



New Directions in the Mitsunobu Reaction

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During the four years of my PhD study, I have had the privilege of working with excellent co-workers and supervisors and the professional relationships and friendships that I have developed during this time have been pivotal in my own professional development. I have no doubt that without the help of these people, my education throughout my PhD would be much poorer and as such I would like to express my gratitude to them.

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I will forever fondly remember my time spent studying for my PhD, partly due to exciting nature of the work involved, but mostly for the lifelong friends that I have made. Studying for a PhD has been a tough, but joyous experience and it is a period of my life I am certain that I will greatly miss.

Publications Associated with Thesis

1. **R. H. Beddoe**, H. F. Sneddon, R. M. Denton, *Org. Biomol. Chem.* 2018, **16**, 7774–7781. "The catalytic Mitsunobu reaction: a critical analysis of the current state-of-the-art."
2. **R. H. Beddoe**, K. G. Andrews, V. Magné, J. D. Cuthbertson, J. Saska, A. L. Shannon-Little, S. E. Shanahan, H. F. Sneddon, R. M. Denton, *Science*, 2019, **365**, 910–914. "Redox-neutral organocatalytic Mitsunobu reactions."
3. **R. H. Beddoe**, D. C. Edwards, L Goodman, H. F. Sneddon, R. M. Denton, *Chem. Commun.* 2020, **56**, 6480–6483. "Synthesis of ^{18}O-labelled alcohols from unlabelled alcohols."

Overview

The work described in this thesis is broadly focused on new developments in the Mitsunobu reaction. Specifically, this thesis reports our attempts to develop a catalytic and scalable alternative to the Mitsunobu reaction as well as new applications of the Mitsunobu towards a method for ^{18}O-labelling of alcohols.

Chapter 1 provides an introduction to organophosphorus chemistry and organophosphorus-based catalysis. The chapter begins with a theory-based overview of commonly-encountered functional groups within organophosphorus chemistry that are of relevance to the novel work presented in this thesis. This is followed by a review of some of the most common synthesis methods involving organophosphorus reagents and catalysts.

Chapter 2 explores the development of a catalytic Mitsunobu reaction which is predicated on a novel, unprecedented redox-neutral catalytic cycle. The applications of this new organocatalytic Mitsunobu reaction are then explored in the context of forming carbon-oxygen, carbon-nitrogen and carbon-carbon bonds and the design and synthesis of modified catalysts with improved catalytic activities is reported.

Chapter 3 is focused on the development if an ^{18}O-labelling methodology of alcohols by means of a Mitsunobu esterification, followed by an ester hydrolysis. This method is then further explored as a means to access isotopically enriched active pharmaceutical ingredients with potential applications as internal standards for mass spectrometry-based analysis.

I would like to note that, although I had an intellectual input into all of the work reported in this thesis, not all of the practical work was carried out by myself. In some rare cases, certain practical work packages, were carried out by colleagues. I felt it was necessary to include these experiments in this thesis as they influenced the subsequent direction that the projects took. I have made every effort to credit my co-workers in this respect by including a short disclaimer at the end of figure captions which includes work conducted by a colleague.

Abbreviations

Ac	acetyl
ADDM	azodicarbonyldimorpholine
ADDP	1,1'-(azodicarbpnyl)dipiperidine
ADME	absorption, distribution, metabolic and excretion
AIBN	azobisisobutyronitrile
Ar	unspecified aromatic group
ATR	attenuated total reflection
b.p.	boiling point
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
n-Bu	*n*-butyl
t-Bu	*tert*-butyl
Bz	benzoyl
c	centi
CALB	*Candida Antartica* lipase
cat.	catalyst
CBS	Corey-Bakshi-Shibata
CMBP	cyanomethylenetributylphosphorane
CMMP	cyanomethylenetrimethylphosphorane
CPME	cyclopentyl methyl ether
C_q	quaternary carbon
Cy	cyclohexyl
d	doublet
Da	Dalton
dba	dibenzylideneacetone
DCAD	di-4-chlorobenzyl azodicarboxylate
1,2-DCE	1,2-dichloroethane
DEAD	diethyl azodicarboxylate
DEBM	diethylbromomalonate
DHTD	4,7-dimethyl-3,5,7-hexahydro-1,2,4,7-tetrazocin-3,8-dione
DIAD	diisopropyl azodicarboxylate

DMA	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DMEAD	di-2-methoxyethyl azodicarboxylate
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
DMTP	dimethylmalonyltributylphosphorane
DNEAD	di-4-nitrobenzyl azodicarboxylate
DPDS	diphenyldisiloxane
DPEN	1,2-diphenyl-1,2-ethylenediamine
DPPA	diphenylphosphoryl azide
DPPE	1,2-bis(diphenylphosphino)ethane
DTBAD	di-*tert*-butyl azodicarboxylate
EDG	electron donating group
d.e.	diastereomeric excess
d.r.	diastereomer ratio
e.e.	enantiomeric excess
equiv.	equivalents
EDTA	ethylenediaminetetraacetic acid
EI	electron ionisation
ESI	electrospray ionisation
Et	ethyl
EWG	electron withdrawing group
FTIR	Fourier transform infrared spectroscopy
g	gram(s)
GC	gas chromatography
GP	general procedure
h	hour(s)
HMDS	hexamethyldiazasilane
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
Hz	hertz
IPA	isopropyl alcohol

IPr	1,3-bis-(2,6-diisopropylphenyl)imidazole
IR	infrared
J	coupling constant (NMR spectroscopy)
k	reaction rate constant
KHMDS	potassium hexamethyldiazasilane
KIE	kinetic isotope effect
LA	Lewis acid
LDA	lithium diisopropylamide
LED	light-emitting diode
lit.	literature
m	multiplet (NMR spectroscopy); meter(s); milli
M	generic transition metal; $molL^{-1}$; mega
m-	meta-
m.p.	melting point
MBH	Morrison-Brunn-Huisgen
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
min	minute(s)
MPO	4-methoxypyridine *N*-oxide
Ms	methanesulfonyl
MS	molecular sieves; mass spectrometry
MTr	1-*O*-(monomethoxytrityl)
m/z	mass-to-charge ratio
n	nano
NHC	*N*-heterocyclic carbene
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
Ns	2-nitrophenylsulfonyl; 4-nitrobenzylsulfonyl
Nu	generic nucleophile
[O]	generic oxidant
o-	ortho-
n-oct	*n*-octyl
p	pentet

p-	para-
Pc	phthalocyanine
Ph	phenyl
PIDA	phenyliodine(III) diacetate
PMHS	poly(methylhydrosiloxane)
ppm	part(s) per million
i-Pr	*iso*-propyl
n-Pr	*n*-propyl
PS-	polystyrene supported
Py	pyridyl
q	quartet (NMR spectroscopy)
R	unspecified chemical group
R_f	retardation factor
r.t.	room temperature
RDS	rate-determining step
RNA	ribonucleic acid
s	singlet (NMR spectroscopy)
SCS	spin-centre shift
SET	single electron transfer
SFC	supercritical fluid chromatography
S_N2	bimolecular nucleophilic substitution
S_N1	unimolecular nucleophilic substitution
t	triplet (NMR spectroscopy)
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TCT	2,4,6-trichlorotriazine
Tf	trifluorosulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMAD	*N*,*N*,*N'*,*N'*-tetramethyl azodicarboxamide

TMS	trimethlsilyl
TOF	time-of-flight
T_R	retention time
Ts	*para*-toluenesulfonyl
UV	ultraviolet
v/v	volume per unit volume
w/w	weight per unit weight
w/v	weight per unit volume
X	unspecified halogen group
δ	chemical shift
µ	micro
ν_{max}	absorption maximum (IR spectroscopy)

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Chapter 1

An Introduction to Organophosphorus Chemistry and Organophosphorus-Based Catalysis

1.1 Functional Groups in Organophosphorus Compounds

The organic chemistry of phosphorus is based on the existence of numerous stable compounds containing carbon–phosphorus bonds. Since phosphorus, like nitrogen, is in group 15 of the periodic table, it can readily adopt 3-coordinate structures in the phosphorus(III) oxidation state. However, organophosphorus compounds are also stable in the phosphorus(V) oxidation state, where the central phosphorus atom can adopt many different structures and coordination numbers. To help clarify and characterise this structural diversity, the coordination number of organophosphorus compounds is designated by the letter σ and the valency is designated by the letter λ, as a convenient shorthand.

1.1.1 Phosphines

Phosphines are trivalent phosphorus(III) compounds of the general formula PR_3 (σ_3, λ_3, R = aryl or alkyl). Like amines, phosphines possess one lone pair of electrons and as such occupy a trigonal pyramidal geometry. Due to the larger frontier orbitals of phosphorus, the P–R (*ca.* 1.4 Å) bonds in a phosphine are longer than the N–R (*ca.* 1.0 Å) bonds in an analogous amine. The reduced steric clash allows the bonding angle to reduce from 107° in ammonia (NH_3) to 93° in phosphine (PH_3) which results in P–R bonds that are almost unhybridized, instead using orbitals with high p-orbital character to bond with the R group.[1–3]

This reduced bonding angle, increases the activation energy of pyramidal inversion, which occurs through a trigonal planar transition state (figure 1A). This energy barrier to is much greater than is found with analogous amines. For example, the Gibbs energy of activation for the epimerisation of ammonia is 5.78 Kcal/mol, whereas the value for phosphine is much greater at 31.5 Kcal/mol.[4] As such, the vast majority of phosphines with three different substituents attached to the phosphorus can be resolved into stable enantiomers at room temperature whereas amines cannot.[5] This is an important property of phosphines, since chiral *P*-stereogenic phosphines are important in asymmetric catalysis, such as the use of the ligand (*R*,*R*)-DIPAMP in asymmetric hydrogenation reactions as reported by Knowles and co-workers (figure 1B).

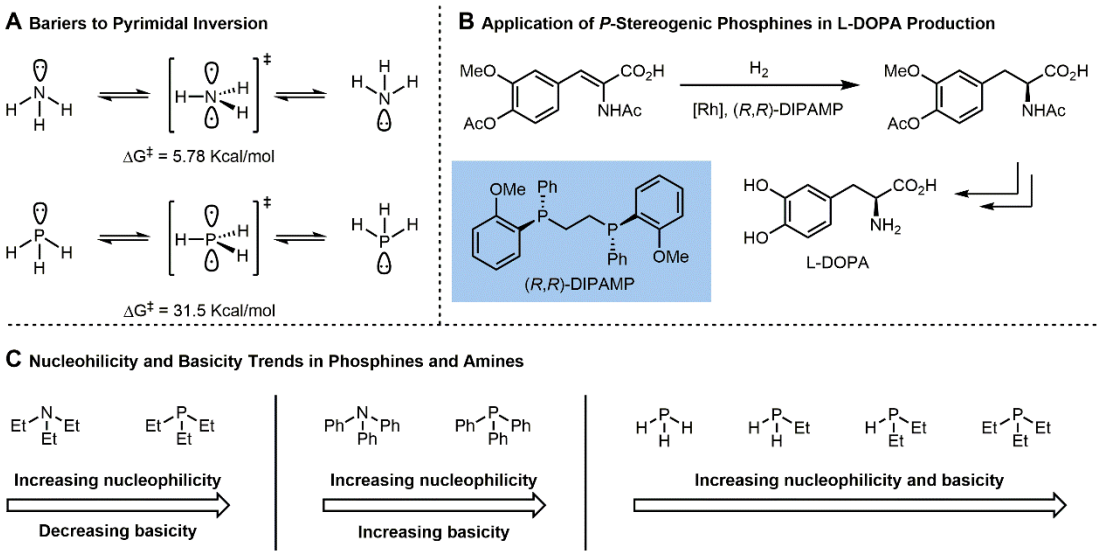


Figure 1. (A) The energy barriers to pyrmidal inversion of ammonia and phosphine; **(B)** The application of the *P*-stereogenic chiral phosphine DIPAMP in the industrial synthesis of L-DOPA; **(C)** Nucleophilicity and basicity trends in phosphines and amines.

Most of the reactivity associated with phosphines is centred on the lone pair, and its availability to form bonds. Phosphines are Brønsted basic—they are slightly less basic than their amine counterparts. For example, the pK_aH of triethylphosphine is 8.6 in water, whereas the pK_aH of triethylamine is 10.8.[6,7] However, this trend is reversed when comparing triaryl phosphines and triarylamines. Unlike triarylamines, overlap between the phosphorus lone pair and the aromatic π- system is inefficient due to the larger frontier orbitals associated with the lone pair and the long P–C bonds.[8] As such triphenylphosphine (pK_aH (H_2O) = 2.8) is significantly more Brønsted basic than triphenylamine (PK_aH (H_2O) = −5.0).[6,7,9,10]

The nucleophilic property of phosphines is fundamental in organophosphorus chemistry as it underpins many classic organophosphorus-mediated reactions. Trialkylphosphines are generally the most nucleophilic, followed by secondary phosphines then primary phosphines—the nucleophilicity decreases with fewer electron releasing substituents attached to the phosphorus. Similarly, triarylphosphines are generally less nucleophilic than trialkylphosphines.[7,11] Nevertheless, triphenylphosphine is still a powerful nucleophile and several common organophosphorus-mediated reactions (eg. Mitsunobu, Appel,

Staudinger) are all initiated with the nucleophilic attack of a phosphine on an electrophilic centre.[12]

1.1.2 Phosphine Oxides

Tertiary phosphine oxides are stable, abundant class of organophosphorus molecules with a chemical formula of R_3PO (R = alkyl or aryl). Generally, they are crystalline, non-toxic solids.[13] The central tetracoordinated phosphorus atom (σ^4, λ^5) has a tetrahedral geometry. Three of the four bonds are made up of σ-bonds which connect the phosphorus atom to the R groups. The phosphoryl (phosphorus-oxygen) bond is known to be relatively short (typically within the range of 1.47–1.59 Å),[1] polar and strong (bond dissociation energies are typically within the range of 128–139 kcal/mol).[14]

The commonly accepted bonding description of the phosphoryl bond involves the donation of a lone pair from the phosphorus to form a σ-bond between the phosphorus and oxygen, to yield a species with a negative charge on the oxygen. The resulting negative charge on the oxygen is back-donated to low-lying orbitals on the phosphorus. Thus, resonance forms **1** and **2** are often said to contribute towards the bonding in the phosphoryl bond (figure 2A).

The nature of the oxygen to phosphorus back-bonding has been the subject of much debate. This back-bonding was once widely thought to involve donation of electrons from the oxygen into vacant d-orbitals of the phosphorus (**3**, figure 2B).[15–17] However, over the last 30 years many *ab initio* studies of the phosphoryl bond, have rendered this view untenable and concluded that d-orbitals have no involvement in back-bonding. Thus, this old bonding description is no longer used.[18–22]

The multiple bonding character of the phosphoryl group is attributed to back-donation of electrons from an oxygen 2p-orbital into vacant σ* antibonding orbitals of the P–R bonds (**4**, figure 2B). Crystallographic evidence for this interaction has been reported by the Orpen group[23] and *ab initio* calculations from Reed and Schleyer has further supported this bonding model.[20] A consequence of this orbital description is that a greater degree of back-bonding occurs for phosphine oxides containing more electronegative R substituents with

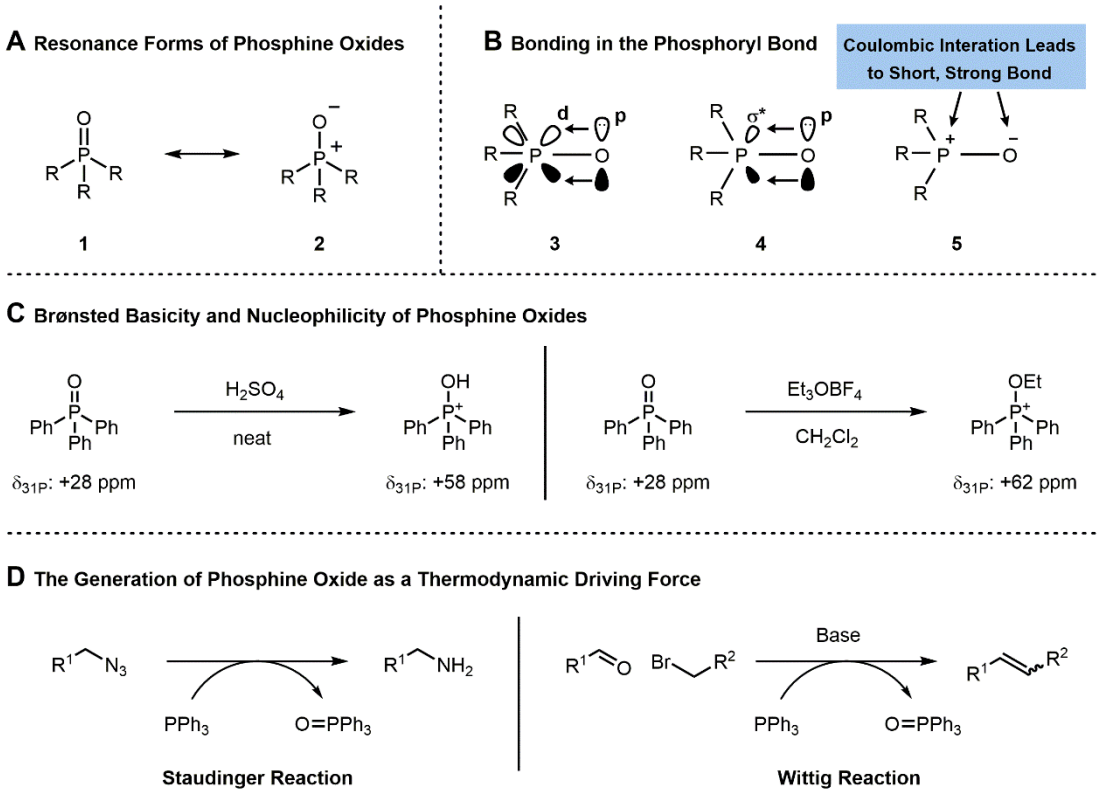


Figure 2. (A) Resonance forms of phosphine oxides; **(B)** Bonding orbitals involved in the phosphoryl bond; **(C)** A demonstration of phosphine oxide basicity and nucleophilicity; **(D)** The generation of triphenylphosphine oxide as a driving force for the Staudinger and Wittig reactions.

lower-energy acceptor orbitals. This phenomenon results in an overall stronger phosphoryl bond. This theory is supported by the decreasing IR stretching frequencies across the series F_3PO (1418 cm^{-1}) < Cl_3PO (1298 cm^{-1}) < Me_3PO (1170 cm^{-1}).[24]

An alternative bonding model has also emerged from *ab-initio* calculations by Sundberg[25] and Chesnut,[26,27] which supports a view that the σ bond between the phosphorus and oxygen leading to a species with an ionic charge on each atom (**2**) was present, however it is the Coulombic interactions between the charged phosphorus and oxygen that strengthens and shortens the P–O bond (**5**, figure 2B). This model dismisses any multiple bonding character in the P–O bond. Regardless of the precise description of the electron distribution in a phosphoryl bond, there is no doubting that the bond is short, strong and highly polar.

Although phosphine oxides are generally unreactive, the phosphoryl oxygen is a weak Brønsted base and nucleophile. For example, the pK_aH of

diphenylmethylphosphine oxide and dimethylphenylphosphine oxide are −3.2 and −2.4 respectively and are both fully protonated in anhydrous sulfuric acid.[14] Furthermore, triphenylphosphine oxide behaves as a nucleophile when reacted with potent electrophiles, such as triethyloxonium tetrafluoroborate to obtain ethoxytriphenyl phosphonium tetrafluoroborate (figure 2C).[28]

Phosphine oxides are often encountered as by-products of reactions mediated by organophosphorus reagents. Since the phosphoryl bond has a high dissociation energy, the generation of a phosphoryl bond, from the oxidation of a phosphine serves as a thermodynamic driving force for many key organophosphorus-mediated reactions, such as the Wittig, Appel and Staudinger reactions (figure 2D).

1.1.3 Phosphoranes

Phosphoranes are pentavalent phosphorus compounds with the general formula PR_5 (σ_5, λ_5), the vast majority of which are arranged in a trigonal bipyramid geometry. In this geometry the axial and equatorial positions are non-equivalent and, as such, certain substituents prefer to occupy axial positions. Without accounting for steric crowing effects of substituents, the axial positions in phosphoranes, whose bonds are longer than the equatorial, tend to be occupied by the most electronegative ligands, whereas π-donor ligands preferentially occupy the equatorial position (figure 3A). Based on these phenomena the preference of different substrates for the axial position follows the ensuing order; F > H > CF_3 > PhO > Cl > MeS > MeO > Me_2N > Me > Ph.[29,30]

Phosphoranes can be fluxional, meaning that groups are not firmly held in a given equatorial or axial position. Many phosphoranes are able to undergo a stereomutation process called *pseudorotation*, wherein axial and equatorial ligands exchange positions. Pseudorotation can occur by one of two mechanisms. The first, known as the Berry mechanism involves the bending of two axial P–R bonds into equatorial positions and two equatorial P–R bonds into axial positions simultaneously.[31] The second, known as the turnstile mechanism, involves the rotation of one axial and one equatorial P–R bond to form a pseudo square-based pyramid intermediate, followed by a second rotation of two pseudoequatorial

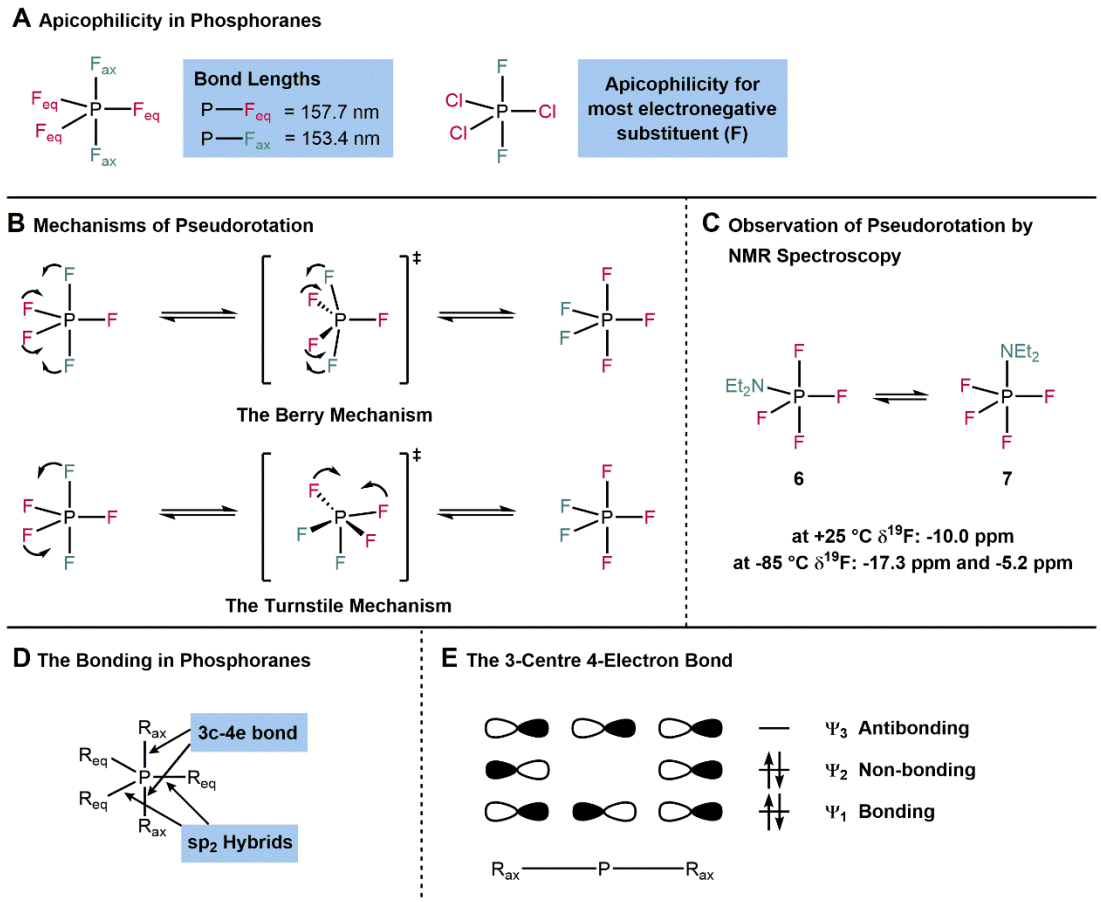


Figure 3. (A) Relative bond lengths and apicophilicity in pentavalent phosphoranes; **(B)** The mechanisms of pseudorotation in phosphoranes, the Berry mechanism (above) and the turnstile mechanism (below); **(C)** The observation of pseudorotation by ^{19}F NMR; **(D)** The different bonds involved in P–R bonds in pentavalent phosphoranes; **(E)** An orbital description of a 3-centre, 4-electron bond.

substituents (figure 3B).[32] This phenomenon can be observed spectroscopically, since the ^{19}F NMR spectrum for (diethylamino)tetrafluorophosphorane contains only a single signal at room temperature, despite the static molecule containing two fluorine environments. This phenomenon is only possible if the fluorine atoms can exchange positions faster than the NMR timescale. At −85 °C however, the rate of pseudorotation is reduced and two signals are present at −5.2 and −17.3 ppm in a 1:1 ratio (figure 3C).[33] This spectrum is consistent with phosphorane **6** which is the most thermodynamically stable pseudorotamer.

As with phosphine oxides, the involvement of d-orbitals in bonding was once invoked to explain the apparent hypervalency of phosphoranes,[34] however, this

has since been discredited.[21] The equatorial P–R bonds are two-centre, two-electron bonds formed by the combination of sp^2 hybrids on the central phosphorus atom at appropriate orbitals on the R group. This model leaves one filled p-orbital on the phosphorus, which forms a bonding interaction with the axial R groups through, three-centre, four-electron bond (figure 3D). The linear combinations of two half-filled p-orbitals on the ligands with the filled p-orbital on the phosphorus, along the co-linear R–P–R axis, affords a bonding orbital, which is doubly occupied and a non-bonding orbital, which is doubly occupied and a vacant antibonding orbital (figure 3E).[35,36]

1.1.4 Phosphonium Salts and Heterophosphonium Salts

Compounds with the formula $[PR_4^+]X^-$ comprise the phosphonium salts. These species are tetrahedral, tetravalent, cationic phosphorus(V) compounds. The bonding consists of four 2-electron σ-bonds emanating from the phosphorus centre to the R groups and the phosphorus carries a positive charge.[36] Phosphonium salts where the R groups are either alkyl or aryl groups are important synthetic in organophosphorus chemistry, as they are commonly employed as precursors to phosphonium ylides in the Wittig reaction. These types of phosphonium salts are commonly synthesised by alkylation of trisubstituted phosphines.

Halophosphonium and oxyphosphonium salts are phosphonium salts where one or more of the carbon substituents is replaced by a halogen or by groups based on oxygen respectively. These species are electrophilic at the phosphorus centre and are known to isomerise through a pentacoordinate phosphorane (figure 4A). If the counterion is sufficiently Lewis basic, it can form a bonding interaction with the phosphorus centre, adopting the role of an axial substituent of the phosphorane.[37,38]

The preference to adopt either a pentacoordinate phosphorane form or a tetracoordinate phosphonium structure is determined by several parameters such as Lewis basicity of the counterion, Lewis acidity of the phosphonium, the thermodynamic stability of the phosphorane and, when in a solution, the polarity of the solvent. For example, Cl_2PPh_3 takes the phosphonium form when it is in the

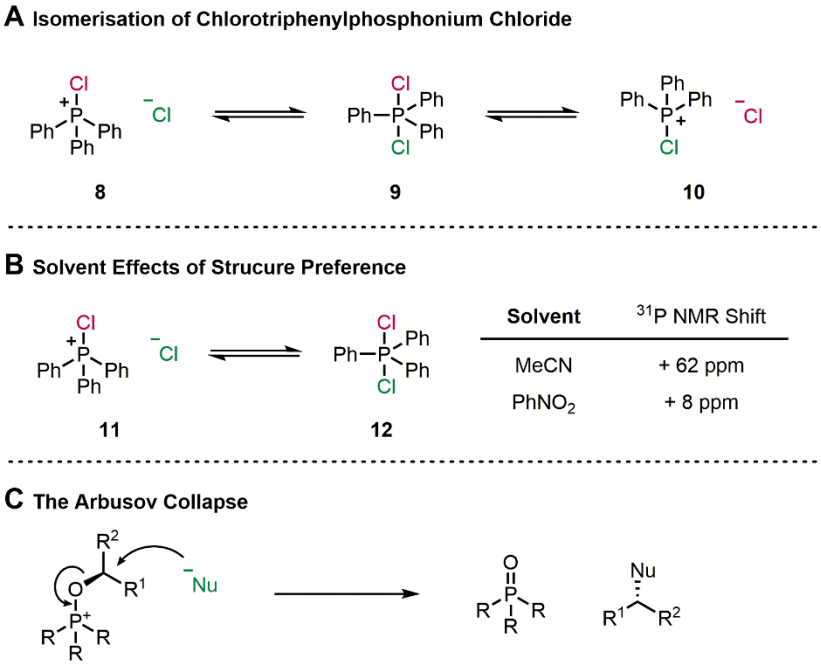


Figure 4. (A) The reversible isomerisation of tetracoordinate phosphonium salt to a pentavalent phosphorane; **(B)** Solvent effects on the phosphonium salt:phosphorane equilibrium; **(C)** The mechanism of the Arbuzov collapse.

solid phase, or dissolved in polar solvents such as acetonitrile,[39,40] but has greater 5-coordinate character in benzene and nitrobenzene (figure 4B).[40,41] Similarly, the 5-coordinate structure $P(OR)_5$ prevails over the phosphonium structure $P(OR)_4^+(OR)^-$ due to the strong Lewis basicity of the alkoxide ion.[41,42] If the counterion is non-nucleophilic, such as BF_4^- or PF_6^- there is no possibility for the 5-coordinate state to exist, therefore the species only exists as the phosphonium salt.[36]

Many alkoxyphosphonium salts with nucleophilic counterions are unstable with respect to nucleophilic substitution. The nucleophilic counterion can attack the α-carbon of the alkoxy group, displacing a phosphine oxide leaving group. This process is commonly referred to as the 'Arbusov collapse' and results in an inversion of stereochemistry at the α-carbon (figure 4C).[43–46] The Arbusov collapse is driven by the generation of a thermodynamically stable phosphoryl bond and is an important mechanistic step, and thermodynamic driving force, in valuable organophosphorus-mediated reactions such as the Appel and Mitsunobu reactions.

1.2 Organophosphorus Chemistry

A wide range of name reactions mediated by organophosphorus reagents have emerged from the past decade of research in the field. Many of these reactions are now a fundamental part of a synthesis chemists' arsenal.[47–49] They are commonly used in the synthesis of highly complex molecules, such as natural products, and are routinely used to synthesise fine chemicals at both laboratory and industrial scales. The next section provides a review of the most important reactions within the field of organophosphorus chemistry.

1.2.1 Wittig Reaction

Since its discovery in1954,[50,51] the Wittig reaction has become one of the most important and effective methods available of synthesising alkenes.[52–59] The reaction uses phosphonium ylide and aldehydes or ketones as reactants and the phosphonium ylides are conventionally synthesised by the deprotonation of a phosphonium salt. The phosphonium salts themselves are generally accessed through the alkylation of a phosphine, usually triphenylphosphine, using an alkyl halide or pseudohalide (figure 5A).

Phosphonium ylides are generally classified into three categories, depending on the identity of the ylide substituents (R^1 and R^2 in figure 5A). The nature of the ylide is known to affect the regioselectivity of the reaction. Stabilized ylides, where the R groups is a strong electron withdrawing group (eg. $-CO_2R$ or $-SO_2R$ etc.) give predominantly *E*-alkenes. Non-stabilized ylides where the R group is electron releasing, such as an alkyl groups, give predominantly *Z*-alkenes. Lastly, semi-stabilized ylides where the R group is an aryl or alkenyl substituent tend to give a mixture of *E* and *Z* regioisomers (figure 5B). A notable exception to this rule is the 'Schlosser modification,' whereby the addition of stoichiometric lithium halide salt to the reaction mixture results in non-stabilized ylides producing alkenes with high diastereoselectivity for the *E* alkene (figure 5C).[60]

Mechanistic studies of this reaction have revealed that the phosphonium ylide and aldehyde or ketone undergo an initial thermal [2+2] cycloaddition (**13**, figure 5D), forming oxyphosphetane intermediate **14**. Subsequent retro-[2+2] of

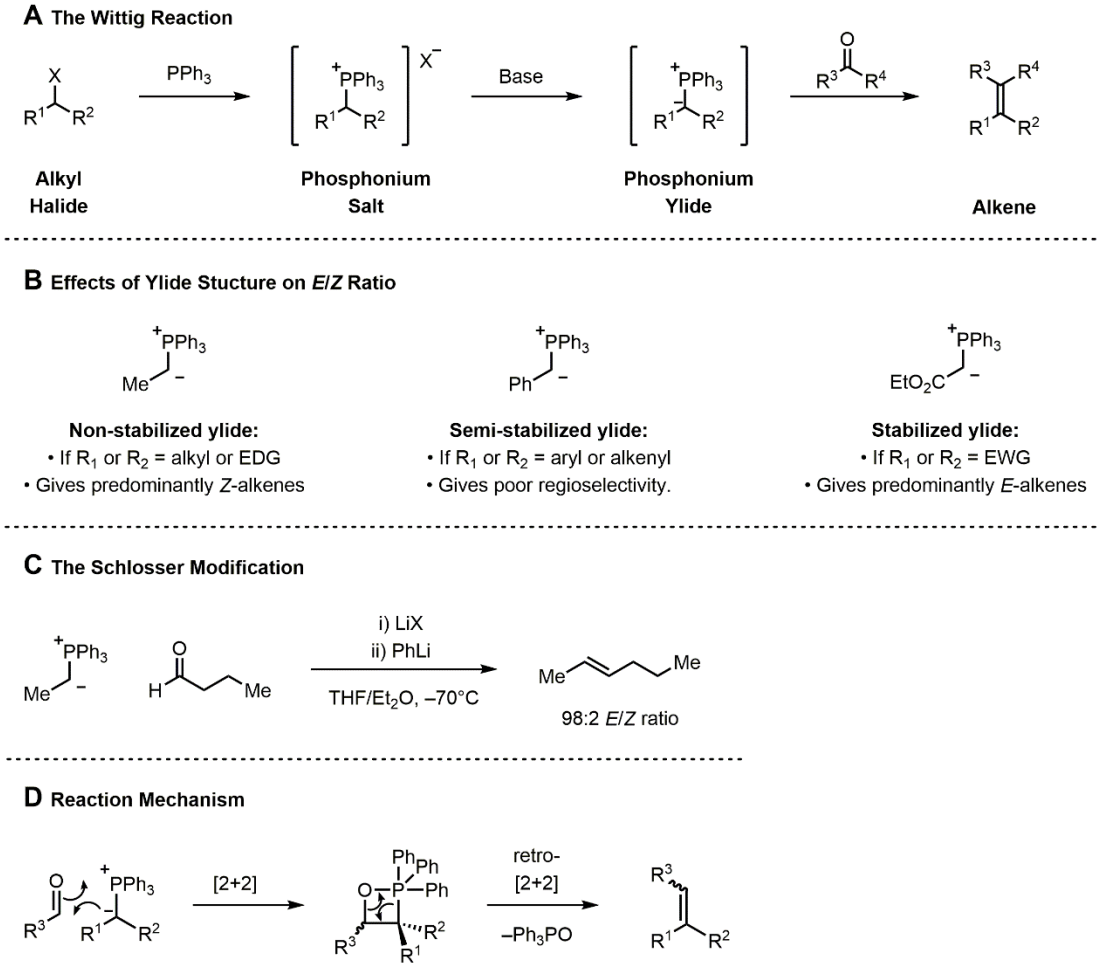


Figure 5. (A) The intermediates involved in the Wittig reaction; **(B)** Different phosphonium ylides and their effects on the regioselectivity of the Wittig reaction; **(C)** The Schlosser modification for the synthesis of *E*-alkenes from non-stabilised ylides; **(D)** The Wittig reaction mechanism.

this intermediate affords the alkene product **15** and phosphine oxide by-product (figure 5D).[61–69] Since the reaction is under kinetic control, the diastereoselectivity of the reaction is determined by the relative orientation of the phosphonium ylide and aldehyde/ketone during the formation of the oxyphosphetane intermediate.[70,71]

1.2.2 Horner-Wadsworth-Emmons Reaction

The Horner-Wadsworth-Emmons reaction is closely related to the Wittig reaction—the difference is that deprotonated phosphonate esters, rather than phosphonium ylides, are coupled with aldehydes or ketones to form alkenes (figure 6A).[59,72–77] The by-product of this reaction is a dialkylphosphonate ester, which, in contrast to triphenylphosphine oxide, can be separated from the

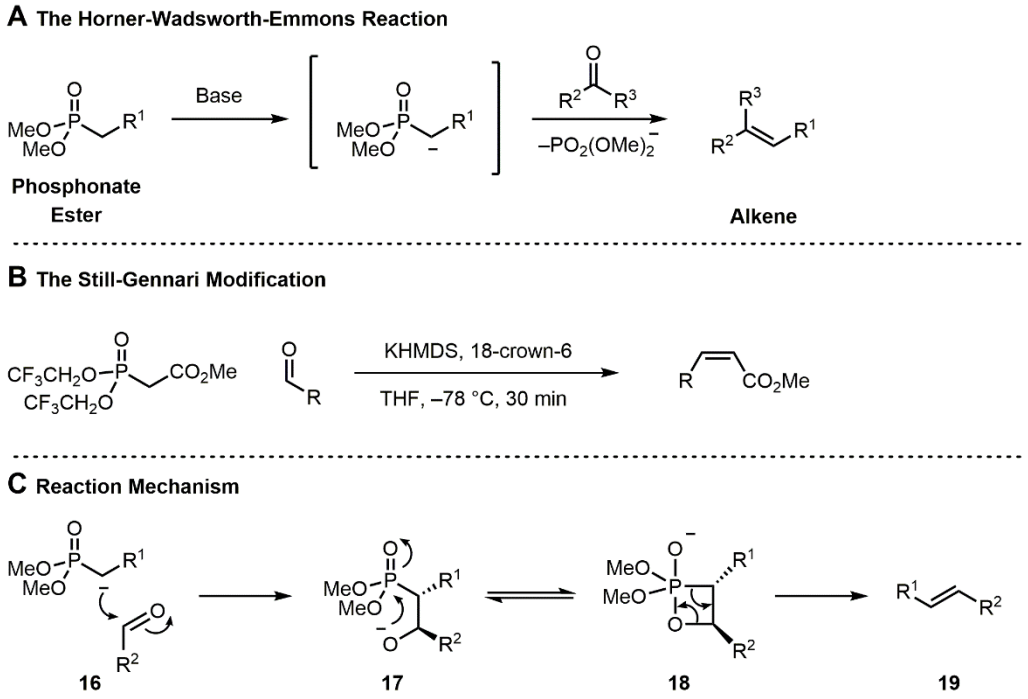


Figure 6. (A) The intermediates involved in the Horner-Wadsworth-Emmons reaction; **(B)** The Still-Gennari modification for the synthesis of Z-alkenes; **(C)** The Horner-Wadsworth-Emmons reaction mechanism.

reaction mixture by aqueous extraction, and is therefore a more practically convenient alternative to the Wittig reaction.

The phosphonate esters are conventionally deprotonated using strong bases, such as sodium hydride, however milder conditions, using weaker bases have been subsequently developed.[78–82] This reaction produces predominantly *E*-alkenes, however *Z*-alkenes can be accessed using the Still-Gennari modification, which involves varying the base and replacing the alkoxy substituents on the phosphonate ester with trifluorothoxy groups (figure 6B).[83] The phosphonate esters are conventionally prepared by either the Arbuzov reaction or the Michaelis-Becker reaction.

The mechanism of this reaction begins with an α-deprotonation of the phosphonate ester (figure 6C) and the resulting nucleophilic carbanion (**16**) undergoes a nucleophilic attack on the aldehyde or ketone. The resulting alkoxyphosphonate (**17**) is in equilibrium with an oxyphosphentane (**18**), which undergoes a retro-[2+2] to afford the alkene product (**19**) and a dialkylphosphonate ester.[59]

1.2.3 Staudinger Reaction

Discovered in 1919,[84] the Staudinger reaction describes the reaction of an organic azide with a phosphine to generate an iminophosphorane with concomitant formation of dinitrogen (figure 7A).[85–89] The mechanism of this transformation begins with a nucleophilic attack of the phosphine to the unsubstituted terminal nitrogen atom of the azide (**20**, figure 7B) to give the corresponding phosphazide (**21**). Next, the iminophosphorane product (**23**) is generated by the expulsion of dinitrogen from a four membered transition state (**22**).

In most cases, the iminophosphoranes are subjected to further chemical manipulation in the same pot. For example, hydrolysis of the generated iminophosphoranes with water affords primary amines (figure 7A). This two-step procedure is commonly referred to as the 'Staudinger reduction' and is a typical method for converting azides into amines. Similarly, if iminophosphoranes are reacted with aldehydes or ketones, an aza-Wittig

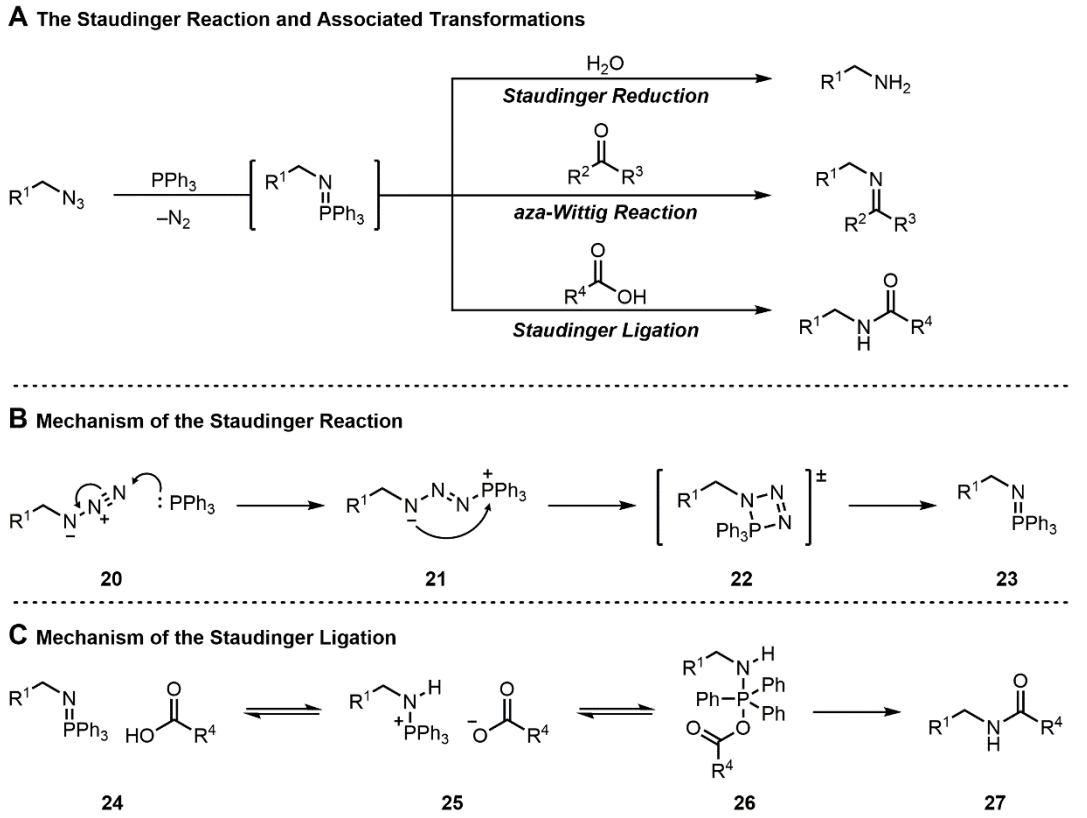


Figure 7. (A) The Staudinger reaction and subsequent transformations of the iminophosphorane; **(B)** The Staudinger reaction mechanism; **(C)** The mechanism of the Staudinger ligation.

reaction occurs, and an imine product is generated (figure 7A).

If the Staudinger reaction is conducted in the presence of a carboxylic acid or ester, *N*-substituted amides are generated. This transformation is often called the 'Staudinger ligation.' It is thought to occur through *O*,*N*-phosphorane (**26**, figure 7C) which rearrange to generate the amide product (**27**) and phosphine oxide by-product. Since this reaction is selective, fast, generally high-yielding and compatible with functional groups found in biological systems, it has become one of the most important and effective methods for bioconjugation.

1.2.4 Appel Reaction

The Appel reaction is a mild method for converting alcohols to alkyl halides with inversion of stereochemistry (figure 8A). The reagents conventionally used are triphenylphosphine and an electrophilic halogen source. The most common halogen sources are carbon tetrachloride and carbon tetrabromide which are used to synthesise alkyl chloride and bromide respectively. For iodination reactions, Sammuelsson's modified conditions are usually the reaction conditions of choice, which uses triphenylphosphine, iodine and imidazole as reagents (figure 8B). Since the Appel reaction is generally milder than other common deoxyhalogenation reagents (such as thionyl chloride and phosphorus tribromide), it has found widespread application in the deoxyhalogenation of complex molecules.

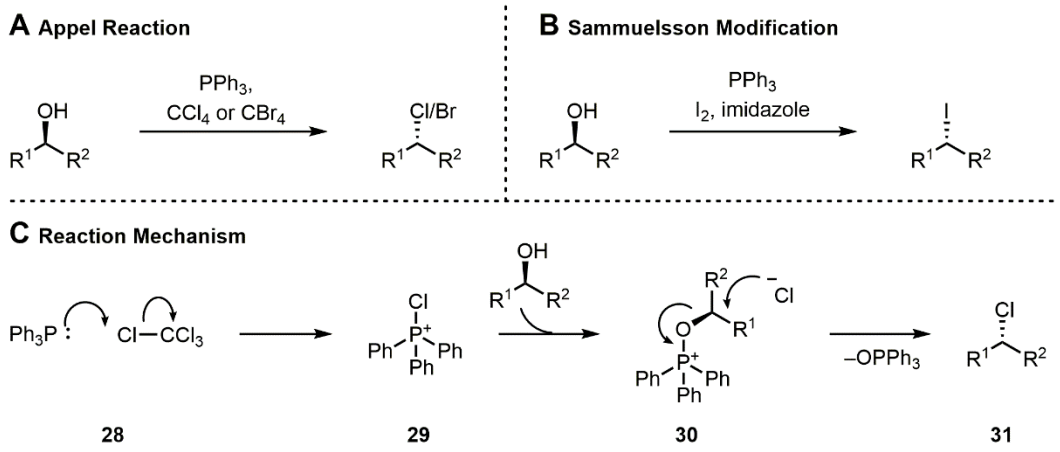


Figure 8. (A) A generic Appel reaction; **(B)** The Sammuelsson modification to the Appel reaction; **(C)** The Appel reaction mechanism, using CCl_4 and triphenylphosphine as representative reagents.

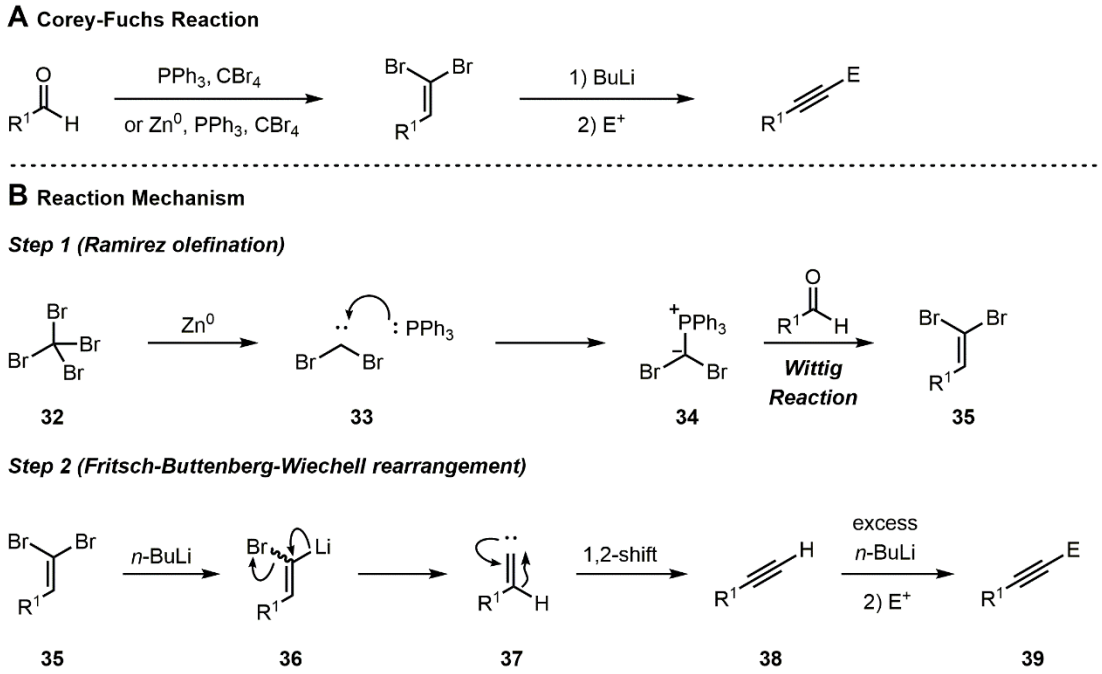


Figure 9. (A) The starting material, reagent, intermediates and product involved in the Corey-Fuchs reaction; **(B)** The Corey-Fuchs reaction mechanism.

The mechanism proceeds by nucleophilic attack of triphenylphosphine to the carbon tetrachloride (**28**, figure 8C) to afford chlorophosphonium species **29**. The chloride substituent is then displaced by the alcohol to form an alkoxyphosphonium chloride (**30**). A subsequent Arbuzov collapse of the affords the alkyl chloride (**31**) and triphenylphosphine oxide.

1.2.5 Corey-Fuchs Reaction

The Corey-Fuchs reaction describes a two-step method to access alkynes from aldehydes (figure 9A).[90–92] The first step of the reaction involves generating a 1,1-dibromoalkene (**35**, figure 9B) *via* the reaction of triphenylphosphine with dibromocarbene (**33**), which can either be generated from the reaction of tetrabromomethane with zinc metal or excess triphenylphosphine, to form a phosphorus ylide (**34**). This ylide then undergoes a Wittig reaction with the aldehyde to generate the 1,1-dibromoalkene (**35**). This step is commonly referred to as the 'Ramirez olefination.'[93] In the second step 1,1-dibromoalkene is treated with *n*-butyllithium, to induce a lithium-halogen exchange followed by α-elimination (**36**). A 1,2-shift of the resulting vinylidene intermediate (**37**) affords the terminal alkyne (**38**).[94] If excess *n*-butyllithium is present in the

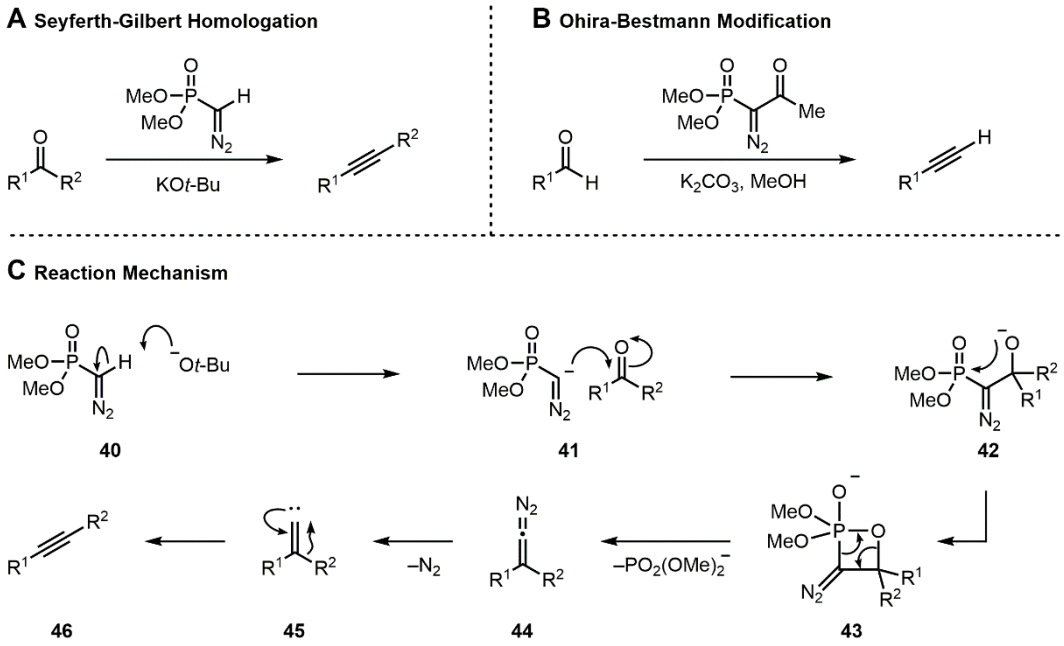


Figure 10. (A) The starting material, reagent and products involved in the Seyferth-Gilbert homologation; **(B)** The Ohira-Bestmann modification; **(C)** The Seyferth-Gilbert homologation reaction mechanism.

reaction mixture, then the terminal alkyne product is deprotonated, and can be therefore be functionalised with myriads of electrophiles to afford di-substituted alkynes (**39**).

1.2.6 Seyferth-Gilbert Homologation

The Seyferth-Gilbert homologation enables alkynes to be prepared from aldehydes or ketones using a dialkylphosphono-diazomethane reagent (figure 10A). The dialkylphosphonodiazomethane is firstly deprotonated (**40**, figure 10C) and the resulting anion attacks the carbonyl group of the aldehyde or ketone, and an oxyphosphetane intermediate is formed (**43**). This intermediate then undergoes a retro-[2+2] to afford a thermally unstable diazoalkane (**44**). After loss of dinitrogen, the resulting vinylidene undergoes a 1,2-shift (**45**) to afford the alkyne (**46**). One drawback of the Seyferth-Gilbert homologation is the requirement for a strong base, usually potassium *tert*-butoxide, for the initial deprotonation. In the Ohira-Bestmann modification, the dialkylphosphonodiazomethyl anion is instead generated from the solvolysis of a dialkyl-1-diazo-2-oxopropylphosphonate using potassium carbonate and

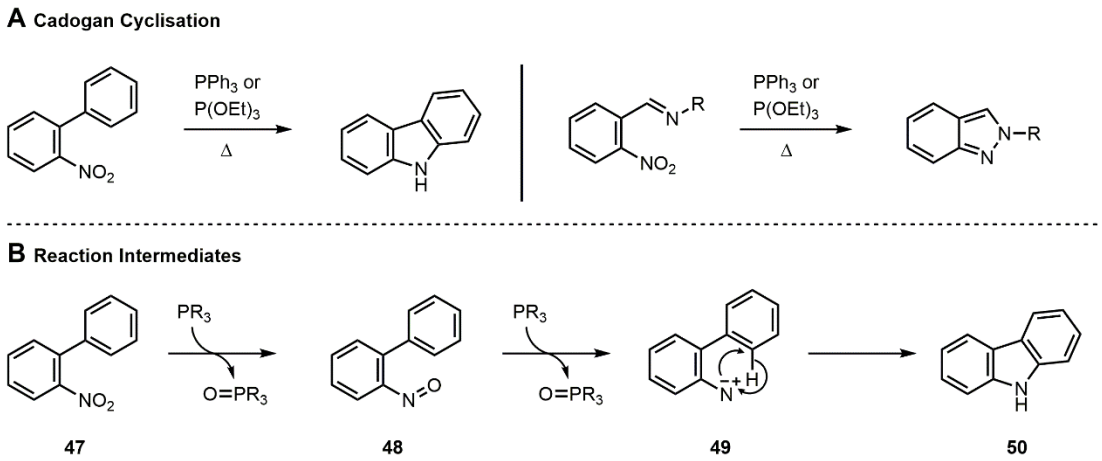


Figure 11. (A) The Cadogan cyclisation for the synthesis of barbazoles and indazoles; **(B)** The reaction mintermediates involved in the Cadogan cyclisation.

methanol (figure 10B). These modified conditions offer a much wider functional group tolerance and are usually the conditions of choice for carrying out this transformation.

1.2.7 Cadogan Cyclisation

The Cadogan cyclisation is a powerful method for intramolecular reductive functionalisations of nitroarenes. The reaction is commonly used to synthesise carbazoles or indazoles from nitroarene precursors (figure 11A). The reaction occurs by initial reduction of the nitroaryl, using stoichiometric phosphine or phosphite, to the analogous nitrosoarene (**48**, figure 11B), followed by a second reduction to a nitrene (**49**). This reduction is followed by the intramolecular trapping of the nitrene to form cyclic products. In the example shown in figure 11B, the nitrene undergoes a C–H insertion to form a carbazole product (**50**).

A major issue with this method is the requirement for high temperatures and super-stoichiometric phosphine/phosphite. In Cadogan's original reports,[95–108] the reaction was conducted in neat refluxing triethylphosphite (b.p. 156 °C) and despite further practical improvements,[109–111] the reaction still requires elevated temperatures and super-stoichiometric quantities of a phosphine or phosphite.

1.3 The Mitsunobu Reaction

The Mitsunobu reaction enables the nucleophilic substitution of alcohols, by a redox combination of a phosphine (usually triphenylphosphine) and azo reagent (usually diethylazodicarboxylate (DEAD) or diisopropylazodicarboxylate (DIAD)). Since its discovery in 1967,[112–114] this reaction has occupied a privileged role within synthetic organic chemistry and is often used as a key step in the synthesis of complex molecules such as natural products.[115] The reaction is widely regarded as the state-of-the art method for the nucleophilic substitution of alcohols due to its wide functional group tolerance, and its excellent substrate scope.[116–122]

Primary and secondary alcohols are effective substrates. Although the Mitsunobu coupling of activated tertiary alcohols have been demonstrated,[123] the scope of the tertiary alcohols is very limited, and this transformation is seldom employed in synthesis. When enantiopure, chiral secondary alcohols are used as substrates, in the vast majority of cases the nucleophilic substitution occurs with a full Walden inversion of stereochemistry.

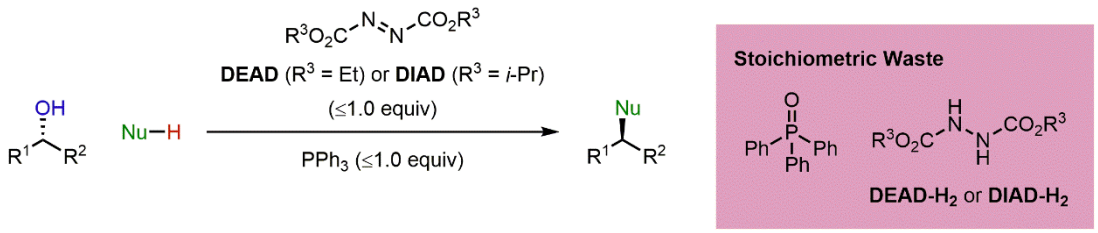


Figure 12. The starting material, reagents, products and by-products involved in the Mitsunobu reaction,

1.3.1 Pro-Nucleophile Scope and Applications in Organic Chemistry

The pro-nucleophiles that are compatible with this reaction are generally compounds containing relatively acidic O–H, N–H, S–H and C–H bonds which permit the formation of C–O, C–N, C–S and C–C bonds respectively. Under the triphenylphosphine/DEAD protocol, the pK_a (in water) for these pro-nucleophiles must be below 11, however, using modified azo reagents, the pK_a of the pro-nucleophile can be increased to 15 and still be effective in the reaction

(this is discussed in more detail on page 24). Although acidic pro-nucleophiles are the most common, some metal salts such as zinc azide and zinc *N*,*N*-dimethyldithiocarbamate are effective as nucleophiles in the Mitsunobu reaction.[124] The next section provides an overview of the type of bond construction permitted and examples of useful applications of the Mitsunobu reaction within synthetic organic chemistry.

Carbon–Oxygen Bond Formations. One of the most common applications of the Mitsunobu reaction is in the synthesis of carboxylic esters, using carboxylic acids as pro-nucleophiles (figure 13).[112,114] Since the Mitsunobu esterification occurs with inversion of stereochemistry, a Mitsunobu esterification-ester hydrolysis sequence is often used for inverting the stereochemistry of a *C*-stereogenic secondary alcohol (figure 13A).[125–129] This reaction sequence is commonly referred to as the 'Mitsunobu inversion' and has found numerous applications in the synthesis of natural products, such as Crimmins' synthesis of (±)-ginkolide B[130] and Kibayashi's synthesis of (±)-fasicularin.[131]

Phenols and phenol derivatives are also competent pro-nucleophiles in the Mitsunobu reaction and can be effectively coupled with primary and secondary alcohols to form phenol ethers.[132] This synthesis method is often used as a base-free alternative to the Williamson ether synthesis. Sulfonic acids[133] and zinc sulfonate salts[134] are good pro-nucleophiles in the Mitsunobu reaction, and can be coupled with alcohols to form sulfonate esters. Similarly, various phosphoric acid esters can be accessed through the Mitsunobu coupling of phosphoric acids and alcohols.[112,114]

Carbon–Nitrogen Bond Formations. Nitrogen pro-nucleophiles can engage in a Mitsunobu reaction, if they are sufficiently acidic (pKa < 13). Thus, several examples of carbon–nitrogen bond forming reaction have been developed using activated amines as pro-nucleophiles. Protected primary amines can be synthesized from alcohols using phthalimide as the pro-nucleophile.[135–137] This is a convenient alternative to the Gabriel synthesis and the phthalimides are routinely deprotected to their analogous primary amines using hydrazine or methylamine (figure 13B).[137]

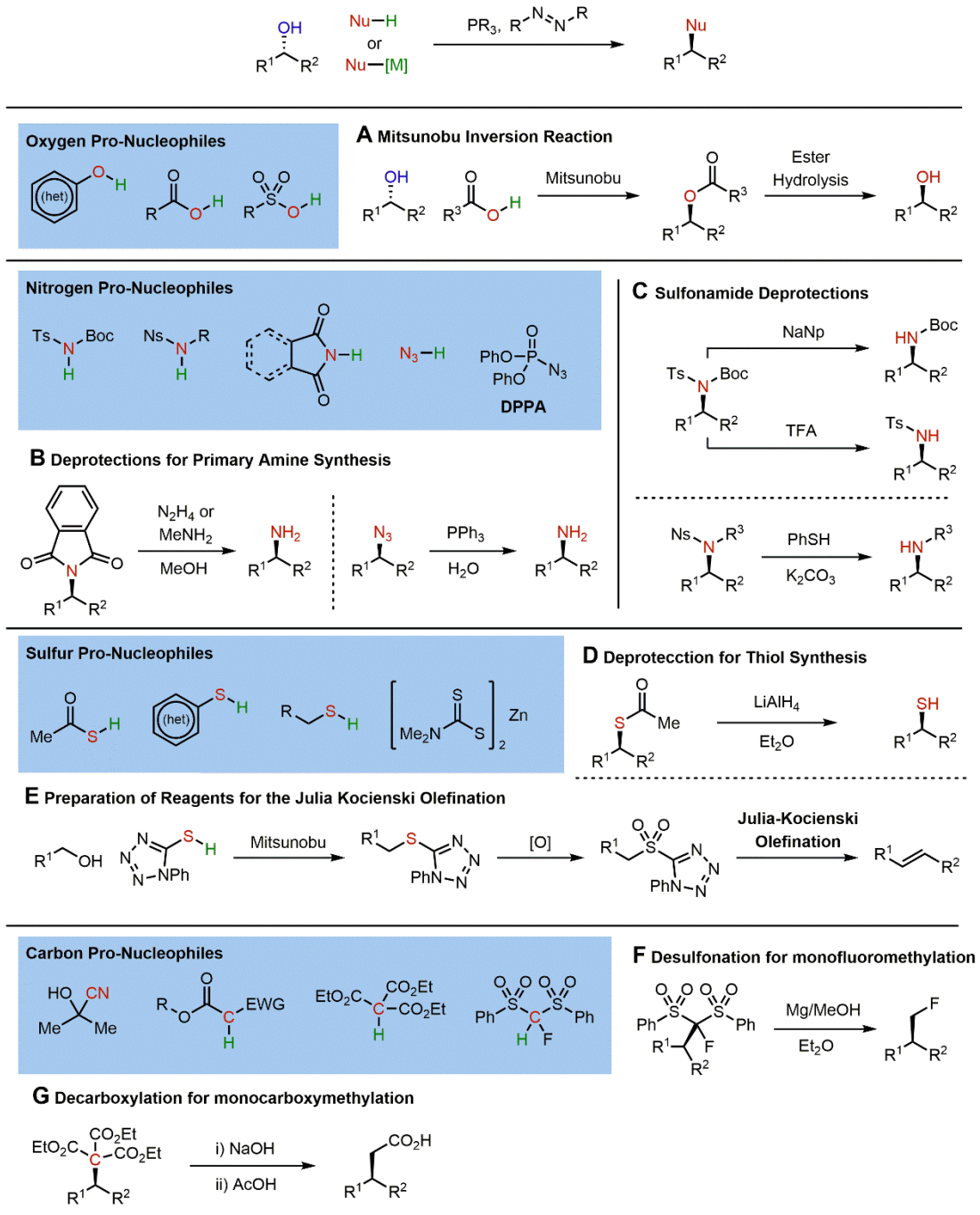


Figure 13. Common compatible Mitsunobu pro-nucleophiles and synthetic applications; (A) The Mitsunobu esterification-hydrolysis sequence for inverting enantiopure, chiral secondary alcohols; **(B)** Deprotections of substituted phthalimides and azides for primary amine synthesis; **(C)** Selective deprotections of sulfonamide Mitsunobu products; **(D)** Deprotection of thioesters for thiol synthesis; **(E)** The use of the Mitsunobu reaction to enable a Julia-Kocienski olefination; **(F)** Reductive desulfonation for the synthesis of fluoromethylalkanes; **(G)** Decarboxylation of triesters for the synthesis of homologated carboxylic acids.

Hydrazoic acid[138] or a safer, more practical azide source such as diphenylphosphoryl azide (DPPA)[139] are commonly used as pro-nucleophiles in the Mitsunobu reaction to afford alkyl azides. This is a convenient method, since azide groups are robust amine surrogates, which can be converted to their analogous amines using the Staudinger reduction, or under hydrogenation conditions.

Using sulfonamides as pro-nucleophiles in the Mitsunobu reaction is a widespread strategy for accessing amine derivatives. For example, Weinreb and co-workers have shown that *N*-Boc-*p*-toluenesulfonamide can be directly coupled with primary and secondary alcohols under Mitsunobu conditions. The Boc-protected amine or the substituted *p*-toluenesulfonamide product can then be afforded through selective deprotection.[140] Similarly, Fukuyama and co-workers reported that the *N*-substituted 2- and 4-nitrobnzenesulfonamides[141,142] as well as *N*-substituted 2,4-dinitrobenzenesulfonamides[143] are effective pro-nucleophiles in the Mitsunobu reaction. After the Mitsunobu coupling, the nitrobenzene sulfonyl moiety can be removed under mild conditions to reveal a secondary amine (figure 13C).[144]

Carbon–Sulfur Bond Formations. Thioacetic acid has been shown to be a competent pro-nucleophile in the Mitsunobu reaction to access thioacetates.[145] Treating the thioacetates with lithium aluminium hydride enables access to the corresponding thiol (figure 13D). Similarly, zinc *N*,*N*-dimethyldithiocarbamate, (which is an inexpensive fungicide also known as ziram,) can engage in a Mitsunobu reaction to afford dithiocarbamates.[146]

Alkyl thiols and thiophenols can be used as Mitsunobu pro-nucleophiles to access thioethers. This reaction is commonly used to access phenyltetrazole thioethers, which upon oxidation to the corresponding sulfone, is an important intermediate for the Julia-Kocienski olefination reaction[147] (figure 13E) and Baran's nickel-catalyzed radical cross-coupling reaction.[148]

Carbon–Carbon Bond Formations. Carbon-carbon bond forming reactions are highly sought after, and the Mitsunobu reaction can be used to fashion such connections. A key challenge in developing such reactions is the requirement for

the carbon pro-nucleophile to have a pKa within the operating regime for a Mitsunobu reaction. Nevertheless, numerous 1,3-dicarbonyl and pseudo-1,3-dicarbonyl compounds have been shown to be effective pro-nucleophiles, such as ethylcyanoacetate,[149] ethyl acetoacetate,[150] Meldrum's acid,[151] bis(2,2,2,-trifluoroethyl)malonates[152] and malonitrile derivatives.[153] Similarly, triethylmethanetricarboxlate is a compatible pro-nucleophile,[154] and the triester product can be derivatised into the doubly homologated carboxylic acid (figure 13G).[155,156]

Another useful pro-nucleophile in the Mitsunobu reaction is 1-fluoro-bis(phenylsulfonyl)methane. The product of the carbon-carbon bond forming Mitsunobu reaction can be readily subjected to a reductive desulfonation, thus providing convenient access to a fluoromethyl moiety (figure 13F).[157] Alkyl nitriles can also be accessed from the Mitsunobu coupling of alcohols and hydrogen cyanide.[158] Moreover, the safer and more practical reagent, acetone cyanohydrin can be used in place of hydrogen cyanide to access alkyl nitriles.[159] As the alkylnitrile product can be further derivatised this reaction is commonly used for the one-carbon homologation of alcohols.[160–163]

1.3.2 Phosphine and Azo Reagents in the Mitsunobu Reaction

The use of triphenylphosphine and DEAD/DIAD as redox reagents in the Mitsunobu reaction results in the generation of triphenylphosphine oxide and one of two hydrazide by-products, diethyl hydrazide-1,2-dicarboxylate (DEAD-H_2) or diisopropyl hydrazide-1,2-dicarboxylate (DIAD-H_2). Separating these by-products from the reaction product, is challenging, in most cases requiring carefully planned column chromatography. This makes the Mitsunobu reaction unappealing to preparative chemists and limits its application in parallel library syntheses and process chemistry.

To address these issues, modified phosphine and azo reagents have been developed that enable facile purification of crude reaction mixtures by phase-separation, rather than column chromatography.[164,165] Furthermore, some modified azo reagents have resulted in a broadened pro-nucleophile scope (see azodicarboxamide reagents, page 24).

Modified Azodicarboxylate Reagents. DEAD-H_2 and DIAD-H_2 are difficult to separate from product of the Mitsunobu reaction because they are soluble in most organic solvents, and often co-elute with the reaction product during flash column chromatography. Furthermore, they have poor aqueous solubility therefore cannot be removed from the reaction mixture by an aqueous extraction. Analogues of DEAD and DIAD that can be easily removed from the reaction mixture have therefore been developed. Many of these are now commercially available and commonly used instead of DEAD or DIAD.

Replacing the ethyl groups of DEAD with *tert*-butyl groups furnishes di-*tert*-butyl azodicarboxylate (DTBAD).[166] Both DTBAD and its hydradine analogue DTBAD-H_2 are sensitive to acid, which converts them to gaseous by-products

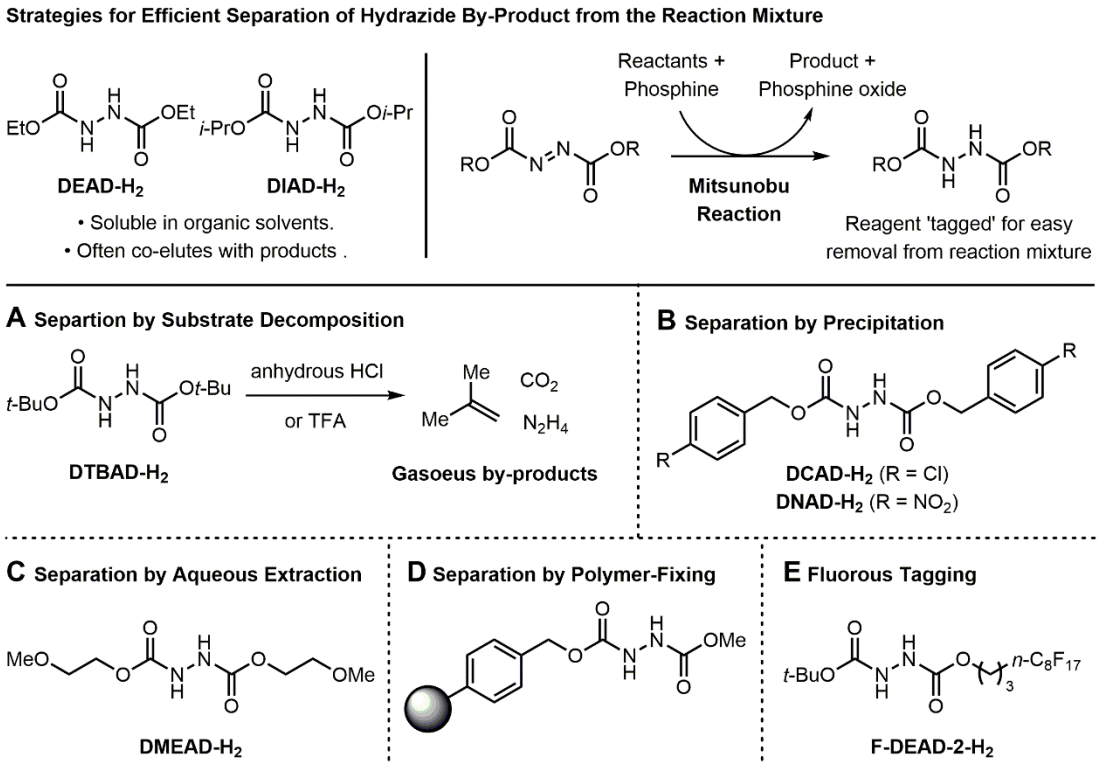


Figure 14 Modifications of azo reagents for easy removal from a reaction mixture. (A) The acid-mediated decomposition of DTBAD-H_2 to gaseous by-product as an effective separation strategy; **(B)** DCAD-H_2 and DNAD-H_2 which are separated from the reaction mixture by precipitation and filtration; **(C)** DMEAD-H_2—a hydrazide by-product which is removed from a reaction mixture by aqueous extraction; **(D)** Polymer-bound hydrazide by-product which is separated from the reaction mixture by phase separation; **(E)** Hydrazide by-products tagged with a fluorous tail, which is separated from a reaction mixture by fluorous chromatography.

(figure 14A). Thus, the hydrazide by-product can be removed from the reaction mixture by treating the reaction mixture with an acid (usually TFA or anhydrous HCl).

Replacing the ethyl groups of DEAD with either 4-chlorobenzyl or 4-nitrobenzyl groups gives di-4-chlorobenzyl azodicarboxylate (DCAD)[167] and di-4-nitrobenzyl azodicarboxylate (DNAD)[168] respectively. These azodicarboxylate reagents are air-stable solids, and their hydrazide by-products can be removed by precipitation from dichloromethane (figure 14B). Another notable DEAD analogue is di-2-methoxyethyl azodicarboxylate (DMEAD). The hydrazide by-product (DMEAD-H_2) is highly polar and can be removed from the reaction mixture by an aqueous extraction (figure 14C).[169,170]

A polystyrene-bound DEAD analogue has been successfully employed in a Mitsunobu reaction, and the insoluble polymeric hydrazide by-product is separated from the reaction mixture by filtration (figure 14D).[171] Fluorous analogues of DEAD can also be employed in the Mitsunobu reaction and the fluorous hydrazide by-product can be removed by fluorous chromatography (figure 14E).[172–174]

Azodicarboxamide Reagents. The pro-nucleophile scope of a Mitsunobu reaction using azodicarboxylate reagents is generally limited to those with a pKa < 11. This is because the basicity of the Morrison-Brunn-Hisguen betaine (see page 28 for discussion of mechanism) is not sufficiently basic to deprotonate pro-nucleophiles with a pKa above 11. In order to expand the pro-nucleophile scope, Tsunoda has developed a series of azocarboxamide reagents as alternatives to DEAD or DIAD, namely 1,1'-(azodicarbonyl)dipiperidine (ADDP),[175] *N*,*N*,*N'*,*N'*-tetramethylazodicarboxamide (TMAD)[176] and 4,7-dimethyl-3,5,7-hexahydro-1,2,4,7-tetrazocin-3,8-dione (DHTD) (figure 15A).[150] As the MBH betaine for these azo reagents are stronger bases, pro-nucleophiles with a pKa of up to 13 can engage in a Mitsunobu reaction, such as amides and malonates (figure 15B). Generally, trialkylphosphines such as tri(*n*-butyl)phosphine are used in combination with azodicarboxamide reagents.

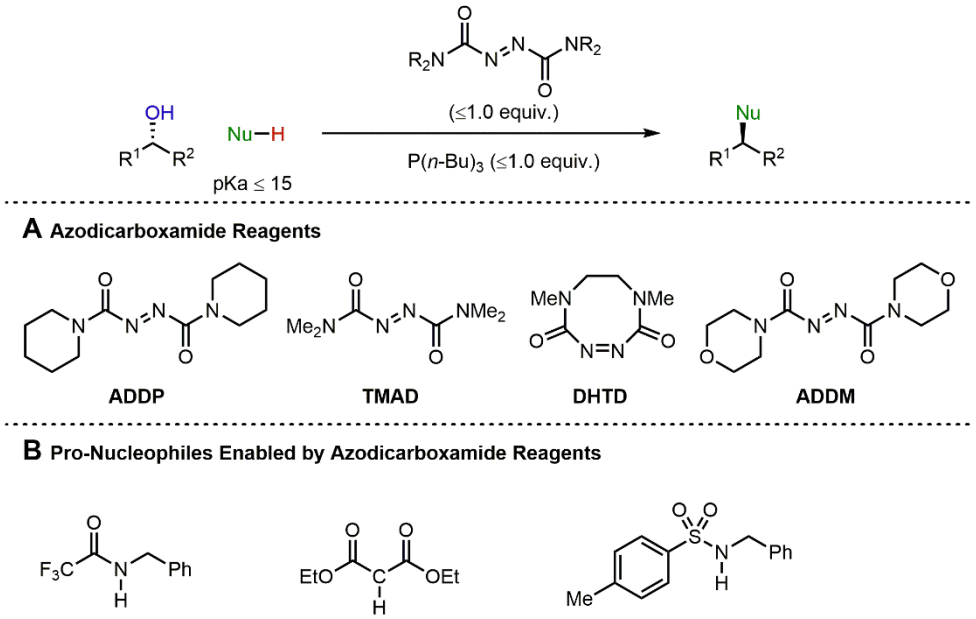


Figure 15. The use of azodicarboxamide reagents in the Mitsunobu reaction; (A) The various azodicarboxamide reagents commonly used; **(B)** The pro-nucleophiles that are effective in the Mitsunobu reaction when azodicarboxamide reagents are used instead of azodicarboxylate reagents.

Like DIAD and DEAD, the use of ADDP is complicated by the generation of a hydrazide by-product, ADDP-H_2 and column chromatography is typically required to purify reaction mixtures involving ADDP. Fletcher and co-workers have therefore developed azodicarbonyldimorpholine (ADDM) (figure 15A).[177] The hydrazide by-product ADDM-H_2 is water-soluble and may be removed from the reaction mixture by a simple aqueous extraction.

New Phosphine Reagents. Triphenylphosphine oxide is notoriously difficult to remove from a crude reaction mixture, since it often co-elutes with the reaction product during column chromatography and cannot be removed from a reaction mixture by aqueous extraction.

Tri(*n*-butyl)phosphine can be used as a replacement for triphenylphosphine, and tri(*n*-butyl)phosphine oxide can be removed from the reaction by aqueous extraction (figure 16A). However, this is often disfavoured on the grounds that tri(*n*-butyl)phosphine is pyrophoric and malodorous, and is notorious for giving unwanted side reactions in the Mitsunobu reaction.[178]

The use of bis(diphenylphosphino)ethane (DPPE) can be effectively used as an alternative to triphenylphosphine.[179] The associated bis-phosphine oxide is

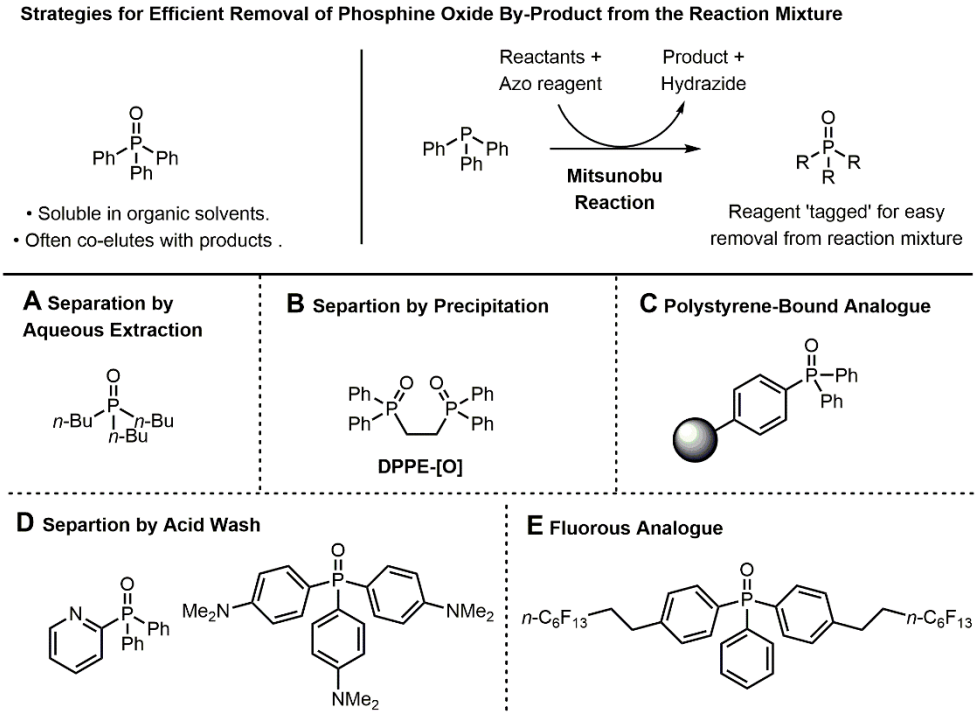


Figure 16. Phosphine modifications for easy removal of phosphine oxide by-product; (A) Tri(*n*-butyl)phopshine oxide, which can be removed from the reaction mixture by aqueous extraction; **(B)** DPPE-[O], which is conventionally removed from the reaction mixture by precipitation; **(C)** Polystyrene-bound triphenylphosphine, whose phosphine oxide by-product is removed from the reaction mixture by phase separation; **(D)** Brønsted base-tagged phosphine oxides for separation using acid wash; **(E)** Phosphine oxide by-products tagged with a fluorous tail, which is separated from a reaction mixture by fluorous chromatography.

highly polar and insoluble so can be removed from the reaction mixture by filtration (figure 16B). Additionally, polymer-bound triphenylphosphine can be effectively used in a Mitsunobu reaction, and the phosphine oxide by-product can be separated from the reaction mixture by phase separation (figure 16C).[180–183]

Triphenylphosphine is commonly tagged with a Brønsted base functional group which allows for the separation from the reaction mixture by extraction into an aqueous phase upon protonation. Examples of these kinds of phosphines are diphenyl-2-pyridylphosphine developed by Jenkins[184] and (*p*-dimethylaminophenyl) diphenylphosphine, developed by von Itzstein[185] (figure 16D). Additionally, fixing triphenylphosphine with a fluorous tag, allows the phosphine oxide by-product to be separated by fluorous chromatography (figure 16E).[173]

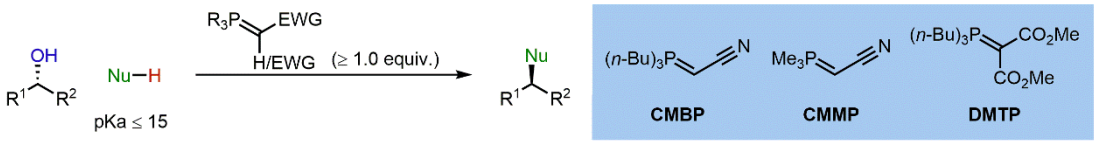


Figure 17. Phosphorane reagents used as alternatives to phosphine-azodicarboxylate reagent combinations in the Mitsunobu reactions.

Combination of Modified Phosphines and Azo Reagents. The combined use of modified phosphine and modified azo reagent have enabled the development of chromatography-free Mitsunobu reactions.[166,186–191] For example, diphenyl-2-pyridylphosphine is commonly used in combination with DTBAD since the associated phosphine oxide and hydrazide by-products are removed from the reaction mixture by treatment with acid (and a subsequent aqueous extraction in the case of diphenyl-2-pyridylphosphine oxide).[166] These developments in chromatography-free synthesis, especially the advent of polymer-bound reagents, have enabled the Mitsunobu reaction to be used in parallel library syntheses, where simple and facile purification of reaction mixtures are neccessary.[192–195]

Phosphoranes as Mitsunoubu Reagents. Tsunoda and co-workers have developed cyanomethylenetri(*n*-butyl)phosphorane (CMBP)[196] and cyanomethylenetrimethylphosphorane (CMMP),[197,198] which are phosphorus (V) reagents that serve as both the phosphine and azo reagent in the Mitsunobu reaction (figure 17, see page 33 for mechanism). A key benefit of using these reagents is that the by-products are tributylphosphine oxide or trimethylphosphine oxide and acetonitrile which are easily removed from the reaction mixture. Similarly, McNulty and co-workers have developed dimethylmalonyltributylphosphorane (DMTP) as a Mitsunobu reagent which can facilitate the Mitsunobu esterification of a range of different alcohols.[199] The caveat of these reagents is that they are moisture sensitive and therefore require specialist reaction setups (figure 17).

1.3.3 Mechanism of the Mitsunobu Reaction

Probing the mechanism of the Mitsunobu reaction has been the subject of dozens of publications since the reaction's discovery. Although much is known now about the mechanism, certain mechanistic details, particularly, the precise nature of some of the intermediates are still subject to debate. The general mechanistic understanding of the Mitsunobu reaction have largely emerged from investigations into the reaction of carboxylic acids and alcohols, using triphenylphosphine and either DEAD or DIAD. As such, unless explicitly stated, the mechanistic discussion in this part of the thesis concerns only the Mitsunobu *esterification* reaction.

The mechanism is often described in three different stages, **1)** the formation of the Morrison-Brunn-Huisgen betaine, **2)** the generation of the key alkoxyphosphonium intermediate and **3)** the Arbusov collapse. In the ensuing section, a detailed mechanistic description is given for each of three steps. Alternative mechanistic explanations are explored, and the respective reasons for their redundancy is given.

The Generation of the Morrison-Brunn-Huisgen Betaine. The reaction of a phosphine with an azo-dicarboxylate species affords a kinetically stable betaine adduct of the structure **53** (figure 18). This adduct was first prepared by Morrison in 1958[200] and subsequently investigated by Brunn and Huisgen in 1969.[201] It is commonly referred to as the 'Morrison-Brunn-Huisgen betaine' (MBH betaine). This betaine has been characterised by mass spectrometry,[202] and ^{31}P NMR (δ_P = +44.9 ppm, THF-d^8).[203,204]

One mechanistic proposal for the generation of the MBH betaine, proposed by Jenkins,[205] involves a single electron oxidation of the phosphine by the azodicarboxylate, followed by the addition of the phosphorus-centred radical cation to another molecule of azodicarboxylate (**51**, figure 18A). Single electron reduction of the nitrogen-centred radical by a radical chain mechanism subsequently affords the MBH intermediate (**53**). Jenkins provided evidence of an electronic paramagnetic resonance spectrum which he assigned to the nitrogen-centred radical **52**, however subsequent investigations by Eberson,[206]

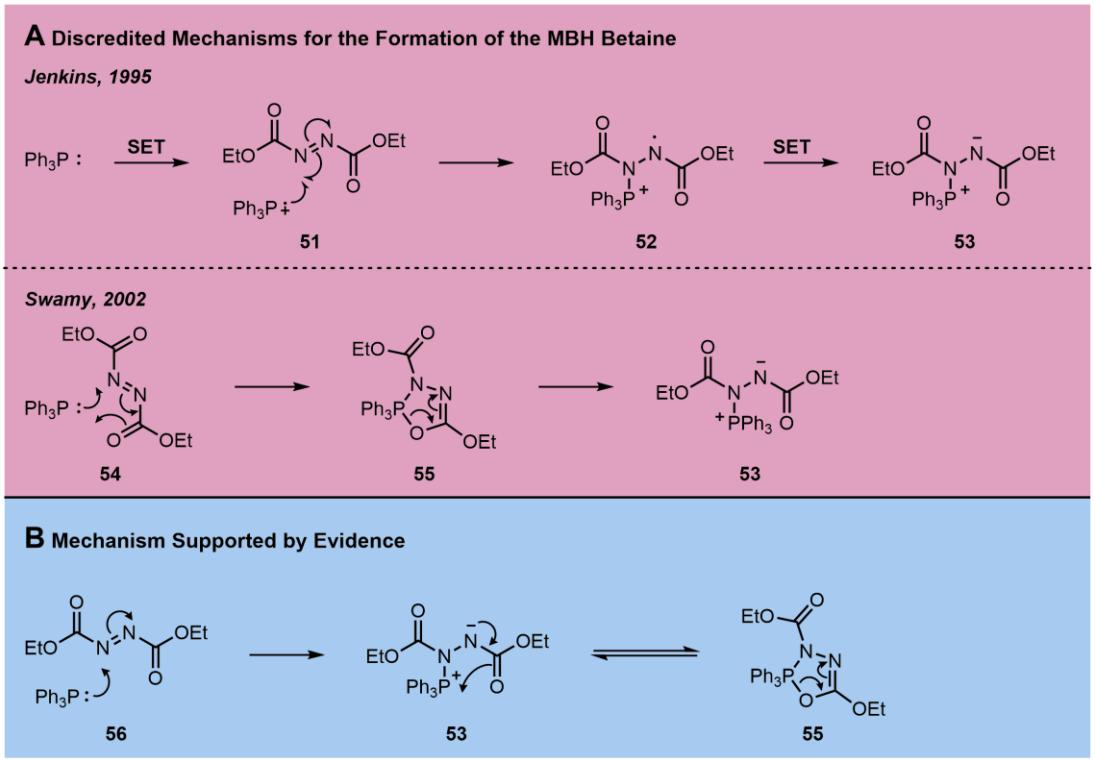


Figure 18. Postulated mechanisms for the formation of the Morrison; **(A)** Two previously postulated mechanisms for the formation of the MBH betaine which have since been discredited; **(B)** The mechanism for the formation of the MBH betaine.

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and Jenkins[207] demonstrated that this spectrum had been miss-assigned, and was instead consistent with a different P–O adduct. The P–O adduct, which can form under Mitsunobu reaction conditions, is now thought to be the product of an unproductive side-reaction and does not result in the generation of the MBH betaine.

Another possible mechanism for the formation of the MBH betaine invokes a (4+1) chelotropic reaction between the phosphine and the azodicarboxylate (**54**), followed by ring opening. Swamy and co-workers have isolated and characterised a series of *O,N*-phosphoranes based on postulated intermediate **55** which they hypothesised to be intermediates in the formation of the MBH betaine.[208] However, a study by Jenkins and co-workers showed that this pathway was not operative since strained phosphines are shown to be less reactive than triphenylphosphine which is unexpected in this mechanism.[209]

The currently accepted mechanism entails an irreversible, conjugate addition of the nucleophilic phosphine to the azodicarboxylate (**56**) to generate the MBH adduct (figure 18B).[210] This is consistent with the second-order reaction kinetics of this step.[211] The propensity for the azodicarboxylate group to react this way is due to the weak N=N bond and the electrophilicity of the conjugated acceptor site. For these reasons, this betaine is kinetically and thermodynamically stable with respect to elimination back to the phosphine and azodicarboxylate.

Ab initio calculations by the Eberson group have revealed that the MBH betaine is stabilised by lone-pair donation of the carbonyl group to the σ* orbital of the phosphorus atom.[212] The species should therefore be thought of as a resonance of both the betaine form and a cyclic *O*,*N*-phosphorane (**55**).

Generation of an Alkoxyphosphonium Intermediate. The next stage of the reaction mechanism involves the exchange of the hydrazide group of the MBH betaine with an alcohol to generate an alkoxyphosphonium intermediate. This occurs through a series of exchanges *via* phosphorane and phosphonium salt intermediates. The order in which these groups exchange, and the identities of the species involved, has been thoroughly studied.

From analysis of the reaction by ^{31}P NMR, it is known that if one equivalent of an alcohol is added to the MBH betaine, equimolar quantities of a di(alkoxy)phosphorane (**58**) and unreacted MHB betaine are generated (figure 19A).[203,204,213,214] Subsequent addition of a carboxylic acid has been shown to generate a myriad of different intermediates, namely protonated MBH betaine (**59**),[215,216] a di(alkoxy)phosphorane (**58**),[216,217] an alkoxyphosphonium carboxylate salt (**60**)[215–217] and an (acyloxy)alkoxyphosphorane (**61**).[216]

Addition of a carboxylic acid to the MBH betaine results in the protonation of the MBH betaine to generate phosphonium salt **63** (figure 19B).[215,217,218] Subsequent addition of the alcohol has been shown to generate a di(alkoxy)phosphorane (**64**),[217,218] an (alkoxy)phosphonium carboxylate salt (**66**)[215] and a (acyloxy)alkoxyphosphorane (**65**).[216] In both cases, the relative molar distribution of each generated species is governed by several factors, such as

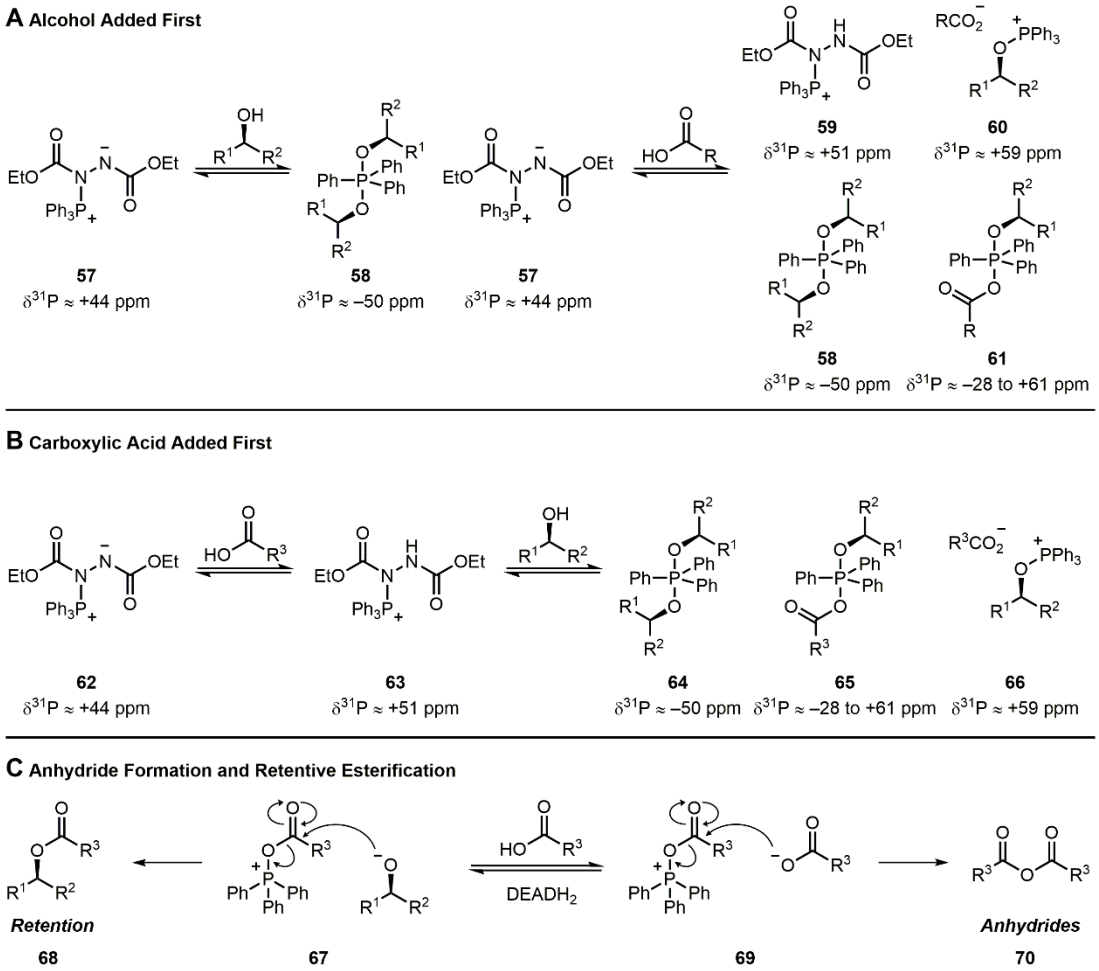


Figure 19. Intermediates involved in the mechanism of the Mitsunobu reaction; **(A)** The intermediates observed when the alcohol is added to the MBH betaine; **(B)** The intermediates observed when the carboxylic acid is added to the MBH betaine; **(C)** The mechanistic rationale for the generation of esters with retention of stereochemistry and anhydrides as side-products in the Mitsunobu reaction.

solvent polarity, alcohol stoichiometry, carboxylic acid stoichiometry and acidity.[178,215–218]

It is therefore clear that the generation of the (alkoxy)phosphonium carboxylate salt (**60**/**66**) from the MBH betaine does not follow a single, well-defined mechanistic pathway. Instead, there are several different pathways accessible and the extent to which any given pathway is involved is governed by several different factors. These factors include order of reagent addition, alcohol stoichiometry, steric crowding surrounding the hydroxyl of the alcohol, carboxylic acid stoichiometry, acidity of the carboxylic acid and solvent polarity.

Further evidence confirming the presence of the oxyphosphorane intermediates in the mechanism of the Mitsunobu reaction was reported out by Watanabe and co-workers. They used chiral *P*-stereogenic phosphine instead of triphenylphosphine, and analysed the enantiomeric excess of the resulting phosphine oxide.[219] As a consequence of the pseudorotation which occurs with phosphoranes, the resulting phosphine oxide by-products were isolated as racemates. Interestingly, carboxylic acids of low pKa, e.g. 3,5-dinitrobenzoic acid, yielded phosphine oxide by-products with an inversion of stereochemistry. Presumably due to the poor nucleophilicity of the carboxylate anion, any phosphorane generated during the mechanism was very short-lived.

The Arbuzov Collapse. The final stage of the Mitsunobu reaction is the irreversible Arbuzov collapse whereby the alkoxyphosphonium salt undergoes a concerted nucleophilic displacement with its counterion acting as a nucleophile. Since the nucleophile approaches the sp^3 centre *via* a backside attack, the Arbuzov collapse leads to a full Walden inversion of stereochemistry. This step is often incorrectly referred to as an S_N2 process. Hughes and co-workers have shown that this step is first-order with respect to the oxyphosphonium, however is zero-order with respect to the carboxylate, thus first-order overall.[220] This is because both the nucleophile and electrophile are tightly held as an ion pair before the nucleophilic substitution can occur. When the reaction is run in a concentrated salt solution of *n*-$Bu_4N^+BF_4^-$, both nucleophile and electrophile are freely dissolved in solution and the reaction displays second-order reaction kinetics, thus resembling a typical S_N2 reaction.

Mechanistic Rationale for Common Side Reactions. In some rare cases, the Mitsunobu reaction has been known to generate esters with retention of steretochemistry,[221–223] or anhydrides.[224] This occurs because, when Arbuzov collapse is slow, the alkoxyphosphonium carboxylates are known to undergo rearrangements to their analogous (acyloxy)phosphonium salts (**67**, figure 19C) *via* a (acyloxy)alkoxyphosphorane intermediate.[225,226] The generated (acyloxy)phosphonium salts are electrophilic at the carbonyl carbon, and are prone to nucleophilic displacement by a carboxylate or alkoxide nucleophile (figure 19C). The retentive esterification reaction is often an unwanted minor

side reaction in the invertive Mitsunobu esterification, which resultsin loss of enantiomeric excess of the ester product.[225] Additionally, anhydrides can be generated under the reaction conditions trough a similar mechanism, involving the acylation of a carboxylate salt by an acylphosphonium intermediate (**69** to **70**, figure 19C).

Currently Accepted Mechanism. Considering these mechanistic observations, the Mitsunobu reaction mechanism that is most commonly accepted by the synthetic chemistry community, depicted in figure 20, is as follows. Firstly, the MBH betaine (**71**) is generated from the irreversible, conjugate addition of the phosphine to the azodicarboxylate. The MBH betaine may then either react with two molecules of alcohol to produce a dialkoxyphosphorane (**72**), or be deprotonated to afford a protonated MBH betaine (**73**). In the first pathway the dialkoxyphosphorane (**72**) intermediate reacts reversibly with the carboxylic acid to form an alkoxyphosphonium carboxylate (**74**). In the second pathway the alkoxyphosphonium salt (**74**) is generated from the irreversible reaction of the protonated MBH betaine and alcohol. The alkoxyphosphonium salts then undergoes a unimolecular Arbuzov collapse to afford the inverted carboxylic ester product and triphenylphosphine oxide by-product (**77**). The alkoxyphosphonium salt however, is in equilibrium with an (acyloxy)phosphonium salt (**76**) which is generated through an (acyloxy)alkoxyphosphorane intermediate (**75**). This unproductive pathway leads to side-products, namely esters with retention of configuration, and anhydrides.

Mechanism of CMMP and CMBP mediated Mitsunobu Reactions. The mechanism of Mitsunobu reactions mediated by CMMP and CMBP is less studied that the analogous triphenylphosphine and DIAD/DEAD system. Nevertheless, Tsunoda and Itô have postulated that the CMMP and CMBP have similar reactivities to the MBH intermediate. They have suggested that CMPP initially deprotonates the pro-nucleophile to form phosphonium salt **78** (figure 20B). Acetonitrile is then displaced from this phosphosnium salt to form alkoxyphosphonium salt **79**. Subsequent Arbusov collapse affords the Mitusnobu product, as well as the phosphine oxide by-product (**80**).[227]

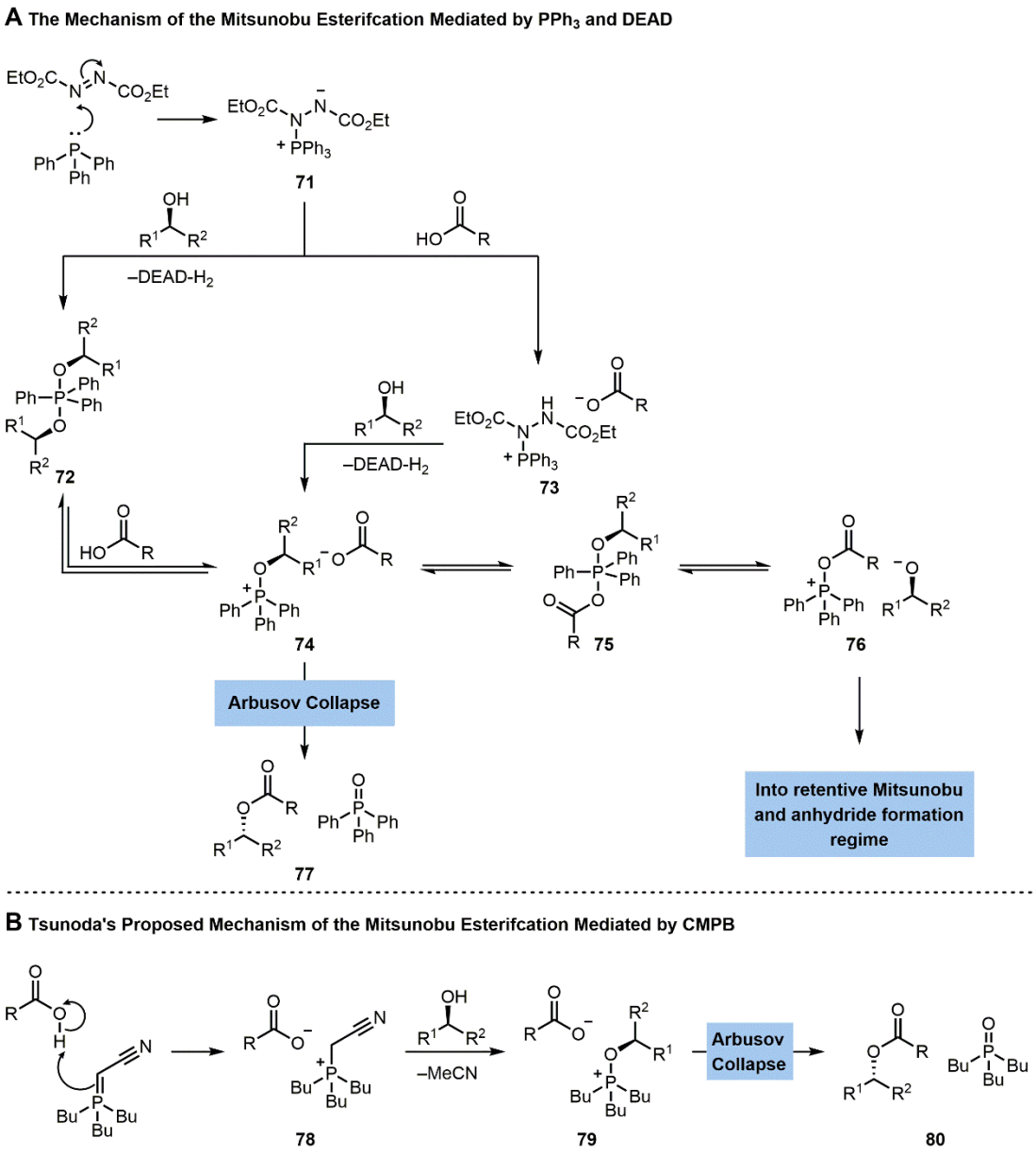


Figure 20. (A) The currently accepted mechanism for the Mitsunobu esterification reaction; (B) The currently accepted mechanism for the CMPB-mediated Mitsunobu esterification reaction.

1.4 Organophosphorus Catalysis

Despite the widespread use of reactions mediated by organophosphorus reagents, they suffer from notable drawbacks. The reactions all require stoichiometric quantities of the organophosphorus reagent since the driving force of these reactions is the generation of a thermodynamically stable phosphoryl bond. This requirement for a stoichiometric quantity of a high-molecular weight reagent is detrimental to these reactions' atom economies. Furthermore, the stoichiometric waste generated in these reactions often require specialist purification procedures to remove these unwanted by-products (see pages 22–27 for discussion of chromatography-free Mitsunobu reactions.) In an effort to address these issues, much of the latest research in the field of organophosphorus chemistry has concerned the development of reactions that are *catalytic* in an organophosphorus species.[228]

Strategies in Organophosphorus Catalysis. Within this field, two major strategies towards organophosphorus catalysis have emerged, the redox-active approach and the redox-neutral approach (figure 21).[229,230] Redox-active organophosphorus catalysis describes organophosphorus catalysis manifolds whereby the phosphorus oxidation state is shuttled between the P(III) and P(V) oxidation states throughout the catalytic cycle. This field is largely focused on achieving catalytic turnover through the *in situ* reduction of a phosphine oxide (or similar P(V) compound) to a phosphine using a stoichiometric reductant. Since hydrosilanes are known to act as chemoselective reductants of phosphine oxides, they are, with little exception, the most often used terminal reductants (figure 21).

An alternative to this approach is the redox-neutral approach whereby the organophosphorus catalyst remains in the P(V) oxidation state throughout the catalytic cycle. Generally, a phosphine oxide is activated to a reactive phosphorus (V) reagent, which the facilitates a desired transformation, with a concomitant return to its stable phosphine oxide form. The benefit here is that a reductant is not necessary to achieve catalytic turnover, however in most cases an external, stoichiometric activating reagent is required to access the reactive P(V) species

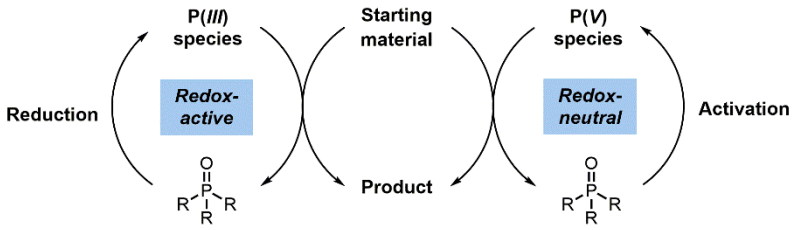


Figure 21. Generic catalytic cycles for redox-active and redox-neutral organophosphorus catalysis manifolds.

(figure 21). The next sections of this chapter provide an overview to some approaches towards organophosphorus catalysis using both redox-active and redox-neutral strategies.

1.4.1 Redox-Active Catalysis

Catalytic Staudinger Reactions. Developing a catalytic Staudinger reduction, using a redox-active approach is challenging as silanes are incompatible with the water required to hydrolyse the phosphorane intermediate (figure 22A). However, redox-active catalytic manifolds for this transformation have been developed where turnover is achieved by reducing the *iminophosphorane* (**81**) to the analogous phosphine (**82**) rather than the phosphine oxide. Thus, water is not required in the mechanism.

In 2012, Rutjes and van Delft reported the first example of such a reaction (figure 22B).[231] Using 10 mol% of phospholene **83**, in combination with phenylsilane as a reductant in refluxing 1,4-dioxane (b.p. 101 °C), the catalytic Staudinger reduction of both alkyl and aryl azides to their analogous amines was demonstrated. In 2018, Mecinović and co-workers reported a modified process, using 3 mol% triphenylphosphine catalyst, and stoichiometric poly(methylhydrosiloxane) (PMHS) as a reductant (figure 22C).[232] The reactions were conducted in refluxing CPME (b.p. 106 °C) and were effective in converting alkyl, allyl and aryl azides to amines. This publication was shortly followed by a second report by Mecinović of a room temperature catalytic Staudinger reaction (figure 22D). These new conditions employed triphenylphosphine as a catalyst and diphenyldisiloxane (DPDS) as a terminal reductant and had a similarly wide substrate scope as the preceding publication.[233]

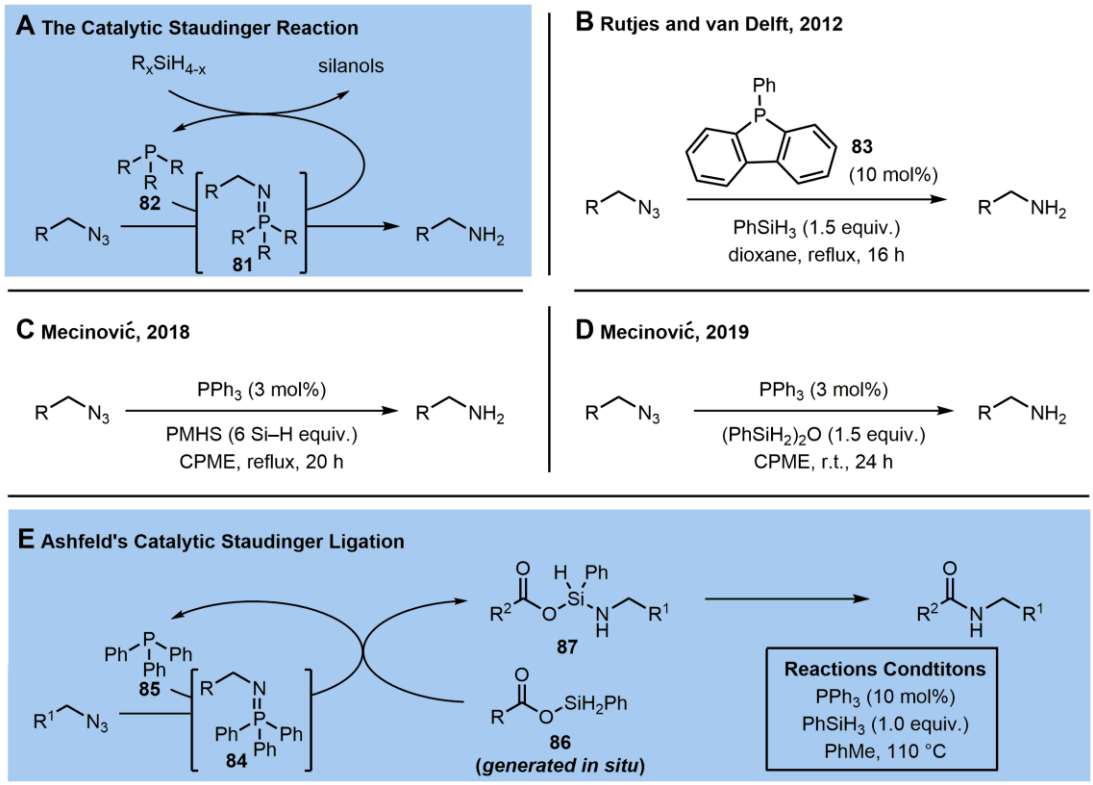


Figure 22. (A) The catalytic cycle for redox-active catalytic Staudinger reductions; **(B)** Rutjes and van Delft's catalytic Staudinger protocol; **(C)** Mecinović's catalytic Staudinger protocol; **(D)** Mecinović's room temperature catalytic Staudinger protocol; **(E)** The catalytic cycle for Ashfeld's redox active catalytic Staudinger ligation.

A redox-active catalysis strategy can also be applied to the Staudinger ligation reaction. Ashfeld and co-workers have reported a Staudinger ligation with triphenylphosphine as a catalyst and phenylsilane as a terminal reductant (figure 22E).[234] The mechanism of this catalysis manifold has been the subject of debate. In separate publications, the Denton and Mecinović groups have demonstrated that an iminophosphorane (**84**) is reduced by an *in situ* generated silyl ester (**86**), to form an aminosilyl ester (**87**) and regenerate the triphenylphosphine. The aminosilylester (**87**) subsequently rearranges into the amide product and silanol by-product. This mechanism does not invoke the intermediacy of a phosphine oxide and the silane is intrinsically involved in the amidation mechanism.[235,236]

Catalytic Wittig Reactions. Another notable redox-active manifold is the catalytic Wittig reaction (figure 23).[237,238] This reaction is predicated on the generation phosphonium ylide **88** from the deprotonation of a phosphonium salt generated from a nucleophilic substitution reaction of an alkyl halide with the phosphine catalyst. A subsequent Wittig reaction affords the alkene product and a phosphine oxide (**89**). Catalytic turnover is then achieved by the reduction of the phosphine oxide, to regenerate the phosphine (**90**).

The first example of this catalytic reaction was reported in 2009 when O'Brien and co-workers reported a Wittig reaction that was catalytic in phospholane oxide **91** (figure 23A).[239] Using 10 mol% of this catalyst, in combination with a diphenylsilane reductant, the Wittig coupling of aldehydes and activated alkyl halides were successfully carried out to afford alkene products with high selectivity for the *E*-regioisomer. However, only alkyl halides that were activated with an adjacent electron withdrawing group were effective substrates in this reaction. A such, the scope of the reaction was limited.[240,241]

The main cause of this limitation was the incompatibility of the reaction with the strong bases required to form the phosphonium ylide. However, subsequent work by the O'Brien group showed that using phosphine oxides **92a–d** as catalysts enabled both benzyl halides and unactivated alkyl iodides to successfully engage in the reaction give alkenes with predominantly the *E*-regioisomer (figure 23B).[242] In 2019, work by the Werner group showed that the phosphetane oxide catalyst **93** could be used to enable a catalytic Wittig reaction at room temperature.[243] As with O'Brien's first publication, only alkyl halides that were activated with an adjacent electron withdrawing group were effective substrates.[244–249]

Despite these key developments, future opportunities within this field include the advent of catalysts that can control regioselectivity. Some progress has been made in this field with Werner and co-workers developing an enantioselective Wittig reaction using phosphine **94** as catalyst and triethoxysilane as a reductant. Using this chiral phosphine catalyst, a pro-chiral diketone was effectively desymmetrised in a modest yield but with good enantioselectivity (figure 23D).[250]

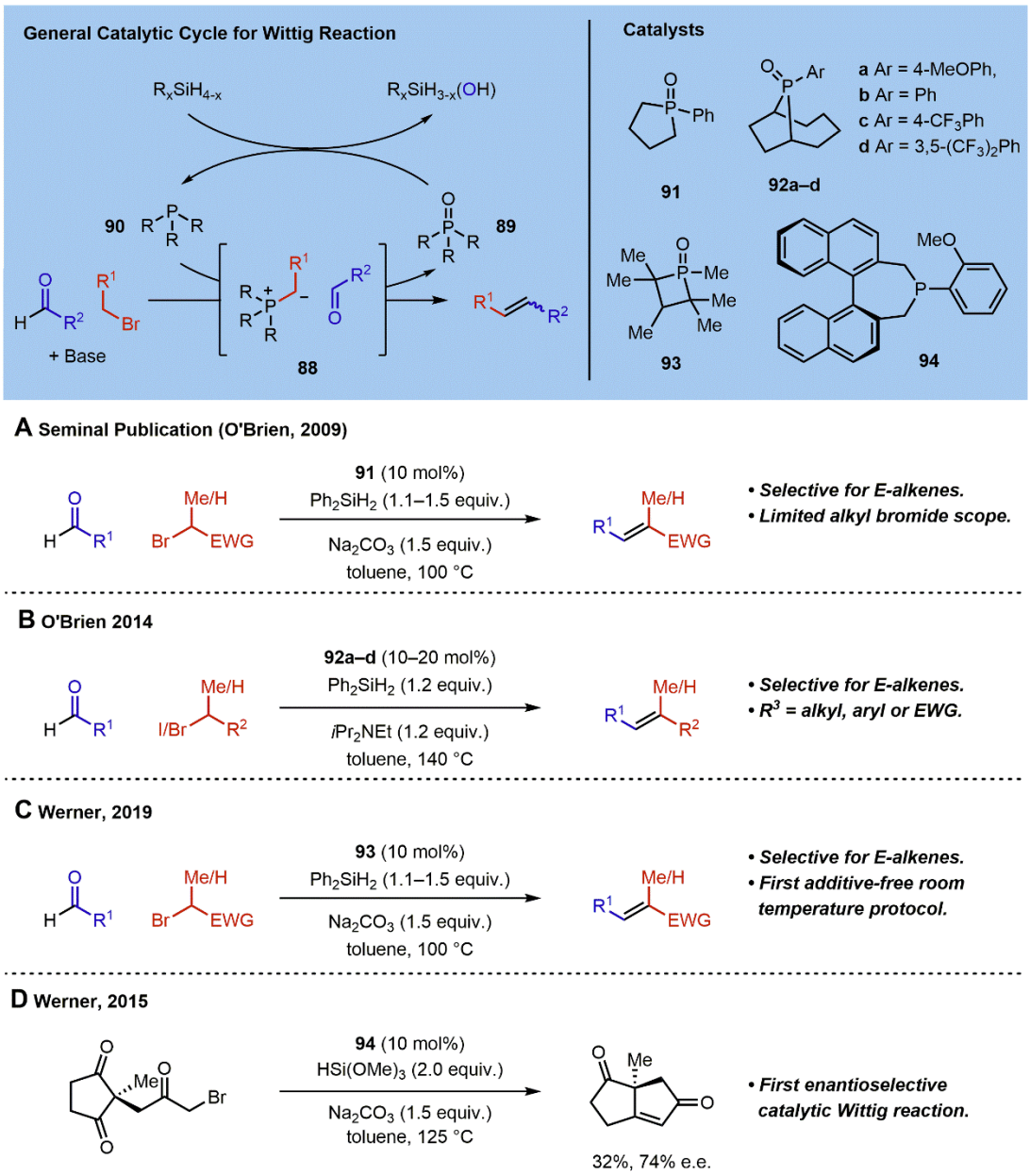


Figure 23. The redox-active catalytic Wittig reactions; **(A)** O'Brien's seminal catalytic Wittig protocol; **(B)** O'Brien's improved protocol, which enables non-activated alkyl halides to be used as substrates; **(C)** Werner's room temperature catalytic Wittig protocol; **(D)** Werner's enantioselective catalytic Wittig reaction.

Catalytic Aza-Wittig. The first redox-active catalytic aza-Wittig reaction was reported by van Delft and co-workers in 2013.[251] They disclosed a method for accessing benzoxazoles and benzodiazepine by an intramolecular aza-Wittig reaction using a phospholene oxide catalyst and diphenylsilane as a terminal reductant. This method has since been extended to the synthesis of [1,3]oxazin-

4-ones,[252] 4-benzylidene-2-aryloxazol-5(4H)-ones[252] and 4H-3,1-benzoxazines[253] by Ding and co-workers.[254]

Recently, Kwon and co-workers have reported the first enantioselective catalytic aza-Wittig reaction using an enantiopure phosphine catalyst and phenylsilane as a terminal reductant.[255] In this reaction, pro-chiral 1,3-diketones were desymmetrised to provide heterocyclic imines with high enantiomeric excess. This method represents a rare example of an enantioselective redox-active organophosphorus catalysis manifold with high enantiomeric excess.

Reductive Functionalisation of Nitro Compounds. The Cadogan cyclisation is a powerful method for the reductive functionalisation of nitroarenes, however, it is rarely used by synthetic chemists, due to its two major limitations. The reaction requires stoichiometric phosphine or phosphite and high temperatures. In Cadogan's original publication, the reaction was conducted in neat refluxing triethylphosphite (b.p. 156 °C) and even with further practical improvements, the reaction still requires elevated temperatures and super-stoichiometric quantities of a phosphine or phosphite.

Radosevich and co-workers realised that strained phosphines, such as **95**, have smaller HOMO-LUMO gaps[256–258] than their acyclic counterparts, and therefore the activation energy for the reduction of nitro groups to nitrenoids was lower. With this insight, they developed a modified Cadogan cyclisation using phosphetane oxide **96** as a catalyst and phenylsilane as a terminal reductant (figure 24).[259,260] Using this reagent/catalyst combination, the authors were able to access indazoles, benzotriazoles, carbazoles and indoles with a wide range of substitution patterns (figure 24A). Critically, these reactions were conducted with 15–20 mol% catalyst and at a lower temperature of 100–120 °C. This case study is exemplary of how a phosphine can be tuned and optimised for specific reactions, where the practicality of the reaction is unaffected since a low catalyst loading is sufficient. This catalytic method now represents the state of the art for the Cadogan cyclization with respect to atom economy and practicality, greatly improving the original protocol.

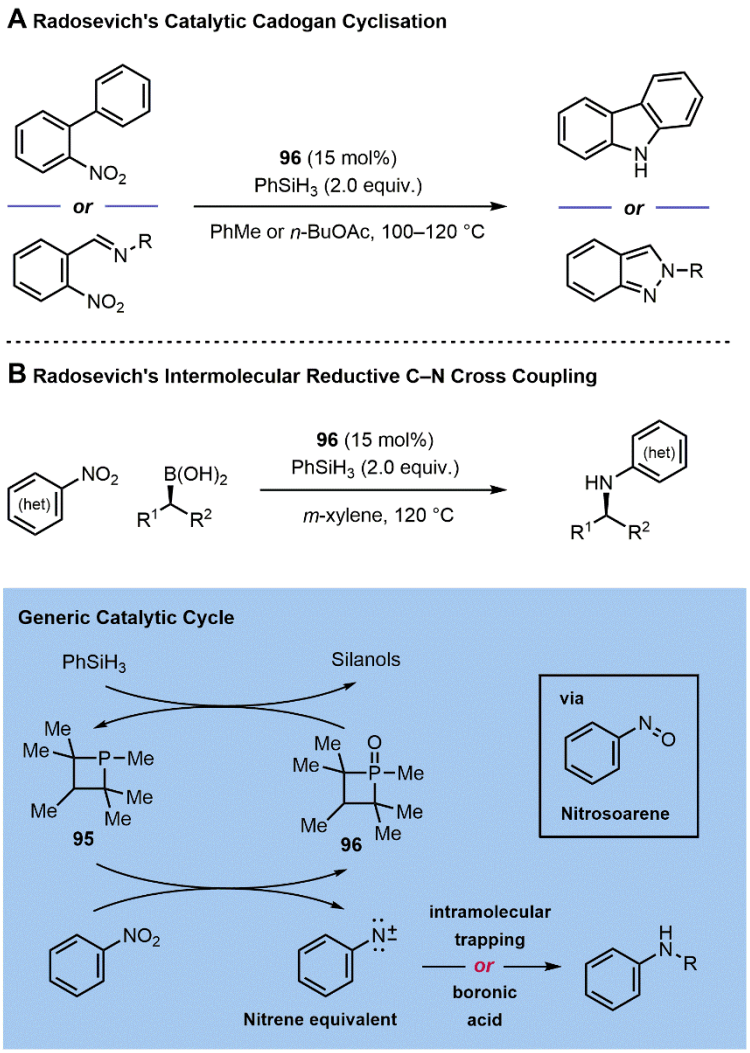


Figure 24. (A) A redox-active approach towards catalytic Cadogan cyclisation; **(B)** A redox-active organophosphorus catalysis manifold for the reductive coupling of nitroaromatics and boronic acids.

Concurrent with these studies, Radosevich investigated the introduction of an exogenous coupling partner to the redox-active catalytic manifold, to facilitate an *intermolecular* coupling reaction. From these studies, a phosphine-catalysed reductive carbon–nitrogen cross coupling of nitroarenes and boronic acids was discovered (figure 24B).[261,262] This powerful transformation represented a new means of forming carbon nitrogen bonds and could be used orthogonally to the Chan-Lam and Buchwald-Hartwig reactions. Furthermore, the use of this reaction, in tandem with an intramolecular cyclisation enables the construction of various azaheterocycles, such as oxindoles, indoles and benzimidazoles.[263]

Redox-Active Catalytic Mitsunobu and Appel Reactions. Developing redox-active catalytic methods for the Mitsunobu and Appel reactions is challenging, since the reactions require a stoichiometric oxidant (halogen donor or azodicarboxylate) as well as a phosphine to operate. Under redox-active catalysis, the terminal silane reductant must be therefore be compatible with the oxidant to create a working catalytic system (figure 25A).

Van Delft and co-workers reported the first example of a catalytic Appel bromination reaction in 2011.[264] Using diethylbromomalonate (DEBM) as a bromonium source along with 10 mol% of phosphine catalyst **97**, and diphenylsilane as a terminal reductant was shown to be effective in the deoxybromination of primary, secondary and tertiary alcohols (figure 25B). An analogous redox-active catalytic Appel chlorination reaction was subsequently reported by Werner and co-workers (figure 25C).[265] This method used trioctylphosphine as a catalyst with trichlorotoluene as chlorine source and phenylsilane as a terminal reductant and was effective for a variety of primary and secondary alcohols.

The sole example of a redox-active organophosphine catalysed Mitsunobu reaction was reported by Aldrich in 2015.[266] In this reaction, a phospholene oxide (**91**) was shown to be an effective catalyst for the Mitsunobu coupling of alcohols

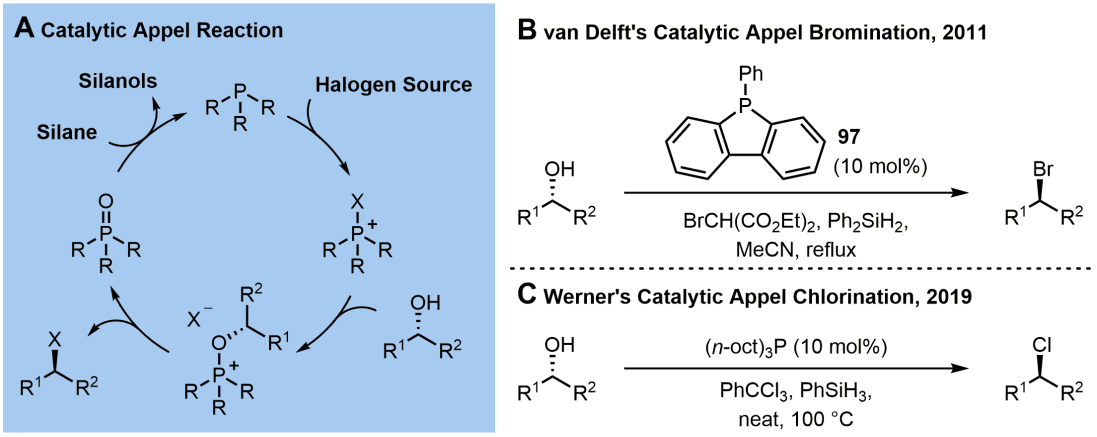


Figure 25. (A) A catalytic cycle for redox-active Appel reactions; **(B)** van Delft's protocol for a catalytic Appel bromination; **(C)** Werner's protocol for a catalytic Appel chlorination.

and various oxygen- and nitrogen-centred pro-nucleophiles. The reaction required stoichiometric phenylsilane as a terminal reductant, and a stoichiometric DIAD as the azo oxidant. A more in-depth analysis of Aldrich's redox-active catalytic Mitsunobu reaction is provided in chapter 2.

1.4.2 Redox-Neutral Catalysis

Redox-Neutral Catalytic Aza-Wittig Reaction. The first example of a redox-neutral catalytic system was published in 1962 by Campbell and co-workers when they reported a phosphine oxide-catalysed synthesis of symmetrical carbodiimides by the dimerization of isocyanates (figure 26A).[267–269] The proposed mechanism involves an initial metathesis reaction between phosphine oxide (**98**) and isocyanate to generate an iminophosphorane intermediate (**99**), expelling carbon dioxide as a by-product. The iminophosphorane intermediate then undergoes an aza-Wittig reaction with a second equivalent of isocyanate to form a carbodiimide and regenerate the phosphine oxide catalyst.

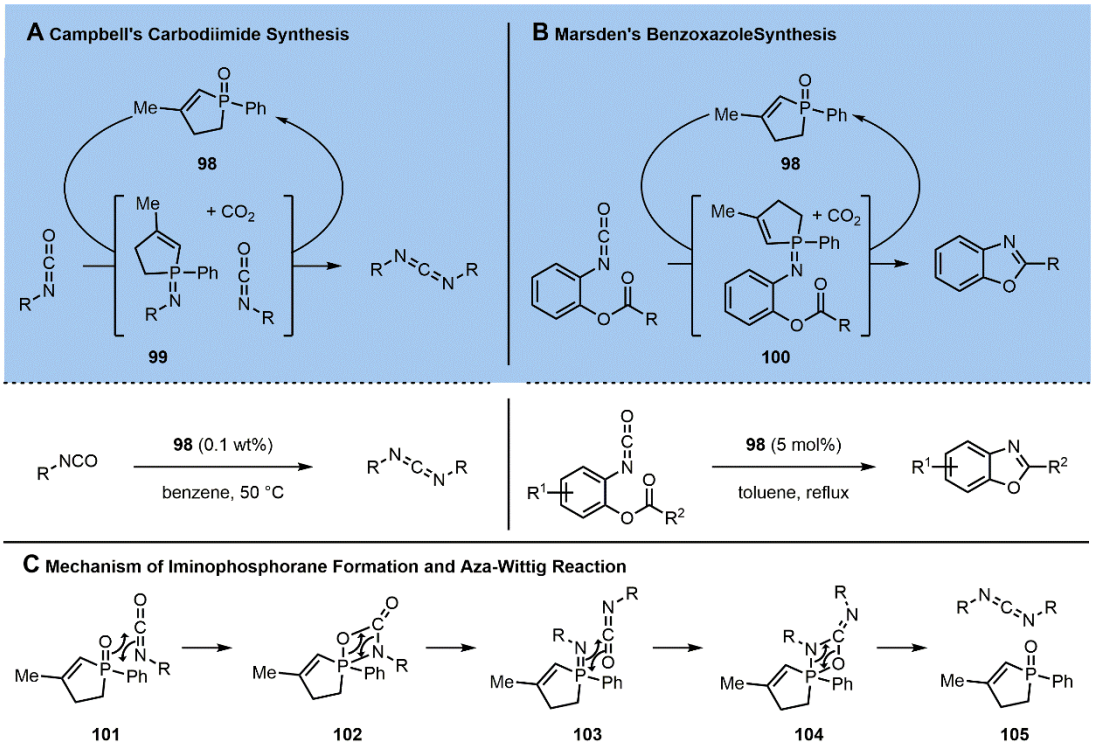


Figure 26. (A) Campbell's redox-neutral aza-Wittig reaction for the synthesis of carodiimides; **(B)** Marsden's redox-neutral catalytic aza-Wittig reaction for the synthesis of benzisoxazoles; **(C)** Mechanism of iminophosphorane formation and aza-Wittig reaction.

Since this seminal study, this type of catalytic manifold remained unexplored until it was revisited by Marsden and co-workers 2008 (figure 26B). They published a method to access phenanthridine and benzoxazoles using a redox-neutral phosphine oxide catalysed intramolecular aza-Wittig reaction.[270] The mechanism proposed involves a metathesis reaction between phosphine oxide (**98**) and an isocyanate, generating an iminophosphorane intermediate (**100**) and carbon dioxide. The iminophosphorane then undergoes an intramolecular aza-Wittig reaction with a neighbouring ester to afford a benzoxazole product and regenerates the phosphine oxide. This method has since been applied as a key step towards the general synthesis of 1,4-benzodiazepin-5-ones and benzimidazoles.[271]

Redox-Neutral Catalytic Appel Reaction and other Halogenations. Using a redox-neutral phosphine oxide catalysis strategy, Denton and co-workers reported a triphenylphosphine oxide catalysed Appel reaction (figure 27A).[272,273] In their catalytic strategy, a triphenylphosphine oxide catalyst (**106**) is firstly activated by oxalyl chloride to afford a cholorophosphonium chloride intermediate (**107**). This electrophilic intermediate undergoes an Appel chlorination with the alcohol substrate, regenerating triphenylphosphine oxide.

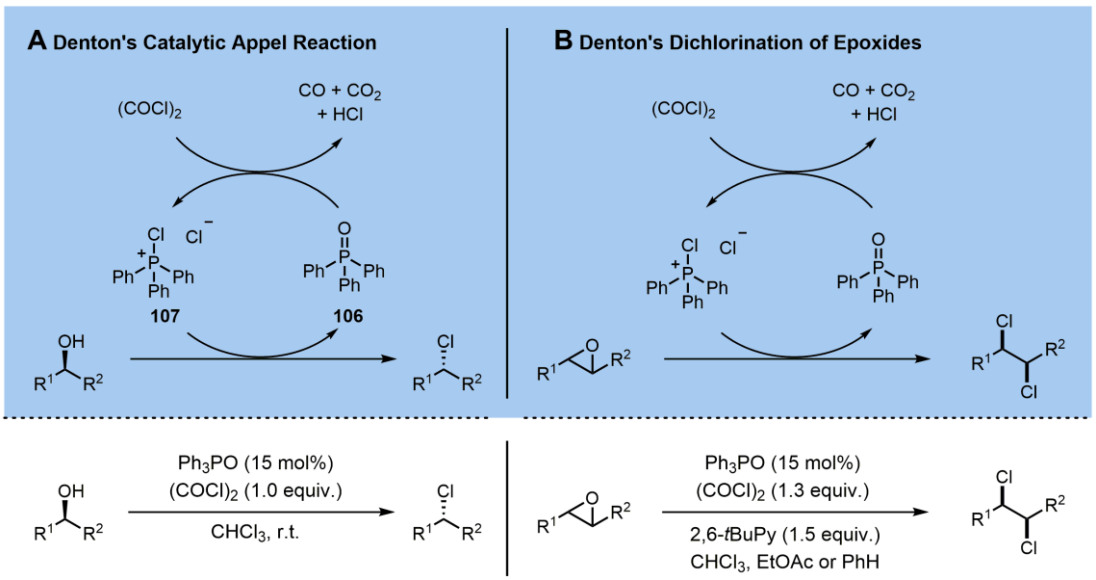


Figure 27. (A) Denton's redox neutral catalytic Appel reaction; **(B)** Denton's redox-neutral catalytic dichlorination of epoxides.

Moreover, the addition of stoichiometric lithium bromide to the reaction mixture results in the generation of alkyl bromides. This reaction has continued to be investigated for practical improvements. The phosphine oxide catalyst can be immobilised to a solid-sate resin for efficient recovery and re-use,[274] and the reaction can be performed using dimethylcarbonate as an environmentally benign alternative solvent.[275] Additionally, the reaction has been used by the McGarrigle group to access a series of glycosyl chlorides.[276]

Denton and co-workers have also reported a phosphorus mediated vicinal dichlorination of epoxides that is catalysed by triphenylphosphine oxide, using oxalyl chloride as the chlorinating reagent (figure 27B).[277] The reaction occurs with inversion at both stereogenic centres. Using this method as a key strategy, Denton's groups realized the total synthesis of the chlorosulfolipid malhamensilipin A.[278] Additionally, the Denton group have shown that aldehydes can be converted into geminal dichloroalkanes under the triphenylphosphine oxide catalysis.[279] Other reported halogenation reactions under redox-neutral catalysis have been reported by Xu and co-workers, namely a 1,3-dichlorination of α,β-unsaturated ketoesters[280] and a 1,2-dibrominaion of α,β-unsaturated ketoesters.[281]

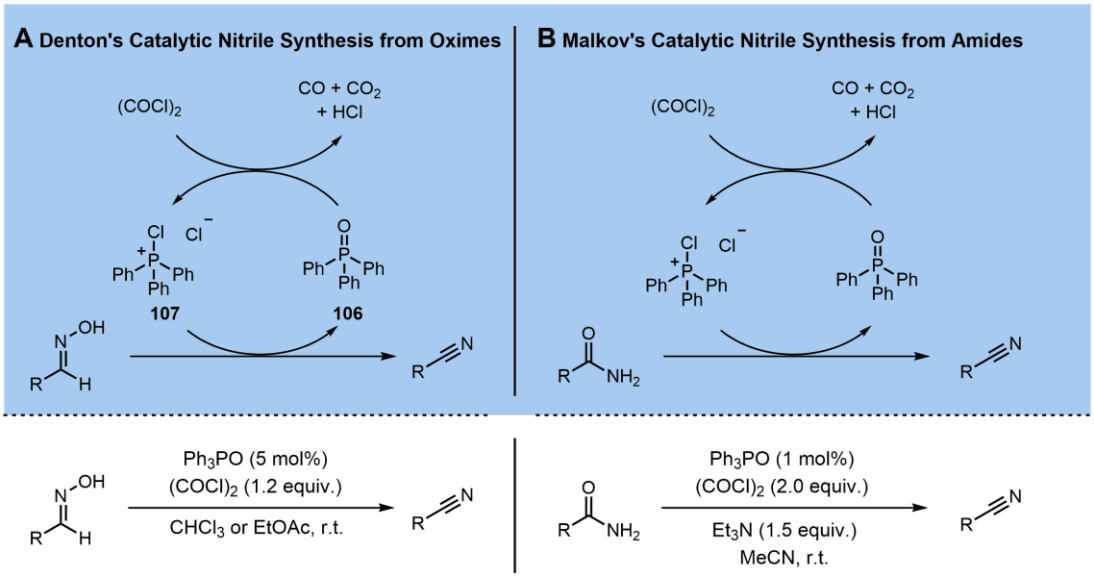


Figure 28. (A) Denton's triphenylphosphine oxide-catalysed dehydration of oximes to nitriles; **(B)** Malkov's triphenylphosphine oxide-catalysed dehydration of primary amides to nitriles.

Catalytic Dehydrative Syntheses of Nitriles. The Denton group have applied their catalytic Appel reaction conditions towards the synthesis of nitriles by the dehydration of oximes (figure 28A).[282] The dehydration reaction was shown to occur via *in situ* activation of the oxime with oxayl chloride, followed by a chlorophosphonium salt-catalysed decomposition to product. In 2018, Malkov and co-workers reported a method for the dehydration of primary amides under redox-neutral organophosphorus catalysis (figure 28B).[283] The combination of triphenylphosphine oxide catalyst and oxalyl chloride as a stoichiometric activating reagent enables the *in situ* activation and dehydration of both aromatic and aliphatic primary amides to nitriles.

1.5 References

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Chapter 2

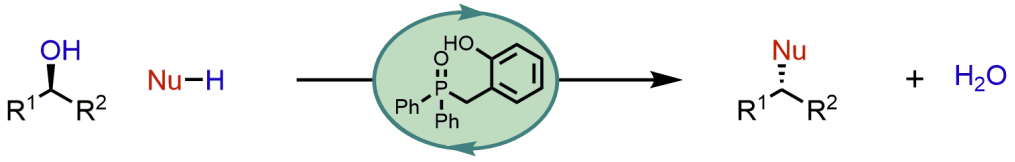
The Development of a Catalytic Mitsunobu Reaction

Abstract

Despite its well-reported issues with atom economy and requirement for toxic and explosive reagents, the Mitsunobu reaction remains the state-of-the-art method for nucleophilic substitutions of alcohols on the laboratory scale. Nevertheless, due to these drawbacks, the reaction is often neglected by process chemists for use in large scale synthesis. The development of alternative protocols that removes the requirement for toxic stoichiometric reagents are therefore highly desired by synthetic organic chemists.

In this chapter, an unprecedented approach towards a catalytic Mitsunobu is reported. A specially designed phosphine oxide organocatalyst has been shown to promote the Mitsunobu coupling of alcohols with a variety of pro-nucleophiles, enabling the formation of numerous examples of carbon–oxygen, carbon–nitrogen and carbon–sulfur bonds. The only by-product generated under the catalytic conditions is water, therefore this method represents a significant improvement in atom economy. The application of this new method towards streamlining the synthesis of active pharmaceutical ingredients is also reported. Furthermore, though catalyst structure-activity relationship studies, new catalysts have been identified with enhanced reactivity.

A New Catalytic Mitsunobu Reaction



Features of New Protocol	**Chapter Contents**
• Produces H_2O as sole by-product.	• Substrate scope evaluation.
• New catalysis manifold.	• Applications in API synthesis.
• Brench-stable phosphine oxide organocatalyst.	• Mechanistic Studies.
	• Catalyst Modification Studies.

2.1 Introduction

2.1.1 Activation of Alcohols Towards Nucleophilic Substitution

Alcohols are important feedstocks for chemical synthesis because they are readily available through a variety of industrial processes, generally inexpensive and can be derivatised into a variety of functional groups.[1] One important synthetic transformation of alcohols is the dehydroxylative nucleophilic substitution reaction, which is frequently used in synthesis. The ideal nucleophilic substitution reaction would involve direct substitution of a hydroxyl group with a nucleophile (figure 1). Unfortunately, due to the poor leaving group potential of the hydroxide anion this hypothetical reaction is kinetically disfavoured. In addition, a nucleophile which is also Brønsted basic will usually deprotonate an alcohol rather than displace it. To overcome these issues, an alcohol must typically be converted to a more activated functionality, usually a sulfonate ester or halide before it may be displaced by a nucleophile.[2,3] Due to this prerequisite activation step, the overall transformation suffers from poor step and atom economy and, furthermore, generates stoichiometric quantities of waste.

As a result, a variety of catalytic methods that directly activate the hydroxyl group

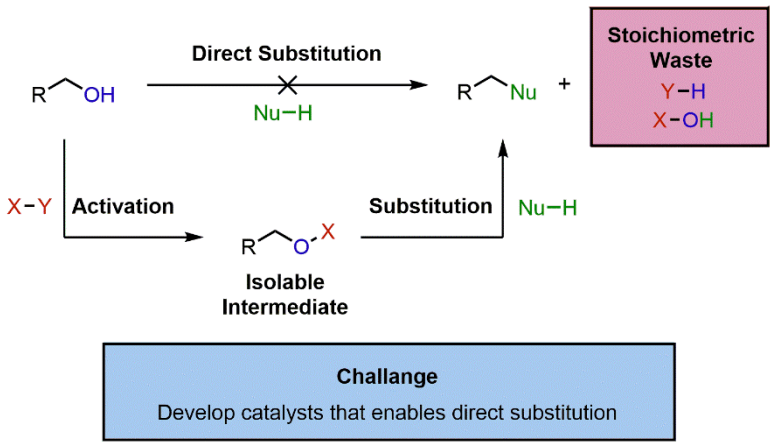


Figure 1. Since direct, uncatalysed substitution of alcohols is impossible, an activation-substitution protocol is typically required for nucleophilic displacement of alcohols. This results in the generation of stoichiometric waste.

of alcohols towards nucleophilic substitution have been developed. Under these catalytic manifolds, the only by-product of the alcohol activation is water. As such they are atom economical alternatives to the established activation-displacement methods. In the next section, the state-of-the-art methods for the catalytic nucleophilic substitution of alcohols are reviewed.

***Borrowing Hydrogen Catalysis*.** One common approach to activate alcohols towards nucleophilic substitution involves the catalytic *in situ* oxidation of the alcohol to an aldehyde or ketone intermediate. The oxidised alcohol then undergoes a specific condensation reaction, before reduction, by the transient transition metal hydride species installs the desired functional group (figure 2A).[4–9] Typically, these reactions employ transition metal catalysts based on osmium, ruthenium, rhodium and iridium, however recent developments within the field have enabled borrowing hydrogen methods based on earth-abundant first row transition metal catalysts.[10]

A common application of this strategy involves the condensation of amines or amides with the aldehyde intermediate to from imines, followed by reduction to form substituted amines.[11] This method was first discovered independently by Grigg[12] and Watanabe in 1981,[13] has been developed into a robust method of for the formal alkylation of amines using alcohols as electrophiles.

The borrowing hydrogen catalysis approach is not exclusively used to synthesise amines. The transient aldehyde or ketone can also be subjected to aldol condensations followed by *in situ* reduction to afford allyl alcohols.[14,15] Additionally, the generated aldehyde or ketone can be subjected to Knovenagel condensation[16] or Wittig olefination[17,18] with subsequent reduction of the generated alkene as a method to displace hydroxyl groups with carbon nucleophiles.

Transition Metal Catalysed Nucleophilic Allylic Substitution. *Allylic* alcohols are common precursors to transition metal π-allyl compounds and are therefore often used as electrophiles in transition metal catalysed nucleophilic allylic substitution (figure 2B).[19] Transition metal catalysts based on palladium, iridium or ruthenium are effective in this transformation and the method can be used to

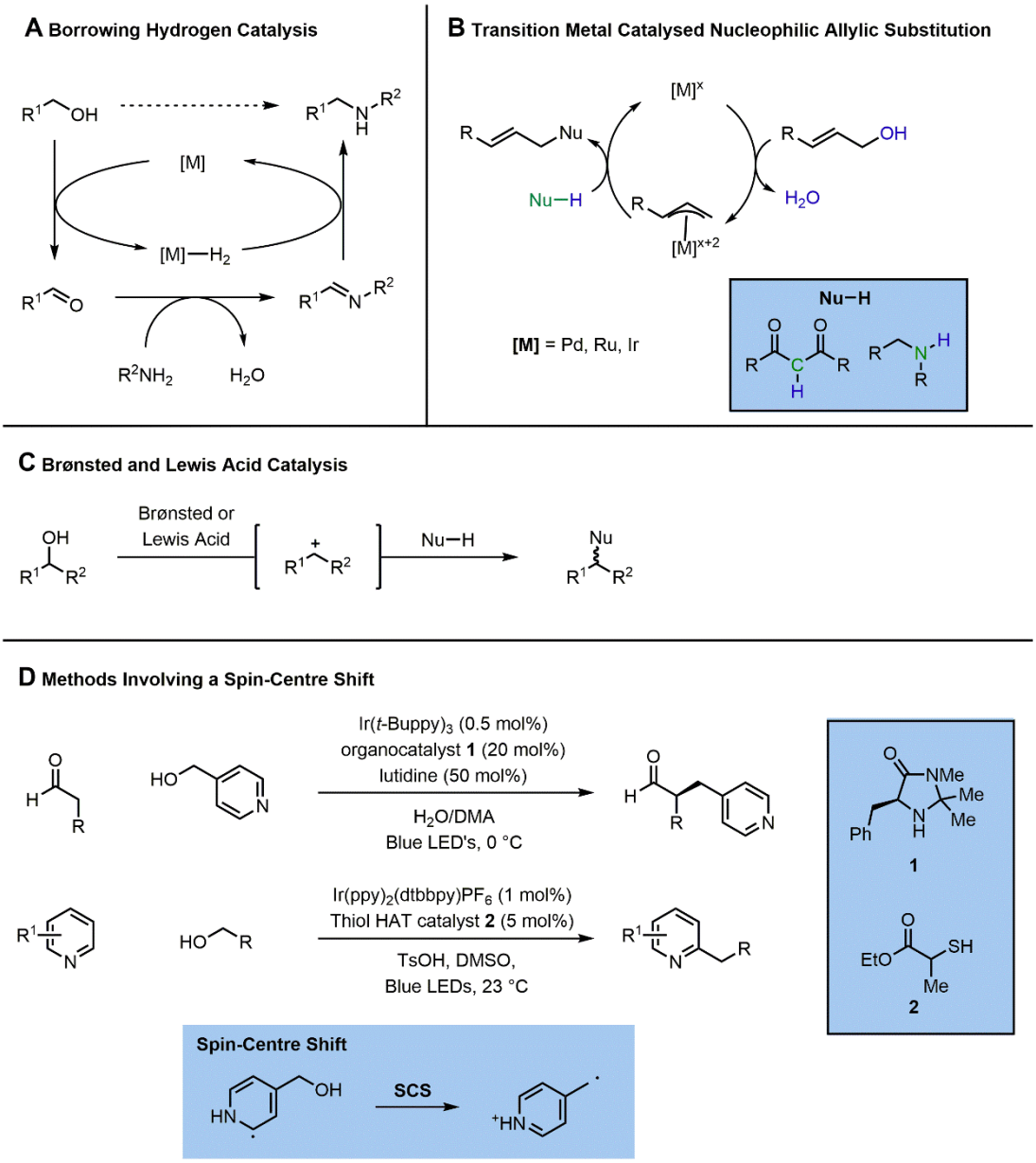


Figure 2. Different strategies for the catalysed dehydroxylative nucleophilic substitution of alcohols. (A) Synthesis of amines by borrowing hydrogen catalysis; **(B)** Transition metal-catalysed nucleophilic substitution of allylic alcohols via π-allyl intermediates; **(C)** Brønsted and Lewis acid catalysed nucleophilic substitution of alcohols, through carbocation intermediates; **(D)** Dehydroxylative nucleophilic substitution of alcohols mediated by a spin-centre shift mechanism.

forge numerous carbon–oxygen,[20] carbon–nitrogen,[21] carbon–carbon[22,23] and carbon–sulfur[20,24] bonds. Although the reaction occurs through an achiral π-allyl transition metal complexes, in many cases high enantioselectivity can be induced through use of chiral phosphine ligands.[25–27]

Brønsted and Lewis Acid Catalysis. The use of Brønsted acids or oxophilic Lewis acids is often used to induce S_N1-type reactions using alcohols as electrophiles (figure 2C).[28,29] A wide variety of Lewis acids are known to induce this type of reactivity, including zinc(II) salts,[30] bismuth (III) salts,[31–33] copper(II) salts,[34,35] indium (III) salts[36–38] and boron(III) compounds.[39,40] Since this type of alcohol activation results in the generation of a carbocation, only alcohols that generate stable carbocations are compatible, such as π-activated alcohols and tertiary alcohols. Furthermore, since these reactions occur *via* carbocation intermediates, in the vast majority of cases enantiopure chiral secondary and tertiary alcohols are racemised under the reaction conditions (see pages 64–66 for exceptions).

Methods Involving a Spin-Centre Shift. MacMillan and co-workers have reported that the use of photo-redox catalysis enables direct dehydrative alkylation of alcohols (figure 3D). The mechanism underpinning the alcohol activation invokes the generation of β-carbon centred hydroxyradicals, which undergoes a β–C–O scission with the elimination of a molecule of water to generate a second carbon-centred radical. This mechanism is commonly referred to as a 'spin-centre shift,' and the β-carbon centred hydroxyradicals are usually generated through a single electron reduction of 4-pyridinemethanol derivatives, or by hydrogen atom transfer of an alcohol. This novel means of activating alcohols towards nucleophilic substitution has so far been applied to the alkylation of electron poor heteroarenes using alcohols,[41] and the enantioselective α-alkylation of aldehydes using 4-pyridinemethanol derivatives as alkylating agents.[42]

2.1.2 Catalytic Nucleophilic Substitution of Alcohols with Inversion of Stereochemistry

Although the methods reviewed so far in this chapter are effective in the dehydrative nucleophilic substitution of alcohols, they all occur through achiral intermediates and, necessarily generate racemic products when used with enantiopure chiral alcohols. The development of catalytic methods that enable *stereospecific bimolecular* nucleophilic substitution of enantiopure chiral alcohols remains a major challenge in contemporary synthetic organic chemistry.

Recently, three major strategies have emerged for addressing the challenge of developing such reactions, Lewis base catalysis, Brønsted/Lewis acid catalysis and catalytic Mitsunobu reactions.

2.1.2.1 Lewis Base Catalysis

One solution to this problem has emerged in the field of Lewis base catalysis.[43–45] In these catalytic cycles (figure 3) the lone pair of the Lewis base catalyst (**3**) initially attacks an electrophilic site on the activating reagent (**4**), releasing a nucleophile. The activated catalyst (**5**) then activates the alcohol to yield an electrophilic intermediate **6.** This intermediate will then undergo a nucleophilic displacement by the nucleophilic counterion to yield the nucleophilic substitution product (**7**) with full Walden inversion of stereochemistry.

Selenium Dioxide Catalysis. The first example of this kind of catalysis manifold, and to date the only example of selenoxide catalysis was reported in 1988 by Lee and co-workers (figure 4A).[46] They demonstrated that 2 mol% selenium dioxide and stoichiometric chlorotrimethylsilane enabled the deoxychlorination of both primary and secondary alcohols in mostly excellent yields.

Sulfoxide Catalysis. In 1995, Snyder reported a procedure for alcohol deoxychlorination, which employed dimethyl sulfoxide as a Lewis base catalyst

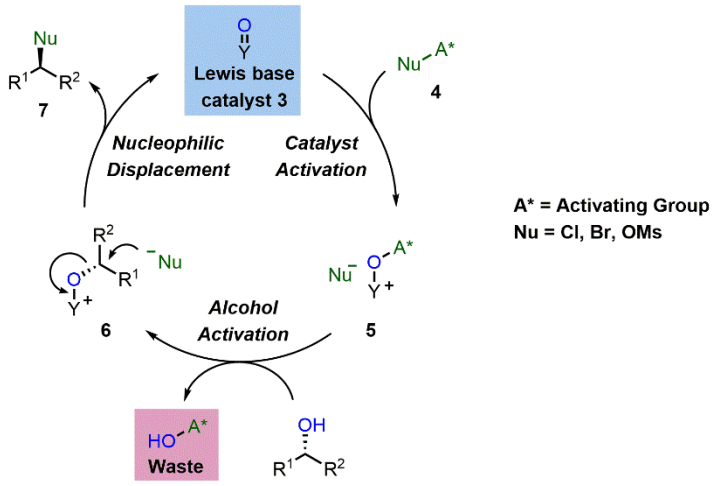


Figure 3. A generic catalytic cycle for the Lewis Base catalysed dehydroxylative nucleophilic substitution of alcohols with inversion of stereochemistry.

and chlorotrimethylsilane as an activating reagent and chloride source (figure 4B).[47] This work remained largely unexplored until 2008, when Li and co-workers reported that it was also possible to use 2,4,6-trichlorotriazine (TCT) as an activating reagent and chloride source, in concert with dimethylsulfoxide as a Lewis base catalyst.[48]

In 2018, Huy and co-workers performed a systematic evaluation of several sulfoxide and selenoxide catalysis for the deoxychlorination of alcohols.[49] In these studies, they identified that *ortho*-anisyl methylsulfoxide gave superior catalytic activity to dimethylsufoxide, and was able to catalyse the deoxychlorination of a wide range of alcohols when used with benzoyl chloride as the activating reagent.

Phosphine Oxide Catalysis. As previously described, Denton and co-workers have developed a chlorodehydration of alcohols (catalytic Apple reaction, see chapter 1, page 44), catalysed by triphenylphosphine oxide (figure 4C).[50] They further demonstrated that the activated phosphonium intermediate could be intercepted by a bromide anion, from the addition of stoichiometric lithium bromide, to afford the alkyl bromide products.[51] Further studies have showed that this reaction can be used for the preparation of glycosyl chlorides,[52] carried out using a polymeric phosphine oxide catalyst,[53] and can be performed on large scales, using environmentally benign solvents.[54]

Aromatic Ketone Catalysis. Owing to their aromaticity, the oxygen atom of cyclopropenones and tropones have greater Lewis basicity then typical ketones and can therefore react with oxalyl chloride to form 1,1-dichlorocyclopropenes and 1,1-dichlorocycloheptatriene repectively.[55–57] This unique reactivity makes them ideal Lewis base catalysts for the deoxychlorination of alcohols. Lambert and co-workers, have designed a deoxychlorination, using a diarylcyclopropenone catalyst, with oxalyl chloride as the electrophilic activating reagent and chloride source (figure 4D).[58] Under the same catalytic blueprint, Lambert and co-workers have reported a diphenylcyclopropenone catalysed deoxy-mesylation of alcohols, using methanesulfonic anhydride as the activating reagent and source of mesylate anion.[59] Finally, Huy and co-workers have recently conducted an evaluation of different cyclopropenone catalysts for the

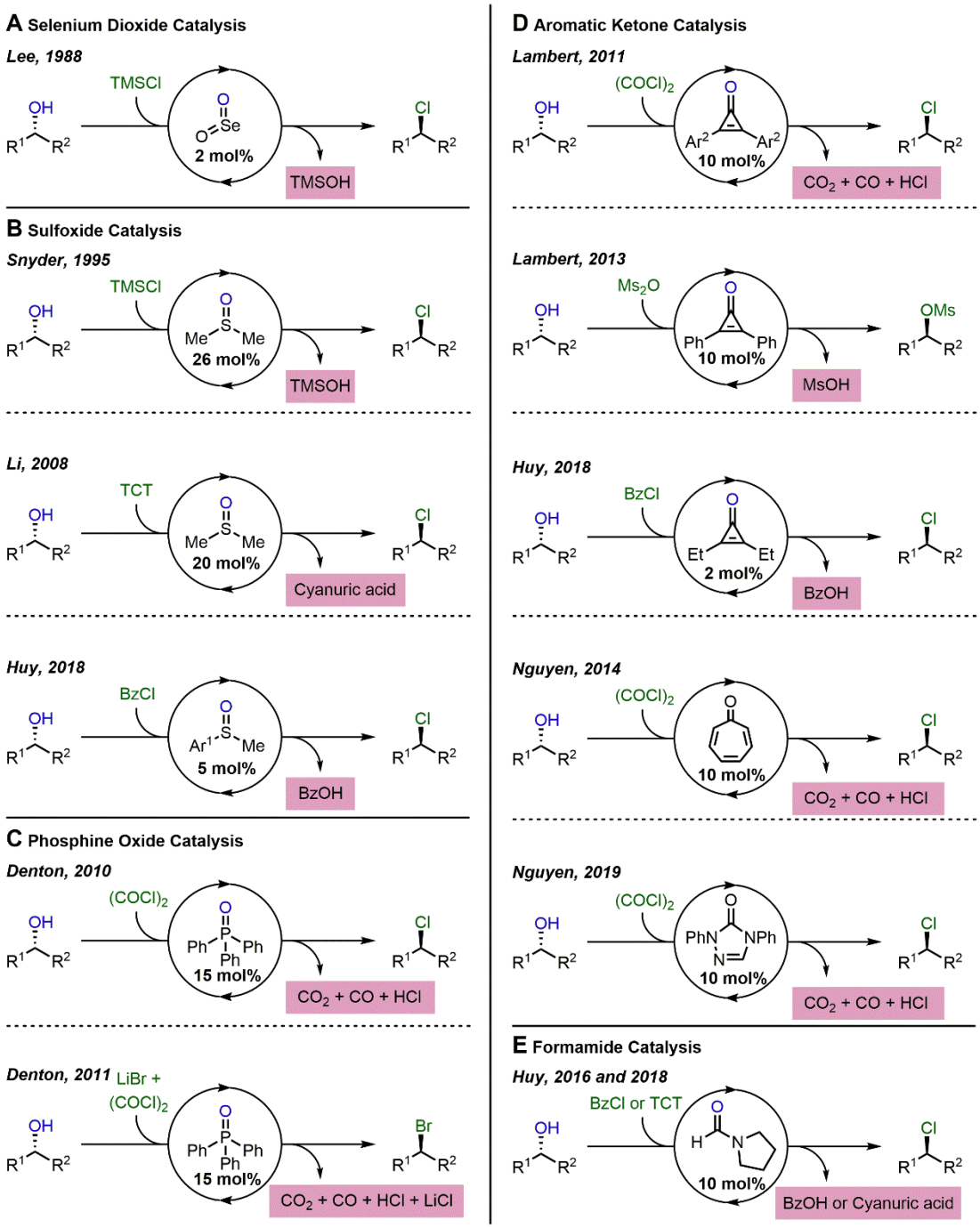


Figure 4. Examples of Lewis Base catalysed nucleophilic substitution of alcohols. (A) Selenoxide-cataysed deoxychlorination of alcohols; **(B)** Sulfoxide catalysed deoxychlorination of alcohols; Ar^1 = 2-anisyl; **(C)** Phosphine oxide catalysed deoxychlorination and deoxybromination of alcohols; **(D)** Dehydroxylative nucleophilic substitution of alcohols catalysed by cyclopropenones, tropone and 2,3,5-triazolinones; Ar^2 = 4-anisyl; **(E)** Amide catalysed deoxychlorination of alcohols.

deoxychlorination of alcohols using benzoyl chloride as the activating reagent and chloride source.[60] They identified diethylcyclopropenone as the optimal

catalyst for this transformation and the deoxychlorination of a wide range of alcohols were carried out using as little as 2 mol% catalyst.

Nguyen and co-workers reported a deoxychlorination of alcohols catalysed by tropone, with oxalyl chloride as the electrophilic activating reagents and chloride source.[61] They further demonstrated that the addition of super-stoichiometric bromide salt to the reaction mixture afforded the alkyl bromide products instead of alkyl chlorides. Additionally, Nguyen and co-workers have shown that 2,3,5-triazolinones are effective Lewis base catalysts for the deoxychlorination and deoxybromination of alcohols using stoichiometric oxalyl chloride and oxalyl bromide respectively.[62]

Formamide Catalysis. Formamides, in particular *N*-formylpyrrolidine, has been demonstrated by Huy and co-workers to be an effective Lewis base catalyst for the deoxychlorination of alcohols, using benzoyl chloride as the electrophilic activating reagent and chloride source (figure 4E).[63] In a second publication, they further demonstrated that TCT could be used as an alternative activating reagent and chloride source.[64]

In general, these methods offer safe and atom economical alternatives to typical methods of achieving invertive deoxyhalogenation, such as the Appel reaction. Nevertheless, a significant drawback in that stochiometric activating reagents are always required, which results in the generation stoichiometric by-products. Furthermore, in the first step of the catalyst cycles the Lewis base catalysts are activated by nucleophilic attack on to the electrophilic activating reagent, releasing the latent nucleophile as a leaving group. As more powerful nucleophiles tend to be poorer leaving groups, this type methodology becomes increasingly difficult when using more powerful nucleophiles. This inherent flaw in this catalytic strategy is evident by the limitation of the nucleophile scope to halogens and pseudohalogens.

2.1.2.2 Brønsted and Lewis Acid Catalysis

As previously discussed, alcohols can be activated towards nucleophilic substitution using Brønsted or Lewis acid catalysis. However, these reactions occur through carbocation intermediates and, in most cases, generate racemic

products. However, there are notable examples of Brønsted or Lewis acid catalysed intramolecular nucleophilic substitution reactions of alcohols occurring with inversion of stereochemistry. This can occur for one of two reasons (figure 5). Firstly, the C–O bond breaks concurrently with the formation of the Nu–C bond though a trigonal bipyramid S_N2-type transition (**8**) state giving a Walden inversion of stereochemistry (**10**). In the second case, the C–O bond breaks to form a transient close-contact ion pair (**9**) with a single enantiotopic face blocked by the anion. The carbocation is then trapped by an incipient nucleophile approaching the carbocation from the unhindered face. In the next section of this these, the literature examples of Brønsted and Lewis acid catalysed invertive nucleophilic substitution reactions are reviewed.

Brønsted Acid Catalysis. In 2015, Samec and co-workers demonstrated that using phosphinic acid as a Brønsted Acid catalyst enabled the condensation of a nucleophile tethered to a stereogenic enantiopure secondary alcohols to give cyclic products with inversion of configuration (figure 5A).[65] Although numerous oxygen-, nitrogen-, and sulfur-centred nucleophiles were shown to be effective, the reaction conditions only enabled the formation of 5-membered rings *via* a 5-*exo*-*tet* cyclisation. The authors have proposed a S_N2-type trigonal bipyramid transition state for this transformation, which was supported by *ab initio* studies.

Lewis Acid Catalysis. In 2019, Cook and co-workers reported that an iron(III) chloride pre-catalyst could affect the intramolecular condensation of a nucleophile tethered to stereogenic enantiopure secondary or tertiary alcohols to give cyclic products with inversion of configuration (figure 5B).[66] Sulfonamides were shown to be effective nucleophiles in this transformation, however, only substituted pyrrolidine products could be accessed *via* a 5-*exo*-*tet* cyclisation. The authors proposed that the reaction occurred through a transient ion pair as depicted in figure 5.

Concurrent with this report, Samec and co-workers reported a similar iron(III) triflate catalysed intramolecular condensation with inversion of configuration (figure 5C).[67] Enantiopure secondary and tertiary alcohols were shown to be

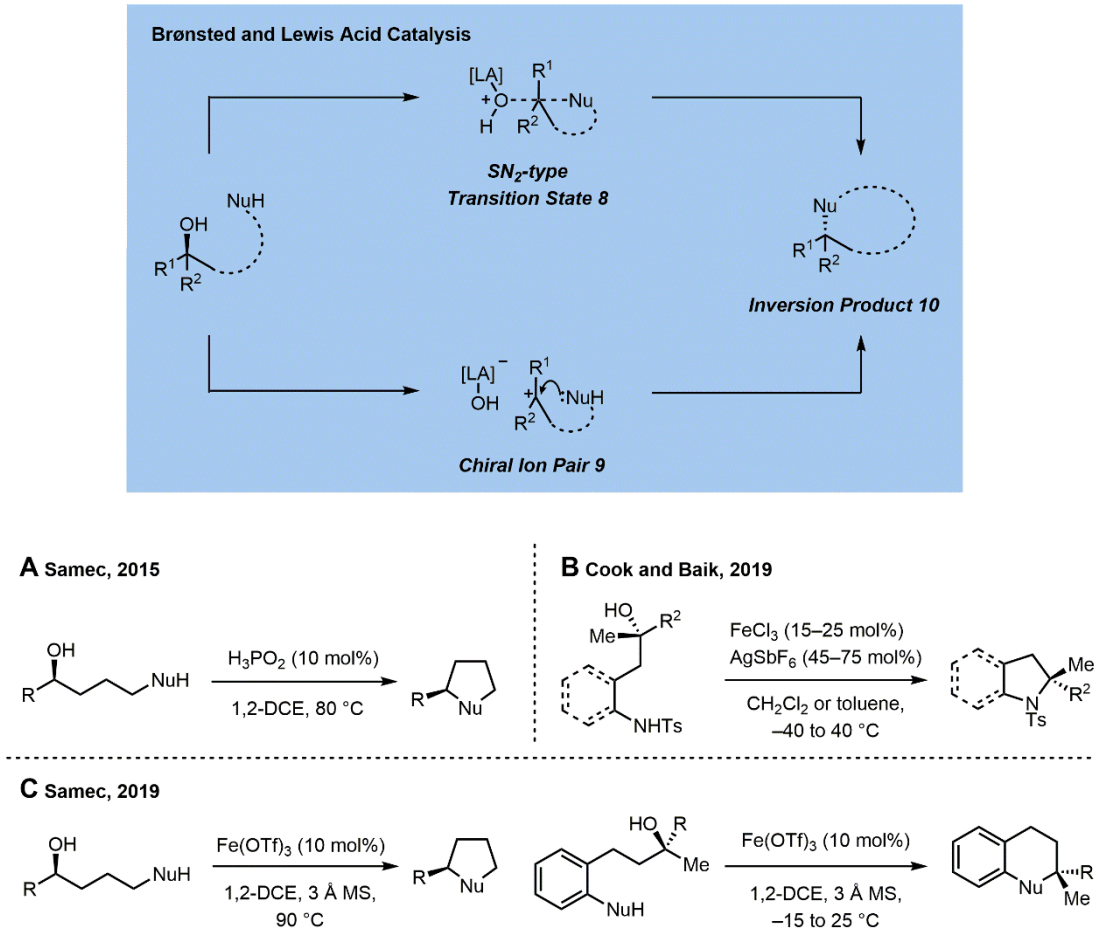


Figure 5. Brønsted and Lewis acid catalysed nucleophilic substitution of alcohols with inversion of stereochemistry. (A) Samec's phosphinic acid catalysed intramolecular nucleophilic substitution of secondary alcohols, to form five-membered saturated heterocycles; **(B)** Cook and Baik's iron(III) catalysed intramolecular nucleophilic substitution of tertiary alcohols, to form five-membered pyrrolidine; **(C)** Samec's iron(III) catalysed intramolecular nucleophilic substitution of secondary and tertiary alcohols to form five- and six-membered saturated heterocycles.

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good substrates for the transformation. Under these reaction conditions, oxygen-, nitrogen-, and sulfur-centred nucleophiles were shown to be effective internal pro-nucleophiles and both five and six-membered rings could be accessed by 5-*exo-tet* and 6-*exo-tet* cyclisation reactions respectively. The authors proposed that for *secondary alcohols* the reaction occurred through a S_N2-type trigonal bipyramid transition state for this transformation, which was supported by *ab initio* studies.

2.1.3 Redox-Active Catalytic Mitsunobu Reactions

Much of the research on catalytic bimolecular nucleophilic substitution of alcohols has centred on the development of catalytic Mitsunobu reactions. In these reactions, the required stoichiometric phosphine and azo reagents are recycled *in situ* by mild terminal reductants and oxidants. As the reagents are regenerated *in situ*, this approach therefore allows sub-stoichiometric loadings of azo reagent or phosphine.

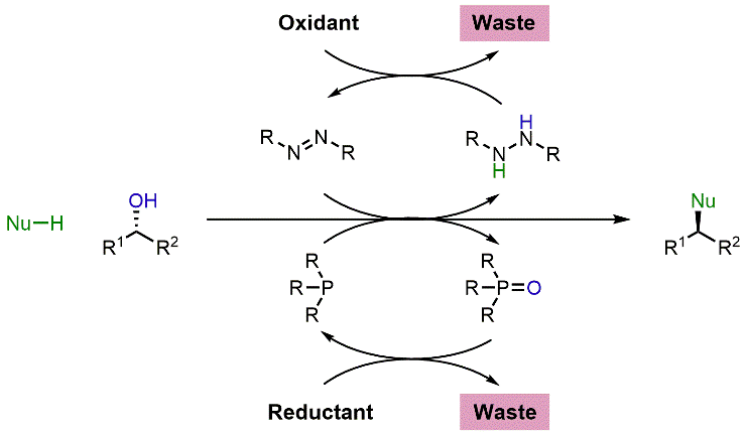


Figure 6. Generic catalytic blueprint for redox-active catalytic Mitsunobu reactions, where the required phosphine and azo compounds are recycled *in situ* by terminal reductants or oxidants.

Methods Catalytic in the Azo Species. Much of the work in this field has focused on developing Mitsunobu reactions that are catalytic in an azo species through *in situ* oxidation of the hydrazide using a terminal, stoichiometric oxidant. To develop a working reaction under this manifold, it is imperative that the hydrazide is selectively re-oxidised in the presence of an oxidizable phosphine.

The first reaction of this kind was reported by Toy and co-workers in 2006 (figure 7A).[68] Their strategy used DEAD as a catalyst which could be efficiently recycled using phenyliodine(III) diacetate (PIDA) as the terminal oxidant.[69] The typical hydrazide waste by-product associated with the Mitsunobu reaction was therefore replaced by iodobenzene and acetic acid, which can be removed from a reaction mixture by distillation, rather than chromatography.

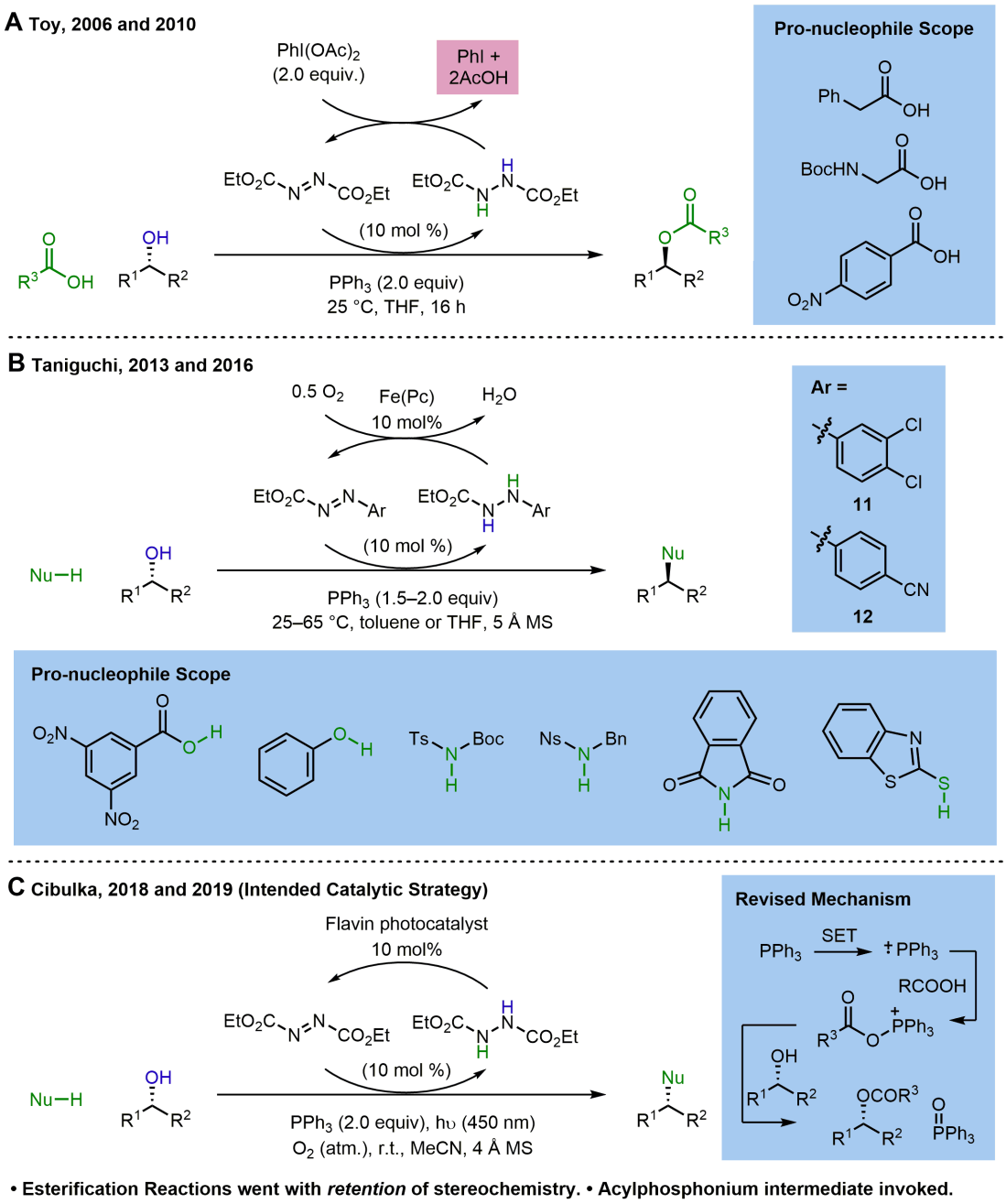


Figure 7. Literature-known Mitsunobu reactions that are catalytic in an azo species. (A) Toy's azo recycling strategy using PIDA as the terminal oxidant; **(B)** Taniguchi's azo recycling strategy using air and Fe(Pc) co-catalyst as the oxidation system; **(C)** Cibulka's catalytic design for photo-redox-mediated oxidation system for recycling azo species.

Despite being an important conceptual breakthrough in the field, from a practical perspective, there are some notable issues with this method. A background redox-coupling reaction between the triphenylphosphine and PIDA resulted in the requirement for super-stoichiometric (2.0 molar equivalents) quantities of

these reagents. Furthermore, a by-product of this method, acetic acid, is itself an effective pro-nucleophile in the Mitsunobu reaction, which limits the pro-nucleophile scope to a narrow selection of carboxylic acids and in contrast to the rich substrate scope of the Mitsunobu reaction.[70]

This research area received no further attention until 2013, when Taniguchi and co-workers reported an alternative azo recycling system for a catalytic Mitsunobu reaction (figure 7B).[71–73] Building on their own work on the aerobic oxidation of carbazates, they developed a system whereby a Mitsunobu-active arylazocarboxylate (**11** and **12**) was instead turned over, using an iron phthalocyanine co-catalyst with oxygen as the terminal oxidant. When this oxidation system was used, in a Mitsunobu reaction with triphenylphosphine, the only by-product from azodicarboxylate recycling was water.

Under these conditions, the pro-nucleophile scope was broad, encompassing a range of phthalimide, sulfonamide, thiol and phenol pro-nucleophiles. Furthermore, the Mitsunobu coupling of sterically encumbered secondary alcohols, such as menthol, was demonstrated with high yields and inversion of configuration.

Cibulka and co-workers have also attempted to develop a catalytic Mitsunobu, whereby the azodicarboxylate is recycled using a photo-redox oxidation system based on a flavin-derived photocatalyst, with oxygen as the terminal oxidant (figure 7C).[74,75] Upon light excitation, the flavin photocatalyst was reported to oxidise hydrazides to azodicarboxylates, thus achieving catalytic turnover. The use of this oxidation system, with stoichiometric triphenylphosphine was shown to give ester products from the coupling of carboxylic acids and alcohols.

However, when applied to enantiopure chiral secondary alcohols, the ester products were obtained with retention of stereochemistry. The authors suggested that an alternative reaction mechanism was occurring, involving a triphenylphsophonium radical cation, which was generated from the single-electron oxidation of triphenylphosphine by the flavin-based photo-redox oxidation system (figure 7C). They proposed that an acyloxyphosphonium salt was generated from the radical cation, which resulted in the retentive acylation

of the alcohol.[76] This study therefore demonstrates that designing and implementing an alternative oxidation system, that is unreactive to the oxidisable phosphine, is highly challenging.

Methods Catalytic in Phosphine. The work described in the foregoing section describes the advances in Mitsunobu reactions catalytic in the azo reagents. This allows for the Mitsunobu reaction to be run without the requirement for a high-energy, potentially explosive stoichiometric reagent. However, the Mitsunobu reaction is also notorious for producing stoichiometric quantities of a phosphine oxide by-product. As such, the development of Mitsunobu reactions that are catalytic in phosphine, by means of a redox-active organophosphorus catalysis manifold (figure 8A), are also at the forefront of research endeavours into organophosphorus catalysis.

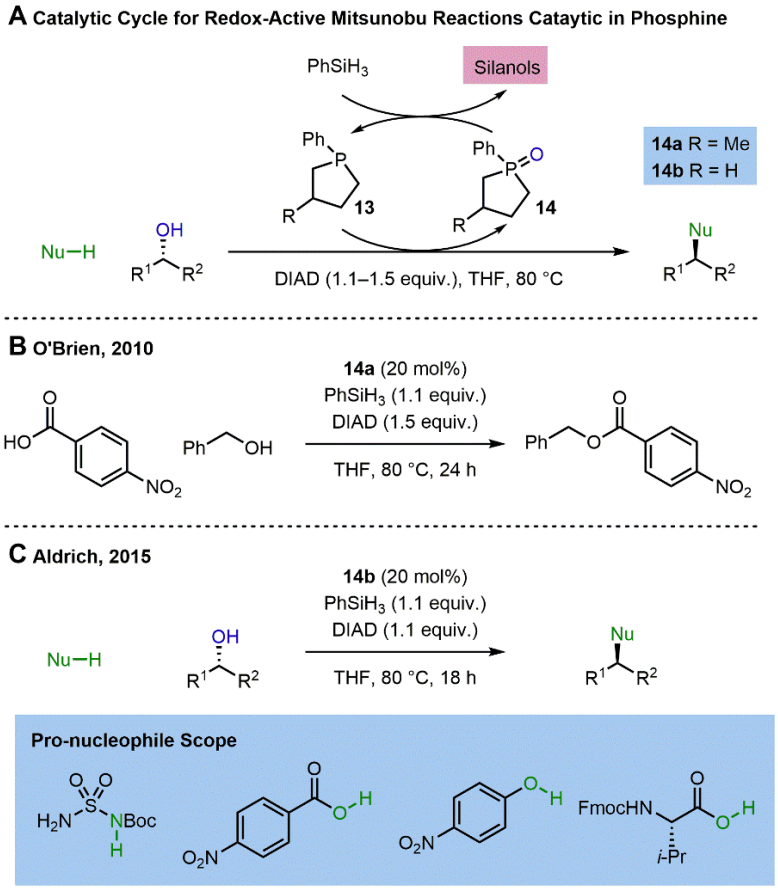


Figure 8. (A) A catalytic strategy for redox-active phosphine/phosphine oxide catalysed Mitsunobu reactions; **(B)** O'Brien's protocol for a redox-active phosphine oxide catalysed Mitsunobu reaction; **(C)** Aldrich's protocol for a redox-active phosphine oxide catalysed Mitsunobu reaction.

The first application of this strategy to the Mitsunobu reaction was reported in the patent literature by O'Brien in 2010 (figure 8B).[77] A Mitsunobu reaction was described using 20 mol% phospholene oxide **14a** as a catalyst in combination with phenylsilane as the terminal reductant. The stoichiometric azo reagent used was DIAD. The patent provided one example of the esterification of benzyl alcohol and 4-nitrobenzoic acid. Although the esterification had occurred with a good yield, an inversion of stereochemistry—a key attribute of a Mitsunobu reaction—was not demonstrated. Therefore, the possibility of the reaction occurring through an alternative, retentive esterification pathway could not be ruled out.

The work was revisited by Aldrich and co-workers in 2015, when they reported a similar Mitsunobu protocol catalysed by phospholene oxide **14b**, with phenylsilane as the terminal reductant and DIAD as the stoichiometric azo reagent (figure 8C).[78] Under this new protocol, a wider pro-nucleophile and alcohol scope was reported, with both carbon-nitrogen and carbon-oxygen bond forming reactions being demonstrated. Critically, when enantiopure, chiral secondary alcohols were used as substrates, the products were obtained with inversion of stereochemistry.

Methods Catalytic in Phosphine and the Azo Species. In seeking a protocol catalytic in both the phosphine and azo species, Aldrich and co-workers developed a Mitsunobu protocol, whereby Taniguchi's azo oxidation system was conflated with their own redox-active phosphine recycling system (figure 9A).[78] In this system, both the azo oxidant and phosphine reductant were in sub-stoichiometric quantities.

However, the substrate scope of this reaction was limited to the esterification of two primary benzylic alcohols with 4-nitrobenzoic acid, and there was no demonstration of an inversion of a chiral non-racemic secondary alcohol (figure 9B). However, subsequent investigations by Taniguchi and co-workers revealed that this doubly catalytic esterification gave near identical yields of ester in the absence of the azo reagent (figure 9C).[79] They further demonstrated that when (−)-ethyl lactate was used as the alcohol substrate, the ester product was obtained in a very low yield (4–7% over three runs) with 68–82% enantiomeric excess in favour of the retention product. The intended mechanistic pathway,

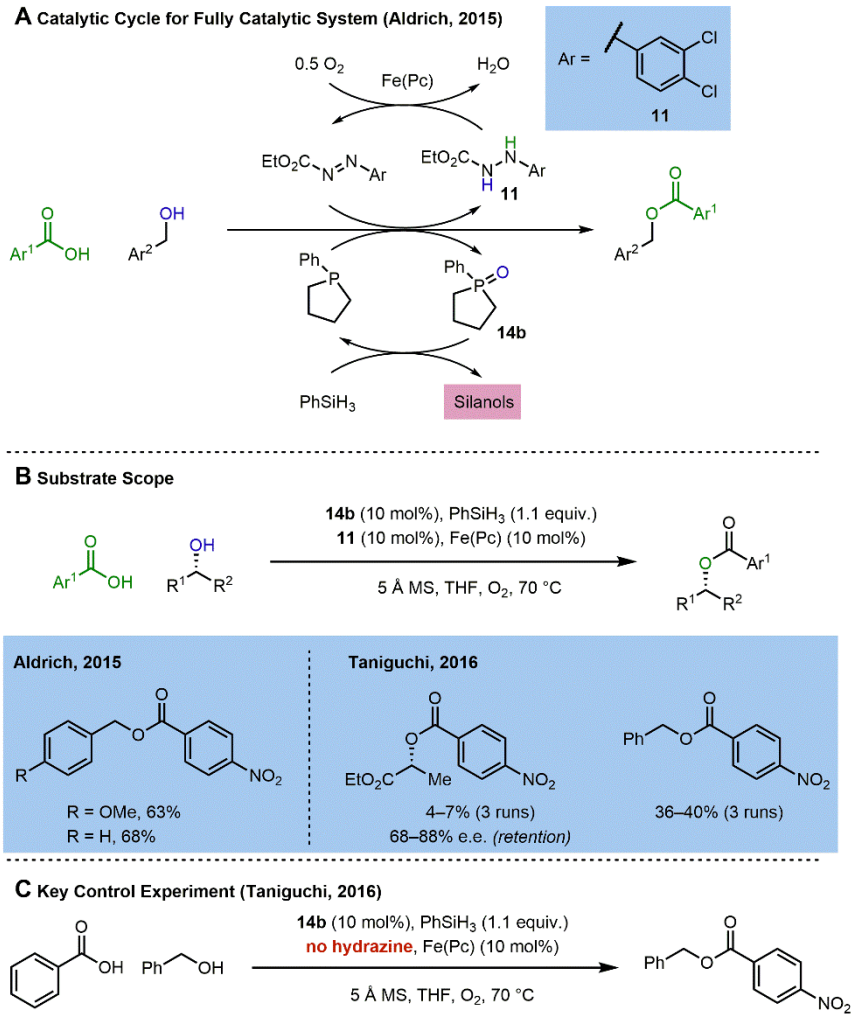


Figure 9. (A) The catalytic blueprint for Aldrich's fully catalytic Mitsunobu reaction; **(B)** The substrate scope for the fully catalytic Mitsunobu reaction from the groups of Aldrich and Taniguchi; **(C)** Taniguchi's key control experiment which demonstrates that the reaction works in the absence of a hydrazide species, thus cannot proceed through a Mitsunobu-type mechanism.

depicted in figure 9A, was clearly not the mechanism responsible for this esterification reaction.

Efficiency of the Catalytic Reactions. Since the Mitsunobu reaction is a 'redox dehydration,'[80] any catalytic manifold predicated on redox recycling will always require a stoichiometric terminal reductant and oxidant. As such, the generation of stoichiometric waste is unavoidable, and the nature and quantity of the waste generated is intrinsically liked to the nature and stoichiometry of the terminal oxidant or reductant. For example, although the Toy procedure allows for a Mitsunobu reaction to operate with sub-stoichiometric quantities of DEAD, to

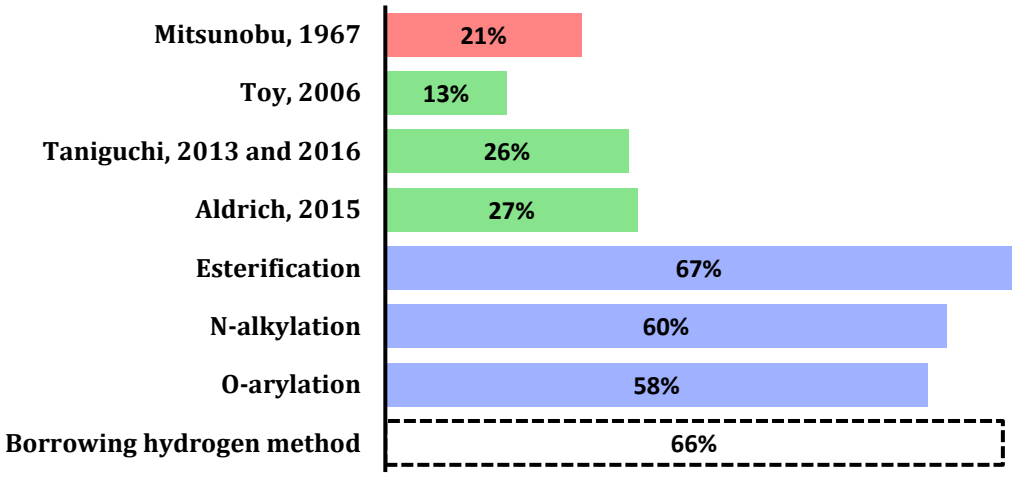


Figure 10. A bar graph comparing the reaction mass efficiencies (RMEs) of the literature catalytic Mitsunobu reactions, including a comparison with other methods for similar bond construction.

achieve facile recycling, two equivalents of PIDA is required, increasing the overall quantity of waste generated. In contrast, Taniguchi's procedure, which uses oxygen as the terminal oxidant, turns over the azo species with much better mass efficiently. Nevertheless, the Taniguchi procedure still requires super-stoichiometric quantities of triphenylphosphine.

To demonstrate the differences in efficiency quantitatively, the reaction mass efficiency (RME) of each of the catalytic Mitsunobu reactions was calculated and compared (figure 10).[81] This metric is an extension of Trost's atom economy metric,[82,83] however additional variables account for stoichiometry of reagents and any unrecovered catalyst. The RME value of a conventional stoichiometric Mitsunobu reaction (from selected examples from ref. 116 from chapter 1)[84] was calculated to be 21%. In comparison with this benchmark figure the Toy procedure gave a reduced RME score (13%), because of the requirement for super-stoichiometric triphenylphosphine and terminal oxidant. Only modest improvements in RME scores were seen for both the Taniguchi procedure and Aldrich's method catalytic exclusively in the phosphine reagent procedure with RME scores of 26% and 27% respectively.[85]

Given that the Mitsunobu reaction is often used for esterification, the *O*-alkylation of phenols and *N*-alkylation, the RME values for the catalytic Mitsunobu reactions were compared with other established methods for this type of bond construction. In 2002, Constable and co-workers surveyed and calculated the RME values for reaction types grouped by the type of bond construction that they facilitate.[81] In this study, esterification, *N*-alkylation and *O*-arylation methods were calculated to be 67%, 60% and 58% respectively. Comparison of these calculated values with those of the reviewed catalytic Mitsunobu reactions reveal a significant efficiency gap between the catalytic Mitsunobu reactions and existing methods to carry out similar bond construction. Finally, an *N*-alkylation reaction using the 'borrowing hydrogen' method was calculated to have a RME value of 66%. An efficiency gap is therefore also observed when the catalytic Mitsunobu reactions are compared to a mature, well-developed catalytic alcohol activation method, such as the 'borrowing hydrogen' protocol of Williams and co-workers.[84]

It should be noted that the comparative methods do not share all the same attributes as the Mitsunobu reaction, such as providing inversion of stereochemistry. This efficiency gap can therefore be offset somewhat by considering this added value of the Mitsunobu reaction. Nevertheless, there is still much room for improvement and efficiency gain.

2.1.4 Redox-Neutral Catalytic Mitsunobu Reactions

As redox-active catalytic Mitsunobu reactions require both a stoichiometric reductant and oxidant, a redox-neutral catalysis manifold, which is free of redox reagents, is arguably a more suitable strategy. Since the Mitsunobu reaction itself is a redox neutral transformation—there is no oxidation or reduction of the *reactants*, only the *reagents*—it is well suited for redox-neutral organophosphorus catalysis manifolds. Furthermore, the efficiency ceiling placed on redox-active catalytic Mitsunobu reactions is not present in an analogous redox-neutral manifold since stoichiometric oxidants and reductants are not essential for catalytic turnover.

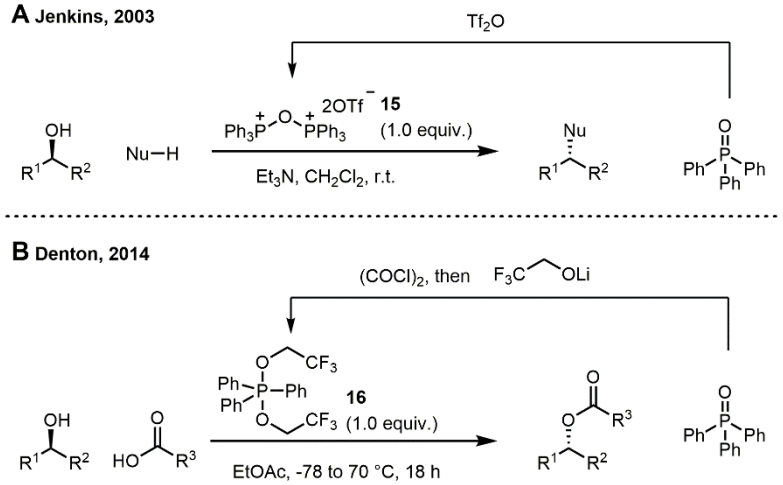


Figure 11. Redox-neutral Mitsunobu reactions using stoichiometric reagents. (A) The use of Hendrickson's reagent as a Mitsunobu reagent by Jenkins and co-workers; **(B)** The use of the Ishikawa phosphorane as a Mitsunobu reagent by Denton and co-workers.

Apart from publications pertaining to the work reported in this thesis, to date there are no reported redox-neutral catalytic Mitsunobu reactions. However, there are literature-known examples of redox-neutral Mitsunobu reactions using stoichiometric phosphorus(V) reagents. In these reactions the stoichiometric phosphorus(V) reagent, which facilitates the Mitsunobu reaction, is generated from a phosphine oxide. Since the by-product of the Mitsunobu reaction is a phosphine oxide, the phosphorus species remains in the phosphorus(V) oxidation state throughout the generation of the reagent and the subsequent Mitsunobu reaction.

In 2003, Jenkins and co-workers showed that the Hendrickson reagent (triphenylphosphonium anhydride trifluoromethanesulfonate, **15**) facilitated the Mitsunobu coupling of primary alcohols with 4-nitrobenzoic acid, thioacetic acid and sodium azide in excellent yields (figure 11A).[86] Under these conditions, secondary alcohols were predominantly dehydrated to the analogous alkene, but also gave low yields of inverted Mitsunobu products. Critically, the Hendrickson reagent was accessed from triphenylphosphine oxide and trifluoromethanesulfonic anhydride, therefore in principle, the Hendrickson reagent could be regenerated and recycled using the triphenylphosphine oxide

by-product of the Mitsunobu step without leaving the phosphorus(V) oxidation state.

In 2014, the Denton group reported a Mitsunobu reaction which used the Ishikawa phosphorane (**14**) as the sole stoichiometric reagent (figure 11B).[87] The protocol enabled the coupling of various carboxylic acid pro-nucleophiles with primary and secondary alcohols. Comparable to the work of Jenkins, the Ishikawa phosphorane was accessed from the phosphine oxide, *via* the dichlorophosphorane, therefore the phosphorus remained in the phosphorus(V) oxidation state during the generation of the reagent, and throughout the Mitsunobu reaction.

Designing a Redox-Neutral Catalytic Mitsunobu Reaction. Building on the work of Jenkins and Denton, we sought to develop a redox-neutral catalytic Mitsunobu reaction. Such a catalytic manifold would require the unconventional step of accessing a phosphorane, which can facilitate a Mitsunobu reaction, from a phosphine oxide in a catalytic sense.

In 1978, Hellwinkel and Krapp reported a rare example of an acid mediated dehydration of a phosphine oxide (**17**, figure 12A) to generate a spirocyclic dioxyphosphorane (**18**).[88] This unusual reactivity was intriguing for two reasons, the breaking of a stable phosphoryl bond is seemingly contra-thermodynamic, and certain dialkoxyphosphoranes are known intermediates in the Mitsunobu reaction.[89–91]

Based on this reaction, a catalytic cycle for a redox-neutral Mitsunobu reaction was envisaged, whereby the spirocyclisation of phosphine oxide **17** was induced by the acidic pro-nucleophile substrate (figure 12B). In the presence of a pro-nucleophile and alcohol, dioxyphosphorane **18** would subsequently ring-open to afford alkoxyphosphonium **19**, through a similar mechanistic pathway to the Mitsunobu reaction when the alcohol is added before the pro-nucleophile (see chapter 1, pages 28–34 for discussion). Subsequent Arbuzov collapse of alkoxyphosphonium **19** would yield the nucleophilic substitution product and regenerate the phosphine oxide (**17**), thereby closing the catalytic cycle.

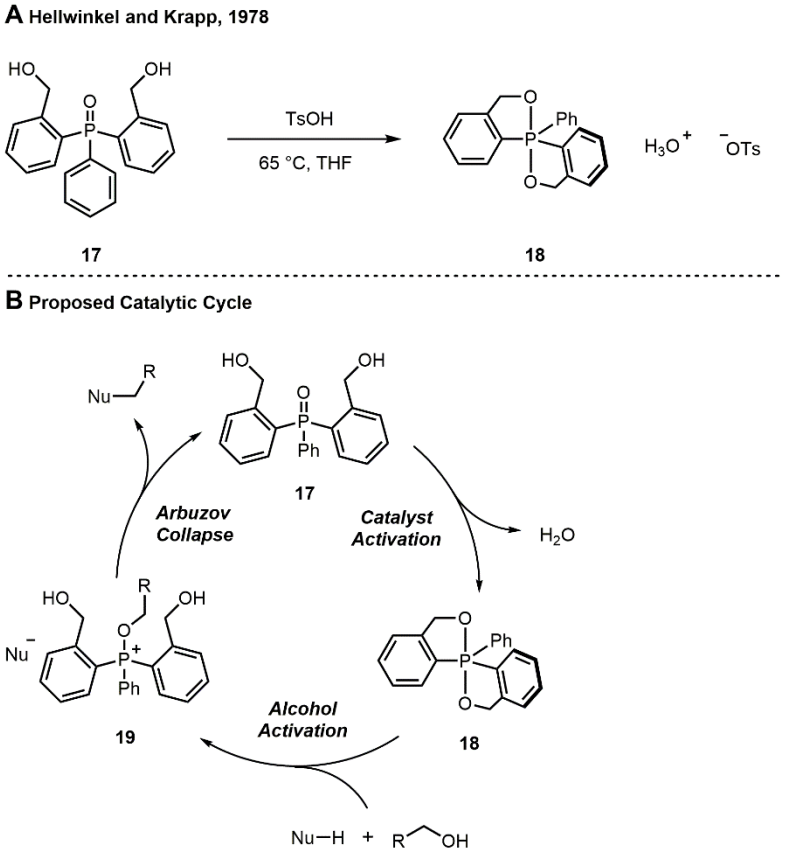


Figure 12. (A) Hellwinkel and Krapp's acid mediated dehydrative dioxyphosphorane synthesis; **(B)** A proposed redox-neutral catalytic Mitsunobu reaction, which uses Hellwinkel and Krapp's dehydrative spirocyclisation as a catalytic step.

Unpublished Work Within the Denton Group. Attempts to develop a working catalytic system based on this plan have been ongoing within the Denton group since the early 2010s. In this work spirocyclic phosphorane **18** was adjudged to be too kinetically stable with respect to ring opening and substitution with alcohols. However, when investigating this issue, a second-generation phosphine oxide (**C1**) was identified, who's corresponding spirocyclic phosphorane could ring open in the presence of strong Bronsted or Lewis acids (figure 13A).

Using this new catalyst the esterification of 1-decanol using triflic acid was attempted, however, due to the strongly electrophilic nature of the triflate ester product, a subsequent nucleophilic displacement from an incipient decanol nucleophile occurred, yielding didecyl ether (figure 13A). Nevertheless, by using sub-stoichiometric quantities of both phosphine oxide **C1** and triflic acid, as well as Dean-Stark apparatus for continued water removal, the dehydrative homo-

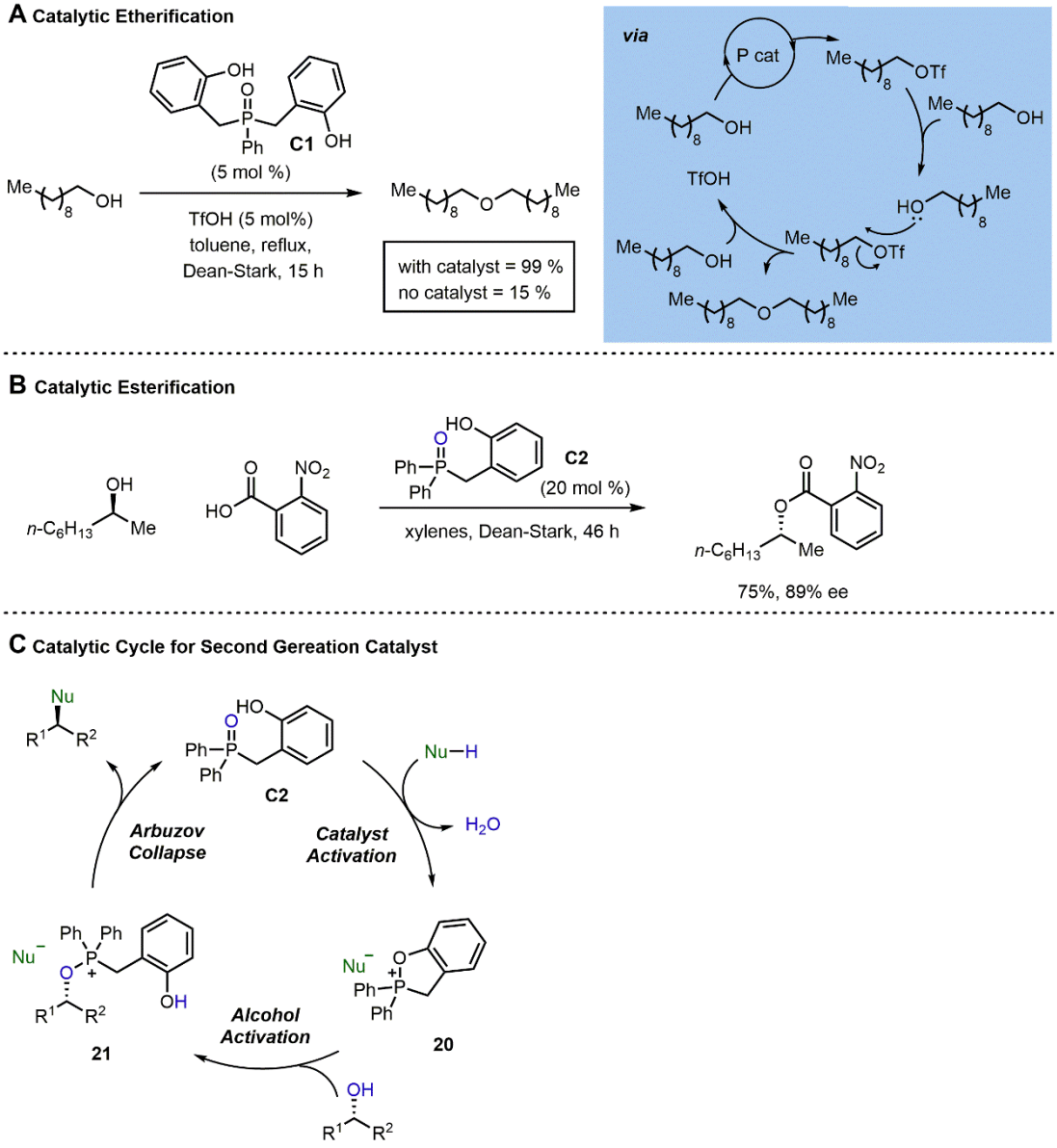


Figure 13. (A) A catalytic homo-etherification under a redox-neutral catalytic Mitsunobu manifold, developed by the Denton group; **(B)** An invertive esterification under a redox-neutral catalytic Mitsunobu manifold, developed by the Denton group; **(C)** A proposed catalytic cycle for the catalytic invertive esterification.

coupling of 1-decanol, was demonstrated to occur at enhanced rates compared to a control reaction.

Despite this success, the high kinetic stability of the dioxyphosphorane intermediate was hindering the catalyst turnover. This prompted further catalyst modification studies, which revealed that only a single phenol internal nucleophile was required for the desired Mitsunobu activity. This second-

generation catalyst (**C2**) was shown to be far more active and could couple less acidic pro-nucleophiles with alcohols (figure 13B).

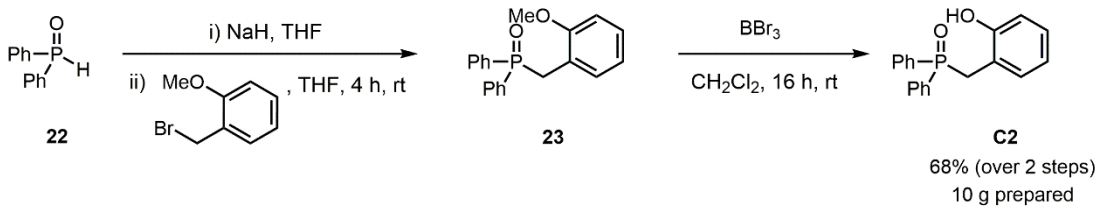
Using this new catalyst, the first example of a catalytic esterification reaction was demonstrated. When a solution of (*S*)-(+)-2-octanol and 2-nitrobenzoic acid in xylenes was heated to reflux and held for 46 hours with 20 mol% of **C2**, a catalytic Mitsunobu esterification reaction was observed with a high yield and the inverted ester was obtained with 89% e.e. (figure 13B). An alternative catalytic cycle is proposed for catalyst **C2** (figure 13C). Here, the catalyst is activated by the acid mediated dehydration of **C2** to oxyphosphosphonium **20**, which then undergoes a substitution reaction with the alcohol substrate to form a second oxyphosphonium intermediate (**21**). Subsequent Arbuzov collapse yields the desired substitution product, regenerating the catalyst.

Prior to starting the work described in this thesis, this method had only been exemplified in the coupling of the model substrates shown in figure 13B. This study will therefore firstly seek to expand the substrate scope, through optimisation of reaction conditions and catalyst modifications. This chapter documents the progress made in developing this catalytic Mitsunobu procedure, as well as investigations aiming to identify new, more active phosphine oxide organocatalysts based on **C2**.

2.2 Results and Discussion

2.2.1 Developing a Catalytic Esterification Reaction

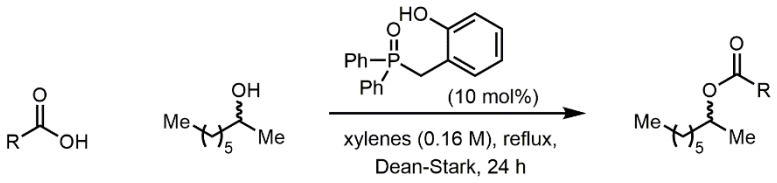
In seeking to develop a scalable and operationally simple synthesis of catalyst **C2**, a new strategy involving a Michaelis-Becker reaction, using diphenylphosphine oxide (**22**) as a nucleophile, was investigated. Deprotonation of diphenylphosphine oxide, followed by nucleophilic substitution using 2-methoxybenzyl bromide as the electrophile afforded a methoxy-protected catalyst (**23**). Subsequent deprotection using boron tribromide yielded a multi-gram batch of the desired phosphine oxide (**C2**) with an overall yield of 68%. Since this route did not require any column chromatography—only a trituration after each step were required for purification—it is a highly practical and amenable to further scale-up.

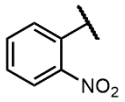
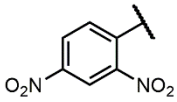
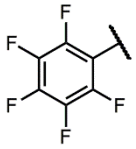
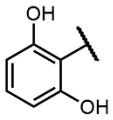
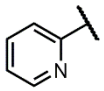
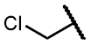


Scheme 1. A new scalable synthesis of catalyst **C2** using a strategy based on a Michaelis-Becker reaction of diphenylphosphine oxide and 2-methoxybenzyl bromide.

Next, attempts to broaden the substrate scope of the catalytic Mitsunobu esterification reaction were investigated. In traditional Mitsunobu reactions several studies have shown that the carboxylic acid identity can have drastic effects on the yield and inversion levels obtained.[92,93] In order to probe which carboxylic acids were effective pro-nucleophiles under the reaction conditions, a screening of different carboxylic acid pro-nucleophiles was conducted. The test conditions consisted of heating a solution of 10 mol% catalyst, and an equimolar quantity of both carboxylic acid and alcohol in xylenes for 24 hours using Dean-Stark apparatus for water removal (table 1). Yields were determined by ^{1}H NMR using an internal standard.

Table 1. The effect of alternating the carboxylic acid coupling partner on reaction yield. Reaction yield was determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane as an internal standard.

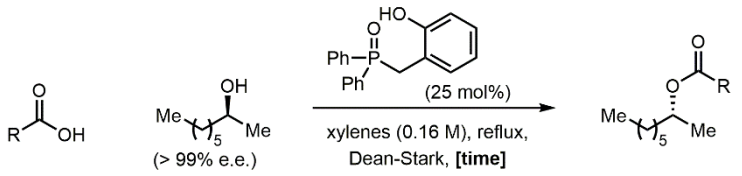


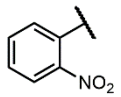
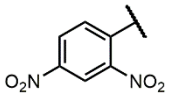
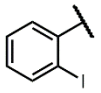
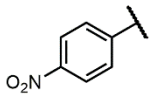
Entry	R	pKa	NMR Yield (%)	Alcohol Remaining (%)	Yield in Absence of Catalyst (%)
1		2.17	39	46	8
2		1.70	81	3	12
3		1.75	70	26	14
4		1.22	20	71	-
5		5.25	9	84	-
6		0.66	52	39	43
7		2.86	43	53	30

The general trend observed was that carboxylic acids with lower pKa values gave better yields of ester products. The greatest yield (81%) was observed when 2,4-dinitrobenzoic acid was used as the pronucleophile (table 1, entry 2), which is more acidic that 2-nitrobenzoic acid, as the pro-nucleophile. Furthermore, pentafluorobenzoic acid (entry 3) gave an enhanced yield compared to 2-nitrobenzoic acid. When the reactions were run in the absence of a catalyst, a background esterification reaction, between the alcohol and pro-nucleophile was observed, presumably occurring *via* a Fischer-type esterification mechanism. The NMR yield of ester was 8%, 12% and 14% for 2-nitrobenzoic acid, 2,4-dinitrobenzoic acid and pentafluorobenzoic acid respectively.

When 2,6-dihydroxybenzoic acid, was tested as a pro-nucleophile (entry 4), the ester product was obtained with an ^{1}H NMR yield of 20%. Picolinic acid, which is

Table 2. An optimisation table comparing the invertive esterification of different carboxylic acid pro-nucleophile with (*S*)-(+)-2-octanol.



Entry	R	Isolated Yield (%)	Reaction time (hours)	Product e.e. (%)
1		74	48	94
2		76	20	96
3		68	20	89
4		25 (based on 33% conversion)	20	90
5		24 (based on 50% conversion)	48	91

commonly used as a pro-nucleophile for the Mitsunobu inversion,[93] gave poor conversion to product (entry 5). Due to the relatively poor yields for these substrates, the background reactions were not investigated.

Using trichloroacetic acid (entry 6) and chloroacetic acid (entry 7) as pro-nucleophiles gave ester products with yields of 52% and 43% respectively. However, when the reactions were run in the absence of a catalyst, the esters were formed with relatively high yields of 43% and 30%. This observation suggests that the predominant esterification mechanism for these substrates was an off-cycle mechanism and therefore these results were not investigated further.

Having identified a number of carboxylic acid pro-nucleophiles compatible with our catalytic system, their capacities to invert the stereochemistry of an enantiopure secondary alcohol were investigated (table 2). Using (*S*)-(+)-2-octanol as a model substrate, various substituted benzoic acid pro-nucleophiles were evaluated as pro-nucleophiles, using an increased 25 mol% catalyst loading.

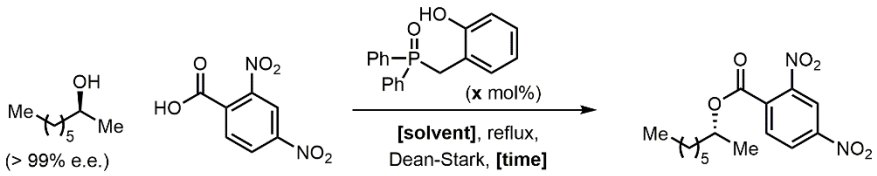
When 2-nitrobenzoic acid, 2,4-dinitrobenzoic acid and pentafluorobenzoic acid were tested (table 2, entries 1–3) as pro-nucleophiles, the reactions were held until full conversion to product was reached. Of the three pro-nucleophiles, 2,4-dinitrobenzoic acid (entry 2) was shown to be the best pro-nucleophile since it gave an ester product with the highest enantiomeric excess for the inversion product (96% e.e.), shortest reaction times (complete after 20 hours) and highest isolated yield (76%). Pentafluorobenzoic acid (entry 3) gave a similarly short reaction time of 20 hours, a high yield of 68% and a high enantiomeric excess for the inverted product (89% e.e.). Using 2-nitrobenzoic acid as a pro-nucleophile (entry 1) gave similarly good inversion of stereochemistry and high yield however, a longer reaction time was required to allow the reaction to reach completion.

2-Iodobenzoic acid (entry 4) and 4-nitrobenzoic acid (entry 5) were also tested as pro-nucleophiles, however these reactions proceeded at a much slower rate and were therefore the reactions were stopped before full conversion. As such, the isolated yields were low (25% and 24% respectively). Nevertheless, both carboxylic acids afforded inverted ester products with high enantiomeric excess, namely 90% e.e. for 2-iodobenzoic acid and 91% e.e. for 4-nitrobenzoic acid.

Since using 2,4-dinitrobenzoic acid as a pro-nucleophile gave superior results to the other carboxylic acids, its reaction with (*S*)-2-octanol was subjected to further optimisation studies (table 3). Changing the solvent from xylenes (entries 1–5) to toluene (entries 6–9) generally resulted in prolonged reaction times and no significant improvement in yield or enantiomeric excess of product. Furthermore, lowering the catalyst loading to 10 mol% did not greatly affect reaction time, yield or enantiomeric excess of product.

The most profound trend observed was that lowering the reaction concentration to 0.080 M resulted in a greater enantiomeric excess and yield, whereas increasing the reaction concentration to 0.40 M resulted in a lower yield and enantiomeric excess (entries 7-9). From these studies the optimal conditions were adjudged to consist of using 10 mol% catalyst, using xylenes as the solvent and conducting the reaction at a concentration of 0.080 M (entry 7). These

Table 3. The optimisation of the catalytic Mitsunobu esterification of 2,4-dinitrobenzoic acid with (S)-(+)-2-octanol. The effects of changing solvent, reaction concentration, catalyst loading and reaction temperature are investigated,



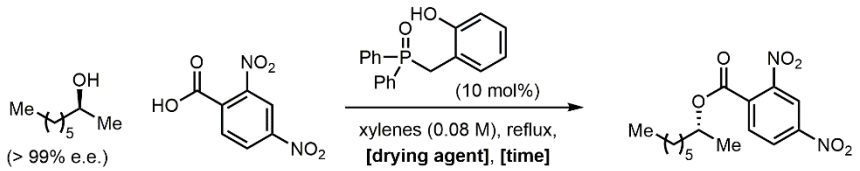
Entry	Concentration / (M)	Solvent	Catalyst loading / (mol%)	Reaction duration / (hours)	Isolated yield / (%)	Product e.e. / (%)
1	0.080	toluene	25	96	75	96
2	0.16	toluene	25	72	77	90
3	0.40	toluene	10	96	72	89
4	0.080	toluene	10	72	56	98
5	0.16	toluene	10	72	54	96
6	0.16	xylenes	25	20	76	97
7	0.080	xylenes	10	30	84	98
8	0.16	xylenes	10	24	74	96
9	0.40	xylenes	10	24	65	91

reaction conditions provided the inverted ester product with 98% e.e. and an 84% yield.

Despite achieving near-full inversion of configuration, some erosion of enantiomeric excess was observed during the transformation (2% e.e.). To investigate where the enantiomeric excess was lost the reaction was run in the absence of the catalyst which gave the desired ester in 10% isolated yield after 30 hours with 19% e.e. for the retention product (table 4, entry 2). The implies that the background reaction goes *via* two different mechanisms, a minor retentive Fischer-type esterification mechanism and a major racemising S_N1-type mechanism. We reasoned that keeping the concentration of acid low may reduce the background reaction, therefore the addition the acid in portions throughout the reaction was investigated. Adding the acid portion-wise over 48 hours and 72 hours gave almost identical yields and enantiomeric excess to the standard optimised conditions (entries 3 and 4).

Without a Dean-Stark trap, the reaction gave poor yield of 5% and 82% e.e. for the retention product (entry 5), thus demonstrating that a method for water

Table 4. The optimisation of the catalytic Mitsunobu esterification of 2,4-dinitrobenzoic acid with (S)-(+)-2-octanol. The use of a portion-wise acid addition protocol and alternative drying agents are investigated. *Reactions carried out in microwave vials at 1.0 mmol scale.



Entry	Deviation from Standard Conditions	Reaction duration / (hours)	Isolated yield / (%)	Product e.e. / (%)
1	None	30	84	98 (*inversion*)
2	No catalyst used	30	10	19 (*retention*)
3	Acid added in equal portions at 0, 8 and 24 hours.	48	82	98 (*inversion*)
4	Acid added in equal portions at 0, 24 and 48 hours.	72	82	98 (*inversion*)
5	No drying agent used*	30	5	82 (*retention*)
6	$MgSO_4$ used as drying agent*	30	5	82 (*retention*)
7	Na_2SO_4 used as drying agent*	30	6	71 (*retention*)
8	3 Å molecular sieves used as drying agent*	30	4	56 (*retention*)
9	4 Å molecular sieves used as drying agent*	30	3	37 (*retention*)
10	5 Å molecular sieves used as drying agent*	30	13	33 (*inversion*)

removal is essential. The use of alternative drying agents for water removal was therefore investigated. Using magnesium sulfate or sodium sulfate as *in situ* desiccants was detrimental to the reaction, giving poor yields of 5% and 6% respectively (entries 6 and 7). Furthermore, using molecular sieves, of various pore sizes, as *in situ* desiccants also gave poor yields and did not give a clean inversion of stereochemistry (entries 8–10).

2.2.2 Substrate Scope Evaluation

With optimised conditions in hand, the scope of this catalytic Mitsunobu esterification reaction, with respect the alcohol substrate was investigated (figure 14). To scope some functional group tolerance, primary alcohols were subjected to the reaction conditions. As shown in figure 14, substrates bearing a wide variety of functional groups including ester (**24a**), amide (**24b**), phthalimide (**24c**) and nitrile (**24d**) functional groups were esterified under the reaction conditions. When β-citronellol (**24e**) was subjected to the reaction

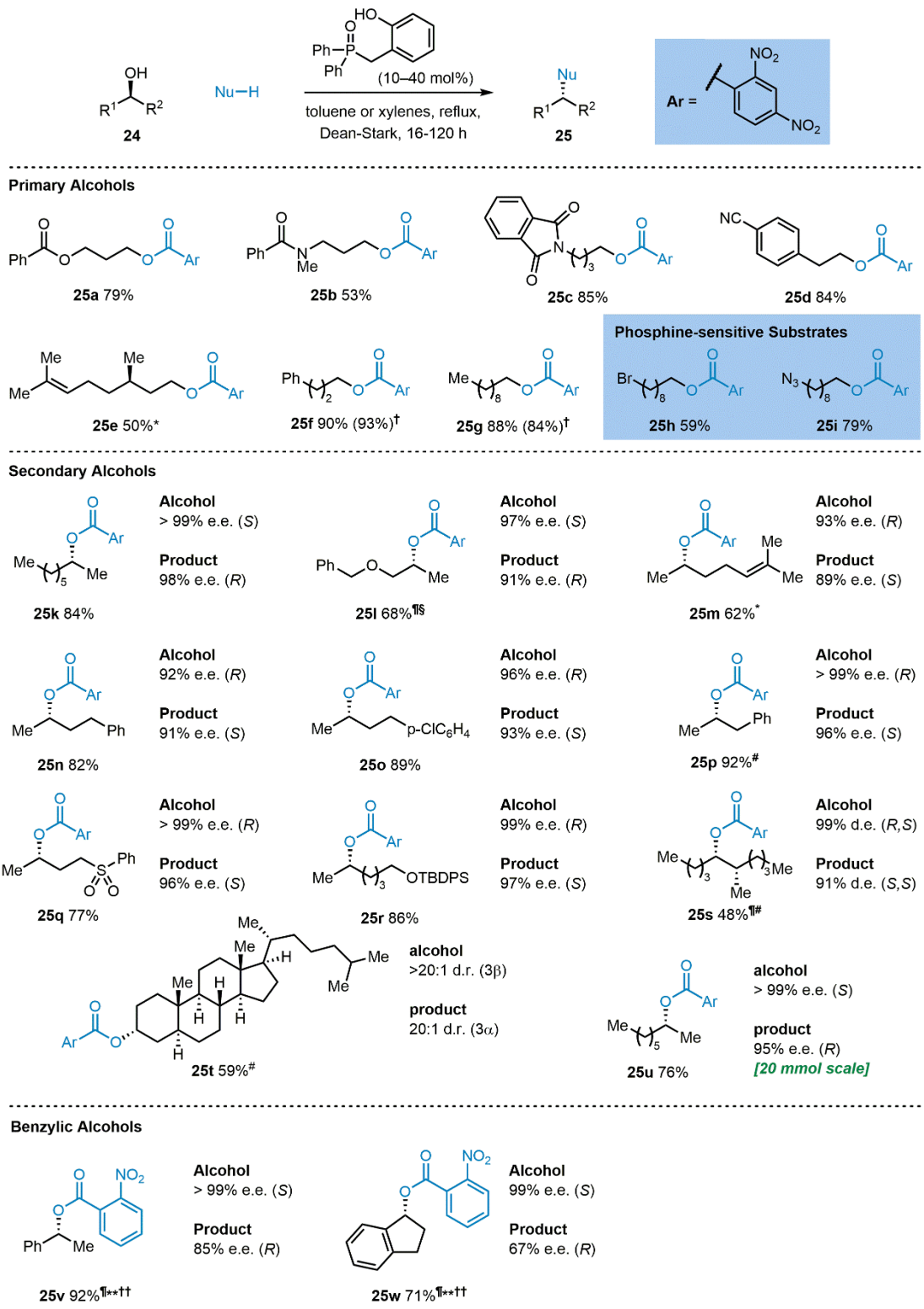
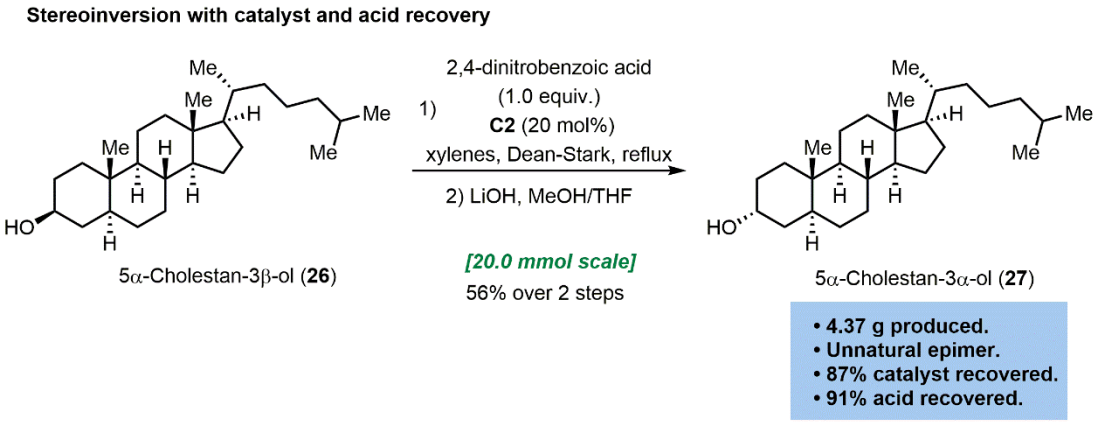


Figure 14. The substrate scope for the catalytic Mitsunobu esterification. *Isomerisation of alkene accounts for *ca.* 10% of the yield. †Reactions performed with reclaimed acid and catalyst. §40 mol% catalyst used. ¶Portion-wise addition of the acid. #20 mol% catalyst used. **25 mol% catalyst used. ††2 equivalents of alcohol used; The synthesis of alcohol **24s** was conducted by Dr. Keith Andrews.

conditions, the analogous ester was formed, although this occurred with some isomerisation of the acid-sensitive internal alkene. Hydrocinnamyl alcohol (**24f**) and 1-decanol (**24g**) were also shown to be competent substrates in the reaction, affording their respective ester products with high yields. Notably, substrates containing phosphine-sensitive functional groups such as alkyl bromide (**24h**) and azide (**24i**) were efficiently coupled under the reaction conditions. Since these functional groups are known to react with phosphines, attempting to access these products under classical Mitsunobu conditions or under redox-active catalytic Mitsunobu manifolds would likely be problematic.

Numerous enantiopure, chiral secondary alcohols were also effectively coupled with 2,4-dinitrobenzoic acid under the reaction conditions, affording inverted esters with high enantiomeric excess. Substrates containing ether (**25l**), alkene, (**24m**), aryl chloride (**24o**), sulfone (**24q**) and silyl ether (**24r**) functional groups afforded the corresponding inverted esters (**25k–r**) in good to excellent yields. In the case of the electron deficient alcohol, **24l**, its lower reactivity could be overcome by increasing the catalyst loading to 40 mol%, which gave the inverted ester product with excellent yields and selectivity. When 5α-cholestan-3β-ol (**24v**) was subjected to the reaction conditions, the corresponding inverted ester (**25v**) was also obtained. When (*S*)-(+)-2-octanol and 2,4-dinitrobenzoic acid were coupled under the catalytic conditions, at an increased scale of 20.0 mmol, the inverted ester product was obtained with a slightly reduced yield (76%) and enantiomeric excess (95% e.e.).

Benzylic alcohols, such as **24t,** were challenging substrates since they have a tendency undergo an unproductive background S_N1 coupling, which resulted in an erosion of enantiomeric excess. However, exchanging 2,4-dinitrobenzoic acid for the less acidic 2-nitrobenzoic acid, increasing the catalyst loading to 20 mol%, exchanging the solvent from xylenes to toluene and prolonging the reaction time gave the inverted ester in 92% yield and 85% e.e. Under these modified conditions, (*S*)-(+)-1-indanol (**24u**) was also converted into its corresponding inverted ester (**25u**) in a 71% yield, albeit with a reduced enantiomeric excess of 67%.



Scheme 2. A multi-gram one-pot two-step Mitsunobu inversion of 5α-cholestan-3β-ol, to access the non-natural epimer 5α-cholestan-3α-ol.

In the 'Mitsunobu inversion' (see chapter 1, page 19) the ester products formed from the Mitsunobu coupling are subsequently hydrolysed to yield the inverted alcohol. We sought to investigate using the catalytic esterification conditions for a Mitsunobu inversion in order to to access a non-natural epimer of a chiral secondary alcohol natural product (scheme 2). Thus, the non-natural epimer of the steroid 5α-cholestan-3β-ol was synthesised on a multi-gram scale, in two steps by using a catalytic Mitsunobu esterification protocol, followed by ester hydrolysis in an overall yield of 56%. The catalyst and 2,4-dinitrobenzoic acid were then recovered from the final reaction mixture in 87% and 91% yield, respectively. The recovered catalyst and acid were subsequently used in the catalytic esterification of substrates **24f** and **25f** (see figure 14) with no significant loss of yield, thereby demonstrating that a Mitsunobu inversion could be conducted without generating any stoichiometric waste products.

In the case of *exo*-norborneol (**28a**, figure 15) and cholesterol (**28b**), the corresponding esters were afforded with *retention* of stereochemistry. In the absence of catalyst, the esters are not formed. This is presumably due to the substrates reacting in an S_N1-like manner, mediated by the phosphine oxide catalyst. Under this hypothesis, the generated carbocation is trapped by the nucleophile attacking from the least hindered face.

In the case of *exo*-norborneol, the 2-norbornyl cation has exceptional stability, arising from overlap between the bridging carbon–carbon σ-bond and the empty

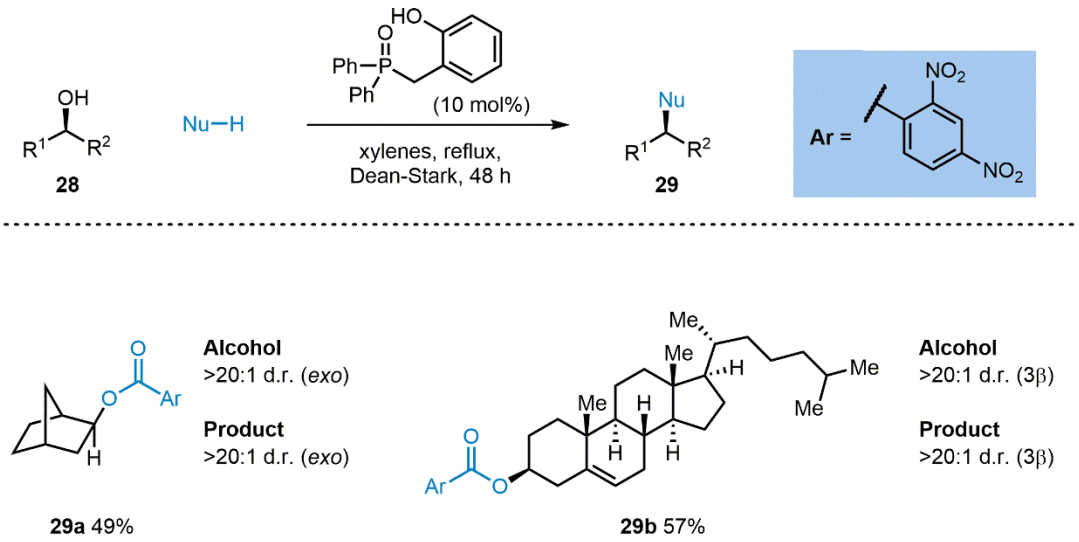


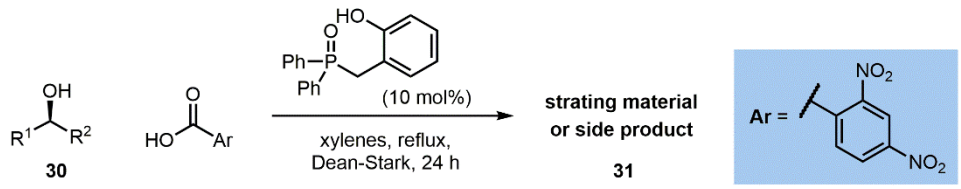
Figure 15. Examples of catalytic Mitsunobu esterification reactions which went with retention of stereochemistry.

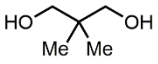
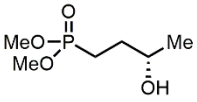
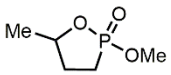
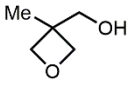
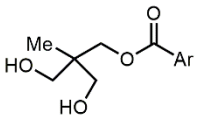
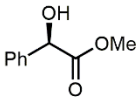
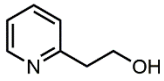
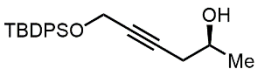
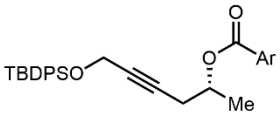
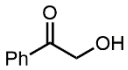
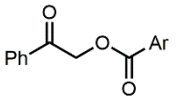
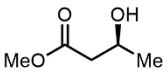
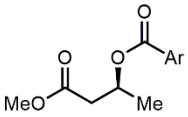
p-orbital of the carbocation.[94,95] With cholesterol, the generated carbocation is stabilised by anchimeric assistance of the adjacent alkene.[96] In many cases, cholesterol is known to undergo phosphorus-mediated deoxyhalogenation reactions with retention of stereochemistry, therefore this result was unsurprising.[96]

During the evaluation of the substrate scope, several alcohol substrates did not react, or gave unwanted side reactions under the reaction conditions (table 5). Hindered primary alcohols **30a** and **30b** both failed to give the desired ester product. This is unsurprising, since they are structurally similar to neopentyl alcohol, which is known to be too hindered to undergo facile Arbusov collapse and as such is a poor substrate in the Mitsunobu reaction.[97] Alcohol **30a** failed to react and after 24 hours, only starting material was visible by ^{1}H NMR. In the case of alcohol **30b**, under the reaction conditions the acid-sensitive oxetane underwent a ring opening to form diol **31b** as the major product.

Pyridine-containing alcohol **30c** failed to give an ester product when subjected to the reaction conditions. Instead, the alcohol decomposed to a complex mixture of unidentifiable side-products. It is likely that in this instance, the catalytic Mitsunobu reaction is inhibited by the Brønsted basicity of the pyridine moiety.

Table 5. Examples of alcohols that either gave unwanted side-products or failed to react when subjected to the catalytic Mitsunobu esterification reaction.



Alcohol Substrate	Reaction Outcome	Alcohol Substrate	Reaction Outcome
 **30a**	Starting material recovered	 **30e**	 **31e** (*ca.* 80% conversion)
 **30b**	 **31b** (*ca.* 85% yield)	 **30f**	No conversion to product
 **30c**	Complex mixture of products	 **30g**	 **31g** (*ca.* 15% conversion)
 **30d**	 **25b** (*ca.* 3% conversion)	 **30h**	 **31h** (13% NMR yield)

Hydroxyacetophenone (**30d**) also gave very poor conversion to product, presumably due to the electron-deficient nature of the alcohol.

When secondary alcohol **30e** was subjected to the reaction conditions, the cyclic phosphonate ester **31e** was obtained, rather than the desired carboxylic ester, probably *via* an acid-mediated internal trans-esterification mechanism. Furthermore, methyl (*R*)-(−)-mandelate (**30f**) gave no conversion to product, presumably since the alcohol has poor nucleophilicity.

Alcohols **30g** and **30h** both gave poor conversions to product, and analysis of the crude reaction mixture by ^{31}P NMR revealed that the signal corresponding to the catalyst was mostly replaced with a new signal at 30.8 ppm. This new phosphorus

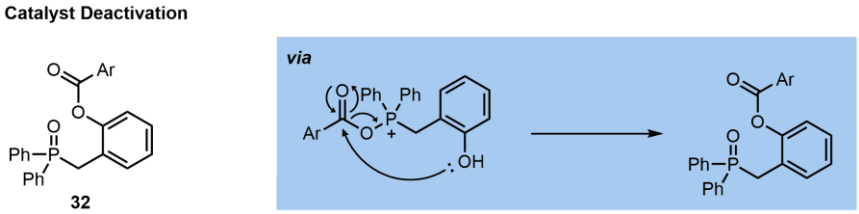


Figure 16. A proposed mechanism with which the catalyst undergoes a deactivating esterification reaction.

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species was isolated and identified as the product of the esterification of catalyst and 2,4-dinitrobenzoic acid (**32**, figure 16). This phosphine oxide is likely to form by an acylation of the catalyst *via* an acylphosphonium intermediate. In fact, this catalyst deactivation side reaction can be observed to a small extent in many of the examples shown in figure 14, however there is no apparent trend between alcohol structure and rate of catalyst deactivation.

This substrate scope investigation suggested that the reactions limitations are as follows: **a)** inverted esters with poor enantiomeric excess were obtained when using enantiopure benzylic alcohols as substrates, however the enantiomeric excess could be increased by using toluene as a solvent, increasing the catalyst loading and using 2-nitrobenzoic acid as the pro-nucleophile; **b)** if stable carbocations are readily generated from the alcohols, then the reaction may go with retention of configuration; **c)** sterically hindered alcohols are poorly tolerated; **d)** some acid-sensitive functional groups may decompose under the reaction conditions and **e)** functional groups which are Brønsted bases are poorly tolerated.

Nevertheless, several inverted esters (figure 14) were successfully formed with high enantiomeric excesses. When non-activated alcohols were used as substrates, between 1 and 8% e.e. was eroded during the reaction. Overall, the yields obtained were good-to-excellent ranging from 48–92%.

2.2.3 Mechanistic Studies

Isotope Labelling Study. The mechanism of the catalytic Mitsunobu esterification was investigated using an isotope labelling experiment. In this study, ^{18}O-enriched 1-decanol and 2,4-dinitrobenzoic acid were subjected to the reaction conditions with 15 mol% catalyst (figure 17A). The ester product was formed with high ^{16}O incorporation of 88% and the recovered catalyst was obtained with 66% yield and found to contain 74% of the ^{18}O label. This result is consistent with the expected oxygen transfer from the alcohol to the catalyst during the Arbuzov collapse step of the catalytic cycle. Furthermore, as the carboxylate is the nucleophile in this reaction, the ^{16}O label of the carboxylate is fully transformed to the ester product. This result is fully consistent with the proposed catalytic cycle (figure 13C).

Catalyst Structure Activity Relationship. The effect of structural changes to the catalyst on the reaction outcome was investigated. An analogue of the catalyst, where the hydroxyl group is replaced by a methoxy (figure 17B, entry 3), and a second analogue where the methylene linker between the phenol and phosphorus atom is removed (entry 4) were tested for their abilities to catalyse the Mitsunobu coupling of (*S*)-(+)-2-octanol and 2,4-dinitrobenzoic acid. In both cases, the reactions gave similar results to the background reaction (entry 1), namely low isolated yields and formation of the retention product with low enantiomeric excess.

With both phosphine oxides, the formation of the five-membered oxyphosphonium intermediate is precluded, thereby, shutting down the catalytic cycle. Furthermore, the phosphine oxide where the methylene linker between the phenol and phosphorus atom is removed (entry 4) has a similar ^{31}P NMR shift (39.4 ppm) to the catalyst, indicating a similar amount of phosphoryl activation (phosphonium character). The lack of catalytic activity therefore discredits a possible mechanistic pathway, whereby the phenol hydroxyl group acts as a hydrogen-bond donor to activate the alcohol towards nucleophilic substitution.

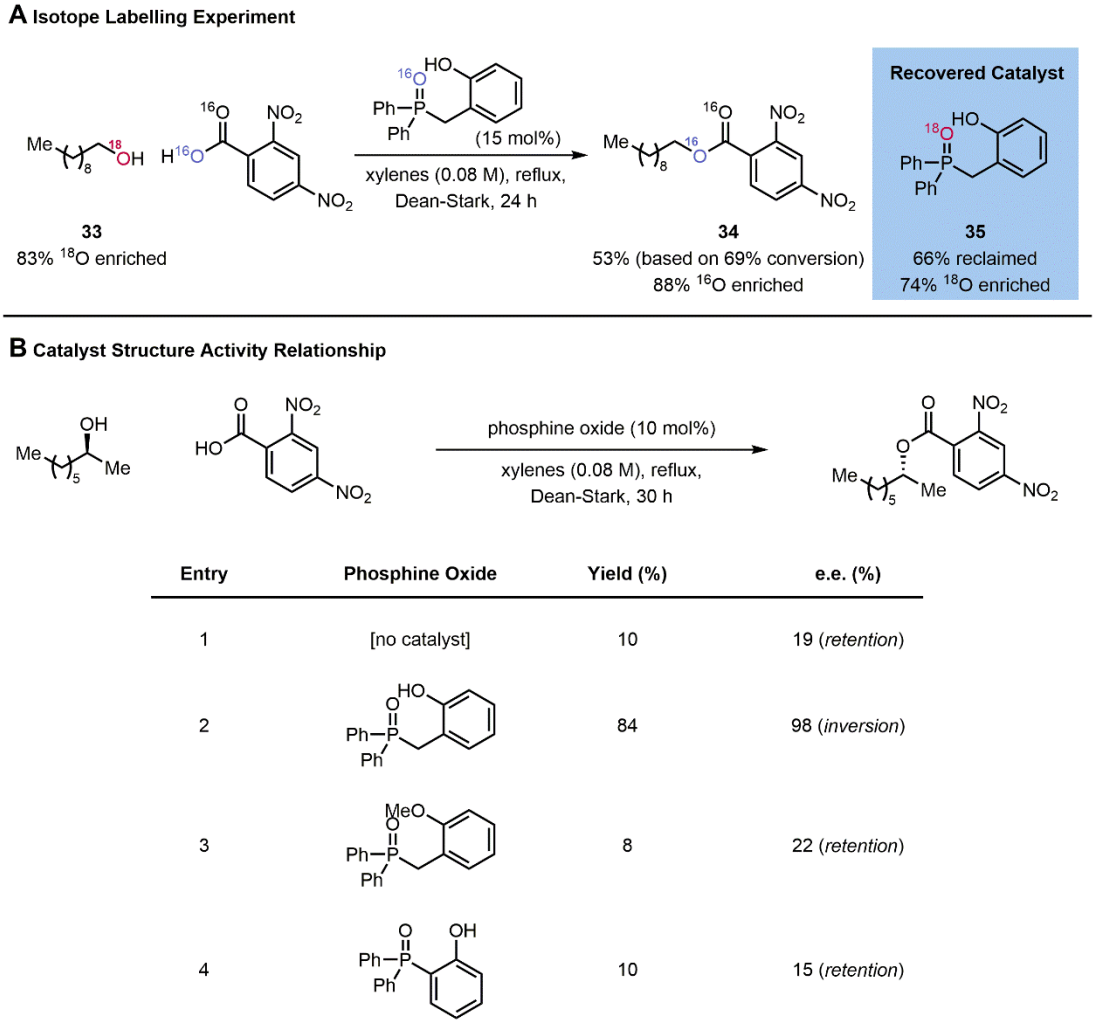


Figure 17. (A) An isotope labelling experiment showing transfer of oxygen from the alcohol substrate to the catalyst; Experiment was conducted by myself and Dr Keith Andrews; **(B)** Structure-activity relationships of the catalyst; The practical work associated with entry 4 was conducted by Dr Valentin Magné..

Catalyst Resting State. To determine the catalyst's resting state, we sought to monitor the coupling of 2-octanol and 2,4-dinitrobenzoic acid by *in situ* monitoring. However, since the reaction setup requires a Dean-Stark trap, *in situ* monitoring by NMR spectroscopy was not possible. Furthermore, attempts to monitor the reaction using FTIR (ReactIR) was impossible due to cross-signal interferences.

Analysis of *aliquots* of the reaction mixture by ^{31}P NMR and ^{1}H NMR revealed that only the phosphine oxide was observable (figure 18A and 18B), which suggests that the phosphine oxide is the resting state of the catalyst. However, since the

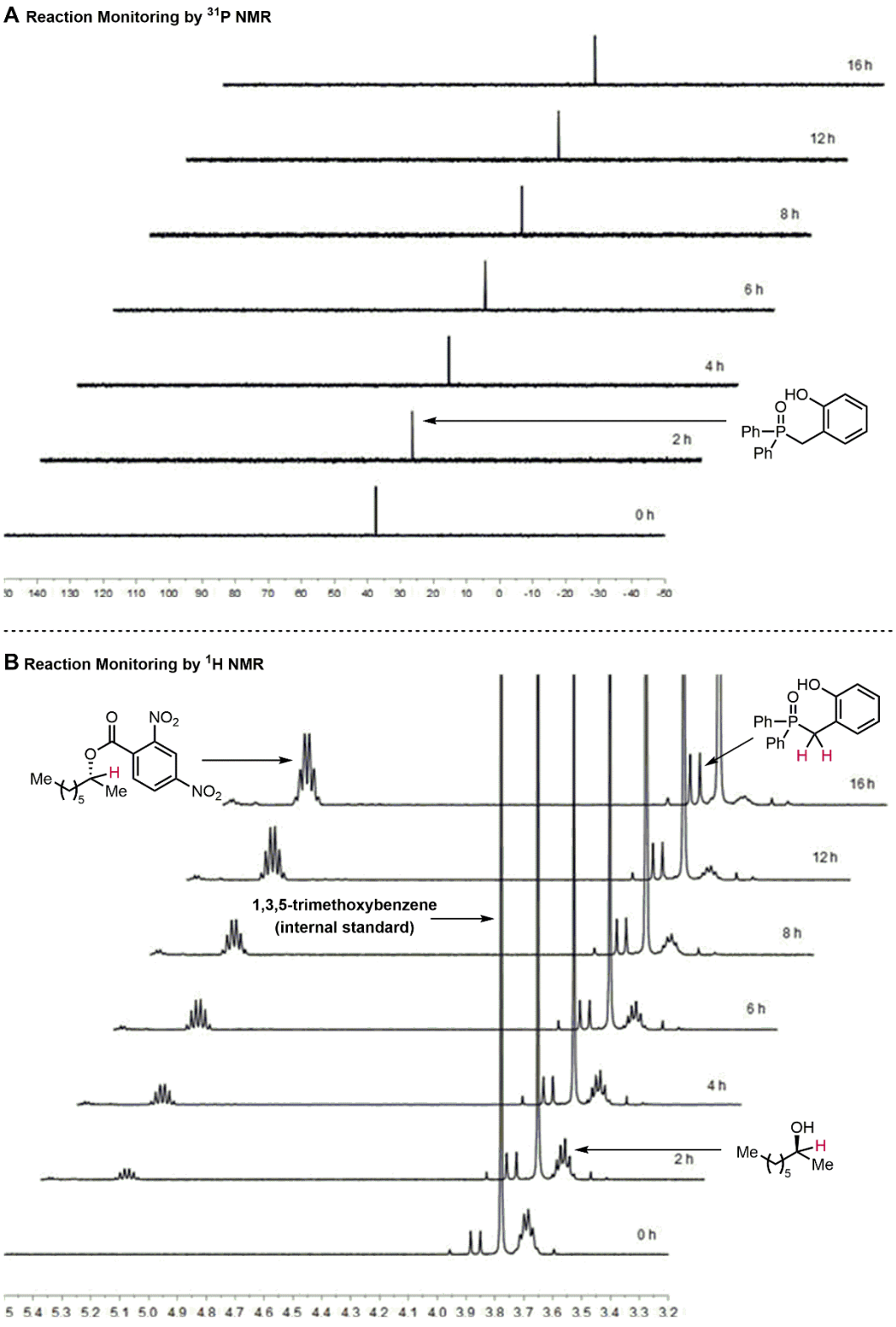


Figure 18. (A) ^{31}P NMR spectra of aliquots of the reaction mixture taken at specified intervals; **(B)** ^{1}H NMR of aliquots of the reaction mixture, shown between 5.5 ppm and 3.2 ppm, taken at specified intervals.

reaction could not be monitored directly, the possibility cannot be ruled out that the phosphine oxide is only observed as a result of the rapid hydrolysis of different catalytic intermediate upon preparation of the NMR sample. Therefore, if the catalyst resting state is highly hydrolytically sensitive, it is unlikely to be observed in this experiment.

2.2.4 Catalytic Sulfonation

The work described in the previous section describes the development and application of a catalytic Mitsunobu esterification using carboxylic acids as pro-nucleophiles. However, other pro-nucleophiles that are sufficiently acidic are compatible with the catalytic manifold. For example, previous work within the group has demonstrated that *p*-toluenesulfonic acid is a competent pro-nucleophile for the tolsylation of 1-decanol under the catalytic Mitsunobu reaction. This catalytic tosylation reaction was therefore further investigated.

Using aspects of the new reaction conditions developed for the catalytic esterification reaction, namely a reaction concentration of 0.08 M concentration, the tolysation of 1-decanol was shown to afford the corresponding 1-decyl

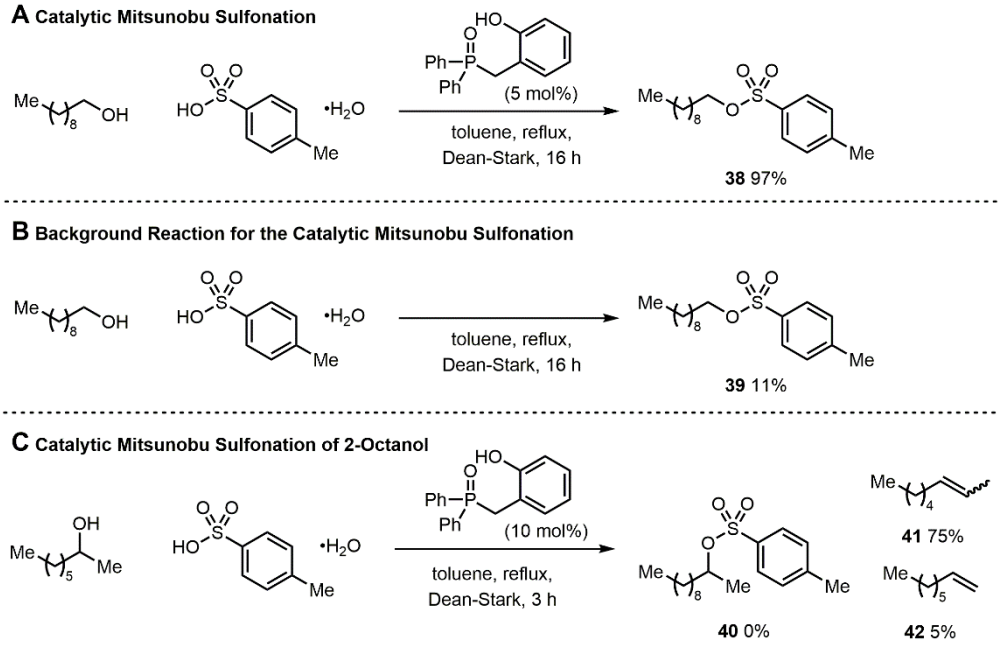
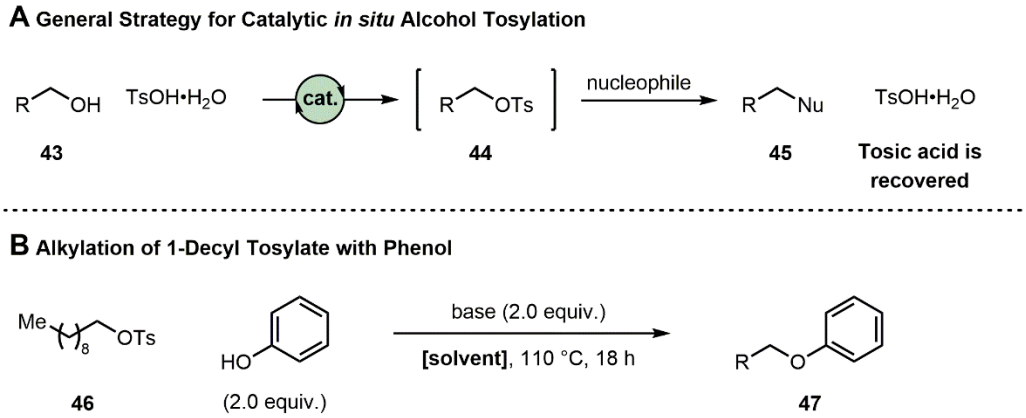


Figure 19. (A) The catalytic Mitsunobu tosylation of 1-decanol; **(B)** The background coupling of the 1-decanol and tosic acid; **(C)** The catalytic Mitsunobu tosylation of 2-octanol.



Entry	Base	Solvent	Conversion / (%)
1	K_2CO_3	toluene	33
2	K_2CO_3	1:1 toluene/DMF	n/a*
3	Cs_2CO_3	toluene	67
4	Cs_2CO_3	1:1 toluene/DMF	100

Figure 20. (A) An application of the catalytic Mitsunobu tosylation reaction for activating primary alcohols towards nucleophilic substitution *in situ*; **(B)** The optimisation of the alkylation of phenol with 1-decyl tosylate. *Decomposition of starting material observed.

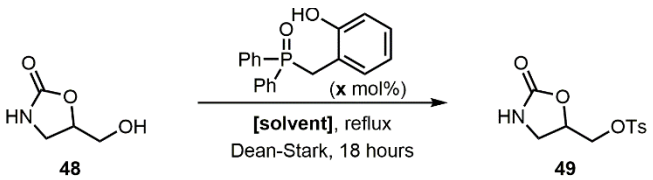
tosylate (**38**) with a near-quantitative yield after 16 hours, using 5 mol% catalyst (figure 19A). In the absence of a catalyst, the sulfonation reaction till occurs, albeit at a much slower rate, with only a 11% yield after 16 hours (figure 19B). Unfortunately, attempting to apply these conditions for the tosylation of 2-octanol, did not afford the desired 2-octyl tosylate product (figure 19C), instead giving the dehydration products, 2-octene (**41**) and 1-octene (**42**).

Encouraged by the high yield obtained for the tosylation of 1-decanol, this reaction was then investigated as a strategy for activating alcohols towards nucleophilic substitution *in situ* (figure 20A). Under this proposal a primary alcohol (**43**) and *p*-toluenesulfonic acid are coupled under the catalytic Mitsunobu conditions to form a sulfonate ester intermediate (**44**) *in situ*. Once the intermediate is fully formed, the addition of a nucleophile causes a nucleophilic displacement reaction, affording the product (**45**) and *p*-toluenesulfonate by-product. The significance of this strategy is that the *p*-toluenesolfonic acid by-product can be recovered and isolated by protonating the sulfonate by-product then recycled.

This strategy was investigated with the aim of using phenols as nucleophiles to access phenol ethers. This one-pot etherification protocol would provide a convenient and atom economical alternative to existing phenol alkylation methods and avoids the use of stoichiometric activating reagents such as *p*-toluenesulfonyl chloride and phosphorus tribromide. Firstly, the alkylation of phenol with 1-decyl tosylate was investigated and optimised (figure 20B). As the alkylation was required to be conducted in the same pot as the Mitsunobu step, the reactions were all conducted using toluene or toluene/DMF mixtures as solvents. The optimisation study revealed that caesium carbonate was the optimal base, and that a 1:1 mixture of toluene/DMF was the optimal solvent (entry 4). Under these conditions the phenol product was afforded with 100% conversion.

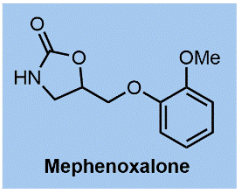
Having validated the elementary steps of the *in situ* activation-alkylation strategy, its application for the synthesis of the muscle relaxant mephenoxalone was investigated. which would involve the *in situ* tosylation of 5-(hydroxymethyl)-1,3-oxazolidin-2-one (**48**, table 6), followed by alkylation using guaiacol as a nucleophile. Unfortunately, this strategy was unsuccessful, as the catalytic tosylation of 5-(hydroxymethyl)-1,3-oxazolidin-2-one was slow, resulting in a poor NMR yield (table 5, entry 1). Increasing the catalyst loading and changing the solvent from toluene to xylenes had little effect on the yield (entries 2–3). This investigation was therefore abandoned.

Table 6. The attempted tosylation of 5-(hydroxymethyl)-1,3-oxazolidin-2-one using a catalytic Mitsunobu protocol in the synthesis of mephenoxalone.

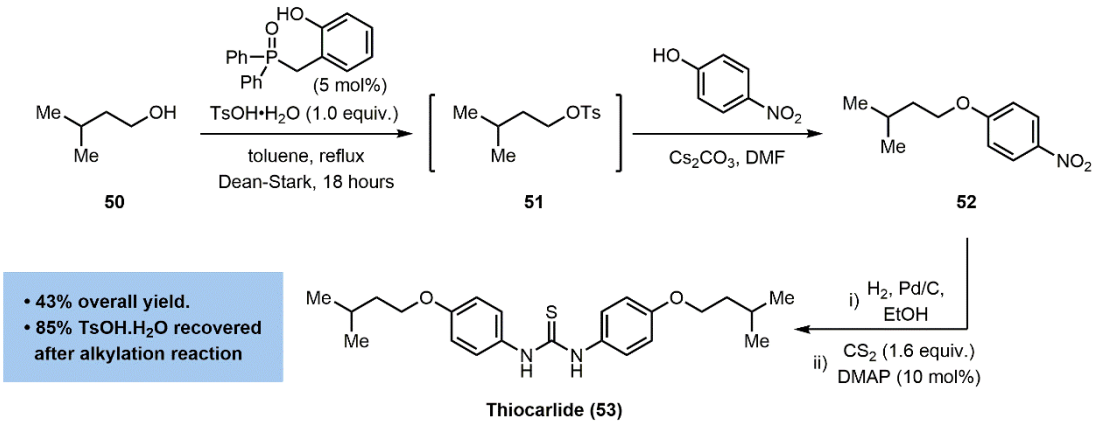


48 **49**

Entry	Solvent	Catalyst Loading (mol%)	NMR Yield (%)
1	toluene	10	8
2	toluene	20	13
3	xylenes	20	15



Mephenoxalone



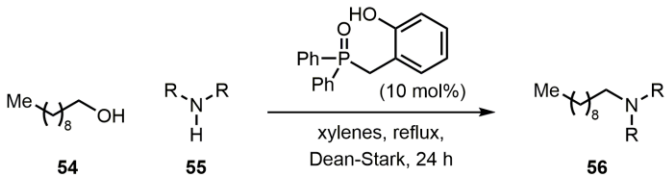
Scheme 3. A two-pot one four-step synthesis of thiocarlide, involving a catalytic Mitsunobu tosylation-nucleophilic substitution strategy.

An alternative active pharmaceutical ingredient was therefore targeted, and Thiocarlide, the anti-tuberculosis drug, was viewed as a promising candidate. A catalytic Mitsunobu reaction between isoamyl alcohol (**50**, scheme 3) and *p*-toluenesulfonic acid monohydrate afforded isoamyl tosylate (**51**) with quantitative conversion. The isoamyl tosylate was then reacted with 4-nitrophenol and ceasium carbonate *in situ* to afford the phenol ether product (**52**). As *p*-toluenesulfonic acid monohydrate was recovered from the crude reaction mixture with 87% recovery, the only stoichiometric waste generated in this two-step procedure was the waste associated with the ceasium carbonate base. Subsequent reduction and thiourea formation afforded Thiocarlide (**53**) in an overall yield of 43%.

2.2.5 Carbon–Nitrogen and Carbon–Sulfur Bond Formations

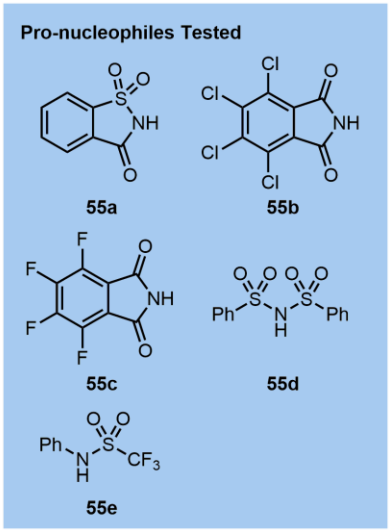
As carbon–nitrogen bond forming Mitsunobu reactions are highly valuable to synthetic organic chemists (see chapter 1, figure 13), the identification of suitable nitrogen-centred pro-nucleophile (**55**) for the catalytic Mitsunobu reaction was investigated (table 7). Several potential pro-nucleophiles, containing exceptionally acidic N–H bonds were screened for their capacity to undergo a Mitsunobu coupling with 1-decanol. The reaction conditions, which were adopted from the optimised conditions for the catalytic esterification reaction, consisted of heating 1-decanol and the nitrogen-centred pro-nucleophile for 24 hours in xylenes under reflux, using a Dean-Stark apparatus.

Table 7. A screen aiming to identify a compatible nitrogen-centred pro-nucleophiles for the catalytic Mitsunobu reaction.



54 55 56

Entry	Pro-nucleophile	NMR Yield (%)
1	55a	15
2	55b	0
3	55c	2
4	55d	54 (84 after 48 hours)
5	55e	2



Saccharin (**55a**) was shown to give the desired Mitsunobu coupling product, albeit as a low yield of 15% (table 7, entry 1). Unfortunately, 3,4,5,6-tetrachlorophthalimide (**55b**) and 3,4,5,6-tetrafluorophthalimide (**55c**) failed to react as pro-nucleophiles under the catalytic conditions (entries 2 and 3). Using dibenzenesulfonimide (**55d**) as a pro-nucleophile gave a 54% NMR yield after 24 hours, however the reaction had not reached full conversion. The reaction was therefore held for a further 24 hours, which resulted in an 82% NMR yield (entry 4). Lastly, 1,1,1-trifluoro-*N*-phenylmethanesulfonamide (**55e**) gave negligible yield of the desired product under the reaction conditions (entry 5).

Having identified dibenzenesulfonimide as a competent pro-nucleophile, the scope of this catalytic carbon–nitrogen bond forming reaction, with respect to the alcohol substrate was investigated (figure 21). 1-Decanol (**57a**) and 5-hexyn-1-ol (**57b**) were coupled with dibenzenesulfonimide (**55d**) under the catalytic Mitsunobu conditions with yields of 83% and 47% respectively. The utility of this reaction was demonstrated in the synthesis of the orthogonally protected diamine (**58c**) from an amino alcohol starting material (**57c**) with a yield of 88%. Unfortunately, geraniol (**57d**) decomposed under the reaction conditions, with no product formation observed, and sugar derivative **57e** failed to react. The reaction of (*S*)-(+)-2-octanol (**57f**) with dibenzenesulfonimide gave the corresponding substituted sulfonimide (**58f**) in a very poor yield, however, this

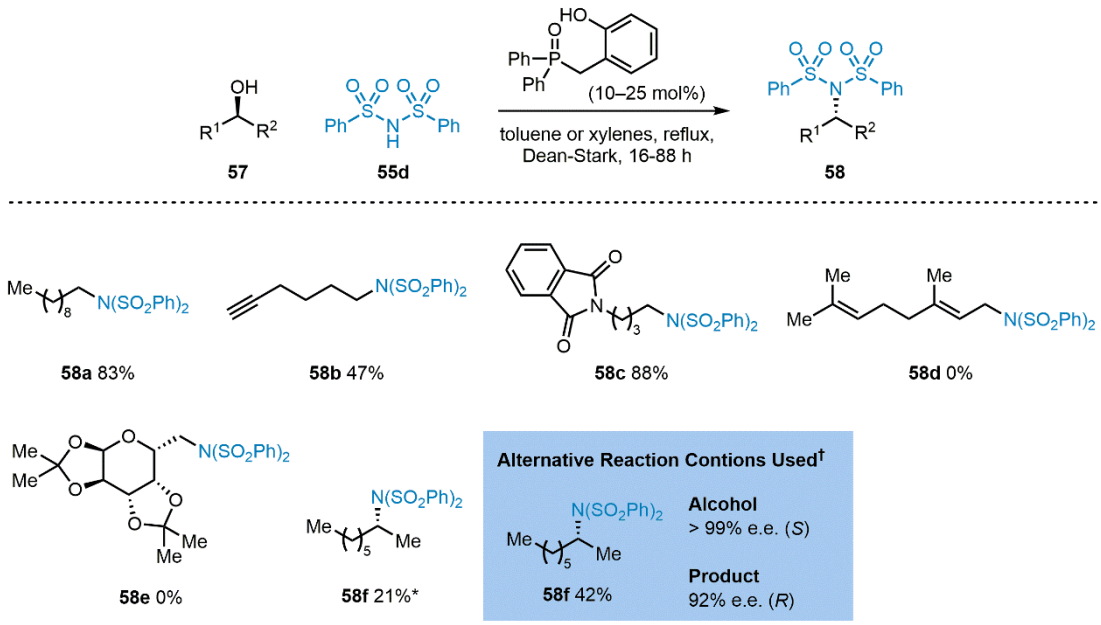


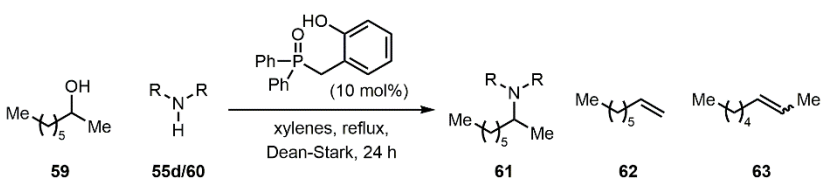
Figure 21. The substrate scope for the catalytic Mitsunobu sulfonimidation using dibenzenesulfinimide. *NMR yield after full consumption of alcohol. †Conditions: (*S*)-(+)-2-octanol (2.0 equiv.), dibenzenesulfonimide (1.0 equiv.), catalyst (25 mol%), toluene, reflux, 88h; Substrate **58b** was synthesisied by Dr Valentin Magné.

yield was increased to 42% by switching the solvent to toluene, doubling the alcohol stoichiometry and increasing the catalyst loading to 25%. This reaction went with inversion of stereochemistry, affording the product with 92% e.e. Critically, in the cases of 1-decanol and (*S*)-(+)-2-octanol, repeating the reaction in the absence of the catalyst gave 0% and 1% of product respectively, demonstrating that the catalyst is involved in the sulfonimide formation mechanism.

Upon examining the ^{1}H NMR spectrum of the reaction mixture of coupling of (*S*)-(+)-2-octanol and dibenzenesulfonimide, it was apparent that significant quantities of the dehydration products, 1-octene (**62**) and 2-octene (both *E* and *Z* isomers, **63**) were formed under the reaction conditions (table 8, entry 1). In seeking to improve the low yield of sulfonimide obtained for this coupling reaction, alternative nitrogen-centred pro-nucleophiles were tested for their capacities to engage in a carbon–nitrogen bond forming reaction with 2-octanol.

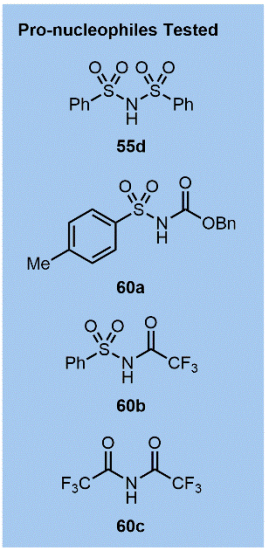
When benzyl tosylcarbamate (**60a**) was used as a pro-nucleophile, the only product observed was the transesterification product **64** (entry 2). This transesterification has previously been observed upon heating alcohols and

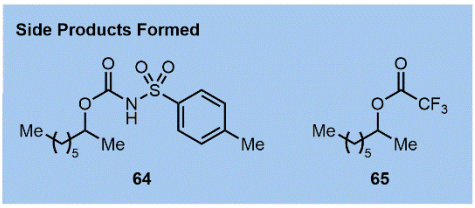
Table 8. A screen seeking to identify compatible nitrogen-centred pro-nucleophiles which can be coupled with 2-octanol under the catalytic Mitsunobu protocol.



59 55d/60 61 62 63

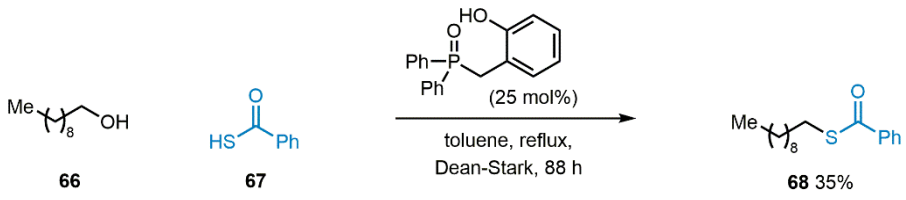
Entry	Pro-nucleophile	NMR Yield (%)	Terminal Alkene (%)	Internal Alkene (%)	Side Product (%)
1	55d	21	8	31	0
2	60a	0	0	0	55
3	60b	0	10	34	0
4	60c	0	0	0	59





substituted carbamates.[98] Using trifluoroacetylsulfonamide (**60b**) as a pro-nucleophile gave both 2-octene and 1-octene with yields of 34% and 10% respectively (entry 3). Finally, when bis-trifluoroacetylamine (**60c**) was used as a pro-nucleophile, the desired Mitsunobu coupling was not observed, and the pro-nucleophile reacted as a trifluoroacetyl donor, forming trifluoroacetoxy ester **65** instead (entry 4).

Looking to further expand the pro-nucleophile scope, the identification of a compatible sulfur-centred pro-nucleophile was investigated. Thioester **68** could thus be accessed by using thiobenzoic acid (**67**) and 1-decanol (**66**) as coupling partners, demonstrating the viability of carbon-sulfur bond formation. Unfortunately, the yield of this reaction was low at 35% (scheme 4).



66 67 **68** 35%

Scheme 4. The use of thiobenzoic acid as a pro-nucleophile in the catalytic Mitsunobu reaction enabling the formation of a carbon-sulfur bond.

2.2.6 Catalyst Optimisation Studies

The work described in the foregoing section describes the development and applications of a catalytic Mitsunobu reaction using a single phosphine oxide catalyst. During these investigations, it became apparent that this protocol had major limitations, namely that the pro-nucleophile was required to be especially acidic (pKa (H_2O) ≲ 3.0) and high temperatures were required for catalysis to occur. A potential way to alleviate this limitation is to design and implement rational structural modifications to the phosphine oxide catalyst. If distinctive structure-activity relationships can be identified, then catalysts with better catalytic activities can potentially be accessed.

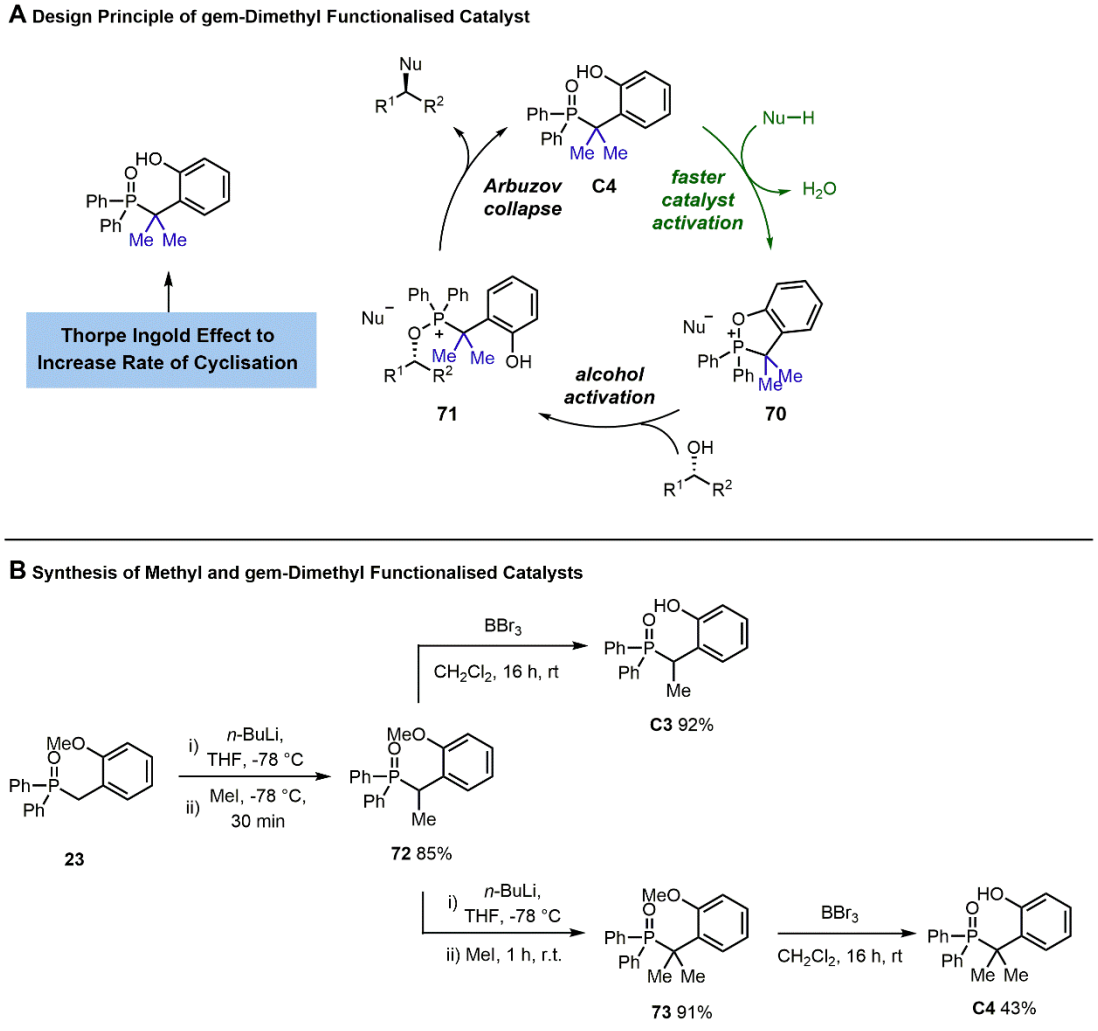


Figure 22. (A) A proposed geminal-dimethyl modification to the catalyst structure and it's potential effects on the catalytic cycle; **(B)** The synthesis of phosphine oxides C3 and C4 via an α-alkylation of **23**, followed by deprotection.

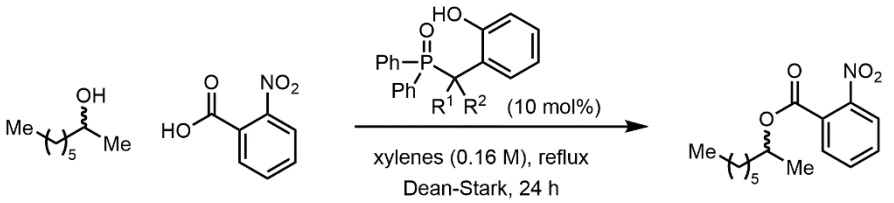
Firstly, a group of phosphine oxides, based on functionalising the structure of catalyst **C2**, were synthesised and their catalytic activities evaluated. The first round of modification comprised functionalising the methylene unit separating phosphorus atom and the phenol moiety with methyl groups (figure 22A). This modification was designed to increase the rate of the internal dehydration step in the catalytic cycle by the Thorpe-Ingold effect imposed by the methyl groups. Phosphine oxide targets **C3** and **C4** were therefore synthesised and evaluated for their catalytic activities.

The synthesis of phosphine oxides **C3** and **C4** was achieved by the deprotonation then alkylation of intermediate **23** using *n*-butyllithium followed by iodomethane, yielding monomethylated phosphine oxide **72** with a yield of 85% (figure 22B). Subsequent methylation of **72**, using *n*-butyllithium, then iodomethane afforded gem-dimethyl phosphine oxide **73** with a yield of 91%. Deprotection of phosphine oxides **73** and **73**, using boron tribromide, yielded the desired phosphine oxides **C3** and **C4** with yields of 92% and 43% respectively.

To quantitatively compare the methylated phosphine oxide's catalytic activities, their capacities to catalyse a Mitsunobu esterification reaction were evaluated (table 9). Specifically, the phosphine oxides (10 mol%) were tested for their abilities to facilitate the Mitsunobu coupling of 2-octanol and 2-nitrobenzoic acid. The reaction conditions used xylenes (at reflux) as the reaction solvent and the reactions were conducted using a Dean-Stark apparatus. After 24 hours the reaction was stopped, and the NMR yield was determined, using an internal standard as a reference.

Under these reaction conditions, the unfunctionalized catalyst **C2** was able to catalyse the Mitsunobu coupling of 2-octaol and 2-ntrobenzoic acid with a yield of 39% after 24 hours (table 9, entry 2). In the absence of phosphine oxide, the background esterification of 2-octanol and 2-nitrobenzoic acid occurred with 8% yield (entry 1). The methylated phosphine oxides **C3** and **C4**, however, gave diminished yields of 30% and 10%, compared with **C2**. Moreover, phosphine oxide **C4** gave no rate enhancement compared to the background reaction.

Table 9. The evaluation of phosphine oxides **C3** and **C4** as catalysts in the Mitsunobu esterification reaction.



Entry	R^1	R^2	NMR yield / (%)	Alcohol Remaining / (%)
1	No catalyst (control)		8	85
2	H	H	39	46
3	Me	H	30	59
4	Me	Me	10	64

The ^{31}P NMR shifts of phosphine oxides **C3** and **C4** are centred at 41.6 ppm and 47.6 ppm respectively. These figures suggest that there is an increased electron density on the phosphorus atom compared with **C2** (38.3 ppm), which likely stems from the increased hyperconjugation afforded by the methyl groups. This increased electron density at the phosphorus reduces the phosphoryl bond dipole moment, lowering the electrophilicity of the phosphorus centre. This presumably slows the nucleophilic ring closing activation step, thus hindering catalyst turnover. Additionally, the increased steric crowding around the phosphorus atom of the oxyphospholene catalytic intermediate (**70**, figure 25A) could result in a slower reaction with the alcohol, thus slowing the catalytic cycle.

Having observed the profound effect that the electronic nature of the phosphorus atom had on catalytic activity, the possibility of fine tuning of the phosphorus centres electron richness, leading to improved catalytic activity, was investigated. The phenyl groups bonded to the phosphorus were therefore functionalised at the para position, with groups of varying electron withdrawing/donating abilities.

The Reed and Scheyler bonding model for phosphine oxides (see chapter 1, figure 2B) predicts that electron donating groups increase the energy of the P–C σ* orbitals, which are used as acceptor orbitals for back-donation. This would result in less back-donation and therefore a weaker phosphoryl bond, which would presumably aid the dehydrative catalyst activation step. However,

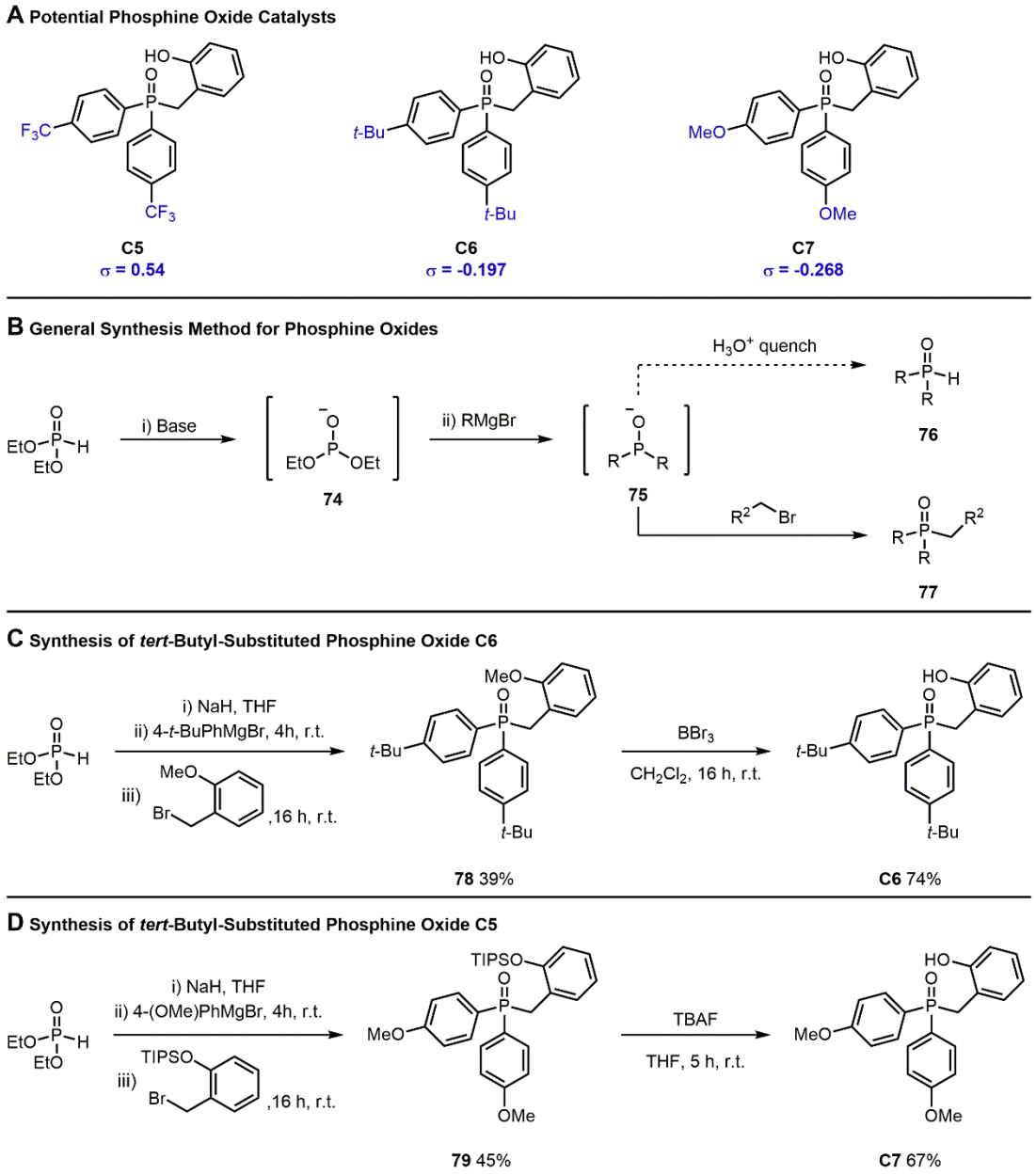


Figure 23. (A) Proposed phosphine oxides with Hammett σ values of the added *para*-substituents.; **(B)** A new one-pot synthesis strategy towards phosphine oxides **C6** and **C7**; **(C)** The synthesis of **C6** using the one-pot three-component reaction; **(D)** The synthesis of **C7** using the one-pot three--component reaction; Catalyst **C5** was synthesised by Dr Jan Saska.

electron withdrawing groups would presumably withdraw electron density from the phosphorus, thus further polarising the phosphoryl bond, which could encourage nucleophilic attack from the internal phenol nucleophile.

To probe some structure-activity relationships, catalysts **C5**, **C6** and **C7** which contained substituents of varying Hammett σ values, were targeted (figure 23A).

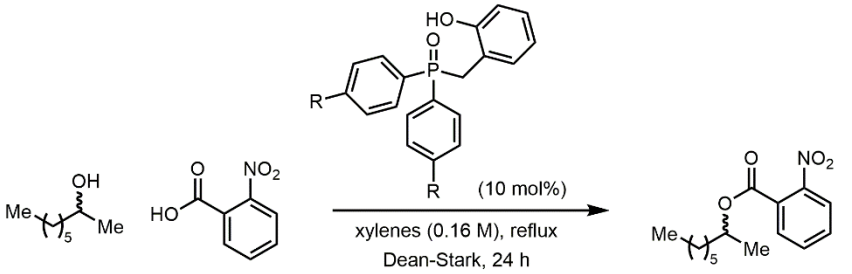
Fortunately, substantial quantities of catalyst **C5** had been previously synthesised within the group and was available to use. For the synthesis of catalysts **C6** and **C7**, we considered the previously established alkylation of the relevant diarylphosphine oxide (see scheme 1). Unfortunately, attempts to synthesise di(paramethoxyphenyl)phosphine oxide, the corresponding diarylphosphine oxide for the synthesis of phosphine oxide **C5**, was impeded by the high polarity and poor solubility of di(paramethoxyphenyl)phosphine oxide. This intermediate was difficult to purify using common purification techniques, and as such, this synthetic approach was abandoned.

The conventional synthesis of diarylphosphine oxides involves deprotonating diethylphosphite to yield the phosphite anion **74** (figure 23B), followed by nucleophilic substitution of the ethoxy substituents with a Grignard reagent.[99] Usually, intermediates such as **75**, are then protonated to yield the corresponding diarylphosphine oxides (**76**), however phosphinite intermediates such as **75** are known to undergo alkylation to afford tertiary phosphine oxides such as **77**.[99] We therefore theorised that phosphine oxides **C6** and **C7** could be synthesised using a one-pot strategy, from diethylphosphite.

Using this synthesis strategy, the 4-tertbutylphenyl groups and 2-methoxybenzyl group were installed sequentially to diethylphosphite to afford to methoxy protected intermediate **78** in a single-pot reaction (figure 23C). The poor yield (39%) of this step is perhaps unsurprising considering the multi-step nature of the synthesis sequence. Subsequent deprotection of intermediate **78** using boron tribromide afforded phosphine oxide **C6** with a yield of 74%. A re-design of this synthetic route was required to synthesise phosphine oxide **C7**, as the boron tribromide deprotection step would be incompatible with the required methoxy groups. An alternative phenol protecting group was therefore sought. TIPS-protected phosphine oxide **79** was synthesised with a 45% yield. Deprotection of intermediate **79** with tetrabutylammonium fluoride afforded the phosphine oxide **C7** with a yield of 67%.

Having synthesised the phosphine oxides, their activities were tested using the previously employed reaction conditions, the results of which are shown in

Table 10. The evaluation of phosphine oxides **C5**, **C6** and **C7** as catalysts in the Mitsunobu esterification reaction.



Entry	R	NMR yield / (%)	Alcohol Remaining / (%)
1	No catalyst (control)	8	85
2	H	39	46
3	OMe	44	45
4	*t*-Bu	42	43
5	CF_3	34	56

table 10. The yields after 24 hours show a well-defined structure-activity relationship. Electron donating groups, such as methoxy- and *tert*-butyl (entries3 and 4) were shown to enhance catalyst activity. Conversely, electron poor groups (CF_3, entry 5) resulted in poorer catalyst activity. These results support the view that electron donating groups, reduces back-donation in the phosphoryl bond, weakening the bond and this effect seemingly increases catalyst activity.

Encouraged by these results, another structure-activity relationship, which involved altering the electron richness of the phenol ring of the catalyst, by changing the substituent para to the hydroxyl group was investigated (figure 24A). By varying electron donating/withdrawing abilities of the substituents allowed for the nucleophilicity and acidity of the phenol to be tuned. Electron donating groups would enhance the nucleophilicity of the phenol which may encourage the required nucleophilic attack, on to the phosphoryl group, in the catalyst activation step. Similarly, a more acidic phenol, could potentially result in a faster rate of proton transfer from the phenol to the phosphine oxide, which is a requirement for the catalyst activation step.

The synthesis of the trifluoromethyl- and fluoro-substituted analogue began with the deoxychlorination of commercially available alcohols **80** and **82**, with yields of 91% and 57% respectively (figures 24B and 24C). The alkylation of

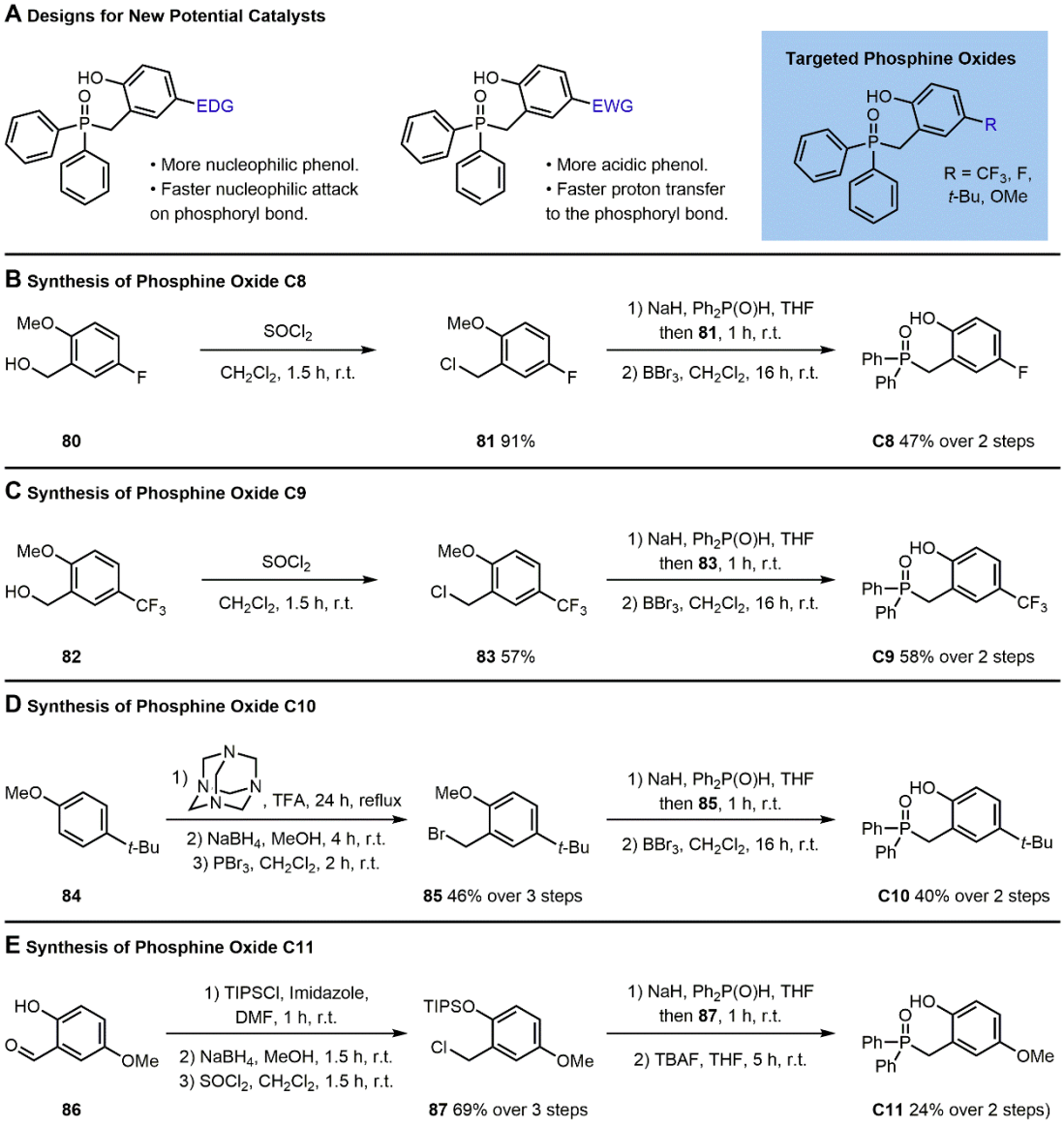
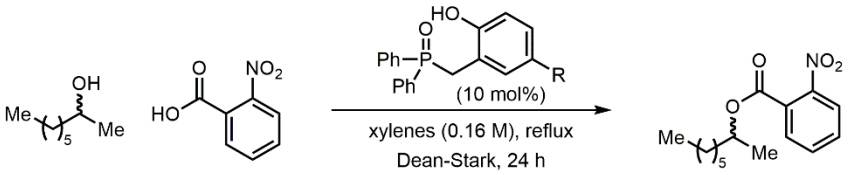


Figure 24. (A) Proposed phosphine oxides aiming to probe the effect of phenol nucleophilicty on catalyst activity; **(B)** The synthesis of **C8** by the alkylation of diphenylphosphine oxide; **(C)** The synthesis of **C9** by the alkylation of diphenylphosphine oxide; **(D)** The synthesis of **C10** by the alkylation of diphenylphosphine oxide; **(E)** The synthesis of **C11** by the alkylation of diphenylphosphine oxide.

diphenylphosphine oxide using benzyl chlorides **81** and **83**, followed by deprotection of the methoxy group using boron tribromide afforded catalysts **C8** and **C9** with overall yields of 47% and 58% respectively.

For the synthesis of the *tert*-butyl-substituted analogue, the analogous alcohol starting material was not available from commercial sources. The required

Table 11. The evaluation of phosphine oxides **C8**, **C9**, **C10** and **C11** as catalysts in the Mitsunobu esterification reaction.



Entry	R	NMR yield / (%)	Alcohol Remaining / (%)
1	No catalyst (control)	8	85
2	H	39	46
3	OMe	36	62
4	*t*-Bu	40	52
5	F	36	61
6	CF_3	35	58

benzyl alcohol was therefore accessed by a Duff reaction of 4-*tert*-butylanisole (**84**, figure 24D), which installed the requisite aldehyde functional group *ortho* to the methoxy group. The aldehyde was subsequently reduced with sodium borohydride to access the alcohol. A subsequent deoxybromination using phosphorus tribromide afforded methoxy-protected benzyl bromide **85** with a 46% yield over the three steps. Alkylation of diphenylphoshine oxide, using benzyl bromide **85** followed by a boron tribromide-mediated deprotection yielded the desired phosphine oxide **C10** with an overall yield of 40%.

To synthesise the methoxy-substituted analogue, 5-methoxysalicylaldehyde was firstly protected with chlorotriisopropylsilane (TIPSCl), then the TIPS-protected phenol was reacted with sodium borohydride to access the requisite benzyl alcohol. The benzyl alcohol was then reacted with thionyl chloride to afford benzyl chloride **87** with a yield of 69% over three steps. The alkylation of diphenylphosphine oxide with benzyl chloride **87**, followed by TIPS-deprotection using tetrabutylammonium fluoride afforded methoxy-substituted phosphine oxide **C11** with a yield of 24% over 2 steps (figure 24E).

With the synthesised phosphine oxides in hand, their activities were assessed, using the previously employed reaction conditions, the results of which are shown in table 11. The distribution of yields for the tested phosphine oxide catalysts was narrow, however, both highly electron-donating (OMe, entry 3) and

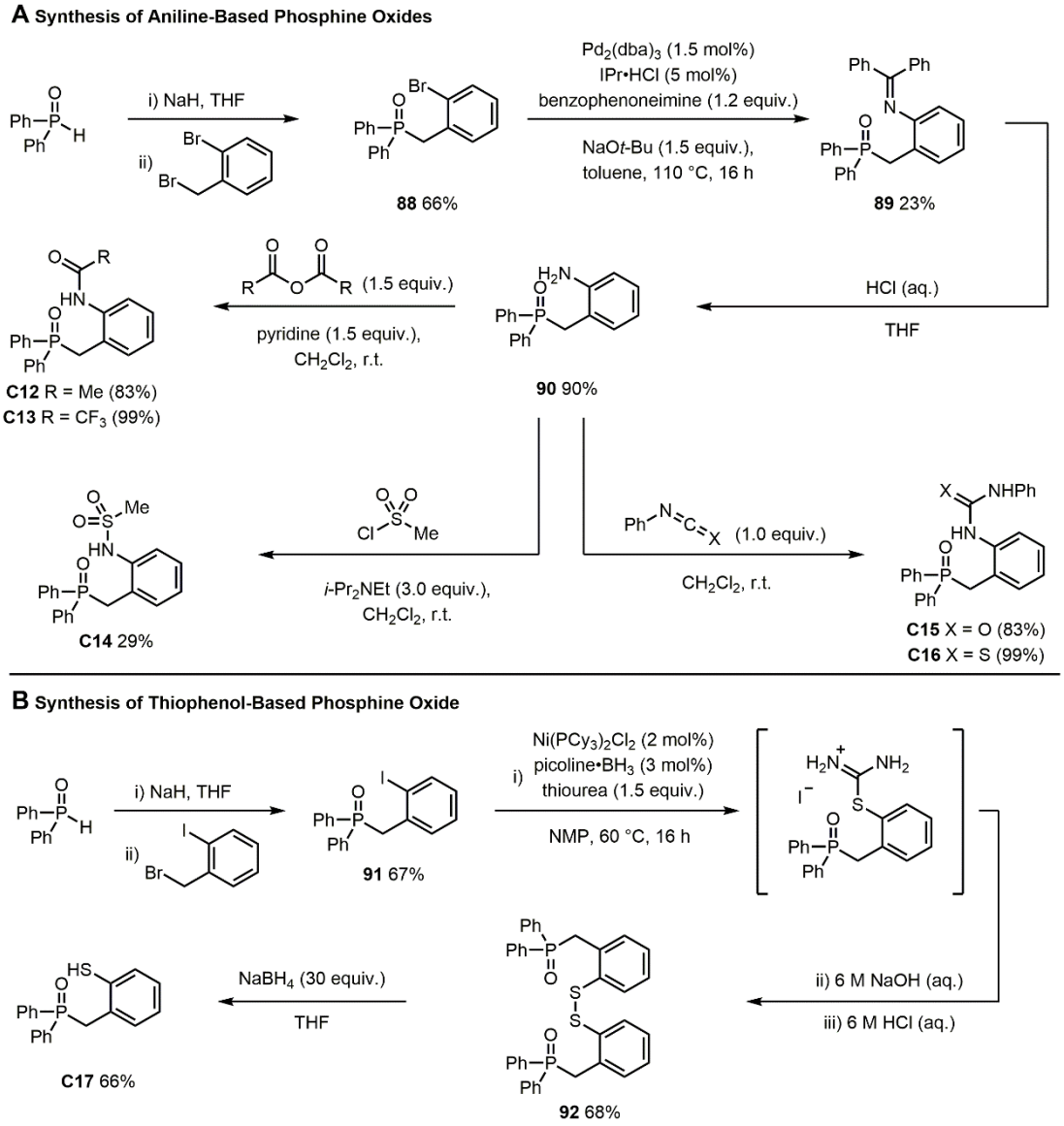


Figure 25. (A) The synthesis of phosphine oxides, **C12**, **C13**, **C14**, **C15** and **C16** through a common aniline intermediate (**90**); The synthesis of phosphine oxide **C17** through the cross-coupling of a hydrogen sulfide surrogate.

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electron withdrawing (CF_3, entry 6) substituent were shown to be detrimental to catalytic activity. The *tert*-butyl-substituted phosphine oxide **C10** (entry 4), however gave a comparable yield to the unfunctionalized catalyst **C2** (entry 2).

Since the nucleophilicity of the phenol is known to subtly affect the activity of the catalyst (see table 11), changing the phenol nucleophile to nitrogen- or sulfur-based nucleophiles was investigated. To test this hypothesis, numerous aniline and thiophenol derivatives of catalyst **C2** were synthesised and tested.

The synthesis of aniline derivatives **C12–C16** was achieved by an initial alkylation of diphenylphosphine oxide with 2-bromobenzyl bromide to afford tertiary phosphine oxide **88** with a 66% yield (figure 25A). The aryl bromide was then subjected to a Buchwald-Hartwig amination using benzophenone imine—a common ammonia surrogate[100]—to form substituted benzophenoneimine **89**, which was hydrolysed under acidic conditions to reveal the analogous aniline with an overall yield of 21%.

The aniline intermediate was then derivatised into amide, sulfonamide, urea and thiourea derivatives. The reaction of aniline **90** with acetic anhydride and pyridine as the base afforded acetylamide derivative **C12** with a yield of 83%. Similarly, the reaction of aniline **90** with trifluoroacetic anhydride and pyridine afforded trifluoroacetamide derivative **C13** with a quantitative yield. Lastly, the reaction of aniline **90** with methane sulfonyl chloride and Hünig's base afforded sulfonamide derivative **C14** with a poor yield of 29%.

Since urea and thiourea-containing organic molecules are known to activate substrates hydrogen bond donation in organocatalysis,[101] the possibility of using a catalyst analogue, with contained thiourea or urea for both activating the phosphoryl group and acting as internal nucleophile was explored. To synthesise these targets, aniline **90** was reacted with phenyl isocyanate and phenyl isothiocyanate urea derivative **C15** and thiourea derivative **C16** were obtained with yields of 83% and 99% respectively.

The thiophenol analogue of catalyst **C17** was also viewed as a promising target. This catalyst design was intriguing as thiophenols are more nucleophilic than their phenol counterparts, but thiophenolates are better leaving groups than phenolates and these properties may be well suited towards the requirements of the catalytic cycle.

The synthesis of thiophenol analogue **C17** was achieved by alkylating diphenylphosphine oxide with 2-iodobenzyl bromide to form tertiary phosphine oxide **91**. This intermediate was then subjected to a cross-coupling reaction with a hydrogen sulfide surrogate. Initial attempts to apply Peñéñory's copper-catalysed cross-coupling of potassium thioacetate with aryl iodides[102] was

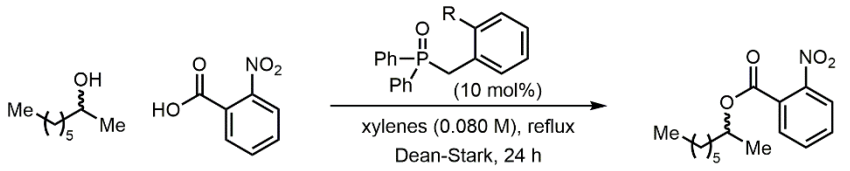
unsuccessful, giving very poor conversion to product. The application of the Ball group's nickel-catalysed cross-coupling of thiourea and aryl iodides,[103] however successfully furnished the desired isothiouronium product, however attempts to hydrolyse this intermediate *in situ* to its analogous thiophenol afforded the disulfide product **92** instead. Treating disulfide **92** with a vast excess of sodium borohydride in de-gassed tetrahydrofuran afforded the corresponding thiophenol derivative **C17** with an overall yield of 45% (figure 25B).

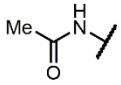
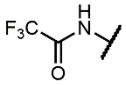
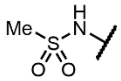
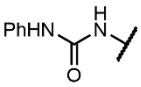
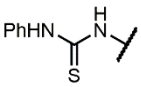
Firstly, the catalytic activities of phosphine oxides **C12**, **C13**, **C14**, **C15** and **C16**, which all contain a nitrogen-centred internal nucleophile, were tested. The reaction conditions used to test these catalysts differed from the conditions used in tables 8–10 and were run with a lower reaction concentration. This was because lower dilutions have previously resulted in greater stereochemical inversion (see page 84) and secondly, under more dilute conditions, less mass of phosphine oxide is required to test its capacity to catalyse a Mitsunobu reaction. Under the reaction conditions, each phosphine oxide containing a nitrogen-centred nucleophile failed to catalyse the Mitsunobu esterification of 2-octanol and 2-nitrobenzoic acid to any greater extent than the background esterification reaction (table 10, entries 3–7). Furthermore, using thiophenol-containing phosphine oxide (entry 8) as the catalyst resulted very poor conversion after 24 hours.

Finally, some of the intermediates accessed on the route towards phosphine oxides **C12**–**C17** were tested. When the phenol nucleophile is replaced with analogous aryl bromide (**88**) and aryl iodide (**91**) no catalytic Mitsunobu esterification activity was observed, beyond the background esterification reaction (entries 10–11). Furthermore, the phosphine oxide afforded from replacing the phenol moiety with an analogous aniline (**90**) also gave no catalytic activity, beyond the background esterification reaction (entry 9).

The late stage derivatisation strategy used for the synthesis of the various aniline-based phosphine oxides (**C12**–**C16**) enabled facile access to numerous phosphine oxides from a common aniline intermediate. Since *para*-substitution of the innocent phenyl rings of the catalyst was shown to positively affect catalyst

Table 12. The evaluation of phosphine oxides **C12**, **C13**, **C14**, **C15**, and **C16** as catalysts in the Mitsunobu esterification reaction. Intermediates **88**, **90** and **91** are also evaluated.



Entry	R	NMR yield / (%)	Alcohol Remaining / (%)
1	No catalyst (control)	6	93
2		36	58
3		3	97
4		4	94
5		7	90
6		11	86
7		5	79
8		3	96
9		2	96
10		4	88
11		4	95

activity (see table 10), an investigation into introducing various groups by a similar late stage derivatisation strategy was investigated.

This was achieved using a procedure described by Tartinov and co-workers[104] whereby a solution of 2-hydroxybenzyl alcohol and triethylphosphite in toluene was heated for 64 hours to form cyclic phosphonate **93** (figure 26A). This phosphonate intermediate was then reacted with various Grignard reagents to access analogues of catalyst **C2** with alternative substituents in the R position. Using this method, phosphine oxides containing ethyl (**C18**) 2-methoxyphenyl-

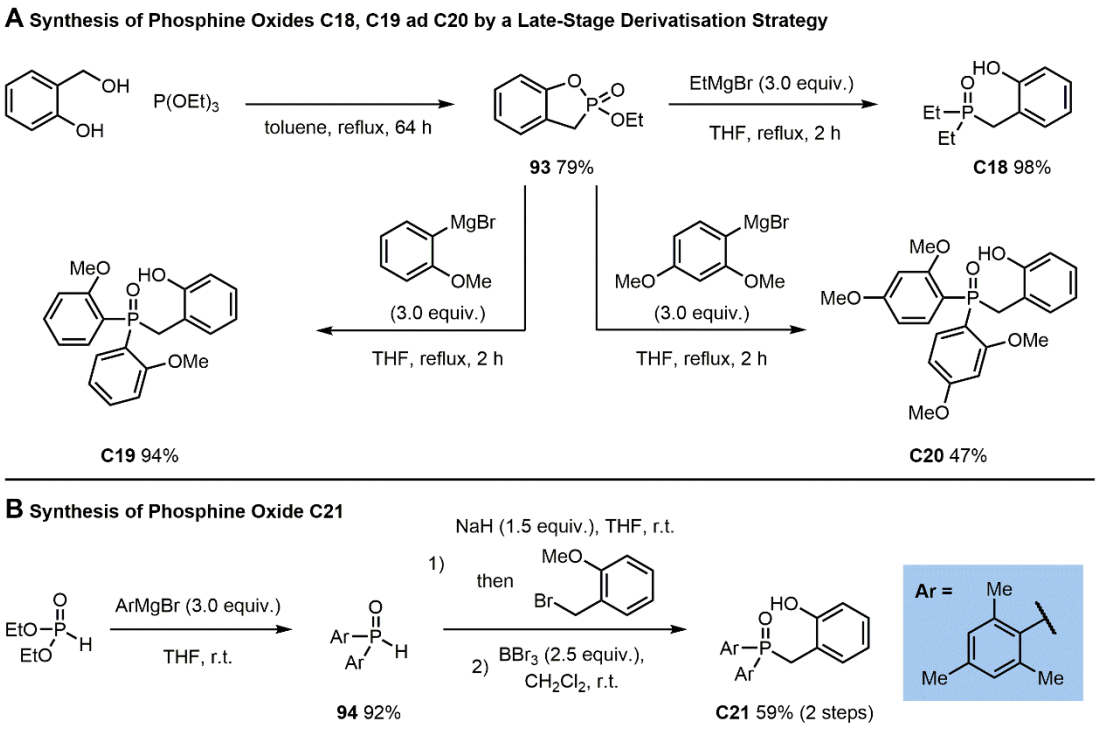


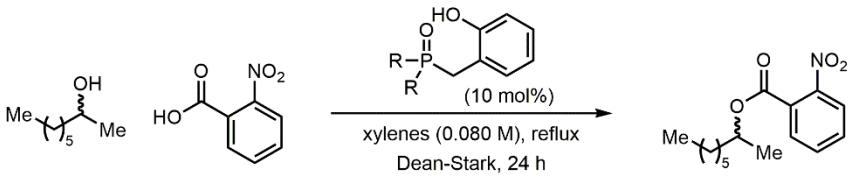
Figure 26. (A) The synthesis of phosphine oxides **C18**, **C19** and **C20** by the derivatisation of common intermediate **93**; **(B)** The synthesis of phosphine oxide **C21** through the alkylation of dimesitlyphosphine oxide.

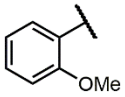
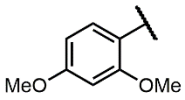
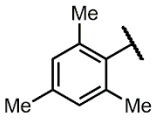
(**C19**) and 2,4-dimethoxyphenyl- (**C20**) groups in place of the usual phenyl groups with yields of 98%, 94% and 47% yield, respectively.

Attempts to synthesise mesityl-substituted phosphine oxide **C21** using this method was unsuccessful, presumably due to the high steric bulk of the required 2-mesitylmagnesium bromide Grignard reagent, and the poor reactivity of the electrophile. This phosphine oxide was instead synthesised *via* the *P*-alkylation of dimesitylphosphine oxide, followed by a deprotection of the methoxy group using boron tribromide with an overall yield of 59% (figure 26B).

With the new phosphine oxides in hand, their capacities to catalyse the Mitsunobu esterification of 2-octanol and 2-nitrobenzoic acid were evaluated (table 13). Ethyl-substituted phosphine oxide **C18** (entry 3) gave modest catalytic activity, however the catalytic activity was inferior to parent phosphine oxide **C2** (entry 2). When the phenyl group is replaced by electron-rich aromatic groups,

Table 13. The evaluation of phosphine oxides **C18**, **C19**, **C20** and **C21** as catalysts in the Mitsunobu esterification reaction.

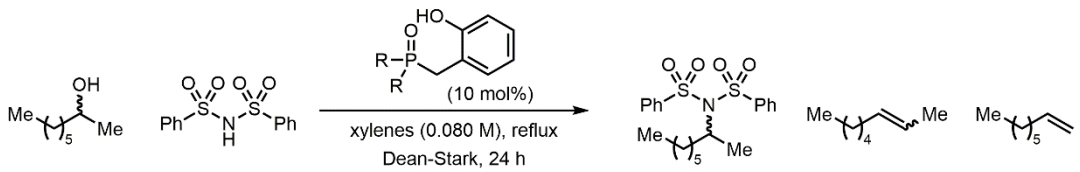


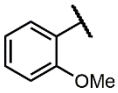
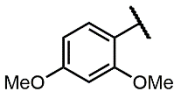
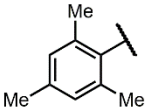
Entry	R	NMR yield / (%)	Alcohol Remaining / (%)
1	No catalyst (control)	6	93
2		36	58
3		24	72
4		45	57
5		42	54
6		17	80

namely 2-methoxyphenyl (**C19**, entry 4) and 2,4-dimethoxyphenyl (**C20**, entry 5) groups, a subtle improvement in catalytic activity is observed, compared to phosphine oxide **C2**. Lastly, mesityl-substituted phosphine oxide **C21** gave modest catalytic activity but was substantially inferior to catalyst **C2**.

The capacity of these phosphine oxides to catalyse the Mitsunobu coupling of 2-octanol and dibenzenesulfonimide was also investigated (table 14). In the absence of any phosphine oxide catalyst, no product formation is observed (entry 1). As previously established (see **58f**, figure 21) when catalyst **C2** was used, after 24 hours the substituted sulfonimide product was obtained with 21% yield and the formation of 2-octene and 1-octene accounting for the 31% and 8% of the yield respectively (entry 2). Ethyl-substituted catalyst (**C18**) afforded the sulfonimide product with a reduced 18% yield with the dehydration products, 2-octene and 1-octene, accounting for the 15% and 4% of the yield respectively (entry 3).

Table 14. The evaluation of phosphine oxides **C18**, **C19**, **C20** and **C21** as catalysts in the Mitsunobu sulfonimidation reaction.



Entry	R	NMR yield / (%)	Internal Alkene / (%)	Terminal Alkene / (%)	Alcohol Remaining / (%)
1	No catalyst (control)	0	0	0	99
2		21	31	8	35
3		18	15	4	59
4		17	14	3	35
5		14	25	6	55
6		0	0	0	92

When phosphine oxides **C19** and **C20** were tested, the substituted sufonimide products were obtained with similar yields of 17% and 14% respectively with significant concomitant formation of 1-octene and 2-octene (entries 4 and 5). Lastly, mesityl-substituted catalyst (**C21**) was seemingly too sterically encumbered to be catalytically active and gave a 0% yield for both the sulfonimide and dehydration products (entry 5). The alcohol starting material was the major observable species in the reaction mixture.

2.3 Conclusions

The work presented in this chapter describes an organocatalytic, reagent-free Mitsunobu reaction which is founded on an unprecedented redox-neutral organophosphorus catalytic cycle. This catalytic strategy has been demonstrated to enable the Mitsunobu coupling of pro-nucleophiles, including carboxylic acids, sulfonic acids, sulfonimide and thiocarboxylic acids, with primary and secondary alcohols. An organocatalytic Mitsunobu Inversion protocol has also been developed and applied to the large-scale synthesis of the unnatural epimer β-cholestanol. Additionally, a catalytic sulfonation has been developed as a way of activating alcohols in situ towards nucleophilic substitution. This protocol was applied to the streamlining of the synthesis of the anti-tuberculosis active pharmaceutical ingredient, thiocarlide.

Catalyst modification studies, aiming to identify well-defined structure-activity trends, have identified five phosphine oxides with improved catalytic activities (figure 27B). Notably, improvement in catalyst activity can be attained from replacing the innocent phenyl rings of the parent catalyst with electron-rich aromatic groups. This was especially prominent when the phenyl groups were replaced by analogous 2-methoxyphenyl, 4-methoxyphenyl and 2,4-dimethoxyphenyl groups which were the most active catalysts to date.

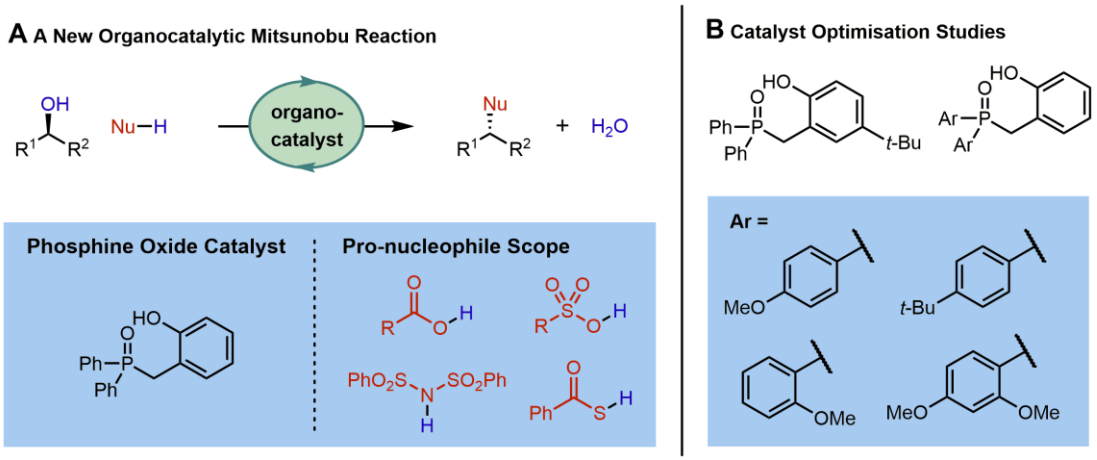


Figure 27. (A) An unprecedented phosphine oxide-catalysed Mitsunobu reaction; **(B)** Catalyst optimisation studies have identified five phosphine oxides with improved catalytic activities.

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Chapter 3

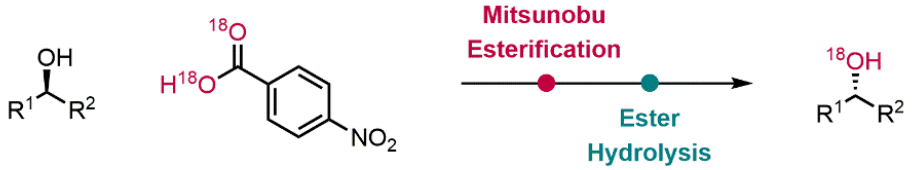
Synthesis of ^{18}O-Labelled Alcohols from Unlabelled Alcohols Using a Mitsunobu Esterification-Based Strategy

Abstract

^{18}O-labelled alcohols are often used as tools for studying reaction mechanisms in synthetic organic chemistry. However, synthesising ^{18}O-labelled alcohols is challenging, since commercially available ^{18}O-labelled building blocks are limited. Furthermore, since there is a dearth of literature-known general methods for accessing ^{18}O-labelled alcohols, *de novo*, substrate-specific synthesis routes are usually required.

This work describes a new method for synthesising ^{18}O-labelled alcohols using a Mitsunobu esterification with an ^{18}O-labelled carboxylic acid, followed by hydrolysis of the labelled ester. This protocol represents a highly practical and synthetically useful means of accessing a range of primary and secondary ^{18}O-labelled alcohols with high (up to 96%) isotopic purity. The method is further exemplified in the labelling of the active pharmaceutical ingredient, Dropropizine and is shown to be tolerant of second-generation separation-friendly Mitsunobu reagents.

A New Method for the ^{18}O-Labelling of Alcohols



Features of New Protocol
- Isotopic purity up to 96%.
- Does not require *de novo* syntheses.
- All reagents are bench-stable and commercially available.

Chapter Contents
- ^{18}O-labelled carboxylic acid synthesis.
- Substrate scope evaluation.
- Applications in synthesis of labelled active pharmaceutical ingredients.

3.1 Introduction

3.1.1 Stable Isotope-Labelled Compounds in Mechanistic Studies

Stable isotope-labelled compounds have a variety of roles in the organic and bioorganic sciences. One important role in synthetic organic chemistry is that they are often used as tools to probe mechanisms through measuring kinetic isotope effects and isotope tracing.[1–4] In the first part of this chapter, these techniques for studying reaction mechanisms are reviewed with reference to relevant literature examples of ^{18}O-labelled substrates being used.

Isotope Tracing Studies. In mechanistic studies, substrates are often labelled with a non-native isotope at a specific position and then subjected to the studied reaction. The resulting position and distribution of the isotope in the product can give vital information on the mechanism of the reaction and rule out any mechanism that do not account for the results obtained. The studied substrates are commonly labelled with stable isotopes such as ^{2}H, ^{13}C or ^{14}C for this purpose.

A notable historic example of using isotope tracing to ascertain information on a reaction mechanism was reported by Roberts and co-workers in 1953 (figure 1).[5] They studied the reaction of chlorobenzene (**1**) and potassium amide in liquid ammonia, which affords aniline (**2**) as the major product. Roberts and co-workers repeated this reaction, using chlorobenzene where the *ipso*-carbon was labelled with the ^{14}C isotope. When the reaction was run using the isotopically labelled chlorobenzene (**3**), the aniline product was afforded with the ^{14}C labelled scrambled between the *ipso*- (**4**) and *ortho*- (**5**) positions (figure 1A). The authors deduced that the result was not consistent with an S_NAr type mechanism, involving a Messenheimer complex (**7**) intermediate (shown in figure 1B), since an S_NAr mechanism would result in the ^{14}C label present at only the *ipso*-position. The result of the labelling experiment instead supports a mechanism which involves a benzyne intermediate (**10**, figure 1C). Since the amide anion can attack the benzyne from either the carbon containing the ^{14}C label, or the unlabelled carbon, this mechanism was consistent with the observed scrambling of the ^{14}C label position (**11** and **12**).

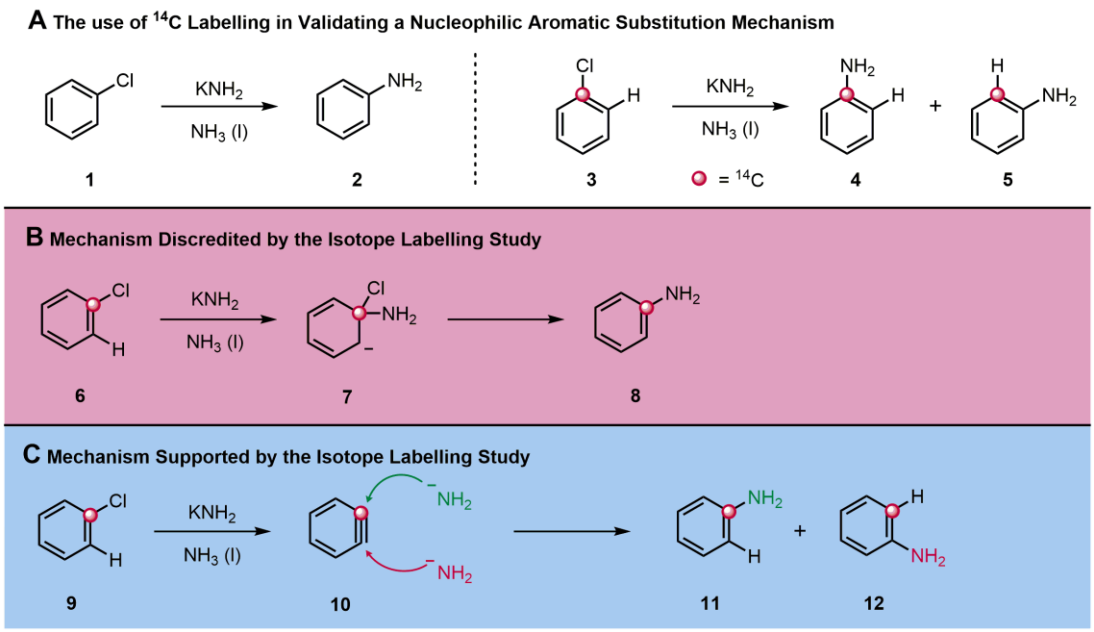


Figure 1. The use of ^{14}C-labelled compounds to probe the nature of the reaction intermediate in the nucleophilic aromatic substitution of chlorobenzene with potassium amide by Roberts and co-workers.

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^{18}O-labelled substrates are also commonly used in isotope labelling studies (figure 2). For example, to develop a mechanistic understanding for the LDA-mediated rearrangement of aryl triflate **13** to sulfone **14**, Lloyd-Jones and co-workers, conducted the reaction with ^{18}O-labelled aryl triflate **13**.[6] The product was afforded with the ^{18}O-label fully incorporated into the hydroxyl position of the phenol product (**14**). This result ruled out the possibility of a mechanism involving the initial dehydration of the starting material to a benzyne intermediate (figure 2B, **16**), since this would involve the scrambling of the ^{18}O label access all three oxygens of the product. Aided by this mechanistic insight, and having subsequently conducted further mechanistic studies, the authors determined that the mechanism occurred by an *ortho*-deprotonation, followed by a thia-Fries rearrangement (figure 2C).

Another example of the use of a ^{18}O-labelled substrate in isotope-labelling studies was reported by Taniguchi in 2011 (figure 3).[7] In their publication they reported an iron-catalysed, triphenylphosphine-mediated esterification of alcohols and carboxylic acids. One proposed mechanism for this transformation involved the generation of an alkoxyphosphonium carboxylate, followed by an Arbuzov

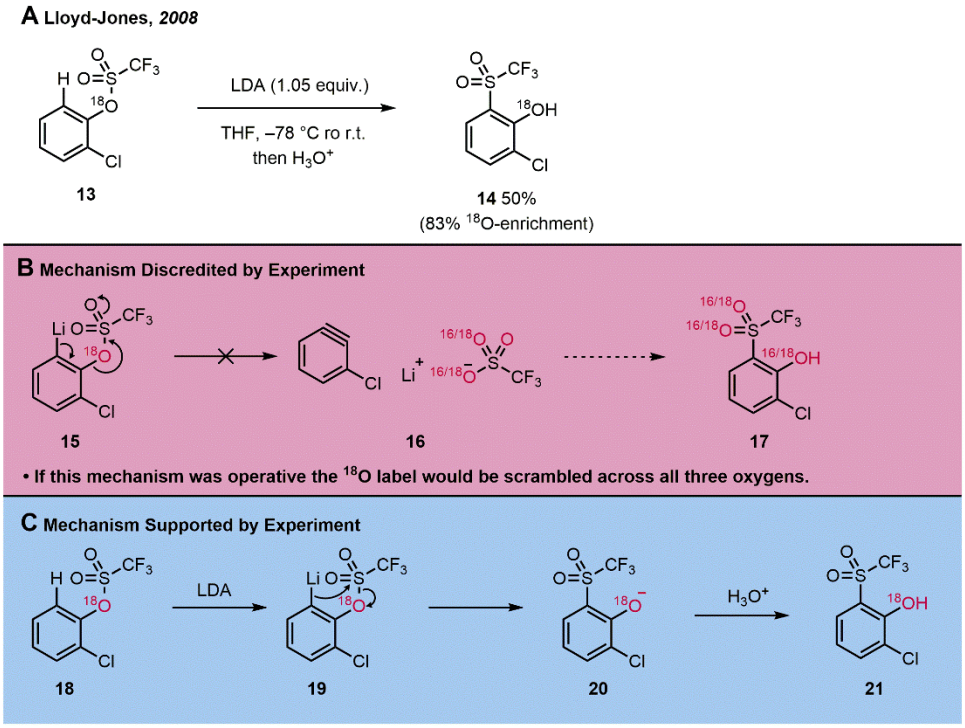


Figure 2. The use of ^{18}O-labelled aryl triflate to probe the mechanism of the rearrangement of **13** to **14** when treated with LDA by Lloyd-Jones and co-workers.

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collapse, akin to the Mitsunobu reaction mechanism. To investigate this possibility, ^{18}O-labelled 1-phenylpropan-3-ol (**22**) and 4-nitrobenzoic acid (**23**) were subjected to the reaction conditions, and the ester product was afforded with complete incorporation of the ^{18}O-label (**24**). Furthermore, when the 4-nitrobenzoic acid was labelled with an ^{18}O-label (**27**), the label was distributed amongst both the product (**28**) and phosphine oxide by-product (**29**). These results show unequivocally that the reaction does not proceed *via* an Arbuzov collapse of an alkoxyphosphonium carboxylate (shown in figure 3B). The authors have instead postulated that the reaction occurs through the single-electron oxidation of the triphenylphosphine to form the phosphorus-centred radical cation. The combination of the radical cation and carboxylate then generates an acylphosphonium salt (**34**, figure 3C), which reacts as an activated ester, with nucleophilic catalysis of the pyridine *N*-oxide co-catalyst, to form the ester product. The result of the isotope labelling study is in agreement with this result.

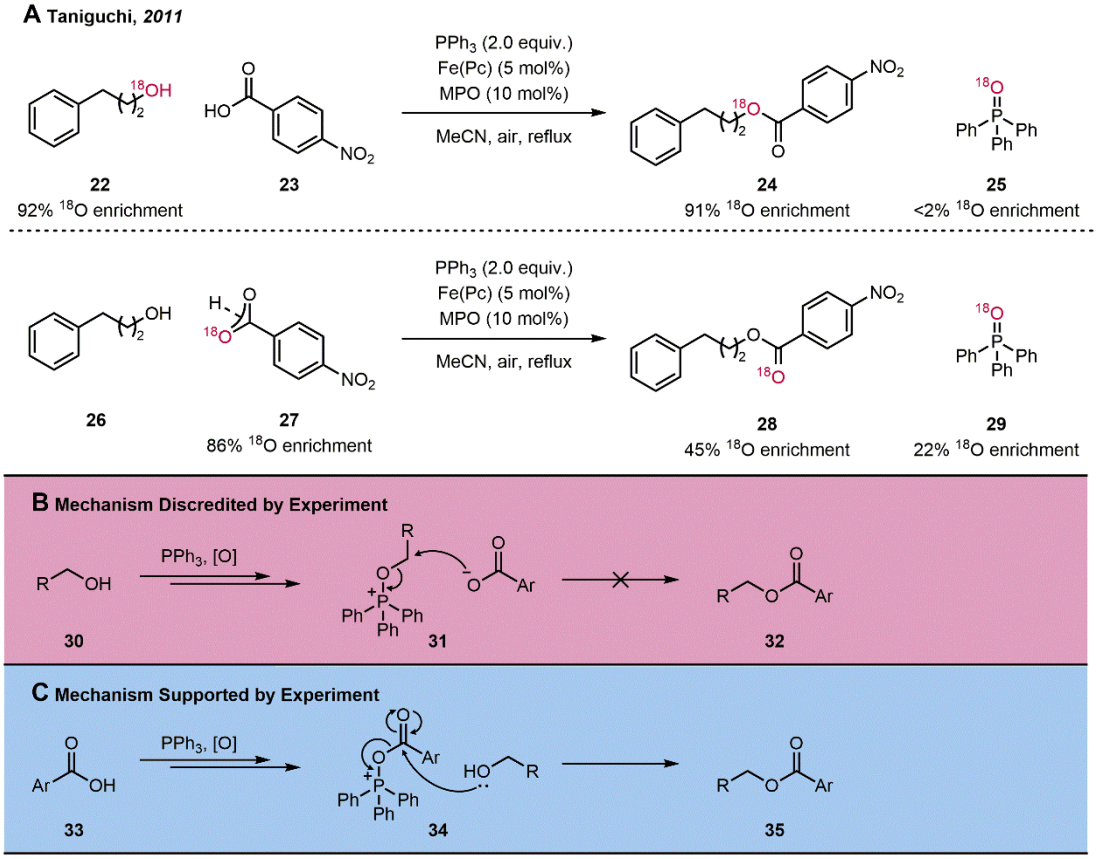


Figure 3. The use of ^{18}O-labelled compounds to investigate whether the reaction proceeds through an alkoxyphosphonium (**31**) or acylphosphonium (**34**) intermediate by Taniguchi and co-workers.

Kinetic Isotope Effects. A kinetic isotope effect is a phenomenon where the rate of a given chemical reaction, changes when one of the atoms of a reactant is replaced with a different isotope. If a bond to an isotopically labelled atom is broken during the rate-determining step of a reaction, then a primary kinetic isotope effect is observed. Thus, much information can be attained on the rate-determining step of a reaction by studying kinetic isotope effects.

Historically, kinetic isotope effect studies have provided fundamental information required for determining reaction mechanisms. For example, the Diels-Alder reaction of isoprene and maleic anhydride shows a $^{13}C/^{12}C$ kinetic isotope effect on the terminal alkene carbons, which demonstrates that the rate-determining step involving bonds being forged to both carbon atoms simultaneously (figure 4).[8] This mechanistic observation therefore discredits a non-concerted, step-wise mechanism and supports a concerted mechanism for the Diels-Alder cycloaddition.

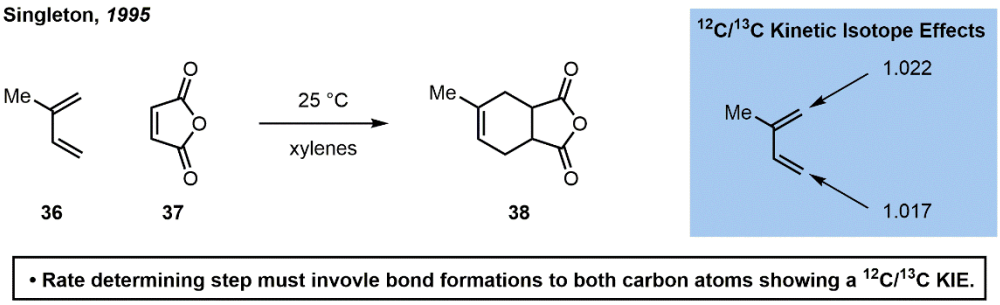


Figure 4. The use of $^{12}C/^{13}C$ kinetic isotope effects as evidence in the determination of the mechanism of the Diels-Alder reaction.

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^{18}O-labelled substrates are much less frequently used to measure kinetic isotope effects than their ^{13}C-labelled and ^{2}H-labelled counterparts. Nevertheless, with advancements in high-accuracy kinetic profiling,[9] it is possible to measure kinetic isotope effects between ^{18}O-labelled substrates and unlabelled ^{16}O-enriched substrates. In attempting to investigate the mechanism of the Ribonuclease A catalysed cleavage of RNA strands, Cleland and co-workers have identified a $^{18}O/^{16}O$ kinetic isotope effect in the internal transesterification of uridine ester **39** (figure 5) to afford cyclic phosphoric acid ester **40**.[10,11] Uridine ester **39** was designed to mimic an RNA strand with the 3-nitrobenzoxy group possessing similar leaving group ability to a polynucleotide oligomer. The observed kinetic isotope effect demonstrated that the loss of the 3-nitrobenzoxy group was a rate determining step in the substitution mechanism.

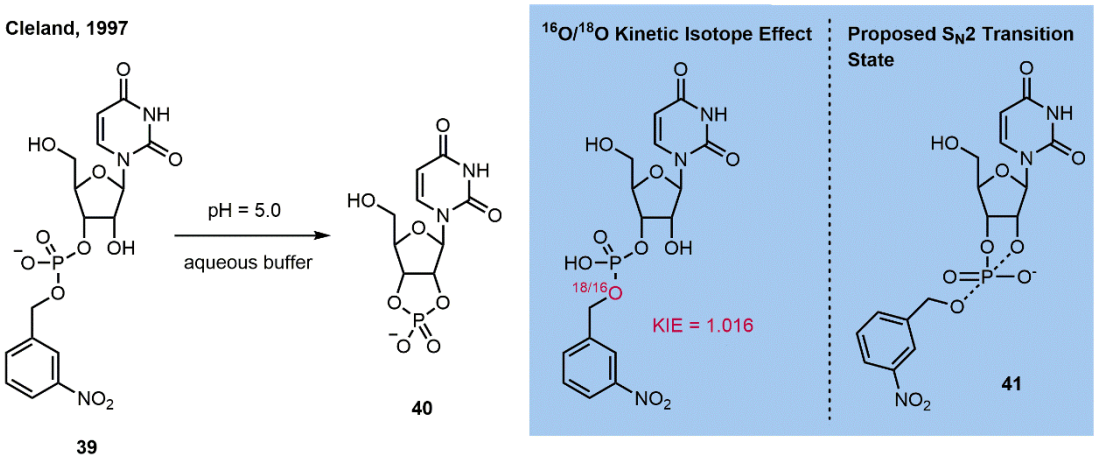


Figure 5. The use of ^{18}O-labelled uridine derivative to measure $^{18}O/^{16}O$ kinetic isotope effects for the study of the biochemical mechanism of RNA hydrolysis.

This result was a key constituent of a wider mechanistic investigation, that was consistent with concerted S_N2-type mechanism of substitution for the transesterification. The authors postulated that the reaction went through a trigonal bypyramidal transition state (**41**), but this phosphorane species was not a stable intermediate in the mechanism. Since this report, Cleland and co-workers have used $^{16}O/^{18}O$ kinetic isotope effect studies to develop a mechanistic understanding of the hydrolysis of phosphate esters.[12]

3.1.2 Stable Isotope Labelled Compounds in Pharmaceutical Studies

Isotopically labelled compounds are critical to the drug development process. For example, active pharmaceutical ingredients and drug candidates labelled with radioactive isotopes so that the compounds can be tracked *in vivo*.[13] Active pharmaceutical ingredients labelled with stable isotopes also have numerous roles such as internal standards for mass spectrometry-based analysis.[14,15] Additionally, the incorporation of deuterium into a drug molecule has been shown to affect metabolic stability.[16] The following section provides an in-depth discussion of the roles of stable isotope-labelled active pharmaceutical ingredients in the pharmaceutical sciences.

Stable Isotope Labelled Compounds in Pharmaceutical Sciences. Pharmaceutical compounds labelled with non-native stable isotopes are widely used as internal standards for quatitative mass-spectrometry based analysis of various pharmacokinetic and pharmacodynamic properties.[13,14] This is particularly advantageous in biological assays, where adding an additional known quantity of the assayed substrate, labelled with non-native isotopes, allows for accurate measurement of substrate concentration using mass spectrometry (figure 6).[15] This provides a useful means of measuring various important pharmacokinetic and pharmacodynamic parameters during absorption, distribution, metabolism and excretion (ADME) studies of drug candidates.

If stable-isotope labelled analogues of active pharmaceutical ingredients are to be used as internal standards for mass-spectrometry based analysis, they must conform to certain specifications. Firstly, the most abundant isotope in a labelled

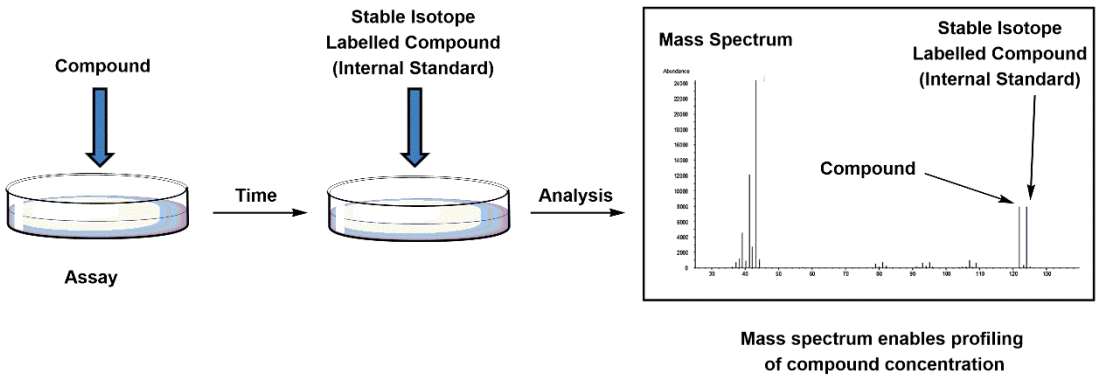


Figure 6. A pictoral depiction of how stable isotope-labelled active pharmaceutical ingredients are used as internal standards for mass spectrometry-based analysis during pharmaceutical development.

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active pharmaceutical ingredient sample must be at least four mass units heavier than the unlabelled isotopologue. Secondly, the sample should contain no greater than 0.5 mol% of the parent, unlabelled isotopologue.[17] These specifications are vital to prevent cross-signal interferences when interpreting the mass spectra.

The synthesis of stable isotope labelled active pharmaceutical ingredients is usually achieved by *de novo* synthesis using building blocks labelled with specific stable isotopes (most commonly ^{2}H, ^{13}C or ^{15}N).[13] However, recent developments in synthetic methodology have resulted in new methods that can exchange specific hydrogen atoms of an active pharmaceutical ingredient with deuterium isotopes. This approach offers cost- and time- efficient means of labelling an active pharmaceutical ingredient, which does not rely on *de novo* syntheses.

Iridium catalysts based on Crabtree's catalyst are known to be effective catalysts for hydrogen/deuterium exchange reactions and are widely used for the preparation of deuterium labelled active pharmaceutical ingredients.[18] However, in general the hydrogen/deuterium exchange is limited to aromatic C–H bonds adjacent to a directing group. Chirik and co-workers have demonstrated that pharmaceutical molecules can be labelled with deuterium isotopes by iron-catalysed hydrogen isotope exchange (figure 7A).[19] This deuteration reaction occurs with different site-selectivity to the iridium-catalysed systems described and thus the iron-catalysed and iridium-catalysed systems are complimentary strategies for accessing deuterium labelled active pharmaceutical ingredients.

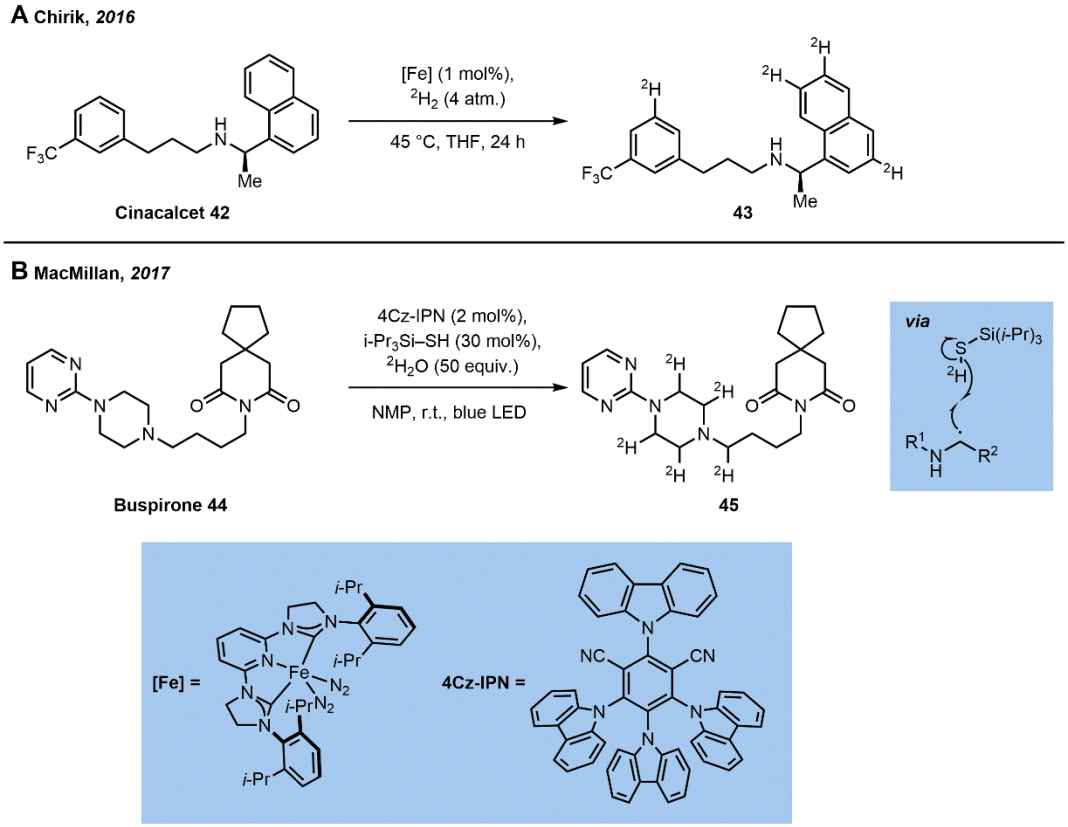


Figure 7. The synthesis of deuterium labelled active pharmaceutical ingredients by hydrogen-deuterium exchange. **(A)** An iron(II)-catalysed hydrogen-deuterium exchange at aromatic C–H bonds; **(B)** A photo-redox catalysis-mediated hydrogen-deuterium exchange at aliphatic C–H bonds α to heteroatoms.

MacMillan and co-workers have recently described a dual photo-redox and hydrogen atom transfer catalysis strategy for selectively exchanging the hydrogen atoms of sp^3 C–H with deuterium isotopes (figure 7B).[20] This occurs *via* the photo-redox catalysis-mediated generation of α-amino radicals, which undergoes a hydrogen atom transfer with an *in situ* generated deuterated thiol. This protocol enables access to numerous active pharmaceutical ingredients with deuterium labels installed α to nitrogen and oxygen atoms.

Although oxygen-containing functional groups are common in pharmaceutical molecules, compounds labelled with the ^{18}O isotope are rarely used as internal standards for mass-spectrometry based analysis. This due to the poor availability of the ^{18}O-labelled building blocks required for the *de novo* syntheses of these ^{18}O-labelled targets.[13] However, recently some important progress has been made in this field. Reilly and co-workers have reported a method for labelling

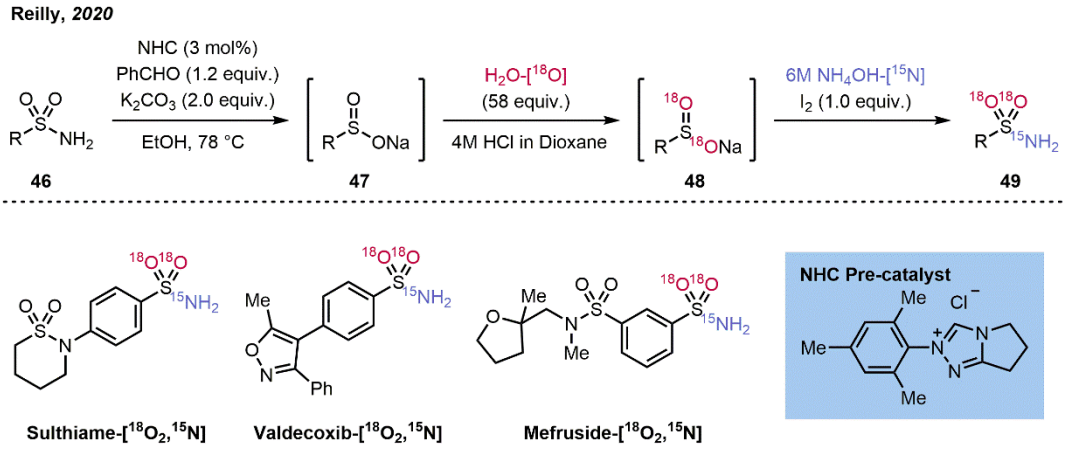


Figure 8. The labelling of sulfonamide-containing active pharmaceutical ingredients with two ^{18}O labels and one ^{15}N label as reported by Reilly and co-workers.

primary sulfonamide functional groups of active pharmaceutical ingredients with two ^{18}O labels and one ^{15}N label (figure 8). This method involves the initial transformation of the primary sulfonamide (**46**) to the analogous sulfinate salt by an *N*-heterocyclic carbene-catalysed process (**47**), followed by acid-mediated $^{16}O/^{18}O$ exchange with H_2O-[^{18}O], to form ^{18}O-labelled sulfinate salt (**48**). The ^{18}O-labelled sulfinate salt is then subjected to oxidative sulfonamidation, using $^{15}NH_4OH$ and iodine to afford the isotopically labelled sulfonamide (**49**). This protocol has enabled the labelling of numerous sulfonamide-containing active pharmaceutical ingredients, with high isotopic purity, without having to resort to *de novo* syntheses.

3.1.3 Methods for Synthesising ^{18}O-Labelled Alcohols

The development of robust synthesis methods towards the ^{18}O-labelled compounds is critical, given their widespread application. Developing such synthesis routes presents numerous unique challenges.[21,22] The pool of commercially available isotopically labelled starting materials from which the ^{18}O-labelled substrates can be synthesised from is limited (figure 9A). The isotopically labelled starting materials which are commonly used are ^{18}O-labelled water, which is commercially available at 97% and 99% isotopic purity for £2.35 and £20.62 per mmol respectively, and ^{18}O labelled carbon monoxide and oxygen gas which are both commercially available at £12.12 and

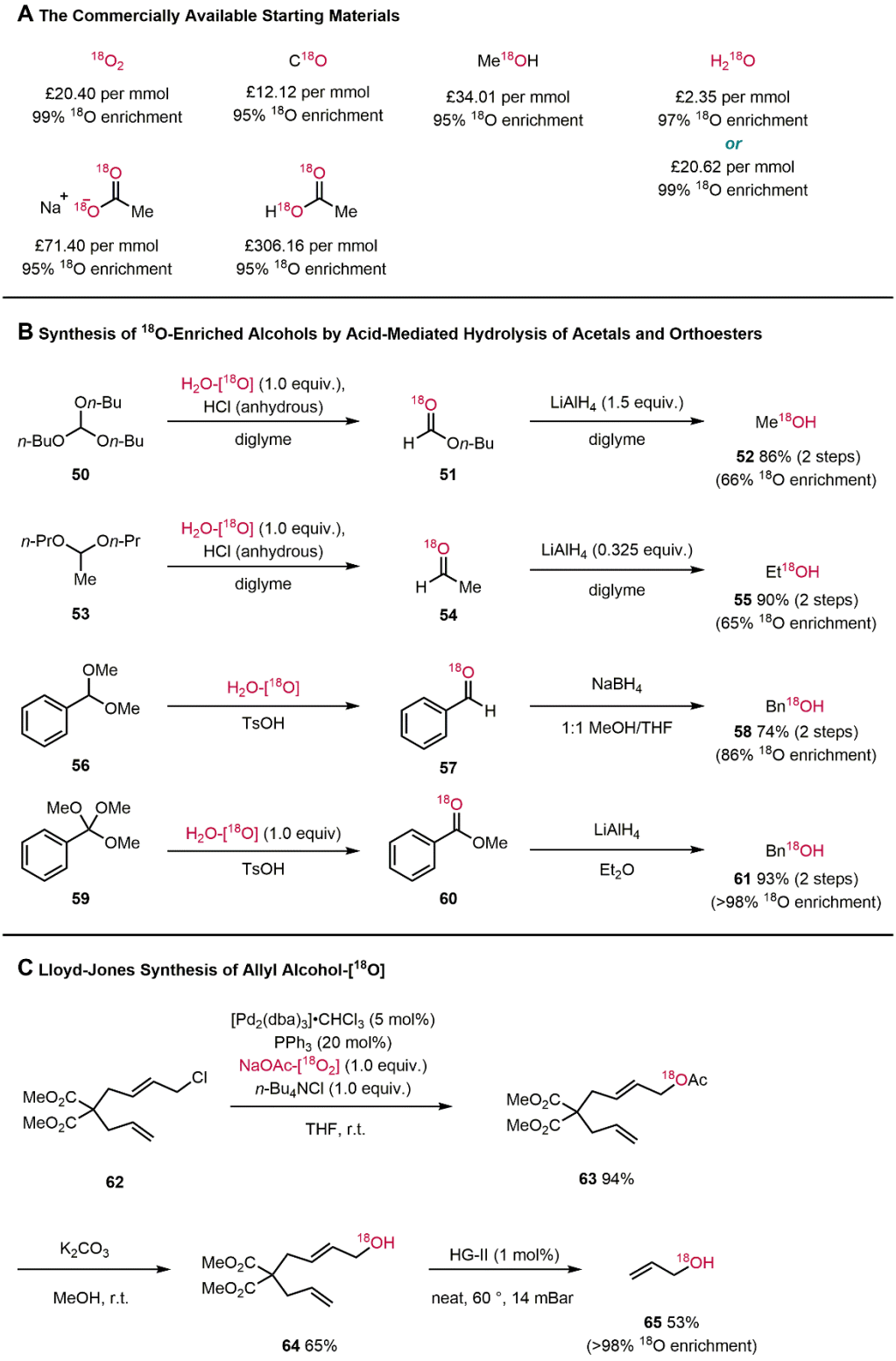


Figure 9. Substrate-specific methods for synthesising ^{18}O-labelled alcohols. (A) The commonly used building blocks for incorporating the ^{18}O-isotope into molecules. Prices and ^{18}O-enrichment are quoted from Sigma Aldrich for the largest available quantity; **(B)** Literature methods for synthesising ^{18}O-labelled alcohols by acid-mediated hydrolysis of acetals and orthoesters; **(C)** Lloyd-Jones' method of accessing allyl alcohol-[^{18}O] using a ring closing metathesis strategy.

£20.40 per mmol respectively. Other commercially available isotopically labelled starting materials include ^{18}O labelled methanol, sodium acetate and acetic acid, however, these are significantly more expensive.

Substrate-Specific Methods for the Synthesis of ^{18}O-Labelled Alcohols. Sawyer and co-workers have reported a high yielding synthesis of both methanol-[^{18}O] (figure 9B, **52**) and ethanol-[^{18}O] (**55**).[23] Methanol-[^{18}O] was prepared in a two-step synthesis, by the initial hydrochloric acid-catalysed hydrolysis of tri-*n*-butyl orthoformate (**50**) using H_2O-[^{18}O], to form *n*-butyl formate-[^{18}O] (**51**). This label formate ester was subsequently reduced by lithium aluminium hydride to afford methanol-[^{18}O] (**52**) with an overall yield of 86%. Similarly, ethanol-[^{18}O] was prepared by the by the initial hydrochloric acid-catalysed hydrolysis of acetaldehyde dipropylacetal (**53**), to form acetaldehyde-[^{18}O] (**54**), followed lithium aluminium hydride-mediated reduction to afford ethanol-[^{18}O] (**55**) with an overall yield of 90%. The isotopic purities obtained were 66% and 65% respectively.

This method was adapted by Carlsen and Ystenes and applied towards the synthesis of benzyl alcohol-[^{18}O] (**58**), where benzaldehyde dimethyl acetal (**56**) was hydrolysed with H_2O-[^{18}O], under *p*-toluenesulfonic acid catalysis, to afford benzaldehyde-[^{18}O] (**57**).[24] Subsequent reduction using sodium borohydride then afforded benzyl alcohol-[^{18}O] (**58**) with an overall yield of 74% and an ^{18}O isotope incorporation of 86%. Young and Robinson have also developed a similar synthesis method to access benzyl alcohol-[^{18}O], except in their case, methyl orthobenzoate (**59**) was hydrolysed with H_2O-[^{18}O], under *p*-toluenesulfonic acid catalysis, to afford methyl benzoate-[^{18}O] (**60**).[25] Subsequent reduction of the ester, using lithium aluminium hydride afforded benzyl alcohol-[^{18}O] (**61**) with a yield of 93%.

In 2011, Lloyd-Jones and co-workers were seeking to develop a preparative method for ^{18}O-labelled allyl alcohol (figure 9C, **65**).[26] A notable challenge was that the labelled allyl alcohol product was highly volatile, therefore purification by distillation from common reaction solvents would be challenging, Their solution was to use a solvent-free ring-closing metathesis strategy, using

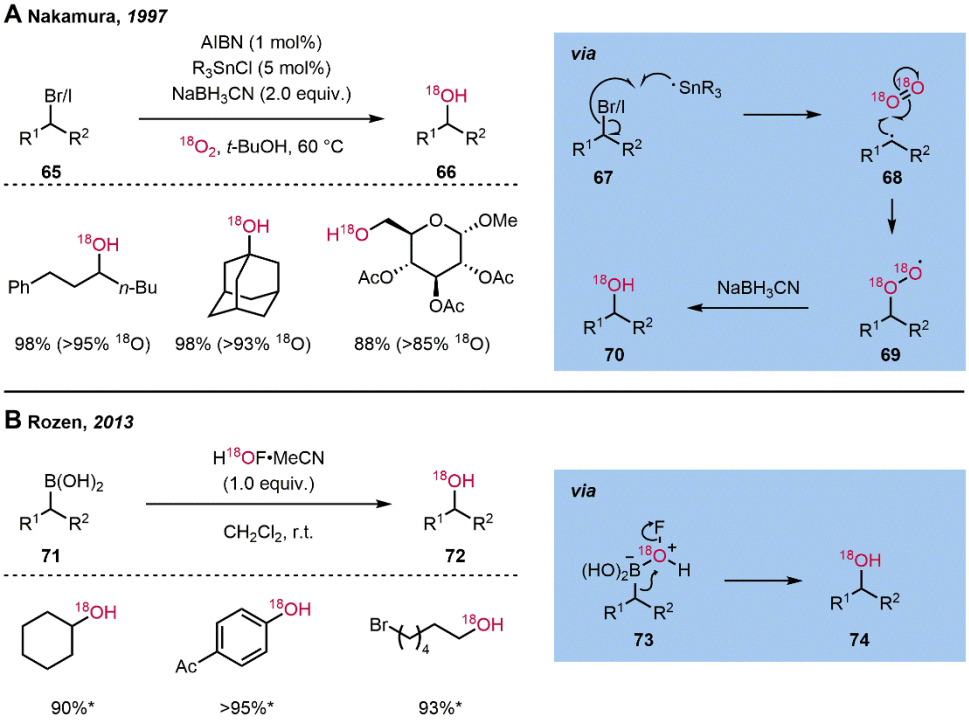


Figure 10. General synthesis methods for accessing ^{18}O-labelled alcohols. **(A)** Nakamura's method for converting alkyl bromides and alkyl iodides to ^{18}O-labelled alcohols; **(B)** Rozen's method for converting boronic acids to ^{18}O-labelled alcohols. *Yield were not quoted in the manuscript for ^{18}O-labelled substrates. Yields are therefore quoted for ^{16}O-enriched substrates using unlabelled HOF•MeCN.

substituted ^{18}O-labelled allylic alcohol **64**, releasing the labelled allyl alcohol (**65**) as a product, which could be purified by distillation.

^{18}O-labelled allylic alcohol **64** was accessed in two steps. Firstly, a palladium-calalysed allylic nucleophilic substitution of the analogous allyl chloride (**62**), using ^{18}O-labelled sodium acetate as the nucleophile, was performed. Subsequent hydrolysis of the resultant ester afforded the ^{18}O-labelled substituted allylic alcohol (**63**). Although this method was highly effective in accessing high purity and isotopically-labelled ^{18}O-allyl alcohol, it be noted that although sodium acetate is commercially available, its' high cost (£71.40 per mmol from Sigma Aldrich, figure 9A), may make this method prohibitively expensive for some larger-scale syntheses.

General Methods for the Synthesis of ^{18}O-Labelled Alcohols. Apart from publications pertaining to work presented in this thesis, only two *general*

methods of accessing ^{18}O-labelled alcohols have been reported in the literature to date. In 1997, Nakamura and co-workers reported a method for converting alkyl iodides and bromides to ^{18}O-labelled alcohols (figure 10A).[27] The reaction is facilitated by a tin-centred radical, which is generated *in situ* from the reduction of tin chloride using sodium cyanoborohydride. The *in situ*-generated tin-mediated generation of a carbon-centred radical (**68**), which undergoes radical combination with $^{18}O_2$ forming a peroxy-radical (**69**). The peroxy radical is subsequently reduced by the excess sodium cyanoborohydride. Using this method, the authors were able to access primary, secondary and tertiary ^{18}O-labelled alcohols with yields ranging between 88–98% and an isotopic purity of 85–95%.

In 2013, Rozen and co-workers reported a method of accessing ^{18}O-labelled alcohols from boronic acids using the hypofluorous acid complex [$H^{18}OF$•MeCN] (figure 10B).[28] This reagent, which serves as both the oxidant and ^{18}O source, is prepared using fluorine gas, ^{18}O-labelled water and acetonitrile. In their report, the authors demonstrated the ^{18}O-labelling of alcohols by oxidative hydroxylation of aryl and alkyl boronic acid, which enabled access to isotopically labelled phenols, as well as primary and secondary alcohols. The authors did not measure the isotopic purity of the alcohol products, however qualitative analysis of the mass spectra graphics presented in the publication suggested that isotopic purity values were high (>75%).

^{18}O-Labelling by a Mitsunobu Reaction. In this work, the development of a new method for accessing ^{18}O-labelled alcohols, using a Mitsunobu esterification reaction, are explored. As a result of the Arbusov collapse, which is a key mechanistic feature of the Mitsunobu reaction (see chapter 1, page 32), using a carboxylic acid pro-nucleophile labelled with two ^{18}O-isotopes, will result in the incorporation of the ^{18}O label in the ester product. Subsequent hydrolysis of this ester intermediate will then afford the ^{18}O-labelled alcohol.

This concept has been explored before in order to make specific ^{18}O-labelled alcohols as part of wider mechanistic studies (figure 11). Cleland and co-workers have synthesised ^{18}O-labelled 3-nitrobenzylalcohol-[^{18}O,^{15}N] (figure 11A, **78**) by the Mitsunobu esterification of 3-nitrobenzylalcohol-[^{15}N] (**75**) with benzoic

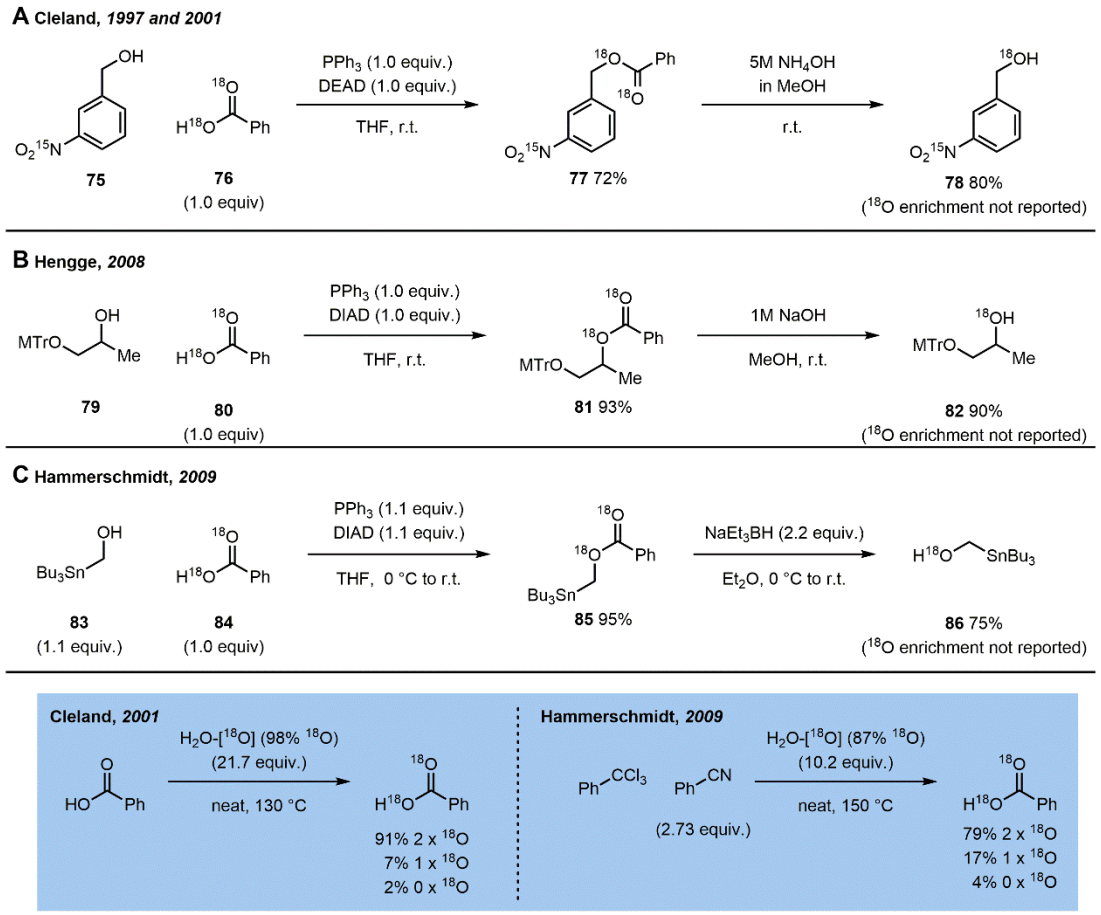


Figure 11. Current literature examples of the synthesis of ^{18}O-labelled alcohols using a Mitsunobu esterification reaction, followed by an ester hydrolysis. *MTr = 1-*O*-(monomethoxytrityl).

acid-[$^{18}O_2$] (**76**), followed by ester hydrolysis.[10,12] The authors did not comment on the isotopic purity of the alcohol ^{18}O-enrichment, and an notable issue with this method is that the benzoic acid-[$^{18}O_2$] was required to be synthesised by heating benzoic acid with 21.7 molar equivalents of H_2O-[^{18}O].

Similarly, Hengge and co-workers have synthesised ^{18}O-labelled alcohol **82** (figure 11B) using a similar Mitsunobu esterification-hydrolysis sequence, using benzoic acid-[$^{18}O_2$] (**80**) as the pro-nucleophile.[11] In this report, the authors did not report an isotopic purity value, and did not state how the benzoic acid-[$^{18}O_2$] was synthesised. Finally, Hammerschmidt and co-workers have synthesised tributylstannylmethanol-[^{18}O] (figure 11C, **86**) using a Mitsunobu esterification-ester reduction sequence.[29] This protocol uses benzoic acid-[$^{18}O_2$] as a pro-nucleophile, which was accessed by the hydrolysis of a mixture of benzonitrile and α,α,α-trichlorotoluene with 10.2 molar equivalents of H_2O-[^{18}O]. The authors

did not comment of the isotopic purity of the tributylstannylmethanol-[^{18}O] product, however the new preparative method for benzoic acid-[$^{18}O_2$] gave an 82% yield and an isotopic purity of 79%.

There are notable practical issues with these examples, including the poor isotopic purity of the products, as well as the requirement of super-stoichiometric quantities of H_2O-[^{18}O] (between 10.2 and 21.7 equivalents) Furthermore, this concept has never been explored as a general means for accessing ^{18}O-labelled alcohols, only as a means of accessing specific substrates.

Given these results, it is clear that; a) a single general method for the Mitsunobu esterification-mediated ^{18}O-labelling is required that can reliably and consistently deliver labelled alcohols with high ^{18}O incorporation and b) an improved synthesis of a suitable carboxylic acid pro-nucleophile, that is efficient with respect to molar equivalents of H_2O-[^{18}O], are required.

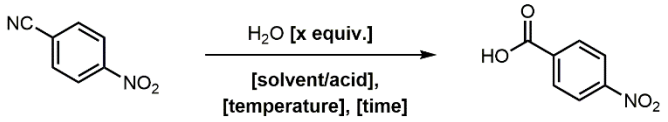
3.2 Results and Discussion

3.2.1 Synthesis of an ^{18}O-Labelled Carboxylic Acid

Firstly, the challenge of developing a method to access a suitable ^{18}O-labelled carboxylic acid pro-nucleophile was addressed. Since 4-nitrobenzoic acid has been demonstrated to be an especially high-yielding pro-nucleophile in the Mitsunobu esterification reaction,[30] it was chosen as a suitable carboxylic acid. The synthesis of its doubly ^{18}O-labelled counterpart, 4-nitrobenzoic acid-[$^{18}O_2$], was therefore targeted, by an acid-mediated hydrolysis of 4-nitrobenzonitile using H_2O-[^{18}O].

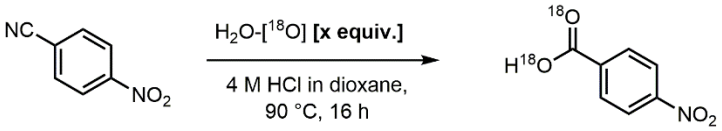
To ensure a high incorporation of the ^{18}O isotope into the carboxylic acid, the proton source was required to be anhydrous, to limit any contamination with the ^{16}O isotope present in unlabelled water. However, for the initial reaction discovery and optimisation phase, shown in table 1, unlabelled water was used, due to the high cost associated with H_2O-[^{18}O]. Thus, the hydrolysis of 4-nitrobenzonitrile was attempted using 1 M hydrochloric acid in diethyl ether at room temperature in DMF, toluene and DMSO (table 1, entries 1–3). In each case no conversion to the carboxylic acid product was observed. Using Amberlyst 15 as an alternative anhydrous proton source and running the reaction at 85 °C

Table 1. The discovery and optimisation of an acid-mediated hydrolysis of 4-nitrobenoitrile towards the synthesis of 4-nitrobenzoic acid-[$^{18}O_2$]. *Yield was not determined due to significant product decomposition.



Entry	H_2O equiv.	Solvent/Acid	Temperature / (°C)	Time / (h)	Conc. / (M)	Yield / (%)
1	2.50	20% *v/v* 1 M HCl in diethyl ether in DMF	25	24	0.5	0
2	2.50	20% *v/v* 1 M HCl in diethyl ether in toluene	25	24	0.5	0
3	2.50	20% *v/v* 1 M HCl in diethyl ether in DMSO	25	24	0.5	0
4	2.50	5% *w/v* Amberlyst® 15 in 1,2-DCE	85	24	0.5	< 5
5	2.20	35% *v/v* TfOH in dioxane	90	24	2.0	85
6	2.50	4 M HCl in dioxane	90	16	0.5	83
7	2.50	4 M HCl in dioxane	90	16	1.8	91
8	2.50	4 M HCl in dioxane	90	16	2.8	n/a*

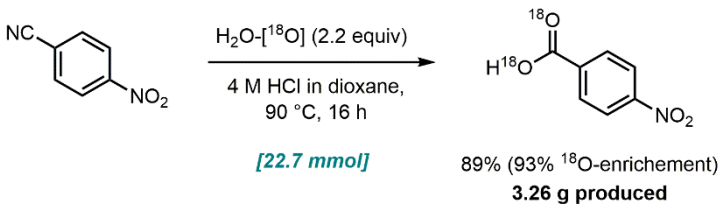
Table 2. The optimisation of an acid-mediated hydrolysis of 4-nitrobenzonitrile using H_2O-[^{18}O].



Entry	H_2O-[^{18}O] equivalents	Yield / (%)	Isotopic Purity / (%)
1	2.50	91	92
2	2.20	92	93
3	2.00	84	89

resulted in minimal conversion to product (entry 4). Furthermore, using trifluoromethylsulfonic acid as the proton source resulted in formation of product with a high NMR yield of 85% (entry 5), however, the product could not be isolated as a pure sample and alternative reaction conditions were trialled. When the reaction was conducted in 4 M HCl in dioxane at 90 °C, the product was obtained with a high yield of 83% (entry 6). Attempts to run the reaction at higher concentration resulted in a superior yield of 91% at 1.8 M (entry 7), however when the reaction was run at a concentration of 2.8 M (entry 8), significant starting material decomposition was observed, and the product could not be isolated as a pure sample.

The reaction conditions were further investigated for their capacity to efficiently label the carboxylic acid with H_2O-[^{18}O] (table 2). When 4-nitrobenzonitrile was reacted with 2.50 molar equivalents of H_2O-[^{18}O] in 4 M hydrochloric acid in dioxane at 90 °C, the carboxylic acid was afforded with an isotopic purity of 92% (entry 1). The singly labelled carboxylic acid accounted for the remaining 8%. When the molar equivalents of H_2O-[^{18}O] was reduced to 2.20 equivalents, the yield and isotopic purity increased to 92% and 93% respectively (entry 2),



Scheme 1. A scale-up of the acid-mediated hydrolysis of 4-nitrobenzonitrile with H_2O-[^{18}O]

however, using 2.00 molar equivalents H_2O-[^{18}O] had a detrimental effect on both yield and isotopic purity (entry 3). Using the optimal conditions (entry 2) the preparation of 4-nitrobenzoic acid-[$^{18}O_2$] was performed at a 22.7 mmol scale, which resulted in the formation of 3.26 g of product. The 4-nitrobenzoic acid-[$^{18}O_2$] was afforded with an 89% yield and 93% isotopic purity (scheme 1).

3.2.2 Substrate Scope Evaluation

With a convenient method to access 4-nitrobenzoic acid-[^{18}O]$_2$ in hand, the use of this carboxylic acid in the Mitsunobu esterification-ester protocol was investigated (figure 12). A range of primary and secondary alcohols were subjected to standard Mitsunobu esterification conditions, followed by an ester hydrolysis using lithium hydroxide to yield the corresponding ^{18}O-labelled alcohol.

Firstly, the benzylic alcohols 1-naphthalenemethanol (**87a**) and **87b** were converted into their ^{18}O-labelled isotopologues with yields of 73% and 36% respectively and excellent isotopic purity of 94% and 95% respectively. Additionally, the ^{18}O isotopologues for indole-containing alcohol **87c** and amino acid derivative **87d** were both accessed in fair-to-excellent yields and with a high isotopic purity of 96%. Ferrocenemethanol-[^{18}O] (**89e**) was also accessed with a good yield using this protocol, however the isotopic purity was slightly lower at 87%, presumably due to post hydrolysis S_N1-type hydroxyl exchange. Sugar derivative **87f** was effectively labelled with the ^{18}O isotope with a yield of 67% and an excellent isotopic purity of 95%. The ^{18}O-labelling of the monoterpinoids geraniol (**87g**) and (1*R*-(−)-myrtenol (**87h**) were also performed, and their ^{18}Olabelled counterparts (**89g** and **89h**) were afforded with pleasing yields (59% and 57% respectively) and excellent isotopic purity (92% and 93% respectively).

^{18}O-labelled (±)-Neomenthol (**89i**) was afforded when (±)-menthol (**87i**) was subjected to the reaction conditions, demonstrating the inversion of stereochemistry associated with the Mitsunobu esterification. Similarly, *epi*-cholesterol-[^{18}O] (**89k**) was obtained when the reaction conditions were applied to cholesterol (**87k**). Additionally, the ^{18}O-labelled acetal-protected adenosine

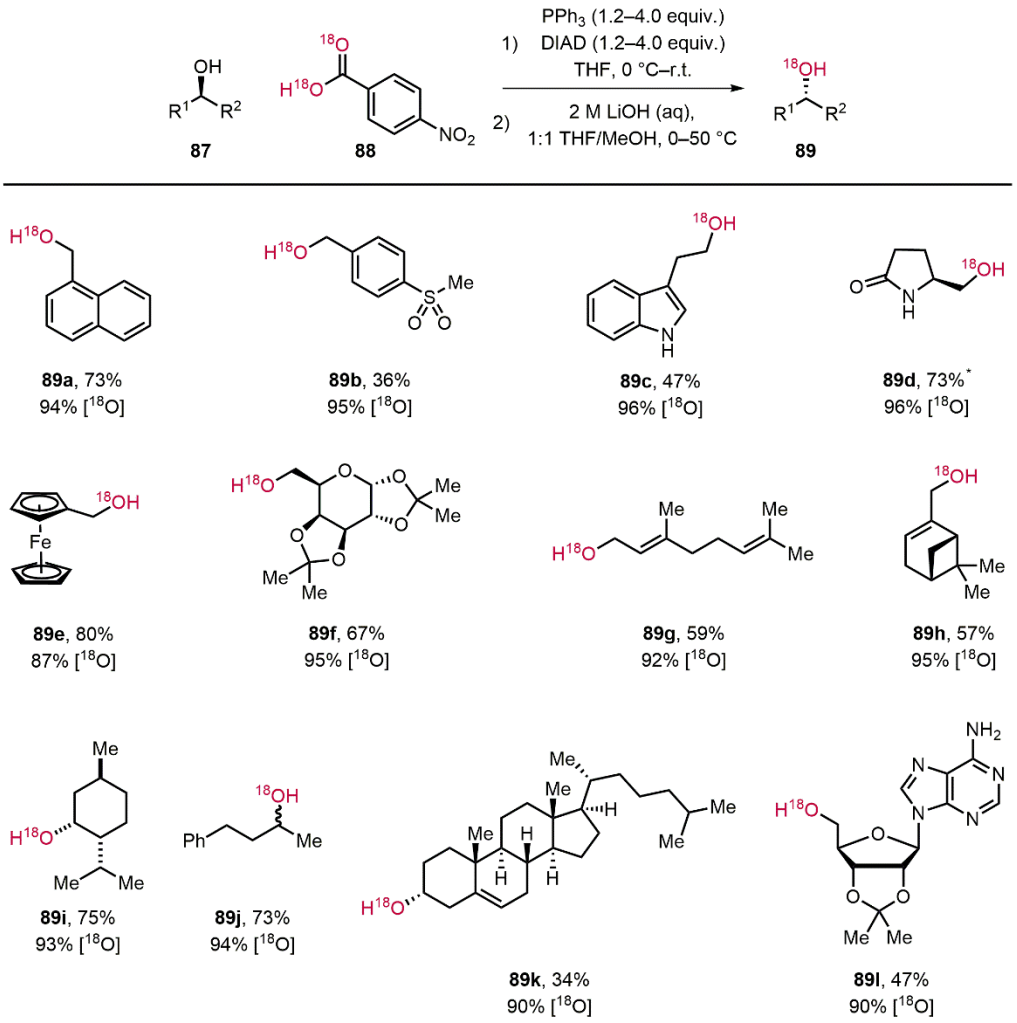


Figure 12. The substrate scope for the Mitsunobu esterification-hydrolysis mediated synthesis of ^{18}O-labelled alcohols. Yields are quoted as yield of the two-step process; *K_2CO_3 in MeOH/H_2O was used for the hydrolysis step; [^{18}O] = ^{18}O isotopic purity; Substrates **89a**, **89b** and **89c** were synthesised by Daniel Edwards; Substrates **89d**, **89g**, **89i**, **89k** and **89l** were synthesised by Louis Goodman.

87l was produced with an excellent isotopic purity of 90% albeit with a poor yield of 47%. Although the yields of different substrates were varied, pleasingly, the isotopic purity for each example remained excellent throughout, ranging from 87–96%.

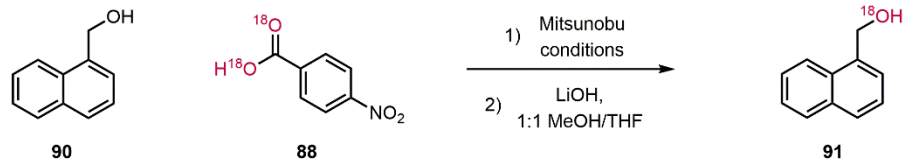
The Use of Alternative Mitsunobu Reagents. The reagents used in this labelling protocol (DIAD and triphenylphosphine) suffer from well-documented drawbacks (see chapter 1, page 22), specifically, the production of stoichiometric triphenylphosphine oxide and hydrazine by-products. Furthermore, DIAD is thermally unstable and its use is generally avoided on scale. Since second-generation, separation friendly Mitsunobu reagents, allows for Mitsunobu

reactions to be carried with facile removal of the reaction by-products (see pages 22–27), their use in the ^{18}O-labelling protocol was explored.

Firstly, the use of DTBAD in conjunction with diphenyl-2-pyridylphosphine, followed by hydrolysis, enabled the ^{18}O-labelling of 1-naphthalenemethanol with comparable yields and isotopic purity (77% and 92% respectively) to the DIAD/triphenylphosphine system (figure 13A, entry 2). Critically, the addition of hydrochloric acid successfully converted the hydrazide by-product into gaseous products, and the phosphine oxide was successfully removed using an aqueous acid wash. Similarly, the use of DCAD, with polystyrene-supported triphenylphosphine, followed by hydrolysis, afforded 1-naphthalenemethanol-[^{18}O] with comparable isotopic purity of 92% albeit at a poorer yield of 49% (figure 13A, entry 3). Both hydrazine and phosphine oxide by-products were separated from the reaction mixture by precipitation from dichloromethane.

Using CMBP, instead of DIAD and triphenylphosphine, followed by hydrolysis, enabled access to 1-naphthalenemethanol-[^{18}O] with an excellent isotopic purity

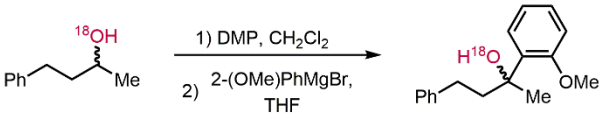
A The Use of Alternative Mitsunobu Conditions



90 **88** **91**

Entry	Conditions	Yield	[^{18}O]
1	DIAD, PPh_3, THF	73%	94%
2	DTBAD, PPh_2Py, THF	77%	92%
3	DCAD, PS-PPh_3, CH_2Cl_2	49%	92%
4	CMBP, toluene, 100 °C	61%	93%
5	ADDP, PBu_3, toluene, 60 °C	50%	88%

B Synthesis of an ^{18}O-Enriched Tertiary Alcohol



89j

92 67% (2 steps)
93% [^{18}O]

Figure 13. (A) The use of alternative separation-friendly Mitsunobu reagents for the ^{18}O-labelling of 1-naphthalenemethanol; **(B)** The synthesis of ^{18}O-labelled tertiary alcohol through the subsequent oxidation then Grignard addition of ^{18}O-labelled alcohol **89j**.

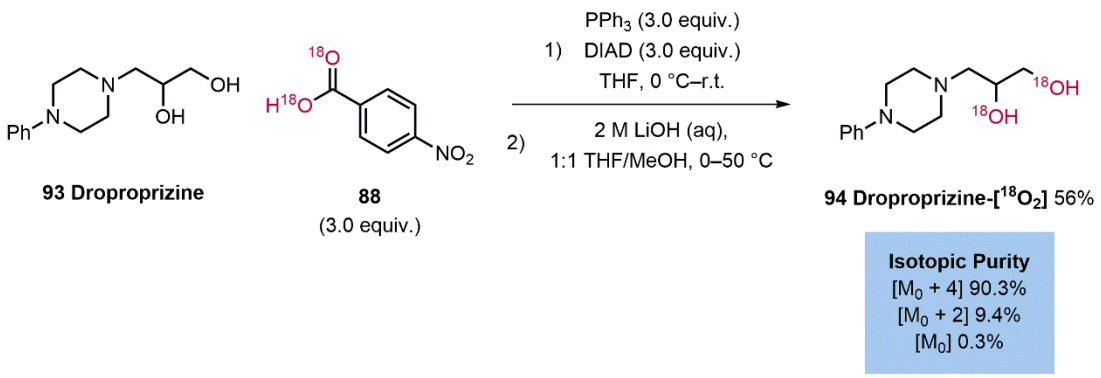
of 93% and a yield of 61% (figure 3A, entry 4). Finally, the commonly used reagent combination of ADDP with tributylphosphine (figure 13A, entry 5), with subsequent hydrolysis, afforded 1-naphthalenemethanol-[^{18}O] albeit with reduced yield of 50% and isotopic purity of 88%. Overall, these experiments demonstrate that the use of the potentially hazardous DIAD, and the chormatographic removal of triphenylphosphine oxide and hydrazide by-products from the reaction mixture can be avoided in the Mitsunobu esterification-hydrolysis protocol.

Synthesis of an ^{18}O-Labelled Tertiary Alcohol; Since tertiary alcohols are generally unreactive to the Mitsunobu reaction, ^{18}O-labelled tertiary alcohols cannot be accessed directly using the described Mitsunobu-based protocol. In seeking to address this shortcoming in the ^{18}O-labelling method, the synthesis of an ^{18}O-labelled tertiary alcohol by the initial oxidation of an ^{18}O-labelled secondary alcohol, followed by nucleophilic addition of a carbon-centred nucleophile, was investigated (figure 13A). Thus, the oxidation of ^{18}O-labelled secondary alcohol **89j,** to its corresponding ketone, using the Dess-Martin periodinane, followed by a Grignard reaction using 2-methoxyphenylmagnesium bromide afforded the tertiary alcohol **92** in a yield of 67% over two steps with minimal erosion of isotopic purity (figure 13B).

3.2.3 Synthesis of ^{18}O-Labelled Active Pharmaceutical Ingredients

The application of this method towards active pharmaceutical ingredients, so that stable isotope-labelled active pharmaceutical ingredients with potential applications in pharmaceutical sciences was then investigated. This method would be valuable for synthesising ^{18}O-labelled active pharmaceutical ingredients by a two-step ^{16}O/^{18}O exchange using the Mitsunobu esterification-hydrolysis protocol. Thus ^{18}O-labelled active pharmaceutical ingredients can be accessed without having to resort to *de novo* syntheses.

As previously stated (see pages 129–130), for stable-isotope analogues of active pharmaceutical ingredient to serve as internal standards for mass spectrometry-based analysis the most abundant isotope is required to be at least four mass units greater than the parent unlabelled isotopologue ([M_0 + 4]). In the context of



Scheme 2. The ^{18}O-labelling of Dropropizine using the Mitsunobu esterification-ester hydrolysis sequence.

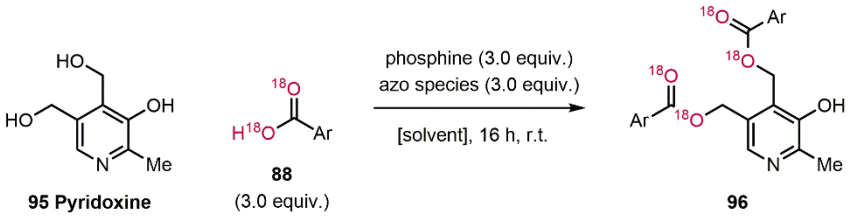
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^{18}O labels, to satisfy this requirement, the most abundant isotopologue must contain a minimum of two ^{18}O labels. Additionally, the internal standard should contain no more than 0.5 mol% of the parent, unlabelled isotopologue ([M_0]).

The cough suppressant, Dropropizine, was chosen as an appropriate substrate, since it contains two hydroxyl groups which are potentially reactive towards a Mitsunobu esterification reaction. Using the Mitsunobu esterification-hydrolysis protocol, Dropropizine-[^{18}O]$_2$ was obtained with a two-step yield of 56% (scheme 2). Mass spectrometry analysis of the product indicated that the doubly-labelled isotopologue ([M_0 + 4]) accounted for 90.3% of the sample, the singly-labelled isotopologue ([M_0 + 2]) accounted for 9.4%, and only 0.3% of the unlabelled substrate ([M_0]) was present. This demonstrates that our method can be effectively used as a means to access mass spectrometry internal standards.

The Mitsunobu esterification of Pyridoxine (vitamin B_6, **95**, table 3), using the ^{18}O-labelled carboxylic acid was investigated next. When triphenylphosphine and DIAD were used as reagents, using either tetrahydrofuran or chloroform as solvents, the diester product was obtained with a very low yield (entries 1–2). Using tri(*n*-butyl)phosphine with either ADDP and DIAD in both tetrahydrofuran and chloroform did not yield any diester (**96**) product (entries 3–5). Finally, the use of polystyrene supported triphenylphosphine and DIAD as reagents were unsuccessful, with no product formation observed (entry 6).

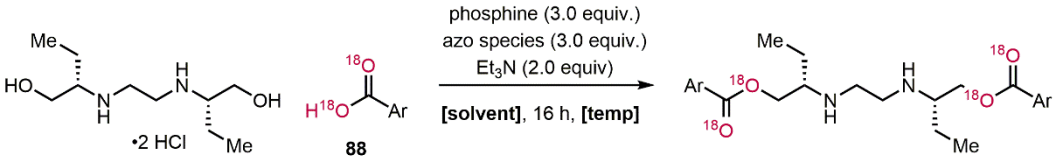
Table 3. The attempted ^{18}O-labelling of Pyridoxine using the Mitsunobu esterification-ester hydrolysis sequence.



95 Pyridoxine | **88** (3.0 equiv.) | **96**

Entry	Phosphine	Azo Species	Solvent	Yield / %
1	PPh_3	DIAD	THF	< 5
2	PPh_3	DIAD	$CHCl_3$	< 5
3	$P(n\text{-}Bu)_3$	ADDP	THF	0
4	$P(n\text{-}Bu)_3$	ADDP	$CHCl_3$	0
5	$P(n\text{-}Bu)_3$	DIAD	$CHCl_3$	0
6	PS-PPh_3	DIAD	$CHCl_3$	0

Table 4. The attempted ^{18}O-labelling of Ethambutol using the Mitsunobu esterification-ester hydrolysis sequence.

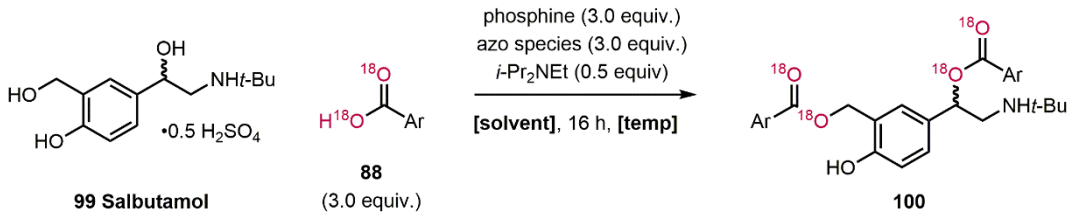


97 Ethambutol | **88** (3.0 equiv.) | **98**

Entry	Phosphine	Azo Species	Solvent	Temperature / °C	Yield / %
1	PPh_3	DIAD	THF	r.t.	< 5
2	PPh_3	DIAD	$CHCl_3$	r.t.	0
3	PPh_3	DIAD	toluene	r.t.	0
4	PPh_3	DIAD	THF	40	< 5
5	PPh_3	DIAD	THF	66	< 5

The attempted labelling of Ethanbutol (**97**, table 4) was also precluded by its inability to engage in the Mitsunobu esterification step. Attempting to couple Ethanbutol with ^{18}O-labelled 4-nitrobenzoic acid using triphenylphosphine and DIAD in THF gave the corresponding diester with a very poor yield (< 5%). However, changing the solvent to chloroform or toluene resulted no formation of diester product (entries 2 and 3). Attempting to run the reaction in tetrahydrofuran at higher temperatures of 40 °C and 66 °C both afforded the product with a very low yield of < 5% (entries 4 and 5).

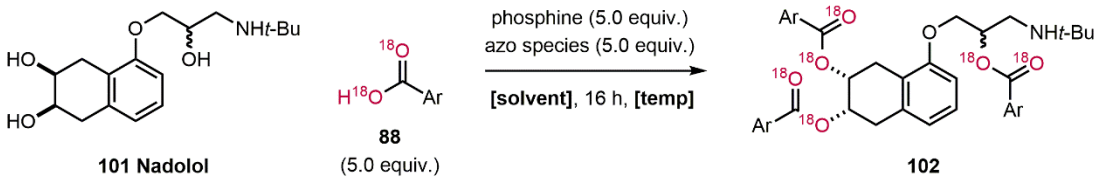
Table 5. The attempted ^{18}O-labelling of Salbutamol using the Mitsunobu esterification-ester hydrolysis sequence.



99 Salbutamol **88** (3.0 equiv.) **100**

Entry	Phosphine	Azo Species	Solvent	Temperature / °C	Yield / %
1	PPh_3	DIAD	THF	r.t.	0
2	PPh_3	DIAD	toluene	r.t.	0
3	PPh_3	DIAD	DMF	r.t.	0
4	PPh_3	DIAD	THF	66	0
5	PPh_3	DIAD	toluene	66	0
6	P(*n*-Bu)$_3$	ADDP	THF	r.t.	0
7	P(*n*-Bu)$_3$	ADDP	toluene	r.t.	0

Table 6. The attempted ^{18}O-labelling of Nadolol using the Mitsunobu esterification-ester hydrolysis sequence.



101 Nadolol **88** (5.0 equiv.) **102**

Entry	Phosphine	Azo Species	Solvent	Temperature / °C	Yield / %
1	PPh_3	DIAD	THF	r.t.	0
2	PPh_3	DIAD	toluene	r.t.	0
3	PPh_3	DIAD	$CHCl_3$	r.t.	< 5
4	PPh_3	DIAD	$CHCl_3$	66	< 5
5	PPh_3	DEAD	THF	r.t.	0
6	PPh_3	DEAD	$CHCl_3$	r.t.	0
7	PPh_3	DEAD	$CHCl_3$	66	0
8	P(*n*-Bu)$_3$	DEAD	THF	r.t.	0
9	P(*n*-Bu)$_3$	DEAD	$CHCl_3$	r.t.	0
10	P(*n*-Bu)$_3$	ADDP	toluene	r.t.	0

The ^{18}O-labelling of Salbutamol (**99**, table 5) was then investigated, beginning with the attempted Mitsunobu esterification of Salbutamol with ^{18}O-labelled 4-nitrobenzonitrile to form diester **100**. Attempts to facilitate the Mitsunobu coupling with triphenylphosphine and DIAD reagent combination proved

unsuccessful in numerous solvents, at both room temperature and at 66 °C (entries 1–5). Using the reagent combination of tri(*n*-butyl)phosphine and ADDP also proved to be unsuccessful with no product being obtained (entries 6 and 7).

Finally, in seeking to form labelled triester **102** (table 6), the β-blocker Nadolol (**101**) was subject to a Mitsunobu esterification with ^{18}O-labelled 4-nitrobenzonitrile. The Mitsunobu coupling was initially attempted using triphenylphosphine and DIAD as reagents. The reaction gave no product when conducted in tetrahydrofuran or toluene (entries 1 and 2), however a low yield (< 5%) of product was obtained when the reaction was conducted in chloroform, at both room temperature and 66 °C (entries 3 and 4). However, attempts to improve on this result, by altering the solvent, reaction temperature, phosphine and azo species were unsuccessful, with each attempt giving 0% yield (entries 5–10).

3.3 Conclusion

A Mitsunobu esterification-ester hydrolysis sequence using a doubly ^{18}O-labelled carboxylic acid as a pronucleophile has enabled the development of a protocol for the ^{18}O-labelling of primary and secondary alcohols. The synthesis of a ^{18}O-labelled tertiary alcohol was also achieved by the derivatisation of an ^{18}O-labelled secondary alcohol. The Mitsunobu coupling approach allows abundant unlabelled alcohols to be used as substrates whilst also providing stereo-control. The conditions were shown to be tolerant of a wide range of functional groups. Furthermore, we have demonstrated that alternative Mitsunobu reagents, which simplify purification, are compatible with this protocol.

The ^{18}O-labelling protocol was also applied to the labelling of the active pharmaceutical ingredient Dropropizine. The labelled substrate was accessed with sufficient isotopic purity to make it appropriate as an internal standard for mass spectrometry-based analysis which is essential for pharmaceutical developments. Attempts to label other active pharmaceutical ingredients, namely Pyridoxine, Ethanbutol, Salbutamol and Nadolol, using this protocol were unsuccessful, with the Mitsunobu step giving very poor yields of diester and triester products.

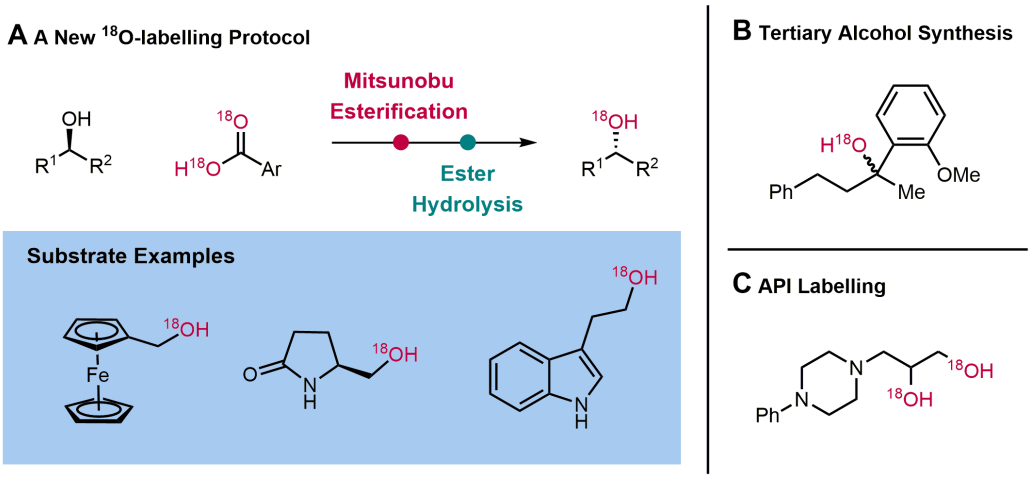


Figure 14. (A) A Mitsunobu esterification-hydrolysis based protocol for accessing ^{18}O-labelledd alcohols; **(B)** Derivatisation of 18O-labelled secondary alcohols to of ^{18}O-labelled tertiary alcohols; **(C)** Application of the ^{18}O-labelling protocol towards the synthesis of ^{18}O-labelled active pharmaceutical ingredients.

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Experimental

General Information

Reagents and solvents, unless otherwise noted, reagents were purchased from commercial suppliers and used directly without further purification. Unless indicated, technical grade solvents were purchased from commercial suppliers and used without further purification. Petrol refers to 40-60 petroleum ether. Unless otherwise stated, all toluene was dried by passing over two columns of activated alumina and kept over sodium wire. All water was deionised before use. Unless stated, all reactions were carried out in conventional glassware. 'Room temperature' can vary between 18 °C and 25 °C. For chapter 3, 4 M HCl in dioxane was purchased from Acros (product code: MFCD00011324). 4-nitrobenzonitrile was dried in an Abderhalden drying pistol using $CaCl_2$ as the desiccant at 50 °C for 24 hours before use. H_2O-[^{18}O] (98% isotopic purity) was purchased from Sercon Ltd. (product code: F03-0027).

Analysis and Characterization

Analytical thin layer chromatography (TLC) was performed on Merck aluminium-backed silica gel 60 F254 plates (product code: 105554.) Developed TLC plates were visualized by ultraviolet (UV) irradiation (254 nm) or by staining with a solution of potassium permanganate. Column chromatography was carried out according to Still's method, using Fluorochem silica gel 60 Å, 40–63 mesh (product code = LC401). Melting points were measured using a Stuart SMP3 (Sigma Aldrich product Z645729.) Fourier transform infrared spectrometry (FTIR) was carried out using a Bruker Tensor 27 using an attenuated total reflection (ATR) attachment and peaks are reported in terms of frequency of absorption (cm^{-1}). High-resolution mass spectrometry HRMS were acquired using a Bruker microTOF II with Electron Spray Ionization (ESI-TOF). HRMS data were quoted to four decimal places (0.1 mDa). Specific rotations ([α]D T) were measured using an Anton Paar MCP 100 Modular Circular Polarimeter. All NMR spectra were recorded at 298 K on either a Bruker AV 400, Bruker AV 3400 or Bruker Ascent 500 and are internally referenced to residual solvent signals ($CDCl_3$ is referenced at δ 7.26 and 77.16 for ^1H and ^{13}C NMR respectively, DMSO-*d*$_6$ is referenced at δ 2.50 and 39.52 for ^1H and ^{13}C NMR respectively, CD_3OD is

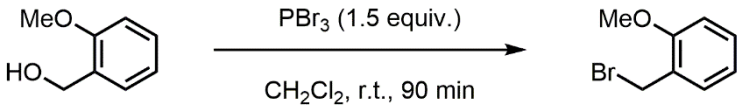
referenced at δ 3.31 and 49.00 for ^{1}H and ^{13}C NMR respectively). All NMR chemical shifts (δ) were reported in parts per million (ppm) and coupling constants (J) are given in Hertz (Hz). The ^{1}H NMR spectra are reported as follows: δ (multiplicity, coupling constant J, number of protons.) All chiral HPLC and SFC was carried out by Reach Separations (BioCity Nottingham, Pennyfoot Street, Nottingham, NG1 1GF - http://www.reachseparations.com.

Chapter 2

The Development of a Catalytic Mitsunobu Reaction

Preparation of Catalyst C2

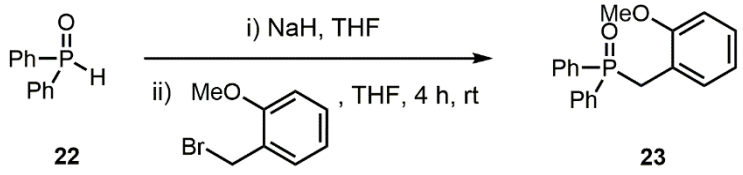
1-(Bromomethyl)-2-methoxybenzene (S1)



S1

To a solution of 2-methoxybenzyl alcohol (6.65 mL, 50.0 mmol) in CH_2Cl_2 (100 mL) was added phosphorus tribromide (7.05 mL, 75.0 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1.5 hours. The reaction was re-cooled to 0 °C, quenched with H_2O (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with a saturated $NaHCO_3$ solution (2 × 100 mL) then a saturated brine solution (100 mL), dried over $MgSO_4$ and concentrated in vacuo to afford the title compound as an off-white solid (10.03 g, 99%).* **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.36 – 7.28 (m, 2H), 6.94 (apparent td, *J* = 7.5, 1.0 Hz, 1H), 6.89 (dd, *J* = 8.3, 1.0 Hz, 1H), 4.59 (s, 2H), 3.91 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 157.6 (C_q), 131.0 (CH), 130.3 (CH), 126.2 (C_q), 120.8 (CH), 111.1 (CH), 55.7 (CH_3), 29.2 (CH_2); **HRMS** (GC/MS-EITOF) *m/z* calc'd for $C_8H_9{}^{79}BrO$ $[M]^{+\cdot}$: 199.9831 found 199.9829; **m.p.** 46–48 °C (lit. = 47–49 °C). Data are consistent with those reported in the literature.[1] *The compound was stored at −20 °C under argon.

(2-Methoxybenzyl)diphenylphosphine Oxide (23)

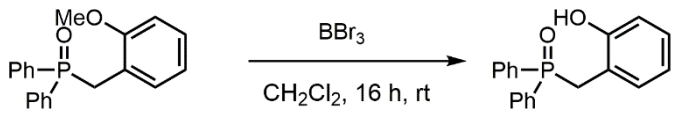


22 **23**

To a solution of diphenylphosphine oxide (8.43 g, 41.6 mmol) in anhydrous THF (120 mL) was added sodium hydride (2.50 g, 62.5 mmol of a 60% *w*/*w* dispersion in oil) in portions at 0 °C. The suspension was warmed to room temperature, and after 30 minutes. The reaction mixture was then cooled to 0 °C before 1-(bromomethyl)-2-methoxybenzene (**S1**) (10.0 g, 50.0 mmol) was added and the mixture was warmed to room temperature and stirred for a further 1 hour.

The reaction mixture was then quenched with H_2O at 0 °C and extracted with EtOAc (3 × 150 mL). The combined organic extracts were washed with a saturated brine solution (150 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by trituration with Et_2O to afford the title compound as an off-white solid. (11.05 g, 82%) **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.75 – 7.66 (m, 4H), 7.50 – 7.44 (m, 2H), 7.43 – 7.34 (m, 5H), 7.17 – 7.11 (m, 1H), 6.89 – 6.83 (m, 1H), 6.65 (d, *J* = 8.2 Hz, 1H), 3.75 (d, *J* = 14.2 Hz, 2H), 3.44 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 156.9 (d, *J* = 5.4 Hz, C_q), 133.0 (d, *J* = 98.8 Hz, C_q), 131.8 (d, *J* = 4.7 Hz, CH), 131.6 (d, *J* = 3.0 Hz, CH), 131.3 (d, *J* = 9.2 Hz, CH), 128.4 – 128.2 (m, 2 × CH), 120.7 (d, *J* = 2.8 Hz, CH), 119.9 (d, *J* = 8.2 Hz, C_q), 110.3 (d, *J* = 2.8 Hz, CH), 55.0 (s, CH_3), 31.2 (d, *J* = 68.0 Hz, CH_2); **^{31}P{^{1}H} NMR** (162 MHz, $CDCl_3$) δ_P 30.1; **HRMS (ESI-TOF)** *m/z* calc'd for $C_{20}H_{20}O_2P$ $[M + H]^+$: 337.1352, found 337.1349; **TLC** R_f; 0.38 (4:1 EtOAc/petrol); **FTIR** (neat) ν_{max}/cm^{-1} 3074, 2930, 2834, 1616, 1488, 1457, 1435, 1242, 1198, 1142, 1118, 1091, 1021; **m.p.** 109–110 °C. Data are consistent with those reported in the literature.[2]

(2-Hydroxybenzyl)diphenylphosphine Oxide (C2)



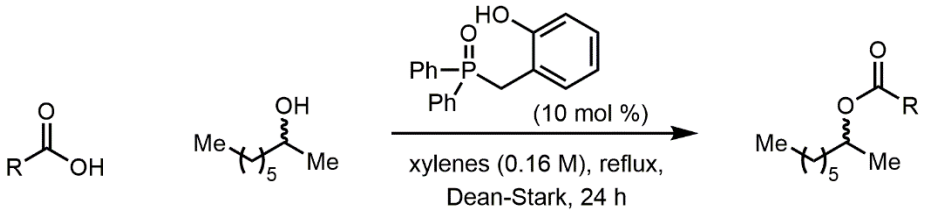
23 **C2**

To a solution of **23** (11.0 g, 34.3 mmol) in CH_2Cl_2 (75 mL) was added 1 M boron tribromide in CH_2Cl_2 (75 mL, 75.0 mmol) dropwise at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 hours, after which reaction was quenched with H_2O (50 mL). The pH of the aqueous layer was adjusted to pH 8 using a saturated aqueous solution of NaHCO3 (30 mL) before being extracted with CH_2Cl_2 (3 × 75 mL). The combined organic extracts were washed with a saturated aqueous solution of NaHCO3 (75 mL), then a saturated brine solution (75 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by trituration with Et_2O to afford the title compound as a colourless solid (8.95 g, 84%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.81 (s, 1H) 7.76 – 7.68 (m, 4H) 7.58-7.52 (m, 2H) 7.50 – 7.44 (m, 4H) 7.14 – 7.08 (m, 1H) 7.00 (dd, *J* = 8.1, 1,2 Hz,) 6.77 (apparent dt, *J* = 7.6, 1.9 Hz, 1H) 6.69 (apparent td, *J* = 7.6, 1.2 Hz, 1H) 3.71

(d, J = 12.9 Hz); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 156.7 (d, J = 3.9 Hz, C_q), 132.6 (d, J = 3.0 Hz, CH), 131.8 (d, J = 6.3 Hz, CH), 131.1 (d, J = 9.7 Hz, CH), 130.7 (d, J = 100.5 Hz, C_q), 129.1 (d, J = 2.9 Hz, CH), 128.9 (d, J = 12.2 Hz, CH), 120.7 (d, J = 1.9 Hz, CH), 119.7 (d, J = 2.3 Hz, CH), 119.5 (d, J = 8.5 Hz, C_q), 35.6 (d, J = 67.4 Hz, CH_2); **^{31}P{^{1}H} NMR** (162 MHz, $CDCl_3$) δ_P 38.3; **HRMS** (ESI-TOF) m/z calc'd for $C_{19}H_{18}O_2P$ $[M + H]^+$: 309.1039; found 309.1048; **FTIR** (neat) ν_{max}/cm^{-1} 3077, 2955, 2925, 1580, 1484, 1439, 1246, 1219, 1152, 1124, 1096, 1070; **TLC** R_f; 0.35 (1:1 EtOAc/petrol); **m.p.** 167–169 °C. Data are consistent with those reported in the literature.[3]

Optimization of the Catalytic Mitsunobu Reaction

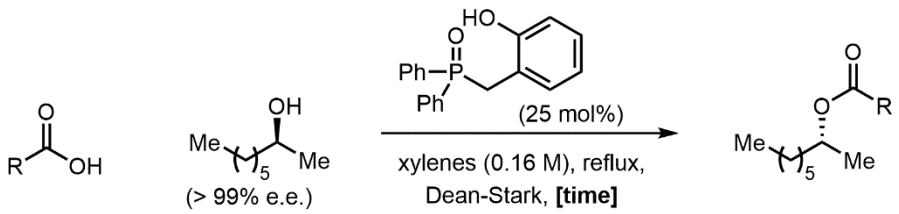
Evaluation of Different Carboxylic Acids (Table 1)



A suspension of (±)-2-octanol (316 µL, 2.00 mmol), carboxylic acid (2.00 mmol) and catalyst **C2** (62 mg, 200 µmol) in xylenes (12.5 mL) was heated to reflux in a Dean-Stark apparatus and stirred for 24 hours. The reaction mixture was cooled to room temperature, and 1,1,2,2-tetrachloroethane (216 µL, 2.00 mmol) was added as an NMR internal standard and the reaction mixture was stirred for five minutes. An aliquot was taken and subject to ^{1}H NMR analysis to determine the NMR yield.

For examples showing promising results, (Entries 1,2,3,6 and 7) the extent of the background esterification was monitored. The protocols were as follows; A suspension of (±)-2-octanol (316 µL, 2.00 mmol) and carboxylic acid (2.00 mmol) in xylenes (12.5 mL) was heated to reflux in a Dean-Stark apparatus, and stirred for 24 hours. The reaction mixture was cooled to room temperature, and 1,1,2,2,-tetrachloroethane (216 µL, 2.00 mmol) was added as an NMR internal standard and the reaction mixture was stirred for five minutes. An aliquot was taken and subject to ^{1}H NMR analysis to determine the NMR yield.

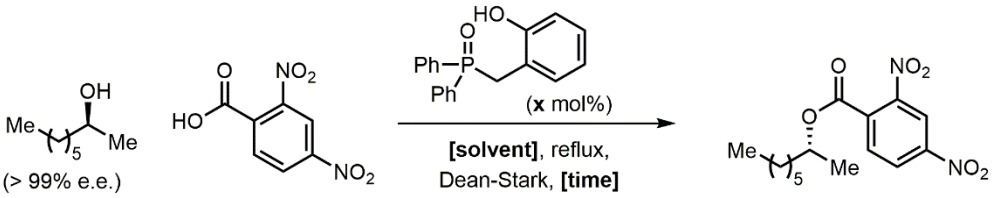
Evaluation of Different Carboxylic Acids for Invertive Esterification (Table 2)



A suspension of (*S*)-(+)-2-octanol (316 µL, 2.00 mmol), carboxylic acid (2.00 mmol) and catalyst **C2** (154 mg, 500 µmol) in xylenes (12.5 mL) was heated to reflux in a Dean-Stark apparatus, and stirred for the stated time period. The

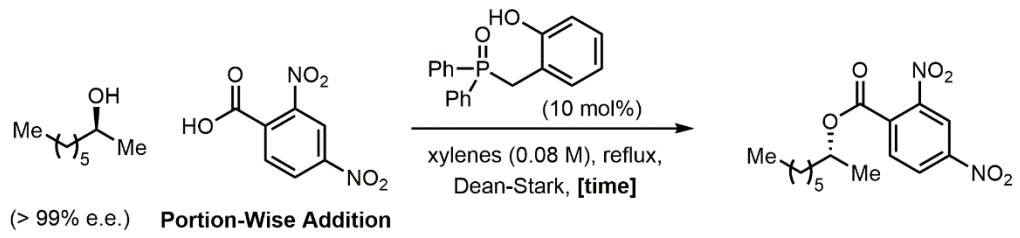
reaction mixture was cooled to room temperature, diluted with EtOAc (20 mL) and washed with NaOH (2 × 10 mL of a 1.0 M solution in H_2O) solution twice then brine (10 mL). The organic phase was dried over $MgSO_4$ and concentrated. The crude residue was purified by flash column chromatography to afford the ester product. Enantiomeric excess was determined by chiral HPLC or SFC comparing with both a racemic sample and a sample with retention of stereochemistry.

Evaluation of Solvent, Reaction Duration and Concentration (Table 3)



(*S*)-(+)-2-Octanol, 2,4-dinitrobenzoic acid and catalyst **C2** were suspended in xylenes or toluene to the appropriate concentration and catalyst loading. The mixture was then heated to reflux in a Dean-Stark apparatus and stirred until the alcohol was fully consumed. The reaction mixture was cooled to room temperature, diluted with EtOAc and washed with NaOH (10-20 mL of a 1.0 M solution in H_2O) twice then brine (10-20 mL of a saturated solution in H_2O.) The organic phase was dried over $MgSO_4$ and concentrated. The crude residue was purified by flash column chromatography to afford the ester product. Enantiomeric excess was determined by chiral HPLC or SFC comparing with both a racemic sample and a sample with retention of stereochemistry.

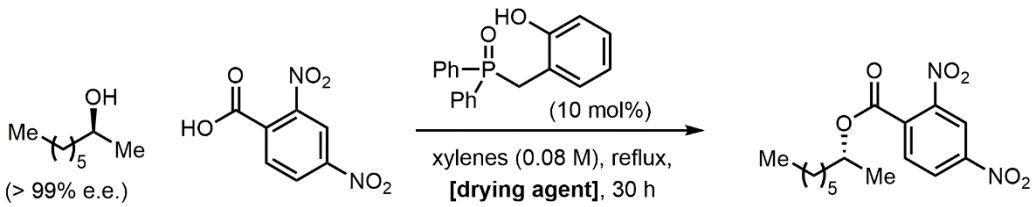
Evaluation of Portion-Wise Acid Addition (Table 4, entries 3–4)



A suspension of (*S*)-(+)-2-octanol (316 µL, 2.00 mmol), 2,4-dinitrobenzoic acid (141 mg, 0.666 mmol) and catalyst **C2** (61 mg, 0.20 mmol) in xylenes (25 mL) was heated to reflux in a Dean-Stark apparatus, and stirred for the stated time period. After the first time point a further addition of 2,4-dinitrobenzoic acid

(141 mg, 0.666 mmol) was made. After the second time point a further addition of 2,4-dinitrobenzoic acid (141 mg, 0.666 mmol) was made and the reaction was stirred until the states endpoint. The reaction mixture was cooled to room temperature, diluted with EtOAc (20 mL) and washed with NaOH (2 × 10 mL of a 1.0 M solution in H_2O) solution twice then brine (10 mL). The organic phase was dried over $MgSO_4$ and concentrated. The crude residue was purified by flash column chromatography to afford the ester product. Enantiomeric excess was determined by chiral HPLC or SFC comparing with both a racemic sample and a sample with retention of stereochemistry.

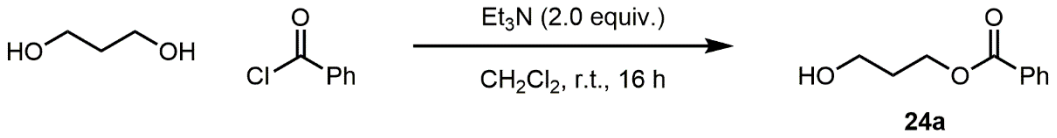
Evaluation of Different Drying Agents (Table 4, entries 5–10)



To a 25 mL microwave vial was added of (*S*)-(+)-2-octanol (158 µL, 1.00 mmol), 2,4-dinitrobenzoic acid (212 mg, 1.00 mmol), catalyst **C2** (31 mg, 0.10 mmol), xylenes (12.5 mL) and a specified drying agent (100 mg). The vials were capped and heated to 145 °C and stirred for 30 hours. The reaction mixture was cooled to room temperature, diluted with EtOAc (20 mL) and washed with 1 M aqueous NaOH solution (2 × 10 mL) twice then a saturated brine solution (10 mL). The organic phase was dried over $MgSO_4$ and concentrated. The crude residue was purified by flash column chromatography to afford the ester product. Enantiomeric excess was determined by chiral HPLC or SFC comparing with both a racemic sample and a sample with retention of stereochemistry.

Preparation of the Alcohol Starting Materials

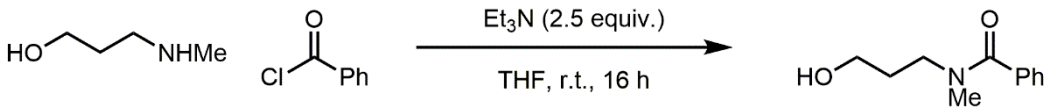
3-Hydroxypropyl Benzoate (24a)



24a

To a solution of 1,3-propanediol (3.25 mL, 45.0 mmol) and triethylamine (4.18 mL, 30.0 mmol) in CH_2Cl_2 (75 mL) was added benzoyl chloride (1.74 mL, 15.0 mmol) dropwise at 0 °C. The solution was warmed to room temperature and stirred for 16 h. The reaction mixture was then diluted with H_2O (75 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was washed with a saturated brine solution (75 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, 1:1 EtOAc/petrol) to afford the title compound as a colourless oil (1.91 g, 70%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.06 – 8.01 (m, 2H), 7.59 – 7.53 (m, 1H), 7.47 – 7.40 (m, 2H), 4.49 (t, *J* = 6.1 Hz, 2H), 3.77 (t, *J* = 6.1 Hz, 2H), 2.18 (s, 1H), 2.01 (apparent p, *J* = 6.1 Hz, 2H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 167.1 (C_q), 133.2 (CH), 130.2 (C_q), 129.7 (CH), 128.5 (CH), 61.9 (CH_2), 59.3 (CH_2), 32.0 (CH_2); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{10}H_{12}NaO_3$ $[M + Na]^+$ = 203.0679 found 203.0677; **TLC** R_f; 0.34 (1:1 EtOAc/petrol). Data are consistent with those reported in the literature.[4]

***N*-(3-Hydroxypropyl)-*N*-methylbenzamide (24b)**

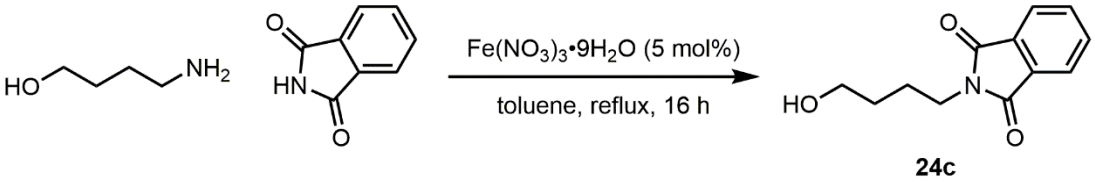


24b

To a solution of 3-(methylamino)propan-1-ol (1.00 g, 11.2 mmol) and triethylamine (3.91 mL, 28.1 mmol) in THF (20 mL) was added benzoyl chloride (1.09 mL, 9.35 mmol) in THF (10 mL) *via* dropping funnel over 30 minutes at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 hours. The reaction mixture was then concentrated *in vacuo*, diluted with H_2O (100 mL) and extracted with EtOAc (4 × 50 mL). The combined organic extracts were washed with a saturated brine solution (100 mL), dried over $MgSO_4$ and

concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, 1:24 MeOH/CH_2Cl_2) to afford the title compound as a colourless oil (1.57 g, 87%). **^{1}H NMR** (400 MHz, DMSO-d_6, 353 K) δ_H 7.45 – 7.40 (m, 3H), 7.40 – 7.34 (m, 2H), 4.20 (t, *J* = 5.2 Hz, 1H), 3.55 – 3.28 (m, 4H), 2.93 (s, 3H), 1.73 (apparent p, *J* = 6.6 Hz, 2H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 172.8 (C_q), 135.9 (C_q), 129.9 (CH), 128.5 (CH), 127.0 (CH), 58.2 (CH_2), 43.8 (CH_2), 37.5 (CH_3), 29.3 (CH_2); **HRMS** (ESI-TOF) *m/z* calc'd for $C_{11}H_{16}NO_2$ $[M + H]^+$: 194.1176 found 194.1172; **FTIR** (neat) ν_{max}/cm^{-1} 3398, 2937, 2837, 1611, 1576, 1503, 1479, 1446, 1401, 1301, 1262, 1056, 1026; **TLC** R_f; 0.26 (1:19 MeOH/CH_2Cl_2).

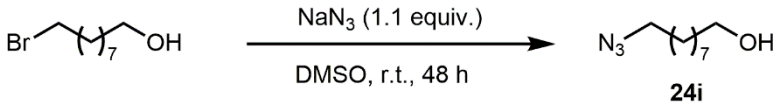
2-(4-Hydroxybutyl)isoindoline-1,3-dione (24c)



24c

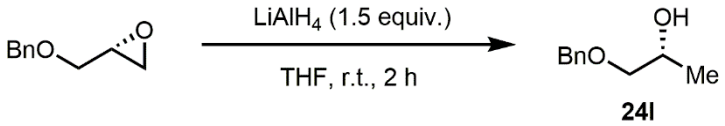
According to an adapted literature procedure,[5] 4-amino-1-butanol (891 mg, 10.0 mmol), phthalimide (2.94 g, 20.0 mmol) and $Fe(NO_3)_3{\cdot}9H_2O$ (202 mg, 500 µmol) were suspended in toluene (10.0 mL). The reaction mixture was heated to reflux and stirred for 16 hours, before the reaction mixture was diluted with EtOAc (20 mL), filtered through celite and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 0:100 to 1:49 gradient, MeOH/ CH_2Cl_2) afforded the title compound as an off-white solid (1.81 g, 83%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.82 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.70 (dd, *J* = 5.5, 3.0 Hz, 2H), 3.72 (t, *J* = 7.1 Hz, 2H), 3.68 (t, *J* = 6.5 Hz, 2H), 1.82 – 1.72 (m, 3H), 1.65 – 1.56 (m, 2H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 168.6 (C_q), 134.1 (CH), 132.2 (C_q), 123.3 (CH), 62.4 (CH_2), 37.8 (CH_2), 29.9 (CH_2), 25.2 (CH_2); **HRMS** (ESI-TOF) *m/z* calc'd for $C_{12}H_{14}NO_3$ $[M + H]^+$: 220.0968 found 220.0974; **TLC** R_f; 0.28 (1:49 MeOH:CH_2Cl_2); **m.p.** 54–55 °C (lit.[6] = 52–53 °C). Data are consistent with those reported in the literature.[6]

9-Azidononan-1-ol (24i)



To a solution of 9-bromo-1-nonanol (1.67 g, 7.50 mmol) in DMSO (75 mL) was added sodium azide (536 mg, 8.25 mmol) in portions at room temperature and the reaction mixture was stirred for 48 hours. The reaction mixture was then diluted with H_2O (200 mL) and extracted with Et_2O (3 × 200 mL). The combined organic extracts were washed with a saturated brine solution (200 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 Et_2O/petrol) afforded the title compound as a colourless oil (1.31 g, 94%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.62 (t, *J* = 6.6 Hz, 2H), 3.24 (t, *J* = 7.0 Hz, 2H), 1.63 – 1.51 (m, 4H), 1.41 (s, 1H), 1.38 – 1.25 (m, 10H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 63.1 (CH_2), 51.6 (CH_2), 32.9 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 28.9 (CH_2), 26.8 (CH_2), 25.8 (CH_2); **HRMS** (ESI-TOF) *m/z* calc'd for $C_9H_{19}N_3NaO$ $[M + Na]^+$: 208.1420 found 208.1420; **TLC** R_f; 0.22 (1:1 Et_2O/petrol). Data are consistent with those reported in the literature.[7]

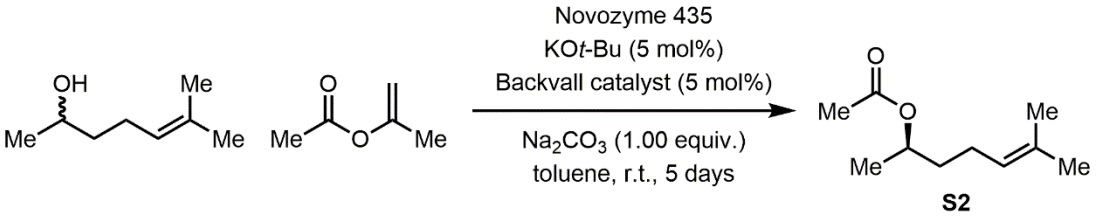
(*S*)-1-(Benzyloxy)propan-2-ol (24l)



To a solution of (*S*)-benzyl glycidyl ether (1.86 mL, 12.0 mmol) in THF (10.0 mL) was added lithium aluminium hydride (683 mg, 18.0 mmol) in portions at 0 °C, under an argon atmosphere. The reaction mixture was warmed to room temperature and stirred for 2 hours. The reaction was then diluted with Et_2O (20 mL) and cooled to 0 °C before H_2O (0.70 mL) was added dropwise, followed by a 15% *w/v* aqueous NaOH solution (0.70 mL) then H_2O (2.1 mL). The reaction was warmed to room temperature and stirred for 15 minutes, before $MgSO_4$ (5 g) was added and the reaction mixture stirred for a further 15 minutes then passed through a pad of celite, then a short pad of silica, eluting with EtOAc. The solvent was removed *in vacuo* to afford the title compound as a colourless liquid (1.80 g, 90%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.39 – 7.27 (m, 5H), 4.56 (s, 2H), 4.01 (dqd, *J*

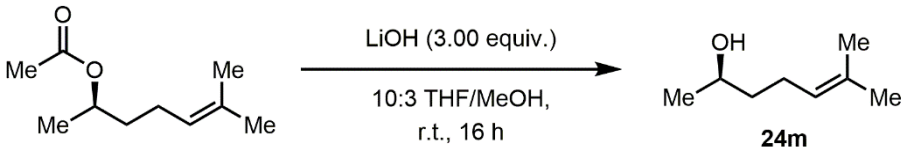
= 8.1, 6.4, 3.1 Hz, 1H), 3.48 (dd, *J* = 9.4, 3.1 Hz, 1H), 3.29 (dd, *J* = 9.4, 8.1 Hz, 1H), 1.15 (d, *J* = 6.4 Hz, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 138.1 (C_q), 128.6 (CH), 127.9 (CH), 127.9 (CH), 75.9 (CH_2), 73.4 (CH_2), 66.6 (CH), 18.8 (CH_3); **HRMS** (ESI-TOF) *m/z* calc'd for $C_{10}H_{14}NaO_2$ $[M + Na]^+$: 189.0886 found 189.0888; **FTIR** (neat) ν_{max}/cm^{-1} 3393, 2970, 2859, 1453, 1369, 1091. **TLC** R_f; 0.21 (1:4 EtOAc/petrol); e.e. = 97% (determined by chiral SFC of the 2,4-dintitrobenzoate ester, see **S21**) Data are consistent with those reported in the literature.[8]

(*R*)-6-Methylhept-5-en-2-yl Acetate (S2)



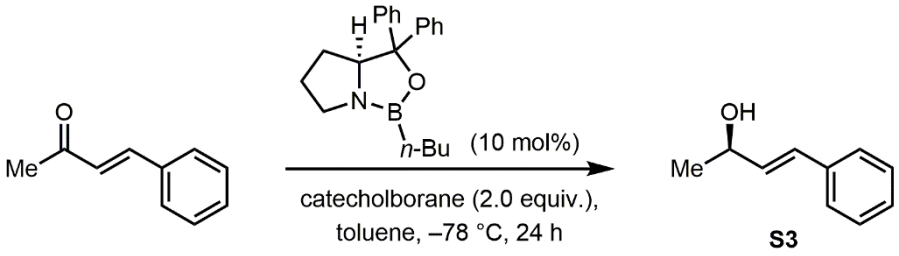
Synthesized according to an adapted literature procedure.[9] To a flame-dried Schlenk tube was added 1.0 M potassium *tert*-butoxide in THF (300 µL, 300 µmol), and the solvent was evaporated *in vacuo* using a Schlenk line. *Candida Antartica* Lipase (CALB, also known as Novozyme 435, 6 mg), Bäckvall catalyst (**S8**) (see pages 175–176 for synthesis, 191 mg, 300 µmol) and sodium carbonate (636 mg, 6.00 mmol) were added, before toluene (12 mL) was added and the reaction mixture was stirred for 6 minutes. (±)-6-methyl-5-hepten-2-ol (769 mg, 6.00 mmol) was added and the reaction mixture was stirred for 4 minutes, then isopropenyl acetate (978 µL, 9.00 mmol) was added and the reaction mixture was stirred at 25 °C for 5 days. The reaction mixture was then filtered, and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:19 EtOAc:petrol) afforded the title compound as a colourless oil. (798 mg, 78%) **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.11 – 5.05 (m, 1H), 4.88 (dqd, *J* = 7.7, 6.2, 5.2 Hz, 1H), 2.06 – 1.95 (m, 5H), 1.68 (s, 3H), 1.66 – 1.60 (m, 1H), 1.59 (s, 3H), 1.56 – 1.42 (m, 1H), 1.21 (d, *J* = 6.2 Hz, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 170.9 (C_q), 132.3 (C_q), 123.6 (CH), 70.8 (CH), 36.1 (CH_2), 25.8 (CH_3), 24.2 (CH_2), 21.5 (CH_3), 20.1 (CH_3), 17.7 (CH_3); **TLC** R_f; 0.21 (1:19 EtOAc/petrol); Data are consistent with those reported in the literature.[10]

(*R*)-6-Methylhept-5-en-2-ol (24m)



To a solution of **S2** (341 mg, 2.00 mmol) in 10:3 THF:MeOH (13 mL) was added 2.0 M aqueous solution of lithium hydroxide (3.0 mL, 6.0 mmol) at room temperature and the reaction mixture was stirred for 16 hours, after which the mixture was diluted with NaOH (20 mL, 1.0 M solution in H_2O) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:3 EtOAc:petrol) afforded the title compound as a colourless liquid. (150 mg, 59%) **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.14 – 5.10 (m, 1H), 3.83 – 3.78 (m, 1H), 2.14 – 2.00 (m, 2H), 1.66 (s, 3H), 1.61 (s, 3H), 1.53-1.38 (m, 3H), 1.18 (d, *J* = 6.0 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 132.0 (C_q), 124.0 (CH), 68.0 (CH), 39.1 (CH_2), 25.6 (CH_3), 24.4 (CH_2), 23.4 (CH_3), 17.6 (CH_3); **TLC** R_f; 0.32 (1:3 EtOAc:petrol); **$[\alpha]_D^{25}$** −8.0; (*c.* 1.0, $CHCl_3$) **(lit.**[10] **$[\alpha]_D^{22}$** −11.7 (*c.* 1.01, $CHCl_3$)); e.e = 93% (determined by chiral SFC of the 2,4-dinitrobenzoate ester, see **S23**). Data are consistent with those reported in the literature.[10]

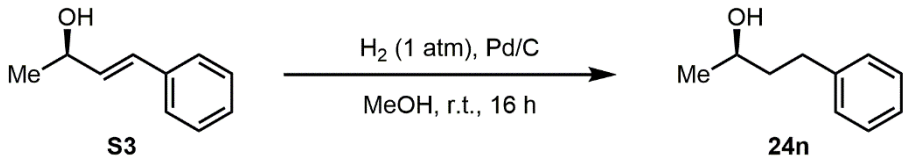
(*R*,*E*)-4-Phenylbut-3-en-2-ol (S3)



To a solution of 4-phenyl-3-buten-2-one (1.46 g, 10.0 mmol) in toluene (10.0 mL) was added (*S*)-(−)-2-butyl-CBS-oxazaborolidine (1.0 mL, 1.0 mmol, 1.0 M solution in toluene) and the reaction mixture was stirred at room temperature for 15 minutes before being cooled to −78 °C and a solution of catecholborane (2.40 g, 20.0 mmol) in toluene (7.0 mL) was added by syringe over 20 minutes. The reaction mixture stirred at −78 °C for a further 24 hours before being

quenched with a 1.0 M aqueous NaOH solution (60 mL). The quenched reaction mixture was diluted with water then extracted with EtOAc (3 × 50 mL). The combined organic extracts were successively washed with a 1.0 M aqueous NaOH solution (60 mL) until the aqueous washings were colourless. The organic fraction was then washed with brine (50 mL), dried over $MgSO_4$ then concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, 1:4 EtOAc:petrol) to afford the title compound as an off-white solid (1.04 g, 70%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.43 – 7.39 (m, 2H), 7.37 – 7.32 (m, 2H), 7.30 – 7.24 (m, 1H), 6.60 (dd, *J* = 15.9, 1.1 Hz, 1H), 6.29 (dd, *J* = 15.9, 6.4 Hz, 1H), 4.52 (apparent p, *J* = 6.4 Hz, 1H), 1.83 (s, 1H), 1.41 (d, *J* = 6.4 Hz, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 136.8 (C_q), 133.7 (CH), 129.5 (CH), 128.7 (CH), 127.7 (CH), 126.6 (CH), 69.0 (CH), 23.5 (CH_3); **TLC** R_f; 0.21 (1:4 EtOAc:petrol); **m.p.** 58–60 °C; **$[\alpha]_D^{25}$: +**29.9 (*c.* 1.0, $CHCl_3$) **(lit.**[11] **$[\alpha]_D^{20}$**: –28.6 (*c.* 1.4, $CHCl_3$) *S*-stereoisomer 90% e.e.); **Chiral SFC** column: Lux C1 (4.6 mm × 250 mm, 5 μm); mobile phase: 3:7 EtOH:CO_2 (0.2% *v*/*v* NH_3); flow rate: 4 mL/min; temperature: 40 °C; T_R (min) 1.91 (major), 2.56 (minor); 95% e.e.;. Data are consistent with those reported in the literature.[12]

(*R*)-4-Phenylbutan-2-ol (24n)

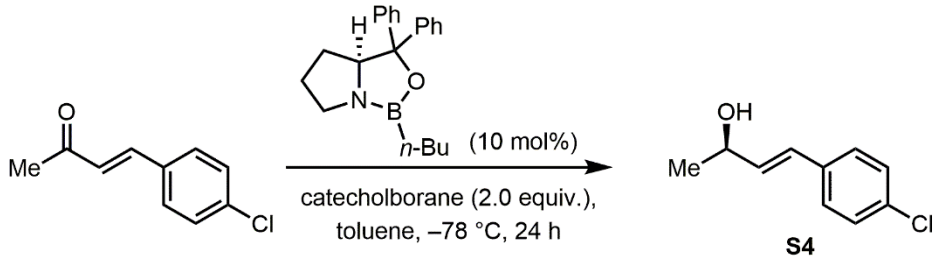


S3 **24n**

A suspension of **S3** (889 mg, 6.00 mmol) and palladium hydroxide (89 mg, 84 μmol, 10% *w*/*w* on carbon) in MeOH was charged with hydrogen gas (1 atm) and stirred for 16 hours after which time the reaction mixture was filtered through celite and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, 1:9 EtOAc:petrol) to afford the title compound as a pale orange oil (682 mg, 76%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.33 – 7.26 (m, 2H), 7.23 – 7.17 (m, 3H), 3.84 (apparent sextet, *J* = 6.2 Hz, 1H), 2.81 – 2.63 (m, 2H), 1.84 – 1.71 (m, 2H), 1.35 (s, 1H), 1.24 (d, *J* = 6.2 Hz, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 142.2 (C_q), 128.6 (4 × Ar-C, CH), 126.0 (CH), 67.7 (CH), 41.0 (CH_2), 32.3 (CH_2), 23.8 (CH_3); **TLC** R_f; 0.23 (1:4 EtOAc:petrol); **$[\alpha]_D^{25}$** –13.8 (*c.* 1.0, $CHCl_3$)

(lit.[13] **[α]$_D^{25}$** +15.0 (*c.* 1.0, $CHCl_3$) *S*-stereoisomer, 96% e.e.); **Chiral SFC** column: Lux C1 (4.6 mm × 250 mm, 5 μm); mobile phase: 3:17 EtOH:CO_2 (0.2% *v*/*v* NH_3); flow rate: 4 mL/min; temperature: 40 °C; T_R (min) 1.56 (major), 1.88 (minor) 92% e.e. Data are consistent with those reported in the literature.[14]

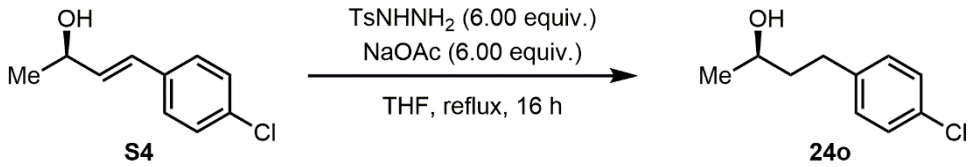
(*R*)-(*E*)-4-(4-Chlorophenyl)but-3-en-2-ol (S4)



To a solution of 4-(4-chlorophenyl)-3-butanone (2.35 g, 13.0 mmol) in toluene (17.0 mL) was added (*S*)-(−)-2-butyl-CBS-oxazaborolidine (1.3 mL, 1.0 mmol, 1.0 M solution in toluene) and the reaction mixture was stirred at room temperature for 15 minutes before the reaction mixture was cooled to −78 °C and a solution of catecholborane (3.12 g, 26.0 mmol) in toluene (5.0 mL) was added by syringe over 20 minutes. The reaction mixture stirred at −78 °C for a further 24 hours before being quenched with a 1.0 M aqueous NaOH solution (60 mL). The quenched reaction mixture was diluted with water then extracted with EtOAc (3 × 50 mL). The combined organic extracts were successively washed with a 1.0 M aqueous NaOH solution (60 mL) until the aqueous washings were colourless. The organic fraction was then washed with a saturated brine solution (50 mL), dried over $MgSO_4$ then concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, 3:7 EtOAc:petrol) to afford the title compound as an off-white solid (1.61 g, 68%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 4H), 6.52 (d, *J* = 15.9 Hz, 1H), 6.23 (dd, *J* = 15.9, 6.3 Hz, 1H), 4.48 (apparent p, *J* = 6.3 Hz, 1H), 1.75 (s, 1H), 1.37 (d, *J* = 6.3 Hz, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 135.3 (C_q), 134.3 (CH), 133.3 (C_q), 128.9 (CH), 128.2 (CH), 127.8 (CH), 68.9 (CH), 23.5 (CH_3); **m.p.** 57–59 °C (lit.[15] 55–58 °C); **TLC** R_f; 0.31 (4:6 EtOAc:petrol); **[α]$_D^{25}$** +25.8 (*c.* 1.0 $CHCl_3$) **(lit.**[15] **[α]$_D^{20}$** +27.3 (*c.* 0.6, $CHCl_3$)); **Chiral SFC** column: Lux A2 (4.6 mm × 250 mm, 5 μm); mobile phase: 1:9 EtOH:CO_2 (0.2% *v*/*v* NH_3); flow rate: 4 mL/min; temperature: 40 °C; T_R (min) 2.08

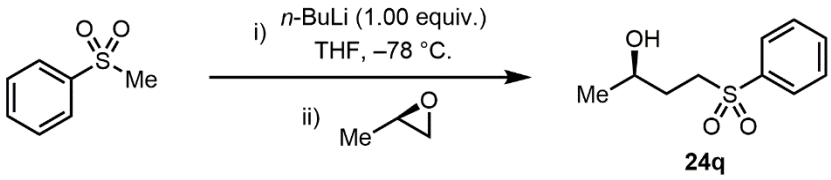
(minor), 2.20 (major) e.e. = 96%; Data are consistent with those reported in the literature.[16]

(*R*)-4-(4-Chlorophenyl)butan-2-ol (24o)



A suspension of **S4** (1.10 g, 6.00 mmol), *p*-toluenesulfonylhydrazine (6.70 g, 36.0 mmol) and sodium acetate (2.95 g, 36.0 mmol) in THF (40 mL) was heated to reflux and stirred 16 hours before the reaction mixture was cooled to room temperature and concentrated *in vacuo*. The crude residue was diluted with H_2O (60 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with a 2.0 M aqueous NaOH solution (100 mL) then a saturated brine solution (100 mL), dried over $MgSO_4$ and concentrated. Purification by flash column chromatography (SiO_2, 1:3 EtOAc/petrol) afforded the title compound as a colourless oil (974 mg, 88%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.24 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 3.74 – 3.86 (m, 1H), 2.77 – 2.59 (m, 2H), 1.81 – 1.64 (m, 3H), 1.22 (d, *J* = 6.2 Hz, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 140.6 (C_q), 131.6 (C_q), 129.8 (CH), 128.6 (CH), 67.4 (CH), 40.8 (CH_2), 31.5 (CH_2), 23.8 (CH_3); **TLC** R_f; 0.35 (3:7 EtOAc/petrol); **$[\alpha]_D^{25}$** −7.5 (c. 1.0, $CHCl_3$); **Chiral SFC** column: Lux A2 (4.6 mm × 250 mm, 5 μm); mobile phase: 1:19 EtOH:CO_2 (0.2% *v*/*v* NH_3); flow rate: 4 mL/min; temperature: 40 °C; T_R (min) 2.80 (major), 2.94 (minor) e.e. = 96%. Data are consistent with those reported in the literature.[17]

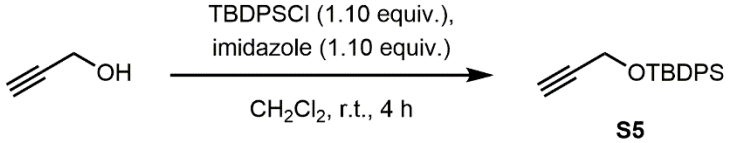
(*R*)-4-(Phenylsulfonyl)butan-2-ol (24q)



To a solution of methyl phenyl sulfone (781 mg, 5.00 mmol), in THF (6.0 mL) was added a 2.40 M solution of *n*-butyllithium in hexanes (2.08 mL, 5.00 mmol) dropwise at −78 °C. The reaction mixture was stirred at −78 °C for 15 minutes,

then warmed to room temperature and stirred for a further 10 minutes. The reaction mixture was then cooled to −78 °C and (*R*)-(+)-propylene oxide (524 μL, 7.50 mmol) was added dropwise. The reaction mixture was then warmed to room temperature and stirred for 16 hours, after which the reaction was quenched with a saturated aqueous NH_4Cl solution (10 mL) at 0 °C, diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic fractions were washed with a saturated aqueous NH_4Cl solution (40 mL) then a saturated brine solution (40 mL), dried over $MgSO_4$ and concentrated. The crude residue was purified by flash column chromatography (SiO_2, 6:4 EtOAc:petrol) to afford the title compound as a colourless oil, which solidified on standing (802 mg, 75%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.94 – 7.88 (m, 2H), 7.69 – 7.63 (m, 1H), 7.60 – 7.54 (m, 2H), 3.97 – 3.85 (m, 1H), 3.30 (ddd, *J* = 14.0, 10.1, 5.3 Hz, 1H), 3.20 (ddd, *J* = 14.0, 10.1, 5.8 Hz, 1H), 2.16 (s, 1H), 1.91 (dddd, *J* = 13.9, 9.8, 5.8, 1.7 Hz, 1H), 1.78 (dddd, *J* = 13.9, 10.3, 8.5, 5.3 Hz, 1H), 1.20 (dd, *J* = 6.2, 1.1 Hz, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 139.3 (C_q), 133.9 (CH), 129.5 (CH), 128.1 (CH), 66.3 (CH), 53.3 (CH_2), 31.7 (CH_2), 23.8 (CH_3); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{10}H_{15}O_3S$ $[M + H]^+$: 215.0736 found 215.0734; **FTIR** (neat) ν_{max}/cm^{-1} 3482, 2971, 2927, 1448, 1421, 1393, 1286, 1260, 1146, 1118, 1086, 1072, 1055; **m.p.** 47–48 °C; **TLC:** R_f; 0.26 (6:4 EtOAc:petrol); **$[\alpha]_D^{25}$** −18.2 (*c.* 1.0 $CHCl_3$) **(lit.[18] $[\alpha]_D^{21}$** −21.1 (*c.* 0.97, $CHCl_3$) *R*-stereoisomer, >95% e.e.); **Chiral SFC** column: Amy-C (4.6 mm × 250 mm, 5 μm), mobile phase: 1:4 EtOH:CO_2 (0.2% *v*/*v* NH_3), flow rate: 4 mL/min, temperature: 40 °C, T_R: 2.46 (major), 2.79 (minor), >99% e.e.

tert-Butyldiphenyl(prop-2-yn-1-yloxy)silane (S5)

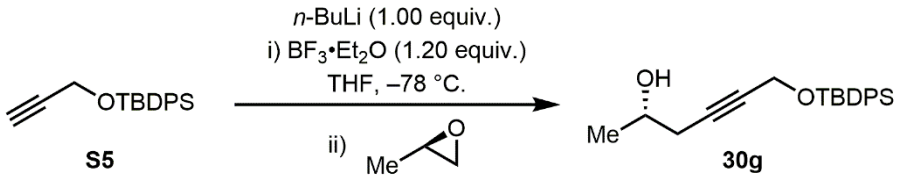


S5

To a solution of propargyl alcohol (2.33 mL, 40.0 mmol) and imidazole (3.00 g, 44.0 mmol) in CH_2Cl_2 (25.0 mL) was added *tert*-butyl(chloro)diphenylsilane (11.4 mL, 44.0 mmol) dropwise. The reaction was stirred for four hours, before the reaction mixture was diluted with Et_2O (100 mL) and washed with H_2O (2 × 100 mL), then a saturated brine solution (100 mL). The organic layer was

dried over anhydrous $MgSO_4$ and concentrated. The crude residue was purified by flash column chromatography (SiO_2, 1:99 EtOAc/petrol) to afford the title compound as a colorless liquid which solidified upon standing (10.96 g, 93%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.74 – 7.69 (m, 4H), 7.48 – 7.36 (m, 6H), 4.32 (d, *J* = 2.4 Hz, 2H), 2.39 (t, *J* = 2.4 Hz, 1H), 1.07 (s, 9H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 135.7 (C_q), 133.1 (CH), 130.0 (CH), 127.9 (CH), 82.2 (C_q), 73.2 (CH), 52.6 (CH_2), 26.8 (CH_3), 19.3 (C_q); **HRMS** (GC/MS-EI-TOF) *m*/*z* calc'd for $C_{15}H_{13}OSi$ $[M - t\text{-Bu}]^{\cdot+}$: 237.0730 found 237.0735; **m.p.** 58–59 °C (lit.[19] 58–60 °C); **TLC** R_f; 0.49 (1:19 EtOAc:petrol). Data are consistent with those reported in the literature.[19]

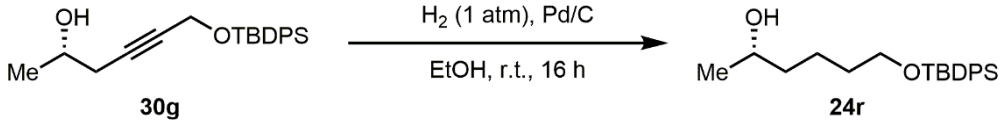
(*R*)-6-((*tert*-Butyldiphenylsilyl)oxy)hex-4-yn-2-ol (30g)



To a solution of **S5** (4.42 g, 15.0 mmol) in THF (50 mL) was added a 2.40 M solution of *n*-butyllithium in hexanes (6.25 mL, 15.0 mmol) at −78 °C and the reaction mixture was stirred for 30 minutes. Boron trifluoride diethyl etherate (2.22 mL, 18.0 mmol) was added dropwise followed by (*R*)-(+)-propylene oxide (1.52 mL, 22.5 mmol) and the reaction was held at −78 °C and stirred for two hours. The reaction was then quenched with a saturated aqueous NH_4Cl solution (20 mL), then concentrated *in vacuo*. The residue was diluted with H_2O (30 mL), then extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with a saturated brine solution (70 mL), dried over $MgSO_4$ then concentrated. The crude residue was loaded onto a short silica plug and eluted with 1:4 EtOAc:petrol to remove polymerised THF, then purified by flash column chromatography (SiO_2, 1:9 to 1:4 gradient, EtOAc:petrol). The resulting oil was re-purified by flash column chromatography (SiO_2, 3:7 Et_2O:petrol) to afford the title compound as a colorless oil. (3.09 g, 58%) **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.77 – 7.67 (m, 4H), 7.47 – 7.36 (m, 6H), 4.35 (t, *J* = 2.2 Hz, 2H), 3.85 (dqd, *J* = 6.7, 6.3, 4.6 Hz, 1H), 2.36 (ddt, *J* = 16.5, 4.6, 2.2 Hz, 1H), 2.27 (ddt, *J* = 16.5, 6.7, 2.2 Hz, 1H), 1.82 (s, 1H), 1.20 (d, *J* = 6.3 Hz, 3H), 1.06 (s, 9H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$)

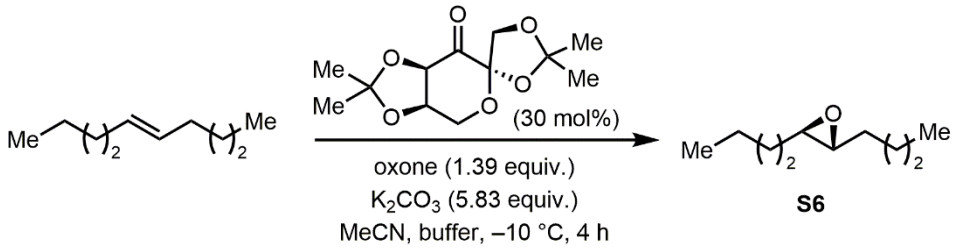
δ_C 135.8 (C_q), 133.4 (CH), 129.9 (CH), 127.8 (CH), 82.0 (C_q), 81.3 (C_q), 66.4 (CH), 53.0 (CH_2), 29.5 (CH_2), 26.8 (CH_3), 22.4 (CH_3), 19.3 (CH_q); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{22}H_{28}NaO_2Si$ $[M + Na]^+$: 375.1751 found 375.1761; **TLC** R_f; 0.26 (1:4 EtOAc:petrol); **$[\alpha]_D^{25}$:** +18.8 (*c.* 1.0, $CHCl_3$); **Chiral HPLC** column: Lux C1 (4.6 mm × 250 mm, 5 μm), mobile phase: 19:1 heptane:IPA (0.2% *v*/*v* NH_3), flow rate: 1 mL/min, temperature: 22 °C, T_R: 5.84 (major), 6.15 (minor), 96% e.e. Data are consistent with those reported in the literature.[20]

(*R*)-6-((*tert*-Butyldiphenylsilyl)oxy)hexan-2-ol (24r)



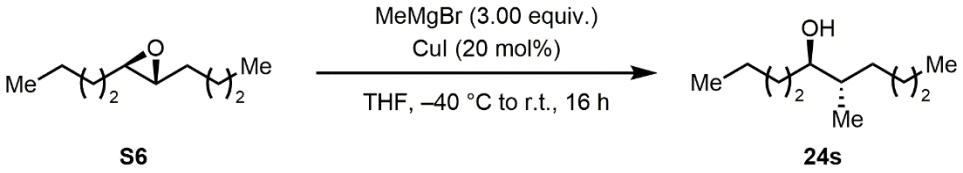
A suspension of **30g** (1.23 g, 3.50 mmol) and 10% *w*/*w* palladium on carbon with 50% *w*/*w* H_2O (204 mg, 95.8 μmol,) in EtOH (10 mL) was charged with hydrogen gas (1 atm) and stirred for 16 hours before the reaction mixture was filtered through celite and concentrated *in vacuo.* The crude residue was purified by flash column chromatography (SiO_2, 1:4 EtOAc:petrol) to afford the title compound as a colourless oil (870 mg, 70%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.72 – 7.67 (m, 4H), 7.46 – 7.36 (m, 6H), 3.83 – 3.74 (m, 1H), 3.69 (t, *J* = 6.4 Hz, 2H), 1.65 – 1.55 (m, 2H), 1.53 – 1.36 (m, 4H), 1.18 (d, *J* = 6.2 Hz, 3H), 1.07 (s, 9H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 135.7 (C_q), 134.2 (CH), 129.7 (CH), 127.7 (CH), 68.2 (CH), 63.9 (CH_2), 39.1 (CH_2), 32.6 (CH_2), 27.0 (CH_3), 23.5 (CH_2), 22.1 (CH_3), 19.3 (C_q); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{22}H_{32}NaO_2Si$ $[M + Na]^+$: 379.2064 found 379.2061; **FTIR** (neat) ν_{max}/cm^{-1} 3330, 2930, 2857, 1471, 1427, 1389, 1106; **TLC** R_f: 0.21 (1:4 EtOAc:petrol); **$[\alpha]_D^{25}$: +**17.8 (*c.* 1.0, $CHCl_3$); e.e.: 99% (determined by chiral HPLC of the derivatised 2,4-dinitrobenzoic ester **S33**). Data are consistent with those reported in the literature.[21]

(*R,R*)-2,3-Dibutyloxirane (S6)



According to an adapted literature procedure,[22] to a solution of (*E*)-dec-5-ene (730 µL, 5.16 mmol) in MeCN (75 mL) was added a buffer solution of $Na_2(EDTA)\cdot 2H_2O$ (8 mg, 0.02 mmol) and $Na_2B_4O_7\cdot 10H_2O$ (520 mg, 1.36 mmol) dissolved in H_2O (52 mL). Added to this stirring solution was tetrabutylammonium hydrogensulfate (78 mg, 0.23 mmol) and the Shi epoxidation catalyst, D-epoxone (400 mg, 1.55 mmol). The reaction was stirred vigorously under an air atmosphere, then cooled to −10 °C. In two separate syringes, using a syringe pump was added a) potassium carbonate (4.16 g, 30.1 mmol) in H_2O (34 mL), and b) oxone (4.42 g, 7.19 mmol) in H_2O (34 mL) containing $Na_2(EDTA)\cdot 2H_2O$ (5.5 mg, 0.015 mmol) simultaneously, over 2 hours. The reaction was warmed to ambient temperature and stirred for 2 hours. The reaction mixture was diluted with H_2O (100 mL) and extracted with pentane (3 × 100 mL). The combined organic extracts were washed with a saturated brine solution (100 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, 0:100 to 1:9 gradient, Et_2O:petrol) to afford the title compound as a colourless oil (495 mg, 61%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 2.69 – 2.61 (m, 2H), 1.57 – 1.29 (m, 12H), 0.91 (t, *J* = 7.1 Hz, 6H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 58.9 (CH), 31.8 (CH_2), 28.2 (CH_2), 22.5 (CH_2), 14.0 (CH_3); **FTIR** (neat) ν_{max}/cm^{-1} 2958, 2929, 2872, 2860, 1465, 1377, 1229, 1217; **TLC** R_f: 0.33 (1:9 Et_2O:petrol). Data are consistent with those reported in the literature.[23]

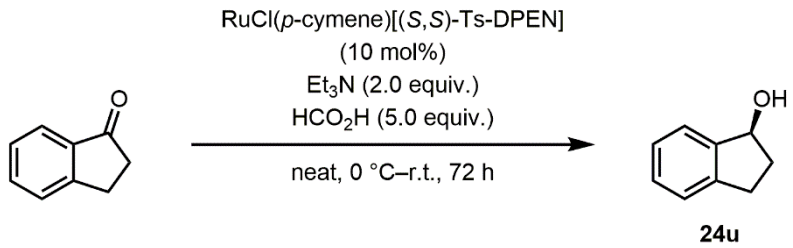
(5*R*,6*S*)-6-Methyldecan-5-ol (24s)



S6 **24s**

To a suspension of CuI (116 mg, 606 μmol) in THF (8 mL) was added a 3.0 M solution of methylmagnesium bromide in Et_2O (3.0 mL, 9.1 mmol) then a solution of **S6** (474 mg, 3.03 mmol) in THF (10 mL) at −40 °C under an argon atmosphere. The reaction was warmed to room temperature and stirred for 16 hours before the reaction was quenched with a 1.0 M aqueous solution of NH_4Cl (10 mL) at 0 °C, diluted with H_2O (20 mL) and the reaction was stirred for 1 hour then extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with a saturated brine solution (2 × 40 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, 1:19 EtOAc:petrol) to afford the title compound as a colourless oil (491 mg, 94%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.43 (ddd, *J* = 7.9, 5.0, 2.7 Hz, 1H), 1.57 – 1.02 (m, 13H), 0.96 – 0.84 (m, 9H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 72.8 (CH), 41.8 (CH), 41.6 (CH_2), 32.4 (CH_2), 27.0 (CH_2), 26.1 (CH_2), 23.6 (CH_2), 23.3 (CH_2), 22.7 (CH_3), 14.1 (CH_3), 14.1 (CH_3); **FTIR** (neat) ν_{max}/cm^{-1} 3359, 2956, 2928, 2872, 2859, 1461, 1378, 1001; **TLC** R_f: 0.31 (1:19 EtOAc:petrol); **$[\alpha]_D^{25}$:** +9.2 (c. 0.1 $CHCl_3$); 99% d.e. (determined by SFC analysis of the derivatised 2,4-dinitrobenzoic ester **S35**) 90% e.e. (determined by SFC analysis of the derivatised 2,4-dinitrobenzoic ester **S35**).

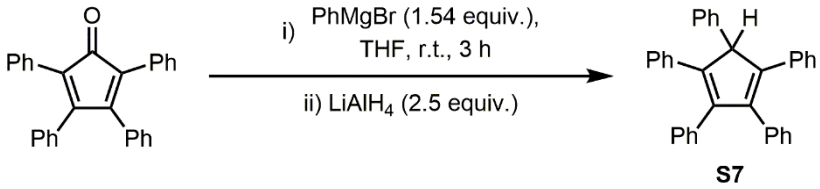
(*S*)-(+)-1-Indanol (24u)



24u

Formic acid (1.9 mL, 50 mmol) was added dropwise at 0 °C to triethylamine (2.8 mL, 20 mmol). The solution was brought to room temperature before adding indanone (1.32 g, 10.0 mmol) and RuCl(*p*-cymene)[(*S*,*S*)-Ts-DPEN] (64 mg, 0.10 mmol) under vigorous stirring (gas evolving). The reaction was stirred for 72 hours before a saturated aqueous solution of NH_4Cl (10 mL) was added and the organics were extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, CH_2Cl_2) afforded the title compound as a white solid (1.14 g, 85%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.45 – 7.39 (m, 1H), 7.30 – 7.21 (m, 3H), 5.25 (dd, *J* = 6.8, 5.3 Hz, 1H), 3.07 (ddd, *J* = 16.1, 8.5, 4.8 Hz, 1H), 2.83 (ddd, *J* = 15.9, 8.3, 6.6 Hz, 1H), 2.50 (dddd, *J* = 13.2, 8.3, 6.9, 4.8 Hz, 1H), 1.95 (dddd, *J* = 13.6, 8.5, 6.6, 5.3 Hz, 1H), 1.72 (s, 1H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 145.1 (C_q), 143.5 (C_q), 128.5 (CH), 126.9 (CH), 125.1 (CH), 124.3 (CH), 76.6 (CH), 36.1 (CH_2), 29.9 (CH_2); **FTIR** (neat) ν_{max}/cm^{-1} 3319, 3074, 3021, 2966, 1478, 1457, 1336, 1050, 1034, 765; **m.p.** 50–52 °C; **TLC** R_f: 0.15 (CH_2Cl_2); **[α]$_D^{20}$:** +30.9 (*c*. 1.0, $CHCl_3$); **Chiral HPLC** column: chiralcel OD-H (4.6 mm × 250 mm, 5 μm), mobile phase: 97:3 isohexane:IPA, flow rate 1 mL/min, temperature: ambient; T_R (min) 14.83 (major), 17.06 (minor), 99% e.e. Data are consistent with those reported in the literature.[24]

Cyclopenta-1,3-diene-1,2,3,4,5-pentaylpentabenzene (S7)

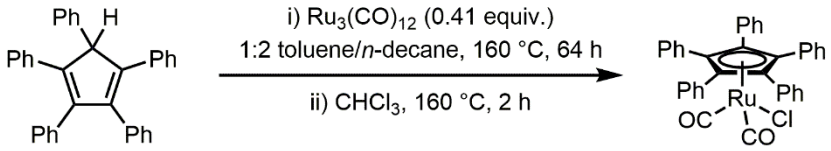


S7

To a suspension of magnesium turnings (389 mg, 16.0 mmol) and iodine (2 crystals) in anhydrous THF (5.0 mL) was added bromobenzene (1.98 mL, 18.8 mmol) in anhydrous THF (17.5 ml) at room temperature and the reaction mixture was stirred for one hour. Tetraphenylcyclopentadienone (4.01 g, 10.4 mmol) in THF (17.5 ml) was added dropwise, and the reaction mixture was stirred for a further 2 hours. The reaction mixture was then cooled to 0 °C, lithium aluminium hydride (987 mg, 26.0 mmol) was added in portions and the reaction was stirred for 16 hours at room temperature. The reaction mixture was quenched with a saturated aqueous NH_4Cl solution (20 mL), diluted with H_2O (100 mL) and extracted with hot CH_2Cl_2* (400 mL). The organic phase was dried over $MgSO_4$ and concentrated. The crude residue was purified by trituration with MeCN to afford the title compound as an off-white solid (3.78 g, 81%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.24 – 6.94 (m, 25H), 5.09 (s, 1H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 146.7 (C_q), 144.1 (C_q), 138.2 (C_q), 136.3 (C_q), 135.9 (C_q), 130.3 (CH), 129.2 (CH), 128.7 (CH), 128.6 (CH), 128.0 (CH), 127.8 (CH), 126.8 (CH), 126.7 (CH), 126.5 (CH), 62.8 (CH); **m.p.** 254–256 °C (lit.[9] = 251–252 °C). Data are consistent with those reported in the literature.[9]

*The extraction was initially carried out at ambient temperature which resulted in the undissolved compound being suspended throughout both phases. Upon heating the separating funnel with a heat gun, the solid was dissolved and the layers were easily separable.

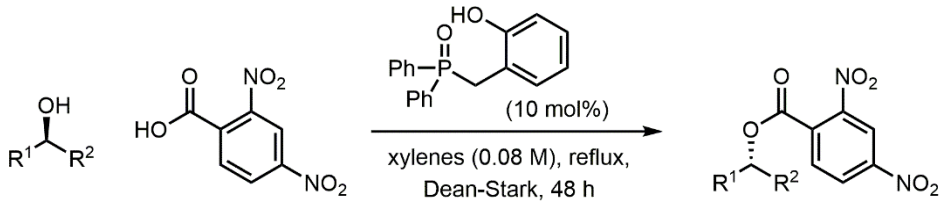
Bäckvall Catalyst (S8)



S8

S7 (491 mg, 1.10 mmol) and triruthenium dodecacarbonyl (237 mg, 370 μmol) was suspended in toluene (2.0 mL) and *n*-decane (4.0 mL) and heated at 160 °C in a sealed tube for 64 hours, before $CHCl_3$ (0.60 mL) was added and the reaction mixture was heated for a further 2 hours. The reaction mixture was then cooled to room temperature and pentane (25 mL) was added and the precipitate collected by filtration. Purification by flash column chromatography (SiO_2, 1:1 CH_2Cl_2/ petrol) afforded the title compound as a yellow solid (330 mg, 47%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.19 (tt, *J* = 7.4, 1.3 Hz, 5H), 7.10 (t, *J* = 7.8 Hz, 10H), 7.04-7.02 (m, 10H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 197.0 (C_q), 132.3 (C_q), 129.7 (CH), 128.5 (CH), 128.0 (CH), 106.6 (C_q); **FTIR (neat)** ν_{max}/cm^{-1} 3055, 2036, 1984, 1600, 1577, 1502, 1444, 1074, 1029, 738, 695, 559; **m.p.** decomposed. Data are consistent with those reported in the literature.[9]

General Procedure for the Catalytic Mitsunobu Reaction



A suspension of alcohol (1.0 equiv.), 2,4-dinitrobenzoic acid (1.0 equiv.) and catalyst **C2** (5-25 mol%) in xylenes (12.5 mL per mmol of alcohol) was heated to reflux in a Dean-Stark apparatus and stirred for 48 hours. The reaction mixture was then cooled to room temperature, diluted with EtOAc and washed with a 1 M aqueous NaOH solution twice then a saturated aqueous brine solution. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography to afford the inverted ester product.*

*If desired, the catalyst can be recovered by flash column chromatography. The catalyst elutes with 1:1 EtOAc:petrol and is usually recovered with 50–90% yield (dependent on the substrate).

Enantiomeric excesses and diastereomeric excesses are determined by either chiral SFC or chiral HPLC. Stereochemistry is assigned by comparing the chromatograms to analogous ester products with retention of stereochemistry (see pages 198–218 for syntheses). In the cases of substrates **25t**, **29a** and **29b**, the diastereomer ratio is determined by ^1H NMR, through comparing relevant peak areas. The epimer is assigned by comparing the NMR spectra to analogous ester products with retention of stereochemistry.

Graphical Supporting Information for the Catalytic Mitsunobu Reaction

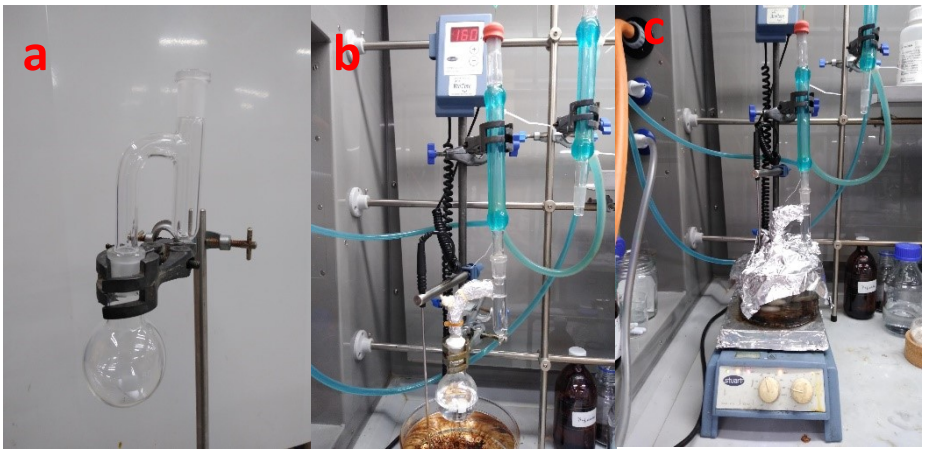


Figure S1. a) A 50 mL or 25 mL round-bottomed flask with a small Dean-Stark trap is required. **b)** The starting materials and catalyst are added to the round-bottomed flask. Solvent is added so that the flask is half-filled (12.5 mL in a 25 mL RBF or 25mL in a 50 mL RBF.) The round bottomed flask is connected to the Dean Stark trap, which is connected to a condenser which is open to air, *via* a rubber septum pierced with a needle. The joints are sealed with Teflon tape to prevent solvent leakage. **c)** The round bottomed flask is immersed in an oil bath set to approx. 160–165 °C, (paraffin oil will discolor and become viscous after repeated use, silicone oil is recommended) until the solvent is seen to be condensing into the Dean-Stark trap. The oil bath is covered with aluminum-foil and Dean-Stark trap is covered with cotton wool and aluminum foil for insulation. A high rate of stirring is recommended.

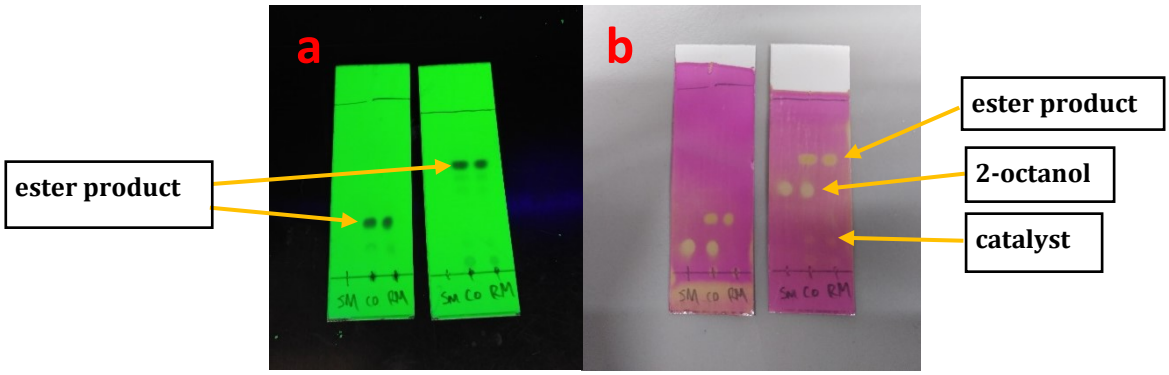
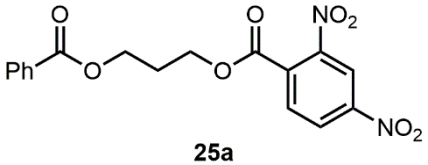


Figure S2. TLC of the reaction mixture after 48 hours of the reaction of (S)-2-octanol with 2,4-dinitrobenzoic acid. **a)** Developed TLC plates visualized using UV light (254 nm.) TLCs were run using 1:9 EtOAc/petrol (left) and 1:1 EtOAc/petrol (right.) The ester product is easily visualized by UV light. **b)** Developed TLC plates visualized by staining with $KMnO_4$. TLCs were run using 1:9 EtOAc/petrol (left) and 1:1 EtOAc/petrol (right.) Alcohols and ester products are generally easily visualized by $KMnO_4$. The catalyst can be visualized by both UV and $KMnO_4$, however due to the low catalyst concentration in the reaction mixture, it can appear quite faint.

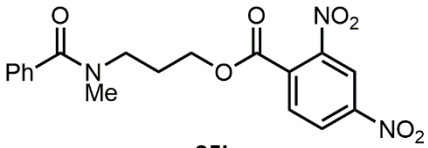
3-(Benzoyloxy)propyl 2,4-Dinitrobenzoate (25a)



25a

Synthesized according to the general procedure using 3-hydroxypropyl benzoate **(24a)** (180 mg, 1.00 mmol), 2,4-dinitrobenzoic acid (212 mg, 1.00 mmol), catalyst **C2** (31 mg, 0.10 mmol) and xylenes (12.5 mL). Purification by flash column chromatography (SiO_2, 3:17, EtOAc:petrol) afforded the title compound as a pale yellow solid (296 mg, 79%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.76 (d, *J* = 2.2 Hz, 1H), 8.48 (dd, *J* = 8.4, 2.2 Hz, 1H), 8.02 – 7.98 (m, 2H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.58 – 7.52 (m, 1H), 7.44 – 7.39 (m, 2H), 4.57 (t, *J* = 6.2 Hz, 2H), 4.45 (t, *J* = 6.1 Hz, 2H), 2.24 (apparent p, *J* = 6.2 Hz, 2H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 166.5 (C_q), 163.8 (C_q), 149.1 (C_q), 148.1 (C_q), 133.2 (CH), 132.9 (C_q), 131.4 (CH), 130.0 (C_q), 129.7 (CH), 128.5 (CH), 127.6 (CH), 119.7 (CH), 64.3 (CH_2), 61.3 (CH_2), 27.9 (CH_2); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{17}H_{15}N_2O_8$ $[M + H]^+$: 375.0823 found 375.0829; **FTIR** (neat) ν_{max}/cm^{-1} 3108, 3081, 3057, 2962, 1729, 1706, 1548, 1533, 1367, 1351, 1332, 1260, 1111, 1063, 1026; **m.p.** 80–82 °C; **TLC** R_f: 0.49 (4:6 EtOAc/petrol).

3-(*N*-Methylbenzamido)propyl 2,4-Dinitrobenzoate (25b)

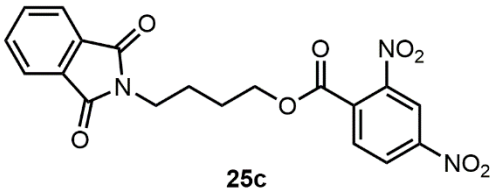


25b

Synthesized according to the general procedure using *N*-(3-hydroxypropyl)-*N*-methylbenzamide **(24b)** (193 mg, 1.00 mmol), 2,4-dinitrobenzoic acid (212 mg, 1.00 mmol), catalyst **C2** (31 mg, 0.10 mmol) and xylenes (12.5 mL). The crude reaction mixture was purified twice by flash column chromatography (SiO_2, 1:49, MeOH:CH_2Cl_2 then 1:1 EtOAc/petrol) afforded the title compound as a pale orange oil (272 mg, 53%) (sample contaminated with 1 molar equivalent of $CHCl_3$. 53% yield has accounted for this). **^{1}H NMR** (400 MHz, 353 K, DMSO-d_6) δ_H 8.79 (d, *J* = 2.2 Hz, 1H), 8.61 (dd, *J* = 8.4, 2.3 Hz, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.41

– 7.29 (m, 7H), 4.43 – 4.32 (m, 3H), 3.56 – 3.43 (m, 3H), 2.94 (s, 4H), 2.02 (p, *J* = 6.7 Hz, 3H); **$^{13}C\{^{1}H\}$ NMR** (101 MHz, 353 K, DMSO-d_6) δ_C 170.1 (C_q), 162.7 (C_q), 148.8 (C_q), 147.3 (C_q), 136.4 (C_q), 131.2 (CH), 130.8 (C_q), 128.6 (CH), 127.7 (CH), 127.6 (CH), 126.1 (CH), 119.2 (CH), 64.1 (CH_2), 25.8 (CH_2) (2 peaks are obscured by solvent peaks so are not reported); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{18}H_{18}N_3O_7$ $[M + H]^+$: 388.1139 found 388.1143; **FTIR** (neat) ν_{max}/cm^{-1} 3107, 2996, 2886, 1735, 1626, 1603, 1536, 1402, 1346, 1281, 1244, 1113, 1056; **TLC** R_f: 0.27 (1:49 $MeOH/CH_2Cl_2$).

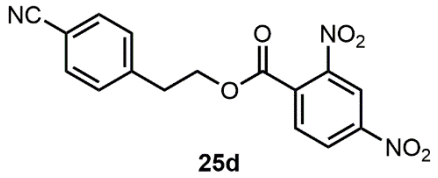
4-(1,3-Dioxoisoindolin-2-yl)butyl 2,4-Dinitrobenzoate (25c)



25c

Synthesized according to the general procedure using 2-(4-hydroxybutyl)isoindoline-1,3-dione **(24c)** (438 mg, 2.00 mmol), 2,4-dinitrobenzoic acid (424 mg, 2.00 mmol), catalyst **C2** (62 mg, 0.20 mmol) and xylenes (25 mL). Purification by flash column chromatography (SiO_2, gradient of 1:199 to 1:99 $MeOH:CH_2Cl_2$) afforded the title compound as a pale yellow solid. (703 mg, 85%) **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.76 (d, *J* = 2.2 Hz, 1H), 8.52 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.82 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.71 (dd, *J* = 5.5, 3.1 Hz, 2H), 4.45 – 4.39 (m, 2H), 3.76 – 3.70 (m, 2H), 1.84 – 1.75 (m, 4H); **$^{13}C\{^{1}H\}$ NMR** (101 MHz, $CDCl_3$) δ_C 168.5 (C_q), 163.8 (C_q), 149.0 (C_q), 148.1 (C_q), 134.1 (CH), 133.1 (C_q), 132.1 (C_q), 131.4 (CH), 127.6 (CH), 123.4 (CH), 119.7 (CH), 66.7 (CH_2), 37.4 (CH_2), 25.7 (CH_2), 25.2 (CH_2); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{19}H_{16}N_3O_8$ $[M + H]^+$: 414.0932, found 414.0935; **FTIR** (neat) ν_{max}/cm^{-1} 3102, 3076, 2912, 1732, 1703, 1532, 1400, 1351, 1288, 1251, 1139, 1038, 1025; **m.p.** 118–119 °C; **TLC** R_f: 0.23 (CH_2Cl_2).

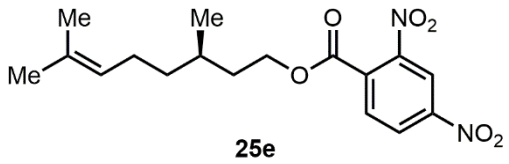
4-Cyanophenethyl 2,4-Dinitrobenzoate (25d)



25d

Synthesized according to the general procedure using 4-(2-hydroxyethyl)benzonitrile (147 mg, 1.00 mmol), 2,4-dinitrobenzoic acid (212 mg, 1.00 mmol), catalyst **C2** (31 mg, 0.10 mmol) and xylenes (12.5 mL). Purification by flash column chromatography (SiO_2, 9:11, EtOAc:petrol) afforded the title compound as a pale yellow solid (286 mg, 84%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.76 (d, *J* = 2.2 Hz, 1H), 8.52 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 4.62 (t, *J* = 6.8 Hz, 2H), 3.13 (t, *J* = 6.8 Hz, 2H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 163.6 (C_q), 149.1 (C_q), 148.2 (C_q), 142.7 (C_q), 132.6 (C_q), 132.6 (CH), 131.3 (CH), 129.7 (CH), 127.7 (CH), 119.8 (CH), 118.8 (C_q), 111.0 (C_q), 66.6 (CH_2), 34.7 (CH_2); **HRMS (ESI-TOF)** *m*/*z* calc'd for $C_{16}H_{12}N_3O_6$ $[M + H]^+$: 342.0721 found 342.0717; **FTIR** (neat) ν_{max}/cm^{-1} 3107, 3085, 3058, 2968, 2936, 2224, 1730, 1707, 1606, 1533, 1353, 1276, 1248, 1127, 1109, 1060, 1025; **m.p.** 111–112 °C; **TLC** R_f: 0.55 (1:1 EtOAc/petrol).

(*S*)-3,7-Dimethyloct-6-en-1-yl 2,4-Dinitrobenzoate (25e)

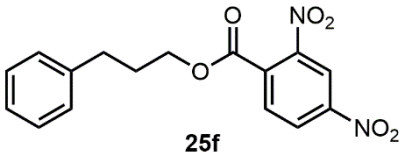


25e

Synthesized according to the general procedure using (*S*)-(−)-β-citronellol (365 µL, 2.00 mmol), 2,4-dinitrobenzoic acid (424 mg, 2.00 mmol), catalyst **C2** (62 mg, 0.20 µmol) and xylenes (25 mL). Purification by flash column chromatography (SiO_2, 3:7 CH_2Cl_2:petrol) afforded the title compound as a yellow oil. Product was isolated as a 88:12 ratio of the internal and terminal alkene respectively (348 mg, 50%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.77 (d, *J* = 2.2 Hz, 1H), 8.52 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 5.11 – 5.03 (m, 0.88H, internal alkene), 4.70 – 4.63 (m, 0.24H, terminal alkene), 4.49 – 4.35 (m, 2H), 2.08 – 1.88 (m, 3H), 1.85 – 1.71 (m, 1H), 1.66 (s, 3H), 1.59 (s, 3H), 1.57 – 1.48 (m, 2H), 1.43 –

1.31 (m, 1H), 1.26 – 1.14 (m, 1H), 0.94 (d, *J* = 6.3 Hz, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 163.8 (C_q), 149.0 (C_q), 148.3 (C_q), 146.0 (C_q), 131.6 (C_q), 131.4 (CH), 127.5 (CH), 124.5 (CH), 119.7 (CH), 66.1 (CH_2), 37.0 (CH_2), 35.1 (CH_2), 29.5 (CH), 25.8 (CH_3), 25.5 (CH_2), 19.4 (CH_3), 17.8 (CH_3) (^{13}C NMR shown for major product only); **HRMS** (ESI-TOF) *m/z* calc'd for $C_{17}H_{23}N_2NaO_6$ $[M + Na]^+$: 373.1370 found 373.1356; **TLC** R_f: 0.18 (1:9 EtOAc:petrol).

3-Phenylpropyl 2,4-Dinitrobenzoate (25f)

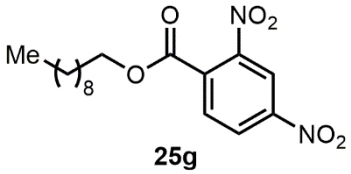


25f

Synthesized according to the general procedure using 3-phenylpropan-1-ol (272 µL, 2.00 mmol), 2,4-dinitrobenzoic acid (424 mg, 2.00 mmol), catalyst **C2** (62 mg, 0.20 mmol) and xylenes (25 mL). Purification by flash column chromatography (SiO_2, 1:4 EtOAc:petrol) afforded the title compound as a pale orange solid (594 mg, 90%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.78 (d, *J* = 2.2 Hz, 1H), 8.52 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.33 – 7.27 (m, 2H), 7.23 – 7.17 (m, 3H), 4.41 (t, *J* = 6.4 Hz, 2H), 2.73 (t, *J* = 7.6 Hz, 2H), 2.08 (tt, *J* = 7.6 Hz, 6.4 Hz, 2H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_c 163.7 (C_q), 149.0 (C_q), 148.3 (C_q), 140.8 (C_q), 132.9 (C_q), 131.4 (CH), 128.6 (CH), 128.5 (CH), 127.5 (CH), 126.3 (CH), 119.6 (CH), 66.8 (CH_2), 32.2 (CH_2), 29.9 (CH_2); **HRMS** (ESI-TOF) *m/z* calc'd for $C_{16}H_{14}N_2NaO_6$ $[M + Na]^+$: 353.0744 found 353.0730; **FTIR** (neat) ν_{max}/cm^{-1} 3118, 3092, 3059, 2924, 1721, 1531, 1370, 1353, 1289, 1138; **m.p.** 61–63 °C; **TLC** R_f: 0.36 (3:7 EtOAc:petrol).

Reaction was repeated using 2,4-dinitrobenzoic acid and catalyst **C2** recovered from epimerization of 5α-cholestan-3β-ol (see figure 2 from manuscript) to afford the title compound as a pale yellow solid (612 mg, 93%).

1-Decyl 2,4-Dinitrobenzoate (25g)

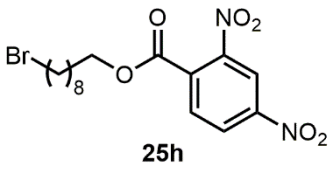


25g

Synthesized according to the general procedure using 1-decanol (382 μL, 2.00 mmol), 2,4-dinitrobenzoic acid (424 mg, 2.00 mmol), catalyst **C2** (62 mg, 0.20 mmol) and xylenes (25 mL). Purification by flash column chromatography (SiO_2, 1:19 EtOAc:petrol) afforded the title compound as a pale yellow oil (628 mg, 88%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.78 (d, *J* = 2.2 Hz, 1H), 8.53 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 4.38 (t, *J* = 6.7 Hz, 2H), 1.74 (apparent p, *J* = 6.7 Hz, 2H), 1.43 – 1.21 (m, 14H), 0.88 (t, *J* = 6.8 Hz, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 163.9 (C_q), 149.1 (C_q), 148.4 (C_q), 133.3 (C_q), 131.4 (CH), 127.6 (CH), 119.7 (CH), 67.8 (CH_2), 32.0 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.3 (CH_2), 25.9 (CH_2), 22.8 (CH_2), 14.3 (CH_3); **HRMS** (ESI-TOF) m/z calc'd for $C_{17}H_{24}N_2NaO_6$ $[M + Na]^+$: 375.1527 found 375.1315; **FTIR** (neat) ν_{max}/cm^{-1} 3106, 3054, 2919, 2851, 1728, 1608, 1543, 1466, 1357, 1293, 1256, 1161, 1139, 1063; **TLC** R_f: 0.22 (1:9 EtOAc:pentane).

Reaction was repeated using 2,4-dinitrobenzoic acid and catalyst **C2** recovered from epimerization of 5α-cholestan-3β-ol (see figure 2 from manuscript) to afford the title compound as a pale yellow solid (592 mg, 84%).

9-Bromononyl 2,4-Dinitrobenzoate (25h)

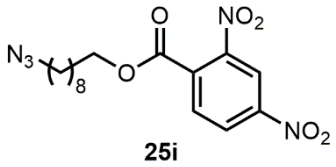


25h

Synthesized according to the general procedure using 9-bromo-1-nonanol (446 mg, 2.00 mmol), 2,4-dinitrobenzoic acid (424 mg, 2.00 mmol), catalyst **C2** (62 mg, 0.20 mmol) and xylenes (25 mL). Purification by flash column chromatography (SiO_2, 0:100 to 2:25 gradient, EtOAc:petrol) afforded the title compound as a pale yellow oil (492 mg, 59%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.78

(d, *J* = 2.2 Hz, 1H), 8.53 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 4.38 (t, *J* = 6.7 Hz, 2H), 3.41 (t, *J* = 6.8 Hz, 2H), 1.85 (apparent p, *J* = 6.8 Hz, 2H), 1.74 (apparent p, *J* = 6.7 Hz, 2H), 1.47 – 1.27 (m, 10H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 163.8 (C_q), 149.0 (C_q), 148.3 (C_q), 133.1 (C_q), 131.4 (CH), 127.5 (CH), 119.6 (CH), 67.6 (CH_2), 34.1 (CH_2), 32.8 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 28.7 (CH_2), 28.2 (CH_2), 28.1 (CH_2), 25.7 (CH_2); **HRMS** (ESI-TOF) *m/z* calc'd for $C_{16}H_{21}{}^{79}BrN_2NaO_6$ $[M + Na]^+$: 439.0475, found 439.0474; **FTIR** (neat) ν_{max}/cm^{-1} 3115, 3071, 3051, 2929, 2852, 1730, 1537, 1351, 1282, 1058; **TLC** R_f: 0.40 (1:4 EtOAc:petrol).

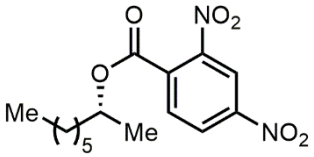
9-Azidononyl 2,4-Dinitrobenzoate (25i)



25i

Synthesized according to the general procedure using 9-azidononan-1-ol **(24i)** (185 mg, 1.00 mmol), 2,4-dinitrobenzoic acid (212 mg, 1.00 mmol), catalyst **C2** (31 mg, 0.10 mmol) and xylenes (12.5 mL). Purification by flash column chromatography (SiO_2, 1:9, EtOAc:petrol) afforded the title compound as a pale yellow oil (296 mg, 79%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.77 (d, *J* = 2.2 Hz, 1H), 8.53 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 4.38 (t, *J* = 6.8 Hz, 2H), 3.25 (t, *J* = 6.8 Hz, 2H), 1.74 (apparent p, *J* = 6.8 Hz, 2H), 1.60 (apparent p, *J* = 6.8 Hz, 2H), 1.44 – 1.27 (m, 10H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 163.9 (C_q), 149.1 (C_q), 148.4 (C_q), 133.2 (C_q), 131.4 (CH), 127.6 (CH), 119.7 (CH), 67.7 (CH_2), 51.6 (CH_2), 29.4 (CH_2), 29.1 (CH_2), 28.9 (2 × CH_2), 28.3 (CH_2), 26.8 (CH_2), 25.8 (CH_2); **HRMS** (ESI-TOF) *m/z* calc'd for $C_{16}H_{22}N_5O_6$ $[M + H]^+$ = 380.1565 found 380.1566; **FTIR** (neat) ν_{max}/cm^{-1} 3108, 2929, 2856, 2093, 1733, 1604, 1536, 1465, 1347, 1279, 1244, 1131, 1109, 1057; **TLC** R_f: 0.29 (1:9 EtOAc/petrol).

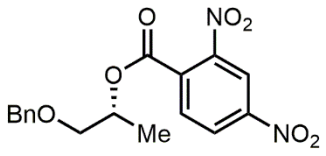
(*R*)-Octan-2-yl 2,4-Dinitrobenzoate (25k)



25k

Synthesized according to the general procedure using (*S*)-(+)-2-octanol (317 μL, 2.00 mmol), 2,4-dinitrobenzoic acid (424 mg, 2.00 mmol), catalyst **C2** (62 mg, 0.20 mmol) and xylenes (25 mL) with the exception that the reaction time was 30 hours. Purification by flash column chromatography (SiO_2, 1:19 EtOAc:petrol) afforded the title compound as a pale yellow solid (545 mg, 84%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.76 (d, *J* = 2.1 Hz, 1H), 8.51 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 5.19 (apparent sextet, *J* = 6.3 Hz, 1H), 1.76 – 1.65 (m, 1H), 1.63 – 1.51 (m, 1H), 1.40 – 1.22 (m, 9H), 0.90 – 0.84 (m, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 163.4 (C_q), 148.9 (C_q), 148.1 (C_q), 133.7 (C_q), 131.3 (CH), 127.5 (CH), 119.6 (CH), 75.4 (CH), 35.6 (CH_2), 31.8 (CH_2), 29.2 (CH_2), 25.3 (CH_2), 22.7 (CH_2), 19.4 (CH_3), 14.2 (CH_3); **HRMS** (ESI-TOF) *m/z* calc'd for $C_{15}H_{20}N_2NaO_6$ $[M + Na]^+$; 347.1214, found 347.1197; **FTIR** ν_{max}/cm^{-1} 3108, 2930, 2858, 1730, 1604, 1537, 1460, 1346, 1346, 1284, 1245; **m.p.** 44–46 °C; **TLC** R_f: 0.29 (1:19 EtOAc/petrol); **$[\alpha]_D^{26}$** –64.0 (*c.* 1.0, $CHCl_3$); **Chiral SFC** column: Amy-C (4.6 mm × 250 mm, 5 μm); mobile phase: 1:4 MeOH:CO_2, flow rate: 4 mL/min; temperature: 40 °C; T_R (min) 1.14 (major), 1.39 (minor), 98% e.e.

(*R*)-1-(Benzyloxy)propan-2-yl 2,4-Dinitrobenzoate (25l)

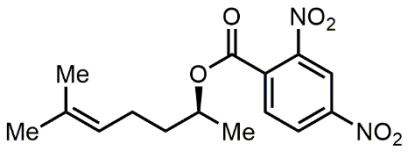


25l

A solution of (*S*)-1-(benzyloxy)propan-2-ol **(24l)** (332 mg, 2.00 mmol), 2,4-dinitrobenzoic acid (141 mg, 666 μmol) and catalyst **C2** (123 mg, 0.400 mmol) in xylenes (25 mL) was heated to reflux in a Dean-Stark apparatus and stirred. After 24 hours, a further addition of 2,4-dinitrobenzoic acid (141 mg, 666 μmol) was

made. After 66 hours a further addition of 2,4-dinitrobenzoic acid (141 mg, 666 μmol) and catalyst **C2** (62 mg, 0.20 mmol) was made. After 114 hours a further addition of catalyst **C2** (62 mg, 0.20 mmol) was made. After 192 hours, the reaction mixture was cooled to room temperature, diluted with EtOAc (20 mL) and washed with a 2.0 M aqueous NaOH solution (2 × 20 mL) then a saturated brine solution (20 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 EtOAc:petrol) afforded the title compound as an orange oil (490 mg, 68%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.79 (d, *J* = 2.2 Hz, 1H), 8.50 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.41 – 7.27 (m, 5H), 5.42 (apparent qt, *J* = 6.4, 5.1 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 3.61 (apparent d, *J* = 5.1 Hz, 2H), 1.40 (d, *J* = 6.5 Hz, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 163.4 (C_q), 148.9 (C_q), 148.0 (C_q), 137.9 (C_q), 133.3 (C_q), 131.4 (CH), 128.5 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 119.6 (CH), 73.3 (CH_2), 73.1 (CH), 72.0 (CH_2), 16.1 (CH_3); **HRMS** (ESI-TOF) *m/z* calc'd for $C_{17}H_{16}N_2NaO_7$ $[M + Na]^+$: 383.0850 found 361.0846; **FTIR** (neat) ν_{max}/cm^{-1} 3105, 2984, 2871, 1730, 1535, 1346, 1281, 1244, 1112, 1091; **TLC** R_f: 0.29 (1:4 EtOAc:petrol); **[α]$_D^{25}$** −44.0 (*c.* 1.0, $CHCl_3$); **Chiral SFC** column: Amy-C (4.6 mm × 250 mm, 5 μm); mobile phase: 1:3 MeOH:CO_2; flow rate: 4 mL/min; temperature: 40 °C; T_R (min) 1.70 (major), 2.00 (minor) 91% e.e.

(*S*)-6-Methylhept-5-en-2-yl 2,4-Dinitrobenzoate (25m)

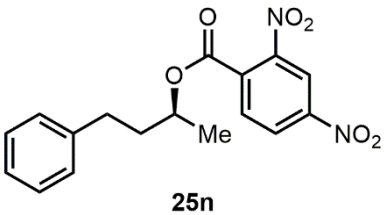


25m

Synthesized according to the general procedure using (*R*)-6-methylhept-5-en-2-ol **(24m)** (128 mg, 1.00 mmol), 2,4-dinitrobenzoic acid (212 mg, 1.00 mmol), catalyst **C2** (31 mg, 0.10 mmol) and xylenes (12.5 mL). Purification by flash column chromatography (SiO_2, 1:9 EtOAc:petrol) afforded the title compound as a yellow oil. (201 mg, 62%). NMR analysis showed that the compound was a 91:9 mixture of the internal and terminal alkene. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.77 (d, *J* = 2.2 Hz, 1H), 8.52 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 5.20 (apparent

sextet, *J* = 6.3 Hz, 1H), 5.14 – 5.05 (m, 0.91H, internal alkene), 4.75 – 4.64 (m, 0.18H, terminal alkene), 2.05 (q, *J* = 7.6 Hz, 2H), 1.82 – 1.55 (m, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.37 (d, *J* = 6.2 Hz, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 163.4 (C_q), 149.0 (C_q), 148.3 (C_q), 133.6 (C_q), 132.7 (C_q), 131.4 (CH), 127.5 (CH), 123.1 (CH), 119.7 (CH), 75.0 (CH), 35.7 (CH_2), 25.8 (CH_3), 24.0 (CH_2), 19.5 (CH_3), 17.8 (CH_3) (^{13}C NMR shown for major product only); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{15}H_{18}N_2NaO_6$ $[M + Na]^+$: 345.1057, found 345.1057; **TLC** R_f: 0.47 (1:4 EtOAc:petrol); **Chiral SFC** column: Amy-C (4.6 mm × 250 mm, 5 μm), mobile phase: 1:9 MeOH:CO_2 (0.2% *v*/*v* NH_3), flow rate: 4 mL/min, temperature: 40 °C, T_R (min) 1.49 (minor), 1.86 (major), 89% e.e.

(*S*)-4-Phenylbutan-2-yl 2,4-Dinitrobenzoate (25n)

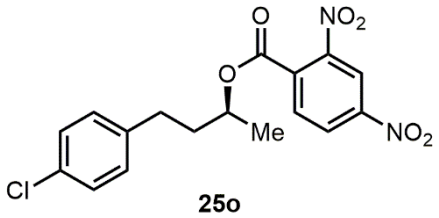


25n

Synthesized according to the general procedure using (*R*)-4-phenylbutan-2-ol **(24n)** (150 mg, 1.00 mmol), 2,4-dinitrobenzoic acid (212 mg, 1.00 mmol), catalyst **C2** (31 mg, 0.10 mmol) and xylenes (12.5 mL). Purification by flash column chromatography (SiO_2, 1:19 to 1:9 gradient, EtOAc:petrol) afforded the title compound as a pale orange oil. (282 mg, 82%) **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.76 (d, *J* = 2.2 Hz, 1H), 8.50 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.32 – 7.26 (m, 2H), 7.22 – 7.16 (m, 3H), 5.25 (dqd, *J* = 7.6, 6.3, 4.9 Hz, 1H), 2.78 – 2.63 (m, 2H), 2.07 (dddd, *J* = 14.0, 9.2, 7.6, 6.5 Hz, 1H), 1.94 (dddd, *J* = 14.2, 9.2, 6.8, 4.9 Hz, 1H), 1.42 (d, *J* = 6.3 Hz, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 163.4 (C_q), 148.9 (C_q), 148.2 (C_q), 141.2 (C_q), 133.4 (C_q), 131.4 (CH), 128.6 (CH), 128.5 (CH), 127.5 (CH), 126.2 (CH), 119.6 (CH), 74.8 (CH), 37.2 (CH_2), 31.7 (CH_2), 19.5 (CH_3); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{17}H_{16}N_2NaO_6$ $[M + Na]^+$: 367.0901, found 367.0899; **FTIR** (neat) ν_{max}/cm^{-1} 3105, 2981, 2863, 1730, 1538, 1346, 1282, 1244, 1154, 1130, 1049; **TLC** R_f: 0.31 (1:9 EtOAc:petrol); **$[\alpha]_D^{25}$ +**56.0 (*c.* 1.0, $CHCl_3$); **Chiral SFC** column: Amy-C (4.6 mm × 250 mm, 5 μm), mobile phase: 1:3

MeOH:CO_2, flow rate: 4 mL/min, temperature: 40 °C, T_R (min) 1.89 (minor), 2.17 (major), 91% e.e.

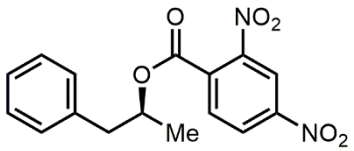
(*S*)-4-(4-Chlorophenyl)butan-2-yl 2,4-Dinitrobenzoate (25o)



25o

Synthesized according to the general procedure using (*R*)-4-(4-chlorophenyl)butan-2-ol **(24o)** (369 mg, 2.00 mmol), 2,4-dinitrobenzoic acid (424 mg, 2.00 mmol), catalyst **C2** (62 mg, 0.20 mmol) and xylenes (25 mL). Purification by flash column chromatography (SiO_2, 1:9 EtOAc:petrol) afforded the title compound as a pale yellow solid (678 mg, 89%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.75 (d, *J* = 2.2 Hz, 1H), 8.51 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 5.23 (dqd, *J* = 7.5, 6.3, 4.7 Hz, 1H), 2.74 – 2.61 (m, 2H), 2.09 – 1.98 (m, 1H), 1.90 (dddd, *J* = 14.0, 9.0, 7.0, 4.7 Hz, 1H), 1.40 (d, *J* = 6.3 Hz, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 163.3 (C_q), 149.0 (C_q), 148.2 (C_q), 139.6 (C_q), 133.2 (C_q), 131.9 (CH), 131.4 (C_q), 129.8 (CH), 128.8 (CH), 127.5 (CH), 119.6 (CH), 74.6 (CH), 37.1 (CH_2), 31.1 (CH_2), 19.5 (CH_3); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{17}H_{15}{}^{35}ClN_2NaO_6$ $[M + Na]^+$: 401.0511; found 401.0501; **FTIR** (ATR) ν_{max}/cm^{-1} 3104, 2983, 2941, 1725, 1604, 1534, 1488, 1344, 1279, 1242, 1052; **m.p.** 68–70 °C; **TLC** R_f: 0.35 (1:4 EtOAc:petrol); **$[\alpha]_D^{25}$** +64.0 (*c.* 1.0, $CHCl_3$); **Chiral SFC** column: Chiralpak IG (4.6 mm × 250 mm, 5 μm); mobile phase: 4:6 MeOH:CO_2 (0.2% *v*/*v* NH_3); flow rate: 4 mL/min; temperature: 40 °C; T_R (min) 2.08 (minor), 2.28 (major), 93% e.e.

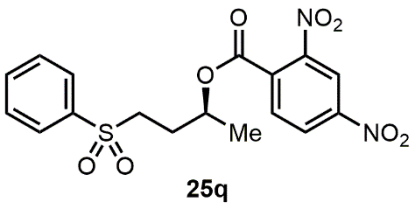
(*S*)-1-Phenylpropan-2-yl 2,4-Dinitrobenzoate (25p)



25p

Synthesized according to the general procedure using (*R*)-4-(phenylsulfonyl)butan-2-ol (214 mg, 1.00 mmol), 2,4-dinitrobenzoic acid (212 mg, 1.00 mmol), catalyst **C2** (62 mg, 0.20 mmol) and xylenes (12.5 mL), however the reaction was continued for a further 24 hours (72 hours overall.) Purification by flash column chromatography (SiO_2, 3:17 EtOAc:petrol) afforded the title compound as a yellow oil (302 mg, 92%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.78 (d, *J* = 2.2 Hz, 1H), 8.48 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.36 – 7.25 (m, 3H), 7.24 – 7.15 (m, 2H), 5.44 (apparent dp, *J* = 7.2, 6.3 Hz, 1H), 3.04 (dd, *J* = 13.8, 7.2 Hz, 1H), 2.89 (dd, *J* = 13.8, 6.3 Hz, 1H), 1.40 (d, *J* = 6.3 Hz, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 163.4 (C_q), 148.9 (C_q), 147.9 (C_q), 137.0 (C_q), 133.6 (C_q), 131.2 (CH), 129.5 (CH), 128.7 (CH), 127.6 (CH), 127.0 (CH), 119.7 (CH), 75.4 (CH), 42.0 (CH_2), 19.2 (CH_3); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{16}H_{14}N_2NaO_6$ $[M + Na]^+$: 353.0744 found 353.0741; **FTIR** (neat) ν_{max}/cm^{-1} 3106, 3029, 2982, 2934, 1730, 1604, 1536, 1454, 1346, 1281, 1245,1130, 1111, 1055, 1030; **TLC** R_f: 0.33 (1:4 EtOAc:petrol); **[α]$_D^{25}$** +6.7 (*c.* 1.0, $CHCl_3$); **Chiral SFC** column: Amy-C (4.6 mm × 250 mm, 5 μm); mobile phase: 1:4 MeOH:CO_2, flow rate: 4 mL/min; temperature: 40 °C; T_R (min) 1.63 (minor), 1.80 (major), 96% e.e.

(*S*)-4-(Phenylsulfonyl)butan-2-yl 2,4-Dinitrobenzoate (25q)

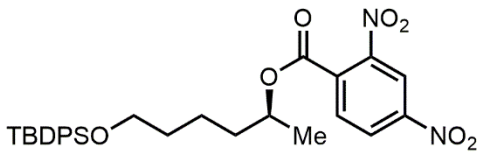


25q

Synthesized according to the general procedure using (*R*)-4-(phenylsulfonyl)butan-2-ol **(24q)** (214 mg, 1.00 mmol), 2,4-dinitrobenzoic acid (212 mg, 1.00 mmol), catalyst **C2** (31 mg, 0.10 mmol) and xylenes (12.5 mL). Purification by flash column chromatography (SiO_2, 3:7 EtOAc:petrol) afforded

the title compound as a pale yellow oil. (316 mg, 77%) **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.76 (d, *J* = 2.2 Hz, 1H), 8.52 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.94 – 7.87 (m, 3H), 7.71 – 7.64 (m, 1H), 7.62 – 7.55 (m, 2H), 5.32 – 5.23 (m, 1H), 3.26 – 3.11 (m, 2H), 2.20 – 2.01 (m, 2H), 1.38 (d, *J* = 6.3 Hz, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 163.3 (C_q), 149.1 (C_q), 147.9 (C_q), 138.9 (C_q), 134.1 (CH), 132.9 (C_q), 131.5 (CH), 129.6 (CH), 128.2 (CH), 127.8 (CH), 119.7 (CH), 72.8 (CH), 52.4 (CH_2), 28.7 (CH_2), 19.4 (CH_3); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{17}H_{16}N_2NaO_8S$ $[M + Na]^+$: 431.0520, found 431.0518; **FTIR** (neat) ν_{max}/cm^{-1} 3105, 2941, 2921, 1727, 1604, 1535, 1447, 1346, 1279, 1243, 1141, 1087, 1051; **TLC** R_f: 0.18 (3:7 EtOAc:petrol); **$[\alpha]_D^{25}$** +44.0 (*c.* 1.0, $CHCl_3$); **Chiral SFC** column: Lux C4 (4.6 mm × 250 mm, 5 μm); mobile phase: 1:1 MeOH:CO_2 (0.2% *v*/*v* NH_3), flow rate: 4 mL/min; temperature: 40 °C; T_R (min) 2.36 (major), 2.86 (minor), 96% e.e.

(*S*)-6-((*tert*-Butyldiphenylsilyl)oxy)hexan-2-yl 2,4-Dinitrobenzoate (25r)

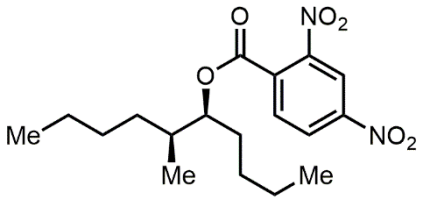


25r

Synthesized according to the general procedure (*R*)-6-((*tert*-butyldiphenylsilyl)oxy)hexan-2-ol **(24r)** (357 mg, 1.00 mmol), 2,4-dinitrobenzoic acid (212 mg, 1.00 mmol), catalyst **C2** (31 mg, 0.10 mmol) and xylenes (12.5 mL). Purification by flash column chromatography (SiO_2, 1:9 EtOAc:petrol) afforded the title compound as a yellow oil (475 mg, 86%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.77 (d, *J* = 2.2 Hz, 1H), 8.45 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.70 – 7.62 (m, 4H), 7.46 – 7.35 (m, 6H), 5.27 – 5.17 (m, 1H), 3.70 (t, *J* = 6.2 Hz, 2H), 1.78 – 1.68 (m, 1H), 1.66 – 1.42 (m, 5H), 1.37 (d, *J* = 6.3 Hz, 3H), 1.05 (s, 9H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 163.5 (C_q), 148.9 (C_q), 148.1 (C_q), 135.7 (C_q), 134.1 (CH), 133.7 (C_q), 131.3 (CH), 129.7 (CH), 127.7 (CH), 127.5 (CH), 119.6 (CH), 75.2 (CH), 63.6 (CH_2), 35.3 (CH_2), 32.3 (CH_2), 27.0 (CH_3), 21.7 (CH_2), 19.4 (CH_2), 19.4 (C_q); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{29}H_{38}N_3O_7Si$ $[M + NH_4]^+$: 568.2474 found 568.2482; **FTIR** (neat) ν_{max}/cm^{-1} 3072, 2932, 2858, 1731, 1604, 1538, 1346, 1284, 1245, 1105, 1056; **TLC** R_f: 0.20 (1:4 EtOAc:petrol); **$[\alpha]_D^{25}$** +28.0 (*c.* 1.0, $CHCl_3$); **Chiral HPLC** column: Lux C1 (4.6 mm × 250 mm, 5 μm); mobile

phase: 19:1 heptane:IPA (0.2% *v*/*v* NH_3); flow rate: 1 mL/min; temperature: ambient; T_R (min) 14.35 (major), 15.51 (minor), 97% e.e.

(5*S*,6*S*)-6-Methyldecan-5-yl 2,4-Dinitrobenzoate (25s)

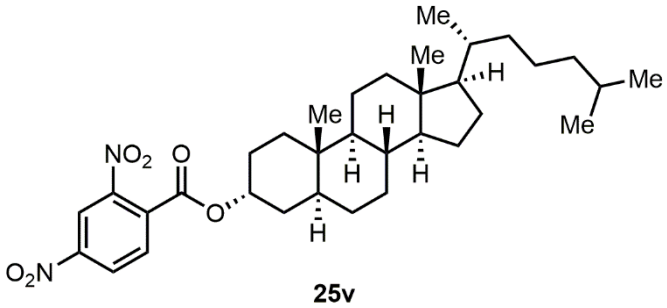


25s

A solution of (5*R*,6*S*)-6-methyldecan-5-ol **(24s)** (345 mg, 2.00 mmol), 2,4-dinitrobenzoic acid (141 mg, 666 μmol) and catalyst **C2** (123 mg, 0.40 mmol) in xylenes (25 mL) was heated to reflux in a Dean-Stark apparatus and stirred. After 8 hours, a further addition of 2,4-dinitrobenzoic acid (141 mg, 666 μmol) was made. After a further 16 hours another addition of 2,4-dinitrobenzoic acid (141 mg, 666 μmol) was made and the reaction was continued for a further 24 hours. The reaction mixture was then cooled to room temperature, diluted with EtOAc (20 mL) and washed with a 1.0 M aqueous NaOH solution (2 × 20 mL) then a saturated brine solution (20 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 3:97 EtOAc:petrol) afforded the title compound as a yellow oil (355 mg, 48%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.73 (d, *J* = 2.2 Hz, 1H), 8.51 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 5.16 (ddd, *J* = 8.4, 5.1, 3.7 Hz, 1H), 1.84 – 1.54 (m, 3H), 1.45 – 1.23 (m, 9H), 1.22 – 1.12 (m, 1H), 0.96 – 0.85 (m, 9H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 163.5 (C_q), 149.0 (C_q), 148.4 (C_q), 133.4 (C_q), 131.4 (CH), 127.3 (CH), 119.6 (CH), 81.8 (CH), 36.1 (CH), 32.6 (CH_2), 30.6 (CH_2), 29.6 (CH_2), 28.0 (CH_2), 23.0 (CH_2), 22.7 (CH_2), 14.4 (CH_3), 14.2 (CH_3), 14.1 (CH_3); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{18}H_{26}N_2O_6$ $[M + Na]^+$: 389.1683 found 389.1670; **FTIR** (neat) ν_{max}/cm^{-1} 3108, 2957, 2930, 2860, 1730, 1604, 1537, 1465, 1346, 1280, 1245, 1155, 1128, 1108, 1057; **TLC** R_f: 0.17 (1:19 EtOAc:petrol); **$[\alpha]_D^{25}$** +12.0 (*c.* 1.0, $CHCl_3$); **SFC for d.e. determination** Amy-C (4.6 mm × 250 mm, 5 μm); mobile phase: 1:19 CO_2:EtOH (0.2% *v*/*v* HCO_2H); flow rate: 4 mL/min; temperature: 40 °C; T_R (min) 1.81 (minor), 1.94 (major), 91% d.e.; **Chiral SFC for e.e. determination** Lux C4

(4.6 mm × 250 mm, 5 μm); mobile phase: 3:97 MeOH:CO_2 (0.2% *v*/*v* HCO_2H); flow rate: 4 mL/min; temperature: 40 °C; T_R (min) 5.43 (minor), 5.91 (major), 91% e.e.

5α-Cholestan-3α-yl 2,4-Dinitrobenzoate (25t)

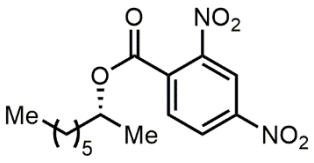


25v

A suspension of 5α-cholestan-3β-ol (389 mg, 1.00 mmol), 2,4-dinitrobenzoic acid (212 mg, 1.00 mmol) and catalyst **C2** (62 mg, 0.20 mmol) in xylenes (12.5 mL) was heated to reflux in a Dean-Stark apparatus and stirred for 72 hours. The reaction mixture was then cooled to room temperature, MeCN (150 mL) was added and the precipitate was collected by filtration. The filtrate was washed with MeCN (20 mL) and allowed to dry under vacuum suction, affording the title compound as an off-white solid (343 mg, 59%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.75 (d, *J* = 2.2 Hz, 1H), 8.53 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 5.40 – 5.30 (m, 1H), 2.01 – 1.42 (m, 12H), 1.41 – 0.93 (m, 19H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.86 (dd, *J* = 6.6, 1.8 Hz, 6H), 0.81 (s, 3H), 0.65 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 163.2 (C_q), 149.0 (C_q), 148.3 (C_q), 133.6 (C_q), 131.6 (CH), 127.4 (CH), 119.6 (CH), 74.8 (CH), 56.6 (CH), 56.4 (CH), 54.3 (CH), 42.7 (CH), 40.3 (C_q), 40.1 (CH_2), 39.7 (CH_2), 36.3 (CH_2), 36.0 (CH), 35.8 (CH), 35.6 (CH), 33.1 (CH_2), 32.7 (CH_2), 32.0 (CH_2), 28.5 (CH_2), 28.4 (CH_2), 28.2 (CH), 26.1 (CH_2), 24.3 (CH_2), 24.0 (CH_2), 23.0 (CH_3), 22.7 (CH_2), 20.9 (CH_2), 18.8 (CH_3), 12.2 (CH_3), 11.5 (CH_3); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{34}H_{54}N_3O_6$ $[M + NH_4]^+$: 600.4007 found 600.4005; **FTIR** (neat) ν_{max}/cm^{-1} 3123, 3105, 3060, 2961, 2876, 1715, 1607, 1531, 1373, 1346, 1288, 1257, 1156, 1129, 1062; **m.p.** 198-201 °C; **$[\alpha]_D^{25}$ +**12.8 (*c.* 1.0, $CHCl_3$) Analysis of the crude reaction mixture by ^{1}H NMR indicated a 20:1 d.r. in favour of inversion based on integrating the signals centred at 5.31 ppm (inversion) and 5.01 ppm (retention).

^{1}H and ^{13}C NMR does not correspond to the retention product **S60**, indicating that this is not the retention product. The ^{13}C NMR signal centered on 74.8 ppm and the ^{1}H NMR signal centered on 5.45 ppm gave good agreement with the analogous inverted 4-nitrobenzoyl ester.[25] Hydrolysis of the ester confirmed this assignment (see pages 219–220).

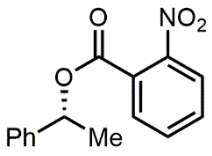
(*R*)-Octan-2-yl 2,4-Dinitrobenzoate (25u) at 20 mmol Scale



25k

A suspension of (*S*)-(+)-2-octanol (3.17 mL, 20.0 mmol), 2,4-dinitrobenzoic acid (4.24 g, 20.0 mmol) and catalyst **C2** (617 mg, 2.00 mmol) in xylenes (250 mL) was heated to reflux in a Dean-Stark apparatus and stirred for 72 hours. The reaction mixture was then cooled to room temperature, diluted with EtOAc (100 mL) and washed with a 1.0 M aqueous NaOH solution (2 × 100 mL) then a saturated brine solution (100 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, 3:97 EtOAc:petrol) to afford the title compound as a pale yellow solid (4.91 g, 76%) **^{1}H NMR** and **^{13}C{^{1}H} NMR** data matches compound **25k**. **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{15}H_{20}N_2NaO_6$ $[M + Na]^+$: 347.1214 found 347.1203; **Chiral SFC** column: Amy-C (4.6 mm × 250 mm, 5 μm); mobile phase: 4:1 MeOH:CO_2 (0.2% *v*/*v* NH_3); flow rate: 4 mL/min; temperature: 40 °C; T_R (min) 1.17 (major), 1.42 (minor), 95% e.e.

(*R*)-1-Phenylethyl 2-Nitrobenzoate (25v)

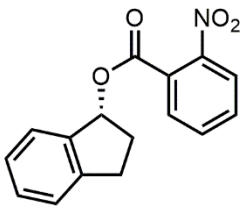


25t

A suspension of (*S*)-(−)-1-phenylethanol (241 μL, 2.0 mmol), 2-nitrobenzoic acid (84 mg, 0.50 mmol), and catalyst **C2** (77 mg, 0.25 mmol) in toluene (12.5 mL) was

heated to reflux in a Dean Stark apparatus and stirred. After 20 hours, a further addition of 2-nitrobenzoic acid (84 mg, 0.50 mmol) was made and the reaction was continued for a further 20 hours. The reaction mixture was then cooled to room temperature, diluted with EtOAc (20 mL) and washed with a 1.0 M aqueous NaOH solution (2 × 20 mL) then a saturated brine solution (20 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:4 EtOAc:petrol) afforded the title compound as a pale yellow oil (248 mg, 92%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.93 – 7.86 (m, 1H), 7.77 – 7.70 (m, 1H), 7.64 (m, 2H), 7.43 – 7.27 (m, 5H), 6.13 (q, *J* = 6.6 Hz, 1H), 1.67 (d, *J* = 6.6 Hz, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 164.7 (C_q), 148.5 (C_q), 140.7 (C_q), 132.9 (CH), 131.8 (CH), 130.1 (CH), 128.7 (CH), 128.4 (CH), 127.8 (CH), 126.4 (CH), 123.9 (CH), 75.1 (CH), 21.7 (CH_3); **HRMS** (ESI-TOF) *m/z* calc'd for $C_{15}H_{17}N_2O_4$ $[M + NH_4]^+$: 289.1183 found 289.1182; **FTIR** (neat) ν_{max}/cm^{-1} 2982, 1727, 1607, 1579, 1533, 1350, 1283, 1254, 1129, 1059, 761, 734, 698; **TLC** R_F: 0.36 (1:4 EtOAc:petrol); **$[\alpha]_D^{25}$** −58.0 (*c*. 1.0, $CHCl_3$); **Chiral HPLC** column chiralpak AD-H (4.6 mm × 250 mm, 5 μm), mobile phase: 4:1 *iso*-hexane:EtOH, flow rate 1 mL/min, temperature: ambient, T_R (min) 6.73 (major), 8.69 (minor), 85% e.e.

(*R*)-2,3-Dihydro-1H-inden-1-yl 2-Nitrobenzoate (25w)

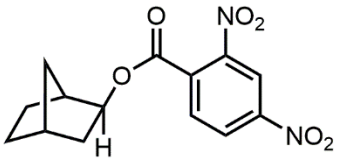


25u

A suspension of (*S*)-(+)-1-indanol **(24w)** (268 mg, 2.00 mmol), 2-nitrobenzoic acid (84 mg, 0.50 mmol), and catalyst **C2** (77 mg, 0.25 mmol) in toluene (12.5 mL) was heated to reflux in a Dean Stark apparatus and stirred. After 20 hours, a further addition of 2-nitrobenzoic acid (84 mg, 0.50 mmol) was made and the reaction was continued for a further 20 hours. The reaction mixture was then cooled to room temperature, diluted with EtOAc (20 mL) and washed with a 1.0 M aqueous NaOH solution (2 × 20 mL) then a saturated brine solution (20 mL). The organic phase was dried over MgSO4 and concentrated *in vacuo*.

Purification by flash column chromatography (SiO_2, 1:9 EtOAc:petrol) afforded the title compound as a pale yellow oil (200 mg, 71%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.93 – 7.86 (m, 1H), 7.77 – 7.70 (m, 1H), 7.69 – 7.55 (m, 2H), 7.54 – 7.47 (m, 1H), 7.36 – 7.19 (m, 3H), 6.45 (dd, *J* = 6.9, 3.4 Hz, 1H), 3.18 – 3.10 (m, 1H), 2.93 (ddd, *J* = 16.2, 8.7, 4.4 Hz, 1H), 2.64 – 2.58 (m, 1H), 2.30 (dddd, *J* = 14.2, 8.3, 4.4, 3.3 Hz, 1H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 165.6 (C_q), 148.3 (C_q), 144.9 (C_q), 140.1 (C_q), 133.0 (CH), 131.7 (CH), 130.0 (CH), 129.5 (CH), 128.2 (CH), 127.0 (CH), 126.0 (CH), 125.0 (CH), 124.0 (CH), 81.0 (CH), 32.0 (CH_2), 30.4 (CH_2); **HRMS** (ESI-TOF) *m/z* calc'd for $C_{16}H_{13}NNaO_4$ $[M + Na]^+$: 306.0737 found 306.0732; **FTIR** (neat) ν_{max}/cm^{-1} 3098, 2941, 1725, 1608, 1531, 1285, 1251, 1124, 1071, 1011, 756, 736; **TLC** R_f: 0.27 (1:9 EtOAc:petrol); **$[\alpha]_D^{25}$**: −17.9 (*c*. 1.0, $CHCl_3$); **Chiral HPLC** column chiralpak IC (4.6 mm × 250 mm, 5 μm), mobile phase: 90:10 isohexane:IPA, flow rate 1 mL/min, temperature: ambient, T_R (min) 10.88 (minor), 13.50 (major), 67% e.e.

exo-Norbornyl 2,4-Dinitrobenzoate (29a, figure 15))



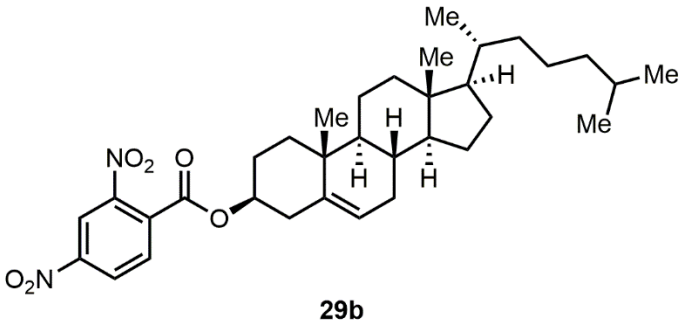
29a

Synthesized according to the general procedure using *exo*-norborneol (224 mg, 2.00 mmol), 2,4-dinitrobenzoic acid (424 mg, 2.00 mmol), catalyst **C2** (62 mg, 0.20 mmol) and xylenes (12.5 mL). Purification by flash column chromatography (SiO_2, 1:19, EtOAc:petrol) afforded the title compound as a pale yellow solid (303 mg, 49%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.73 (d, *J* = 2.2 Hz, 1H), 8.51 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 4.90 (d, *J* = 7.0 Hz, 1H), 2.46 (d, *J* = 5.0 Hz, 1H), 2.37 – 2.31 (m, 1H), 1.82 (ddd, *J* = 13.9, 7.0, 2.5 Hz, 1H), 1.67 – 1.53 (m, 2H), 1.53 – 1.41 (m, 2H), 1.28 – 1.08 (m, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 163.2 (C_q), 149.0 (C_q), 148.4 (C_q), 133.3 (C_q), 131.6 (CH), 127.4 (CH), 119.6 (CH), 81.3 (CH), 41.4 (CH), 39.0 (CH_2), 35.5 (1 × CH_2, 1 × CH), 28.1 (CH_2), 24.2 (CH_2); **HRMS** (ESI-TOF) *m/z* calc'd for $C_{14}H_{14}N_2NaO_6$ $[M + Na]^+$: 329.0744 found 329.0734; **FTIR** (neat) ν_{max}/cm^{-1} 3123, 3104, 3062, 2962, 2879, 1716, 1607, 1529, 1373,

1362, 1345, 1310, 1286, 1250, 1156, 1129, 1117, 1061; **m.p.** 102–103 °C; **TLC** R_f: 0.32 (1:9 EtOAc/petrol).

^{1}H and ^{13}C NMR matches retention compound **S43**.

Cholesteryl 2,4-Dinitrobenzoate (29b, figure 15)

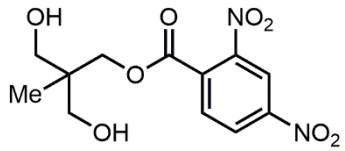


29b

A suspension of cholesterol (773 mg, 2.00 mmol), 2,4-dinitrobenzoic acid (424 mg, 2.00 mmol) and catalyst **C2** (62 mg, 0.20 mmol) in xylenes (25 mL) was heated to reflux in a Dean-Stark apparatus and stirred for 24 hours. The reaction mixture was then cooled to room temperature, MeCN (150 mL) was added and the precipitate was collected by filtration. The filtrate was washed with MeCN (20 mL) and allowed to dry under vacuum suction, affording the title compound as an off-white solid (660 mg, 57%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.78 (d, *J* = 2.2 Hz, 1H), 8.52 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 5.50 – 5.38 (m, 1H), 4.92 (tt, *J* = 11.0, 5.0 Hz, 1H), 2.52 – 2.34 (m, 2H), 2.07 – 0.95 (m, 29H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.86 (dd, *J* = 6.5, 1.9 Hz, 6H), 0.68 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 163.3 (C_q), 148.9 (C_q), 148.2 (C_q), 139.0 (C_q), 133.6 (CH), 131.4, (C_q), 127.6 (CH), 123.6 (CH), 119.7 (CH), 77.8 (CH), 56.8 (CH), 56.3 (CH), 50.2 (CH), 42.5 (C_q), 39.9 (CH_2), 39.7 (CH_2), 37.6 (CH_2), 37.0 (CH_2), 36.7 (CH_2), 36.3 (CH_2), 35.9 (CH), 32.1 (CH_2), 32.0 (CH), 28.4 (CH_2), 28.2 (CH), 27.4 (CH_2), 24.4 (CH_2), 24.0 (CH_2), 23.0 (CH_3), 22.7 (CH_3), 21.2 (CH_2), 19.4 (CH_3), 18.9 (CH_3), 12.0 (CH_3); **HRMS** (ESI-TOF) *m/z* calc'd for $C_{34}H_{48}N_2NaO_6$ $[M + Na]^+$: 603.3405 found 603.3411; **FTIR** (neat) ν_{max}/cm^{-1} 3107, 3083, 3056, 2930, 2867, 1714, 1606, 1550, 1538, 1372, 1353, 1299, 1134; **m.p.** 174-178 °C; **$[\alpha]_D^{25}$ +**15.5 (*c.* 1.0, $CHCl_3$); **TLC:** R_f: 0.26 (1:9 EtOAc/petrol).

^{1}H and ^{13}C NMR matches the retention product **S44**.

3-Methyl-3-oxetanemethanol (table 5, 31b)



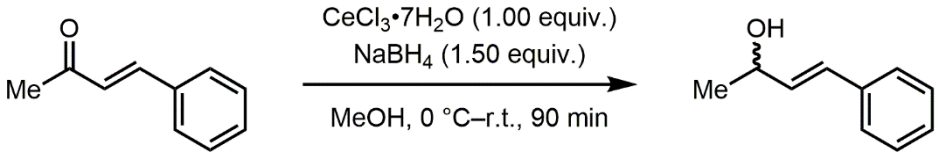
31b

Synthesized according to the general procedure using (*R*)-4-phenylbutan-2-ol **(24n)** (150 mg, 1.00 mmol), 2,4-dinitrobenzoic acid (212 mg, 1.00 mmol), catalyst **C2** (31 mg, 0.10 mmol) and xylenes (12.5 mL). Purification by flash column chromatography (SiO_2, 1:19 to 1:9 gradient, EtOAc:petrol) afforded the title compound as a pale orange oil. (282 mg, 82%) **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.77 (d, *J* = 2.2 Hz, 1H), 8.55 (dd, *J* = 8.4, 2.2 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 4.48 (s, 2H), 3.65 (t, *J* = 9.9 Hz, 5H), 2.34 (s, 2H), 0.89 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 164.2 (C_q), 149.3 (C_q), 148.5 (C_q), 132.6 (C_q), 131.9 (CH), 127.6 (CH), 119.7 (CH), 69.7 (CH), 67.8 (CH), 40.8 (CH), 16.9 (CH); **HRMS** (ESI-TOF) m/z calc'd for $C_{12}H_{15}N_2O_8$ $[M + H]^+$: 315.0823 found 315.0820; **FTIR** (neat) ν_{max}/cm^{-1} 3276, 3101, 3077, 2974, 2945, 2903, 2882, 1726, 1605, 1547, 1529, 1371, 1349, 1289, 1246, 1156, 1135, 1052, 1034; **m.p.** 103–105 °C.

Preparation of Chiral HPLC and SFC Standards

To determine the enantiomeric excesses of the products of the catalytic Mitsunobu method, chiral HPLC or SFC was used. Therefore, racemic samples of each product were required, as well as the ester products with retention, so that we could demonstrate that our products were made with inversion of stereochemistry. The syntheses of these standards are described below.

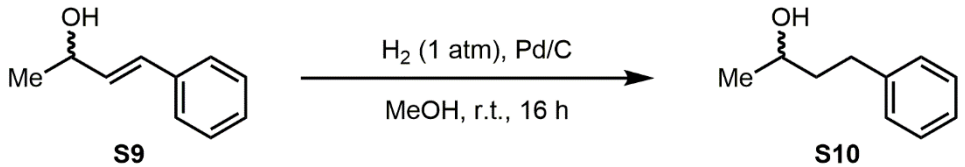
(±,*E*)-4-Phenylbut-3-en-2-ol (S9)



S9

To a suspension of 4-phenyl-3-buten-2-one (1.46 g, 10.0 mmol) and cerium trichloride heptahydrate (3.73 g, 10.0 mmol) in MeOH (7.0 mL) was added sodium borohydride (567 mg, 15.0 mmol) in portions at 0 °C. The reaction mixture was warmed to room temperature and stirred for 90 minutes, after which the reaction was quenched with a saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with a saturated brine solution (30 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound as an off-white solid (1.31 g, 89%). **^{1}H NMR** and **^{13}C{^{1}H} NMR** matched compound **S3**; **TLC** R_f: 0.21 (1:4 EtOAc:petrol); **m.p.** 58–60 °C;

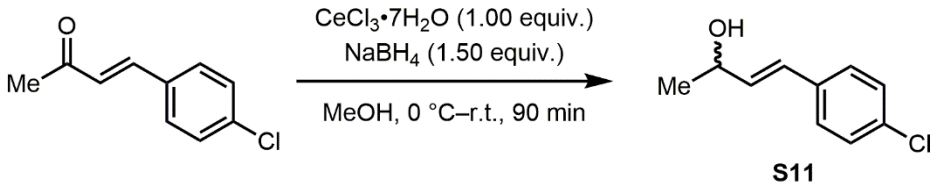
(±)-4-Phenylbutan-2-ol (S10)



S9 **S10**

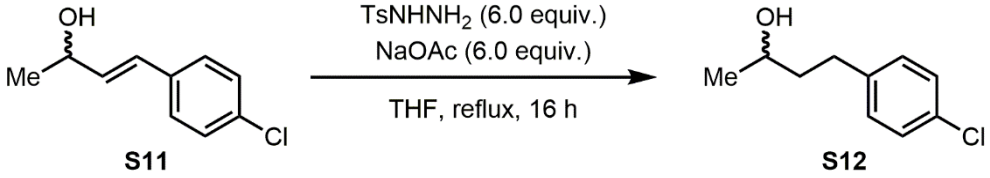
Prepared according to the same procedure as (*S*)-4-phenylbutan-2-ol **(24n)** on a 6.0 mmol scale. Purification by flash column chromatography (SiO_2, 1:9 EtOAc:petrol) afforded the title compound as a colourless oil (700 mg, 78%). **^{1}H NMR** and **^{13}C{^{1}H} NMR** matched compound **24n**; **TLC** R_f: 0.23 (1:4 EtOAc:petrol).

(±,*E*)-4-(4-Chlorophenyl)but-3-en-2-ol (S11)



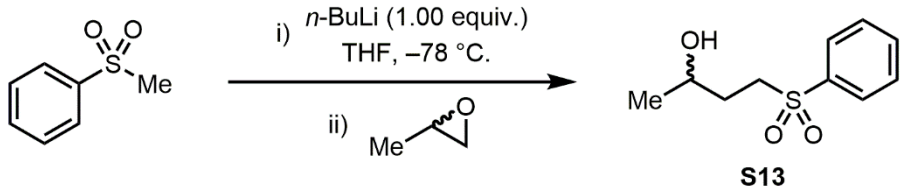
To a suspension of 4-(4-chlorophenyl)-3-buten-2-one (1.81 g, 10.0 mmol) and cerium trichloride heptahydrate (3.73 g, 10.0 mmol) in MeOH (7.0 mL) was added sodium borohydride (567 mg, 15.0 mmol) in portions at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 hours, after which the reaction was quenched with a saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with a saturated brine solution (30 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound as a colourless solid (1.52 g, 83%). **^{1}H NMR** and **^{13}C{^{1}H} NMR** matched compound **S4**; **m.p.** 57–59 °C; **TLC** R_f: 0.31 (4:6 EtOAc:petrol).

(±)-4-(4-Chlorophenyl)butan-2-ol (S12)



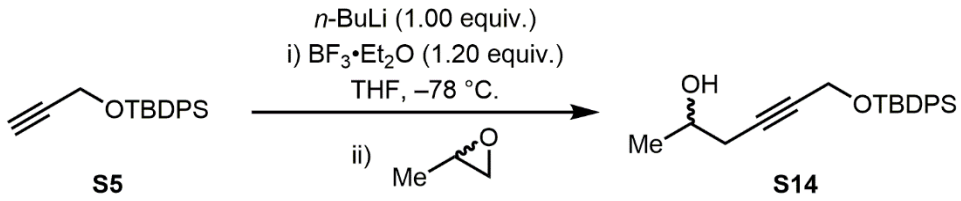
Prepared according to the same procedure as (*R*)-4-(4-chlorophenyl)butan-2-ol **(24o)** on a 6.0 mmol scale. Purification by flash column chromatography (SiO_2, 3:7 EtOAc/petrol) afforded the title compound as a colourless oil. (1.09 g, 92%) **^{1}H NMR** and **^{13}C{^{1}H} NMR** data matched compound **24o**; **TLC** R_f: 0.35 (3:7 EtOAc:petrol).

(±)4-(Phenylsulfonyl)butan-2-ol (S13)



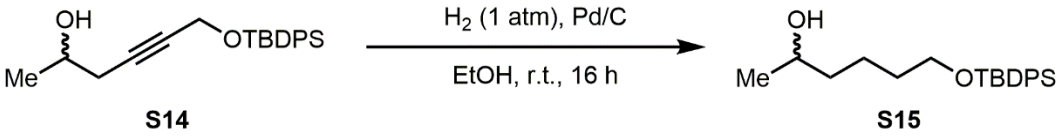
Prepared according to the same procedure as (*R*)-4-(phenylsulfonyl)butan-2-ol **(24q)**, with (±)-propylene oxide on a 3.0 mmol scale. Purification by flash column chromatography (SiO_2, 6:4 EtOAc:petrol) afforded the title compound as a colourless oil. (484 mg, 75%) **^{1}H NMR** and **^{13}C{^{1}H} NMR** data matched compound **24q**; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{10}H_{15}O_3S$ $[M + H]^+$: 215.0736 found 215.0734; **TLC** R_f: 0.26 (6:4 EtOAc:petrol).

(±)-6-((*tert*-Butyldiphenylsilyl)oxy)hex-4-yn-2-ol (S14)



Prepared according to the same procedure as (*R*)-6-((*tert*-butyldiphenylsilyl)oxy)hex-4-yn-2-ol **(30g)**, with (±)-propylene oxide on a 8.0 mmol scale. Purification by flash column chromatography (SiO_2, 1:9 EtOAc:petrol) afforded the title compound as a pale orange oil. (1.49 g, 53%) **^{1}H NMR** and **^{13}C{^{1}H} NMR** data matched compound **30g**; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{22}H_{28}NaO_2Si$ $[M + Na]^+$: 375.1751 found 375.1750; **TLC** R_f: 0.26 (1:4 EtOAc:petrol).

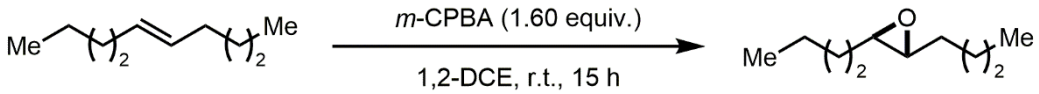
(±)-6-((*tert*-Butyldiphenylsilyl)oxy)hexan-2-ol (S15)



S14 **S15**

Prepared according to the same procedure as (*R*)-6-((*tert*-butyldiphenylsilyl)oxy)hexan-2-ol **(24r)** on a 1.2 mmol scale. Purification by flash column chromatography (SiO_2, 1:4 EtOAc/petrol) afforded the title compound as a colourless oil. (234 mg, 67%) **^{1}H NMR** and **^{13}C{^{1}H} NMR** data matched compound **24r**; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{22}H_{32}NaO_2Si$ $[M + Na]^+$: 379.2064 found 379.2069; **TLC** R_f: 0.21 (1:4 EtOAc:petrol).

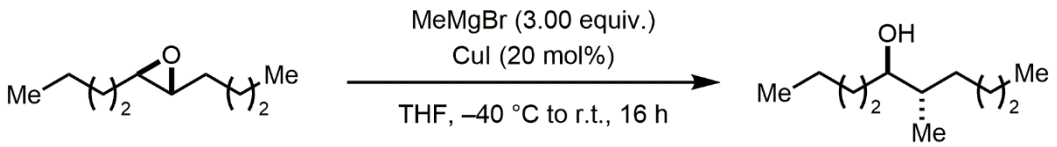
(±)-*cis*-2,3-Dibutyloxirane (S16)



S16

To a solution of (*E*)-dec-5-ene (1.54 g, 11.0 mmol) in 1,2-dichloroethane (60 mL) and added was added a 77% *w*/*w* aqueous *meta*-chloroperoxybenzoic acid solution (3.94 g, 17.6 mmol) and the reaction was stirred at ambient temperature for 15 hours. The reaction was quenched with a 5% *w*/*w* aqueous sodium sulfite solution (50 mL) and stirred for a further 10 minutes. The layers were separated, and the organic layer was washed with further 5% *w*/*w* aqueous sodium sulfite solution (50 mL) then a saturated aqueous $NaHCO_3$ solution (50 mL). The organic layer was dried over $MgSO_4$, then concentrated *in vacuo*, to afford the title compound as a colourless oil (1.39 g, 81%). **^{1}H NMR** and **^{13}C{^{1}H} NMR** spectra match with compound **S6**.

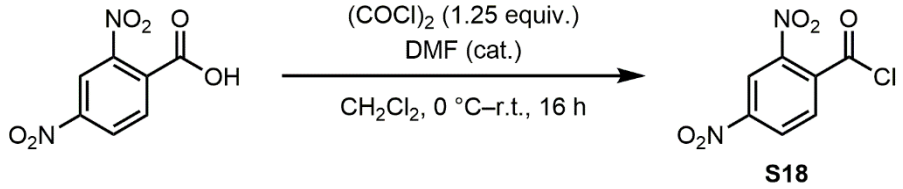
(±)-*trans*-6-Methyldecan-5-ol (S17)



S16 **S17**

Prepared according to the same procedure as (5*R*,6*R*)-6-methyldecan-5-ol **(24s)** on a 8.90 mmol scale, affording the title compound as a colourless oil (1.02 g, 73%). **^{1}H NMR** and **^{13}C{^{1}H} NMR** spectra match with compound **24s**.

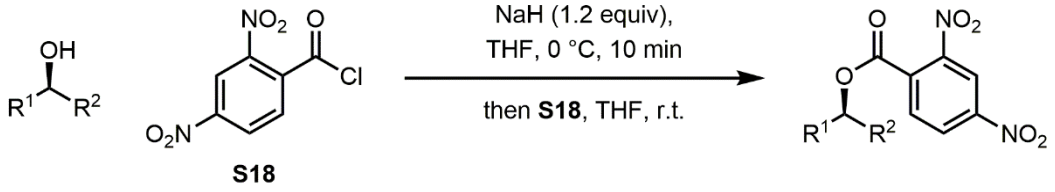
2,4-Dinitrobenzyol Chloride (S18)



S18

To a stirring solution of 2,4-dinitrobenzoic acid (2.12 g, 10.0 mmol) and DMF (2 drops) in CH_2Cl_2 (25 mL) was added oxalyl chloride (1.06 mL, 12.5 mmol) dropwise at 0 °C. The reaction mixture was warmed to ambient temperature and stirred of 16 hours. The reaction mixture was then concentrated *in vacuo* to afford the title compound as a pale-yellow oil, which solidified upon standing (2.26 g, 99%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.99 (d, *J* = 2.2 Hz, 1H), 8.66 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 164.5 (C_q), 149.4 (C_q), 145.3 (C_q), 137.1 (C_q), 129.4 (CH), 128.9 (CH), 120.5 (CH); **FTIR (neat)** ν_{max}/cm^{-1} 3109, 1780, 1715, 1601, 1530, 1418, 1339, 1202, 1149, 1065; **m.p.** 34–38 °C

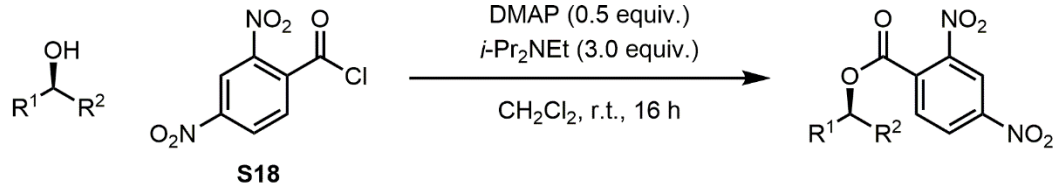
General Procedure 1 (GP1)



S18

To a solution of alcohol (1.0 equiv.) in THF (2.0 mL per mmol) was added sodium hydride (1.2 equiv., 60% *w*/*w* dispersion in mineral oil) at 0 °C and the mixture was stirred for 10 minutes. 2,4-dinitrobenzoyl chloride **(S18)** (1.0 equiv.) in THF (1.0 mL per mmol) was subsequently added and the reaction was warmed to ambient temperature and stirred for 16 hours. The reaction mixture was then quenched with H_2O and extracted with EtOAc three times. The combined organic extracts were washed with a saturated brine solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography afforded the title compound.

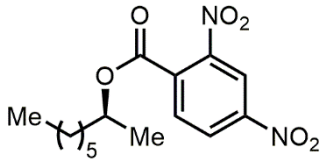
General Procedure 2 (GP2)



S18

To a solution of alcohol (1.0 equiv.), 2,4-dinitrobenzoyl chloride **(S18)** (1.0 equiv.), and 4-dimethylaminopyridine (0.5 equiv.), in CH_2Cl_2 (2,0 mL per mmol) was added *N*,*N*-diisopropylethylamine (3.0 equiv.) and the reaction mixture was stirred at ambient temperature for 16 hours. The reaction mixture was then diluted with EtOAc and the organic layer washed with water, then a 10% *w*/*v* aqueous $CuSO_4$ solution twice, then a saturated brine solution, then dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography afforded the title compound.

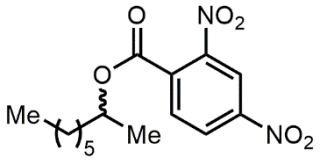
(*S*)-Octan-2-yl 2,4-Dinitrobenzoate (S19)



S19

Synthesized according to GP1 from (*S*)-(+)-2-octanol (158 µL, 1.00 mmol), sodium hydride (48 mg, 1.20 mmol, 60% *w*/*w* dispersion in mineral oil) and 2,4-dinitrobenzoyl chloride **(S18)** (231 mg, 1.00 mmol). Purification by flash column chromatography (SiO_2, 1:19 EtOAc:petrol) afforded the title compound as a pale yellow solid (265 mg, 82%). **^{1}H NMR** and **^{13}C{^{1}H} NMR** spectra match with compound **25k**; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{15}H_{20}N_2NaO_6$ $[M + Na]^+$: 347.1214, found 347.1219; **m.p.** 45–48 °C; **Chiral SFC** column: Amy-C (4.6 mm × 250 mm, 5 µm); mobile phase: 1:4 MeOH:CO_2, flow rate: 4 mL/min; temperature: 40 °C; T_R (min) 1.14 (minor), 1.38 (major), >99% e.e.

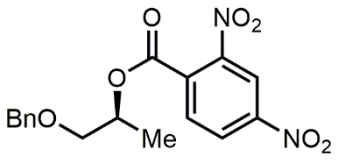
(±)-Octan-2-yl 2,4-Dinitrobenzoate (S20)



S20

Synthesized according to GP1 from (±)-2-octanol (158 µL, 1.00 mmol), sodium hydride (48 mg, 1.20 mmol, 60% *w*/*w* dispersion in mineral oil) and 2,4-dinitrobenzoyl chloride **(S18)** (231 mg, 1.00 mmol). Purification by flash column chromatography (SiO_2, 1:19 EtOAc:petrol) afforded the title compound as a pale yellow solid (224 mg, 69%). **^{1}H NMR** and **^{13}C{^{1}H} NMR** spectra match with compound **25k**; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{15}H_{20}N_2NaO_6$ $[M + Na]^+$: 347.1214, found 347.1199.

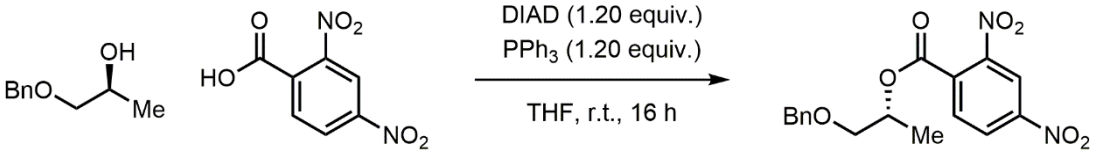
(*S*)-1-(Benzyloxy)propan-2-yl 2,4-Dinitrobenzoate (S21)



S21

Synthesized according to GP1 using (*S*)-1-(benzyloxy)propan-2-ol **(24l)** (166 mg, 1.00 mmol), sodium hydride (48 mg, 1.2 mmol, 60% *w*/*w* dispersion in mineral oil) and 2,4-dinitrobenzoyl chloride **(S18)** (230 mg, 1.00 mmol). Purification by flash column chromatography (SiO_2, 1:9 EtOAc:petrol) afforded the title compound as a pale orange oil (101 mg, 28%) **^{1}H NMR** and **^{13}C{^{1}H} NMR** spectra match with compound **25l**; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{17}H_{16}N_2NaO_7$ $[M + Na]^+$: 383.0850 found 361.0848; **Chiral SFC** column: Amy-C (4.6 mm × 250 mm, 5 µm); mobile phase: 1:3 MeOH:CO_2; flow rate: 4 mL/min; temperature: 40 °C; T_R (min) 1.70 (minor), 2.00 (major) e.e. = 97%.

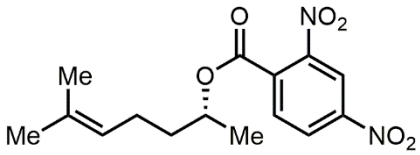
(*R*)-1-(Benzyloxy)propan-2-yl 2,4-Dinitrobenzoate (S22)



S22

To a solution of (*S*)-1-(benzyloxy)propan-2-ol **(24l)** (166 mg, 1.00 mmol), 2,4-dinitrobenzoic acid (212 mg, 1.00 mmol) and triphenylphosphine (315 mg, 1.20 mmol) in THF (1.0 mL) was added diisopropyl azodicarboxylate (236 µL, 1.20 mmol) dropwise at 0 °C. The reaction was warmed to room temperature and stirred for 16 hours. The reaction mixture was diluted with EtOAc (10 mL) and the organic layer was washed with H_2O (2 × 10 mL) then a saturated brine solution (10 mL). The organic layer was then dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:99 to 1:9 gradient, EtOAc:petrol) afforded the title compound as a pale yellow oil (272 mg, 75%). **^{1}H NMR** and **^{13}C{^{1}H} NMR** spectra match with compound **25l**; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{17}H_{16}N_2NaO_7$ $[M + Na]^+$: 383.0850 found 361.0857. A racemic sample for chiral SFC was obtained by using a 1:1 mixture of compounds **S21** and **S22**.

(*R*)-6-Methylhept-5-en-2-yl 2,4-Dinitrobenzoate (S23)

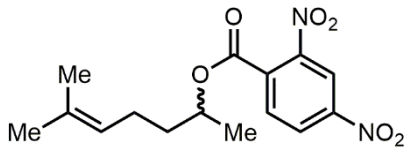


S23

Synthesized according to GP2 from (*R*)-6-methylhept-5-en-2-ol **(24m)** (13 mg, 100 µmol), 2,4-dinitrobenzoyl chloride **(S18)** (23 mg, 100 µmol), *N*,*N*-diisopropylethylamine (52 µL, 300 µmol) and 4-dimethylaminopyridine (6.0 mg, 50 µmol). Purification by flash column chromatography (SiO_2, 1:19 EtOAc:petrol) afforded the title compound as a pale yellow oil (13 mg, 42%). **^{1}H NMR** and **^{13}C{^{1}H} NMR** spectra match with compound **25m**; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{15}H_{18}N_2NaO_6$ $[M + Na]^+$: 345.1057, found 345.1052; **Chiral SFC** column: Amy-C (4.6 mm × 250 mm, 5 µm); mobile phase: 1:9 MeOH:CO_2 (0.2% *v*/*v* NH_3);

flow rate: 4 mL/min; temperature: 40 °C; T_R (min) 1.49 (major), 1.86 (minor), 93% e.e.

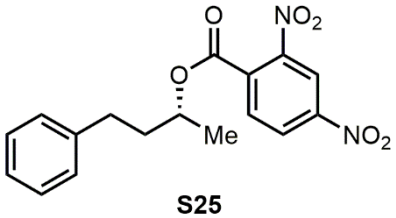
(±)-6-Methylhept-5-en-2-yl 2,4-Dinitrobenzoate (S24)



S24

Synthesized according to GP2 from (±)-6-methylhept-5-en-2-ol (26 mg, 200 µmol), 2,4-dinitrobenzoyl chloride **(S18)** (46 mg, 200 µmol), *N*,*N*-diisopropylethylamine (105 µL, 600 µmol) and 4-dimethylaminopyridine (12 mg, 100 µmol). Purification by flash column chromatography (SiO_2, 1:19 EtOAc:petrol) afforded the title compound as a pale yellow oil (50 mg, 81%). **^{1}H NMR** and **^{13}C{^{1}H} NMR** spectra match with compound **25m**; **HRMS** (ESI-TOF) m/z calc'd for $C_{15}H_{18}N_2NaO_6$ $[M + Na]^+$: 345.1057, found 345.1055.

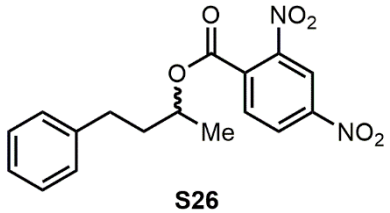
(*R*)-4-Phenylbutan-2-yl 2,4-Dinitrobenzoate (S25)



S25

Synthesized according to GP1 from (*R*)-4-phenylbutan-2-ol **(24n)** (75 mg, 500 µmol), sodium hydride (60% *w*/*w* dispersion in mineral oil, 30 mg, 750 µmol) and 2,4-dinitrobenzoyl chloride **(S18)** (115 mg, 500 µmol). Purification by flash column chromatography (SiO_2, 1:19 to 1:9 EtOAc:petrol gradient) afforded the title compound as a pale yellow oil (98 mg, 56%). **^{1}H NMR** and **^{13}C{^{1}H} NMR** spectra match with compound **25n**; **HRMS** (ESI-TOF) m/z calc'd for $C_{17}H_{20}N_3O_6$ $[M + NH_4]^+$: 362.1364, found 362.1347**; Chiral SFC** column: Amy-C (4.6 mm × 250 mm, 5 µm), mobile phase: 1:3 MeOH:CO_2, flow rate: 4 mL/min, temperature: 40 °C, T_R (min) 1.89 (major), 2.17 (minor), 94% e.e.

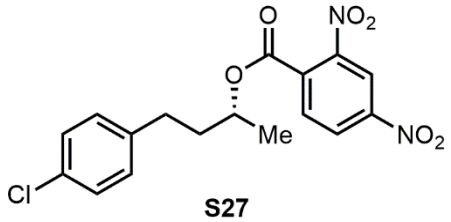
(±)-4-Phenylbutan-2-yl 2,4-Dinitrobenzoate (S26)



S26

Synthesized according to GP2 from (±)-4-phenylbutan-2-ol **(S10)** (75 mg, 500 µmol), 2,4-dinitrobenzoyl chloride **(S18)** (115 mg, 500 µmol), *N*,*N*-diisopropylethylamine (261 µL, 1.50 mmol) and 4-dimethylaminopyridine (30 mg, 250 µmol). Purification by flash column chromatography (SiO_2, 1:19 EtOAc:petrol) afforded the title compound as a pale yellow oil (101 mg, 59%). **^{1}H NMR** and **^{13}C{^{1}H} NMR** spectra match with compound **25n**; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{17}H_{16}NaN_2O_6$ $[M + Na]^+$: 367.0901, found 367.0901.

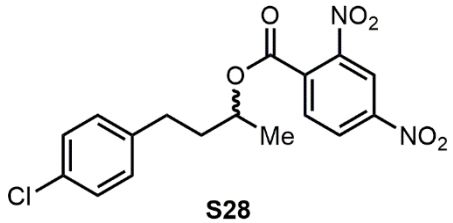
(*R*)-4-(4-Chlorophenyl)butan-2-yl 2,4-Dinitrobenzoate (S27)



S27

Synthesized according to GP1 from (*R*)-4-(4-chlorophenyl)butan-2-ol **(24o)** (92 mg, 500 µmol), sodium hydride (30 mg, 750 µmol, 60% *w*/*w* dispersion in mineral oil,) and 2,4-dinitrobenzoyl chloride **(S18)** (115 mg, 500 µmol). Purification by flash column chromatography (SiO^2, 1:19 to 1:9 gradient, EtOAc:petrol) afforded the title compound as a pale yellow solid (39 mg, 21%). **^{1}H NMR** and **^{13}C{^{1}H} NMR** spectra match with compound **25o**; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{17}H_{15}{}^{35}ClN_2NaO_6$ $[M + Na]^+$: 401.0511, found 401.0510; **Chiral SFC** column: Chiralpak IG (4.6 mm × 250 mm, 5 µm); mobile phase: 2:3 MeOH:CO_2 (0.2% *v*/*v* NH_3); flow rate: 4 mL/min; temperature: 40 °C; T_R (min) 2.07 (major), 2.28 (minor), 96% e.e.

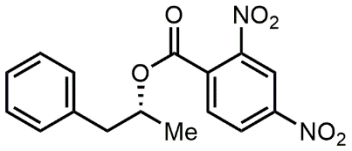
(±)-4-(4-Chlorophenyl)butan-2-yl 2,4-Dinitrobenzoate (S28)



S28

Synthesized according to GP2 from (±)-4-(4-chlorophenyl)butan-2-ol **(S12)** (92 mg, 500 µmol), 2,4-dinitrobenzoyl chloride **(S18)** (115 mg, 500 µmol), *N*,*N*-diisopropylethylamine (261 µL, 1.50 mmol) and 4-dimethylaminopyridine (30 mg, 250 µmol). Purification by flash column chromatography (SiO_2, 1:19 EtOAc:petrol) afforded the title compound as a pale yellow oil (109 mg, 58%). **^{1}H NMR** and **^{13}C{^{1}H} NMR** spectra match with compound **25o**; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{17}H_{15}{}^{35}ClN_2NaO_6$ $[M + Na]^+$: 401.0511, found 401.0514;

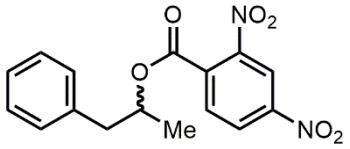
(*R*)-1-Phenylpropan-2-yl 2,4-Dinitrobenzoate (S29)



S29

Synthesized according to GP2 using (*R*)-1-phenyl-propan-2-ol (68 mg, 500 µmol), 2,4-dinitrobenzoyl chloride **(S18)** (115 mg, 500 µmol), *N*,*N*-diisopropylethylamine (261 µL, 1.50 mmol) and 4-dimethylaminopyridine (30 mg, 250 µmol). Purification by flash column chromatography (SiO_2, 3:17 EtOAc:petrol) afforded the title compound as a pale yellow oil (128 mg, 78%). **^{1}H NMR** and **^{13}C{^{1}H} NMR** spectra match with compound **25p**; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{16}H_{14}N_2NaO_6$ $[M + Na]^+$: 353.0744 found 353.0740; **Chiral SFC** column: Amy-C (4.6 mm × 250 mm, 5 µm); mobile phase: 1:4 MeOH:CO_2, flow rate: 4 mL/min; temperature: 40 °C; T_R (min) 1.63 (major), 1.80 (minor), >99% e.e.;

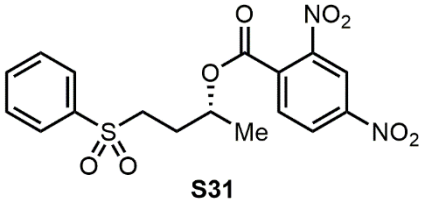
(±)-1-Phenylpropan-2-yl 2,4-Dinitrobenzoate (S30)



S30

Synthesized according to GP2 using (±)-1-phenyl-propan-2-ol (27mg, 200 μmol), 2,4-dinitrobenzoyl chloride **(S18)** (46 mg, 200 μmol), *N*,*N*-diisopropylethylamine (105 μL, 600 μmol) and 4-dimethylaminopyridine (12 mg, 100 μmol). Purification by flash column chromatography (SiO_2, 3:17 EtOAc:petrol) afforded the title compound as a pale yellow oil (58 mg, 88%). **^{1}H NMR** and **^{13}C{^{1}H} NMR** spectra match with compound **25p**; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{16}H_{14}N_2NaO_6$ $[M + Na]^+$: 353.0744 found 353.0748;

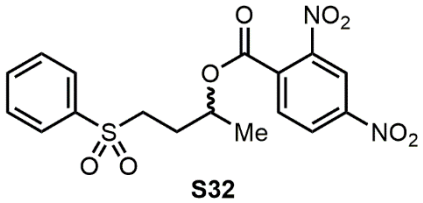
(*R*)-4-(Phenylsulfonyl)butan-2-yl 2,4-Dinitrobenzoate (S31)



S31

Synthesized according to GP2 (*R*)-4-(phenylsulfonyl)butan-2-ol **(24q)** (107mg, 500 μmol), 2,4-dinitrobenzoyl chloride **(S18)** (115 mg, 500 μmol), *N*,*N*-diisopropylethylamine (261 μL, 1.50 mmol) and 4-dimethylaminopyridine (30 mg, 250 μmol). Purification by flash column chromatography (SiO_2, 3:7 EtOAc:petrol) afforded the title compound as a pale yellow oil (124 mg, 61%) **^{1}H NMR** and **^{13}C{^{1}H} NMR** spectra match with compound **25q**; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{17}H_{16}N_2NaO_8S$ $[M + Na]^+$: 431.0520, found 431.0518; **Chiral SFC** column: Lux C4 (4.6 mm × 250 mm, 5 μm); mobile phase: 1:1 MeOH:CO_2 (0.2% *v*/*v* NH_3), flow rate: 4 mL/min; temperature: 40 °C; T_R (min) 2.36 (minor), 2.85 (major), 99% e.e.

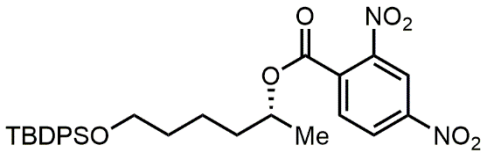
(±)-4-(Phenylsulfonyl)butan-2-yl 2,4-Dinitrobenzoate (S32)



S32

Synthesized according to GP2 (±)-4-(phenylsulfonyl)butan-2-ol **(S13)** (107mg, 500 μmol), 2,4-dinitrobenzoyl chloride **(S18)** (115 mg, 500 μmol), *N*,*N*-diisopropylethylamine (261 μL, 1.50 mmol) and 4-dimethylaminopyridine (30 mg, 250 μmol). Purification by flash column chromatography (SiO_2, 3:7 EtOAc:petrol) afforded the title compound as a pale yellow oil (118 mg, 58%). **^{1}H NMR** and **^{13}C{^{1}H} NMR** spectra match with compound **25q**; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{17}H_{16}N_2NaO_8S$ [M + Na]$^+$: 431.0520, found 431.0518.

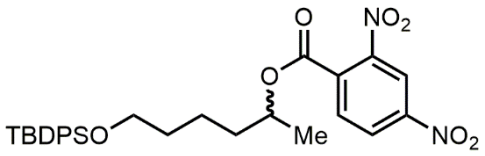
(*R*)-6-((*tert*-Butyldiphenylsilyl)oxy)hexan-2-yl 2,4-Dinitrobenzoate (S33)



S33

Synthesized according to GP2 using (*R*)-6-((*tert*-butyldiphenylsilyl)oxy)hexan-2-ol **(24r)** (71 mg, 200 μmol), 2,4-dinitrobenzoyl chloride **(S18)** (46 mg, 200 μmol), *N*,*N*-diisopropylethylamine (105 μL, 600 μmol) and 4-dimethylaminopyridine (12 mg, 100 μmol). Purification by flash column chromatography (SiO_2, 1:9 EtOAc:petrol) afforded the title compound as a pale yellow oil (91 mg, 83%). **^{1}H NMR** and **^{13}C{^{1}H} NMR** spectra match with compound **25r**; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{29}H_{34}N_2NaO_7Si$ [M + Na]$^+$: 573.2033 found 573.2037; **Chiral HPLC** column: Lux C1 (4.6 mm × 250 mm, 5 μm); mobile phase: 19:1 heptane:IPA (0.2% *v*/*v* NH_3); flow rate: 1 mL/min; temperature: ambient; T_R (min) 14.45 (minor), 15.56 (major), 99% e.e.

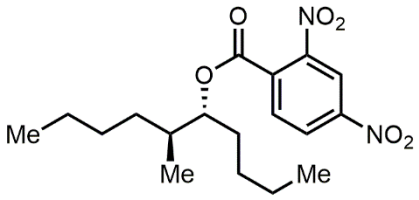
(±)-6-((*tert*-Butyldiphenylsilyl)oxy)hexan-2-yl 2,4-Dinitrobenzoate (S34)



S34

Synthesized according to GP2 using (±)-6-((*tert*-butyldiphenylsilyl)oxy)hexan-2-ol **(S15)** (71 mg, 200 µmol), 2,4-dinitrobenzoyl chloride **(S18)** (46 mg, 200 µmol), *N*,*N*-diisopropylethylamine (105 µL, 600 µmol) and 4-dimethylaminopyridine (12 mg, 100 µmol). Purification by flash column chromatography (SiO_2, 1:9 EtOAc:petrol) afforded the title compound as a pale yellow oil (74 mg, 67%). **^{1}H NMR** and **^{13}C{^{1}H} NMR** spectra match with compound **25r**; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{29}H_{34}N_2NaO_7Si$ $[M + Na]^+$: 573.2033 found 573.2036;

(5*R*,6*S*)-6-Methyldecan-5-yl 2,4-Dinitrobenzoate (S35)

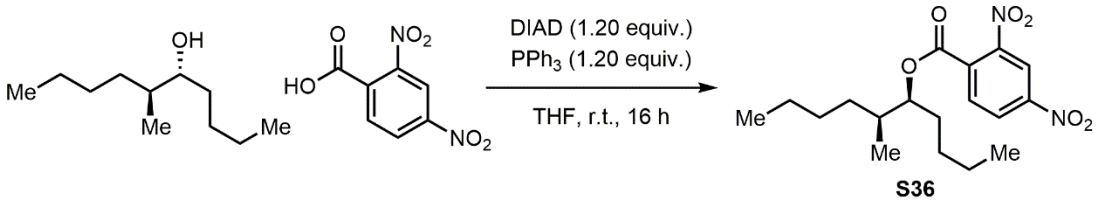


S35

Synthesized according to GP2 using (5*R*,6*S*)-6-methyldecan-5-ol **(24s)** (86 mg, 500 µmol), 2,4-dinitrobenzoyl chloride **(S18)** (115 mg, 500 µmol), *N*,*N*-diisopropylethylamine (261 µL, 1.50 mmol) and 4-dimethylaminopyridine (30 mg, 250 µmol). Purification by flash column chromatography (SiO_2, 1:19 EtOAc:petrol) afforded the title compound as a pale yellow oil (39 mg, 21%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.75 (d, *J* = 2.2 Hz, 1H), 8.52 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 5.13 (dt, *J* = 8.6, 4.4 Hz, 1H), 1.94 – 1.82 (m, 1H), 1.71 – 1.05 (m, 12H), 0.97 – 0.84 (m, 9H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 163.6 (C_q), 149.0 (C_q), 148.3 (C_q), 133.6 (C_q), 131.4 (CH), 127.4 (CH), 119.7 (CH), 82.4 (CH), 36.1 (CH), 32.0 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 27.9 (CH_2), 23.0 (CH_2), 22.7 (CH_2), 15.1 (CH_3), 14.2 (CH_3), 14.1 (CH_3); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{29}H_{34}N_2NaO_7Si$ $[M + Na]^+$: 573.2033 found 573.2036; **FTIR** (neat) ν_{max}/cm^{-1} 3108, 2957, 2930, 2860, 1730, 1604, 1538, 1465, 1347, 1245, 1155, 1130, 1109,

1057; **SFC for d.e. determination** column: Amy-C (4.6 mm × 250 mm, 5 μm); mobile phase: 1:19 CO_2:EtOH (0.2% *v*/*v* HCO_2H); flow rate: 4 mL/min; temperature: 40 °C; T_R (min) 1.79 (major), 1.95 (minor), 99% d.e. **Chiral SFC for e.e. determination** column: Amy-C (4.6 mm × 250 mm, 5 μm); mobile phase: 19:1 CO_2:EtOH (0.2% *v*/*v* HCO_2H); flow rate: 4 mL/min; temperature: 40 °C; T_R (min) 1.86 (minor), 1.98 (major), 90% e.e.

(5*S*,6*S*)-6-Methyldecan-5-yl 2,4-Dinitrobenzoate (S36)

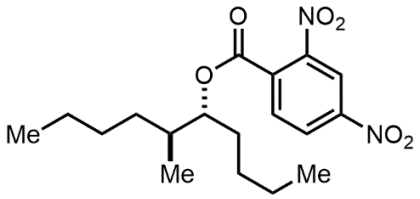


S36

To a solution of (5*R*,6*S*)-6-methyldecan-5-yl **(24s)** (166 mg, 1.00 mmol), 2,4-dinitrobenzoic acid (212 mg, 1.00 mmol) and triphenylphosphine (315 mg, 1.20 mmol) in THF (2.0 mL) was added diisopropyl azodicarboxylate (236 μL, 1.20 mmol) dropwise at 0 °C. The reaction was warmed to room temperature and stirred for 16 hours. The reaction mixture was diluted with EtOAc (10 mL) and the organic layer was washed with H_2O (2 × 10 mL) then a saturated brine solution (10 mL). The organic layer was then dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:99 to 1:9 gradient, EtOAc:petrol) afforded the title compound as a pale yellow oil (272 mg, 75%). **^{1}H NMR** and **^{13}C{^{1}H} NMR** spectra match with compound **25s**; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{18}H_{26}N_2O_6$ $[M + Na]^+$: 389.1683 found 389.1681.

A diastereomer mixture for SFC analysis was acquired by mixing compounds **S35** and **S36**.

(*cis*)-6-Methyldecan-5-yl 2,4-Dinitrobenzoate (S37)

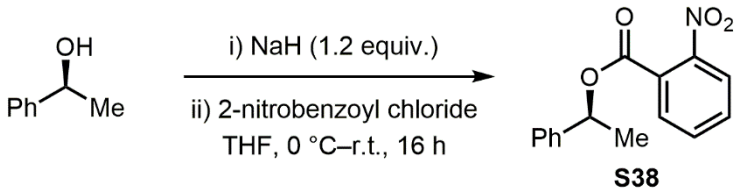


S37

Synthesized according to GP2 using *cis*-6-methyldecan-5-ol **(S17)** (86 mg, 500 µmol), 2,4-dinitrobenzoyl chloride **(S18)** (115 mg, 500 µmol), *N*,*N*-diisopropylethylamine (261 µL, 1.50 mmol) and 4-dimethylaminopyridine (30 mg, 250 µmol). Purification by flash column chromatography (SiO_2, 1:19 EtOAc:petrol) afforded the title compound as a pale yellow oil (48 mg, 26%). **^{1}H NMR** and **^{13}C{^{1}H} NMR** spectra match with compound **S35; HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{18}H_{26}N_2O_6$ $[M + Na]^+$: 389.1683 found 389.1680.

Used as a racemic standard for chiral SFC analysis of compound **25s**.

(*S*)-1-Phenylethyl 2-Nitrobenzoate (S38)

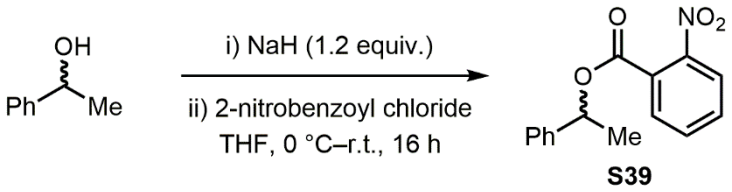


S38

To a solution of (*S*)-1-phenylethanol (120 µL, 1.00 mmol) in THF (1 mL) at 0 °C was carefully added sodium hydride (48 mg, 60% *w*/*w*, 1.2 mmol). The solution was warmed to room temperature and was stirred for 30 minutes. The reaction mixture was cooled again to 0 °C and a solution of 2-nitrobenzoyl chloride (223 mg, 1.2 mmol) in THF (2 mL) was added dropwise. The reaction was stirred at room temperature for 16 hours. A saturated aqueous NH_4Cl solution (10 mL) was added and the mixture was extracted with CH_2Cl_2 (2 × 10 mL), the combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:4 EtOAc:petrol) afforded the title compound as a pale yellow oil (176 mg, 65%). **^{1}H NMR** and **^{13}C{^{1}H} NMR** spectra match with compound **25t; HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{15}H_{17}N_2NaO_4$

[M + NH_4]$^+$: 289.1183 found 298.1186; **Chiral HPLC** column chiralpak AD-H (4.6 mm × 250 mm, 5 μm), mobile phase: 4:1 *i*-hexane:EtOH, flow rate 1 mL/min, temperature: ambient, T_R (min) 6.73 (minor), 8.69 (major), >99% e.e.

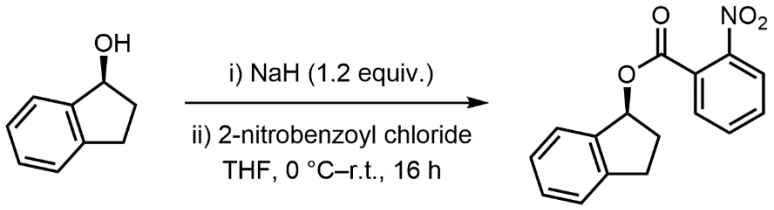
1-Phenylethyl 2-Nitrobenzoate (S38)



S39

Synthesized according to the same protocol as (*S*)-1-phenylethyl 2-nitrobenzoate **(S38)** using 1-phenylethanol (120 μL, 1.00 mmol), THF (1 mL) and sodium hydride (48 mg, 60% *w*/*w*, 1.2 mmol), to yield the title compound as a pale yellow oil (206 mg, 76%) **^{1}H NMR** and **^{13}C{^{1}H} NMR** spectra match with compound **25t; HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{15}H_{17}N_2NaO_4$ [M + NH_4]$^+$: 289.1183 found 298.1184.

(*S*)-Indanyl 2-Nitrobenzoate (S40)

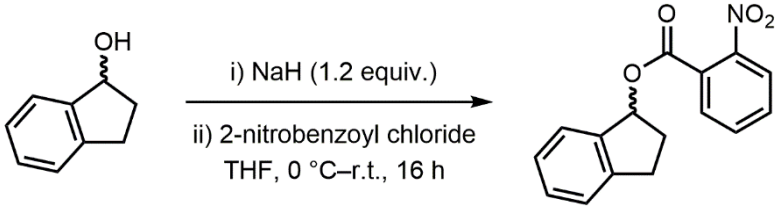


S40

To a solution of (*S*)-indanol (134 mg, 1.00 mmol) in THF (1 mL) at 0 °C was added sodium hydride (48 mg, 60% *w*/*w*, 1.2 mmol). The solution was warmed to room temperature and was stirred for 30 minutes. The reaction mixture was cooled again to 0 °C and a solution of 2-nitrobenzoyl chloride (223 mg, 1.2 mmol) in THF (2 mL) was added dropwise. The reaction was stirred at room temperature for 16 hours. A saturated aqueous NH_4Cl solution (10 mL) was added and the mixture was extracted with CH_2Cl_2 (2 × 10 mL), the combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 EtOAc:petrol) afforded the title compound as a pale yellow oil (199 mg, 70%). **^{1}H NMR** and **^{13}C{^{1}H} NMR** spectra match with

compound **25u**. **HRMS** (ESI-TOF) *m/z* calc'd for $C_{16}H_{13}NNaO_4$ $[M + Na]^+$: 306.0737 found 306.0738; **Chiral HPLC** column chiralpak IC (4.6 mm × 250 mm, 5 μm), mobile phase: 90:10 isohexane:IPA, flow rate 1 mL/min, temperature: ambient, T_R (min) 10.88 (major), 13.50 (minor), 98% e.e.

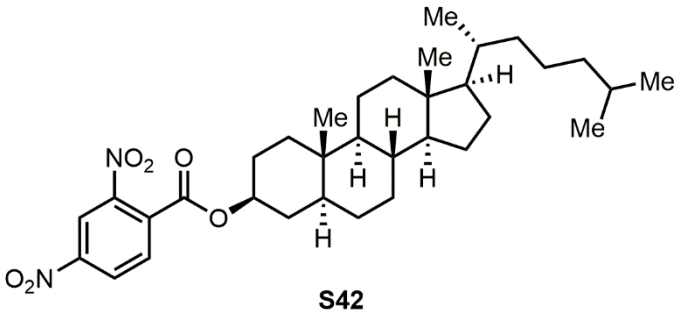
Indanyl 2-Nitrobenzoate (S41)



S41

Synthesized according to the same protocol as (*S*)-indanyl 2-nitrobenzoate **(S40)** using indanol (134 mg, 1.00 mmol), THF (1 mL) and sodium hydride (48 mg, 60% *w*/*w*, 1.2 mmol), to yield the title compound as a pale yellow oil (175 mg, 62%). **^{1}H NMR** and **^{13}C{^{1}H} NMR** spectra match with compound **25u**. **HRMS** (ESI-TOF) *m/z* calc'd for $C_{16}H_{13}NNaO_4$ $[M + Na]^+$: 306.0737 found 306.0735.

5α-Cholestan-3β-yl 2,4-Dinitrobenzoate (S42)

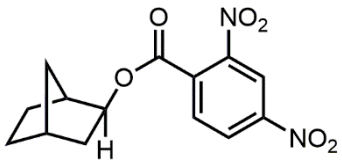


S42

A solution of 5α-cholestan-3β-ol (78 mg, 0.20 mmol) and 2,4-dinitrobenzoyl chloride **(S18)** (47 mg, 0.20 mmol) in 1:9 pyridine/$CHCl_3$ (2 mL) heated to 65 °C in a microwave vial and stirred for 16 h. The reaction mixture was then cooled to room temperature and concentrated *in vacuo*. The crude residue was triturated with MeCN to afford the title compound as an off-white solid (44 mg, 38%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.78 (d, *J* = 2.2 Hz, 1H), 8.51 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 5.01 (tt, *J* = 11.4, 4.9 Hz, 1H), 2.02 – 1.89 (m, 3H), 1.87 – 1.40 (m, 9H), 1.40 – 0.94 (m, 19H), 0.92 – 0.88 (m, 3H), 0.86 (dd, *J* = 6.6, 1.8 Hz,

6H), 0.83 (s, 3H), 0.65 (s, 3H); **$^{13}C\{^{1}H\}$ NMR** (101 MHz, $CDCl_3$) δ 163.4 (C_q), 148.9 (C_q), 148.2 (C_q), 133.7 (CH), 131.4 (C_q), 127.5 (CH), 119.7 (CH), 77.7 (CH), 56.6 (CH), 56.4 (CH), 54.3 (CH), 44.8 (C_q), 42.7 (CH), 40.1 (CH_2), 39.7 (CH_2), 36.8 (CH_2), 36.3 (CH_2), 36.0 (CH_2), 35.6 (CH_2), 33.5 (CH_2), 32.1 (CH_2), 28.7 (CH_2), 28.4 (CH_2), 28.2 (CH), 27.1 (CH_2), 27.1 (CH_2), 24.4 (CH_2), 24.0 (CH_2), 23.0 (CH_3), 22.7 (CH_2), 21.4 (CH_3), 18.8 (CH_3), 12.4 (CH_3), 12.2 (CH_3); **HRMS** (ESI-TOF) *m/z* calc'd for $C_{34}H_{52}N_2O_6$ $[M + NH_4]^+$: 600.4007 found 600.4002; **m.p.** 174–177 °C.

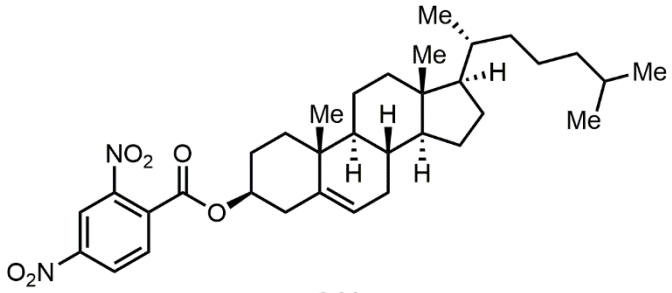
exo-Norbornyl 2,4-Dinitrobenzoate (S43)



S43

A solution of *exo*-norborneol (22 mg, 0.20 mmol) and 2,4-dinitrobenzoyl chloride **(S18)** (47 mg, 0.20 mmol) in 1:9 pyridine/$CHCl_3$ (2 mL) heated to 65 °C in a microwave vial and stirred for 16 h. The reaction mixture was then cooled to room temperature and concentrated in vacuo. The crude residue was purified by flash column chromatography (SiO_2, 1:19 EtOAc/petrol) to afford the title compound as a pale yellow oil (8 mg, 13%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.74 (d, *J* = 2.1 Hz, 1H), 8.51 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 4.92 (d, *J* = 7.0 Hz, 1H), 2.47 (d, *J* = 5.0 Hz, 1H), 2.38 – 2.29 (m, 1H), 1.83 (ddd, *J* = 13.8, 7.1, 2.5 Hz, 1H), 1.66 – 1.55 (m, 2H), 1.53 – 1.42 (m, 2H), 1.25 – 1.10 (m, 3H); **$^{13}C\{^{1}H\}$ NMR** (101 MHz, $CDCl_3$) δ_C 163.3 (C_q), 149.0 (C_q), 148.5 (C_q), 133.4 (C_q), 131.6 (CH), 127.4 (CH), 119.6 (CH), 81.3 (CH), 41.4 (CH), 39.0 (CH_2), 35.5 (1 × CH_2, 1 × CH), 28.2 (CH_2), 24.3 (CH_2); **HRMS** (ESI-TOF) *m/z* calc'd for $C_{14}H_{14}N_2NaO_6$ $[M + Na]^+$: 329.0744 found 329.0744.

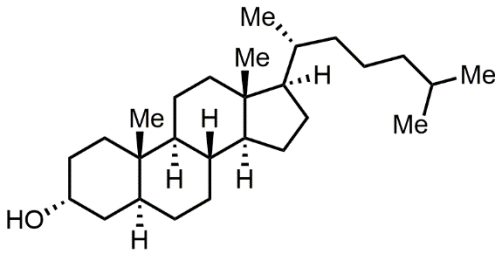
Cholesteryl 2,4-Dinitrobenzoate (S44)



S44

A solution of cholesterol (77 mg, 0.20 mmol) and 2,4-dinitrobenzoyl chloride **(S18)** (47 mg, 0.20 mmol) in 1:9 pyridine/$CHCl_3$ (2 mL) heated to 65 °C in a microwave vial and stirred for 16 h. The reaction mixture was then cooled to room temperature and concentrated in vacuo. The crude residue was triturated with MeCN to afford the title compound as an off-white solid (90 mg, 78%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.78 (d, *J* = 2.2 Hz, 1H), 8.52 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 5.50 – 5.38 (m, 1H), 4.92 (tt, *J* = 11.4, 4.9 Hz, 1H), 2.51 – 2.35 (m, 2H), 2.09 – 0.95 (m, 29H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.87 (dd, *J* = 6.5, 1.9 Hz, 6H), 0.68 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 163.3 (C_q), 148.9 (C_q), 148.2 (C_q), 139.0 (C_q), 133.6 (CH), 131.4 (C_q), 127.6 (CH), 123.6 (CH), 119.7 (CH), 77.8 (CH), 56.8 (CH), 56.3 (CH), 50.2 (CH), 42.5 (C_q), 39.9 (CH_2), 39.7 (CH_2), 37.7 (CH_2), 37.0 (CH_2), 36.7 (CH_2), 36.3 (CH_2), 35.9 (CH), 32.1 (CH_2), 32.0 (CH), 28.4 (CH_2), 28.2 (CH), 27.4 (CH_2), 24.4 (CH_2), 24.0 (CH_3), 23.0 (CH_3), 22.7 (CH_3), 21.2 (CH_2), 19.5 (CH_3), 18.9 (CH_3), 12.0 (CH_3); **HRMS** (ESI-TOF) *m/z* calc'd for $C_{34}H_{48}N_2NaO_6$ $[M + Na]^+$: 603.3405 found 603.3409.

Epimerization of 5α-Cholestan-3β-ol (27)



27

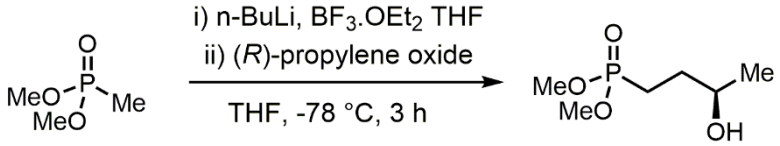
A suspension of 5α-cholestan-3β-ol (7.77 g, 20.0 mmol), 2,4-dinitrobenzoic acid (4.24 g, 20.0 mmol) and catalyst **C2** (1.23 g, 4.00 mmol) in xylenes (250 mL) was heated to reflux in a Dean-Stark apparatus and stirred for 192 hours, then the reaction mixture was cooled to room temperature and concentrated *in vacuo*. The crude residue was dissolved in 3:1 THF/MeOH (100 mL), cooled to 0 °C and a 2.0 M aqueous lithium hydroxide solution (30 mL, 60 mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 5 hours. The reaction mixture was then concentrated, the residue was diluted with a 2.0 M aqueous NaOH solution (300 mL) and extracted with CH_2Cl_2 (2 × 300 mL).* The combined organic extracts were washed with a saturated brine solution (200 mL), dried over $MgSO_4$ and concentrated. Purification by flash column chromatography (SiO_2, 3:17 EtOAc/petrol)** afforded an off-white solid, which was triturated with MeCN to afford the title compound as a white solid (4.37 g, 56%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.05 – 4.01 (m, 1H), 1.96 (dt, *J* = 12.5, 3.4 Hz, 1H), 1.87 – 1.74 (m, 1H), 1.73 – 1.42 (m, 9H), 1.41 – 0.93 (m, 20H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.86 (dd, *J* = 6.6, 1.9 Hz, 6H), 0.77 (s, 3H), 0.65 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 66.8 (CH), 56.7 (CH), 56.4 (CH), 54.5 (CH), 42.7, 40.2 (CH_2), 39.7 (CH_2), 39.3 (CH), 36.3 (CH_2), 36.2 (CH_2), 36.1 (CH_2), 36.0 (CH), 35.7 (CH), 32.4 (CH_2), 32.2 (CH_2), 29.2 (CH_2), 28.8 (CH_2), 28.4 (CH_2), 28.2 (CH), 24.3 (CH_2), 24.0 (CH_2), 23.0 (CH_3), 22.7 (CH_3), 20.9 (CH_2), 18.8 (CH_3), 12.2 (CH_3), 11.3 (CH_3); **m.p.** 175–178 °C; **TLC** R_f: 0.24 (1:4 EtOAc/petrol). Data are consistent with those reported in the literature.[26] ^{13}C{^{1}H} NMR signal for C_3 of 5α-cholestan-3β-ol = 71.4. ^{13}C NMR signal for C_3 of 5α-cholestan-3α-ol: 66.5[26]. For a comparison of ^{13}C{^{1}H} NMR data for different hydroxysteroids, see the following report.[27]

*After the extraction, the aqueous layer was acidified to pH 1 with a 6.0 M aqueous HCl solution and extracted with EtOAc (3 × 300 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated. The crude residue was triturated with $CHCl_3$ to afford 2,4-dinitrobenzoic acid as an orange solid (3.86 g, 91%). **^{1}H NMR** (400 MHz, CD_3OD) δ_H 8.74 (d, *J* = 2.2 Hz, 1H), 8.57 (dd, *J* = 8.4, 2.2 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H); **^{13}C{^{1}H} NMR** (101 MHz, CD_3OD) δ_C 166.5 (C_q), 150.4 (C_q), 149.8 (C_q), 134.3 (C_q), 132.5 (CH), 128.5 (CH), 120.5 (CH). NMR data are consistent with a commercial sample.

The solvent polarity was subsequently increased to 4:6 EtOAc/petrol, which eluted catalyst **C2 as an off-white solid, which was triturated with Et_2O to afford a pure sample of catalyst **C2** (1.07 g, 87%) **^{1}H NMR, ^{13}C{^{1}H} NMR and ^{31}P{^{1}H} NMR** data are consistent with catalyst **C2**.

Failed Substrates (Table 5)

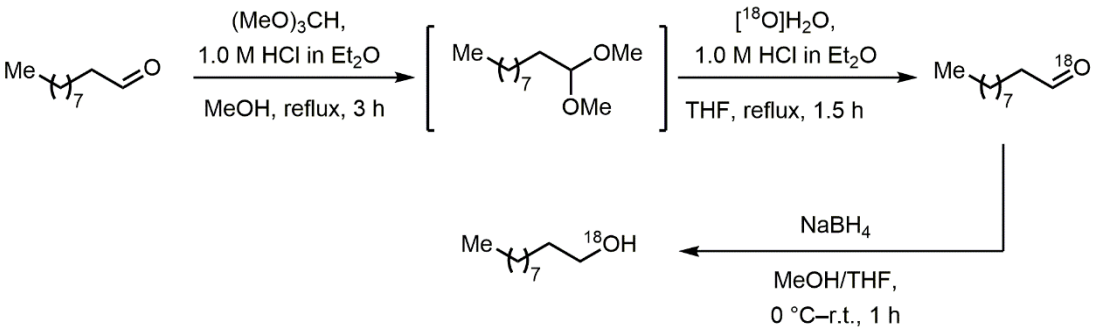
Dimethyl (*R*)-(3-Hydroxybutyl)phosphonate (30e)



30e

To a solution of dimethyl phosphonate (2.60 mL, 24.0 mmol) in anhydrous THF (10 mL) was added a 2.40 M *n*-butyllithium solution in hexanes (10.0 mL, 24.0 mmol) dropwise at −78 °C. The reaction mixture was stirred at −78 °C for 30 minutes, after which (*R*)-propylene oxide (560 µL, 8.00 mmol) was added then boron trifluoride diethyl etherate (3.85 mL, 31.2 mmol) was added dropwise. The reaction mixture was stirred at −78 °C for 3 hours, after which the reaction was quenched with a saturated $NaHCO_3$ (10 mL), then concentrated *in vacuo*. The aqueous suspension was diluted with water (20 mL) and extracted with 1:1 $CHCl_3$:IPA (6 × 25 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:19 MeOH:CH_2Cl_2) afforded the title compound as a colourless oil (1.08 g, 74%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.90 – 3.81 (m, 1H), 3.76 (d, *J* = 1.8 Hz, 3H), 3.73 (d, *J* = 1.8 Hz, 3H), 1.99 – 1.62 (m, 4H), 1.21 (d, *J* = 6.2 Hz, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 67.7 (d, *J* = 14.0 Hz), 52.7 – 52.5 (m), 31.7 (d, *J* = 4.7 Hz), 23.4 (s), 21.2 (d, *J* = 141.7 Hz); **^{31}P{^{1}H} NMR** (162 MHz, $CDCl_3$) δ_P 35.8; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_6H_{15}O_4PNa$ $[M + Na]^+$: 205.0606 found 205.0610; **FTIR** (neat) ν_{max}/cm^{-1} 3381, 2958, 2929, 2853, 1457, 1409, 1375, 1314, 1281, 1233, 1214, 1184, 1245, 1026; **TLC** R_f: 0.32 (1:9 MeOH:CH_2Cl_2)

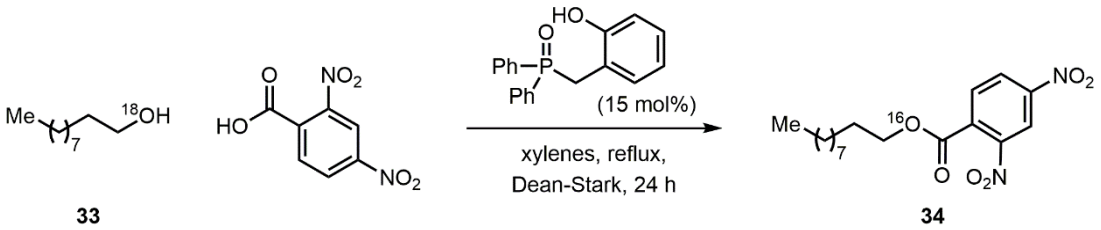
1-Decanol-[^{18}O] (33, Figure 17A)



To a solution of 1-decanal (3.09 g, 16.4 mmol) and trimethylorthoformate (4.38 mL, 40 mmol) in MeOH (10 mL) was added a 1.0 M solution of HCl in Et_2O (500 µL) and the reaction was refluxed for 3 hours, forming a dimethylacetal, then concentrated *in vacuo*. The crude residue was then dissolved in anhydrous THF (5 mL) and H_2O-[^{18}O] (370 µL, 20.5 mmol) was added, followed by a 1.0 M solution of HCl in Et_2O (100 µL). The reaction flask was fitted with an empty Dean-Stark trap and run under argon. The reaction was refluxed for 1.5 hours, after which the solvents were partially evaporated to reduce the MeOH:H_2O-[^{18}O] ratio. Additional anhydrous THF (10 mL), 1.0 M HCl in Et_2O (100 µL) and H_2O-[^{18}O] (100 µL, 5.5 mmol) were added and the reaction mixture was refluxed for a further 1.5 hours. The reaction was concentrated *in vacuo*, and the crude residue was dissolved in anhydrous THF (5 mL) under argon and cooled to 0 °C. Sodium borohydride (1.15 g, 30.4 mmol), was added, and anhydrous MeOH (5 mL) was then added slowly over 15 min. The reaction was stirred for 1 h, then diluted with Et_2O (30 mL). The organic phase was washed with H_2O (30 mL), a 1.0 M aqueous HCl solution (30 mL), then a saturated brine solution (30 mL), dried over $MgSO_4$, then concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, 1:19 to 7:13 gradient, Et_2O:pentane) to afford the title compound as a pale yellow oil (1.40 g, 54%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 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{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 63.09 (CH_2, 0.17C, C^{16}O), 63.07 (CH_2, 0.83C, C^{18}O), 32.8 (CH_2), 31.9 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 25.7 (CH_2), 22.7 (CH_2), 14.1 (CH_3); **FTIR** (neat) ν_{max}/cm^{-1} 3317, 2955, 2922, 2853, 1465, 1378, 1122, 1045, 1014; **HRMS** (GC/MS-EI-TOF) *m*/*z* calc'd for $C_{10}H_{21}{}^{18}O$

[M]$^{+\cdot}$: 159.1629 found 159.1640; 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.

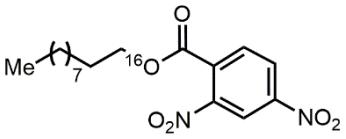
Isotopic Labelling Experiment (Figure 17A)



33 **34**

A suspension of ^{18}O-enriched 1-decanol **(33)** (320 mg, 2.00 mmol), 2,4-dinitrobenzoic acid (424 mg, 2.00 mmol) and catalyst **1** (93 mg, 300 μmol) in xylenes (25 mL) was heated to reflux and stirred for 24 hours in a Dean-Stark apparatus. ^{1}H NMR analysis showed 69% conversion. The reaction was then cooled, diluted with EtOAc (20 mL) and washed with water (2 × 20 mL), then brine (20 mL). The organic layer was dried over $MgSO_4$ then concentrated. The crude residue was purified by flash column chromatography (SiO_2, 1:9 EtOAc:petrol) to afford the ^{16}O-enriched ester **(34)** as a pale yellow oil (374 mg, 53%.) The eluting solvent polarity was increased to 1:1 EtOAc:petrol, which afforded the ^{18}O-enriched catalyst **(35)** as an off-white solid (62 mg, 66%.)

1-Decyl 2,4-Dinitrobenzoate-[^{16}O] (34)

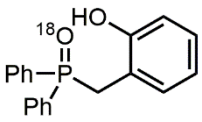


34

(34) ^{1}H NMR spectrum matches compound **25k**; **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 163.8 (C_q), 149.0 (C_q), 148.3 (C_q), 133.2 (C_q), 131.4 (CH), 127.5 (CH), 119.6 (CH), 67.65 (CH_2, 0.88 C(^{16}O)), 67.61 (CH_2, 0.12(C^{18}O)), 32.0 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 28.3 (CH_2), 25.8 (CH_2), 22.8 (CH_2), 14.2 (CH_3). **^{13}C NMR** indicated 88% ^{16}O enrichment by integration of the two peaks at 67.65 and 67.61 ppm. The peak at 67.65 was identified as the ^{16}O-enriched compound, as upon addition of the non-enriched compound **25k** to the NMR sample, the relative integration of the peak at 67.65 ppm increased; **HRMS** (ESI-TOF) m/z

calc'd for $C_{17}H_{24}N_2Na^{16}O_6$ [M +N a]$^+$: 375.1532, found 375.1538; also *m*/*z* calc'd for $C_{17}H_{24}N_2Na^{16}O_5{}^{18}O$ [M + Na]$^+$: 377.1575, found 375.1565. A ratio of peak intensities for the relevant isotopologues was 90:10 $C_{17}H_{24}N_2Na^{16}O_6$:$C_{17}H_{24}N_2Na^{16}O_5{}^{18}O$

(2-Hydroxybenzyl)diphenylphosphine Oxide-[^{18}O] (35)

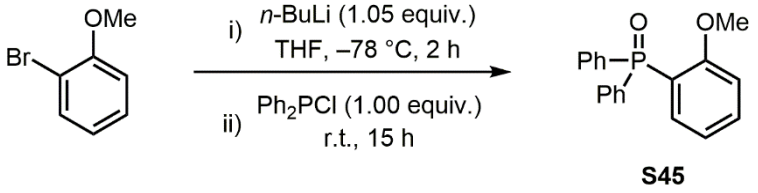


35

^{1}H NMR and **^{13}C{^{1}H} NMR** spectra match compound **C2**. **^{31}P{^{1}H} NMR** (162 MHz, $CDCl_3$) δ_P 38.27 (0.26 P(^{16}O)), 38.24 (0.74 P(^{18}O)). **^{31}P{^{1}H} NMR** indicated 74% ^{18}O incorporation by integration of the two peaks at 38.27 and 38.24 ppm. The peak at 38.24 was identified as the ^{18}O-enriched catalyst, as upon addition of the non-enriched catalyst **C2** to the NMR sample, the relative integration of the peak at 38.27 ppm increased; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{19}H_{18}{}^{16}O^{18}O$ [M + H]$^+$: 311.1087, found 311.1090; also *m*/*z* calc'd for $C_{19}H_{18}{}^{16}O_2$ [M + H]$^+$: 309.1044, found 309.1041. A ratio of peak intensities for the relevant isotopologues was 76:24 $C_{19}H_{18}{}^{16}O^{18}O$:$C_{19}H_{18}{}^{16}O_2$

Procedures for the Catalyst Structure/Activity Relationship Experiments

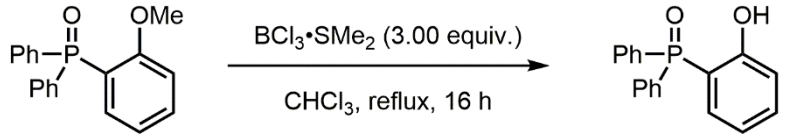
(2-Methoxyphenyl)diphenylphosphine Oxide (S45)



S45

1-bromo-2-methoxybenzene (364 µL, 2.92 mmol) was dissolved in THF (5 mL) and cooled to –78 °C. A 2.5 M solution of *n*-butyllithium in hexanes (1.22 mL, 3.06 mmol) was added dropwise over 20 min and the reaction was stirred at –78 °C for 2 h. Chlorodiphenylphosphine (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 and stirred for 15 h. The reaction was quenched with H_2O (10 mL) and diluted with EtOAc (30 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated to 5 mL. H_2O_2 (12% *w*/*v*, 2 mL) was added and the reaction was stirred for 3 h. The reaction was then diluted with EtOAc (50 mL), washed successively with 6.0 M aqueous sodium hydroxide solution (30 mL), a 1.0 M aqueous HCl solution (30 mL), a saturated aqueous $NaHCO_3$ solution (30 mL), then a saturated brine solution (30 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated to give a white solid. The solid was dissolved in CH_2Cl_2 (10 mL) and petrol added dropwise to induce crystallisation. After standing for 72 h, the solids were filtered and washed with $CHCl_3$. Concentration of the filtrate gave the phosphine oxide as a white solid (625 mg, 70%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 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); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 160.8 (d, *J* = 3.2 Hz, C_q), 134.9 (d, *J* = 7.0 Hz, CH), 134.2 (d, *J* = 2.2 Hz, CH), 133.2 (d, *J* = 107.0 Hz, C_q), 131.8 (d, *J* = 10.0 Hz, CH), 131.4 (d, *J* = 2.9 Hz, CH), 128.1 (d, *J* = 12.2 Hz, CH), 120.9 (d, *J* = 11.5 Hz, CH), 119.6 (d, *J* = 103.9 Hz, C_q), 111.4 (d, *J* = 6.4 Hz, CH), 55.2 (s, CH_3); **^{31}P{^{1}H} NMR** (162 MHz, $CDCl_3$) δ_P 27.3; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{19}H_{18}O_2P$ $[M + H]^+$: 309.1039, found 309.1035; **FTIR** (neat) ν_{max}/cm^{-1} 2972, 2839, 1591, 1577, 1478, 1463, 1432, 1277, 1252, 1163; **m.p.** = 160–164 °C (lit.[28] 164–167 °C).

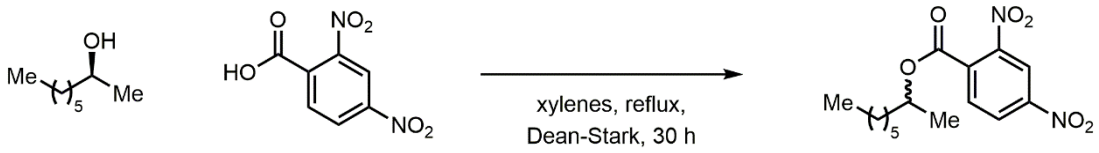
(2-Hydroxyphenyl)diphenylphosphine Oxide (S46)



S45 **S46**

(2-Methoxyphenyl)diphenylphosphine oxide **(S45)** (611 mg, 2.00 mmol) was dissolved in $CHCl_3$ (20 mL) and boron trichloride dimethyl sulfide (1.10 g, 6.00 mmol). The reaction was heated to reflux and stirred for 16 h. A saturated aqueous $NaHCO_3$ solution (10 mL) was then added and the reaction was stirred at room temperature for a further 1 h. The reaction was then acidified to pH 3 with a 1.0 M aqueous HCl solution and extracted with $CHCl_3$ (2 × 50 mL), washed with a 1.0 M aqueous HCl solution (50 mL) and a saturated brine solution (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound as a white crystalline solid (440 mg, 76%). **^{1}H NMR** (400MHz, $CDCl_3$) δ_H 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{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 163.9 (d, *J* = 2.9 Hz, C_q), 134.3 (d, *J* = 2.2 Hz, CH), 132.5 (d, *J* = 2.8 Hz, CH), 132.0 (d, *J* = 10.4 Hz, CH), 132.0 (d, *J* = 105.7 Hz, C_q), 131.9 (d, *J* = 10.0 Hz, CH), 128.7 (d, *J* = 12.3 Hz, CH), 119.0 (d, *J* = 12.3 Hz, CH), 118.6 (d, *J* = 7.6 Hz, CH), 111.1 (d, *J* = 104.0 Hz, C_q); **^{31}P{^{1}H} NMR** (162 MHz) δ_P 39.4 ppm; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{18}H_{16}O_2P$ $[M + H]^+$: 295.0882, found 295.0880; **FTIR** (neat) ν_{max}/cm^{-1} 3691, 3606, 3011, 1606, 1578, 1457, 1438, 1247, 1120; **m.p.** 228–230 °C (lit.[29] 226–228 °C).

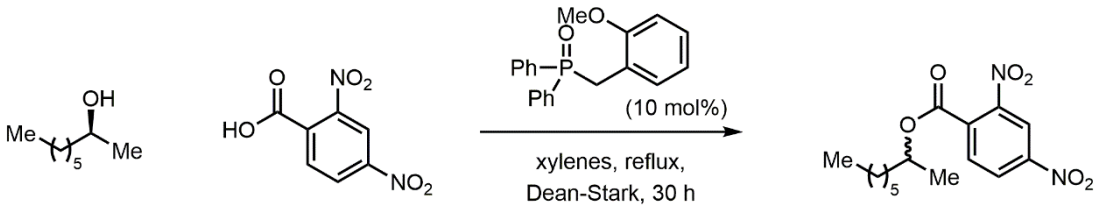
Reaction in the Absence of Catalyst (figure 17, entry 1)



A suspension of (*S*)-(−)-2-octanol (317 µL, 2.00 mmol) and 2,4-dinitrobenzoic acid (424 mg, 2.00 mmol) in xylenes (25 mL) was heated to reflux in a Dean-Stark apparatus and stirred for 30 hours. The reaction mixture was then cooled to room temperature, diluted with EtOAc (20 mL) and washed with a 1.0 M aqueous

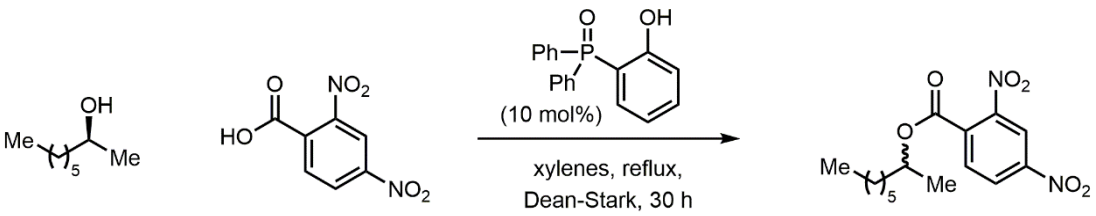
NaOH solution (2 × 20 mL) then a saturated brine solution (20 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, 3:97 EtOAc:petrol) to afford the title compound as a pale yellow oil (64 mg, 10%). **^{1}H NMR** and **^{13}C{^{1}H} NMR** spectra both matched compound **25k; HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{15}H_{20}N_2NaO_6$ $[M + Na]^+$: 347.1214, found 347.1209; **Chiral SFC** column: Chiralpak IG (4.6 mm × 250 mm, 5 μm); mobile phase: 3:17 MeOH:CO_2 (0.2% *v*/*v* NH_3), flow rate: 4 mL/min; temperature: 40 °C; T_R (min) 1.44 (minor), 1.70 (major), 19% e.e.

Reaction with Methoxy Catalyst (figure 17, entry 3)



A suspension of (*S*)-(−)-2-octanol (317 μL, 2.00 mmol), 2,4-dinitrobenzoic acid (424 mg, 2.00 mmol) and phosphine oxide **23** (64 mg, 200 μmol) in xylenes (25 mL) was heated to reflux in a Dean-Stark apparatus and stirred for 30 hours. The reaction mixture was then cooled to room temperature, diluted with EtOAc (20 mL) and washed with a 1.0 M aqueous NaOH solution (2 × 20 mL) then a saturated brine solution (20 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, 3:97 EtOAc:petrol) to afford the title compound as a pale yellow oil (54 mg, 8%). **^{1}H NMR** and **^{13}C{^{1}H} NMR** spectra were in agreement with compound **25k**; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{15}H_{20}N_2NaO_6$ $[M + Na]^+$: 347.1214, found 347.1201; **Chiral SFC** column: Chiralpak IG (4.6 mm × 250 mm, 5 μm); mobile phase: 3:17 MeOH:CO_2 (0.2% *v*/*v* NH_3), flow rate: 4 mL/min; temperature: 40 °C; T_R (min) 1.44 (minor), 1.70 (major), 22% e.e.

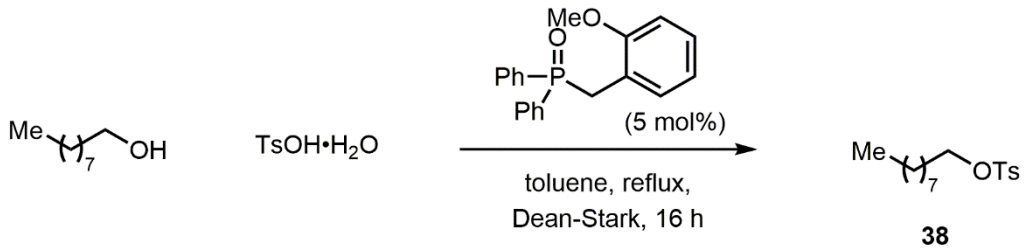
Reaction with Phosphine Oxide S46



A suspension of (*S*)-(−)-2-octanol (158 µL, 1.00 mmol), 2,4-dinitrobenzoic acid (212 mg, 1.00 mmol) and phosphine oxide **S46** (29 mg, 0.10 mmol) in xylenes (12.5 mL) was heated to reflux in a Dean-Stark apparatus and stirred for 30 hours. The reaction mixture was then cooled to room temperature, diluted with EtOAc (20 mL) and washed with a 1.0 M aqueous NaOH solution (2 × 20 mL) then a saturated brine solution (20 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, 5:95 EtOAc:petrol) to afford the title compound as a pale yellow oil (32 mg, 10%). **^{1}H NMR** and **^{13}C{^{1}H} NMR** spectra both gave good agreement with compound **25k**; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{15}H_{20}N_2NaO_6$ $[M + Na]^+$: 347.1214, found 347.1205; **Chiral HPLC** column chiralpak AD-H (4.6 mm × 250 mm, 5 µm), mobile phase: 4:1 *iso*-hexane:EtOH, flow rate 1 mL/min, temperature: ambient, T_R (min) 5.58 (minor), 7.15 (major), 15% e.e.

Catalytic Mitsunobu Tosylation

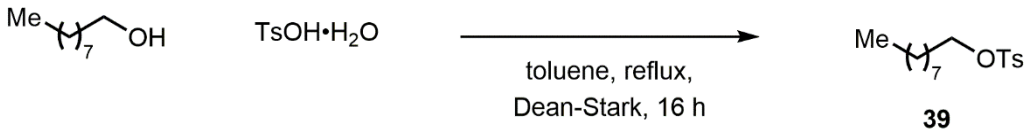
Decyl 4-Methylbenzenesulfonate (38, figure 22 A)



38

A suspension of 1-decanol (1.91 mL, 10.0 mmol), *p*-toluenesulfonic acid monohydrate (1.90 g, 10.0 mmol) and catalyst **C2** (154 mg, 0.500 mmol) in toluene (125 mL) was heated to reflux in a Dean-Stark apparatus and stirred for 16 hours. The reaction mixture was then cooled to room temperature, diluted with EtOAc (300 mL) and washed with a 1.0 M aqueous NaOH solution (2 × 300 mL) then a saturated brine solution (300 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, 1:24 EtOAc/petrol) to afford the title compound as a colourless oil (3.04 g, 97%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.79 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 4.01 (t, *J* = 6.5 Hz, 2H), 2.44 (s, 3H), 1.62 (apparent p, *J* = 6.6 Hz, 2H), 1.33 – 1.13 (m, 14H), 0.87 (t, *J* = 6.9 Hz, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 144.7 (C_q), 133.4 (C_q), 129.9 (CH), 128.0 (CH), 70.8 (CH_2), 32.0 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 25.5 (CH_2), 22.8 (CH_2), 21.7 (CH_2), 14.2 (CH_3); **HRMS** (ESI-TOF) *m/z* calc'd for $C_{17}H_{28}NaO_3S$ $[M + Na]^+$: 335.1651 found 335.1659; **TLC** R_f: 0.17 (1:19 EtOAc/petrol; Data are consistent with those reported in the literature.[30]

Background Reaction (39, figure 22B)

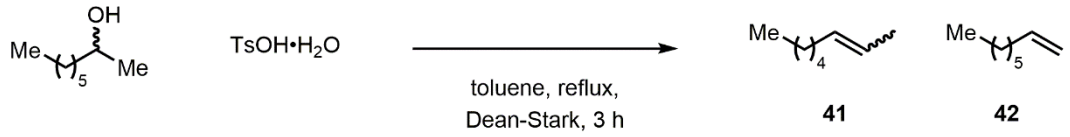


39

A suspension of 1-decanol (382 µL, 2.00 mmol) and *p*-toluenesulfonic acid monohydrate (380 mg, 2.00 mmol) in toluene (25 mL) was heated to reflux in a Dean-Stark apparatus and stirred for 16 hours. 1,1,2,2-tetrachloroethane

(216 µL, 2.00 mmol) was added as an internal NMR standard and an aliquot was analysed by ^{1}H NMR. The product was formed with a yield of 11%.

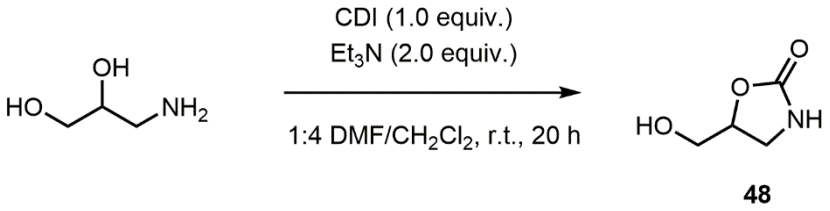
Reaction of 2-Octanol with *p*-Toluenesulfonic Acid (41, 42, figure 22C)



A suspension of 1-decanol (635 µL, 4.00 mmol), *p*-toluenesulfonic acid monohydrate (760 mg, 4.00 mmol) and catalyst **C2** (123 mg, 0.400 mmol) in toluene (25 mL) was heated to reflux in a Dean-Stark apparatus and stirred for 3 hours. 1,3,5-tetimethoxybenzene (244 mg, 1.33 mmol) was added as an internal NMR standard and an aliquot was analysed by ^{1}H NMR. No sulfonate ester was observed. 5% 1-octene (indicative ^{1}H NMR (400 MHz, MeCN-d_3) signal: δ_H 4.99 – 4.93 (m)). 75% 2-octene (mixture of regioisomers, indicative ^{1}H NMR (400 MHz, MeCN-d_3) signal: δ_H 5.55 – 5.37 (m)).

Synthesis of API Targets

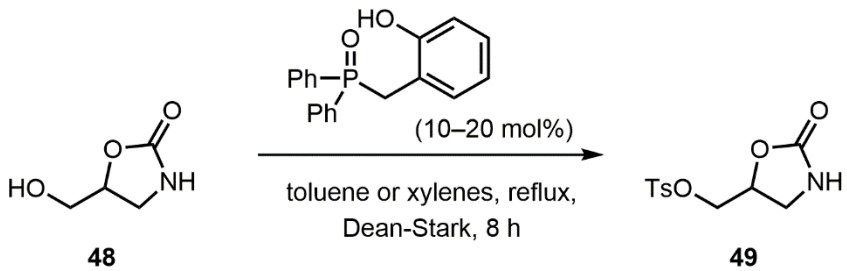
5-(Hydroxymethyl)oxazolidin-2-one (48)



48

To a solution of (±)-3-amino-1,2,propanediol (1.28 g, 14.0 mmol) and triethylamine (2.79 mL, 20.0 mmol) in 4:1 CH_2Cl_2/DMF (50 mL) was added 1,1'-carbonyldiimidazole (1.62 g, 10.0 mmol) at room temperature and the reaction mixture was stirred for 20 hours, then concentrated *in vacuo*. The reaction mixture was diluted with H_2O (200 mL), then extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with a saturated brine solution (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:19 MeOH/EtOAc) afforded the title compound as a colourless oil (687 mg, 59%). **^{1}H NMR** (400 MHz, CD_3OD) δ_H 4.63 – 4.75 (m, 1H), 3.76 (dd, *J* = 12.4, 3.8 Hz, 1H), 3.69 – 3.57 (m, 2H) 3.43 (dd, *J* = 8.6, 6.1 Hz, 1H); **^{13}C{^{1}H} NMR** (101 MHz, CD_3OD) δ_C 162.5 (C_q), 78.4 (CH), 63.2 (CH_2), 42.5 (CH_2); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_4H_7NNaO_3$ $[M + Na]^+$ = 140.0318 found 140.0320; **TLC** Rf: 0.19 (1:19 MeOH/EtOAc). Data are consistent with those reported in the literature.[31]

Catalytic Mitsunobu Coupling of 5-(Hydroxymethyl)oxazolidin-2-one with I-Toluenesulfonic Acid Monohydrate (49)

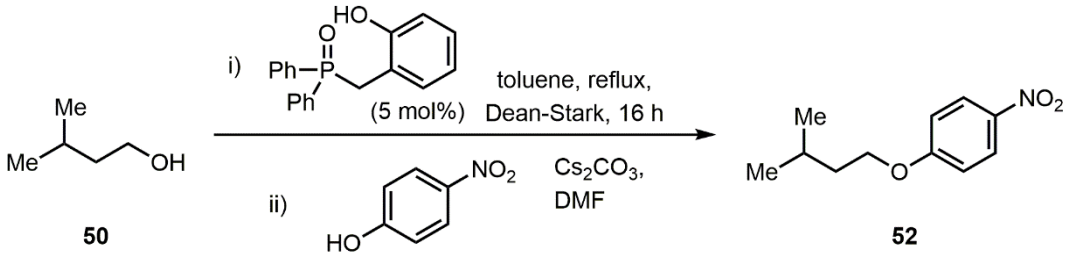


48 **49**

A suspension of 5-(hydroxymethyl)oxazolidin-2-one (117 mg, 1.00 mmol), *p*-toluenesulfonic acid monohydrate (190 mg, 1.00 mmol) and catalyst **C2** (0.10 mmol or 0.20 mmol) in the designated solvent (12.5 mL) was heated to

reflux in a Dean-Stark apparatus and stirred for 8 hours. 1,3,5-tetimethoxybenzene (56 mg, 0.33 mmol) was added as an internal NMR standard and an aliquot was analysed by ^{1}H NMR. The results are shown in chapter 2, table 6.

1-(Isopentyloxy)-4-Nitrobenzene (52)

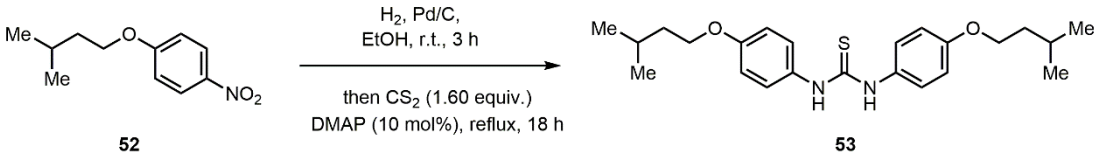


A suspension of isoamyl alcohol (1.31 mL, 12.0 mmol), *p*-toluenesulfonic acid monohydrate (2.28 g, 12.0 mmol) and catalyst **C2** (185 mg, 0.600 mmol) in toluene (75 mL) was heated to reflux in a Dean-Stark apparatus and stirred for 16 hours. Afterwards, the reaction mixture was cooled, 4-nitrophenol (2.00g, 14.4 mmol), caesium carbonate (4.69 g, 14.4 mmol) and DMF (30 mL) was added and the reaction was heated to reflux and stirred for 3 hours. The reaction mixture was concentrated, CH_2Cl_2 (300 mL) was added and the yellow precipitate was collected by filtration.* The filtrate was concentrated and the crude residue was purified by flash column chromatography (SiO_2, 1:9 EtOAc/petrol) to afford the title compound as a colorless oil (2.16 g, 86%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 8.19 (d, *J* = 9.3 Hz, 2H), 6.94 (d, *J* = 9.3 Hz, 2H), 4.08 (t, *J* = 6.7 Hz, 2H), 1.90 – 1.80 (m, 1H), 1.72 (apparent q, *J* = 6.7 Hz, 2H), 0.98 (d, *J* = 6.7 Hz, 6H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 164.4 (C_q), 141.5 (C_q), 126.1 (CH), 114.5 (CH), 67.4 (CH_2), 37.8 (CH_2), 25.1 (CH), 22.7 (CH_3); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{11}H_{15}N_1NaO_3$ $[M + Na]^+$ = 232.0944 found 232.0944; **FTIR** (neat) ν_{max}/cm^{-1} 3116, 3086, 2956, 2872, 1591, 1509, 1472, 1330, 1297, 1255, 1171, 1110, 1006; **TLC** R_f: 0.32 (1:9 EtOAc/petrol)

*The yellow precipitate was partitioned between a 1.0 M aqueous HCl solution (300 mL) and EtOAc (300 mL). The aqueous layer was concentrated *in vacuo* to afford an off-white solid, which was then suspended in EtOH (100 mL). A 48% *w*/*w* aqueous HBr solution (2.0 mL, 17.8 mmol) was added and the mixture was

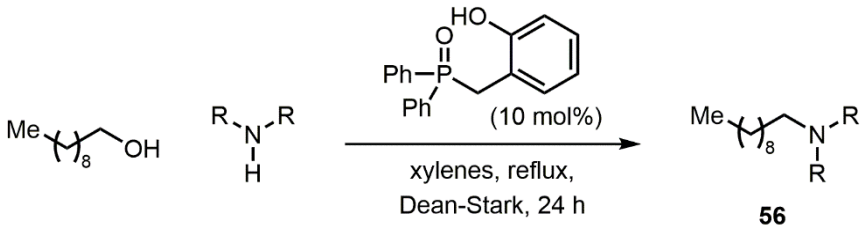
stirred at room temperature for 48 hours. The reaction mixture was passed through a short pad of celite, and the filtrate was concentrated to afford *p*-toluenesulfonic acid monohydrate as an off-white solid. (1.94 g, 85%); **^{1}H NMR** (400 MHz, CD_3OD) δ_H 7.71 (d, *J* = 7.9 Hz, 1H), 7.25 (d, *J* = 7.9 Hz, 1H), 2.37 (s, 1H); **^{13}C{^{1}H} NMR** (101 MHz, CD_3OD) δ_C 142.9 (C_q), 142.1 (C_q), 129.9 (CH), 126.9 (CH), 21.3 (CH_3); **m.p.** 102–107 °C. Data are consistent with commercial sample.

Thiocarlide (53)



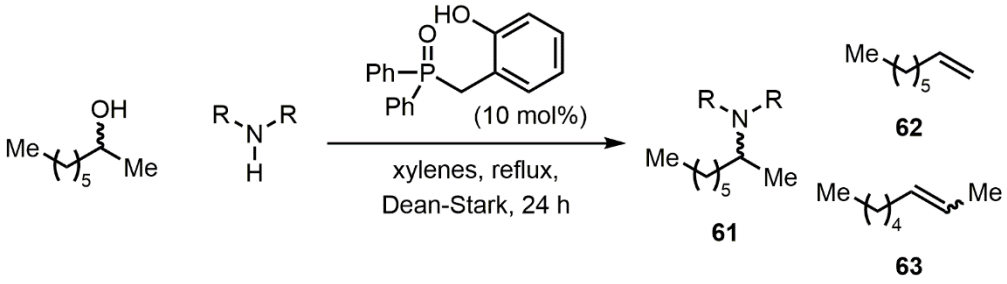
A round-bottomed flask containing a solution of 1-(isopentyloxy)-4-nitrobenzene **(52)** (1.67 g, 8.00 mmol), and 10% *w*/*w* palladium on carbon (167 mg) in EtOH (30 mL) was filled with a H_2 atmosphere (1 atm, balloon) and stirred for 3 hours at room temperature. The balloon was removed, and a reflux condenser fitted to the round-bottomed flask. Carbon disulfide (770 µL, 12.8 mmol) and 4-dimethylaminopyridine (98 mg, 0.80 mmol) was then added and the reaction was heated to reflux and stirred for 18 hours. The reaction mixture was filtered through celite and the filtrate concentrated. The crude residue was purified by flash column chromatography twice (SiO_2, 1:19, EtOAc:petrol to 1:4 EtOAc/petrol gradient then 1:4 Et_2O/petrol) to afforded the title compound as an off-white solid. (796 mg, 50%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.60 (s, 2H), 7.25 (d, *J* = 9.0 Hz, 4H), 6.90 (d, *J* = 9.0 Hz, 4H), 3.98 (t, *J* = 6.6 Hz, 4H), 1.90 – 1.76 (m, 2H), 1.67 (apparent q, *J* = 6.7 Hz, 4H), 0.96 (d, *J* = 6.7 Hz, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 181.2 (C_q), 158.4 (C_q), 129.7 (C_q), 127.7 (CH), 115.4 (CH), 66.8 (CH_2), 38.0 (CH_2), 25.2 (CH), 22.7 (CH_3); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{23}H_{33}N_2O_2S$ $[M + H]^+$ = 401.2257 found 401.2259; **FTIR** (neat) ν_{max}/cm^{-1} 3271, 2953, 2928, 2867, 1614, 1595, 1540, 1506, 1465, 1385, 1344, 1297, 1226, 1168, 1111, 1060, 1029, 1009; **m.p.** 139–140 °C; **TLC** R_f: 0.38 (3:7 EtOAc/petrol). Data are consistent with those reported in the literature.[32]

Screening for Compatible Nitrogen-Centred Pro-Nucleophiles Using 1-Decanol as the Alcohol Substrate (table 7)



A suspension of 1-decanol (190 μL, 1.00 mmol), nitrogen-centered pro-nucleophile (1.00 mmol), and catalyst **C2** (31 mg, 0.10 mmol) in xylenes (12.5 mL) was heated to reflux in a Dean-Stark apparatus and stirred for 24 hours. The reaction mixture was cooled to room temperature, and 1,1,2,2,-tetrachloroethane (216 μL, 2.00 mmol) was added as an NMR internal standard and the reaction mixture was stirred for five minutes. An aliquot was taken and subject to ^{1}H NMR analysis to determine the NMR yield. The results are shown in chapter 2, table 7.

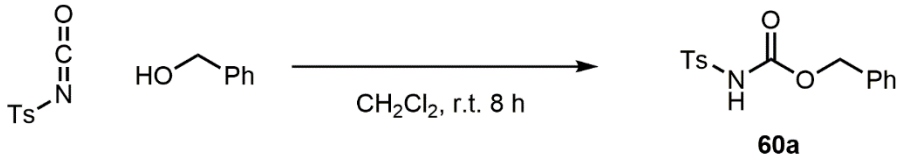
Screening for Compatible Nitrogen-Centred Pro-Nucleophiles Using 2-Octanol as the Alcohol Substrate



A suspension of 2-octanol (159 μL, 1.00 mmol), nitrogen-cantered pro-nucleophile (1.00 mmol), and catalyst **C2** (31 mg, 0.10 mmol) in xylenes (12.5 mL) was heated to reflux in a Dean-Stark apparatus and stirred for 24 hours. The reaction mixture was cooled to room temperature, and 1,1,2,2,-tetrachloroethane (216 μL, 2.00 mmol) was added as an NMR internal standard and the reaction mixture was stirred for five minutes. An aliquot was taken and subject to ^{1}H NMR analysis to determine the NMR yield. The results are shown in chapter 2, table 8.

Synthesis of Nitrogen-Centred Pro-Nucleophiles

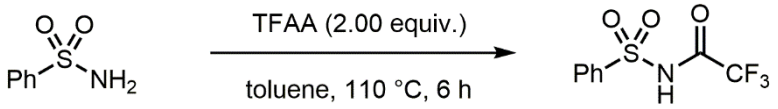
Benzyl Tosylcarbamate (60a)



60a

To a solution of *p*-toluenesulfonyl isocyanate (1.53 mL, 10.0 mmol) in CH_2Cl_2 (40 mL) was added benzyl alcohol (983 µL, 9.50 mL) at 0 °C. The reaction mixture was stirred at room temperature for 8 hours. The reaction mixture was then concentrated *in vacuo*. The crude mixture was recrystalised from CH_2Cl_2/Et_2O to afford the title compound as a colourless solid (2.22g, 77%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.94 – 7.85 (m, 3H), 7.35 – 7.30 (m, 3H), 7.30 – 7.21 (m, 4H), 5.09 (s, 2H), 2.43 (s, 3H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 150.5 (C_q), 145.2 (C_q), 135.5 (C_q), 134.5 (C_q), 129.7 (CH), 128.8 (CH), 128.7 (CH), 128.51 (CH), 128.49 (CH), 68.7 (CH_2), 21.8 (CH_3); **HRMS** (ESI-TOF) *m/z* calc'd for $C_{15}H_{15}NNaO_4S$ $[M + Na]^+$: 328.0614 found 328.0617. Data are consistent with those reported in the literature.[33]

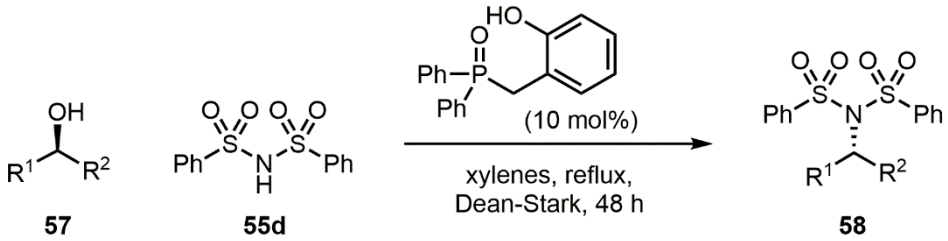
2,2,2-Trifluoro-*N*-(phenylsulfonyl)acetamide (60b)



60b

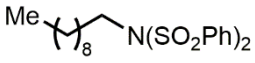
To a microwave vial was added benzenesulfonamide (314 mg, 2.00 mmol) and toluene (1.5 mL) followed by trifluoroacetic anhydride (556 µL, 4.00 mmol). The vial was capped, and the reaction mixture was heated to 110 °C and stirred for 6 hours. The reaction mixture was cooled to room temperature, which resulted in the formation of a colourless precipitate. The precipitate was collected by filtration, washed with toluene and dried under suction to afford the title compound as a colourless solid (490 mg, 97%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.14 – 8.08 (m, 2H), 7.77 – 7.71 (m, 1H), 7.65 – 7.57 (m, 2H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 156.1 (q, *J* = 16.2 Hz, C_q), 140,2 (C_q), 129.5 (CH), 128,6 (CH), 121.1 (CH), 116 (q, *J* = 251.4 Hz, C_q); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ_F –75.1; **HRMS** (ESI-TOF) *m/z* calc'd for $C_8H_6NNaO_3S$ $[M + Na]^+$ = 275.9913 found 275.9927. Data are consistent with those reported in the literature.[34]

General Procedure for *N,N*-Bis-sulfonamidation (figure 24)



A suspension of dibenzenesulfonimide (297 mg, 1.00 mmol), alcohol (1.00 mmol) and catalyst **C2** (31 mg, 0.10 mmol) in xylenes (12.5 mL) was heated to reflux in a Dean-Stark apparatus and stirred for 48 hours. The reaction mixture was then concentrated *in vacuo* and purified by flash column chromatography to afford the *N*-substituted *N,N*-bis-sulfonamide.

***N*-Decyl-*N*-(phenylsulfonyl)benzenesulfonamide (58a)**

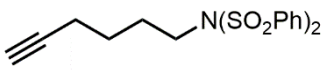


58a

Synthesized according to the general procedure using dibenzenesulfonimide (297 mg, 1.00 mmol), 1-decanol (191 µL, 1.00 mmol), catalyst **C2** (31 mg, 0.10 mmol) and xylenes (12.5 mL). Purification by flash column chromatography (SiO_2, 1:1 CH_2Cl_2:petrol) afforded the title compound as a white solid (364 mg, 83%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.06 – 8.02 (m, 4H), 7.67 – 7.62 (m, 2H), 7.58 – 7.53 (m, 4H), 3.71 – 3.64 (m, 2H), 1.73 – 1.61 (m, 2H), 1.34 – 1.16 (m, 14H), 0.89 (t, *J* = 6.8 Hz, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 140.2 (C_q), 133.9 (CH), 129.2 (CH), 128.2 (CH), 49.8 (CH_2), 32.0 (CH_2), 30.0 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.1 (CH_2), 26.7 (CH_2), 22.8 (CH_2), 14.3 (CH_3); **HRMS** (ESI-TOF) *m/z* calc'd for $C_{22}H_{32}NO_4S_2$ $[M + H]^+$: 438.1767 found 438.1764; **FTIR** (neat) ν_{max}/cm^{-1} 2964, 2919, 2855, 1450, 1365, 1349, 1160, 1084, 1054; **m.p.** 52–55 °C; **TLC** R_f: 0.26 (1:1 CH_2Cl_2/petrol)

In the absence of catalyst, the reaction gave 0% yield by ^{1}H NMR.

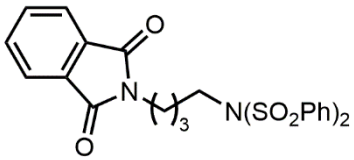
***N*-(Hex-5-yn-1-yl)-*N*-(phenylsulfonyl)benzenesulfonamide (58b)**



58b

Prepared according to the general procedure using 5-hexyn-1-ol (98 mg, 1.0 mmol), dibenzenesulfonimide (297 mg, 1.00 mmol), catalyst **C2** (31 mg, 0.10 mmol) and xylenes (12.5 mL). Purification by flash chromatography (SiO_2, 1:1 CH_2Cl_2:petrol) afforded the title compound as a colorless solid (176 mg, 47%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.05 (dd, J = 8.5, 1.3 Hz, 4H), 7.70 – 7.63 (m, 2H), 7.56 (apparent dd, J = 8.4, 7.0 Hz, 4H), 3.77 – 3.69 (m, 2H), 2.16 (td, J = 7.0, 2.7 Hz, 2H), 1.95 (t, J = 2.7 Hz, 1H), 1.87 – 1.76 (m, 2H), 1.48 (dt, J = 14.5, 7.1 Hz, 2H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 140.1 (C_q), 134.0 (CH), 129.3 (CH), 128.3 (CH), 83.7 (C_q), 69.0 (CH), 49.1 (CH_2), 29.0 (CH_2), 25.5 (CH_2), 18.1 (CH_2); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{18}H_{19}NNaO_4S_2$ $[M + Na]^+$: 400.0648 found 400.0643; **FTIR** (neat) ν_{max}/cm^{-1} 3305, 2941, 1447, 1367, 1350, 1166, 1083, 1049, 922, 803, 758, 718; **m.p.** 88–89 °C; **TLC** R_f: 0.55 (1:1 CH_2Cl_2:petrol).

***N*-(4-(1,3-Dioxoisoindolin-2-yl)butyl)-*N*-(phenylsulfonyl)benzenesulfonamide (58c)**

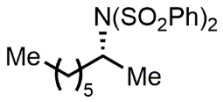


58c

Synthesized according to the general procedure using dibenzenesulfonimide (297 mg, 1.00 mmol), 2-(4-hydroxybutyl)isoindoline-1,3-dione **(24c)** (219 mg, 1.00 mmol), catalyst **C2** (31 mg, 0.10 mmol) and xylenes (12.5 mL). Purification by flash column chromatography (SiO_2, CH_2Cl_2) afforded the title compound as a colourless oil (440 mg, 88%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 – 7.99 (m, 4H), 7.85 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.73 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.66 – 7.59 (m, 2H), 7.57 – 7.51 (m, 4H), 3.75 – 3.70 (m, 2H), 3.65 (t, *J* = 6.9 Hz, 2H), 1.77 – 1.68 (m, 2H), 1.68 – 1.59 (m, 2H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 168.2, 139.8, 134.0, 133.9, 132.0, 129.1, 128.1, 123.2, 48.8, 37.1, 27.1, 25.5; **HRMS** (ESI-TOF) *m*/*z* calc'd for

$C_{24}H_{23}N_2O_6S_2$ [M + H]$^+$: 499.0992 found 499.0995; **FTIR** (neat) ν_{max}/cm^{-1} 2953, 2925, 2855, 1767, 1703, 1444, 1397, 1359, 1322, 1166, 1085, 1039; **TLC** R_f: 0.31 (CH_2Cl_2)

(*R*)-*N*-(Octan-2-yl)-*N*-(phenylsulfonyl)benzenesulfonamide (58f)



58f

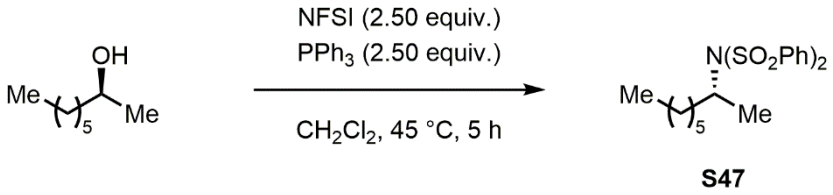
A suspension of dibenzenesulfonimide (594 mg, 2.00 mmol), *S*-(+)-2-octanol (521 mg, 4.00 mmol) catalyst **C2** (154 mg, 0.500 mmol) in toluene (25 mL) was heated to reflux in a Dean-Stark apparatus and stirred for 88 hours. The reaction mixture was then concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, 1:1 CH_2Cl_2/petrol) to afford the title compound as a colourless oil (348 mg, 42%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.05 (d, *J* = 7.6 Hz, 4H), 7.68 – 7.60 (m, 2H), 7.58 – 7.51 (m, 4H), 4.17 – 4.05 (m, 1H), 1.92 – 1.70 (m, 2H), 1.38 (d, *J* = 6.9 Hz, 3H), 1.29 – 0.97 (m, 9H), 0.85 (t, *J* = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 140.5 (C_q), 133.8 (CH), 129.1 (CH), 128.5 (CH), 61.3 (CH), 35.7 (CH_2), 31.7 (CH_2), 29.0 (CH_2), 27.4 (CH_2), 22.6 (CH_2), 19.9 (CH_3), 14.2 (CH_3); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{20}H_{28}NO_4S_2$ [M + H]$^+$: 410.1454 found 410.1454; **FTIR** (neat) ν_{max}/cm^{-1} 2956, 2929, 2858, 1448, 1365, 1350, 1166, 1084; **TLC** R_f: 0.26 (1:1 CH_2Cl_2/petrol); **$[\alpha]_D^{25}$** -0.2 (*c.* 1.0, $CHCl_3$); **Chiral HPLC** column: chiralpak IC (4.6 mm × 250 mm, 5 µm), mobile phase: 1:4 IPA:*iso*-hexane, flow rate: 1 mL/min, temperature: ambient, T_R (min) 8.21 (major), 9.34 (minor), 92% e.e.

In the absence of catalyst, the reaction gave 0% yield by ^{1}H NMR.

^{13}C NMR signal centered at 140.5 appears very broad. This has been previously observed with *sec*-alkylsulfonimides.[35]

Synthesis of Chiral HPLC Samples

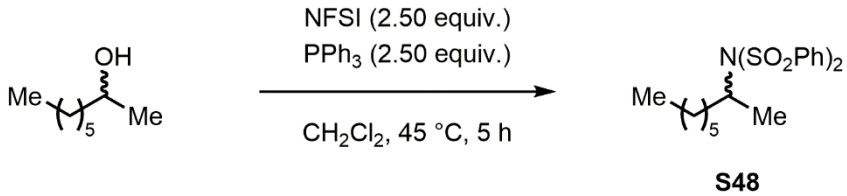
(*R*)-*N*-(Octan-2-yl)-*N*-(phenylsulfonyl)benzenesulfonamide (S47)



S47

According an adapted literature procedure,[36] to a solution of (*S*)-(+)-2-octanol (26 mg, 0.20 mmol) and *N*-fluorobenzenesulfonimide (158 mg, 0.500 mmol) in anhydrous CH_2Cl_2 (3 mL) was added triphenylphosphine (131 mg, 0.500 mmol) in a sealed tube. The reaction mixture was heated to 45 °C and stirred for 5 hours. The reaction mixture was then cooled to room temperature and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, 1:1 CH_2Cl_2/petrol), to afford the title compound as a colourless oil (73 mg, 89%). **^{1}H NMR** and **^{13}C{^{1}H} NMR** data matches with **58f**; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{20}H_{27}NNaO_4S_2$ $[M + Na]^+$: 432.1274 found 432.1267; **Chiral HPLC** column: chiralpak IC (4.6 mm × 250 mm, 5 μm), mobile phase: 1:4 IPA:*iso*-hexane, flow rate: 1 mL/min, temperature: ambient, T_R (min) 8.21 (major), 9.34 (minor), 76% e.e.

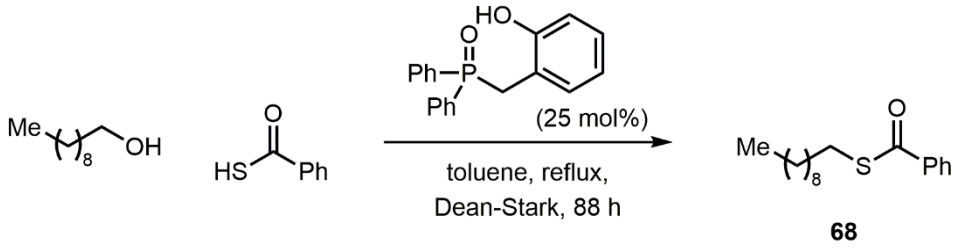
***N*-(Octan-2-yl)-*N*-(phenylsulfonyl)benzenesulfonamide (S48)**



S48

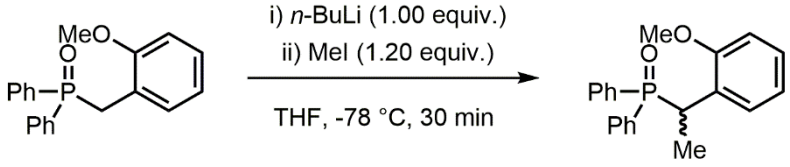
Synthesized according to the procedure for *N*-(octan-2-yl)-*N*-(phenylsulfonyl)benzenesulfonamide **(S47)** using 2-octanol (26 mg, 0.20 mmol), *N*-fluorobenzenesulfonimide (158 mg, 0.500 mmol), CH_2Cl_2 (3 mL) triphenylphosphine (131 mg, 0.500 mmol) to afford the title compound as a colourless oil (78 mg, 95%). **^{1}H NMR** and **^{13}C{^{1}H} NMR** data matches with **58f**; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{20}H_{27}NNaO_4S_2$ $[M + Na]^+$: 432.1274 found 432.1271.

_S_-Decyl Benzothioate (68)



A suspension of thiobenzoic acid (276 mg, 2.00 mmol), 1-decanol (382 μL, 2.00 mmol) catalyst **C2** (154 mg, 0.500 mmol) in toluene (25 mL) was heated to reflux in a Dean-Stark apparatus and stirred for 88 hours. The reaction mixture was then concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, 1:19 Et_2O/petrol) to afford the title compound as a colourless oil (348 mg) which was a mixture of thioester and ester in a 54:46 ratio (35% yield for thioester.) Molar ratios were acquired by integrating the triplets at 3.07 ppm (thioester) and 4.32 (ester) of the ^1H NMR spectrum. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.08 – 8.02 (m, 0.83H), 8.00 – 7.93 (m, 1.11H), 7.58 – 7.52 (m, 1H), 7.47 – 7.40 (m, 2H), 4.32 (t, *J* = 6.7 Hz, 0.92H), 3.07 (t, *J* = 7.3 Hz, 1.08H), 1.77 (apparent p, *J* = 6.7 Hz, 0.88H), 1.67 (apparent p, *J* = 7.4 Hz, 1.09H), 1.49 – 1.18 (m, 14H), 0.88 (t, *J* = 6.7 Hz, 3H). Key signals indicative of thioester: 8.00 – 7.93 (m, 1.11H), 3.07 (t, *J* = 7.3 Hz, 1.08H), 1.67 (apparent p, *J* = 7.4 Hz, 1.09H). Key signals indicative of ester: 8.08 – 8.02 (m, 0.83H), 4.32 (t, *J* = 6.7 Hz, 0.92H), 1.77 (apparent p, *J* = 6.7 Hz, 0.88H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 192.1 (C_q), 166.7 (C_q), 137.3 (C_q), 133.2 (C_q), 132.8 (CH), 130.6 (CH), 129.5 (CH), 128.5 (CH), 128.3 (CH), 127.2 (CH), 65.2 (CH_2), 31.9 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 28.7 (CH_2), 26.1 (CH_2), 22.7 (CH_2), 14.1 (CH_3). Key signals indicative of thioester: 192.1, 137.3; Key signals indicative of ester: 166.7; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{17}H_{28}OS$ $[M + H]^+$: 279.1777 found 279.1766; ; **FTIR** (neat) ν_{max}/cm^{-1} 2923, 2859, 1720, 1664, 1450, 1272, 1205, 1175, 1111; **TLC** R_f: 0.56 (1:19 Et_2O/petrol) (both spots have same R_f value)

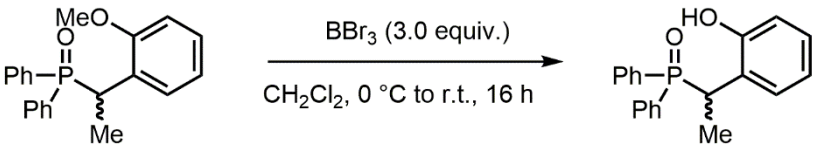
(1-(2-Methoxyphenyl)ethyl)diphenylphosphine oxide (72)



23 **72**

To a flame dried round-bottomed flask was added a solution of **23** (875 mg, 2.50 mmol) in anhydrous THF (10 mL). A 2.0 M solution of *n*-butyllithium in hexanes (1.14 mL, 2.50 mmol) was added dropwise at −78 °C, to give a deep red solution. The reaction was kept at −78 °C and stirred for 15 minutes, then iodomethane (186 µL, 3.00 mmol) was added dropwise, causing an immediate discolouration. The reaction mixture was kept at −78 °C and stirred for a further 30 minutes, after which the reaction was quenched with H_2O (10 mL) and extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with a saturated brine solution (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, 17:3 EtOAc/petrol), to afford the title compound as a pale-yellow solid (712 mg, 85%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.01 – 7.93 (m, 2H), 7.70 (apparent dt, *J* = 7.7, 2.0 Hz, 1H), 7.60 – 7.51 (m, 3H), 7.49 – 7.42 (m, 2H), 7.34 – 7.27 (m, 1H), 7.21 (apparent td, *J* = 7.7, 2.8 Hz, 2H), 7.15 (apparent td, *J* = 7.7, 1.7 Hz, 1H), 6.97 (apparent t, *J* = 7.5 Hz, 1H), 6.61 (d, *J* = 8.2 Hz, 1H), 4.36 (apparent p, *J* = 7.4 Hz, 1H), 3.50 (s, 3H), 1.53 (dd, *J* = 16.1, 7.4 Hz, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δc 156.0 (d, *J* = 6.2 Hz, C_q), 132.7 (d, *J* = 98.5 Hz, C_q), 132.5 (d, *J* = 93.0 Hz, C_q), 131.7 (d, *J* = 2.5 Hz, CH), 131.5 (d, *J* = 8.4 Hz, CH), 131.1 – 130.9 (m, 2 × CH), 129.8 (d, *J* = 4.6 Hz, CH), 128.7 (d, *J* = 11.0 Hz, CH), 127.9 (d, *J* = 2.8 Hz, CH), 127.7 (d, *J* = 11.6 Hz, CH), 126.7 (d, *J* = 5.4 Hz, C_q), 121.0 (d, *J* = 2.8 Hz, CH), 109.9 (d, *J* = 2.2 Hz, CH), 55.1 (s, CH_3), 31.1 (d, *J* = 68.4 Hz, CH), 14.7 (d, *J* = 3.1 Hz, CH_3); **^{31}P{^{1}H} NMR** (162 MHz, $CDCl_3$) δ_P 34.2; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{21}H_{21}O_2PNa$ $[M+Na]^+$: 359.1171; found 359.1177; **FTIR** (neat) ν_{max}/cm^{-1} 3049, 2982, 2929, 1493, 1435, 1247, 1184, 1163, 1114, 1101, 1024; **m.p.** 121–123 °C; **TLC** R_f: 0.25 (4:6 EtOAc/petrol).

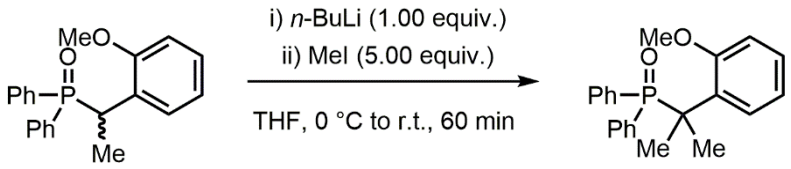
(1-(2-Hydroxyphenyl)ethyl)diphenylphosphine oxide (C3)



72 **C3**

To a solution of **72** (202 mg, 0.60 mmol) in CH_2Cl_2 (6.0 mL) was added a 1.0 M solution of boron tribromide in CH_2Cl_2 (1.8 mL, 1.8 mmol) dropwise at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 hours, after which reaction was quenched with H_2O (20 mL). The aqueous layer was basicified with a saturated $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with a saturated $NaHCO_3$ solution (20 mL), then a saturated brine solution (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound as an off-white solid (178 mg, 92%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.91 – 9.84 (m, 2H), 7.67 – 7.51 (m, 5H), 7.45 – 7.39 (m, 1H), 7.38 – 7.31 (m, 2H), 7.11 – 7.05 (m, 1H), 6.95 (dd, *J* = 8.1, 1.3 Hz, 1H), 6.82 (dd, *J* = 7.7, 1.6 Hz, 1H), 6.67 (apparent t, *J* = 7.4 Hz, 1H), 3.63 (dq, *J* = 9.1, 7.5 Hz 1H), 1.59 (dd, *J* = 15.9, 7.5 Hz, 3H); **^{13}C{H^1} NMR** (101 MHz, $CDCl_3$) δ_C 156.5 (d, *J* = 4.2 Hz, C_q), 132.5 (d, *J* = 2.9 Hz, CH), 132.2 (d, *J* = 3.1 Hz, CH), 131.4 – 131.3 (m, 2 × C_q), 131.1 – 130.9 (m, 2 x CH), 129.0 (d, *J* = 11.5 Hz, CH), 128.7, (d, *J* = 12.1 Hz, CH), 124.6 (d, *J* = 5.5 Hz, C_q), 120.3 (s, CH) 120.1 (d, *J* = 2.0 Hz, CH), 41.0 (d, *J* = 67.2 Hz, CH), 13.0 (d, *J* = 2.0 Hz, CH_3); **^{31}P{^{1}H} NMR** (162 MHz, $CDCl_3$) δ_P 41.7; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{20}H_{19}O_2PNa$ $[M + Na]^+$: 345.1015, found 345.1014; **FTIR** (neat) ν_{max}/cm^{-1} 3058, 2961, 1449, 1436, 1155, 1118, 1090, 1063; **m.p.** 188–190 °C.

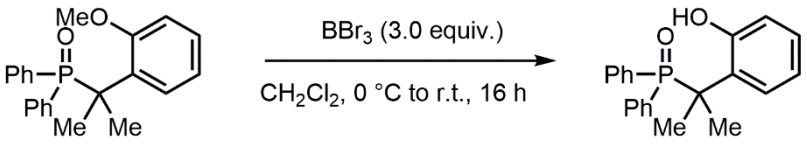
(2-(2-Methoxyphenyl)propan-2-yl)diphenylphosphine oxide (73)



72 **73**

To a flame dried round-bottomed flask was added a solution of **72** (336 mg, 1.00 mmol) in anhydrous THF (4 mL). was added a 2.20 M solution of *n*-butyllithium in hexanes (455 μL, 1.00 mmol) at −78 °C, giving a deep red solution. The reaction was warmed to 0 °C and iodomethane (311 μL, 5.00 mmol) was added dropwise, which caused an immediate discolouration. The reaction mixture was kept at 0 °C and stirred for a further 60 minutes, after which the reaction was quenched with a 1.0 M aqueous HCl solution (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with a saturated brine solution (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, 6:4 EtOAc:petrol), to afford the title compound as a pale-yellow oil (319 mg, 91%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_C 7.64 – 7.57 (m, 4H), 7.45 – 7.39 (m, 2H), 7.37 – 7.30 (m, 4H), 7.28 – 7.23 (m, 1H), 7.21 (apparent dt, *J* = 7.9, 2.0 Hz, 1H), 6.91 (apparent ddt, *J* = 8.0, 7.3, 1.1 Hz, 1H) 6.63 (dd, *J* = 8.1, 1.3 Hz, 1H), 2.98 (s, 3H), 1.74 (d, *J* = 14.8 Hz, 6H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 158.5 (d, *J* = 3.3 Hz, C_q), 132.3 (d, *J* = 8.0 Hz, C_q), 131.1 (d, *J* = 2.8 Hz, CH), 130.4 (d, *J* = 5.2 Hz, CH), 129.2 (d, *J* = 92.8 Hz, C_q), 128.9 (d, *J* = 2.9 Hz, CH), 127.8 (d, *J* = 11.6 Hz, CH), 120.2 (d, *J* = 2.2 Hz, CH), 110.9 (d, *J* = 2.7 Hz, CH), 53.6 (s, CH_3), 42.9 (d, *J* = 65.0 Hz, CH_2), 24.9 (s, CH_3); **^{31}P{^{1}H} NMR** (162 MHz, $CDCl_3$) δ_P 34.5; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{22}H_{24}O_2P$ $[M + H]^+$: 351.1508, found 351.1508; **FTIR** (neat) ν_{max}/cm^{-1} 3056, 2959, 2929, 2871, 2835, 1594, 1579, 1492, 1461, 1435, 1249, 1175, 1150, 1110, 1094, 1082, 1026; **TLC** R_f: 0.25 (6:4 EtOAc/petrol).

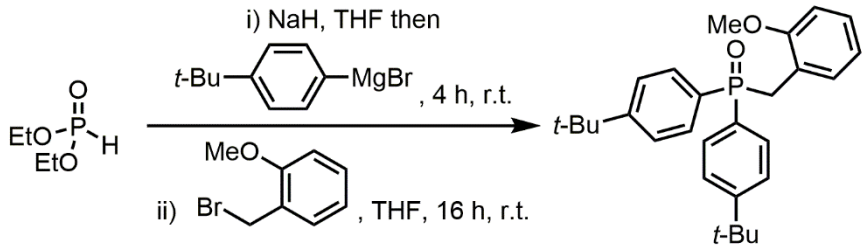
(2-(2-Hydroxyphenyl)propan-2-yl)diphenylphosphine Oxide (C4)



73 **C4**

To a solution of **C4** (300 mg, 0.86 mmol) in CH_2Cl_2 (10 mL) was added a 1.0 M solution of boron tribromide in CH_2Cl_2 (2.6 mL, 2.6 mmol) dropwise at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 hours, after which reaction was quenched with water (20 mL). The aqueous layer was basicified with a saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with a saturated aqueous $NaHCO_3$ solution (20 mL), then a saturated brine solution (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, 1:4 EtOAc/petrol) to afford the title compound as an off-white solid (125 mg, 43%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.84 – 7.75 (m, 4H), 7.56 – 7.50 (m, 2H), 7.47 – 7.40 (m, 4H), 7.16 (apparent ddt, *J* = 8.5, 7.2, 1.5 Hz, 1H), 7.09 (apparent dt, *J* = 8.0, 1.8 Hz, 1H), 7.00 (dd, *J* = 8.1, 1.4 Hz, 1H), 6.79 (ddt, *J* = 8.6, 7.8, 1.1 Hz, 1H), 1.66 (d, *J* = 15.6 Hz, 6H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 157.3 (d, *J* = 3.2 Hz, C_q), 132.7 (d, *J* = 8.4 Hz, C_q), 132.4 (d, *J* = 3.0 Hz, CH), 129.4 (d, *J* = 93.6 Hz, C_q), 129.2 (d, *J* = 2.2 Hz, CH), 128.6 (d, *J* = 3.1 Hz, CH), 128.5 (d, *J* = 11.4 Hz, CH), 127.8 (d, *J* = 5.3 Hz, CH), 121.0 (d, *J* = 2.0 Hz, CH), 120.0 (s, CH), 42.2 (d, *J* = 64.6 Hz, CH_2), 23.7 (s, CH_3); **^{31}P NMR** (162 MHz, $CDCl_3$) δ_P 48.0 – 47.2 (m); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{21}H_{22}O_2P$ $[M + H]^+$ = 337.1352, found 337.1355; **FTIR** (neat) ν_{max}/cm^{-1} 3056, 2929, 2844, 2775, 2617, 1617, 1573, 1485, 1461, 1435, 1409, 1333, 1285, 1242, 1155, 1132, 1111, 1083, 1070, 1026; **m.p.** 120–121 °C; **TLC** R_f: 0.22 (1:4 EtOAc:petrol).

bis(4-(*tert*-Butyl)phenyl)(2-methoxybenzyl)phosphine Oxide (78)

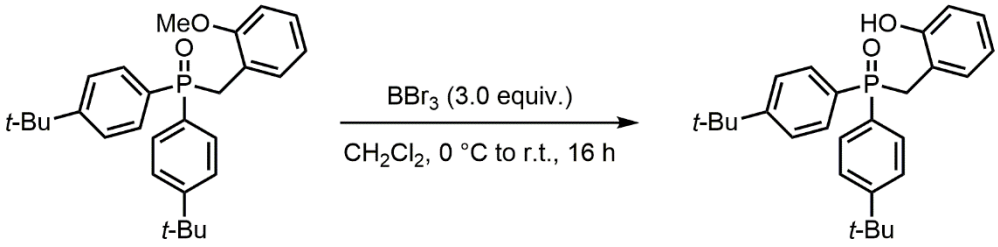


78

To a flame dried flask (flask 1) was added anhydrous THF (5.0 mL), magnesium turnings (146 mg, 6.00 mmol) and iodine (1 crystal). 4-bromo-tertbutylbenzene (1.04 mL, 6.00 mmol) was then added dropwise and stirred for 60 minutes until the exothermic reaction was complete and the magnesium was consumed. In a separate flask (flask 2), to a suspension of sodium hydride (60% *w*/*w* in mineral oil, 110 mg, 2.75 mmol) in anhydrous THF (5.0 mL) was added diethylphosphite (322 μL, 2.50 mmol) dropwise at 0 °C. The reaction mixture was kept at 0 °C and stirred for 30 minutes, after which the Grignard reagent solution from flask 1 was added dropwise at 0 °C. The reaction mixture was warmed to room temperature and stirred for 90 minutes. The mixture was then cooled to 0 °C and a solution of **S1** (602 mg, 3.0 mmol) in anhydrous THF (2.0 mL) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 16 hours, then quenched with a 1.0 M aqueous HCl solution (10 mL), and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with a saturated brine solution (20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, gradient from 1:4 EtOAc:petrol to 1:1 EtOAc:petrol) to afford the title compound as a white solid (420 mg, 39%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.65 – 7.58 (m, 4H), 7.44 – 7.35 (m, 5H), 7.14 (apparent tt, *J* = 7.6, 1.9 Hz, 1H), 6.87 (apparent t, *J* = 7.6 Hz, 1H), 6.64 (d, *J* = 8.2 Hz, 1H), 3.70 (d, *J* = 14.3 Hz, 2H), 3.41 (s, 3H), 1.30 (s, 18H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 156.8 (d, *J* = 5.4 Hz, C_q), 154.7 (d, *J* = 2.6 Hz, C_q), 131.8 (d, *J* = 4.7 Hz, CH), 131.1 (d, *J* = 9.3 Hz, CH), 129.8 (d, *J* = 101.2 Hz, C_q), 128.0 (d, *J* = 3.1 Hz, CH), 125.1 (d, *J* = 11.7 Hz, CH), 120.5 (d, *J* = 3.0 Hz, CH), 120.2 (d, *J* = 7.7 Hz, C_q), 110.1 (d, *J* = 2.4 Hz, CH), 54.8 (s, CH_3), 34.9 (s, C_q), 31.4 (d, *J* = 67.7 Hz, CH_2) 31.1 (s, CH_3); **^{31}P{^{1}H} NMR** (162 MHz, $CDCl_3$) δ_P 30.8; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{28}H_{36}O_2P$ $[M + H]^+$: 435.2447, found 435.2448; **FTIR** (neat) ν_{max}/cm^{-1}

2954, 2902, 2865, 2829, 1599, 1556, 1495, 1459, 1435, 1361, 1318, 1288, 1267, 1226, 1191, 1172, 1114, 1090, 1051; **m.p.** 139–142 °C; **TLC** R_f: 0.30 (1:1 EtOAc/petrol)

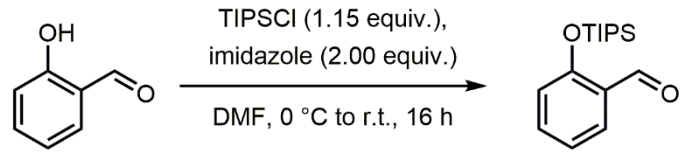
bis(4-(*tert*-Butyl)phenyl)(2-hydroxybenzyl)phosphine Oxide (C6)



78 **C6**

To a solution of **C6** (348 mg, 0.80 mmol) in CH_2Cl_2 (10 mL) was added a 1.0 M solution of boron tribromide in CH_2Cl_2 (2.4 mL, 2.4 mmol) dropwise at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 hours, after which reaction was quenched with water (10 mL). The aqueous layer was basicified with a saturated aqueous $NaHCO_3$ solution (5 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with a saturated aqueous $NaHCO_3$ solution (20 mL), then a saturated brine solution (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude organic residue was purified by flash column chromatography, (SiO_2, 4:6 EtOAc/petrol), to afford the title compound as a white solid (243 mg, 74%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 10.02 (s, 1H), 7.68 – 7.60 (m, 4H), 7.51 – 7.44 (m, 4H), 7.11 (apparent ddt, *J* = 8.9, 7.4, 1.8 Hz, 1H), 7.00 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.82 (apparent dt, *J* = 7.6, 1.8 Hz, 1H), 6.71 (apparent tt, *J* = 7.5, 1.0 Hz, 1H), 3.67 (d, *J* = 13.0 Hz, 2H), 1.31 (s, 18H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 156.9 (d, *J* = 3.8 Hz, C_q), 156.0 (d, *J* = 3.0 Hz, C_q), 131.9 (d, *J* = 6.6 Hz, CH), 131.0 (d, *J* = 9.9 Hz, CH), 129.0 (d, *J* = 2.9 Hz, CH), 127.6 (d, *J* = 102.2 Hz, C_q), 125.9 (d, *J* = 12.2 Hz, CH), 120.6 (s, CH), 119.9 (d, *J* = 8.4 Hz, C_q), 119.7 (d, *J* = 2.2 Hz, CH), 35.9 (d, *J* = 67.4 Hz, CH_2), 35.2 (s, C_q), 31.2 (s, CH_3); **^{31}P{^{1}H} NMR** (162 MHz, $CDCl_3$) δ_P 38.3; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{27}H_{33}NaO_2P$ $[M + Na]^+$: 443.2110, found 443.2119; **FTIR** (neat) ν_{max}/cm^{-1} 2962, 2905, 2868, 2636, 1599, 1579, 1487, 1458, 1393, 1363, 1316, 1269, 1251, 1229, 1204, 1158, 1139, 1108, 1093, 1016; **m.p.** 203–205 °C; **TLC** R_f: 0.26 (4:6 EtOAc/petrol).

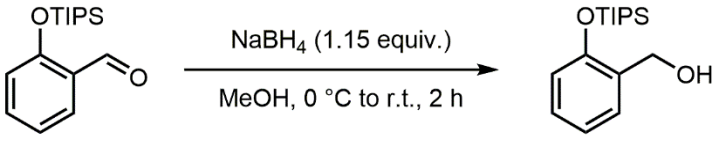
2-((Triisopropylsilyl)oxy)benzaldehyde (S49)



S49

To a solution of salicylaldehyde (2.13 mL, 20.0 mmol) and imidazole (2.72 g, 40.0 mmol) in DMF (40 mL) was added chlorotriisopropylsilane (4.92 mL, 23.0 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 hours after which, a further addition of chlorotriisopropylsilane (1.50 mL, 7.0 mmol) was made at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 hours. The reaction mixture was then diluted with Et_2O (200 mL) and washed with water (5 × 100 mL), then a saturated brine solution (2 × 100 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2 gradient from petrol to 1:99 EtOAc:petrol) to afford the title product as a colourless liquid (5.42 g, 97%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 10.56 (d, *J* = 0.9 Hz, 1H), 7.81 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.44 (ddd, *J* = 8.3, 7.2, 1.9 Hz, 1H), 7.01 (apparent ddt, *J* = 8.1, 7.3, 1.0 Hz, 1H), 6.90 (dd, *J* = 8.4, 1.0 Hz, 1H), 1.41 – 1.29 (m, 3H), 1.13 (d, *J* = 7.4 Hz, 18H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 190.4 (CH), 159.6 (C_q), 135.9 (CH), 128.5 (CH), 127.0 (C_q), 121.3 (CH), 119.9 (CH), 18.1 (CH_3), 13.2 (CH); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{16}H_{27}O_2Si$ $[M + H]^+$ = 279.1780, found 279.1777; **FTIR** (neat) ν_{max}/cm^{-1} 2943, 2892, 2866, 1681, 1666, 1599, 1478, 1458, 1388, 1277, 1250, 1154, 1014; **TLC** R_f: 0.30 (1:9 EtOAc/petrol).

(2-((Triisopropylsilyl)oxy)phenyl)methanol (S50)

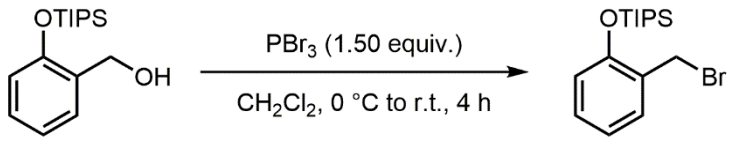


S49 **S50**

To a solution of **S49** (5.29 g, 19.0 mmol) in MeOH (60 mL) was added sodium borohydride (863 mg, 22.8 mmol), in portions, at 0 °C. The reaction mixture was warmed to ambient temperature and stirred for 2 hours. The reaction was

quenched with a 1.0 M aqueous HCl solution (20 mL), then extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with a saturated brine solution (100 mL), dried over $MgSO_4$, and concentrated *in vacuo* to afford the title compound as a colourless liquid (4.99 g, 94%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.30 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.15 (td, *J* = 7.8, 1.8 Hz, 1H), 6.93 (apparent td, *J* = 7.5, 1.1 Hz, 1H), 6.82 (dd, *J* = 8.0, 1.0 Hz, 1H), 4.71 (s, 2H), 1.40 – 1.25 (m, 3H), 1.12 (d, *J* = 7.4 Hz, 18H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 154.0 (C_q), 131.2 (C_q), 128.9 (CH), 128.8 (CH), 121.2 (CH), 118.1 (CH), 62.4 (CH_2), 18.2 (CH_3), 13.2 (CH); **HRMS** (ESI-TOF) *m/z* calc'd for $C_{16}H_{29}O_2Si$ $[M + H]^+$: 281.1937, found 281.1938. Data are consistent with those reported in the literature.[37]

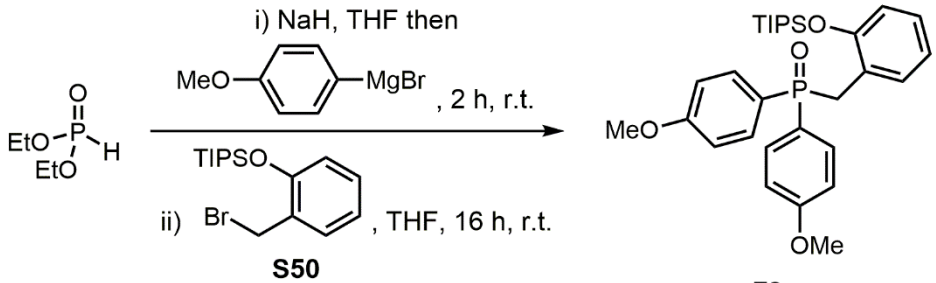
(2-(Bromomethyl)phenoxy)triisopropylsilane (S51)



S50 **S51**

To a solution of **S50** (1.76 g, 17.0 mmol) in CH_2Cl_2 (12 mL) was added phosphorus tribromide (2.40 mL, 25.5 mmol) at 0 °C dropwise. The reaction mixture was stirred at 0 °C for 10 minutes, then warmed to room temperature and stirred for a further three hours. The reaction mixture was re-cooled to 0 °C and quenched with water (5 mL). The aqueous phase was basicified with a saturated aqueous $NaHCO_3$ solution (20 mL) and the organic phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with a saturated aqueous $NaHCO_3$ solution (20 mL), then a saturated brine solution (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound as a pale-yellow oil (5.60 g, 96%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.32 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.16 (ddd, *J* = 8.1, 7.4, 1.8 Hz, 1H), 6.89 (apparent td, *J* = 7.5, 1.1 Hz, 1H), 6.81 (dd, *J* = 8.2, 1.1 Hz, 1H), 4.57 (s, 2H), 1.42 – 1.30 (m, 3H), 1.15 (d, *J* = 7.5 Hz, 18H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 154.4 (C_q), 131.3 (C_q), 130.0 (CH), 128.0 (CH), 118.4 (CH), 121.1 (CH), 27.7 (CH_2), 18.2 (CH_3), 13.2 (CH); **HRMS** (GC/MS-EITOF) *m/z* calc'd for $C_{16}H_{27}{}^{79}BrOSi$ $[M]^{+\cdot}$: 342.1015 found 342.1011; **FTIR** (neat) ν_{max}/cm^{-1} 2946, 2891, 2866, 1599, 1582, 1488, 1454, 1286, 1270, 1218, 1086.

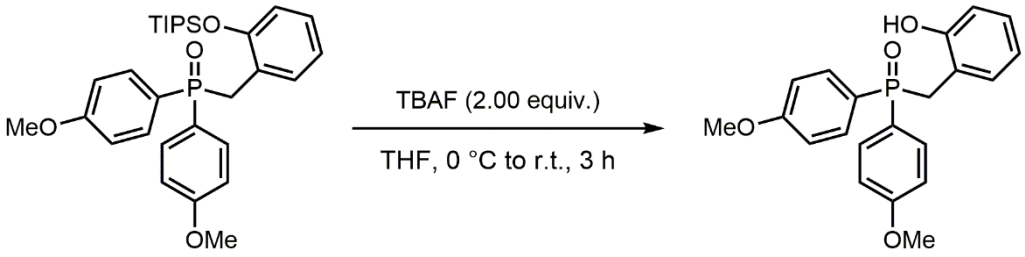
bis(4-Methoxyphenyl)(2-((triisopropylsilyl)oxy)benzyl)phosphine Oxide (79)



To a flame dried flask (flask 1) was added anhydrous THF (5 mL), magnesium turnings (146 mg, 6.00 mmol) and iodine (1 crystal). 4-bromo-anisole (751 µL, 6.00 mmol) was then added dropwise and stirred for 60 minutes until the exothermic reaction was complete and the magnesium was consumed. In a separate flask (flask 2), to a suspension of sodium hydride (60% *w*/*w* in mineral oil, 110 mg, 2.75 mmol) in anhydrous THF (5 mL) was added diethylphosphite (322 µL, 2.50 mmol) dropwise at 0 °C. The reaction mixture was kept at 0 °C and stirred for 30 minutes, after which the Grignard reagent solution from flask 1 was added dropwise at 0 °C. The reaction mixture was warmed to room temperature and stirred for two hours. The mixture was then re-cooled to 0 °C and a solution of **S51** (858 mg, 2.50 mmol) in anhydrous THF (2 mL) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 16 hours, then quenched with MeOH (10 mL) and concentrated *in vacuo*. The residue was dissolved in EtOAc (50 mL), the organic phase was washed with water (30 mL), then extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with a saturated brine solution (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, 7:3 EtOAc:petrol) to afford the title compound as a colourless oil (584 mg, 45%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.56 (dd, *J* = 10.9, 8.8 Hz, 4H), 7.51 (dt, *J* = 7.6, 2.0 Hz, 1H), 7.03 (ddt, *J* = 9.1, 7.7, 1.8 Hz, 1H), 6.91 – 6.81 (m, 5H), 6.70 (dt, *J* = 8.2, 1.1 Hz, 1H), 3.80 (s, 6H), 3.70 (d, *J* = 14.7 Hz, 2H), 1.29 – 1.20 (m, 3H), 1.04 (d, *J* = 7.3 Hz, 18H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 162.2 (d, *J* = 2.9 Hz, C_q), 153.6 (d, *J* = 6.5 Hz, C_q), 133.0 (d, *J* = 10.5 Hz, CH), 131.8 (d, *J* = 4.4 Hz, CH), 127.8 (d, *J* = 2.8 Hz, CH), 124.6 (d, *J* = 105.1 Hz, C_q), 122.5 (d, *J* = 7.1 Hz, C_q), 121.1 (d, *J* = 2.6 Hz, CH), 118.0 (d, *J* = 2.0 Hz, CH), 114.0 (d, *J* = 12.9 Hz, CH), 55.4 (s, CH_3), 31.1 (d, *J* = 69.8 Hz, CH_2), 18.2 (s, CH_3), 13.1 (s, CH);

$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$) δ_P 30.7; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{30}H_{42}O_4PSi$ $[M + H]^+$: 525.2584, found 525.2592; **FTIR** (neat) ν_{max}/cm^{-1} 2944, 2865, 1596, 1570, 1502, 1491, 1451, 1292, 1253, 1197, 1117, 1026; **TLC** R_f: 0.20 (1:1 EtOAc/petrol).

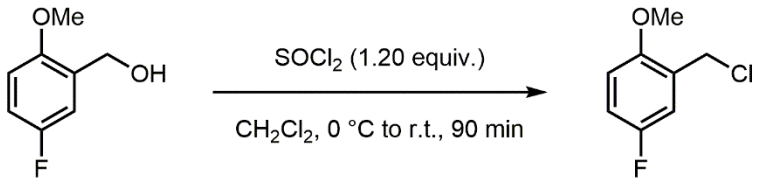
(2-Hydroxybenzyl)bis(4-methoxyphenyl)phosphine Oxide (C7)



79 **C7**

To a solution of **79** (525 mg, 1.2 mmol) in anhydrous THF (3 mL) was added a 1.0 M solution of tetrabutylammonium fluoride in THF (2.4 mL, 2.4 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for three hours. The reaction was quenched with a 1.0 M aqueous HCl solution (5 mL), and the organic phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with a saturated brine solution (10 mL), dried over $MgSO_4$, then concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, 1:1 EtOAc/petrol) to afford the title compound as a colourless solid (297 mg, 67%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.61 (dd, *J* = 11.2, 8.8 Hz, 4H), 7.11 (apparent ddt, *J* = 7.9, 7.2, 1.8 Hz, 1H), 7.00 (dd, *J* = 8.1, 1.3 Hz, 1H), 6.96 (dd, *J* = 8.9, 2.3 Hz, 4H), 6.76 (apparent dt, *J* = 7.6, 1.9 Hz, 1H), 6.70 (apparent tt, *J* = 7.3, 1.2 Hz, 1H), 3.83 (s, 6H), 3.63 (d, *J* = 13.0 Hz, 2H); **$^{13}C\{^{1}H\}$ NMR** (101 MHz, $CDCl_3$) δ_C 162.9 (d, *J* = 2.9 Hz, C_q), 156.8 (d, *J* = 3.8 Hz, C_q), 133.0 (d, *J* = 11.0 Hz, CH), 131.8 (d, *J* = 6.5 Hz, CH), 128.9 (d, *J* = 2.8 Hz, CH), 122.1 (d, *J* = 106.9 Hz, C_q), 120.6 (d, *J* = 1.8 Hz, CH), 120.0 (d, *J* = 8.2 Hz, C_q), 119.7 (d, *J* = 2.7 Hz, CH), 114.5 (d, *J* = 12.7 Hz, CH), 55.5 (s, CH_3), 36.2 (d, *J* = 68.3 Hz, CH_2); **$^{31}P\{^{1}H\}$ NMR** (162 MHz, $CDCl_3$) δ_P 38.3; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{21}H_{21}O_4PNa$ $[M + Na]^+$: 391.1070; found 391.1074; **FTIR** (neat) ν_{max}/cm^{-1} 2929, 2844, 1595, 1570, 1503, 1453, 1296, 1252, 1180, 1158, 1119, 1097, 1022; **m.p.** 154–156 °C; **TLC** R_f: 0.24 (1:1 EtOAc/petrol).

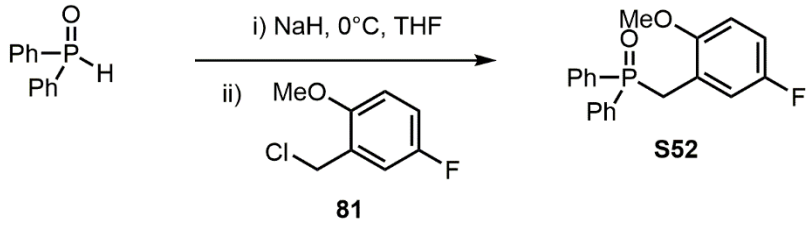
2-(Chloromethyl)-4-fluoro-1-methoxybenzene (81)



81

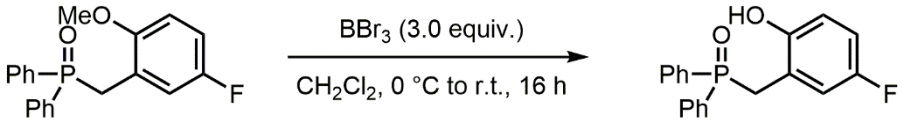
To a solution of 5-fluoro-2-methoxybenzyl alcohol (1.34 g, 8.58 mmol) in CH_2Cl_2 (15 mL) was added thionyl chloride (751 μL, 10.3 mmol) at 0 °C dropwise. The reaction mixture was stirred at 0 °C for 30 minutes, then warmed to room temperature and stirred for a further 90 minutes. The reaction mixture was cooled to 0 °C and quenched with water (5 mL). The aqueous phase was basicified with a saturated aqueous $NaHCO_3$ solution (20 mL) and the organic phase was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were washed with a saturated aqueous $NaHCO_3$ solution (40 mL), then a saturated brine solution (40 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound as a colourless solid (1.36 g, 91%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.11 (dd, *J* = 8.6, 3.1 Hz, 1H), 6.99 (ddd, *J* = 9.0, 8.0, 3.1 Hz, 1H), 6.82 (dd, *J* = 9.0, 4.3 Hz, 1H), 4.61 (s, 2H), 3.86 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 156.8 (d, *J* = 238.9 Hz, C_q), 153.5 (d, *J* = 2.5 Hz, C_q), 127.3 (d, *J* = 7.3 Hz, C_q), 117.2 (d, *J* = 23.8 Hz, CH), 115.9 (d, *J* = 22.9 Hz, CH), 111.8 (d, *J* = 8.0 Hz, CH), 56.2 (s, CH_3), 41.0 (s, CH_2); **^{19}F NMR** (376 MHz, $CDCl_3$) δ_H −123.5 (ddd, *J* = 9.0, 8.6, 4.3 Hz); **HRMS** (GC/MS-EI-TOF) *m*/*z* calc'd for $C_8H_8{}^{35}ClFO$ $[M]^{+\cdot}$: 174.0248 found 174.0256; **FTIR** (neat) ν_{max}/cm^{-1} 3067, 3014, 2971, 2950, 2915, 2842, 1497, 1459, 1426, 1264, 1220, 1183, 1143, 1023; **m.p.** 49–50 °C.

(5-Fluoro-2-methoxybenzyl)diphenylphosphine Oxide (S52)



To a stirring solution of diphenylphosphine oxide (404 mg, 2.00 mmol) in anhydrous THF (7 mL) was added sodium hydride (60% *w*/*w* in oil, 120 mg, 3.00 mmol) in portions at 0 °C. The suspension was held at 0 °C and stirred for 30 minutes. **81** (2.82 g, 14.4 mmol) was added and the mixture was then warmed to room temperature and stirred for a further 1 hour. The reaction mixture was then quenched with water (10 mL) at 0 °C and the organic phase were extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with a saturated brine solution (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by trituration with Et_2O to afford the title compound as a colourless solid (394 mg, 60%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.74 – 7.66 (m, 4H) 7.51 – 7.46 (m, 2H) 7.44 – 7.39 (m, 4H) 7.11 (apparent dt, *J* = 9.0, 2.9 Hz, 1H) 6.82 (apparent dt, J = 8.4, 2.3 Hz, 1H) 6.58 (dd, *J* = 9.0, 4.4 Hz, 1H) 3.71 (d, J = 14.1 Hz, 2H) 3.44 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 156.7 (dd, *J* = 238.9, 3.4 Hz, C_q), 153.2 (dd, *J* = 5.5, 2.1 Hz, C_q), 132.7 (d, *J* = 99.5 Hz, C_q), 131.8 (d, *J* = 2.6 Hz, CH), 131.3 (d, *J* = 9.2 Hz, CH), 128.4 (d, *J* = 12.1 Hz, CH), 121.7 (apparent t, *J* = 8.0 Hz, C_q), 118.5 (dd, *J* = 24.0, 4.8 Hz, CH) 114.2 (dd, *J* = 22.9, 3.1 Hz, CH), 111.0 (dd, *J* = 8.4, 2.9 Hz, CH), 55.5 (s, CH_3), 31.2 (d, *J* = 66.9 Hz, CH_2); **^{19}F NMR** (376 MHz, $CDCl_3$) δ_F −123.4 (apparent dt, *J* = 10.3, 6.4 Hz); **^{31}P{^{1}H} NMR** (162 MHz, $CDCl_3$) δ_P 29.7; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{20}H_{19}FO_2P$ $[M + H]^+$: 341.1101, found 341.1104; **FTIR** (neat) ν_{max}/cm^{-1} 2961, 2920, 2837, 1500, 1436, 1275, 1227, 1180, 1119, 1105, 1090, 1036; **m.p.** 98–100 °C.

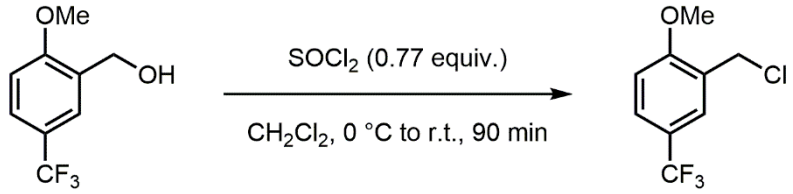
(5-Fluoro-2-hydroxybenzyl)diphenylphosphine Oxide (C8)



S52 **C8**

To a solution of **S52** (340 mg, 1.00 mmol) in CH_2Cl_2 (10 mL) was added a 1.0 M solution of boron tribromide in CH_2Cl_2 (3.0 mL, 3.0 mmol) dropwise at 0 °C. The reaction mixture was warmed to ambient temperature and stirred for 16 hours, after which reaction was quenched with water (5 mL). The aqueous layer was basicified with a saturated aqueous $NaHCO_3$ solution (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with a saturated aqueous $NaHCO_3$ solution (10 mL), then a saturated brine solution (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by trituration with Et_2O to afford the title compound as an off-white solid (258 mg, 79%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.64 (s, 1H), 7.75 – 7.68 (m, 4H), 7.60 – 7.54 (m, 2H), 7.52 – 7.46 (m, 4H), 6.94 (dd, *J* = 8.9, 5.0 Hz, 1H), 6.83 – 6.76 (m, 1H), 6.46 (dt, *J* = 8.8, 2.4 Hz, 1H), 3.66 (d, *J* = 13.0 Hz, 2H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 156.8 (dd, *J* = 237.8, 2.1 Hz, C_q), 152.8 (dd, *J* = 4.4, 1.5 Hz, C_q), 132.8 (d, *J* = 2.9 Hz, CH), 131.1 (d, *J* = 9.3 Hz, CH), 130.3 (d, *J* = 100.4 Hz, C_q), 129.0 (d, *J* = 12.0 Hz, CH), 120.9 (apparent t, *J* = 8.4 Hz, C_q), 120.6 (dd, *J* = 8.1, 2.4 Hz, CH), 117.6 (dd, *J* = 23.1, 6.2 Hz, CH), 115.4 (dd, *J* = 22.1, 2.2 Hz, CH), 35.4 (d, *J* = 67.0 Hz, CH_2); **^{19}F NMR** (376 MHz, $CDCl_3$) δ_F −124.3 – −124.5 (m); **^{31}P{^{1}H} NMR** (162 MHz, $CDCl_3$) δ_P 38.1; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{19}H_{18}FO_2P$ $[M + H]^+$: 327.0945, found 327.0946; **FTIR** (neat) ν_{max}/cm^{-1} 3060, 2925, 1508, 1435, 1170, 1120, 1103; **m.p.** 177–179 °C.

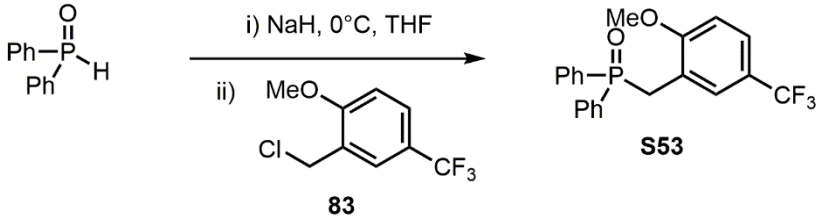
2-(Chloromethyl)-1-methoxy-4-(trifluoromethyl)benzene (83)



83

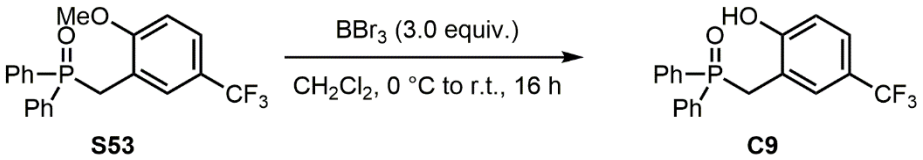
To a solution of 2-methoxy-5-(trifluoromethyl)benzyl alcohol (1.09 g, 7.0 mmol) in CH_2Cl_2 (12 mL) was added thionyl chloride (613 µL, 5.40 mmol) at 0 °C dropwise. The reaction mixture was stirred at 0 °C for 30 minutes, then warmed to room temperature and stirred for a further 16 hours. The reaction mixture was cooled to 0 °C and quenched with water (5 mL). The aqueous phase was basicified with a saturated aqueous $NaHCO_3$ solution (5 mL) and the organic phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with a saturated aqueous $NaHCO_3$ solution (10 mL), then a saturated brine solution (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, 3:17 EtOAc/petrol), to afford the title compound as a colourless oil (673 mg, 57%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.63 (d, *J* = 2.0 Hz, 1H), 7.58 (dd, *J* = 8.6, 2.0 Hz, 1H), 6.96 (d, *J* = 8.6 Hz, 1H), 4.65 (s, 2H), 3.93 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 159.8 (s, C_q), 127.7 (q, *J* = 3.6 Hz, CH), 127.4 (q, *J* = 3.8 Hz, CH), 126.6 (s, C_q), 124.3 (q, *J* = 271.3 Hz, C_q), 123.0 (q, *J* = 33.0 Hz, C_q), 110.7 (s, CH), 56.0 (s, CH_3), 40.9 (s, CH_2); **^{19}F{^{1}H} NMR** (376 MHz, $CDCl_3$) δ_F –61.60 (s); **HRMS** (GC/MS-EITOF) *m*/*z* calc'd for $C_9H_8{}^{35}ClF_3O$ $[M]^{+\cdot}$: 224.0216 found 224.0220; **FTIR** (neat) ν_{max}/cm^{-1} 2972, 2845, 1618, 1509, 1331, 1283, 1262, 1157, 1112, 1080, 1025; **TLC** R_f: 0.29 (3:17 EtOAc/petrol)

(2-methoxy-5-(trifluoromethyl)benzyl)diphenylphosphine oxide (S53)



To a stirring solution of diphenylphosphine oxide (404 mg, 2.00 mmol) in anhydrous THF (7 mL) was added sodium hydride (60% *w*/*w* in oil, 120 mg, 3.00 mmol) in portions at 0 °C. The reaction was held at 0 °C and stirred for 30 minutes. **83** (505 mg, 2.36 mmol) was added and the mixture was then warmed to ambient temperature and stirred for a further 1 hour. The reaction mixture was then quenched with water (10 mL) at 0 °C and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with a saturated brine solution (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude organic residue was purified by trituration with Et_2O to afford the title compound as an off-white solid (713 mg, 91%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.74 – 7.66 (m, 4H), 7.53 – 7.46 (m, 2H), 7.46 – 7.39 (m, 6H), 6.73 (d, *J* = 8.5 Hz, 1H), 3.75 (d, *J* = 14.1 Hz, 2H), 3.53 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 159.5 (d, *J* = 5.3 Hz, C_q), 132.6 (d, *J* = 99.0 Hz, C_q), 131.9 (d, *J* = 2.8 Hz, CH), 131.3 (d, *J* = 9.4 Hz, CH), 128.9 – 128.7 (m, CH), 128.5 (d, *J* = 11.6 Hz, CH), 125.8 – 125.6 (m, CH), 124.3 (q, *J* = 271.6 Hz, C_q), 122.8 (qd, J = 32.8, 2.9 Hz, C_q), 120.9 (d, *J* = 8.4 Hz, C_q), 110.2 (d, *J* = 2.7 Hz, CH), 55.4 (s, CH_3), 31.6 (d, *J* = 66.8 Hz, CH_2); **^{19}F NMR** (376 MHz, $CDCl_3$) δ_F −61.6 (s); **^{31}P{^{1}H} NMR** (162 MHz, $CDCl_3$) δ_P 29.2; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{21}H_{20}F_3O_2P$ $[M + H]^+$: 391.1069, found 391.1074; **FTIR** (neat) ν_{max}/cm^{-1} 2969, 2912, 2840, 1616, 1511, 1438, 1330, 1290, 1260, 1190, 1177, 1147, 1113, 1026; **m.p.** 135–137 °C.

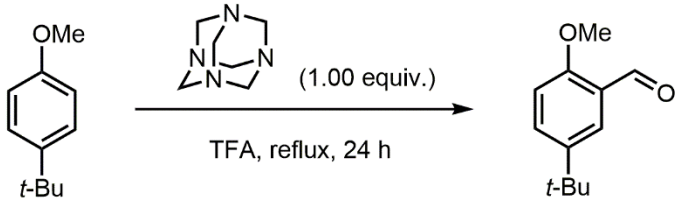
(2-Hydroxy-5-(trifluoromethyl)benzyl)diphenylphosphine Oxide (C9)



S53 **C9**

To a solution of **S53** (585 mg, 1.50 mmol) in CH_2Cl_2 (15 mL) was added a 1.0 M solution of boron tribromide in CH_2Cl_2 (4.5 mL, 4.5 mmol) dropwise at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 hours, after which reaction was quenched with water (10 mL). The aqueous layer was basicified with a saturated aqueous $NaHCO_3$ solution (5 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with a saturated aqueous $NaHCO_3$ solution (20 mL), then a saturated brine solution (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude organic residue was purified by trituration with Et_2O to afford the title compound as a light brown solid (361 mg, 64%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 10.44 (s, 1H), 7.76 – 7.67 (m, 4H), 7.61 – 7.55 (m, 2H), 7.53 – 7.45 (m, 4H), 7.36 – 7.31 (m, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.96 (d, *J* = 2.1 Hz, 1H), 3.73 (d, *J* = 12.9 Hz, 2H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 159.7 (s, C_q), 132.8 (d, *J* = 2.4 Hz, CH), 130.9 (d, *J* = 9.6 Hz, CH), 129.8 (d, *J* = 100.6 Hz, C_q), 128.9 (d, *J* = 12.3 Hz, CH), 128.8 – 128.6 (m, CH), 126.3 – 126.0 (m, CH), 123.9 (q, *J* = 322.4 Hz, C_q) 120.8 (qd, J = 31.4, 3.1 Hz, C_q) 119.7 (d, *J* = 8.1 Hz, C_q), 119.5 (d, *J* = 2.4 Hz, CH) 35.4 (d, *J* = 66.7 Hz, CH_2); **^{31}P{^{1}H} NMR** (162 MHz, $CDCl_3$) δ_P 38.4; **^{19}F NMR** (376 MHz, $CDCl_3$) δ_F −61.1 (s); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{20}H_{17}F_3O_2P$ $[M + H]^+$ = 377.0918, found 377.0920; **FTIR** (neat) ν_{max}/cm^{-1} 2989, 2968, 2912, 2841, 1616, 1511, 1439, 1429, 1330, 1290, 1260, 1190, 1176, 1147, 1112, 1101, 1078, 1026; **m.p.** 134–136 °C.

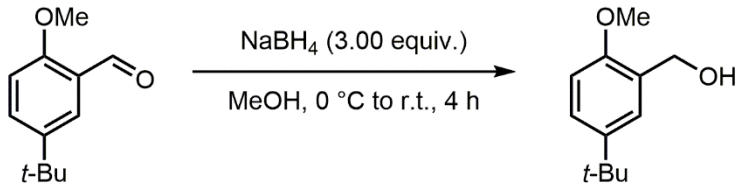
5-(*tert*-Butyl)-2-methoxybenzaldehyde (S54)



S54

A solution of 4-*tert*-butylanisole (1.75 mL, 10.0 mmol) and hexamethylenetetramine (1.40 g, 10.0 mmol) in TFA (20 mL) was heated to reflux and stirred for 24 hours. The reaction mixture was then diluted with EtOAc (150 mL), washed with water (2 × 100 mL), followed by a saturated aqueous $NaHCO_3$ solution (100 mL), then a saturated brine solution (100 mL). The organic layer was separated, dried over $MgSO_4$ concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, 1:19 EtOAc/petrol), to afford the title compound as a colourless oil (1.07 g, 56%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 10.45 (s, 1H), 7.84 (d, *J* = 2.7 Hz, 1H), 7.58 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.92 (d, *J* = 8.7 Hz, 1H), 3.89 (s, 3H), 1.30 (s, 9H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 190.2 (CH), 160.0 (C_q), 143.6 (C_q), 133.3 (CH), 125.1 (CH), 124.2 (C_q), 111.5 (CH), 55.8 (CH_3), 34.3 (C_q), 31.4 (CH_3); **HRMS** (ESI-TOF) *m/z* calc'd for $C_{12}H_{17}O_2$ $[M + H]^+$: 193.1223, found 193.1222; **TLC** R_f: 0.25 (1:19 EtOAc: petrol) 0.25. Data are consistent with those reported in the literature.[38]

5-(*tert*-Butyl)-2-methoxybenzyl Alcohol (S55)

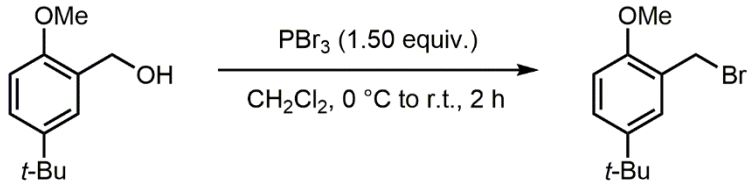


S54 **S55**

To a solution of **S54** (1.02 g, 5.30 mmol) in MeOH (10 mL) was added sodium borohydride (601 mg, 15.9 mmol), in portions, at 0 °C. The reaction mixture was warmed to room temperature and stirred for four hours. The reaction was quenched with a 1.0 M aqueous HCl solution (10 mL), then extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with a saturated brine

solution (20 mL), dried over $MgSO_4$, and concentrated *in vacuo* to yield the title compound as a colourless oil (1.01 g, 98%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.31 – 7.26 (m, 2H), 6.83 (d, *J* = 9.3 Hz, 1H), 4.68 (d, *J* = 6.5 Hz, 2H), 3.85 (s, 3H), 2.32 (apparent t, *J* = 6.5 Hz, 1H), 1.30 (s, 9H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 155.4 (C_q), 143.5 (C_q), 128.4 (C_q), 126.2 (CH), 125.5 (CH), 109.9 (CH), 62.7 (CH_2), 55.4 (CH_3), 34.2 (C_q), 31.6 (CH_3); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{12}H_{18}NaO_2$ $[M + H]^+$: 217.1199, found 217.1202; **FTIR** (neat) ν_{max}/cm^{-1} 3376, 2955, 2912, 2868, 2839, 1614, 1504, 1462, 1439, 1362, 1330, 1290, 1260, 1245, 1191,1177, 1110, 1027.

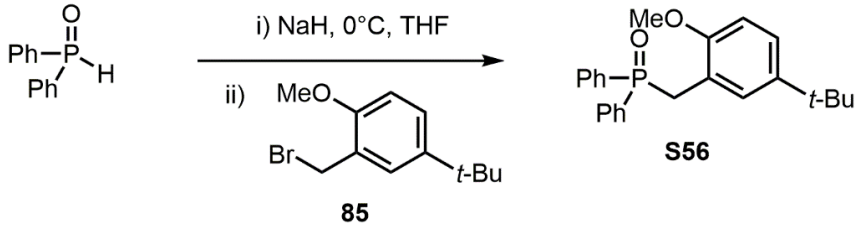
2-(Bromomethyl)-4-(*tert*-butyl)-1-methoxybenzene (85)



S55 **85**

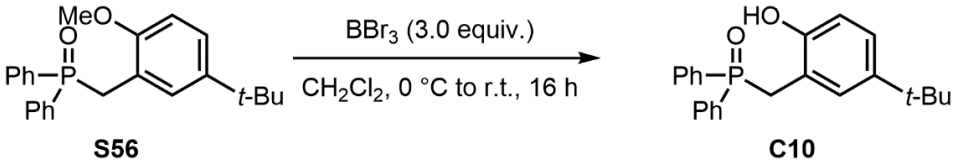
To a solution of **S55** (972 mg, 5.00 mmol) in CH_2Cl_2 (12 mL) was added phosphorus tribromide (705 µL, 7.50 mmol) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 30 minutes, then warmed to room temperature and stirred for a further 2 hours. The reaction mixture was cooled to 0 °C and quenched with water (5 mL). The aqueous phase was basicified with a saturated aqueous $NaHCO_3$ solution (10 mL) and the organic phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with a saturated aqueous $NaHCO_3$ solution (20 mL), then a saturated brine solution (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* afford the title compound as a pale orange oil (1.09 g, 84%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.34 (d, *J* = 2.6 Hz, 1H), 7.31 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.82 (d, *J* = 8.5 Hz, 1H), 4.58 (s, 2H), 3.88 (s, 3H), 1.30 (s, 9H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 155.4 (C_q), 143.6 (C_q), 128.1 (C_q), 127.1 (CH), 125.5 (CH), 110.7 (CH), 55.8 (CH_3), 34.2 (C_q), 31.6 (CH_3), 29.9 (CH_2); **HRMS** (GC/MS-EITOF) *m*/*z* calc'd for $C_{12}H_{17}{}^{79}BrO$ $[M]^{+\cdot}$: 256.0463 found 256.0457; **FTIR** (neat) ν_{max}/cm^{-1} 2954, 2904, 2836, 1610, 1503, 1462, 1442, 1393, 1362, 1243, 1140, 1034.

(5-(*tert*-Butyl)-2-methoxybenzyl)diphenylphosphine Oxide (S56)



To a stirring solution of diphenylphosphine oxide (404 mg, 2.00 mmol) in anhydrous THF (5 mL) was added sodium hydride (60% *w*/*w* in oil, 120 mg, 3.00 mmol) in portions at 0 °C. The reaction was held at 0 °C and stirred for 30 minutes. **85** (566 mg, 2.20 mmol) was added and the mixture was then warmed to ambient temperature and stirred for 5 hours. The reaction mixture was then quenched with a 1.0 M aqueous HCl solution (5 mL) at 0 °C, extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with a saturated brine solution (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude organic residue was purified by flash column chromatography (SiO_2, 6:4 EtOAc/petrol), to afford the title compound as a white solid (323 mg, 43%). **^{1}H NMR** (400 MHz, $CDCl_3$) 7.73 – 7.66 (m, 4H), 7.50 – 7.45 (m, 2H), 7.43 – 7.37 (m, 4H), 7.18 – 7.11 (m, 2H), 6.62 (d, *J* = 8.4 Hz, 1H), 3.75 (d, *J* = 14.4 Hz, 2H), 3.49 (s, 3H), 1.18 (s, 9H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 155.0 (d, *J* = 5.4 Hz, C_q), 143.1 (*J* = 2.9 Hz, C_q), 133.1 (d, *J* = 98.4 Hz, C_q), 131.6 (d, *J* = 2.9 Hz, CH), 131.4 (d, *J* = 9.5 Hz, CH), 129.0 (d, *J* = 4.6 Hz, CH), 128.3 (d, *J* = 11.3 Hz, CH), 124.7 (d, *J* = 3.0 Hz, CH), 119.2 (d, *J* = 8.0 Hz, C_q), 110.0 (d, *J* = 2.3 Hz, CH), 55.2 (s, CH_3), 34.1 (s, C_q), 31.6 (d, J = 67.9 Hz, CH_2), 31.5 (s, CH_3); **^{31}P{^{1}H} NMR** (162 MHz, $CDCl_3$) δ_P 30.0; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{24}H_{27}NaO_2P$ $[M + H]^+$: 401.1641, found 401.1643; **FTIR** (neat) ν_{max}/cm^{-1} 2987, 2961, 1610, 1509, 1428, 1279, 1162, 1140, 1131, 1095, 1060; **m.p.** 126–127 °C; **TLC** R_f; 0.30 (8:2 EtOAc/petrol).

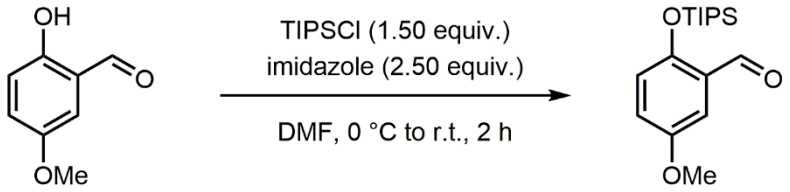
(5-(*tert*-Butyl)-2-hydroxybenzyl)diphenylphosphine Oxide (C10)



S56 **C10**

To a solution of **S56** (292 mg, 0.77 mmol) in CH_2Cl_2 (10 mL) was added a 1.0 M solution of boron tribromide in CH_2Cl_2 (2.4 mL, 2.4 mmol) dropwise at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 hours, after which reaction was quenched with water (10 mL). The aqueous layer was basicified with a saturated aqueous $NaHCO_3$ solution (5 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with a saturated aqueous $NaHCO_3$ solution (20 mL), then a saturated brine solution (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, 4:6 EtOAc/petrol), to afford the title compound as a white solid (263 mg, 94%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.35 (s, 1H), 7.75 – 7.67 (m, 4H), 7.57 – 7.51 (m, 2H), 7.49 – 7.42 (m, 4H), 7.10 (apparent dt, *J* = 8.4, 2.2 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.66 (apparent t, *J* = 2.2 Hz, 1H), 3.68 (d, *J* = 12.7 Hz, 2H), 1.11 (s, 9H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 154.3 (d, *J* = 4.0 Hz, C_q), 143.4 (d, *J* = 2.2 Hz, C_q), 132.5 (d, *J* = 2.8 Hz, CH), 131.2 (d, *J* = 9.5 Hz, CH), 131.2 – 130.2 (m, 2 × CH), 125.7 (d, *J* = 2.9 Hz, CH), 119.2 (d, *J* = 2.4 Hz, CH), 118.9 (d, *J* = 8.8 Hz, C_q), 35.7 (d, *J* = 66.9 Hz, CH_2), 33.9 (s, C_q), 31.5 (s, CH_3); **^{31}P{^{1}H} NMR** (162 MHz, $CDCl_3$) δ_P 38.3; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{23}H_{26}O_2P$ $[M + H]^+$: 365.1665, found 365.1673; **FTIR** (neat) ν_{max}/cm^{-1} 3040, 2959, 2901, 1606, 1509, 1427, 1280, 1169, 1139, 1118, 1098; **m.p.** 168–169 °C; **TLC** R_f: 0.25 (4:6 EtOAc:petrol).

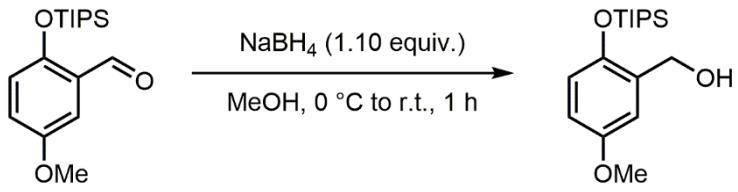
5-Methoxy-2-((triisopropylsilyl)oxy)benzaldehyde (S57)



S57

To a solution of 2-hydroxy-5-methoxybenzaldehyde (1.25 mL, 10.0 mmol) and imidazole (1.70 g, 25.0 mmol) in DMF (30 mL) was added chlorotriisopropylsilane (3.21 mL, 15.0 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for two hours. The reaction was then diluted with EtOAc (200 mL) and the organic layer was washed with water (3 × 200 mL), then a saturated brine solution (2 × 200 mL), then dried over $MgSO_4$ and concentrated *in vacuo*. The crude organic residue was purified by flash column chromatography (SiO_2, 1:19 EtOAc:petrol), to afford the title compound as a colourless oil (2.48 g, 80%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 10.50 (s, 1H), 7.27 (d, *J* = 3.4 Hz, 1H), 7.04 (dd, *J* = 9.0, 3.4 Hz, 1H), 6.83 (d, *J* = 9.0 Hz, 1H), 3.80 (s, 3H), 1.39 – 1.26 (m, 3H), 1.12 (d, *J* = 7.4 Hz, 18H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 190.2 (CH) , 154.1 (C_q), 153.9 (C_q), 126.7 (C_q), 124.1 (CH), 121.1 (CH), 109.6 (CH), 55.9 (CH_3), 18.1 (CH_3), 13.1 (CH); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{17}H_{29}O_3Si$ $[M + H]^+$: 309.1880; found 309.1880; **FTIR** (neat) ν_{max}/cm^{-1} 2945, 2867, 1681, 1488, 1463, 1390, 1333, 1271, 1258, 1216, 1152, 1117, 1081, 1037; **TLC** R_f: 0.74 (1:1 EtOAc:petrol).

(5-Methoxy-2-((triisopropylsilyl)oxy)phenyl)methanol (S58)

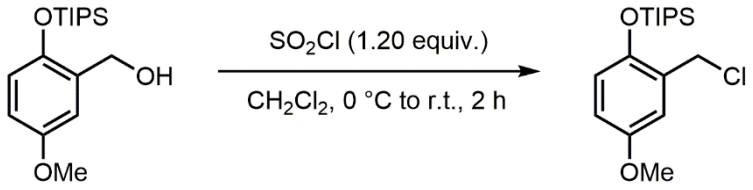


S57 **S58**

To a solution of **S57** (2.16 g, 7.00 mmol) in MeOH (30 mL) was added sodium borohydride (291 mg, 7.70 mmol), in portions, at 0 °C. The reaction mixture was warmed to ambient temperature and stirred for 60 minutes. The reaction was

then quenched with water (20 mL), then extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo* to yield the title compound as a colourless oil (2.10 g, 6.79 mmol, 97%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.88 (d, *J* = 3.1 Hz, 1H), 6.74 (d, *J* = 8.8 Hz, 1H), 6.68 (dd, *J* = 8.8, 3.1 Hz, 1H), 4.68 (d, *J* = 3.3 Hz, 2H), 3.77 (s, 3H), 2.14 (s, 1H), 1.35 – 1.24 (m, 3H), 1.11 (d, *J* = 7.4 Hz, 18H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 153.9 (C_q), 147.7 (C_q), 131.9 (C_q), 118.6 (CH), 114.1 (CH), 113.5 (CH), 62.4 (CH_2), 55.8 (CH_3), 18.2 (CH_3), 13.1 (CH); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{17}H_{31}O_3Si$ $[M + H]^+$: 311.2037; found 311.2049; **FTIR** (neat) ν_{max}/cm^{-1} 2944, 2866, 1682, 1489, 1463, 1422, 1390, 1271, 1215, 1152, 1122, 1037.

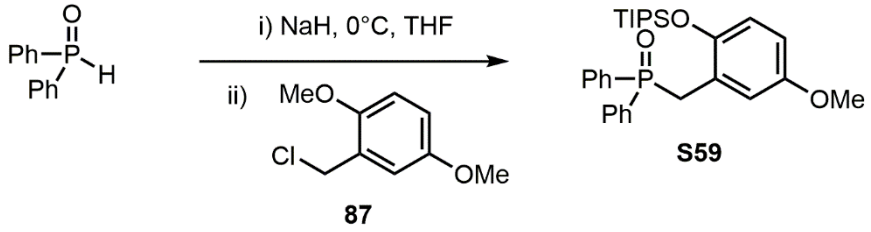
(2-(Chloromethyl)-4-methoxyphenoxy)triisopropylsilane (87)



S58 **87**

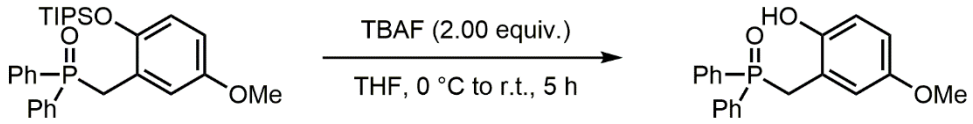
To a solution of **87** (1.86 g, 6.00 mmol) in CH_2Cl_2 (10 mL) was added thionyl chloride (525 µL, 7.20 mmol) at 0 °C dropwise. The reaction mixture was stirred at 0 °C for 30 minutes, then warmed to room temperature and stirred for a further 90 minutes. The reaction mixture was then cooled to 0 °C and quenched with water (5 mL). The organic phase was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were washed with a saturated aqueous $NaHCO_3$ solution (20 mL), then a saturated brine solution (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* afford the title compound as a colourless oil (1.76 g, 89%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.92 (d, *J* = 2.4 Hz, 1H), 6.78 – 6.71 (m, 2H), 4.64 (s, 2H), 3.77 (s, 3H), 1.39 – 1.26 (m, 3H), 1.13 (d, *J* = 7.5 Hz, 18H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 153.6 (C_q), 148.0 (C_q), 128.2 (C_q), 118.9 (CH), 115.7 (CH), 115.2 (CH), 55.8 (CH_3), 42.2 (CH_2), 18.2 (CH_3), 13.1 (CH); **HRMS** (GC/MS-EITOF) *m*/*z* calc'd for $C_{17}H_{29}{}^{35}ClO_2Si$ $[M]^{+\cdot}$: 328.1625 found 328.1630; **FTIR** (neat) ν_{max}/cm^{-1} 2944, 2892, 2866, 1583, 1498, 1463, 1420, 1385, 1367, 1275, 1227, 1159, 1118, 1043, 1015.

(5-Methoxy-2-((triisopropylsilyl)oxy)benzyl)diphenylphosphine Oxide (S59)



To a stirring solution of diphenylphosphine oxide (809 mg, 4.00 mmol) in anhydrous THF (10 mL) was added sodium hydride (60% *w*/*w* in oil, 240 mg, 6.00 mmol) in portions at 0 °C. The stirring suspension was held at 0 °C and stirred for 15 minutes. A solution of **87** (1.58 g, 4.80 mmol) in anhydrous THF (5 mL) was added and the mixture was then warmed to room temperature and stirred for 60 minutes. The reaction mixture was then quenched with a 1.0 M aqueous HCl solution (5 mL) at 0 °C and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with a saturated brine solution (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude organic residue was purified by flash column chromatography (SiO_2, 7:3 EtOAc/petrol) to afford the title compound as a pale-yellow oil (1.23 g, 62%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.73 – 7.65 (m, 4H), 7.49 – 7.43 (m, 2H), 7.42 – 7.35 (m, 4H), 7.06 (apparent t, *J* = 2.8 Hz, 1H), 6.63 (d, *J* = 8.9 Hz, 1H), 6.59 (ddd, *J* = 8.9, 2.8, 1.6 Hz, 1H), 3.75 (d, *J* = 14.7 Hz, 2H), 3.66 (s, 3H), 1.29 – 1.16 (m, 3H), 1.04 (d, *J* = 7.4 Hz, 18H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 153.4 (d, *J* = 3.0 Hz, C_q), 147.5 (d, *J* = 6.9 Hz, C_q), 133.0 (d, *J* = 98.9 Hz, C_q), 131.7 (d, *J* = 2.5 Hz, CH), 131.2 (d, *J* = 9.2 Hz, CH), 128.5 (d, *J* = 11.6 Hz, CH), 122.5 (d, *J* = 7.4 Hz, C_q), 118.6 (d, *J* = 2.2 Hz, CH), 115.6 (d, *J* = 4.5 Hz, CH), 114.4 (d, *J* = 3.0 Hz, CH), 55.7 (s, CH_3), 31.0 (d, *J* = 68.9 Hz, CH_2), 18.2 (s, CH_3), 13.1 (s, CH); **^{31}P{^{1}H} NMR** (162 MHz, $CDCl_3$) δ_P 30.9; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{29}H_{40}O_3PSi$ $[M + H]^+$: 495.2479; found 495.2488; **FTIR** (neat) ν_{max}/cm^{-1} 2943, 2892, 2865, 1608, 1498, 1463, 1436, 1417, 1271, 1230, 1218, 1200, 1118, 1104, 1070, 1038, 1015; **TLC** R_f: 0.20 (7:3 EtOAc/petrol)

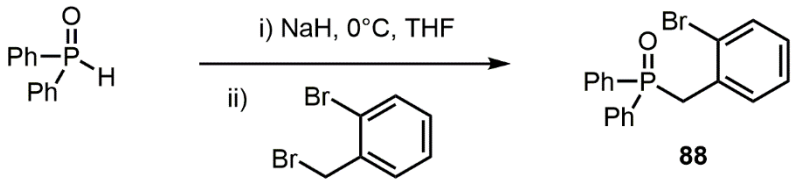
(2-Hydroxy-5-methoxybenzyl)diphenylphosphine Oxide (C11)



S59 **C11**

To a solution of **S59** (1.09 g, 2.20 mmol) in anhydrous THF (10 mL) was added a 1.0 M solution of tetrabutylammonium fluoride in THF (4.4 mL, 4.4 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for five hours. The reaction mixture was then diluted with EtOAc (40 mL), washed with H_2O (3 × 20 mL), then a saturated brine solution (20 mL). The organic layer was dried over $MgSO_4$, concentrated *in vacuo* then purified by flash column chromatography (SiO_2, 1:1 EtOAc/petrol), to afford the title compound as an off-white solid (292 mg, 39%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.29 (s, 1H), 7.76 – 7.67 (m, 4H), 7.59 – 7.52 (m, 2H), 7.51 – 7.44 (m, 4H), 6.94 (d, *J* = 8.8 Hz, 1H), 6.67 (dt, *J* = 8.8, 2.3 Hz, 1H), 6.30 (t, *J* = 2.3 Hz 1H), 3.67 (d, *J* = 12.9 Hz, 2H), 3.60 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 153.5 (d, *J* = 2.2 Hz, C_q), 150.5 (d, *J* = 4.0 Hz, C_q), 132.6 (d, *J* = 3.0 Hz, CH), 131.1 (d, *J* = 9.8 Hz, CH), 130.7 (d, *J* = 99.7 Hz, C_q), 128.9 (d, *J* = 11.6 Hz, CH), 120.5 (d, *J* = 9.0 Hz, C_q), 120.3 (d, *J* = 2.9 Hz, CH), 117.2 (d, *J* = 6.3 Hz, CH), 113.9 (d, *J* = 3.0 Hz, CH), 55.8 (s, CH_3), 35.5 (d, *J* = 67.3 Hz, CH_2); **^{31}P{^{1}H} NMR** (162 MHz, $CDCl_3$) δ_P 38.0; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{20}H_{20}O_3P$ $[M + H]^+$: 339.1150, found 339.1150; **FTIR** (neat) ν_{max}/cm^{-1} 2957, 2905, 2886, 2831, 1590, 1508, 1468, 1451, 1432, 1376, 1271, 1215, 1190, 1164, 1132, 1117, 1096, 1068, 1035; **m.p.** 209–210 °C; **TLC** R_f: 0.30 (1:1 EtOAc/petrol).

(2-Bromobenzyl)diphenylphosphine Oxide (88)

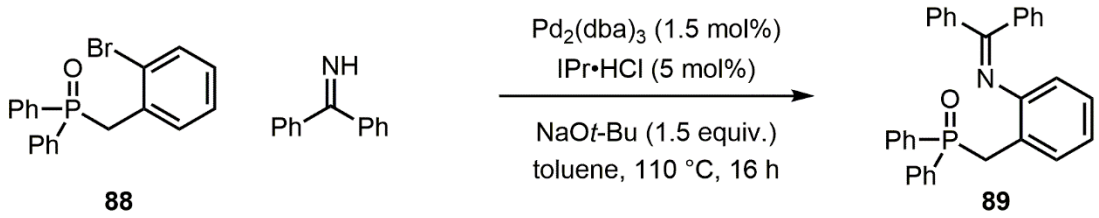


88

To a solution of diphenylphosphine oxide (2.02 g, 10.0 mmol) in anhydrous THF (30 mL) was added sodium hydride (60% *w*/*w* in oil, 600 mg, 15.0 mmol) at 0 °C. The reaction mixture was kept at 0 °C and stirred for 30 minutes. 2-bromobenzyl bromide (3.00 g, 12.0 mmol) in anhydrous THF (1 mL) was then added and the reaction mixture was stirred for 16 hours. The reaction was quenched with MeOH

(10 mL) then concentrated *in vacuo*. The residue was then suspended in H_2O (30 mL) and extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with a saturated brine solution (30 mL) and dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O, then purified by flash column chromatography (SiO_2, gradient from 7:3 EtOAc/petrol to 80:18:2 EtOAc/petrol/10% *v*/*v* NH_4OH in MeOH) afforded the tile compound as a colourless solid (1.54 g, 41%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.74 – 7.67 (m, 4H), 7.58 (apparent dt, *J* = 7.8, 2.0 Hz, 1H), 7.52 – 7.47 (m, 2H), 7.45 – 7.39 (m, 5H), 7.20 (apparent td, *J* = 7.5, 1.3 Hz, 1H), 7.07 – 6.99 (m, 1H), 3.89 (d, *J* = 13.9 Hz, 2H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 132.8 (d, *J* = 1.9 Hz, CH), 132.2 (d, *J* = 99.8 Hz, C_q), 132.1 – 131.9 (m, 2 × CH), 131.7 (d, *J* = 7.3 Hz, C_q), 131.3 (d, *J* = 9.8 Hz, CH), 128.58 (d, *J* = 2.6 Hz, CH), 128.57 (d, *J* = 11.7 Hz, CH), 127.6 (d, *J* = 2.5 Hz, CH), 125.4 (d, *J* = 7.3 Hz, C_q), 37.4 (d, *J* = 66.3 Hz, CH_2); **^{31}P{^{1}H} NMR** (162 MHz, $CDCl_3$) δ_P 29.4; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{19}H_{17}{}^{79}BrOP$ $[M + H]^+$: 371.0195; found 371.0192; **FTIR** (neat) ν_{max}/cm^{-1} 3056, 2952, 2909, 1590, 1567, 1468, 1436, 1405, 1229, 1189, 1145, 1118, 1107, 1023; **m.p.** 117–120 °C; **TLC** R_f: 0.33 (4:1 EtOAc/cyclohexane)

(2-((Diphenylmethylene)amino)benzyl)diphenylphosphine Oxide (89)

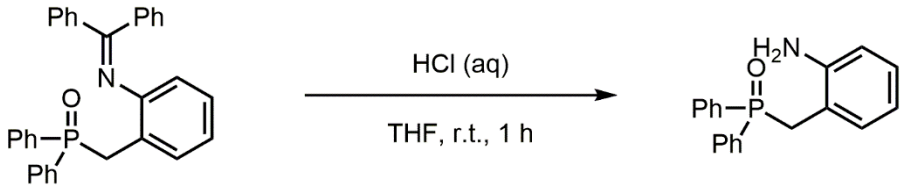


88 **89**

A suspension of **88** (4.83 g, 13.0 mmol), benzophenone imine (2.62 mL, 15.6 mmol), sodium *tert*-butoxide (1.87 g, 19.5 mmol), $Pd_2(dba)_3$•$CHCl_3$ (101 mg, 97.5 µmol) and 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (138 mg, 325 µmol) in degassed toluene (52 mL) was heated to reflux and stirred for 16 hours. A further addition of $Pd_2(dba)_3$•$CHCl_3$ (101 mg, 97.5 µmol) and 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (138 mg, 325 µmol) was made and the reaction mixture was stirred, at reflux, for a further 8 hours. The reaction mixture was then concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, gradient from 1:1 EtOAc/petrol to EtOAc) to afford the title compound as a yellow solid (1.43 g, 23%). **^{1}H NMR** (500 MHz,

$CDCl_3$) δ_H 7.80 – 7.70 (m, 6H), 7.54 – 7.47 (m, 2H), 7.46 – 7.39 (m, 4H), 7.33 (apparent td, *J* = 7.6, 2.8 Hz, 4H), 7.26 – 7.21 (m, 1H), 7.15 (apparent t, *J* = 7.6 Hz, 2H), 6.89 (apparent t, *J* = 7.4 Hz, 1H), 6.79 (apparent t, *J* = 7.7 Hz, 2H), 6.75 (d, *J* = 7.2 Hz, 2H), 6.15 (d, *J* = 7.9 Hz, 1H), 3.95 (d, *J* = 13.9 Hz, 2H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 167.4 (s, C_q), 148.7 (d, *J* = 6.3 Hz, C_q), 140.0 (s, C_q), 135.8 (s, C_q), 133.5 (d, *J* = 98.1 Hz, C_q), 131.7 (d, *J* = 2.7 Hz, CH), 131.5 (d, *J* = 4.5 Hz, CH), 131.4 (d, *J* = 9.1 Hz, CH), 130.8 (s, CH), 129.6 (d, *J* = 9.2 Hz, CH), 128.8 (s, CH), 128.6 (s, CH), 128.5 (s, CH), 128.2 (s, CH), 128.0 (s, CH), 126.9 (d, *J* = 2.8 Hz, CH), 125.5 (d, *J* = 7.7 Hz, C_q), 124.3 (d, *J* = 2.8 Hz, CH), 120.4 (d, *J* = 2.5 Hz, CH), 32.5 (d, *J* = 68.2 Hz, CH_2); **^{31}P{^{1}H} NMR** (202 MHz, $CDCl_3$) δ_P 30.0; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{32}H_{27}NOP$ $[M + H]^+$: 472.1825, found 472.1835; **FTIR** (neat) ν_{max}/cm^{-1} 3055, 1612, 1590, 1569, 1481, 1436, 1391, 1315, 1293, 1270, 1117, 1105; **m.p.** 126–128 °C; **TLC** R_f: 0.42 (EtOAc).

(2-Aminobenzyl)diphenylphosphine oxide (90)

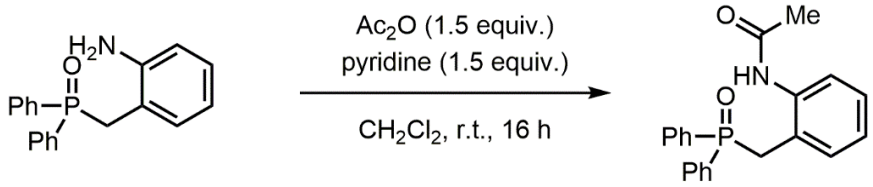


89 **90**

To a solution of **89** (471 mg, 1.00 mmol) in THF (3.33 mL) was added a 2.0 M aqueous HCl solution (167 µL) at room temperature, and the reaction was stirred for 1 hour. The reaction mixture was then diluted with a 0.5 M aqueous HCl solution (10 mL) and the benzophenone by-product was extracted with 2:1 *v*/*v* hexane:EtOAc (10 mL). The aqueous layer was basicified with a 6.0 M aqueous NaOH solution (5 mL) and the organics were extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with a saturated brine solution (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound as a colourless solid (277 mg, 90%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.76 – 7.70 (m, 4H), 7.56 – 7.50 (m, 2H), 7.49 – 7.43 (m, 4H), 6.98 (apparent tt, *J* = 7.6, 1.8 Hz, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 6.57 (apparent dt, *J* = 7.5, 1.9 Hz, 1H), 6.50 (apparent t, *J* = 7.4 Hz, 1H), 4.69 (s, 2H), 3.65 (d, *J* = 12.8 Hz, 2H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 147.3 (d, *J* = 3.6 Hz, C_q), 132.1 (d, *J* = 98.1 Hz, C_q), 132.1 (d, *J* = 2.7 Hz, CH), 131.8 (d, *J* = 5.5 Hz, CH), 131.2 (d, *J* = 9.2 Hz, CH), 128.7 (d, *J* =

11.7 Hz, CH), 128.1 (d, *J* = 2.9 Hz, CH), 118.7 (d, *J* = 2.7 Hz, CH), 117.8 (d, *J* = 8.3 Hz, C_q), 117.5 (d, *J* = 2.7 Hz, CH), 35.5 (d, *J* = 68.0 Hz, CH_2); **$^{31}P\{^1H\}$ NMR** (202 MHz, $CDCl_3$) δ_P 33.8; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{19}H_{19}NOP$ $[M + H]^+$: 308.1199, found 308.1203; **FTIR** (neat) ν_{max}/cm^{-1} 3401, 3302, 3076, 3051, 3024, 3011, 2942, 2888, 1638, 1601, 1582, 1495, 1459, 1436, 1268, 1230, 1171, 1121, 1070; **m.p.** 204–205 °C.

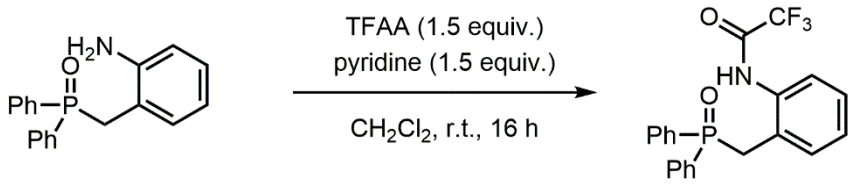
N-(2-((Diphenylphosphoryl)methyl)phenyl)acetamide (C12)



90 **C12**

To a solution of **90** (120 mg, 0.39 mmol) and pyridine (48 μL, 0.59 mmol) in CH_2Cl_2 (3 mL) was added acetic anhydride (58 μL, 0.59 mmol) and the reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was then diluted with CH_2Cl_2 (10 mL) and the organic phase was washed with a 10% *w*/*v* aqueous copper(II) sulfate solution (2 × 10 mL), then a saturated brine solution (10 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by trituration using 1:1 Et_2O/petrol afforded the title compound as a colourless solid (136 mg, 83%). **^1H NMR** (500 MHz, $CDCl_3$) δ_H 10.47 (s, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.72 – 7.67 (m, 4H), 7.57 – 7.52 (m, 2H), 7.50 – 7.45 (m, 4H), 7.19 (apparent d, *J* = 15.5 Hz, 1H), 6.85 (apparent t, *J* = 7.5 Hz, 1H), 6.69 (d, *J* = 7.6 Hz, 1H), 3.66 (d, *J* = 12.9 Hz, 2H), 2.25 (s, 3H); **$^{13}C\{^1H\}$ NMR** (126 MHz, $CDCl_3$) δ_C 169.4 (s, C_q), 137.8 (d, *J* = 3.7 Hz, C_q), 132.5 (d, *J* = 2.7 Hz, CH), 131.5 (d, *J* = 6.3 Hz, CH), 131.0 (d, *J* = 9.4 Hz, CH), 130.9 (d, *J* = 99.9 Hz, C_q) 128.9 (d, *J* = 11.8 Hz, CH), 128.0 (d, *J* = 2.9 Hz, CH), 125.8 (d, *J* = 3.2 Hz, CH), 124.9 (d, *J* = 2.6 Hz, CH), 123.8 (d, *J* = 8.5 Hz, C_q), 35.9 (d, *J* = 66.3 Hz, CH_2), 24.5 (s, CH_3); **$^{31}P\{^1H\}$ NMR** (202 MHz, $CDCl_3$) δ_P 36.0; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{21}H_{21}NO_2P$ $[M + H]^+$: 350.1304, found 350.1296; **FTIR** (neat) ν_{max}/cm^{-1} 3237, 3076, 3055, 3011, 2955, 2917, 2896, 2849, 1682, 1587, 1526, 1453, 1434, 1365, 1302, 1268, 1243, 1224, 1169, 1142, 1118; **m.p.** 197–198 °C.

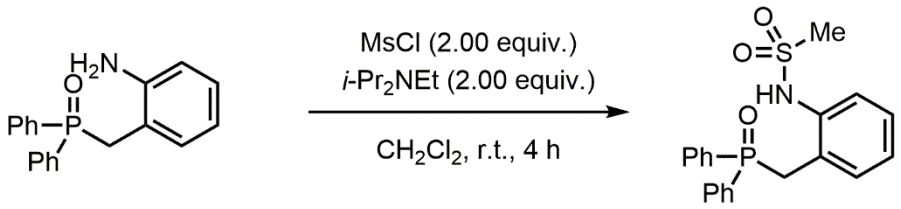
***N*-(2-((Diphenylphosphoryl)methyl)phenyl)-2,2,2-trifluoroacetamide (C13)**



90 **C13**

To a solution of **90** (120 mg, 0.39 mmol) and pyridine (48 µL, 0.59 mmol) in CH_2Cl_2 (3 mL) was added trifluoroacetic anhydride (82 µL, 0.59 mmol) and the reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was then diluted with a 10% *w*/*v* aqueous copper(II) sulfate solution (10 mL), and the organics were extracted with EtOAc (3 × 10 mL) The combined organic extracts were washed with a 10% *w*/*v* aqueous copper(II) sulfate solution (10 mL), then a saturated brine solution (10 mL). The organic solution was dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by trituration using 1:1 Et_2O/petrol to afford the title compound as an off-white solid (157 mg, 99%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 11.82 (s, 1H), 7.76 – 7.68 (m, 5H), 7.59 – 7.54 (m, 2H), 7.52 – 7.46 (m, 4H), 7.28 – 7.23 (m, 2H), 6.98 (apparent t, *J* = 7.5 Hz, 1H), 6.80 (apparent d, *J* = 7.7 Hz, 1H), 3.65 (d, *J* = 12.7 Hz, 2H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 156.4 (q, *J* = 37.4 Hz, C_q), 135.34 (d, *J* = 4.2 Hz, C_q), 132.7 (d, *J* = 2.8 Hz, CH), 131.7 (d, *J* = 5.5 Hz, CH), 131.0 (d, *J* = 9.8 Hz, CH), 130.4 (d, *J* = 100.1 Hz, C_q), 129.0 (d, *J* = 11.9 Hz, CH), 128.3 (d, *J* = 3.3 Hz, CH), 126.7 (d, *J* = 2.7 Hz, CH), 126.0 (d, *J* = 2.7 Hz, CH), 125.1 (d, *J* = 9.0 Hz, C_q), 116.5 (q, *J* = 288.6 Hz, C_q), 35.8 (d, *J* = 65.6 Hz, CH_2); **^{19}F NMR** (376 MHz, $CDCl_3$) δ_F −75.4 (s); **^{31}P{^{1}H} NMR** (202 MHz, $CDCl_3$) δ_P 36.5; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{21}H_{18}F_3NO_2P$ $[M + H]^+$: 404.1022, found 404.1019; **FTIR** (neat) ν_{max}/cm^{-1} 2956, 2918, 2850, 1720, 1588, 1543, 1485, 1456, 1438, 1407, 1287, 1254, 1180, 1146, 1119, 1077; **m.p.** 163–165 °C.

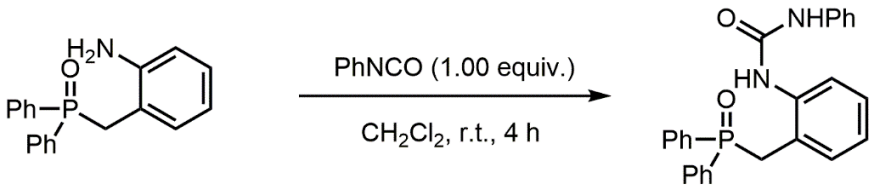
***N*-(2-((Diphenylphosphoryl)methyl)phenyl)methanesulfonamide (C14)**



90 **C14**

To a solution of **90** (120 mg, 0.39 mmol) and diisopropylethylamine (264 µL, 1.17 mmol) in CH_2Cl_2 (3 mL) was added methanesulfonyl chloride (30 µL, 0.39 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 hours. A further addition of methanesulfonyl chloride (30 µL, 0.39 mmol) at 0 °C and the reaction mixture was warmed to room temperature and stirred for a further 2 hours. The reaction mixture was then diluted with a 1.0 M aqueous HCl solution (10 mL) and the organics were extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with a saturated brine solution (10 mL), then dried over $MgSO_4$ and concentrated *in vacuo*. The crude organic residue was purified by flash column chromatography (SiO_2, 4:6 acetone/petrol) to afford the title compound as colourless solid (43 mg, 29%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 10.02 (s, 1H), 7.74 – 7.68 (m, 4H), 7.58 – 7.53 (m, 2H), 7.50 – 7.44 (m, 5H), 7.21 (apparent tt, *J* = 7.8, 1.8 Hz, 1H), 6.93 (apparent t, *J* = 7.5 Hz, 1H), 6.77 (apparent dt, *J* = 7.7, 1.9 Hz, 1H), 3.77 (d, *J* = 12.9 Hz, 2H), 3.17 (s, 3H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 137.5 (d, *J* = 4.5 Hz, C_q), 132.6 (d, *J* = 2.7 Hz, CH), 132.1 (d, *J* = 5.5 Hz, CH), 131.1 (d, *J* = 9.1 Hz, CH), 130.7 (d, *J* = 100.1 Hz, C_q), 128.9 (d, *J* = 11.9 Hz, CH), 128.6 (d, *J* = 3.5 Hz, CH), 126.1 (d, *J* = 9.0 Hz, C_q), 125.8 (d, *J* = 2.7 Hz, CH), 125.0 (d, *J* = 2.7 Hz, CH), 42.0 (s, CH_3), 36.0 (d, *J* = 65.5 Hz, CH_2); **^{31}P{^{1}H} NMR** (202 MHz, $CDCl_3$) δ_P 36.3; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{20}H_{21}NO_3PS$ $[M + H]^+$: 386.0974, found 386.0968; **FTIR** (neat) ν_{max}/cm^{-1} 3155, 2929, 1489, 1439, 1388, 1320, 1273, 1242, 1149, 1122; **m.p.** 233–235 °C; **TLC** R_f: 0.24 (1:1 acetone/petrol)

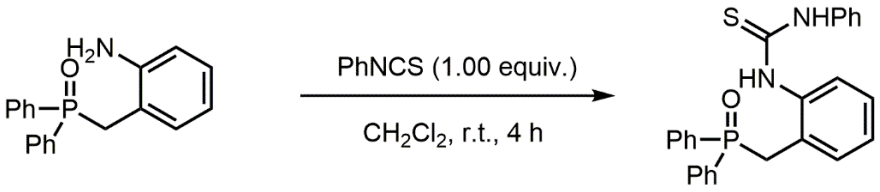
1-(2-((Diphenylphosphoryl)methyl)phenyl)-3-phenylurea (C15)



90 **C15**

To a solution of **90** (120 mg, 0.39 mmol) in CH_2Cl_2 (3 mL) was added phenyl isocyanate (42 µL, 0.39 mmol) at room temperature and the reaction mixture was stirred for four hours. The reaction mixture was then concentrated *in vacuo* to afford the title compound as an off-white solid (138 mg, 83%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 9.61 (s, 1H), 7.80 (apparent d, *J* = 8.0 Hz, 1H), 7.72 – 7.66 (m, 4H), 7.58 – 7.53 (m, 2H), 7.51 – 7.45 (m, 6H), 7.30 – 7.27 (m, 2H), 7.19 (apparent t, *J* = 7.8 Hz, 1H), 7.06 (s, 1H), 7.01 (apparent t, *J* = 7.4 Hz, 1H), 6.83 (apparent t, *J* = 7.5 Hz, 1H), 6.69 (apparent d, *J* = 7.7 Hz, 1H), 3.72 (d, *J* = 12.9 Hz, 2H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 153.3 (s. C_q), 139.1 (s, C_q), 138.4 (d, *J* = 3.8 Hz, CH), 132.5 (d, *J* = 2.7 Hz, CH), 131.4 (d, *J* = 6.1 Hz, CH), 130.9 (d, *J* = 9.3 Hz, CH), 130.7 (d, *J* = 99.9 Hz, C_q), 128.9 (s, CH), 128.8 (d, *J* = 12.2 Hz, CH), 128.0 (d, *J* = 2.9 Hz, CH), 125.0 (d, *J* = 2.5 Hz, CH), 123.9 (d, *J* = 2.5 Hz, CH), 123.3 (d, *J* = 9.1 Hz, C_q), 122.7 (s, CH), 119.3 (s, CH); **^{31}P{^{1}H} NMR** (202 MHz, $CDCl_3$) δ_P 36.6; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{26}H_{24}N_2O_2P$ $[M + H]^+$: 427.1570, found 427.1565; **FTIR** (neat) ν_{max}/cm^{-1} 3325, 3237, 3185, 3123, 3052, 3033, 2949, 2905, 2849, 1680, 1597, 1537, 1497, 1473, 1437, 1292, 1238, 1221, 1175, 1157, 1139, 1112, 1073; **m.p.** 212–214 °C.

1-(2-((Diphenylphosphoryl)methyl)phenyl)-3-phenylthiourea (C16)

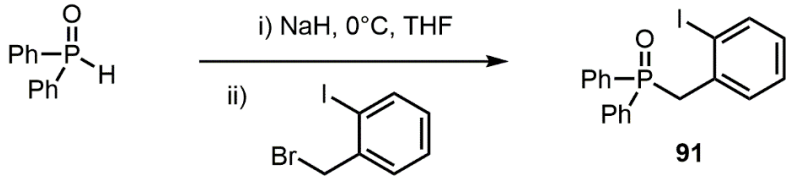


90 **C16**

To a solution of **90** (120 mg, 0.39 mmol) in CH_2Cl_2 (3 mL) was added phenyl isothiocyanate (47 µL, 0.39 mmol) at room temperature and the reaction mixture was stirred for 16 hours. The reaction mixture was then concentrated *in vacuo*. The crude residue was purified by trituration, using Et_2O, to afford the title

compound as an off-white solid (170 mg, 99%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 9.87 (s, 1H), 8.02 (s, 1H), 7.67 (apparent d, *J* = 8.0 Hz, 1H), 7.62 – 7.54 (m, 6H), 7.52 – 7.43 (m, 6H), 7.40 – 7.35 (m, 2H), 7.32 – 7.24 (m, 2H), 7.02 (apparent t, *J* = 7.5 Hz, 1H), 6.72 (apparent d, *J* = 7.6 Hz, 1H), 3.65 (d, *J* = 12.3 Hz, 2H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 181.3 (s, C_q), 139.4 (d, *J* = 4.2 Hz, CH), 137.3 (s, C_q), 132.4 (d, *J* = 2.8 Hz, CH), 131.3 (d, *J* = 6.7 Hz, CH), 131.2 (d, *J* = 99.7 Hz, C_q), 131.1 (d, *J* = 9.3 Hz, CH), 129.6 (s, CH), 128.8 (d, *J* = 11.9 Hz, CH), 129.0 (d, *J* = 2.6 Hz, CH), 127.9 (d, *J* = 3.3 Hz, CH), 127.4 (d, *J* = 9.3 Hz, C_q), 127.0 (d, *J* = 2.8 Hz, CH), 126.91 (s, CH), 125.32(s, CH), 35.25 (d, *J* = 65.4 Hz, CH_2); **^{31}P{^{1}H} NMR** (202 MHz, $CDCl_3$) δ_P 33.2; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{26}H_{24}N_2OPS$ $[M + H]^+$: 443.1341, found 443.1340; **FTIR** (neat) ν_{max}/cm^{-1} 3140, 3057, 2954, 2917, 2849, 1589, 1509, 1490, 1450, 1435, 1353, 1312, 1233, 1192, 1164, 1121, 1101; **m.p.** 174–176 °C.

(2-Iodobenzyl)diphenylphosphine oxide (91)

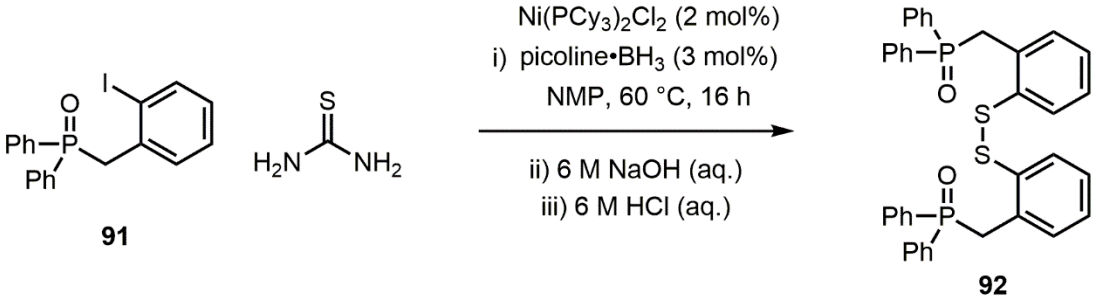


91

To a solution of diphenylphosphine oxide (1.10 g, 5.44 mmol) in anhydrous THF (20 mL) was added sodium hydride (60% *w*/*w* in oil, 327 mg, 8.17 mmol) at 0 °C. The reaction mixture was kept at 0 °C and stirred for 30 minutes. 2-iodobenzyl bromide (1.94 g, 6.53 mmol) was then added and the reaction mixture was stirred for 4 hours. The reaction was quenched with MeOH (10 mL) then concentrated *in vacuo*. The residue was then suspended in H_2O (30 mL) and extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with a saturated brine solution (30 mL) and dried over $MgSO_4$ and concentrated *in vacuo*. The residue was triturated with Et_2O, then purified by flash column chromatography (SiO_2, gradient from 7:3 EtOAc/petrol to 4:1 EtOAc/petrol) afforded the tile compound as a colourless solid (1.48 g, 65%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.74 – 7.65 (m, 5H), 7.58 (apparent dt, *J* = 7.8, 2.0 Hz, 1H), 7.54 – 7.48 (m, 2H), 7.46 – 7.40 (m, 4H), 7.25 (apparent td, *J* = 7.6, 1.3 Hz, 1H), 6.87 (apparent tt, *J* = 7.5, 1.7 Hz, 1H), 3.90 (d, *J* = 13.8 Hz, 2H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 139.6 (d, *J* = 2.2 Hz, CH), 135.2 (d, *J* = 7.4 Hz, C_q), 132.1 (d, *J* = 2.9 Hz, CH), 132.0 (d, *J* = 99.9 Hz, C_q)

131.4 (d, *J* = 9.5 Hz, CH), 131.1 (d, *J* = 4.4 Hz, CH), 128.7 (d, *J* = 3.0 Hz, CH), 128.6 (d, *J* = 11.8 Hz, CH), 128.5 (d, *J* = 2.7 Hz, CH), 102.5 (d, *J* = 7.6 Hz, C_q), 42.4 (d, *J* = 66.0 Hz, CH_2); **$^{31}P\{^1H\}$ NMR** (162 MHz, $CDCl_3$) δ_P 29.7; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{19}H_{16}IOP$ $[M + H]^+$: 419.0056, found 419.0065; **FTIR** (neat) ν_{max}/cm^{-1} 3050, 2944, 2906, 1585, 1562, 1462, 1435, 1403, 1227, 1189, 1143, 1117, 1070, 1012; **m.p.** 109–112 °C; **TLC** R_f: 0.25 (4:1 EtOAc/petrol)

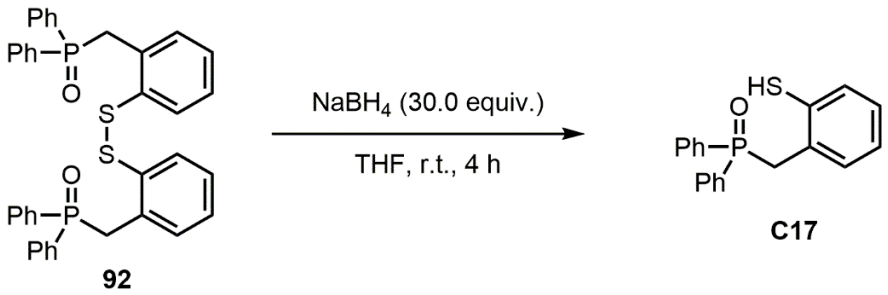
((Disulfanediylbis(2,1-phenylene))bis(methylene))bis(diphenylphosphine Oxide) (92)



According to an adapted literature procedure,[39] a solution of **91** (418 mg, 1.00 mmol), thiourea (114 mg, 1.50 mmol), $Ni(PCy_3)Cl_2$ (14 mg, 20 µmol) and picoline borane (3.2 mg, 30 µmol) in degassed NMP (1.0 mL) was heated to 60 °C and stirred for 16 hours under argon. A degassed 6.0 M aqueous solution of NaOH (2 mL) was added and the reaction mixture was heated to 90 °C and stirred for 24 hours. The reaction mixture was then cooled to room temperature, and a degassed 12.0 M aqueous solution of HCl (2 mL) was added. The organics were extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with a saturated brine solution (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude organic residue was purified by flash column chromatography (SiO_2, gradient from 3:97 MeOH/CH_2Cl_2 to 2:48 MeOH/CH_2Cl_2) to afford the title compound as a colourless solid (220 mg, 68%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.62 – 7.55 (m, 4H), 7.51 – 7.45 (m, 2H), 7.43 – 7.34 (m, 5H), 7.31 (apparent d, *J* = 7.7 Hz, 1H), 7.18 (apparent td, *J* = 7.5, 1.4 Hz, 1H), 7.10 (apparent tt, *J* = 7.5, 1.7 Hz, 1H), 3.67 (d, *J* = 13.7 Hz, 2H); **$^{13}C\{^1H\}$ NMR** (126 MHz, $CDCl_3$) δ_C 137.0 (d, *J* = 6.4 Hz, C_q), 133.5 (d, *J* = 2.4 Hz, CH), 133.4 (d, *J* = 8.0 Hz, C_q), 132.0 (d, *J* = 99.6 Hz, C_q), 131.9 (d, *J* = 2.5 Hz, CH), 131.2 (d, *J* = 9.2 Hz, CH), 128.9 (d, *J* = 2.7 Hz, CH), 128.5 (d, *J* = 12.0 Hz, CH), 127.9 (d, *J* = 3.2 Hz, CH), 35.1 (d, *J* = 65.8 Hz, CH_2);

$^{31}P\{^{1}H\}$ NMR (202 MHz, $CDCl_3$) δ_P 29.4; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{38}H_{33}O_2P_2S_2$ $[M + H]^+$: 647.1392, found 647.1387; **FTIR** (neat) ν_{max}/cm^{-1} 3047, 3040, 2941, 2901, 2892, 1582, 1542, 1461, 1442 1431, 1403, 1310 1287, 1222, 1179, 1161, 1120, 1089, 1066, 1011; **m.p.** 210–218 °C; **TLC** R_f: 0.33 (1:19 $MeOH/CH_2Cl_2$).

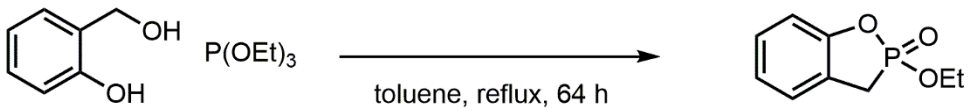
(2-Mercaptobenzyl)diphenylphosphine oxide (C17)



92 C17

To a solution of **92** (200 mg, 0.310 mmol) in degassed THF (10 mL) was added sodium borohydride (332 mg, 9.30 mmol) and the reaction mixture was stirred at room temperature for 4 hours. The reaction was then quenched with water (5 mL), and the organics were extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with a saturated brine solution (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, 3:7 EtOAc/petrol) to afford the title compound as a colourless solid (170 mg, 66%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.76 – 7.67 (m, 5H), 7.57 – 7.51 (m, 2H), 7.49 – 7.43 (m, 5H), 7.40 (apparent d, *J* = 7.7 Hz, 1H), 7.07 (apparent tt, *J* = 7.7, 2.1 Hz, 1H), 7.03 – 6.96 (m, 2H), 4.42 (s, 1H), 3.93 (d, *J* = 13.4 Hz, 2H); **$^{13}C\{^{1}H\}$ NMR** (126 MHz, $CDCl_3$) δ_C 133.4 (d, *J* = 2.7 Hz, CH), 132.6 (d, *J* = 6.4 Hz, C_q), 132.2 (d, *J* = 96.7 Hz, C_q), 132.1 (d, *J* = 3.3 Hz, C_q), 131.3 (d, *J* = 9.2 Hz, CH), 128.7 (d, *J* = 11.7 Hz, CH), 127.6 (d, *J* = 3.5 Hz, CH), 126.9 (d, *J* = 2.7 Hz, CH), 36.9 (d, *J* = 66.5 Hz, CH_2); **$^{31}P\{^{1}H\}$ NMR** (202 MHz, $CDCl_3$) δ_P 31.4; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{19}H_{18}OPS$ $[M + H]^+$: 325.0806, found 325.0810; **FTIR** (neat) ν_{max}/cm^{-1} 3052, 3023, 2947, 2907, 2445, 1588, 1565, 1467, 1436, 1406, 1229, 1171, 1144, 1121, 1102; **m.p.** 116–118 °C.

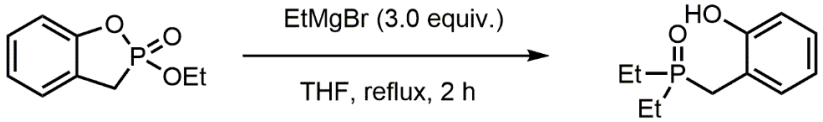
2-Ethoxy-3H-benzo[d][1,2]oxaphosphole 2-Oxide (93)



93

A solution of 2-hydoxybenzyl alcohol (6.21 g, 50.0 mmol) and triethylphosphite (8.57 mL, 50. 0 mmol) in toluene (100 mL) was heated to reflux and stirred for 64 hours. The reaction mixture was then concentrated *in vacuo*. The residue wass purified by Kugelrohr distillation, to afford the title compound as a colourless solid (8.14 g, 74%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.26 – 7.18 (m, 2H), 7.06 – 6.96 (m, 2H), 4.34 – 4.20 (m, 2H), 3.21 – 3.02 (m, 2H), 1.36 (apparent t, *J* = 7.1 Hz, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 153.3 (d, *J* = 12.0 Hz, C_q), 129.1 (s, CH), 127.3 (d, *J* = 18.9 Hz, CH), 123.4 (d, *J* = 1.3 Hz, CH), 122.6 (d, *J* = 3.6 Hz, C_q), 113.4 (d, *J* = 12.4 Hz, CH), 63.4 (d, *J* = 7.0 Hz, CH_2), 24.6 (d, *J* = 124.2 Hz, CH_2), 16.5 (d, *J* = 5.8 Hz, CH_3); **^{31}P{^{1}H} NMR** (162 MHz, $CDCl_3$) δ_P 45.8; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_9H_{11}NaO_3P$ $[M + H]^+$: 221.0338, found 221.0337. Data are consistent with those reported in the literature.[40]

Diethyl(2-hydroxybenzyl)phosphine Oxide (C18)

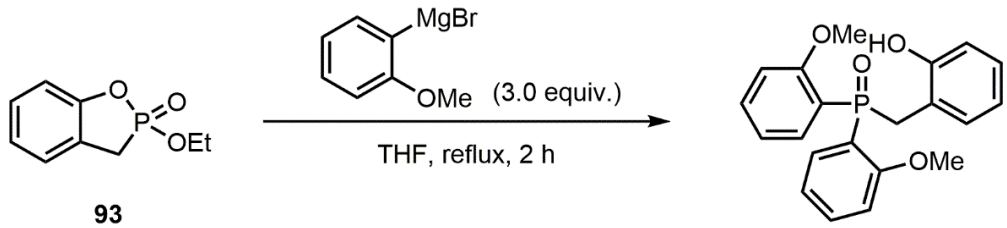


93 **C18**

From an adapted literature procedure,[40] in a microwave vial, to a solution of **93** (279 mg, 1.41 mmol) in anhydrous THF (2 mL) was added a 3.0 M solution of ethylmagnesium bromide in Et_2O (1.41 mL, 4.24 mmol). The vial was capped, and the reaction was heated to 60 °C and stirred for 2 hours. The reaction mixture was then cooled to room temperature, and the reaction was quenched with water (5 mL), then acidified with a 2.0 M aqueous HCl solution (5 mL) and the organics were extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with a saturated brine solution (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by trituration, using Et_2O to afford the title compound as a colourless solid (293 mg, 98%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.18 (apparent t, *J* = 7.7 Hz, 1H), 7.01 (apparent dd, *J* = 8.0, 1.3 Hz, 1H),

6.97 (apparent d, *J* = 7.5 Hz, 2H), 6.84 (apparent t, *J* = 7.4 Hz, 1H), 3.14 (d, *J* = 12.0 Hz, 2H), 1.78 (dqd, *J* = 11.5, 7.7, 4.1 Hz, 4H), 1.17 (dt, *J* = 16.9, 7.7 Hz, 6H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 156.5 (d, *J* = 3.7 Hz, C_q), 131.1 (d, *J* = 5.6 Hz, C_q), 129.2 (d, *J* = 2.3 Hz, CH), 120.8 (d, *J* = 1.2 Hz, CH), 119.9 – 119.8 (m, 2 × 1.40 CH), 32.3 (d, *J* = 61.0 Hz, CH_2), 19.7 (d, *J* = 65.5 Hz, CH_2), 5.8 (d, *J* = 5.3 Hz, CH_3); **^{31}P{^{1}H} NMR** (202 MHz, $CDCl_3$) δ_P 58.9; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{11}H_{17}NaO_2P$ $[M + Na]^+$: 235.0858, found 235.0858; **FTIR** (neat) ν_{max}/cm^{-1} 3041, 2973, 2942, 2912, 2882, 2709, 2610, 1595, 1506, 1455, 1390, 1374, 1279, 1248, 1176, 1106, 1086, 1039, 1028; **m.p.** 109–114 °C.

(2-Hydroxybenzyl)bis(2-methoxyphenyl)phosphine Oxide (C19)

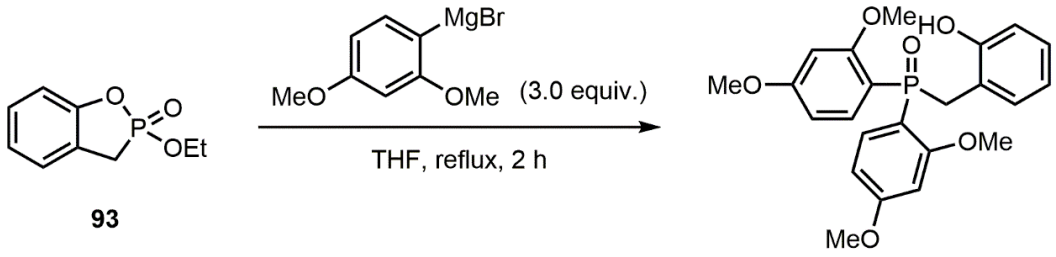


93 **C19**

From an adapted literature procedure,[40] in a microwave vial, to a solution of **93** (279 mg, 1.41 mmol) in anhydrous THF (2 mL) was added a 0.90 M solution of 2-methoxyphenylmagnesium bromide in THF (4.71 mL, 4.24 mmol). The vial was capped, and the reaction was heated to 60 °C and stirred for 2 hours. The reaction mixture was then cooled to room temperature, and the reaction was quenched with water (5 mL), then acidified with a 2.0 M aqueous HCl solution (5 mL) and the organics were extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with a saturated brine solution (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by trituration, using Et_2O to afford the title compound as a colourless solid (483 mg, 94%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.53 (ddd, *J* = 13.5, 7.6, 1.8 Hz, 2H), 7.50 – 7.45 (m, 2H), 7.02 (apparent tt, *J* = 7.4, 1.9 Hz, 1H), 6.99 – 6.91 (m, 5H), 6.72 (apparent d, *J* = 7.5 Hz, 1H), 6.60 (apparent t, *J* = 7.4 Hz, 1H), 4.03 (d, *J* = 15.2 Hz, 2H), 3.84 (s, 6H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 160.8 (d, *J* = 3.3 Hz, C_q), 156.6 (d, *J* = 4.1 Hz, C_q), 134.3 (d, *J* = 7.2 Hz, CH), 134.2 (d, *J* = 1.9 Hz, CH), 131.1 (d, *J* = 7.2 Hz, CH), 128.5 (d, *J* = 3.4 Hz, CH), 121.3 (d, *J* = 9.1 Hz, C_q), 121.0 (d, *J* = 11.7 Hz, CH), 120.2 (d, *J* = 2.4 Hz, CH), 119.1 (d, *J* = 2.7 Hz, CH), 118.8 (d, *J* = 101.8 Hz, C_q), 111.0 (d, *J* = 6.5 Hz, CH), 55.7

(s, CH_3), 34.5 (d, J = 70.0 Hz, CH_2); **$^{31}P\{^1H\}$ NMR** (202 MHz, $CDCl_3$) δ_P 39.6; **HRMS** (ESI-TOF) m/z calc'd for $C_{21}H_{22}O_4P$ $[M + H]^+$: 369.1250, found 369.1256; **FTIR** (neat) ν_{max}/cm^{-1} 3060, 2968, 2939, 2838, 2738, 1590, 1574, 1475, 1456, 1430, 1278, 1249, 1238, 1168, 1168, 1135, 1091, 1071, 1044, 1024, 1011; **m.p.** 205–214 °C.

Bis(2,4-dimethoxyphenyl)(2-hydroxybenzyl)phosphine Oxide (C20)

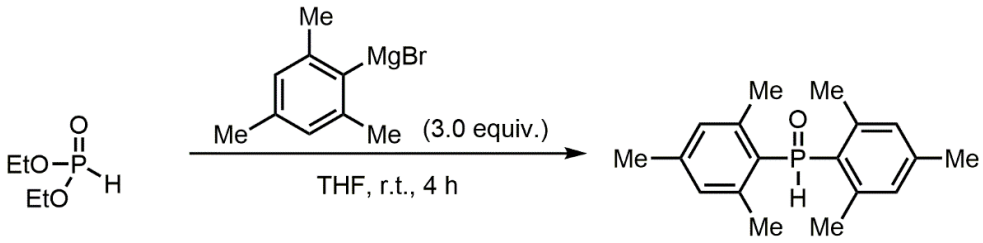


93 **C20**

From an adapted literature procedure,[40] to a solution of 1-bromo-2,4-dimethoxybenzene (920 mg, 4.24 mmol) in anhydrous THF (4 mL) was added magnesium turnings (103 mg, 4.24 mmol) then iodine (1 crystal) and the reaction mixture was stirred for 1 hours. This solution was then added *via* syringe to a solution of **93** (279 mg, 1.41 mmol) in anhydrous THF (2 mL) in a microwave vial. The vial was capped, and the reaction was heated to 60 °C and stirred for 2 hours. The reaction mixture was then cooled to room temperature, and the reaction was quenched with water (5 mL), then acidified with a 2.0 M aqueous HCl solution (5 mL) and the organics were extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with a saturated brine solution (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by trituration, using Et_2O to afford the title compound as a colourless solid (282 mg, 47%). **^1H NMR** (400 MHz, $CDCl_3$) δ_H 10.20 (s, 1H), 7.46 – 7.37 (m, 2H), 7.02 (apparent t, J = 7.7 Hz, 2H), 6.92 (apparent d, J = 7.6 Hz, 1H), 6.73 (apparent d, J = 7.5 Hz, 2H), 6.62 (apparent t, J = 7.3 Hz, 1H), 6.49 – 6.43 (m, 4H), 3.95 (d, J = 15.3 Hz, 2H), 3.84 (s, 6H), 3.81 (s, 6H); **$^{13}C\{^1H\}$ NMR** (101 MHz, $CDCl_3$) δ_C 164.7 (d, J = 2.3 Hz, C_q), 162.4 (d, J = 4.5 Hz, C_q), 156.7 (d, J = 4.1 Hz, C_q), 135.9 (d, J = 8.0 Hz, CH), 131.1 (d, J = 7.2 Hz, CH), 128.3 (d, J = 3.4 Hz, CH), 121.7 (d, J = 8.8 Hz, C_q), 120.1 (d, J = 1.7 Hz, CH), 119.0 (d, J = 2.9 Hz, CH), 110.9 (d, J = 107.9 Hz, C_q), 105.1 (d, J = 12.3 Hz, CH), 98.6 (d, J = 7.8 Hz, CH), 55.7 (s, CH_3), 55.6 (s, CH_3), 34.9

(d, J = 71.1 Hz, CH_2); **$^{31}P\{^1H\}$ NMR** (162 MHz, $CDCl_3$) δ_P 39.2; **HRMS** (ESI-TOF) m/z calc'd for $C_{23}H_{25}NaO_6P$ $[M + Na]^+$ = 451.1281, found 451.1277; **FTIR** (neat) ν_{max}/cm^{-1} 2944, 2839, 2732, 2628, 1594, 1572, 1494, 1456, 1435, 1403, 1313, 1285, 1251, 1208, 1170, 1147, 1115, 1086, 1071, 1023; **m.p.** 174–181 °C.

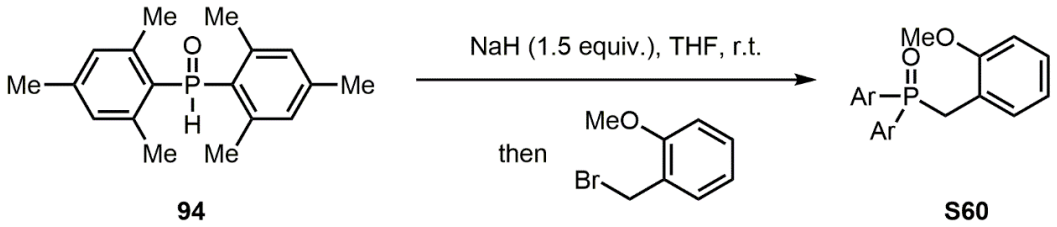
Dimesitylphosphine Oxide (94)



94

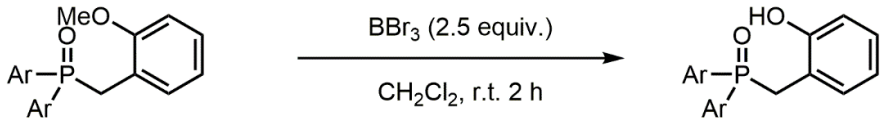
Under an argon atmosphere, to a solution of diethylphosphite (1.29 mL, 10.0 mmol) in THF (30 mL) was added a 1.0 M solution of 2-mesitylmagnesium bromide in THF (30 mL, 30 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 hours. The reaction was the quenched with a 1.0 M aqueous HCl solution (50 mL) at 0 °C and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with a saturated brine solution, dried over $MgSO_4$ and concentrated *in vacuo* and the residue was purified by recrystalization from hexane to afford the title compound as a colourless solid (2.32 g, 81%). **^1H NMR** (400 MHz, $CDCl_3$) δ_H 8.25 (d, J = 476.1 Hz, 1H), 6.85 (d, J = 3.9 Hz, 4H), 2.39 (s, 12H), 2.28 (s, 6H); **$^{13}C\{^1H\}$ NMR** (101 MHz, $CDCl_3$) δ_C 142.0 (d, J = 2.6 Hz, C_q), 141.8 (d, J = 10.5 Hz, C_q), 130.6 (d, J = 10.7 Hz, CH), 126.5 (d, J = 100.0 Hz, C_q), 21.3 (s, CH_3), 20.9 (d, J = 7.8 Hz, CH_3); **$^{31}P\{^1H\}$ NMR** (162 MHz, $CDCl_3$) δ_P 10.2; **HRMS** (ESI-TOF) m/z calc'd for $C_{18}H_{24}OP$ $[M + H]^+$: 287.1559, found 287.1558. Data are consistent with those reported in the literature.[41]

Dimesityl(2-methoxybenzyl)phosphine Oxide (S60)



To a solution of dimesitylphosphine oxide **94** (286 mg, 1.00 mmol) in anhydrous THF (7 mL) was added sodium hydride (60% *w*/*w* dispersion in oil, 60 mg, 1.5 mmol) at room temperature. The reaction mixture was stirred for 30 minutes, after which **23** (241 mg, 1.20 mmol) in anhydrous THF (2 mL) was added and the reaction mixture was stirred for a further 2 hours. The reaction mixture was then heated to 50 °C and stirred for a further 16 hours, after which the reaction was quenched with water (2 mL). The organics were extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were washed with a saurated brine solution (20 mL) and concentrated *in vacuo*. The crude organic residue was purified by trituration with Et_2O to afford the title compound as a colourless solid (304 mg, 75%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.47 (apparent dt, *J* = 7.5, 2.1 Hz, 2H), 7.14 (apparent tt, *J* = 7.8, 2.0 Hz, 1H), 6.87 (apparent t, *J* = 7.5 Hz, 1H), 6.70 (d, *J* = 3.5 Hz, 4H), 6.51 (apparent d, *J* = 8.2 Hz, 1H), 3.84 (d, *J* = 12.4 Hz, 2H), 3.19 (s, 3H), 2.22 (s, 6H), 2.20 (s, 12H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 157.3 (d, *J* = 5.3 Hz, C_q), 141.6 (d, *J* = 10.0 Hz, C_q), 140.2 (d, *J* = 2.7 Hz, C_q), 133.5 (d, *J* = 4.6 Hz, CH), 130.6 (d, *J* = 93.7 Hz, C_q), 130.5 (d, *J* = 11.1 Hz, CH), 128.1 (d, *J* = 3.6 Hz, CH), 120.7 (d, *J* = 8.5 Hz, C_q), 120.1 (d, *J* = 3.4 Hz, CH), 109.6 (d, *J* = 3.1 Hz, CH), 54.6 (s, CH_3), 36.3 (d, *J* = 60.7 Hz, CH_2), 22.8 (d, *J* = 3.9 Hz, CH_3), 21.0 (d, *J* = 1.5 Hz, CH_3); **^{31}P{^{1}H} NMR** (162 MHz, $CDCl_3$) δ_P 36.7; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{26}H_{32}O_2P$ $[M + H]^+$: 407.2134, found 407.2128; **FTIR** (neat) ν_{max}/cm^{-1} 2999, 2965, 2925, 2855, 2836, 1602, 1494, 1460, 1439, 1396, 1289, 1244, 1187, 1167, 1140, 1090, 1050, 1027; **m.p.** 203–205 °C.

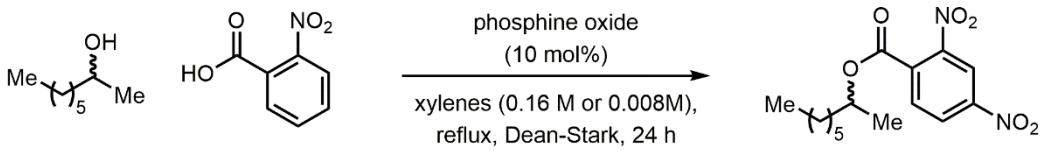
(2-Hydroxybenzyl)dimesitylphosphine Oxide (C21)



S60 **C21**

To a solution of **S60** (280 mg, 0.689 mmol) in CH_2Cl_2 (5 mL) was added a 1.0 M solution of boron tribromide in CH_2Cl_2 (1.72 mL, 1.72 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 hours. The reaction was then quenched with water (5 mL) at 0 °C and the organics were extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with a saturated aqueous $NaHCO_3$ solution (20 mL) then a saturated brine solution (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude organic residue was purified by trituration with Et_2O to afford the title compound as a colourless solid (210 mg, 78%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.08 (apparent ddt, *J* = 9.3, 7.3, 1.9 Hz, 1H), 6.99 (apparent dd, *J* = 8.0, 1.3 Hz, 1H), 6.77 (d, *J* = 3.7 Hz, 4H), 6.53 (apparent tt, *J* = 7.4, 1.2 Hz, 1H), 6.30 (apparent dt, *J* = 7.5, 2.0 Hz, 1H), 3.84 (d, *J* = 11.4 Hz, 2H), 2.26 (s, 12H), 2.24 (s, 6H); **^{13}C{^{1}H} NMR** (101 MHz, CDC_3) δ_C 156.9 (d, *J* = 3.8 Hz, C_q), 141.5 (d, *J* = 2.4 Hz, C_q), 141.2 (d, *J* = 10.2 Hz, C_q), 131.8 (d, *J* = 5.8 Hz, CH), 131.2 (d, *J* = 11.4 Hz, CH), 128.9 (d, *J* = 3.2 Hz, CH), 128.3 (d, *J* = 94.8 Hz, C_q), 121.2 (d, *J* = 8.8 Hz, C_q), 120.4 (d, *J* = 2.4 Hz, CH), 119.3 (d, *J* = 3.0 Hz, CH), 40.2 (d, *J* = 60.9 Hz, CH_2), 22.7 (d, *J* = 4.3 Hz, CH_3), 21.1 (s, CH_3); **^{31}P{^{1}H} NMR** (162 MHz, $CDCl_3$) δ_P 48.2; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{25}H_{30}O_2P$ $[M + H]^+$: 393.1978, found 393.1978; **FTIR** (neat) ν_{max}/cm^{-1} 3023, 2966, 2919, 2849, 1605, 1485, 1452, 1396, 1381, 1244, 1141, 1122, 1070, 1035; **m.p.** 210–212 °C.

Evaluation of Phosphine Oxides as Organocatalysts (tables 9–11)

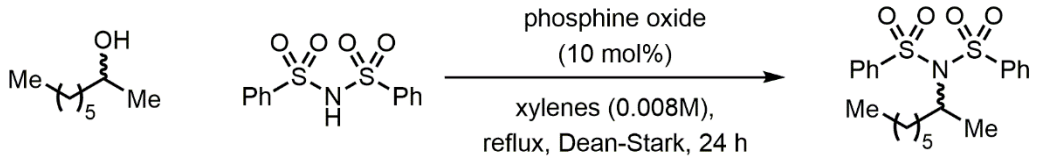


A suspension of (±)-2-octanol (316 µL, 2.00 mmol), 2-nitrobenzoic acid (334 mg, 2.00 mmol) and phosphine oxide (0.20 mmol) in xylenes (12.5 mL) was heated to reflux in a Dean-Stark apparatus, and stirred for 24 hours. The reaction mixture was cooled to room temperature, 1,1,2,2-tetrachloroethane (211 µL, 2.00 mmol) was added as an NMR standard and the yield was determined by ^{1}H NMR.

Evaluation of Phosphine Oxides as Organocatalysts (tables 12–13)

A suspension of (±)-2-octanol (158 µL, 1.00 mmol), 2-nitrobenzoic acid (167 mg, 1.00 mmol) and phosphine oxide (0.10 mmol) in xylenes (12.5 mL) was heated to reflux in a Dean-Stark apparatus, and stirred for 24 hours. The reaction mixture was cooled to room temperature, 1,1,2,2-tetrachloroethane (211 µL, 2.00 mmol) was added as an NMR standard and the yield was determined by ^{1}H NMR.

Evaluation of Phosphine Oxides as Organocatalysts (tables 12–13)

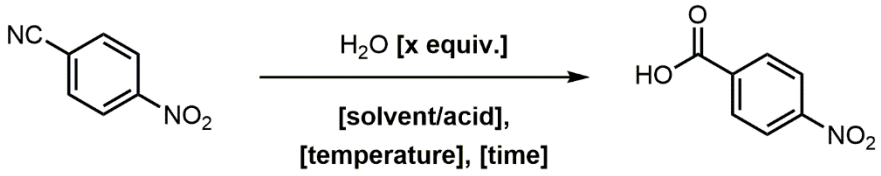


A suspension of (±)-2-octanol (158 µL, 1.00 mmol), dibenzenesulfonimide (297 mg, 1.00 mmol) and phosphine oxide (0.10 mmol) in xylenes (12.5 mL) was heated to reflux in a Dean-Stark apparatus, and stirred for 24 hours. The reaction mixture was cooled to room temperature, 1,1,2,2-tetrachloroethane (211 µL, 2.00 mmol) was added as an NMR standard and the yield was determined by ^{1}H NMR.

Chapter 3

Synthesis of ^{18}O-Labelled Alcohols from Unlabelled Alcohols Using a Mitsunobu Esterification-Based Strategy

General Procedure for the Hydrolysis of 4-Nitrobenzonitrile (table 1)

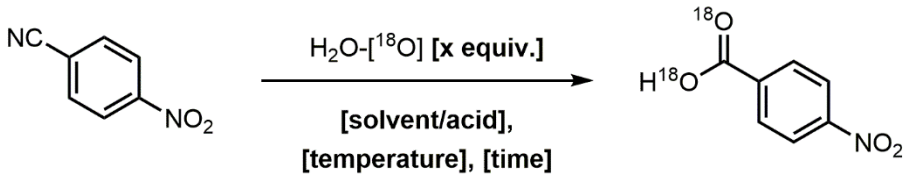


Reactions were run at scales varying from 0.50 mmol to 10.0 mmol. To a Biotage® microwave vial was added 4-nitrobenzonitrile (1 equiv.), the designated solvent and anhydrous acid source then H_2O (2.20–2.50 equiv.) The microwave vial was capped, heated to the indicated temperature and stirred for the indicated amount of time.

Entries 1–5: Yields were determined by ^1H NMR spectroscopy, using 1,1,2,2-tetrachloroethane as an internal standard.

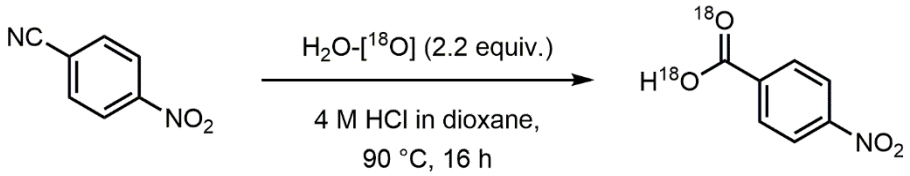
Entries 6–8: Yields are quoted as isolated yields. The reaction mixture was diluted with $CHCl_3$ (2 × volume of reaction solvent) and the precipitate was collected by filtration. The filter cake was washed with $CHCl_3$ and the solid was dried under vacuum, to afford the pure 4-nitrobenzoic acid.

General Procedure for the Hydrolysis of 4-Nitrobenzonitrile (table 2)



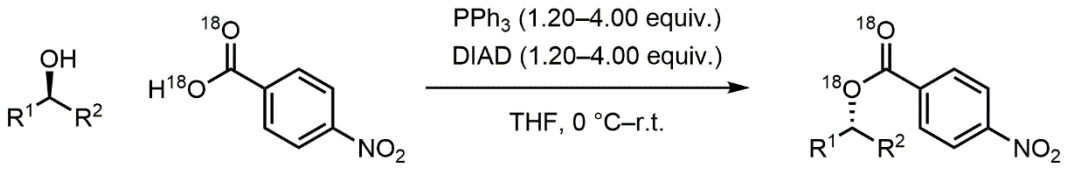
A 0.5–2 mL Biotage® microwave vial (Biotage® product code: 352016) containing a magnetic stirrer bar was dried in an oven at 130 °C for 24 hours. 4-Nitrobenzonitrile (148 mg, 1.00 mmol) was then added and the vial was capped with a Biotage® cap with septum (Biotage® product code: 352298). The vial was purged with argon and allowed to cool to room temperature under an argon atmosphere. 4 M HCl in dioxane (0.4 mL) was added followed by H_2O-[^{18}O] (2.00–2.50 equiv.). The reaction mixture was heated to 90 °C and stirred for 16 hours. The reaction mixture was then cooled to room temperature, diluted with $CHCl_3$ (0.8 mL) and the precipitate was collected by filtration. The filter cake was washed with $CHCl_3$ and the solid was dried under vacuum, to afford pure ^{18}O-enriched 4-nitrobenzoic acid. Yields are quoted as isolated yields.

Preparation of ^{18}O-Enriched 4-Nitrobenzoic acid (2)



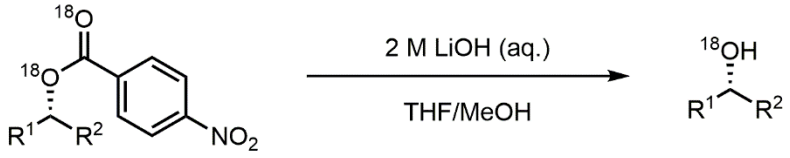
A 10–20 mL Biotage® microwave vial (Biotage® product code: 354833) containing a magnetic stirrer bar was dried in an oven at 130 °C for 24 hours. 4-Nitrobenzonitrile (3.36 g, 22.7 mmol) was then added and the vial was capped with a Biotage® cap with septum (Biotage® product code: 352298). The vial was purged with argon then allowed to cool to room temperature under an argon atmosphere. 4 M HCl in dioxane (9 mL) was added *via* the septum followed by H_2O-[^{18}O] (900 μL, 50.0 mmol). The reaction mixture was heated to 90 °C and stirred for 16 hours. The reaction mixture was cooled to room temperature, $CHCl_3$ (18 mL) was then added and the precipitate was collected by filtration. The filter cake was washed with $CHCl_3$ and the solid was dried under vacuum, to afford the title compound as an off-white solid (3.46 g, 89%). **^{1}H NMR** (400 MHz, CD_3OD) δ_H 8.33 (d, *J* = 8.9 Hz, 2H), 8.24 (d, *J* = 8.9 Hz, 2H); **^{13}C{^{1}H} NMR** (101 MHz, CD_3OD) δ_C 167.5 (C_q), 152.0 (C_q), 137.6 (C_q), 131.9 (CH), 124.5 (CH); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_7H_4N^{16}O_2{}^{18}O_2$ [M − H]$^-$: 170.0231; found 170.0233. also *m*/*z* calc'd for $C_7H_4N^{16}O_3{}^{18}O$ [M − H]$^-$: 168.0188; found 168.0188. The ratio of relative peak intensities for the relevant isotopologues was 93:7 ($C_7H_4N^{16}O_2{}^{18}O_2$:$C_7H_4N^{16}O_3{}^{18}O$). No *m*/*z* corresponding to the unlabelled substrate was detected; **m.p.** 236–239 °C (lit. m.p. = 237–239 °C).[42] Data are consistent with those reported in the literature.[43]

General Procedure for the Synthesis of ^{18}O-Enriched Esters



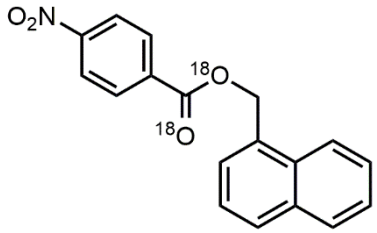
To a solution of alcohol (1.00 equiv.), 4-nitrobenzoic acid-[$^{18}O_2$] (1.00–4.00 equiv.) and triphenylphosphine (1.20–4.00 equiv.) in THF (2–10 mL) was added diisopropyl azodicarboxylate (1.20–4.00 equiv.) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2–48 hours. The reaction mixture was then diluted with a saturated aqueous $NaHCO_3$ solution (10–20 mL) and extracted with EtOAc (3 × 10–20 mL). The combined organic extracts were washed with a saturated brine solution (10–20 mL) dried over $MgSO_4$ and concentrated. The crude residue was purified by flash column chromatography to afford the ^{18}O-enriched ester.

General Procedure for the Hydrolysis of ^{18}O-Enriched Esters



To a solution of ^{18}O-labelled ester (1.00 equiv.) in a THF/MeOH (1–10 mL) solvent mixture was added a 2.0 M aqueous LiOH solution (2.00–3.00 equiv.) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2–24 hours. The reaction mixture was then diluted with a 1.0 M aqueous NaOH solution (10–20 mL) and extracted with EtOAc (3 × 10–20 mL). The combined organic extracts were washed with a saturated brine solution (10–20 mL), dried over $MgSO_4$ and concentrated. When required, the reaction was purified by flash column chromatography.

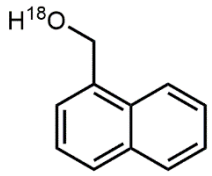
Naphthalen-1-ylmethyl 4-Nitrobenzoate-[$^{18}O_2$] (S61)



S61

Synthesised according to the general procedure using 1-naphthalenemethanol (79 mg, 0.50 mmol), 4-nitrobenzoic acid-[$^{18}O_2$] (86 mg, 0.50 mmol), triphenylphosphine (157 mg, 0.600 mmol) and diisopropyl azodicarboxylate (120 µL, 0.600 mmol) in THF (2 mL). The reaction mixture was stirred at room temperature for 4 hours. Purification by flash column chromatography (SiO_2, 3:17 Et_2O:petrol) afforded the title compound as a colourless solid (121 mg, 78%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 8.25 (d, *J* = 9.1 Hz, 2H), 8.21 (d, *J* = 9.1 Hz, 2H), 8.13 – 8.07 (m, 1H), 7.95 – 7.88 (m, 2H), 7.64 (dd, *J* = 7.0, 1.3 Hz, 1H), 7.62 – 7.53 (m, 2H), 7.50 (dd, *J* = 8.3, 7.0 Hz, 1H), 5.87 (s, 2H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 164.7 (C_q), 150.7 (C_q), 135.6 (C_q), 134.0 (C_q), 131.9 (C_q), 131.0 (C_q), 130.9 (CH), 130.0 (CH), 129.1 (CH), 128.2 (CH), 127.0 (CH), 126.3 (CH), 125.5 (CH), 123.7 (CH), 123.5 (CH), 66.2 (CH_2); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{18}H_{13}NaN^{16}O_2{}^{18}O_2$ $[M + Na]^+$: 334.0822; found 334.0819. also *m*/*z* calc'd for $C_{18}H_{13}NaN^{16}O_3{}^{18}O_1$ $[M + Na]^+$: 332.0779; found 332.0788. The ratio of relative peak intensities for the relevant isotopologues was 92:8 ($C_{18}H_{13}NaN^{16}O_2{}^{18}O_2$:$C_{18}H_{13}NaN^{16}O_3{}^{18}O_1$); **m.p.** 120–122 °C (lit.[44] m,p, = 121 °C); **TLC** R_f: 0.80 (4:1 Et_2O/petrol). Data are consistent with those reported in the literature.[44]

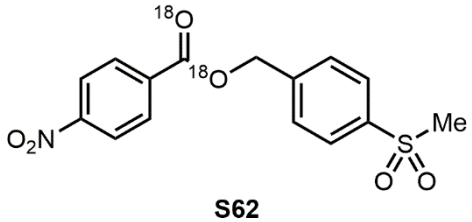
1-Naphthalenemethanol-[^{18}O] (89a)



89a

Synthesised according to the general procedure using **S61** (40 mg, 0.13 mmol) in 1:1 THF/MeOH (2 mL) and a 2.0 M aqueous LiOH solution (190 µL, 0.380 mmol). The reaction mixture was stirred for 2 hours. No additional purification procedures were required, and the title compound was afforded as a colourless solid (19 mg, 93%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.2 Hz, 1H), 7.91 – 7.86 (m, 1H), 7.84 – 7.80 (m, 1H), 7.58 – 7.49 (m, 3H), 7.46 (dd, *J* = 8.2, 7.0 Hz, 1H), 5.16 (s, 2H), 1.86 (s, 1H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 136.4(C_q), 133.9(C_q), 131.4(C_q), 128.8 (CH), 128.7 (CH), 126.5 (CH), 126.0 (CH), 125.5 (CH), 125.5 (CH), 123.8 (CH), 63.8 (CH_2); **HRMS** (ESI-TOF) *m/z* calc'd for $C_{11}H_{10}Na^{18}O$ $[M + Na]^+$: 183.0666; found 183.0672. also *m/z* calc'd for $C_{11}H_{10}Na^{16}O$ $[M + Na]^+$: 181.0624; found 181.0641. The ratio of relative peak intensities for the relevant isotopologues was 94:6 ($C_{11}H_{10}Na^{18}O$: $C_{11}H_{10}Na^{16}O$); **m.p.** 62–64 °C (lit.[45] m.p. 61–63 °C); **TLC** R_f: 0.50 (4:1 Et_2O/petrol). Data are consistent with those reported in the literature.[46]

(4-(Methylsulfonyl)phenyl)methanyl 4-Nitrobenzoate-[$^{18}O_2$] (S62)

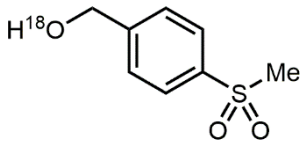


S62

Synthesised according to the general procedure using 4-(methylsulfonyl)benzyl alcohol (93 mg, 0.50 mmol), 4-nitrobenzoic acid-[$^{18}O_2$] (86 mg, 0.50 mmol), triphenylphosphine (157 mg, 0.600 mmol) and diisopropyl azodicarboxylate (120 µL, 0.600 mmol) in THF (2 mL). The reaction mixture was stirred at room temperature for 4 hours. Purification by flash column chromatography (SiO_2,

9:11 EtOAc:petrol) afforded the title compound as a colourless solid (68 mg, 40%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 9.1 Hz, 2H), 8.25 (d, *J* = 9.1 Hz, 2H), 8.00 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 8.5 Hz, 2H), 5.49 (s, 2H), 3.07 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 164.4 (C_q), 151.0 (C_q), 141.6 (C_q), 140.9 (C_q), 135.0 (C_q), 131.0 (CH), 129.0 (CH), 128.1 (CH), 123.9 (CH), 66.4 (CH_2), 44.7 (CH_3); **HRMS** (ESI-TOF) *m/z* calc'd for $C_{15}H_{17}N_2{}^{16}O_4{}^{18}O_2S$ $[M + NH_4]^+$: 357.0887; found 357.0883. also *m/z* calc'd for $C_{15}H_{17}N_2{}^{16}O_5{}^{18}OS$ $[M + NH_4]^+$: 355.0844; found 355.0846. The ratio of relative peak intensities for the relevant isotopologues was 91:9 ($C_{15}H_{17}N_2{}^{16}O_4{}^{18}O_2S$:$C_{15}H_{17}N_2{}^{16}O_5{}^{18}OS$); **FTIR** (neat) ν_{max}/cm^{-1} 3112, 3022, 2920, 1691, 1603, 1524, 1322, 1247, 1145, 1089, 1010; **m.p.** 156–158 °C; **TLC** R_f: 0.24 (7:3 EtOAc/petrol).

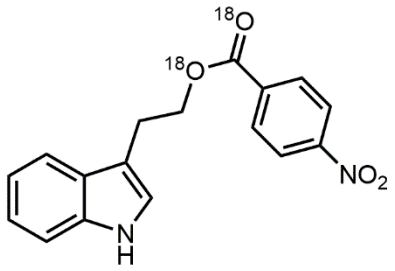
(4-(Methylsulfonyl)phenyl)methanol-^{18}O (89b)



89b

Synthesised according to the general procedure using **S62** (62 mg, 0.18 mmol) in 1:1 THF/MeOH (2 mL) and a 2.0 M aqueous LiOH solution (270 µL, 0.520 mmol). The reaction mixture was stirred for 2 hours. No additional purification procedures were required, and the title compound was afforded as a colourless solid (30 mg, 90%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 4.82 (s, 2H), 3.04 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ 147.4 (C_q), 139.6 (C_q), 127.7 (CH), 127.4 (CH), 64.3 (CH_2), 44.7 (CH_3); **HRMS** (ESI-TOF) *m/z* calc'd for $C_8H_{10}Na^{16}O_2{}^{18}OS$ $[M + Na]^+$: 211.0285, found 211.0285, also *m/z* calc'd for $C_8H_{10}Na^{16}O_3S$ $[M + Na]^+$: 209.0243; found 209.0247. The ratio of relative peak intensities for the relevant isotopologues was 95:5 ($C_8H_{10}Na^{16}O_2{}^{18}OS$:$C_8H_{10}Na^{16}O_3S$); **m.p.** 82–86 °C (lit.[47] m.p. 82–84 °C); **TLC** R_f: 0.62 (7:3 EtOAc/petrol). Data are consistent with those reported in the literature.[47]

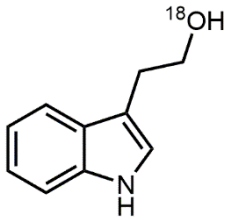
2-(1*H*-Indol-3-yl)ethyl 4-Nitrobenzoate-[^{18}O]$_2$ (S63)



S63

Synthesised according to the general procedure using 3-(2-hydroxyethyl)indole (81 mg, 0.50 mmol), 4-nitrobenzoic acid-[$^{18}O_2$] (86 mg, 0.50 mmol), triphenylphosphine (157 mg, 0.600 mmol) and diisopropyl azodicarboxylate (120 µL, 0.600 mmol) in THF (2 mL). The reaction mixture was stirred at room temperature for 4 hours. Purification by flash column chromatography (SiO_2, 11:9 CH_2Cl_2:petrol) afforded the title compound as a bright orange solid (82 mg, 51%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 9.0 Hz, 2H), 8.18 (d, *J* = 9.0 Hz, 2H), 8.04 (s, 1H), 7.67 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.39 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.23 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.18 – 7.09 (m, 2H), 4.66 (t, *J* = 7.1 Hz, 3H), 3.27 (td, *J* = 7.1, 1.0 Hz, 2H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ 164.9 (C_q), 150.7 (C_q), 136.4 (C_q), 135.9 (C_q), 130.9 (CH), 127.5 (C_q), 123.7 (CH), 122.5 (CH), 122.2 (CH), 119.8 (CH), 118.9 (CH), 111.9 (C_q), 111.4 (CH), 66.1 (CH_2), 24.9 (CH_2); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{17}H_{14}N_2Na^{16}O_2{}^{18}O_2$ [M + Na]$^+$: 337.0931; found 337.0935. also *m*/*z* calc'd for $C_{17}H_{14}N_2Na^{16}O_3{}^{18}O$ [M + Na]$^+$: 335.0888; found 335.0885. The ratio of relative peak intensities for the relevant isotopologues was 92:8 ($C_{17}H_{14}N_2Na^{16}O_2{}^{18}O_2$:$C_{17}H_{14}N_2Na^{16}O_3{}^{18}O$); **FTIR** (neat) ν_{max}/cm^{-1} 3373, 1679, 1599, 1362, 1311, 1222, 1099, 1011; **m.p.** 151–152 °C; **TLC** R_f: 0.56 (4:1 Et_2O/petrol).

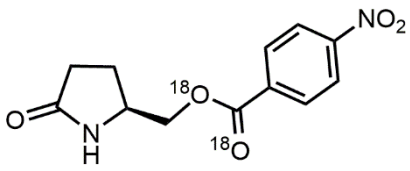
2-(1*H*-Indol-3-yl)ethanol-[^{18}O] (89c)



89c

Synthesised according to the general procedure using **S63** (50 mg, 0.16 mmol) in 1:1 THF/MeOH (2 mL) and a 2.0 M aqueous LiOH solution (240 µL, 0.480 mmol). The reaction mixture was stirred for 2 hours before workup. No additional purification procedures were required, and the title compound was afforded as a colourless solid (24 mg, 92%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.04 (s, 1H), 7.63 (apparent dt, *J* = 7.9, 1.0 Hz, 1H), 7.38 (apparent dt, *J* = 8.2, 1.0 Hz, 1H), 7.24 – 7.19 (m, 1H), 7.17 – 7.07 (m, 2H), 3.92 (t, *J* = 6.3 Hz, 2H), 3.05 (td, *J* = 6.3, 0.8 Hz, 2H), 1.60 (s, 1H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 136.6 (C_q), 127.6 (C_q), 122.6 (CH), 122.4 (CH), 119.6 (CH), 119.0 (CH), 112.5 (C_q), 111.4 (CH), 62.8 (CH_2), 28.9 (CH_2); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{10}H_{12}N^{18}O$ $[M + H]^+$: 164.0956; found 164.0960. also *m*/*z* calc'd for $C_{10}H_{12}N^{16}O$ $[M + H]^+$: 162.0913; found 162.0920. The ratio of relative peak intensities for the relevant isotopologues was 96:4 ($C_{10}H_{12}N^{18}O$:$C_{10}H_{12}N^{16}O$); **m.p.** 58–60 °C (lit.[48] m.p. 56–59 °C); **TLC** R_f: 0.24 (4:1 Et_2O/petrol). Data are consistent with those reported in the literature.[49]

(*S*)-(5-Oxopyrrolidin-2-yl)methyl 4-Nitrobenzoate-[^{18}O]$_2$ (S64)

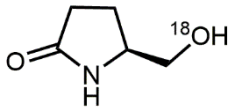


S64

Synthesised according to the general procedure using (*S*)-(+)-5-hydroxymethyl-2-pyrrolidinone (115 mg, 1.00 mmol), 4-nitrobenzoic acid-[$^{18}O_2$] (216 mg, 1.20 mmol), triphenylphosphine (315 mg, 1.20 mmol) and diisopropyl azodicarboxylate (236 µL, 1.200 mmol) in THF (2 mL). The reaction mixture was stirred at room temperature for 48 hours. Purification by flash column

chromatography (SiO_2, 4:96 MeOH:EtOAc) afforded the title compound as a colourless solid (203 mg, 76%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.29 (d, *J* = 9.1 Hz, 2H), 8.24 (d, *J* = 9.1 Hz, 2H), 7.01 (s, 1H), 4.51 (dd, *J* = 11.2, 3.8 Hz, 1H), 4.19 (dd, *J* = 11.2, 7.5 Hz, 1H), 4.12 – 4.04 (m, 1H), 2.44 – 2.32 (m, 3H), 1.99 – 1.86 (m, 1H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 178.5 (C_q), 164.5 (C_q), 150.9 (C_q), 135.0 (C_q), 131.1 (CH), 123.8 (CH), 68.4 (CH_2), 53.0 (CH), 29.8 (CH_2), 23.3 (CH_2); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{12}H_{13}N_2{}^{16}O_3{}^{18}O_2$ $[M + H]^+$: 269.0904; found 269.0897. also *m*/*z* calc'd for $C_{12}H_{13}N_2{}^{16}O_4{}^{18}O_1$ $[M + H]^+$: 267.0861; found 267.0856. The ratio of relative peak intensities for the relevant isotopologues was 91:9 ($C_{12}H_{13}N_2{}^{16}O_3{}^{18}O_2$: $C_{12}H_{13}N_2{}^{16}O_4{}^{18}O_1$); **FTIR** (neat) ν_{max}/cm^{-1} 3205, 3075, 2984, 1703, 1679, 1606, 1520; **m.p.** 164–166 °C; **TLC** R_f: 0.18 (3:97 MeOH/CH_2Cl_2).

(*S*)-(5-Oxopyrrolidin-2-yl)methanol (89d)

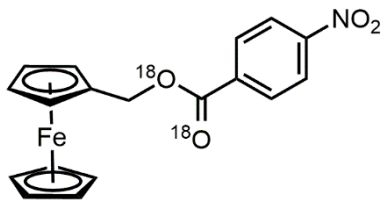


89d

To a solution of **S64** (81 mg, 0.28 mmol) in 1:1 MeOH/H_2O (2 mL) was added potassium carbonate (104 mg, 0.75 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 5 hours. The reaction mixture was then diluted with a 1.0 M aqueous NaOH solution (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with a saturated brine solution (10 mL), dried over $MgSO_4$ and concentrated. The crude residue was purified by flash column chromatography (SiO_2, 1:5 MeOH/EtOAc) to afford the title compound as a colourless oil (38 mg, 96%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.51 (s, 1H), 4.66 (s, 1H), 3.79 – 3.71 (m, 1H), 3.62 (dd, *J* = 11.4, 3.3 Hz, 1H), 3.41 (dd, *J* = 11.4, 6.9 Hz, 1H), 2.39 – 2.23 (m, 2H), 2.17 – 2.06 (m, 1H), 1.75 (dddd, *J* = 12.9, 9.6, 7.2, 5.4 Hz, 1H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 179.6 (C_q), 65.7 (CH_2), 56.6 (CH), 30.4 (CH_2), 22.7 (CH_2); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_5H_9NNa^{16}O^{18}O$ $[M + Na]^+$: 140.0568; found 140.0596. also *m*/*z* calc'd for $C_5H_9NNa^{16}O_2$ $[M + Na]^+$: 138.0525; found 138.0524. The ratio of relative peak intensities for the relevant isotopologues was 96:4

($C_5H_9NNa^{16}O^{18}O$:$C_5H_9NNa^{16}O_2$); **TLC** R_f: 0.25 (1:5 MeOH/EtOAc). Data are consistent with those reported in the literature.[50]

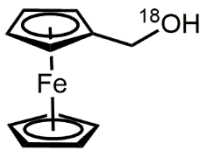
Ferrocenemethanyl 4-Nitrobenzoate-[^{18}O]$_2$ (S65)



S65

To a solution of ferrocenemethanol (108 mg, 0.500 mmol), 4-nitrobenzoic acid-[$^{18}O_2$] (128 mg, 0.750 mmol) and triphenylphosphine (197 mg, 0.750 mmol) in THF (2.5 mL) was added diisopropyl azodicarboxylate (148 µL, 0.750 mmol) at 0 °C. The reaction was warmed to room temperature and stirred for 8 hours. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with a saturated brine solution (10 mL) dried over $MgSO_4$ and concentrated. As the product was unstable to SiO_2 the reaction mixture was carried through to the hydrolysis step without further purification. Characteristic NMR signals: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.26 (d, *J* = 9.0 Hz, 2H), 8.19 (d, *J* = 9.0 Hz, 2H), 5.20 (s, 2H), 4.36 (t, *J* = 1.8 Hz, 2H), 4.23 (t, *J* = 1.8 Hz, 2H), 4.20 (s, 5H); **TLC:** R_f; 0.16 (1:9 Et_2O/petrol).

Ferrocenemethanol-[^{18}O] (89e)

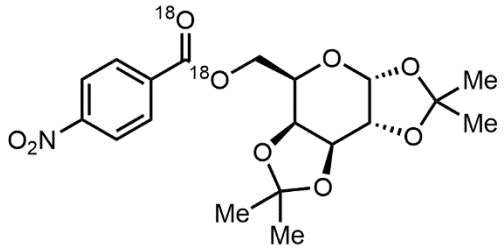


89e

The crude reaction mixture of **S66** was dissolved in 1:1 THF/MeOH (5 mL) and a 2.0 M aqueous LiOH solution (750 µL, 1.50 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 hours. The reaction mixture was then diluted with a 1.0 M aqueous NaOH solution (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with a saturated brine solution (10 mL), dried over $MgSO_4$ and concentrated. The crude residue

was purified twice by flash column chromatography (SiO_2, 1:3 EtOAc/petrol then 1:99 MeOH/CH_2Cl_2 to afford the title compound as an orange solid (87 mg, 80%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 4.33 (d, *J* = 5.8 Hz, 2H), 4.24 (t, *J* = 1.8 Hz, 2H), 4.20 – 4.15 (m, 7H), 1.53 (t, *J* = 5.8 Hz, 1H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 88.6 (C_q), 68.5 (CH), 68.4 (CH_2), 68.0 (CH), 60.9 (CH). **HRMS** (ESI-TOF) *m/z* calc'd for $C_{11}H_{12}{}^{56}FeNa^{18}O$ $[M + Na]^+$: 241.0172; found 241.0163. also *m/z* calc'd for $C_{11}H_{12}{}^{56}FeNa^{16}O$ $[M + Na]^+$: 239.0130; found 239.0157. The ratio of relative peak intensities for the relevant isotopologues was 87:13 ($C_{11}H_{12}{}^{56}FeNa^{18}O$:$C_{11}H_{12}{}^{56}FeNa^{16}O$); **m.p.** 75–80 °C (lit.[51] m.p. 78–81 °C); **TLC** R_f: 0.33 (4:6 EOAc/petrol). Data are consistent with those reported in the literature.[52]

1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranose 4-Nitrobenzoate-[^{18}O]$_2$ (S66)

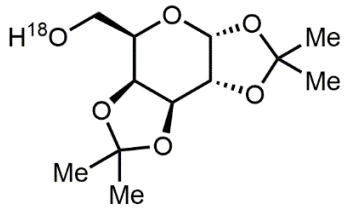


S66

Synthesised according to the general procedure using 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (130 mg, 0.500 mmol), 4-nitrobenzoic acid-[$^{18}O_2$] (256 mg, 1.50 mmol), triphenylphosphine (524 mg, 2.00 mmol) and diisopropyl azodicarboxylate (394 µL, 2.00 mmol) in THF (3 mL). The reaction mixture was stirred at room temperature for 7 hours. Purification by flash column chromatography (SiO_2, 3:7 Et_2O:petrol) afforded the title compound as a colourless oil (142 mg, 69%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.29 (d, *J* = 8.9 Hz, 2H), 8.22 (d, *J* = 8.9 Hz, 2H), 5.57 (d, *J* = 5.0 Hz, 1H), 4.66 (dd, *J* = 7.8, 2.5 Hz, 1H), 4.57 (dd, *J* = 11.6, 4.4 Hz, 1H), 4.49 (dd, *J* = 11.6, 7.8 Hz, 1H), 4.36 (dd, *J* = 5.0, 2.5 Hz, 1H), 4.32 (dd, *J* = 7.8, 1.9 Hz, 1H), 4.22 – 4.16 (m, 1H), 1.51 (s, 3H), 1.48 (s, 3H), 1.36 (s, 3H), 1.34 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 164.7 (C_q), 150.7 (C_q), 135.6 (C_q), 131.0 (CH), 123.7 (CH), 110.0 (C_q), 109.0 (C_q), 96.5 (CH), 71.3 (CH), 70.9 (CH), 70.6 (CH), 66.2 (CH), 65.0 (CH_2), 26.2 (CH_3), 26.1 (CH_3), 25.1 (CH_3),

24.6 (CH_3); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{19}H_{23}NNa^{16}O_7{}^{18}O_2$ [M + Na]$^+$: 436.1350; found 436.1347. also *m*/*z* calc'd for $C_{19}H_{23}NNa^{16}O_8{}^{18}O$ [M + Na]$^+$: 434.1307; found 434.1318. The ratio of relative peak intensities for the relevant isotopologues was 91:9 ($C_{19}H_{23}NNa^{16}O_7{}^{18}O_2$:$C_{19}H_{23}NNa^{16}O_8{}^{18}O$); **FTIR** (neat) ν_{max}/cm^{-1} 2987, 2937, 1696, 1608, 1528, 1382, 1373, 1347, 1265, 1211, 1166, 1092, 1066, 1004; **TLC** R_f: 0.22 (3:7 Et_2O/petrol).

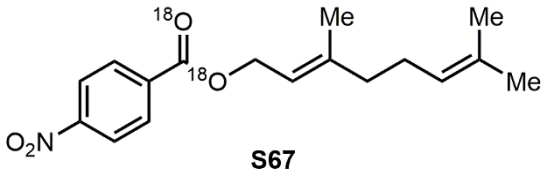
1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranose-[^{18}O] (89f)



89f

Synthesised according to the general procedure using **S66** (82 mg, 0.20 mmol) in 1:1 THF/MeOH (5 mL) and a 2.0 M aqueous LiOH solution (300 μL, 0.600 mmol). The reaction mixture was stirred for 16 hours before workup. The crude residue was purified by flash column chromatography (SiO_2, 4:6 EtOAc/petrol) to afford the title compound as a colourless oil (51 mg, 97%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.57 (d, *J* = 5.0 Hz, 1H), 4.61 (dd, *J* = 7.9, 2.4 Hz, 1H), 4.34 (dd, *J* = 5.0, 2.4 Hz, 1H), 4.27 (dd, *J* = 7.9, 1.6 Hz, 1H), 3.90 – 3.83 (m, 2H), 3.78 – 3.70 (m, 1H), 2.11 (d, *J* = 8.0 Hz, 1H), 1.53 (s, 3H), 1.46 (s, 3H), 1.34 (apparent s, 6H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 109.6 (C_q), 108.8 (C_q), 96.5 (CH), 71.8 (CH), 70.9 (CH), 70.7 (CH), 68.2 (CH), 62.6 (CH_2), 26.2 (CH_3), 26.1 (CH_3), 25.1 (CH_3), 24.5 (CH_3); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{12}H_{20}Na^{16}O_5{}^{18}O$ [M + Na]$^+$: 285.1195; found 285.1199. also *m*/*z* calc'd for $C_{12}H_{20}Na^{16}O_6$ [M + Na]$^+$: 283.1152; found 283.1162. The ratio of relative peak intensities for the relevant isotopologues was 95:5 ($C_{12}H_{20}Na^{16}O_5{}^{18}O$:$C_{12}H_{20}Na^{16}O_6$); **TLC** R_f; 0.24 (1:1 EtOAc/petrol). Data are consistent with those reported in the literature.[53]

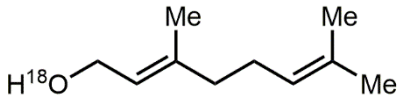
Geranyl 4-Nitrobenzoate-[$^{18}O]_2$ (S67)



S67

Synthesised according to the general procedure using geraniol (154 mg, 1.00 mmol), 4-nitrobenzoic acid-[$^{18}O_2$] (171 mg, 1.00 mmol), triphenylphosphine (315 mg, 1.20 mmol) and diisopropyl azodicarboxylate (236 μL, 1.200 mmol) in THF (2 mL). The reaction mixture was stirred at room temperature for 18 hours. Purification by flash column chromatography (SiO_2, 1:19 EtOAc:petrol) afforded the title compound as a colourless oil (231 mg, 76%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.28 (d, *J* = 9.0 Hz, 2H), 8.21 (d, *J* = 9.0 Hz, 2H), 5.47 (tp, *J* = 7.1, 1.3 Hz, 1H), 5.09 (ddq, *J* = 6.8, 5.3, 1.5 Hz, 1H), 4.89 (d, *J* = 7.1 Hz, 2H), 2.15 – 2.05 (m, 4H), 1.78 (d, *J* = 1.3 Hz, 3H), 1.67 (d, *J* = 1.3 Hz, 3H), 1.61 (d, *J* = 1.3 Hz, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 164.8 (C_q), 150.6 (C_q), 143.6 (C_q), 136.1 (C_q), 132.1 (C_q), 130.9 (CH), 123.6 (CH), 123.6 (CH), 117.8 (CH), 62.9 (CH_2), 39.7 (CH_2), 26.4 (CH_2), 25.8 (CH_3), 17.9 (CH_3), 16.7 (CH_3); **HRMS** (ESI-TOF) *m/z* calc'd for $C_{17}H_{21}NNa^{16}O_2{}^{18}O_2$ $[M + Na]^+$: 330.1448; found 330.1453. also *m/z* calc'd for $C_{17}H_{21}NNa^{16}O_3{}^{18}O$ $[M + Na]^+$: 328.1405; found 328.1426. The ratio of relative peak intensities for the relevant isotopologues was 90:10 ($C_{17}H_{21}NNa^{16}O_2{}^{18}O_2$:$C_{17}H_{21}NNa^{16}O_3{}^{18}O$); **m.p.** 37–41 °C (lit.[54] m.p. 37.8–38.2 °C); **TLC** R_f: 0.18 (3:97 MeOH/CH_2Cl_2). Data are consistent with those reported in the literature.[55]

Geraniol-[^{18}O] (89g)

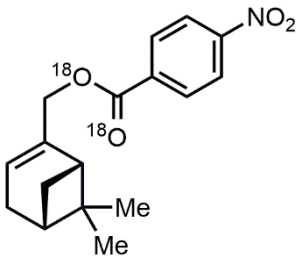


89g

Synthesised according to the general procedure using **S67** (50 mg, 0.16 mmol) in 1:1 THF/MeOH (2 mL) and a 2.0 M aqueous LiOH solution (500 μL, 1.00 mmol). The reaction mixture was stirred for 18 hours before workup. No additional purification procedures were required, and the title compound was afforded as a

colourless oil (61 mg, 78%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.45 – 5.39 (m, 1H), 5.12 – 5.06 (m, 1H), 4.15 (d, *J* = 6.9 Hz, 2H), 2.15 – 2.06 (m, 2H), 2.06 – 1.98 (m, 2H), 1.69 – 1.65 (m, 6H), 1.60 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 140.0 (C_q), 131.9 (C_q), 124.0 (CH), 123.5 (CH), 59.6 (CH_2), 39.7 (CH_2), 26.5 (CH_2), 25.8 (CH_3), 17.8 (CH_3), 16.4 (CH_3); **HRMS** (ESI-TOF) *m/z* calc'd for $C_{10}H_{18}Na^{18}O$ $[M + Na]^+$: 179.1292; found 179.1291. also *m/z* calc'd for $C_{10}H_{18}Na^{18}O$ $[M + Na]^+$: 177.1250; found 177.1243. The ratio of relative peak intensities for the relevant isotopologues was 92:8 ($C_{10}H_{18}Na^{18}O$:$C_{10}H_{18}Na^{18}O$); **TLC** R_f: 0.33 (1:4 EtOAc/petrol). Data are consistent with those reported in the literature.[56]

(1*R*)-(−)-Myrtenyl 4-Nitrobenzoate-[^{18}O]$_2$ (S68)

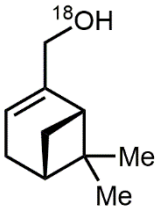


S68

Synthesised according to the general procedure using (1*R*)-(−)-myrtenol (80 µL, 0.50 mmol), 4-nitrobenzoic acid-[$^{18}O_2$] (86 mg, 0.50 mmol), triphenylphosphine (157 mg, 0.600 mmol) and diisopropyl azodicarboxylate (120 µL, 0.600 mmol) in THF (2 mL). The reaction mixture was stirred at room temperature for 4 hours. Purification by flash column chromatography (SiO_2, 1:39 Et_2O:petrol) afforded the title compound as a colourless solid (91 mg, 60%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 8.29 (d, *J* = 8.9 Hz, 2H), 8.19 (d, *J* = 8.9 Hz, 2H), 5.71 – 5.67 (m, 1H), 4.75 – 4.73 (m, 2H), 2.45 (dt, *J* = 8.7, 5.6 Hz, 1H), 2.33 (q, *J* = 18.1 Hz, 2H), 2.22 (td, *J* = 5.6, 1.5 Hz, 1H), 2.17 – 2.11 (m, 1H), 1.31 (s, 3H), 1.23 (d, *J* = 8.7 Hz, 1H), 0.86 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 164.7 (C_q), 150.7 (C_q), 142.5 (C_q), 136.0 (C_q), 130.8 (CH), 123.7 (CH), 122.9 (CH), 68.6 (CH_2), 43.9 (CH), 40.8 (CH), 38.3 (C_q), 31.7 (CH_2), 31.5 (CH_2), 26.3 (CH_3), 21.3 (CH_3); **HRMS** (ESI-TOF) *m/z* calc'd for $C_{17}H_{19}NNa^{16}O_2{}^{18}O_2$ $[M + Na]^+$: 328.1291; found 328.1289. also *m/z* calc'd for $C_{17}H_{19}NNa^{16}O_3{}^{18}O$ $[M + Na]^+$: 326.1249; found 326.1255. The ratio of relative peak intensities for the relevant isotopologues was 92:8

($C_{17}H_{19}NNa^{16}O_2{}^{18}O_2$:$C_{17}H_{19}NNa^{16}O_3{}^{18}O$); **FTIR** (neat) ν_{max}/cm^{-1} 3117, 2982, 2937, 2912, 2885, 2831, 1680, 1597, 1520, 1456, 1344, 1262, 1083, 1010; **m.p.** 76–78 °C; **TLC** R_f: 0.34 (1:9 Et_2O/petrol)

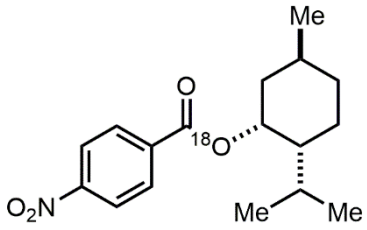
(1*R*)-(–)-Myrtenol-[^{18}O] (89h)



89h

Synthesised according to the general procedure using **S68** (80 mg, 0.26 mmol) in 1:1 THF/MeOH (2 mL) and a 2.0 M aqueous LiOH solution (390 µL, 0.780 mmol). The reaction mixture was stirred for 6 hours before workup. The crude residue was purified by flash column chromatography (SiO_2, 3:7 Et_2O/petrol) to afford the title compound as a colourless oil (38 mg, 95%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.50 – 5.44 (m, 1H), 4.01 – 3.95 (m, 2H), 2.41 (dt, *J* = 8.6, 5.6 Hz, 1H), 2.28 (qt, *J* = 17.9, 2.4 Hz, 2H), 2.17 – 2.08 (m, 2H), 1.29 (s, 3H), 1.18 (d, *J* = 8.6 Hz, 1H), 0.84 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 147.8 (C_q), 117.9 (CH), 66.0 (CH_2), 43.4 (CH), 40.9 (CH), 38.0 (C_q), 31.6 (CH_2), 31.1 (CH_2), 26.1 (CH_3), 21.1 (CH_3); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{10}H_{16}Na^{18}O$ $[M + Na]^+$: 177.1136; found 177.1126. also *m*/*z* calc'd for $C_{10}H_{16}Na^{16}O$ $[M + Na]^+$: 175.1083; found 175.1074. The ratio of relative peak intensities for the relevant isotopologues was 95:5 ($C_{10}H_{16}Na^{18}O$:$C_{10}H_{16}Na^{16}O$); **TLC** R_f; 0.11 (3:7 Et_2O/petrol). Data are consistent with those reported in the literature.[57]

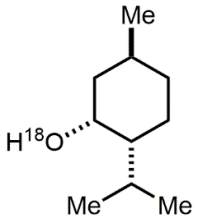
(±)-Neomenthyl 4-Nitrobenzoate-[$^{18}O]_2$ (S69)



87i

Synthesised according to the general procedure using (±)-menthol (78 mg, 0.50 mmol), 4-nitrobenzoic acid-[$^{18}O_2$] (342 mg, 2.00 mmol), triphenylphosphine (524 mg, 2.00 mmol) and diisopropyl azodicarboxylate (392 µL, 2.00 mmol) in THF (2 mL). The reaction mixture was stirred at room temperature for 24 hours. Purification by flash column chromatography (SiO_2, 1:19 EtOAc:petrol) afforded the title compound as pale yellow oil (122 mg, 79%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 8.29 (d, *J* = 8.8 Hz, 2H), 8.20 (d, *J* = 8.8 Hz, 2H), 5.51 – 5.48 (m, 1H), 2.09 (dq, *J* = 14.5, 3.3 Hz, 1H), 1.91 – 1.80 (m, 2H), 1.75 – 1.63 (m, 1H), 1.58 – 1.45 (m, 2H), 1.23 – 1.11 (m, 2H), 1.06 – 0.96 (m, 1H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.91 – 0.86 (m, 6H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 164.1 (C_q), 150.6 (C_q), 136.5 (C_q), 130.8 (CH), 123.7 (CH), 73.3 (CH), 47.1 (CH), 39.3 (CH_2), 34.9 (CH_2), 29.6 (CH), 27.0 (CH), 25.5 (CH_2), 22.3 (CH_3), 21.1 (CH_3), 20.9 (CH_3); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{17}H_{23}NNa^{16}O_2{}^{18}O_2$ $[M + Na]^+$: 332.1604; found 332.1602. also *m*/*z* calc'd for $C_{17}H_{23}NNa^{16}O_3{}^{18}O$ $[M + Na]^+$: 330.1562; found 330.1559. The ratio of relative peak intensities for the relevant isotopologues was 84:16 ($C_{17}H_{23}NNa^{16}O_2{}^{18}O_2$:$C_{17}H_{23}NNa^{16}O_3{}^{18}O$); **TLC** R_f: 0.31 (1:19 EtOAc/petrol). Data are consistent with those reported in the literature.[58]

(±)-Neomenthol-[^{18}O] (89i)

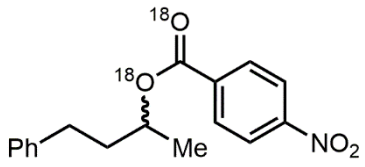


89i

Synthesised according to the general procedure using **S69** (74 mg, 0.24 mmol) in 1:1 THF/MeOH (1 mL) and a 2.0 M aqueous LiOH solution (500 µL, 1.00 mmol). The reaction mixture was stirred for 18 hours before workup. The crude residue was purified by flash column chromatography (SiO_2, 1:9 EtOAc/petrol) to afford the title compound as a colourless oil (36 mg, 95%).* **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.10 (q, *J* = 2.9 Hz, 1H), 1.83 (dq, *J* = 13.7, 3.4 Hz, 1H), 1.78 – 1.61 (m, 3H), 1.52 (dp, *J* = 9.3, 6.7 Hz, 1H), 1.33 – 1.18 (m, 2H), 1.08 (ddd, *J* = 13.8, 12.1, 2.6 Hz, 1H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.88 – 0.83 (m, 4H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 67.9 (CH_2), 48.1 (CH), 42.7 (CH_2), 35.2 (CH_2), 29.3 (CH), 26.0 (CH), 24.3 (CH_2), 22.5 (CH_3), 21.3 (CH_3), 20.9 (CH_3); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{10}H_{20}Na^{18}O$ $[M + Na]^+$: 181.1449; found 181.1449. also *m*/*z* calc'd for $C_{10}H_{20}Na^{16}O$ $[M + Na]^+$: 179.1406; found 179.1406. The ratio of relative peak intensities for the relevant isotopologues was 93:7 ($C_{10}H_{20}Na^{18}O$:$C_{10}H_{20}Na^{16}O$); **TLC** R_f: 0.25 (1:9 EtOAc/petrol). Data are consistent with those reported in the literature.[59] ^{13}C NMR data does not match the retention product (menthol).[60]

*Sample contained 7 mol% CH_2Cl_2 95% yield accounts for this.

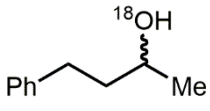
4-Phenylbutan-2-yl 4-Nitrobenzoate-[$^{18}O]_2$ (S70)



S70

Synthesised according to the general procedure using 4-phenyl-2-butanol (451 mg, 3.00 mmol), 4-nitrobenzoic acid-[$^{18}O_2$] (514 mg, 3,00 mmol), triphenylphosphine (944 mg, 3.60 mmol) and diisopropyl azodicarboxylate (709 µL, 3.60 mmol) in THF (5 mL). The reaction mixture was stirred at room temperature for 8 hours. Purification by flash column chromatography (SiO_2, 3:97 Et_2O:petrol) afforded the title compound as a colourless oil (719 mg, 80%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 8.28 (d, *J* = 8.9 Hz, 2H), 8.16 (d, *J* = 8.9 Hz, 2H), 7.27 (dd, *J* = 8.2, 6.9 Hz, 2H), 7.19 (d, *J* = 7.3 Hz, 3H), 5.23 (dqd, *J* = 7.8, 6.2, 4.8 Hz, 1H), 2.82 – 2.67 (m, 2H), 2.14 (dddd, *J* = 14.0, 9.1, 7.7, 6.7 Hz, 1H), 2.00 (dddd, *J* = 14.0, 9.1, 6.7, 4.9 Hz, 1H), 1.42 (d, *J* = 6.2 Hz, 3H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 164.3 (C_q), 150.6 (C_q), 141.3 (C_q), 136.2 (C_q), 130.8 (CH), 128.6 (CH), 128.4 (CH), 126.2 (CH), 123.6 (CH), 72.7 (CH), 37.6 (CH_2), 32.0 (CH_2), 20.2 (CH_3); **HRMS** (ESI-TOF) *m/z* calc'd for $C_{17}H_{17}NNa^{16}O_2{}^{18}O_2$ $[M + Na]^+$: 326.1135; found 326.1134. also *m/z* calc'd for $C_{17}H_{17}NNa^{16}O_3{}^{18}O$ $[M + Na]^+$: 324.1092; found 324.1089. The ratio of relative peak intensities for the relevant isotopologues was 91:9 ($C_{17}H_{17}NNa^{16}O_2{}^{18}O_2$:$C_{17}H_{17}NNa^{16}O_3{}^{18}O$); **TLC** R_f: 0.28 (1:19 Et_2O/petrol). Data are consistent with those reported in the literature.[61]

4-Phenyl-2-butanol-[^{18}O] (89j)

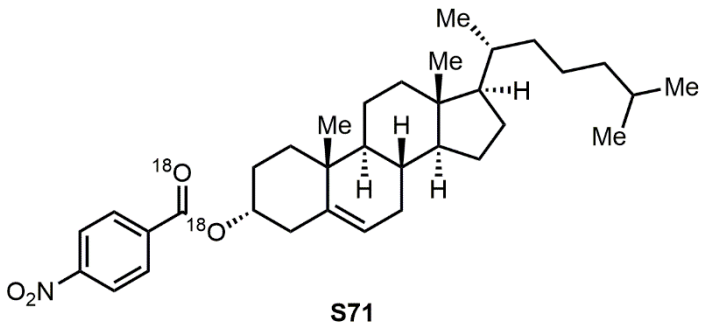


89j

Synthesised according to the general procedure using **S70** (680 mg, 2.25 mmol) in 1:1 THF/MeOH (8 mL) and a 2.0 M aqueous LiOH solution (3.38 mL, 6.75 mmol). The reaction mixture was stirred for 5 hours before workup. The crude residue was purified by flash column chromatography (SiO_2, 1:9

EtOAc/petrol) to afford the title compound as a colourless oil (310 mg, 91%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.31 – 7.27 (m, 2H), 7.22 – 7.17 (m, 3H), 3.83 (apparent sextet, *J* = 6.2 Hz, 1H), 2.76 (ddd, *J* = 13.7, 9.2, 6.3 Hz, 1H), 2.68 (ddd, *J* = 13.7, 9.2, 7.1 Hz, 1H), 1.85 – 1.71 (m, 2H), 1.33 (s, 1H), 1.23 (d, *J* = 6.2 Hz, 3H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 142.2 (C_q), 128.5 (4 × CH), 126.0 (CH), 67.7 (CH), 41.0 (CH_2), 32.3 (CH_2), 23.8 (CH_3); **HRMS** (ESI-TOF) *m/z* calc'd for $C_{10}H_{14}Na^{18}O$ $[M + Na]^+$: 175.0979; found 175.0982. also *m/z* calc'd for $C_{10}H_{14}Na^{16}O$ $[M + Na]^+$: 173.0937; found 173.0939. The ratio of relative peak intensities for the relevant isotopologues was 94:6 ($C_{10}H_{14}Na^{18}O$:$C_{10}H_{14}Na^{16}O$); **TLC** R_f: 0.18 (1:4 EtOAc/petrol). Data are consistent with those reported in the literature.[14]

epi-Cholesteryl 4-Nitrobenzoate-[^{18}O]$_2$ (S71)



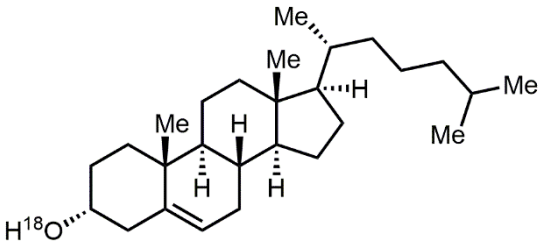
S71

Synthesised according to the general procedure using cholesterol (194 mg, 0.500 mmol), 4-nitrobenzoic acid-[$^{18}O_2$] (128 mg, 0.750 mmol), triphenylphosphine (196 mg, 0.750 mmol) and diisopropyl azodicarboxylate (148 µL, 0.750 mmol) in THF (2 mL). The reaction was mixtutre was stirred at room temperature for 18 hours prior to workup. Purification by flash column chromatography (SiO_2, 1:19 EtOAc:petrol) afforded the title compound as an off-white solid (110 mg, 37%).* **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.28 (d, *J* = 8.9 Hz, 2H), 8.15 (d, *J* = 8.9 Hz, 2H), 5.35 – 5.31 (m, 1H), 5.31 – 5.26 (m, 1H), 2.66 – 2.58 (m, 1H), 2.36 (dt, *J* = 15.4, 2.6 Hz, 1H), 2.08 – 1.67 (m, 6H), 1.64 – 0.96 (m, 23H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.86 (dd, *J* = 6.6, 1.8 Hz, 6H), 0.70 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 160.1 (C_q), 150.5 (C_q), 138.3 (C_q), 136.7 (C_q), 130.7 (CH), 123.7 (CH), 122.8 (CH), 72.6 (CH), 56.9 (CH), 56.3 (CH), 50.6 (CH), 42.5 (C_q), 39.9 (CH_2), 39.7 (CH_2), 37.3 (CH_2), 36.6 (CH_2), 36.3 (CH_2), 36.0 (CH), 34.1 (CH_2), 32.1

(CH_2), 32.0 (CH), 28.4 (CH_2), 28.2 (CH), 24.4 (CH_2), 24.0 (CH_2), 23.0 (CH_3), 22.7 (CH_3), 21.0 (CH_2), 19.1 (CH_3), 18.9 (CH_3), 12.0 (CH_3); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{34}H_{53}N^{16}O_2{}^{18}O_2$ $[M + NH_4]^+$: 557.4085; found 557.4085; **TLC** R_f: 0.27 (1:19 EtOAc/petrol).

*sample contained 25 mol% DIAD•H_2. The 37% yield accounts for this.

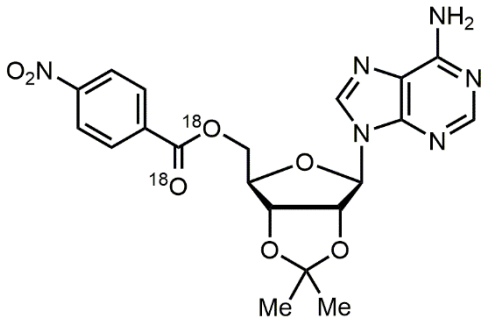
epi-Cholesterol-[^{18}O] (89k)



89k

Synthesised according to the general procedure using **S71** (55 mg, 93 µmol) in 1:1 THF/MeOH (2 mL) and a 2.0 M aqueous LiOH solution (500 µL, 1.00 mmol). The reaction mixture was stirred for 18 hours before workup. The crude residue was purified by flash column chromatography (SiO_2, 1:9 EtOAc/petrol) to afford the title compound as a colourless oil (33 mg, 92%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.43 – 5.38 (m, 1H), 4.01 (t, *J* = 2.9 Hz, 1H), 2.60 – 2.53 (m, 1H), 2.07 (dt, *J* = 14.7, 2.7 Hz, 1H), 2.05 – 1.94 (m, 2H), 1.83 (dtd, *J* = 13.3, 9.5, 5.8 Hz, 1H), 1.77 – 0.95 (m, 27H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.87 (dd, *J* = 6.6, 2.3 Hz, 6H), 0.68 (s, 3H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 138.7 (C_q), 124.2 (CH), 67.3 (CH), 56.9 (CH), 56.3 (CH), 50.5 (CH), 42.5 (C_q), 40.0 (CH_2), 39.9 (CH_2), 39.7 (CH_2), 37.5 (CH_2), 36.3 (CH_2), 35.9 (CH), 33.4 (CH_2), 32.1 (CH_2), 32.0 (CH), 29.1 (CH_2), 28.4 (CH_2), 28.2 (CH), 24.4 (CH_2), 24.0 (CH_2), 23.0 (CH_3), 22.7 (CH_3), 20.9 (CH_3), 18.9 (CH_3), 18.8 (CH_3), 12.0 (CH_3); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{27}H_{46}Na^{18}O$ $[M + Na]^+$: 411.3483; found 411.3475. also *m*/*z* calc'd for $C_{27}H_{46}Na^{16}O$ $[M + Na]^+$: 409.3441; found 409.3423. The ratio of relative peak intensities for the relevant isotopologues was 90:10 ($C_{27}H_{46}Na^{18}O$:$C_{27}H_{46}Na^{16}O$); **TLC** R_f: 0.30 (1:4 EtOAc/petrol); Data are consistent with those reported in the literature.[62] **^{13}C{^{1}H} NMR** data does not match the retention product (cholesterol).[63]

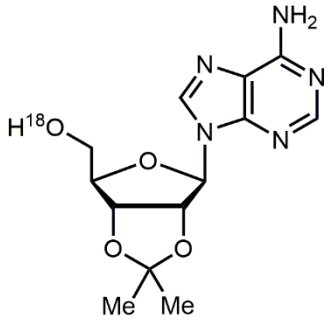
2',3'-*O*-Isopropylideneadenosyl 4-Nitrobenzoate-[^{18}O]$_2$ (S72)



S72

Synthesised according to the general procedure using 2',3'-*O*-isopropylideneadenosine (154 mg, 0.500 mmol) 4-nitrobenzoic acid-[$^{18}O_2$] (171 mg, 1.00 mmol), triphenylphosphine (262 mg, 1.00 mmol) and diisopropyl azodicarboxylate (197 µL, 1.00 mmol) in THF (2 mL). Purification by flash column chromatography (SiO_2, 1:19 MeOH:EtOAc) afforded a 1:2.0 mixture of the title compound and triphenylphosphine oxide respectively (324 mg of mixture, 147 mg, 64% effective yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.30 (s, 1H), 8.23 (d, *J* = 8.9 Hz, 2H), 8.11 (d, *J* = 8.9 Hz, 2H), 7.87 (s, 1H), 6.10 (d, *J* = 1.9 Hz, 1H), 5.69 (s, 2H), 5.60 (dd, *J* = 6.3, 1.9 Hz, 1H), 5.23 (dd, *J* = 6.3, 3.6 Hz, 1H), 4.68 (dd, *J* = 11.3, 4.0 Hz, 1H), 4.60 (dt, *J* = 6.1, 3.8 Hz, 1H), 4.53 (dd, *J* = 11.3, 6.1 Hz, 1H), 1.64 (s, 3H), 1.42 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 164.3 (C_q), 155.6 (C_q), 153.3 (CH), 150.8 (C_q), 149.3 (C_q), 140.2 (CH), 135.0 (C_q), 130.9 (CH), 123.6 (CH), 120.6 (C_q), 114.9 (C_q), 91.2 (CH), 85.2 (CH), 84.2 (CH), 81.8 (CH), 65.2 (CH_2), 27.4 (CH_3), 25.6 (CH_3); **HRMS** (ESI-TOF) *m/z* calc'd for $C_{20}H_{21}N_6{}^{16}O_5{}^{18}O_2$ $[M + H]^+$: 461.1551; found 461.1540. also *m/z* calc'd for $C_{20}H_{21}N_6{}^{16}O_6{}^{18}O$ $[M + H]^+$: 459.1509; found 459.1500. The ratio of relative peak intensities for the relevant isotopologues was 80:20 ($C_{20}H_{21}N_6{}^{16}O_5{}^{18}O_2$:$C_{20}H_{21}N_6{}^{16}O_6{}^{18}O$); **FTIR** (neat) ν_{max}/cm^{-1} 3325, 3167, 3055, 2987, 1697, 1639, 1596, 1526; **TLC** R_f: 0.72 (1:9 MeOH/CH_2Cl_2).

2',3'-*O*-Isopropylideneaenosine-[^{18}O] (89l)

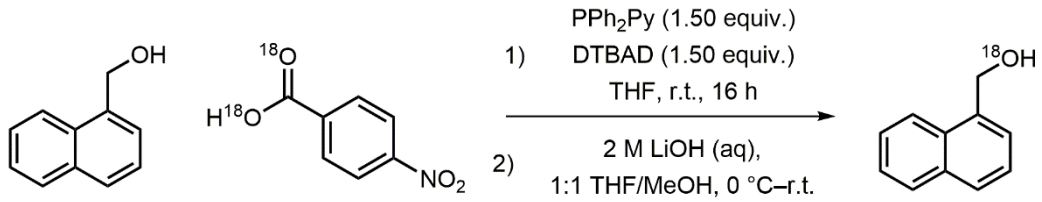


89l

Synthesised according to the general procedure using **S72** (100 mg of a 1:2 mixture with triphenylphosphine oxide, 99 μmol) in 1:1 THF/MeOH (1 mL) and a 2.0 M aqueous LiOH solution (500 μL, 1.00 mmol). The reaction mixture was stirred for 24 hours before workup. The crude residue was purified by flash column chromatography (SiO_2, 1:19 MeOH/EtOAc) to afford the title compound as a colourless oil (23 mg, 74%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.32 (s, 1H), 7.84 (s, 1H), 6.54 (d, *J* = 11.6 Hz, 1H), 5.85 (d, *J* = 5.0 Hz, 1H), 5.80 (s, 2H), 5.21 (t, *J* = 5.4 Hz, 1H), 5.12 (d, *J* = 5.9 Hz, 1H), 4.54 (s, 1H), 4.04 – 3.94 (m, 1H), 3.86 – 3.71 (m, 1H), 1.65 (s, 3H), 1.38 (s, 3H); **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 156.1 (C_q), 152.8 (CH), 148.6 (C_q), 140.5 (CH), 121.4 (C_q), 114.2 (C_q), 94.6 (CH), 86.2 (CH), 83.1 (CH), 81.9 (CH), 63.6 (CH_2), 27.8 (CH_3), 25.4 (CH_3); **HRMS** (ESI-TOF) *m/z* calc'd for $C_{13}H_{17}N_5Na^{16}O_3{}^{18}O$ $[M + Na]^+$: 332.1215; found 332.1214. also *m/z* calc'd for $C_{13}H_{17}N_5Na^{16}O_4$ $[M + Na]^+$: 330.1173; found 330.1170. The ratio of relative peak intensities for the relevant isotopologues was 90:10 ($C_{13}H_{17}N_5Na^{16}O_3{}^{18}O$:$C_{13}H_{17}N_5Na^{16}O_4$); **m.p.** 219–221 °C (lit.[64] m.p. 218–220 °C); **TLC** R_f: 0.14 (1:19 MeOH/EtOAc). Data are consistent with those reported in the literature.[64,65]

Investigating Alternative Mitsunobu Conditions

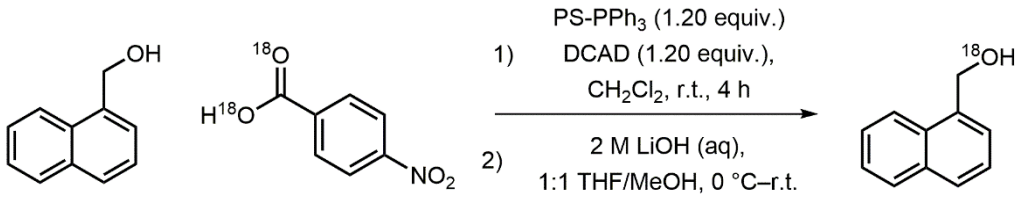
1-Naphthalenemethanol-[^{18}O] (figure 13A, entry 2)



Synthesised according to an adapted literature procedure.[66] To a solution of 1-napthalenemethanol (79 mg, 0.50 mmol), 4-nitrobenzoic acid-[$^{18}O_2$] (128 mg, 0.75 mmol) and diphenyl-2-pyridylphosphine (197 mg, 0.75 mmol) in THF (2 mL) was added di-*tert*-butyl azodicarboxylate (173 mg, 0.75 mmol) and the reaction mixture was stirred at room temperature for 16 hours. A 4.0 M solution of HCl in dioxane (2 mL) was subsequently added and the reaction was stirred for a further 1 hour. The reaction was diluted with a 2.0 M aqueous HCl solution (10 mL) was added and the organics were extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with a saturated brine solution (10 mL), dried over $MgSO_4$ and concentrated. Purification by flash column chromatography (SiO_2, 1:9 Et_2O/cyclohexane) afforded the title compound as a colourless solid (124 mg, 80%). **^{1}H** and **^{13}C{^{1}H} NMR** spectra matched with compound **S61**.

To the ^{18}O-enriched ester product (78 mg, 0.25 mmol) in 1:1 MeOH/THF (2 mL) was added a 2.0 M aqueous LiOH solution (375 µL, 0.750 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 hours. The reaction mixture was then diluted with a 1.0 M aqueous NaOH solution (10 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with a saturated brine solution (10 mL), dried over $MgSO_4$ and concentrated to afford the title compound as a colourless solid (38 mg, 96%). **^{1}H** and **^{13}C{^{1}H} NMR** spectra matched with compound **89a**; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{11}H_{10}Na^{18}O$ $[M + Na]^+$: 183.0666; found 183.0663. also *m*/*z* calc'd for $C_{11}H_{10}Na^{16}O$ $[M + Na]^+$: 181.0624; found 181.0631. The ratio of relative peak intensities for the relevant isotopologues was 92:8 ($C_{11}H_{10}Na^{18}O$: $C_{11}H_{10}Na^{16}O$).

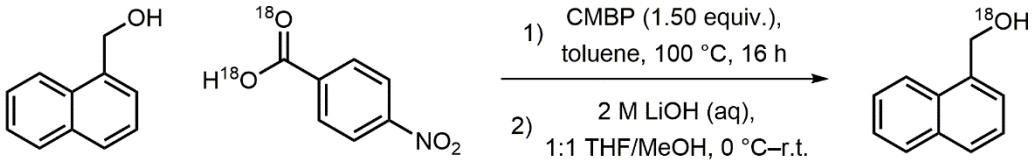
1-Naphthalenemethanol-[^{18}O] (figure 13A, entry 3)



Synthesised according to an adapted literature procedure.[67] To a solution of 1-napthalenemethanol (79 mg, 0.50 mmol), 4-nitrobenzoic acid-[$^{18}O_2$] (103 mg, 0.600 mmol) and polymer-bound triphenylphosphine (200 mg, 3 mmol/g triphenylphosphine loading, 0.600 mmol) in CH_2Cl_2 (2 mL) was added di-(4-chlorobenzyl)azodicarboxylate (220 mg, 0.600 mmol) in CH_2Cl_2 (2 mL) and the reaction mixture was stirred at room temperature for 4 hours, then diluted with CH_2Cl_2 (2 mL) and the suspension was filtered through a pad of celite. The filtrate was concentrated and purified by flash column chromatography (SiO_2, 1:9 Et_2O/cyclohexane) to afford the title compound as a colourless solid (80 mg, 51%). **^{1}H** and **^{13}C{^{1}H} NMR** spectra matched with compound **S61**.

To the ^{18}O-enriched ester product (62 mg, 0.20 mmol) in 1:1 MeOH/THF (2 mL) was added a 2.0 M aqueous LiOH solution (300 µL, 0.600 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 3 hours. The reaction mixture was then diluted with a 1.0 M aqueous NaOH solution (10 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with a saturated brine solution (10 mL), dried over $MgSO_4$ and concentrated to afford the title compound as a colourless solid (31 mg, 97%). **^{1}H** and **^{13}C{^{1}H} NMR** spectra matched with compound **89a**; **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{11}H_{10}Na^{18}O$ $[M + Na]^+$: 183.0666; found 183.0666. also *m*/*z* calc'd for $C_{11}H_{10}Na^{16}O$ $[M + Na]^+$: 181.0624; found 181.0637. The ratio of relative peak intensities for the relevant isotopologues was 92:8 ($C_{11}H_{10}Na^{18}O$:$C_{11}H_{10}Na^{16}O$).

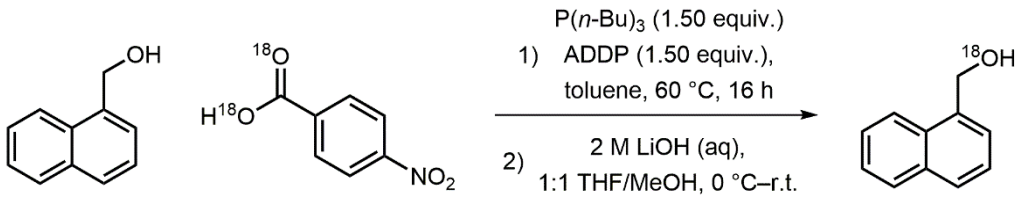
1-Naphthalenemethanol-[^{18}O] (figure 13A, entry 4)



Synthesised according to an adapted literature procedure.[68] Under an atmosphere of argon, to a solution of 1-napthalenemethanol (79 mg, 0.50 mmol) and 4-nitrobenzoic acid-[$^{18}O_2$] (128 mg, 0.750 mmol) in anhydrous toluene (2 mL) was added a 1.0 M solution of cyanomethylenetributylphosphorane in toluene (750 µL, 0.750 mmol) The reaction mixture was heated to 100 °C and stirred for 16 hours. The reaction mixture was then concentrated and the residue was purified by flash column chromatography (SiO_2, 1:9 Et_2O/cyclohexane) to afford the title compound as a colourless solid (102 mg, 65%). **^{1}H** and **^{13}C{^{1}H} NMR** spectra matched with compound **S61**.

To the ^{18}O-enriched ester product (62 mg, 0.20 mmol) in 1:1 MeOH/THF (2 mL) was added a 2.0 M aqueous LiOH solution (300 µL, 0.600 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 3 hours. The reaction mixture was then diluted with a 1.0 M aqueous NaOH solution (10 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with a saturated brine solution (10 mL), dried over $MgSO_4$ and concentrated to afford the title compound as a colourless solid (30 mg, 94%). **^{1}H** and **^{13}C{^{1}H} NMR** spectra matched with compound **89a**; **HRMS** (ESI-TOF) m/z calc'd for $C_{11}H_{10}Na^{18}O$ [M + Na]$^+$: 183.0666; found 183.0670. also m/z calc'd for $C_{11}H_{10}Na^{16}O$ [M + Na]$^+$: 181.0624; found 181.0644. The ratio of relative peak intensities for the relevant isotopologues was 93:7 ($C_{11}H_{10}Na^{18}O$:$C_{11}H_{10}Na^{16}O$).

1-Naphthalenemethanol-[^{18}O] (figure 13A, entry 5)

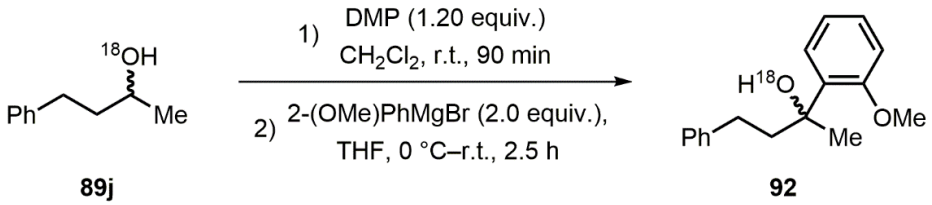


Synthesised according to an adapted literature procedure.[69] Under an atmosphere of argon, to a solution of naphthalenemethanol (79 mg, 0.50 mmol), 4-nitrobenzoic acid-[$^{18}O_2$] (128 mg, 0.75 mmol) and tri(*n*-butyl)phosphine (187 µL, 0.75 mmol) in toluene (1 mL) was added 1,1'-(azodicarbonyl)dipiperidine (173 mg, 0.75 mmol) in toluene (1 mL). The reaction mixture was heated to 60 °C and stirred for 16 hours. The reaction mixture was then diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with a saturated brine solution (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:9 Et_2O/cyclohexane) afforded the title compound as a colourless solid (83 mg, 53%). **^{1}H** and **^{13}C{^{1}H} NMR** spectra matched with compound **S61**.

To the ^{18}O-enriched ester product (62 mg, 0.20 mmol) in 1:1 MeOH/THF (2 mL) was added a 2.0 M aqueous LiOH solution (300 µL, 0.600 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 3 hours. The reaction mixture was then diluted with a 1.0 M aqueous NaOH solution (10 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated to afford the title compound as a colourless solid (30 mg, 94%). **^{1}H** and **^{13}C{^{1}H} NMR** spectra matched with compound **89a**; **HRMS** (ESI-TOF) *m/z* calc'd for $C_{11}H_{10}Na^{18}O$ $[M + Na]^+$: 183.0666; found 183.0669. also *m/z* calc'd for $C_{11}H_{10}Na^{16}O$ $[M + Na]^+$: 181.0624; found 181.0698. The ratio of relative peak intensities for the relevant isotopologues was 88:12 ($C_{11}H_{10}Na^{18}O$:$C_{11}H_{10}Na^{16}O$).

Synthesis of ^{18}O-enriched Tertiary Alcohol

2-(2-Methoxyphenyl)-4-phenylbutan-2-ol-[^{18}O] (92)



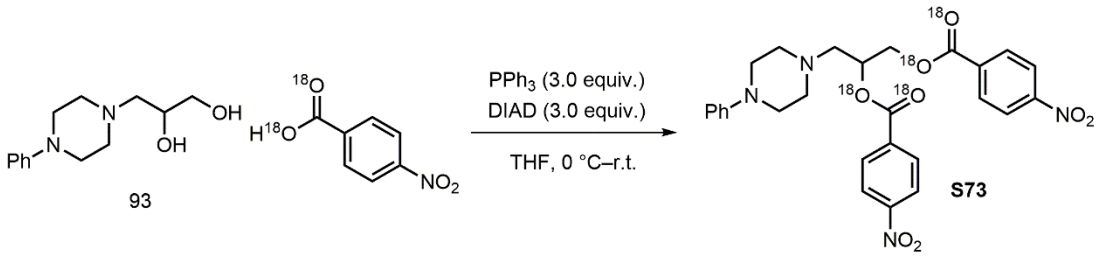
89j **92**

Synthesised according to an adapted literature procedure.[70] To a solution of alcohol **89j** (76 mg, 0.50 mmol) in anhydrous CH_2Cl_2 (8 mL) was added Dess-Martin periodinane (254 mg, 0.60 mmol) at room temperature and the reaction mixture was stirred for 90 minutes. The reaction mixture was then concentrated, 1:9 EtOAc/cyclohexane (5 mL) was added, and the suspension was filtered through a pad of celite. The filtrate was concentrated *in vacuo*, and the residue was purified by flash column chromatography (SiO_2, 8:92 EtOAc/cyclohexane) afforded the ketone as a colourless oil.

The ketone was dissolved in anhydrous THF (3 mL) and a 0.90 M solution of 2-methoxyphenylmagnesium bromide in 2-MeTHF (1.11, 1.00 mmol), was added at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2.5 hours. The reaction mixture was quenched with a 1.0 M aqueous NH_4Cl solution (5mL), diluted with H_2O (10 mL) and extracted with EtOAc (3 × 10mL). The combined organic extracts were washed with a saturated brine solution (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 5:95 to 8:92 gradient of acetone/cyclohexane) afforded the title compound as a colourless oil (87 mg, 67% over 2 steps). **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.35 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.28 – 7.22 (m, 3H), 7.17 – 7.11 (m, 3H), 6.98 (td, *J* = 7.5, 1.2 Hz, 1H), 6.93 (dd, *J* = 8.3, 1.2 Hz, 1H), 3.90 (s, 3H), 2.65 – 2.50 (m, 2H), 2.30 (ddd, *J* = 13.5, 11.7, 5.3 Hz, 1H), 2.16 (ddd, *J* = 13.5, 11.7, 5.5 Hz, 1H), 1.64 (s, 3H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 157.0 (C_q), 142.9 (C_q), 134.7 (C_q), 128.5 (CH), 128.4 (CH), 128.4 (CH), 126.9 (CH), 125.7 (CH), 121.1 (CH), 111.5 (CH), 75.2 (C_q), 55.5 (CH_3), 44.1 (CH_2), 31.1 (CH_2), 27.7 (CH_3); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{17}H_{20}Na^{16}O^{18}O$ $[M + Na]^+$: 281.1398; found 281.1379. also *m*/*z* calc'd for $C_{17}H_{20}Na^{16}O_2$ $[M + H]^+$: 279.1356; found 279.1352. The ratio

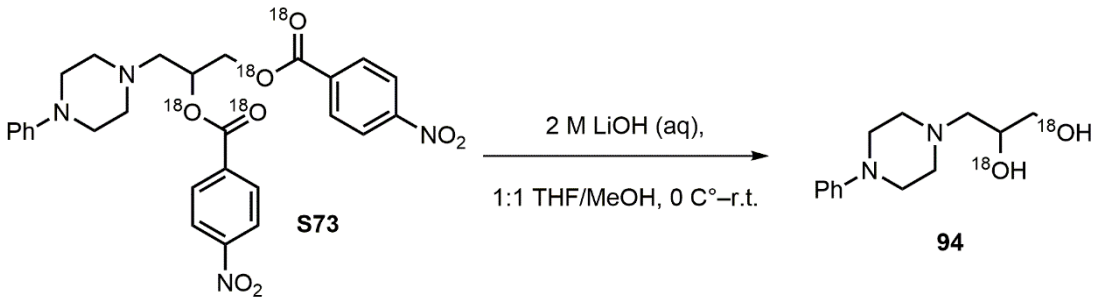
of relative peak intensities for the relevant isotopologues was 93:7 ($C_{17}H_{20}Na^{16}O^{18}O$:$C_{17}H_{20}Na^{16}O_2$); **FTIR** (neat) ν_{max}/cm^{-1} 3444, 2975, 2933, 1496, 1420, 1120, 1048; **TLC** R_f: 0.18 (1:9 acetone/petrol).

Dropropizine bis(4-Nitrobenzoate)-[$^{18}O_4$] (S73)



To a solution of Dropropizine (118 mg, 0.500 mmol), 4-nitrobenzoic acid-[$^{18}O_2$] (257 mg, 1.50 mmol) and triphenylphosphine (393 mg, 1.50 mmol) in THF (6 mL) was added diisopropyl azodicarboxylate (295 µL, 1.50 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2–48 hours. The reaction mixture was then diluted with a saturated aqueous $NaHCO_3$ solution (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with a saturated brine solution (20 mL) dried over $MgSO_4$ and concentrated. Purification by flash column chromatography (SiO_2, 3:97 (10% *v*/*v* NH_4OH in MeOH):petrol) afforded the title compound as a pale yellow solid (180 mg, 57%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 8.31 – 8.26 (m, 4H), 8.22 – 8.15 (m, 4H), 7.29 – 7.23 (m, 2H), 6.91 (d, *J* = 8.2 Hz, 2H), 6.86 (t, *J* = 7.3 Hz, 1H), 5.71 (apparent qd, *J* = 6.6, 2.8 Hz, 1H), 4.82 (dd, *J* = 12.1, 2.9 Hz, 1H), 4.65 (dd, *J* = 12.2, 7.0 Hz, 1H), 3.21 – 3.14 (m, 4H), 2.87 – 2.79 (m, 2H), 2.78 – 2.73 (m, 4H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 164.5 (C_q), 164.2 (C_q), 151.2 (C_q), 150.9 (C_q), 135.3 (C_q), 135.1 (C_q), 130.9 (CH), 130.9 (CH), 129.3 (CH), 123.8 (CH), 120.1 (CH), 116.2 (CH), 70.8 (CH), 65.6 (CH_2), 58.3 (CH_2), 53.9 (CH_2), 49.4 (CH_2); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{27}H_{27}N_4{}^{16}O_4{}^{18}O_4$ $[M + H]^+$: 543.1993; found 543.1990; **TLC** R_f: 0.68 (1:49 $MeOH/CH_2Cl_2$).

Dropropizine-[$^{18}O_2$]



To a solution of **S73** (74 mg, 0.24 mmol) in 1:1 MeOH/THF (1 mL) was added a 2.0 M aqueous LiOH solution (500 1.00 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 18 h. The reaction mixture was then diluted with a 1.0 M aqueous NaOH solution (10 mL) and extracted with EtOAc (30 mL). The combined organic extracts were washed with a saturated brine solution (10 mL), dried over $MgSO_4$ and concentrated. The crude residue was purified by flash column chromatography (SiO_2, 7:93 (10% *v*/*v* NH_4OH in MeOH)/petrol) to afford the title compound as a colourless solid (35 mg, 98%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.30 – 7.24 (m, 2H), 6.93 (d, *J* = 8.1 Hz, 2H), 6.87 (t, *J* = 7.3 Hz, 1H), 3.87 (dd, *J* = 9.3, 4.5 Hz, 1H), 3.76 (dd, *J* = 11.4, 3.6 Hz, 1H), 3.53 (dd, *J* = 11.4, 4.5 Hz, 1H), 3.26 – 3.16 (m, 4H), 2.88 – 2.56 (m, 5H), 2.42 (dd, *J* = 12.4, 3.9 Hz, 1H); **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 151.2 (C_q), 129.2 (CH), 120.1 (CH), 116.3 (CH), 67.1 (CH), 65.0 (CH_2), 60.4 (CH_2), 53.5 (CH_2), 49.4 (CH_2); **HRMS** (ESI-TOF) *m*/*z* calc'd for $C_{13}H_{21}N_2{}^{18}O_2$ $[M + H]^+$: 241.1682; found 241.1680. also *m*/*z* calc'd for $C_{13}H_{21}N_2{}^{16}O{}^{18}O$ $[M + H]^+$: 239.1640; found 239.1634; also *m*/*z* calc'd for $C_{13}H_{21}N_2{}^{16}O_2$ $[M + H]^+$: 237.1598; found 237.1534. The ratio of relative peak intensities for the relevant isotopologues was 90.3:9.4:0.3 ($C_{13}H_{21}N_2{}^{18}O_2$:$C_{13}H_{21}N_2{}^{16}O{}^{18}O$:$C_{13}H_{21}N_2{}^{16}O_2$); **m.p.** 98-102 °C; **TLC** R_f: 0.26 (7:93 (10% *v*/*v* NH_4OH in MeOH)/petrol). Data are consistent with those reported in the literature.[71]

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