.59 (t, *J* = 7.2 Hz, 2H), 1.45 (d, *J* = 12.6 Hz, 13H), 1.28 (h, *J* = 4.8, 3.8 Hz, 4H); **¹³C NMR** (101 MHz, CDCl₃) δ 156.6, 156.0, 132.3, 130.6, 129.4, 125.9 (q, *J* = 281.0 Hz), 112.9, 112.0, 79.0, 55.5, 54.6 (q, *J* = 30.3 Hz), 54.4, 52.5, 40.5, 30.0, 28.4, 27.3, 26.7–26.4 (m, 2C); **¹⁹F NMR** (376 MHz, CDCl₃) δ -69.43 (t, *J* = 9.6 Hz); **IR** (cm⁻¹) (neat) 2934, 2860, 1696, 1487, 1366, 1269, 1248, 1169, 1135, 1082; **HRMS** (ESI⁺): Exact mass calcd for C₂₁H₃₂BrF₃N₂NaO₃ [M+Na], 519.1441. Found 519.1434, σ = 0.0017.

1-(3-((3,7-dimethyloct-6-en-1-yl)(2,2,2-trifluoroethyl)amino)propyl)pyrrolidin-2-one (39)

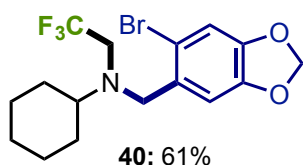


Title compound prepared using general alkylative-trifluoroethylation method B. Purified using standard work-up and flash column chromatography (20-50% EtOAc in pentane); isolated as a clear oil (94 mg, 52%).

¹H NMR (400 MHz, CDCl₃) 5.15 – 5.02 (m, 1H), 3.37 (t, *J* = 7.0 Hz, 2H), 3.30 (t, *J* = 7.4 Hz, 2H), 3.00 (q, *J* = 9.6 Hz, 2H), 2.69 – 2.52 (m, 4H), 2.37 (t, *J* = 8.1 Hz, 2H), 2.09 – 1.86 (m, 4H), 1.78 – 1.55 (m, 8H), 1.54 – 1.38 (m, 2H), 1.37 – 1.08 (m, 3H), 0.87 (d, *J* = 6.3 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 174.9, 131.2 (C_{quat}), 125.8 (q, *J* = 280.9 Hz), 124.7 (=CH), 55.0 (q, *J* = 30.4 Hz), 53.2 (CH₂), 52.6 (CH₂), 47.2 (CH₂), 40.5 (CH₂), 37.1 (CH₂), 34.1 (CH₂), 31.0 (CH₂), 30.3 (CH), 25.7 (CH₂), 25.4 (CH₂), 19.6 (2 x CH₃), 17.9 (CH₂), 17.6 (CH₃); **¹⁹F NMR** (376 MHz, CDCl₃) δ -70.13 (t, *J* = 9.5 Hz); **IR** (cm⁻¹)

(neat) 2958, 2926, 2857, 1671, 1464, 1427, 1269, 1137, 1086; **HRMS** (ESI+): Exact mass calcd for $C_{19}H_{34}F_3N_2O$ $[M+H]$, 363.2617. Found 363.2628, $\sigma = 0.0026$.

***N*-((6-bromobenzo[d][1,3]dioxol-5-yl)methyl)-*N*-(2,2,2-trifluoroethyl)cyclohexanamine (40)**

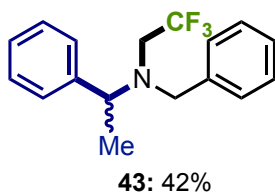


Title compound prepared using general alkylative-trifluoroethylation method A. Purified using standard work-up and flash column chromatography (2-5% EtOAc in pentane); isolated as a pale yellow oil (121 mg, 61%).

^1H NMR (400 MHz, $CDCl_3$) δ 7.15 (s, 1H), 6.95 (s, 1H), 5.97 (s, 2H), 3.83 (s, 2H), 3.12 (q, $J = 9.3$ Hz, 2H), 2.40 (tt, $J = 11.2, 3.6$ Hz, 1H), 1.92 – 1.74 (m, 4H), 1.67 – 1.57 (m, 1H), 1.30 – 0.99 (m, 5H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.5, 147.1, 132.3, 125.8 (q, $J = 279.0$ Hz), 113.3, 112.2, 109.7, 101.5, 60.1, 56.0, 51.5 (q, $J = 31.3$ Hz), 29.2, 26.0, 25.9; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -71.29 (t, $J = 9.3$ Hz); **IR** (cm^{-1}) (neat) 2929, 2855, 1503, 1475, 1230, 1137, 1101, 1073, 1037; **HRMS** (ESI+): Exact mass calcd for $C_{16}H_{20}BrF_3NO_2$ $[M+H]$, 394.0624. Found 394.0619, $\sigma = 0.0152$.

2.22 Full data: compounds 43-46 (ketones)

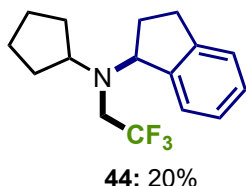
***N*-benzyl-2,2,2-trifluoro-*N*-(1-phenylethyl)ethan-1-amine (43)**



Title compound prepared using general alkylative-trifluoroethylation method E. Purified using standard work-up and flash column chromatography (1-6% dichloromethane in pentane); isolated as a clear oil (61 mg, 42%).

^1H NMR (400 MHz, CDCl_3) δ 7.40 – 7.32 (m, 8H), 7.31 – 7.25 (m, 2H), 4.05 (q, J = 6.9 Hz, 1H), 3.80 (d, J = 14.0 Hz, 1H), 3.75 (d, J = 14.0 Hz, 1H), 3.24 (dq, J = 15.4, 9.4 Hz, 1H), 2.98 (dq, J = 15.4, 9.4 Hz, 1H), 1.44 (d, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 142.1, 139.0, 128.7, 128.3, 128.2, 127.8, 127.2, 127.2, 126.0 (q, J = 281.1, Hz), 58.1, 55.3, 50.2 (q, J = 30.9 Hz), 15.7; ^{19}F NMR (376 MHz, CDCl_3) δ -69.15 (t, J = 9.4 Hz); IR (cm^{-1}) (neat) 3063, 3030, 2975, 1494, 1453, 1432, 1268, 1134, 1097, 1070; HRMS (ESI $^{+}$): Exact mass calcd for $\text{C}_{17}\text{H}_{18}\text{F}_3\text{NNa}$ [$\text{M}+\text{Na}$], 316.1284. Found 316.1293, σ = 0.0160.

***N*-(3-phenylpropyl)-*N*-(2,2,2-trifluoroethyl)-2,3-dihydro-1H-inden-1-amine (44)**

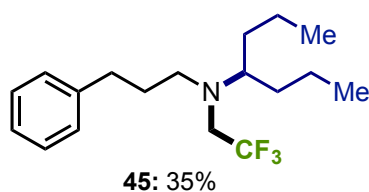


Title compound prepared using general alkylative-trifluoroethylation method E. Purified using standard work-up and flash column chromatography (1-4% EtOAc in pentane); isolated as a clear oil (28 mg, 20%).

^1H NMR (400 MHz, CDCl_3) 7.38 – 7.31 (m, 1H), 7.24 – 7.17 (m, 3H), 4.56 (dd, J = 9.1, 8.1 Hz, 1H), 3.25 – 3.18 (m, 1H), 3.14 (q, J = 9.3 Hz, 2H), 2.92 (ddd, J = 16.1, 9.1, 2.9 Hz, 1H), 2.76 (ddd, J = 16.1, 8.9 Hz, 8.1, 1H), 2.28 (dddd, J = 12.8, 8.9, 8.1, 2.9 Hz, 1H), 1.87

(dddd, $J = 12.8, 9.1, 9.1, 8.9$ Hz, 1H), 1.81 – 1.67 (m, 2H), 1.67 – 1.31 (m, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ 144.1, 143.2, 127.3, 126.5 (q, $J = 279.7$ Hz), 126.3, 124.8, 124.6, 67.0, 61.2, 49.9 (q, $J = 31.6$ Hz), 31.6, 30.0, 29.5, 29.4, 24.1, 23.3; ^{19}F NMR (376 MHz, CDCl_3) δ -70.79 (t, $J = 9.3$ Hz); IR (cm^{-1}) (neat) 2953, 2870, 1477, 1458, 1267, 1131, 1097, 1023; **HR-GC-EIMS**: rt = 12.30 min. Exact mass calcd for $\text{C}_{16}\text{H}_{20}\text{NF}_3$, 283.15424. Found 283.15300, (mass difference: -4.35 ppm).

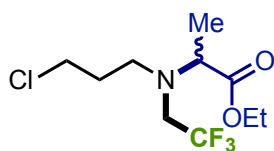
***N*-(3-phenylpropyl)-*N*-(2,2,2-trifluoroethyl)heptan-4-amine (45)**



Title compound prepared using general alkylative-trifluoroethylation method E. Purified using standard work-up and flash column chromatography (1-3% EtOAc in pentane); isolated as a clear oil (55 mg, 35%).

^1H NMR (400 MHz, CDCl_3) δ 7.33 – 7.25 (m, 2H), 7.22 – 7.15 (m, 3H), 3.00 (q, $J = 9.5$ Hz, 2H), 2.68 – 2.61 (m, 2H), 2.59 (t, $J = 7.1$ Hz, 2H), 2.50 (h, $J = 6.6$ Hz, 1H), 1.80 – 1.68 (m, 2H), 1.50 – 1.16 (m, 8H), 0.90 (t, $J = 6.9$ Hz, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ 142.5, 128.3, 128.3, 126.0 (q, $J = 279.2$ Hz), 125.6, 61.7, 52.9 (q, $J = 31.0$ Hz), 51.1, 33.6, 33.3, 31.1, 20.2, 14.2; ^{19}F NMR (376 MHz, CDCl_3) δ -71.21 (t, $J = 9.5$ Hz); IR (cm^{-1}) (neat) 3027, 2958, 2931, 2871, 1455, 1270, 1134, 1088; **HRMS** (ESI+): Exact mass calcd for $\text{C}_{18}\text{H}_{29}\text{F}_3\text{N}$ $[M+H]^+$, 316.2247. Found 316.2255, $\sigma = 0.0066$.

ethyl *N*-(3-chloropropyl)-*N*-(2,2,2-trifluoroethyl)alaninate (46)



46: 41%

Title compound prepared using general alkylative-trifluoroethylation method E. Purified using standard work-up and flash column chromatography (5-10% EtOAc in pentane); isolated as a clear oil (57 mg, 41%).

¹H NMR (400 MHz, CDCl₃) δ 4.17 (q, *J* = 7.1 Hz, 2H), 3.60 (t, *J* = 6.4 Hz, 2H), 3.56 (q, *J* = 7.3 Hz, 1H), 3.36 – 3.17 (m, 2H), 2.86 (t, *J* = 6.6 Hz, 2H), 1.94 – 1.85 (m, 2H), 1.34 (d, *J* = 7.3 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 173.6, 126.0 (q, *J* = 279.4 Hz), 60.6, 59.8, 53.3 (q, *J* = 31.8 Hz), 50.7, 42.3, 31.7, 16.6, 14.3; **¹⁹F NMR** (376 MHz, CDCl₃) δ -71.99 (t, *J* = 9.5 Hz); **IR** (cm⁻¹) (neat) 2985, 2941, 1730, 1271, 1138, 1109, 833; **HRMS** (ESI⁺): Exact mass calcd for C₁₀H₁₈ClF₃NO₂ [M+H], 276.0973. Found 276.0983, σ = 0.0764.

3.0 Supporting Experiments

3.01 – Figure S1: Optimization Table

entry	solvent	time (reflux) /h	TFA equiv	PhSiH ₃ equiv.	additives/conditions	amide %	amine %
1	toluene	16	1.00	1.00	-	18	42
2	toluene	16	1.00	2.00	-	43	39
3	toluene	4	2.00	2.00	-	9	85
4	toluene	4	1.00	2.00	amine.HCl	17	52
5	toluene	4	1.00	2.00	amine.HCl + 1 drop Et ₃ N	31	50
6	THF	4	1.50	2.00	-	22	71
7	THF	4	1.75	2.00	-	8	84
8	THF	4	1.75	2.00	open to air/undried solvent	8	78
9	THF	3	1.75	2.00	Fig 4C in manuscript	6	80
10	THF	3	1.00	2.00	Fig 4C in manuscript	54	0

**0.5 mL solvent containing phenylsilane and trifluoroacetic acid. Heat to temperature, remove from heat to add amine (0.5 mmol), then return to heat for time required. Cooled and concentrated and conversion determined by ¹H-NMR relative to 1,1,2,2-tetrachloroethane as an internal standard.*

3.02 – Azide tolerance (Scheme 6)

The standard alkylation-trifluoroethylation reaction was performed in the presence of one equivalent of 1-(azidomethyl)naphthalene to test the stability of azides to the reductive conditions. After 16 h at 70 °C, the reaction was concentrated and the conversions to products deduced by inspection of the ¹H-NMR spectrum and comparison to 1,1,2,2-tetrachloroethane as an internal standard, in chloroform. Analysis suggested full tolerance of the azide to the conditions, which did not interfere with the desired transformation, which still ran to 86% conversion to the alkylated-trifluoroethylated amine.

3.03 – Figure S2: Competition Experiments (Scheme 13)

Experiment A (Scheme 13A):

Primary amines give amide; secondary amines give amine, even in the same pot, suggesting a distinct intermediate leads to amine, rather than a general active reductant

Benzylamine (0.25 mmol) and *N*-methyl-1-phenylmethanamine (0.25 mmol) were combined in a flask and toluene (0.5 mL) and phenylsilane (1.00 mmol) added. The reaction was heated to reflux and trifluoroacetic acid (0.875 mmol) was added and the reaction stirred for 16 h. After this time, the reaction was concentrated and the conversion to each product determined by integration of convenient ¹H-NMR signals and comparison to 0.25 mmol of 1,1,2,2-tetrachloroethane as an internal standard. The analysis indicated that there was a 46% conversion of the available primary amine to amide, and no detectable trifluoroethylated amine. A 92% conversion of the available secondary amine to the trifluoroethylated amine was observed, and no appreciable level of amide.

Experiment B (Scheme 13B):

In the absence of excess acidity, only amide is observed. Secondary amines outcompete primary amines.

Benzylamine (0.50 mmol) and *N*-methyl-1-phenylmethanamine (0.50 mmol) were combined in a flask and toluene (0.5 mL) and phenylsilane (1.00 mmol) added. The reaction was heated to reflux and trifluoroacetic acid (0.875 mmol) was added and the reaction stirred for 16 h. After this time, the reaction was concentrated and the conversion to each product determined by integration of convenient ¹H-NMR signals and comparison to 0.25 mmol of 1,1,2,2-tetrachloroethane as an internal standard. The analysis indicated that there was a 60% conversion of the available primary amine to amide, and no detectable trifluoroethylated amine. A 95% conversion of the available secondary amine to the trifluoroacetamide was observed, and no appreciable level of amine.

3.04 – Figure S3: Resubjection of amide to the reaction conditions (Scheme 9)

Scheme 9a: *Amide is not reduced to amine under the reaction conditions. Typical background amide formation of ~5% observed.*

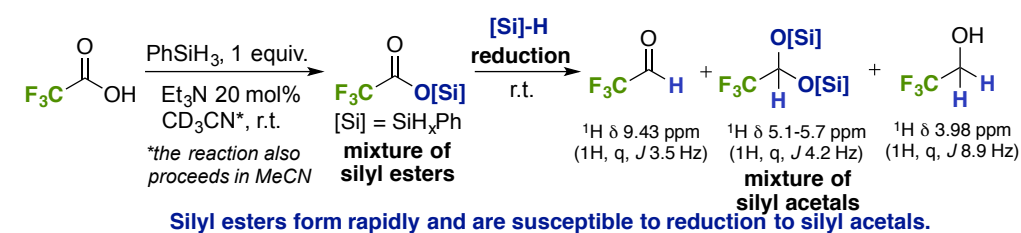
N-benzyl-2,2,2-trifluoro-*N*-methylacetamide (0.50 mmol) and *N*-methyl-1-phenylmethanamine (0.50 mmol) were combined in a flask and toluene (0.5 mL) and phenylsilane (1.00 mmol) added. The reaction was heated to reflux and trifluoroacetic acid (0.875 mmol) was added and the reaction stirred for 16 h. After this time, the reaction was concentrated and the conversion to each product determined by integration of convenient ¹H-NMR signals and comparison to 0.25 mmol of 1,1,2,2-tetrachloroethane as an internal standard. The analysis indicated that there was a 70% conversion of secondary amine to the

trifluoroethylated amine. 1.05 equivalents of amide were observed, which is consistent with no reduction of amide + 5% background reaction (see [optimization table](#)). To rule out a coincidental result and show that amide is not reduced, experiment D utilised a different secondary amine.

Scheme 9b: *Amide is not reduced to amine under the reaction conditions*

N-benzyl-2,2,2-trifluoro-*N*-methylacetamide (0.50 mmol) and piperidine (0.50 mmol) were combined in a flask and toluene (0.5 mL) and phenylsilane (1.00 mmol) added. The reaction was heated to reflux and trifluoroacetic acid (0.875 mmol) was added and the reaction stirred for 16 h. After this time, the reaction was concentrated and the conversion to each product determined by integration of convenient ¹H-NMR signals and comparison to 0.25 mmol of 1,1,2,2-tetrachloroethane as an internal standard. The analysis indicated that there was a 73% conversion of secondary amine to the trifluoroethylated piperidine. 1.00 equivalent of amide was observed, ruling out the reduction of free amide by an external reductant as the mechanism of reduction.

3.05 – Attempts to observe trifluoroacetaldehyde (Scheme 10, Figure 6)



Trifluoroacetic acid (0.60 mmol) and phenylsilane (0.20 mmol) were mixed in deuterated acetonitrile in an NMR tube at rt. Triethylamine (0.02 mmol) was added and the reaction followed by NMR. Hydrogen evolution was observed, and dissolved hydrogen identified at 4.57 ppm. The reaction was briefly heated to reflux with a heat gun, and allowed to stand at

rt for 30 min. Species consistent with previously observed silyl ester species⁹ were noted at 5.02 and 5.67 ppm, and traces of acetal type species were also apparent, suggesting the rates of formation and reduction of the trifluoroacetoxysilyl esters were similar. (Note that acetals are not observed if the reaction is repeated with acetic acid.) No trifluoroacetaldehyde was observed at this point. After 4 h of standing, the initially observed silyl ester species had begun to react further, and evidence of polymeric siloxy species were deduced by the observation of multiple overlapping peaks between 4 and 7 ppm, indicative of a range of silyl hydride species. After standing at room temperature in the NMR tube overnight, a small amount of trifluoroacetaldehyde was visible (9.43 ppm); as was trifluoroethanol (3.98 ppm) and possible derivatives. Importantly, several species consistent with known trifluoroacetaldehyde bis-silyl acetals were identifiable (q, 5.2-5.7 ppm).¹⁰

Aldehydes with strong electron withdrawing groups are known to exist preferentially as the corresponding hydrate.^{1,11} Amines are also known to form the hemiaminals with trifluoroacetaldehyde.¹¹ Such behaviour of carbonyl groups is a function of the electron withdrawing capabilities of the R (e.g. CF₃) group, and it appears to be the electron deficient nature of these acids that promote in situ reduction in this reaction, consistent with the p*K*_a study.

3.06 – Carboxylic acid competition experiment (Scheme 12)

Benzoic acid (0.50 mmol), trifluoroacetic acid (0.50 mmol) and *N*-methyl-1-phenylmethanamine (0.50 mmol) were combined in a flask and THF (0.5 mL) added. The reaction was heated to reflux for 1 min, phenylsilane (1.00 mmol) added, and the reaction stirred for 4 h. After this time, the reaction was concentrated and the conversion to each

product determined by integration of convenient ^1H -NMR signals and comparison to 0.25 mmol of 1,1,2,2-tetrachloroethane as an internal standard. The analysis indicated that there was a 54% conversion to the trifluoroethylated amine, with 31% present as the trifluoroacetamide, composed as two rotamers. The benzamide was present in small amounts, again present as rotamers.

3.07 – HPLC - Enantiopurities

Enantiopurities were determined off-site by Reach Separations. The spectra are available in the appendix.

3.1 – Anilines and primary amines (Scheme 17)

further details available in the masters report of Paige Rist

3.10 Attempted Trifluoroethylation of aniline

According to the typical trifluoroethylation protocol, aniline and phenylsilane were combined in many variations with variable TFA equivalents, in THF or toluene or neat TFA, but the desired product was not observed.

3.11 Attempted Trifluoroethylation of benzylamine

According to the typical trifluoroethylation protocol, benzylamine, TFA and phenylsilane were refluxed in THF over 16 h, but the desired product was not observed.

3.12 Successful trifluoroacetamidation of aniline

According to the typical trifluoroethylation protocol, aniline (1.00 equiv), TFA (1.75 equiv) and phenylsilane (2.00 equiv) were refluxed in THF (0.6 mL) over 16 h. Trifluoroacetamide was generated quantitatively according ^1H -NMR analysis.

3.13 Iridium catalysed reduction of trifluoroacetanilide: Scheme 18B

2,2,2-trifluoro-*N*-phenylacetamide (0.5 mmol) was dissolved in toluene and $[\text{Ir}(\text{COD})\text{Cl}]_2$ (3 mol%, 10 mg) and diethylsilane (259 μL , 2 mmol) were added and the reaction heated at reflux for a 16 h. After this time, the reaction was concentrated and TCE added as an internal standard. The conversion to amine was deduced to be ~60% from the ^1H -NMR spectrum.

3.14 Iridium catalysed trifluoroethylation of 4-bromoaniline: Scheme 18C

4-bromoaniline (86 mg, 0.50 mmol) was combined in toluene (0.5 mL) with trifluoroacetic acid (38 μL , 0.5 mmol) and phenylsilane (62 μL , 0.50 mmol) and heated at reflux for 16 h. After this time, $[\text{Ir}(\text{COD})\text{Cl}]_2$ (3 mol%, 10 mg) and diethylsilane (259 μL , 2 mmol) and the reaction heated at reflux for a further 16 h. The reaction mixture was concentrated, diluted in EtOAc and washed with saturated aqueous sodium bicarbonate solution and the organics dried and concentrated. The residue was subjected to chromatography (20% EtOAc in petrol) and two partially pure fractions were collected, containing the desired trifluoroethylaniline **70** and also a species consistent with silylated hemiaminal **71**. Further details are given in Scheme 18C.

6.0 References

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- 1 H. Mimura, K. Kawada, T. Yamashita, T. Sakamoto and Y. Kikugawa, *J. Fluor. Chem.*, 2010, **131**, 477–486.
 - 2 R. L. Hansen, *J. Org. Chem.*, 1965, **30**, 4322–4324.
 - 3 C. Ates, Z. Janousek and H. G. Viehe, *Tetrahedron Lett.*, 1993, **34**, 5711–5714.

- 4 J. M. Bailey, H. Booth, H. A. R. Y. Al-Shirayda and M. L. Trimble, *J. Chem. Soc. Perkin Trans. 2*, 1984, **0**, 737–743.
- 5 M. Sekiya, O. Matsuda and K. Ito, *Chem. Pharm. Bull. (Tokyo)*, 1975, **23**, 1579–1585.
- 6 K. Yoshida, K. Nakayama, Y. Yokomizo, M. Ohtsuka, M. Takemura, K. Hoshino, H. Kanda, K. Namba, H. Nitani, J. Z. Zhang, V. J. Lee and W. J. Watkins, *Bioorg. Med. Chem.*, 2006, **14**, 8506–8518.
- 7 G. Le Bihan, F. Rondu, A. Pelé-Tounian, X. Wang, S. Lidy, E. Touboul, A. Lamouri, G. Dive, J. Huet, B. Pfeiffer, P. Renard, B. Guardiola-Lemaître, D. Manéchez, L. Pénicaud, Alain Ktorza and J.-J. Godfroid, *J. Med. Chem.*, 1999, **42**, 1587–1603.
- 8 P. J. Riss and F. I. Aigbirhio, *Chem. Commun.*, 2011, **47**, 11873–11875.
- 9 K. G. Andrews, D. M. Summers, L. J. Donnelly and R. M. Denton, *Chem. Commun.*, 2016, **52**, 1855–1858.
- 10 JP2016084310 (A), 2016.
- 11 S. M. Landge, D. A. Borkin and B. Török, *Tetrahedron Lett.*, 2007, **48**, 6372–6376.

Chapter 5

Phosphine Oxide Reductions Using Activated Silanes

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Silanes have a long history of use in the reduction of phosphorus(V) compounds, yet the mainstream understanding of these processes are far from complete. In this Chapter, we attempt to clarify what we perceive to be misgivings about the reactivity of hydridosilanes, and the activation of phosphine oxides with respect to reduction. We do this by first introducing the historical literature, and then through a brief study of a recently published catalytic Wittig reaction. Finally, we exemplify our findings in the development of a new phosphine oxide reduction methodology.

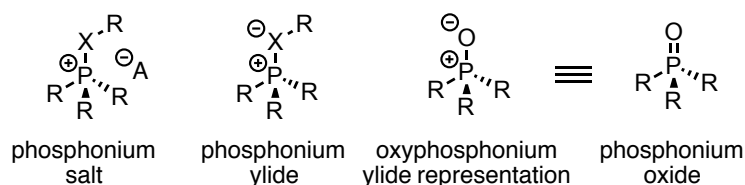
Introduction

Reactivity in Phosphorus(V) Compounds

Phosphorus(V) compounds come in a variety of forms. Despite their apparent diversity, it is often useful to consider these forms as gradations on a single scale. At the reactive end are the phosphonium salts. These have four ligands around a P(V) centre, with a non-coordinating counteranion. Still reactive, but clearly more stabilised, are the tetravalent phosphonium ylides and betaines. In ylides the counterion is localised at the alpha position of one of the ligands, whereas betaines have a more distal negatively charged functionality – they may appear to be a zwitterion.

At the stable end of the spectrum is a specialised pseudo ylide; the phosphine oxide.¹ Phosphines are remarkable oxygen atom storage molecules. In their electron deficient P(V) oxidation state, it is hard to design a better stabilising ligand than oxide; O²⁻. The result is a phosphoryl bond (P=O), but in accordance with the theory of hypercoordination, maintaining the octet of electrons around phosphorus means a formal oxyphosphonium ylide depiction of phosphine oxides; a single P–O bond. But the lack of a second group on oxygen, unlike the true ylides, allows additional orbital interactions with the electron deficient phosphorus(V) centre *via* antibonding orbitals, giving rise to a very strong P–O bond (Figure 1).

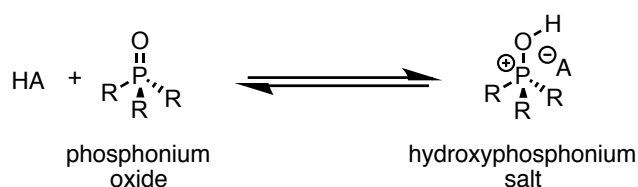
Figure 1. Several important types of phosphorus(V) species.



Gilheany² and others³ have discussed the nature of this P=O phosphoryl bond, and various models have been proposed to describe its structure and electron distribution. Most consider there to be a single sigma bond accompanied by various extents of back-bonding, possibly with some ionic character. Gilheany advocates using the most commonly used description in notation – a P=O double bond – arguing that it is the most useful depiction as the bond is strong and formally unsaturated; the valency shows that addition reactions can occur across the bond,² although there are arguments against this formulation from a theoretical stance.^{3,4} Irrespective of representation or true bonding, it is useful for our purposes here to describe the bond, in an arguably unorthodox way, as a highly stabilised phosphonium ylide.

The reactivity of chemical groups depends on both their thermodynamic and kinetic stability. In the case of phosphine oxides we note that although the bond is polar – normally a sign of the propensity for reactivity – we must admit that the kinetic barrier to reactivity is significantly raised by a deactivation of the phosphonium salt form. The simplest way to depict this is, of course, by drawing the covalent P=O form.

Evidence, theory and formality notwithstanding, the reason we draw attention to the phosphonium ylide representation is that in order to ‘reactivate’ the polarity of this bond, much like carbonyl compounds, we can add a coordinating Lewis or Brønsted acid at oxygen. Indeed, titrating a strong acid into a solution of phosphine oxide results in a continuous downfield shift in the ³¹P-NMR spectrum (more positive δ). This, it must be remembered, is the average chemical shift over the measurement time as hydrogen bonds form and break (Scheme 1).



Scheme 1. Equilibrium between phosphine oxides and hydroxyphosphonium salts in the presence of a strong acid.

In the presence of one equivalent of a superacid, e.g. triflic acid, the whole population of phosphine oxide is essentially continuously protonated, and so the species is best drawn as a full phosphonium salt – the hydroxyphosphonium triflate. That such a strong acid is required to force the equilibrium all the way is testament to the thermodynamic strength of the phosphoryl bond. Recalling our description of the phosphonium salt as the most reactive of the P(V) forms described, reaction *at phosphorus* on a phosphoryl group, therefore, is likely to occur from a very low concentration of activated molecules.

Data on the basicity of phosphine oxides are not widely available, but triphenylphosphine oxide is reported to have a $\text{p}K_{\text{aH}}$ of -2.10 . In other words, phosphine oxides have very low basicities.⁵ This makes hydroxyphosphonium salts a special case in terms of stability; there is essentially a barrierless (proton transfer) mechanism to return to the phosphine oxide, as distinct from, for example, alkoxyphosphonium salts, which require the breaking of an O–R bond to form the oxide. This is indicative of the extent to which phosphorus(V) species need electron stabilisation at phosphorus, and so it comes as little surprise to learn that the oxides – which have a close contact covalent and ionic stabilising effect – are some of the most thermodynamically stable P(V) species.

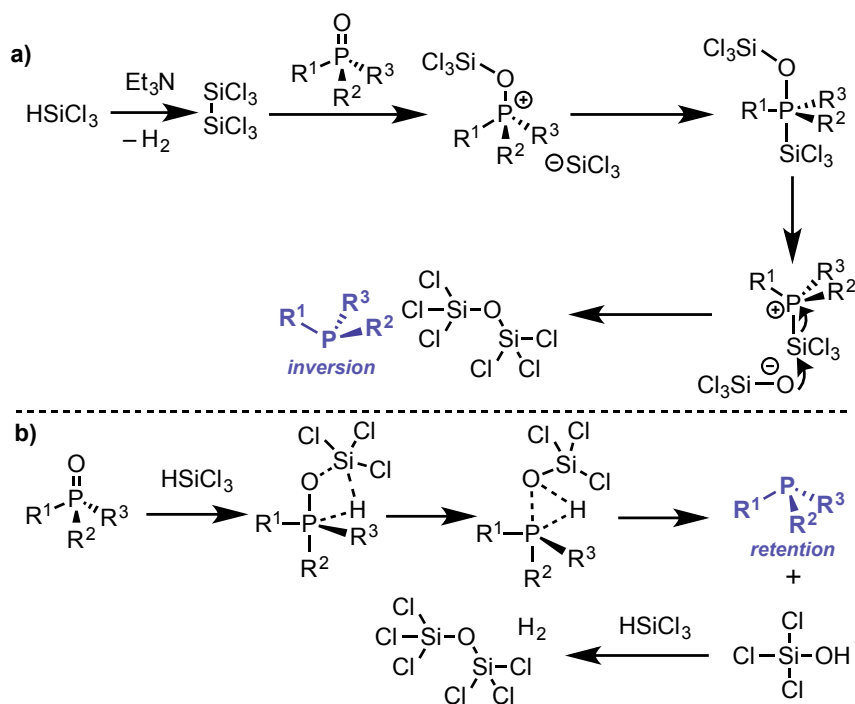
As such, to return the phosphine oxide to the phosphine is difficult, but of immense importance in synthesis, particularly in the field of phosphine-ligand synthesis for asymmetric catalysis,⁶ but also in the context of designing organocatalytic phosphorus-mediated reactions.⁷ The extraction of atomic oxygen is required, generally realised by the

reduction to a water surrogate and the P(III) phosphine. One of the most successfully employed water surrogates are siloxanes, which can store oxygen atoms in stabilised polymeric chains. That hydrosilanes have a hydridic nature due to the inherent electronegativity difference between Si and H makes silanes particularly suitable reagents for the reduction of P(V) oxides to P(III) species.

Mechanism of Phosphine Oxide Reduction Using Hydrosilanes

A recent review describes the history of the reduction of phosphine oxides with silanes.⁸ It would be fair to suggest that our *precise* mechanistic understanding of these reactions is incomplete; early mechanisms lack rigour, whilst more recent studies are limited and take their basis from the under-developed historical suggestions. Perhaps the most up to date work and appraisal in current understanding is given in a computational study by Krenske.⁹

The first class of silanes used to reduce phosphine oxides were the highly Lewis acidic chlorohydrosilanes, e.g. HSiCl_3 .¹⁰ The dominant approach of mechanistic interrogation involves explaining the observed retention or inversion of optically active phosphine oxides under various conditions.^{11–13} Two specific cases arose when using HSiCl_3 : the first case resulted in retention of stereochemistry, whilst the second, with a triethylamine additive, resulted in inversion. Shown below are deemed the most likely representations of the proposed mechanisms adapted from Krenske's interpretations (Scheme 2).

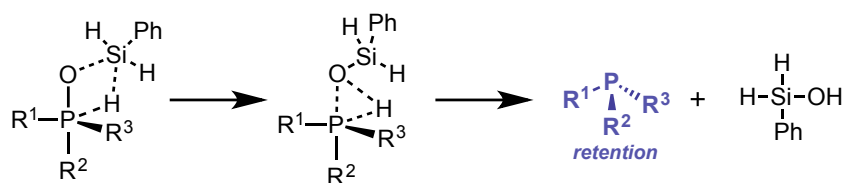


Scheme 2. a) Reduction of phosphine oxides with hexachlorodisilane, formed in situ from hexachlorosilane in the presence of triethylamine, gives inversion of stereochemistry. b) Reduction of phosphine oxides with chlorosilane gives retention of stereochemistry.

What should be noted is that the mechanisms share a general pattern of reactivity; the silane is activated by a Lewis base and the phosphine oxide is activated by a Lewis acid. The adduct can then either *stabilise* the high-energy phosphonium species intramolecularly *via* hydride donation (b), or in the absence of hydride (a), a rearrangement can occur to this end. The resulting pentavalent phosphorus species, in which the stereochemistry has been set, collapses to the thermodynamic products rapidly, before any stereochemical rearrangement can occur (i.e. pseudorotation). For (a), other mechanisms are possible, such as a second silylation of the Si–O–P oxygen atom prior to leaving phosphorus; the key is that the most electronegative atom (P>Si and P>H) takes the electrons.

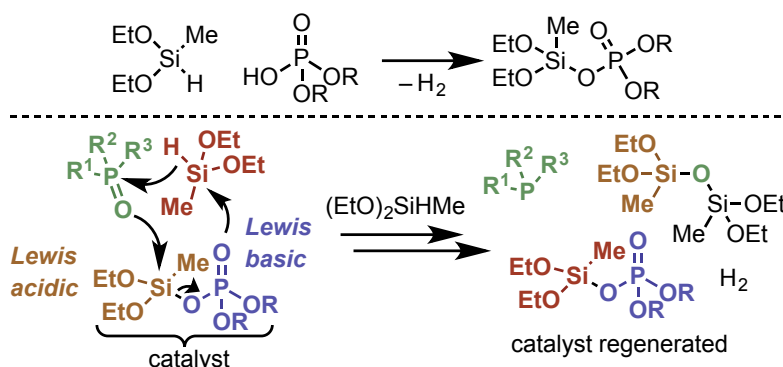
The reaction is favourable because the silane, used in excess, is a high-energy species, which is able to absorb the oxygen into a highly stable water surrogate. Calculations by Krenske⁹ suggest that trimethylphosphine oxide and hexachlorodisilane convert to

trimethylphosphine and hexachlorosiloxane with a 50 kcal/mol energy decrease. The calculations also seem to suggest that, generally, the most energy intensive step is the initial activation of the kinetically stabilised phosphine oxide. Thus, utilisation of a highly reactive Lewis acidic silane is key to achieving high reactivity. Retention in Scheme 2b occurs *via* an intramolecular hydride transfer and *syn* reductive elimination – the same mechanism believed to occur when phenylsilane is used. Inversion inevitably requires a non-hydride-containing Lewis acid, such as hexachlorodisilane.¹² Reduction must involve a backside attack on the P–O bond for inversion to occur. Krenske's proposed mechanism is shown in Scheme 2a. Phenylsilane gives retention of stereochemistry (Scheme 3).¹¹



Scheme 3. Reduction of phosphine oxides with phenylsilane gives retention of stereochemistry.

The importance of activation cannot be overstated; once activated as a phosphonium salt, however, the P(V) species can be readily reduced by even sodium borohydride at room temperature.¹⁴ More recently, a metal free chemoselective reduction of phosphine oxides with silanes was reported by the group of Beller, utilising a bisalkylated phosphoric acid as a catalyst. Scheme 4 depicts a schematic interpretation of Beller's textual analysis;¹⁵ a similar analysis was presented in a recent review.⁸

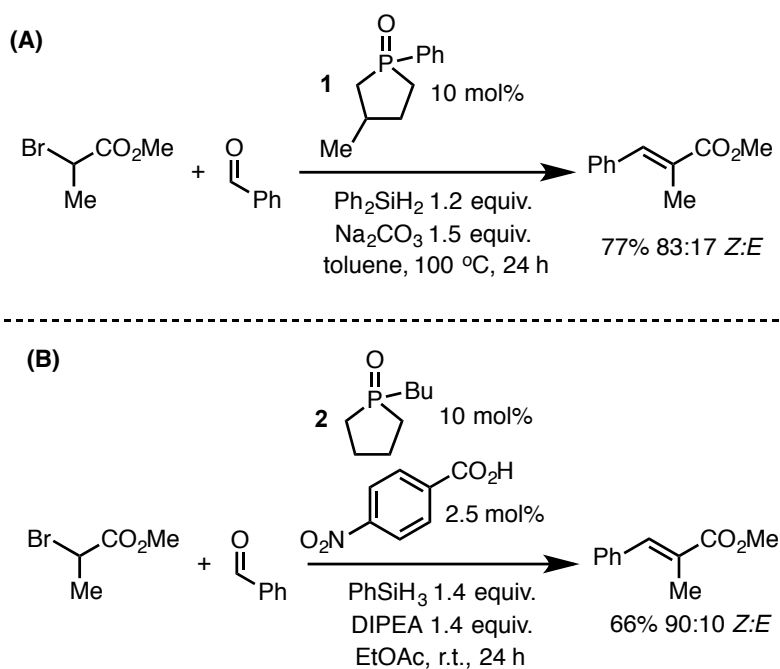


Scheme 4. An interpretation of Beller's proposed mechanism for a phosphoric acid catalysed reduction of phosphine oxides.

This mechanism is perceptive for several reasons; it simultaneously highlights the requirement for a Lewis acidic reductant and a Lewis base to activate it. It begins with dehydrogenative phosphoric silyl ester formation to generate a highly Lewis acidic silicon centre, a species that was observed by ^{31}P -NMR. It is interesting to note that the intention was to use an acid to activate the phosphoryl group. However, investigation demonstrated that the reaction works through an entirely different mechanism, contingent on the formation of an *in situ*-generated Lewis acidic silane. The following results demonstrate that a similar, unappreciated, activation occurs in the recently reported catalytic Wittig reaction.

Silane Activation in O'Brien's Catalytic Wittig Reaction

O'Brien and co-workers have recently developed a catalytic Wittig reaction, in which phosphine oxide reduction is purported to occur to regenerate the phosphine catalyst, similar to the Ashfeld chemistry discussed in Chapter 1. The first procedure they reported utilised diphenylsilane at reflux in toluene over 24 h in the presence of phosphine oxide catalyst **1** (Scheme 5a).¹⁶



Scheme 5. a) O'Brien's organocatalytic Wittig reaction.¹⁶ b) O'Brien's room temperature organocatalytic Wittig reaction.¹⁷

Electron rich (e.g. alkyl) phosphines are prone to oxidation so are less desirable reagents in practical chemistry in terms of storage and handling.¹ This is clearly not a problem in a reaction that requires that the phosphine oxide is reduced. Indeed, more electronically activated phosphine oxides are more easily reduced. The presence of greater electron density at phosphorus both raises the energy of the phosphine (lone pair) with respect to aerobic oxidation and increases the basicity of the phosphine oxide, making it more susceptible to Lewis acid activation. The catalytic Wittig reaction gave good yields and reasonable levels of the *Z*-alkene were isolated (*in situ* isomerisation may be a contributor).

The next report from the O'Brien group was an impressively improved procedure; the reaction now ran at ambient temperature (Scheme 5b).¹⁷ Whilst the catalytic Wittig reaction represents an academically interesting step forward, the most intriguing aspect from our point of view was the facile reduction of the normally difficult to reduce phosphine oxide phosphoryl bond. As mentioned, the replacement of a P-Ph with a P-Bu in the catalyst **2**

makes P more electron-rich and thus the oxide more readily reduced. The authors conducted an excellent study of the reactivity of the phosphine oxide reduction, (independently of the Wittig reaction itself) which was confined to the detailed supporting information.

In this case, a pair of reagents were determined to be required to observe the enhanced phosphine oxide reduction in the presence of silanes; a carboxylic acid and tertiary amine. Stronger acids gave faster reductions. The authors offered a cursory explanation of the rate enhancement focusing on the oxide. The explanation offered was one of 'proton activation'. As discussed in the introduction, in the presence of acids, phosphine oxides can be partially protonated to give hydroxyphosphonium salts, which are undoubtedly more electrophilic at phosphorus. However, in the presence of basic silicon hydrides,¹⁸ the proton of the hydroxyphosphonium salt is the most reactive target ($pK_aH < 0$) rather than phosphorus itself. Indeed, as demonstrated during our work on silyl ester formation (Chapters 1 and 2), the quenching of protic acidity occurs rapidly, especially in polar solvents where more extensive proton transfer occurs (less-solvated anion). The explanation that the carboxylic acid **4** activates the phosphine oxide **3** through protonation must, at this point, be simplistic at best. Although the protonation of the phosphoryl group would indeed activate the P(V) centre, it overlooks the system as a whole. First, it ignores the role of the amine **5**, which as Table 1 shows, is required for rate acceleration.

Table 1. O'Brien's demonstration that acid alone does not activate phosphine oxides for reduction.

Entry	DIPEA (equiv.)	Acid (equiv.)	Conversion (%)
1	14.0	1.0	61
2	14.0	–	6
3	–	1.0	0

^aThe same reactivity pattern was observed under various conditions, using both PhSiH_3 and Ph_2SiH_2 , and with different phosphine oxides.

Although the addition of amine would result in a prohibitively competitive proton abstraction, it is crucial in enhancing the reaction rate. Second, it omits to describe how such a weak and fleeting activation of the phosphine oxide **1** would result in hydride delivery from the silane; in the absence of any additives, phenylsilane takes days at reflux in toluene to reduce many phosphine oxides. Thirdly, all of the mechanisms of silane reduction proposed in the previous literature proceed through phosphoryl attack at silicon, or in the case of Ti catalysts, attack of Ti–H species, achieving the same result.⁸ Evidently, this attack is required at some point in a reaction that requires oxygen transfer; protonating the oxygen atom would presumably inhibit its nucleophilicity. Rutjes and Marsi both comment upon the enhanced reduction of more Lewis basic phosphine oxides by silanes.^{11,19}

Results and Discussion

Probing the O'Brien Phosphine Oxide Reduction Reaction

From our point of view, the system as a whole appeared conducive to silane activation and silyl ester formation. We explored this proposal in a series of experiments in which the

reduction of triphenylphosphine oxide **7**, a difficult reduction substrate, was investigated with different silanes and additives (Table 2).

Table 2. The reduction of triphenylphosphine with various hydridosilanes and additives.

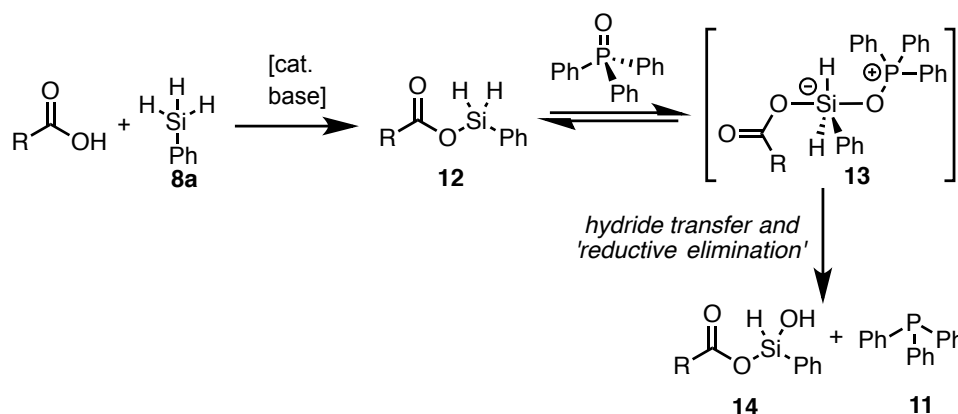
Entry	Acid equiv.	Amine equiv.	Silane equiv. (8)	Ratio of phosphine : oxide	Phosphine oxide shift δ ppm
1	–	–	1.00 (a)	0:100	25.1
2	1.00	–	1.00 (a)	0:100	28.8
3	1.00	1.00	1.00 (a)	5:96	24.9
4	– ^b	–	0.85 (b) ^c	9:91	28.6
5	–	–	1.00 (c)	1:99	25.1
6	1.00 ^d	–	1.00 (a)	0:100	25.3
7	–	–	1.00 (d)	29:71	25.9

^aAll reactions were carried out on a 0.08 mmol scale in 0.5 mL C_6D_6 . ^bpotassium benzoate used in formation of **b**; some free benzoic acid/potassium benzoate present. ^c0.15 equiv. of disiloxane **c** present as a result of hydrolysis. ^dpotassium benzoate used instead of benzoic acid.

In the absence of acid **9** or amine **5**, no reduction occurred (entries 1-2). When both were present, some reduction was seen (entry 3). Preforming the silyl ester **8b** (from the chlorosilane **8d** and carboxylate **10**) led to increased reduction, indicating that the primary role of the base is to catalyse silyl ester formation (entry 4). Because the preformed silyl ester **8b** contained some disiloxane **8c** due to competing hydrolysis during its formation, the disiloxane was independently prepared and tested, showing only trace oxide reduction, ruling this out as the active reductant (entry 5). A further experiment with potassium

benzoate **10** (entry 6) corroborates the importance of the silyl ester in mediating reduction (although solubility limits the true concentration of salt here). In the absence of a proton donor, this intermediate cannot form; any potential reduction process mediated by a carboxylate/phenylsilane adduct does not occur under these conditions.

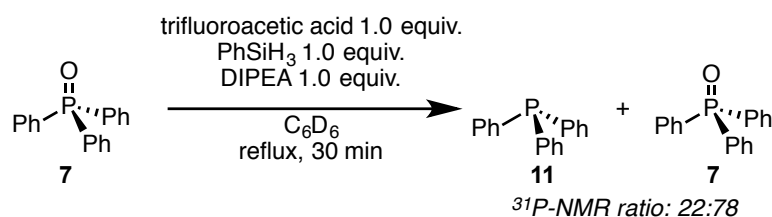
Chlorophenylsilane **8d** proved to be the best reductant of all (entry 7), consistent with a mechanism involving phosphine oxide attack at a more Lewis acidic silicon centre. With the latter result in mind, and given the presence of bromide ions in the catalytic Wittig reaction (Scheme 5), we speculate that bromide ions are able to displace carboxylate from the silyl ester to reform the acid catalyst and generate a bromosilane, which may be the active reductant. Any such equilibrium is only made possible by the initial activation of phenylsilane as a silyl ester (Scheme 6). Silanol products (e.g. **14**) may also displace carboxylate to regenerate the acid catalyst.



Scheme 6. Proposed mechanism of enhanced phosphine oxide reduction *via* in situ silyl ester formation.

Recalling an important study by Corriu in which the stability of amine $\rightarrow$ R₃Si-X ate complexes was determined to be the following: X = R < OR < H < F, SR < OAc, Cl, Br;²⁰ we reasoned that increasing the polarisability of the carboxylate ligand would enhance the phosphine oxide/silane Lewis acid/base interaction, and hence reduction *via* the resultant ate complex. On this basis, trifluoroacetic acid was investigated as an additive. As expected,

the level of reduction (Scheme 7) approached that found with chlorophenylsilane (i.e. entry 7, Table 2).



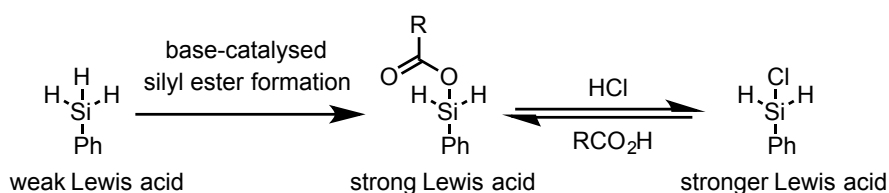
Scheme 7. Demonstration of TFA as a species that forms a Lewis-basic silyl ester.

In the absence of DIPEA, the reduction was only 2%. As demonstrated in Beller's reduction of phosphine oxides,¹⁵ it is possible that more acidic acids can undergo activation with silanes to produce species that accelerate reduction of the phosphine oxides. In the absence of an activating species, such mechanisms advocate the formation of high energy R_3Si^+ species when hydride is transferred. The catalytic formation of activated silanes, however, undoubtedly makes mechanistic and chemical sense, avoiding both the silicenium cation and deactivated oxygen atom problems. In the case of trifluoroacetic acid, the phosphine oxide may become partially protonated. But this does not lead to enhanced reduction, and should not be termed 'proton activation' or even 'phosphine oxide activation.' This is, in fact, '*carboxylate activation*', which leads to silyl ester formation and dehydrogenation of the acidic proton. The resulting silyl ester then reduces the phosphine oxide. Note that in cases with no added base, it might be expected that the more basic (than the oxide) phosphine product can lead to an autocatalytic acceleration in the reaction rate. With the theoretical grounding in place, we sought to exemplify these findings with an improved procedure for the reduction of phosphine oxides to phosphines.

Activated Silanes as Phosphine Oxide Reductants

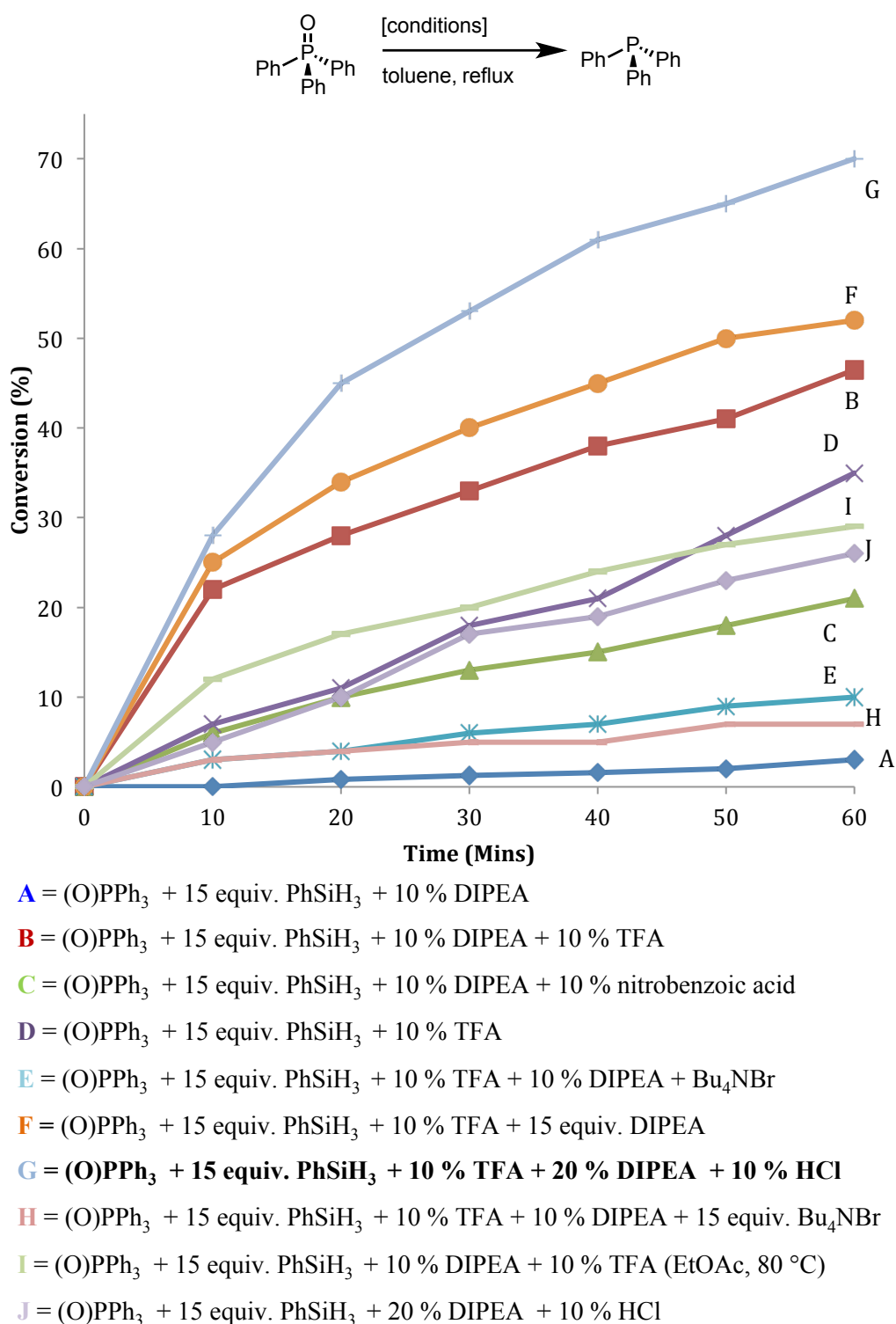
The following work was completed in conjunction with Charlotte Chapman in the group; for full details, consult the relevant Thesis.²¹ First, we studied in more detail the reduction of triphenylphosphine oxide by varying the additives. It is clear from the chart below (Figure 2) that although trifluoroacetic acid does catalyse the reduction of triphenylphosphine oxide by phenylsilane (run D), the reaction is enhanced dramatically by addition of a base catalyst (run B). Phosphine oxides are slightly more basic than carbonyl compounds, one reason being, presumably, that phosphorus is slightly less electronegative than carbon. This Brønsted-base activation can generate a carboxylate anion, which almost certainly promotes the dehydrogenative formation of a silyl ester, which then acts as the reductant in the reaction, as described above.

Of further interest is that a small amount of HCl, introduced as a solution in diethyl ether, enhances the reaction (run J). However, this species alone is inferior to the reaction in which silyl esters can be generated (run F). Carboxylate represents an intermediate acidity; weak enough to retain enough nucleophilicity to attack silicon, but strong enough to operate in an electron-accepting capacity, both in the unstable pentavalent silicon intermediate and in increasing the Lewis acidity of the silicon in the resulting silyl ester. Chloride (from HCl) although an effective additive once present as the chlorosilane, is presumably too weak a nucleophile to activate silicon effectively initially. A synergy between the two (Figure 2) thus creates an effective reagent combination (run G).



Scheme 8. Possibility of the formation of highly Lewis-acid silyl esters in the presence of carboxylate, base and HCl

Figure 2. Chapman's conversion of the reduction of triphenylphosphine as a function of time and additives



The formation of silyl esters is clear in the following result (Table 1, entry 2). If the stoichiometry of TFA:silane is 3:1, the hydride source is exhausted rapidly and only trace phosphine reduction is observed, whereas moderate silyl ester formation gives the active

system. If the reaction were specifically acid promoted, increased acid loadings should lead to a faster reduction rate.

Table 3. Chapman's demonstration the formation of silyl esters may consume all available hydride sources.

$ \begin{array}{c} \text{O} \\ \parallel \\ \text{Ph}-\text{P}-\text{Ph} \\ \\ \text{Ph} \end{array} \xrightarrow[\text{toluene, 100 } ^\circ\text{C, 1 h}]{\begin{array}{l} \text{PhSiH}_3 \text{ [equiv.]} \\ \text{TFA [equiv.]} \\ \text{DIPEA [equiv.]} \end{array}} \begin{array}{c} \text{Ph}-\text{P}-\text{Ph} \\ \\ \text{Ph} \end{array} $									
Entry	Equiv. of PhSiH ₃	Equiv. of TFA	Equiv. of DIPEA	10 mins. (%)	20 mins. (%)	30 mins. (%)	40 mins. (%)	50 mins. (%)	1 hr (%)
1	1	1	1	22	31	38	43	46	48
2	1	3	1	3	3	3	4	3	3

Subsequent optimisation of the system led to a final set of conditions that was exemplified on a modest range of phosphine oxides (Table 4).

Table 4. Chapman's scope of the enhanced reduction methodology

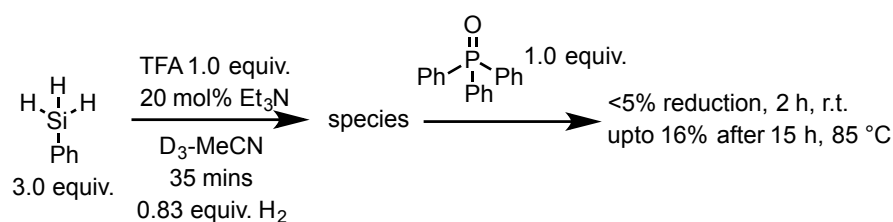
$ \begin{array}{c} \text{O} \\ \parallel \\ \text{R}^1\text{-P}\text{-R}^3 \\ \mid \\ \text{R}^2 \end{array} \xrightarrow[\text{toluene, 100 } ^\circ\text{C, 6 h}]{\begin{array}{l} \text{PhSiH}_3 \text{ 3 equiv.} \\ \text{TFA 2 mol\%} \\ \text{DiPEA 20 mol\%} \\ \text{10 mol\% HCl (in ether)} \end{array}} \begin{array}{c} \text{O} \\ \parallel \\ \text{R}^1\text{-P}\text{-R}^3 \\ \mid \\ \text{R}^2 \end{array} $					
Entry	Phosphine Oxide	Conversion 1hr (%)	Conversion 4hrs (%)	Conversion 6hrs (%)	Yield (%)
1		No reaction	No reaction	No reaction	0
2		100	-	-	15*
3		52	89	97	60*
4		39	68	80	55
5		63	100	-	40*
6		100	-	-	80*
7		No reaction	No reaction	No reaction	0
8		37	66	81	48*

*phosphines isolated as the phosphine-borane complex.

This concludes the presentation of supporting results reported in the Thesis of Charlotte Chapman²¹ based on ideas developed in the first part of this chapter.

Further Mechanistic Experiments

Given that O'Brien's catalytic Wittig reaction operates at room-temperature, we were interested to discover whether the new reaction could operate at these lower temperatures with triphenylphosphine oxide. The data in the SI for the room-temperature Wittig reaction show that the alternative, electron-rich, catalyst is effectively reduced at room temperature. Triphenylphosphine oxide, however, is reported only at reflux in toluene. Scheme 9 shows that only a small amount of reduction ($\sim 5\%$) is observed at room temperature when using preformed silyl esters. Even after heating for 15 h, the level of reduction remained low. However, it does show reduction at room temperature, which would not be observed in the absence of the silyl esters present.



Scheme 9. Demonstration of silyl ester formation and some oxide reduction at room temperature

Presumably, even with activated Lewis acids, the strong phosphoryl bond is slow to attack at silicon. Electron rich phosphines are rapidly reduced, suggesting that this is more important than the rate of hydride transfer, which might be expected to be slower for electron rich phosphine oxides.

Summary

Silane-mediated reductions of phosphine oxides have been reviewed, and the importance of the Lewis basicity of the phosphoryl group discussed. But of equal importance, and sometimes neglected in the literature, is the Lewis acidity of the silane. O'Brien's room-temperature Wittig reaction achieves the reduction of phosphine oxides at ambient

temperature. But proton activation as an explanation of the enhanced reduction has been called into question; instead ‘carboxylate activation’ may occur, promoted by an additional base, or by the Lewis-basic phosphine oxide/phosphine product in the absence of additional base. The resulting carboxylate ion undergoes dehydrogenative silylation to form a Lewis acidic reductant, which facilitates the reduction of the phosphine oxide. With this knowledge, an improved phosphine oxide reduction procedure has been developed in which trifluoroacetic acid acts as the source of carboxylate to generate an enhanced reductant. Although the exact workings of the mechanism have yet to be fleshed out, the data presented suggest that activated silanes play an important role in enhanced reductions.

References

- 1 L. D. Quin, *A Guide to Organophosphorus Chemistry*, John Wiley & Sons, 2000.
- 2 D. G. Gilheany, *Chem. Rev.*, 1994, **94**, 1339–1374.
- 3 W. Kutzelnigg, *Angew. Chem. Int. Ed.*, 1984, **23**, 272–295.
- 4 D. W. Smith, *J. Chem. Educ.*, 2005, **82**, 1202.
- 5 M. Liler, *Reaction Mechanisms in Sulphuric Acid and other Strong Acid Solutions*, Elsevier Science, 2012.
- 6 K. M. Pietrusiewicz and M. Zablocka, *Chem. Rev.*, 1994, **94**, 1375–1411.
- 7 H. A. van Kalker, F. L. van Delft and F. P. J. T. Rutjes, *ChemSusChem*, 2013, **6**, 1615–1624.
- 8 D. Hérault, D. H. Nguyen, D. Nuel and G. Buono, *Chem. Soc. Rev.*, 2015, **44**, 2508–2528.
- 9 E. H. Krenske, *J. Org. Chem.*, 2012, **77**, 3969–3977.
- 10 L. Horner and W. D. Balzer, *Tetrahedron Lett.*, 1965, **6**, 1157–1162.
- 11 K. L. Marsi, *J. Org. Chem.*, 1974, **39**, 265–267.

- 12 K. Naumann, G. Zon and K. Mislow, *J. Am. Chem. Soc.*, 1969, **91**, 7012–7023.
- 13 G. Zon, K. E. DeBruin, K. Naumann and K. Mislow, *J. Am. Chem. Soc.*, 1969, **91**, 7023–7027.
- 14 K. V Rajendran and D. G. Gilheany, *Chem. Commun.*, 2012, **48**, 817–819.
- 15 Y. Li, L.-Q. Lu, S. Das, S. Pisiewicz, K. Junge and M. Beller, *J. Am. Chem. Soc.*, 2012, **134**, 18325–18329.
- 16 C. J. O'Brien, J. L. Tellez, Z. S. Nixon, L. J. Kang, A. L. Carter, S. R. Kunkel, K. C. Przeworski and G. a Chass, *Angew. Chem. Int. Ed.*, 2009, **48**, 6836–6839.
- 17 C. J. O'Brien, F. Lavigne, E. E. Coyle, A. J. Holohan and B. J. Doonan, *Chem. Eur. J.*, 2013, **19**, 5854–5858.
- 18 L. H. Sommer and W. D. Korte, *J. Am. Chem. Soc.*, 1967, **89**, 5802–5806.
- 19 H. a van Kalker, S. H. a M. Leenders, C. R. a Hommersom, F. P. J. T. Rutjes and F. L. van Delft, *Chem. Eur. J.*, 2011, **17**, 11290–11295.
- 20 R. J. P. Corriu, G. Royo and A. Saxce, De, *J. Chem. Soc. Chem. Commun.*, 1980, 892–894.
- 21 C. G. Chapman, University of Nottingham, 2015.

Chapter 5

Experimental Section

Contents

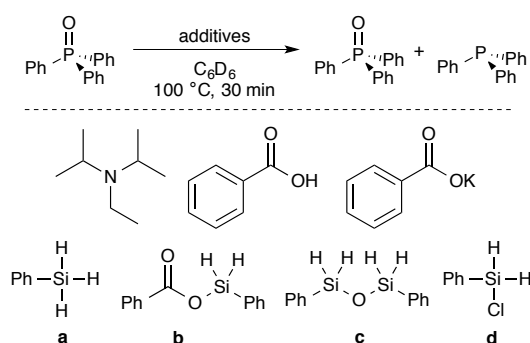
1. General Information.....	340
2. Experimental Details	340
2.1 Triphenylphosphine oxide reduction experiments (Table 2)	340
2.2 Phosphine Oxide Data	341
Attempted room temperature reduction, scheme 9	341

1. General Information

See chapter 1.

2. Experimental Details

2.1 Triphenylphosphine oxide reduction experiments (Table 2)



Entry	Acid (equiv.)	DIPEA (equiv.)	Silane equiv.	Phosphine % (δ ppm)	Phosphine oxide % (δ ppm)
1	–	–	1.00 (a)	0	100 (25.1)
2	1.0	–	1.00 (a)	0	100 (28.8)
3	1.0	1.0	1.00 (a)	5 (-5.2)	95 (24.9)
4	1.0 ^a	–	0.85 (b), 0.15 (c), <0.01 (d)	9 (-5.2)	91 (28.6)
5	–	–	1.00 (c)	1 (-5.2)	99 (25.1)
6	–	–	1.00 (d)	29 (-5.2)	71 (25.9)
7	1.0 ^b	–	1.00 (a)	0	100 (25.3)
8	1.0 ^c	1.0	1.00 (a)	22 (-5.2)	78 (25.0)
9	1.0 ^c	–	1.00 (a)	2 (-5.2)	98 (32.9)

^apotassium benzoate used in formation of **b**; some free benzoic acid/potassium benzoate present. ^bpotassium benzoate used instead of benzoic acid. ^cTrifluoroacetic acid used instead of benzoic acid.

Triphenylphosphine oxide (22.2 mg, 0.0800 mmol) was dissolved in C₆D₆ (0.5 mL) in a flask fitted with a water condenser and added were the requisite additives from; benzoic acid (9.7 mg, 0.080 mmol); *N,N*-diisopropylethylamine (13.2 μ L, 0.0800 mmol); potassium benzoate (12.8 mg, 0.0800 mmol), trifluoroacetic acid (6.1 μ L, 0.080 mmol). In

each case, the reaction was heated to 100 °C before adding the requisite silane; phenylsilane (13.2 μ L, 0.0800 mmol) or chlorophenylsilane (10.6 μ L, 0.0800 mmol). For the preformed silyl ester experiment, phenylsilyl benzoate was formed as the major species as described in Chapter 1 and 2 (0.0800 mmol), and the triphenylphosphine added last. (The ratio of the relevant silanes present from the preformation reaction is shown for entry 4, estimated from the ^1H -NMR spectrum.)

The reaction was heated for 30 min timing from the addition of the silane (or the phosphine oxide in the case of the preformed silyl ester) before cooling rapidly and immediately recording the ^{31}P -NMR spectrum. The ratios shown are approximate relative amounts of phosphine and phosphine oxide based on the direct comparison of the integrals of the two peaks in the ^{31}P -NMR spectrum. The ^1H -NMR after this time showed diphenylsiloxane ($\delta = 5.28$ ppm) as the major Si-H species, as well as others, including some monosilyl ester ($\delta = 5.36$ ppm).

Data for silyl species reported in Chapters 1 and 2.

2.2 Phosphine Oxide Data

See Thesis of Charlotte Chapman, referenced in the main text.

Attempted room temperature reduction, scheme 9

Phenylsilane (369 μ L, 3.00 mmol) was combined in deuterated acetonitrile (2.00 mL) with 20 mol% triethylamine (28 μ L) and TFA (76.5 μ L, 1.00 mmol) and the reaction stirred for 35 min. Hydrogen evolution was monitored by gas-collection, as described in chapter 2, and 0.85 equivalents of hydrogen were collected. After 110 min, triphenylphosphine oxide was added (1.00 mmol), and after 2 h at 25 °C, ^{31}P -NMR demonstrated 5% reduction to the phosphine. After 15 h at 85 °C, 16% phosphine was visible by NMR. Evidence of reduction

of the trifluoroacetic acid to various derivatives was apparent however, so it may be that the active species were destroyed before they could reduce the phosphine oxide.

Chapter 6

A Fully Catalytic Mitsunobu Reaction

Contributing authors: Keith G. Andrews, Andrew L. Shannon-Little, Jan Saska, Ross M. Denton

The Mitsunobu reaction remains state-of-the-art for the inversion of secondary alcohols, despite its atom inefficiency and use of toxic reagents. Recent attempts to develop a catalytic Mitsunobu reaction have focused on augmenting the oxidant and phosphine activator (e.g. DEAD, DIAD, etc). Whilst reducing the amount of this toxic and explosive species is a welcome step forward, the reaction remains stoichiometric in phosphorus, and often requires increased loadings of this reaction component. An ideal approach would be to remove the activator altogether, and instead find a phosphorus system that is amenable to catalysis. In this Chapter, we demonstrate the first example of a fully-catalytic Mitsunobu reaction, a reaction that operates without additives, with a low phosphorus content, and that is able to effect the inversion of secondary alcohols. These first steps herald a new class of reagents for the catalytic inversion of secondary alcohols.

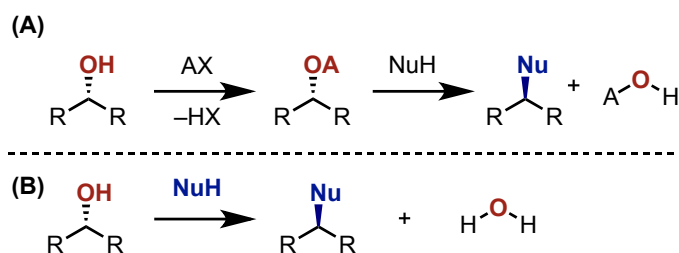
Introduction

Alcohol Activation

Typical alcohol C–OH bonds are reasonably strong, at about 93 kcal/mol. This is weaker than C–H bonds (103, 98, 95, 93 kcal/mol for Me, Et, ⁱPr, ^tBu respectively) and fluoride bonds (110 kcal/mol), but stronger than C–X for X = halogens, NH₂, and other alkyl groups.^{1,2} But these homolytic strengths do not necessarily reflect their kinetic stabilities with respect to the heterolytic dissociation more commonly encountered in organic synthesis. Despite the inherent electronegativity differences (C = 2.55, O = 3.44)³ the C–O bond is kinetically quite stable. At 143 pm, the C–O bond is very short for a single bond, a reasonable marker of its stability. Breaking such a short bond requires large percentage increases in the length, during which the bonding electrons are torn between stabilising the incipient positive charge at carbon and the relatively low valence orbitals of the hydroxide anion. In the case that a nucleophile is approaching the C–O antibonding orbital, the hydroxide ion is destabilised by the lack of a counter-cation and, being such a densely charged unit, is a very poor leaving group. This makes direct substitution reactions on alcohols very difficult. One approach to stabilising the hydroxide leaving group is by using acid to convert the group to water directly. This approach works, to some extent, when it is desirable to replace the OH group with the counterion of the acid; the halogens, for example. The limitations to this approach are clear; more interesting nucleophiles are out of the question, preferring to abstract a proton rather than act as a nucleophile. Additionally, optically active alcohols may succumb to racemisation due to S_N1 pathways in the presence of acid.

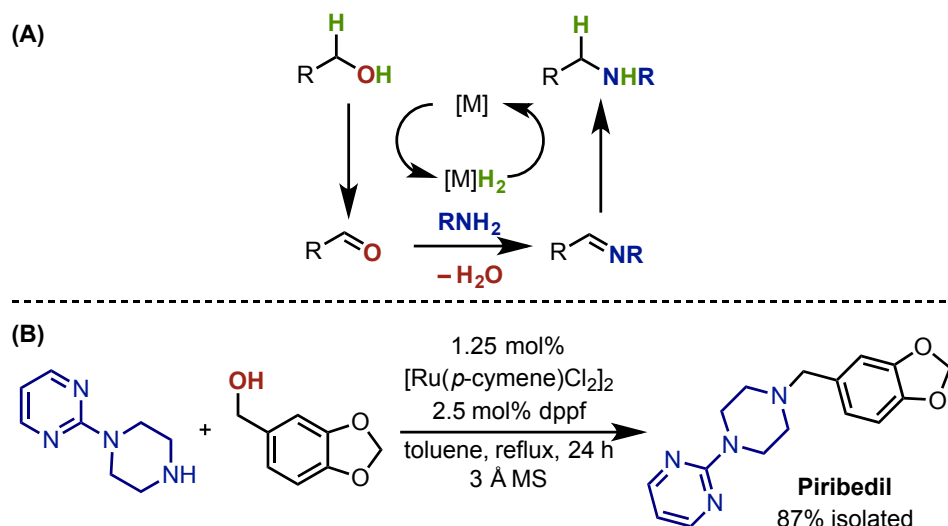
Therefore, typical methods for substituting an alcohol rely on activating the hydroxyl group, often as a tosylate, triflate or halide. The pseudo-halides (OTf, OTs) weaken the C–O bond by withdrawing electron density, and in doing so polarise it, lowering the LUMO and so activating it for attack by a nucleophile. Further, the leaving group has a low charge density. Such reactions often provide good yields, and with good stereo-inversion.

However, activation is inefficient in terms of step and atom economy, generates additional waste, and the activated products are often toxic alkylating agents and are routinely isolated and purified (Scheme 1A); the ideal reaction would involve catalytic activation *in situ*, with water as the sole by-product (Scheme 1B).



Scheme 1. (A) Commonly used substituted manifold *via* activation. (B) Ideal alcohol substitution manifold.

There are several methods of catalytic activation of alcohols. Of note, the groups of Grigg,⁴ Watanabe,⁵ and later notably Williams,⁶ and others, have developed the ‘borrowing hydrogen’ methodology. This method exploits the reactivity of the corresponding carbonyl chemistry. Carbonyl groups are inherently polarised, and their unsaturated nature allows the addition of nucleophiles in order to favourably transfer electron density to oxygen. The alcohol is oxidised *in situ* by a metal catalyst to give a carbonyl compound, which then reacts with the nucleophile, typically an amine, before the resulting imine/iminium ion is reduced back to the saturated compound using the original hydride atom (Scheme 2).

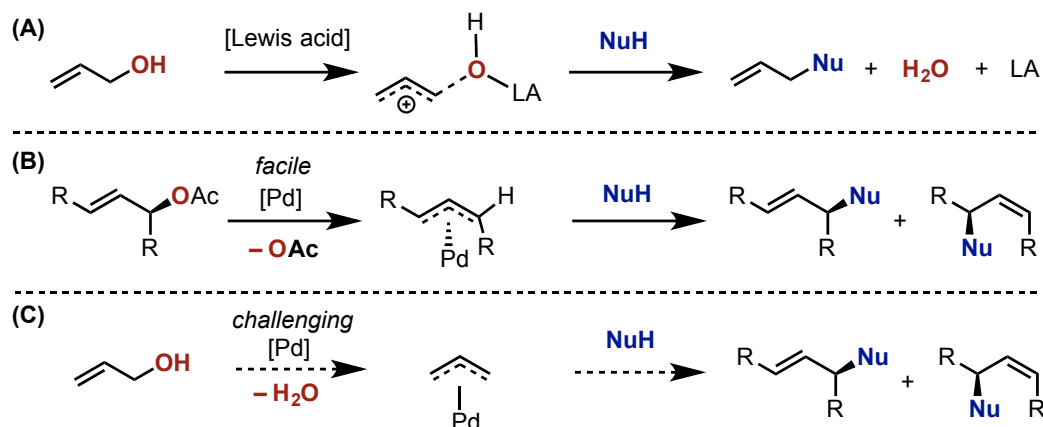


Scheme 2. (A) General scheme for the borrowing hydrogen manifold. (B) Williams' application of this manifold to the synthesis of dopamine agonist, Piribedil.⁶

The chemistry of hemiaminals promotes the required proton transfers to release water, thus overcoming the problem of displacing hydroxide. Interestingly, although molecular sieves were used in initial work to manipulate the equilibrium and remove water, the group of Williams later showed that this was not necessary.⁶ In this case, because the key equilibrium in which water is removed lies on the side of free water, the reaction is essentially irreversible, making removal of water from the reaction mixture unnecessary. The water also does not seem to interfere with the active metal hydrides formed in the reaction. Thermodynamically, the reaction is favourable; Williams states that the alkylation of methylamine with methanol releasing water and *N,N*-dimethylamine has an overall enthalpy change of approximately -7 kcal/mol.⁶ In this case, the reaction appears to be driven by the strength of HO–H bonds over H₂N–H bonds (~ 11 kcal/mol in favour of water, BDEs).⁷ Remarkably, this means the production of water drives the reaction in this case.

There is also a wide range of chemistry performed on the so-called 'activated alcohols'. Benzyl, propargyl and allyl cations are stabilised with respect to alkyl cations, and so there is a lower barrier to loss of water from the respective alcohols. More frequently, water is lost as

an M-OH species, where M is a strong Lewis acid, often a metal species, from which water is released to regenerate the catalyst.^{8–10} Palladium and other transition metals have been used to good effect, especially for allyl alcohol derivatives, resulting in asymmetric methods;^{11–14} even here, however, using free alcohols directly still remains a challenge, and the alcohol is normally activated as an ester or derivative (Scheme 3).¹⁴

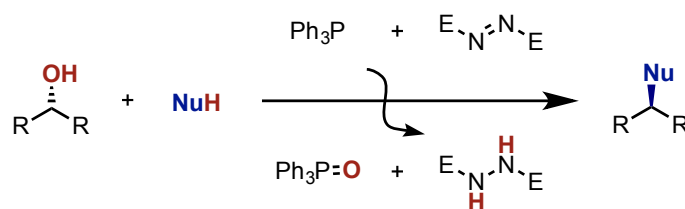


Scheme 3. (A) Use of a Lewis acid to substitute a C–OH bond; (B) Asymmetric palladium on allyl alcohol derivatives; (C) Difficult Pd transformation on π -activated alcohol with no stabilising group on oxygen.

General activation of alcohols requires two steps; the activation step, from which the intermediate is usually isolated and purified to some extent, and the substitution step. Thus, it is unsurprising that the Mitsunobu reaction, which achieves both steps in one pot with stereo-integrity, remains among the state of the art for substitution reactions of alcohols with acidic nucleophiles.

The Mitsunobu Reaction: Origins

The Mitsunobu reaction was developed by Oyo Mitsunobu in 1967.^{15–18} The reaction involves the substitution of a hydroxyl group, usually a secondary alcohol, with an acidic pronucleophile. The hydroxyl group of the alcohol, along with the proton of the nucleophile, are incorporated into by-products; a formal dehydration (Scheme 4).

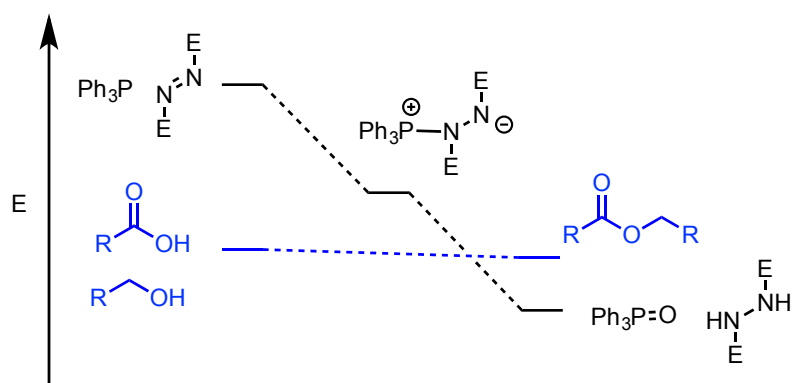


Scheme 4. The form of the Mitsunobu reaction

Because the alcohol oxygen is lost (largely) through an $\text{S}_{\text{N}}2$ reaction, the reaction normally proceeds with (Walden) inversion¹⁹ of stereochemistry at the alcohol carbon centre. The dehydration is made thermodynamically favourable by sequestration of the oxygen atom at phosphorus, in a strong $\text{P}=\text{O}$ (phosphoryl) bond (130 kcal/mol).²⁰ The two protons end up on a reduced hydrogen acceptor, usually as a hydrazine. Thus, the Mitsunobu reaction formally requires an oxidant and a reductant. Mukaiyama originally described the reaction as a ‘redox-dehydration’.^{21,22}

Like many useful classical transformations, the efficiency and success of the Mitsunobu reaction is driven by an exaggerated downhill electronic pathway. This is achieved by using highly reactive starting materials, and forming highly stabilised by-products. Such reactions are robust and reliable for the reason that the substrates are not a major component in the thermodynamic equation (Figure 1), so can be varied without affecting the overall favourability.

Figure 1. The largest energetic change in the Mitsunobu reaction occurs in the phosphine and diazo compounds, whilst the substrates remain roughly the same (qualitative diagram only).



In other words, *we can perform unfavourable reactions with respect to the substrate transformation*, because energy is gained in converting reactive co-reagents. However, in the case of an esterification reaction, where the transformation is favoured by about ~ 1 kcal/mol (for $\text{AcOH} \rightarrow \text{EtOAc}$), the Mitsunobu reaction uses a large thermodynamic driving force to gain a kinetic advantage which, although convenient, is arguably energetically wasteful. This transformation highlights another problem with C-O bond substitution; a lack of an inherent thermodynamic driving force. In the Mitsunobu reaction, the thermodynamic driving force is produced using two reagents.

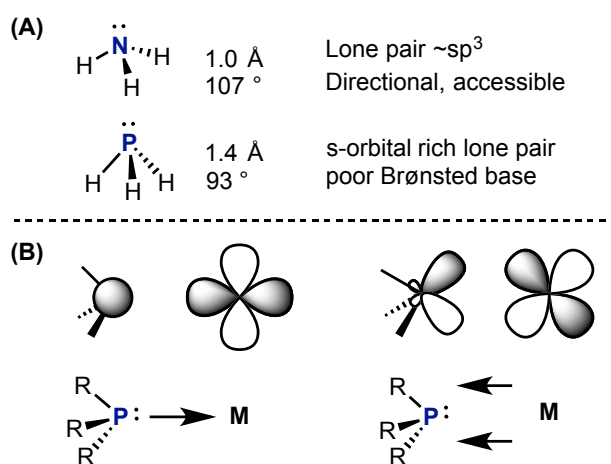
The Redox-Dehydration

In the context of a Mitsunobu reaction, a “redox dehydration” is a redox transformation that absorbs water. The first component, and which ultimately performs the desired breaking of the C-O bond, is a phosphine, typically triphenylphosphine. Phosphines have the interesting property that they are good Lewis bases, but poor Brønsted bases, in contrast to their group 15 analogues, amines. This behaviour results from their position on the second row, where the larger, higher-energy frontier orbitals result in longer P-R bonds. Ammonia, for instance, has an N-H bond length of about $1.0 \text{ \AA}$, whilst phosphine (PH_3) has a P-H bond length of closer to $1.4 \text{ \AA}$. The decreased steric clashes and different orbital energies allow the bond angles to significantly decrease in PH_3 relative to NH_3 , from $\sim 107^\circ$ to $\sim 93^\circ$ (Figure 2A).

The result is a p-orbital heavy contribution to the P-R bonds, and a concomitant increase in s-character in the phosphine lone pair. This gives the lone pair undefined directionality, and makes it relatively inaccessible as it is closer to the P atom. When acting as a ligand, the reasonably high energy (3s) of the lone pair may be a better match for metal acceptor

orbitals than protons, and perhaps more importantly, the p-orbital-rich P-R anti-bonding orbitals make phosphines (particularly arylphosphines) excellent pi-acceptors (matching the orbital symmetry at the metal) (Figure 2B).

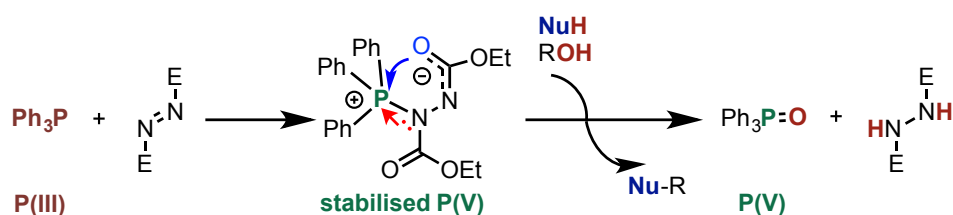
Figure 2. (A) Ammonia vs phosphine; (B) Metal-phosphine bonding orbitals (other d-orbitals possible, e.g. dz^2).



The relatively low electronegativity of phosphorus (2.2) leaves almost no electron excess at phosphorus in PR_3 molecules (unlike the nitrogen atom in ammonia, which holds excess electron density) and so there is little electrostatic motivation to act as a Brønsted base. Additionally, unlike metal centres, protons provide no stabilising back-donation, critical to replenish the electron deficient nature of a protonated phosphine. This is also why alkyl phosphines are better Lewis-bases; hyperconjugation from alkyl ligands helps make the lone pair more available. Alternatively, Bent's rule would say there is less p-character in the P-R bonds, and more in the lone pair, leading to a higher higher energy lone pair. *In terms of reactivity, therefore, phosphines tend to react only by donating their lone pair when there is a suitable electrostatic or covalent stabilisation of the resulting electron deficient P centre.* This theoretical groundwork is essential for understanding the relative stabilities of various phosphonium salts, species in which a positive phosphorus centre is present.

The second key reagent in the Mitsunobu reaction is the phosphine-activation agent, and as such, needs to satiate the demands made above. Firstly, it must have a suitably positioned acceptor orbital to oxidise the phosphine(III) species to P(V) (accept the lone pair), and secondly, it must simultaneously stabilise the incipient P⁺ centre. As noted in the main introduction, phosphorus(V) is typically the most useful P species in terms of mediating reactivity due to the relatively kinetically labile nature of the (hypervalent) P-X bonds, which facilitate substitution reactions.

The most commonly used activating agent is a diazo compound, typically a diazodicarboxylate, although others have been developed.^{23–26} This species has a suitably weak N=N bond (~60 kcal/mol for the pi-component), and a conjugated acceptor group, which allows the lone pair electron transfer to be both favourable and also immediately stabilising for the new P(V) centre due to the locality of the counterion. Additionally, the reaction reveals a lone pair on the adjacent N atom to further stabilise the P(V) centre (Scheme 5).



Scheme 5. Stabilisation of P(V) by the hydrazine ligand, and demonstration of the 'water surrogate' nature of the reagents

As well as generating suitably reactive species, the phosphine and hydrazine pair are ultimately utilised as a surrogate for water. The O²⁻ is secured as a phosphine oxide, whilst the two protons are stored across the hydrazine. Between the stages of the highly reactive starting materials and highly stabilised by-products, is a stage of balanced reactivity,

ultimately a result of the hypervalent chemistry of the involved $P(V)$ species, the focus of the next section.

Mitsunobu Reaction – Mechanism

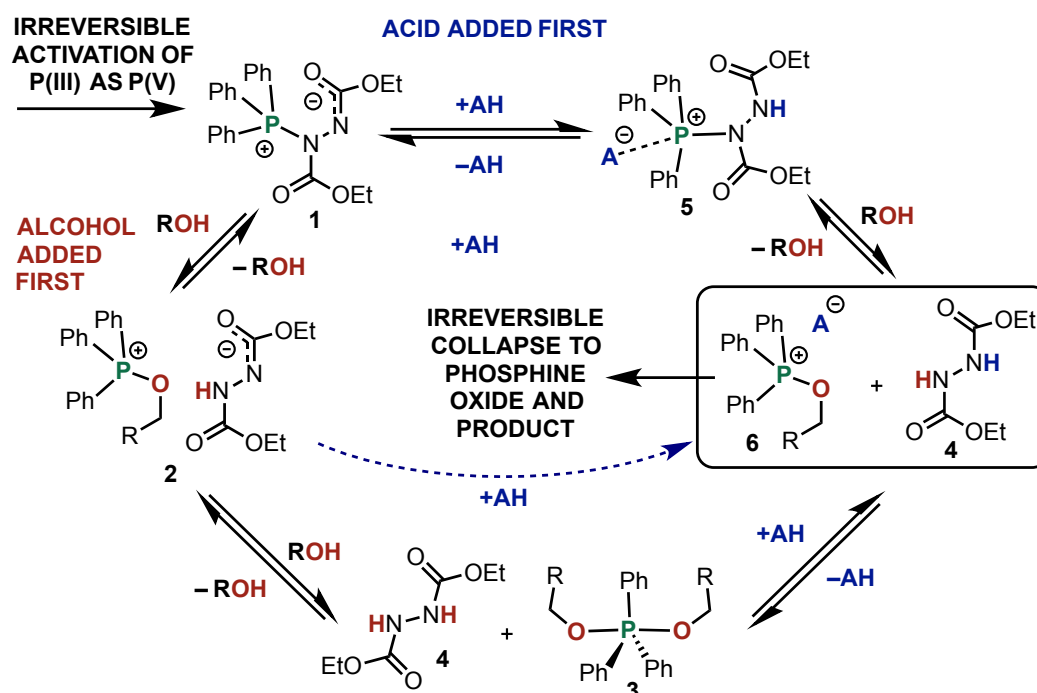
The success of the Mitsunobu reaction depends on several properties of the two reagents used. The kinetic reactivity of the starting reagents is one, and the thermodynamic driving force is another. But these properties would be irrelevant if the intermediate activated species did not interact with the substrates. The reaction hinges on two key reactivity differentials: firstly, the fact that the hydrazine ligand of the betaine **1** is easily displaced by the alcohol to form an alkoxyphosphonium salt **2**; and, secondly, that the acidic component is deprotonated by the resulting hydrazide anion, replacing it as counterion to give **6** and the free hydrazodicarboxylate **4**. That this must be the case is clear, but the explanation is slightly more nuanced.

Phosphonium salts display a range of reactivities. As discussed in Chapter 4, the phosphine oxide may be considered a pseudo-phosphonium salt. Its stability arises from the close contact electrostatic interaction between P and O groups, perhaps better described through secondary covalent bonding interactions. It is no surprise, then, that alcohols make good donors, due to the availability of the oxygen lone pairs for secondary stabilising effects. In other words, the group best able to stabilise the $P(V)^+$ centre through covalent bonding should prevail thermodynamically in any given mixture (until decomposition to the phosphine oxide occurs).

The fifth component of a $P(V)^+$ species (in addition to four that make up the R_3P^+ -donor salt) can vary hugely. The role of this component (counterion or ligand) is determined by its electron-donating power; the result is a species existing somewhere (on average) between

tetrahedral and trigonal-bipyramidal structures. The (trigonal-bipyramidal) phosphorane is favoured for basic donors of high charge density, whilst the (tetrahedral) salt is favoured for weakly basic anions of dispersed charge (sterics may result in deviation from these rules). This variation is due to a trade off between disrupting the existing bonding in the tetrahedral shape (weakening the bonds) and stabilising the excess electrons of the (anionic) fifth component. In the Mitsunobu reaction, the presence of an acidic component (*stabilised* anion) allows the phosphonium salt form to prevail.

Typically this is representative – there are few phosphoranes that are stable in the presence of reasonable acidity (e.g. kinetically stable phosphoranes with intramolecular donors or bulky ligands). Various historical attempts to describe the Mitsunobu reaction have focused on the order of addition of the various components (Scheme 6).^{27–38}



Scheme 6. Following the activation of the phosphine by the hydrazine, a dynamic equilibrium is set up, which is eventually exited by formation of the phosphine oxide. The intermediate species enter into a (pseudo)-thermodynamic equilibrium dictated by the stability of the P(V) species.

Whilst the order of addition does indeed impinge on the precise species present initially, ultimately a (pseudo)-thermodynamic mixture tends to prevail for typical substrates. (*Here, (pseudo)-thermodynamic means that, irrespective of order of addition, the reagents are added sufficiently quickly to allow a dynamic equilibrium to arise before any formation of phosphine oxide*). The outcome of the reaction relies heavily on the resulting equilibrium. The diazo component, whilst activating the phosphine initially, appears to make both a relatively poor donor and a relatively poor acceptor in the hydrazide form (**4**). This ensures it is outcompeted by the alcohol as a donor, *and* the acidic component as the counterion. The result is that alkoxyphosphonium salt **6** will form, with the best available donor, and the best available counterion. Ultimately, this species is kinetically unstable with respect to formation of the phosphine oxide and the desired product.

It is worth briefly mentioning the other possible species; firstly, the dialkoxyphosphorane **3**. Such phosphoranes exist as a juxtaposition of the size and electronegativity of oxygen. The high electron density of an alkoxide anion (classically, a 'hard' anion) is *unstable* with respect to charge delocalisation. However, the phosphorane only retains *stability* because the oxygen atom can accept the excess electrons in the 3-centre-4-electron bonds in the axial dimension. The conclusion is that the alkoxide wants to rid itself of the charge density, but only half of it!

As such, the alkoxide ligands retain basicity, presumably somewhere between an alkoxide and an alcohol. In the presence of moderate acids, therefore, the phosphorane is thermodynamically unstable with respect to protonation, and ligand exchange. If the incoming ligand is more acidic than the outgoing ligand, a phosphonium salt will prevail. If the incoming ligand is less acidic, a (more robust) phosphorane will prevail. Kinetically, these reactions are different. Because in the first case (adding acid to phosphorane) the

reaction is favourably dissociative, whilst the second (adding a better donor to phosphorane) is disfavourably disassociative (or disfavourably associative), phosphoranes are much faster to exchange in the presence of acids than they are to rearrange to other phosphoranes under neutral conditions. Fortunately, all of these observations are consistent with the desired outcome of the Mitsunobu reaction.

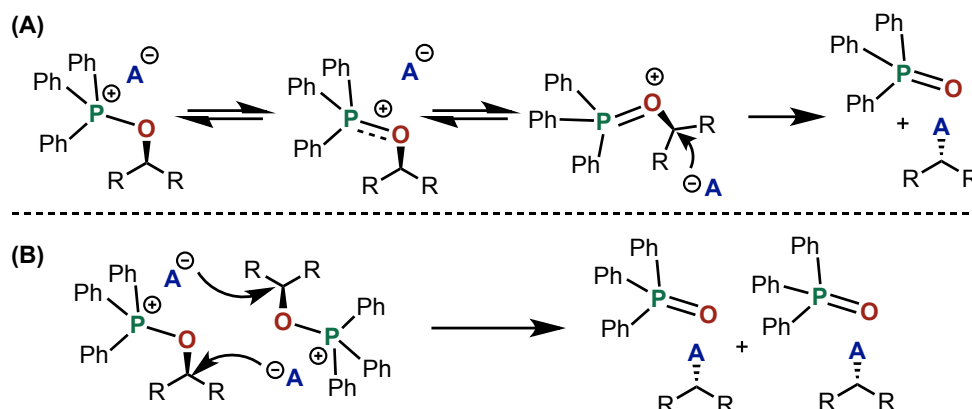
With the precursor alkoxyphosphonium salt **6** formed, the Arbuzov collapse is all that remains to complete the reaction and release the products.

Collapse: Substitution, Stereoinversion and Competing Processes

Alkoxyphosphonium salts are reactive intermediates for one key reason; the P–O bond is persistently in a state of partial double bond character. This makes the bond unstable with respect to many transformations, all of which seek to convert this partial double bond character into a full phosphoryl bond. Reactions include direct C–O bond substitution, elimination to alkenes, and other cascades; but all are driven by the incipient phosphoryl bond.

In the context of alcohol activation, it is apparent that the reactivity in the Mitsunobu reaction is due to the enforced polarisation of the C–O bond. Alkoxyphosphonium salts have several important advantages over other modes of activation. Firstly, unlike activation methods that require a second component (e.g. a Lewis acid catalyst), the polarisation is permanent due to the strong P–O covalent bond, which gives an entropic advantage. Secondly, unlike alkyl halides, for instance, which only generate partial charge polarisation, the P⁺–O bond tends towards a full positive charge on phosphorus, particularly as during the displacement itself, the anion is distal, as it is involved in the substitution. (*Note, however, evidence has been amassed that suggests pairs of phosphonium salts come together to*

exchange anions in non-polar solvents – such behaviour explicitly seeks to minimise P^+/A^- ion pair separation by sharing anions. This also explains why it is so difficult to engage phosphonium salts with external nucleophiles; the $P-O$ bond is less electrostatically polarised when the anion is not distal to the P^+ centre, as is the case in the typical Arbuzov collapse. Collapse has been measured to be first order in phosphonium salt) (Scheme 7).^{27,34}



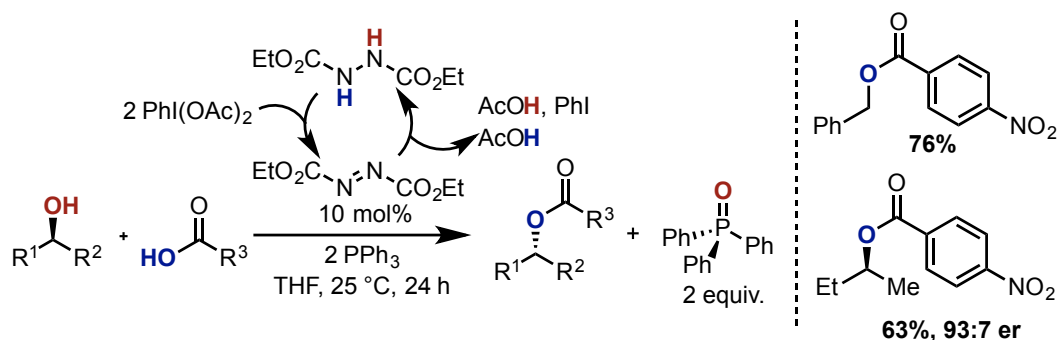
Scheme 7. (A) Depiction of the incipient phosphoryl (double) bond and the migration of the nucleophilic counterion to give stereoinversion; (B) In non-polar solvents, nucleophiles may be exchanged to reduce ion pair separation.

The result is that, from this alkoxyphosphonium species, stereoinversion is guaranteed. However, loss of optical purity is possible at earlier stages, notably when the counterion is weakly acidic (aliphatic acids are less efficient substrates), and so spends time coordinated to phosphorus. This activates it as an electrophile rather than a nucleophile, and so a retention pathway, in which the alcohol retains its original oxygen atom, can occur. More acidic acids are therefore preferred for inversion purposes.^{33,39–41} The reasons the Mitsunobu is so robust and effective are exactly the same reasons that make designing a catalytic version so desirable – but also so difficult.

Existing “Catalytic Mitsunobu” Methodologies

In 2006, Toy and co-worker published what might be considered the first of a recent class of catalytic Mitsunobu reactions.⁴² The reaction is catalytic to the extent that the hydrazine

activator, DEAD, is present at only 10 mol% loading, and is regenerated using (diacetoxyiodo)benzene as a terminal oxidant (Scheme 8).

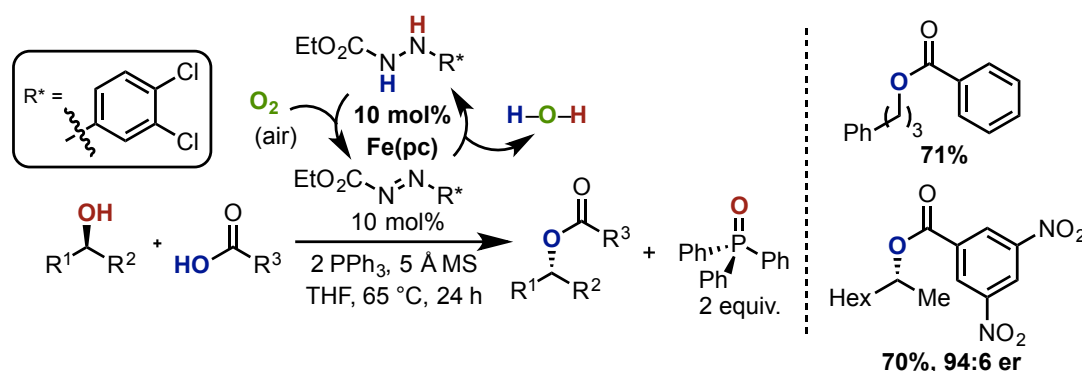


Scheme 8. Toy's Mitsunobu reaction, substoichiometric in hydrazine with DAIB terminal oxidant (2006)⁴²

The reaction requires two equivalents of triphenylphosphine oxide due to competing oxidation. This oxidation meant an 18% background reaction occurred in the absence of hydrazine (some productive oxidation of P(III) to P(V)). The background reaction could be outcompeted by adding the excess PPh₃ in portions for slower (secondary) substrates. Attempts to replace DEAD with other commonly used hydrazines led to reduced conversions. The reaction gave competitive levels of inversion relative to the stoichiometric hydrazine version, with yields ~3/4 the level of the stoichiometric yield (54-88%). A limited range (3) of acids was reported (mostly 4-nitrobenzoic acid), whilst the alcohols ranged from benzyl and alkyl alcohols. Of note, optically active substrates comprised: α -methylbenzyl alcohol (59%, 84:16 er), ethyl lactate (65%, 100:0 er), and butan-2-ol (63%, 93:7 er).

In 2013, Taniguchi and co-workers developed a similar version, in which Fe(Pc) (10 mol%) was used as a co-catalyst alongside substoichiometric hydrazine (10 mol%), with oxygen in the air now acting as the terminal oxidant (Scheme 9).⁴³ Fourteen aryl-hydrazines were explored to find a suitable reactivity level. An electron deficient dichloroaryl species was found to work well with the Fe(Pc) oxidant. Molecular sieves were crucial, suggested to

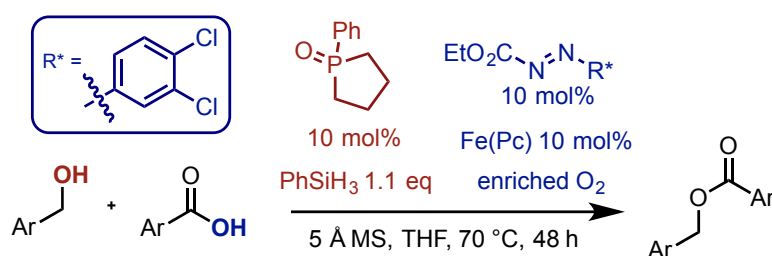
remove water, or peroxide from the oxidation. Again, two equivalents of triphenylphosphine were required.



Scheme 9. Taniguchi's Mitsunobu reaction, substoichiometric in hydrazine, with Fe(Pc)/air terminal oxidant system.

The reaction was shown to be effective for acidic acids (e.g. nitrobenzoic acid 50%, whereas dinitrobenzoic acid gave 79% with ethyl lactate) and a range of secondary alcohols, with e.r. values typically in the 90s (84-98% e.e.). Taniguchi's group followed this report with a detailed study with improved conditions and expanded substrate scope,⁴⁴ in which phenols were also tolerated, as well as cyclic aminoalcohols and arylthiols. In addition, a study using ¹⁵N-labelled hydrazine demonstrated that the phosphine attacked the nitrogen atom adjacent to the aryl group, as expected. The dichloroarylhydrazine was shown to have an improved thermal stability profile relative to typical Mitsunobu hydrazines.

In 2015, Aldrich and Buonomo reported that they had achieved a 'fully catalytic' Mitsunobu reaction, in which both the hydrazine and phosphine were substoichiometric (Scheme 10).⁴⁵



Scheme 10. Aldrich's "Fully catalytic Mitsunobu system",⁴⁵ later discredited by Taniguchi.⁴⁶

The reaction used Taniguchi's oxidation system (hydrazine and Fe(Pc)/air),⁴³ alongside O'Brien's phosphine oxide/phenylsilane P(III)-P(V) catalyst system (recall Chapter 4).^{47,48} Although the phosphine turnover system appeared to give a Mitsunobu reaction that was substoichiometric in phosphine (oxide), Taniguchi and co-workers later demonstrated that the reactions which claimed to be 'fully-catalytic' were flawed, as the reaction gave a background reaction without hydrazine, which is likely linked to the benzyl alcohol substrate choice.⁴⁶

Challenges in Designing a Catalytic Mitsunobu Reaction

As the attempts to design various 'catalytic' Mitsunobu reactions above have demonstrated, the task is an onerous one. What follows is an analysis of the existing protocols, and a summary of the challenges to overcome, which will be referred back to throughout the rest of this Chapter.

Firstly, it is worth noting that many of the so-called 'catalytic' variations of classical reactions fail to deliver from an energetic perspective. Many just shift any redox problems to another reagent. Toy's Mitsunobu, for example, substitutes 0.9 equivalents of hydrazine for 2 equivalents of DAIB and an additional equivalent of phosphine (and generates two equivalents of acetic acid and iodobenzene as waste). For this reason, such processes are disingenuous to claim a 'sustainability' ethos. Although the metrics of progressive chemistry ('i.e., as set out in the 'green chemistry principles') include a focus on improving safety, which many catalytic versions do seek to address, there are a large number of such reactions that would be hard pressed to defend accusations of *increasing* atom inefficiency. Toy's reaction, then, is sold from a 'safety' perspective (although it is never clear that the synthesis

chemist benefits from the reduced loading: it is debatable whether there is a difference in the exposure risk in retrieving 1 mL vs 10 mL of a toxic reagent from an open bottle.)

Taniguchi's reaction, on the other hand, uses air as the oxidant, and requires only 10 mol% of the Fe catalyst to mediate the oxidation. Again, they require increased loadings of phosphine, but they have clearly attempted a smart choice of oxidant to increase atom efficiency where the hydrazine is concerned, as well as the safety aspect.

Other advantages sought include improving practicality of execution or purification. Much has been made of the difficulty of removing the triphenylphosphine oxide by-product in the Mitsunobu reaction, which may streak during chromatography, or co-elute with the desired product. There are now countless methods to address this problem, including aqueous soluble phosphorus sources and polymer-supported variants.⁴⁹ Such methods are, perhaps, infrequently used by practising chemists due to cost and availability of functionalised variants. In terms of sustainability, water-soluble by-products are arguably harmful for the environment or may require special disposal. More complex stoichiometric reagents still require synthesising, and can just shift the focus of the atom economy to a different point in the synthesis chain. Polymers can be regenerated, but have a limited life-time. Arguably, the best approach is still to recrystallise the triphenylphosphine oxide product and utilise it in further transformations. Indeed, there are now several methods to perform Mitsunobu reactions from the oxide itself.^{38,50} Such approaches rely on the fact that a phosphorus(V) oxide is already in the correct oxidation state, removing the requirement for any exogenous redox components. It is therefore unquestionable that an idealised strategy would avoid P(III), given that all the useful reactivity occurs in the P(V) state. This is in contrast to the Staudinger reaction, where the useful reactivity arises from the selective reaction of P(III) with an azido group.

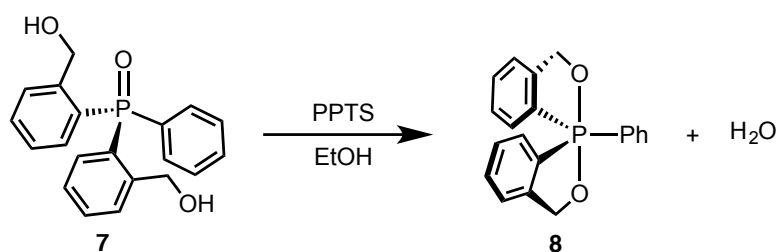
With the above description of the Mitsunobu reaction in mind, and the lessons learned from recent attempts to make the reaction more efficient, the following challenges to designing a catalytic Mitsunobu reaction can be summarised:

1. Reactivity arises from an incipient phosphoryl group, but stability of the phosphoryl group drives the reaction, and makes turnover of any phosphoryl-based catalyst difficult.
2. The reaction is a redox dehydration, which means turnover has to;
 - a. remove water from the reaction by storing it elsewhere. This requires either a water removal approach, or a stoichiometric desiccant, largely devaluing other substoichiometric advantages.
 - b. one component is oxidised, and one reduced. Turning over the two reagents orthogonally means including a stoichiometric oxidant and reductant of even higher energetic potential but which do not react themselves, an approach that seems to largely devalue any substoichiometric advantages of using a catalyst.
3. Strategies that introduce a P(V) catalyst need:
 - a. to form an alkoxyphosphonium salt under the reaction conditions.
 - b. to be a bench stable reagent.
4. Strategies that introduce P(V) *as the phosphine oxide* also require:
 - a. a method to activate the phosphine oxide as a phosphonium salt.
 - b. any reagents used in the turnover to avoid reaction with the substrates.
 - c. conditions in which the formal by-product (water) is removed, to avoid quenching.

Examining the difficulties encountered by groups that have already attempted to generate such a reaction, and considering the above challenges, there remained one clear approach, yet unexplored, but with hints of precedent. Fortunately, this approach is very close to the ideal reaction, and it is here that we began our efforts.

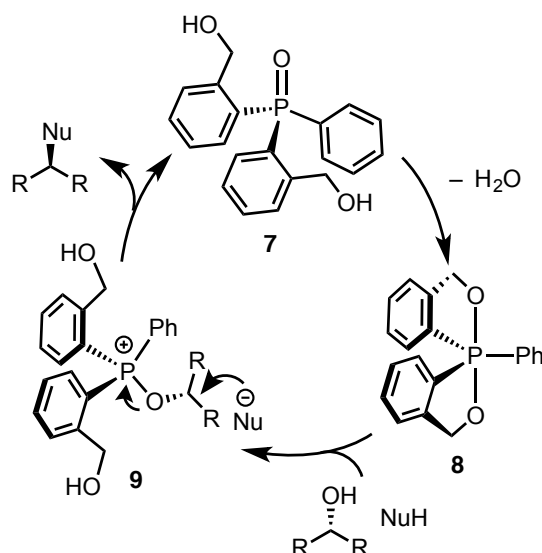
Autodehydration Phosphine Oxide Catalysis

In 2011, Kielbasinski and co-workers definitively observed that phosphine oxide **7** spontaneously dehydrated in the presence of catalytic acid to give dialkoxyphosphorane **8** (Scheme 11).⁵¹



Scheme 11. Kielbasinski's autodehydrating phosphine oxide **7**.⁵¹

Such a molecule was intriguing to us for two key reasons; firstly, it appeared to be achieving with ease the problem of recycling a phosphoryl bond to release water; and, secondly, the resulting species is a phosphorane – some phosphoranes are known to be Mitsunobu active.^{52–58} In other words, the species was putatively achieving *both turnover and activation of its own accord*. Such an observation allowed the following putative catalytic cycle to be devised (Scheme 12).



Scheme 12. Putative catalytic cycle for a Mitsunobu reaction using the Kielbasinski phosphine oxide **7**

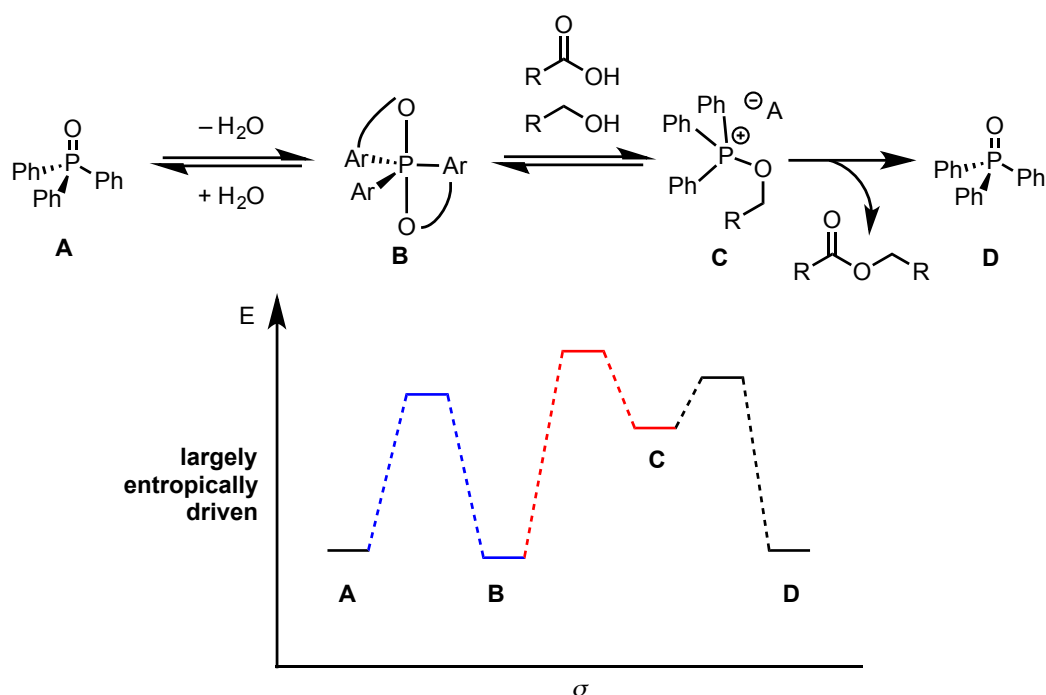
Of course, a species that seems to spontaneously transform from stability to reactivity is redolent of claims of a perpetual motion machine. With the benefit of further investigation, the following caveats have been collated.

- The equilibrium favours dehydration under acidic conditions.
- This is either because the dioxaphosphorane **8** is more stable than the oxide **7**, or that the entropic contribution can dictate the thermodynamic equilibrium. In this case, two molecules (phosphorane and water) are formed at the cost of the rotational restriction of a single molecule (the oxide). The presence of acid may also stabilise the ejected water by solvation.
- The phosphorane **9** must to be similar in internal energy to the phosphine oxide for an appreciable concentration of phosphorane to form over a given time period. The Hammond postulate suggests that if the phosphorane is too much higher in energy (too reactive), the kinetic barrier to dehydration will also be higher, making it less likely to be compensated for by entropic and solvation effects.

- Specifically, Kielbasinski's phosphine oxide **8** may overcome the strength of its phosphoryl bond in the following ways:
 - The acid (PPTS) activates the phosphine oxide by drawing electron density away from phosphorus, increasing its electrophilicity. In other words, the kinetic barrier to loss of water is lowered by the acid. There may also be partial activation by the hydroxyl groups (H-bonding).
 - The molecule has a high population of states that leads to dehydration (unimolecular), relative to the low number of states that lead to hydration (bimolecular).
 - Removal of water from the equilibrium can drive the formation of phosphorane.

Therefore, we must accept that if the phosphorane is thermodynamically less stable than the oxide, it is probably kinetically more stable with respect to substitution. In other words, the reasons the phosphorane forms (entropically driven chelate effect) will also make the phosphorane resistant to desirous reactivity, because species **9** in Scheme 12 ***must be more reactive with respect to phosphorane formation than the oxide is.*** Indeed, in Chapter 1, we were suspicious of the idea that an oxide would be reduced whilst more reactive P(V) species were not. It is not surprising, therefore, that a catalytic cycle in which a phosphoryl bond is degraded whilst more sensitive species are permitted to react productively has been difficult to manage (Figure 3).

Figure 3. The dehydration of A to B is largely entropically driven. For this reason, formation of C must involve a larger energy barrier, requiring three species to come together to form a single reactive species. The reason A can form B is the reason C is such an unlikely species to form. The protocol would be benefited (as depicted) by a smaller barrier to reach D than return to B.

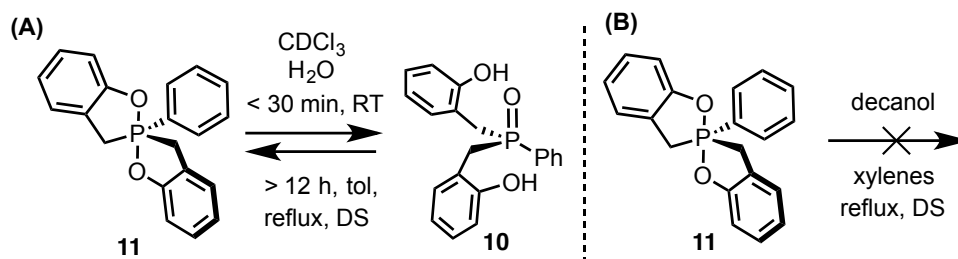


Mitsunobu Catalysis: Previous Work in the Group

A full account of the background and detailed initial experiments to reach this point can be found in the thesis of Andrew L. Shannon-Little, Denton Group, 2015.⁵⁹ The rest of this introduction describes work from that thesis.

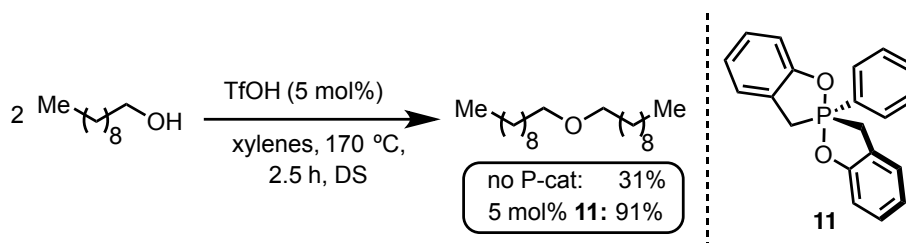
Despite successfully dehydrating, the Kielbasinski spirocyclic dioxyposphorane proved unreactive towards Mitsunobu chemistry under a number of conditions. The phosphorane was adjudged to be too kinetically stable with respect to exchange with a free alcohol. To investigate the factors of this stability, a second-generation catalyst (**10**) was synthesised in which the benzyloxy positions were reversed (phenols instead of benzyl alcohols). This catalyst would also pre-emptively alleviate any competing and deactivating Arbuzov collapse of the catalyst itself. The group demonstrated that this phosphine oxide **10** dehydrates

under Dean-Stark conditions in xylenes to form diphenoxyphosphorane **11** in the absence of acid. However, this species was shown to be robust with respect to substitution by alcohols, and no Mitsunobu activity was observed (Scheme 13).



Scheme 13. Phosphine oxide **10** dehydrated under neutral Dean-Stark conditions, but failed to react with an alcohol.

Here, the problem of the differential activity is apparent; a catalyst which is able to dehydrate a phosphine oxide is unsurprisingly unreactive with respect to forming an unstable phosphonium salt. Drawing on work by the group of Evans,⁵⁷ strong acids such as triflic acid and tetrafluoroboric acid were shown to open the phosphorane **11**, and thus drive the equilibrium to a phosphonium salt. Note that the oxide also exists as a phosphonium salt in such acidic conditions, which removes the requirement for a reactive species to survive for longer than the oxide. By combining the acidic conditions with Dean-Stark dehydration, the etherification of decanol to didecylether was shown to be possible under Dean-Stark water removal conditions in xylenes on a 20 g scale (Scheme 14).



Scheme 14. The first *P*-catalytic Mitsunobu reaction in the etherification of decanol with phosphorane **18** and triflic acid co-catalyst.

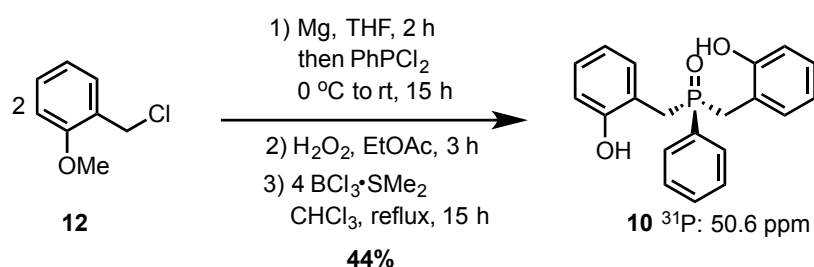
In the presence of TfOH, the *P*-catalytic reaction was shown to give an elevated alkylation (91% ether) with respect to a control reaction (31%). With this proof of concept in hand, we

set about optimising and improving the reaction, including understanding how diethyl ether is formed in this reaction.

RESULTS AND DISCUSSION

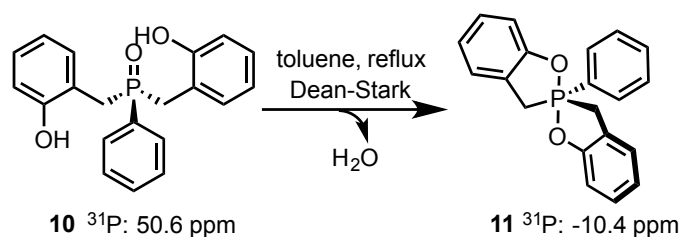
Exploring the Reactivity of Legacy Phosphine Oxide Catalyst **10**

Although the legacy phosphine oxide **10** appeared to reproduce Mitsunobu chemistry (the reactivity is dependent on the presence of the phosphorus catalyst), the mechanism was yet to be proven. Thus work began by synthesising the legacy catalyst **10** and confirming the results reported previously in the group (Scheme 15).⁵⁹



Scheme 15. Synthesis of legacy catalyst **10**

Double addition of the Grignard reagent of **12** to *P,P*-dichlorophenylphosphine followed by oxidation and demethylation afforded a multigram batch of phosphine oxide **10**. It was found that refluxing **10** under Dean-Stark conditions in toluene afforded the phosphorane **11** relatively rapidly, previously only observed with xylene (Scheme 16). (*Note: Although a quantitative dehydration has never been observed in toluene (in this or previous work), it is suspected that this is due to the ease of hydrolysis of the species during manipulation between the sample and recording of the NMR spectra. Thus the lengthy dehydration time quoted in the legacy work is probably related to this practical difficulty. Dehydration was not observed to occur in chloroform.*)



Scheme 16. Dehydration of catalyst **10** under Dean-Stark conditions (15 h) in toluene.

Using toluene would allow the temperature to be brought down from 170 °C to 130 °C, a clear practical boon. When utilising the Dean-Stark apparatus, the elevated heating temperatures (above the boiling point of the solvent) are required to enforce an adequate temperature gradient up through the insulated glassware to prevent condensation before reaching the trap mechanism. This allows an efficient water removal rate. The stirring rate is also important with respect to a consistent reflux turnover, so this was controlled in all experiments.

We continued utilising decanol (**13**) as a non-volatile, inexpensive primary alcohol, and explored the etherification reaction in the presence of a number of acids. Practically speaking, conversions to product were determined by concentrating the reaction mixture to ~dryness, and recording an NMR spectrum of the resulting mixture. The decanol and its derivatives were used to quantify the ratio of products, assuming no losses due to evaporation. To ensure this method was robust, a mass balance experiment was undertaken, in which the contents of the Dean-Stark trap were concentrated as well as the reaction flask. Insignificant mass losses were observed (<1%) both overall, and in terms of decanol/derivatives in the trap rather than the flask. The results are shown in Table 1.

In the absence of an acid additive, no alkylation was observed (entry 1) when catalyst **10** was present. Tosic acid was ineffective, whilst HBF_4 reacted with the decanol to form a species consistent with the trialkoxyborate (entries 3-4). Triflic acid, however, produced 96.5%

didecyl ether and 7 % decyl triflate after 15 h reflux under Dean-Stark conditions in toluene (entry 5).

Table 1. Homoetherification of decanol using phosphine oxide catalyst **10 in the presence of various acidic additives.**

2 $\text{Me}-(\text{CH}_2)_8\text{OH}$ **13** $\xrightarrow[\text{15 h, Dean-Stark}]{\text{toluene, reflux}}$ $\text{Me}-(\text{CH}_2)_8\text{O}-(\text{CH}_2)_8\text{Me}$ **14**

Entry	Pcat (mol%)	Add. (mol%)	t /h	14 (%)
1	10 (5)	- -	15	0
2	10 (10)	TsOH (10)	15	0
3	10 (10)	HBF ₄ (10)	3	0 ^b
4	- -	HBF ₄ (10)	3	0 ^b
5	10 (10)	TfOH (10)	15	96, 7^c
6	- -	TfOH (5)	15	15
7	10 (10)	TfOH (10)	3	57, 4 ^c
8	- -	TfOH (10)	3	4
9 ^d	10 (5)	TfOH (5)	4	12
10 ^e	10 (5)	TfOH (5)	15	34

^aAll experiments performed with 0.296 mmol catalyst **10** in 17 mL solvent and 11.84 mmol alcohol (10% experiments run with 5.92 mmol alcohol). Catalyst loading quoted with respect to product mmol.

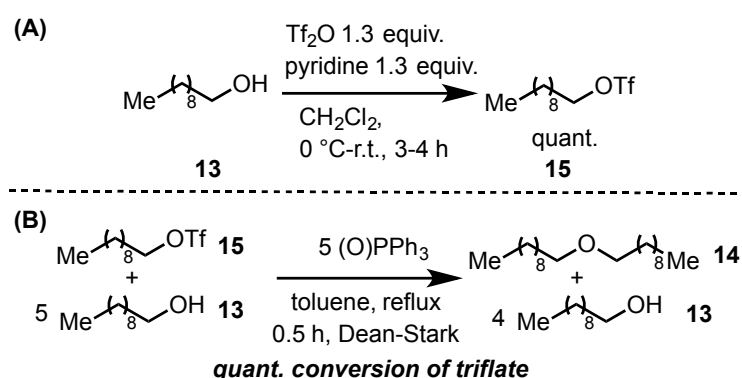
^bdecomposition of acid. ^cdecyl triflate. ^dbenzene as solvent. ^ecyclohexane as solvent.

The conversion to ether was only 15% under the same conditions in the absence of catalyst **10** (entry 6), demonstrating the role of the phosphorus centre in the catalysis. A second pair of experiments performed over 3 h indicated that catalyst **10** afforded a ~1.5/mol% rate enhancement (~15 fold acceleration with 10 mol% loading) over the background acid-catalysed reaction (entries 7-8). Other lower boiling solvents were investigated briefly, but suffered from catalyst-solubility problems (entries 9-10) and a lower activity, although catalysis was still viable.

Of particular interest was the observation of decyl triflate in the reaction mixture. Symmetrical ether synthesis is known using triflic anhydride, proceeding via the triflate.⁶⁰

But in the case of entry 5, the triflate present at the end of the reaction was rather close to the mol% loading of triflic acid. This suggested that the reaction might be proceeding through decyl triflate and subsequent alkylation, which was rate determining. Indeed, after 3 h (entry 7), triflate was visible in the reaction medium, suggesting it was forming faster than it was being consumed. The most likely alternative possibility was that external decanol could undergo alkylation with the decoxyphosphonium triflate, but such reactions involving external nucleophiles have been infrequently documented, certainly from phosphonium salts that have internal nucleophiles as counteranions.

We therefore sought to corroborate whether decyl triflate (**15**) was a viable alkylating agent under the reaction conditions. Thus, freshly prepared decyl triflate **15** was heated for 30 min in the presence of five equivalents each of decanol **13** and triphenylphosphine oxide **16** as a non-interfering Lewis base. (In the absence of the Lewis base Friedel-Crafts reactions were observed, *vide infra*). In order to match the observed rate of formation of ether in the catalytic reaction (c.f. Table 1, entry 7), the triflate should undergo full conversion to ether in 30 min, which turned out to be the case (Scheme 17).

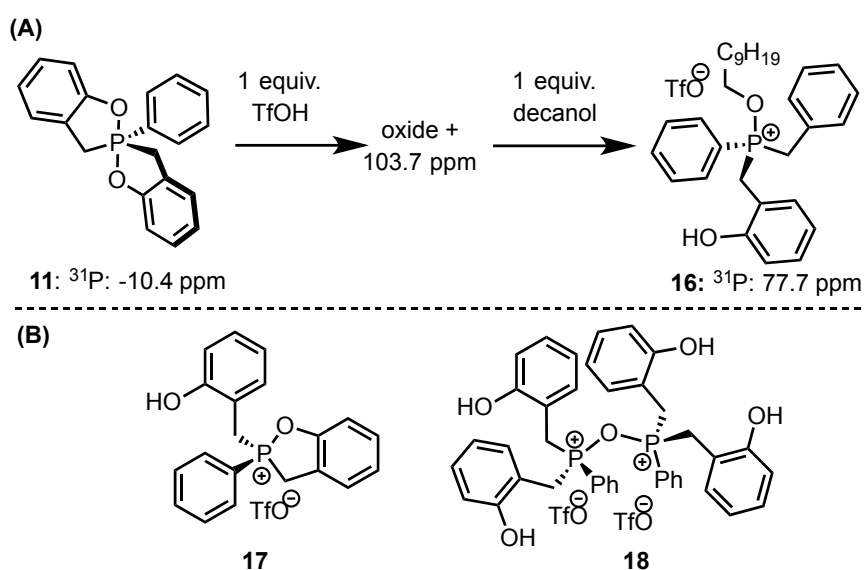


Scheme 17. (A) synthesis of decyl triflate; (B) reaction of decyl triflate with decanol under Dean-Stark conditions.

If alkylation were occurring through triflate **15**, then it would appear to be the rate-determining step. Else, it is expected that the triflate would be consumed by the remaining decanol towards the end of the reaction, approaching an asymptote of conversion calculable

from the relative rates of activation and alkylation. That the majority was present as the decyl triflate suggests that dehydration occurs rapidly, and consumes the remaining decanol before alkylation can occur.

In order to obtain evidence of any active phosphorus species, triflic acid was added to a toluene solution containing phosphorane **11** at room temperature in toluene. Problems with competing hydrolysis restricted the attainment of a pure sample, but the major species obtained was a phosphonium-like species with a ^{31}P -NMR shift of 103.7 ppm (Scheme 18).

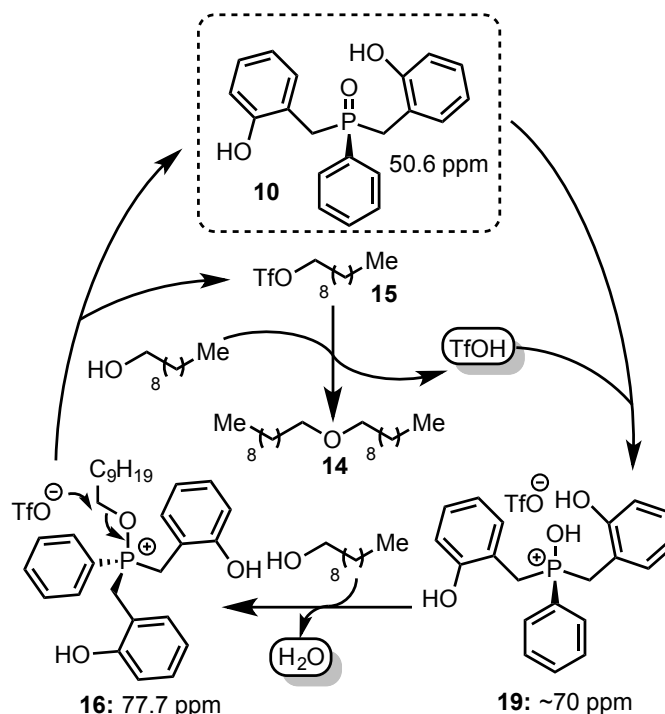


Scheme 18. (A) Formation of the proposed alkoxyphosphonium salt from the phosphorane, triflic acid and decanol; (B) Potential species with shift at 103.7 ppm. (Note that all species have variable shifts (est. ± 1 ppm) in the presence of different concentrations of H-bonding impurities, more so for the protonated oxide.)

Addition of decanol to the species with shift 103.7 ppm led to the formation of the decyloxyphosphonium triflate **16** with a shift of 77.7 ppm, in good agreement with known phosphonium salts. This species undergoes conversion to the decyl triflate and the phosphine oxide upon heating. Heating for 5 min gave 4% decyl triflate, with $\sim 15\%$ after 1 h, along with 8% diethyl ether (not shown). These values should not be taken as quantitative, as competing hydrolysis and the resultant possibility of background conversion from the resulting triflic acid must be considered. Nonetheless, they support a Mitsunobu-type

Arbuzov collapse of the decylphosphonium triflate to the triflate, as would be expected. The rate may be slower than typical (e.g. chloride) substitution rates, as triflate is a poorer nucleophile. Evidence was also accrued that suggested that the phosphine oxide could react directly with the decyl triflate to form the alkoxyphosphonium salt, suggesting the Arbuzov collapse reaction is reversible (not shown).

On balance, the species at 103.7 ppm is likely to be **17**. Initially, this assignment was doubted due to a single benzyl resonance in the ^{13}C spectrum, but a similar species has been observed to form from a different compound where the identity is less dubitable. We currently believe that the species is sufficiently fluxional to average to one benzyl carbon signal. For now it suffices to say that species 103.7 ppm is Mitsunobu active, forming the decylphosphonium triflate **16** when mixed with decanol. Thus a likely catalytic reaction manifold is shown in Scheme 19.



Scheme 19. Plausible mechanism for the *P*-catalysed conversion of decanol to decyl triflate.

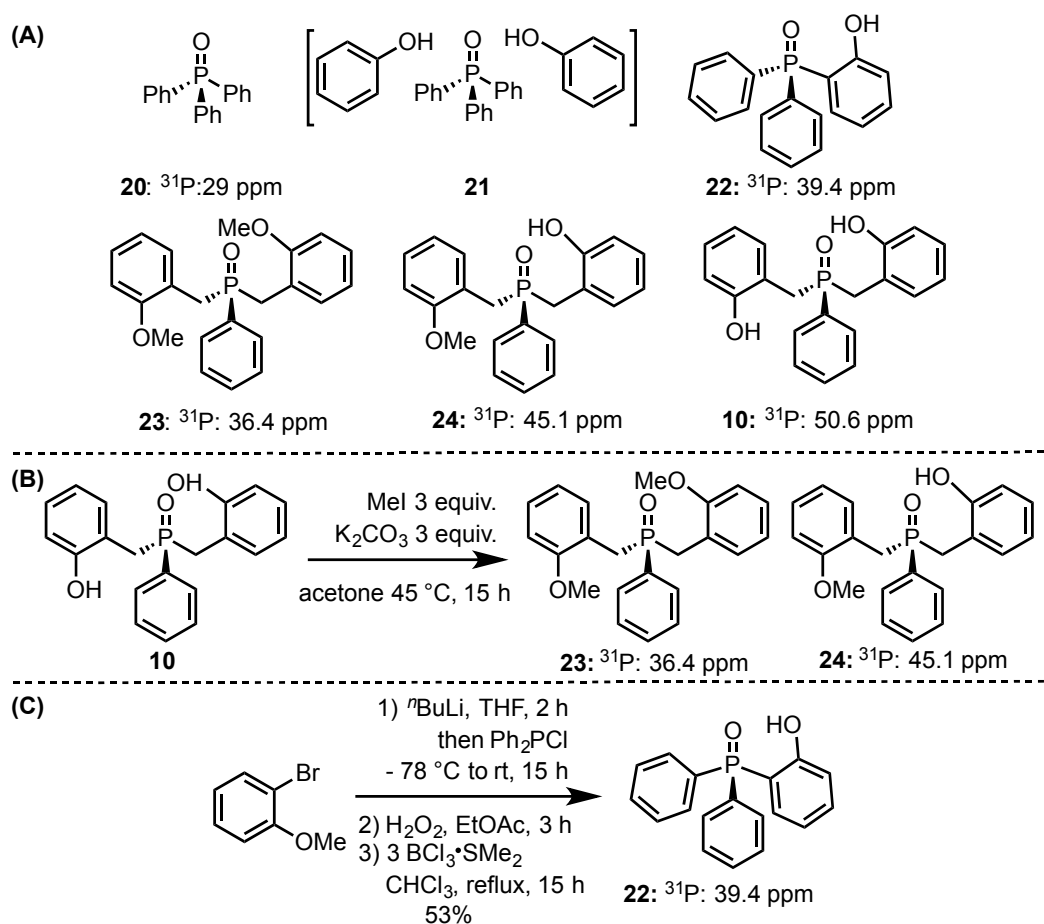
The oxide **10** is protonated in the presence of triflic acid (**19**, observed when oxide and triflic acid are mixed 1:1), which aids dehydration. Although we have shown that in the absence of decanol a reactive phosphonium species exists (104 ppm), in the presence of decanol it is uncertain whether this species exists or whether the alkoxyphosphonium triflate **16** is formed directly. That the triflic acid is largely present as decyl triflate at the end of the reaction indicates that oxide **10** and the alkyl triflate may be the resting state of the system. Indeed, the triflate is visible throughout the reaction; as is the oxide. Given that in the absence of triflic acid the reaction does not proceed (**16** is not formed; c.f. Table 1, entry 1), but that catalyst **10** can dehydrate, it seems unlikely that the alkyl triflate is an off pathway intermediate. The triflate anion is known to be more nucleophilic than methanol.⁶¹

We decreased the loading of the catalyst to interrogate its activity in a large scale preparative reaction. Over 15 h, a 1 mol% loading of oxide **10** was able to form 93% didecyl ether on a 6 g scale, equating to a minimum turnover number of 50. Whilst the phosphorus catalyst remains reasonably pure at a high loading, analysis of the phosphorus species present at 1 mol% loading indicated measurable degradation at this scale. Alkylation of the catalyst phenol groups was observed by ³¹P-NMR and confirmed by mass spectrometry (mostly mono; ~18%, ³¹P: 45.2 ppm, m/z 479). It is uncertain whether the alkylation occurs intramolecularly, or via an alkylation of an external decyl triflate, but given the general success of the reaction and the dependence of degradation on catalyst loading, an external alkylation seems most likely.

It is clear from the originally proposed manifold that the internal hydroxyl groups are necessary to dehydrate the catalyst, but Scheme 19 indicates that only one of these might be required, suggesting mono-alkylation would not deactivate the catalyst. Thus we designed a series of experiments to interrogate this theory.

Interrogation of the internal hydroxyl group requirements for dehydration of the catalyst

In order to ascertain whether both pendant hydroxyl groups are required for dehydration of the phosphine oxide in the presence of acid, we varied the position and number of hydroxyl groups in various potential catalyst systems, shown in Scheme 20.



Scheme 20. (A) The six different catalyst systems compared. (B) Synthesis of oxides 23 and 24. (C) Synthesis of phosphine oxide 22.

We then conducted the same etherification reaction with the new set of potential catalysts for comparison to the active oxide **17** (Table 2). Entries 1 and 2 in Table 2 demonstrate the legacy catalyst **10** and the background result: 5 mol% triflic acid alone produces a 15% conversion to ether over 15 h (entry 2), whilst 5 mol% catalyst **10** gives 99% conversion to the ether (entry 1). Note that the presence of a Lewis base (e.g. phosphine oxide **20**) may

reduce the background reaction (15% down to 7%) by vitiating the acidity of free triflic acid (entry 3).

Table 2. Comparison of different oxide catalysts in the homoetherification of decanol

$$\begin{array}{ccc}
 2 \text{ Me}-(\text{CH}_2)_8\text{OH} & \xrightarrow[\text{15 h, Dean-Stark}]{\text{conditions}} & \text{Me}-(\text{CH}_2)_8\text{O}-(\text{CH}_2)_8\text{Me} \\
 \mathbf{13} & & \mathbf{14} \\
 & \text{toluene, reflux} &
 \end{array}$$

Entry	Pcat (mol%)	Add. (mol%)	t /h	14 (%)
1 ^c	10 (5)	TfOH (5)	15	99, 1 ^b
2	– –	TfOH (5)	15	15
3	20 (10)	TfOH (10)	15	7
4	21 (5)	TfOH (5)	15	6
5	22 (5)	TfOH (5)	15	11
6	23 (5)	TfOH (5)	15	9
7	24 (5)	TfOH (5)	15	99, 1 ^b

^aAll experiments performed with 0.296 mmol catalyst in 17 mL solvent, 11.84 mmol alcohol (10% experiments run with 5.96 mmol alcohol). ^bdecyl triflate. ^cReaction performed by J. Saska.

Triphenylphosphine oxide was not a catalyst (entry 3), even in the presence of an external phenol source (**21**, entry 4). The catalytic effect cannot be simply due to an electronic effect of a dialkyl phosphine oxide (vs. triaryl), as di-protected analogue of the active catalyst **23** did not promote the reaction (entry 6). However, mono-protected analogue **24** did promote efficient catalysis (entry 7). The position of this functionality was shown to be key; in system **22** in which the internal phenol group cannot readily access the phosphorus centre (would be a 4-membered ring), no catalysis was observed (entry 5). These results all pointed to the requirement for one internal hydroxyl group (that can form a 5-membered-ring at phosphorus) to promote dehydration of the phosphine oxide.

These results demonstrated that mono-alkylation of the catalyst should not result in its deactivation, but also that singly functionalised catalysts might be worth exploring. First, however, the reactivity of the legacy catalyst **10** was explored in a number of other scenarios.

Further Reactivity of the Legacy Catalyst **10**

Motivation: Alongside our studies of the hydroxyl requirements of the catalyst system, the legacy catalyst **10** was trialled in a number of other experiments. The following reactivity types were considered:

- a) Reactivity of diols
- b) Secondary alcohols; inversion and elimination
- c) The investigation of other acidic nucleophiles

In terms of developing a catalytic system that might have some practical value, homoetherification represents a limited field. Although a clear rate enhancement was observed in the presence of phosphorus relative to triflic acid, it is questionable whether the current protocol offers an advantage over acidic heterogeneous catalysis methods. Indeed, industrial processes tend to use solid-supported acid catalysts, which offer longer lifetimes and higher catalyst turnover numbers, as well as ease of purification. It also seemed unlikely that our process could be adapted to couple two different alcohols (e.g. R^1OH and R^2OH); more nucleophilic alcohols would both be faster to become activated, and faster to react with the resulting triflate species, and so a mixture of alcohols R^1OH and R^2OH would likely tend towards a mixture of R^1-O-R^1 and R^2-O-R^2 , impure with R^1-O-R^2 depending on relative reactivity factors.

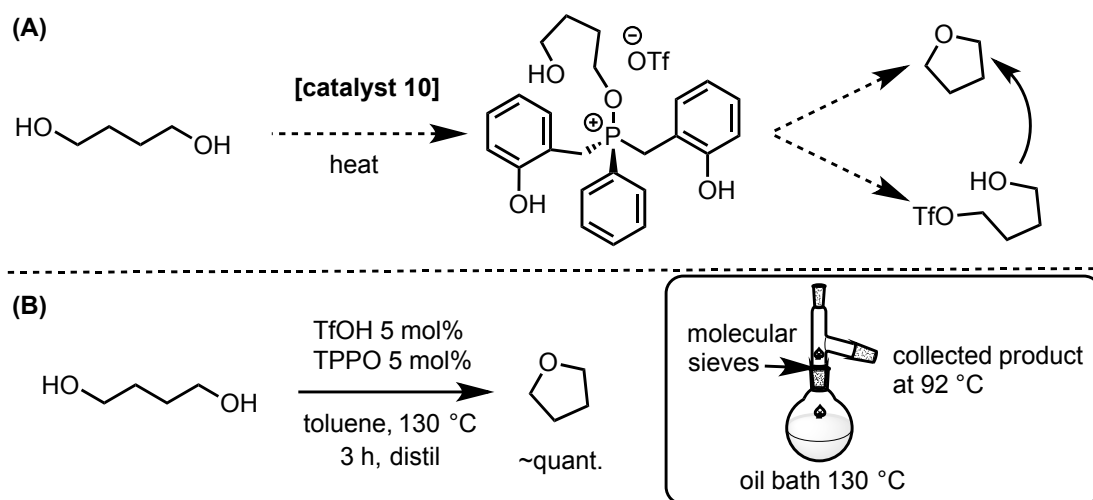
One way of overcoming the anticipated selectivity problems would be by using diols, which should form cyclic species preferentially (kinetically). Of most interest was the possibility of an inversion of a secondary alcohol to generate a cyclic ether bearing a stereocentre. Efficient general methods for alcohol inversion in general remain limited to multistep processes of activation and S_N2 inversion, or the classic Mitsunobu reaction. Achieving inversion would also mean exploring other acidic nucleophiles that didn't result in activated esters like triflates, thus moving away from etherification. Finally, the possibility of clean elimination reactions of alcohols to alkenes was also considered as a desirable transformation for which limited atom-efficient methods exist.

Further Reactivity of the Legacy Catalyst, 10: a) Reactivity Towards Diols

This reactivity manifold was simple in design: the reaction would be performed as usual, with the expectation that the diol would either act as its own internal nucleophile onto the alkoxyphosphonium intermediate, or close subsequently onto a triflate (Scheme 21a). 1,4-butanediol was chosen as a convenient diol that would generate THF. This was deemed of interest, as industrial methods of THF production use solid-supported acid catalysts such as aluminium oxide at temperatures above 100 °C.⁶² The reaction was performed as a distillation, with a desiccant (MS) packed in between the flask and condensing unit, collecting at 92 °C at the top (Scheme 21, box).

In the event, the background reaction with triflic acid was far too quick (Scheme 21b) to envisage obtaining an appreciable rate enhancement; essentially quantitative THF collection was obtained within 3 h, contaminated with water and toluene. The desiccant was of little use, as the water distilled over with the THF. This result suggested that the role of a

phosphorus catalyst would be over-shadowed by the simple acid catalysed regime (at double loading (10 mol%), the catalyst **10** only gives 60% conversion to didecyl ether over 3 h).



Scheme 21. (A) Possible reaction manifolds; (B) Reactivity of 1,4-butanediol.

Next, the reaction was performed in xylenes, with the hope that the solvent would remain, unlike when the reaction was performed in toluene. Indeed, THF could be collected pure (free from solvent) if the reaction was run in xylenes at 130 °C, but did not collect at lower temperatures. Again, oxide catalyst **10** was not required for a rapid rate. The problem with this approach is twofold: firstly, Dean-Stark azeotroping only works with the bulk solvent, as it is the condensing of this bulk solvent that heats the glassware and internal atmosphere sufficiently to allow reflux. Without this heat, the water and/or THF do not distil efficiently. Following from this point, even if the catalyst could give a rate enhancement at lower temperatures, water removal would be difficult. Dehydrating the catalyst at lower temperatures is much slower, as observed in benzene (recall Table 1, entry 9).

The conclusion here is that a rate enhancement is difficult because:

- a) intramolecular diols are much faster to react with the acid due to locality (entropic) effects – i.e. background is too fast;

- b) Lowering temperatures means requiring a much more active catalyst with faster dehydration rates;
- c) Removal of water at lower temperatures means a suitable desiccant is required as azeotroping no longer works.

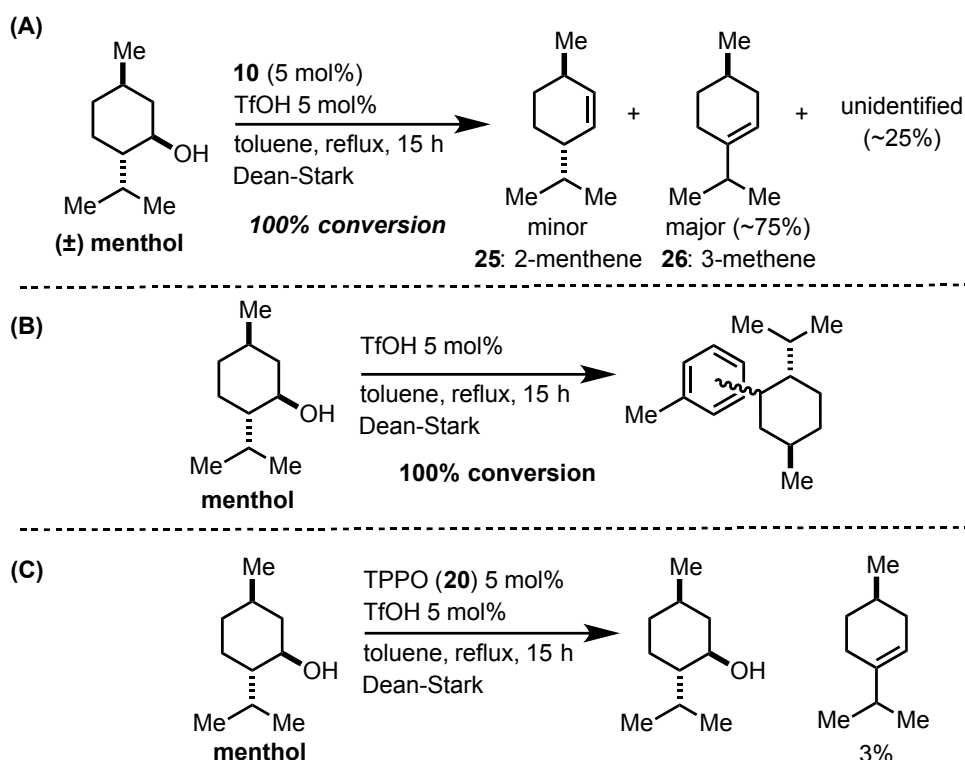
Given that solid-supported catalysts can perform quantitative catalysis, this reaction will be of limited interest unless the reaction can be shown to be highly productive at temperatures below 100 °C.

Further Reactivity of the Legacy Catalyst, 10: b) Elimination Reactions of Secondary Alcohols

Menthol was investigated as an optically active secondary alcohol. In the proposed triflic acid manifold, any homoetherification would be accompanied by retention of stereochemistry (double inversion) for one of the stereocentres. In the presence of 10 mol% oxide **10** and 10 mol% triflic acid, reaction in benzene over 15 h under Dean-Stark conditions was limited, with mostly menthol recovered. However, the same reaction performed in toluene (higher temperature) led to quantitative conversion of the starting material. After chromatography, a mixture of inseparable alkenes was recovered, in high yield. 3-Menthene **26** was the major species (~75%), by comparison of the alkene signals to literature values.⁵⁰ Although a minor amount of 2-menthene **25** was observed, the other remaining major species (~25%, based on integration of key signals) has eluded identification Scheme 22.

In the absence of a phosphorus catalyst, but in the presence of triflic acid, however, *the methenes were not observed*. Full conversion of the menthol starting material was noted, but

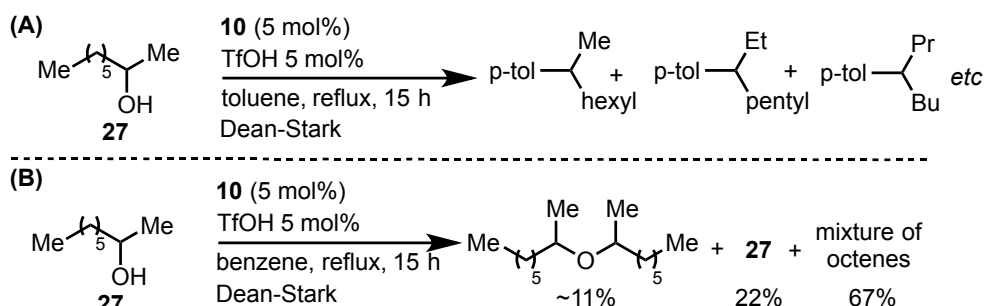
no alkene signals remained in the reaction mixture. Friedel-Crafts reactions were evident by the number of benzyl signals (toluene derivatives) at ~ 2.4 ppm.



Scheme 22. (A) In the presence of oxide **10**, menthol was largely dehydrated to 3-menthene; (B) The background reaction with TfOH led to Friedel-Crafts reactions; (C) Using triphenylphosphine oxide **20** as a Lewis-base additive prevents the Friedel-Crafts reactions.

The control reaction using triphenylphosphine oxide **20** proved interesting; apart from $\sim 3\%$ alkene, the starting material (menthol) was the major compound observed in the crude reaction mixture. This indicates that the Lewis basic phosphine oxide is sufficient to attenuate the acidity of the triflic acid additive in this case, *and that the dehydration to alkene in the above case is likely mediated by the phosphorus catalyst 10*. It is important to note, however, that if a stoichiometric acid is used (i.e. a higher loading than the catalyst), the phosphine oxide is unlikely to be as effective at reducing the background rate, certainly for stronger acids.

Next, the elimination reaction was attempted with 2-octanol in the presence of 5 mol% **10** and TfOH in toluene. After 15 h, the reaction showed extensive decolouration and ^1H -NMR analysis indicated Friedel-Crafts reactions with the solvent (Scheme 23A).



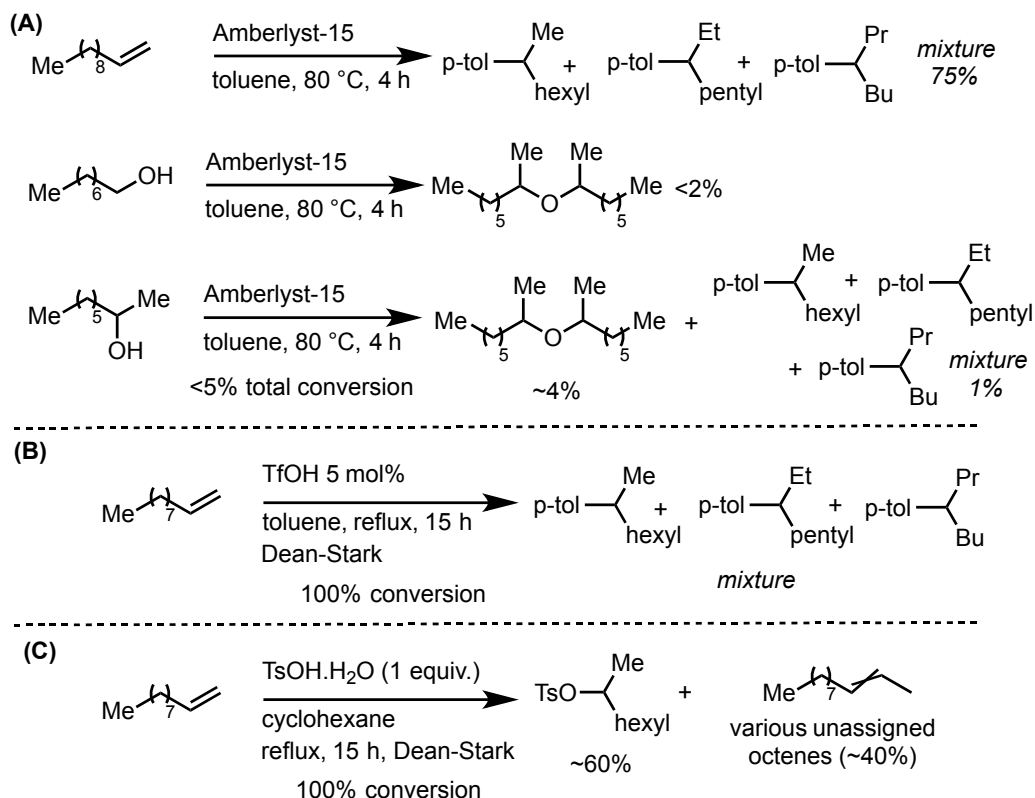
Scheme 23. (A) 2-octanol undergoes Friedel-Crafts chemistry with **A1**; (B) Use of benzene prevents Friedel-Crafts but the rate is slowed and alkenes migration is observed.

Repeating the reaction in benzene, a less nucleophilic aromatic solvent, at a lower temperature (DS, $\sim 100^\circ\text{C}$ oil bath, relative to; DS with toluene $\sim 135^\circ\text{C}$ oil bath), reduced the Friedel-Crafts reactivity (Scheme 23B). There was evidence of dioctyl ether, but octanol **27** and a mixture of variously-migrated octene products made up most of the mixture. Whilst the menthol reaction was relatively well-behaved, in this case the alkenes were prone to internal migration. (*This might suggest that the major (most-substituted alkene) menthene product above is simply the thermodynamic alkene after migration.*)

These results all suggested that the reaction was leading to dehydration and subsequent acid-catalysed Friedel-Crafts reactions of the resulting alkene with the solvent. Such reactions are known with Amberlyst-15, supporting this analysis (Scheme 24A).⁶³

Indeed, decene underwent quantitative Friedel-Crafts reactions in the presence of 5 mol% TfOH and the absence of any phosphine oxide (Scheme 24b). It appeared that some alkene chain isomerisation occurred before alkylation in some cases, as ~ 6 benzyl ^1H multiplets were observed in addition to at least 4 benzyl Ar-CH₃ groups. Comparing the integration of Ar-H signals to Ar-Me signals suggested that essentially only monoalkylation had occurred.

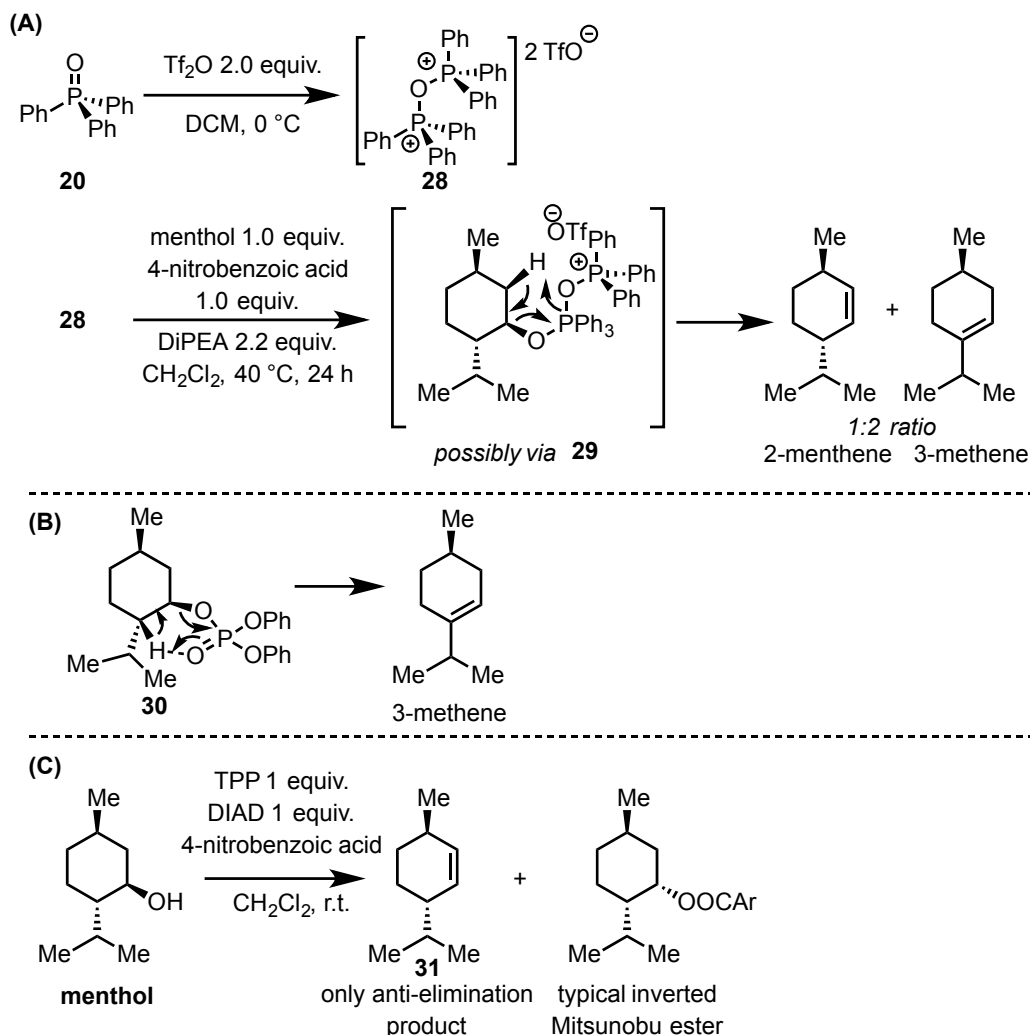
This result confirms that alkenes are the most likely precursor to the observed Friedel-Crafts reactions, and that the more hindered menthenes are less prone to Friedel-Crafts reactions in the presence of a phosphine oxide Lewis base. Even in cyclohexane, with a less acidic acid (tosic acid), migration occurred, as well as acid-promoted addition reactions of tosic acid (Scheme 24C).



Scheme 24. a) Lachter's Friedel-Crafts alkylation of toluene with octene using an Amberlyst-15 catalyst.⁶³ b) Friedel-Crafts alkylation of toluene with decene in the presence of 5 mol% triflic acid. c) Decene reacted with TsOH in cyclohexane to give migrated alkenes.

These results indicated limited applicability of the P-catalysed elimination reaction. Menthene is especially prone to elimination due to its conformational rigidity, as demonstrated in the literature reactions shown in Scheme 25 using the Hendrickson reagent **28** and diphenylphosphate (via species **30**).

Whatever the mechanism, the strength of the acid appeared to be the driver of the elimination chemistry. Thus, attempts to reduce the acidity were made to allow isolation of the inverted alcohols.



Scheme 25. Relevant Hendrickson reagent results: a) Jenkins' proposed mechanism for the Hendrickson reagent-promoted dehydration of menthol.⁵⁰ b) A similar mechanism was proposed for the *syn*-elimination of menthol with diphenylphosphate.⁶⁴ c) Jenkins' demonstration that the analogous reaction with the Mitsunobu conditions leads to a different outcome, namely esterification with inversion or *anti*-elimination.⁵⁰

Further Reactivity of the Legacy Catalyst, 10: c) Inversion of Secondary Alcohols

When 1 equivalent of benzoic acid was utilised in toluene over 15 h without any catalyst (Scheme 26), 84% starting material remained. The reacted material appeared to be migrated

alcohols – no more than trace ester (5.19 ppm) or ether (3.41 ppm) were observed. With a strong acid, tosic acid, again catalyst free, the reaction became strongly discoloured and full consumption of the alcohol was observed. There was again evidence of Friedel-Crafts reactions, suggesting that the optimum reactivity zone for the inversion of secondary alcohols would lie between benzoic and tosic acids.

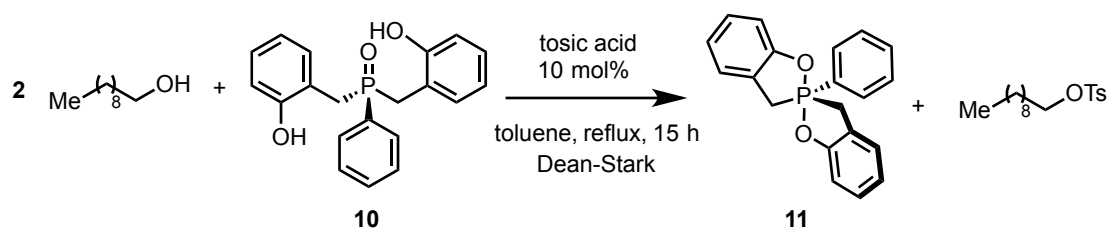


Scheme 26. Even lower acidity acids (benzoic acid) led to migrated alcohols in the absence of phosphine oxide

These reactions were at the time perhaps misleadingly discouraging, as they suggested unruly background reactions that would be hard to tame. But future work would begin to generate evidence that the acidic conditions could be tempered by two factors: Firstly, the Lewis basic phosphine oxide catalyst and its hydroxyl groups, and secondly the productive reaction itself; *if catalysis is fast enough, the acidity of the reaction will tend towards neutrality, thus slowing the decomposition reactions.* (note: this means that e.e.s should always be slightly higher than predicted using the background rate). A key problem with the background reactions is that the reactions are acid-catalysed. Thus, as the reaction proceeds, the apparent acidity gets higher with respect to remaining alcohol. Because the desired reactivity pathways lead to a neutral solution, the relative acidity remains constant (or, in fact, decreases relative to the constant oxide catalyst), and so it may be possible to outcompete this acidity if the catalyst is active enough.

Failure to realise this strategy earlier hindered development of the reaction with respect to secondary alcohol inversion experiments. They did, however, drive development of better

catalysts that would be active with lower acidity acids. Recalling entry 2 from Table 1, tosic acid failed to be an effective co-catalyst for forming ether (Scheme 27).

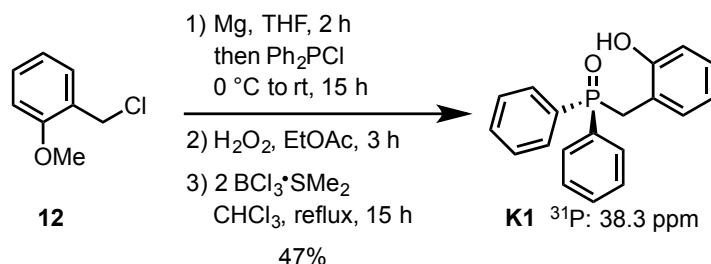


Scheme 27. Tosic acid fails to disrupt the stable dioxaphosphorane **11** and so catalyse tosylate/ether formation.

Crucially, at the end of the reaction, the phosphorane **11** was visible. This suggested that the tosic acid was insufficiently acidic to allow the phosphorane to engage with the decanol (albeit it at only 10% loading). This conclusion was subsequently over-turned; the tosic acid is present entirely as decyl tosylate at the end of the reaction, meaning there is no acid remaining to open the phosphorane, and that the catalyst likely performed the role of tosylation. At the time, however, this result misled us to believe the dioxaphosphorane was kinetically stable in the presence of tosic acid (which may or may not be the case). The positive result with the mono-protected analogue **24** offered a way forward, although this required that dehydration of the oxide wouldn't be limited in the presence of a weaker acid. Fortunately, it was not, and research using a new catalyst began.

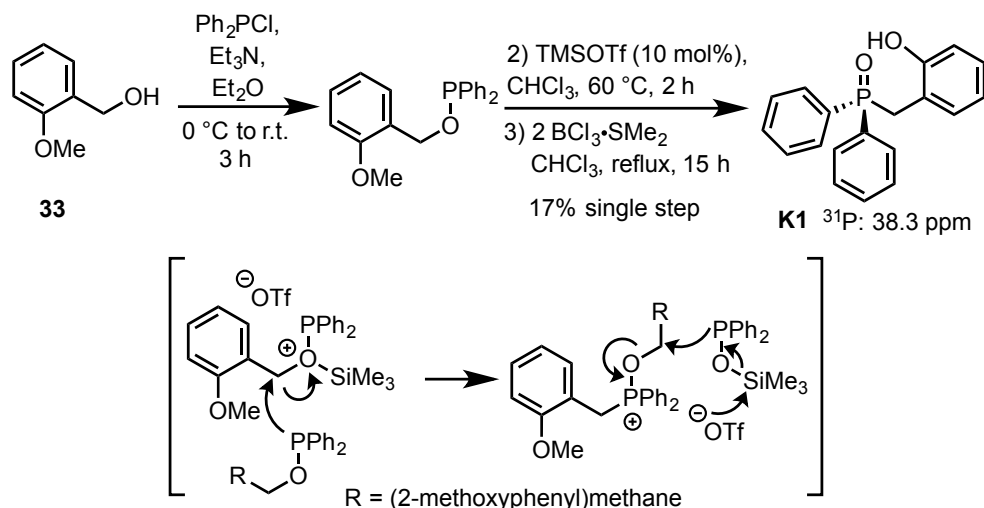
K1: Monohydroxyl Phosphine Oxide Catalyst

To confirm the reactivity of the mono-protected catalyst in a more easily accessible compound, catalyst **K1** was synthesised in an analogous method to the previous oxide catalyst **10** from benzyl chloride (Scheme 28).



Scheme 28. Synthesis of monohydroxyl catalyst K1.

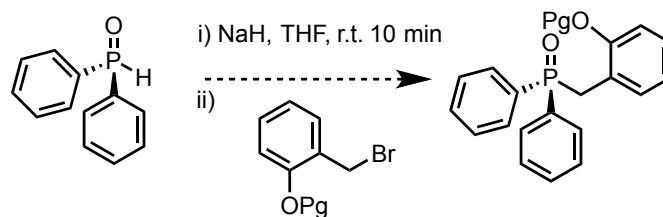
This approach was limited by the efficiency of the Grignard reaction, which was unoptimised for time/temperature etc here. Several other approaches proved to be viable synthesis methods, including the Lewis acid-catalysed Arbuzov rearrangement procedure developed by Renard and co-workers directly from the halide-precursor, alcohol **33** (Scheme 29).⁶⁵



Scheme 29. Synthesis of K1 via a Lewis acid catalysed Arbuzov sequence, and Renard's proposed mechanism.

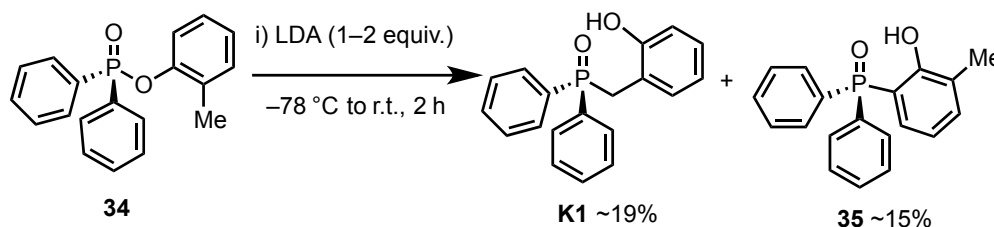
The reaction was proposed to work as shown at the bottom of Scheme 29. In this idealised scenario, two molecules of phosphinite swap their benzyloxy groups. Practically, after stirring alcohol **33** with the chlorophosphine, the phosphinite is obtained in ether solution by careful filtration of the amine salt and used immediately, as it is sensitive to oxidation and hydrolysis. Performed carefully, this sequence should give between 80-90% yield. In an attempt to streamline the synthesis, however, a single rearrangement and deprotection step was attempted (as both involve Lewis-acidic conditions in chloroform), but yielded only

17% over the three steps after chromatography and recrystallization. Losses tend to come about from an incomplete initial phosphinite formation, which can be hindered by temperature control (r.t. should properly be 25 °C) and inefficient stirring due to the initial precipitation of salts. Another approach that came to light late in the day, and so remains untested, is shown in Scheme 30.



Scheme 30. Another possible route to the general catalyst structure.

The reaction is expected to work efficiently for Pg = Me. A final route involved a speculative phospho-Fries rearrangement on phosphonate **34**, easily produced from the chlorophosphine and *o*-cresol (2-methylphenol) followed by *in situ* oxidation (not shown). The resulting species **34** is stable to chromatography. The subsequent reaction hinges on the selective deprotonation of the benzyl position on the *o*-cresol derived phosphinate by LDA, and internal substitution releasing the more stable phenoxy species (although such anions are sometimes sensitive to aryl oxidation reactions which may hinder this reaction) (Scheme 31).



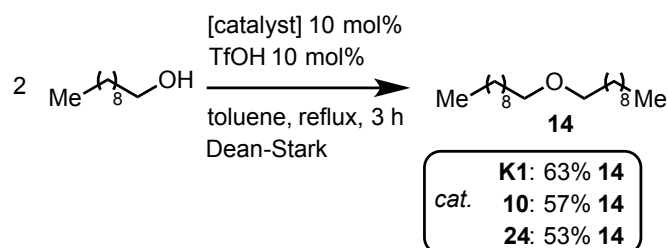
Scheme 31. Phospho-Fries rearrangement approach to K1

In the event, the reaction was not as selective as expected. Following the addition of freshly prepared LDA and warming to room temperature, the two major species recovered after chromatography were the desired phosphine oxide **K1** (19%) and a mixture containing *o*-

cresol and phosphine oxide **35** (15%). The release of *o*-cresol presumably forms along with diphenylphosphinic acid. This reaction is also unoptimised, and it is expected that the rate of warming, equivalents of base and length of reaction may adjust the product ratio. After considering commercially available materials, the optimum route will likely be either the alkylation of the benzyl bromide, or the Arbuzov rearrangement. In any case, the catalyst is readily accessible in only a few steps from commercially available materials.

K1: Reactivity

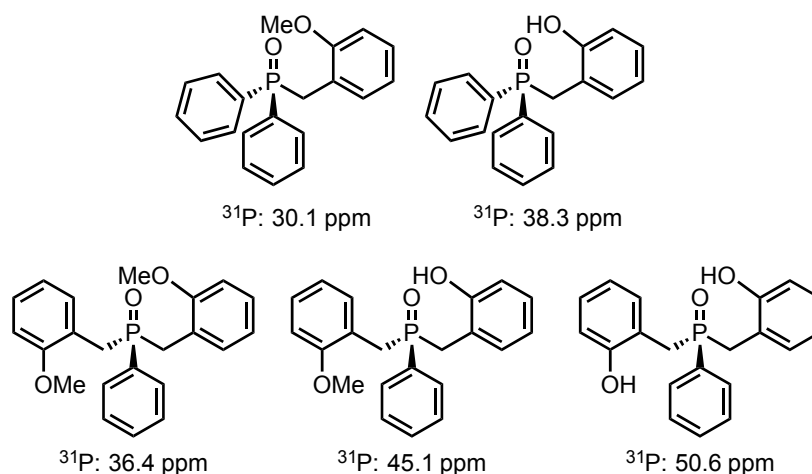
In the triflic acid co-catalysed etherification reaction, **K1** performed at least as well as either **10** or its mono-protected analogue **24**, demonstrating that a single hydroxyl group is sufficient for both dehydration and catalysis (Scheme 32).



Scheme 32. **K1** and TfOH catalysed etherification of decanol, compared to legacy catalyst **10** and its mono-phenoxy-protected analogue **24**.

Free from the possibility of forming a stable dioxyphosphorane intermediate, we next attempted catalysis of **K1** with tosic acid and decanol. Initial catalyst designs had interpreted the role of the hydroxyl groups as both forming the phosphorane, but also aiding activation of the phosphoryl bond via H-bonding. Indeed, the ^{31}P shifts of the oxides demonstrate the effect of intramolecular hydrogen bonds on the phosphoryl bond strength (Figure 4). This meant there was the possibility that using a monohydroxyl group catalyst with a less acidic acid might result in the loss of activity, as acid also activates phosphoryl bonds.

Figure 4. The effect of hydrogen-bonding on the strength of the phosphoryl bond in a series of phosphine oxides



We first tried the etherification reaction, assuming that decyl tosylate would undergo reaction with decanol as for the triflate. Using 5 mol% TsOH monohydrate, decanol and 2.5 mol% **K1**, decyl tosylate **36** was formed in 5% conversion, a quantitative conversion with respect to tosic acid. Didecyl ether **21** was only formed in 1% yield, clearly indicating a very slow alkylation reaction with this less reactive electrophile. This suggested we might be able to catalyse the formation of decyl tosylate instead of ether, a much more enticing prospect. And so 1 equivalent of tosic acid monohydrate and decanol were combined to attempt to form the decyl tosylate stoichiometrically.

The results of the catalytic and control reactions are given in Table 3. Entries 3 and 4 indicate clear catalysis in the presence of **K1** (85% tosylate) relative to no P-catalyst (21% tosylate), equal to roughly a 3-fold rate enhancement at a 2.5 mol% catalyst loading (1.2 x acceleration/mol%). A control reaction with triphenylphosphine oxide served to confirm the specific role of **K1** in the increased rate (entry 5). At these loadings, there did not appear to be a reduced background rate due to the Lewis base action of the phosphine oxide. The reaction occurred in benzene, but was predictably slower, highlighting the requirement for temperature (entry 6).

Table 3. Reaction of decanol and tosic acid with and without oxide catalyst K1

$ \begin{array}{c} \text{Me}-(\text{CH}_2)_8-\text{OH} \\ \mathbf{13} \end{array} \xrightarrow[\text{toluene, reflux, [time]}]{\begin{array}{c} \text{[catalyst, 2.5 mol\%]} \\ \text{TsOH} \cdot \text{H}_2\text{O 1 equiv.} \\ \text{Dean-Stark} \end{array}} \begin{array}{c} \text{Me}-(\text{CH}_2)_8-\text{OH} \\ \mathbf{13} \end{array} + \begin{array}{c} \text{Me}-(\text{CH}_2)_8-\text{OTs} \\ \mathbf{36} \end{array} + \begin{array}{c} \text{Me}-(\text{CH}_2)_8-\text{O}-(\text{CH}_2)_8-\text{Me} \\ \mathbf{14} \end{array} $						
Entry	Pcat (mol%)	t /h	decanol 13 (%)	ether 14 (%)	tosylate 36 (%)	
1	K1 (2.5)	5	46	5	44	
2	–	5	80	4.5	11	
3	K1 (2.5)	15	0	7.5	85	
4	–	15	58	10.5	21	
5	TPPO (2.5)	15	60	9.5	21	
6 ^b	K1 (2.5)	15	85	2	11	

^aAll experiments performed with 0.148 mmol catalyst in 17 mL toluene, 5.92 mmol alcohol, under Dean-Stark conditions. ^breaction performed in benzene 17 mL (note that each ether molecule has consumed 2 molecules of decanol)

Attempts to increase the tosylate:ether ratio by increasing the loading of **K1** proved unsuccessful. Doubling the catalyst loading to 5 mol% **K1** still gave only 86% tosylate (Table 4, entry 1), relative to the 85% with 2.5 mol%.

Table 4. Increase the tosic acid loading to 1.5 equivalents led to no catalytic enhancement, but increased the background reaction

$ \begin{array}{c} \text{Me}-(\text{CH}_2)_8-\text{OH} \\ \mathbf{13} \end{array} \xrightarrow[\text{toluene, reflux, [time]}]{\begin{array}{c} \text{[catalyst, 2.5 mol\%]} \\ \text{TsOH} \cdot \text{H}_2\text{O [equiv]} \\ \text{Dean-Stark} \end{array}} \begin{array}{c} \text{Me}-(\text{CH}_2)_8-\text{OH} \\ \mathbf{13} \end{array} + \begin{array}{c} \text{Me}-(\text{CH}_2)_8-\text{OTs} \\ \mathbf{36} \end{array} + \begin{array}{c} \text{Me}-(\text{CH}_2)_8-\text{O}-(\text{CH}_2)_8-\text{Me} \\ \mathbf{14} \end{array} $						
Entry	Pcat (mol%)	TsOH.H ₂ O (eq.)	t /h	decanol 13 (%)	ether 14 (%)	tosylate 36 (%)
1	K1 (5)	1.0	15	0	7	86
2	K1 (5)	1.5	15	6	8.5	77
3	–	1.5	15	31	11.5	46

^aAll experiments performed with 0.148 mmol catalyst in 17 mL toluene, 5.92 mmol alcohol, under Dean-Stark conditions.

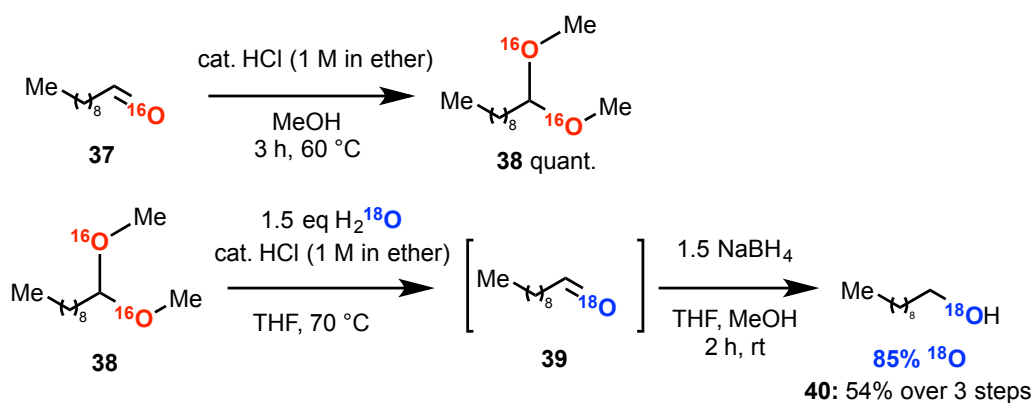
This result suggested that small percentage catalyst increases would not improve the rate over the background. Using 1.5 equiv TsOH did not improve the overall conversion to tosylate either (but the background increased); when 5 mol% **K1** was present, the ether and tosylate yields were about the same as with 1.0 equiv TsOH (entry 2 and 3).

An idea that has not been tested would be to allow a 1.5 h delay before adding the decanol to remove water, which hinders the catalytic reaction but not the etherification reaction, leading to a lower tosylate yield.

Despite our failure thus far to push the conversion of tosylate higher, the current results already show a ~4 times rate acceleration over the background, including a reduced conversion to ether side-product. With these promising results assured, we investigated the reactivity of **K1** in different scenarios.

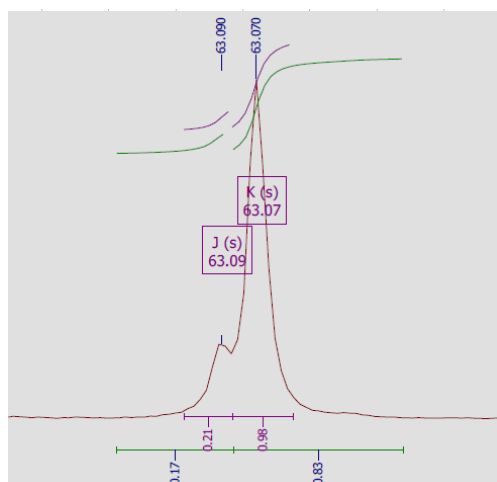
K1: Confirming the mechanism of the activation of primary alcohols

It was important for our long-term goal of secondary alcohol inversion that the activity of **K1** was due to dehydration and Arbuzov collapse of an alkoxyphosphonium salt. Although it was difficult to envisage a separate *P*-catalysed reaction that didn't involve Arbuzov collapse of an alkoxyphosphonium tosylate, we endeavoured to obtain further evidence of this step. We therefore designed an isotope labelling experiment to track the provenance of the oxygen atoms in the reaction. First, ^{18}O -decanol was synthesised as shown in Scheme 33.

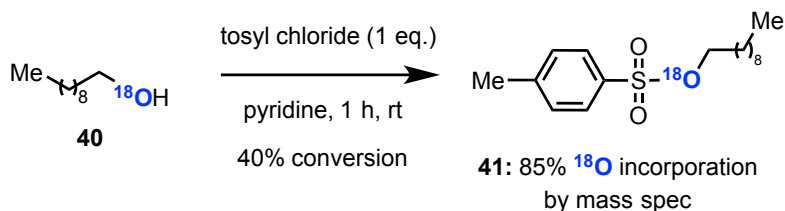


Scheme 33. Synthesis of ^{18}O -decanol from ^{16}O -decanal using labelled water.

First, ^{16}O -decanal **37** was dehydrated under acid catalysis to give its dimethylacetal **38**. This acetal was separated from remaining aldehyde and dried by chromatography, before performing a careful partial hydrolysis in the presence of $\text{H}_2[\text{O}]^{18}$ and dry HCl in ether to give ^{18}O -decanal **39**. In the same pot, to avoid exchange with atmospheric moisture, the labelled aldehyde was reduced with sodium borohydride in THF. This reaction is normally performed with water present to aid solubility, but this was not possible here. Instead, small amounts of methanol were added to help dissolve and activate the sodium borohydride. Following chromatography, pure ^{18}O -decanol **40** was obtained in 54% yield over the three steps. The extent of labelling was examined by quantitative ^{13}C NMR analysis, suggesting an 83% label incorporation by comparison of the alpha carbon shift integrations, which were reasonably separated at 125 MHz (Figure 5).

Figure 5. The alpha carbon ^{13}C -NMR signal of decanol 40 at 125 MHz showing ^{18}O incorporation.

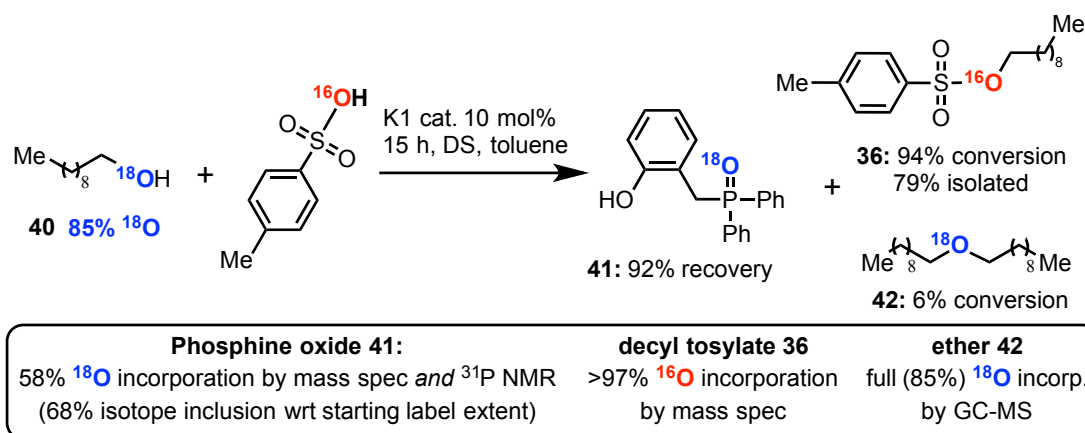
Conversion of a small amount of decanol to its tosylate allowed a quantitative mass spectrometry analysis (decanol itself is a poor mass-spectrometry substrate). Isotopic analysis of the resulting decyl tosylate indicated 85% ^{18}O inclusion, in good agreement with the ^{13}C NMR analysis (Scheme 34).



Scheme 34. The extent of decanol labelling was also determined by mass-spec analysis of the corresponding tosylate, generated from tosyl chloride. (The low conversion is due to the scale rather than kinetic isotope effects.)

With the labelled decanol **40** in hand, the alcohol was subjected to the typical Dean-Stark tosylation conditions with **K1**. If Arbuzov collapse was occurring, the ^{18}O label should be transferred during the reaction to the phosphoryl group of the catalyst. At the end of the reaction, it was hoped that a significant level of the oxide would remain (no acid to autodehydrate the catalyst), and analysis would confirm the presence of the labelled atom. Similarly, all tosylate should be free of ^{18}O -labelled oxygen, whilst the ether, speculated to be

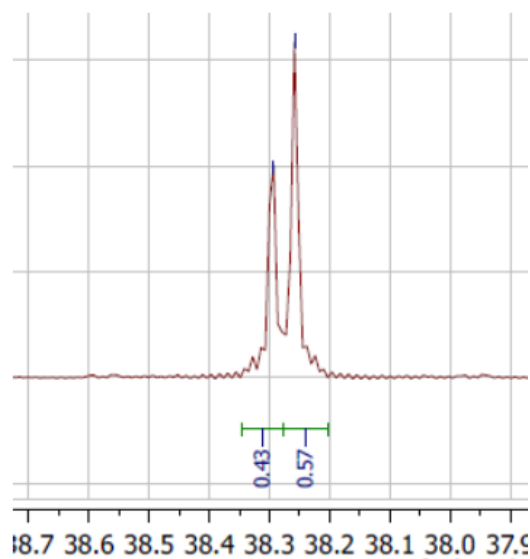
formed from the acid-catalysed reaction of two alcohol molecules would contain ^{18}O (Scheme 35).



Scheme 35. K1-catalysed tosylation using ^{18}O -labelled decanol **40**. The label distribution, including incorporation of the label into the reclaimed catalyst, supports the Arbuzov-collapse mechanism.

In the event, the distribution of labelled (isotopic) oxygen supported the hypotheses, and provided a further proof of concept that alcohol inversion might be possible under the right conditions. Specifically, ^{18}O was transferred to phosphorus and ^{16}O to the tosylate product. Integration of the two phosphoryl shifts of reclaimed catalyst were in good agreement with mass spectrometry ratios, and indicated a $\sim 58\%$ ^{18}O -label incorporation into the catalyst (Figure 6).

Figure 6. The ^{18}O -phosphoryl shift can be used to determine the extent of ^{18}O -label incorporation onto the catalyst oxide (162 MHz).



It is not expected that full incorporation would occur, as any moisture in the reaction mixture would rehydrolyse any activated catalyst, and so exchange the label (and the decanol was only at 85% label inclusion to begin with). Meanwhile, almost complete incorporation of the ^{16}O label to the tosylate suggested both that Arbuzov collapse had occurred, and also that the background reaction is largely as previously predicted (i.e., the tosic acid attacks a protonated alcohol to release water, retaining the sulfonate oxygen atom). With strong evidence that catalyst activation and subsequent Arbuzov collapse were occurring in hand, we sought to explore further reactivity of the catalyst, with the specific goal of stereoinversion of a secondary alcohol.

K1: Additional reactivity; the stereoinversion of 2-octanol

K1, which is unable to sit as a stable phosphorane like legacy catalyst **10**, was hoped to be amenable to dehydration with less acidic acids (triflic acid led to Friedel-Crafts/elimination). So, 2-octanol was subjected to a number of different acids to explore its tolerance to the acidity under Dean-Stark conditions (Table 5).

Table 5. Carboxylic acid screen: the reaction of decanol with carboxylic acids of varying pK_a under different temperatures and conditions

Reaction scheme: 2-octanol (**13**) + $R^1-COOH \xrightarrow{[solvent], [temp], [time], \text{Dean-Stark}}$ $R^1-COO-2\text{-octyl}$

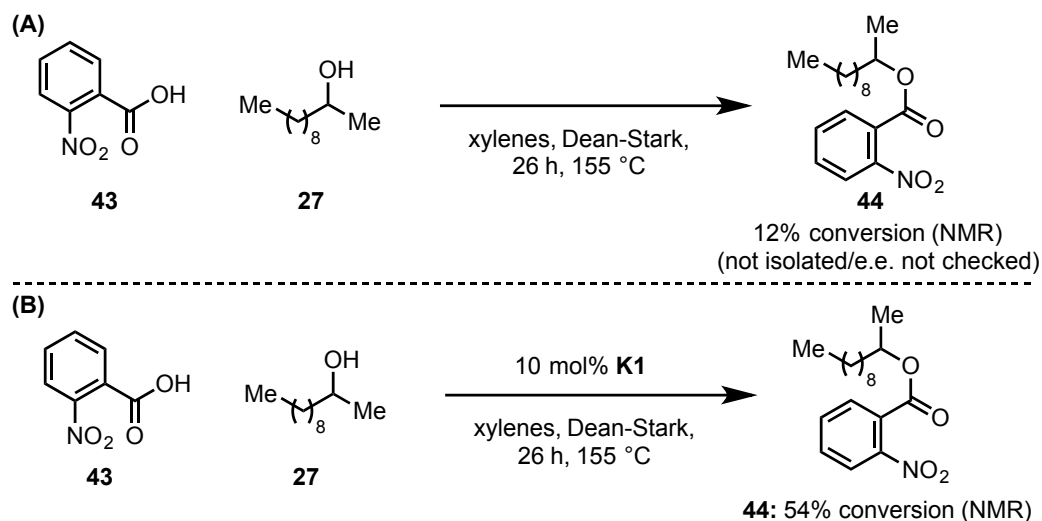
entry	acid	time /h	solvent	catalyst	result
1	benzoic	15	tol		0% ester
2	benzoic	15	tol	2.5 mol K1	0% ester
3	Benzoic + 0.5 mol % TfOH	15	tol	–	45% ester
4	4-nitrobenzoic	15	tol	–	>1%
5	trichloroacetic	15	tol	–	88%
6	trichloroacetic	15	cyclohexane	K1	~72% ester
7	trichloroacetic	17	cyclohexane	–	~70% ester
8	TCAA, amberlyst	15	tol, 90 °C	–	83% ester
9	Benzoic + SSSA	17.5	tol	–	27%
10	Benzoic + SSSA	17.5	tol	K1	No catal.
11	Phenol, amberlyst	2	tol, 90 °C	–	No react.
12	HCl, benzoic	16	tol	–	No react.

SSSA = silica supported sulfuric acid (co-catalyst); TCAA trichloroacetic acid

Again, however, with tosic acid, 2-octanol underwent full conversion, ultimately to Friedel-Crafts type products, presumably via the alkene (not shown). This result lead to a strategic rethink; instead, acids would be trialled against decanol until the background reaction was present, but very low, and where there was a hint of catalysis at least. This was predicted to

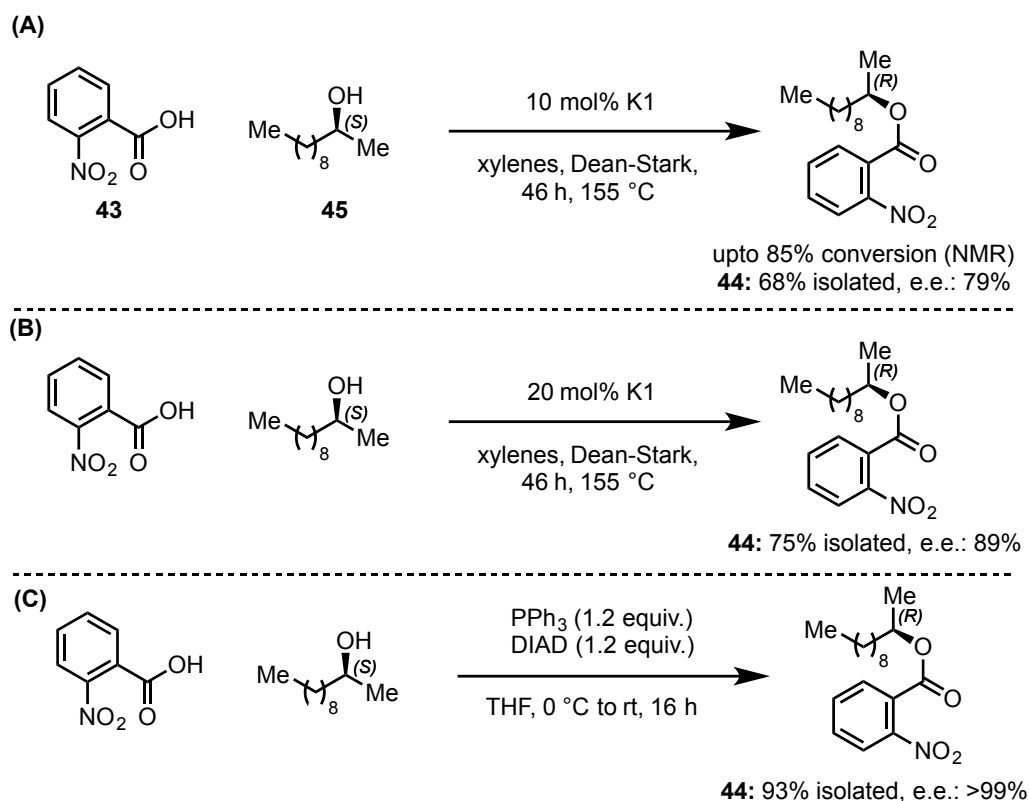
give a rough acidity window where secondary testing could begin without too much dehydration. Use of benzoic acid ($pK_a \sim 4.2$, water) with decanol gave no background ester (entry 1), and was insufficiently acidic to dehydrate the catalyst and give any catalysis (entry 2). The addition of 0.5 mol% TfOH led to a huge background reaction (entry 3). 4-Nitrobenzoic acid ($pK_a = 3.4$, water) gave no reaction with decanol in the absence of catalyst (entry 4). Trichloroacetic acid ($pK_a \sim 0.7$, water), on the other hand, gave a very large background reaction in cyclohexane (b.p. 81 °C) over 15 h (entry 7), which was not noticeably improved by the addition of 2.5 mol% **K1** (entry 6). These two results suggested lowering the acidity could decrease elimination reactions. However, the problem of the fast background remained, even at lower temperature. Further experiments in which external acids were added to the reaction were not successful (entries 8-12).

The likely pK_a window for useful catalysis with **K1** was therefore deemed to be between 0.7 and 3.4. There are not a lot of convenient carboxylic acids that fall into this window, but eventually 2-nitrobenzoic acid (pK_a 2.2) was trialled. The position of the nitro group on this benzoic acid has a surprisingly strong effect on the acidity, being a full 1.2 log units more acidic than the 4-nitro isomer. Initial experiments with 2-octanol and 2-nitrobenzoic acid in toluene over 14 h showed hints of a possible rate acceleration, but it was difficult to rule out experimental uncertainty at this point. In order to try and stretch out any differences, the reaction was run for longer (26 h), in xylenes. Over this time period, a clear rate acceleration was obtained ($\sim 4\times$ formation of ester, Scheme 36).



Scheme 36. First hint of successful catalysis with **K1** and a secondary alcohol (B) relative to the control reaction (A).

With these promising signs of catalysis, optically pure 2-octanol was trialled in xylenes with 10% **K1** over 46 h (Scheme 37A).



Scheme 37. (A) Catalysis (10 mol% **K1**) with inversion of 2-octanol; (B) Catalysis (20 mol% **K1**) with inversion of 2-octanol; (C) Standard Mitsunobu reaction.

The enantiomeric excess was checked for all reactions via chiral-phase HPLC and compared to a standard Mitsunobu reaction with both chiral and racemic 2-octanol-derived esters

(Scheme 37B and C). The **K1** catalysis gave 79% e.e. with 68% isolated yield compared to the regular Mitsunobu which gave 93% isolated yield and >99% e.e.. Increasing the catalyst loading to 20 mol% increased the yield to 75% with 89% e.e. now achieved (this equates to 95:5 e.r., comparable to the methodologies described in Schemes 8-9). To obtain such an impressive enantioselectivity with the first active catalyst designed demonstrates the huge potential of this manifold. At the time of writing, these results are unoptimised and, given the analysis in the previous section, may benefit from pre-drying the solvent/alcohol to enhance the catalyst manifold at the start of the reaction. Given that the catalyst is reclaimed at ~80% levels during the chromatography at the end of the reaction, increasing the loading to achieve a higher e.e. also looks both feasible and worthwhile.

To show the benefit of our approach, some metrics were calculated, including E-factor⁶⁶ (kg waste/kg product) and effective mass yield⁶⁷ (mass useful atoms out/mass atoms in, excluding water). Table 6 shows that the catalysis is far more atom efficient than the original Mitsunobu protocol, as long as the solvent and catalyst are reclaimed. These are arguably trivial procedures as the Dean-Stark is an automatic distillation device and the catalyst elutes cleanly after the product during chromatography.

In calculating the values for the standard Mitsunobu, it is assumed that ~ 80% of triphenylphosphine oxide may be usefully recovered from trituration. Both metrics implicitly include the yield in the calculation, so the theoretical maximum values are included, including full yield and 80% phosphorus recovery. For **K1** catalysis (entry 1, top table), the missing 7% in the effective mass yield is 2% catalyst and 5% water. The second table shows E-factors; typical values in the pharmaceutical industry as calculated by Sheldon are in the range of 25-100. Clearly then, a theoretical maximum value of 0.02 for this reaction

including catalyst and solvent recycling against the 21.2 of a typical non-recycled Mitsunobu reaction represents a significant advancement (1000 fold decrease in waste).

Table 6. Effective mass yield and E-factor metrics for the catalysis vs typical Mitsunobu

<i>Effective Mass Yield</i>					
REACTION	yield ^b	No ^c reclaim	without solvent ^d	reclaim P ^e	theoretical max ^e
10 mol% K1	67%	2%	57%	70%	93%
20 mol% K1	75%	3%	58%	83%	92%
Mitsunobu	93%	4%	28%	57%	67%

^aEffective mass yield = useful mass isolated/total mass in. ^byield obtained in experiment; ^cvalue using only the product as useful mass; ^dvalue discounting reaction solvent; ^evalue if 80% of the phosphorus used is reclaimed and solvent discounted; ^ftheoretical maximum value assuming 100% yield, solvent fully recovered, and 80% phosphorus components reclaimed usefully.

<i>E-Factor</i>					
REACTION	yield	No reclaim	without solvent	reclaim P	theoretical max ^b
10 mol% K1	67%	43.17	0.69	0.56	0.02
20 mol% K1	75%	38.79	0.66	0.42	0.02
Mitsunobu	93%	21.20	2.25	1.11	0.40

^aE-factor = waste mass/useful mass. Other definitions as above. ^btheoretical max for 100% yield, all solvent reclaimed, and with 80% phosphorus recovery.

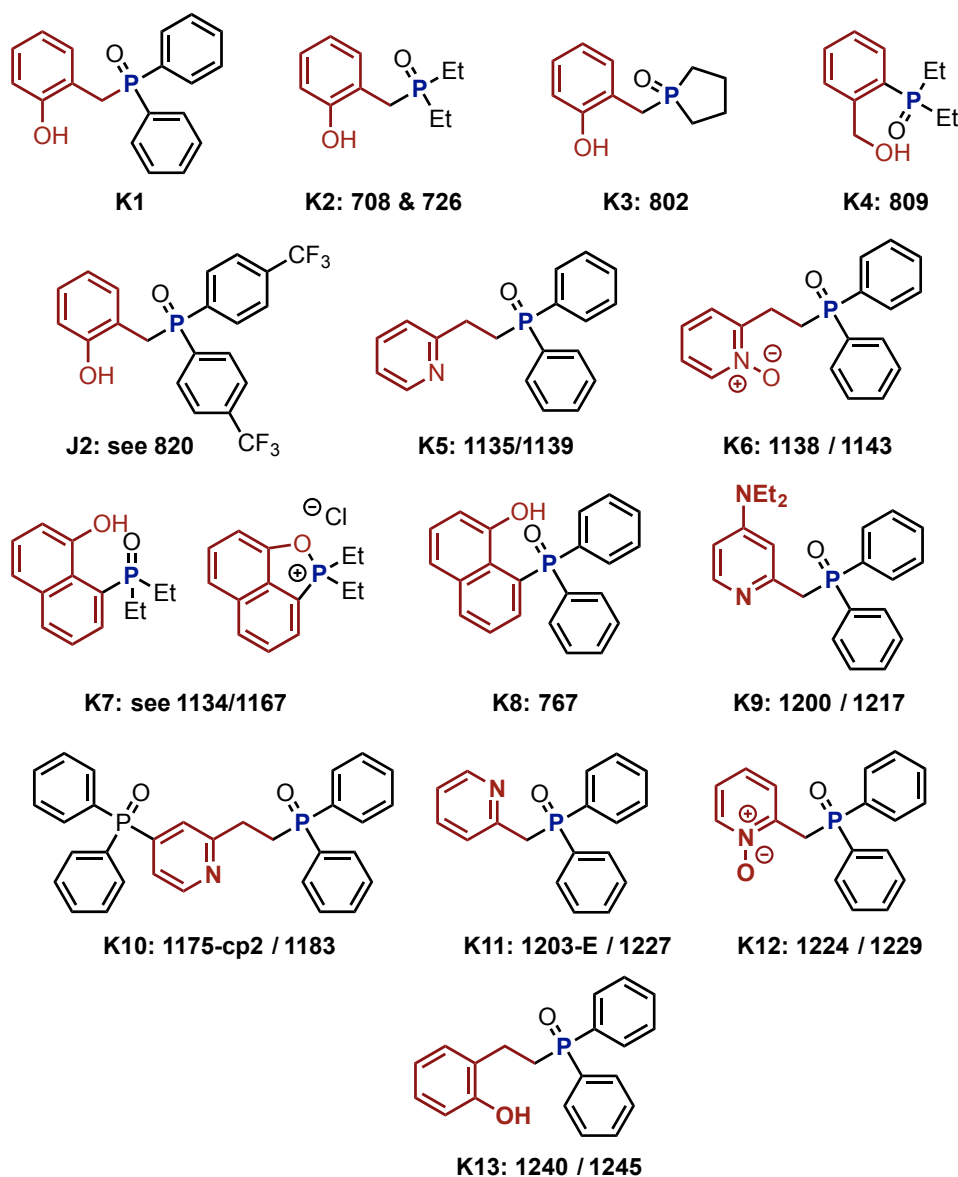
This reactivity was discovered late in the experimental process, and is under further investigation in the group (4-nitrobenzoic acid has since been shown to be viable in the presence of a catalyst). As it stands, the reaction represents the first *P*-catalytic Mitsunobu

reaction, and indeed the first catalytic method for the inversion of alkyl alcohols. Currently, the procedure is limited in scope in terms of sensitivity towards acids. Also, the scope of the acid is clearly pK_a limited. However, the process is to be viewed as a catalytic inversion of alcohols (certainly, the method would not be a sensible general etherification reaction), and so holds promise in this respect.

Catalyst Development

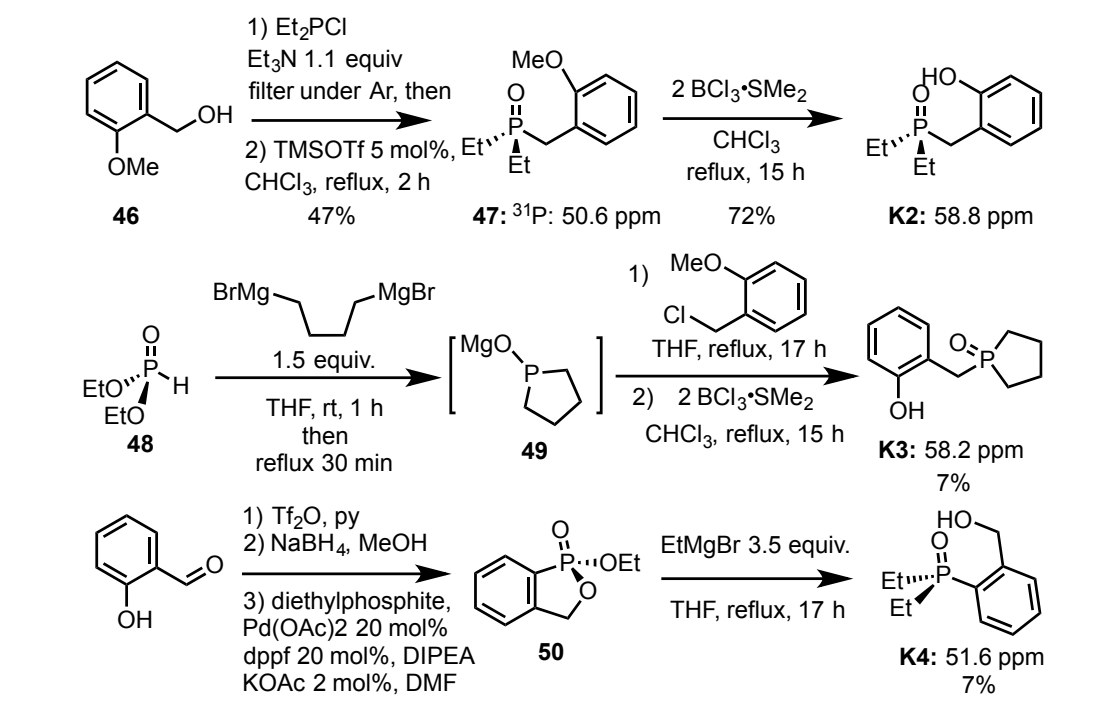
Alongside the studies into the reactivity of **K1**, analogues of **K1** were designed, synthesised, and tested in the tosylation of decanol over 5 or 15 h in toluene. As **K1** gave about 44% conversion of decanol over 5 h, this gave a suitable midpoint around which to rank different catalysts. For the less active species, 15 h allowed a better distinction. All of the following catalyst syntheses are unoptimised and, for efficiency of time, followed the hallowed Med-Chem doctrine of '*All you need is some.*' A summary of the catalysts is given in Figure 7.

Figure 7. A summary of the catalysts tested. (laboratory NB experiment numbers given)



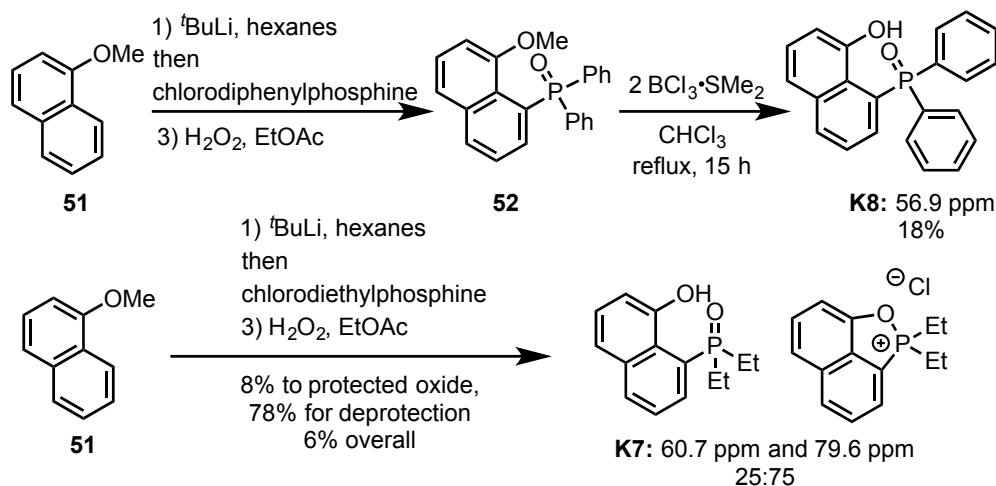
A summary of the synthesis routes is given in Schemes 39-43. **K2** was synthesised using the Lewis-acid catalysed Arbuzov rearrangement of a phosphinite⁶⁵ previously discussed, giving an overall yield of 34% (Scheme 38). **K3** was synthesised using an adapted double Grignard protocol (Scheme 38). The excess Grignard reacts initially to remove the proton at P. Then a double addition onto the Mg-phosphorus species is proposed, releasing two equivalents of MgOEt. The remaining *in situ* anion is then used as a nucleophile, reacting with the appropriate benzyl chloride. Following methoxy deprotection, the product **K3** was isolated

in 7% overall yield. Synthesis of **K4**, in which the linker is inverted, involved a speculative palladium-catalysed (Hirao)⁶⁸ cross coupling using salicylaldehyde-derived 2-(hydroxymethyl)phenyl triflate using a literature protocol.⁶⁹ The protocol wasn't reported to work with either triflate groups or free alcohols, but a low yield of cyclic intermediate **50** was recovered from the mixture. After forcing conditions with an excess of ethyl magnesium Grignard, the desired diethyl phosphine oxide was isolated in 7% overall yield.



Scheme 38. Synthesis of **K2**, **K3** and **K4**.

The synthesis of **K8** began with 1-methoxynaphthylene **51** (Scheme 39). Thermodynamic deprotonation at room temperature overnight with *tert*-butyllithium afforded the 8-lithiated naphthylene derivative, which performed nucleophilic attack on chlorodiphenylphosphine. After oxidation to oxide **52** and purification, deprotection with boron trichloride afforded the desired phosphine oxide in 18% overall yield after recrystallization from hot DMSO/MeCN. This oxide was largely insoluble in most solvents at room temperature, and only sparingly soluble in DMSO.



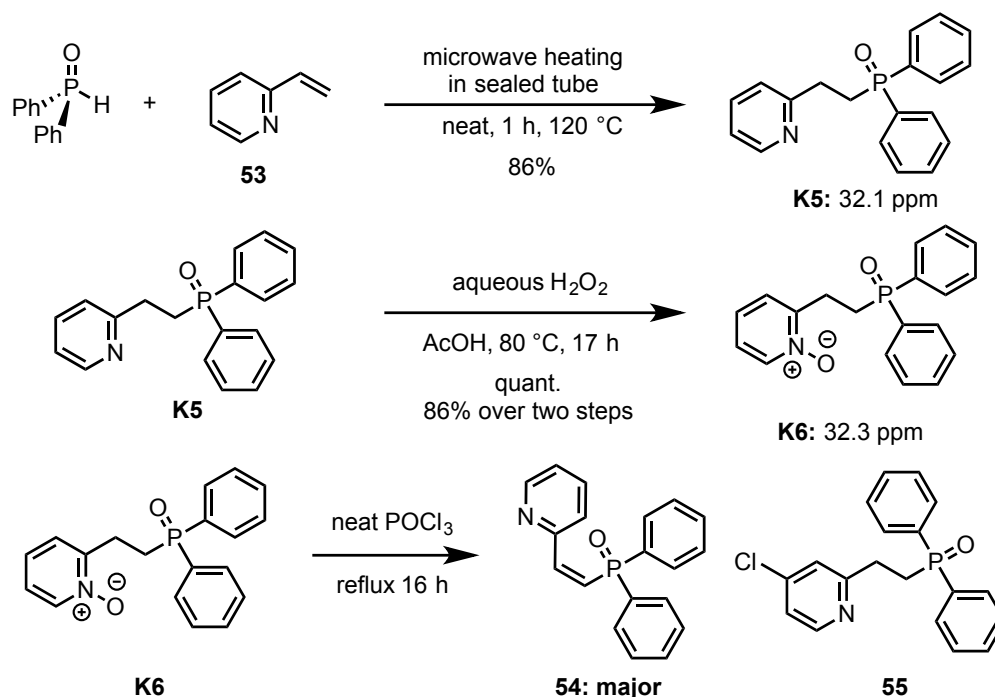
Scheme 39. Synthesis of K7 and K8

The diethyl analogue of **K8**, **K7**, was synthesised analogously. Surprisingly, upon deprotection of the methoxy-phenol group, the oxide was isolated directly after workup as a mixture of the oxide and its phosphonium salt (75:25 ratio). The counterion was speculated to be chloride from the boron trichloride, but is unconfirmed. Initially, chromatography was attempted but, unsurprisingly, the phosphonium salt was difficult to isolate in this manner. A mixture of the two species was isolated after work-up and used directly.

A group of pyridine-based catalysts was also synthesised (Scheme 40). **K5** and **K6** both have ethyl linkers, whereas **K11** and **K12** have benzyl linkers. In these species, the nucleophile to drive dehydration would be the pyridine, or the *N*-oxide. Pyridine **K5** was isolated cleanly after work-up following a microwave conjugate-addition reaction of the sensitive 2-vinyl pyridine with the P(III) tautomer of diphenylphosphine oxide. **K5** was converted to **K6** via pyridine oxidation to the *N*-oxide using peroxide in acetic acid.

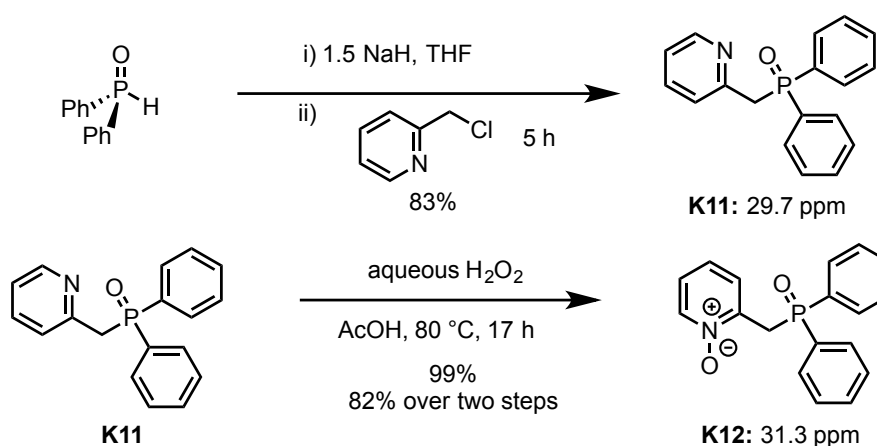
A sample of **K6** was refluxed in POCl_3 for 16 h, a reaction reported to yield some para-chloro pyridine if pyridine *N*-oxide is the substrate. The resulting chloropyridine would allow access to para-substituted analogues of **K6**. In the event, although a small amount of the desired chloropyridine **55** was generated, the majority was *cis*-alkene **54**, perhaps

formed via phosphorylation of the N-oxide followed by sequential proton abstractions from the ethyl chain to reduce the N-O bond.



Scheme 40. Synthesis of oxide catalysts K5, K6.

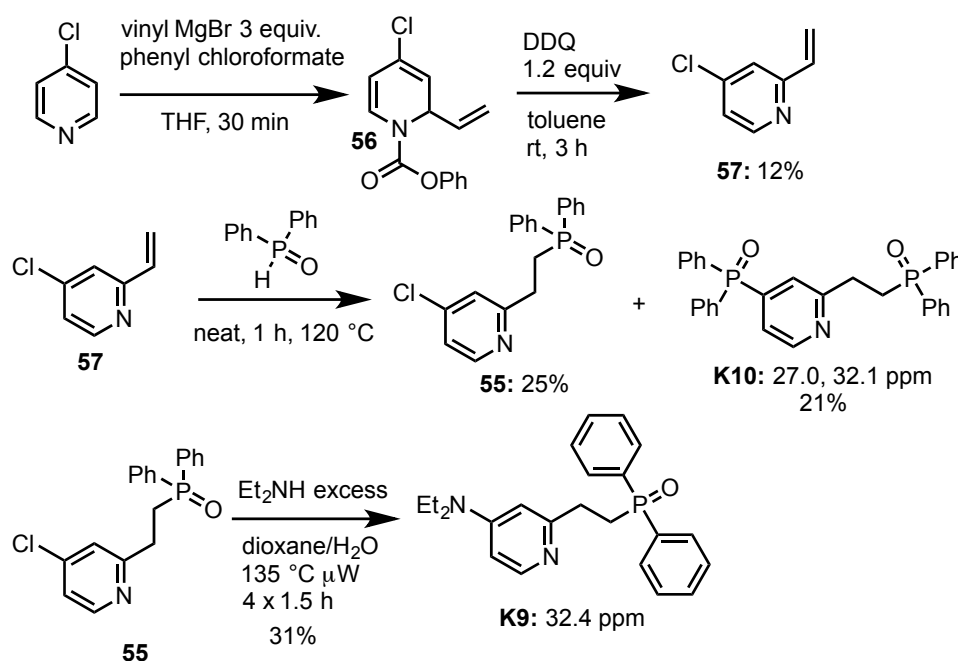
The **K6** oxide series with a benzyl linker was also synthesised. Deprotonation of diphenylphosphine oxide with sodium hydride and reaction with 2-(chloromethyl)pyridine gave **K11** directly. Oxidation of pyridine **K11** gave **K12** (Scheme 41).



Scheme 41. Synthesis of oxide catalysts K11 and K12.

Due to the low yield of chloropyridine **55** above, synthesis of DMAP analogue **K9** began again by synthesising chlorovinylpyridine **56** from 4-chloropyridine (Scheme 42). Vinyl

magnesium bromide adds relatively selectively to the 2-position when the pyridine is activated with phenyl chloroformate.⁷⁰ Oxidation of the resulting dihydropyridine **56** with DDQ (*p*-chloranil proved ineffective) afforded light and temperature sensitive vinyl pyridine **57** in 12% yield. This vinyl pyridine was subjected to the same microwave S_NAr conditions used in the synthesis of **K5**. Competing nucleophilic attack of the phosphine oxide led to diphosphorus containing species **K10** as well as the desired chloropyridine phosphine oxide **55**. Microwave heating under pressure in the presence of dioxane/water and diethylamine as a nucleophile gave diethylaminopyridine (DEAP) based catalyst **K9** in 1% overall yield.

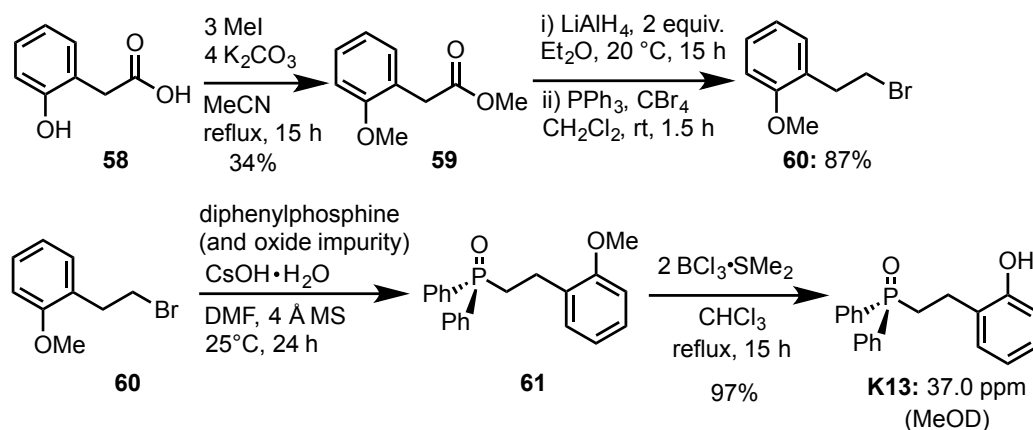


Scheme 42. Synthesis of oxide catalysts **K10** and **K9**

Finally, ethyl-linked **K1**-analogue **K13** was synthesised. First, 2-bromoethylphenol derivative **60** was generated from commercially available hydroxyphenyl acetic acid **58** by a sequence of bismethylation, reduction, and bromination (Scheme 43).

The initial dimethylation of **58** was marred by hydrolysis of the ester during an ill-judged work-up procedure, but reduction and bromination of the resultant alcohol proceeded as expected to give bromide **60**. Bromide **60** was then stirred with a mixture of

diphenylphosphine and its oxide impurity under basic conditions. It was supposed that the oxide in the contaminated phosphine would also react productively to give the desired oxide **61**. Oxidation was not required at the end of the reaction. Typical boron trichloride demethylation of the resulting mixture containing methoxyphenol phosphine oxide **61** gave **K13** in 1.5% overall yield.



Scheme 43. Synthesis of oxide catalyst K13

Catalyst Design Features

Following the early promising results of **K1**, further catalyst design considered the following opposing parameters, which will be referred to through the following discussion:

1. *Electron density at phosphorus:* More electron density means a weaker phosphoryl group and lower barrier to (protonation and) water loss, but also a decreased electrophilicity with respect to incoming nucleophiles.
2. *Nucleophilicity of the internal nucleophile:* A better nucleophile means a faster dehydration but also a more stabilised cyclic phosphonium salt (or phosphorane).
3. *The identity of the nucleophile,* and number of associated protons/basicity etc.
4. *The ring size of the putative cyclic phosphonium salt intermediate:* a smaller ring means faster kinetics of closing, but a potentially more stable intermediate.

5. *The sterics around phosphorus:* ring strain might drive geometry preference and therefore various exchange rates.

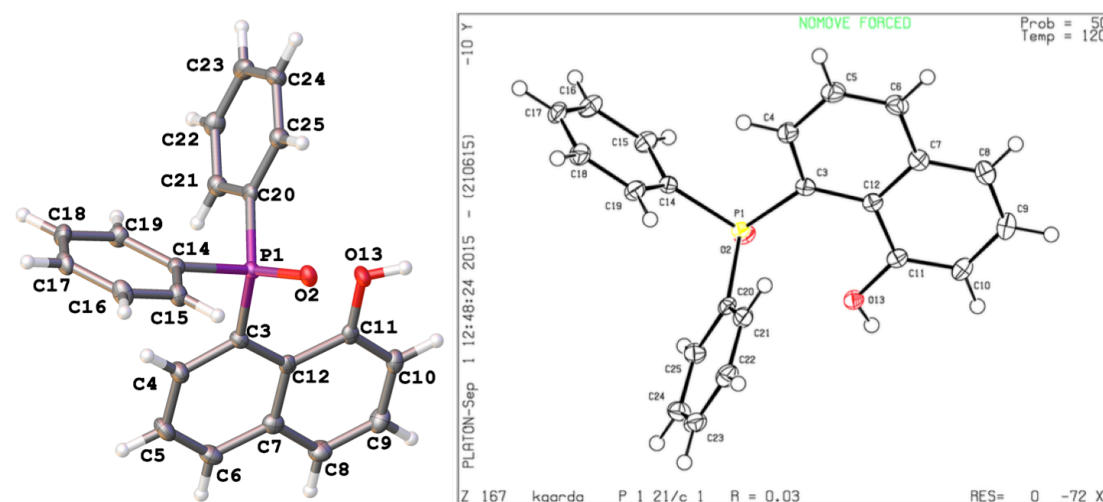
A summary of the results of testing the catalysts described above is summarised in Figure 9, below (*copy also provided at back of Thesis*). The results will be described in the order they were tested (not necessarily numerically sensible!) First, we designed **K2** as a more electron rich phosphine oxide. This would allow us to investigate Design Point 1. Subjected to the tosylation reaction over 15 h, **K2** demonstrated a 50% acceleration over the background reaction, but was far inferior to **K1** (~4x rate). This suggested electron rich phosphorus centres were slower to dehydrate, and that electron poor species might be beneficial.

Next, cyclic structure **K3** was tested. It was supposed that such a species might dehydrate more easily due to a destabilised phosphine oxide. Indeed, its shift of 77.6 ppm indicated a weak phosphoryl bond with low double bond character (shift is more like a phosphonium salt). After 15 h in the tosylation reaction, **K3** showed a similar enhancement over the background as **K2**. However, ^{31}P -NMR analysis showed two new species with shifts of 119 and 102 ppm. These may be the ring-closed phosphonium tosylate, and possibly the decyloxyphosphonium tosylate (or protonated oxide). This hints at a fast dehydration, but a reasonably stabilised internal phosphonium species. Additionally, it would seem that the Arbuzov collapse is slow (conversion is not high), hinting at low double bond character in the alkoxyphosphonium tosylate species, as seen for the oxide. This might be less of a problem with less acidic acids (which would be better nucleophiles). These two results exemplify the different forms of electronic donation at phosphorus; alkyl groups increase the electron density at phosphorus, but in certain geometries (e.g. 5-ring in **K3**), a reduction in secondary orbital contributions from donor ligands (e.g. alkoxy), leads to an electron deficiency.

K4 is an electron rich phosphine oxide with an inverted linker (benzyl alcohol nucleophile instead of phenol). It showed no enhancement over the background tosylation, and inspection of the ^{31}P -NMR spectrum at the end of the reaction showed that the catalyst was present as its dehydrated internal phosphonium form with a shift of 119 ppm. Benzyl alcohol is almost as good a donor as decanol, and certainly better than phenol. With the chelate effect to boost it, it is unsurprising that the species is relatively stable with respect to external nucleophile exchange.

Naphthol-based **K8** is an interesting structure; it has three aryl groups, but a high phosphorus shift of 57 ppm. In addition to any geometrically forced hydrogen bonding from the hydroxyl group, the phosphorus atom is connected to a relatively electron rich biaryl group (although not in conjugation with the OH). A crystal structure was obtained (Figure 8), confirming the connectivity of the naphthyl group. In addition, the structure showed that the hydroxyl group participated in intermolecular hydrogen bonding rather than internal bonding to the oxide, which may explain the low solubility of **K8**.

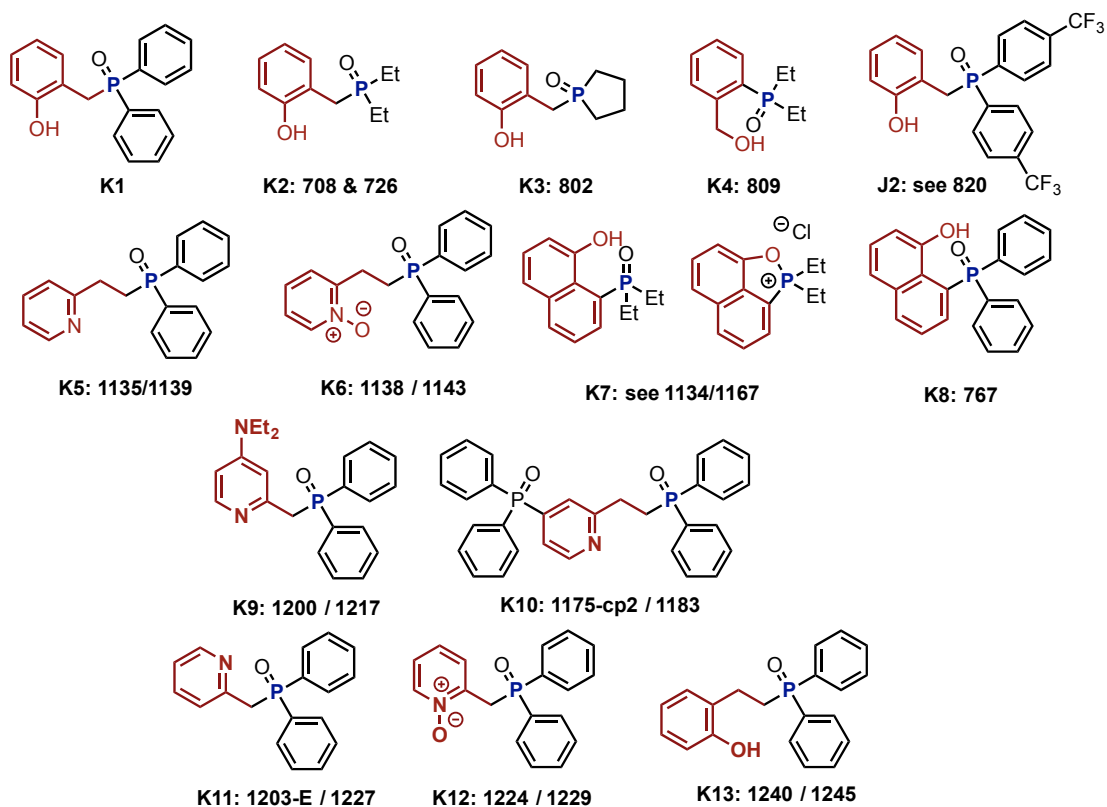
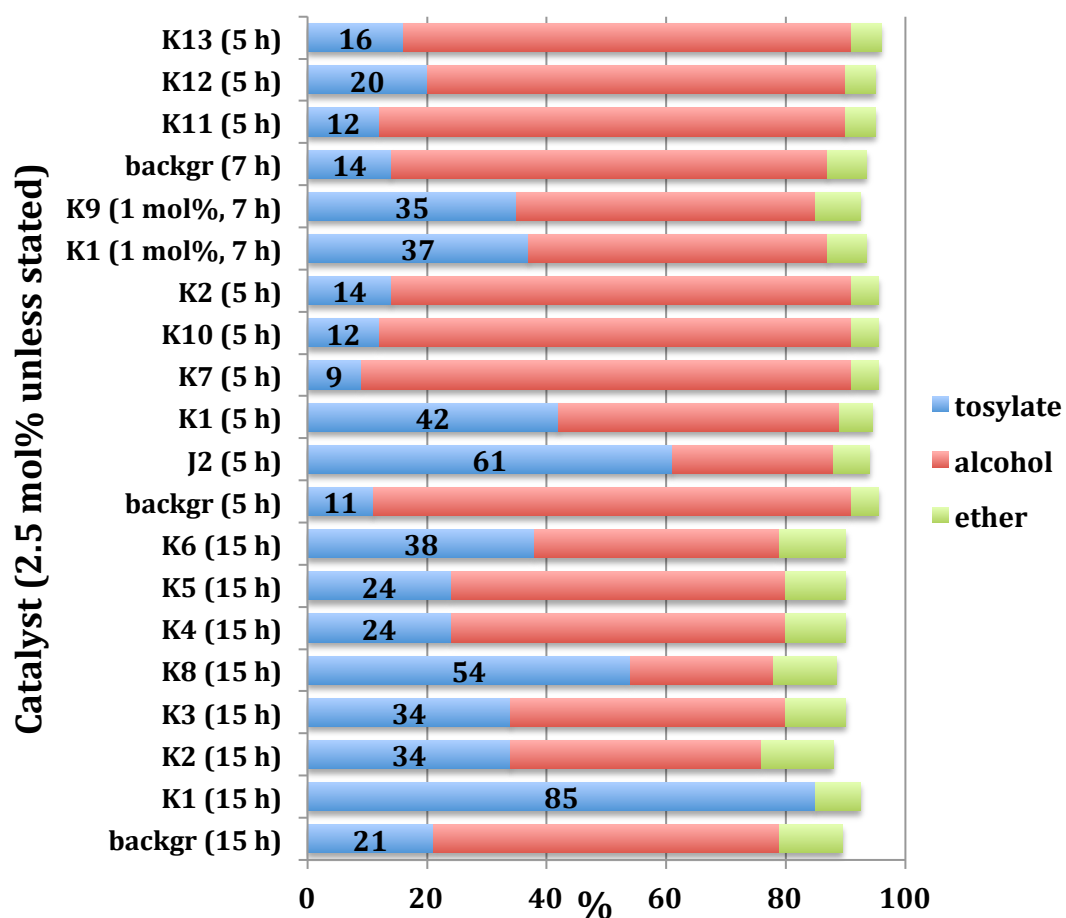
Figure 8. Crystal structure of **K8**, obtained by Will Lewis.



In the tosylation experiment, **K8** performed well (~2.6x acceleration over the background tosylation), but still significantly lower than **K1**. It is uncertain how much the poor solubility may have contributed to this result, but the catalyst appeared to be soluble in the refluxing Dean-Stark conditions. A dramatic difference was seen for **K7**, the diethyl analogue of **K8**. **K7** underwent partial autodehydration during the BCl_3 -promoted deprotection of the methoxy precursor. Simple molecular modelling suggests that for the less hindering ethyl groups, the naphthyl group can access a favourable position for direct attack of the phosphine oxide more readily than in the diphenyl analogue. **K7** did show catalysis, and at the end of reaction was sitting entirely as the phosphonium salt, ^{31}P δ 83 ppm. This ended the first stage of catalyst development. It was concluded that a better catalyst:

- would be electron poor from induction by the two ancillary aryl groups
- would have an internal nucleophile ideally slightly more nucleophilic than phenol, but less nucleophilic than benzyl alcohol.
- may have a distorted geometry, but probably not the *P*-cyclopentyl group. Geometry more likely to be favourably utilised by reducing nucleophile degrees of freedom.

In collaboration with Jan Saska in the group, these design specifications were applied to a small range of further catalysts. Impressively, electron poor phosphine oxide **J2** showed an approximate 50% rate enhancement over **K1**, clearly demonstrating the success of our rationally implemented SAR strategy, and indicating that further improvements should be readily achieved.

Figure 9. Results for the tosylation of decanol with various catalyst oxides (*copy also provided at back of Thesis*).

In the meantime, it was decided to explore some further chemical space. Phosphine oxide **K5** has a pyridine group positioned such that it might form a 5-ring interaction at the phosphorus centre. Although this species has no proton to assist water removal, and is a poorer donor to phosphorus than alkoxide, it has the opportunity to artificially enhance the local acid concentration as the most basic species in the reaction mixture. Additionally, it should not form stable internal cyclic phosphonium species. A 15 h tosylation reaction with **K5** demonstrated no activity, however. Its *N*-oxide, **K6**, on the other hand, which is able to form a 6-ring cyclic species, showed a rate enhancement of ~1.6x over the background. At the end of the reaction, the oxide was present in 90% along with 10% of an unknown species with shift 71 ppm.

Pyridine *N*-oxides are used as Lewis basic nucleophiles in catalysis and some DMAP *N*-oxide analogues are up to 50 times more active than DMAP species in sulfonyl transfer reactions.⁷¹ Importantly, they are far less basic than pyridines, which may result in a reduced competition with the oxide for acid, which needs to activate the phosphoryl bond for dehydration.

The analogues of **K5** and **K6** with a single carbon spacer between pyridine and phosphine oxide were also prepared. Pyridine **K11** showed no catalysis (possibly slight negative effect), whilst pyridine *N*-oxide **K12** showed a possible catalytic enhancement ($x \sim 1.4$). Because of the low differentials relative to the background, these data would benefit from longer experiment times for quantification (see **K2** data over 15 h and 5 h relative to backgrounds). However, the catalysts are clearly less reactive than **K1**.

To boost the nucleophilicity of the pyridine, the DMAP-type analogue was synthesised (**K9**). This had a single carbon spacer, two phenyl groups at phosphorus, and used ethyl groups instead of methyl on the amino group (DEAP rather than DMAP – this was because

diethylamine was easier to incorporate in the microwave than dimethylamine.) **K9** showed remarkable activity in the tosylation test, almost equalling **K1** over 7 h at only 1% loading (x2.5 acceleration over background). Currently, there is no evidence that the catalysis is *P*-catalysed (rather than DEAP catalysed), and so it would be worth running a *P*-free background reaction with 1% DMAP/DEAP present.

During the synthesis of **K9**, a dimerization-type reaction occurred when another molecule of diphenylphosphine oxide participated in a nucleophilic substitution reaction of the chloropyridine. The resulting phosphine oxide was designated as **K10** and duly put through its paces. Over 5 h, **K10** showed significantly lower activity than **K9**, with any rate enhancement indistinguishable from the realms of experimental error. The final catalyst to be tested was **K13**, the ethyl-linker analogue of **K1**. The activity of 5 and 6-ring species had been similar for the *N*-oxides catalysts **K12** (5 ring, ~ x1.8 accel.) and **K6** (6 ring, ~x1.8 accel.). When **K13** was subjected to the tosylation reaction over 5 h, a modest acceleration of ~ x1.5 was observed, just about high enough to be accepted against experimental error, but much lower than the 5-ringed **K1**. This is another catalyst whose activity could be better ranked with a longer reaction time.

Catalyst activity: Discussion and Future Improvements

A summary of the catalytic tosylate formation results is given in Table 7.

Table 7. Summary of yield enhancements for the tosylation of decanol when various phosphine oxide catalysts were present relative to the background.

cat ID	ring size	internal nucleo.	time	mol%	Yield enhancement %/mol/h
K1	5	PhOH	5	2.5	2.5
K1	5	PhOH	7	1	3.3
K1	5	PhOH	15	2.5	1.7
K2	5	PhOH	5	2.5	0.2
K2	5	PhOH	15	2.5	0.3
K3	5	PhOH	15	2.5	0.3
K4	5	BnOH	15	2.5	0.1
K5	5	Py	15	2.5	0.1
K6	6	Py-O	15	2.5	0.5
K7	5	NpOH	5	2.5	-0.2
K8	5	NpOH	15	2.5	0.9
K9	5	Py	7	1	3.0
K10	5	Py	5	2.5	0.1
K11	4	Py	5	2.5	0.1
K12	5	Py-O	5	2.5	0.7
K13	6	PhOH	5	2.5	0.4

*The **yield enhancement %/mol/h** is the % product formed above the relevant background tosylate formation per mol% catalyst per hour. Red values are within experimental error and thus are not clearly enhancing or hindering. Highlighted rows show the most significant activity. The variation in activity of **K1** over different times highlights both possible experimental error and also the fact that different relative background/catalysis rates occur at different phases of the reaction, as discussed in the simulation section. (initial phase slow due to water, final phase slow due to low concentration of decanol/acid).*

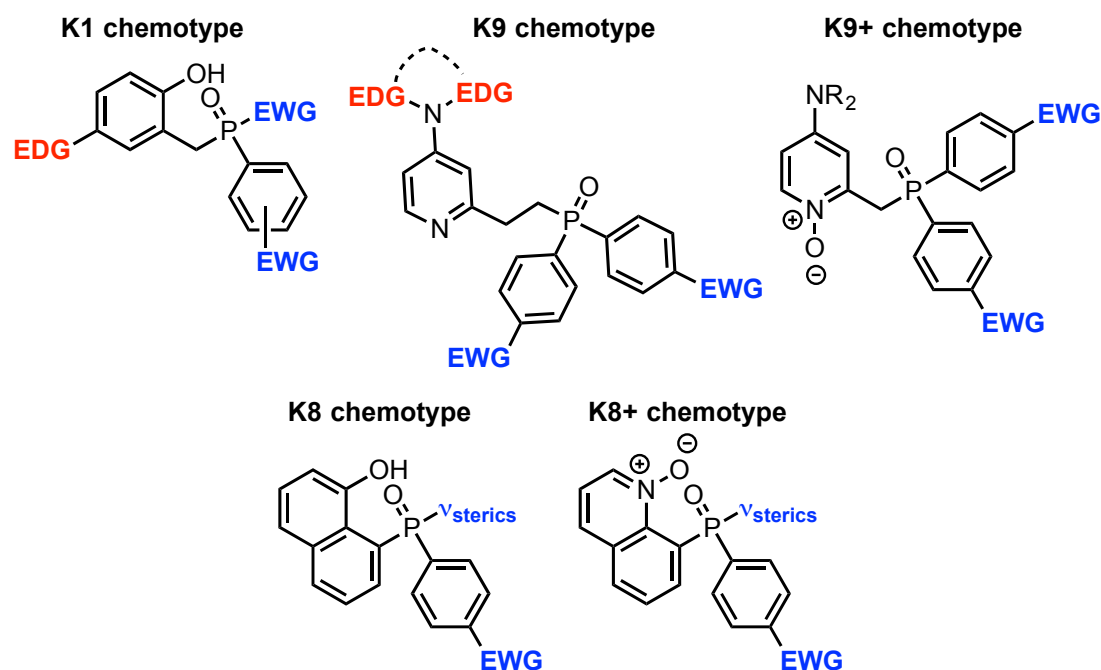
The final column is normalised for time and catalyst loading. It therefore shows the % product above the relevant background tosylate formation per mol% catalyst per hour of

reaction. All reactions were run at the same concentration. A value of 0 is equal to the background. A positive value indicates a yield enhancement over the background. The grey shaded entries indicate an entry with reasonable activity. The red entries are too close to experimental error to be definitively assigned as active/inactive, but have a low activity either way.

The only catalyst that showed a higher activity than **K1** in the tosylation reaction was **J2**, which has the **K1** chemotype and additional electron withdrawing groups on the ancillary ligands. Of the catalysts tested, a surprising number are active – a remarkable 8 out of 13 showing some activity. Of the 5 that showed no activity, two successfully dehydrated and became stuck at the phosphorane (**K4**, **K7**). Of the different chemotypes; phenols, naphthols, pyridines and pyridine *N*-oxides all showed activity and inactivity, highlighting the complex relationship between the differing catalyst components. Of the catalysts tested, the 5-membered rings performed better than analogous 6-ring species: so **K12** was at least as good as **K6**, and **K1** significantly outperformed **K13**.

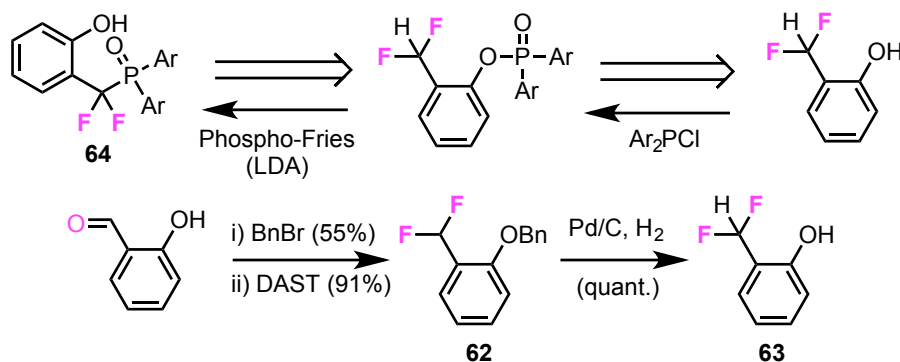
The most promising nucleophilic chemotypes and their expansion potential are shown in Figure 10.

Figure 10. Some possible future catalyst directions.



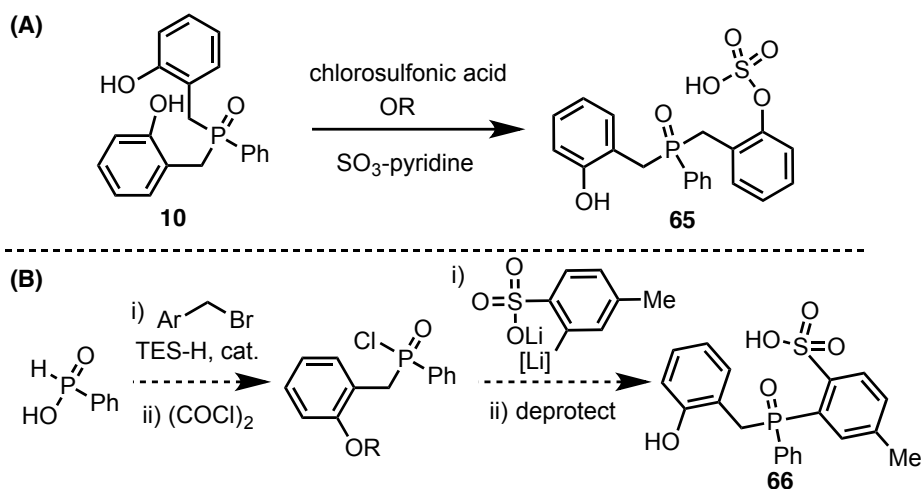
An additional chemotype is included, labelled **K9+**. This chemotype would be significantly easier to synthesise (from the commercially available 4-chloropyridine-2-carboxylic acid or picoline⁷²) than **K9**, and switches the pyridine for an *N*-oxide, which has been shown to be more nucleophilic than the pyridine alone.⁷³ Combined into a DMAP-type structure with a 5-ring motif, this could be a powerful catalyst. Likewise, the promising naphthol moiety of **K8** could be exchanged for an *N*-oxide (**K8+**), which would perhaps decrease the stability of the phosphonium salt (as seen with **K7**) whilst retaining the geometric benefits.

A different approach to phosphine oxide activation might be to include an electron-withdrawing group on the benzyl CH₂ position of **K1**. An attempt at synthesising the precursor fragment **63** was successful, but attempts at incorporation into a catalyst (**64**) have yet to be completed. The rough outline is as follows in Scheme 46. The fluorination and deprotection steps proceeded smoothly; (in this case, the trivial benzyl protection was marred by the poor quality of the benzyl bromide.)



Scheme 44. Synthesis of difluoro-benzyl chemotype 64. Precursor phenol 63 synthesised successfully as shown.

With the key phenol **63** so readily prepared, the phospho-Fries should be tried to compare the activity of this interesting **K1** analogue. It might be expected that the deprotonation step in the phospho-Fries reaction should occur more easily than the typical benzyl analogue, which gave ~19% in an unoptimised **K1** synthesis from *o*-cresol (*vide supra*, Scheme 31). This difluoro compound would represent a novel class of reagents that might display interesting reactivity. It is uncertain what their stability would be. It is also uncertain how the ability of electron poor catalysts to dehydrate will change with lower acidity acids. It seems likely that the rate acceleration of **J2** is due to a faster dehydration due to a faster reaction at the electron deficient phosphorus by the internal nucleophile. However, such phosphine oxides have a lower Lewis basicity, which may in turn lead to a *rate decrease* when lower acidity acids are used to activate them. Higher temperatures and weaker acids may therefore require electron rich phosphine oxides. A final approach in which internal activation was examined was to include sulfuric acid into the catalyst itself (Scheme 45).

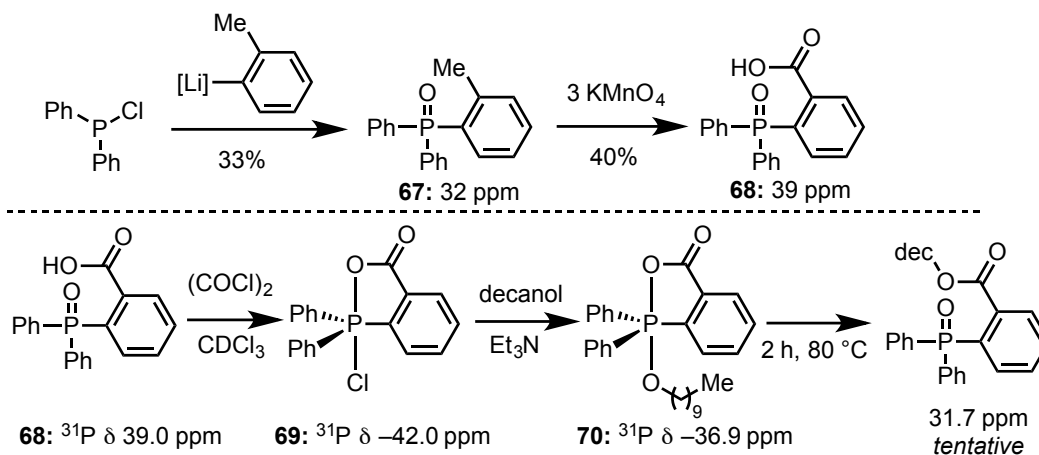


Scheme 45. (A) Attempted synthesis of sulfonic acid-containing catalyst **65**; B) Possible route to a different sulfonic acid analogue.

Brief attempts towards this goal involved mono-sulfonation of the legacy catalyst oxide **10**. This approach appeared to give some product, but isolation from the pyridine reaction medium proved difficult. A related species, **66**, might be a better target. Its synthesis might involve addition of the dianion of tosic acid formed by directed lithiation to a chlorophosphine.⁷⁴ This approach might be better if the free phenol is allowed to ring close on the phosphoryl chloride species; this phenoxy leaving group should still make the *P*-centre an electrophile in the next step, and would remove the need for a deprotection in the presence of a free sulfonic acid later on. Other existing related species suggest feasibility too.⁷⁵ The logic behind this design is clear; the local presence of the acid might promote facile dehydration. Indeed, the species may exist as the phosphorane or phosphonium salt in the same way the Kielbasinski oxide **7** did in the presence of acid.

The carboxylic acid containing species **68** was also investigated briefly (Scheme 46A). This species was synthesised by complete benzyl oxidation of *o*-tolyl containing phosphine oxide **67**. This species formed a chlorophosphorane in solution in the presence of oxalyl chloride (Scheme 46B). After the addition of decanol, a phosphonium salt was observed (48.6 ppm, not shown), which converted to a phosphorane on the addition of base (to prevent an

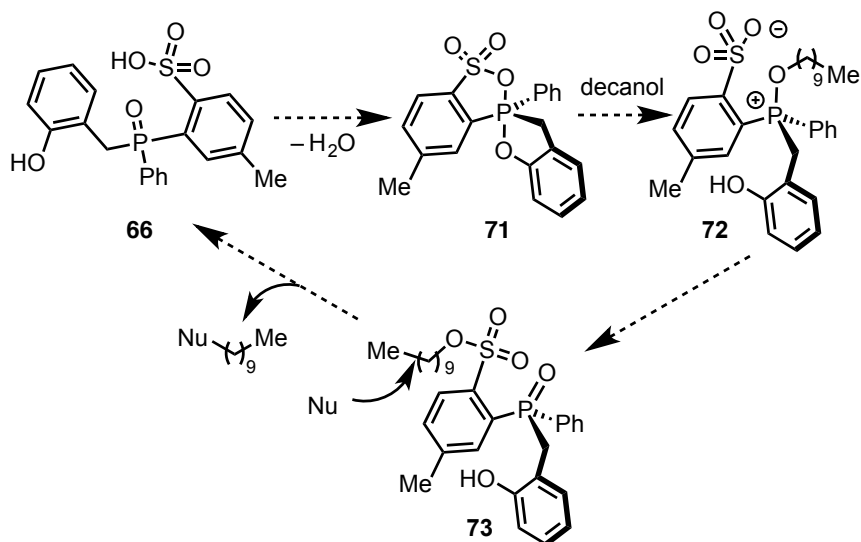
Appel). This species suffered from probable esterification after heating. No attempt to dehydrate this catalyst thermally (i.e. Dean-Stark conditions) was made, but it may be interesting to see whether more acidic acids can exchange with the local benzoate ion to give a productive phosphonium salt and outcompete catalyst deactivation.



Scheme 46. (A) synthesis of phosphine oxide **68**. b) reaction of phosphine oxide **68** with oxalyl chloride and decanol led to an esterified catalyst.

This observation of internal esterification suggests that a sulfonic acid derivative (e.g. **66**) might self-alkylate. However, unlike the esterified analogue of **68**, the sulfonic acid may act as an electrophile in the right circumstances, thus allowing autodehydration and alcohol activation in a single system (Scheme 47).

However, there is always the danger with a double 5-ringed phosphorane (e.g. **71**) that kinetic stability will hinder exchange with external alcohols. In this case, however, neither phenol or sulfonate group are great donors, and the sulfonate is a sufficiently stable counterion.



Scheme 47. Plausible sulfonic acid/*P*-catalyst manifold in which the sulfonic acid group acts as an acid to dehydrate the phosphine oxide, a counterion/nucleophile in a phosphonium salt, and then an alcohol activating group.

Clearly, there is still much chemical space to be explored here, and given the hit rate amongst the catalysts already designed, and the success of **K1**, broad and uninhibited exploration of a range of catalysts probably offers the most efficient route forward. Many of these catalysts may perform completely differently under different temperatures and with less acidic acids, so may be worth revisiting in the context of secondary alcohol inversion experiments.

K1: Other Reactivity Manifolds

This section ties off the loose ends from the above discussions. Each heading represents a goal that was attempted. The bullet points report the attempted reactions. The reactions are grouped into themed attempts.

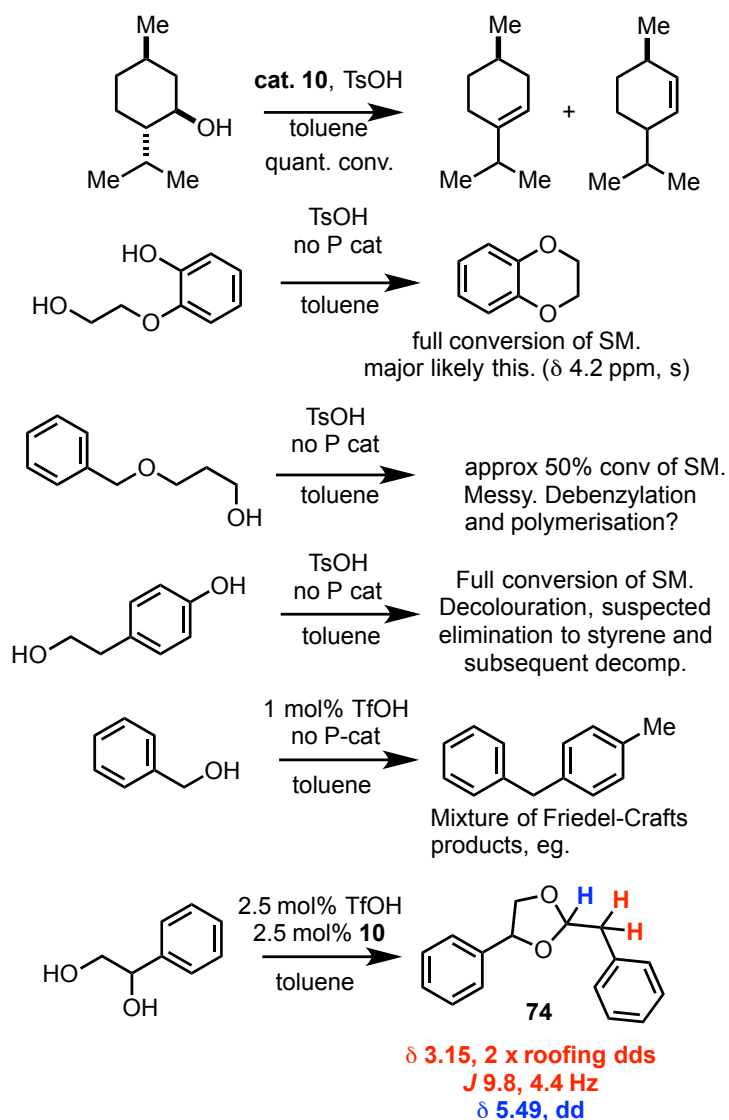
- 1) **Goal:** *homoetherification via the tosylate to give a catalytic etherification with substoichiometric tosic acid and K1, using decanol. Catalyst is not present unless stated.*

- Electrophile decyl nosylate **did not** undergo etherification when heated under toluene/Dean-Stark conditions in the presence of decanol and 1 equivalent of triphenylphosphine oxide as a Lewis base over 30 min.
 - The addition of 10 mol% DMAP **did not** change this outcome.
 - The addition of 10 mol% tetrabutyl ammonium iodide **did** lead to iodide, but this species was also slow to undergo alkylation.
 - **K1** (2.5 mol%), TsOH.H₂O (10 mol%), TBAI (10 mol%) reacted with decanol under toluene/Dean-Stark conditions over 15 h to give ~9% (~quant.) iodide and only 2% didecyl ether. It is assumed that the Bu₄N⁺ OTs salt formed means the reaction stops due to a lack of acidity to turnover the catalyst.
 - Decyl nosylate and phenol **did** undergo a mixed ether (5%) formation under toluene/Dean-Stark conditions over 2 h in the presence of 50 mg amberlyst(OH), whereas the background reaction (no amberlyst) gave no ether.
 - However, the reaction gave **no** additional ether over 15 h, suggesting the acidic by-product disrupts the solid-supported basic-catalyst.
 - Using MgO as base gave no ether in the same reaction.
 - In a reaction with **K1** (5 mol%), amberlyst(OH) (100 mg), TsOH.H₂O (20 mol%), and phenol, decanol underwent tosylation (to 17%, 85% of the max) under toluene/Dean-Stark conditions but failed to give any phenolic ether over 15 h. The use of both a base and an acid is clearly a difficult balance to strike.
- 2) **Goal:** *K1 catalysed iodination of decanol via the tosylate using a stiochiometric iodide source and catalytic tosic acid.*

- See result above indicating acid depletion problem: the reaction is formally the addition of HI to HO-R to give water and I-R, and therefore needs stoichiometric acid.
- Background iodination (no P-cat) under toluene/Dean-Stark conditions, 15 h: decanol, TBAI (1 equiv), 10% TsOH, amberlyst 15 (~1 equiv). The theory here was to use amberlyst as the acid source. Gave a high (29%) amount of iodide.
- Same as above, but with 2.5 mol% **K1**. Also gave 29% iodide, suggesting acid limiting, and a competent background reaction.
- Stoichiometric TsOH, TBAI and decanol were heated under toluene/Dean-Stark conditions for 16 h (no P-cat). Background iodide formation was 62% (incredibly high, indicating the *in situ* formation of HI that possibly forms the iodide independent of the tosylate.)
- Concluded that the background rate is too high to see significant rate acceleration in this regime. Could try over a shorter time, but further catalyst development probably required for lower acidity acid and with lower temperature to reduce background.

3) **Goal:** *use other secondary alcohols in the tosylation reaction with **K1**.*

- Unsuccessful background reactions – *did not* try **K1** unless stated (Scheme 48). Unlikely that **K1** would decrease apparent acidity because is at a low loading relative to acid, unlike in the triflic acid experiments.



Scheme 48. Other attempted substrates with competing background reactions.

Reaction of 2-phenyl-ethandiol with catalytic TfOH and catalyst oxide **10** did not lead to epoxide, but rather to many species. A major product (**74**) was the result of an acidic-catalysed 1,3-hydride shift to the aldehyde and subsequent acetal formation. The aldehyde was also visible. The hydride shift is known.⁷⁶

5. Goal: THF formation from butanediol.

- Overall conclusion: background is much too fast due to intramolecular trapping of partial cations.
- Neat reactions (run in butanediol) do not show catalysis.

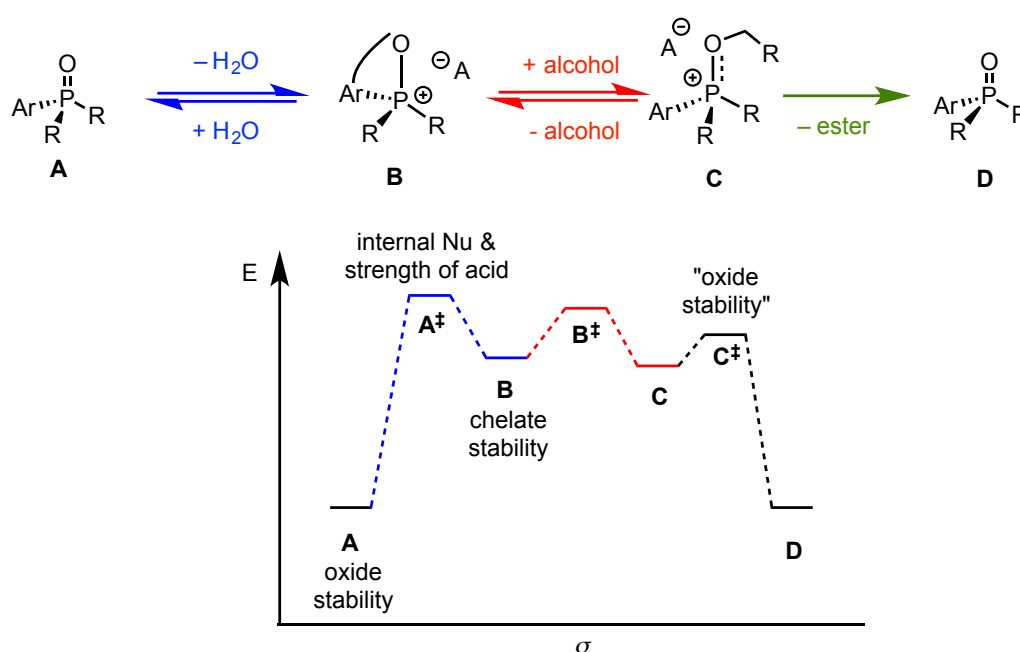
- Cooling the reaction leads to incomplete water removal, which will shut down catalysis.

Whilst there is a wide scope of reactivity waiting to be discovered, more useful breakthroughs will come with more active catalysts that allow weaker acids to be tolerated.

Final Thoughts

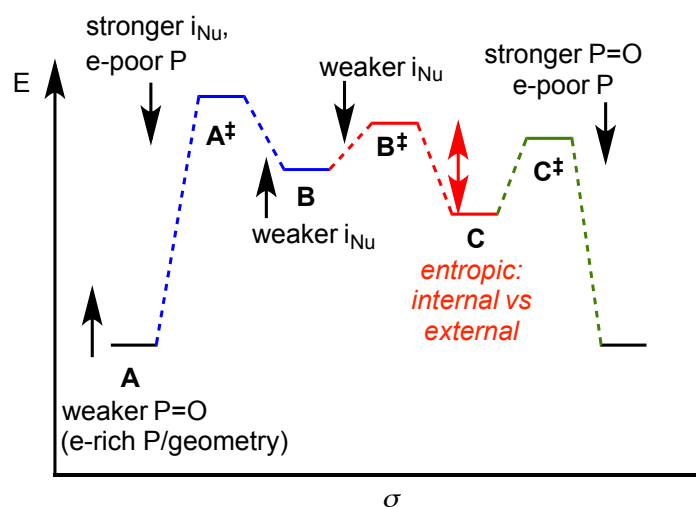
It was stated that the discussion of the different catalysts tried might not be applicable in the present of weaker acids and higher temperatures. This is because the acid and temperature are directly responsible for the various kinetic barriers in the catalytic cycle. In Figure 3 (*vide supra*), a rough energy coordinate diagram was presented to discuss the different energetic barriers in the cycle. It is worth reanalysing these kinetics in light of the new (non-phosphorane) cycle. Figure 11 shows a qualitative energy diagram with some approximate energy levels sketched in. Catalysis is made up of three operations; dehydration ($A^\ddagger$), alcohol exchange ($B^\ddagger$), and Arbuzov collapse ($C^\ddagger$).

Figure 11. The kinetics of the catalytic cycle



To improve catalysis, the largest barrier must be decreased by destabilising intermediates and stabilising transition states. The depth of **A** in the diagram is primarily dictated by the strength of the phosphoryl bond. To destabilise **A** (and so decrease $\mathbf{A}^\ddagger$), a weaker phosphoryl bond is required, which can be tuned electronically and geometrically. However, a weaker phosphoryl bond will raise the energy of $\mathbf{C}^\ddagger$, by lessening the double bond character of the incipient P=O. Weaker acids would raise $\mathbf{A}^\ddagger$ but lower $\mathbf{C}^\ddagger$. An electron poor phosphorus centre would strengthen the phosphoryl bond but increase the electrophilicity with respect to attack by the internal nucleophile i_{Nu} (conflicting contributors to the height of $\mathbf{A}^\ddagger$). The success of **J2** seems to suggest that these effects *are not balanced*. A summary of barrier heights and effects is shown in Figure 12.

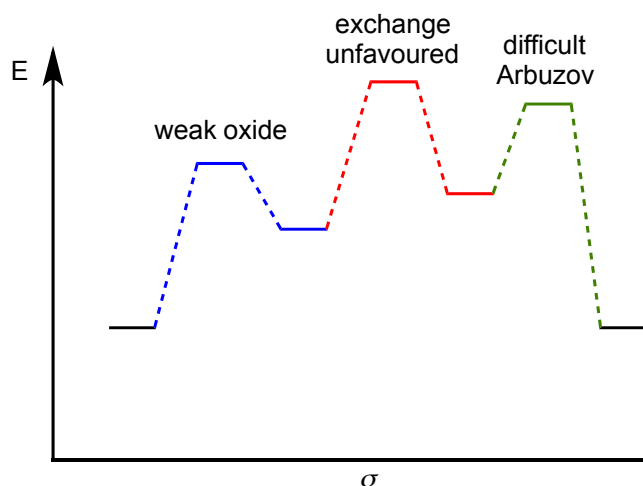
Figure 12. Factors affecting the different kinetic barriers in the catalytic cycle



Unlike the phosphorane catalyst **10**, the energy of dehydrated species **B** for **K1** is much higher, having lost its kinetic (bis-chelate) stability. However, the stronger the internal nucleophile i_{Nu} , the more stable **B** with respect to exchange. On the other hand, a stronger internal nucleophile will lower $\mathbf{A}^\ddagger$, the barrier to dehydration. In turn, the stability of **B** will impinge on the ease of substitution; a stronger i_{Nu} will decrease the rate of exchange for a free alcohol. The exchange of the internal nucleophile for an external alcohol is dictated by

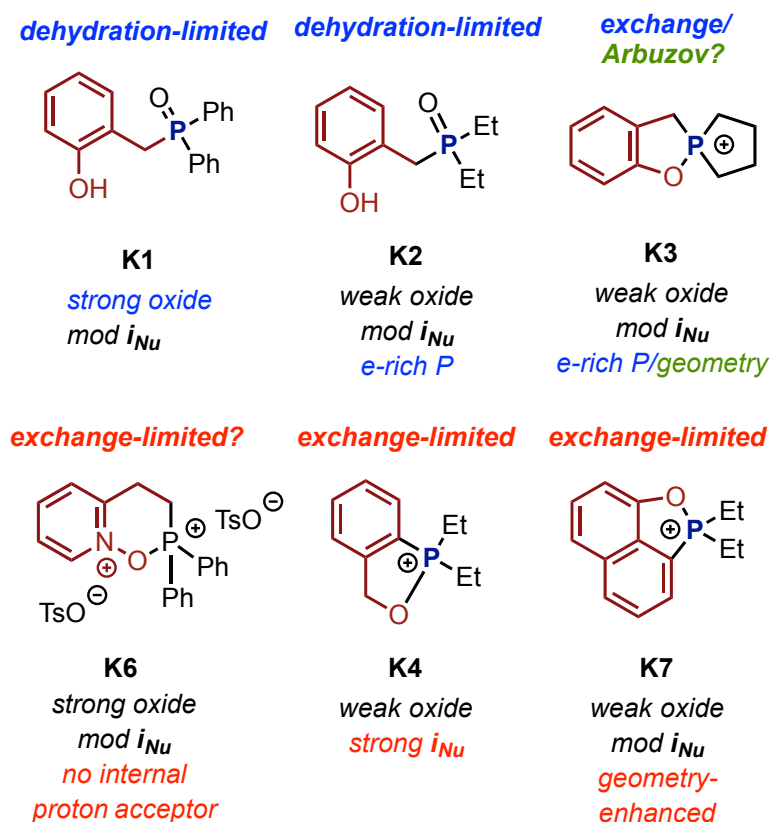
$B^\ddagger$. This exchange becomes important when the dehydration and Arbuzov collapse steps are fast. Whilst weakening the oxide may increase dehydration, if it simply passes the differential to another energetic barrier, the reaction will not necessarily increase in rate as expected (Figure 13).

Figure 13. The catalytic cycle may be kinetically limited by any of the three barriers.

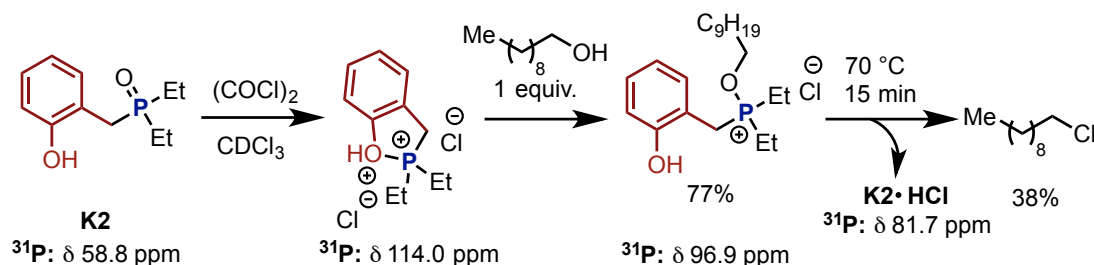


Interestingly, it is the dehydration-limited catalysts that perform best. This may be because the step is made irreversible by the removal of water from the reaction mixture. It is uncertain how higher temperatures, will affect the barriers (water removal easier? Bimolecular reactions more favourable?). Nonetheless, there are examples in this study of catalysts that appear to be limited by different barriers (Figure 14). It may be that a computational study would provide some clues as to which element of the catalytic cycle to focus on.

Figure 14. Examples of catalysts that appear to be limited by different barriers in the cycle – the forms shown are species seen at the end of the reaction (tosylation of decanol), supporting the limiting factor in the cycle



Experimentally, the rates of Arbuzov collapse could be investigated for each catalyst by generating in isolation the alkoxyphosphonium chloride from the catalyst and oxalyl chloride and the alcohol and measuring the different rates of collapse to the alkyl chloride. For instance, **K2** reacted as shown in Scheme 49. Note that proton NMR indicates the presence of a proton (δ 8.0 ppm) on the cyclic species with shift ^{31}P δ 114.0 ppm.



Scheme 49. Arbuzov collapse of **K2** to chlorodecane measured against time: could be used as a method to interrogate the rate of this part of the catalytic cycle.

If this technique was perfected, the relative rates of Arbuzov could be studied in isolation for the different catalyst contenders, although the rates relative rates may be different when chloride is not a ligand. Additionally, the second equivalent of HCl may distort the reaction away from ideal conditions.

Summary

The work presented in this Chapter concerns the development of an additive-free, phosphine oxide-catalysed Mitsunobu reaction that would generate only water waste. The design approach involves an internal nucleophile capable of dehydrating a phosphine oxide core, thus activating it as a phosphonium salt towards Mitsunobu chemistry. This approach has now been realised.

Phosphine oxide **K1** was developed from the originally designed oxide **10**, which was discovered to be kinetically stable as the phosphorane in the presence of weak acid. **K1** was shown to be a competent autodehydration phosphine oxide in the presence of acids up to a pK_a of 2.2 (2-nitrobenzoic acid). This reactivity has allowed both the catalytic homoetherification of primary alcohols (TfOH), the catalytic formation of decyl tosylate (TsOH), and, most significantly, the esterification and inversion of 2-octanol (2-nitrobenzoic acid) (at an e.r of 95:5).

In order to improve the reactivity, a range of different phosphine oxides with different internal nucleophile chemotypes were designed, synthesised and tested as catalysts in the tosylation of decanol. Of these, 8 of 13 showed some form of rate acceleration, suggesting that the general approach discussed here could be very powerful with the right catalyst.

Future work will involve further catalyst improvements, followed by exemplification of a wider range of secondary alcohols. Several suggestions have been described.

References

- 1 R. T. Sanderson, *Polar covalence*, Academic Press, New York, 1983.
- 2 R. T. Sanderson, *Chemical bonds and bond energy*, Academic Press, New York, 2d ed., 1976.
- 3 A. L. Allred, *J. Inorg. Nucl. Chem.*, 1961, **17**, 215–221.
- 4 R. Grigg, T. R. B. Mitchell, S. Sutthivaiyakit and N. Tongpenyai, *J. Chem. Soc. Chem. Commun.*, 1981, **0**, 611–612.
- 5 Y. Watanabe, Y. Tsuji, H. Ige, Y. Ohsugi and T. Ohta, *J. Org. Chem.*, 1984, **49**, 3359–3363.
- 6 M. H. S. A. Hamid, C. L. Allen, G. W. Lamb, A. C. Maxwell, H. C. Maytum, A. J. A. Watson and J. M. J. Williams, *J. Am. Chem. Soc.*, 2009, **131**, 1766–1774.
- 7 J. S. Wright and K. U. Ingold, *J. Chem. Educ.*, 2000, **77**, 1062.
- 8 M. Bandini and M. Tragni, *Org. Biomol. Chem.*, 2009, **7**, 1501–1507.
- 9 E. Emer, R. Sinisi, M. G. Capdevila, D. Petruzzello, F. De Vincentiis and P. G. Cozzi, *European J. Org. Chem.*, 2011, **2011**, 647–666.
- 10 M. Rueping and B. J. Nachtsheim, *Beilstein J. Org. Chem.*, 2010, **6**, 6–30.
- 11 B. M. Trost and D. L. Van Vranken, *Chem. Rev.*, 1996, **96**, 395–422.
- 12 J. Muzart, *European J. Org. Chem.*, 2007, **2007**, 3077–3089.
- 13 B. M. Trost and M. L. Crawley, *Chem. Rev.*, 2003, **103**, 2921–2944.
- 14 M. Bandini, *Angew. Chem. Int. Ed.*, 2011, **50**, 994–995.

- 15 O. Mitsunobu, M. Yamada and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 1967, **40**, 935–939.
- 16 T. Mukaiyama, O. Mitsunobu and T. Obata, *J. Org. Chem.*, 1965, **30**, 101–105.
- 17 O. Mitsunobu, *Synthesis*, 1981, **1981**, 1–28.
- 18 O. Mitsunobu and M. Eguchi, *Bull. Chem. Soc. Jpn.*, 1971, **44**, 3427–3430.
- 19 P. Walden, *Berichte der Dtsch. Chem. Gesellschaft*, 1896, **29**, 133–138.
- 20 C. T. (Colin T. Mortimer, *Reaction heats and bond strengths*, Elsevier, 2017 revis., 1960.
- 21 T. Mukaiyama, I. Kuwajima and Z. Suzuki, *J. Org. Chem.*, 1963, **28**, 2024–2027.
- 22 T. Mukaiyama, *Angew. Chem. Int. Ed.*, 2004, **43**, 5590–5614.
- 23 T. Tsunoda, Y. Yamamiya and S. Itô, *Tetrahedron Lett.*, 1993, **34**, 1639–1642.
- 24 B. H. Lipshutz, D. W. Chung, B. Rich and R. Corral, *Org. Lett.*, 2006, **8**, 5069–5072.
- 25 N. Iranpoor, H. Firouzabadi, D. Khalili and S. Motevalli, *J. Org. Chem.*, 2008, **73**, 4882–4887.
- 26 A. G. M. Barrett, R. S. Roberts and J. Schröder, *Org. Lett.*, 2000, **2**, 2999–3001.
- 27 D. Camp, P. J. Harvey and I. D. Jenkins, *Tetrahedron*, 2015, **71**, 3932–3938.
- 28 R. Guthrie and I. Jenkins, *Aust. J. Chem.*, 1982, **35**, 767–774.
- 29 D. Camp and I. D. Jenkins, *J. Org. Chem.*, 1989, **54**, 3049–3054.
- 30 D. Camp and I. D. Jenkins, *J. Org. Chem.*, 1989, **54**, 3045–3049.
- 31 D. Camp, M. von Itzstein and I. D. Jenkins, *Tetrahedron*, 2015, **71**, 4946–4948.

- 32 D. L. Hughes, *Org. Prep. Proced. Int.*, 1996, **28**, 127–164.
- 33 S. Schenk, J. Weston and E. Anders, *J. Am. Chem. Soc.*, 2005, **127**, 12566–12576.
- 34 D. L. Hughes, R. A. Reamer, J. J. Bergan and E. J. J. Grabowski, *J. Am. Chem. Soc.*, 1988, **110**, 6487–6491.
- 35 M. Varasi, K. A. M. Walker and M. L. Maddox, *J. Org. Chem.*, 1987, **52**, 4235–4238.
- 36 J. A. Dodge, J. I. Trujillo and M. Presnell, *J. Org. Chem.*, 1994, **59**, 234–236.
- 37 D. Crich, H. Dyker and R. J. Harris, *J. Org. Chem.*, 1989, **54**, 257–259.
- 38 X. Tang, C. Chapman, M. Whiting and R. Denton, *Chem. Commun.*, 2014, **50**, 7340–7343.
- 39 S. F. Martin and J. A. Dodge, *Tetrahedron Lett.*, 1991, **32**, 3017–3020.
- 40 J. E. Green, D. M. Bender, S. Jackson, M. J. O'Donnell and J. R. McCarthy, *Org. Lett.*, 2009, **11**, 807–810.
- 41 M. Saïah, M. Bessodes and K. Antonakis, *Tetrahedron Lett.*, 1992, **33**, 4317–4320.
- 42 T. Y. S. But and P. H. Toy, *J. Am. Chem. Soc.*, 2006, **128**, 9636–9637.
- 43 D. Hirose, T. Taniguchi and H. Ishibashi, *Angew. Chem. Int. Ed.*, 2013, **52**, 4613–4617.
- 44 D. Hirose, M. Gazvoda, J. Košmrlj and T. Taniguchi, *Chem. Sci.*, 2016, **7**, 5148–5159.
- 45 J. A. Buonomo and C. C. Aldrich, *Angew. Chem. Int. Ed.*, 2015, **127**, 13233–13236.
- 46 D. Hirose, M. Gazvoda, J. Košmrlj and T. Taniguchi, *Org. Lett.*, 2016, **18**, 4036–

- 4039.
- 47 C. J. O'Brien, F. Lavigne, E. E. Coyle, A. J. Holohan and B. J. Doonan, *Chem. Eur. J.*, 2013, **19**, 5854–5858.
- 48 PCT Int. Appl., WO2010/118042A2, 2010.
- 49 M. Figlus, N. Wellaway, A. W. J. Cooper, S. L. Sollis and R. C. Hartley, *ACS Comb. Sci.*, 2011, **13**, 280–285.
- 50 K. E. Elson, I. D. Jenkins and W. A. Loughlin, *Org. Biomol. Chem.*, 2003, **1**, 2958–2965.
- 51 S. Kaczmarczyk, M. Kwiatkowska, L. Madalińska, A. Barbachowska, M. Rachwalski, J. Błaszczyk, L. Sieroń and P. Kielbasiński, *Adv. Synth. Catal.*, 2011, **353**, 2446–2454.
- 52 A. Pautard-Cooper and S. A. Evans, *J. Org. Chem.*, 1989, **54**, 2485–2488.
- 53 J. W. Kelly and S. A. Evans, *J. Am. Chem. Soc.*, 1986, **108**, 7681–7685.
- 54 P. L. Robinson, C. N. Barry, S. W. Bass, S. E. Jarvis and S. A. Evans, *J. Org. Chem.*, 1983, **48**, 5396–5398.
- 55 A. M. Pautard and S. A. Evans, *J. Org. Chem.*, 1988, **53**, 2300–2303.
- 56 W. T. Murray, J. W. Kelly and S. A. Evans, *J. Org. Chem.*, 1987, **52**, 525–529.
- 57 W. T. Murray and S. A. Evans, *J. Org. Chem.*, 1989, **54**, 2440–2446.
- 58 P. L. Robinson, C. N. Barry, J. W. Kelly and S. A. Evans, *J. Am. Chem. Soc.*, 1985, **107**, 5210–5219.
- 59 A. L. Shannon-Little, Nottingham University, 2015.

- 60 T. Nishiyama, H. Kameyama, H. Maekawa and K. Watanuki, *Can. J. Chem.*, 2011.
- 61 B. Dhakal, L. Bohé and D. Crich, *J. Org. Chem.*, 2017, [acs.joc.7b01850](#).
- 62 H. Müller, in *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2011.
- 63 E. R. Lachter, R. A. da Silva San Gil, D. Tabak, V. G. Costa, C. P. S. Chaves and J. A. dos Santos, *React. Funct. Polym.*, 2000, **44**, 1–7.
- 64 H. Quast and T. Dietz, *Synthesis*, 1995, **1995**, 1300–1304.
- 65 P.-Y. Renard, P. Vayron, E. Leclerc, A. Valleix and C. Mioskowski, *Angew. Chem. Int. Ed.*, 2003, **42**, 2389–2392.
- 66 R. A. Sheldon, *Green Chem.*, 2007, **9**, 1273.
- 67 D. J. C. Constable, A. D. Curzons and V. L. Cunningham, *Green Chem.*, 2002, **4**, 521–527.
- 68 T. Hirao, T. Masunaga, Y. Ohshiro and T. Agawa, *Tetrahedron Lett.*, 1980, **21**, 3595–3598.
- 69 M. Kalek, M. Jezowska and J. Stawinski, *Adv. Synth. Catal.*, 2009, **351**, 3207–3216.
- 70 R. Yamaguchi, Y. Nakazono, T. Matsuki, E. Hata and M. Kawanisi, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 215–222.
- 71 A. R. Katritzky, B. L. Duell, D. Rasala, B. Knier and H. D. Durst, *Langmuir*, 1988, **4**, 1118–1122.
- 72 T. W. Koenig and J. S. Wiczorek, *J. Org. Chem.*, 1968, **33**, 1530–1532.
- 73 J. I. Murray, R. Woscholski and A. C. Spivey, *Chem. Commun.*, 2014, **50**, 13608–

- 13611.
- 74 Z. Shen and R. F. Jordan, *J. Am. Chem. Soc.*, 2010, **132**, 52–53.
- 75 T. M. J. Anselment, C. Wichmann, C. E. Anderson, E. Herdtweck and B. Rieger, *Organometallics*, 2011, **30**, 6602–6611.
- 76 G. Gelbard, *Ind. Eng. Chem. Res.*, 2005, **44**, 8468–8498.

Chapter 6

Experimental Section

Contents

1. General Information	437
2. Experimental Details	437
2.0 Dean Stark Protocol and Diagram	437
2.1 Synthesis and Experiments of Legacy Catalyst Phosphine Oxide 10	438
2.11 Scheme 17 – Confirmation that decanol is alkylated by decyl tosylate 15 to form ether 14	442
2.12 Representative catalytic etherification reaction using catalyst 10 (Table 1)	444
2.13 Experiments to interrogate the requirement for an internal hydroxyl group (Scheme 20)	445
2.14 Etherification reactions, Table 2	448
2.2 Further Reactivity of Legacy Catalyst 10	448
2.21 THF synthesis (Scheme 21)	448
2.22 Elimination reactions: Menthol (Scheme 22)	449
2.23 Elimination reactions: 2-octanol and decene (Scheme 23, 24, 26)	450
2.3 Synthesis and Experiments of K1	451
2.31 Demethylation reaction to give (2-hydroxybenzyl)diphenylphosphine oxide (K1) ⁷	452
2.32 Lewis-acid-catalysed Arbuzov rearrangement to synthesis K1 (Scheme 29)	453
2.33 Phospho-Fries Sequence to give K1 and 35 (Scheme 31)	454
2.34 Phospho-Fries Rearrangement attempt to generate K1 and 35 (Scheme 31)	455
2.35 Catalytic etherification of decanol with K1 and triflic acid to form didecyl ether (Scheme 32)	457
2.36 Catalytic tosylation of decanol with K1 and tosic acid to form decyl tosylate 36 (Table 3)	457

2.37 Screen of carboxylic acids for the esterification of decanol or 2-octanol with K1 (Table 10).....	457
2.4 K2: Synthesis and Experiments.....	458
2.41 Reaction of K2 with oxalyl chloride and decanol (Scheme 49)	460
2.5 Synthesis and experiments of Catalysts K3-K12	462
2.51 Synthesis and Experiments of K3 and K4.....	462
2.52 Synthesis and Experiments of K5 and K6.....	466
2.53 Attempted <i>p</i> -pyridyl chlorination of K6.....	468
2.54 Synthesis and Experiments of K7.....	469
2.55 Synthesis and Experiments of K8.....	471
2.56 Synthesis and Experiments of K9 and K10 (Scheme 42)	474
2.57 Synthesis and Experiments of K11 and K12 (Scheme 41).....	477
2.58 Synthesis and Experiments of K13 (Scheme 43)	479
2.6 Additional Catalyst Syntheses.....	483
2.60 Synthesis of gemdifluoro K1 catalyst precursor sequence (Scheme 44).....	484
2.61 Phospho-Fries rearrangement precursor: 2-(difluoromethyl)phenyl diphenylphosphinate (64a).....	486
2.62 Attempted synthesis of sulfonic acid augmented catalyst 10, (65).....	487
2.63 Attempted Iodination of decanol (Goal 2, ~p87).....	487
2.7 Oxygen-18 Labelling Experiments (Schemes 33-35)	488
2.71 K1-catalysed tosylation of ^{18}O decanol to trace final location of ^{18}O	492
2.72 The ^{16}O tosylate (with oxygen incorporation from tosyl):.....	492
2.73 The ^{18}O - <i>P</i> -catalyst, ^{18}O -K1, from a Mitsunobu reaction, $\text{S}_{\text{N}}2$	493
2.74 1-(decyloxy)decane- ^{18}O (42), demonstrating ether formation from nucleophilic decanol.....	495
2.8 Inversion of 2-octanol with K1.....	495
2.81 Chiral HPLC determination of enantiomeric excess of ester 44:	497
3.0 Experimental References For Chapter 6	501

1. General Information

See Chapter 1.

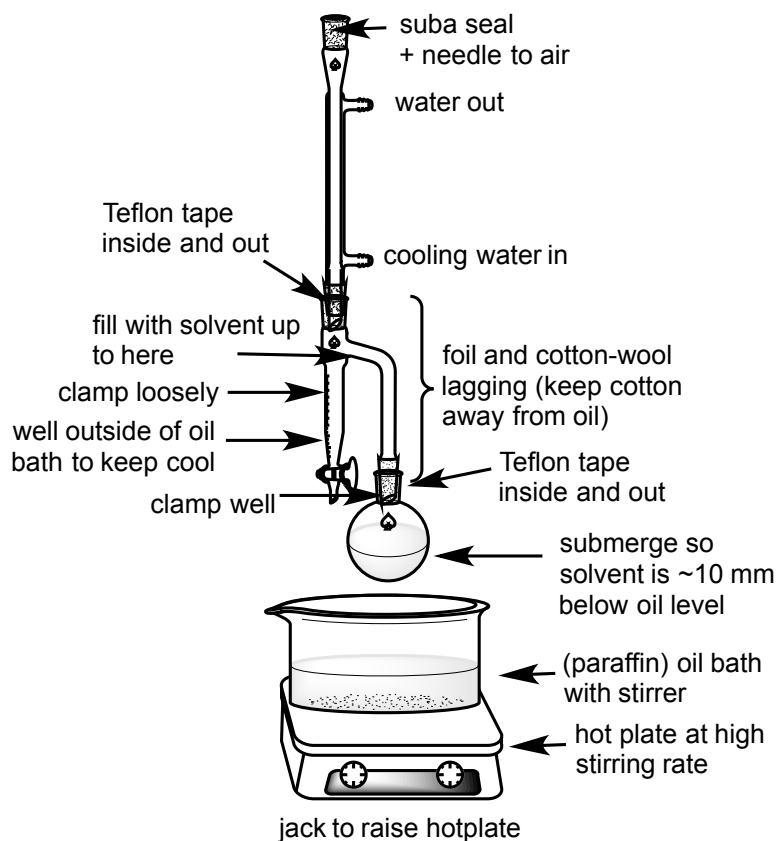
2. Experimental Details

2.0 Dean Stark Protocol and Diagram

All Dean-Stark procedures were performed as follows:

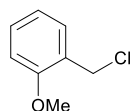
A 50 mL B14 round-bottomed flask was equipped with a medium-sized stirrer bar (~15 mm) and charged with the reagents and solvent. A Dean-Stark trap with B14 ground glass joints bearing a single diameter of Teflon tape was twisted firmly into the flask. The flask was clamped above a large oil bath containing a large magnetic stirrer bar, positioned on a hotplate. The hotplate was secured onto a jack to raise the reaction above the fumehood floor to reduce cooling from the air-flow, and set at a rapid stirring rate (stirring rate effects reflex efficiency). The Dean-Stark trap with a closed tap was filled with the requisite solvent (Winchester grade). A B14 water condenser bearing a single diameter of Teflon tape on its male joint was twisted into the top of the Dean Stark trap. The top of the condenser was fitted with a B14 suba seal and a needle to air perforated through the seal to ensure pressure equalisation with atmospheric pressure. The horizontal cross-bar of the Dean-Stark trap was wrapped with a thin layer of cotton wool, which was sealed around the glass with aluminium foil lagging. Further foil was added to insulate the top of the flask up to the first bend of the DS trap, and a further piece of foil added up to the condenser. The flask was submerged into the oil bath (preheated) and timing started immediately. The solvent level in the flask was at least 1 cm below the oil level to ensure efficient heating of the glass to contain a continuous reflex to the trap. For toluene, the oil bath was set to 130-135 °C; for

xylene, the oil bath was set to 155 °C. These temperatures affect the reflux efficiency by heating the glass; different temperatures may be required for efficient reflux if r.t. varies (r.t. here 10-25 °C). A diagram is shown below:



2.1 Synthesis and Experiments of Legacy Catalyst Phosphine Oxide 10

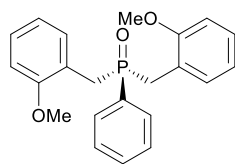
1-(chloromethyl)-2-methoxybenzene¹ (12)



(2-methoxyphenyl)methanol (10.0 g, 72.4 mmol) was dissolved in dichloromethane (200 mL) and the reaction cooled to – 20 °C. Thionyl chloride (10.5 mL, 145 mmol) was added over 10 min ensuring the reaction remained cool. The reaction was then removed from the ice bath and placed in a water bath at room temperature and the reaction stirred for 3 h.

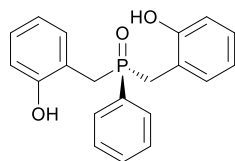
After this time, the reaction was quenched cautiously with water and the layers separated. The organic layer was washed carefully with saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate and concentrated *in vacuo* to give a clear oil (10.9 g, 96%) which gave data consistent with that previously reported. The oil was stored in the freezer under argon before use without further purification. (Note: Care should be taken to remove all by-products (acid) during the work-up procedure as the compound is unstable with respect to storage in the presence of acid.) ^1H NMR (400 MHz, CDCl_3) δ 7.41 – 7.24 (m, 2H), 6.99 – 6.85 (m, 2H), 4.68 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 157.3, 130.5, 130.0, 125.8, 120.6, 110.8, 55.5, 41.6; IR (cm^{-1}) (CDCl_3) 3069, 3008, 2967, 2942, 2840, 1603, 1495, 1465, 1440, 1252.

bis(2-methoxybenzyl)(phenyl)phosphine oxide (23)



Magnesium turnings (2.30 g, 94.6 mmol) were stirred overnight rapidly in a flame-dried 500 mL two-necked flask in the presence of an abrasive broken pipette under an argon atmosphere. An iodine crystal was added and the flask heated to induce vaporisation. THF (5 mL) was added and the solvent heated briefly to reflux. Further THF was added (150 mL) and the solvent heated to reflux and removed from the heat. Benzyl chloride **12** (13.8 g, 88.1 mmol) was added in THF (5 mL) over 1 h with stirring, allowing the reaction to heat under its own exotherm. The reaction was stirred ambiently for a further 2 h and then cooled to 0 °C in an ice bath. Dichloro(phenyl)phosphane (5.98 mL, 44.1 mmol) was added dropwise in THF (10 mL) over 20 min and the reaction stirred warming to room temperature overnight. The reaction was concentrated by 50% and diluted with EtOAc

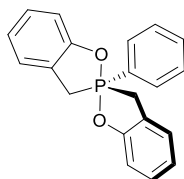
(100 mL). The organic layer was washed sequentially with 1 M NaOH, 1 M HCl, saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate, filtered and concentrated. The crude residue was redissolved in EtOAc (30 mL) and aqueous hydrogen peroxide (12% w/v, 10 mL) added and the mixture stirred for 3 h. The reaction was diluted with EtOAc and washed with 1 M HCl, saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate, filtered and concentrated. The crude residue was dry loaded onto silica and a very short flash column chromatography performed using 200 mL of each 25%, 35%, 40%, 45% (collection started), 50%, 55% EtOAc in petrol to remove the majority of the impurities. The partially purified product (13.7 g) was taken to the next step. 500 mg was purified further (45%-100% EtOAc/petrol) to give acceptable characterisation data (260 mg of a colourless sticky residue). Alternatively, the dimethyl ether could be prepared cleanly by dimethylation of clean phosphine oxide **10** (see preparation of compound **24**). **¹H NMR** (400 MHz, CDCl₃) δ 7.55 – 7.46 (m, 2H), 7.41 – 7.34 (m, 1H), 7.31 – 7.25 (m, 4H), 7.19 – 7.11 (m, 2H), 6.89 – 6.82 (m, 2H), 6.74 – 6.69 (m, 2H), 3.58 (s, 6H), 3.48 – 3.40 (m, 4H); **¹³C NMR** (101 MHz, CDCl₃) δ 156.8 (d, *J* = 5.3 Hz), 132.3 (d, *J* = 94.1 Hz), 131.5 (d, *J* = 4.7 Hz), 131.2-131.0 (m, 2C), 127.9 (d, *J* = 3.2 Hz), 127.4 (d, *J* = 11.5 Hz), 120.6 (d, *J* = 2.8 Hz), 120.4 (d, *J* = 7.6 Hz), 110.2 (d, *J* = 2.8 Hz), 54.9, 30.8 (d, *J* = 63.8 Hz); **³¹P NMR** (162 MHz, CDCl₃) (¹H-decoupled) δ 36.4 ppm; **HRMS** (ESI⁺): Exact mass calcd for C₂₂H₂₄O₃P [M+H], 367.1458. Found 367.1454, *σ* = 0.0023; **IR** (cm⁻¹) (CDCl₃) 2970, 2838, 1495, 1466, 1438, 1250.

bis(2-hydroxybenzyl)(phenyl)phosphine oxide (10)

Phosphine oxide **23** (13.0 g, 35.5 mmol) was dissolved in chloroform (130 mL) and added was boron trichloride dimethylsulfide complex (25.0 g, 139 mmol). The reaction was heated at reflux for 16 h, and then checked for full conversion by ^{31}P NMR (36 ppm consumed) after washing an aliquot of the reaction mixture with water. The reaction mixture was diluted with chloroform 200 mL and isopropanol added with shaking until the solution was homogenous/fully dissolved. The reaction mixture was then washed with saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate, filtered and concentrated. The crude material was dry-loaded onto silica and purified by short flash column chromatography (25-100% EtOAc in petrol) to give a white solid that crystallised from the eluent with standing (6.7 g, 45% over three steps (from the benzyl chloride)). The solid could be recrystallised from hot acetonitrile. ^1H NMR (400 MHz, CDCl_3) δ 8.59 (s, 2H), 7.71 – 7.59 (m, 2H), 7.57 – 7.48 (m, 1H), 7.48 – 7.39 (m, 2H), 7.17 – 7.06 (m, 2H), 6.99 – 6.90 (m, 2H), 6.89 – 6.80 (m, 2H), 6.79 – 6.69 (m, 2H), 3.58 (dd, J = 15.1, 13.3 Hz, 2H), 3.35 (dd, J = 15.1, 11.3 Hz, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 155.7 (d, J = 4.1 Hz), 132.7 (d, J = 2.9 Hz), 131.4 (d, J = 6.1 Hz), 130.4 (d, J = 9.4 Hz), 129.2 (d, J = 2.9 Hz), 128.9 (d, J = 11.8 Hz), 127.5, 121.0 (d, J = 2.9 Hz), 119.3 (d, J = 2.9 Hz), 118.4 (d, J = 8.8 Hz), 33.8 (d, J = 63.1 Hz); ^{31}P NMR (162 MHz, CDCl_3) (^1H -decoupled) δ 50.6 ppm; HRMS (ESI+): Exact mass calcd for $\text{C}_{20}\text{H}_{20}\text{O}_3\text{P}$ [$\text{M}+\text{H}$], 339.1145. Found 339.1138, σ = 0.0008; IR (cm^{-1}) (CDCl_3) 3691, 3604, 3154, 3011, 1602, 1582, 1488, 1246; **Mp** 186-188 °C (from MeCN).

2-phenyl-2,3,3'-trihydro-2λ5-2,2'-spirobi[benzo[d][1,2]oxaphosphole]

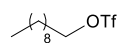
(11)



Phosphine oxide **10** (100 mg, 0.296 mmol) was heated under Dean-Stark conditions in toluene (10 mL) for 15 h. The toluene was removed *in vacuo* and the resulting white solid characterised immediately in C₆D₆. The compound is unstable with respect to hydrolysis back to the parent oxide, but stable in anhydrous solvent; ¹H NMR (400 MHz, C₆D₆) δ 8.01 – 7.84 (m, 2H), 7.05 – 7.00 (m, 2H), 6.96 – 6.88 (m, 7H), 6.73 – 6.68 (m, 2H), 3.39 (dd, ³J_{HH}=19.7, ³J_{PH}=18.5 Hz, 2H, P-CH₂H + P-CH₂H), 3.28 (dd, ³J_{PH}=21.0, ³J_{HH}=19.7 Hz, 2H, P-CH₂H + P-CH₂H); ¹³C NMR (101 MHz, C₆D₆) (selected signals only, due to solvent overlap) δ 157.5 (d, *J* = 5.4 Hz), 133.2 (d, *J* = 11.1 Hz), 131.2 (d, *J* = 3.9 Hz), 125.8 (d, *J* = 21.5 Hz), 119.6, 111.9 (d, *J* = 4.1 Hz), 29.9 (d, *J* = 114.8 Hz); ³¹P NMR (162 MHz, C₆D₆) δ -10.4 ppm.

2.11 Scheme 17 – Confirmation that decanol is alkylated by decyl tosylate **15** to form ether **14**

Synthesis of decyl trifluoromethanesulfonate (**15**)²



Trifluoromethanesulfonic anhydride (415 μL, 2.46 mmol) was dissolved in dichloromethane (4 mL) at 0 °C and added was pyridine (200 μL, 2.46 mmol). Added was decanol (300 mg, 1.90 mmol) and the reaction stirred at room temperature for 4 h. The reaction was quenched with water, the organics separated and washed with saturated

aqueous sodium bicarbonate solution and brine and dried over magnesium sulfate, filtered and concentrated. The crude residue, which contained some solid, was added neat to a short silica pad and rapidly eluted with diethyl ether (3 column volumes); the solid remained undissolved on top of the column. The eluent was concentrated to give the desired triflate as a clear oil (537 mg, 98%) The triflate was generally used immediately, but was viable after storage under argon and refrigeration for a few days. ^1H NMR (400 MHz, CDCl_3) δ 4.53 (t, J = 6.5 Hz, 2H), 1.90 – 1.75 (m, 2H), 1.49 – 1.36 (m, 2H), 1.36 – 1.16 (m, 12H), 0.97 – 0.79 (m, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 118.7 (q, J = 319.7 Hz), 77.7, 31.8, 29.4, 29.3, 29.2 (2C), 28.8, 25.0, 22.6, 14.1; ^{19}F NMR (377 MHz, CDCl_3) δ -74.9 ppm.

Decanol (1.85 mmol) was heated in toluene (10 mL) with triphenylphosphine oxide as a Lewis base (515 mg, 1.85 mmol) under the Dean-Stark conditions for 30 min. The fresh triflate (0.348 mmol) was added, and the reaction reheated for 30 min, before cooling and concentration. ^1H -NMR relative to TCE as internal standard (and relative to the decanol) indicated full conversion to ether, which is sufficient to account for the conversion rate observed in a typical etherification reaction.

When oxide **10** (50.0 mg, 0.148 mmol) was heated in toluene (17 mL) for 1 h, followed by 1 h heating in the presence of decyl triflate (43 mg), 19% of the alkoxy phosphonium salt with ^{31}P shift 77 ppm was observed. In the ^1H -NMR, 19% CH_2 (3.96 ppm, 2H, app q (dt, J = ~6 Hz, small J not measurable)). These results suggested some degree of reversibility in the Arbuzov reaction.

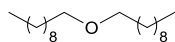
When oxide **10** (100 mg, 0.296 mmol) was heated in toluene (15 mL) for 16 h under Dean-Stark conditions (to form the dioxypyphosphorane **11**), followed by the addition of 1

equivalent of decanol (0.296 mmol) and heating for 1 h, and the addition of triflic acid (0.296 mmol) and heating at 130 °C for 5 min, the following species were observed: the same phosphonium salt (^{31}P : 77 ppm, ^1H : 4.10 ppm, dt, ~17%); decyl triflate (4%, 4.62 ppm); and the balance as decanol and phosphine oxide. After 1 h further heating, 15% triflate and 12% alkoxyphosphonium salt were present, along with 8% ether.

2.12 Representative catalytic etherification reaction using catalyst **10** (Table 1)

To phosphine oxide **10** (100 mg, 0.296 mmol, 5 mol%) was added decanol (2.260 mL, 11.84 mmol) and toluene (17 mL). Finally triflic acid (26.1 μL , 0.296 mmol, 5 mol%) was added and the flask attached to a Dean-Stark apparatus fitted with a water-condenser. All joints were sealed with Teflon tape inside and out, and the apparatus well-lagged to promote a strong reflux through to the condenser. The reaction was heated in an oil bath set at 130 °C for 15 h. The depth the flask was submerged, the lagging and the stirring rate were controlled for, as varying these lead to varying reflux efficiencies. After 15 h, the reaction was cooled, concentrated and the conversion to ether calculated by comparing the integration of the O- CH_2 signals in the ^1H -NMR. Conversion to ether was 96%, with the mass balance of decanol present as the triflate in accordance with independently prepared material above. The liquid residue was pipetted away from a sticky insoluble residue and loaded neat onto a short pad of silica and the ether product flushed with diethyl ether to obtain pure didecyl ether after concentration. The sticky residue was then loaded onto a short silica column in a small amount of EtOAc and purified with 35%-55% EtOAc in petrol to reclaim the catalyst. Alternatively, diphenolic-catalyst **10** could be reclaimed by dissolving the residue in a diethyl ether solution, washing with water, then extraction of the organic layer into aqueous sodium hydroxide, acidification with HCl and re-extraction with

chloroform:isopropanol (4:1). The material was generally recrystallised from hot acetonitrile to give reusable material.

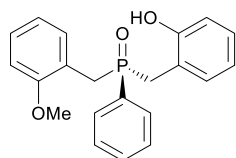


Didecyl ether³ had the followed data: ¹H NMR (400 MHz, CDCl₃) δ 3.38 (t, *J* = 6.8 Hz, 2H), 1.56 (tt, *J* = 6.8 Hz, 2H), 1.39 – 1.18 (m, 14H), 0.88 (d, *J* = 7.1 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 71.0, 31.9, 29.8, 29.6, 29.6, 29.5, 29.3, 26.2, 22.7, 14.1; HRMS (ESI+): Exact mass calcd for C₂₀H₄₃O [M+H], 299.3308. Found 299.3307, σ = 0.0026; IR (cm⁻¹) (CDCl₃) 2999, 2929, 2856, 1467, 1105.

These reactions were repeated with different acids and phosphines as described in **Table 1**.

2.13 Experiments to interrogate the requirement for an internal hydroxyl group (Scheme 20)

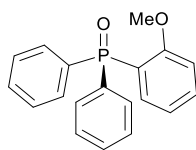
(*R/S*)-(2-hydroxybenzyl)(2-methoxybenzyl)(phenyl)phosphine oxide (**24**)



Phosphine oxide **10** (400 mg, 1.18 mmol) was suspended in acetone (9 mL) with potassium carbonate (655 mg, 4.74 mmol) and added was methyl iodide (295 μL, 4.74 mmol) and the reaction stirred at 50 °C for 16 h. The conversion was checked by ³¹P NMR to ensure no starting material remained and was found to be roughly 1:4 monomethyl oxide (**24**):dimethyl oxide (**23**). The reaction was concentrated, suspended in EtOAc and filtered and the filtrate partitioned between EtOAc and water. The organic layer was washed with 1 M HCl and brine, dried over magnesium sulfate and concentrated. The

crude residue was purified by flash column chromatography (10-70% EtOAc-petrol). The monomethyl oxide **24** eluted first (~40% EtOAc, co-elutes with oxide **10**) followed by the dimethyl oxide **23**. **24** was isolated as a colourless residue (50 mg, 15 %) and gave data as follows; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.58 – 7.50 (m, 2H), 7.49 – 7.42 (m, 1H), 7.41 – 7.31 (m, 2H), 7.24 – 7.15 (m, 2H), 7.11 – 7.04 (m, 1H), 6.97 – 6.92 (m, 1H), 6.92 – 6.85 (m, 1H), 6.84 – 6.79 (m, 1H), 6.77 – 6.67 (m, 2H), 3.59 (s, 3H), 3.55 – 3.45 (m, 3H), 3.26 (dd, $J = 15.0, 11.1$ Hz, 1H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 156.8 (d, $J = 4.7$ Hz), 156.5 (d, $J = 3.9$ Hz), 132.0 (d, $J = 3.0$ Hz), 131.5 (d, $J = 6.2$ Hz), 131.4 (d, $J = 4.9$ Hz), 130.7 (d, $J = 9.1$ Hz), 129.8 (d, $J = 95.4$ Hz), 128.8 (d, $J = 3.0$ Hz), 128.7 (d, $J = 3.4$ Hz), 128.2 (d, $J = 11.6$ Hz), 120.8 (d, $J = 3.1$ Hz), 120.37, 119.47 (d, $J = 9.0$ Hz), 119.42 (d, $J = 2.8$ Hz), 119.1 (d, $J = 7.7$ Hz), 110.7 (d, $J = 3.0$ Hz), 55.0, 33.9 (d, $J = 63.9$ Hz), 31.2 (d, $J = 63.7$ Hz); $^{31}\text{P NMR}$ (162 MHz, CDCl_3) (^1H -decoupled) δ 45.1 ppm; **HRMS** (ESI+): Exact mass calcd for $\text{C}_{21}\text{H}_{22}\text{O}_3\text{P}$ $[\text{M}+\text{H}]$, 353.1301. Found 353.1305, $\sigma = 0.0007$; **IR** (cm^{-1}) (CDCl_3) 3695, 2964, 1601, 1582, 1489, 1250.

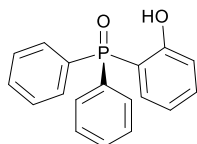
(2-methoxyphenyl)diphenylphosphine oxide (MeO-22)⁴



1-bromo-2-methoxybenzene (364 μL , 2.92 mmol) was dissolved in THF (5 mL) and cooled to -78°C . Added dropwise over 20 min was $n\text{BuLi}$ (2.5 M in hexanes, 1.22 mL, 3.06 mmol) and the reaction stirred at -78°C for 2 h. Chlorodiphenylphosphane (540 μL , 2.92 mmol) dissolved in THF (4 mL) was added dropwise over 30 min and the reaction then allowed to warm to room temperature over 15 h. The reaction was quenched with water and diluted with EtOAc (30 mL). The organic layer was separated, dried over magnesium

sulfate and concentrated to 5 mL. Added was aqueous hydrogen peroxide (12% w/v, 2 mL) and the reaction stirred for 3 h. The reaction was diluted with EtOAc (50 mL), washed with 6 M aqueous sodium hydroxide solution, 1 M HCl, saturated aqueous sodium carbonate solution, brine, and the organics dried over magnesium sulfate, filtered and concentrated to give a white solid. The solid was dissolved in dichloromethane and petrol added dropwise to induce crystallisation. After standing for 72 h, there were two clear, individual solid species. The solids were filtered and the desired dissolved away from the impurity (off-white solid beads) using chloroform. Concentration of the filtrate gave the phosphine oxide as a white solid (625 mg, 70%). **¹H NMR** (400 MHz, CDCl₃) δ 7.82 – 7.74 (m, 1H), 7.73 – 7.66 (m, 4H), 7.53 – 7.46 (m, 3H), 7.45 – 7.37 (m, 4H), 7.12 – 7.02 (m, 1H), 6.95 – 6.85 (m, 1H), 3.54 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 160.8 (d, *J* = 3.2 Hz), 134.9 (d, *J* = 7.0 Hz), 134.2 (d, *J* = 2.2 Hz), 133.2 (d, *J* = 107.0 Hz), 131.8 (d, *J* = 10.0 Hz), 131.4 (d, *J* = 2.9 Hz), 128.1 (d, *J* = 12.2 Hz), 120.9 (d, *J* = 11.5 Hz), 119.6 (d, *J* = 103.9 Hz), 111.4 (d, *J* = 6.4 Hz), 55.2; **³¹P NMR** (162 MHz) (¹H-decoupled) δ 27.3 ppm; **HRMS** (ESI⁺): Exact mass calcd for C₁₉H₁₈O₂P [M+H], 309.1039. Found 309.1035, σ = 0.0097; **IR** (cm⁻¹) (CDCl₃) 2972, 2839, 1591, 1577, 1478, 1463, 1432, 1277, 1252, 1163; **Mp** 160-164 °C (lit.⁴ 164-167 °C).

(2-hydroxyphenyl)diphenylphosphine oxide (22)⁵



Phosphine oxide **MeO-22** (611 mg, 2.00 mmol) was dissolved in chloroform (20 mL) and added was boron trichloride dimethylsulfide complex (1.1 g, 6.0 mmol). The reaction was stirred at reflux for 16 h. The reaction was stirred for 1 h with saturated aqueous sodium

bicarbonate solution, acidified to pH3 and extracted twice with chloroform, washed with 1M HCl and brine, dried over magnesium sulfate, filtered and concentrated to give a white crystalline solid (440 mg, 76%) ~95:5 ratio of **30:MeO-30** by ^{31}P -NMR. ^1H NMR (400 MHz, CDCl_3) δ 11.14 (s, 1H), 7.75 – 7.63 (m, 4H), 7.62 – 7.54 (m, 2H), 7.53 – 7.44 (m, 4H), 7.44 – 7.36 (m, 1H), 7.04 – 6.94 (m, 2H), 6.87 – 6.78 (m, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 163.9 (d, $J = 2.9$ Hz), 134.3 (d, $J = 2.2$ Hz), 132.5 (d, $J = 2.8$ Hz), 132.0 (d, $J = 10.4$ Hz), 132.0 (d, $J = 105.7$ Hz), 131.9 (d, $J = 10.0$ Hz), 128.7 (d, $J = 12.3$ Hz), 119.0 (d, $J = 12.3$ Hz), 118.6 (d, $J = 7.6$ Hz), 111.1 (d, $J = 104.0$ Hz); ^{31}P NMR (162 MHz) (^1H -decoupled) δ 39.4 ppm; HRMS (ESI+): Exact mass calcd for $\text{C}_{18}\text{H}_{16}\text{O}_2\text{P}$ [M+H], 295.0882. Found 295.0880, $\sigma = 0.0071$; IR (cm^{-1}) (CDCl_3) 3691, 3606, 3011, 1606, 1578, 1457, 1438, 1247, 1120; **Mp** 228-230 °C (lit.⁵ 226-228 °C).

2.14 Etherification reactions, Table 2

These reactions were performed using the procedure described for Table 1, above.

2.2 Further Reactivity of Legacy Catalyst 10

2.21 THF synthesis (Scheme 21)

The setup was as depicted in the main text: The reaction was performed as a distillation, with a desiccant (MS) packed in between the flask and condensing unit, collecting at 92 °C at the top. Triphenylphosphine oxide (5 mol%, 82.8 mg) and triflic acid (5 mol%, 26.1 μL) were added toluene (17 mL) along with 1,4-butanediol (11.84 mmol, 1.05 mL) and heated at 130 °C for 3 h. The conversion to THF was quantitative as adjudged by recording the ^1H -NMR of the clear liquid that collected in the distillation trap.

The reaction was repeated in xylenes (17 mL). The temperature was gradually increased, starting at 105 °C. No liquid distilled until the temperature reached 130 °C. At this

temperature, a mixture of water and THF was collected in the distillation trap. This was determined to be because the glassware did not reach temperature until the bulk solvent reached close to boiling point.

2.22 Elimination reactions: Menthol (Scheme 22)

According to the representative catalytic ether formation, menthol (11.84 mmol) was reacted in the presence of 5 mol% triflic acid and 5 mol% catalyst oxide **10** (100 mg) over 15 h in toluene (17 mL) under Dean-Stark conditions. The reaction was adjudged to give a mixture of menthenes; 75% was 3-menthene, with ~3 % 2-menthene. The remaining major product remains unidentified. The spectra showing a mixture of these species after chromatography (EtOAc:petrol, 0%-50%) are depicted in the appendix. 3-menthene has a characteristic alkene signal at 5.37 ppm at 1.2 integration, (relative to the 6H doublet at 0.99 ppm), of which ~0.2 is a second unknown species. 2-menthene is visible at 5.53 ppm. The remaining alkene signals are unassigned.

The reaction was repeated without any phosphorus species; menthol (11.84 mmol) was reacted in the presence of 5 mol% triflic acid with no phosphorus catalyst over 15 h in toluene (17 mL) under Dean-Stark conditions. The reaction was adjudged to give Friedel-Crafts products by observation of a several tolyl methyl peaks. The result indicates mostly monoalkylation (spectra in appendix). No alkene was present.

The reaction was repeated with menthol (11.84 mmol), 5 mol% triflic acid with 5 mol%, and triphenylphosphine oxide (5 mol%) over 15 h in toluene (17 mL) under Dean-Stark conditions. No extensive reaction was observed, with largely starting material and small amounts of alkene (~4-5%) observed, indicating that the phosphine oxide acted as a Lewis

base and inhibited Friedel-Crafts reactivity of the triflic acid. The alkene products appear to be a roughly 3:2 ratio of 3-menthene to 2-menthene.

2.23 Elimination reactions: 2-octanol and decene (Scheme 23, 24, 26)

According to the representative catalytic ether formation, 2-octanol (11.84 mmol) was reacted in the presence of 5 mol% triflic acid and 5 mol% catalyst oxide **17** (100 mg) over 15 h in toluene (17 mL) under Dean-Stark conditions. The reaction was adjudged to give Friedel-Crafts products, determined from the crude NMR spectrum shown.

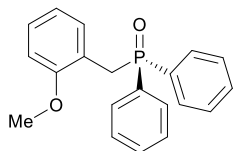
According to the representative catalytic ether formation, 2-octanol (11.84 mmol) was reacted in the presence of 5 mol% triflic acid and 5 mol% catalyst oxide **17** (100 mg) over 15 h in benzene under Dean-Stark conditions. The reaction was adjudged to give the desired ether and alkene material, determined from the crude NMR spectrum shown. The ether is proposed to be present at 3.43 ppm, with starting material 2-octanol identified at 3.86 ppm. There are several alkene containing species between 4.9 and 5.7 ppm.

According to the representative catalytic ether formation, decene and 5 mol% triflic acid were heated over 15 h in cyclohexane under Dean-Stark conditions. The crude reaction mixture showed ~40% alkenes (some migrated) and ~60% decyl tosylate.

According to the representative catalytic ether formation, 2-octanol and benzoic acid were reacted in the absence of any additional acid or catalyst over 15 h in toluene under Dean-Stark conditions. The spectra in the appendix show a mixture containing mostly 2-octanol, and two unknown species, most likely migrated secondary alcohols. No ester or ether was identified in the mixture.

2.3 Synthesis and Experiments of K1

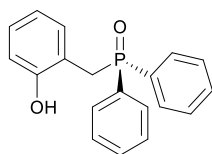
(2-methoxybenzyl)diphenylphosphine oxide (MeO-K1)⁶ (Scheme 28)



Magnesium turnings (183 mg, 7.53 mmol) were stirred overnight rapidly in a flame-dried 500 mL two-necked flask in the presence of an abrasive broken pipette under an argon atmosphere. An iodine crystal was added and the flask heated to induce vaporisation. THF (1 mL) was added and the solvent heated briefly to reflux. Further THF was added (12 mL) and the solvent heated to reflux and removed from the heat. Benzyl chloride **12** (1.07 g, 6.85 mmol) was added in THF (2 mL) over 1 h with stirring, allowing the reaction to heat under its own exotherm. The reaction was stirred ambiently for a further 3 h and then cooled to 0 °C in an ice bath. Chloro(diphenyl)phosphane (1.26 mL, 6.85 mmol) was added dropwise in THF (10 mL) over 20 min and the reaction stirred warming to room temperature overnight. The reaction was concentrated by 50% and diluted with EtOAc. The organic layer was washed sequentially with 1 M NaOH, 1 M HCl, saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate, filtered and concentrated. The crude residue was redissolved in EtOAc (5 mL) and an excess of aqueous hydrogen peroxide (12% w/v, 2 mL) added and the mixture stirred for 3 h. The reaction was diluted with EtOAc and washed with 1 M HCl, saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate, filtered and concentrated. The crude residue was dry loaded onto a short silica and a very short flash column chromatography performed using 50 mL of each 30%, 30%, 40%, 50%, 60%, 70, 70% EtOAc in petrol to remove the majority of the impurities. The partially purified product

(1.36 g, 62%) was taken to the next step. ^1H NMR (400 MHz, CDCl_3): δ 7.75 – 7.65 (m, 4H), 7.54 – 7.33 (m, 8H), 7.19 – 7.11 (m, 1H), 6.86 (t, J = 7.5 Hz, 1H), 6.65 (d, J = 8.1 Hz, 1H), 3.75 (d, J = 14.2 Hz, 2H), 3.44 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 156.7 (d, J = 5.5 Hz), 132.8 (d, J = 98.7 Hz), 131.6 (d, J = 4.7 Hz), 131.5 (d, J = 3.0 Hz), 131.2 (d, J = 9.2 Hz), 128.3 – 128.0 (m), 120.6 (d, J = 2.6 Hz), 119.8 (d, J = 8.1 Hz), 110.1 (d, J = 2.8 Hz), 54.8, 31.0 (d, J = 67.6 Hz). ^{31}P NMR (162 MHz) δ 30.1; HRMS (ESI+): Exact mass calcd for $\text{C}_{20}\text{H}_{20}\text{O}_2\text{P}$ $[\text{M}+\text{H}]$, 323.1195. Found 323.1197, σ = 0.0006.

2.31 Demethylation reaction to give (2-hydroxybenzyl)diphenylphosphine oxide (K1)⁷



Phosphine oxide **MeO-K1** (1.22 g, 3.78 mmol) was dissolved in chloroform (15 mL) and added was boron trichloride dimethylsulfide complex (1.50 g, 8.44 mmol). The reaction was heated at reflux for 16 h, and then checked for full conversion by ^{31}P NMR (30 ppm consumed) after washing an aliquot of the reaction mixture with water. The reaction mixture was diluted with chloroform 15 mL and quenched cautiously with saturated aqueous sodium bicarbonate solution and stirred for 1 h. The organic layer was separated, and then washed with saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate, filtered and concentrated. The crude material was dry-loaded onto silica and purified by short flash column chromatography (25-100% EtOAc in petrol) to give a white solid, collected in an initial pure batch, and a second ~95% pure batch (by ^{31}P -NMR) (total: 902 mg, ~77%, 47% over three steps (from the benzyl chloride)). ^1H NMR (400 MHz, CDCl_3): δ 9.82 (s, 1H), 7.76 – 7.68 (m, 4H), 7.59 – 7.52 (m, 2H), 7.51 – 7.44 (m,

4H), 7.14 – 7.07 (m, 1H), 7.00 (dd, $J = 8.1, 1.3$ Hz, 1H), 6.79 – 6.74 (m, 1H), 6.72 – 6.66 (m, 1H), 3.71 (d, $J = 12.9$ Hz, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 156.6 (d, $J = 3.8$ Hz), 132.4 (d, $J = 3.0$ Hz), 131.6 (d, $J = 6.7$ Hz), 130.9 (d, $J = 9.7$ Hz), 130.5 (d, $J = 100.0$ Hz), 128.9 (d, $J = 2.6$ Hz), 128.8 (d, $J = 12.2$ Hz), 120.6 (d, $J = 1.7$ Hz), 119.6 (d, $J = 2.9$ Hz), 119.3 (d, $J = 8.5$ Hz), 35.4 (d, $J = 67.4$ Hz); ^{31}P NMR (162 MHz, CDCl_3) δ 38.3; HRMS (ESI+): Exact mass calcd for $\text{C}_{19}\text{H}_{17}\text{NaO}_2\text{P}$ $[\text{M}+\text{Na}]$, 331.0858. Found 331.0856, $\sigma = 0.0043$; IR (cm^{-1}) (CDCl_3) 3694, 1602, 1488, 1195; **Mp** 167.5-168.5 °C.

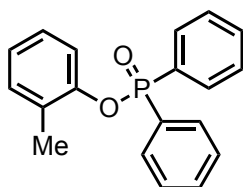
2.32 Lewis-acid-catalysed Arbuzov rearrangement to synthesis K1 (Scheme 29)

According to a literature procedure,⁶ (2-methoxyphenyl)methanol **33** (1.44 mL, 10.8 mmol) and triethylamine (1.65 mL, 11.9 mmol) were added to dry, degassed ether (4.3 mL) and cooled to 0 °C. Added dropwise over 30 min was *P*-chloro-diphenylphosphine (2.00 mL, 10.8 mmol) in diethyl ether (5 mL) over 30 min. The reaction was warmed to ambient temperature (20 °C) and stirred for 2 h. (The white suspension gradually broke up and was eventually stirring fluidly, which is a reasonable indicator of completion. It is better to leave this reaction slightly longer to make sure it is complete). The material was carefully filtered into a new flask under argon and the solid washed with a little dry ether. The reaction was concentrated by rotary evaporation and immediately returned to an atmosphere of argon. Chloroform (11 mL) was added and Ar bubbled through the solution for 10 min. TMS-triflate (5 mol%, 98 μL) was added, and the reaction stirred at 60 °C for 15 h, before boron trichloride dimethylsulfide complex (21.6 mmol, 4.7 g) was added and the reaction refluxed under argon for 16 h. After cooling to rt, the reaction was cautiously quenched with an aqueous sodium bicarbonate solution. After the work-up described for the demethylation reaction above, the solution was left to stand, and the white solid was collected by filtration. After recrystallization from hot MeCN (standing in the fridge

overnight), **K1** was isolated as a white solid (556 mg, 17%). Impurities removed by recrystallisation include the diphenylphosphinic acid and diphenylphosphine oxide, presumably from an incomplete initial alkylation reaction.

2.33 Phospho-Fries Sequence to give **K1** and **35** (Scheme 31)

***o*-tolyl diphenylphosphinate (34)**



1145-A-cp2

According to adapted literature procedures,^{8,9} *ortho*-cresol (1.17 mL, 10.8 mmol) and triethylamine (1.51 mL, 10.8 mmol) were added to dry, degassed ether (4.5 mL) and cooled to 0 °C. Added dropwise over 30 min was *P*-chloro-diphenylphosphine (2.00 mL, 10.8 mmol) in diethyl ether (5 mL) and the reaction stirred over 3 h warming to ambient temperature (23 °C). (The white suspension gradually broke up and was eventually stirring fluidly, which is a reasonable indicator of completion). The material was carefully filtered into a new flask and immediately subjected to oxidation with an excess of aqueous hydrogen peroxide (~ 2 mL). After stirring for 30 min at ambient temperature, the organic layer was separated, the aqueous extracted with further ether, and the combined ether layers washed with aqueous sodium bicarbonate and water, and dried over magnesium sulfate and concentrated to give a crude yellow oil (3.4 g). The oil began to precipitate a white solid on standing. The partially solidified residue was suspended in a small amount of EtOAc and loaded onto a silica column, with the assumption that the solid was undesired diphenyl phosphinic acid. The desired oxide **34** was eluted with EtOAc:petrol 50:50 as a white solid (1.98 g, 59%); ¹H NMR (400 MHz, Chloroform-*d*) δ 7.94 – 7.84 (m, 4H), 7.58 –

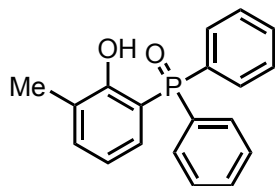
7.51 (m, 2H), 7.50 – 7.43 (m, 4H), 7.26 – 7.22 (m, 1H), 7.17 – 7.12 (m, 1H), 7.06 – 6.94 (m, 2H), 2.31 (s, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 149.6 (d, J = 8.2 Hz), 132.4 (d, J = 2.9 Hz), 131.7 (d, J = 10.7 Hz), 131.3 (d, J = 138.2 Hz), 131.3, 129.1 (d, J = 5.7 Hz), 128.6 (d, J = 13.2 Hz), 126.9, 124.4, 120.2 (d, J = 3.7 Hz), 16.8; ^{31}P NMR (162 MHz, Chloroform-*d*) δ 29.9; **HRMS** (ESI+): Exact mass calcd for $\text{C}_{19}\text{H}_{17}\text{NaO}_2\text{P}$ [$\text{M}+\text{Na}$], 331.0858. Found 331.0861, σ = 0.0029; **AT-IR** (neat): 3061, 2982, 2949, 2916, 1586, 1492, 1464, 1438, 1381, 1226, 1175, 1126, 1109 cm^{-1} ; **Mp**: 72-73 °C.

2.34 Phospho-Fries Rearrangement attempt to generate K1 and 35 (Scheme 31)

A synthesis of **K1** was attempted using a phospho-Fries rearrangement. A solution of *o*-tolyl diphenylphosphinate **34** (1.00 g, 3.24 mmol) in THF (15 mL) was added dropwise over 10 min at – 78°C to a solution of LDA, made by adding butyl lithium (1.6 M in hexanes, 2.25 mL, 3.56 mmol) to a THF solution (15 mL) of freshly distilled diisopropylamine (545 μL , 3.89 mmol) and stirring for 10 min. After stirring for 2 h warming to ambient temperature, the reaction was quenched with 1 M ammonium chloride solution. The reaction was diluted with dichloromethane and the organic layer separated and washed with a 1 M HCl solution. The crude material was combined with a second attempt (6.42 mmol scale) and purified by flash column chromatography using EtOAc/petrol 50:50. **K1** was isolated as a white solid (550 mg, 19%).

The second major product was the product of *ortho* aryl deprotonation and rearrangement:

(2-hydroxy-3-methylphenyl)diphenylphosphine oxide (35)



1178/1146

Peaks selected from impure mixture (610 mg) containing this compound (57%) and *ortho*-cresol (43%); ^1H NMR (300 MHz, Chloroform-*d*) δ 11.23 (s, 1H), 7.75 – 7.65 (m, 4H), 7.62 – 7.54 (m, 2H), 7.53 – 7.43 (m, 4H), 6.78 – 6.70 (m, 1H), 2.28 – 2.25 (s, 3H); ^{31}P NMR (121 MHz, Chloroform-*d*) δ 40.0; ^{13}C NMR (75 MHz, Chloroform-*d*) δ 162.1 (d, $J = 3.0$ Hz), 135.2 (d, $J = 2.3$ Hz), 132.5 (d, $J = 2.8$ Hz), 132.0 (d, $J = 10.4$ Hz), 131.7 (d, $J = 119.1$ Hz), 129.5 (d, $J = 10.3$ Hz), 128.6 (d, $J = 12.2$ Hz), 127.7 (d, $J = 7.5$ Hz), 118.5 (d, $J = 13.6$ Hz), 110.0 (d, $J = 104.1$ Hz), 16.0 (d, $J = 1.7$ Hz); HRMS (ESI+): Exact mass calcd for $\text{C}_{19}\text{H}_{18}\text{O}_2\text{P}$ [M+H], 309.1039. Found 309.1042, $\sigma = 0.0002$; AT-IR (neat): 3168, 3058, 2951, 1591, 1459, 1437, 1419, 1264, 1246, 1231, 1185, 1158, 1131, 1119, 1079, 1042, 1028 cm^{-1} .

ortho-cresol: ^1H NMR (300 MHz, Chloroform-*d*) δ 7.19 – 7.03 (m, 2H), 6.87 (td, $J = 7.4, 1.2$ Hz, 1H), 6.79 (dd, $J = 7.9, 1.2$ Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 153.7, 131.0, 127.1, 123.8, 120.7, 114.9, 15.7.

2.35 Catalytic etherification of decanol with K1 and triflic acid to form didecyl ether (Scheme 32)

According to the representative catalytic ether formation, decanol (11.84 mmol) was heated with 5 mol% triflic acid and 5 mol% catalyst oxide **17** (100 mg) over 15 h in toluene (17 mL) under Dean-Stark conditions. NMR analysis indicated 63% ether.

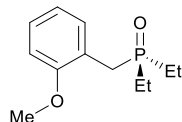
2.36 Catalytic tosylation of decanol with K1 and tosic acid to form decyl tosylate **36** (Table 3)

K1 (45.7 mg, 0.148 mmol, 2.5 mol% wrt product), decanol (1.13 mL, 5.91 mmol) and tosic acid monohydrate (1.13 g, 5.91 mmol) were combined in toluene (17 mL) under Dean-Stark conditions for 15 h. The product was decyl tosylate, formed in 85% conversion, with 15% of the O-CH₂ signals present as ether. The signals for the decyl tosylate were extracted from the crude spectrum and are as follows: ¹H NMR (400 MHz, CDCl₃) δ 7.82 – 7.77 (m, 2H), 7.38 – 7.32 (m, 2H), 7.30 – 7.24 (m, 3H), 7.21 – 7.15 (m, 3H), 4.03 (t, *J* = 6.5 Hz, 2H), 2.36 (s, 3H), 1.68 – 1.59 (m, 2H), 1.33 – 1.18 (m, 14H), 0.89 (t, *J* = 6.9 Hz, 3H).

2.37 Screen of carboxylic acids for the esterification of decanol or 2-octanol with K1 (Table 10)

According to the general catalytic procedure, the acids, solvents and temperatures were combined as stated in Table 10.

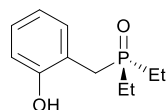
2.4 K2: Synthesis and Experiments

diethyl(2-methoxybenzyl)phosphine oxide (MeO-K2, 47)¹⁰

Chlorodiethylphosphane (1.0 mL, 8.2 mmol) was added dropwise over 30 min, to an ice-cold solution of (2-methoxyphenyl)methanol (1.13 g, 8.2 mmol) and triethylamine (1.26 mL, 9.0 mmol) in degassed diethyl ether (3.5 mL). After stirring for a further 30 min at room temperature, the reaction was filtered under argon to remove the amine-HCl salt. The filtrate was concentrated on a Schlenk line, maintaining an argon atmosphere immediately after the ether had evaporated. The liquid was dissolved immediately in chloroform (8 mL) and added was trimethylsilyl trifluoromethanesulfonate (74 μ L, 0.41 mmol, 5.0 mol%). The reaction was stirred at 60 °C for 2 h, and concentrated. The residue was dissolved in dichloromethane, washed with saturated aqueous sodium bicarbonate solution, 1 M HCl solution and brine, dried over magnesium sulfate, filtered and concentrated. The crude material was dry-loaded onto silica and purified by flash column chromatography (9:1 dichloromethane/acetone) to give a semi pure colourless residue (800 mg, 43%). Selected data from this semi pure spectrum; ¹H NMR (400 MHz, CDCl₃): δ 7.30 – 7.22 (m, 1H), 7.23 – 7.17 (m, 1H), 6.94 – 6.88 (m, 1H), 6.87 – 6.82 (m, 1H), 3.81 (s, 3H), 3.20 (d, J = 15.4 Hz, 2H), 1.69 – 1.54 (m, 4H), 1.16 (t, J = 7.8 Hz, 3H, P-CH(H')(H')-Me), 1.12 (t, J = 7.8 Hz, 3H, P-CH(H')(H')-Me). ¹³C NMR (101 MHz, CDCl₃) δ 156.7 (d, J = 4.6 Hz), 131.2 (d, J = 4.5 Hz), 128.1 (d, J = 3.1 Hz), 121.8 – 119.8 (m), 110.4 (d, J = 2.9 Hz), 55.1, 29.0 (d, J = 60.5 Hz), 19.8 (d, J = 66.4 Hz), 5.5 (d, J = 5.1 Hz); ³¹P NMR (162 MHz) δ 50.6; HRMS

(ESI+): Exact mass calcd for $C_{12}H_{19}NaO_2P$ $[M+Na]$, 249.1015. Found 249.1022, $\sigma = 0.0008$; **IR** (cm^{-1}) ($CDCl_3$) 3072, 3011, 1602, 1249, 1139.

diethyl(2-hydroxybenzyl)phosphine oxide (K2)¹¹



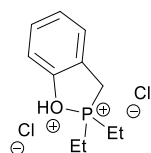
Phosphine oxide **MeO-K2**, **47** (800 mg, 3.54 mmol) was dissolved in chloroform (10 mL) and added was boron trichloride dimethylsulfide complex (1.27 g, 7.08 mmol). The reaction was heated at reflux for 16 h. The reaction mixture was diluted with chloroform 15 mL and quenched cautiously with saturated aqueous sodium bicarbonate solution and stirred for 1 h. The organic layer was separated, and then washed with saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate, filtered and concentrated. The crude material was dry-loaded onto silica and purified by short flash column chromatography (20-100% EtOAc in petrol, then eluting with DCM/acetone 9:1) to give a white solid (500 mg, 72%). **¹H NMR** (400 MHz, $CDCl_3$) δ 9.72 (s, 1H), 7.22 – 7.12 (m, 1H), 7.04 – 6.92 (m, 2H), 6.89 – 6.79 (m, 1H), 3.14 (d, $J = 12.1$ Hz, 2H), 1.94 – 1.58 (m, 5H), 1.18 (t, $J = 7.8$ Hz, 3H), 1.14 (t, $J = 7.7$ Hz, 3H); **¹³C NMR** (101 MHz, $CDCl_3$) 156.3 (d, $J = 3.8$ Hz), 131.0 (d, $J = 6.1$ Hz), 128.9 (d, $J = 2.7$ Hz), 120.6 (d, $J = 1.3$ Hz), 119.7 (d, $J = 8.4$ Hz), 119.5 (d, $J = 2.6$ Hz), 32.0 (d, $J = 60.8$ Hz), 19.5 (d, $J = 65.9$ Hz), 5.6 (d, $J = 4.6$ Hz); **³¹P NMR** (162 MHz, $CDCl_3$) δ 58.8; **HRMS** (ESI+): Exact mass calcd for $C_{11}H_{17}NaO_2P$ $[M+Na]$, 235.0858. Found 235.0862, $\sigma = 0.0006$; **IR** (cm^{-1}) ($CDCl_3$) 3692, 1602, 1488, 1270, 1249, 1148, 1127. **Mp** 124.5-125.5 °C. (lit. 127 °C).⁹

According to the representative catalytic tosylation reaction, **K2** (31.4 mg) was used in **K1**'s place, and gave 34% tosylate, 42% decanol and 24% ether by integration of the O-CH₂ 2H triplet signals.

2.41 Reaction of K2 with oxalyl chloride and decanol (Scheme 49)

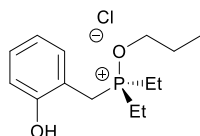
Phosphine oxide **K2** (10 mg, 0.047 mmol) was dissolved in CDCl₃ (0.5 mL) in a dry NMR tube under argon and added was oxalyl chloride (4.0 µL, 0.047 mmol). The reaction was warmed gently until more no gas was observed to be evolved. NMR data was recorded immediately:

Unknown species, potentially:



2,2-diethyl-2,3-dihydro-1H-benzo[d][1,2]oxaphosphole-1,2-diium dichloride

¹H NMR (400 MHz, CDCl₃): δ 8.03 (s, 1H), 7.38 – 7.35 (m, 1H), 7.32 – 7.27 (m, 1H), 7.15 – 7.10 (m, 1H), 7.06 – 7.02 (m, 1H), 4.34 (d, *J* = 13.1 Hz, 2H), 3.42 – 2.55 (m, 2H), 1.38 (t, *J* = 7.6 Hz, 3H), 1.33 (t, *J* = 7.6 Hz, 3H). (Note that the signal at 3.06 does not integrate to the expected 4H, and appears as a broad doublet, *J* = 119.8 Hz); ¹³C NMR (101 MHz, CDCl₃) δ 155.8 (d, *J* = 2.4 Hz), 130.0 (br. s), 127.0 (d, *J* = 15.4 Hz), 124.5, 120.9 (d, *J* = 2.2 Hz), 113.3 (d, *J* = 8.4 Hz), 29.7 (d, *J* = 61.4 Hz), 22.8 (d, *J* = 61.0 Hz, 2C), 5.4 (d, *J* = 7.2 Hz, 2C); ³¹P NMR (162 MHz, CDCl₃) δ 114.0.

diethyl(2-hydroxybenzyl)(propoxy)phosphonium chloride

Decanol was then added to the above species in the NMR tube and the reaction mixed with shaking. Immediate NMR analysis showed the following selected signals, consistent with a phosphonium chloride salt. The mixture contained roughly 3.3:1 ratio of this salt to oxide/decanol (formed by hydrolysis).

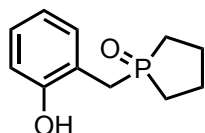
^1H NMR (400 MHz, CDCl_3): δ 9.37 (s, 2H), 7.42 – 7.35 (m, 1H), 7.19 – 7.06 (m, 2H), 6.82 – 6.69 (m, 1H), 4.20 (dt, J = 6.2 Hz, 2H), 3.88 (t, J = 6.2, 5.6 Hz, 2H), 2.57 – 2.27 (m, 4H), 1.68 – 1.53 (m, 2H), 1.38 – 1.09 (m, 20H), 0.86 (t, J = 6.7 Hz, 3H); **^{13}C NMR** (101 MHz, CDCl_3) δ 155.6 (d, J = 4.7 Hz), 131.0 (d, J = 5.6 Hz), 130.0 (d, J = 3.4 Hz), 120.1 (d, J = 2.9 Hz), 117.3 (d, J = 2.6 Hz), 113.2 (d, J = 8.0 Hz), 71.2 (d, J = 8.6 Hz), 31.8, 30.3 (d, J = 6.3 Hz), 29.5 (d, J = 4.2 Hz), 29.4, 29.3, 29.2, 29.0, 25.2, 22.6, 16.0 (d, J = 58.6 Hz), 14.1, 5.0 (d, J = 5.5 Hz). **$^{31}\text{P}\{\text{H}\}$ NMR** (162 MHz, CDCl_3) δ 97.0.

The NMR tube mixture was then heated at 70 °C for 15 min, and the mixture checked by ^1H -NMR spectroscopy. The conversion to chlorodecane was 38%, with 62% remaining phosphonium salt by integration of the CH_2 groups on the decyl chain in the ^1H -NMR spectrum. Chlorodecane was identified from the following key shifts from the Cl-CH_2 -group: **^1H NMR** (400 MHz, CDCl_3): δ 3.51 (t, J = 6.8 Hz, 2H); **^{13}C NMR** (101 MHz, CDCl_3) δ 45.3.

2.5 Synthesis and experiments of Catalysts K3-K12

2.51 Synthesis and Experiments of K3 and K4

1-(2-hydroxybenzyl)phospholane 1-oxide (K3)



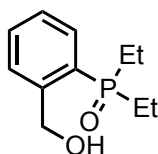
K3: 802

(As depicted in Scheme 38) According to an adapted literature procedure,¹² magnesium turnings (510 mg, 21 mmol) was activated by stirring with an iodine crystal in THF (7.5 mL). 1,4-dibromobutane (1.12 mL, 10 mmol) dissolved in THF (2.5 mL) was added dropwise to the solution over 45 min to give a thick, grey solution. After stirring for a further 15 min, diethylphosphite (859 μ L, 6.66 mmol) in THF (4 mL) was added over 5 min (large exotherm), and the reaction stirred at ambient temperature for 1 h, followed by 30 min at reflux. The solids dissolved over this time. Then, benzyl chloride **12** (1.04 g, 6.66 mmol) was added in a minimum of THF, and the reaction refluxed for 17 h. The reaction was quenched with saturated ammonium chloride solution, and the mixture extracted twice with an excess of ethyl acetate. The combined organics were washed with brine, dried over magnesium sulfate and concentration to give a crude residue. The ³¹P-NMR of the crude mixture showed a major peak at 70 ppm. After chromatography (0-100% EtOAc in petrol) the desired had not eluted, and was eventually washed off the column with EtOAc:MeOH (4:1) giving a clear oil (820 mg) with major ³¹P-NMR peak at 71.1 ppm. A large shoulder suggested a major impurity of a similar composition. Although unclean, ¹H-NMR showed a clear benzyl doublet with $3J_{\text{PH}}=16$ Hz at 3.36 ppm and multiplets consistent with the desired ring system between 1.5 and 2 ppm. Other fractions contained a mixture of partially

reacted species, including the benzylated diethylphosphite suggesting a greater excess of Grignard might be required.

The above mixture containing an undetermined amount of oxide **MeO-K3** (sample mass: 820 mg, mas: 2.68 mmol) was dissolved in chloroform (11 mL) with boron trichloride dimethylsulfide complex (1.31 g, 5.36 mmol) and heated at reflux for 15 h. After this time, the reaction was cooled and washed with saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate, filtered and concentrated. Analysis of the crude material before purification suggested some decomposition of some of the components of the mixture and confirmation of the shoulder impurity. The crude material was dry-loaded onto silica and purified by flash column chromatography (dichloromethane:acetone 90:10→ 85:15) to give a clear oil (142 mg, 91% pure by ^{31}P -NMR, 7% overall yield.) ^1H NMR (400 MHz, Chloroform-*d*) δ 9.57 (s, 1H), 7.12 – 7.01 (m, 2H), 6.92 (dd, J = 8.1, 1.2 Hz, 1H), 6.78 (tt, J = 7.4, 1.0 Hz, 1H), 3.27 (d, J = 14.0 Hz, 2H), 2.01 – 1.84 (m, 4H), 1.79 – 1.55 (m, 2H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 155.7 (d, J = 4.5 Hz), 130.9 (d, J = 5.3 Hz), 128.6 (d, J = 3.0 Hz), 120.1 (d, J = 2.6 Hz), 119.1 (d, J = 8.3 Hz), 117.7 (d, J = 2.8 Hz), 33.6 (d, J = 57.7 Hz), 25.8 (d, J = 64.5 Hz), 24.2 (d, J = 8.5 Hz); ^{31}P NMR (162 MHz, Chloroform-*d*) δ 77.6; **HRMS** (ESI⁺): Exact mass calcd for $\text{C}_{11}\text{H}_{16}\text{O}_2\text{P}$ [M+H], 211.088243. Found 211.089278, σ = 0.00151.

diethyl(2-(hydroxymethyl)phenyl)phosphine oxide (**K4**)



K4: 809

*A better route to this compound might use the referenced procedure instead.*¹³

(As depicted in Scheme 38) Salicylaldehyde (500 mg, 4.09 mmol) and triethylamine (791 μ L, 9.82 mmol) were dissolved in dichloromethane (7.7 mL) and cooled to 0 °C. Added dropwise to maintain the temperature was triflic anhydride (825 μ L, 4.91 mmol), the ice bath removed, and the reaction stirred warming to room temperature over 2 h. The reaction was quenched with saturated aqueous sodium bicarbonate solution at 0 °C, and the organics separated. The aqueous layer was extracted a further 3 times with dichloromethane and the combined organics dried over magnesium sulfate, filtered, and concentrated. The desired triflated benzylaldehyde **50a** was isolated as a clear oil (1.04 g) by flash column chromatography (10-20% EtOAc in petrol).

According to a literature procedure,¹⁴ aldehyde **50a** was dissolved in methanol (17 mL) and sodium borohydride (246 mg, 6.50 mmol) was added portion-wise with stirring at rt. After 30 min, TLC indicated full conversion of aldehyde to alcohol, and the reaction was concentrated by ~75%, diluted with EtOAc and washed with HCL (1 M, aq), saturated sodium bicarbonate solution and brine, and then dried over magnesium sulfate and concentrated. The residue was loaded onto a short pad of silica with petrol. After washing with a little petrol and petrol:ether (9:1), the desired alcohol was isolated cleanly by flushing off the silica with neat ether to give alcohol **50b** as a clear oil (881 mg, 84% over 2 steps); ¹H NMR (400 MHz, Chloroform-*d*) δ 7.65 – 7.59 (m, 1H), 7.44 – 7.35 (m, 2H), 7.30 – 7.25 (m, 1H), 4.83 – 4.78 (m, 2H); ¹³C NMR (101 MHz, Chloroform-*d*) δ 146.9, 133.6, 130.0, 129.5, 128.7, 121.3, 59.5; ¹⁹F NMR (377 MHz, Chloroform-*d*) δ -73.6; **HRMS** (ESI+): Exact mass calcd for C₈H₇F₃NaO₄S [M+Na], 278.9909. Found 278.9915, σ = 0.0045.

Palladium acetate (157 mg, 0.7 mmol) and potassium acetate (7 mg, 0.07 mmol), and dppf (1,1'-Bis(diphenylphosphino)ferrocene) (388 mg, 0.7 mmol) were dissolved in DMF (3.5

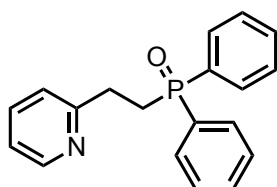
mL) and heated at 60 °C for 30 min. Added was then DiPEA (975 μ L, 5.6 mmol) and diethylphosphite (1.33 mL, 10.3 mmol) and the reaction heated for 15 min. Triflate **50b** (881 mg, 3.44 mmol) was then added slowly as a solution in DMF (14 mL). The reaction was then heated for 12 h at 100 °C. After this time the reaction was concentrated under vacuum, and the residue partitioned between water and diethyl ether. The organic layer was dried over magnesium sulfate and concentrated. After chromatography, a dark residue was isolated which was speculated to be cyclic species **50** (130 mg), having similar data to related compounds.¹³ Other products gave signs that triflate migration to the benzyl alcohol had occurred, followed by alkylation reactions (characteristic P-benzyl doublet at 3.74 ppm, $J = 12.9$ Hz). Species **50** had selected signals: ¹H NMR (400 MHz, Chloroform-*d*) δ 7.77 – 7.67 (m, 1H), 7.58 – 7.51 (m, 1H), 7.47 – 7.38 (m, 1H), 7.31 – 7.25 (m, 1H), 5.23 (roofing dd, $J = 9.1, 14.0$ Hz, 1H), 5.17 (roofing dd, $J = 7.0$ Hz, 14.0 Hz, 1H), 4.18 – 3.97 (m, 2H), 1.18 (t, $J = 7.1$ Hz, 3H); ³¹P NMR (162 MHz, Chloroform-*d*) δ 35.9.

Species **50** (112 mg, 0.458 mmol) was dissolved in THF (2 mL) and added at rt was an excess of ethyl magnesium bromide 3.0 M in ether (0.55 mL, 1.6 mmol) and the reaction refluxed for 15 h. After this time, the reaction was quenched with quenched with saturated ammonium chloride solution, and the mixture extracted twice with ethyl acetate. The combined organics were washed with brine and dried over magnesium sulfate. The material was purified by flash column chromatography (CH₂Cl₂:petrol, then eluted with MeOH:acetone:CH₂Cl₂ 5:20:75) to give **K4** as a residue (50.8 mg, 7% overall yield); ¹H NMR (400 MHz, Chloroform-*d*) δ 7.48 – 7.42 (m, 1H), 7.40 – 7.26 (m, 3H), 5.96 (br. s, 1H, OH), 4.73 (br. s, 2H, CH₂), 2.09 – 1.91 (m, 4H), 1.12 (dt, $J = 17.2, 7.7$ Hz, 6H); ¹³C NMR (101 MHz, Chloroform-*d*) δ 147.4 (d, $J = 5.5$ Hz), 131.9 (d, $J = 2.5$ Hz), 131.2 (d, $J = 9.7$ Hz), 130.6 (d, $J = 12.2$ Hz), 129.5 (d, $J = 87.5$ Hz), 127.5 (d, $J = 11.7$ Hz), 65.3 (d, $J =$

3.2 Hz), 22.8 (d, $J = 69.7$ Hz), 5.5 (d, $J = 5.3$ Hz); ^{31}P NMR (162 MHz, Chloroform- d) δ 51.6; **HRMS** (ESI+): Exact mass calcd for $\text{C}_{11}\text{H}_{18}\text{O}_2\text{P}$ $[\text{M}+\text{H}]$, 213.1039. Found 278.9915, $\sigma = 0.0045$. The data were in good agreement with a related compound.¹⁵

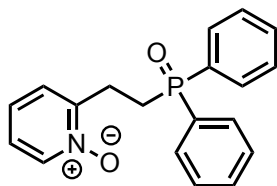
2.52 Synthesis and Experiments of K5 and K6

diphenyl(2-(pyridin-2-yl)ethyl)phosphine oxide (K5)¹⁶

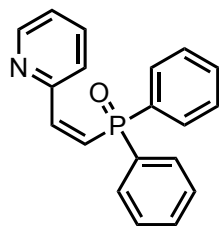


K5: 1135/1139

(As depicted in Scheme 40) According to a literature procedure,¹⁶ 2-vinylpyridine (539 μL , 5.00 mmol) was mixed neat with diphenylphosphine oxide (1.01g, 5.00 mmol) in a microwave vial (~ 10 mL) and the vial sealed and microwave heated for 1 h at 120 $^{\circ}\text{C}$. The resulting solid was triturated in ether/pentane (1:1) to give the title compound as a white solid (1.32 g, 86%); ^1H NMR (400 MHz, Chloroform- d) δ 8.48 (dd, $J = 4.9, 1.7$ Hz, 1H), 7.84 – 7.72 (m, 4H), 7.58 – 7.40 (m, 7H), 7.16 – 7.04 (m, 2H), 3.18 – 3.07 (m, 2H), 2.84 – 2.74 (m, 2H); ^{31}P NMR (162 MHz, Chloroform- d) δ 32.1; ^{13}C NMR (101 MHz, Chloroform- d) δ 160.2 (d, $J = 14.0$ Hz), 149.2, 136.5, 132.8 (d, $J = 98.8$ Hz), 131.7 (d, $J = 2.9$ Hz), 130.8 (d, $J = 9.3$ Hz), 128.6 (d, $J = 11.7$ Hz), 123.1, 121.5, 29.7 (d, $J = 2.9$ Hz), 29.2 (d, $J = 71.8$ Hz); **HRMS** (ESI+): Exact mass calcd for $\text{C}_{19}\text{H}_{18}\text{NNaOP}$ $[\text{M}+\text{Na}]$, 330.1018. Found 330.1020, $\sigma = 0.0013$; **AT-IR** (neat): 3065, 3005, 2988, 2910, 1588, 1568, 1475, 1435, 1175, 1119, 1104 cm^{-1} ; **Mp**: 112-113 $^{\circ}\text{C}$

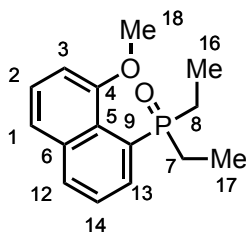
2-(2-(diphenylphosphoryl)ethyl)pyridine 1-oxide (K6)

Pyridine **K5** (1.00 g, 3.25 mmol) was dissolved in AcOH (4 mL) and added was aqueous hydrogen peroxide (excess, 1 mL) and the reaction heated at 80 °C for 17 h. After this time, the reaction was concentrated by 2/3 volume and partitioned between dichloromethane and aqueous sodium bicarbonate. The organic layer was separated, dried over magnesium sulfate and concentrated to give the title compound as a yellow oil that was difficult solidify but clean by ^1H -NMR (mp 85-86 °C) (1.05 g, quant.). ^1H NMR (400 MHz, Chloroform-*d*) δ 8.13 (dd, J = 5.7, 2.1 Hz, 1H), 7.84 – 7.75 (m, 4H), 7.51 – 7.39 (m, 6H), 7.28 – 7.22 (m, 1H), 7.12 – 7.03 (m, 2H), 3.30 – 3.19 (m, 2H), 2.91 – 2.80 (m, 2H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 150.5 (d, J = 12.6 Hz), 139.5, 132.7 (d, J = 99.1 Hz), 131.7 (d, J = 2.9 Hz), 130.6 (d, J = 9.5 Hz), 128.6 (d, J = 11.8 Hz), 126.8, 125.8, 124.2, 25.1 (d, J = 70.9 Hz), 24.9 (d, J = 2.7 Hz); **HRMS** (ESI+): Exact mass calcd for $\text{C}_{19}\text{H}_{18}\text{NNaO}_2\text{P}$ [$\text{M}+\text{Na}$], 346.0967. Found 346.0973, σ = 0.0022; **AT-IR** (neat): 3388, 5057, 2224, 1654, 1489, 1437, 1422, 1237, 1221, 1172, 1119, 1071 cm^{-1} ; **Mp**: 85-86 °C (not a great solid)

2.53 Attempted *p*-pyridyl chlorination of K6**(*Z*)-diphenyl(2-(pyridin-2-yl)vinyl)phosphine oxide****1141-cp3**

The chlorination of pyridine *N*-oxide **K6** in the para-position was attempted as follows: Oxide **K6** (800 mg, 2.48 mmol) was added to neat POCl₃ (5 mL) at 0 °C and then reflux for 16 h at 100 °C. After this time the black mixture was cooled and cautiously quenched with aqueous sodium hydroxide (1 M) and stirred for 2 h. The mixture was extracted with dichloromethane, dried over magnesium sulfate and concentrated to give a black crude residue (730 mg). After chromatography (0–20 % MeOH in EtOAc), chlorinated oxide **55** was isolated as a partially pure residue (84 mg), along with the title compound as a mixture (76% alkene) along with some deoxygenated pyridine. Cis stereochemistry assigned using the alkene coupling constant (14 Hz) and by comparison to the known trans isomer¹⁷ and related cis compound¹⁸ (quoted in Appendix 1). Following peaks extracted from the semi pure NMR spectra; ¹H NMR (400 MHz, Chloroform-*d*) δ 8.40 – 8.32 (m, 1H), 7.92 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.81 – 7.72 (m, 4H), 7.59 (dd, *J* = 39.1, 14.0 Hz, 1H), 7.50 – 7.32 (m, 8H), 7.02 (ddd, *J* = 7.6, 4.8, 1.1 Hz, 1H), 6.55 (dd, *J* = 18.7, 14.0 Hz, 1H); ³¹P NMR (162 MHz, Chloroform-*d*) δ 20.19; **HRMS** (ESI+): Exact mass calcd for C₁₉H₁₈NNaO₂P [M+Na], 306.1042. Found 306.1063, σ = 0.0078.

2.54 Synthesis and Experiments of K7

diethyl(8-methoxynaphthalen-1-yl)phosphine oxide (MeO-K7, 52)**K7: 1036/1134/1167**

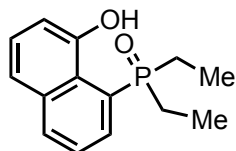
(As depicted in Scheme 39) According to an adapted literature procedure,^{19,20} 1-methoxynaphthalene (1.00 g, 6.32 mmol) was dissolved in hexane (12 mL) and added dropwise at room temperature (20 °C) over 10 min was ^tBuLi 1.7 M in pentanes (4.46 mL, 7.58 mmol). The reaction was stirred at room temperature for 20 h. Trichlorophosphine (1.39 mL, 6.32 mmol) was then added as a solution in hexane (1.5 mL) dropwise over 30 min at –78 °C. The reaction was stirred, warming to ambient temperature over 17 h. The reaction was recooled to 0 °C, and added was ethylmagnesium bromide (3.0 M in ether, commercial) over 60 min. The reaction was allowed to warm to ambient temperature overnight.

The mixture was partitioned between water and ethyl acetate and the organics separated. The organics were partially concentrated to ~ 10 mL solvent and added was an excess of an aqueous hydrogen peroxide solution. The reaction was stirred at ambient temperature for 2 h, and then the layers separated. The organic layer was washed thoroughly with aqueous HCl (1 M), an aqueous sodium bicarbonate solution, and brine, dried over magnesium sulfate, and concentrated. The crude material was subjected to column chromatography 0–20 % methanol in ethyl acetate. Approximately 220 mg of ^tBuP(=O)Et₂ was eluted (³¹P-NMR δ 56.7 ppm) before the desired eluted as a moderately pure white foam (270 mg, 8%)

which was taken to deprotection without further purification. The following data was extracted from the relevant NMR spectra: ^1H NMR (300 MHz, Chloroform-*d*) δ 8.66 (ddd, $J_{H-P} = 14.1, J = 7.3, 1.4$ Hz, *H13*), 7.93 (ddd, $J = 8.3, 1.8, 1.4$ Hz, *H12*), 7.58 (ddd, $J = 8.3, 7.3, 1.2$ Hz, *H14*), 7.52 (ddd, $J = 8.2, 1.8, 1.2$ Hz, *H1*), 7.42 (dd, $J = 8.2, 7.6$ Hz, *H2*), 6.92 (dd, $J = 7.6, 1.2$ Hz, *H3*), 3.95 (s, 3H), 2.25 – 2.11 (m, 4H), 1.06 (dt, $J = 17.8, 7.7$ Hz, 6H); ^{31}P NMR (121 MHz, Chloroform-*d*) δ 50.5; ^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.3, 136.7 (d, $J = 5.4$ Hz), 135.5 (d, $J = 7.7$ Hz), 132.3 (d, $J = 3.0$ Hz), 126.5 (d, $J = 109.1$ Hz), 125.9, 125.7 (d, $J = 11.5$ Hz), 125.0 (d, $J = 6.6$ Hz), 122.4, 106.0, 54.1, 24.0 (d, $J = 73.5$ Hz), 6.4 (d, $J = 5.4$ Hz). **HRMS** (ESI+): Exact mass calcd for $\text{C}_{15}\text{H}_{20}\text{O}_2\text{P}$ [$\text{M}+\text{H}$], 263.1195. Found 263.1202, $\sigma = 0.0027$.

Phosphine oxide **MeO-K7, 52** (270 mg, 1.03 mmol) was dissolved in dry chloroform (3 mL) and added was boron trichloride dimethylsulfide complex (369 mg, 2.06 mmol) and the reaction refluxed for 16 h. After this time, the reaction was quenched cautiously with aqueous sodium bicarbonate solution and stirred for 3 h (not required) at room temperature. The layers were separated and the organic layer washed with further bicarbonate and brine, dried over magnesium sulfate and concentrated. The resulting residue (200 mg, 78%) was a mixture (73:27) of the desired and a species consistent with the phosphonium salt.

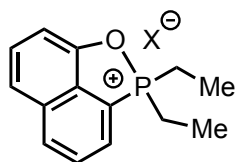
73%: **diethyl(8-hydroxynaphthalen-1-yl)phosphine oxide (K7)**



1134

^1H NMR (400 MHz, Chloroform-*d*) δ 8.00 (dt, J = 8.3, 1.4 Hz, 1H), 7.68 – 7.52 (m, 1H), 7.52 – 7.37 (m, 3H), 7.24 – 7.18 (m, 1H), 2.23 (dq, J = 10.4, 7.6 Hz, 4H), 1.17 (dt, J = 17.6, 7.7 Hz, 6H); ^{31}P NMR (162 MHz, Chloroform-*d*) δ 60.49; HRMS (ESI+): Exact mass calcd for $\text{C}_{14}\text{H}_{18}\text{O}_2\text{P}$ $[\text{M}+\text{H}]$, 249.1039. Found 249.1042, σ = 0.0052. (only this species seen by mass spec, indicating the below species is hydrolysed to oxide.) (*Carbon signals inseparable from the below*)

And: 27%



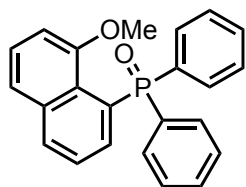
1134

Selected signals from the mixture: Identity of X unknown, probably chloride from the BCl_3 .

^1H NMR (400 MHz, Chloroform-*d*) δ 8.17 (d, J = 7.6 Hz, 1H), 6.73 (d, J = 7.4 Hz, 1H), 2.92 – 2.74 (br. m, 2H), 2.74 – 2.59 (br. m, 2H), 1.37 – 1.04 (m, 6H); ^{31}P NMR (162 MHz, Chloroform-*d*) δ 79.6.

2.55 Synthesis and Experiments of K8

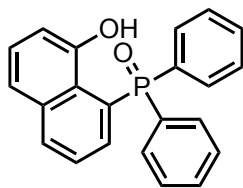
(8-methoxynaphthalen-1-yl)diphenylphosphine oxide (52)



760

(As depicted in Scheme 38) According to an adapted literature procedure,^{19,20} 1-methoxynaphthalene (1.00 g, 6.32 mmol) was dissolved in hexane (12 mL) and added

dropwise at room temperature (20 °C) over 10 min was ^tBuLi 1.7 M in pentanes (4.46 mL, 7.58 mmol). The reaction was stirred at room temperature for 20 h to give a dull yellow/tan suspension. *P*-chlorodiphenylphosphine (1.39 mL, 6.32 mmol) was then added as a solution in hexane (1.5 mL) dropwise over 30 min at room temperature. The reaction was stirred at ambient temperature over 17 h, becoming gradually lighter to give a cream suspension. The mixture was partitioned between water and ethyl acetate and the organics separated. The organics were partially concentrated to ~ 10 mL solvent and added was an excess of an aqueous hydrogen peroxide solution. The reaction was stirred at ambient temperature for 2 h, and then the layers separated. The organic layer was washed thoroughly with aqueous HCl (1 M), an aqueous sodium bicarbonate solution, and brine, dried over magnesium sulfate, and concentrated. The crude material was triturated in diethyl ether and subjected to column chromatography 60:40 EtOAc:petrol. Approximately 650 mg of ^tBuP(=O)Ph₂ was eluted (³¹P-NMR δ 38.9 ppm) before flushing the column with 20% MeOH: EtOAc to give the desired as a moderately pure white foam (870 mg, 38%) which was taken to deprotection without further purification. The following data was extracted from the relevant NMR spectra: ¹H NMR (400 MHz, Chloroform-*d*) δ 8.00 (d, *J* = 8.2 Hz, 1H), 7.76 – 7.37 (m, 14H), 6.79 (d, *J* = 7.5 Hz, 1H), 3.33 (s, 3H); ³¹P NMR (162 MHz, Chloroform-*d*) δ 35.56; ¹³C NMR (101 MHz, Chloroform-*d*) δ 154.8 (d, *J* = 1.5 Hz), 136.4 (d, *J* = 11.7 Hz), 135.7 (d, *J* = 110.0 Hz), 135.5 (d, *J* = 8.3 Hz), 133.2 (d, *J* = 3.0 Hz), 131.0 (d, *J* = 9.4 Hz), 130.7 (d, *J* = 2.6 Hz), 128.2 (d, *J* = 12.3 Hz), 127.0, 126.2 (d, *J* = 5.8 Hz), 126.1 (d, *J* = 101.7 Hz), 125.0 (d, *J* = 14.5 Hz), 121.3, 107.0, 53.7; **HRMS** (ESI⁺): Exact mass calcd for C₂₃H₁₉NaO₂P [M+Na], 381.1015. Found 381.1021, σ = 0.0023.

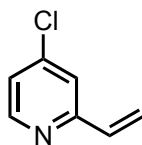
(8-hydroxynaphthalen-1-yl)diphenylphosphine oxide (K8)**K8: 767**

Phosphine oxide **52** (870 mg, 2.43 mmol) was dissolved in dry chloroform (9 mL) and added was boron trichloride dimethylsulfide complex (871 mg, 4.86 mmol) and the reaction refluxed for 16 h. After this time, the reaction was quenched cautiously with aqueous sodium bicarbonate solution and stirred for 15 min at room temperature. The layers were separated and the organic layer washed with further bicarbonate and brine, dried over magnesium sulfate and concentrated. (note: dilute with dichloromethane and isopropanol if having solubility issues at start of work-up.) The resulting residue was triturated with dichloromethane to give a white solid, which was heated in a mixture of hot MeCN/DMSO/EtOH. After cooling, the insoluble solid was collected by filtration and washed with acetonitrile to give the title compound as a white solid (382 mg, 47%). The location of the phosphorus on the naphthyl ring was confirmed by x-ray crystallography. ^1H NMR (400 MHz, DMSO- d_6) δ 11.47 (s, 1H), 8.16 (d, J = 7.4 Hz, 1H), 7.66 – 7.42 (m, 15H), 6.90 (d, J = 7.5 Hz, 1H); ^{31}P NMR (162 MHz, DMSO- d_6) δ 39.86; ^{13}C NMR (126 MHz, DMSO- d_6) δ 153.2 (d, J = 3.2 Hz), 135.9 (d, J = 8.5 Hz), 134.6 (d, J = 11.4 Hz), 134.2 (d, J = 2.9 Hz), 133.2 (d, J = 108.3 Hz), 131.9 (d, J = 2.7 Hz), 131.5 (d, J = 9.9 Hz), 128.8 (d, J = 12.2 Hz), 127.9, 125.5 (d, J = 97.9 Hz), 125.0 (d, J = 6.3 Hz), 124.3 (d, J = 14.3 Hz), 120.3, 113.6; ^1H NMR (400 MHz, Methanol- d_4) δ 8.12 (dt, J = 8.2, 1.5 Hz, 1H), 7.71 – 7.54 (m, 7H), 7.54 – 7.43 (m, 6H), 7.41 (t, J = 7.8 Hz, 1H), 6.84 (dd, J = 7.6, 1.2 Hz, 1H); ^{31}P NMR (162 MHz, Methanol- d_4) δ 41.16; Insufficiently soluble to acquire carbon in

MeOD; **AT-IR** (neat): 2872, 2790, 2683, 2582, 1563, 1522, 1482, 1436, 1430, 1362, 1337, 1304, 1280, 1215, 1152, 1108, 1095, 1028 cm^{-1} ; **HRMS** (ESI⁺): Exact mass calcd for $\text{C}_{22}\text{H}_{18}\text{O}_2\text{P}$ [M+H], 345.1039. Found 345.1040, $\sigma = 0.0022$; **Mp**: 256 °C.

2.56 Synthesis and Experiments of K9 and K10 (Scheme 42)

4-chloro-2-vinylpyridine (57)

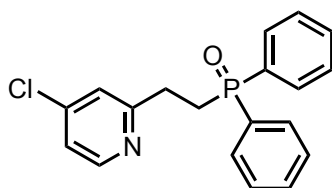


1151-C-cp4

According to an adapted literature procedure,^{21,22} 4-chloropyridine hydrochloride salt (1.00 g, 6.67 mmol) was added to a cooled (0 °C) solution of vinyl magnesium bromide 1 M in THF (20 mL, 20 mmol) in additional THF (40 mL). Phenylchloroformate (815 μL , 6.00 mmol) was added as a solution in THF (4 mL) dropwise over 5 min at 0 °C. After stirring at room temperature for 30 min, the reaction was quenched with a 1 M aqueous ammonium chloride solution and extracted with dichloromethane to give about 2 g of crude residue. The residue was partially purified by flash column chromatography, using a short column and eluting quickly with neat dichloromethane to give 1.25 g of partially purified residue of **56**. This material was immediately subjected to oxidative conditions by stirring for 3 h in toluene (10 mL) at room temperature with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1.3 g, 8.0 mmol), taking care to exclude light from the reaction mixture. The dark mixture was quenched with 1 M aqueous sodium hydroxide solution and stirred for 15 min. Another short column, eluting with neat dichloromethane ($R_f = 0.4$), provided the title pyridine as a yellow oil (111 mg, 12%). The vinyl pyridine was stored refrigerated and under argon to prevent polymerisation; ^1H NMR (300 MHz, Chloroform- d) δ 8.46 (dd, $J =$

5.3, 0.6 Hz, 1H), 7.34 (dd, $J = 2.0, 0.6$ Hz, 1H), 7.17 (dd, $J = 5.3, 2.0$ Hz, 1H), 6.77 (dd, $J = 17.5, 10.8$ Hz, 1H), 6.23 (dd, $J = 17.4, 1.1$ Hz, 1H), 5.54 (dd, $J = 10.8, 1.1$ Hz, 1H); ^{13}C NMR (101 MHz, Chloroform- d) δ 157.2, 150.3, 144.5, 135.8, 122.6, 121.5, 119.8; IR (neat): 3047, 3022, 1794, 1723, 1633, 1571, 1545, 1493, 1207 cm^{-1} .

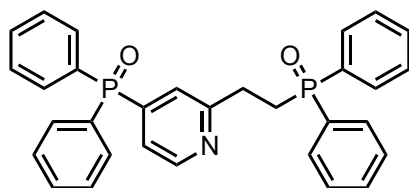
(2-(4-chloropyridin-2-yl)ethyl)diphenylphosphine oxide (55)



1175-A-cp1: 1141-cp2

According to an adapted literature procedure,¹⁶ vinyl pyridine **57** was mixed neat in a (~10 mL) microwave vial containing a stirrer bar. The vial was sealed with a lid, and subjected to microwave heating for 1 h at 120 °C. The mixture regrettably reached 160 °C briefly. The resulting mixture was partitioned between EtOAc and 1 M aqueous sodium hydroxide, and the organics separated and dried with magnesium sulfate. The resulting residue was purified by flash column chromatography using a gradient of 50-100% EtOAc in petrol and finally 1-25% MeOH in EtOAc to give two major products. The first was the desired oxide X, a yellow residue (65 mg, 25%). ^1H NMR (300 MHz, Chloroform- d) δ 8.36 (d, $J = 5.3$ Hz, 1H), 7.76 (ddt, $J = 11.6, 6.5, 1.7$ Hz, 5H), 7.59 – 7.40 (m, 7H), 7.15 – 7.04 (m, 2H), 3.15 – 3.03 (m, 2H), 2.84 – 2.70 (m, 2H); ^{13}C NMR (75 MHz, Chloroform- d) δ 161.8 (d, $J = 13.8$ Hz), 150.1, 144.3, 132.6 (d, $J = 98.9$ Hz), 131.8 (d, $J = 2.6$ Hz), 130.8 (d, $J = 9.3$ Hz), 128.7 (d, $J = 11.6$ Hz), 123.4, 121.9, 29.6 (d, $J = 2.7$ Hz), 28.9 (d, $J = 71.6$ Hz). ^{31}P NMR (121 MHz, Chloroform- d) δ 31.87; ^{31}P NMR (121 MHz, Chloroform- d) δ 31.9; IR (neat): 3055, 2921, 1575, 1555, 1468, 1180, 1118, 1103 cm^{-1} ; HRMS (ESI+): Exact mass calcd for $\text{C}_{19}\text{H}_{17}\text{ClNNaOP}$ [$\text{M}+\text{Na}$], 364.0628. Found 364.0625, $\sigma = 0.0054$.

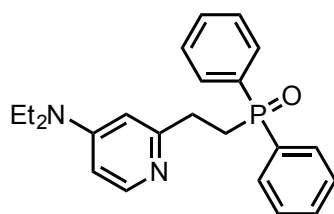
(2-(2-(diphenylphosphoryl)ethyl)pyridin-4-yl)diphenylphosphine oxide
(K10)



K10: 1175-cp2 / 1183

The second product was bis phosphine oxide **K10**, a yellow residue (80 mg, 21% wrt pyridine); ^1H NMR (300 MHz, Chloroform-*d*) δ 8.68 – 8.57 (m, 1H), 7.76 (ddt, J = 11.6, 6.6, 1.6 Hz, 4H), 7.67 – 7.54 (m, 6H), 7.54 – 7.33 (m, 11H), 3.20 – 3.03 (m, 2H), 2.88 – 2.70 (m, 2H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 160.7 (dd, J = 14.8, 10.2 Hz), 149.5 (d, J = 10.2 Hz), 142.6 (d, J = 96.2 Hz), 132.5 (d, J = 2.9 Hz), 132.5 (d, J = 99.2 Hz), 131.9 (d, J = 10.2 Hz), 131.8 (d, J = 2.6 Hz), 130.8 (d, J = 105.5 Hz), 130.8 (d, J = 9.1 Hz), 128.8 (d, J = 11.1 Hz), 128.7 (d, J = 10.3 Hz), 124.9 (d, J = 8.0 Hz), 123.5 (d, J = 7.5 Hz), 29.8, 28.8 (d, J = 71.7 Hz); ^{31}P NMR (121 MHz, Chloroform-*d*) δ 32.07 (alkyl), 26.97 (pyridyl); **AT-IR** (neat): 3054, 2922, 2853, 1586, 1436, 1186, 1118 cm^{-1} ; **HRMS** (ESI+): Exact mass calcd for $\text{C}_{31}\text{H}_{28}\text{NO}_2\text{P}_2$ [$\text{M}+\text{H}$], 508.1590. Found 508.1596, σ = 0.0029.

(2-(4-(diethylamino)pyridin-2-yl)ethyl)diphenylphosphine oxide (K9)



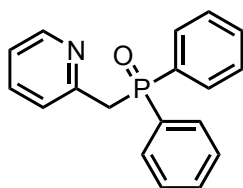
K9: 1200 / 1217

4-Chloropyridine phosphine oxide **55** was dissolved in a mixture of dioxane (0.3 mL), THF (0.3 mL) and water (0.3 mL) in a microwave vial and added was an excess (0.5 mL) of

diethylamine. The reaction was sealed, and microwave heated under pressure (up to 200 PSI) at 135 °C for 1.5 h x 5. LC-MS analysis indicated ~ 70% desired and the reaction was diluted with ethyl acetate and washed thorough with aqueous sodium bicarbonate and water. The organics were dried over magnesium sulfate and purified by column chromatography 0-20% MeOH in EtOAc and finally eluting the desired oxide with 20:1:79 MeOH:Et₃N:EtOAc as a yellow residue (22 mg, 31%); ¹H NMR (400 MHz, Chloroform-*d*) δ 8.07 (d, *J* = 6.1 Hz, 1H), 7.83 – 7.71 (m, 4H), 7.52 – 7.38 (m, 6H), 6.33 (d, *J* = 2.7 Hz, 1H), 6.27 (dd, *J* = 6.1, 2.7 Hz, 1H), 3.29 (q, *J* = 7.1 Hz, 4H), 3.03 – 2.92 (m, 2H), 2.81 – 2.71 (m, 2H), 1.13 (t, *J* = 7.1 Hz, 6H); ³¹P{¹H} NMR (162 MHz, Chloroform-*d*) δ 32.3; ¹³C NMR (101 MHz, Chloroform-*d*) δ 152.6, 149.2, 133.0 (d, *J* = 98.3 Hz), 131.6 (d, *J* = 2.9 Hz), 130.8 (d, *J* = 9.5 Hz), 128.6 (d, *J* = 11.7 Hz), 105.1, 104.4, 43.8, 30.1 (d, *J* = 2.8 Hz), 29.6 (d, *J* = 71.1 Hz), 12.3; **HRMS** (ESI+): Exact mass calcd for C₂₃H₂₈N₂OP [M+H], 379.1934. Found 379.1939, σ = 0.0044; **IR** (neat) 3055, 2971, 2929, 1596, 1538, 1504, 1470, 1180, 1118.

2.57 Synthesis and Experiments of K11 and K12 (Scheme 41)

diphenyl(pyridin-2-ylmethyl)phosphine oxide (K11)

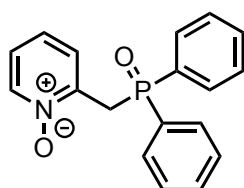


K11: 1203-E / 1227

Diphenylphosphine oxide (303 mg, 1.5 mmol) was suspended in dry THF (4 mL) at 0 °C and added was sodium hydride as a 60% dispersion in mineral oil (90 mg, 2.3 mmol). After stirring for 10 min, added was the freebase of 2-(chloromethyl)pyridine as a solution in THF (1 mL), generated immediately beforehand by extracting from an aqueous solution of

the pyridine hydrochloride salt (270 mg, 1.65 mmol) with ether (3 portions), drying the combined organics over magnesium sulfate and concentrating *in vacuo*. The reaction was then allowed to warm to ambient temperature (23 °C) over 5 h. The reaction was diluted with ethyl acetate, washed with a saturated aqueous sodium carbonate solution and brine, dried over magnesium sulfate and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (sequentially: neat EtOAc; then 0.5:1:98.5 Et₃N, MeOH, EtOAc; then 0.5:5:94.5) to give a white solid (365 mg, 83%). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.40 – 8.35 (m, 1H), 7.80 – 7.70 (m, 4H), 7.55 (ddd, *J* = 7.6, 7.6, 1.8 Hz, 1H), 7.51 – 7.38 (m, 7H), 7.11 – 7.04 (m, 1H), 3.93 (d, *J* = 14.2 Hz, 2H); ¹³C NMR (101 MHz, Chloroform-*d*) δ 152.5 (d, *J* = 7.4 Hz), 149.2, 136.4 (d, *J* = 2.2 Hz), 132.4 (d, *J* = 100.4 Hz), 131.8 (d, *J* = 2.6 Hz), 131.1 (d, *J* = 9.5 Hz), 128.5 (d, *J* = 12.3 Hz), 125.0 (d, *J* = 3.4 Hz), 121.8 (d, *J* = 2.8 Hz), 40.9 (d, *J* = 64.5 Hz). ³¹P{¹H} NMR (162 MHz, Chloroform-*d*) δ 29.73; HRMS (ESI+): Exact mass calcd for C₁₈H₁₇NOP [M+H], 294.1042. Found 294.1042, σ = 0.0035; AT-IR (neat): 3049, 2948, 2904, 1584, 1567, 1476, 1431, 1404, 1323, 1237, 1183, 1165, 1147, 1116, 1070, 1050 cm⁻¹; MP 132-133 °C.

2-((diphenylphosphoryl)methyl)pyridine 1-oxide (K12)



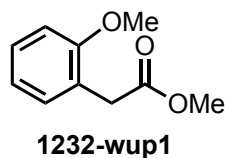
K12: 1224 / 1229

Pyridine **K11** (210 mg, 0.785 mmol) was dissolved in acetic glacial acid (1.5 mL) and added was an excess of hydrogen peroxide (30% wt in water) (1 mL) and the reaction heated at 80 °C for 12 h. The reaction was partially concentrated, diluted in dichloromethane and washed with a saturated aqueous sodium carbonate solution and

brine, dried over magnesium sulfate and concentrated *in vacuo* to give the title compound as an off-white solid (240 mg, 99%); **¹H NMR** (400 MHz, Chloroform-*d*) δ 8.12 (d, *J* = 6.4 Hz, 1H), 7.85 (m, 5H), 7.54 – 7.40 (m, 6H), 7.19 – 7.11 (m, 1H), 7.11 – 7.04 (m, 1H), 4.24 (d, *J* = 13.9 Hz, 2H); **³¹P NMR** (121 MHz, Chloroform-*d*) δ 31.25; **¹³C NMR** (126 MHz, Chloroform-*d*) δ 144.0 (d, *J* = 5.5 Hz), 139.2, 132.1 (d, *J* = 2.9 Hz), 131.9 (d, *J* = 102.1 Hz), 130.8 (d, *J* = 10.0 Hz), 128.6 (d, *J* = 12.2 Hz), 127.8 (d, *J* = 4.1 Hz), 125.6 (d, *J* = 2.4 Hz), 124.2 (d, *J* = 2.3 Hz), 30.7 (d, *J* = 66.4 Hz); **HRMS** (ESI+): Exact mass calcd for C₁₈H₁₇NO₂P [M+H], 310.0991. Found 310.0992, σ = 0.0012; **AT-IR** (neat): 3113, 3089, 3057, 3016, 2988, 2969, 2873, 1489, 1436, 1397, 1263, 1227, 1185, 1155, 1124, 1106 cm⁻¹; **MP** gradual decomp, then melting of residual solid at 184 °C.

2.58 Synthesis and Experiments of K13 (Scheme 43)

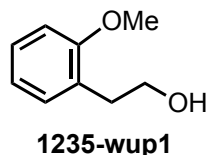
methyl 2-(2-methoxyphenyl)acetate (59)



2-(2-hydroxyphenyl)acetic acid (2.0 g, 13.1 mmol) was dissolved in acetonitrile (8 mL) and added was potassium carbonate (7.24 g, 52.4 mmol) and methyl iodide (816 μ L, 39.3 mmol) and the reaction stirred at reflux for 15 h. Over this time the reaction became yellow. Crude ¹H-NMR analysis suggested full conversion. The reaction was concentrated, diluted with ether and filtered. The ether solution was washed with brine, dried and concentrated to give a yellow oil (800 mg, 34%). [Future attempts should alter the procedure/work-up to avoid decomposition/hydrolysis]; **¹H NMR** (400 MHz, Chloroform-*d*) δ 7.26 (td, *J* = 8.0, 1.8 Hz, 1H), 7.19 (dd, *J* = 7.5, 1.8 Hz, 1H), 6.92 (td, *J* = 7.5, 1.1 Hz, 1H), 6.88 (tt, *J* = 8.3, 0.7 Hz, 1H), 3.82 (s, 3H), 3.69 (s, 3H), 3.64 (s, 2H); **¹³C NMR** (101 MHz,

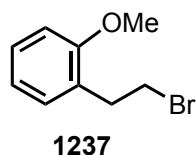
Chloroform-*d*) δ 172.3, 157.5, 130.8, 128.5, 123.0, 120.5, 110.5, 55.4, 51.8, 35.7; **HRMS** (ESI+): Exact mass calcd for $C_{10}H_{12}NaO_3$ [$M+Na$], 203.0679. Found 203.0678, $\sigma = 0.0068$.

2-(2-methoxyphenyl)ethan-1-ol (**59b**)



Methyl ester **59** (800 mg, 4.44 mmol) was dissolved in dry ether (10 mL) and added portionwise was solid lithium aluminium hydride (340 mg, 9.0 mmol) and the suspension stirred at ambient temperature (20 °C) for 15 h. Following the Fieser workup [(where x = g lithal) At 0 °C, add x mL water, add x mL 1 M HCl, add 3x mL water, stir rt 15 min, add magnesium sulfate, stir 15 min, filter)], the resulting solution was washed with brine, dried over magnesium sulfate and concentrated *in vacuo* to give a clear oil (587 mg, 87%); **¹H NMR** (400 MHz, Chloroform-*d*) δ 7.22 (ddd, $J = 8.2, 7.5, 1.8$ Hz, 1H), 7.17 (dd, $J = 7.4, 1.8$ Hz, 1H), 6.91 (ddd, $J = 7.5, 7.4, 1.1$ Hz, 1H), 6.88 (dd, $J = 8.2, 1.1$ Hz, 1H), 3.83 (s, 3H), 3.83 (t, $J = 6.5$ Hz, 1H), 2.91 (t, $J = 6.5$ Hz, 2H); **¹³C NMR** (101 MHz, Chloroform-*d*) δ 157.6, 130.8, 127.8, 127.0, 120.6, 110.4, 62.8, 55.3, 34.0; **HRMS** (ESI+): Exact mass calcd for $C_9H_{12}NaO_2$ [$M+Na$], 175.0730. Found 175.0728, $\sigma = 0.0093$.

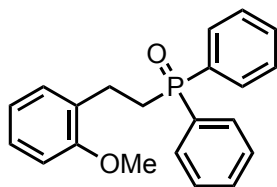
1-(2-bromoethyl)-2-methoxybenzene (**60**)



Alcohol **59b** (580 mg, 3.82 mmol) was dissolved in dichloromethane (7 mL) and added was triphenylphosphine (1.5 g, 5.7 mmol) followed by careful addition (exotherm) of

carbon tetrabromide (1.58 g, 4.78 mmol). The reaction was stirred until no alcohol remained by TLC (~1.5 h) and the reaction was concentrated. The crude material was titrated in ether by scratching with a glass rod and stirring vigorously for 10 min. After filtration and concentration of the liquid, the procedure was repeated twice more (with pentane) to give a solid-free pale yellow liquid (850 mg, quant.), which contained only traces of phosphorus compounds by ^1H -NMR. Compound used as was; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.25 (t, J = 7.8 Hz, 1H), 7.16 (dd, J = 7.4, 1.6 Hz, 1H), 6.91 (t, J = 7.4 Hz, 1H), 6.87 (d, J = 8.2 Hz, 1H), 3.84 (d, J = 0.9 Hz, 3H), 3.58 (t, J = 7.7 Hz, 2H), 3.18 (t, J = 7.7 Hz, 2H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.5, 130.6, 128.3, 127.1, 120.4, 110.4, 55.2, 34.6, 32.1; **AT-IR** (neat): 3019, 2960, 2835, 1600, 1587, 1492, 1462, 1437, 1315, 1288, 1263, 1242, 1214, 1094, 1050, 1029 cm^{-1} .

(2-methoxyphenethyl)diphenylphosphine oxide (61)



1238

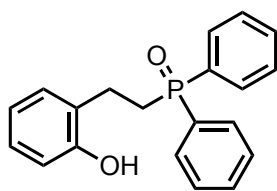
According to an adapted literature procedure,²³ to a stirring solution of caesium hydroxide monohydrate (312 mg, 1.86 mmol) in anhydrous DMF (15 mL) containing 4 Å molecular sieves (500 mg/mmol CsOH) at 25 °C was added a mixture of diphenylphosphine and diphenylphosphine oxide (1:1) (906 mg, ~ 1 equiv phosphine). After stirring for 10 min, alkyl bromide **60** (400 mg, 1.86 mmol) was added as a solution in DMF (1 mL). The reaction was stirred for 24 h at 25 °C. After this time, the reaction diluted with water and extracted with three large portions of dichloromethane, ensuring facile layer separation. The dichloromethane was washed with saturated aqueous sodium bicarbonate and brine,

concentrated under reduced pressure and the residue taken up in ethyl acetate, which was washed with copious brine to remove the DMF. The organic solution was dried over magnesium sulfate and concentrated *in vacuo*. ^{31}P -NMR analysis indicated the material had oxidised *in situ*, obviating the need for an oxidative work-up. The residue was triturated in ethyl acetate, and the solid removed by filtration. The remaining material was purified by flash column chromatography (100% EtOAc) to give two impure fractions containing the desired phosphine oxide, one of which contained large quantities of diphenylphosphine oxide. The following peaks were extracted from the NMR-spectra and the two batches of material immediately taken for deprotection; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.81 – 7.75 (m, 4H), 7.70 – 7.63 (m, 4H), 7.49 – 7.42 (m, 2H), 7.16 (ddd, $J = 8.2, 7.5, 1.8$ Hz, 1H), 7.10 (dd, $J = 7.4, 1.8$ Hz, 1H), 6.84 (ddd, $J = 7.5, 7.4, 1.1$ Hz, 1H), 6.80 (dd, $J = 8.2, 1.1$ Hz, 1H), 3.79 (s, 3H), 2.97 – 2.88 (m, 2H), 2.62 – 2.53 (m, 2H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ was difficult to interpret due to impurities; ^{31}P NMR (162 MHz, Chloroform-*d*) δ 32.5.

Initial experiments suggest that the following alternative procedure will be successful:

Diphenylphosphine oxide (130 mg, 0.65 mmol) was dissolved in THF (5 mL) at 0 °C and added was sodium hydride as a 60% dispersion in mineral oil (40 mg, 1.0 mmol). After 10 min stirring, alkyl bromide **60** (150 mg, 0.65 mmol) was added as a solution in THF (1 ml) and the reaction stirred overnight at ambient temperature. No conversion was noted at this time. The reaction was subjected to heating at 50 °C for 12 h, this time affording 33% conversion to the desired alkyl(diphenyl)phosphine oxide **61**. It is anticipated that a longer, hotter reaction period would give a higher conversion.

(2-hydroxyphenethyl)diphenylphosphine oxide (K13)

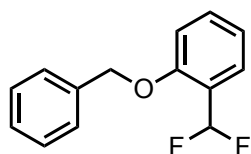
**K13: 1240 / 1245**

Both batches of semi-pure methylated phenol **61** (~70 mg, 0.21 mmol), were successfully deprotected and purified as follows: The methyl-protected phenol phosphine oxide **61** was dissolved in chloroform (16 mL/mmol) and added was boron trichloride dimethylsulfide complex (4 equivalents). The reaction was refluxed for 16 h, cooled, and then quenched cautiously with a saturated aqueous solution of sodium bicarbonate. The mixture was stirred for 15 min at ambient temperature and then diluted with dichloromethane:PrOH (90:10). The organic layer was washed with further bicarbonate solution and the organics dried over magnesium sulfate and concentrated *in vacuo* to give a crude white solid. The solid was triturated with hot ethyl acetate and the remaining solid obtained by filtration. In total, the title compound was obtained as a highly insoluble white solid (65 mg, ~97%); ^1H NMR (300 MHz, Methanol- d_4) δ 7.87 – 7.69 (m, 5H), 7.69 – 7.46 (m, 5H), 7.06 – 6.94 (m, 3H), 6.75 – 6.64 (m, 3H), 2.90 – 2.77 (m, 2H), 2.77 – 2.63 (m, 2H); ^{13}C NMR (101 MHz, Methanol- d_4) δ 155.06, 131.94 (d, J = 2.9 Hz), 131.91 (d, J = 99.6 Hz), 130.46 (d, J = 8.7 Hz), 129.38, 128.58 (d, J = 11.8 Hz), 127.31, 126.93 (d, J = 14.6 Hz), 119.24, 114.55, 28.59 (d, J = 70.1 Hz), 22.67 (d, J = 3.5 Hz); ^{31}P NMR (121 MHz, Methanol- d_4) δ 37.0; **HRMS** (ESI $^+$): Exact mass calcd for $\text{C}_{20}\text{H}_{20}\text{O}_2\text{P}$ [$\text{M}+\text{H}$], 323.1195. Found 323.1194, σ = 0.0016; **AT-IR** (neat): 3056, 2949, 2904, 1594, 1504, 1484, 1161, 1133 cm^{-1} ; **Mp** 230 $^{\circ}\text{C}$

2.6 Additional Catalyst Syntheses

2.60 Synthesis of gemdifluoro K1 catalyst precursor sequence (Scheme 44)

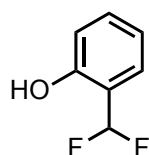
1-(benzyloxy)-2-(difluoromethyl)benzene (62)

**1147-B-cp1**

According to an adapted literature procedure,²⁴ salicylaldehyde (2.00 g, 16.4 mmol) was refluxed in acetone (20 mL) in the presence of benzyl bromide (1.95 mL, 16.4 mmol) and potassium carbonate (2.26 g, 1.64 mmol) for 16 h. After this time, the reaction went yellow (further investigation indicated the benzyl bromide was impure/contained HBr), and the mixture was cooled and filtered. The acetone was evaporated *in vacuo* in a vented hood and the oil partitioned between ether and aqueous saturated sodium carbonate. The organic layer was separated, dried and concentrated to give an impure crude material (3.8 g). Chromatography with 1-10% EtOAc/petrol afforded the title compound as a clear oil (1.9 g, 55%). The oil became a slightly pink solid on storing overnight in the freezer. A portion of the aldehyde (100 mg, 0.47 mmol) was then dissolved in dry dichloromethane (0.3 mL) and added was DAST [(diethylamino)sulfur trifluoride] (106 μ L, 0.799 mmol) and the reaction was activated with 1 drop of methanol. After stirring for 5 h at ambient temperature (23 $^{\circ}$ C), ^{1} H-NMR analysis suggested the mono-fluoro alcohol intermediate was the major species, which reverted to aldehyde on attempt at isolation. Heating the reaction at 40 $^{\circ}$ C for 16 h resulted in essentially complete conversion of to the desired difluoro compound. The mixture was diluted with further dichloromethane and quenched with saturated aqueous sodium bicarbonate solution and the organic layer separated, washed with brine, dried, and concentrated. The residue was purified by flash column

chromatography (5-30% EtOAc/pentane) to give the title compound as a yellow oil (100 mg, 91%); ^1H NMR (400 MHz, Chloroform-*d*) δ 7.63 – 7.57 (m, 1H), 7.46 – 7.31 (m, 6H), 7.08 – 7.03 (m, 1H), 7.02 (t, J = 55.7 Hz, 1H), 7.02 – 6.97 (m, 1H), 5.14 (s, 2H); ^{19}F NMR (376 MHz, Chloroform-*d*) δ -115.37 (d, J = 55.6 Hz); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 156.38 (t, J = 6.1 Hz), 136.38, 131.97 – 131.83 (m, 2C), 128.65, 128.11, 127.18, 126.32 (t, J = 5.6 Hz), 120.90, 112.29, 111.57 (t, J = 235.7 Hz), 70.28; **HRMS** (ESI+): Exact mass calcd for $\text{C}_{14}\text{H}_{12}\text{F}_2\text{NaO}$ [$\text{M}+\text{Na}$], 257.0748. Found 257.0748, σ = 0.0264.

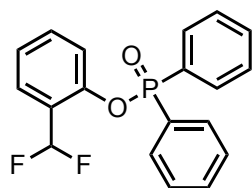
2-(difluoromethyl)phenol (**63**)



1148-B-wup1

According to an adapted literature procedure,²⁴ benzyl protected phenol **62** (100 mg, 0.430 mmol) was dissolved in methanol (2 mL) and placed under an argon atmosphere. Added was 10% Pd/C (20% by wt substrate, 20 mg), and the reaction vessel placed under an atmosphere of hydrogen (triple balloon) by 4 vacuum/refill cycles. The reaction was stirred vigorously for 14 h at ambient temperature (23 °C), leading to complete conversion. After careful filtration through a celite pad, washing with ethanol, the resulting solution was concentrated to give the title compound, which was isolated as a yellow oil (62 mg, quant.). The material is reported to be unstable,²⁴ so was used immediately in the next step. Peaks extracted from crude ^1H -NMR; ^1H NMR (300 MHz, Chloroform-*d*) δ 7.45 (dt, J = 7.7, 1.3 Hz, 1H), 7.39 – 7.30 (m, 1H), 7.00 (t, J = 7.6 Hz, 1H), 6.89 (t, J = 55.4 Hz, 1H), 6.88 – 6.83 (m, 1H).

2.61 Phospho-Fries rearrangement precursor: 2-(difluoromethyl)phenyl diphenylphosphinate (64a)



1148-B-wup1

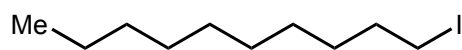
Phenol **63** (62 mg, 0.43 mmol) was dissolved in degassed ether (1 mL) at 0 °C and added was triethylamine (60 μ L, 0.43 mmol). Chlorodiphenylphosphine (80 μ L, 0.43 mmol) was added dropwise over 30 min as a solution in ether (0.5 mL) and the reaction stirred warming to ambient temperature (23 °C) over 3 h. After this time, the reaction was filtered to remove the solids, and stirred for a further 30 min at ambient temperature in the presence of aqueous hydrogen peroxide (excess, 1 mL). The layers were then separated, and the aqueous extracted with a portion of ether. The combined ether layers were then washed with saturated aqueous sodium bicarbonate solution and brine and the organic layer dried over magnesium sulfate and concentrated. The mixture was partially purified by column chromatography (30% EtOAc in petrol) to give a yellow residue (26 mg). The semi pure mixture was analysed as follows; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.98 – 7.88 (m, 4H), 7.62 – 7.56 (m, 3H), 7.54 – 7.43 (m, 5H), 7.36 – 7.30 (m, 1H), 7.25 – 7.16 (m, 1H), 6.98 (t, J = 55.3 Hz, 1H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 149.2 (m), 132.8, 132.1, 132.0, 131.7 (d, J = 10.6 Hz), 130.4 (d, J = 138.0 Hz), 128.8 (d, J = 13.9 Hz), 126.8 (t, J = 6.4 Hz), 124.4, 120.3 (d, J = 4.1 Hz), 111.9 (t, J = 237.6 Hz); ^{31}P NMR (162 MHz, Chloroform-*d*) δ 31.5; **HRMS** (ESI⁺): Exact mass calcd for $\text{C}_{19}\text{H}_{15}\text{F}_2\text{NaO}_2\text{P}$ [$\text{M}+\text{Na}$], 367.0670. Found 367.0670, σ = 0.0040; **AT-IR** (neat) 3060, 2968, 1609, 1592, 1492, 1456, 1439, 1381, 1285, 1222, 1187, 1162, 1128, 1110, 1060, 1026, 912 cm^{-1} .

2.62 Attempted synthesis of sulfonic acid augmented catalyst 10, (65)

According to an adapted literature procedure,²⁵ phosphine oxide **10** (100 mg, 0.296 mmol) was dissolved in pyridine (1 mL) and added was sulfur trioxide pyridine complex (189 mg, 1.18 mmol) and the reaction stirred at 65 °C for 13 h. ³¹P-NMR indicated conversion of starting material, but aqueous work-up from EtOAc did not yield product. Mass spectrometry before isolation suggested the product might be present. This reaction is under-explored at this stage.

2.63 Attempted Iodination of decanol (Goal 2, ~p422)

Iododecane ²⁶



1204-A-cp1

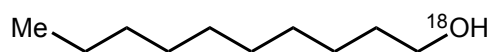
A 50 mL round-bottomed flask with a B14 neck and containing a stirrer bar was charged with decanol (0.950 g, 5.91 mmol), tetrabutylammonium iodide (2.18 g, 5.91 mmol), tosic acid monohydrate (113 mg, 0.591 mmol), amberlyst-15 (dry) ion exchange resin (1.26 g, ~4.7 mmol H⁺/g, 5.91 mmol) and toluene 17 mL. A Dean-Stark apparatus (see general Dean-Stark protocol) fitted with a condenser was attached and the flask submerged to 2/3 depth in an oil bath at 130 °C. The flask was heated for 15 h before concentration of the solvent. Integrating the CH₂ signals alpha to oxygen in the ¹H-NMR spectrum showed 29% iodide, 67% alcohol, and 4% diethyl ether (by extrapolation – peaks are actually under TBA salt signals, can utilise CH₃ triplet at 0.9 ppm as an internal standard).

The reaction was repeated identically, but with inclusion of oxide **K1** (45.5 mg, 2.5 mol%), this time yielding 29% iodide, 63% alcohol, and 8% diethyl ether. This mixture was purified by column chromatography to reclaim K1 (40 mg) and the title compound (370 mg, 23%);

^1H NMR (400 MHz, Chloroform- d) δ 3.19 (t, J = 7.0 Hz, 2H), 1.82 (tt, J = 7.0 Hz, 2H), 1.46 – 1.19 (m, 16H), 0.88 (t, J = 7.0, 6.5 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform- d) δ 33.6, 31.9, 30.5, 29.5, 29.4, 29.3, 28.5, 22.7, 14.1, 7.3 .

2.7 Oxygen-18 Labelling Experiments (Schemes 33-35)

Synthesis of decan-1-ol- ^{18}O (40)



1225-red-cp1

Decanal (3.09 g, 16.4 mmol) was dissolved in methanol (10 mL) with trimethylorthoformate (4.38 mL, 40 mmol) and added was 0.5 mL 1.0 M HCl in ether. The reaction was refluxed for 3 h giving complete conversion to the desired dimethyl acetal. The acetal (16.4 mmol) was dissolved in dry THF (5 mL) and added was H_2^{18}O (370 μL , 20.5 mmol), followed by 0.1 mL 1.0 M HCl in ether. The reaction flask was fitted with an empty Dean-Stark trap and run under argon. The reaction was refluxed for 1.5 h at 70 °C. ^1H -NMR analysis showed 45% aldehyde at this time and contained free methanol. The solvents were partially evaporated to reduce the methanol:water ratio, and then resubjected to the conditions with an additional THF (10 mL), HCl in ether (0.1 mL) and H_2^{18}O (100 μL , 5.5 mmol). ^1H -NMR analysis indicated 81% aldehyde at this point. The reaction was concentrated *in vacuo*, and immediately subjected to the reduction conditions, omitting any work-up. The crude aldehyde was dissolved in THF (5 mL) under argon and cooled to 0 °C. Added was sodium borohydride (1.15 g, 30.4 mmol), and dry methanol (~ 5 mL) was then added slowly over 15 min, controlling the rate of the reaction, which was dependent on methanol to solubilise the reductant. The reaction was stirred for 1 h, and then diluted with ether and washed with water, 1 M aqueous HCl and brine. The organics were dried,

and the crude oil purified by flash column chromatography using a gradient of 5-35% ether in pentane to give the title compound as a pale yellow oil (1.40 g, 54%). High-resolution ^{13}C -NMR (126 MHz) indicated 83% ^{18}O incorporation by integration of the two peaks at 63.09 and 63.07 ppm. ^1H NMR (400 MHz, Chloroform-*d*) δ 3.64 (t, J = 6.6 Hz, 2H), 1.56 (dt, J = 8.0, 6.4 Hz, 2H), 1.39 – 1.21 (m, 14H), 0.95 – 0.82 (m, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 63.1, 32.8, 31.9, 29.6, 29.5, 29.4, 29.3, 25.7, 22.7, 14.1; ^{13}C NMR (126 MHz, Chloroform-*d*) δ 63.09 (0.17C, C^{16}O), 63.07 (0.83C, C^{18}O), 32.78, 31.88, 29.60, 29.54, 29.42, 29.31, 25.71, 22.67, 14.11; **Synthesised decanol- ^{18}O AT-IR** (neat): 3317, 2955, 2922, 2853, 1465, 1378, 1122, 1045, 1014 cm^{-1} ; **Regular Decanol: AT-IR** (neat): 3327, 2955, 2922, 2853, 1465, 1378, 1122, 1056 cm^{-1} .

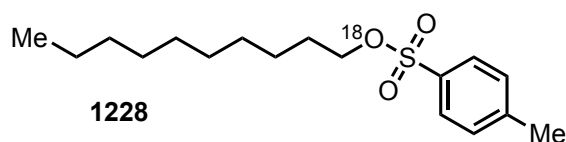
Mass Analysis of oxygen-18 labelled decanol: Due to the poor molecular ion signal in both ESI and GC-EIMS, analysis of O-containing fragments produced during a GC-EIMS run was attempted. This analysis is quite crude due to the low intensity of the ion peaks, giving a low resolution. Nonetheless, the following ^{18}O fragments were located, and the average ^{18}O incorporation was determined to be ~82%, in good agreement with the values calculated from ^{13}C -NMR and the mass ratios of the tosylated analogue (see 1228). The error of the calibration at ~ 30 m/z was estimated at about 20 ppm, whilst at 160 ppm the error is ~10 ppm.

Fragment	Calc	Measured	Peak Integral
H ₃ O	19.01784	19.01754	689.2
H ₃ ¹⁸ O	21.02209	21.02265	4504.63
		¹⁸ O incorp	87%
Fragment			
C ₁₀ H ₂₁ O	157.15869	157.17377	306.2
C ₁₀ H ₂₁ ¹⁸ O	159.16294	159.16397	1011.4
		¹⁸ O incorp	77%
Average ¹⁸O incorp:			82%

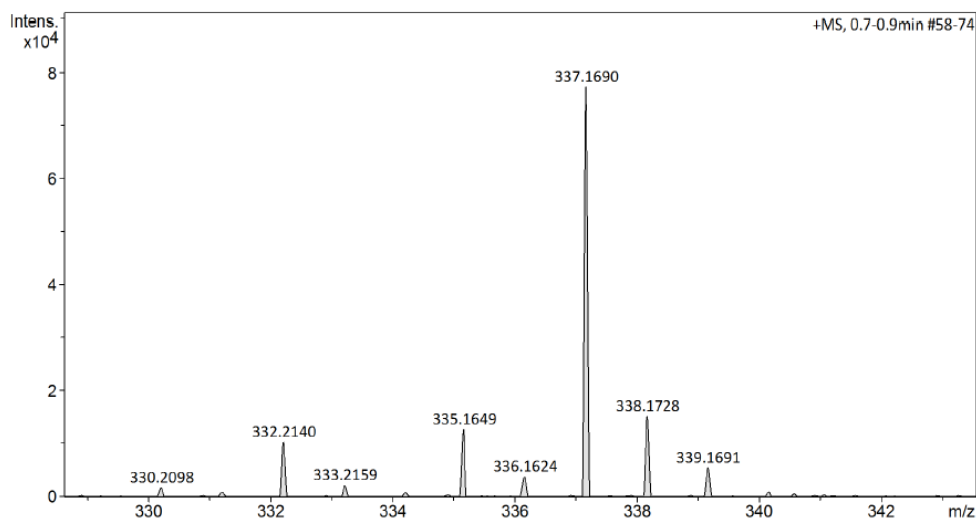
The water ions were present as the protonated form: interestingly, although background water is present in the spectrum, there is no non-protonated ¹⁸O-water, suggesting (little) exchange of ions between fragmentation and measurement.

Conversion of decanol (for label incorporation analysis) to decyl 4-methylbenzenesulfonate-¹⁸O (41)

The above ¹⁸O-decanol **40** (4.6 mg, 0.029 mmol) was analysed for ¹⁸O content by formation of its tosylate by stirring with 1 equiv. tosic acid (5.5 mg, 0.029 mmol) at room temperature in pyridine (100 µL) for 1 h. After dilution with EtOAc and washing with saturate sodium bicarbonate solution and HCl and brine, the mass spectrum of the resulting tosylate indicated:



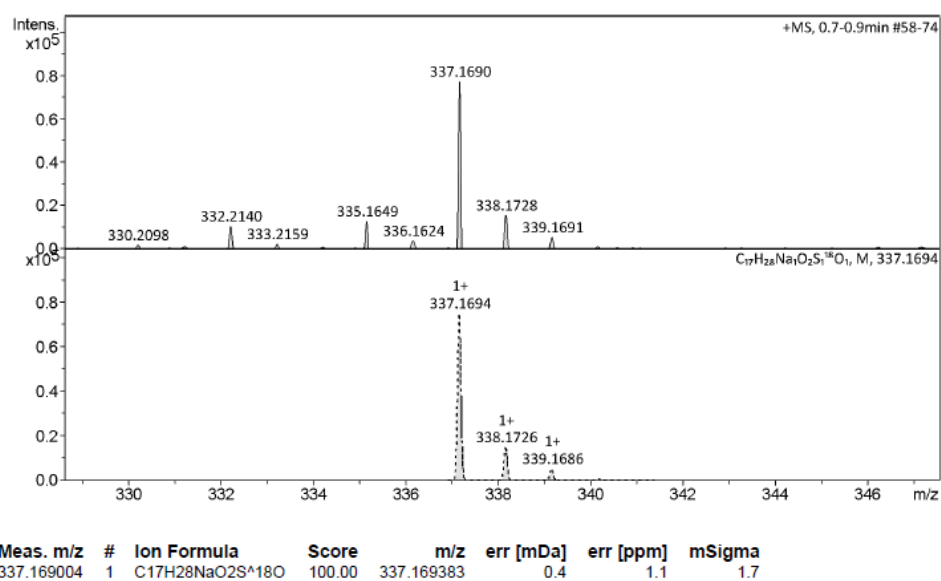
Result: 85% ¹⁸O incorporation: (Chemical Formula: C₁₇H₂₈NaO₂¹⁸OS+ Exact Mass: 337.1694)



m/z	I %	I
102.1282	18.7	14471
229.0257	12.5	9684
245.0110	5.2	3985
247.0355	11.1	8545
261.0520	21.8	16846
262.0539	5.2	4047
263.0493	5.7	4408
279.0897	6.4	4909
291.2581	8.3	6396
332.2140	13.4	10331
335.1649	16.5	12747
337.1690	100.0	77289
338.1728	19.8	15272
339.1691	6.9	5358

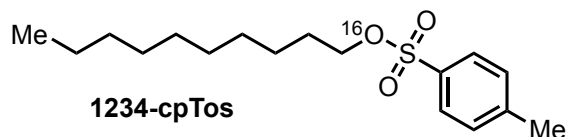
HRMS (ESI+): Exact mass calcd for $C_{17}H_{28}NaO_2S^{18}O$ $[M+Na]$, 337.169004. Found 337.169383, $\sigma = 0.0017$.

Shown below: measured (top) calculated (bottom).



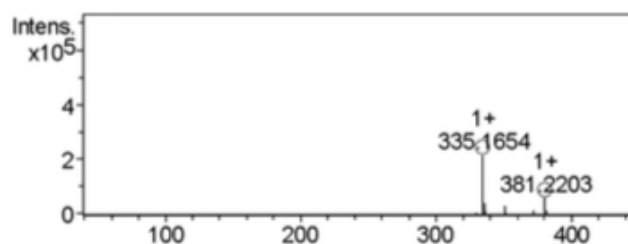
2.71 K1-catalysed tosylation of ^{18}O decanol to trace final location of ^{18}O

Tosic acid monohydrate (377 mg, 1.97 mmol) was suspended in toluene (15 mL) and connected to a Dean-Stark apparatus as described in the general protocol. The reaction was refluxed for 1 h to azeotropically remove the water to avoid label contamination. ^{18}O -decanol (316 mg, 1.97 mmol) was then added to the reaction mixture, along with phosphine oxide K1 (10 mol%, 30.4 mg). The reaction was then heated under Dean-Stark conditions for a further 15 h) and the reaction cooled and concentrated. The residue was dissolved in ethyl acetate and washed with a saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate and concentrated. The residue was purified by flash column chromatography (1-50% EtOAc in pentane) to give the desired tosylate, ether and phosphine oxide catalyst. The compounds are characterised below.

2.72 The ^{16}O tosylate (with oxygen incorporation from tosyl):**decyl 4-methylbenzenesulfonate (36)**²⁷

Isolated as a pale oil (484 mg, 79%). Mass analysis (below) indicated <3% ^{18}O incorporation, indicating that the tosylate oxygen displaced the original ^{18}O label on decanol in the C-O bond forming step; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.84 – 7.73 (m, 2H), 7.39 – 7.29 (m, 2H), 4.02 (t, J = 6.5 Hz, 2H), 2.45 (s, 3H), 1.68 – 1.57 (m, 2H), 1.37 – 1.15 (m, 16H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 144.6, 133.3, 129.8, 127.9, 70.7, 31.8, 29.4, 29.4, 29.2, 28.9, 28.8, 25.3, 22.6, 21.6, 14.1; **AT-IR** (neat): 2924, 2854, 1599, 1466, 1359, 1188, 1175 cm^{-1} ; **HRMS** (ESI+): Exact mass calcd for $\text{C}_{17}\text{H}_{28}\text{NaO}_3\text{S}$ [$\text{M}+\text{Na}$], 335.1651. Found 335.1654, σ = 0.0017. Ratio of ions

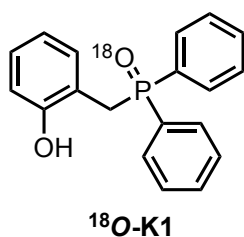
(335:337) = 59.4:4.0, indicating > 97% exclusion of ^{18}O after considering other isotopes/overlapping signals.



#	m/z	I %
1	195.0085	1.0
2	330.2097	1.7
3	335.1654	59.4
4	336.1681	11.9
5	337.1642	4.0
6	351.1388	9.4

2.73 The ^{18}O -P-catalyst, ^{18}O -K1, from a Mitsunobu reaction, $\text{S}_{\text{N}}2$

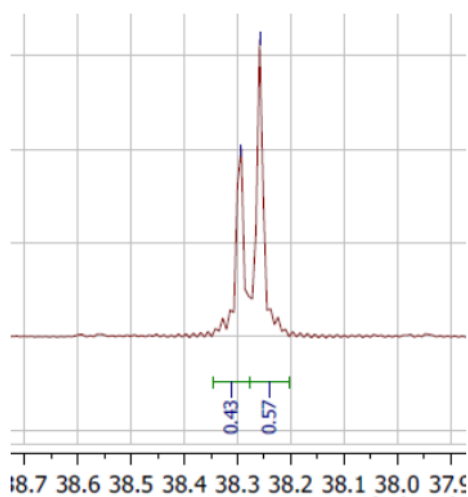
(2-hydroxybenzyl)diphenylphosphine oxide- ^{18}O



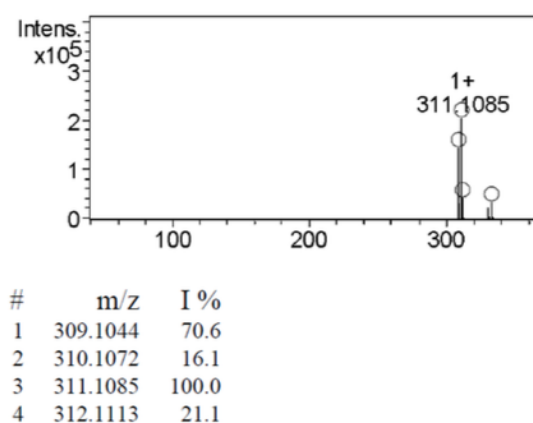
Isolated as a white solid (27.5 mg, 90% recovered). ^{31}P -NMR and mass analysis suggest 57-60% incorporation (~68-71% wrt initial isotope purity of decanol); ^1H NMR (400 MHz, Chloroform- d) δ 9.80 (s, 1H), 7.77 – 7.69 (m, 4H), 7.59 – 7.52 (m, 2H), 7.51 – 7.44 (m, 4H), 7.15 – 7.08 (m, 1H), 7.00 (dd, J = 8.1, 1.2 Hz, 1H), 6.76 (dt, J = 7.6, 1.9 Hz, 1H), 6.69 (tt, J = 7.6, 1.2 Hz, 1H), 3.71 (d, J = 12.9 Hz, 2H); ^{13}C NMR (101 MHz, Chloroform- d) δ 156.6 (d, J = 3.8 Hz), 132.4 (d, J = 2.9 Hz), 131.6 (d, J = 6.5 Hz), 130.9 (d, J = 9.5 Hz), 130.5 (d, J = 100.0 Hz), 128.9 (d, J = 2.6 Hz), 128.8 (d, J = 11.8 Hz), 120.6 (d, J = 1.9 Hz), 119.6 (d, J = 2.7 Hz), 119.3 (d, J = 8.4 Hz), 35.4 (d, J = 67.4 Hz); ^{31}P NMR (162 MHz, Chloroform- d) δ 38.30 (0.43P, P= ^{16}O), 38.26 (0.57P, P= ^{18}O); **AT-IR** (neat): 3058, 2956,

2923, 2852, 1579, 1484, 1438, 1388, 1263, 1245, 1218, 1187, 1177, 1144, 1123, 1092, 1060, 1032, 997 cm^{-1} ; **HRMS** (ESI+): Exact mass calcd for $\text{C}_{19}\text{H}_{18}\text{OP}^{18}\text{O}$ $[\text{M}+\text{H}]$, 311.1081. Found 311.1083, $\sigma = 0.0027$.

Depiction of the ^{31}P -NMR spectrum showing isotope inclusion:

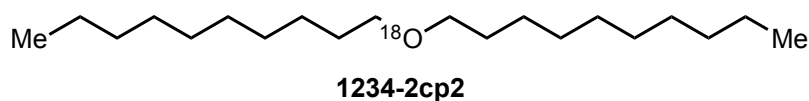


Ratio of 309 to 311 (66.8:100.0) indicates 60% incorporation of ^{18}O label after consideration of other isotopes, which is a 71% incorporation wrt the initial isotope purity of 85%. Note that because the catalyst can dehydrate *in situ*, it is expected that some degradation would occur at the end of the reaction due to adventitious water elsewhere in the system.



Mass spectrum demonstrating ^{18}O -label inclusion in the oxide **K1**.

2.74 1-(decyloxy)decane- ^{18}O (42), demonstrating ether formation from nucleophilic decanol.

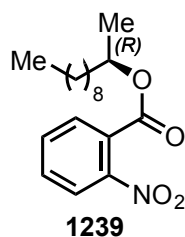


Isolated as a pale oil with a slight contamination by tosylate **36**. Similarly to the ^{18}O -decanol, mass spec analysis of the ether was complicated by low ion intensities and fragmentation under GC-EIMS conditions. Analysis of oxygen containing fragments suggested an 82% incorporation of ^{18}O , which is in excellent agreement with the isotopic purity of the decanol starting material, indicating that in all cases, the oxygen on decanol is transferred to the ether product. Accurate mass calibration errors estimated at 10 ppm.

	Calc	Measured	Peak Integral
$\text{C}_2 \text{H}_5 \text{O}$	45.03349	45.03278	7662.05
$\text{C}_2 \text{H}_5 ^{18}\text{O}$	47.03774	47.03818	31756.66
		^{18}O incorp	81%
$\text{C}_{11} \text{H}_{23} \text{O}$	171.17434	171.17319	9526.36
$\text{C}_{11} \text{H}_{23} ^{18}\text{O}$	173.17859	173.18019	39815.5
		^{18}O incorp	81%
$\text{C}_{14} \text{H}_{29} \text{O}$	213.22129	213.22285	1728.93
$\text{C}_{14} \text{H}_{29} ^{18}\text{O}$	215.22554	215.22754	8998.39
		^{18}O incorp	84%
Average ^{18}O incorp:			82%

2.8 Inversion of 2-octanol with K1

(*R*)-octan-2-yl 2-nitrobenzoate (44)



(*S*)-2-octanol (385 mg, 2.96 mmol) was dissolved in xylenes (15 mL) and added was 2-nitrobenzoic acid (495 mg, 2.96 mmol) and phosphine oxide **K1** at various loadings (x mol%, $x = 0, 10$ or 20) and the reaction flask set-up according to the Dean-Stark protocol. The reaction was heated in an oil bath at 155 °C for 26 h, after which time ^1H -NMR showed the following approximate conversions to the ester: $x=0$ – 12%; $x=10$ – 52%; $x=20$ – 73%). These values are calculated with respect to remaining 2-octanol, and do not take into account any losses in the trap (~1-2% of starting material). For the experiments with $x=10, 20$, the reactions were subjected to a further 20 h heating, and then concentrated at 50 °C under reduced pressure (8 mbar). The material was diluted with ethyl acetate and washed with a saturated aqueous sodium bicarbonate solution and brine. The organics were dried over magnesium sulfate and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (1-50% EtOAc/pentane), eluting the title compound at 10-15% and the phosphine oxide catalyst **K1** at 50% EtOAc. The ester was isolated as a pale yellow oil and the enantiomeric excesses determined by chiral HPLC: ($x=10$, 553 mg, 67%, 79% ee), ($x=20$, 616 mg, 75%, 89% ee). The catalyst was recovered as a white solid ($x=10$, 73 mg, 80%), ($x=20$, 147 mg, 79%). The data for the ester were as follows; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.89 (dd, $J = 7.8, 1.4$ Hz, 1H), 7.73 (dd, $J = 7.5, 1.7$ Hz, 1H), 7.66 (ddd, $J = 7.5, 7.5, 1.4$ Hz, 1H), 7.61 (ddd, $J = 7.8, 7.5, 1.7$ Hz, 1H), 5.16 (tq, $J = 7.0, 6.2$ Hz, 1H), 1.77 – 1.63 (m, 1H), 1.61 – 1.51 (m, 1H), 1.33 (d, $J = 6.2$ Hz, 3H), 1.40 – 1.24 (m, 8H), 0.88 (t, $J = 7.0$, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 165.0, 132.7, 131.4, 129.8, 128.3, 123.8, 73.9, 35.6, 31.7, 29.1, 25.2, 22.6, 19.3, 14.0; **HRMS** (ESI+): Exact mass calcd for $\text{C}_{15}\text{H}_{21}\text{NNaO}_4$ [$\text{M}+\text{Na}$], 302.1363. Found 302.1359, $\sigma = 0.0021$; **AT-IR** (neat): 2930, 2859, 1726, 1534, 1351, 1287, 1254, 1165, 1132, 1116, 1073 cm^{-1} ; for $x = 10$, $[\alpha]^{22.5}_{\text{D}}$ (c 1.0, EtOH) = -31.9° .

To aid the verification of the enantioselectivity of the above catalysis, a typical Mitsunobu reaction was also performed with both (*S*)-2-octanol and racemic 2-octanol as follows:

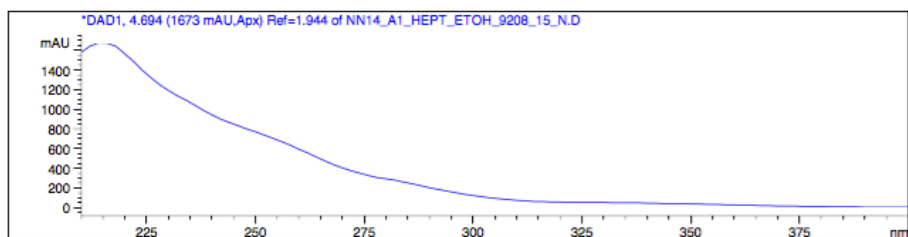
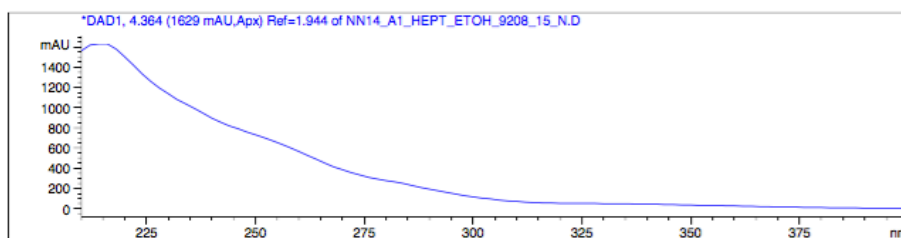
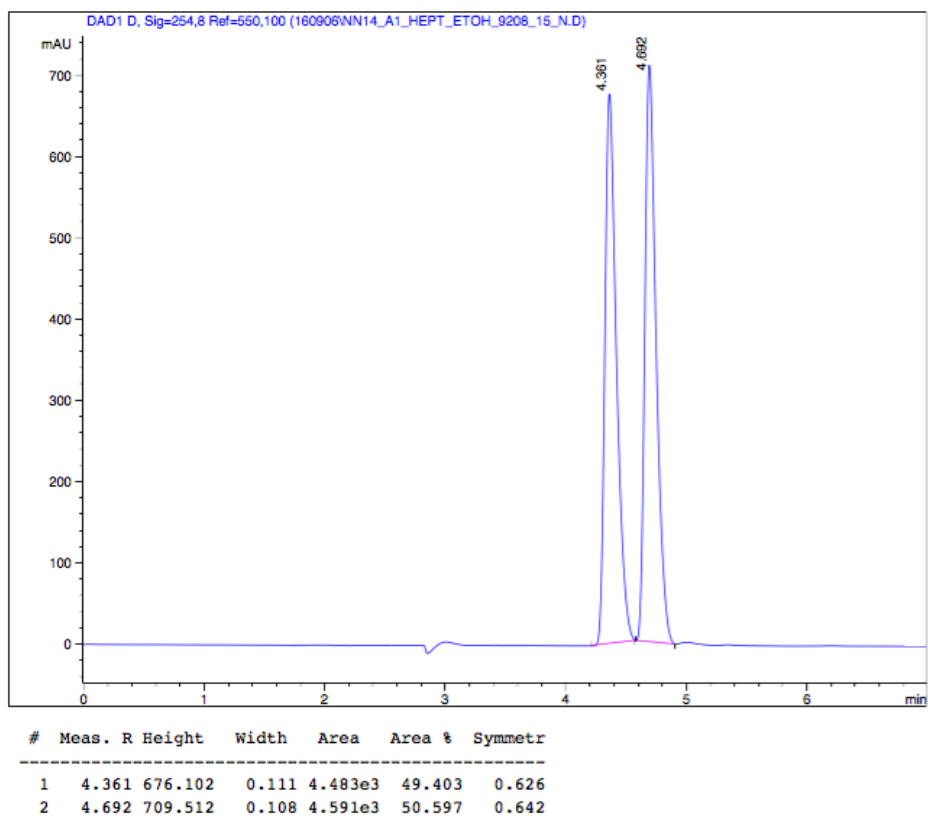
2-octanol (318 μ L, 2.00 mmol), 2-nitrobenzoic acid (334 mg, 2.00 mmol) and triphenylphosphine (630 mg, 2.40 mmol) were dissolved in dry THF (11 mL) and the mixture cooled to 0 °C. DIAD (472 μ L, 2.40 mmol) was added as a solution in THF (1 mL) and the reaction stirred warming to ambient temperature (20 °C) over 15 h. After this time, the reaction was diluted with ether and washed with a saturated aqueous sodium carbonate solution and brine, dried over magnesium sulfate and concentrated *in vacuo*. The resulting residue was triturated in both ether and cold toluene, discarding the solids each time. The remaining liquid was purified further by column chromatography (10-20% EtOAc/pentane), collecting the fraction immediately after the bright yellow material to give the title compound as a pale yellow oil (90-93%, racemate: 1.2% ee – optically active experiment: 99.5% ee) with identical data to the above, except; $[\alpha]^{22.5}_{\text{D}}$ (*c* 1.0, EtOH) = – 49.9°.

2.81 Chiral HPLC determination of enantiomeric excess of ester 44:

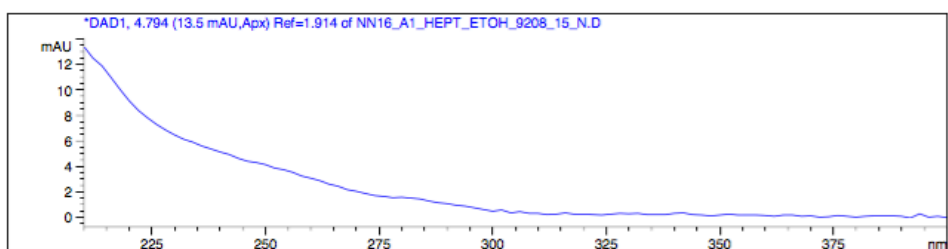
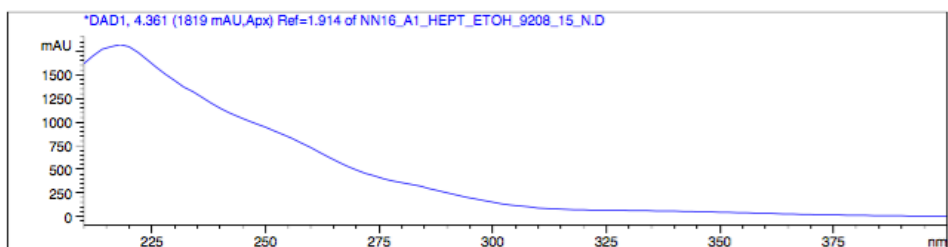
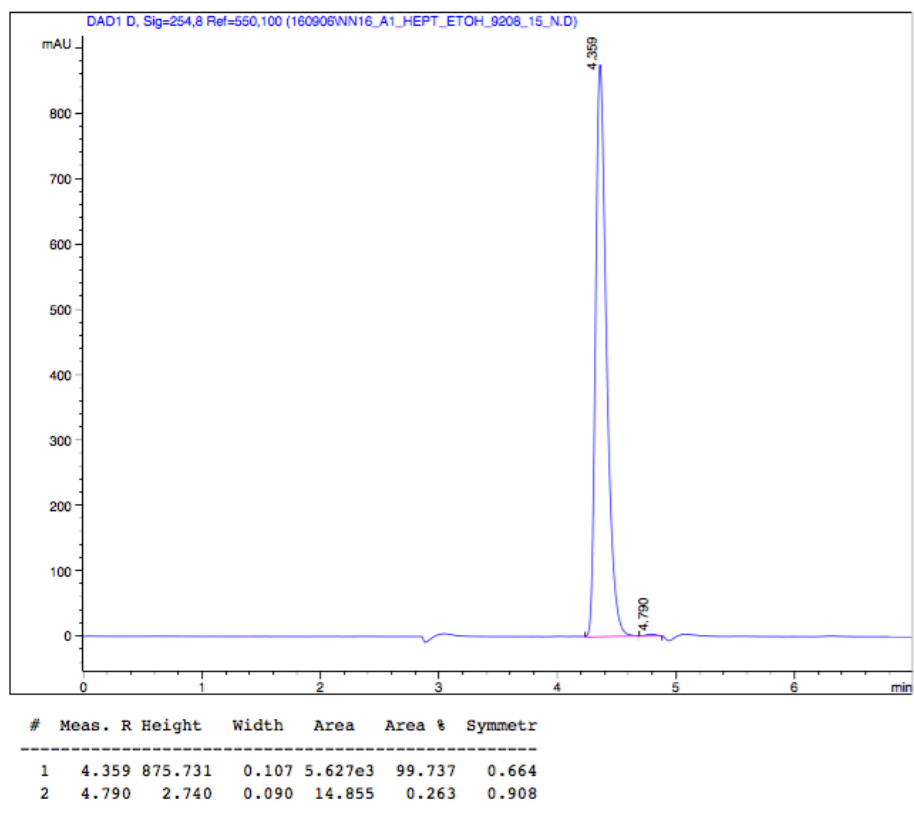
Sample dissolved to 1 mg/mL and subjected to HPLC analysis:

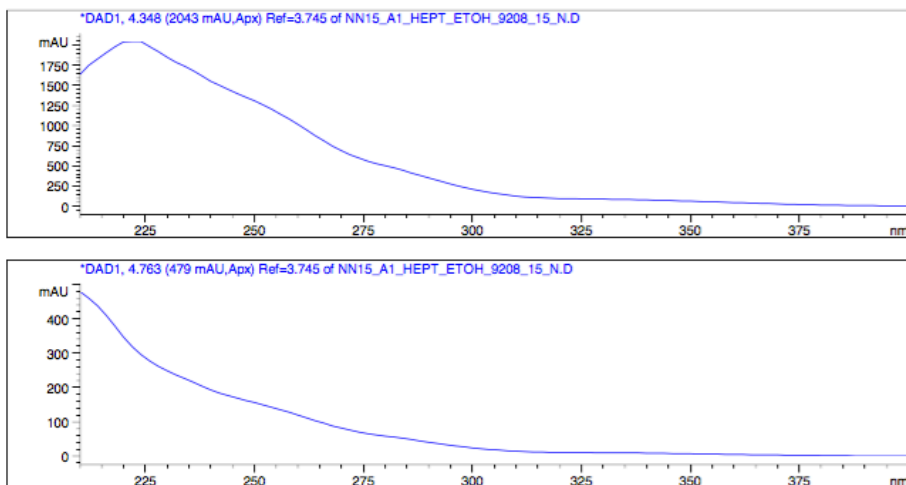
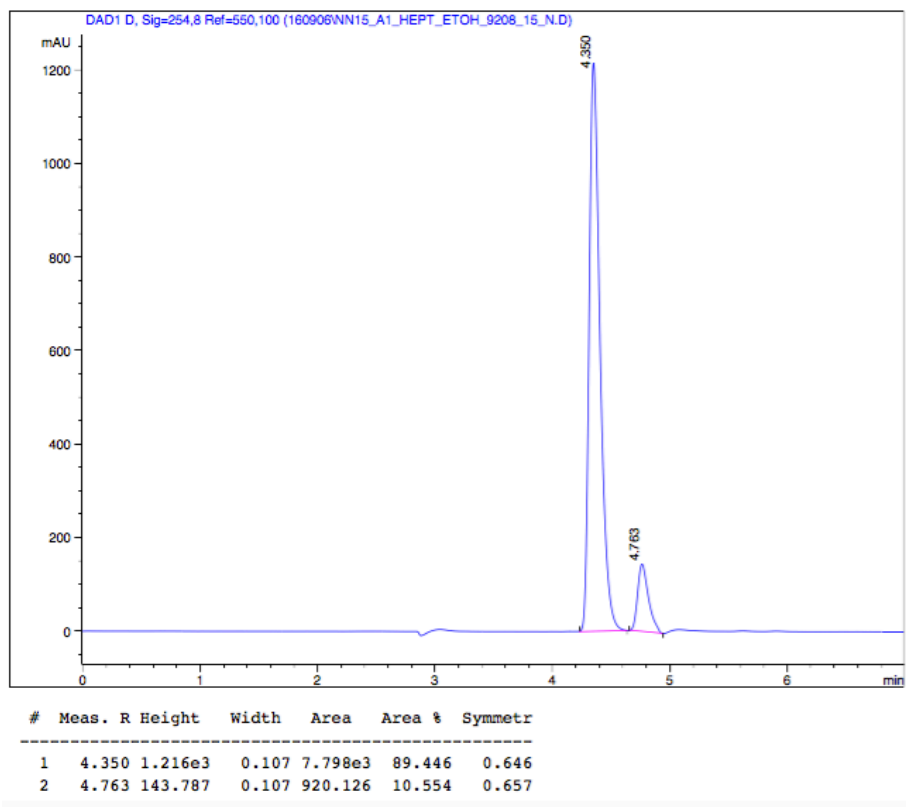
Column Details	Lux A1 (4.6mm x 250mm, 5 μ m)
Column Temperature	Ambient
Flow Rate	1 mL/min
Detector Wavelength	254 nm
Injection Volume	1.0 μ L
Isocratic Conditions	92:08 HEPT:EtOH

Racemate (1.2% ee):



Normal Mitsunobu (99.5% ee)

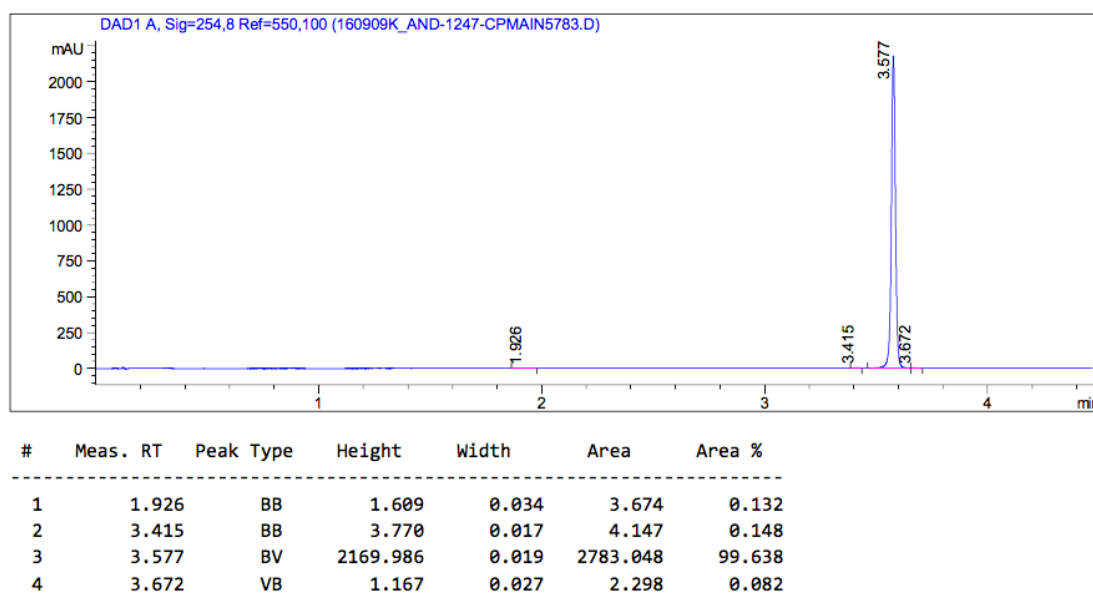


Catalytic Mitsunobu: 10 mol% K1 over 46 h (78.9% ee)**Comments on the UV trace for the chiral HPLC data:**

The UV traces for the two peaks in the racemic mixture are identical. However, both the optically active Mitsunobu and the catalytic material show slightly different traces. LCMS analysis under both acid and base conditions shows all three samples to be >99% pure, and

to only contain a single (shared) peak. It is thought that there may be a stronger UV reporter impurity at the associated retention time in these samples. We have treated any such species as negligible in the analysis of the ee, and so quoted the worst case scenario values (although the other data are all in agreement.)

LC-MS trace of the ester product isolated from the 20 mol% **K1**-catalysed Mitsunobu reaction:



3.0 Experimental References For Chapter 6

- 1 J. Drabowicz, J. Luczak and M. Mikolajczyk, *J. Org. Chem.*, 1998, **63**, 9565–9568.
- 2 A. Esswein, H. Rembold and R. R. Schmidt, *Carbohydr. Res.*, 1990, **200**, 287–305.
- 3 Y.-J. Zhang, W. Dayoub, G.-R. Chen and M. Lemaire, *Tetrahedron*, 2012, **68**, 7400–7407.
- 4 M. Stankevič and A. Włodarczyk, *Tetrahedron*, 2013, **69**, 73–81.
- 5 M. P. Pavan, M. Chakravarty and K. C. Kumara Swamy, *European J. Org. Chem.*,

- 2009, **2009**, 5927–5940.
- 6 P.-Y. Renard, P. Vayron, E. Leclerc, A. Valleix and C. Mioskowski, *Angew. Chem. Int. Ed.*, 2003, **42**, 2389–2392.
 - 7 F. Wang, M. Qu, F. Chen, Q. Xu and M. Shi, *Chem. Commun.*, 2012, **48**, 8580–8582.
 - 8 B. Dhawan and D. Redmore, *J. Org. Chem.*, 1984, **49**, 4018–4021.
 - 9 G. A. Consiglio, S. Failla and P. Finocchiaro, *Mendeleev Commun.*, 2003, **13**, 182–183.
 - 10 E. A. Ishmaeva, A. A. Gazizova, Y. A. Vereshchagina and N. A. Bondarenko, *Russ. J. Gen. Chem.*, 2008, **78**, 1662–1667.
 - 11 US4621123 (A), 1986.
 - 12 T. Ghaffar and A. W. Parkins, *J. Mol. Catal. A Chem.*, 2000, **160**, 249–261.
 - 13 J. A. Miles, R. C. Grabiak and C. Cummins, *J. Org. Chem.*, 1982, **47**, 1677–1682.
 - 14 I. R. Márquez, D. Miguel, A. Millán, M. L. Marcos, L. Á. de Cienfuegos, A. G. Campaña and J. M. Cuerva, *J. Org. Chem.*, 2014, **79**, 1529–1541.
 - 15 M. Stankevič, J. Pisklak and K. Włodarczyk, *Tetrahedron*, 2016, **72**, 810–824.
 - 16 R. A. Stockland, R. I. Taylor, L. E. Thompson and P. B. Patel, *Org. Lett.*, 2005, **7**, 851–853.
 - 17 L. Liu, Y. Wang, Z. Zeng, P. Xu, Y. Gao, Y. Yin and Y. Zhao, *Adv. Synth. Catal.*, 2013, **355**, 659–666.
 - 18 T. Kawashima, M. Nakamura and N. Inamoto, *Heterocycles*, 1997, **44**, 487–507.

- 19 F. R. Knight, A. L. Fuller, A. M. Z. Slawin and J. Derek Woollins, *Polyhedron*, 2010, **29**, 1849–1853.
- 20 S. Kehrli, D. Martin, D. Rix, M. Mauduit and A. Alexakis, *Chem. - A Eur. J.*, 2010, **16**, 9890–9904.
- 21 D. L. Comins and N. B. Mantlo, *J. Org. Chem.*, 1985, **50**, 4410–4411.
- 22 R. Yamaguchi, Y. Nakazono, T. Matsuki, E. Hata and M. Kawanisi, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 215–222.
- 23 M. T. Honaker, B. J. Sandefur, J. L. Hargett, A. L. McDaniel and R. N. Salvatore, *Tetrahedron Lett.*, 2003, **44**, 8373–8377.
- 24 S. R. Hanson, L. J. Whalen and C.-H. Wong, *Bioorg. Med. Chem.*, 2006, **14**, 8386–8395.
- 25 H. Kamiyama, Y. Kubo, H. Sato, N. Yamamoto, T. Fukuda, F. Ishibashi and M. Iwao, *Bioorg. Med. Chem.*, 2011, **19**, 7541–7550.
- 26 Y. Zhao and V. Snieckus, *Org. Lett.*, 2014, **16**, 390–393.
- 27 L. Timko, E. Fischer-Fodor, M. Garajová, M. Mrva, G. Chereches, F. Ondriska, M. Bukovský, M. Lukáč, J. Karlovská, J. Kubincová and F. Devínsky, *Eur. J. Med. Chem.*, 2015, **93**, 263–273.

Final Summary

It is hoped that the work on silyl esters presented in this Thesis, and supporting publications, will help bring to mainstream organic chemistry an understanding of hypercoordination chemistry, specifically the *associative* mechanism that nearly all silicon-based reactions proceed through. For instance, the activation of Si-H and Si-Nu nucleophiles occurs through an initial coordination by a donor at silicon, and this is an often-overlooked and mechanism-affecting step. A second key observation is that hydridosilanes are often non-innocent players in many reactions in which they are described as 'terminal reductants.' The loss of hydrogen from such species when a Lewis basic/Brønsted acidic pair encounters a silicon hydride occurs rapidly and with a very low energy barrier, particularly when silicon is unhindered (as in phenylsilane). Further, the increasing Lewis acidity of silanes upon which (e.g.) a carboxylate group is attached leads to enhanced reactivity of the modified silane. This information should not only aid mechanistic understanding of silane-based reactions, but also in the development of new chemistry.

The amidation/amination chemistry has already generated a lot of interest in industry, and as this reaction is developed further (cheaper silanes and catalysts), it may become widely used, perhaps even replacing reductive amination reactions in some circumstances. Reactions in which tertiary amides are formed and reduced in the presence of secondary amides would be of particular interest.

It is expected that the trifluoroethylation reaction will be modified to operate for α -difluorocarboxylic acids, for which there is arguably a higher demand than the trifluoroethyl species, particularly in pharmaceuticals, agrochemicals, and materials science. Other strongly

acidic carboxylic acids may also be investigated. The reaction should find a home in modular core-generation in drug-discovery.

Finally, the Mitsunobu reaction hopefully heralds the beginning of a powerful new manifold for phosphorus-catalysed reactions. With the inversion of secondary alcohols now demonstrated, work can begin on increasing the reactivity to allow reactions at lower temperatures to take place. The inversion of naturally occurring optically active alcohols through catalysis may find industrial application.

Figure 9. Results for the tosylation of decanol with various catalyst oxides (*copy also provided at back of Thesis*).