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Nickel-Catalysed Arylative Cyclisations of Alkynones & Molecular Editing of Cyclic Ketones

A thesis submitted to The University of Nottingham for the degree of Doctor of Philosophy

By

Harley Green

September 2022

Declaration

I hereby declare that, except for where specific reference is made to other sources, the work contained within this thesis is the original work of my own research and any collaboration is clearly indicated. This thesis has been composed by myself and has not been submitted, in whole or part, for any other degree, diploma or other qualification. I confirm that the work submitted is my own, except work which has formed part of jointly-authored publications. The contributions of myself and other authors to this work have been specifically indicated where relevant. I confirm that appropriate credit has been given with the thesis where references has been made to the work of others.

The following thesis contains results reported in the following publication:

"Enantioselective Nickel-Catalysed *anti*-Arylmetallative Cyclisations onto Acyclic Ketones" Green, H.; Argent, S. P.; Lam, H. W. *Chem. Eur. J.* **2021**, *27*, 5897–5900

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ABBREVIATIONS

acac	acetylacetonate
Acr	acridinium
AIBN	azobisisobutyronitrile
aq	aqueous
atm	atmosphere
BArF	tetrakis(3,5-bis(trifluoromethyl)phenyl)borate
bpy	2,2'-bipyridyl
BTMG	2-*t*-butyl-1,1,3,3-tetramethylguanidine
BQ	benzoquinone
Cbz	benzyloxycarbonyl
Cg	1,3,5,7-tetramethyl-2,4,8-trioxa-6-phosphaadamantane
cod	1,5-cyclooctadiene
conc	concentration
cp	cyclopentadienyl
cp*	pentamethylcyclopentadiene
Cy	cyclohexyl
DBDMH	1,3-dibromo-5,5-Dimethylhydantoin
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DG	directing group
DIAD	diisopropyl azodicarboxylate
DMA	*N*,*N*-dimethylacetamide
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMEDA	*N*,*N*-dimethylethylenediamine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DMT	dimethyl terephthalate
DPEphos	bis[(2-diphenylphosphino)phenyl] ether
DPPA	diphenyl phosphoryl azide
dppb	1,4-bis(diphenylphosphino)butane
dppe	ethylenebis(diphenylphosphine)
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
dtbbpy	4,4 -di-*t*-butyl-2,2 -dipyridyl
DTS	diverted total synthesis
E^+	electrophile
EDC	1-ethyl-3-(-3-dimethylaminopropyl) carbodiimide
ee	enantiomeric excess
equiv	equivalent
Fmoc	fluorenylmethyloxycarbonyl
GF	graphite film
h	hours
HAT	hydrogen atom transfer

HFIP	hexafluoroisopropanol
HPLC	High performance liquid chromatography
HRMS	high-resolution mass spectrometry
hv	light
i	iso
IC_{50}	half maximal inhibitory concentration
IMes	1,3-bis(2,4,6-trimethylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene
Ind*	heptamethyl indenyl
IPA	*i*-propyl alcohol
IR	infrared
KIE	kinetic isotope effect
m	meta
Mes	mesityl
min	minutes
MOM	methoxymethyl
m.p.	melting point
Ms	methanesulfonyl
MS	molecular sieves
m/z	mass to charge ratio
n	normal
NCS	*N*-chlorosuccinimide
ND	not detected
NIS	*N*-iodosuccinimide
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
Ns	nitrobenzenesulfonyl
Nu	nucleophile
o	ortho
p	para
PCET	proton-coupled electron transfer
phen	1,10-phenanthroline
Phox	phosphinooxazoline
PIFA	[bis(trifluoroacetoxy)iodo]benzene
pin	pinacol
PMB	*p*-methoxybenzyl
Py	pyridine
PyBox	pyridine-linked bis(oxazoline)
RCM	ring-closing metathesis
rr	regioisomeric ratio
rt	room temperature
s	sec
SAR	structure-activity relationship
SCX	strong cation exchange chromatography
SDS	sodium *n*-dodecyl sulfate
SET	single electron transfer
STAB	sodium triacetoxyborohydride

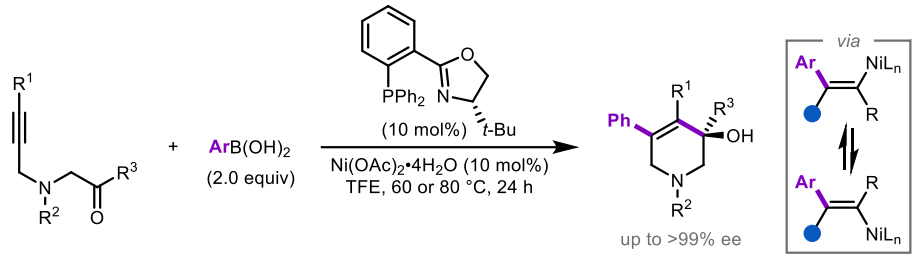
t	tert
t	time
T	temperature
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBHP	*t*-butyl hydroperoxide
TBS	*t*-butyldimethylsilyl
Tc	thiophene-2-carboxylate
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMB	1,3,5-trimethoxybenzene
TMS	trimethylsilyl
Tol	tolyl
Troc	2,2,2-trichloroethoxycarbonyl
Ts	*p*-toluenesulfonyl
UHP	urea hydrogen peroxide
Δ	heat at reflux

Part I and Part II are both numbered and referenced independently.

Abstract

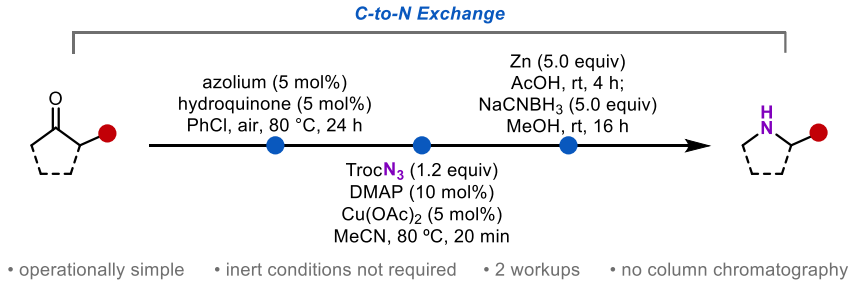
Part I: Nickel-Catalysed *anti*-Arylmetallative Cyclisations onto Ketones

A highly enantioselective and regioselective nickel-catalysed domino reaction of the addition of boronic acids across an alkyne, followed by subsequent cyclisation onto a ketone is reported. The reversible *E*/*Z* isomerization of the alkenylnickel intermediate is key to enable the overall *anti*-arylmetallative cyclisation. The process affords enantioenriched tertiary-alcohol-containing products of which the ring system is featured in several diarylindolizidine alkaloids.



Part II: Molecular Editing of Cyclic Ketones: C-to-N Atom Exchange

A process for the molecular editing of α-substituted cyclic ketones by performing a formal C-to-N atom exchange is reported. The key first step involves ring-opening the ketone, with the ketoacid product being leveraged through a Curtius rearrangement to introduce the nitrogen atom. Finally, a ring closing step forms the C-to-N atom exchanged product. This process involves simple air-tolerant chemistry, and the products themselves can be purified without the need for column chromatography with a preliminary scope of five compounds being reported.



Part I

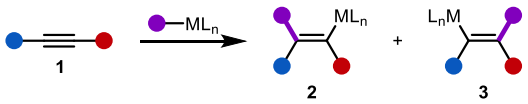
Enantioselective Nickel-Catalysed *anti*-Arylmetallative Cyclisations onto Ketones

1 Introduction

1.1 Carbofunctionalisation Of Alkynes

Alkynes are an incredibly versatile functional group that can be transformed by a plethora of methodology, including metal-catalysed reactions.[1–5] One key transformation of alkynes is the addition of new groups across the triple bond to form alkenes of different substation patterns; these alkene products are valuable, not only for their reactivity which enables further transformation, but they are also featured in a variety of natural products and biologically active compounds.[6–9]

A transformation of interest is the carbometalation of alkynes, which has proved to be a powerful tool to access highly substituted alkenes. Classically, this has been achieved using a stoichiometric organometallic reagent (e.g. Grignard reagents, organozinc reagents, etc.) as pro-nucleophiles along with a metal catalyst.[10–15] More recently there has been a shift to using boronic acids due to their numerous benefits: they are bench stable, easy to handle, have good functional group compatibility, with a vast number commercially available.[16–18] Commonly the organometallic reagent will add across the alkyne in a *syn*-selective manner, this limitation provides inherent control in the resulting stereochemistry of the product. There is however the issue of controlling the regioselectivity when using unsymmetric alkynes (**1**), to avoid a mixture of products **2** and **3** being formed (Scheme 1.1).



Scheme 1.1: *Addition of organometallics across alkynes.*

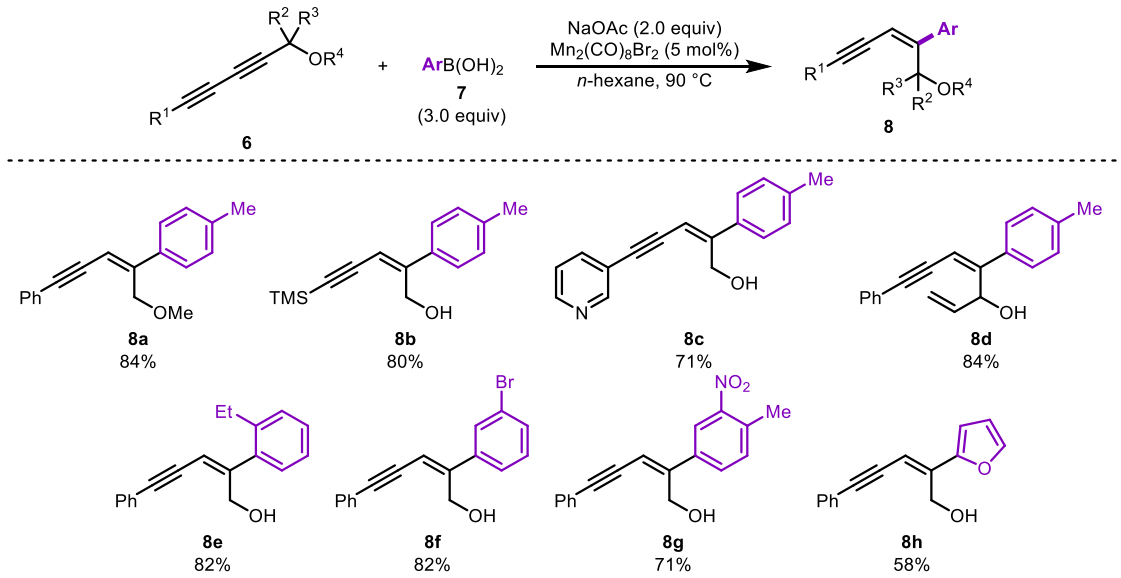
After carbometalation has occurred the alkenylmetal intermediate **2** can undergo further transformation, such as protonolysis to form a trisubstituted alkene **4**, or alternatively trapped with an electrophile to form a tetrasubstituted alkene **5** (Scheme 1.2). There are also cases where the alkenylmetal intermediate **2** can be utilised in metal-catalysed reactions such as Suzuki-type cross-couplings or Heck reactions.[10]



Scheme 1.2: *Reactivity of the alkenylmetal intermediate.*

1.1.1 Manganese-Catalysed

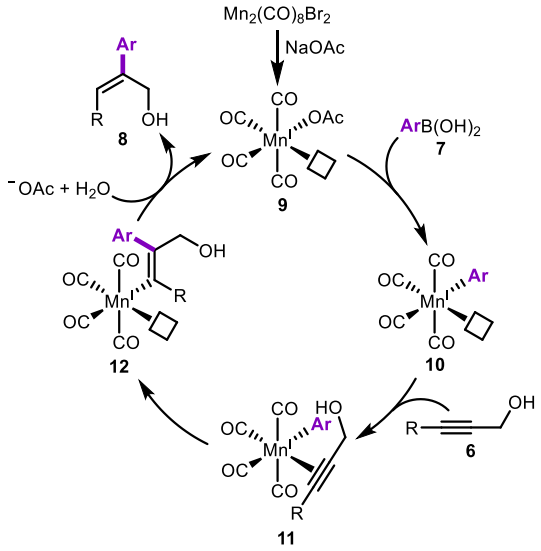
Xie reported one of the first examples of a Mn(I)-catalysed hydroarylation of unsymmetrical diynes **6** to form alkenes **8** as a single regio- and stereoisomer (Scheme 1.3).[19] Previous Mn(I)-catalysed hydroarylation required arylalkynes with preinstalled directing groups on the arene, however, Xie employed a propargylic alcohol/ether as a more versatile directing group.[20,21] The authors also attempted to employ rhodium- and palladium-catalysed hydroarylation conditions to their substrates, however only trace product was observed. Various arylalkynes **6** performed well, along with alkylalkynes and even silylalkynes (**8b**). On the other hand, whilst both primary (**8a–8c**) and secondary propargylic alcohols (**8d**) were successful, tertiary propargylic alcohols were not. With respect to the boronic acid scope both electron-rich (**8a** and **8h**) and electron-poor functional groups (**8g**) worked well along with *ortho*-substitution (**8e**).



Scheme 1.3: *Manganese-catalysed formation of **8**.*

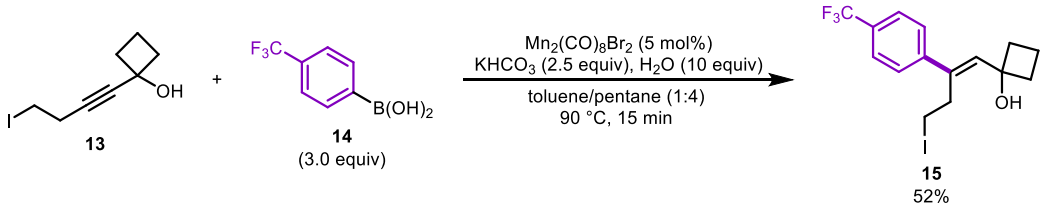
The authors investigated the mechanism, starting with the origin of the regioselectivity. They calculated the natural bond orbital charge distribution which showed that it is unlikely that the electronics are solely responsible. Hydroarylations of various monoalkynes required both an alcohol and an aryl group to retain good regioselectivity. Based on these results a proposed mechanism is outlined in Scheme 1.4.[22,23] First, NaOAc converts the precatalyst into **9** which then undergoes transmetalation to generate **10**. The formation of a **10**-like species was determined through isolation and X-ray crystallography from a reaction with stoichiometric $Mn_2(CO_8)Br_2$. The vacant coordination site of **10** then coordinates to **6**, which followed by migratory insertion into the alkyne forms **12**; the regioselectivity of this step was further investigated through computational calculations which determined a key weak OH–π interaction between the hydroxy group and the

aryl ring on **12** which drives the selectivity.[24] Finally protonolysis completes the cycle and forms the product **8**.



Scheme 1.4: *Proposed mechanism for the formation of* ***8****.*

The Xie group later expanded the scope of their manganese-catalysed hydroarylations to the simple internal alkyne **13** to form the tertiary allylic alcohol **15** (Scheme 1.5).[25] Compared to their previous work where they achieved β-arylation, γ-arylation was observed in this case when using a more sterically encumbered alcohol, all whilst avoiding β-OH elimination to form an allene. Under their developed system a vast number of substrates were successful, with several examples of late-stage functionalisation of complex medicinally derived alkynes, along with functional groups such as alkyl iodides (**13**).

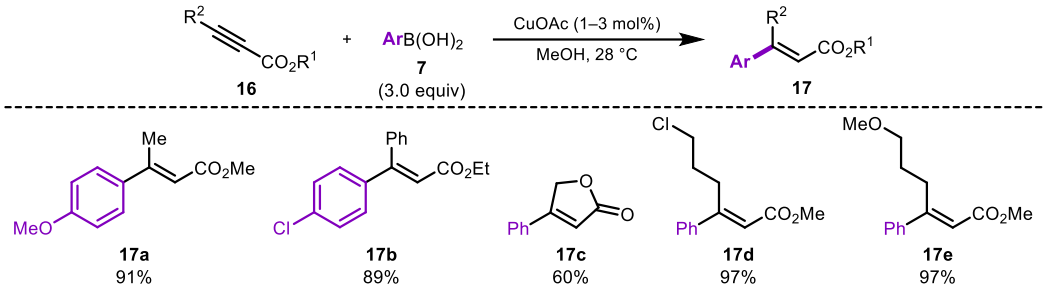


Scheme 1.5: *Manganese-catalysed formation of* ***15****.*

1.1.2 Copper-Catalysed

The copper-catalysed hydroarylation of alkynoates **16** was reported by Yamamoto *et al.* (Scheme 1.6).[26] The use of alkynoates allowed CuOAc to be employed as a catalyst at relatively low loadings without any need for a ligand, making it an economical process compared to earlier work, such as Hayashi's rhodium-catalysed hydroarylation (Scheme 1.9). The alkenes **17** were obtained with excellent regioselectivity, along with tolerating other electrophilic functional groups such as a primary alkyl chloride (**17d**). When using a tethered alcohol, the hydroarylation product underwent lactonisation *in situ* to form **17c**.

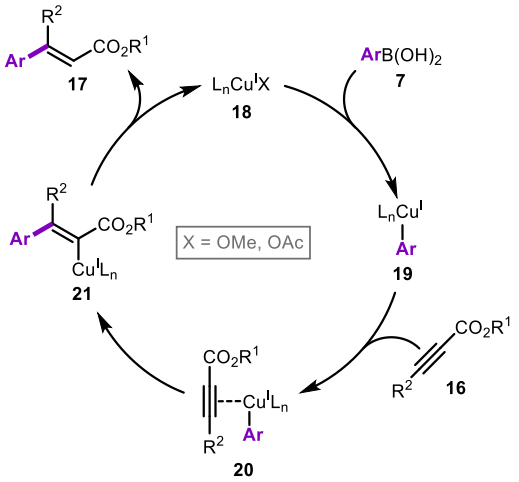
When alkynones were used in place of alkynoates a mixture of *syn*- and *anti*-hydroarylation products were afforded; the authors suggested this may be due to a possible alkenylcopper intermediate facilitating isomerisation through an allenolate intermediate.



Scheme 1.6: *Copper-catalysed hydroarylation of alkynoates* ***16****.*

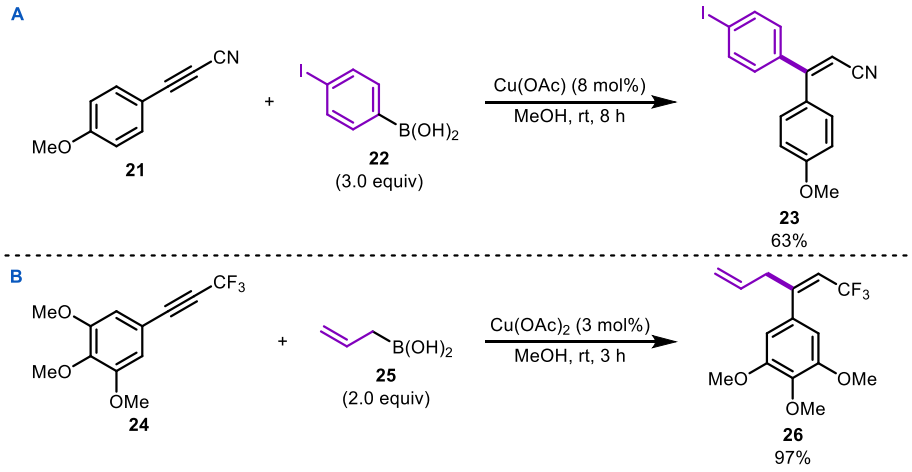
A proposed mechanism is outlined in (Scheme 1.7). First transmetalation of **18** with **7** affords **19**. Coordination to **16** followed by migratory insertion forms the alkenylcopper species **21**, which upon protonolysis gives the product **17** and reforms **18**.[27]

Later work by the Yamamoto group described allylboronates as nucleophiles under these reaction conditions, which was then utilised in the total synthesis of anhydromevalonate-5-phosphate.[28,29]



Scheme 1.7: *Proposed mechanism for the formation of* ***17****.*

Following on from alkynoates the Yamamoto group reported the copper-catalysed hydroarylation of alkynyl nitrile **21** to form acrylonitrile **22** (Scheme 1.8a).[30] Both electron-rich and electron-deficient coupling partners were tolerated, however sterically demanding boronic acids required more forcing conditions. With respect to functional group compatibility aryl iodides worked well, providing further avenues for product derivatisation.

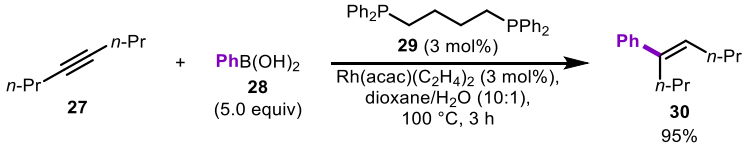


Scheme 1.8: *Copper-catalysed formation of* ***23*** *and* ***26****.*

Finally Yamamoto *et al.* applied their developed copper-catalysed hydroarylation conditions to alkynes with a trifluoromethyl group (**24**) as the products are of interest due to their potential bioactivity (Scheme 1.8b).[31,32] Previous palladium-catalysed methods had moderate to poor regioselectivity, however by using copper-catalysis the desired products were formed in excellent yields and stereoselectivity.[33] Arylboronic acids were employed with sensitive functional groups present such as aldehydes and iodides. Allyl boronic acid **25** could also be employed resulting in hydroallylation of the alkyne **26**.

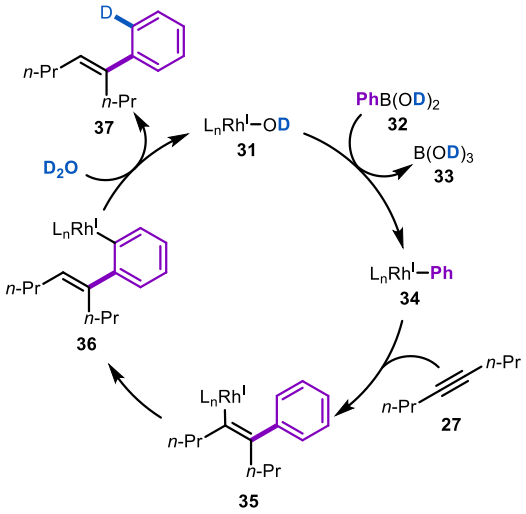
1.1.3 Rhodium-Catalysed

Hayashi reported the first example of the carbometalation of alkynes (**27**) using boronic acids (**28**) as the pro-nucleophile to form trisubstituted alkenes (**30**) utilising rhodium-catalysis (Scheme 1.9).[34] In the case of unsymmetric alkynes those that had an electron-withdrawing group formed the desired products with excellent regioselectivity, however, if there was little electronic bias then the regioselectivity degraded significantly.



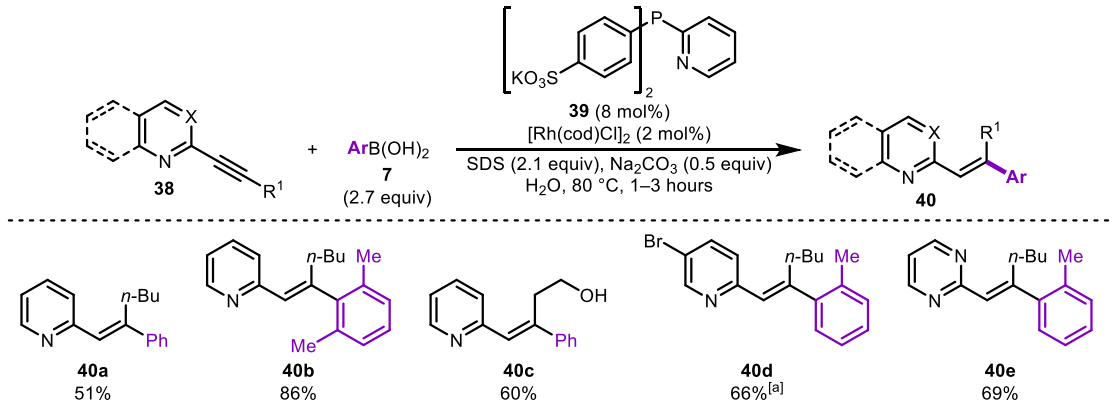
Scheme 1.9: *Rhodium-catalysed carbometalation of* ***27****.*

A proposed mechanism is outlined in Scheme 1.10. First transmetalation of **31** with **32** forms the arylrhodium species **34**. Coordination and migratory insertion into **27** affords the alkenylrhodium species **35**. At this point it was expected that protonolysis would form the product **30** and complete the catalytic cycle, however, deuterium labelling studies showed that once **35** is formed a 1,4-rhodium migration occurs, forming the arylrhodium species **36**. Finally, **36** undergoes protonolysis to complete the cycle and form **37**.



Scheme 1.10: *Proposed mechanism for the formation of* ***37****.*

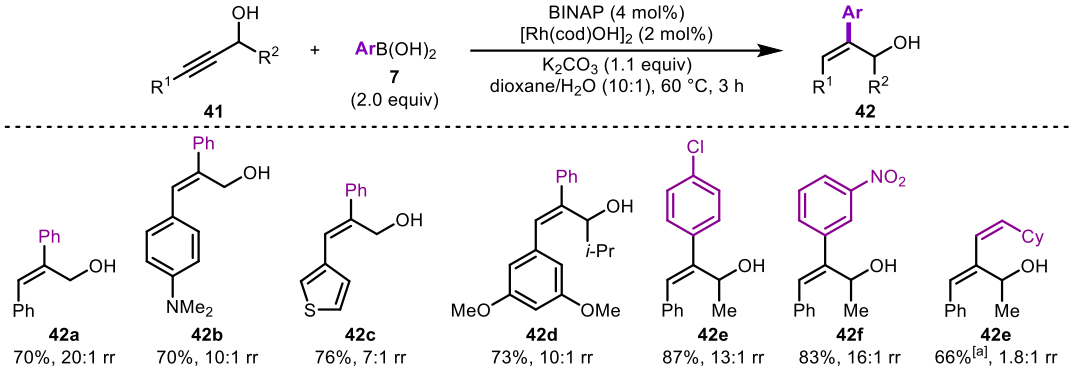
Lautens and co-workers reported the addition of arylboronic acids **7** to alkynes conjugated to electron-deficient heterocycles **38** under aqueous conditions, enabling the hydroarylated products **40** to be accessed in good yields and excellent regioselectivity (Scheme 1.11).[35,36] A novel water soluble ligand (**39**), along with sodium dodecyl sulfate (SDS) as a surfactant, allow for H_2O to be employed as the solvent. The pyridyl group on **39** was found to be key for the desired reactivity as replacing it with either a phenyl or *p*-$SO_3KC_6H_4$ group vastly decreased the yields. Interestingly it was found that *ortho*-substituted boronic acids performed best compared to other substitution patterns. Additionally, the reaction was reported to work excellently on a substrate with a propargylic pyridine showing that direct conjugation to the heteroaromatic ring is not necessary, which may imply that coordination between rhodium and the pyridine nitrogen directs reactivity and regioselectivity rather than the electronics of the alkyne.



Scheme 1.11: *Rhodium-catalysed formation of* ***40****.* [a]*[Rh(COD)Cl]₂ (4 mol%),* ***39*** *(16 mol%) and ArB(OH)₂ (5.0 equiv)*

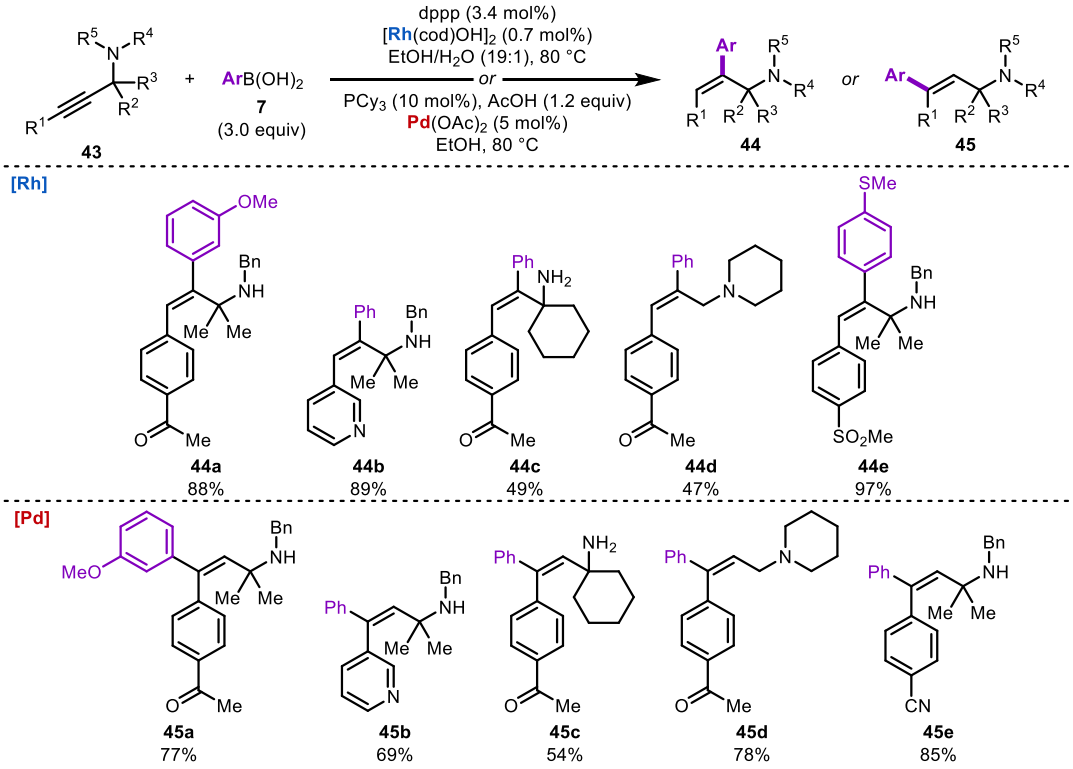
Following on from their previous work Lautens *et al.* sought to address the regioselectivity issues when hydroarylating aryl-alkyl substituted alkynes by using a propargylic

alcohol (**41**) (Scheme 1.12).[37] It is thought that coordination between the alcohol and rhodium facilitates the overall transformation, as subjection of alkynes without a propargylic alcohol to the optimised conditions gave poor conversions. However, when employing propargylic alcohols **41**, allylic alcohols **42** could be accessed in good yields and typically good regioselectivities. The products were subsequently shown to be good precursors for Friedel-Crafts alkylations to form indenes. Subsequent work by the group also demonstrated this methodology on the hydroarylation of propargylic sulfones.[38]



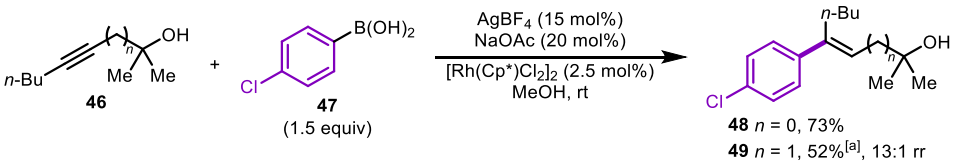
Scheme 1.12: *Rhodium-catalysed formation of* ***42****.* *[a]Combined yield of both regioisomers.*

Miranelli reported a regiodivergent approach for the hydroarylation of propargylic amines **43** with boronic acids **7**, forming **44** when using rhodium-catalysis, or, the opposite regioisomer **45** with palladium-catalysis (Scheme 1.13).[39] An investigation was made to examine the effect of stereoelectronics on the regioselectivity. Propargylic amines of various steric environments gave excellent regioselectivity suggesting that sterics may not be a key factor. As the reaction with rhodium was thought to go through a mechanism analogous to Scheme 1.10 this ruled out the potential for chelation control given that the rhodium would be placed on C_γ (with respect to the alcohol). To probe for electronic effects computational calculations of the charge distribution of the π-complex formed between the arylrhodium and alkyne were carried out. The results showed that C_γ has a greater negative charge than C_β which matched well with rhodium being more positively charged compared to the aryl group; this aligns with the regioselectivity that was observed experimentally. Overall this suggests that electronics play a more important role under these conditions compared to other systems where sterics dominate.[40] Based on these results the authors investigated the use of palladium-catalysis on the alkynes **43** and found the same trend was followed affording the opposite regioisomer **45** due to the difference in the mechanism of the palladium-catalysed hydroarylation (see Scheme 1.17).



Scheme 1.13: *Rhodium-catalysed formation of* ***44*** *and palladium-catalysed formation of* ***45****.*

One omission in the work by Lautens (Scheme 1.12) were tertiary propargylic alcohols as substrates due to the propensity of the alkenylrhodium intermediate undergoing β-OH elimination to form an allene rather than undergoing protonolysis.[41,42] Ma and co-workers found that by utilising Rh(III)-catalysis they were able to take tertiary (homo)propargylic alcohols **46** and obtain the hydroarylation products **48** and **49** in good yields and regioselectivities (Scheme 1.14).[43] Control reactions using β-OH elimination conditions showed that the boron source had an impact on the chemoselectivity with boroxines favouring β-OH elimination compared to boronic acids. Again, in this case it was critical for the alcohol to remain unsubstituted.

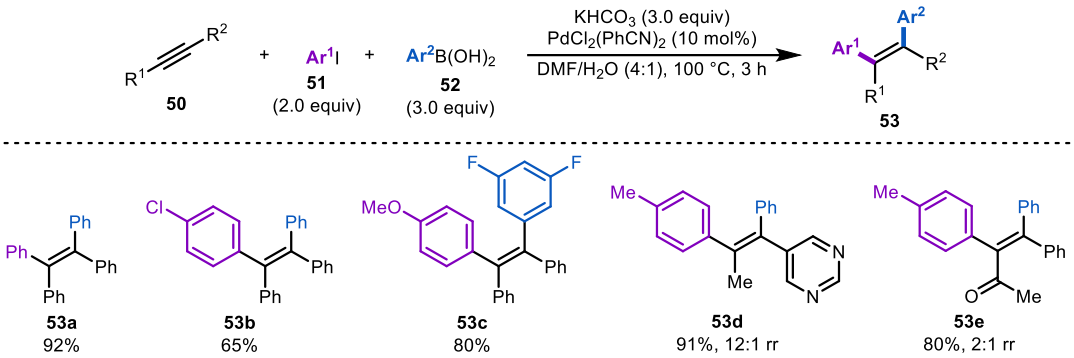


Scheme 1.14: *Rhodium-catalysed formation of* ***48*** *and* ***49****.* *[a]ArB(OH)2 (2.0 equiv)*

1.1.4 Palladium-Catalysed

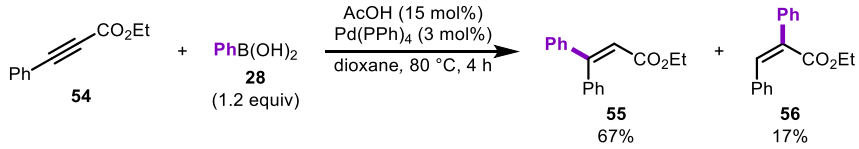
In 2003 Larock described the formation of tetrasubstituted alkenes **53** from a three-component coupling between alkynes **50**, aryl iodides **51** and arylboronic acids **52** (Scheme 1.15).[44,45] The products were obtained in typically good yields, without observing significant Suzuki cross-coupling products, along with functional groups such as aryl

chlorides (**53b**) and heterocycles (**53d**) being tolerated. The regioselectivity of non-symmetric alkynes (**53d**) was described to be under steric control, however, in the case of **53e** mismatched electronics and sterics led to poor regioselectivity.



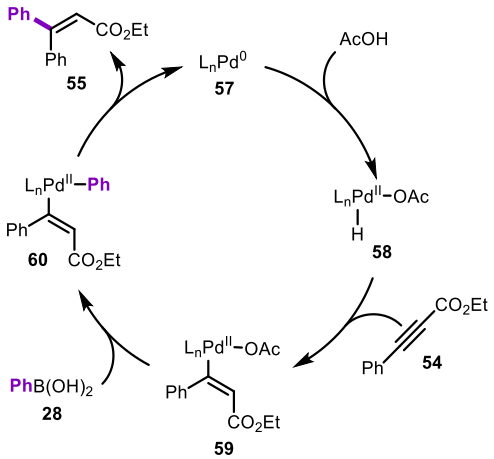
Scheme 1.15: *Palladium-catalysed formation of **53**.*

Oh and co-workers reported the palladium-catalysed hydroarylation of alkynes with boronic acids (Scheme 1.16).[46] When internal/terminal alkynes were used arylation was typically favoured on the carbon with the bulkiest substituent. When alkynoate **54** was used the expected regioisomer **55** was the major product, however, some of the other regioisomer **56** was also observed.



Scheme 1.16: *Palladium-catalysed hydroarylation of alkyne **54** forming regioisomers **55** and **56**.*

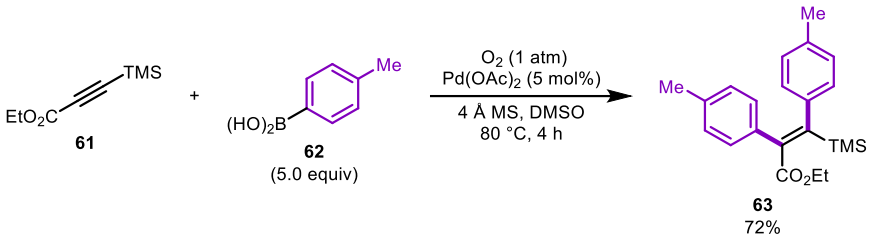
A proposed mechanism for this transformation is outlined in Scheme 1.17.



Scheme 1.17: *Proposed mechanism for the formation of **55**.*

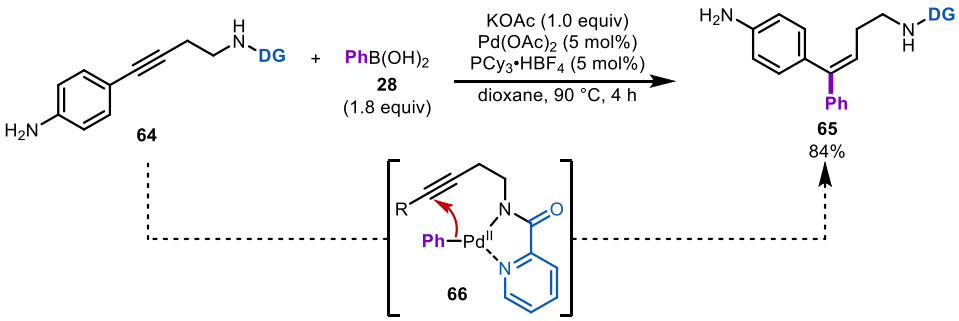
First **57** is thought to undergo oxidative addition with AcOH to form a Pd-H species (**58**) which subsequently inserts across the alkyne forming **59**; this is based on deuterium

labelling studies whereby deuteration of a terminal alkyne was observed when using AcOD without any boronic acid present, indicating an interaction between these components. Intermediate **59** then undergoes a transmetalation/reductive elimination sequence to afford the alkene product **55** and completing the catalytic cycle. Later work by Ogilvie found $Pd(OAc)_2$ in conjunction with small ligands, such as PEt_3, resulted in the complete regioselectivity of **55**.[47]



Scheme 1.18: *Palladium-catalysed diarylation of alkyne* ***61****.*

Under oxidative conditions the diarylation of alkyne **61** affording the tetrasubstituted alkene **63** was achieved by Larock (Scheme 1.18).[48] These conditions allow for carbopalladation of the alkyne rather than hydropalladation, which when followed by a transmetalation/reductive elimination sequence with another equivalent of **62** forms the product **63** along with Pd(0) which is aerobically re-oxidised.[49]



Scheme 1.19: *Palladium-catalysed directed hydroarylation of alkyne* ***64****.*

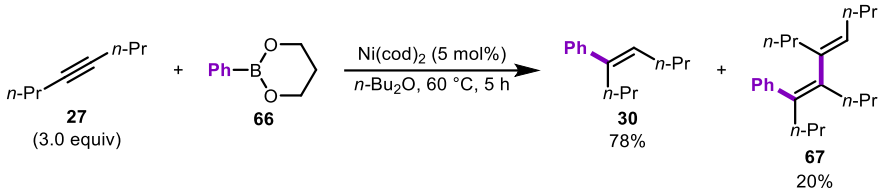
In 2016 Engle and co-workers reported the regioselective hydroarylation of alkynes (**64**) by employing a tethered (removable) directing group (Scheme 1.19).[50] A picolinamide moiety was found to be the most effective directing group, which they proposed can coordinate to the palladium, directing arylation towards the distal end of the alkyne; under the described conditions excellent regioselectivities of >50:1 were obtained. Compared to the mechanism above (Scheme 1.17), Engle hypothesised that this reaction may proceed through a Pd(II) redox-neutral pathway, whereby the presence of a base enables transmetalation to form an arylpalladium species. Upon coordination to the directing group intermediate **66** is formed which is primed for migratory insertion into the alkyne. The reaction tolerated the use of both aryl- and alkylalkynes. In the case of a TMS alkyne,

arylation was observed with a 6:1 ratio of distal/proximal, which is impressive given the sterics of the TMS group generally encourages the reverse regioselectivity, albeit in a reduced yield, likely due to said steric effects. The tether length could also be varied from ethylene to butylene with little loss of regioselectivity, but when a methylene linker was used the regioselectivity was diminished.

In addition to the examples discussed above, the palladium-catalysed carbometalation of alkynes is a thoroughly investigated area with various other examples reported.[51–58]

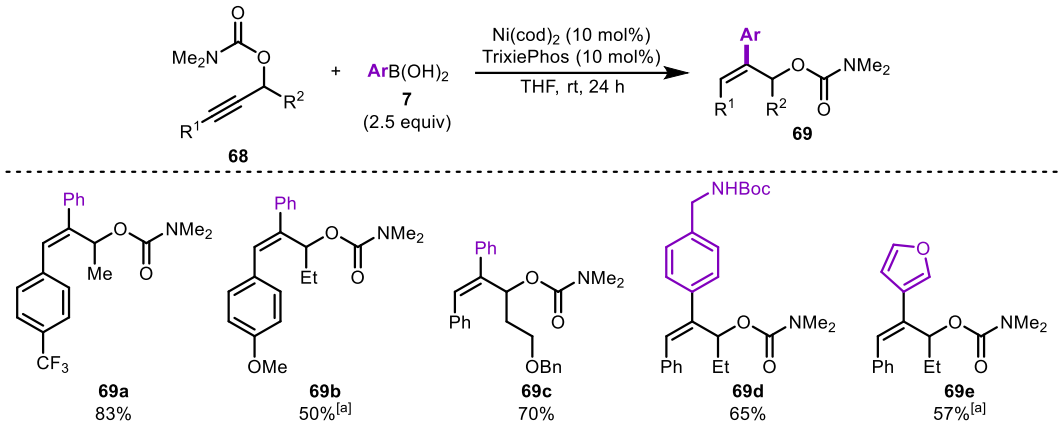
1.1.5 Nickel-Catalysed

Owing to its similar reactivity of palladium, nickel has also been featured extensively in the carbofunctionalisation of alkynes.[59,60] The hydroarylation of internal alkynes (**27**) using arylboronates (**66**) was reported by Shirakawa *et al*. (Scheme 1.20).[61] They also observed the tetrasubstituted alkene **67** as a side product, which under slightly modified conditions, the authors were able to form almost exclusively.



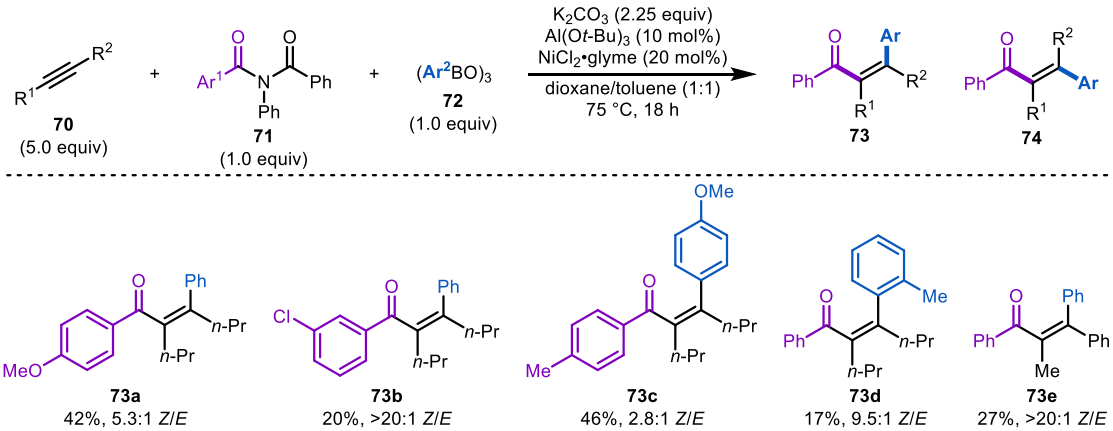
Scheme 1.20: *Nickel-catalysed hydroarylation of **27** to form the trisubstitued alkene **30** and tetrasubstituted alkene **67**.*

Jarvo and co-workers reported the hydroarylation of propargylic carbamates **68** using nickel-catalysis. Typically, free alcohols as a directing group were required in previous reports. Jarvo found that carbamates were an effective directing group forming the allylic carbamate products **69** in good yields and regioselectivities, without any allylic substitution being observed (Scheme 1.21).[62] These reactions proceeded at room temperature, however electron-rich aryl groups on either coupling partner (**69b** and **69e**) required elevated temperatures to get good conversions. The directing group was limited to dimethylcarbamate, either diphenylcarbamate, or the unsubstituted carbamate gave poor yields. Other directing groups, such as pivalates and carbonates, were also tested, however formation of an allene product was favoured over hydroarylation. Deuterium labelling showed that the origin of the hydrogen on the alkyne is from the boronic acid; this suggests that the reaction may occur through the formation of a Ni-H species (formed from the nickel catalyst and the boronic acid) with the mechanism broadly following what was shown in Scheme 1.17. This mechanism would also explain the regioselectivity of addition across the alkyne.



Scheme 1.21: *Nickel-catalysed formation of* ***69****.* [a]*Reaction done at 80 °C.*

The carboacylation of alkynes **70** was reported by Stanley forming enones **73** (Scheme 1.22).[63] During optimisation several challenges were identified. The reaction would stall at ~65% yield, which was thought to be due to the product **73** poisoning the catalyst; this was confirmed *via* a control reaction spiked with **73** which gave a reduced yield of 13%. To mitigate this, they screened Lewis acid additives and found that the addition of Al(O*t*-Bu)$_3$ increased the yield to 90%, however the stereoselectivity was still problematic. Arylboroxines were found to have a positive effect on the stereoselectivity compared to arylboronic acids, this was thought to be due to Ni-H species formed from oxidative addition into the O-H bond of the boronic acid. Once formed the Ni-H then proceeds to isomerise the product **73** to **74**. A control reaction showed that when subjecting pure **73** to the reaction conditions for 4 hours with 5.0 equivalents of a boronic acid the purity degraded to a 2.5:1 mixture of *Z*/*E* isomers.



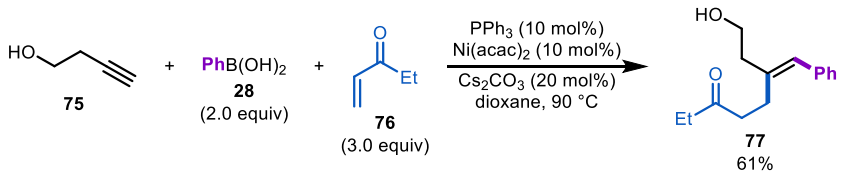
Scheme 1.22: *Nickel-catalysed dicarbofunctionalization of alkynes* ***70*** *with imides* ***71*** *and boroxines* ***72****.*

In conclusion an array of metal-catalysed carbofunctionalisation of alkynes has been described allowing for control of the regiochemistry and stereochemistry of the products. Additionally, this chemistry is amenable to both mono- and dicarbofunctionalization.

These factors allow for the modular approach of alkyne diversification, enabling access to a wide array of valuable alkenes.

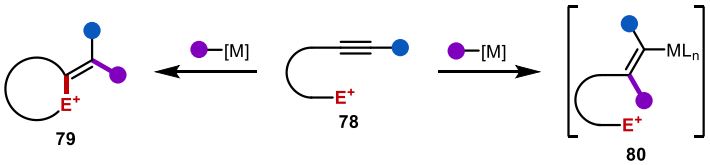
1.2 *Syn*-Carbometallative Arylative Cyclisations of Alkynes

The metal-catalysed reactions of alkynes using organometallics received a lot of attention in the late 1900s which laid the groundwork for the development of more complex reactions using organoboron reagents. For example, with organometallics, alkenylmetal intermediates can be utilised as a nucleophile for the addition into certain electrophiles such as carbonyls.[64] This was eventually translated into using organoboron reagents (**28**) with terminal alkynes (**75**) and enones (**76**) by Reddy and co-workers to form trisubstituted alkenes (**77**) (Scheme 1.23).[65] Multi-component reactions such as this are valuable due to the ability to vary the simple building blocks to access a diverse array of valuable products. Unfortunately, there seldom reports of such multi-component couplings using organoboron reagents due to difficulties overcoming entropy, as well as avoiding premature protonolysis of the alkenylmetal intermediate.



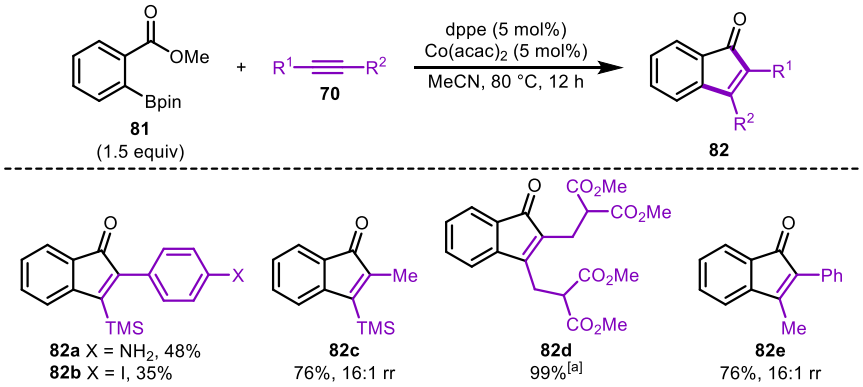
Scheme 1.23: *Intermolecular nickel-catalysed three-component coupling forming the trisubstituted alkene **77**.*

A natural progression from a multi-component intermolecular reaction is to tether two or more of the components together, enabling a domino reaction. For example an alkyne tethered to an electrophile **78** which can undergo carbometalation followed by cyclisation onto the tethered electrophile, forming a complex product **79** in minimal steps (Scheme 1.24).[66–69] By taking this approach not only is the entropic barrier reduced but stereochemistry can also be built into the starting material. Given that migratory insertion into an alkyne **78** is *syn*-selective there are two possible outcomes based on the regioselectivity: if addition occurs proximal to the electrophile, then cyclisation can proceed to form **79**. On the other hand, distal addition furnishes intermediate **80** which due geometric constraints is unable to cyclise, therefore giving this process a further element of control.



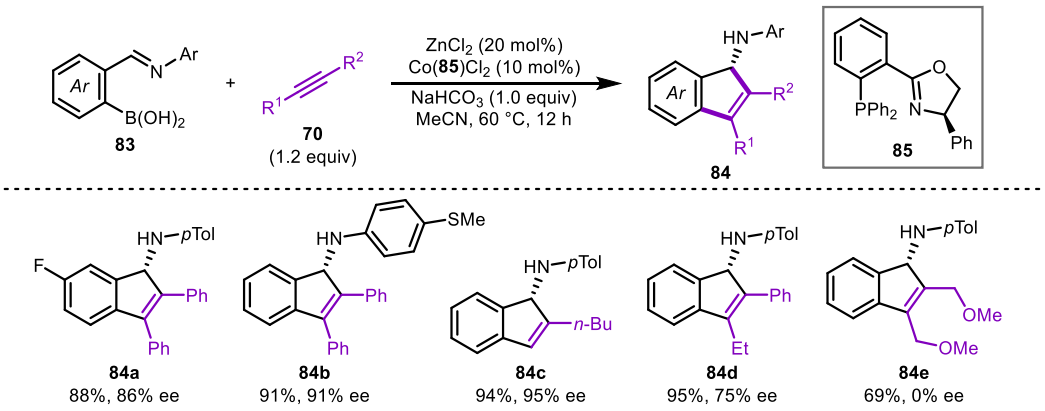
Scheme 1.24: *Syn-selection carbometalation/cyclisation of alkynyl tethered electrophiles.*

1.2.1 Cobalt-Catalysed



Scheme 1.25: *Cobalt-catalysed formation of* ***82****.* [a]*Co(acac)₂ (2 mol%) was used.*

The use of cobalt-catalysis for such domino reactions was not reported until recently when Ueda and co-workers described the synthesis of indenones **82** (Scheme 1.25).[70] In this case rather than using an alkyne tethered to an electrophile, the boronate was tethered to the electrophile. Various alkynes **70** were shown to react with **81**, including both symmetric and asymmetric alkynes. When using TMS-substituted alkynes (**82a–82c**) good regioselectivity was observed with often only a single isomer being isolated. On the other hand, when using an asymmetric alkyne with aryl/alkyl groups (**82e**) the regioselectivity deteriorated. The scope tolerated challenging functionality such as anilines (**82a**) and aryl iodides (**82b**). Monosubstituted malonates (**82d**) were also tolerated giving excellent yields, with no side-reactions occurring at the ester.



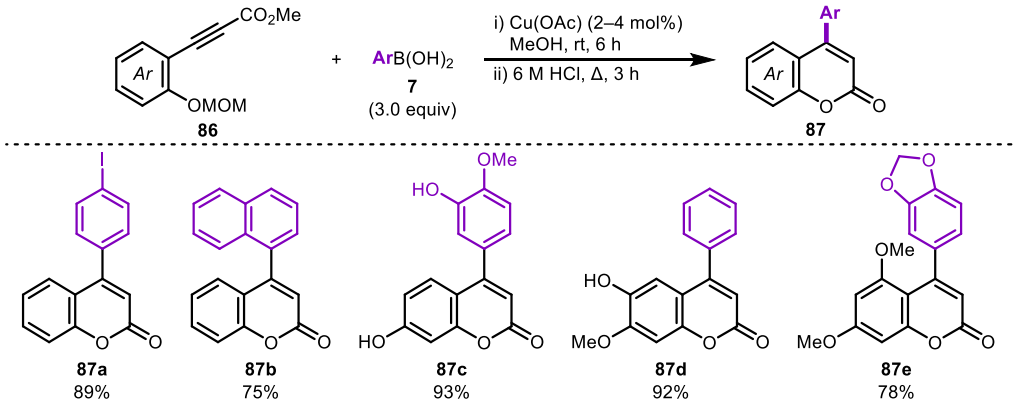
Scheme 1.26: *Cobalt-catalysed formation of indenamines* ***84****.*

Cheng *et al.* reported the enantioselective synthesis of indenamines **84** from boronic acids **83** and alkynes **70** (Scheme 1.26).[71] Both symmetric (**84a** and **84b**) and unsymmetric alkynes were tolerated in excellent yields and typically excellent enantioselectivities. In the case of non-symmetric alkynes, the regioselectivity was excellent. The reaction was also amenable to aryl (pseudo)halides in place of the boronate by simply adding 3.0 equivalents of Zn as a reductant, along with removing the $ZnCl_2$ and $NaHCO_3$. Typically,

under reductive conditions the results were very similar, with the added benefit that they could be ran at 40 °C rather than 60 °C, however it was found that the enantioselectivities were more sensitive to the sterics of the substrate.

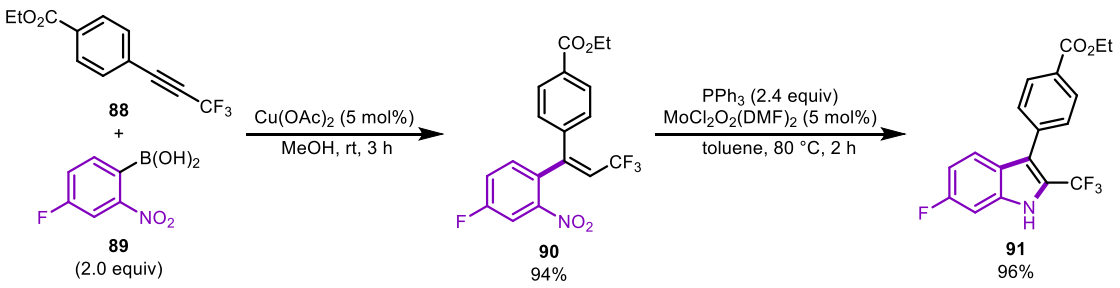
1.2.2 Copper-Catalysed

Yamamoto reported the synthesis of 4-arylcoumarins derivatives **87** through a domino copper-catalysed hydroarylation/acid-mediated cyclisation procedure (Scheme 1.27).[72] Initial attempts were made using an unprotected phenol, however, the presence of the phenol caused side reactions where methanol would add into the starting material. With the MOM protected alcohol a variety of alkynes **86** were successfully converted into coumarins **87**, tolerating a range of arylboronic acids in excellent yields. Substitution of the alkyne partner was also possible, enabling the synthesis of several naturally occurring coumarins (**87d** and **87e**). Zhao has since taken a similar approach and utilised palladium-catalysis with alkynyl phosphonates to access phosphacoumarin derivatives.[73]



Scheme 1.27: *Copper-catalysed formation of 4-arylcoumarins **87**.*

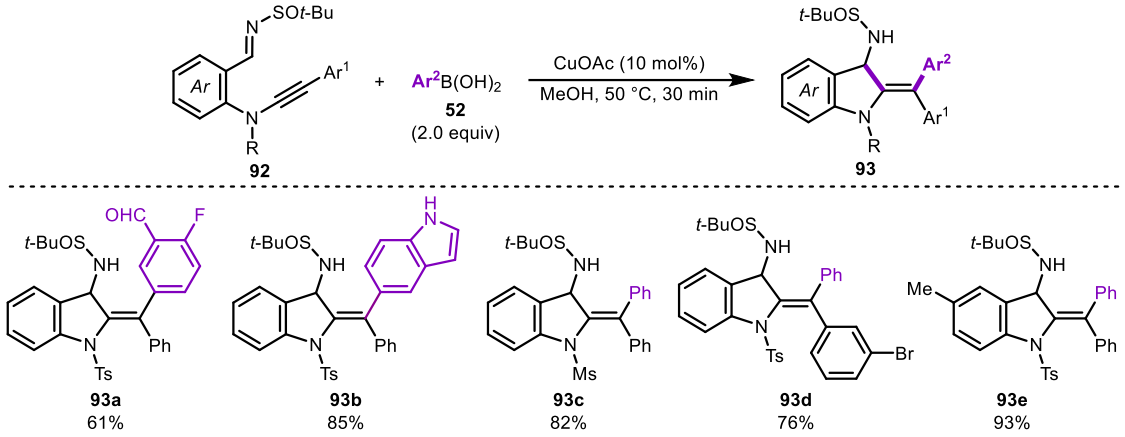
Yamamato *et al.* further utilised their developed methodology for the hydroarylation of alkynes (**88**) with *ortho*-nitro-containing boronic acids (**89**), which primes (**90**) for a Cadogan cyclisation to form indoles (**91**) in excellent yields (Scheme 1.28).[74]



Scheme 1.28: *Copper-catalysed formation of indole **91**.*

Ye and co-workers investigated ynamides **92** as a hydroarylation/cyclisation precursor as at the time they were underreported as substrates for carbometalation (Scheme

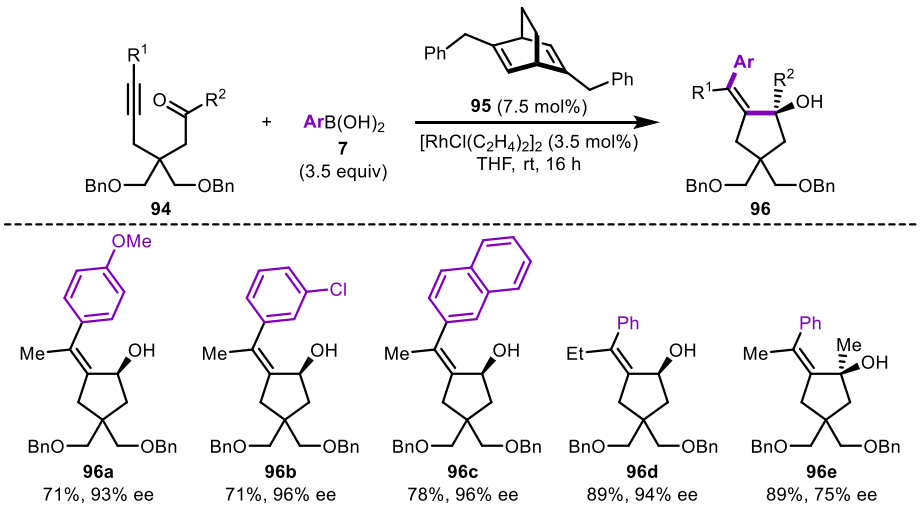
1.29).[75,76] The developed conditions were efficient and quick, affording the products in good yields. Groups such as indoles (**93b**) and aldehydes (**93a**) were tolerated.



Scheme 1.29: *Copper-catalysed hydroarylation/cyclisation of ynamides* ***92****.*

1.2.3 Rhodium-Catalysed

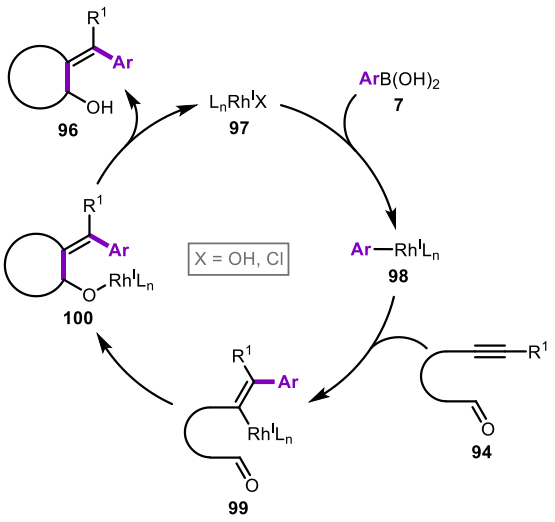
Developing upon their previous work Hayashi and co-workers extended their arylative carbometalation of alkynes using rhodium-catalysis onto alkynones and alkynals **94** (Scheme 1.30).[77] The initial scope afforded racemic products, however, use of the chiral ligand **95** gave a complementary enantioselective variant, affording the 5-*exo*-trig products **96** in good yields and enantioselectivities. Unfortunately, when using ketones the enantioselectivity was diminished as seen in **96e**.



Scheme 1.30: *Rhodium-catalysed arylation/cyclisation of* ***94****.*

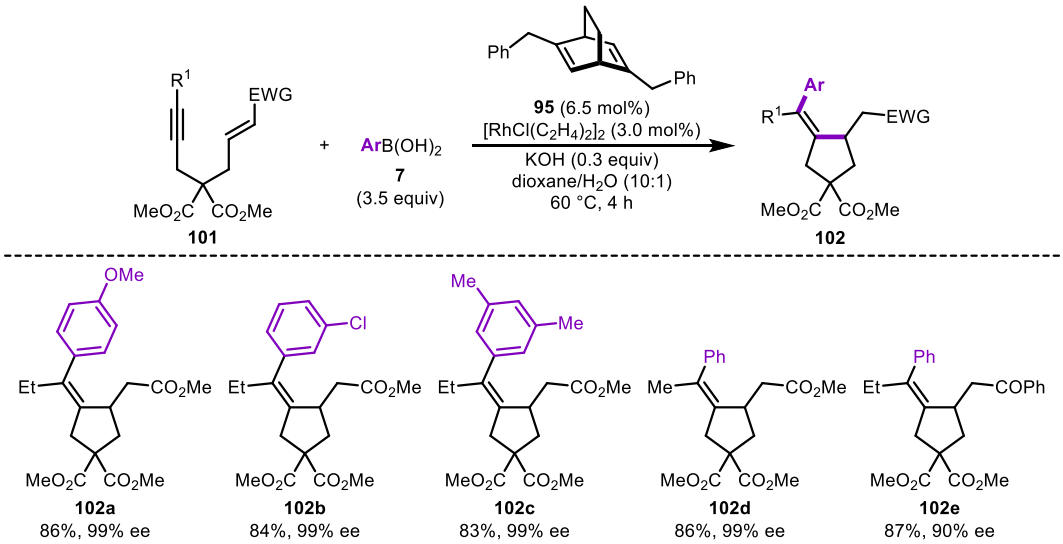
A proposed mechanism is outlined in Scheme 1.31. First transmetalation with the aryl boronic acid **7** yields the aryl rhodium species **98**. *Syn*-carbometalation onto the alkyne **94** places the rhodium proximal to the carbonyl, which followed by addition into the

ketone then forms **100**. Finally, protonolysis affords the product **96** and reforms the active catalyst **97**.



Scheme 1.31: *Proposed mechanism for the formation of* ***96****.*

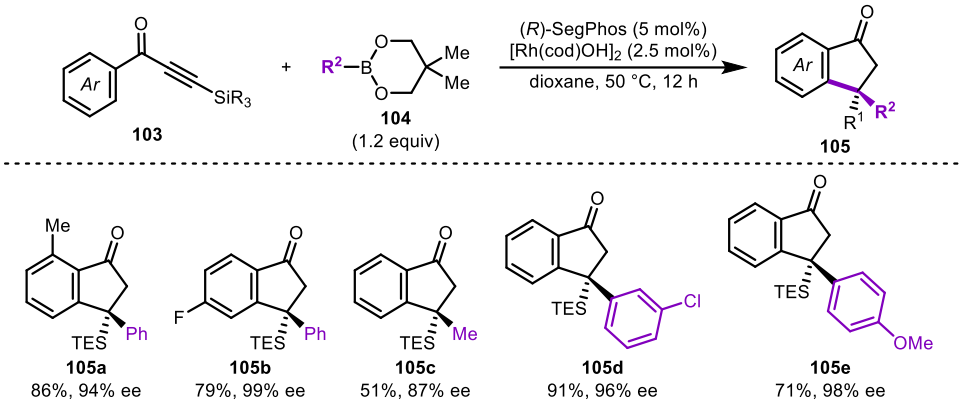
Hayashi has also reported α,β-unsaturated carbonyls tethered to alkynes **101** cyclised *via* a 1,4-addition using similar conditions to their work above (Scheme 1.32).[78] The products **102** were obtained in excellent yields and enantioselectivity, with both alkynoates (**102a–102d**) and alkynones (**102e**) as the electrophile. Unfortunately, the alkyne substituent was limited to simple alkyl groups.



Scheme 1.32: *Rhodium-catalysed arylation/cyclisation of* ***101****.*

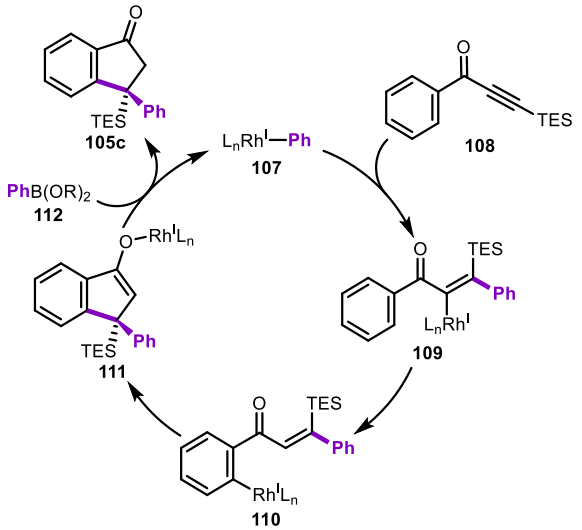
After Hayashi reported the hydroarylation of alkynes using rhodium-catalysis which featured a 1,4-Rh migration (Scheme 1.10) they, along with other groups, set out to further exploit this reactivity.[34,79] Initially in 2005 Hayashi described the work of reacting **103** analogues with arylzinc reagents, utilising a 1,4-rhodium migration to obtain the 1,1-dicarbofunctionalisation of alkynes forming indanones **105**.[80] Unfortunately attempts to

make this chemistry enantioselective were unsuccessful, with 54% ee being their best result. Later in 2007 they reported that by using silylalkynones **103** with aryl- and alkyl-boronates **104**, along with (*R*)-SegPhos as a chiral ligand, indanones **105** could be accessed in good yields and excellent enantioselectivities (Scheme 1.33).[81] Attempts were made to use boronic acids, however the yields were poor; this was appointed to them dehydrating *in situ* and the H_2O formed protonating the alkenylrhodium intermediate. The use of boronates **104** eliminated this possibility, whilst retaining good reactivity towards transmetalation.



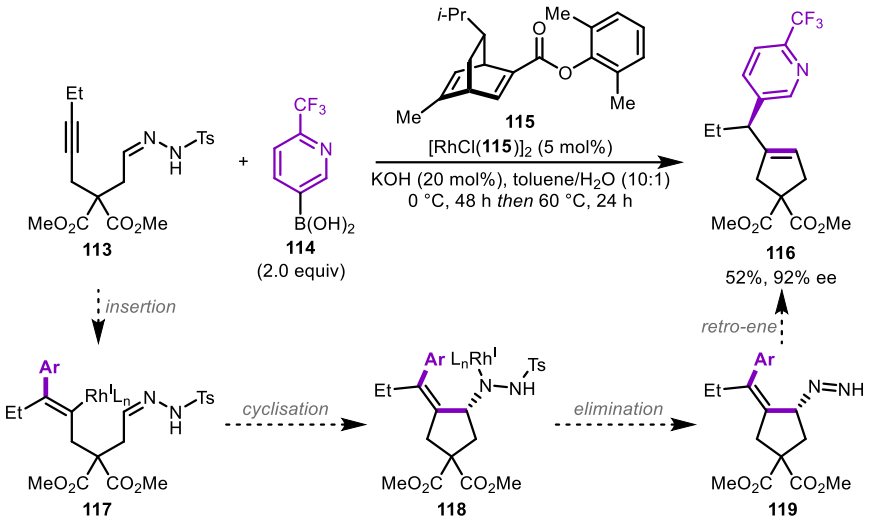
Scheme 1.33: *Rhodium-catalysed formation of indanones* ***105****.*

A proposed mechanism is outlined in Scheme 1.34. The active catalyst **107** is formed from transmetalation with the boronate **112**, and subsequently undergoes a regioselective migratory insertion into the alkyne **108** to give the alkenylrhodium species **109**. A 1,4-rhodium migration forms the arylrhodium species **110** which subsequently undergoes an enantioselective 1,4-addition to form the rhodium enolate **111**. Transmetalation of **111** turns over the catalyst and forms the indanone **105c**.



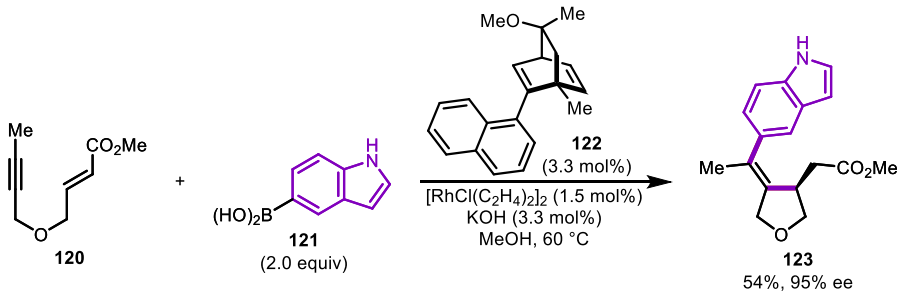
Scheme 1.34: *Proposed mechanism for the formation of indanone* ***105c****.*

Recently Lee *et al.* extended the electrophile scope to *N*-tosylhydrazones (**113**) (Scheme 1.35).[82] First carbometalation of the alkyne forms **117**, which subsequently adds into the hydrazone affording **118**. Rather than **118** undergoing protonolysis elimination to form the allylic diazene **119** occurs. A retro-ene reaction of the allylic diazene simultaneously extrudes N_2 and isomerises the alkene to form the cyclopentene **116**. Notably *N*-Boc hydrazones were also tolerated along with a variety of boronic acids.



Scheme 1.35: *Rhodium-catalysed addition/cyclisation/rearrangment of tosylhydrazone* ***113****.*

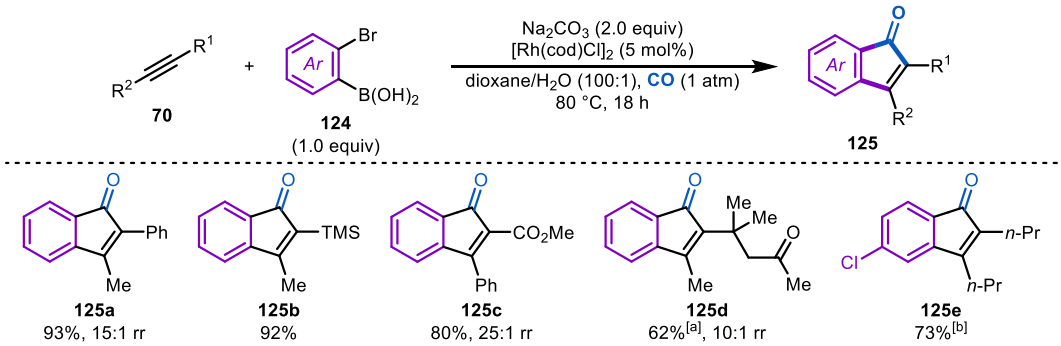
Work done by the Darses' group showed that the linker between the alkyne and the electrophile is also amenable to change. The use of an oxygen tether (**120**) allowed for the enantioselective formation of oxacycles **123** (Scheme 1.36).[83] A wide scope of boronic acids were demonstrated, including heteroaromatic boronic acids (**121**). However, there were limitations with respect to the alkyne substituent, as variation from methyl to *o*-MeC_6H_4 inverted the regioselectivity of the initial insertion into the alkyne, which followed by a rhodium 1,4-migration and cyclisation formed a benzazepine derivative.



Scheme 1.36: *Rhodium-catalysed formation of* ***123****.*

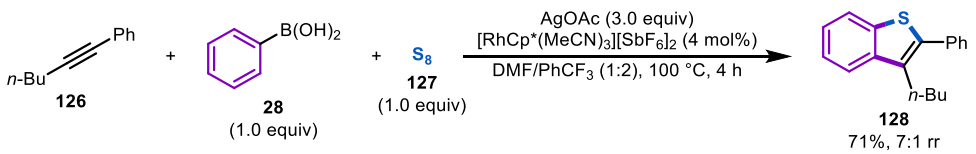
The examples above all proceed *via* a Rh(I) redox-neutral pathway under. The cyclisations mentioned thus far all involve an alkyne tethered to an electrophile, however this reactivity is not limited to such substrates as there are examples of cyclisations occurring where

the alkyne is tethered to an allylic methoxy group or even an unactivated alkene.[84,85] As previously mentioned, the three-component coupling between an alkyne, boronic acid and electrophile is a highly challenging, but desirable, transformation. Chatani *et al.* envisioned that boronic acids with an *ortho*-bromide moiety **124** could undergo an initial carbometalation with alkynes **70**, which followed by subsequent oxidative addition into the aryl bromide would form a Rh(III) intermediate. This intermediate could then undergo a carbonylation/reductive elimination to form **125** (Scheme 1.37).[86] Various alkynes were tolerated, however, those without a strong electronic or steric bias (**125e**) showed deterioration of the regioselectivity. Presence of an electrophile, such as a ketone (**125d**), still led to the formation of the desired product without any ketone addition products being observed. The reaction also works with an aryl bromide tethered to an alkyne to form analogous products to **125** when reacted with boronic acids.



Scheme 1.37: *Rhodium-catalysed formation of* ***125****.* [a]*[Rh] (2.5 mol%) was used.* [b]*ArCl used in place of ArBr.*

Miura and co-workers sought to expand upon their previous rhodium-catalysed oxidative cyclisation methodology to form benzothiophenes (**128**) through a three-component coupling between alkynes (**126**), boronic acids (**28**) and S8 (Scheme 1.38).[87,88] Unlike the work by Chatani (Scheme 1.37), this work utilised a C-H activation step to form a similar rhodacycle intermediate which could then undergo a single sulfur insertion/reductive elimination sequence to form benzothiophenes (**128**). An oxidant was found to be necessary as the formation of said intermediate was postulated to occur *via* Rh(III) rather than Rh(I). Substitution on the boronic acid sometimes led to poor regioselectivity resulting from the C-H activation step. Thankfully the regioselectivity of the hydroarylation step was often good, and the products obtained in moderate to good yields.

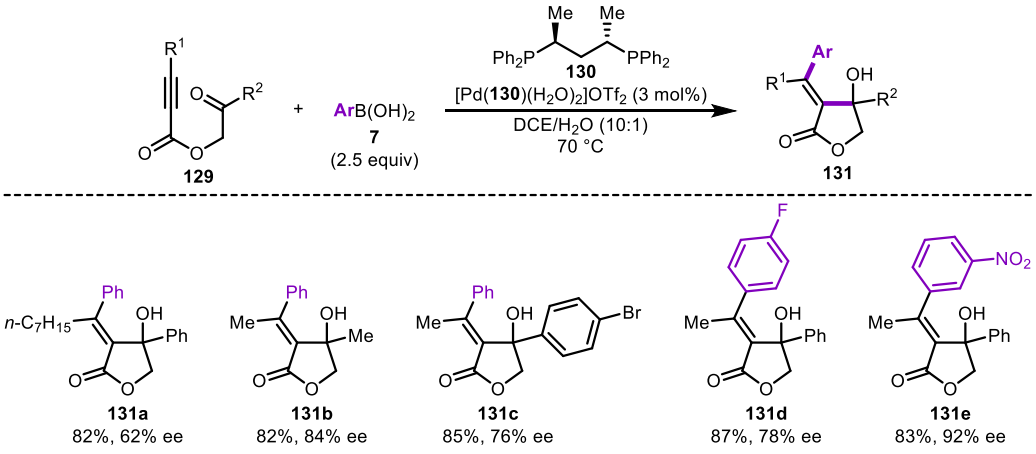


Scheme 1.38: *Rhodium-catalysed formation of benzothiophene* ***128****.*

Beyond the examples shown above the rhodium-catalysed *syn*-carbometallative cyclisation of alkynes has been a thoroughly investigated area with numerous other examples reported.[89–94]

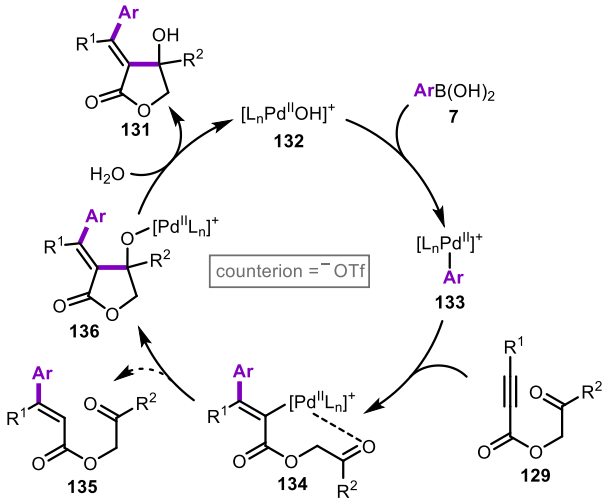
1.2.4 Palladium-Catalysed

Palladium-catalysed cascade cyclisation reactions have been extensively studied.[95] Palladium has been shown to do similar cyclisation reactions as rhodium, however unlike rhodium which typically proceeds through a redox-neutral Rh(I) pathway, both redox-active and redox-neutral pathways are commonly accessed using palladium.[96] For example if a cationic palladium catalyst is employed then it is hypothesised that reactivity occurs *via* a redox-neutral Pd(II) pathway.[97] Ultimately these differences in mechanistic pathways to rhodium allow access to alternate products. The first reported example of a palladium-catalysed arylative cyclisation onto a tethered electrophile was by Lu *et al.* using a cationic palladium species (Scheme 1.39).[97] Alkynones **129** were employed, generating lactones **131** in good yields and moderate to good enantioselectivities. The use of cationic Pd(II) has several advantages compared to neutral Pd(II): vacant coordination sites, stronger Lewis acidity, and harder metal property which help enable the desired reactivity.



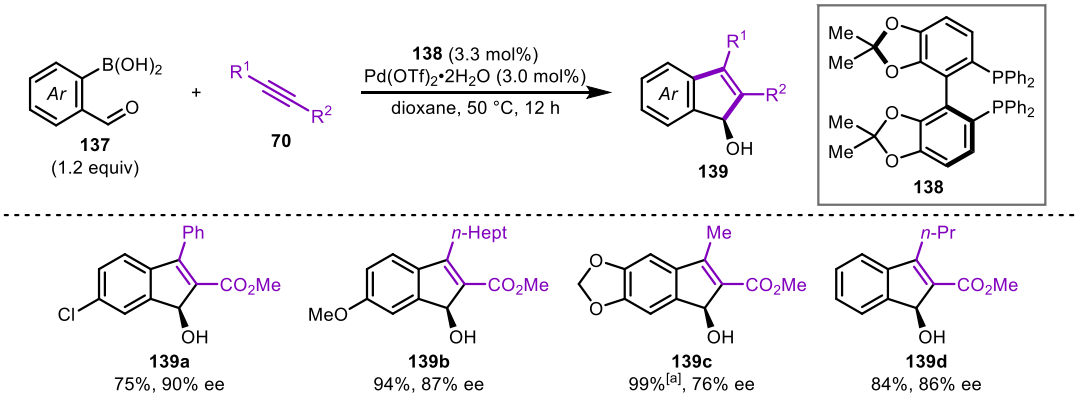
Scheme 1.39: *Palladium-catalysed formations of lactones **131**. Absolute stereochemistry not reported.*

A proposed mechanism is outlined in Scheme 1.40. **123** undergoes transmetalation with the boronic acid **7** affording **133**. Distal *Syn*-carbometalation onto the alkyne **129** forms **134** which can then take two possible paths. The first is protonolysis which forms the side-product **135**, the second is addition into the ketone, which may potentially be activated by the Lewis acidity of the palladium species, forming the lactone **136**. Finally, protonolysis of **136** regenerates the active catalyst **132** and forms the product **131**.



Scheme 1.40: *Proposed mechanism for the formation of* ***131****.*

Another possibility for the *syn*-carbometallative arylative cyclisations of alkynes is to place the electrophile on the boronic acid coupling partner. In 2007 the Lu group reported the coupling of boronic acids **137** with simple alkynes **70** to form enantioenriched indenols **139** in good yields and enantioselectivities (Scheme 1.41).[98] The reaction worked best with alkynoates, as dialkyl substituted alkynes failed to form any product. Likewise, ketones as the electrophile were not fruitful. Xu and co-workers later reported that Phox ligands can be employed with varied success; whilst the enantioselectivities obtained were excellent, asymmetric alkynes suffered from relatively poor regioselectivities.[99]

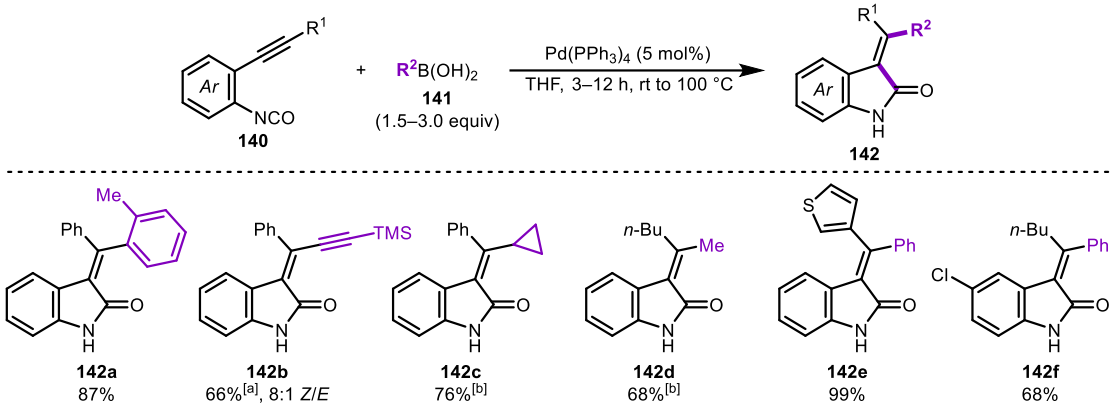


Scheme 1.41: *Palladium-catalysed formation of indenols* ***139****.* [a] *{Pd[(R)-BINAP]•2H2O}(OTf)2 was used.*

The Lu group subsequently reported the use of imines, derived from **137**, to access indenamine analogues of **139**, however to get good enantioselectivity a chiral sulfinamine was employed along with a chiral ligand.[100] Lu and others have since reported various different *syn*-carbometallative cyclisations of alkynes using this cationic palladium paradigm.[101–103]

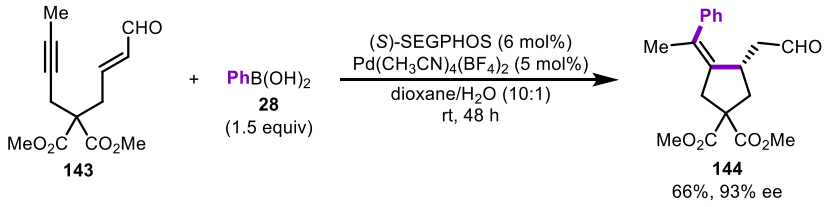
Murakami and co-workers reported that isocyanates **140** can also function as suitable electrophiles. In the presence of boronic acids **141** under palladium-catalysis **140** cyclised

to form the heterocycles **142** in excellent yields, regioselectivity and stereoselectivity (Scheme 1.42).[104] A wide variety of boronic acids were compatible, including those with steric hinderance (**142a**). A large advantage of utilising palladium-catalysis was that alkynylboronic acids (**142b**) and alkylboronic acids (**142c** and **142d**) could be employed to install sp and sp^3 carbons respectively; under their previously developed rhodium-catalysed conditions on analogous substrates this was not possible.[105] Given that all the products were observed as a single regioisomer, along with Pd(II) salts being unreactive, the authors proposed that the reaction may proceed through an oxidative cyclisation to form an oxopalladacycle, which then undergoes a transmetalation/reductive elimination sequence to form the product **142**.



Scheme 1.42: *Palladium-catalysed formation of **142**. [a]$Pd(dba_3)_2$•$CHCl_3$ (2.5 mol%), P(2-furyl)$_3$ (5.0 mol%) was used. [b]Dioxane used as the solvent.*

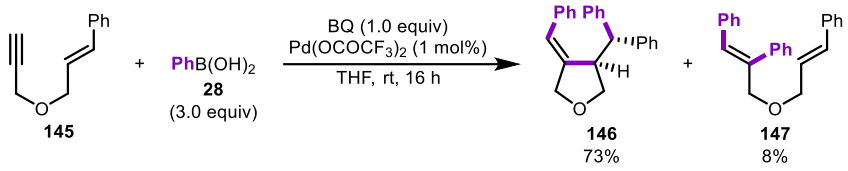
The arylation/1,4-addition to α,β-unsaturated carbonyls (**143**) has also been described by the Lu group using a cationic palladium species. Again only a narrow scope was described with the alkyne group being limited to simple alkyl or aryl units (Scheme 1.43).[106] The linker was variable with malonates, *N*-tosylsulfonamides and oxygen linkers all being tolerated. However, whilst the scope was narrow, the cyclopentanes (**144**) were isolated in good yields and excellent enantioselectivities.



Scheme 1.43: *Palladium-catalysed formation of **144**.*

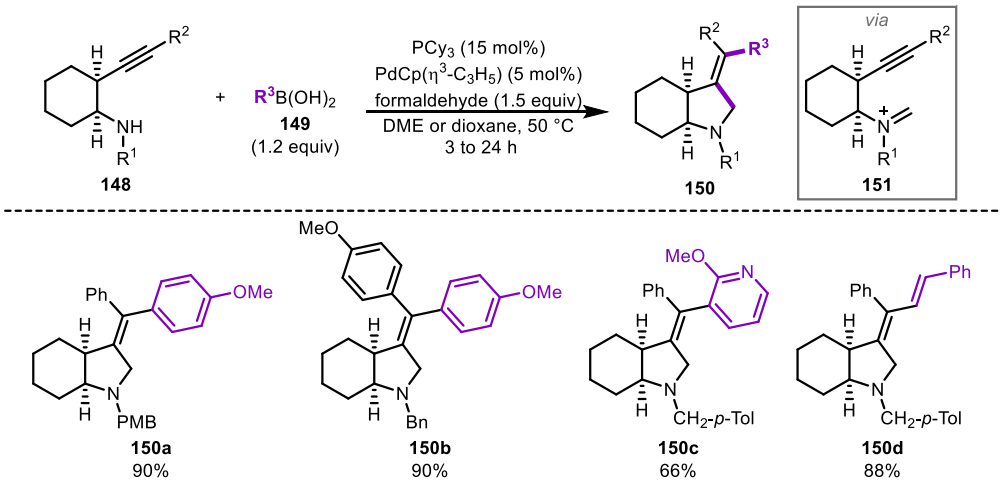
Bäckvall reported the diarylation of enynes (**145**) with boronic acids (**28**) using benzoquinone (BQ) as an oxidant (Scheme 1.44).[96] The authors proposed that after *syn*-carbometalation/cyclisation, the alkyl palladium species undergoes a second transmetalation to install the second aryl group, which followed by reductive elimination forms the

product **146**. The Pd(0) species is then re-oxidised by BQ, reforming the active catalyst and completing the cycle. It is suggested that BQ also coordinates before reductive elimination, accelerating the rate at which it occurs. Reductive elimination also occurred to a lesser extent before cyclisation forming some of the bis-arylated side product **147**.



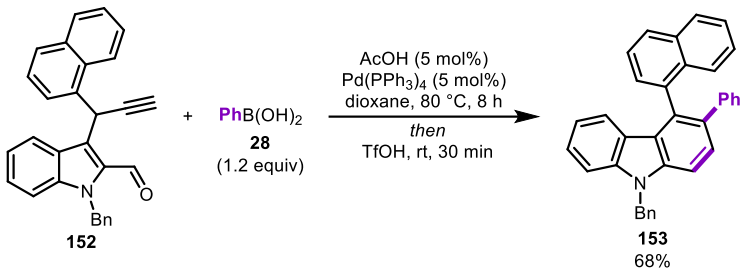
Scheme 1.44: *Palladium-catalysed formation of* ***146*** *and* ***147****.*

In a three-component reaction Doi *et al.* formed the iminium electrophiles **151** *in situ* between the secondary amine **148** and formaldehyde (Scheme 1.45).[107] Retention of stereochemistry and good yields were observed across a number of products **150** using various aryl and alkenyl boronic acids **149**, all whilst avoiding alternative reactivity such at the Petasis borono-Mannich reaction.[108] When linear aminoalkynes were employed the reaction was relatively sluggish with a decreased yield, suggesting that the Thorpe-Ingold effect plays a significant role in this reaction.[109]



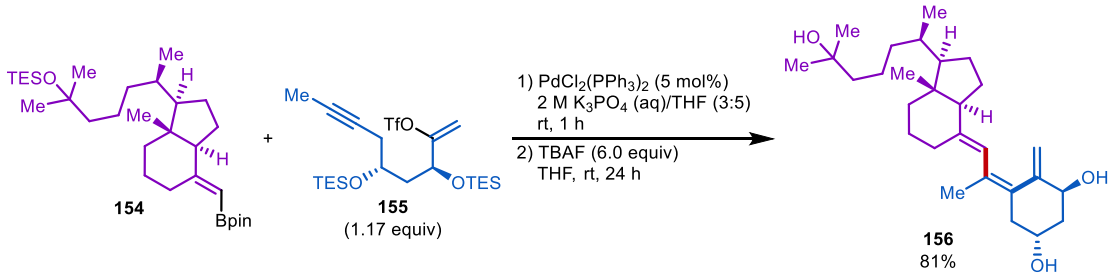
Scheme 1.45: *Palladium-catalysed formation of* ***150****.*

The Reddy group were able to access arylated carbazoles (**153**) from alkynals (**152**) and arylboronic acids (**28**) through a cascade reaction: first palladium-catalysed hydroarylation of the alkyne, followed by an acid-mediated cyclisation/dehydration (Scheme 1.46).[110] Both electron-rich and electron-poor boronic acids gave good yields. It was also shown that ketones can be used in place of the aldehyde as the electrophile, allowing for another point of diversification in the carbazole products.



Scheme 1.46: *Palladium-catalysed formation of carbazole* ***153****.*

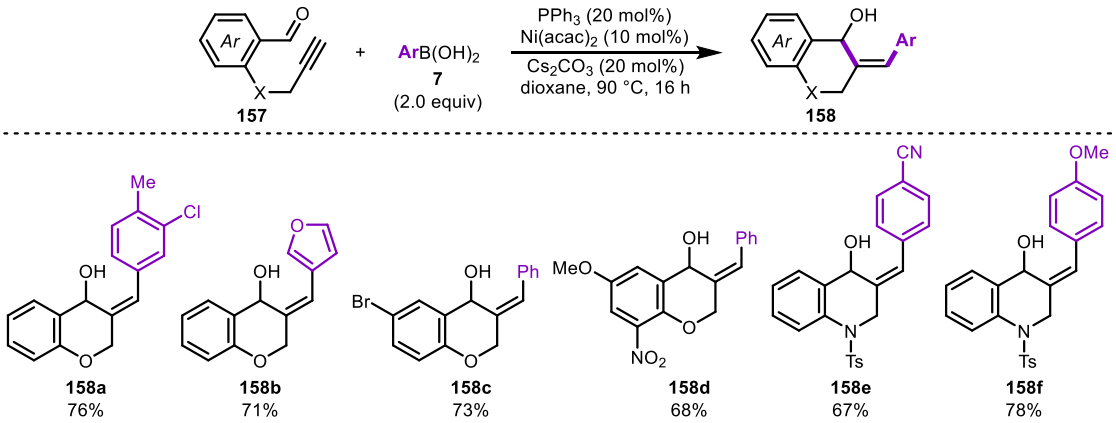
The application of *syn*-carbometallative cyclisations has also found use in total synthesis, such as Mouriño's total synthesis of 1α,25-dihydroxyvitamin $D3_a$ (**156**) (Scheme 1.47).[111] The penultimate step involved a palladium-catalysed cyclisation/alkenylation cascade between an alkenyl boronate **154** and alkynyl triflate **155**, which followed by deprotection of the TES groups to afford the natural product **156** in a 81% yield over two steps.



Scheme 1.47: *Palladium-catalysed formation of 1α,25-Dihydroxyvitamin* D_3 *(****156****).*

1.2.5 Nickel-Catalysed

Whilst the nickel-catalysed carbofunctionalisation of alkynes is well described, the use of nickel-catalysis for the *syn*-carbometallative cyclisations of alkynes was not described until 2018.[112] By using *N*- or *O*-propargyl benzaldehydes Reddy was able to access chromane skeletons **158**, a motif found in several natural products (Scheme 1.48).[113]

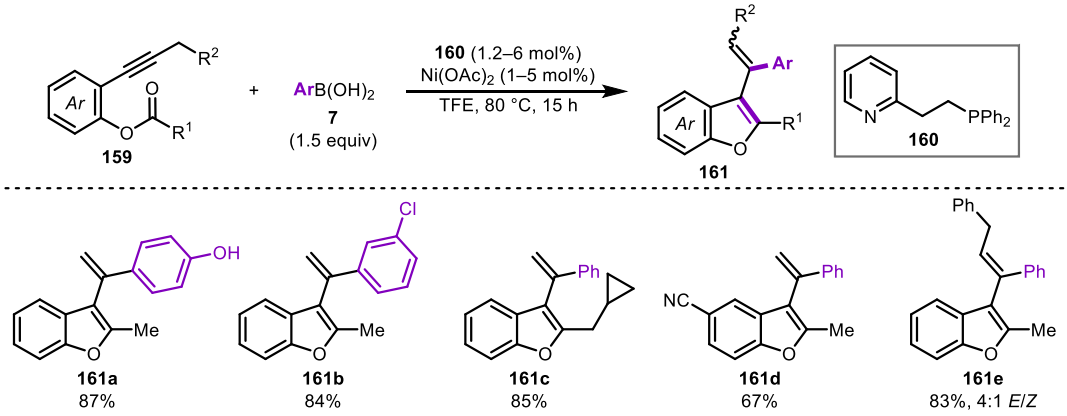


Scheme 1.48: *Nickel-catalysed formation of* ***158****.*

Functional groups such as aryl bromides (**158c**) and nitriles (**158e**) were tolerated, along with heterocycles such as a furan (**158b**). Some examples were also shown using an

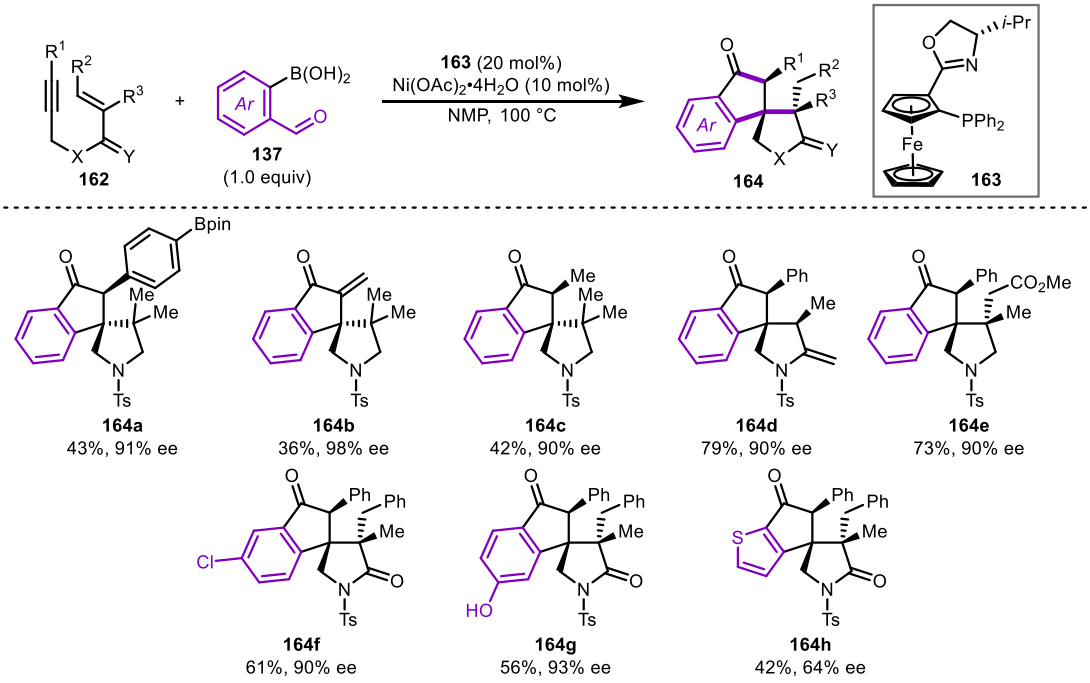
enone as the electrophile affording the 1,4-addition products. Unfortunately, they were limited to only using terminal alkynes with no substituted alkyne examples. Since this seminal report the area of these nickel-catalysed cyclisation reactions has grown rapidly.[114–116]

Cho and co-workers described an umpolung approach towards the formation of benzofurans **161**, whereby the alkyne (**159**) acts as the nucleophile and the ester as an electrophile, compared to conventional methodology which utilises phenols as a nucleophile for oxymetalations of alkynes (Scheme 1.49).[117–119] The mechanism is thought to be analogous to Scheme 1.40 up to the point where the alkenylnickel species adds into the ester to form an alkoxynickel species, which then dehydrates (rather than undergoing protonolysis) to form the benzofurans **161**. The products were formed in excellent yields with functional groups such as aryl chlorides (**161b**) and nitriles (**161d**) being well tolerated. When a trisubstituted alkene (**161e**) was formed a mixture of stereoisomers was isolated, with the *E* isomer being favoured.



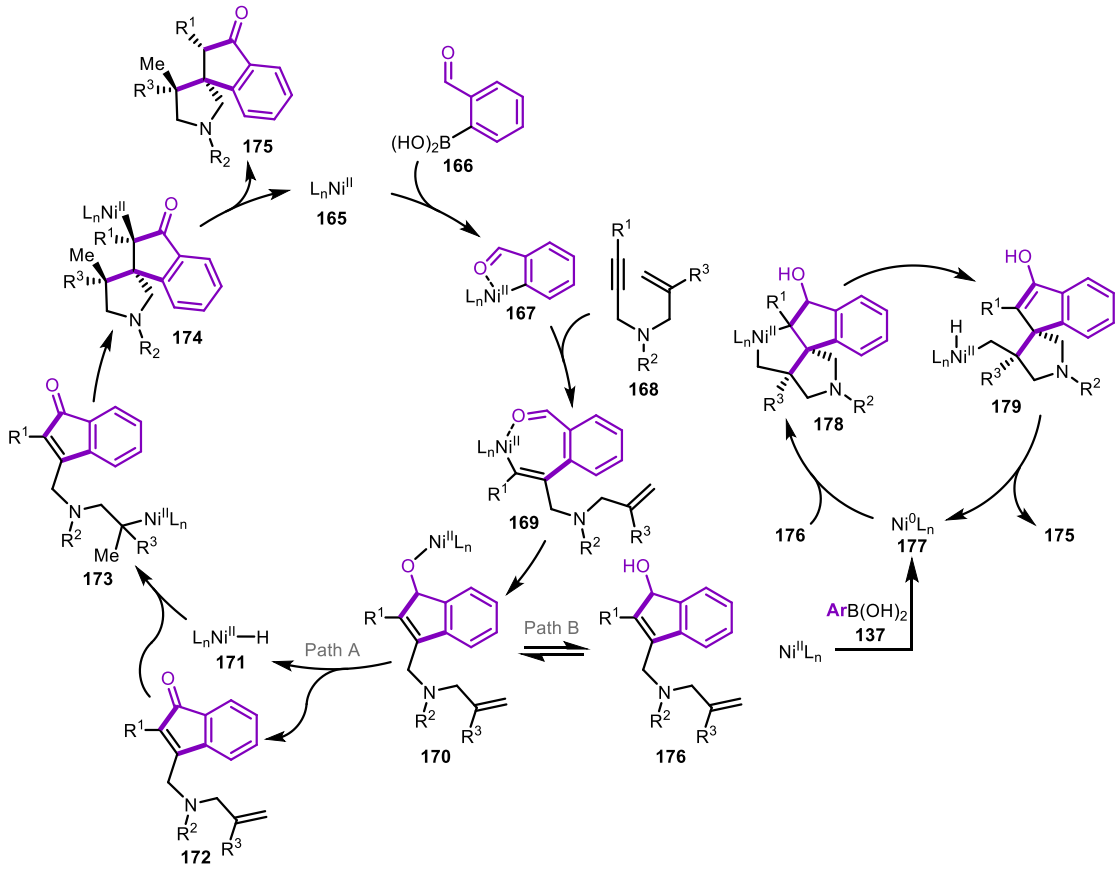
Scheme 1.49: *Nickel-catalysed formation of benzofurans **161**.*

Kong *et al.* reported the enantioselective formation of complex spirocycles **164** through a nickel-catalysed borrowing hydrogen cascade cyclisation (Scheme 1.50).[120] During optimisation they found that polar aprotic solvents such as DMSO, DMA and NMP were critical for the formation of the spirocycle. Meanwhile Phox-type ligands afforded the best yields which led them to using **163**. An extensive scope was displayed with functional groups such as aryl boronates (**164a**) being tolerated, along with nitrogen-containing heterocycles and anilines. Presence of alkenes (**164b** and **164d**) also lead to successful spirocyclisation. The alkyne could also be substituted with alkyl groups (**164c**), as the carbometalation step on such substrates is often challenging under nickel-catalysis.



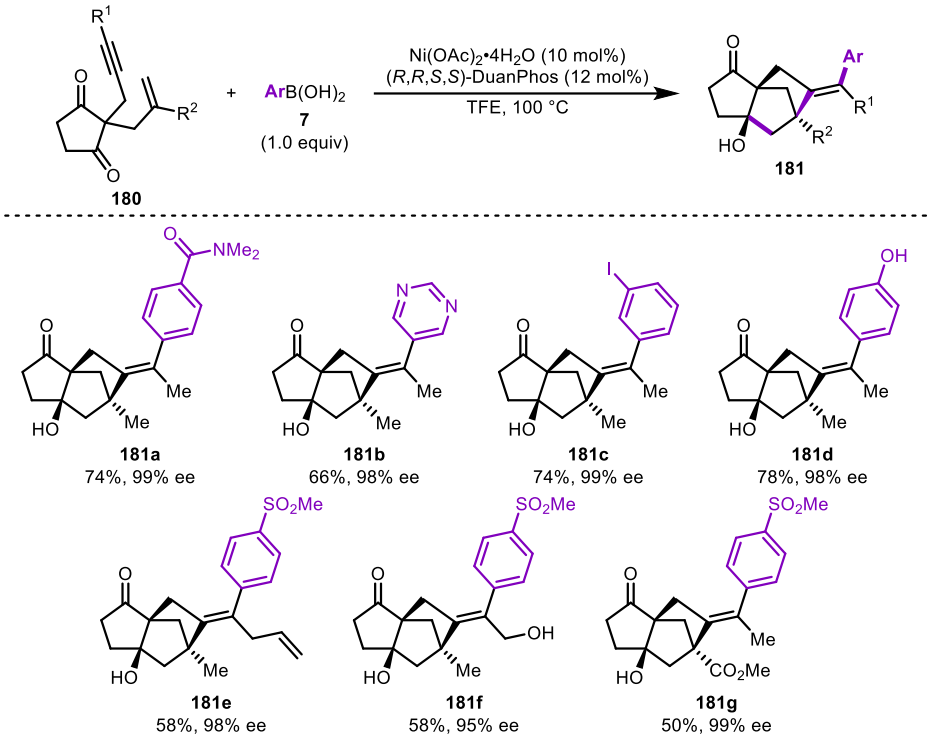
Scheme 1.50: *Nickel-catalysed formation of spirocycles* ***164****.*

A proposed mechanism is outlined Scheme 1.51. First transmetalation of **165** with the boronic acid **166** occurs, with coordination to the aldehyde possibly assisting this step. The arylnickel species **167** then coordinates and inserts into the alkyne **168** to form **169** which primes nickel for addition into the aldehyde to form the alkoxynickel **170**. At this point there are two possible routes that could lead to product formation: in Path A the next step is β-H elimination to form the enone **172** and a nickel hydride **171**. This step was based on KIE studies using a deuterium labelled aldehyde where a KIE of 3.2 was observed, indicating that this may be the rate-determining step of the reaction. The nickel hydride **171** then inserts into the unactivated alkene in **172**; use of a deuterated aldehyde showed high levels of deuterium incorporation at the methyl group providing further evidence. Finally, spirocyclisation forms the nickel enolate **174** which can then undergo protonolysis to form the product **175**. Alternatively (Path B), the alkoxynickel **170** can undergo protonolysis to form the alcohol **176**; this alcohol was observed and isolated from the reaction with time course reactions showing that it was rapidly formed and then subsequently converted into the desired product. The Ni(II) catalyst can then be reduced by the boronic acid to form a Ni(0) species **177** which can then undergo an oxidative cyclisation with **176**, followed by a β-H elimination to form **179**. Finally reductive elimination forms the product **175**.



Scheme 1.51: *Proposed mechanism for the formation of* ***175****.*

Another example of nickel-catalysed enantioselective domino cyclisations reported by Kong used readily accessible starting materials **180**, and boronic acids **7** to form complex scaffolds **181** with three enantioenriched quaternary centres (Scheme 1.52).[121] Due to the complexity of this transformation multiple factors had to be considered during the reaction design, such as the regioselectivity of hydroarylation, which is opposite to that of similar nickel-catalysed hydroarylations.[122] Another challenge is mitigating addition into the electrophilic ketone after hydroarylation, as a Heck-cyclisation onto the unactivated alkene is required prior to addition into the ketone; with respect to this it was found that using TFE as the solvent minimised the undesired reactivity with other solvents forming the undesired product exclusively. The reaction was limited to arylboronic acids, however groups such as pyrimidines (**181b**), aryl iodides (**181c**) and phenols (**181d**) were tolerated. Meanwhile the alkyne substituent could be widely varied, tolerating both aryl- and alkyl groups (**181e**–**181g**). Due to the products **181** have several functional handles, such as a ketone, alcohol and an alkene, the products were amenable to various synthetic modifications, further exemplifying their utility as complex fragments.

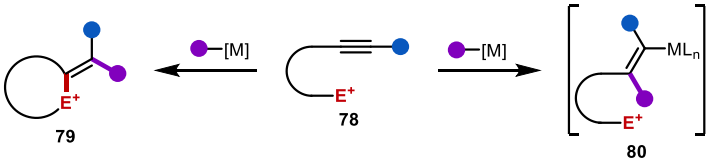


Scheme 1.52: *Nickel-catalysed formation of* ***181****.*

In conclusion exploitation of intermediate alkenylmetal species, often formed from arylation of an alkyne, enables *syn*-carbometallative arylative cyclisations of alkynes, resulting in a wide array of complex, and often enantioenriched, products. The reactivity of these alkenylmetal species is not just limited to addition into electrophiles, but they can also react in Heck cross couplings.

1.3 *Anti*-Carbometalation of Alkynes

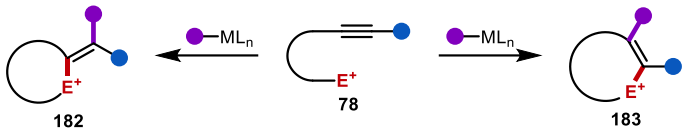
In the previous section the *syn*-carbometalation of alkynes followed by cyclisation onto a variety of tethered electrophiles was discussed. Whilst a variety of complex structures could be formed there are mechanistic limitations to this process with only proximal carbometalation (with respect to the electrophile) leading to the cyclisation of **78** to **79** (Scheme 1.53). Distal carbometalation forms the alkenylmetal species **80** which is unable to undergo cyclisation due to geometric constraints.



Scheme 1.53: *Syn-carbometalation/cyclisation of alkynyl tethered electrophiles.*

On the other hand, if (formal) *anti*-addition occurs then there are two potential products depending on the regioselectivity of carbometalation (Scheme 1.54): if proximal addition

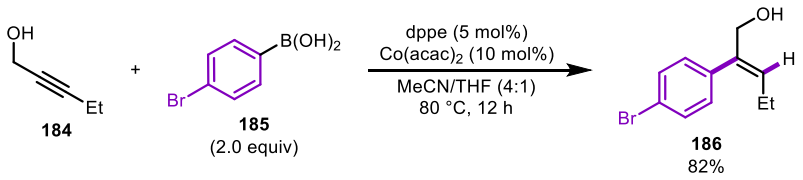
occurs then cyclisation will afford the exocyclic alkene **182** of opposite stereochemistry to the *syn*-addition product **79**. However, if distal addition occurs then cyclisation is also possible forming the endocyclic alkene **183**.



Scheme 1.54: *Anti-carbometalation/cyclisation of alkynyl tethered electrophiles.*

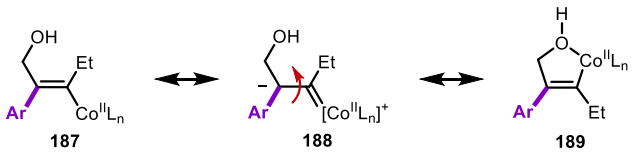
1.3.1 Cobalt-Catalysed

The use of cobalt-catalysis to achieve *anti*-carbometalation of alkynes has been reported by Cheng and co-workers (Scheme 1.55).[123] The majority of the alkynes described were propargylic esters which formed the expected *syn*-hydroarylation product. However, a switch in stereoselectivity was observed if propargylic alcohols (**184**) or propargylic carbamates were employed as the substrate, a trend that has been observed with these substrates under other conditions.[124]



Scheme 1.55: *Cobalt-catalysed formation of **186**.*

The authors proposed that the formal *anti*-carbometalation occurs *via* isomerisation through a cobalt carbene **188**. It is believed that the *Z*-alkene was favoured through chelation of the alcohol (or carbamate) to cobalt **189**. Examples without a chelating group showed a 1:1 mixture of *E*/*Z* isomers. Propargylic esters exclusively forming the *syn*-hydroarylation product was rationalised by the electron-withdrawing nature of the ester, preventing the carbene from forming, thus the alkene stereochemistry is determined through migratory insertion into the alkyne.

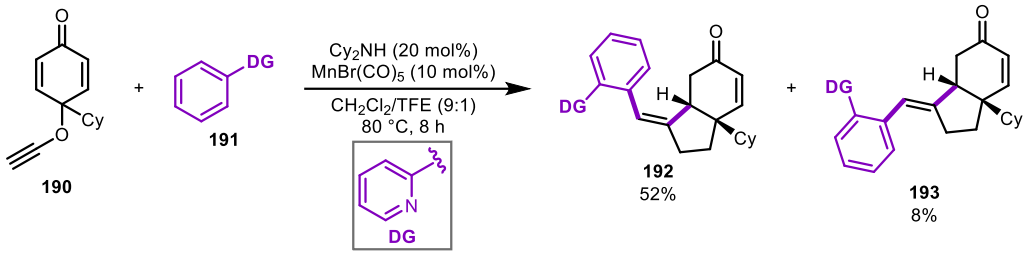


Scheme 1.56: *Proposed mechanism for the E/Z isomersation of **187** to **189**.*

1.3.2 Manganese-Catalysed

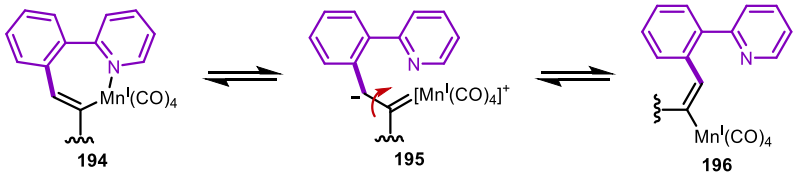
More recently an example has been reported by Lin of manganese exhibiting *anti*-carbometalation behaviour (Scheme 1.57).[125] Rather than a boronic acid being used a biaryl unit with a 2-pyridyl directing group (**191**) is employed as the arylating agent *via*

C-H activation. When reacting **191** with the alkyne **190** under the given conditions the major cyclisation product was the *syn*-carbometalation product **192**, but interestingly they also observed a minor amount of the *anti*-carbometalation product **193**. Screening showed that the solvent had a large impact on the observed ratio of E/Z-isomers, such as DMF affording 1.5:1 (E/Z) compared to the 6.5:1 (E/Z) obtained in the final conditions as shown below.



Scheme 1.57: *Manganese-catalysed formation of* ***192*** *and* ***193****.*

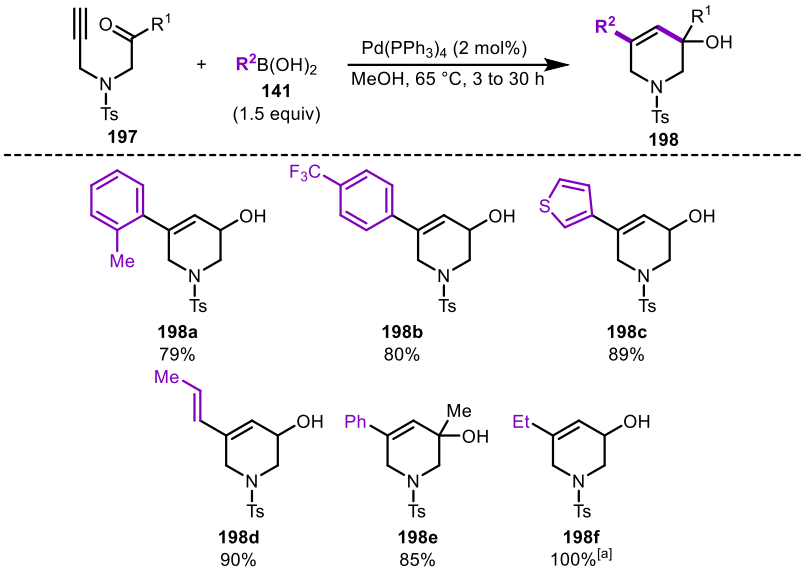
Resubjecting the mixture of products (**192** and **193**) to the reaction conditions had no effect on the ratio of stereoisomers, indicating that the stereoselectivity was intrinsic to the reaction. The authors postulated that the formal *anti*-carbometalation may occur *via* the formation of the manganese carbene **195** (Scheme 1.58).



Scheme 1.58: *Proposed mechanism for the E/Z isomerisation of the manganese complex.*

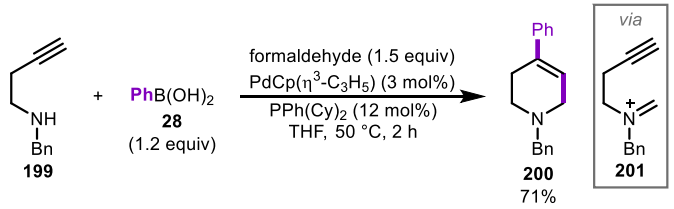
1.3.3 Palladium-Catalysed

Shortly after the initial reports of the palladium-catalysed *syn*-carbometalation of alkynes with boronic acids Kondo and co-workers described an *anti*-carbometalation variation (Scheme 1.59).[126] Terminal alkynes, tethered to an aldehyde or ketone, **197** were reacted with boronic acids **141** to give the *anti*-addition products **198** in excellent yields. A wide boronic acid scope was reported, with alkenylboronic acids (**198d**) and alkylboranes (**198f**) being tolerated. This chemistry is however limited to terminal alkynes, as using substituted alkynes gave a mixture of regioisomers resulting from addition across the alkyne.



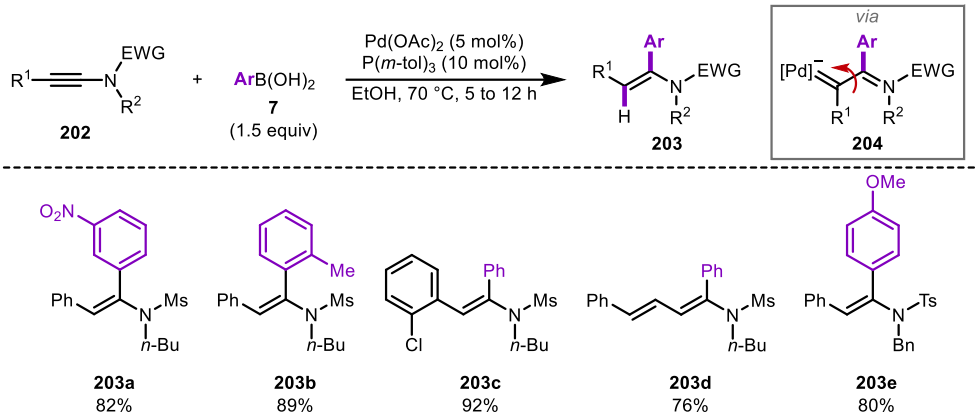
Scheme 1.59: *Palladium-catalysed formation of tetrahydropyridines* ***198****.* [a]*Et_3B (2.0 equiv) was used.*

Analogous to Doi's work, and a continuation to above, Kondo achieved the *anti*-carbometalation of linear aminoalkynes (**199**) in a three-component reaction where an iminium (**201**) formed *in situ* acts as the electrophile accessing a variety of di-substituted tetrahydropyridines **200** (Scheme 1.60).[127] Interestingly the reaction also worked on the allene isomer of **199** giving comparable yields when an alkyne was used; some benefits of using an allene included being able to utilise phenylacetylene and a copper catalyst, to achieve the alkynylation/cyclisation, or B_2Pin_2 to achieve the borylation/cyclisation.



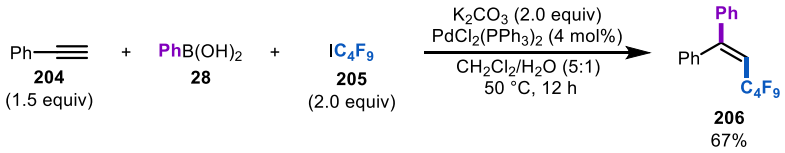
Scheme 1.60: *Palladium-catalysed formation of tetrahydropyridine* ***200****.*

The palladium-catalysed *anti*-addition of arylboronic acids **7** to electron-deficient ynamides **202** to form the corresponding enamides **203** was reported by Zhu and co-workers (Scheme 1.61).[128] Various ynamides were tolerated, along with both electron-rich (**203e**) and electron-deficient (**203a**) boronic acids. The authors proposed that the formation of the *anti*-addition products may proceed through a metallocarbene species **204** where donation of the nitrogen lone pair can push electrons onto palladium, allowing for rotation of the σ-bond to form the *E*-alkene.



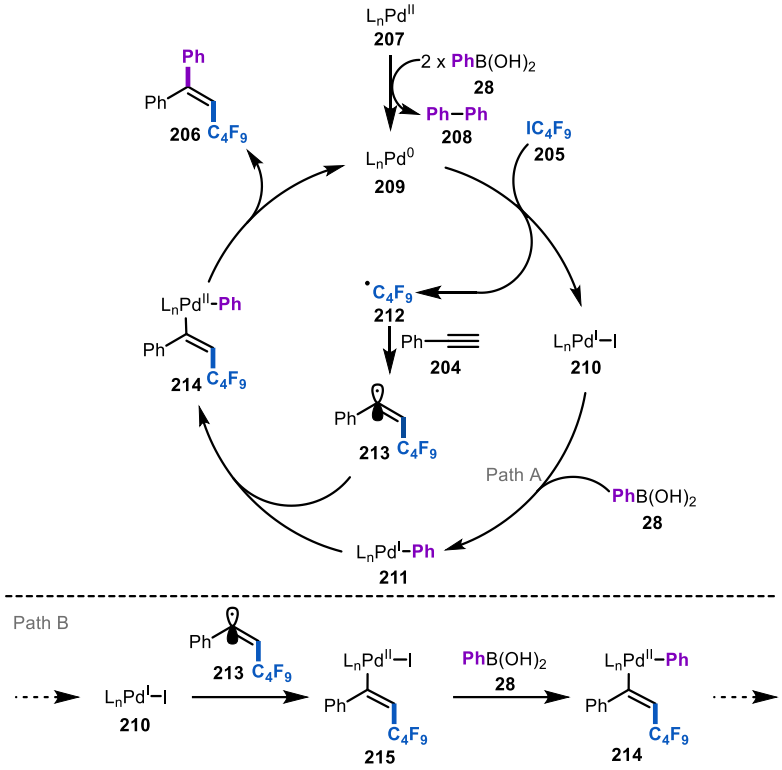
Scheme 1.61: *Palladium-catalysed formation of alkenes* ***204****.*

Nevado *et al.* reported the stereoselective dicarbofunctionalisation of terminal alkynes (**204**) using boronic acids (**28**) and perfluoroalkyl iodides (**205**) to form trisubstituted alkenes (**206**) in good yields, and as a single stereoisomer in most examples (Scheme 1.62).[129] The use of internal alkenes as substrates proved challenging, however Chaładaj showed that it was possible by using a Buchwald palladium precatalyst system.[130]



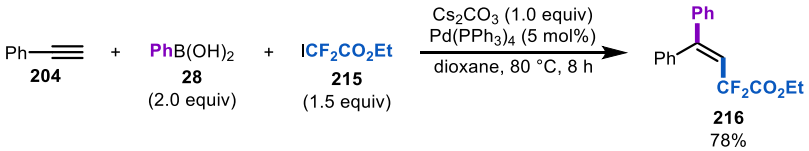
Scheme 1.62: *Palladium-catalysed formation of alkene* ***206****.*

A proposed mechanism for the formation of **206** is shown in Scheme 1.63. To generate the active Pd(0) catalyst **209** the Pd(II) precatalyst **207** undergoes two sequential transmetalation events with the boronic acid **28** followed by reductive elimination forming **208**. Single electron transfer with the alkyl iodide **205** forms the alkyl radical **212**, and a Pd(I) species **210** which then undergoes transmetalation with the boronic acid **28** to form the aryl Pd(I) species **211** (Path A). Meanwhile the alkyl radical **212** combines with the alkyne **204** to form an alkenyl radical **213** which rapidly isomerises.[131] **211** then adds to **213** forming the less hindered alkenylpalladium species **214**. Finally, reductive elimination furnishes the alkene **206** and reforms the Pd(0) catalyst **209**. The authors also propose a second possible pathway, Path B, whereby the alkenyl radical **213** first combines with **210**, and then transmetalation occurs followed by reductive elimination to form the alkene **214**.



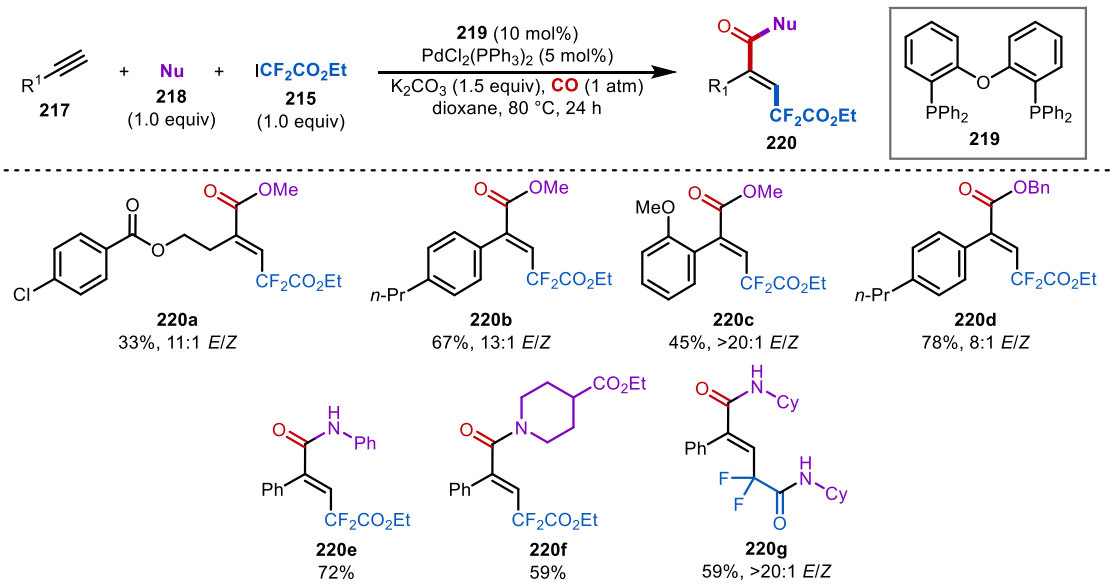
Scheme 1.63: *Proposed mechanism for the formation of alkene* ***206****.*

In the same year Liang reported an analogous system to Nevado's, using ethyl difluoroiodoacetate (**215**) as the sole alkyl halide to obtain aryldifluoroalkylated alkenes (**216**) (Scheme 1.64).[132] Functional groups such as ketones and nitriles were tolerated, however no examples were shown with strong electron-withdrawing groups either on the alkyne or the boronic acid.



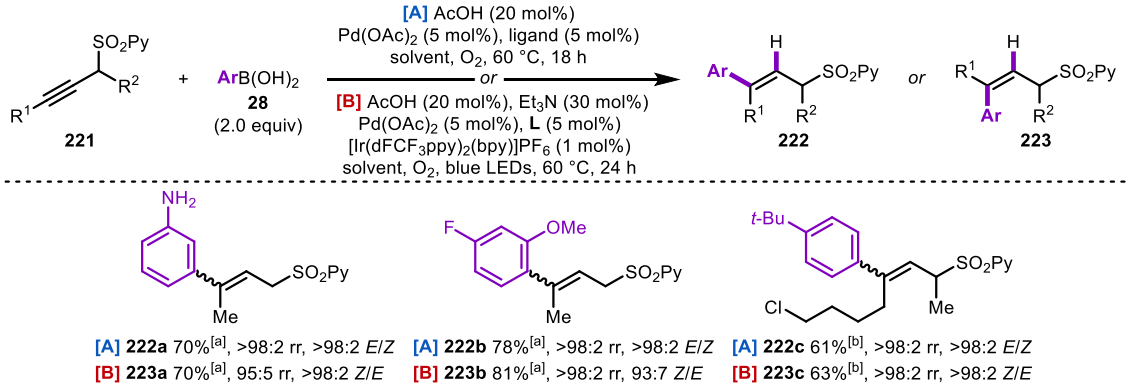
Scheme 1.64: *Palladium-catalysed formation of alkene* ***216****.*

Following up on the three-component couplings shown above both Liang and Skrydstrup reported a four-component coupling utilising a CO atmosphere to add a carbonylation step before arylation with the boronic acid.[133,134] Liang and co-workers explored this further with another four-component coupling where they replaced the boronic acid with a more general nucleophile (**218**), such as an alcohol or amine to form acrylates (**220a–220d**) or acrylamides (**220e–220g**) (Scheme 1.65).[135] Generally the products were formed with good stereoselectivity. A broad range of nucleophiles, including both aliphatic and aromatic nucleophiles, were tolerated, however there were some limitations such as allyl alcohol and *t*-BuOH.



Scheme 1.65: *Palladium-catalysed coupling of alkynes **217**, nucleophiles **218**, iodides **215** and CO.*

With photochemistry's emergence to prominence in the last decade a wealth of methodology has been developed, such as complex dual catalytic cycles being able to take advantage of the benefits of photocatalysis and conventional metal catalysis, to the simple isomerisation of alkenes.[136,137] Carretero and co-workers managed to take advantage of both by taking propargyl sulfones **221** and performing a stereodivergent hydroarylation to form either the *Z*-alkene **222** or *E*-alkene **223** (Scheme 1.66).[138]



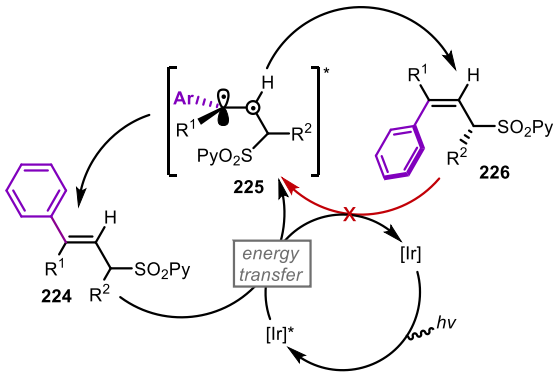
[A] **222a** 70%[a], >98:2 rr, >98:2 *E*/*Z* [A] **222b** 78%[a], >98:2 rr, >98:2 *E*/*Z* [A] **222c** 61%[b], >98:2 rr, >98:2 *E*/*Z*
[B] **223a** 70%[a], 95:5 rr, >98:2 *Z*/*E* [B] **223b** 81%[a], >98:2 rr, 93:7 *Z*/*E* [B] **223c** 63%[b], >98:2 rr, >98:2 *Z*/*E*

Scheme 1.66: *Palladium-catalysed formation of **222** and **223**. [a]ligand = dppe, solvent = THF/MeOH (10:1). [b]ligand = P(p-MeOC6H4)3, solvent = toluene/MeOH (10:1).*

Typically metal-catalysed hydroarylations suffer from lack of regioselectivity when using unsymmetric dialkyl alkynes, however Carretero envisioned the use of a 2-pyridylsulfone as a removable directing group to achieve good regioselectivity. The choice of ligand was also found to be important; when propargylic substitution was present a monodentate ligand [P(*p*-MeOHC$_6$H$_4$)$_3$] was utilised to allow for a coordination site to be freed up enabling better coordination to the pyridyl group, resulting in better regioselectivity. Alternatively, a bidentate ligand (dppe) was used when there was no propargylic substitution. The *syn*-hydroarylated products **222** could be obtained using conditions **[A]**

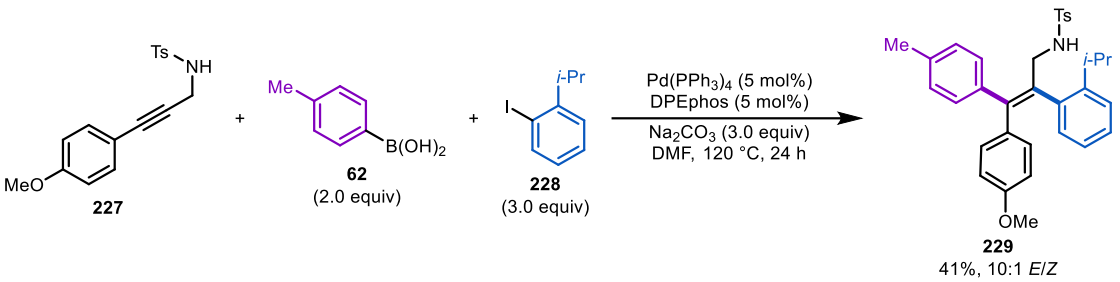
where palladium-catalysis is utilised. Upon investigation the authors found that these products could be efficiently isomerised by applying an iridium photocatalyst and blue LEDs, which led to the development of a one-pot procedure, conditions **[B]**, whereby the *anti*-hydroarylation products **223** could be directly isolated. In both cases the regio- and stereoselectivity were excellent with typically only one stereoisomer being observed. Functional groups such as anilines, heterocycles, alkyl chlorides and nitriles were all well tolerated.

The mechanism for the palladium cycle is thought to broadly follow the mechanism described in Scheme 1.40, with the AcOH being present solely for increasing the solubility of the catalyst. For the isomerisation of **222** into **223** a proposed mechanism is shown in Scheme 1.67. First the iridium photocatalyst is excited, which then allows for energy transfer to **224** to form the excited species **225**. Relaxation to the ground state can then either form **224** or **226**. Due to the steric congestion of **226**, resulting from $A^{1,3}$ strain, energy transfer from the excited photocatalyst is no longer possible due to an energy mismatch. This allows for **225** to be contra-thermodynamically isomerised into **226**.[139] Work has since been reported by Carretero using various electron-withdrawn alkynes, achieving similar regioselectivity and stereoselectivity.[140]



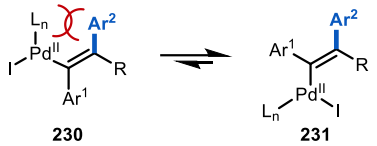
Scheme 1.67: *Palladium-catalysed formation of* ***226****.*

Cheng *et al.* reported the *anti*-dicarbofunctionalisation of alkynes (**227**) using boronic acids (**62**) and aryl iodides (**228**) to form tetrasubstituted alkenes (**229**) in typically good yields and regioselectivities (Scheme 1.68).[141] They also reported that it was possible to replace the boronic acid with $Me_3Si\text{-}SiMe_3$ or B_2pin_2 to introduction a silyl or boronate group, however they also started to observe 1,4-palladium migrations leading to the formation of complex products.



Scheme 1.68: *Palladium-catalysed formation of tetrasubstituted alkene* ***229****.*

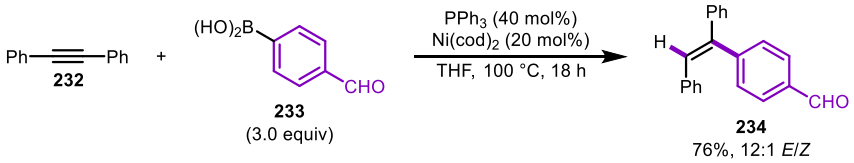
The products **229** obtained are analogous to those obtained by Larock (Scheme 1.15) using very similar reaction conditions whereby the *Z*-alkenes were isolated. The major difference was the choice of the ligand; Cheng found that bulkier ligands, such as DPEphos, favoured the formation of the *E*-alkene product. Based on this they proposed that a steric clash between the ligand and the installed aryl group **230** facilitates the isomerisation to **231**, possibly through a η^2-complex.



Scheme 1.69: *Rationale for the isomerisation of* ***230*** *to* ***231****.*

1.3.4 Nickel-Catalysed

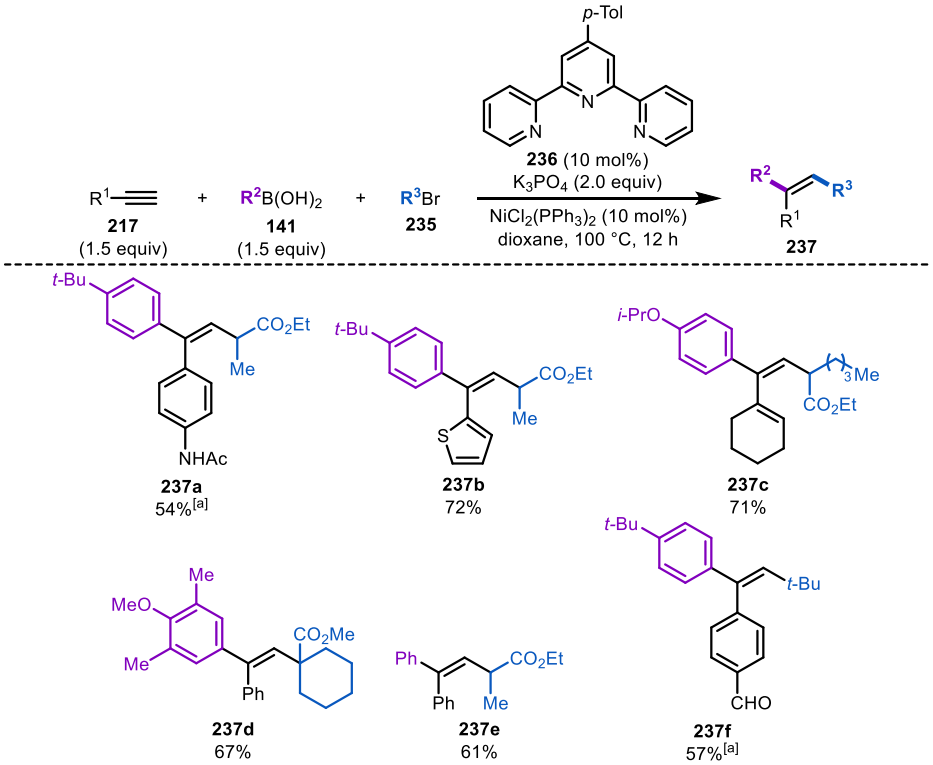
There are examples of *anti*-carbometalation across alkynes using stoichiometric nickel-catalysis dating back as far as the late 1970s, however since then reactions have been developed to use substoichiometric nickel-catalysis.[142–144] Using $Ni(cod)_2$, Hartwig *et al.* observed primarily the *anti*-carbometalation product (**234**) from the hydroarylation of alkynes (**232**) using boronic acids (**233**) (Scheme 1.70).[145] Under reductive conditions aryl halides could be used in place of boronic acids to afford analogous products



Scheme 1.70: *Nickel-catalysed formation of* ***234****.*

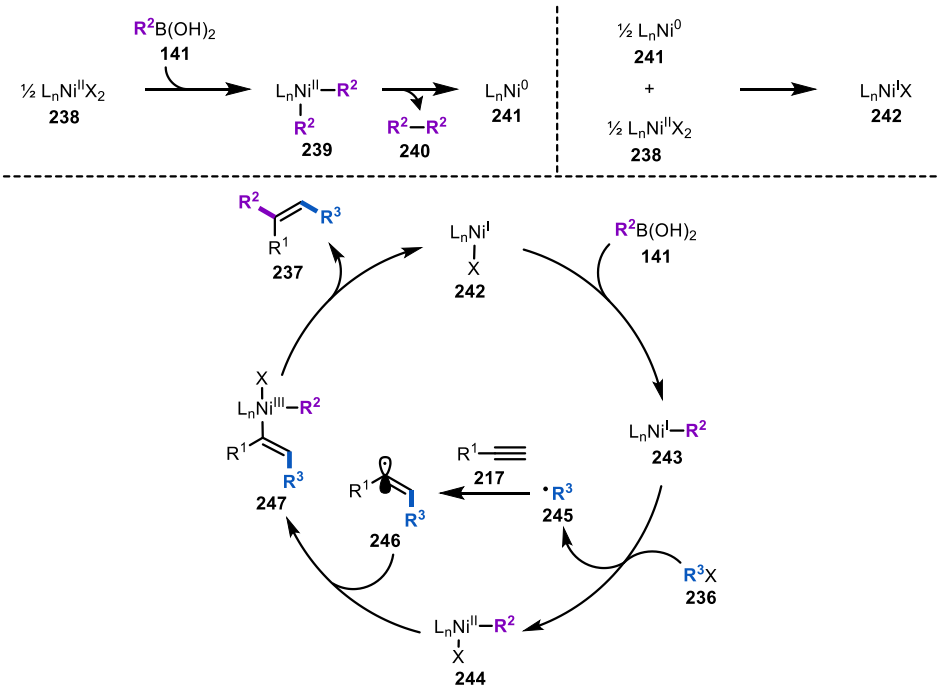
Nevado adapted the previous work they did on the palladium-catalysed stereoselective dicarbofunctionalisation of alkynes (Scheme 1.62) to use nickel-catalysis (Scheme 1.71).[146] Terminal alkynes **217** were reacted with arylboronic acids **141** and activated alkyl bromides **235**, a more general halide source than perfluoroalkyl iodides, to form the trisubstituted alkenes **237** in a stereoselective manner. Tertiary and secondary unact-

ivated (**237f**) alkyl iodides were also tolerated. The use of sulfonyl chlorides in place of alkyl bromides is also possible.[147]



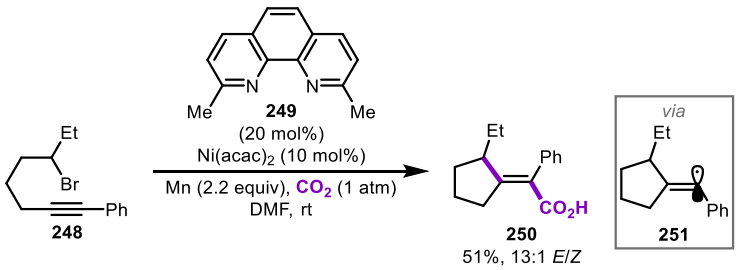
Scheme 1.71: *Nickel-catalysed formation of* ***237****. [a]Alkyne (1.0 equiv), boronic acid (2.0 equiv), t-butyl iodide (2.0 equiv), benzene, 80 °C, 12 h.*

A proposed mechanism for this three-component coupling is shown in Scheme 1.72. The formation of the active Ni(I) catalyst **242** is thought to occur through two sequential transmetalation events of the precatalyst **238** with **141** to give a diaryl Ni(II) species **239**. This then undergoes reductive elimination to form a Ni(0) species **241**. Studies have shown that the Ni(0) species **241** and Ni(II) species **238** can then comproportionate to form the active Ni(I) catalyst **242**.[148] Transmetalation of **242** with the boronic acid **141** affords the aryl Ni(I) species **243**. Reaction with the alkyl halide **236** forms the Ni(II) halide **244**, along with the alkyl radical **245** which then selectively adds into the alkyne **217** at the terminal position. The resultant alkenyl radical **246** undergoes isomerisation allowing for the exclusive *anti*-addition, as guided by sterics, to give the nickel species **247**. Finally, **247** undergoes reductive elimination completing the catalytic cycle forming the alkene product **237**.



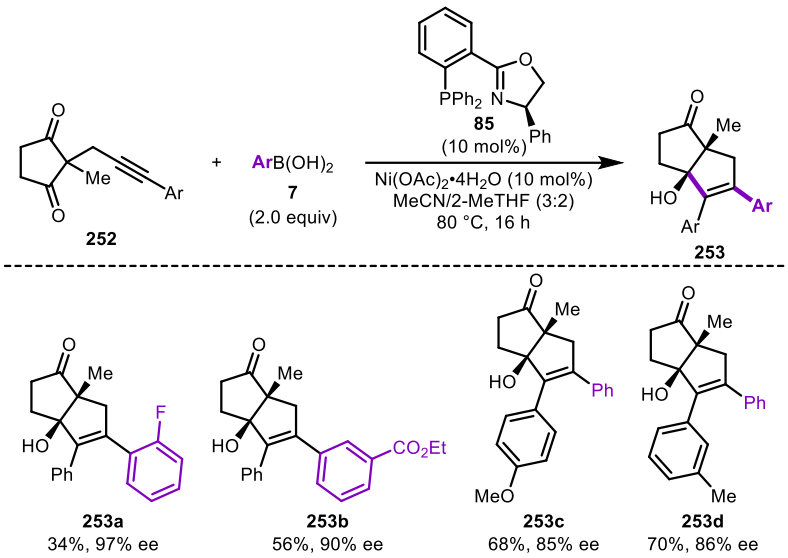
Scheme 1.72: *Proposed mechanism for the formation of* ***237****.*

The difunctionalisation of alkynes has also been achieved using CO_2 as the electrophile under reductive conditions (Scheme 1.73).[149] Whilst both primary and secondary alkyl bromides were tolerated, primary alkyl bromides afforded the *syn*-carbometalation products whereas the added steric bulk in the secondary alkyl bromide **248** favoured *anti*-carbometalation forming **250**. Similar to above, this is believed to proceed through a radical intermediate **251** which facilitates the formal *anti*-addition.



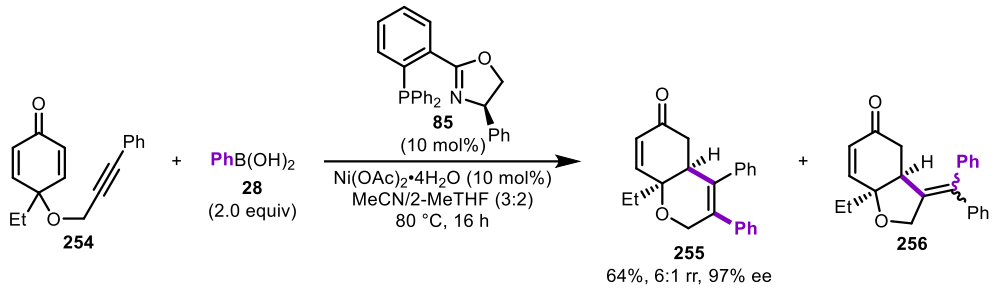
Scheme 1.73: *Nickel-catalysed formation of* ***250*** *via* ***251****.*

The enantioselective intramolecular *anti*-carbometalation of a tethered electrophile using nickel-catalysis has been reported by Lam and co-workers (Scheme 1.74).[122] Alkynyl 1,3-diketones **252** were reacted with arylboronic acids **7** affording the cyclic products **253** in good yields and enantioselectivities. A variety of synthetically useful functional groups were tolerated such as esters (**253b**), nitriles, and aryl chlorides.



Scheme 1.74: *Nickel-catalysed formation of* ***253****.*

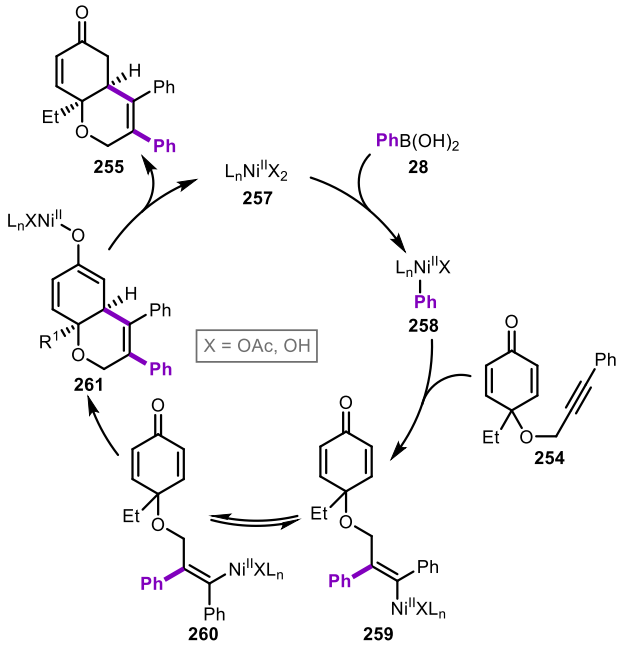
In the same paper Lam also reported the use of alkynes tethered to enones (**254**) which cyclised to give complex bicyclic products (**255**) (Scheme 1.75). Unlike in the previous example where they exclusively formed their product a as a single regioisomer (likely determined through the rate of cyclisation) in this case a mixture of regioisomers was observed. This originates from the regioselectivity of carbometalation. The major product occurs when carbometalation occurs distal with respect to the electrophile, however some product (**256**) was observed where carbometalation occurred proximal with respect to the electrophile.



Scheme 1.75: *Nickel-catalysed formation of* ***255****.*

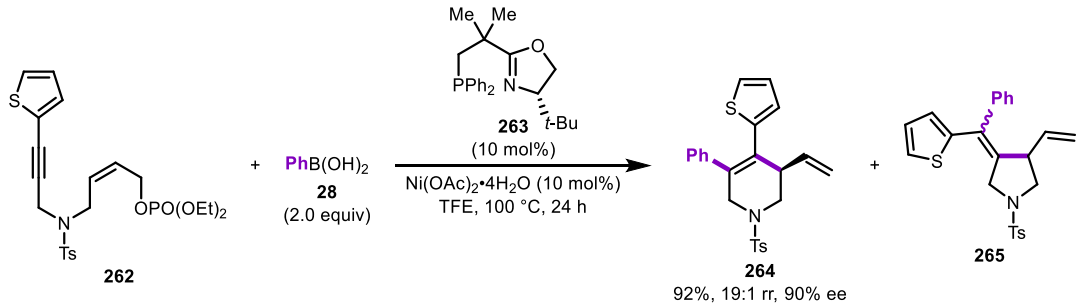
The proposed mechanism for this transformation is shown in Scheme 1.76. First transmetalation of **257** with **28** forms the arylnickel species **258**. *Syn*-carbonickelation onto the alkyne **254** places the nickel at the distal position, forming **259**. The authors propose that the alkenylnickel species **259** undergoes an *E*/*Z* isomerisation, the mechanism of which is currently unknown, to form the formal anti-addition alkenylnickel species **260**. 1,4-addition onto the enone forms the nickel alkoxide **261**, which upon protonolysis releases the product **255** and reforms the Ni(II) catalyst **257**. Unlike the Ni(I)/(III) catalysed *anti*-carbometalation shown in Scheme 1.72 this reaction is postu-

lated to proceed *via* a redox-neutral Ni(II) cycle based on similar nickel/palladium chemistry.



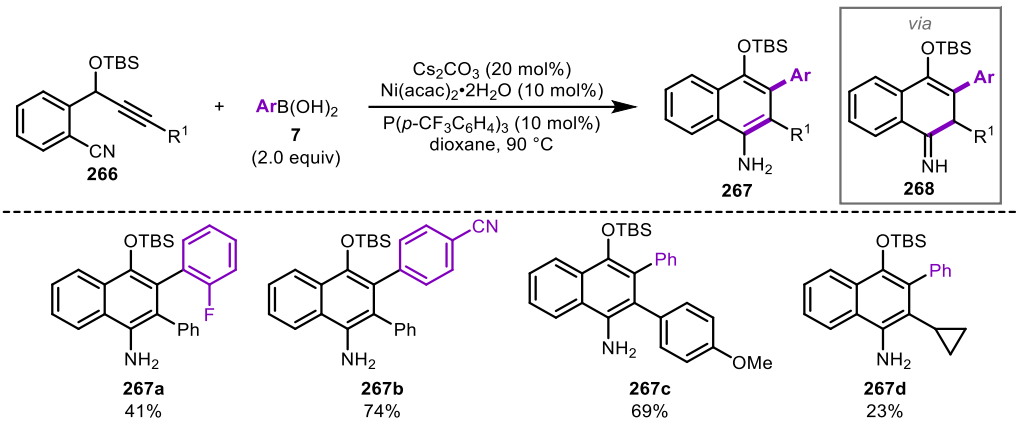
Scheme 1.76: *Proposed mechanism for the formation of* ***255****.*

After the initial report on diones/enones (see above) the substrate scope has been further expanded by Lam and co-workers such as the use of allylic phosphonates (**262**) as the electrophile (Scheme 1.77).[150] The product of this reaction is enantioenriched tetrahydropiperidines containing a vinyl group (**264**), a synthetically useful scaffold enabling further manipulation. The yields and enantioselectivity were good with typically only a small amount of the minor regioisomer (**265**) being observed, which could be separated by column chromatography.



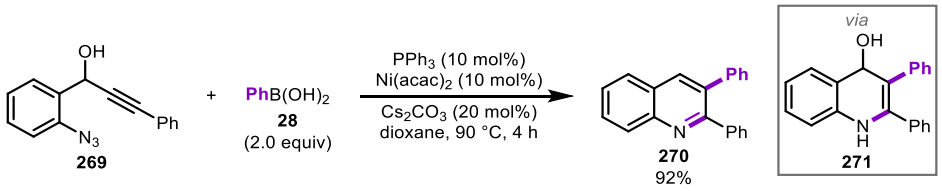
Scheme 1.77: *Nickel-catalysed formation of* ***264****.*

Aryl nitriles with a tethered alkyne **266** have been used by Liu allowing for the formation of 1- napthylamines **267** through tautomerisation of the intermediate imine **268** (Scheme 1.78).[151] One limitation of this chemistry is that the silyl ether group was needed for the desired reactivity.



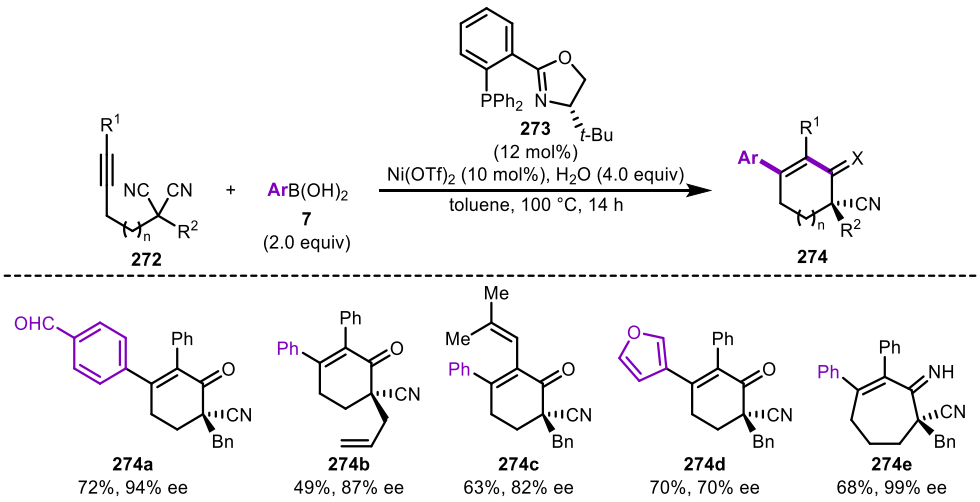
Scheme 1.78: *Nickel-catalysed formation of* ***267****.*

Reddy and co-workers used similar substrates with an azide in place of a nitrile as the electrophile, along with leaving the alcohol unprotected (Scheme 1.79).[152] In this example the cyclisation occurs onto the nitrile **269** to form the enamine **271** and subsequent dehydration of the alcohol allows for aromatisation to form the quinoline product **270**.



Scheme 1.79: *Nickel-catalysed formation of* ***270****.*

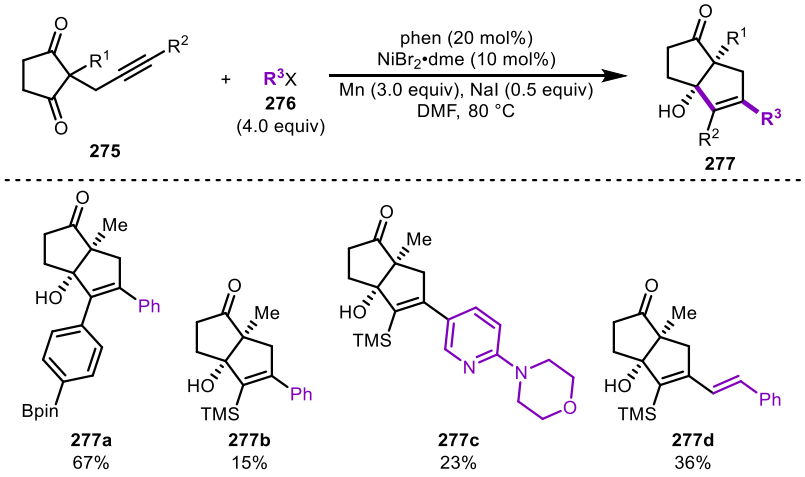
More recently Liu and co-workers reported alkynes tethered to malononitriles **272** reacting with arylboronic acids **7** to form cyclic products with an all-carbon stereocenter containing a nitrile **274** (Scheme 1.80).[153] They showed a large scope including functional groups such as aldehydes (**274a**) and vinyl groups (**274b**) along with heterocycles such as furans (**274d**). The ring size could also be varied to cyclopentanes and cycloheptanes (**274e**). In the case of the cycloheptane products the authors found that the imine formed after addition to the nitrile was not hydrolysed *in-situ*, therefore isolating the imine instead. The reaction even worked with a methyl substituted alkyne, however the opposite regioisomer was preferred resulting from distal carbonickelation (1.5:1 rr). Alternative aryl boron sources could also be used with $(PhBO)_3$ and $PHBF_3K$ both giving similar yields and enantioselectivity to $PhB(OH)_2$, however, attempts to use PhBpin gave no reaction under base-free conditions.



Scheme 1.80: *Nickel-catalysed formation of* ***274****.*

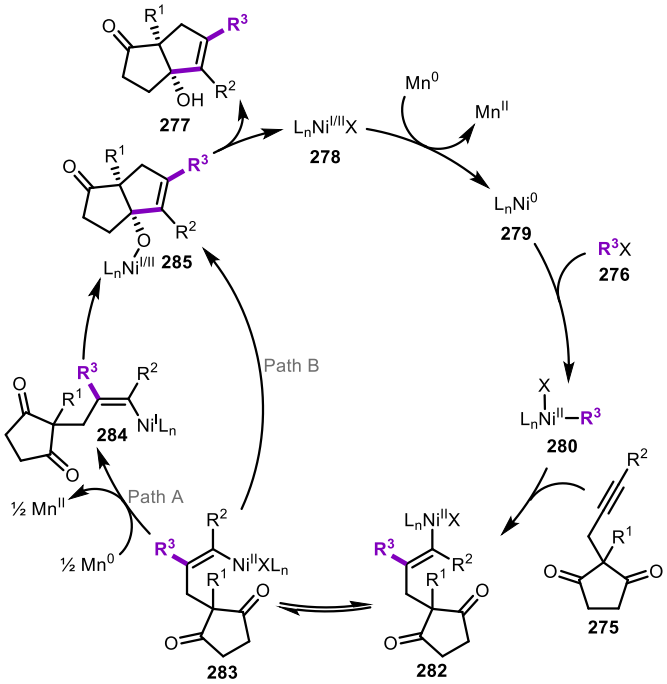
A variety of other reports have taken advantage of this nickel E/Z isomerisation to create a variety of cyclic products by utilising various starting materials and electrophiles such as electron-poor amides, ketones, ynamides and more.[154–161]

Up to this point all of the nickel-catalysed *anti*-arylative cyclisations utilised boronic acids, however in 2020 Kong and co-workers showed that it was also possible to use aryl/alkenyl halides **276** under reductive conditions to form products **277** analogous to those made by Lam (Scheme 1.81).[122,162] The main benefit of a reductive methodology is that the boronic acid coupling partners are relatively expensive compared to aryl halides, whilst also generally being derived from the parent aryl halide. Under these conditions substrates containing either anilines or nitrogen-containing heterocycles (**277c**) were tolerated in varying degrees, along with arylboronates; substrates such as these are seldom reported under redox-neutral conditions using boronic acids. An example was also shown using a chiral Phox ligand on one of the substrates, giving comparable enantioselectivity as reported by Lam.



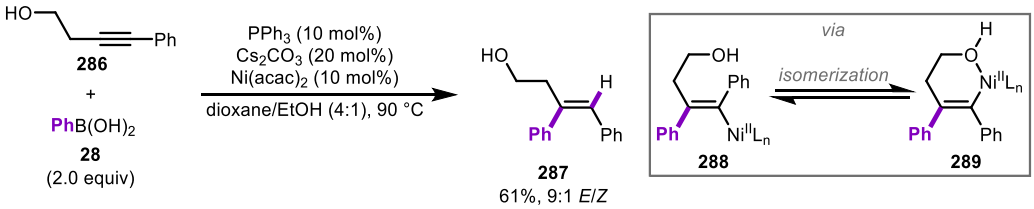
Scheme 1.81: *Nickel-catalysed formation of* ***277****.*

A proposed mechanism for the formation of **277** is outlined in Scheme 1.82. First the reduction of **278** with Mn(0) to **279** allows for oxidative insertion into the aryl halide **276** to give **280**. Migratory insertion into the alkyne **275**, followed by an E/Z isomerisation process forms alkenylnickel species **283**. From here two possible pathways are proposed. Pathway A starts with another reduction to form a Ni(I) species **284** which then cyclises onto the ketone to form the Ni(I) alkoxide **285**. Alternatively, **283** could directly cyclise to form the Ni(II) alkoxide **285**. Finally, protonolysis of **285** forms the desired product **277** and completes the cycle. The authors favour Path A on the basis that the reaction worked on a phthalimide as a weak electrophile, which was previously shown to not work under conditions reported by Lam, suggesting that a more nucleophilic Ni(I) species may be responsible for addition into the carbonyl.



Scheme 1.82: *Proposed mechanism for the formation of **277**.*

The anti-carbometalation of internal alkynes has also been achieved without being directed by a tethered electrophile, but instead by using a tethered alcohol (**286**) (Scheme 1.83).[65] It is thought that due to a steric clash between the nickel and the aryl group promotes isomerisation of **288** to **289** along with favourable chelation between the nickel and the alcohol in **289**.



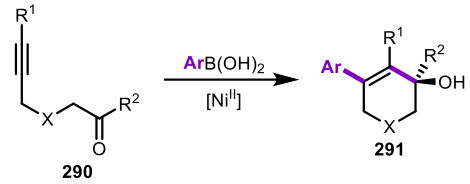
Scheme 1.83: *Nickel-catalysed formation of* ***287****.*

In conclusion numerous examples of both *syn*-carbometalation and *anti*-carbometalation reactions have been described giving an overview of the potential of these types of reactivity, from simple carbometallation to complex enantioselective domino cyclisation reactions. The methods described often used a precious metal as the catalyst; therefore movement to more abundant metals, such as iron and nickel, for this type of chemistry may potentially make it cheaper and more sustainable.[163,164] More recently there has been a lot of focus on achieving this type of reactivity/obtaining similar products through alternative methodologies, such as C-H activation or photochemistry. Both areas have potential for greater atom economy compared to using coupling partners such as boronic acids, whilst also opening doors for alternative reactivity.[1,165–169]

2 Results and Discussions

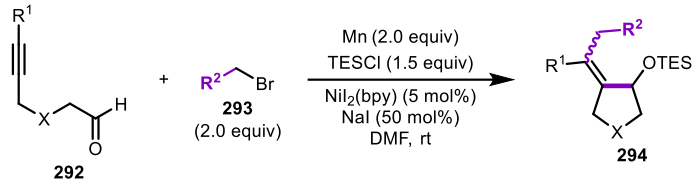
2.1 Project Aims

Previous work by our group described a number of *anti*-carbometallative cyclisations of alkynes onto various tethered electrophiles, such as diones, esters, amides, and enones, with all of the examples carried out asymmetrically where possible.[122,150,170–172]



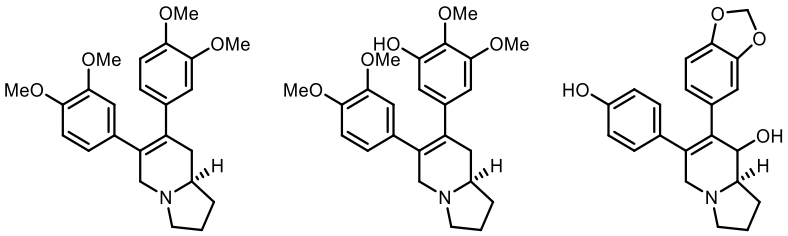
Scheme 2.1: *Proposed nickel-catalysed formation of cyclisation products* ***291****.*

As this nickel-catalysed *anti*-carbometalation/cyclisation sequence is a relatively new discovery it is of great interest to find the limitations of this chemistry, from the manipulation of the nickel intermediates in different ways, such as the work by Kong, to the use of different electrophiles, or substrates, to enable the synthesis of high value fragments.[121] Our aim was to develop the use of simple heteroatom tethered alkynones **290** as substrates in the nickel-catalysed *anti*-arylmetallative cyclisation to form enantioenriched heterocyclic products **291** (Scheme 2.1), extending the chemistry previously developed utilising cyclic diones as the electrophile (Scheme 1.74). Additionally, developing the chemistry on these substrates would provide a complementary methodology as that reported by Montgomery whom showed that analogous alkynylcarbonyls **292** could react with alkyl halides **293** *via* Ni(0)-catalysis, affording the 5-*exo*-trig products **294** through a reductive cyclisation (Scheme 2.2).[173]



Scheme 2.2: *Nickel-catalysed reductive cyclisation of* ***292*** *with alkyl bromides* ***293****.*

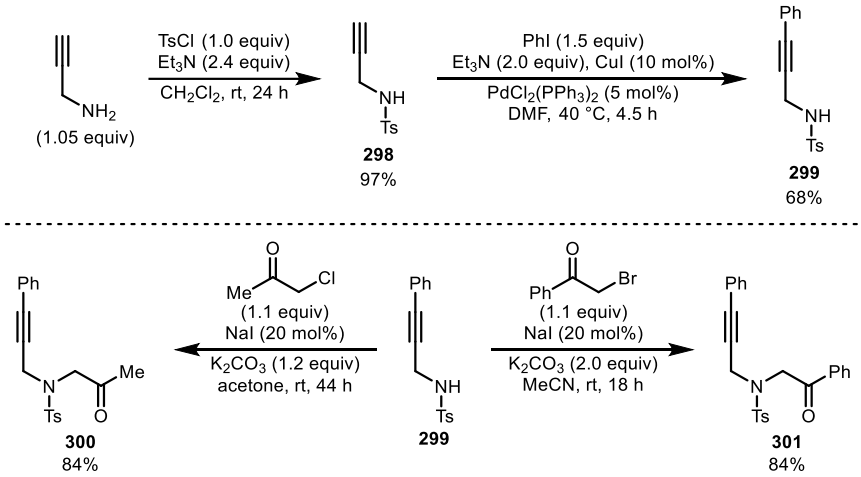
The heterocyclic products formed would also be of value, with the tetrahydropyridine core being featured in several natural products (**295**–**297**), along with having potential therapeutic properties.[174–178]



Scheme 2.3: *Natural products featuring a tetrahydropyridine core with a tetrasubstituted alkene.*

2.2 Reaction Optimisation

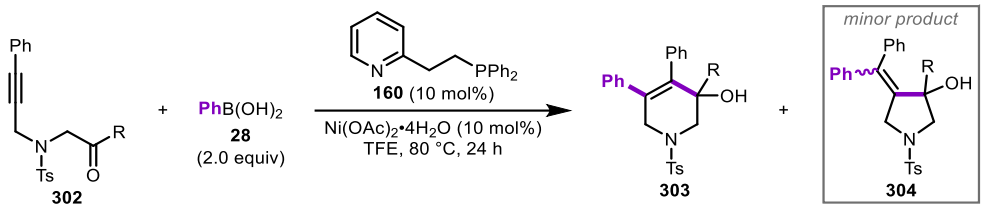
As previous work in the Lam group showed that *N*-tosyl tethered alkynes worked well for the nickel-catalysed *anti*-carbometalation cyclisations onto an allylic electrophile it was proposed that this could be extended to *N*-tosyl linked alkynones. Initial investigations began with the synthesis of the methyl (**300**) and phenyl (**301**) ketones as model substrates to use for optimisation (Scheme 2.4).



Scheme 2.4: *Preparation of alkynones **300** and **301**.*

Tosylation of propargylamine afforded alkyne **298**, which was then subjected to a Sonogashira cross-coupling to yield the key intermediate **299**. Alkylation with various α-halo ketones resulted in alkynones **300** and **301**. With these alkynones in hand they were then subjected to the reported conditions developed by the Lam group using the achiral ligand **160** (Table 2.1).[122] Pleasingly both substrates demonstrated the desired reactivity. Under these conditions **300** (Entry 1) gave a good NMR yield and regioselectivity of the desired tetrahydropyridinyl product **303** to the side product **304** (derived from initial proximal carbometalation on the alkyne). On the other hand, **301** (Entry 2) was lower yielding; the reaction also suffered from low mass recovery with only 13% of unreacted starting material being observed in the crude NMR.

***Table* 2.1:** *Preliminary results.*

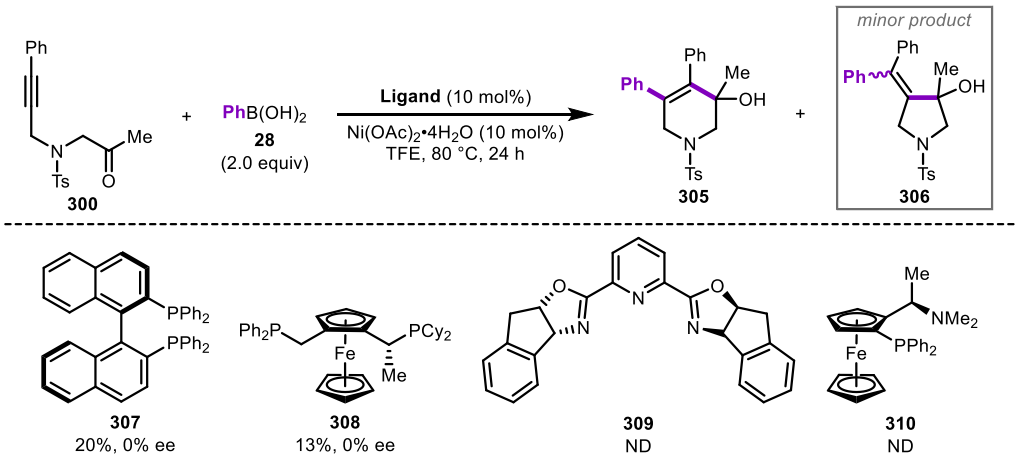


Entry	R	Yield (%)[a]	303:304[b]
1	Me	80	7:1
2	Ph	19	5:1

[a]Determined by ^{1}H NMR analysis using TMB as an internal standard. [b]Determined by ^{1}H NMR analysis of the crude reactions.

Having had initial success using these alkynones the next step taken was to identify a chiral ligand that would give good enantioselectivities along with good yields and regioselectivities. A brief screen of various ligand families was undertaken, including bisphosphines (**307** and **308**), a pyBox derivative (**309**) and a *P,N*-ligand (**310**). Only the bisphosphines (**307** and **308**) showed any reactivity, albeit in low yields, with neither of them inducing any enantioselectivity (Table 2.2).

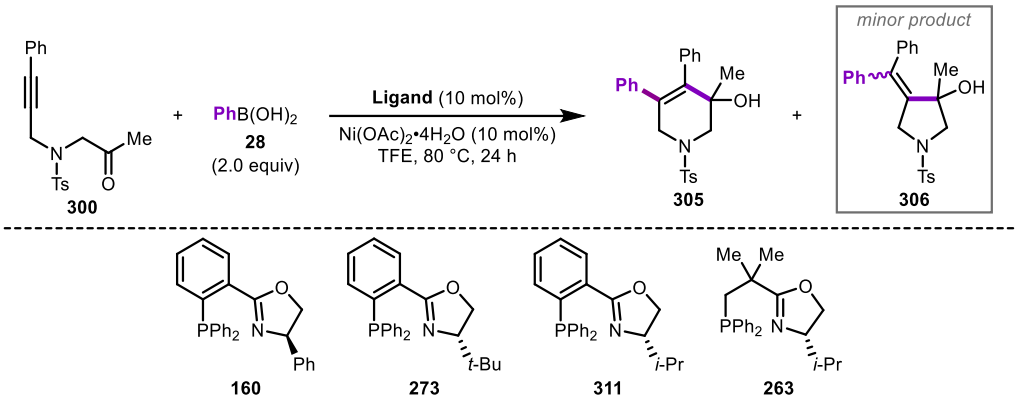
Table 2.2: *Chiral ligand screen.*



Yields determined by ^{1}H NMR analysis using TMB as an internal standard. ND = not detected.

Following the groups previous findings, phosphinooxaziline (Phox) type ligands were also screened with **300** which provided more encouraging results as shown in Table 2.3.

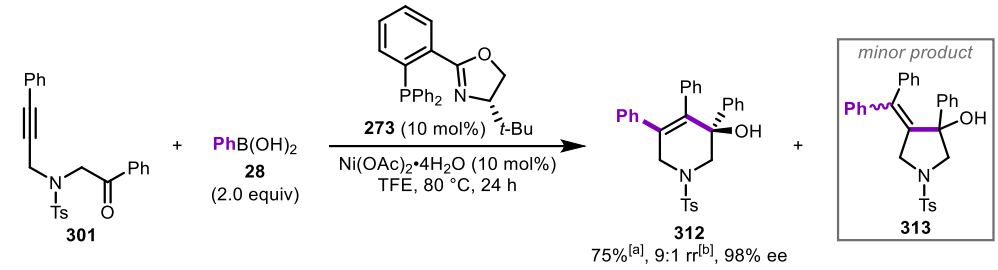
Table 2.3: *Chiral Phox ligand screen.*



Entry	Ligand	Yield (%)[a]	305:306[b]	ee of 306 (%)
1	**160**	62	7:1	–50
2	**273**	63	12:1	75
3	**311**	24	5:1	69
4	**263**	23	7:1	60

[a]Determined by ^{1}H NMR analysis using TMB as an internal standard. [b]Determined by ^{1}H analysis of the crude reactions.

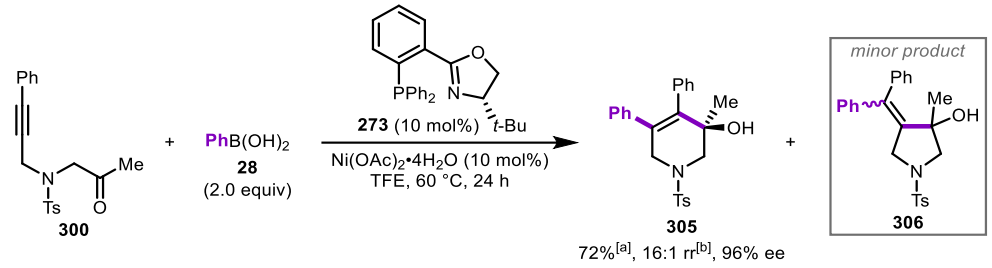
The reaction using **160** gave a good yield of 62%, however, both the regioselectivity and enantioselectivity were lacking (Entry 1). The use of **273** gave very promising results with good yield, regioselectivity and enantioselectivity being observed (Entry 2). The use of **311** was low yielding with poor regioselectivity; pleasingly though it showed moderate enantioselectivity achieving 69% ee (Entry 3). **263** (Entry 4) gave similar results to **311**. From these results **273** appeared to be the best ligand. To confirm this further the reaction was repeated using **301** as the substrate (Scheme 2.5). Pleasingly with the bulkier phenyl group the enantioselectivity was improved to 98% ee whilst retaining a good yield and regioselectivity.



Scheme 2.5: *Nickel-catalysed formation of **312**. [a]Yield determined by ^{1}H NMR analysis using TMB as an internal standard. [b]Determined by ^{1}H analysis of the crude reactions.*

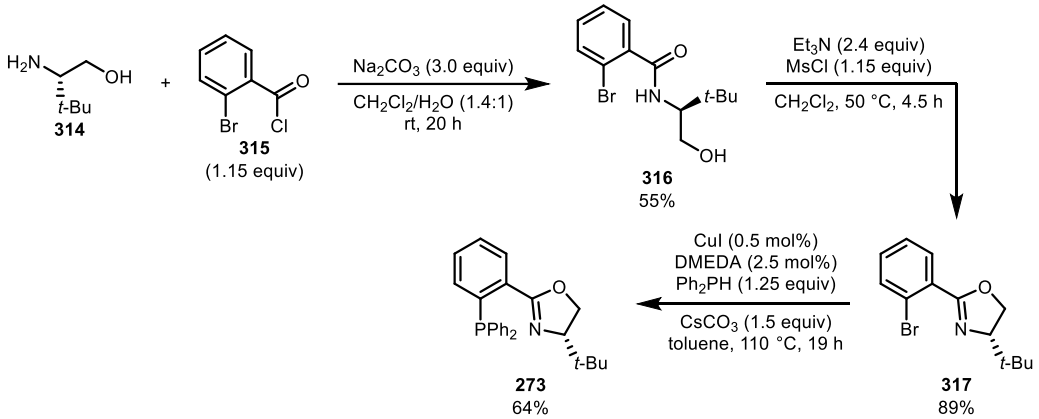
As the enantioselectivity was lower in the case of the methyl ketone **300** versus the phenyl ketone **301** it was thought that the sterics around the ketone may have an important role in determining the enantioselectivity. Based on this result, lowering the temperature

was investigated to improve the enantioselectivity in the absence of steric bulk as with example **300**. Pleasingly repeating the reaction at 60 °C increased the enantioselectivity to 96% ee whilst also having a slight positive effect on the yield and regioselectivity, thus cementing the choice of **273** as the ligand (Scheme 2.6). Attempts were also made to see if the temperature could be lowered when using the phenyl ketone substrate **301**, however in this case this led to significant decreases in the yield.



Scheme 2.6: *Nickel-catalysed formation of **305** at 60 °C. [a]Yield determined by ^{1}H NMR analysis using TMB as an internal standard. [b] Determined by ^{1}H analysis of the crude reactions.*

Whilst **273** is commercially available, it is considerably expensive, therefore we decided to synthesise it according to a procedure reported by Stoltz (Scheme 2.7).[179] The synthesis reported begins by taking L-*t*-leucine as the chiral source which is reduced down to the amino alcohol **314**, however this step was performed by a previous Lam group member. First acylation of **314** with the acyl chloride **315** under Schotten-Baumann conditions afforded the amide **316**, followed by mesylation and then dehydrative cyclisation formed the oxazoline **317**. Finally, copper-catalysed coupling of **317** with Ph_2PH gave the ligand **273** in an overall yield of 32%, providing grams of the ligand quickly and cheaply.[180]

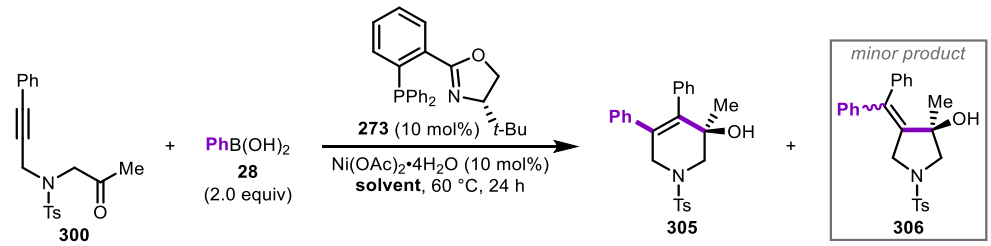


Scheme 2.7: *Synthesis of **273**.*

Given the success of **273**, different solvents were next screened (Table 2.4). As TFE worked well other alcohol solvents were also tested for activity (entries 2–5), however, they all failed to show any reactivity. A selection of polar aprotic solvents was also investigated, including mixtures of MeCN and THF; of these only EtOAc (Entry 7) and THF

(Entry 12) showed any activity, the former gave poor results whilst the latter gave reasonable yields, good regioselectivity and excellent enantioselectivity. As the results using THF were comparable to those of TFE (Entry 1) further optimisation was performed using THF as the solvent in hope that with some modifications it may outperform TFE, whilst also being a more attractive option with respect to cost and sustainability.

Table 2.4: *Solvent Screen.*

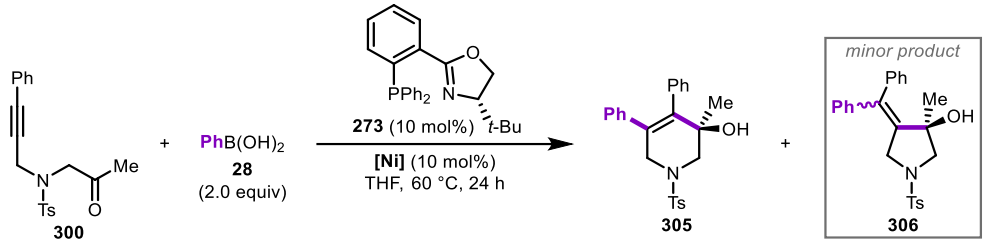


Entry	Solvent	Yield (%)[a]	305:306[b]	ee (%)
1	TFE	72	16:1	96
2	MeOH	ND	-	-
3	EtOH	ND	-	-
4	*t*-BuOH	ND	-	-
5	IPA	ND	-	-
6	dioxane	ND	-	-
7	EtOAc	7	5:1	-
8	DMF	ND	-	-
9	MeCN	ND	-	-
10	MeCN/THF (4:1)	ND	-	-
11	MeCN/THF (3:2)	ND	-	-
12	THF	63	10:1	95

[a]Determined by ^{1}H NMR analysis using TMB as an internal standard. [b]Determined by ^{1}H analysis of the crude reactions. ND = not detected.

Next the catalyst was screened as shown in Table 2.5. Unfortunately, none of the salts screened showed any activity except for $Ni(OTf)_2$ (Entry 6) which was poor yielding, leaving $Ni(OAc)_2•4H_2O$ (Entry 1) as the best option. Other metals, such as cobalt salts, were tested in the reaction, however these also displayed no reactivity.

Table 2.5: *Metal salt screen.*



Entry	Ni(II) salt	Yield (%)[a]	305:306[b]
1	$Ni(OAc)_2 \cdot 4H_2O$	63	10:1
2	$NiCl_2 \cdot 6H_2O$	ND	-
3	$NiCl_2$	ND	-
4	NiI_2	ND	-
5	$Ni(acac)_2$	ND	-
6	$Ni(OTf)_2$	42	7:1
7	$Ni(TFA)_2 \cdot 4H_2O$	ND	-

[a]Determined by ^1H NMR analysis using TMB as an internal standard. [b]Determined by ^1H analysis of the crude reactions. ND = not detected.

Further screening of additives such as bases, Lewis acids, and H_2O were conducted, however none of these provided any improvement. The equivalents of boronic acid were also varied, however this led to mixed results between the two substrates **300** and **301**. A decrease in boronic acid equivalents to 1.2 equivalents gave very minor improvements when using **300**, whereas when using **301** a significant drop in the yield was observed. Therefore, as a compromise 2.0 equivalents of boronic acid was used for all reactions.

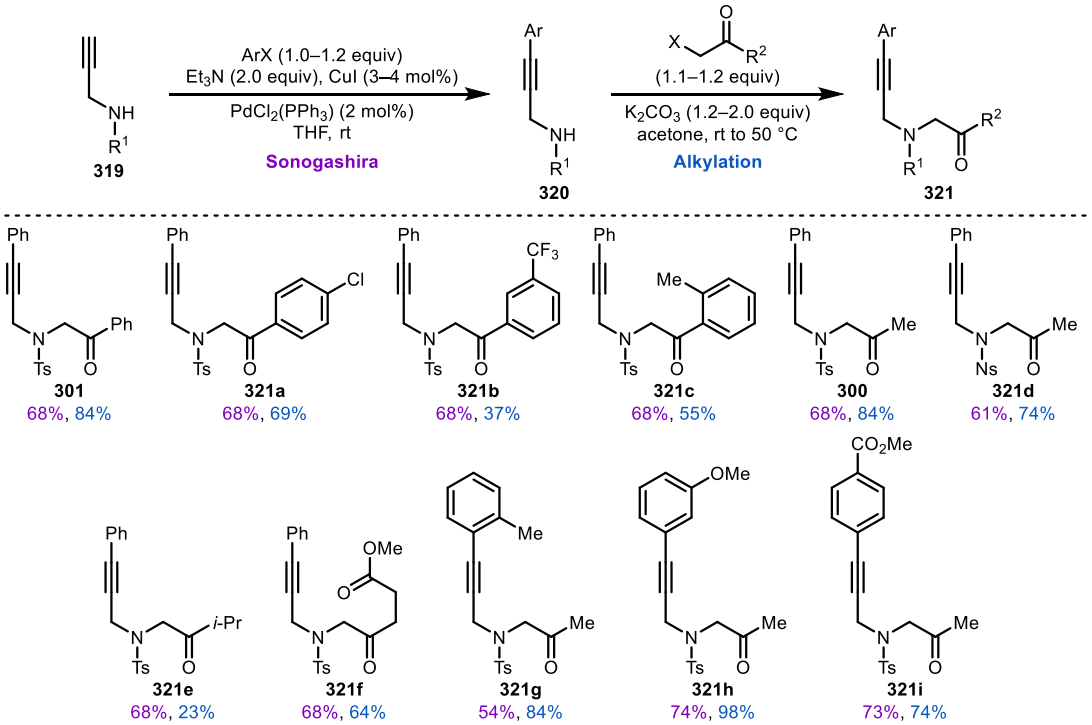
Attempts were also made to lower the catalyst and ligand loading, however reducing this to 2.5 mol% or 5.0 mol% led to drastically lower yields. An increase in catalyst loading to 20 mol% did give slight improvements to the yield however this was not pursued further as it was deemed undesirable to have such a high catalyst loading. Finally, increasing the concentration of the reaction was also briefly examined which unfortunately led to degradation of the yield.

Due to no breakthroughs being made THF as the solvent continued to perform worse compared to TFE. Therefore, we returned to using TFE as the solvent for the final conditions. The overall optimised conditions were those as used in Table 2.4, Entry 1, with the temperature being varied based on the ketone substituent.

2.3 Synthesis of Alkynones

To evaluate the scope of this process a series of alkynones were synthesised containing variations of the tether, alkyne substituent and the ketone substituent. Due to their preliminary success, and ease of synthesis, nitrogen-containing alkynones **321** were utilised as the main class of substrates during this work. The alkynones were synthesised starting from a protected propargylamine **319,** subjecting it first to a Sonogashira reaction installing the alkyne substituent, followed by alkylation of the nitrogen with an α-halo ketone, thereby affording the cyclisation precursors **321** (Table 2.6).

Table 2.6: *Synthesis of the alkynone starting materials* ***321****.*

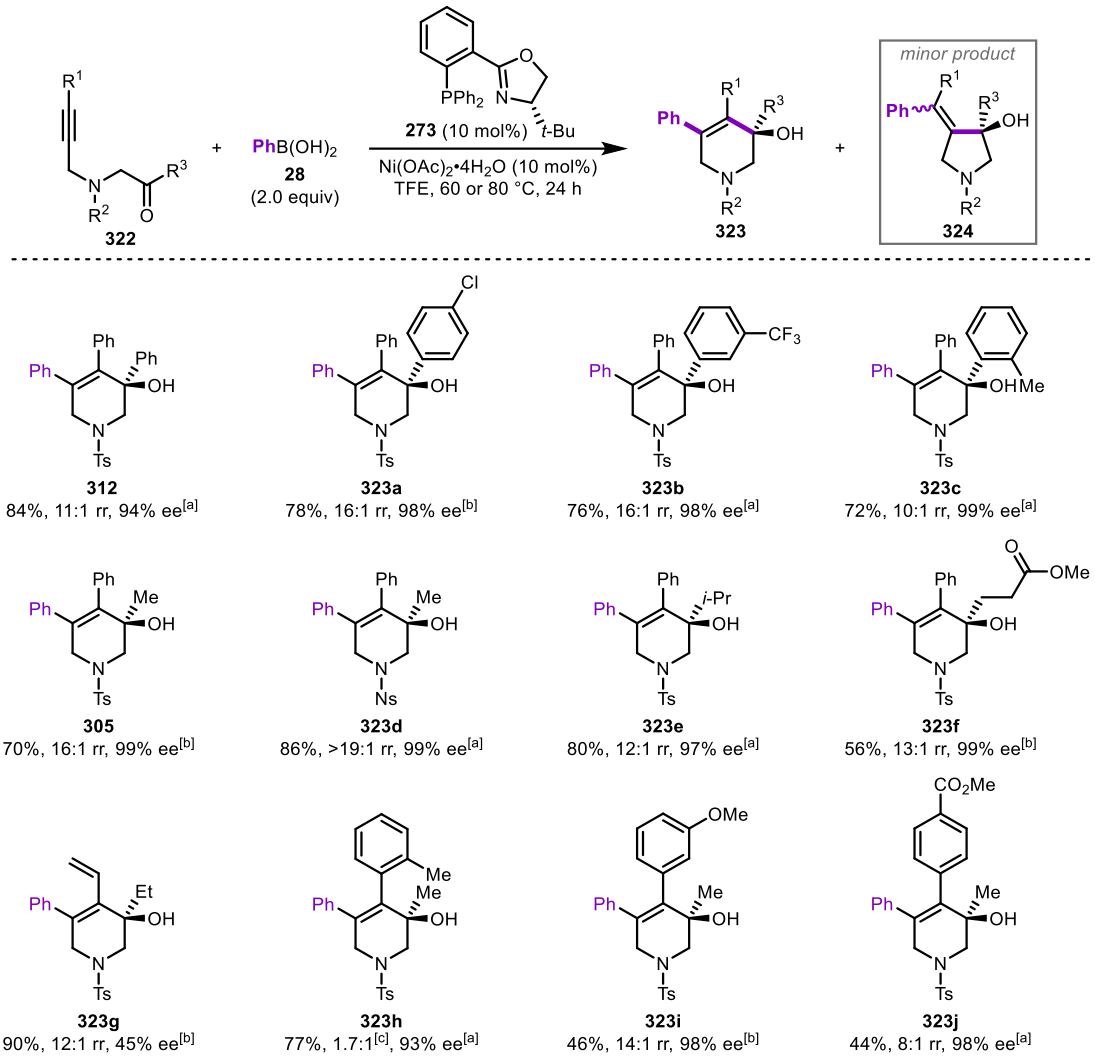


2.4 Alkynone Scope

With alkynones **322** in hand, they were subjected to the optimised conditions utilising phenylboronic acid **28** to afford the cyclisation products **323** as shown in Table 2.7. A range of aromatic ketones were well tolerated, with substrates containing phenyl (**312**), *para*-chlorophenyl (**323a**), (*meta*-trifluoromethyl)phenyl (**323b**), or *ortho*-methylphenyl (**323c**) ketones all giving the desired product. Likewise, dialkyl ketones were also successful substrates with ketones containing a methyl (**323d** and **323h**–**323j**), isopropyl (**323e**) or methyl propanoate (**323f**) all readily cyclising. With **323f** it was thought that the alcohol may lactonise *in situ* to form an enantioenriched spirocycle, however this did not occur. The alkyne substituent was typically aryl with phenyl (**323a**–**323f**), *meta*-methoxyphenyl (**323i**) and (*para*-carbomethoxy)phenyl (**323j**) all being tolerated. A sub-

strate with a vinyl group (**323g**) also reacted well giving an excellent yield, however the enantioselectivity was diminished. The nitrogen protecting group was not just limited to a *para*-tosylsulfonamide, with a *para*-nitrophenylsulfonamide (**323d**) also proceeding to cyclise, allowing for alternative deprotection methods to be utilised.

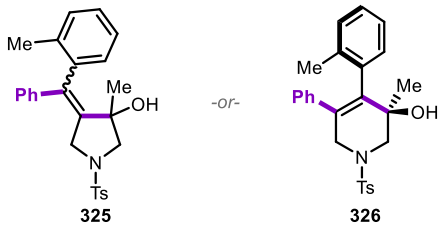
Table 2.7: *Alkynone scope of nickel-catalysed anti-arylmetallative cyclisations.*



Reactions employed 0.30 mmol of ***322****. rr was determined by* ^{1}*H analysis of the crude reactions.* [a]*80 °C.* [b]*60 °C.* [c]*Undistinguishable mixture of regioisomers or diastereomers.*

In the case of **323h** a mixture of two products was observed, both of which having excellent enantioselectivity. These could possibly be a mixture of regioisomers (**325**), as discussed, however due to the added steric hindrance at the *ortho*-position this could also be a mixture of diastereomers (**326**) resulting from atropisomerism (Scheme 2.8). The ^{1}H NMR spectrum of **323h** showed no mixtures of alkenes, which may be present if **325** was formed. Attempts were made to distinguish between these possibilities through derivatisation, such as an osmium-mediated cleavage of the alkene or dehydration/aromatisation of the ring to discriminate between the products, however this was unsuccessful. Typical-

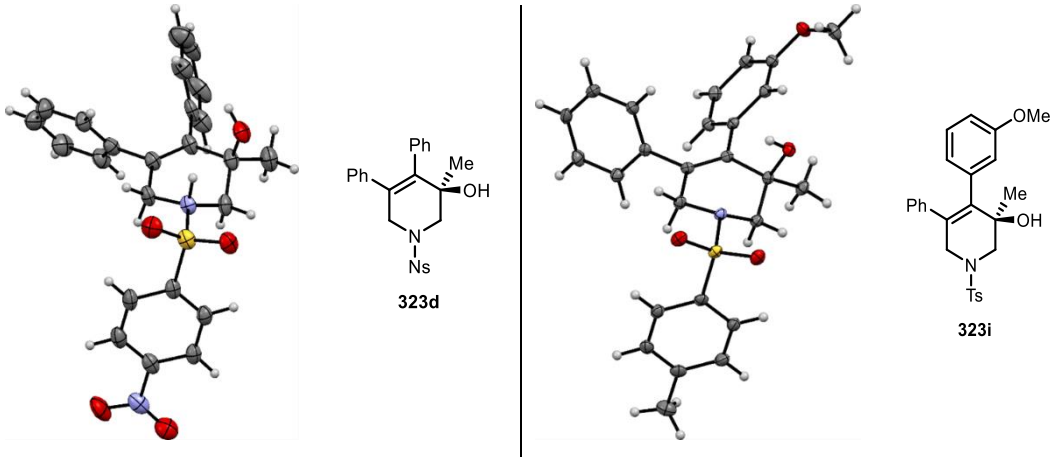
ly, the regioselectivity of carbometalation is often guided by steric effects, whereby the nickel is placed next to the largest substituent, for example when using an alkyne with a TMS substituent the metal gets placed next to the TMS group. This suggests that the mixture may be diastereomers, rather than regioisomers, however further evidence would be required to prove this hypothesis; a crystal structure would be likely be required to distinguish between these two possibilities.



325 **326**

Scheme 2.8: *Possible regioisomer **325** or diastereomer **326** of **323h**.*

The absolute configuration of **323d** and **323i** was determined by X-ray crystallography, with the rest of the products being assigned by analogy (Scheme 2.9).



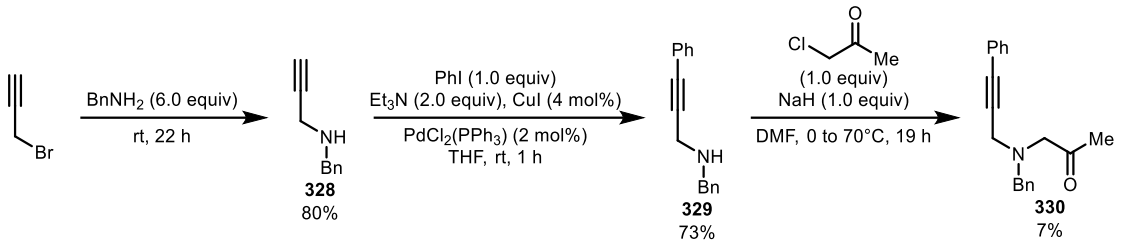
323d **323i**

Scheme 2.9: *Crystal structures of **323d** and **323i**. See experimental section for further details.*

2.5 Further Exploration of Alkynone Scope

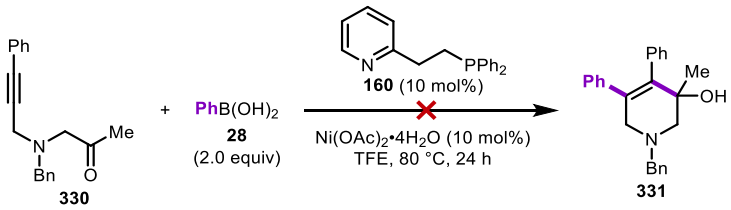
2.5.1 Nitrogen Linker

Further attempts were made to increase the generality of the substrates to the arylative cyclisation methodology developed. To expand the protecting group scope, a substrate with a benzyl protected amine **330** was synthesised (Scheme 2.10). First amination of propargyl bromide with excess benzylamine gave **328**, which was then subjected to a Sonogashira reaction to install a phenyl group on the alkyne **329**. Next alkylation of the amine was attempted resulting in alkynone **330** in a poor yield. This is likely due to various side reactions such as overalkylation or competing deprotonation of the chloroacetone.



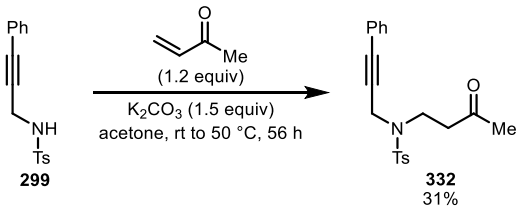
Scheme 2.10: *Synthesis of* ***330****.*

Unfortunately, when **330** was subjected to the racemic arylative cyclisation conditions none of the product **331** could be detected (Scheme 2.11). This may be due to the higher Lewis basicity of the amine compared to the sulfonamide. The sulfonamide may also assist the orientation of alkyne and ketone facilitating the cyclisation step.



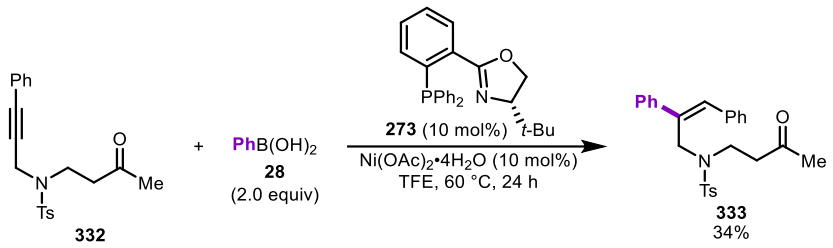
Scheme 2.11: *Attempted nickel-catalysed cyclisation of* ***330****.*

Changing the tether length would allow for different sized rings to be formed. In the case of a nitrogen linker no attempts were made to form a product with a 5-membered ring. This is because either an amide or ynamide would have to be utilised, amides have already been described as an electrophile to form pyrroles, whilst ynamides would likely cause issues in the hydroarylation step due to mismatching electronic and steric factors.[171] On the other hand a viable substrate to form a 7-memebered ring is easily accessible. The key intermediate **299** could undergo an aza-Michael addition to form **332** (Scheme 2.12).



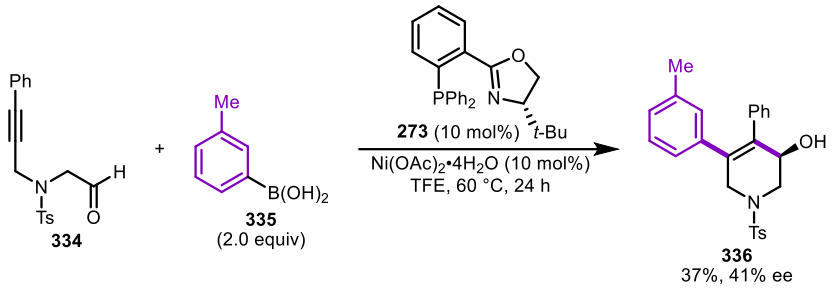
Scheme 2.12: *Synthesis of* ***332****.*

When subjected to the developed conditions **332** did not undergo cyclisation, however, the hydroarylated product **333** was isolated in a 34% yield as a single stereoisomer (Scheme 2.13). This may suggest that isomerisation of the alkenylnickel species is an equilibrium process with the subsequent cyclisation not being kinetically favourable with longer tether lengths.



Scheme 2.13: *Attempted nickel-catalysed cyclisation of* ***332****.*

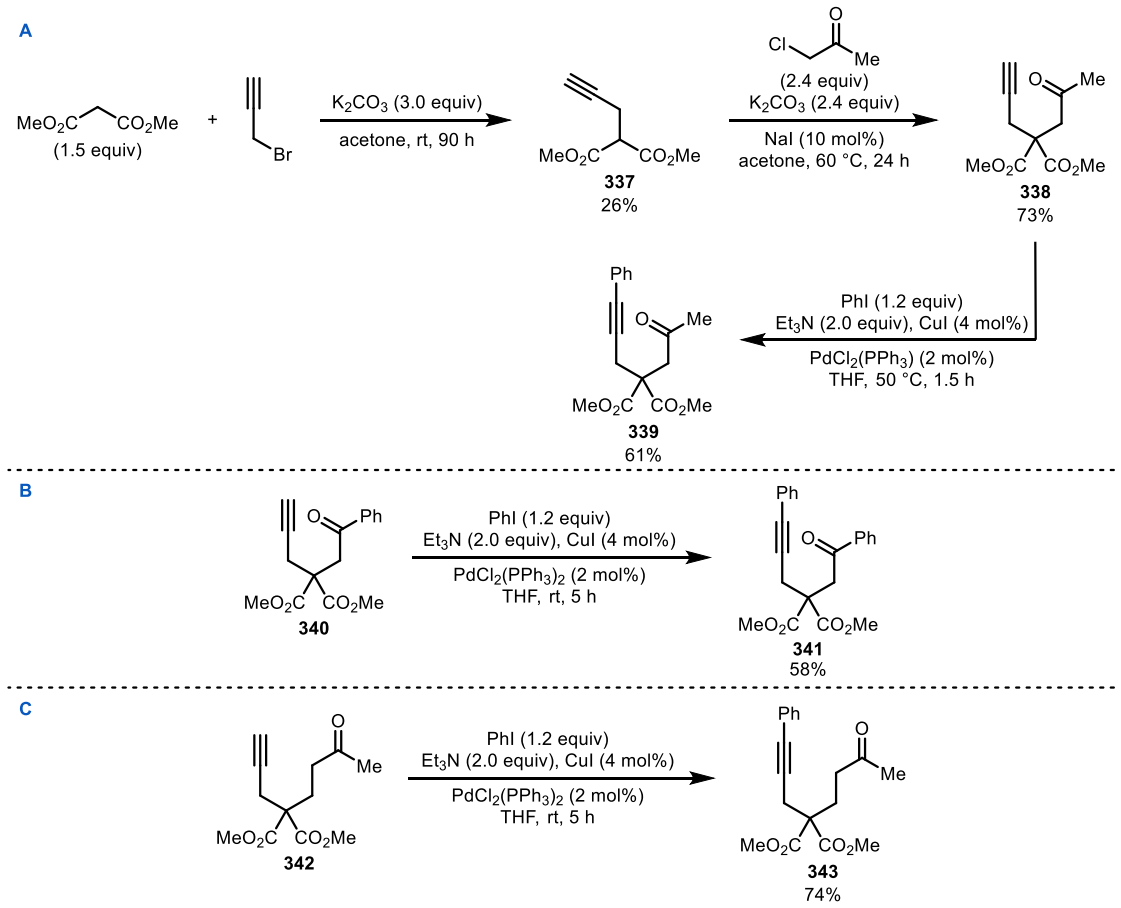
We also investigated changing the electrophile from a ketone to other carbonyls. Whilst an ester could function as the electrophile they would form non-chiral products so it is of relatively little interest (as well as an example already having been reported).[150] However there remains the possibility to use an aldehyde as an electrophile to access enantioenriched secondary alcohols. Subjection of **334** with **335** to the arylative cyclisation conditions afforded the product **336** in a moderate yield and a poor 41% ee.



Scheme 2.14: *Attempted nickel-catalysed cyclisation of* ***334****.* ***334*** *was synthesised by Simone Gillbard.*

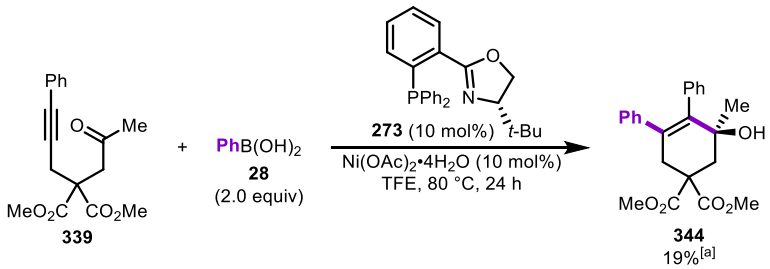
2.5.2 Carbon Linker

As only a nitrogen linker had been used in the examples thus far we wanted to further expand the chemical diversity of the products by utilising a carbon linker, to access carbocyclic products. A malonate unit as the carbon linker allowed for the facile synthesis of the substrates using a similar pathway to before. Using this approach three different substrates were synthesised. First propargylation of dimethyl malonate afforded **337**, which was then alkylated with chloroacetone, followed by arylation of the alkyne through a Sonogashira reaction to afford the cyclisation precursor **339** (Scheme 2.15A). Similarly, arylation of intermediate **340** by a Sonogashira coupling to form the phenyl ketone analogue **341** (Scheme 2.15B). Finally, subjection of intermediate **342** to a Sonogashira coupling gave **343** (Scheme 2.15C).



Scheme 2.15: *A) Synthesis of **339**. B) Synthesis of **341**. C) Synthesis of **343**. **340** and **342** were prepared by Riccardo Di Sanza.*

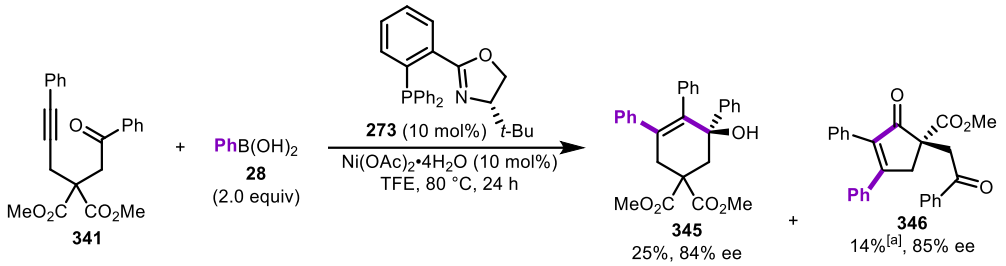
Subjection of **339** to the arylative cyclisation conditions formed **344** in a 19% yield, along with 14% of unreacted starting material being observed, the rest of the mass was unaccounted for (**Scheme 2.16**). In the case of attempting the reaction with ligand **160** none of the desired product could be detected with full consumption of the starting material.



Scheme 2.16: *Attempted nickel-catalysed cyclisation of **339**.* [a]Determined by ^{1}H NMR analysis using TMB as an internal standard.

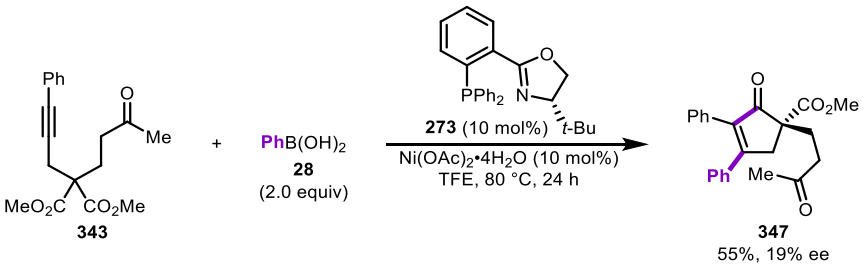
The attempted arylative cyclisation of the phenyl ketone **341** was slightly more successful, with 25% of the desired product **345** being isolated with 84% ee, however, this result was somewhat surprising given that these classes of substrates worked well when a different electrophile was utilised (Scheme 2.17).[150] Interestingly 14% of **346** was observed by NMR, which results in cyclisation onto one of the esters, suggesting that despite the

lower electrophilicity of the ester the kinetic preference to form a 5-membered ring over a 6-membered ring is competitive.



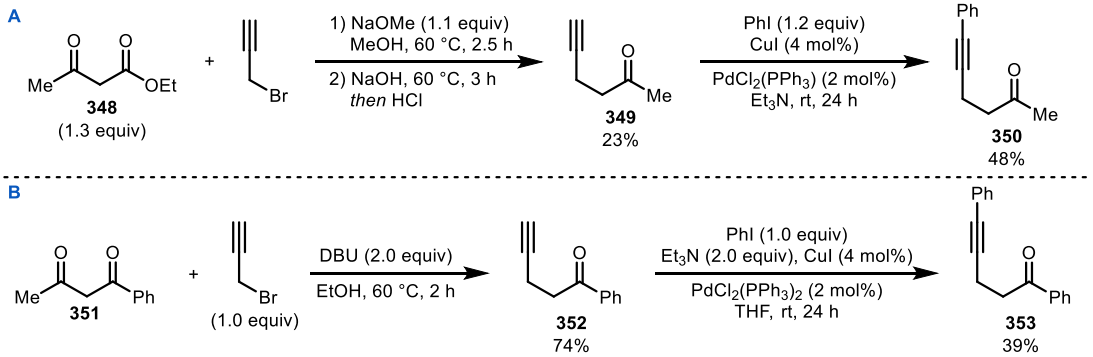
Scheme 2.17: *Attempted nickel-catalysed cyclisation of* ***340****.* [a]Determined by ^{1}H NMR analysis using TMB as an internal standard.

Finally, an attempt was made to form a 7-membered carbocycle using **343**, although like previous efforts none of the desired product was formed. In this case selective formation of **347** outcompeted any cyclisation onto the ketone; surprisingly in this case there was a large drop in the enantioselectivity of **347** with 19% ee being observed compared to the 85% **346** (Scheme 2.18).



Scheme 2.18: *Attempted nickel-catalysed cyclisation of* ***343****.*

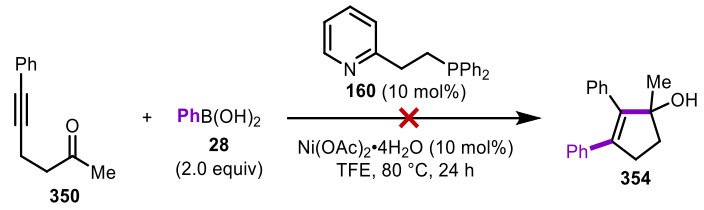
To gain access to 5-membered rings we decided to use a methylene linker. First propargylation of the β-ketoester **348** followed by decarboxylation gave **349**. Subjection to a Sonogashira coupling gave the cyclisation precursor **350** in a 48% yield (Scheme 2.19A).



Scheme 2.19: *A) Synthesis of* ***350****. B) Synthesis of* ***353****.*

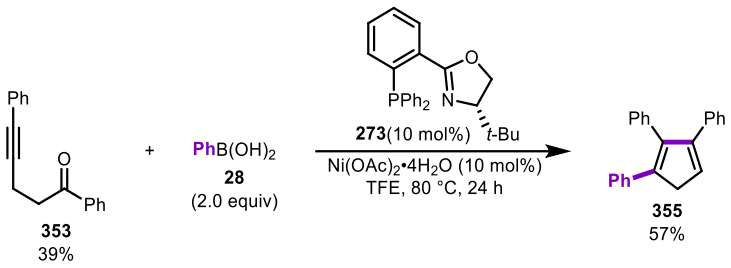
The phenyl ketone analogue **353** was similarly synthesised; first a propargylation/retro-Claisen of the diketone **351**, followed by a Sonogashira to give **353** in a 39% yield (Scheme 2.19B).

Unfortunately, subjection of **350** to the developed reaction conditions resulted in no product **354**, with all the starting material being consumed (Scheme 2.20).



Scheme 2.20: *Attempted nickel-catalysed cyclisation of* ***350****.*

On the other hand, when employing the phenyl ketone **353** arylative cyclisation did occur, but rather than isolating the desired tertiary alcohol, **355** was isolated instead which resulted from *in situ* dehydration (Scheme 2.21).



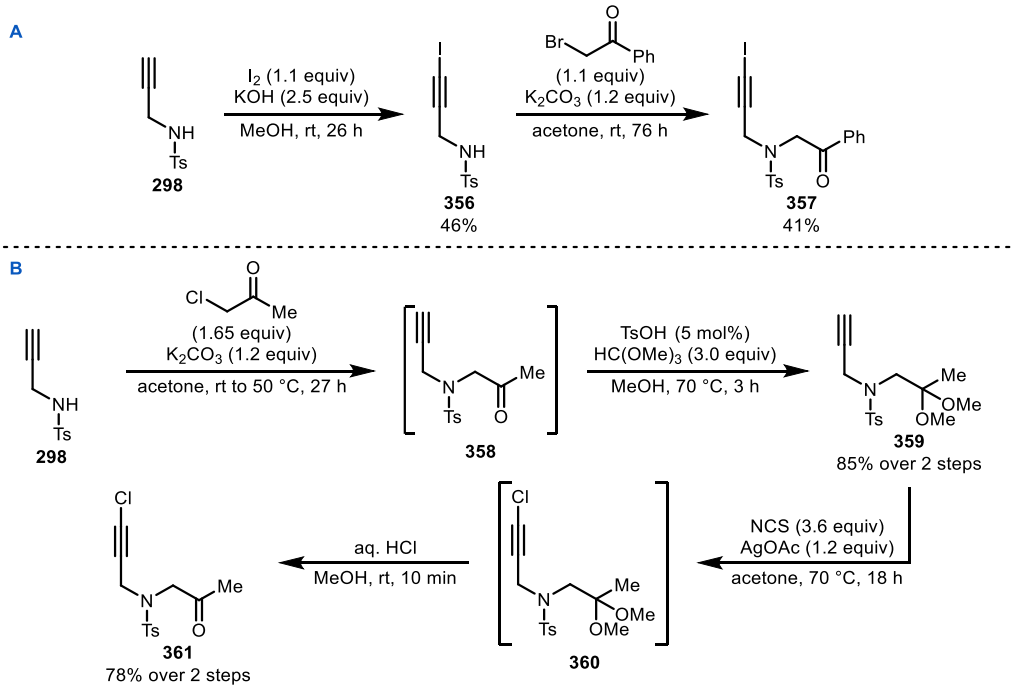
Scheme 2.21: *Attempted nickel-catalysed cyclisation of* ***353****.*

2.5.3 Alkyne Substituent Variation

One of the shortcomings of this methodology is the number of arene groups in the products, with some having up to four arene units. To further expand the methodology and the chemical diversity of the products we aimed to minimise the number of arene units. Specifically, in most cases a 1,2-diaryl alkene is formed which is a moiety that is not prevalent in natural/pharmaceuticals compared to other alkene substitution patterns. One avenue to address this is to change the alkyne substituent to a non-aromatic moiety; this was shown earlier using a vinyl substituted alkyne to form **323g**, however we realised there are various other possibilities we could examine. Any changes to the alkyne substituent would have to be managed carefully as changing this group could lead to changes in the regioselectivity, as it is thought that the stereoelectronics of the aryl group plays a key role in obtaining the desired regioselectivity of carbometalation.[12]

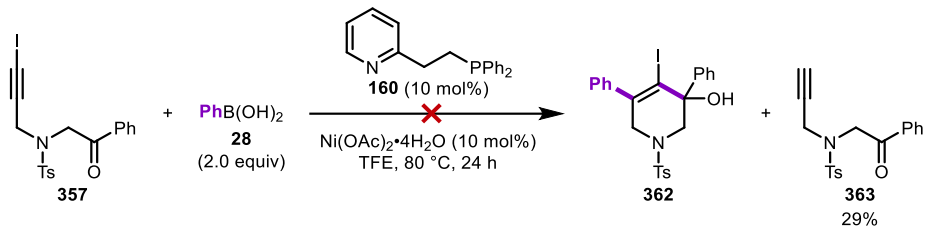
One possibility is replacing the arene with a halide such as an iodide or chloride; this would form a vinyl halide in the product which would be an excellent handle for further derivatisation of the products. The iodide **357** was synthesised by iodination of **298** followed by alkylation with bromoacetophenone (Scheme 2.22A). The chloride analogue **361** was synthesised by a modified route due to incompatibilities of **358** undergoing elec-

trophilic chlorination (Scheme 2.22B). First **298** was alkylated with chloroacetone followed by the protection of **358** as the dimethyl acetal to give **359** in an 85% yield over 2 steps. Chlorination of the alkyne, followed by deprotection under aqueous acidic conditions afforded **361** in 78% yield over 2 steps.



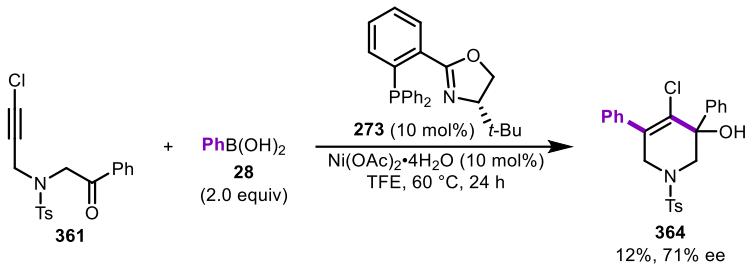
Scheme 2.22: *A) Synthesis of **357**. B) Synthesis of **361**.*

Subjection of **357** to the arylative cyclisation conditions resulted in none of the desired product being formed (Scheme 2.23). Only protodeiodonation (**363**) was observed in a 29% yield with no starting material remaining.



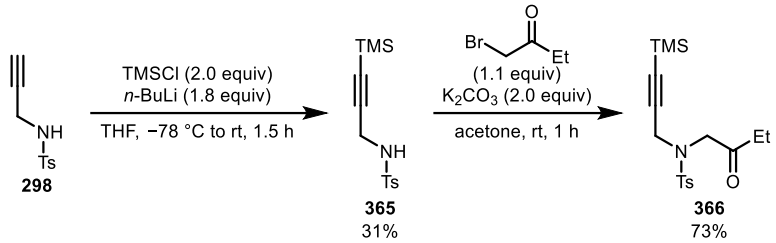
Scheme 2.23: *Attempted nickel-catalysed cyclisation of **357**.*

When subjecting the chloride **361** to the reaction conditions 12% of the product **364** was isolated with a diminished enantioselectivity of 71% ee (Scheme 2.24). ^{1}H NMR spectroscopy of the crude reaction mixture showed that there were significant amounts of starting material remaining, so it may have been possible with extended reaction times or higher catalyst loading to achieve a higher conversion.



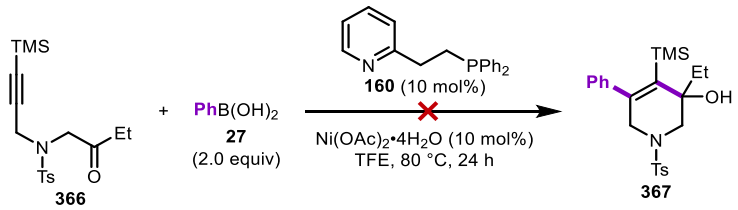
Scheme 2.24: *Attempted nickel-catalysed cyclisation of* ***361****.*

Silyl alkynes were also considered, due to their ease of synthesis and precedence for these being viable substrates as reported by Lam and co-workers in similar nickel-catalysed cyclisations.[150,181] The synthesis begins with silylation of the terminal alkyne **298** followed by alkylation with the α-haloketone to afford the alkynone **366** (Scheme 2.25).



Scheme 2.25: *Synthesis of* ***366****.*

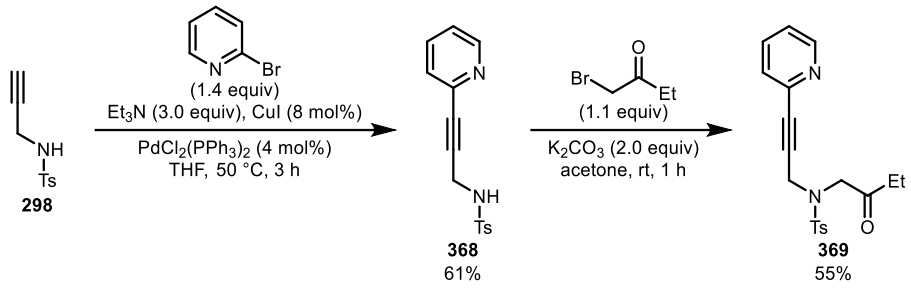
Attempted nickel-catalysed cyclisation of **366** did not give any of the desired product **367**; when using ligand **160** 85% of the starting material remained, whereas when using ligand **273** the reaction formed a complex mixture with no observable starting material or product (Scheme 2.26).



Scheme 2.26: *Attempted nickel-catalysed cyclisation of* ***366****.*

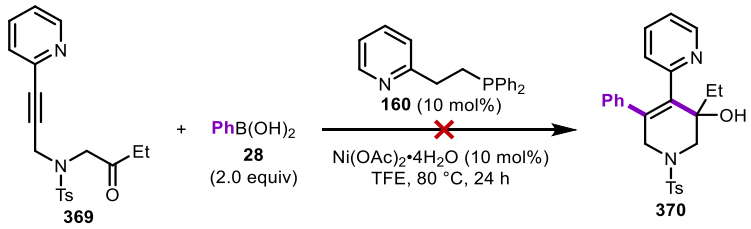
Another area that we were keen to explore was the inclusion of more heteroatoms in the products, either from the boronic acid or from the alkynone. Though was challenging given the distinct lack of heteroatoms from previous papers published in this area, likely due to incompatibility between the nickel catalyst and heteroatoms due to coordination.[122,150] We have demonstrated that both phenol and tertiary alcohols can be tolerated under the developed conditions, so more specifically we investigated whether it was possible to introduce more nitrogen atoms into the products. One attempt to achieve this was by utilising a 2-pyridyl group on the alkyne **369**, which could be synthesised in a similar fashion

of the standard substrates by utilising a Sonogashira reaction followed by alkylation of the sulfonamide (Scheme 2.27).



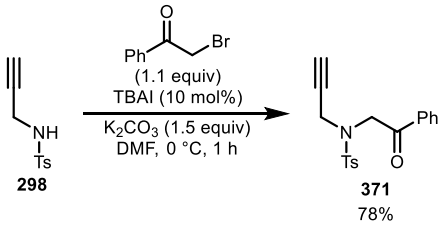
Scheme 2.27: *Synthesis of* ***369****.*

The idea behind this was that even if the nitrogen was to coordinate with the nickel it may subsequently direct it towards the substrate. However, when **369** was subjected to either the racemic or enantioselective conditions a complex mixture was formed (Scheme 2.28).



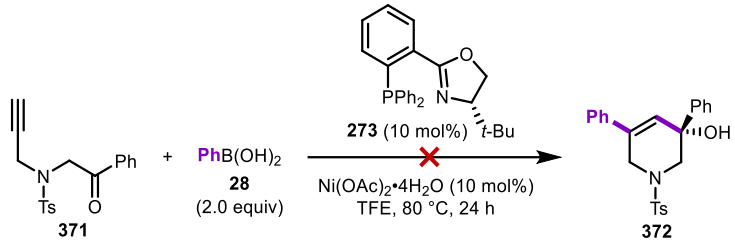
Scheme 2.28: *Attempted nickel-catalysed cyclisation of* ***369****.*

It was also considered that the terminal alkyne **371** could also be utilised as a substrate, which was easily synthesised in one step from **298** (Scheme 2.29).



Scheme 2.29: *Synthesis of* ***371****.*

Attempted cyclisation of **371** with ligand **160** led to only trace product being observed with full consumption of the starting material (Scheme 2.30). When employing ligand **273**, the product **372** was formed in a 23% yield, again with full consumption of starting material. However, in both cases it is likely that any product formed would be the undesired regioisomer given the stereoelectronics of the alkyne, therefore this substrate was pursued no further.[182]

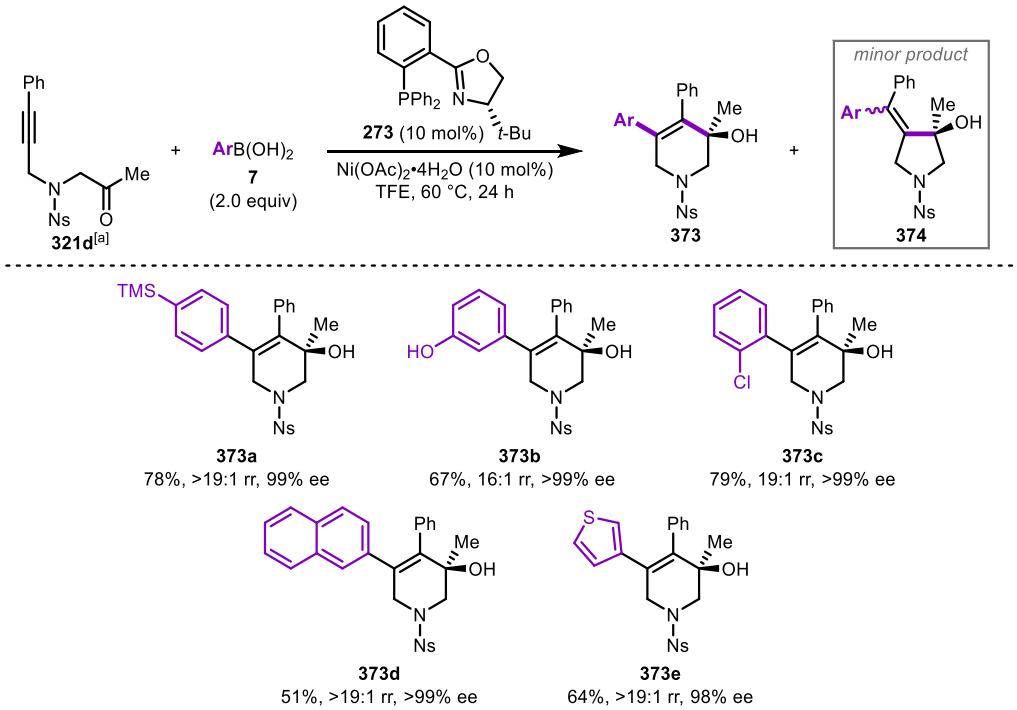


Scheme 2.30: *Attempted nickel-catalysed cyclisation of* ***371****.*

2.6 Boronic Acid Scope

For the boronic acid scope **321d** was utilised to further exemplify the use of a *para*-nitrophenylsulfonamide as a protecting group (Table 2.8). Pleasingly the arylative cyclisation products **373** were obtained in yields up to 79%, and with enantioselectivities of 98% to >99% ee. Boronic acids with various stereoelectronic effects were tolerated, with notable examples including *meta*-hydroxyphenylboronic acid (**373b**) and *ortho*-chlorophenylboronic acid (**373c**). 2-Napthylboronic acid (**373d**) and an example of a heterocycle, 3-thienylboronic acid (**373e**), also successfully formed the desired product.

Table 2.8: *Boronic acid scope of nickel-catalysed anti-arylmetallative cyclisations.*

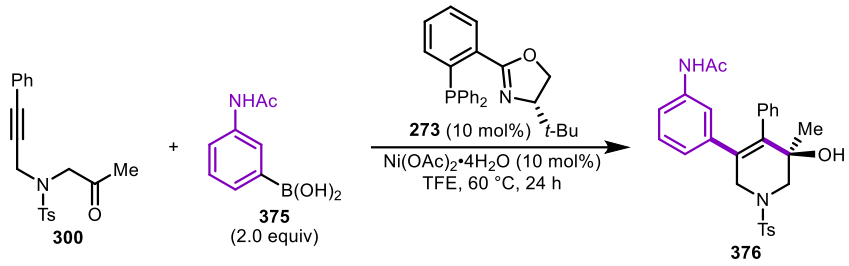


[a]Reactions employed 0.30 mmol of ***321d.*** *rr was determined by* ^{1}*H analysis of the crude reactions.*

2.6.1 Further Boronic Acid Scope

Previously we had tried to incorporate heteroatoms into the product by using **369** as a substrate, however, this was not tolerated in the reaction conditions. Attempts were made to use 3-pyridylboronic acid which led to the formation of complex mixtures. (3-

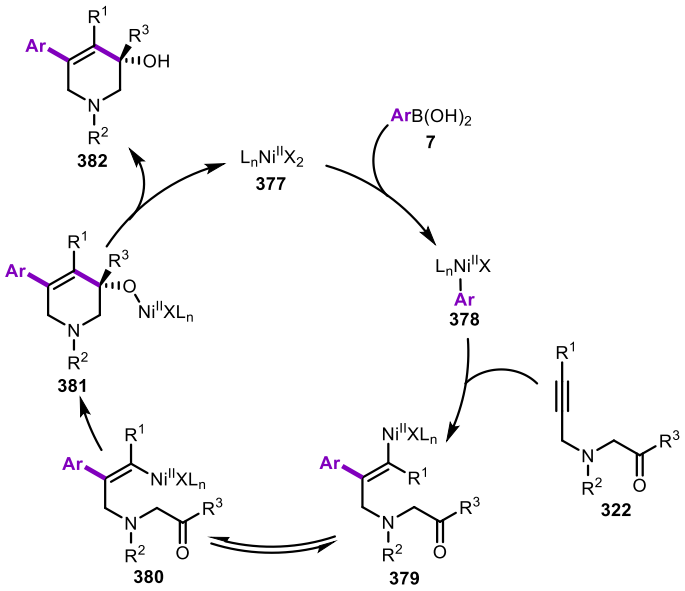
Acetamidophenyl)boronic acid (**375**) was also tested, as shown in Scheme 2.31. Use of this boronic acid would demonstrate tolerance of an amide functionality under the reaction conditions, which can subsequently be hydrolysed to give access to the aniline derivative. Initially this was performed on a 0.05 mmol scale of **300** which formed the desired product **376** in 49% as determined by ^{1}H NMR spectroscopy. Unfortunately, upon scaling the reaction up to 0.30 mmol, despite the crude NMR spectrum looking promising, isolation of **376** was unsuccessful.



Scheme 2.31: *Attempted nickel-catalysed cyclisation of alkynone **300** with boronic acid **375**.*

2.7 Proposed Reaction Mechanism

The proposed mechanism is thought to be analogous to previous cyclisations developed by the Lam group whereby it proceeds *via* a Ni(II) redox-neutral cycle (Scheme 2.32).



Scheme 2.32: *Proposed mechanism for the formation of **382**.*

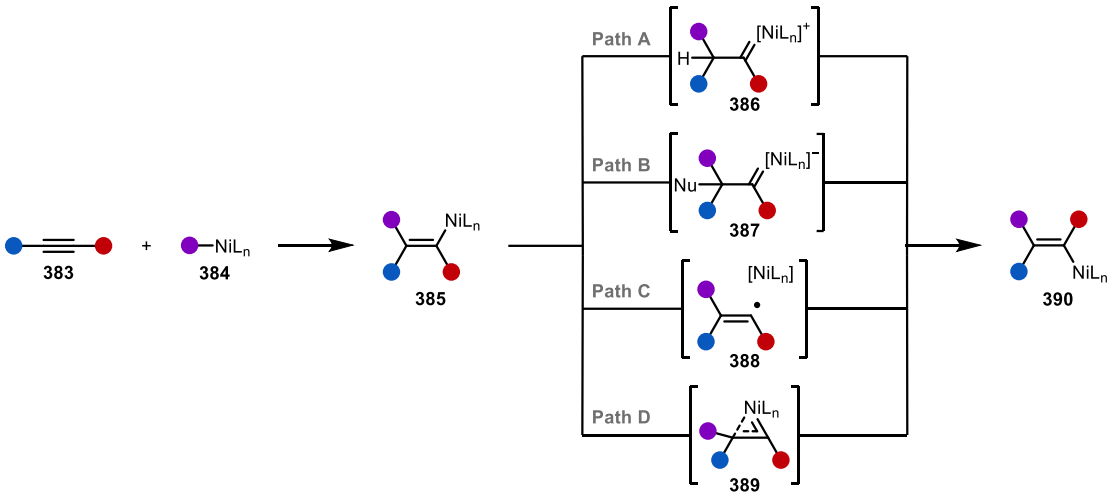
First the catalyst **377** undergoes transmetalation with the boronic acid **7** followed by carbonickelation of the alkyne **322** forming **379**. At this point it is thought that a key isomerisation step occurs, facilitating the formal *anti*-addition observed in the final product. **380** allows the nickel to add into the carbonyl affording **381**. Finally, protonolysis forms the product **382** and completes the catalytic cycle. Liu proposed that under similar

conditions with a base additive that the mechanism may instead proceed *via* a Ni(I) redox-neutral cycle due to the isolation of a Ni(I) intermediate that went on to show catalytic activity in their reaction. Based on the differences in reactivity between the reductive system reported by Kong (Scheme 1.81) to our system it may be more likely that our process occurs through a Ni(II) redox-neutral cycle.

Whilst no investigation into the mechanism was done as part of this work, reports by the Lam group and others on this nickel-catalysed *anti*-carbometalation cyclisation manifold have described some preliminary findings with respect to the mechanism. The step that is of the most interest is the isomerisation step, as being able to understand and control this would allow for transference to alternative nickel-catalysed additions to alkynes.

Bergmann did early studies into the mechanism of the isomerisation of alkenylnickel species formed from the addition of Ni(acac)(PPh_3)Ph and Ni(acac)(PPh_3)Me to alkynes.[142,143] They found that an alkenylnickel species was formed quickly which then equilibrates to form a mixture of isomers. Interestingly the addition of the respective organonickel species above to 1-phenyl-1-propyne or diphenylacetylene both formed the same statistical mixture of the same alkenylnickel product. Based on those results they proposed that both pathways proceed through a common intermediate which can undergo reversible isomerisation, as *anti*-addition or substrate selective *syn*- or *anti*-addition seemed very unlikely. The effect of the phosphine ligand was also investigated with excess phosphine inhibiting addition into the alkyne, suggesting the insertion into the alkyne occurs *via* association of the alkyne to the nickel displacing a phosphine ligand. On the other hand, excess phosphine does not inhibit isomerisation, however it also does not have an impact on the mixture of isomers, which lead them to believe that the phosphine may be involved in both the isomerisation- and product-forming step.

Several possible pathways for the isomerisation of the alkenylnickel intermediate are shown in Scheme 2.33. First *syn*-addition of the organonickel species **384** into **383** affords the intermediate **385**. Whilst direct *anti*-addition across the alkyne has been proposed it seems very unlikely that this would directly occur.[183] Path A proceeds through reversable protonation of **385** to form **386** which allows for isomerisation to occur to form **390**, however this pathway seems unlikely due to hydroarylation products often being observed.



Scheme 2.33: *Possible pathways for the isomerisation of the alkenyl-nickel intermediate.*

Likewise, Path B follows a similar premise but occurs through addition of a nucleophile, such as a phosphine, to **385** yielding **387**; this is the pathway that is favoured by Bergman as discussed above.

The third pathway, Path C, proceeds through a reversible bond homolysis of **385** to form the vinyl radical **388** which can undergo inversion to allow formation of the more sterically favoured alkenylnickel intermediate **390**. Path C seems unlikely as Liu reported that similar nickel-catalysed reactions were not inhibited by TEMPO. However Martin has suggested that this process may be rapid, minimising the chance that TEMPO would have to quench any radicals, in turn making this path difficult to confirm experimentally.[149,151]

Finally, Path D proposes the unimolecular approach of the reversible formation of the haptomer **389**.[184] Path D could also go through a similar unimolecular approach through the formation of a zwitterionic carbenoid.[123,125,162]

In conclusion the mechanism for the isomerisation step is still elusive, though there is still merit for further investigation into the mechanism both experimentally and computationally.

2.8 Conclusions and Future Work

In conclusion the nickel-catalysed *anti*-carbometallative cyclisations developed by the Lam group has been expanded to substrates with an alkyne tethered to an acyclic ketone. Various substrates and boronic acids were demonstrated to afford chiral tertiary alcohol containing products in excellent enantioselectivities. The tetrahydropyridine core formed is of potential value both medicinally and is featured in several natural products. The limitations of this work have also been vastly explored with attempts to form various ring systems and minimising the number of aromatic units in the products.

For future work it would be of interest to further exploit the intermediary alkenylnickel species, such as the work by Kong where they utilise it to undergo a Heck cyclisation.[121] The development of different coupling partners is also of great interest, as moving away from boronic acids may allow for the coupling of alkyl units. As the alkenylnickel species has been proposed to be Ni(I) in some cases it may be possible to combine this chemistry with photocatalysis to allow for the generation of radicals that could add to the alkyne and subsequently follow the reactivity to form *anti*-addition cyclisation products. The mechanism of the palladium-catalysed dicarbofunctionalisation reported by Nevado in Scheme 1.63 shows that a PdX species undergoes transmetalation to form a ArPd species which then recombines with the alkenyl radical; however, if it was possible to utilise the PdX for the recombination then it may be possible to effect an addition of the alkenylpalladium species into an electrophile. This would again provide access to alkyl halides as a coupling partner.

3 EXPERIMENTAL

3.1 GENERAL INFORMATION

All air-sensitive reactions were carried out under an inert atmosphere using oven-dried apparatus. 2,2,2-Trifluoroethanol (TFE) was purchased from Fluorochem and degassed before use using a stream of argon gas (20 min). 2-[2-(Diphenylphosphino)ethyl]pyridine or racemic Ph-PHOX were used as achiral ligands to prepare authentic racemic products for obtaining chiral HPLC assays. All commercially available reagents were used as received unless otherwise stated. Petroleum ether refers to Sigma-Aldrich product 24587 (petroleum ether boiling point 40–60 °C). Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien 60F254 0.2 mm precoated plates. Compounds were visualised by exposure to UV light or by dipping the plates into solutions of potassium permanganate or vanillin followed by gentle heating. Flash column chromatography was carried out using silica gel (Fisher Scientific 60 Å particle size 35-70 micron or Fluorochem 60 Å particle size 40-63 micron).

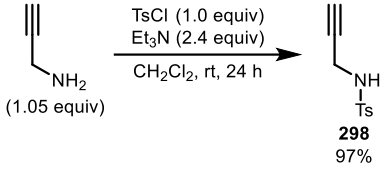
Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. The solvent of recrystallisation is reported in parentheses. Infrared (IR) spectra were recorded on Bruker platinum alpha FTIR spectrometer on the neat compound using the attenuated total reflectance technique. High resolution mass spectra were recorded using electrospray ionisation (ESI) techniques. X-ray diffraction data were collected at 120 K on an Agilent SuperNova diffractometer using CuKα radiation.

NMR spectra were acquired on Bruker Ascend 400 or Ascend 500 spectrometers. ^{1}H and ^{13}C NMR spectra were referenced to external tetramethylsilane *via* the residual protonated solvent (^{1}H) or the solvent itself (^{13}C). ^{19}F NMR spectra were referenced through the solvent lock (^{2}H) signal according to the IUPAC-recommended secondary referencing method following Bruker protocols. All chemical shifts are reported in parts per million (ppm). For $CDCl_3$, the shifts are referenced to 7.26 ppm for ^{1}H NMR spectroscopy and 77.16 ppm for ^{13}C NMR spectroscopy. Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. High resolution mass spectra were recorded using electrospray ionisation (ESI) techniques. Coupling constants are quoted in Hz (J). ^{1}H NMR splitting patterns were designated as singlet (s), doublet (d), triplet (t), quartet (q), pentet (p). Splitting patterns that could not be interpreted or easily visualised were designated as multiplet (m), apparent (app) or broad (br).

3.2 Preparation of Alkynones

3.2.1 Preparation of Key Intermediates

4-Methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (298)



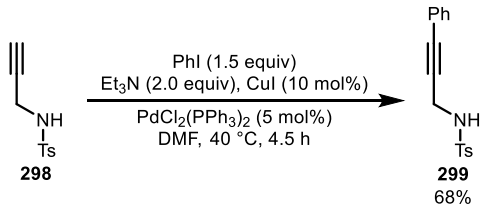
To a solution of propargylamine (5.00 g, 90.8 mmol) in CH_2Cl_2 (100 mL) under an argon atmosphere at 0 °C was added 4-toluenesulfonyl chloride (16.5 g, 86.5 mmol). To the resulting solution Et_3N (29.0 mL, 208 mmol) was added dropwise and the reaction mixture stirred at room temperature for 24 h. The solution was diluted with Et_2O (500 mL), washed with 10% aqueous HCl (300 mL) and brine (100 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give **298** (17.6 g, 97%) as an off-white solid. The analytical data were consistent with those reported previously.[181]

R_f = 0.21 (40% Et_2O/petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82–7.74 (2H, m, Ar**H**), 7.31 (2H, d, *J* = 8.1 Hz, Ar**H**), 4.78 (1H, br t, *J* = 6.0 Hz, N**H**), 3.82 (2H, dd, *J* = 6.1, 2.5 Hz, C**H**$_2$), 2.43 (3H, s, C**H**$_3$), 2.10 (1H, t, *J* = 2.6 Hz, C**H**).

^{13}C NMR (101 MHz, $CDCl_3$): δ 144.0 (C), 136.6 (C), 129.8 (2 × CH), 127.5 (2 × CH), 78.1 (C), 73.1 (CH), 33.0 (CH_2), 21.7 (CH_3).

4-Methyl-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (299)



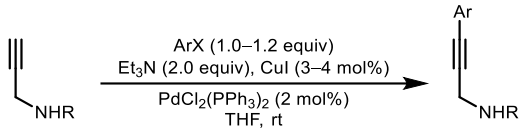
To a suspension of $Pd(PPh_3)_2Cl_2$ (674 mg, 0.96 mmol) and CuI (364 mg, 1.91 mmol) in DMF (16 mL) under an argon atmosphere at room temperature was added iodobenzene (3.20 mL, 28.7 mmol), Et_3N (5.30 mL, 38.2 mmol) and a solution of alkyne **298** (4.00 g, 19.1 mmol) in DMF (24 mL). The resulting mixture was stirred at 40 °C for 4 h. The reaction was diluted with brine (400 mL) and then the aqueous layer extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 × 400 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (20 to 50% EtOAc/petroleum ether) to give **299** (3.71 g, 68%) as a brown solid. The analytical data were consistent with those reported previously.[185]

R_f = 0.22 (20% EtOAc/petroleum ether)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87–7.79 (2H, m, Ar**H**), 7.33–7.20 (5H, m, Ar**H**), 7.17–7.11 (2H, m, Ar**H**), 4.94 (1H, br t, *J* = 6.1 Hz, N**H**), 4.08 (2H, d, *J* = 6.2 Hz, C**H**$_2$), 2.35 (3H, s, C**H**$_3$)
^{13}C NMR (101 MHz, $CDCl_3$): δ 143.8 (C), 137.0 (C), 131.7 (2 × CH), 129.8 (2 × CH), 128.6 (2 × CH), 128.2 (CH), 127.6 (2 × CH), 122.2 (C), 84.8 (C), 83.4 (C), 33.9 (CH_2), 21.6 (CH_3).

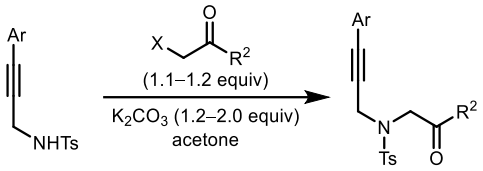
3.2.2 Preparation of Alkynones

General Procedure A: Sonogashira Coupling

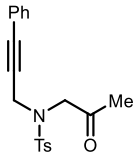


To a suspension of aryl halide (1.0–1.2 equiv), Et_3N (2.0 equiv), $Pd(PPh_3)_2Cl_2$ (2 mol%) and CuI (3–4 mol%) in anhydrous THF under an argon atmosphere at room temperature was added the alkyne (1.0 equiv) and the resulting mixture was stirred at room temperature for the indicated time. The mixture was filtered through celite (using Et_2O as the eluent) and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography to give the title compound.

General Procedure B: Sulfonamide Alkylation



To a suspension of the alkyne (1.0 equiv) and K_2CO_3 (1.2–2.0 equiv) in acetone at room temperature was added the α-haloketone (1.1–1.2 equiv) and the mixture was stirred at the indicated temperature for the indicated time. The mixture was filtered through celite (EtOAc), and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography to give the title compound.



4-Methyl-*N*-(2-oxopropyl)-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (300). Prepared according to General Procedure B, using alkyne **299** (1.79 g, 6.28 mmol), chloroacetone (0.55 mL, 6.91 mmol) and K_2CO_3 (1.04 g, 7.53 mmol) in acetone (18 mL) at room temperature for 44 h. Purification by column chromatography (50% EtOAc/petroleum ether) gave the ketone **300** (1.79 g, 84%) as an orange solid.

R_f = 0.22 (20% EtOAc/petroleum ether).

m.p. 94–96 °C (Et_2O).

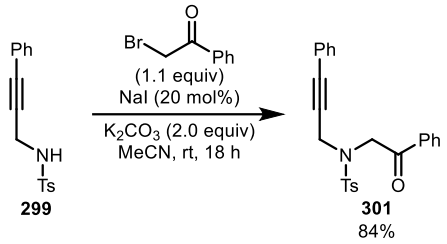
IR 3061, 2923, 1733 (C=O), 1598, 1491, 1349, 1161, 1099, 815, 758 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81–7.71 (2H, m, Ar**H**), 7.35–7.21 (5H, m, Ar**H**), 7.17–7.09 (2H, m, Ar**H**), 4.39 (2H, s, C**H**$_2$C=O), 4.05 (2H, s, C**H**$_2$C≡C), 2.37 (3H, s, ArC**H**$_3$), 2.27 (3H, s, C**H**$_3$C=O).

^{13}C NMR (101 MHz, $CDCl_3$) δ 203.7 (C), 144.1 (C), 135.6 (C), 131.7 (2 × CH), 129.9 (2 × CH), 128.8 (CH), 128.4 (2 × CH), 127.8 (2 × CH), 122.0 (C), 86.4 (C), 81.4 (C), 55.9 (CH_2), 39.1 (CH_2), 27.3 (CH_3), 21.6 (CH_3).

HRMS (ESI) Exact mass calculated for $[C_{19}H_{19}NO_3SNa]^+$ [M+Na]$^+$: 364.0978, found: 364.0976.

4-Methyl-*N*-(2-oxo-2-phenylethyl)-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (301)



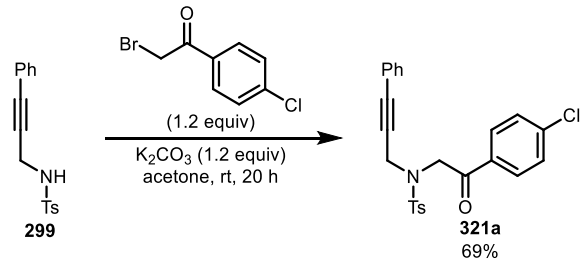
To a solution of alkyne **299** (1.00 g, 3.50 mmol) and 2-bromo-1-phenylethan-1-one (766 mg, 3.85 mmol) in MeCN (11 mL) at room temperature was added K_2CO_3 (967 mg, 7.00 mmol) and NaI (105 mg, 0.70 mmol), and the resulting mixture was stirred at room temperature for 18 h. H_2O (10 mL) was added and the MeCN was removed *in vacuo*. The resulting mixture was extracted with EtOAc (3 × 10 mL), and the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (15% EtOAc/petroleum ether) to give the ketone **301** (1.18 g, 84%) as an orange oil. The analytical data were consistent with those reported previously.[186]

R_f = 0.22 (20% EtOAc/petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81–7.71 (2H, m, Ar**H**), 7.35–7.21 (5H, m, Ar**H**), 7.17–7.09 (2H, m, Ar**H**), 4.39 (2H, s, C**H**$_2$C=O), 4.05 (2H, s, C**H**$_2$C≡), 2.37 (3H, s, C**H**$_3$), 2.27 (3H, s, C**H**$_3$C=O).

^{13}C NMR (101 MHz, $CDCl_3$): δ 203.7 (C), 144.1 (C), 135.5 (C), 131.7 (2 × CH), 129.9 (2 × CH), 128.8 (CH), 128.4 (2 × CH), 127.8 (2 × CH), 122.0 (C), 86.4 (CH), 81.4 (CH), 55.8 (CH_2), 39.1 (CH_2), 27.3 (CH_3), 21.6 (CH_3).

_N_-[2-(4-Chlorophenyl)-2-oxoethyl]-4-methyl-_N_-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (321a)



To a suspension of alkyne **299** (250 mg, 0.88 mmol) and K_2CO_3 (145 mg, 1.05 mmol) in acetone (6 mL) under an argon atmosphere at room temperature was added 2-bromo-4′-chloroacetophenone (245 mg, 1.05 mmol) and the resulting mixture was stirred for 20 h. H_2O (10 mL) and brine (5 mL) were added, and the mixture extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc/petroleum ether) to give the ketone **321a** (265 mg, 69%) as a white solid.

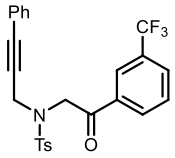
R_f = 0.44 (20% EtOAc/petroleum ether).

m.p. 123–125 °C ($CHCl_3$); IR 2916, 1699 (C=O), 1590, 1490, 1402, 1349, 1225, 1161, 1093, 913 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (2H, d, *J* = 8.7 Hz, Ar**H**), 8.17 (2H, d, *J* = 8.7 Hz, Ar**H**), 7.80 (2H, d, *J* = 8.0 Hz, Ar**H**), 7.34 (2H, d, *J* = 8.0 Hz, Ar**H**), 7.30–7.22 (3H, m, Ar**H**), 7.10 (2H, d, *J* = 7.2 Hz, Ar**H**), 4.76 (2H, s, C**H**$_2$C=O), 4.47 (2H, s, C**H**$_2$C≡C), 2.41 (3H, s, C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 192.6 (C), 144.1 (C), 140.5 (C), 135.9 (C), 133.3 (C), 131.7 (2 × CH), 129.9 (2 × CH), 129.8 (2 × CH), 129.3 (2 × CH), 128.8 (CH), 128.3 (2 × CH), 127.9 (2 × CH), 122.0 (C), 86.5 (C), 81.5 (C), 52.2 (CH_2), 38.5 (CH_2), 21.6 (CH_3).

HRMS (ESI) Exact mass calculated for $[C_{24}H_{20}ClNO_3SNa]^+$ [M+Na]$^+$: 460.0745, found: 460.0744.



4-Methyl-_N_-{2-oxo-2-[3-(trifluoromethyl)phenyl]ethyl}-_N_-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (321b). Prepared according to General Procedure B, using alkyne **299** (500 mg, 1.75 mmol), 2-bromo-1-[3-(trifluoromethyl)phenyl]ethan-1-one (0.35 mL, 2.10 mmol) and K_2CO_3 (484 mg, 3.50 mmol) in acetone (6 mL) at room temperature for 24 h. Purification by column chromatography (0 to 20% EtOAc/petroleum ether) gave the ketone **321b** (307 mg, 37%) as an orange solid.

R_f = 0.26 (10% EtOAc/petroleum ether).

m.p. 118–120 °C ($CHCl_3$).

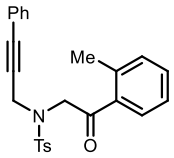
IR 2924, 1706 (C=O), 1612, 1598, 1490, 1327, 1263, 1158, 1126, 1092 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25–8.17 (2H, m, Ar**H**), 7.88–7.77 (3H, m, Ar**H**), 7.63 (1H, t, *J* = 7.8 Hz, Ar**H**), 7.36–7.31 (2H, m, Ar**H**), 7.30–7.20 (3H, m, Ar**H**), 7.15–7.07 (2H, m, Ar**H**), 4.79 (2H, s, C**H**$_2$C=O), 4.46 (2H, s, C**H**$_2$C≡), 2.40 (3H, s, C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 192.6 (C), 144.2 (C), 135.8 (C), 135.5 (C), 131.7 (2 × CH), 131.6 (q, *J* = 33.0 Hz, C), 131.6, (CH), 130.3 (q, *J* = 3.5 Hz, CH), 129.9 (2 × CH), 129.7 (CH), 128.8 (CH), 128.3 (2 × CH), 127.9 (2 × CH), 125.2 (q, *J* = 3.8 Hz, CH), 123.7 (q, *J* = 272.7 Hz, C), 121.9 (C), 86.7 (C), 81.4 (C), 52.4 (CH_2), 38.6 (CH_2), 21.6 (CH_3).

^{19}F NMR (376 MHz, $CDCl_3$) δ −62.8 (s).

HRMS (ESI) Exact mass calculated for $[C_{25}H_{21}F_3NO_3S]^+$ [M+H]$^+$: 472.1189, found: 472.1188.



4-Methyl-*N*-[2-oxo-2-(*o*-tolyl)ethyl]-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (321c). Prepared according to General Procedure B, using alkyne **299** (500 mg, 1.75 mmol), 2-bromo-1-(*o*-tolyl)ethan-1-one (305 µL, 2.10 mmol) and K_2CO_3 (484 mg, 3.50 mmol) in acetone (6 mL) at room temperature for 24 h. Purification by column chromatography (15 to 20% EtOAc/petroleum ether) gave the ketone **321c** (400 mg, 55%) as an orange solid.

R_f = 0.17 (10% EtOAc/petroleum ether).

m.p. 95–97 °C ($CHCl_3$).

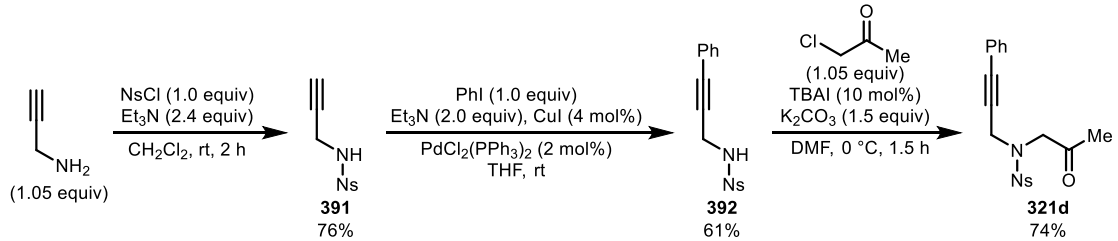
IR 2925, 1695 (C=O), 1598, 1570, 1489, 1347, 1223, 1157, 1091, 1068 cm^{-1}.

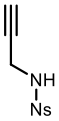
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.77 (2H, m, Ar**H**), 7.67 (1H, dd, *J* = 8.0, 1.4 Hz, Ar**H**), 7.40 (1H, app td, *J* = 7.5, 1.4 Hz, Ar**H**), 7.33–7.20 (7H, m, Ar**H**), 7.16–7.09 (2H, m, Ar**H**), 4.69 (2H, s, C**H**$_2$C=O), 4.52 (2H, s, C**H**$_2$C≡), 2.48 (3H, C**H**$_3$), 2.38 (3H, s, C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.2 (C), 143.9 (C), 138.7 (C), 136.1 (C), 135.5 (C), 132.2 (CH), 132.1 (CH), 131.7 (2 × CH), 129.8 (2 × CH), 128.7 (CH), 128.33 (CH), 128.27 (2 × CH), 127.8 (2 × CH), 125.9 (CH), 122.0 (C), 86.3 (C), 81.7 (C), 53.8 (CH_2), 38.4 (CH_2), 21.6 (CH_3), 21.1 (CH_3).

HRMS (ESI) Exact mass calculated for $[C_{25}H_{24}NO_3S]^+$ [M+H]$^+$: 418.1471, found: 418.1471.

4-Nitro-*N*-(2-oxopropyl)-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (321d)



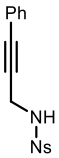


4-Nitro-*N*-(prop-2-yn-1-yl)benzenesulfonamide (391). To a solution of 4-nitrobenzenesulfonyl chloride (3.30 g, 14.9 mmol) in CH_2Cl_2 (75 mL) under an argon atmosphere at 0 °C was added propargylamine (1.00 mL, 15.6 mmol). To the resulting solution was added Et_3N (5.00 mL, 35.7 mmol) dropwise and the reaction was stirred at room temperature for 2 h. The mixture was diluted with Et_2O (100 mL), washed with 10% aqueous HCl (50 mL) and brine (50 mL). The organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (30% EtOAc/petroleum ether) to give **391** (2.71 g, 76%) as an off-white solid. The analytical data were consistent with those reported previously.[187]

R_f = 0.23 (40% Et_2O/petroleum ether).

^{1}H NMR (400 MHz, CD_3CN): δ 8.37–8.33 (2H, m, Ar**H**), 8.08–8.04 (2H, m, Ar**H**), 6.31–6.13 (1H, br m, N**H**), 3.86–3.81 (2H, m, C**H**$_2$), 2.29 (1H, t, *J* = 2.5 Hz, C**H**).

^{13}C NMR (101 MHz, CD_3CN): δ 151.3 (C), 146.9 (C), 129.6 (2 × CH), 125.2 (2 × CH), 78.9 (C), 74.1 (CH), 33.2 (CH_2).

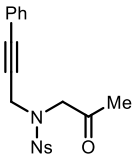


4-Nitro-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (392). Prepared according to General Procedure A, using alkyne **391** (400 mg, 1.67 mmol), phenyl iodide (0.23 mL, 1.67 mmol), Et_3N (1.39 mL, 3.34 mmol), $Pd(PPh_3)_2Cl_2$ (24.0 mg, 0.03 mmol) and CuI (10.0 mg, 0.07 mmol) in anhydrous THF (2 mL) for 1 h. Purification by column chromatography (5% EtOAc/$CHCl_3$) gave **392** (320 mg, 61%) as an orange solid. The analytical data were consistent with those reported previously.[188]

R_f = 0.36 (5% EtOAc/$CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30–8.23 (2H, m, Ar**H**), 8.15–8.09 (2H, m, Ar**H**), Ar, 7.31–7.26 (1H, m, Ar**H**), 7.25–7.20 (2H, m, Ar**H**), 7.11–7.01 (2H, m, Ar**H**), 5.01 (1H, br t, *J* = 5.9 Hz, N**H**), 4.18 (2H, d, *J* = 5.9 Hz, C**H**$_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 150.2 (C), 146.1 (C), 131.4 (2 × CH), 129.2 (CH), 128.9 (2 × CH), 128.5 (2 × CH), 124.4 (2 × CH), 121.5 (C), 85.7 (C), 82.6 (C), 34.0 (CH_2).



4-Nitro-*N*-(2-oxopropyl)-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (321d). To a solution of alkyne **392** (316 mg, 1.00 mmol), chloroacetone (90 µL, 1.05 mmol) and Bu_4NI (37.0 mg, 0.10 mmol) in anhydrous DMF under an argon atmosphere at 0 °C was added K_2CO_3 (207 mg, 1.50 mmol) and the resulting mixture was stirred for 1.5 h. H_2O (5 mL) was added and the mixture extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (50% Et_2O/petroleum ether) to give the ketone **321d** (294 mg, 74%) as an orange solid.

R_f = 0.58 (10% EtOAc/$CHCl_3$).

m.p. 146–148 °C (Et_2O/CH_2Cl_2).

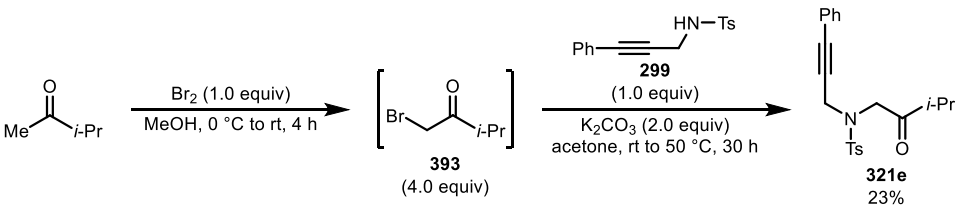
IR 3102 (NH), 1735 (C=O), 1607, 1530, 1351, 1311, 1165, 1105, 1013, 928 cm^{-1}.

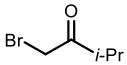
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34–8.29 (2H, m, Ar**H**), 8.08–8.03 (2H, m, Ar**H**), 7.35–7.29 (1H, m, Ar**H**), 7.29–7.22 (2H, m, Ar**H**), 7.17–7.11 (2H, m, Ar**H**), 4.45 (2H, s, C**H**$_2$C=O), 4.21 (2H, s, C**H**$_2$C≡), 2.23 (3H, s, C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.1 (C), 150.3 (C), 144.9 (C), 131.6 (2 × CH), 129.3 (CH), 129.0 (2 × CH), 128.6 (2 × CH), 124.4 (2 × CH), 121.5 (C), 87.0 (C), 80.8 (C), 55.5 (CH_2), 39.0 (CH_2), 27.2 (CH_3).

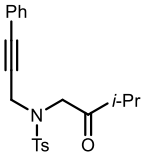
HRMS (ESI) Exact mass calculated for $[C_{18}H_{16}N_2O_5SNa]^+$ $[M+Na]^+$: 395.0672, found: 395.0668.

4-Methyl-*N*-(3-methyl-2-oxobutyl)-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (321e)





1-Bromo-3-methylbutan-2-one (393). To a solution of 3-methylbutan-2-one (3.00 g, 34.8 mmol) in anhydrous MeOH (20 mL) at 0 °C was added Br_2 (1.79 mL, 34.8 mmol) and the resulting solution stirred at 0 °C for 30 min before heating to room temperature and stirring for a further 3.5 h. The reaction was diluted with H_2O (20 mL) and stirred for 30 min. Further H_2O (30 mL) was added, and the mixture extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (30 mL), H_2O (30 mL), brine (30 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product **393** was used without further purification.



4-Methyl-*N*-(3-methyl-2-oxobutyl)-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (321e). Prepared according to a modification of General Procedure B, using alkyne **299** (750 mg, 2.62 mmol), bromide **393** (864 mg, 5.24 mmol) and K_2CO_3 (730 mg, 5.24 mmol) in acetone (8 mL) at room temperature for 4 h and then at 50 °C for 20 h. Further bromide **393** (864 mg, 5.24 mmol) was added, and the mixture stirred for at 50 °C for 6 h. Purification by column chromatography (10% EtOAc/petroleum ether) followed by recrystallisation (EtOAc/petroleum ether) gave the ketone **321e** (222 mg, 23%) as a white solid.

R_f = 0.48 (20% EtOAc/petroleum ether).

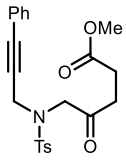
m.p. 74–76 °C ($CHCl_3$).

IR 2960, 2925, 1727 (C=O), 1598, 1490, 1443, 1348, 1161, 1090, 1042 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79–7.72 (2H, m, Ar**H**), 7.33–7.27 (3H, m, Ar**H**), 7.26–7.22 (2H, m, Ar**H**), 7.16–7.09 (2H, m, Ar**H**), 4.41 (2H, s, C**H**$_2$C≡), 4.20 (2H, s, C**H**$_2$C=O), 2.80 (1H, sept, *J* = 6.9 Hz, C**H**(CH$_3$)$_2$), 2.38 (3H, s, ArC**H**$_3$), 1.12 (6H, d, *J* = 6.9 Hz, CH(C**H**$_3$)$_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.7 (C), 144.0 (C), 135.8 (C), 131.7 (2 × CH), 129.8 (2 × CH), 128.8 (CH), 128.4 (2 × CH), 127.9 (2 × CH), 122.1 (C), 86.3 (C), 81.6 (C), 53.1 (CH_2), 38.5 (CH_2), 38.2 (CH), 21.6 (CH_3), 18.3 (2 × CH_3).

HRMS (ESI) Exact mass calculated for $[C_{21}H_{24}NO_3S]^+$ [M+H]$^+$: 370.1471, found: 370.1478.



Methyl 5-{[4-methyl-*N*-(3-phenylprop-2-yn-1-yl)phenyl]sulfonamide}-4-oxopentanoate (321f). Prepared according to General Procedure B, using alkyne **299** (750 mg, 2.62 mmol), methyl 5-bromo-4-oxopentanoate (1.10 g, 5.26 mmol) and K_2CO_3 (730 mg, 5.26 mmol) in acetone (8 mL) at room temperature for 24 h. Purification by column chromatography (20 to 30% EtOAc/petroleum ether) gave the ketone **321f** (693 mg, 64%) as an off-white solid.

R_f = 0.23 (20% EtOAc/petroleum ether).

m.p. 97–99 °C ($CHCl_3$).

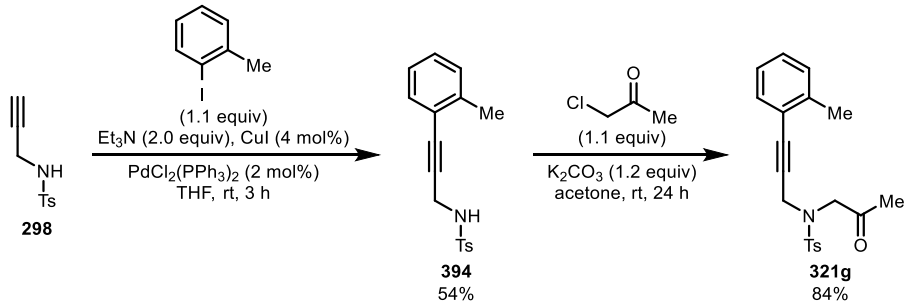
IR 2952, 1730 (C=O), 1598, 1491, 1438, 1411, 1347, 1210, 1160, 1092 cm^{-1}.

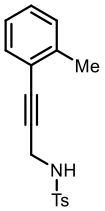
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78–7.73 (2H, m, Ar**H**), 7.33–7.27 (3H, m, Ar**H**), 7.26–7.22 (2H, m, Ar**H**), 7.14–7.10 (2H, m, Ar**H**), 4.40 (2H, s, C**H**$_2$C≡), 4.09 (2H, s, NC**H**$_2$C=O), 3.66 (3H, s, OC**H**$_3$), 2.89 (2H, t, *J* = 6.5 Hz, C**H**$_2$CH$_2$), 2.64 (2H, t, *J* = 6.5 Hz, CH$_2$C**H**$_2$), 2.36 (3H, s, ArC**H**$_3$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 204.5 (C), 173.0 (C), 144.1 (C), 135.4 (C), 131.7 (2 × CH), 129.8 (2 × CH), 128.8 (CH), 128.3 (2 × CH), 127.9 (2 × CH), 122.0 (C), 86.4 (C), 81.3 (C), 55.5 (CH_2), 52.0 (CH_3), 39.2 (CH_2), 34.3 (CH_2), 27.8 (CH_2), 21.6 (CH_3).

HRMS (ESI) Exact mass calculated for $[C_{22}H_{23}NO_5SNa]^+$ [M+Na]$^+$: 436.1189, found: 436.1193.

4-Methyl-*N*-(2-oxopropyl)-*N*-[3-(*o*-tolyl)prop-2-yn-1-yl]benzenesulfonamide (321g)





4-Methyl-*N*-[3-(*o*-tolyl)prop-2-yn-1-yl]benzenesulfonamide (394). Prepared according to General Procedure A, using alkyne **298** (1.05 g, 5.00 mmol), 1-iodo-2-methylbenzene (0.70 mL, 5.50 mmol), Et_3N (1.40 mL, 10.0 mmol), $Pd(PPh_3)_2Cl_2$ (70.0 mg, 0.10 mmol) and CuI (38.0 mg, 0.20 mmol) in anhydrous THF (5 mL) for 3 h. Purification by column chromatography (20 to 50% EtOAc/petroleum ether) gave **394** (815 mg, 54%) as an orange solid.

R_f = 0.61 (30% EtOAc/petroleum ether).

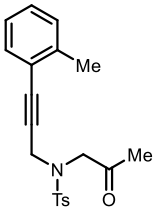
m.p. = 133–135 °C ($CHCl_3$).

IR 3271 (NH), 2922, 1598, 1486, 1432, 1326, 1156, 1092, 1062, 813 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (2H, d, *J* = 7.9 Hz, Ar**H**), 7.29–7.25 (2H, m, Ar**H**), 7.23–7.17 (1H, m, Ar**H**), 7.17–7.04 (3H, m, Ar**H**), 4.77 (1H, t, *J* = 6.1 Hz, N**H**), 4.13 (2H, d, *J* = 6.1 Hz, C**H**$_2$), 2.35 (3H, s, C**H**$_3$), 2.24 (3H, s, C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 143.9 (C), 140.2 (C), 137.0 (C), 132.1 (CH), 129.8 (2 × CH), 129.5 (CH), 128.7 (CH), 127.5 (2 × CH), 125.5 (CH), 122.0 (C), 87.1 (C), 83.8 (C), 34.0 (CH_2), 21.6 (CH_3), 20.6 (CH_3).

HRMS (ESI) Exact mass calculated for $[C_{17}H_{17}NO_2SNa]^+$ [M+Na]$^+$: 322.0872, found: 322.0873.



4-Methyl-*N*-(2-oxopropyl)-*N*-[3-(*o*-tolyl)prop-2-yn-1-yl]benzenesulfonamide (321g). Prepared according to General Procedure B, using alkyne **394** (400 mg, 1.34 mmol), chloroacetone (120 µL, 1.47 mmol) and K_2CO_3 (221 mg, 1.60 mmol) in acetone (4 mL) at room temperature for 24 h. Purification by column chromatography (20% EtOAc/petroleum ether) gave **321g** (398 mg, 84%) as a yellow solid.

R_f = 0.47 (30% EtOAc/petroleum ether).

m.p. = 94–96 °C ($CHCl_3$).

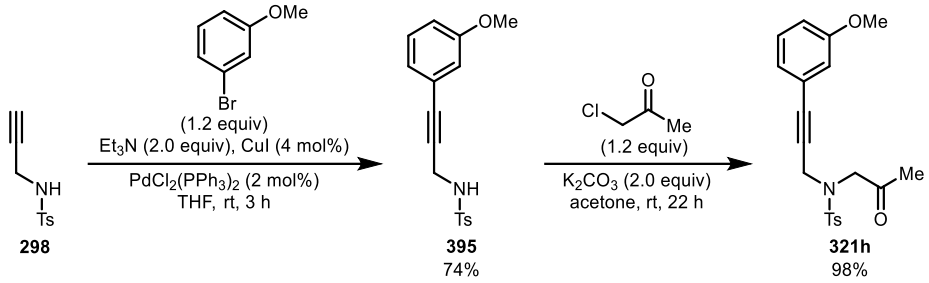
IR 2922, 1633 (C=O), 1598, 1486, 1348, 1252, 1159, 1098, 1012, 926 cm^{-1}.

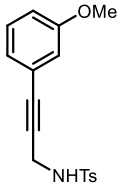
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80–7.74 (2H, m, Ar**H**), 7.31–7.28 (2H, m, Ar**H**), 7.25–7.18 (1H, m, Ar**H**), 7.16 (1H, d, *J* = 7.6 Hz, Ar**H**), 7.13–7.05 (2H, m, Ar**H**), 4.47 (2H, s, C**H**$_2$C≡), 4.09 (2H, s, C**H**$_2$C=O), 2.37 (3H, s, ArC**H**$_3$), 2.29 (3H, s, C**H**$_3$C=O), 2.22 (3H, s, ArC**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 203.6 (C), 144.2 (C), 140.2 (C), 135.6 (C), 132.2 (CH), 129.9 (2 × CH), 129.6 (CH), 128.8 (CH), 127.8 (2 × CH), 125.6 (CH), 121.8 (C), 85.4 (C), 85.1 (C), 55.8 (CH_2), 39.2 (CH_2), 27.3 (CH_3), 21.6 (CH_3), 20.6 (CH_3).

HRMS (ESI) Exact mass calculated for $[C_{20}H_{22}NO_3S]^+$ [M+H]$^+$: 356.1315, found: 356.1319.

***N*-[3-(3-Methoxyphenyl)prop-2-yn-1-yl]-4-methyl-*N*-(2-oxopropyl)benzenesulfonamide (321h)**





***N*-[3-(3-Methoxyphenyl)prop-2-yn-1-yl]-4-methylbenzenesulfonamide (395).** Prepared according to General Procedure A, using alkyne **298** (2.00 g, 9.56 mmol), 3-bromoanisole (1.40 mL, 11.5 mmol), Et_3N (2.70 mL, 19.1 mmol), $PdCl_2(PPh_3)_2$ (134 mg, 0.19 mmol) and CuI (55.0 mg, 0.39 mmol) in anhydrous THF (10 mL) for 3 h. Purification by column chromatography (20% EtOAc/petroleum ether) gave the alkyne **395** (2.22 g, 74%) as an orange solid.

R_f = 0.19 (20% EtOAc/petroleum ether).

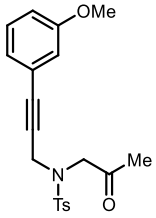
m.p. 109–110 °C ($CHCl_3$).

IR 3274 (NH), 2943, 1598, 1574, 1480, 1427, 1392, 1289, 1156, 1046 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85–7.77 (2H, m, Ar**H**), 7.32–7.24 (2H, m, Ar**H**), 7.15 (1H, app t, *J* = 8.0 Hz, Ar**H**), 6.88–6.80 (1H, m, Ar**H**), 6.73 (1H, app dt, *J* = 7.6, 1.2, Ar**H**), 6.68–6.66 (1H, m, Ar**H**), 4.71–4.64 (1H, br m, N**H**), 4.07 (2H, d, *J* = 6.1 Hz, C $\mathbf{H}_2$), 3.77 (3H, s, OC$\mathbf{H}_3$), 2.36 (3H, s, ArC$\mathbf{H}_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3 (C), 144.0 (C), 137.0 (C), 129.9 (2 × CH), 129.4 (CH), 127.6 (2 × CH), 124.2 (CH), 123.2 (C), 116.9 (CH), 114.9 (CH), 84.8 (C), 83.2 (C), 55.4 (CH_3), 33.9 (CH_2), 21.6 (CH_3).

HRMS (ESI) Exact mass calculated for $[C_{17}H_{17}NO_3SNa]^+$ $[M+Na]^+$: 338.0821, found: 338.0821.



***N*-[3-(3-Methoxyphenyl)prop-2-yn-1-yl]-4-methyl-*N*-(2-oxopropyl)benzenesulfonamide (321h).** Prepared according to a modification of General Procedure B, using alkyne **298** (750 mg, 2.38 mmol), chloroacetone (0.23 mL, 2.85 mmol) and K_2CO_3 (657 mg, 4.76 mmol) in acetone (7 mL) at room temperature for 22 h. Purification by silica plug (50% EtOAc/petroleum ether) gave the ketone **321h** (869 mg, 98%) as a yellow solid.

R_f = 0.42 (30% EtOAc/petroleum ether).

m.p. 72–73 °C ($CHCl_3$).

IR 2941, 1733 (C=O), 1597, 1575, 1481, 1422, 1348, 1290, 1204, 1160 cm^{-1}.

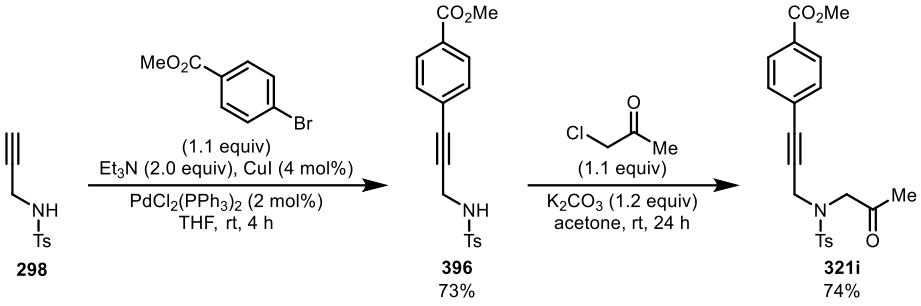
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77–7.73 (2H, m, Ar**H**), 7.33–7.27 (2H, m, Ar**H**), 7.16 (1H, app t, *J* = 8.1 HZ, Ar**H**), 6.87–6.82 (1H, m, Ar**H**), 6.72 (1H, app dt, *J* = 7.6, 1.2 Hz, Ar**H**), 6.67–

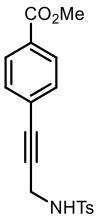
6.64 (1H, m, Ar**H**), 4.38 (2H, s, C**H**$_2$C≡), 4.05 (2H, s, C**H**$_2$C=O), 3.77 (3H, s, OC**H**$_3$), 2.38 (3H, s, C**H**$_3$C=O), 2.26 (3H, s, ArC**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 203.6 (C), 159.3 (C), 144.2 (C), 135.5 (C), 129.9 (2 × CH), 129.4 (CH), 127.8 (2 × CH), 124.1 (CH), 122.9 (C), 117.0 (CH), 114.9 (CH), 86.3 (C), 81.2 (C), 55.8 (CH_2), 55.4 (CH_3), 39.0 (CH_2), 27.3 (CH_3), 21.6 (CH_3).

HRMS (ESI) Exact mass calculated for $[C_{20}H_{22}NO_4S]^+$ $[M+H]^+$: 372.1264, found: 372.1262.

Methyl 4-(3-{[4-methyl-*N*-(2-oxopropyl)phenyl]sulfonamide}prop-1-yn-1-yl)benzoate (321i)



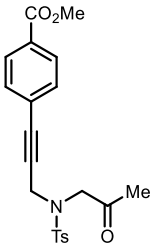


Methyl 4-{3-[(4-methylphenyl)sulfonamide]prop-1-yn-1-yl}benzoate (396). Prepared according to General Procedure A, using alkyne **298** (1.50 g, 7.17 mmol), methyl 4-iodobenzoate (2.07 g, 7.88 mmol), Et_3N (2.00 mL, 14.3 mmol), $Pd(PPh_3)_2Cl_2$ (101 mg, 0.14 mmol) and CuI (55.0 mg, 0.29 mmol) in anhydrous THF (7 mL) for 4 h. Purification by column chromatography (25 to 50% EtOAc/petroleum ether) gave the alkyne **396** (1.80 g, 73%) as an orange solid. The analytical data were consistent with those reported previously.[189]

R_f = 0.14 (20% EtOAc/petroleum ether).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93–7.88 (2H, m, Ar**H**), 7.84–7.79 (2H, m, Ar**H**), 7.27 (2H, d, *J* = 8.3 Hz, Ar**H**), 7.16 (2H, d, *J* = 8.3 Hz, Ar**H**), 4.86 (1H, t, *J* = 6.2 Hz, N**H**), 4.10 (2H, d, *J* = 6.2 Hz, C**H**$_2$), 3.91 (3H, s, C**H**$_3$C=O), 2.35 (3H, s, ArC**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.5 (C), 144.0 (C), 137.0 (C), 131.6 (2 × CH), 129.9 (C), 129.8 (2 × CH), 129.4 (2 × CH), 127.6 (2 × CH), 126.8 (C), 86.4 (C), 84.0 (C), 52.4 (CH_3), 33.8 (CH_2), 21.6 (CH_3).



Methyl 4-(3-{[4-methyl-*N*-(2-oxopropyl)phenyl]sulfonamide}prop-1-yn-1-yl)benzoate (321i). Prepared according to General Procedure B, using alkyne **396** (750 mg, 2.18 mmol), chloroacetone (0.19 mL, 2.40 mmol) and K_2CO_3 (362 mg, 2.62 mmol) in acetone (6 mL) at room temperature for 24 h. Purification by column chromatography (30% EtOAc/petroleum ether) gave the ketone **321i** (645 mg, 74%) as an off-white solid.

R_f = 0.45 (30% EtOAc/petroleum ether).

m.p. 107–109 °C ($CHCl_3$).

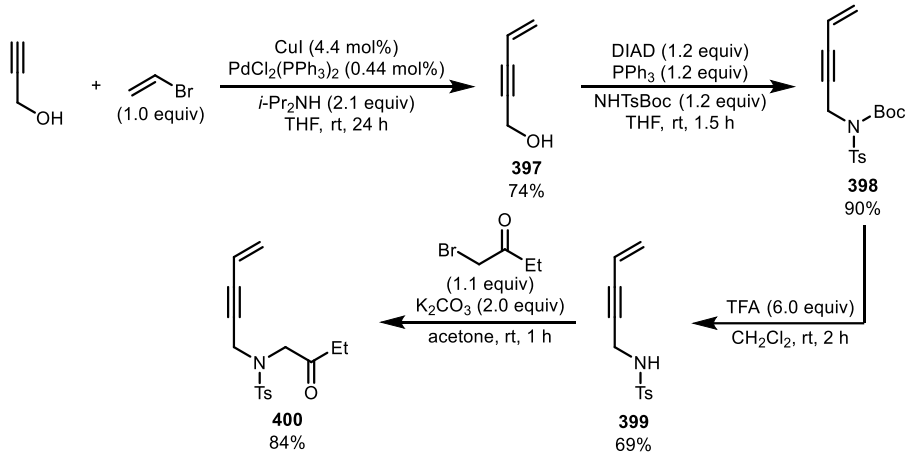
IR 2953, 1720 (C=O), 1606, 1436, 1349, 1308, 1277, 1161, 1106, 1019 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96–7.88 (2H, m, Ar**H**), 7.79–7.72 (2H, m, Ar**H**), 7.29 (2H, d, *J* = 7.8 Hz, Ar**H**), 7.21–7.14 (2H, m, Ar**H**), 4.41 (2H, s, C**H**$_2$C≡), 4.06 (2H, s, C**H**$_2$C=O), 3.91 (3H, s, OC**H**$_3$), 2.37 (3H, s, C**H**$_3$C=O), 2.26 (3H, s, ArC**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 203.4 (C), 166.4 (C), 144.2 (C), 135.5 (C), 131.6 (2 × CH), 130.1 (C), 129.9 (2 × CH), 129.5 (2 × CH), 127.8 (2 × CH), 126.6 (C), 85.5 (C), 84.5 (C), 55.8 (CH_2), 52.4 (CH_3), 39.0 (CH_2), 27.3 (CH_3), 21.6 (CH_3).

HRMS (ESI) Exact mass calculated for $[C_{21}H_{22}NO_5S]^+$ [M+H]$^+$: 400.1213, found: 400.1213.

4-Methyl-*N*-(pent-4-en-2-yn-1-yl)benzenesulfonamide (400)



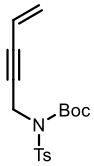


Pent-4-en-2-yn-1-ol (397). To a solution of vinyl bromide (1 M in THF, 25.0 mL, 25.0 mmol), $Pd(PPh_3)_2Cl_2$ (74.0 mg, 0.11 mmol), CuI (218 mg, 1.10 mmol) and diisopropylamine (7.40 mL, 52.5 mmol) at 0 °C was added propargyl alcohol (1.46 mL, 25.0 mmol) and the resulting mixture stirred at room temperature for 24 h. Saturated aqueous NH_4Cl (50 mL) was added and the mixture extracted with Et_2O (4 × 25 mL). The combined organics were washed with H_2O (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (30% Et_2O/pentane) to give **397** (1.52 g, 74%) as an orange oil. The analytical data were consistent with those reported previously.[190]

R_f = 0.36 (30% Et_2O/petroleum ether)

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.82 (1H, ddt, *J* = 17.6, 11.0, 2.0 Hz, **H**C=CH$_a$H$_b$), 5.65 (1H, dd, *J* = 17.6, 2.2 Hz, HC=C**H**$_a$H$_b$), 5.50 (1H, dd, *J* = 11.0, 2.2 Hz, HC=CH$_a$**H**$_b$), 4.39 (2H, dd, *J* = 6.1, 2.0 Hz, C**H**$_2$), 1.89–1.69 (1H, br m, O**H**).

^{13}C NMR (101 MHz, $CDCl_3$): δ 127.7 (CH_2), 116.7 (CH), 88.0 (C), 84.5 (C), 51.6 (CH_2).



***tert*-Butyl pent-4-en-2-yn-1-yl(tosyl)carbamate (398)**. To a solution of alcohol **397** (400 mg, 4.79 mmol), *tert*-butyl tosylcarbamate (1.56 g, 5.75 mmol) and PPh_3 (1.51 g, 5.75 mmol) in anhydrous THF (16 mL) under an argon atmosphere at 0 °C was added DIAD (1.13 mL, 5.75 mmol). The resulting solution was stirred at room temperature for 1.5 h and then concentrated *in vacuo*. The residue was purified by column chromatography (15% Et_2O/petroleum ether) to give the carbamate **398** (1.44 g, 90%) as a white solid.

R_f = 0.27 (15% Et_2O/petroleum ether).

m.p. 116–118 °C (Et_2O).

IR 2982, 2937, 1722 (C=O), 1595, 1350, 1257, 1147, 1087, 908, 838 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.30 (2H, d, *J* = 8.1 Hz, Ar**H**), 5.80 (1H, ddt, *J* = 17.7, 11.0, 1.9 Hz, **H**C=CH_2), 5.63 (1H, dd, *J* = 17.7, 2.2 Hz, =C**H**$_a$H$_b$), 5.51 (1H, dd, *J* = 11.0, 2.2 Hz, =CH$_a$**H**$_b$), 4.74 (2H, d, *J* = 1.9 Hz, NC**H**$_2$), 2.44 (3H, s, ArC**H**$_3$), 1.35 (9H, s, (C**H**$_3$)$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.4 (C), 144.5 (C), 136.9 (C), 129.3 (2 × CH), 128.4 (2 × CH), 127.8 (CH_2), 116.8 (CH), 85.2 (C), 85.0 (C), 82.7 (C), 36.6 (CH_2), 28.0 (3 × CH_3), 21.8 (CH_3).

HRMS (ESI) Exact mass calculated for $[C_{17}H_{21}NO_4SNa]^+$ [M+Na]$^+$: 358.1083, found: 358.1074.

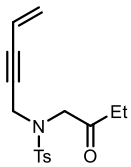


4-Methyl-*N*-(pent-4-en-2-yn-1-yl)benzenesulfonamide (399). To a solution of carbamate **398** (1.00 g, 2.98 mmol) in CH_2Cl_2 (10 mL) under an argon atmosphere at 0 °C was added TFA (1.40 mL, 17.9 mmol). The resulting mixture was stirred at room temperature for 2 h and then concentrated *in vacuo*. The residue was redissolved in EtOAc (15 mL), washed with H_2O (15 mL) and brine (15 mL). The organics were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the sulfonamide **399** (485 mg, 69%) as an off-white solid. The analytical data were consistent with those reported previously.[191]

R_f = 0.33 (30% Et_2O/petroleum ether).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (2H, d, *J* = 8.0 Hz, Ar**H**), 7.31 (2H, d, *J* = 8.0 Hz, Ar**H**), 5.55 (1H, ddt, *J* = 18.0, 10.5, 2.0 Hz, **H**C=CH$_b$H$_a$), 5.44–5.37 (2H, m, HC=**CH$_b$H$_a$**), 4.57 (1H, t, *J* = 6.0 Hz, N**H**), 3.95 (2H, dd, *J* = 6.0, 1.9 Hz, C**H**$_2$), 2.42 (3H, s, C**H**$_3$).

^{13}C NMR (126 MHz, $CDCl_3$): δ 143.9 (C), 136.8 (C), 129.8 (2 × CH), 127.8 (CH_2), 127.6 (2 × CH), 116.3 (CH), 83.9 (C), 83.5 (C), 33.8 (CH_2), 21.7 (CH_3).



4-Methyl-*N*-(2-oxobutyl)-*N*-(pent-4-en-2-yn-1-yl)benzenesulfonamide (400). Prepared according to General Procedure B, using alkyne **399** (175 mg, 0.74 mmol), 1-bromobutan-2-one (84.0 µL, 0.82 mmol) and K_2CO_3 (200 mg, 1.49 mmol) in acetone (3 mL) at room temperature for 1 h. Purification by column chromatography (20% EtOAc/petroleum ether) gave the ketone **400** (189 mg, 84%) as a colourless oil.

R_f = 0.27 (20% EtOAc/petroleum ether).

IR 2978, 1728 (C=O), 1598, 1494, 1411, 1344, 1557, 1103, 1039, 974 cm^{-1}.

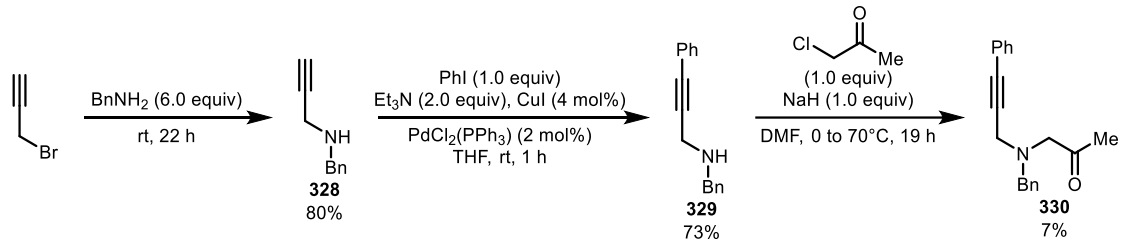
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71–7.65 (2H, m, Ar**H**), 7.30–7.25 (2H, m, Ar**H**), 5.51 (1H, ddt, *J* = 17.1, 11.5, 2.0 Hz, C**H**=CH_2), 5.40–5.32 (2H, m, =C**H**$_2$), 4.24 (2H, d, *J* = 2.0 Hz, C**H**$_2$C≡), 3.97 (2H, s, C**H**$_2$C=O), 2.53 (2H, q, *J* = 7.3 Hz, C**H**$_2$$CH_3$), 2.38 (3H, s, ArC**H**$_3$), 1.04 (3H, t, *J* = 7.3 Hz, CH_2C**H**$_3$).

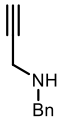
^{13}C NMR (126 MHz, $CDCl_3$) δ 206.1 (C), 143.9 (C), 135.4 (C), 129.7 (2 × CH), 127.9 (CH_2), 127.7 (2 × CH), 116.0 (CH), 84.8 (C), 82.1 (C), 54.7 (CH_2), 38.8 (CH_2), 33.0 (CH_2), 21.5 (CH_3), 7.4 (CH_3).

HRMS (ESI) Exact mass calculated for $[C_{16}H_{20}NO_3S]^+$ [M+H]$^+$: 306.1158, found: 306.1163.

3.3 Further Exploration of Alkynone Scope

1-[Benzyl(3-phenylprop-2-yn-1-yl)amino]propan-2-one (330)



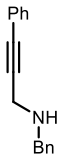


***N*-Benzylprop-2-yn-1-amine (328).** To benzylamine (9.90 mL, 90.0 mmol) at room temperature was slowly added propargyl bromide (80% w/v in toluene, 1.61 mL, 15.0 mmol) and the resulting solution stirred at room temperature for 23 h. The mixture was diluted with Et_2O (50 mL), washed with 2 M aqueous NaOH (50 mL), and the aqueous layer extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (Et_2O) to give **328** as a yellow oil (1.75 g, 80%). The analytical data were consistent with those reported previously.[192]

R_f = 0.36 (Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.31 (4H, m, Ar**H**), 7.30–7.24 (1H, m, Ar**H**), 3.89 (2H, s, C**H**$_2$Ar), 3.44 (2H, d, *J* = 2.5 Hz, C**H**$_2$C≡), 2.26 (1H, t, *J* = 2.4 Hz, C**H**), 1.45 (1H, br s, N**H**).

^{13}C NMR (101 MHz, $CDCl_3$): δ 139.5 (C), 128.6 (2 × CH), 128.5 (2 × CH), 127.3 (CH), 82.2 (C), 71.7 (CH), 52.4 (CH_2), 37.5 (CH_2).

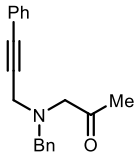


***N*-Benzyl-3-phenylprop-2-yn-1-amine (329).** Prepared according to General Procedure A, using alkyne **328** (730 mg, 5.00 mmol), Phenyl iodide (0.56 mL, 5.00 mmol), Et_3N (1.39 mL, 10.0 mmol), $Pd(PPh_3)_2Cl_2$ (70.0 mg, 0.10 mmol) and CuI (38.0 mg, 0.20 mmol) in anhydrous THF (7 mL) for 1 h. Purification by column chromatography (10 to 30% Et_2O/petroleum ether) gave **329** (809 mg, 73%) as an orange oil. The analytical data were consistent with those reported previously.[193]

R_f = 0.14 (30% Et_2O/petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52–7.44 (2H, m, Ar**H**), 7.43–7.28 (8H, m, Ar**H**), 3.97 (2H, s, C**H**$_2$Ar), 3.68 (2H, s, C**H**$_2$C≡), 1.59 (1H, br s, N**H**).

^{13}C NMR (101 MHz, $CDCl_3$): δ 139.7 (C), 131.8 (2 × CH), 128.5 (4 × CH), 128.4 (2 × CH), 128.1 (CH), 127.2 (CH), 123.3 (C), 87.7 (C), 83.8 (CH), 52.6 (CH_2), 38.4 (CH_2).



1-(Benzyl[3-phenylprop-2-yn-1-yl]amino)propan-2-one (330). To a solution of alkyne **329** (280 mg, 1.26 mmol) in anhydrous DMF (4 mL) under an argon atmosphere at 0 °C was added NaH (60% dispersion in mineral oil, 51.0 mg, 1.26 mmol) and the resulting mixture stirred at 0 °C for 30 min. Chloroacetone (0.10 mL, 1.26 mmol) was slowly added to the suspension and the mixture stirred at room temperature for 1 h and then at 70 °C for 19 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (10 mL). The organic layer was washed with 2 M $Na_2S_2O_3$ (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (0.5% MeOH/CH_2Cl_2) to give **330** (24.0 mg, 7%) as an orange oil.

R_f = 0.27 (0.5% MeOH/CH_2Cl_2).

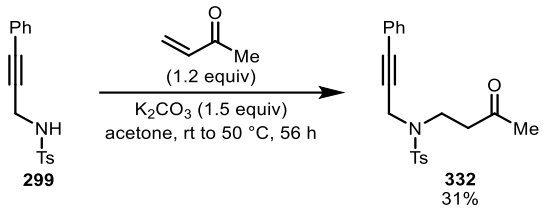
IR 3030, 2918, 1712 (C=O), 1489, 1352, 1322, 1250, 1174, 1074, 755 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48–7.28 (11H, m, Ar**H**), 3.76 (2H, s, C**H**$_2$Ar), 3.65 (2H, s, C**H**$_2$C≡), 3.45 (2H, s, C**H**$_2$C=O), 2.19 (3H, s, C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 207.4 (C), 137.9 (C), 131.9 (2 × CH), 129.4 (2 × CH), 128.6 (2 × CH), 128.4 (2 × CH), 128.3 (CH), 127.6 (CH), 123.1 (C), 86.1 (C), 83.9 (C), 63.4 (CH_2), 58.5 (CH_2), 43.6 (CH_2), 27.9 (CH_3).

HRMS (ESI) exact mass calculated for $[C_{19}H_{20}NO]^+$ $[M+H]^+$: 278.1539, found: 278.1542.

4-Methyl-*N*-(3-oxobutyl)-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (332)



To a suspension of alkyne **299** (500 mg, 1.75 mmol) and K_2CO_3 (363 mg, 2.62 mmol) in acetone (4 mL) at room temperature was added but-3-en-2-one (0.17 mL, 2.10 mmol) and the resulting mixture stirred at room temperature for 36 h and then at 50 °C for 20 h. The mixture was filtered through celite (EtOAc), and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (40% Et_2O/petroleum ether) to give ketone **332** (210 mg, 31%) as an orange oil.

R_f = 0.21 (40% Et_2O/petroleum ether).

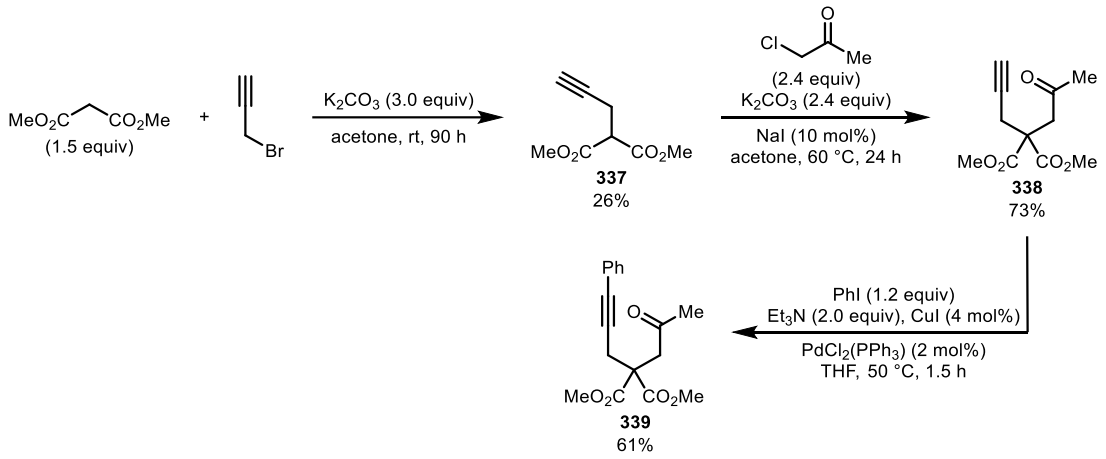
IR 2924, 1715 (C=O), 1598, 1490, 1346, 1158, 1095, 1019, 902, 815 cm^{-1}.

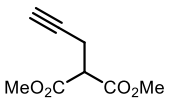
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.73 (2H, m, Ar**H**), 7.31–7.18 (5H, m, Ar**H**), 7.10–7.03 (2H, m, Ar**H**), 4.35 (2H, s, C**H**$_2$C≡), 3.49 (2H, t, *J* = 7.0 Hz, NC**H**$_2$CH$_2$), 2.89 (2H, t, *J* = 7.0 Hz, C**H**$_2$C=O), 2.34 (3H, s, C**H**$_3$C=O), 2.19 (3H, s, ArC**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 206.8 (C), 143.8 (C), 135.6 (C), 131.6 (2 × CH), 129.7 (2 × CH), 128.6 (CH), 128.3 (2 × CH), 128.0 (2 × CH), 122.2 (C), 85.7 (C), 82.1 (C), 43.3 (CH_2), 42.2 (CH_2), 38.9 (CH_2), 30.3 (CH_3), 21.5 (CH_3).

HRMS (ESI) Exact mass calculated for $[C_{20}H_{21}NO_3SNa]^+$ [M+Na]$^+$: 378.1133, found: 378.1133.

6-Phenylhex-5-yn-2-one (339)





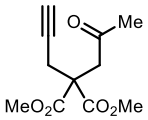
Dimethyl 2-(prop-2-yn-1-yl)malonate (337). To a suspension of dimethyl malonate (1.36 mL, 12.0 mmol) and K_2CO_3 (3.32 g, 24.0 mmol) in acetone (20 mL) at room temperature was added propargyl bromide (80% w/v in toluene, 0.89 mL, 8.00 mmol) and the resulting mixture stirred at room temperature for

90 h. H_2O (30 mL) was added and the aqueous layer extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (10% Et_2O/petroleum ether) to give **337** (523 mg, 26%) as a colourless oil. The analytical data were consistent with those reported previously.[194]

R_f = 0.15 (10% Et_2O/petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.77 (6H, s, 2 × C**H**$_3$), 3.61 (1H, t, *J* = 7.7 Hz, C**H**CH_2), 2.79 (2H, dd, *J* = 7.7, 2.7 Hz, C**H**$_2$), 2.02 (1H, t, *J* = 2.7 Hz, ≡C**H**).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.3 (C), 79.9 (C), 70.6 (CH), 52.9 (2 × CH_3), 51.0 (CH), 18.6 (CH_2).

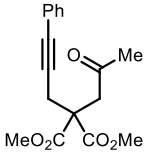


Dimethyl 2-(2-oxopropyl)-2-(prop-2-yn-1-yl)malonate (338). To a solution of **337** (212 mg, 1.25 mmol) in acetone (12 mL) at room temperature was added chloroacetone (0.24 mL, 2.99 mmol), K_2CO_3 (415 mg, 2.99 mmol) and NaI (15.0 mg, 0.12 mmol) and the resulting mixture stirred 60 °C for 24 h. The mixture was filtered and concentrated *in vacuo*. The residue was purified by column chromatography (30% Et_2O/petroleum ether) to give **338** (165 mg, 73%) as a yellow oil. The analytical data were consistent with those reported previously.[195]

R_f = 0.29 (30% Et_2O/petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.70 (6H, s, 2 × OC**H**$_3$), 3.32 (2H, s, 2H, C**H**$_2$C=O), 2.96 (2H, d, *J* = 2.8 Hz, C**H**$_2$C≡), 2.15 (3H, s, C**H**$_3$C=O), 2.00 (1H, t, *J* = 2.7 Hz, C**H**).

^{13}C NMR (101 MHz, $CDCl_3$): δ 205.3 (C), 169.6 (2 × C), 79.2 (C), 71.8 (CH), 54.3 (C), 53.2 (2 × CH_3), 45.4 (CH_2), 30.2 (CH_2), 23.3 (CH_3).



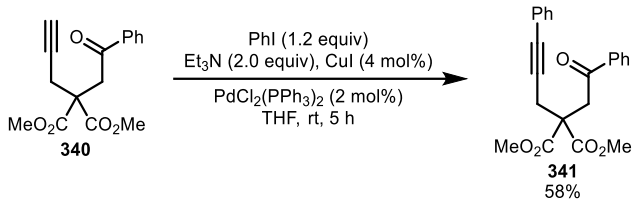
Dimethyl 2-(2-oxopropyl)-2-(3-phenylprop-2-yn-1-yl)malonate (339). Prepared according to a modification of General Procedure A, using alkyne **338** (144 mg, 0.64 mmol), phenyl iodide (90.0 μL, 0.80 mmol), Et_3N (0.19 mL, 1.33 mmol), $Pd(PPh_3)_2Cl_2$ (9.00 mg, 0.013 mmol) and CuI (5.00 mg, 0.027 mmol) in anhydrous THF (1 mL) for 1.5 h at 50 °C. Purification by column chromatography (30% Et_2O/petroleum ether) gave **339** (118 mg, 61%) as an orange oil. The analytical data were consistent with those reported previously.[196]

R_f = 0.31 (30% Et_2O/petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.33 (2H, m, Ar**H**), 7.31–7.26 (3H, m, Ar**H**), 3.76 (6H, s, 2 × OC**H**$_3$), 3.41 (2H, s, C**H**$_2$C=O), 3.22 (2H s, C**H**$_2$C≡), 2.20 (3H, s, C**H**$_3$C=O).

^{13}C NMR (101 MHz, $CDCl_3$): δ 205.5 (C), 169.9 (2 × C), 131.8 (2 × CH), 128.4 (2 × CH), 128.3 (CH), 123.1 (C), 84.6 (C), 84.0 (C), 54.9 (C), 53.3 (2 × CH_3), 45.8 (CH_2), 30.4 (CH_2), 24.4 (CH_3).

Dimethyl 2-(2-oxo-2-phenylethyl)-2-(3-phenylprop-2-yn-1-yl)malonate (341)



To a suspension of iodobenzene (0.40 mL, 3.60 mmol), Et_3N (0.84 mL, 6.00 mmol), $Pd(PPh_3)_2Cl_2$ (42.1 mg, 0.06 mmol) and CuI (22.9 mg, 0.12 mmol) in anhydrous THF (3 mL) under an argon atmosphere at room temperature was added the alkyne **340** (865 mg, 3.00 mmol) and the resulting mixture was stirred at room temperature for the 5 h. The mixture was filtered through celite (Et_2O), and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (0 to 20% EtOAc/cyclohexane) to give the alkyne **341** (633 mg, 58%) as an orange solid.

R_f = 0.43 (20% EtOAc/petroleum ether).

m.p. 78–80 °C ($CHCl_3$).

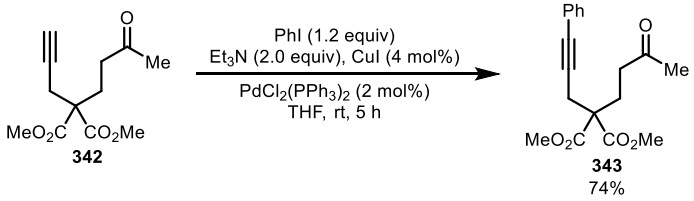
IR 3056, 2953, 1739 (C=O), 1686 (C=O), 1596, 1581, 1448, 1251, 1205, 1183 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07–7.99 (2H, m, Ar**H**), 7.62–7.54 (1H, m, Ar**H**), 7.47 (2H, t, *J* = 7.7 Hz, Ar**H**), 7.33–7.22 (5H, m, Ar**H**), 3.98 (2H, s, C**H**$_2$C=O), 3.80 (6H, s, 2 × OC**H**$_3$), 3.34 (2H, s, C**H**$_2$C≡).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.0 (C), 170.1 (2 × C), 136.5 (C), 133.7 (CH), 131.8 (2 × CH), 128.8 (2 × CH), 128.34 (2 × CH), 128.33 (2 × CH), 128.2 (CH), 123.2 (C), 84.7 (C), 84.1 (C), 55.2 (C), 53.3 (2 × CH_3), 41.4 (CH_2), 24.5 (CH_2).

HRMS (ESI) Exact mass calculated for $[C_{22}H_{20}O_5Na]^+$ [M+Na]$^+$: 387.1203, found: 387.1198.

Dimethyl 2-(3-oxobutyl)-2-(3-phenylprop-2-yn-1-yl)malonate (343)



To a suspension of iodobenzene (0.40 mL, 3.60 mmol), Et_3N (0.84 mL, 6.00 mmol), $Pd(PPh_3)_2Cl_2$ (42.1 mg, 0.06 mmol) and CuI (22.9 mg, 0.12 mmol) in anhydrous THF (3 mL) under an argon atmosphere at room temperature was added the alkyne **342** (721 mg, 3.00 mmol) and the resulting mixture was stirred at room temperature for 5 h. The mixture was filtered through celite (Et_2O), and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (0 to 40% EtOAc/cyclohexane) gave the alkyne **343** (707 mg, 74%) as an orange oil.

R_f = 0.23 (20% EtOAc/petroleum ether).

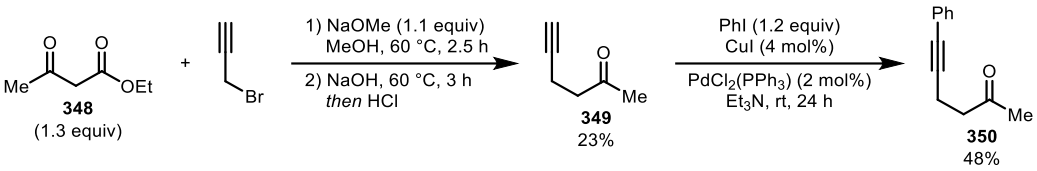
IR 3001, 2964, 1731 (C=O), 1598, 1572, 1491, 1436, 1272, 1198, 1093 cm^{-1}.

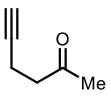
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.33 (2H, m, Ar**H**), 7.29–7.24 (3H, m, Ar**H**), 3.75 (6H, s, 2 × OC**H**$_3$), 3.03 (2H, s, C**H**$_2$C≡), 2.55 (2H, dd, *J* = 8.7, 6.6 Hz, C**H**$_2$C=O), 2.39 (2H, dd, *J* = 8.7, 6.6 Hz, C**H**$_2$CH$_2$C=O), 2.15 (3H, s, C**H**$_3$C=O).

^{13}C NMR (101 MHz, $CDCl_3$) δ 207.2 (C), 170.7 (2 × C), 131.8 (2 × CH), 128.4 (2 × CH), 128.2 (CH), 123.1 (C), 84.0 (C), 83.9 (C), 56.6 (C), 53.0 (2 × CH_3), 38.8 (CH_2), 30.0 (CH_3), 26.8 (CH_2), 24.9 (CH_2).

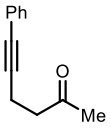
HRMS (ESI) Exact mass calculated for $[C_{18}H_{20}O_5Na]^+$ [M+Na]$^+$: 339.1203, found: 339.1198.

6-Phenylhex-5-yn-2-one (350)





Hex-5-yn-2-one (349). To a solution of ethyl acetoacetate (3.40 mL, 27.0 mmol) and NaOMe (1.12 g, 22.0 mmol) in MeOH (20 mL) at 0 °C was added propargyl bromide (80% w/v in toluene, 2.20 mL, 20.0 mmol) and the resulting mixture stirred at room temperature for 10 mins and then at 60 °C for 2.5 h. Et_2O (20 mL) was added to the mixture and the NaBr filtered off. The filtrate was concentrated *in vacuo*. 1M aqueous NaOH (30 mL) was added to the residue and the mixture stirred at 60 °C for 3 h. The mixture was acidified to pH = 1 with concentrated HCl, and the aqueous layer extracted with Et_2O (3 × 30 mL). The combined organic layers were then washed with saturated aqueous $NaHCO_3$ (30 mL), H_2O (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by distillation under reduced pressure (ca. 20 mbar, room temperature) to give **349** (452 mg, 23%) as colourless liquid containing an inseparable impurity and was used in the next step without further purification.



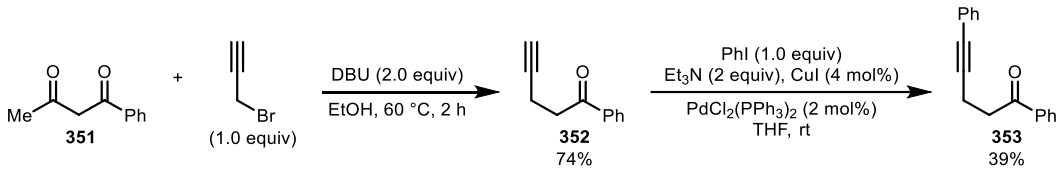
6-Phenylhex-5-yn-2-one (350). A mixture of phenyl iodide (0.33 mL, 2.50 mmol), $Pd(PPh_3)_2Cl_2$ (29.0 mg, 0.04 mmol), CuI (16.0 mg, 0.08 mmol) in Et_3N (4 mL) was purged with argon and stirred at room temperature for 10 min. To the mixture was added alkyne **349** (200 mg, 2.08 mmol) and the reaction mixture stirred at room temperature for 24 h and then concentrated *in vacuo*. The residue was purified by column chromatography (5% Et_2O/pentane) to give **350** (173 mg, 48%) as a yellow oil containing an inseparable impurity. The analytical data were consistent with those reported previously.[197]

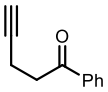
R_f = 0.23 (5% Et_2O/pentane).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.33 (2H, m, Ar**H**), 7.30–7.22 (3H, m, Ar**H**), 2.80–2.69 (2H, m, C**H**$_2$C=O), 2.69–2.59 (2H, m, C**H**$_2$C≡), 2.18 (3H, s, C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 206.6 (C), 131.6 (2 × CH), 128.3 (2 × CH), 127.8 (CH), 123.6 (C), 88.6 (C), 81.0 (C), 42.5 (CH_2), 30.0 (CH_3), 14.0 (CH_2).

Cyclopenta-1,3-diene-1,2,3-triyltribenzene (353)



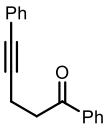


1-Phenylpent-4-yn-1-one (352). To a solution of 1-phenylbutane-1,3-dione (0.46 mL, 3.08 mmol) and propargyl bromide (0.34 mL, 3.08 mmol) in EtOH (20 mL) under an argon atmosphere at room temperature was added DBU (0.92 mL, 6.17 mmol) and the resulting mixture was stirred at 60 °C for 2 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography (1 to 4 % EtOAc/petroleum ether) gave **352** (360 mg, 74%) as a colourless solid. The analytical data were consistent with those previously reported.[198]

R_f = 0.14 (1% EtOAc/petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (2H, m, Ar**H**), 7.60–7.53 (1H, m, Ar**H**), 7.47 (2H, m, Ar**H**), 3.24 (2H, dd, *J* = 8.3, 6.4 Hz, CH_2C=O), 2.63 (2H, dt, *J* = 6.4, 2.7 Hz, C**H**$_2$C≡), 1.98 (1H, t, *J* = 2.7 Hz, C**H**).

^{13}C NMR (101 MHz, $CDCl_3$): δ 197.8 (C), 136.6 (C), 133.4 (CH), 128.8 (2 × CH), 128.1 (2 × CH), 83.5 (C), 68.9 (CH), 37.7 (CH_2), 13.3 (CH_2).



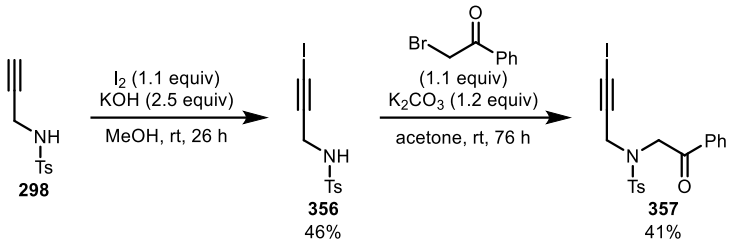
1,5-Diphenylpent-4-yn-1-one (353). Prepared according to General Procedure A, using alkyne **352** (300 mg, 1.90 mmol), phenyl iodide (0.30 mL, 2.28 mmol), Et_3N (0.53 mL, 3.76 mmol), $Pd(PPh_3)_2Cl_2$ (27.0 mg, 0.04 mmol) and CuI (15.0 mg, 0.08 mmol) in anhydrous THF (2 mL) for 24 h. Purification by column chromatography (0 to 20% EtOAc/petroleum ether) gave **353** (174 mg, 39%) as a colourless solid. The analytical data were consistent with those reported previously.[199]

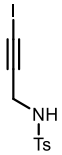
R_f = 0.36 (30% EtOAc/petroleum ether).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04–7.98 (2H, m, Ar**H**), 7.63–7.55 (1H, m, Ar**H**), 7.48 (2H, m, Ar**H**), 7.42–7.35 (2H, m, Ar**H**), 7.32–7.24 (3H, m, Ar**H**), 3.38–3.30 (2H, m, C**H**$_2$C=O), 2.89–2.83 (2H, m, C**H**$_2$C≡).

^{13}C NMR (126 MHz, $CDCl_3$): δ 198.2 (C), 136.7 (C), 133.4 (CH), 131.7 (2 × CH), 128.8 (2 × CH), 128.3 (2 × CH), 128.2 (2 × CH), 127.9 (CH), 123.8 (C), 89.0 (C), 81.2 (C), 38.0 (CH_2), 14.5 (CH_2).

N-(3-Iodoprop-2-yn-1-yl)-4-methyl-*N*-(2-oxopropyl)benzenesulfonamide (357)



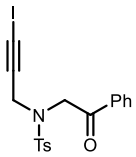


***N*-(3-Iodoprop-2-yn-1-yl)-4-methylbenzenesulfonamide (356).** To a solution of alkyne **6** (1.50 g, 7.17 mmol) in MeOH (2 mL) under an argon atmosphere at room temperature was added KOH (1.00 g, 17.9 mmol) and I_2 (2.00 g, 7.89 mmol) and the resulting mixture stirred at room temperature for 26 h. H_2O (10 mL) was added and the aqueous layer extracted with Et_2O (4 × 10 mL). The combined organic layers were washed with aqueous 2 M $Na_2S_2O_3$ (10 mL), brine (10 mL), dried, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc/petroleum ether) to give **356** (1.10 g, 46%) as a colourless solid. The analytical data were consistent with those reported previously.[200]

R_f = 0.36 (20% EtOAc/petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81–7.72 (2H, m, Ar**H**), 7.37–7.30 (2H, m, Ar**H**), 4.55 (1H, br t, *J* = 6.3 Hz, N**H**), 3.99 (2H, d, *J* = 6.3 Hz, C$\mathbf{H}_2$), 2.44 (3H, s, C$\mathbf{H}_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 144.1 (C), 136.7 (C), 129.9 (CH), 127.7 (CH), 88.2 (C), 77.4 (C), 34.9 (CH_2), 21.8 (CH_3).



***N*-(3-Iodoprop-2-yn-1-yl)-4-methyl-*N*-(2-oxopropyl)benzenesulfonamide (357).** Prepared according to General Procedure B, using alkyne **356** (500 mg, 1.49 mmol), 2-bromoacetophenone (326 mg, 1.64 mmol) and K_2CO_3 (247 mg, 1.79 mmol) in acetone (5 mL) at room temperature for 76 h. Purification by column chromatography (20% EtOAc/petroleum ether) followed by trituration with cold Et_2O gave **356** (277 mg, 41%) as a colourless solid.

R_f = 0.27 (20% EtOAc/petroleum ether).

m.p. = 117–119 °C (Et_2O).

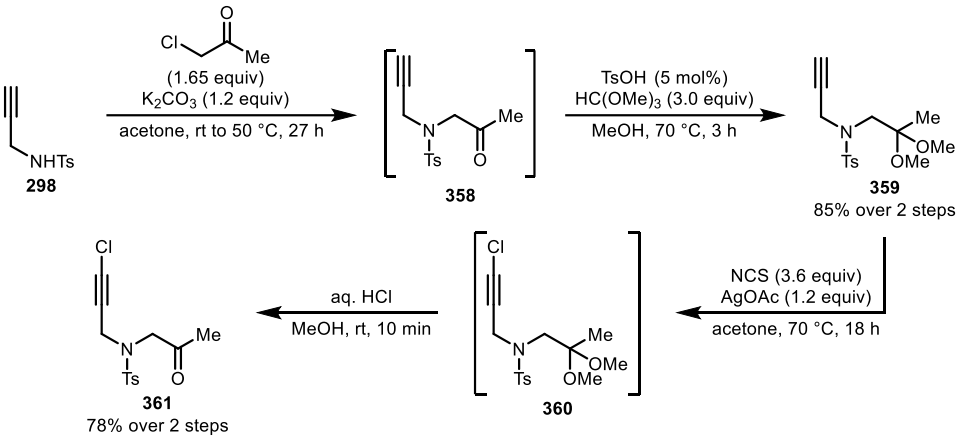
IR 3046, 2961, 1698 (C=O), 1596, 1436, 1325, 1227, 1151, 1065, 908 cm^{-1}.

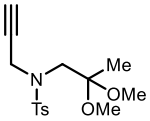
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00–7.91 (2H, m, Ar**H**), 7.80–7.72 (2H, m, Ar**H**), 7.66–7.57 (1H, m, Ar**H**), 7.54–7.44 (2H, m, Ar**H**), 7.38–7.28 (2H, m, Ar**H**), 4.72 (2H, s, C$\mathbf{H}_2$C=O), 4.40 (2H, s, C$\mathbf{H}_2$C≡), 2.45 (3H, s, C$\mathbf{H}_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 193.4 (C), 144.1 (C), 135.9 (C), 135.0 (C), 134.0 (CH), 129.9 (2 × CH), 129.0 (2 × CH), 128.3 (2 × CH), 127.8 (2 × CH), 86.9 (C), 77.4 (C), 52.0 (CH_2), 39.4 (CH_2), 21.8 (CH_3).

HRMS (ESI) exact mass calculated for $[CH_{17}INO_3S]^+$ [M+H]$^+$: 453.9968, found: 453.9960.

***N*-(3-Chloroprop-2-yn-1-yl)-4-methyl-*N*-(2-oxopropyl)benzenesulfonamide (361)**





***N*-(2,2-Dimethoxypropyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (359).** To a suspension of alkyne **S3** (1.00 g, 4.78 mmol) and K_2CO_3 (793 mg, 5.73 mmol) in acetone (15 mL) at room temperature was added chloroacetone (0.42 mL, 5.26 mmol) and the resulting mixture was stirred at room temperature for 24 h. Further chloroacetone (0.21 mL, 2.58 mmol) was added and the mixture was stirred at 50 °C for a further 3 h. The reaction mixture was filtered through celite (EtOAc), and the filtrate concentrated *in vacuo* to leave the ketone **358**, which was used directly in the next step without further purification. The flask containing the ketone **358** was evacuated and backfilled with argon three times, and anhydrous MeOH (25 mL), followed by *p*-toluenesulfonic acid monohydrate (46 mg, 0.24 mmol) were added. The solution was heated to 70 °C and trimethyl orthoformate (1.57 mL, 14.3 mmol) was added, and the mixture was stirred at 70 °C for 3 h. The reaction was cooled to room temperature, diluted with Et_2O (70 mL), and then washed with saturated aqueous $NaHCO_3$ (20 mL), H_2O (20 mL), and brine (20 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (15% EtOAc/petroleum ether) to give the dimethyl acetal **359** (1.26 g, 85% over 2 steps) as a colourless oil.

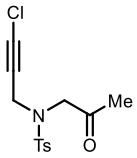
R_f = 0.68 (30% EtOAc/petroleum ether).

IR 3272, 2946, 1598, 1434, 1385, 1348, 1331, 1280, 1158, 1122 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75–7.70 (2H, m, Ar**H**), 7.28 (2H, d, *J* = 8.0 Hz, Ar**H**), 4.30 (2H, d, *J* = 2.4 Hz, C**H**$_2$C≡), 3.33 (2H, s, C**H**$_2$C(OCH$_3$)$_2$), 3.21 (6H, s, 2 × OC**H**$_3$), 2.41 (3H, s, ArC**H**$_3$), 1.93 (1H, t, *J* = 2.4 Hz, ≡C**H**), 1.43 (3H, s, CC**H**$_3$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.7 (C), 136.3 (C), 129.5 (2 × CH), 128.0 (2 × CH), 101.9 (C), 77.3 (C), 73.9 (CH), 48.9 (CH_2), 48.7 (2 × CH_3), 37.4 (CH_2), 21.7 (CH_3), 20.2 (CH_3).

HRMS (ESI) Exact mass calculated for $[C_{15}H_{21}NO_4SNa]^+$ [M+Na]$^+$: 334.1086, found: 334.1086.



***N*-(3-Chloroprop-2-yn-1-yl)-4-methyl-*N*-(2-oxopropyl)benzenesulfonamide (361).** To a solution of acetal **359** (467 mg, 1.50 mmol) in acetone (5 mL) under an argon atmosphere at room temperature was added NCS (721 mg, 5.40 mmol) and $AgNO_3$ (300 mg, 1.80 mmol), and the resulting mixture was stirred at 70 °C for 18 h. The reaction was filtered through celite (EtOAc) and concentrated *in vacuo* to leave the chloroalkyne **360**, which was used directly in the next step without further purification. To the chloroalkyne **360** was added MeOH (5 mL) and 10% aqueous HCl (1 mL) and the resulting suspension was stirred at room temperature for 10 min. Saturated aqueous $NaHCO_3$ (10 mL) was added, and the volatiles were removed *in vacuo*. The mixture was extracted with EtOAc (20 mL), and the organic layer was washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (0 to 20% EtOAc/cyclohexane) to give the ketone **361** (351 mg, 78%) as a colourless solid.

R_f = 0.28 (20% EtOAc/petroleum ether).

m.p. 67–69 °C ($CHCl_3$).

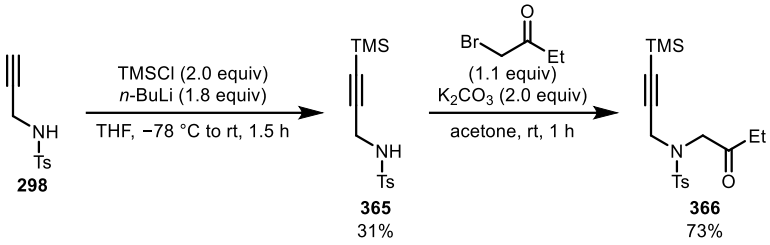
IR 2923, 2242, 1732 (C=O), 1598, 1495, 1418, 1346, 1156, 1101, 1006 cm^{-1}.

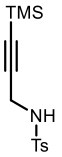
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.33 (2H, d, *J* = 8.1 Hz, Ar**H**), 4.16 (2H, s, C**H**$_2$C≡), 3.99 (2H, s, C**H**$_2$C=O), 2.43 (3H, s, ArC**H**$_3$), 2.22 (3H, s, C**H**$_3$C=O).

^{13}C NMR (101 MHz, $CDCl_3$) δ 203.1 (C), 144.3 (C), 135.4 (C), 129.9 (2 × CH), 127.8 (2 × CH), 64.5 (C), 62.2 (C), 55.6 (CH_2), 38.5 (CH_2), 27.3 (CH_3), 21.7 (CH_3).

HRMS (ESI) Exact mass calculated for $[C_{13}H_{14}NO_3S^{35}ClNa]^+$ [M+Na]$^+$: 322.0275, found: 322.0272.

4-Methyl-*N*-(2-oxobutyl)-*N*-[3-(trimethylsilyl)prop-2-yn-1-yl]benzenesulfonamide (366)



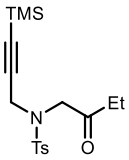


4-Methyl-*N*-[3-(trimethylsilyl)prop-2-yn-1-yl]benzenesulfonamide (365). To a solution of alkyne **298** (2.00 g, 9.56 mmol) in anhydrous THF (25 mL) at −78 °C under an argon atmosphere was added *n*-BuLi (2.7 M in toluene, 6.40 mL, 17.2 mmol) dropwise and the resulting mixture heated to 0 °C and stirred for 45 min (additional anhydrous THF [10 mL] was added after ca. 20 min as the reaction mixture became very viscous). TMSCl (2.40 mL, 19.1 mmol) was added, and the resulting mixture heated to room temperature and stirred for 30 min. The reaction was quenched with H_2O (10 mL) and the mixture extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with H_2O (20 mL), brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (30% Et_2O/petroleum ether) to give **365** (835 mg, 31%) as a colourless solid. The analytical data were consistent with those previously reported.[201]

R_f = 0.31 (30% Et_2O/petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80–7.74 (2H, m, Ar**H**), 7.31 (2H, d, *J* = 8.0 Hz, Ar**H**), 4.61–4.50 (1H, m, N**H**), 3.86 (2H, d, *J* = 6.1 Hz, C**H**$_2$), 2.43 (3H, s, ArC**H**$_3$), 0.03 (9H, s, (C**H**$_3$)$_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 143.8 (C), 136.9 (C), 129.8 (2 × CH), 127.6 (2 × CH), 99.5 (C), 90.1 (C), 34.0 (CH_2), 21.7 (CH_3), -0.3 (CH_3).



4-Methyl-*N*-(2-oxobutyl)-*N*-[3-(trimethylsilyl)prop-2-yn-1-yl]benzenesulfonamide (366). Prepared according to General Procedure B, using alkyne **365** (400 mg, 1.42 mmol), 1-bromobutan-2-one (0.15 mL, 1.56 mmol) and K_2CO_3 (392 mg, 2.84 mmol) in acetone (6 mL) at room temperature for 1 h. Purification by column chromatography (10% EtOAc/petroleum ether) gave **366** (376 mg, 84%) as a colourless solid.

R_f = 0.16 (30% Et_2O/petroleum ether).

m.p. = 73–75 °C ($CHCl_3$/pentane).

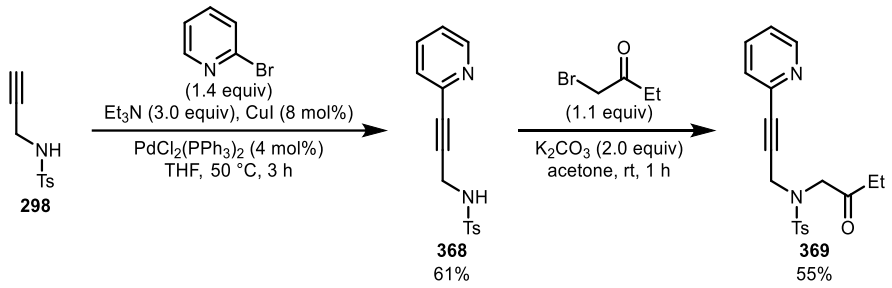
IR 2966, 1732 (C=O), 1596, 1444, 1411, 1350, 1326, 1307, 1249, 1162 cm^{-1}.

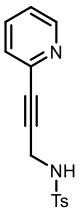
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73–7.66 (2H, m, Ar**H**), 7.30 (2H, d, *J* = 8.0 Ar**H**), 4.17 (2H, s, C**H**$_2$C=O), 3.98 (2H, s. C**H**$_2$C≡), 2.58 (2H, q, *J* = 7.3, C**H**$_2$CH$_3$), 2.42 (3H, s, ArC**H**$_3$), 1.08 (3H, t, *J* = 7.3, CH$_2$C**H**$_3$), 0.02 (9H, s, (C**H**$_3$)$_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 206.3 (C), 144.0 (C), 135.5 (C), 129.8 (2 × CH), 127.81 (2 × CH), 97.5 (C), 92.0 (C), 54.8 (CH_2), 39.1 (CH_2), 33.1 (CH_3), 21.7 (CH_3), 7.6 (CH_3), −0.1 (3 × CH_3).

HRMS (ESI) exact mass calculated for $[C_{17}H_{26}NO_3SSi]^+$ $[M+H]^+$: 352.1397, found: 352.1396.

4-Methyl-*N*-(2-oxobutyl)-*N*-[3-(pyridin-2-yl)prop-2-yn-1-yl]benzenesulfonamide (369)





4-Methyl-*N*-[3-(pyridin-2-yl)prop-2-yn-1-yl]benzenesulfonamide (368). To a suspension of alkyne **298** (1.00 g, 3.50 mmol), 2-bromopyridine (0.47 mL, 4.90 mmol), $Pd(PPh_3)Cl_2$ (98.0 mg, 0.14 mmol), CuI (53.0 mg, 0.28 mmol) in anhydrous THF (1.5 mL) under argon an atmosphere at room temperature was added Et_3N (1.50 mL, 10.5 mmol) and the mixture stirred at 50 °C for 3 h. The mixture was concentrated *in vacuo*. The residue was purified by column chromatography (70% EtOAc/petroleum ether) to give **368** (750 mg, 61%) as a brown solid.

R_f = 0.33 (70% EtOAc/petroleum ether).

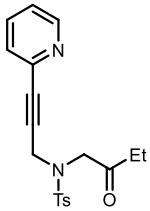
m.p. = 142–144 °C (Et_2O).

IR 3065, 2860, 1584, 1466, 1429, 1326, 1155, 1092, 1070, 812 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (1H, app dt, *J* = 4.7, 1.5 Hz, Ar**H**), 7.82–7.76 (2H, m, Ar**H**), 7.60 (1H, app td, *J* = 7.8, 1.8 Hz, Ar**H**), 7.28–7.18 (3H, m, Ar**H**), 7.11 (1H, app dt, *J* = 7.9, 1.1 Hz, Ar**H**), 5.77 (1H, t, *J* = 6.2 Hz, N**H**), 4.08 (2H, d, *J* = 6.2 Hz, C**H**$_2$), 2.32 (3H, s, C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 150.0 (CH), 143.7 (C), 142.3 (C), 137.1 (C), 136.3 (CH), 129.8 (2 × CH), 127.6 (2 × CH), 127.2 (CH), 123.4 (CH), 84.1 (C), 83.8 (C), 33.6 (CH_2), 21.6 (CH_3).

HRMS (ESI) exact mass calculated for $[C_{15}H_{14}N_2O_2SNa]^+$ $[M+Na]^+$: 309.0668, found: 309.0664.



4-Methyl-*N*-(2-oxobutyl)-*N*-[3-(pyridin-2-yl)prop-2-yn-1-yl]benzenesulfonamide (369). Prepared according to General Procedure B, using alkyne **368** (400 mg, 1.40 mmol), 2-bromo-1-cyclopropylethan-1-one (0.16 mL, 1.54 mmol) and K_2CO_3 (386 mg, 2.79 mmol) in acetone (6 mL) for 1 hour at room temperature. Purification by column chromatography (20% EtOAc/CH_2Cl_2) to give **369** (275 mg, 55%) as a brown solid.

R_f = 0.32 (15% EtOAc/petroleum ether).

m.p. = 84–85 °C ($CHCl_3$).

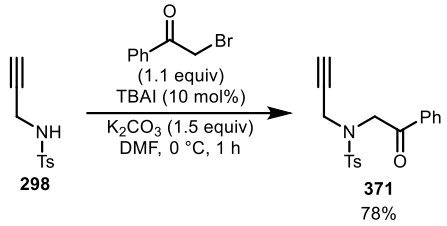
IR 2982, 1729 (C=O), 1598, 1580, 1462, 1426, 1376, 1341, 1308, 1157 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54–8.51 (1H, m, Ar**H**), 7.79–7.72 (2H, m, Ar**H**), 7.60 (1H, app td, *J* = 7.8, 1.8, Ar**H**), 7.31–7.26 (2H, m, Ar**H**), 7.22 (1H, ddd, *J* = 7.7, 4.9, 1.2, Ar**H**), 7.14–7.10 (1H, m, Ar**H**), 4.42 (2H, s, C**H**$_2$C≡), 4.12 (2H, s, C**H**$_2$C=O), 2.56 (2H, q, *J* = 7.3, C**H**$_2$CH$_3$), 2.35 (3H, s, ArC**H**$_3$), 1.07 (3H, t, *J* = 7.3, CH$_2$C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 205.8 (C), 150.0 (CH), 143.9 (C), 142.2 (C), 136.1 (CH), 135.6 (C), 129.7 (2 × CH), 127.7 (2 × CH), 127.1 (CH), 123.2 (CH), 85.4 (C), 81.7 (C), 54.7 (CH_2), 38.6 (CH_2), 33.0 (CH_2), 21.5 (CH_3), 7.4 (CH_3).

HRMS (ESI) exact mass calculated for $[C_{19}H_{21}N_2O_3S]^+$ $[M+H]^+$: 357.1267, found: 357.1281.

4-Methyl-*N*-(2-oxo-2-phenylethyl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide (371)



To a solution of alkyne **298** (500 mg, 2.39 mmol), 2-bromoacetophenone (523 mg, 2.63 mmol) and TBAI (88.0 mg, 0.24 mmol) in anhydrous DMF (5 mL) under an argon atmosphere at 0 °C was added K_2CO_3 (495 mg, 3.58 mmol) and the resulting mixture stirred at 0 °C for 1 h. H_2O (10 mL) was added, and the aqueous layer extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with saturated aqueous NH_4Cl (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (50% Et_2O/petroleum ether) to give **371** (593 mg, 78%) as an off-white solid. The analytical data were consistent with those reported previously.[195]

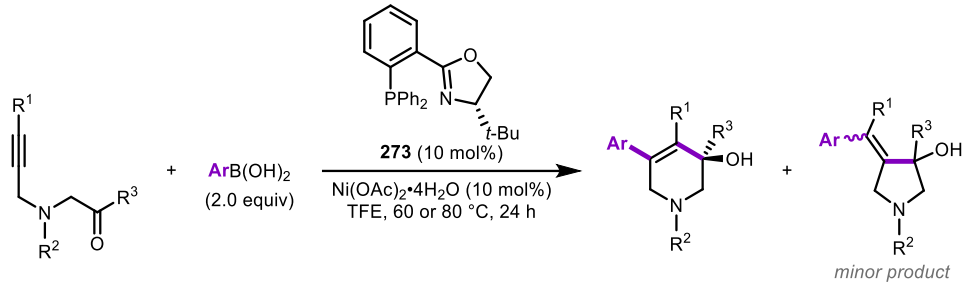
R_f = 0.37 (50% Et_2O/pet ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98–7.91 (2H, m, Ar**H**), 7.81–7.73 (2H, m, Ar**H**), 7.65–7.57 (1H, m, Ar**H**), 7.52–7.44 (2H, m, Ar**H**), 7.35–7.28 (2H, m, Ar**H**), 4.81 (2H, s, C**H**$_2$C=O), 4.29 (2H, d, *J* = 2.5 Hz, C**H**$_2$C≡C), 2.44 (3H, s, C**H**$_3$), 2.11 (1H, t, *J* = 2.5 Hz, C**H**).

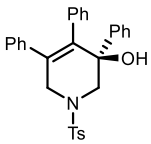
^{13}C NMR (101 MHz, $CDCl_3$): δ 193.4 (C), 144.0 (C), 136.2 (C), 134.9 (C), 134.0 (CH), 129.8 (2 × CH), 129.0 (2 × CH), 128.2 (2 × CH), 127.8 (2 × CH), 76.7 (C), 74.5 (C), 51.6 (CH_2), 37.5 (CH_2), 21.7 (CH_3).

3.4 Enantioselective Nickel-Catalysed Arylative Cyclisation onto Alkynones

General Procedure C



An oven dried microwave vial fitted with a magnetic stirrer bar was charged with the appropriate substrate **1** (0.30 mmol), boronic acid (0.60 mmol), $Ni(OAc)_2{\cdot}4H_2O$ (7.50 mg, 0.03 mmol) and (*S*)-*t*-BuPhox (**L1**, 11.6 mg, 0.03 mmol). The vial was capped with a crimped cap seal and evacuated and backfilled with argon (3 cycles). Freshly degassed TFE (3 mL, using a stream of argon for 20 min) was added, and the mixture was stirred at room temperature for 10 min, and then at the specified temperature for 24 h. The reaction was cooled to room temperature, diluted with EtOAc (5 mL), and washed with brine (10 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography to give the arylative cyclisation product **2**.



(*R*)-3,4,5-Triphenyl-1-tosyl-1,2,3,6-tetrahydropyridin-3-ol (312). Prepared according to General Procedure C, using alkynone **301** (121 mg, 0.30 mmol) and phenylboronic acid (73.0 mg, 0.60 mmol) at 80 °C. ^{1}H NMR analysis of the crude material showed the ratio of major:minor products was 11:1. Purification by column chromatography (CH_2Cl_2) gave **312** (121 mg, 84%) as an off-white solid.

R_f = 0.17 (CH_2Cl_2).

m.p. 198–200 °C (Et_2O).

$[\alpha]_D^{25}$ +16.0 (*c* 1.00, $CHCl_3$).

IR 3530 (OH), 3051, 1596, 1442, 1342, 1248, 1186, 1000, 937, 815 cm^{-1}.

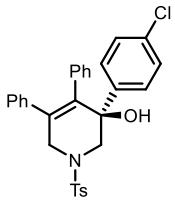
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.60 (2H, m, Ar**H**), 7.49–7.41 (2H, m, Ar**H**), 7.37–7.29 (2H, m, Ar**H**), 7.33–7.21 (2H, m, Ar**H**), 7.25–7.15 (1H, m, Ar**H**), 7.19–7.07 (3H, m, Ar**H**),

7.04–6.95 (2H, m, Ar**H**), 6.95–6.84 (3H, m, Ar**H**), 6.84–6.76 (2H, m, Ar**H**), 4.15 (1H, d, *J* = 16.3 Hz, C**H**$_a$H$_b$C=), 3.91 (1H, d, *J* = 16.3 Hz, CH$_a$**H**$_b$C=), 3.60 (1H, d, *J* = 11.5 Hz, C**H**$_a$H$_b$COH), 3.30 (1H, d, *J* = 11.5 Hz, CH$_a$**H**$_b$COH), 2.82 (1H, s, O**H**), 2.45 (3H, s, ArC**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.2 (C), 142.3 (C), 139.0 (C), 138.9 (C), 136.6 (C), 134.7 (C), 132.9 (C), 130.7 (2 × CH), 130.0 (2 × CH), 128.7 (2 × CH), 128.2 (2 × CH), 128.1 (2 × CH), 128.0 (2 × CH), 127.5 (2 × CH), 127.44 (CH), 127.41 (CH), 126.8 (CH), 126.5 (2 × CH), 74.4 (C), 57.6 (CH_2), 50.1 (CH_2), 21.7 (CH_3).

HRMS (ESI) Exact mass calculated for $[C_{30}H_{27}NO_3SNa]^+$ [M+Na]$^+$: 504.1604, found: 504.1595.

Enantiomeric excess was determined by HPLC using a Chiralpak IC column (80:20 *i*-hexane:*i*-PrOH, 0.5 mL/min, 254 nm, 25 °C); t_r (major) = 26.1 min, t_r (minor) = 28.7 min, 94% ee.



(*R*)-3-(4-Chlorophenyl)-4,5-diphenyl-1-tosyl-1,2,3,6-tetrahydropyridin-3-ol (323a). Prepared according to General Procedure C, using alkynone **321a** (131 mg, 0.30 mmol) and phenylboronic acid (73.0 mg, 0.60 mmol) at 60 °C. ^{1}H NMR analysis of the crude material showed the ratio of major:minor products was 16:1. Purification by column chromatography (5 to 15% EtOAc/pentane) gave **323a** (121 mg, 78%) as an off-white solid.

R_f = 0.21 (15% EtOAc/pentane).

m.p. 143–144°C ($CHCl_3$).

IR 3496 (OH), 2924, 1598, 1491, 1443, 1401, 1348, 1166, 1091, 1038 cm^{-1}.

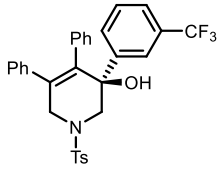
$[\alpha]_D^{25}$ +4.0 (*c* 1.00, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66–7.61 (2H, m, Ar**H**), 7.40–7.37 (2H, m, Ar**H**), 7.33 (2H, d, *J* = 8.0 Hz, Ar**H**), 7.23–7.19 (2H, m, Ar**H**), 7.16–7.11 (3H, m, Ar**H**), 7.00–6.88 (5H, m, Ar**H**), 6.82–6.76 (2H, m, Ar**H**), 4.12 (1H, d, *J* = 16.5 Hz, C**H**$_a$H$_b$C=), 3.94 (1H, d, *J* = 16.5 Hz, CH$_a$**H**$_b$C=), 3.54 (1H, d, *J* = 11.6 Hz, C**H**$_a$H$_b$COH), 3.27 (1H, d, *J* = 11.6 Hz, CH$_a$**H**$_b$COH), 2.80 (1H, s, O**H**), 2.46 (3H, s, C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.3 (C), 141.0 (C), 138.7 (C), 138.5 (C), 136.3 (C), 135.0 (C), 133.3 (C), 132.9 (C), 130.6 (2 × CH), 130.1 (2 × CH), 128.6 (2 × CH), 128.3 (4 × CH, 2 peaks merged into one peak), 127.9 (4 × CH, 2 peaks merged into one peak), 127.7 (2 × CH), 127.5 (CH), 127.0 (CH), 74.1 (C), 57.4 (CH_2), 50.0 (CH_2), 21.8 (CH_3).

HRMS (ESI) Exact mass calculated for $[C_{30}H_{27}{}^{35}ClNO_3S]^+$ [M+H]$^+$: 516.1395, found: 516.1375.

Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column (95:5 *i*-hexane:*i*-PrOH, mL/min, 230 nm, 25 °C); t_r (minor) = 20.4 min, t_r (major) = 23.8 min, 98% ee.



(*R*)-4,5-Diphenyl-1-tosyl-3-[3-(trifluoromethyl)phenyl]-1,2,3,6-tetrahydropyridin-3-ol (323b). Prepared according to General Procedure C, using alkynone **321b** (142 mg, 0.30 mmol) and phenylboronic acid (73.0 mg, 0.60 mmol) at 80 °C. ^{1}H NMR analysis of the crude material showed the ratio of major:minor products was 16:1. Purification by column chromatography (5 to 10% acetone/pentane) gave **323b** (125 mg, 76%) as an off-white solid.

R_f = 0.36 (10% acetone/pentane).

m.p. 164–166 °C ($CHCl_3$).

IR 3491 (OH), 2926, 1598, 1492, 1443, 1327, 1162, 1121, 1091, 1074 cm^{-1}.

$[\alpha]_D^{25}$ +44.0 (*c* 1.00, $CHCl_3$).

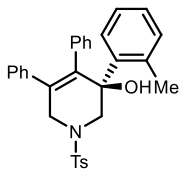
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.62 (4H, m, Ar**H**), 7.46–7.37 (1H, m, Ar**H**), 7.41–7.29 (3H, m, Ar**H**), 7.22–7.08 (3H, m, Ar**H**), 7.05–6.94 (2H, m, Ar**H**), 6.97–6.85 (3H, m, Ar**H**), 6.85–6.75 (2H, m, Ar**H**), 4.19 (1H, d, *J* = 16.4 Hz, C**H**$_a$H$_b$C=), 3.94 (1H, d, *J* = 16.4 Hz, CH$_a$**H**$_b$C=), 3.66 (1H, d, *J* = 11.6 Hz, C**H**$_a$H$_b$COH), 3.22 (1H, d, *J* = 11.6 Hz, CH$_a$**H**$_b$COH), 3.07 (1H, s, O**H**), 2.46 (3H, s, C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.4 (C), 143.3 (C), 138.6 (C), 138.3 (C), 136.3 (C), 135.5 (C), 132.8 (C), 130.5 (2 × CH), 130.3 (q, $J_{C\text{-}F}$ = 31.0 Hz, C), 130.1 (2 × CH), 130.1 (CH), 128.6 (2 × CH), 128.5 (CH), 128.3 (2 × CH), 128.0 (2 × CH), 127.6 (2 × CH); 127.6 (CH), 127.0 (CH), 124.2 (q, $J_{C\text{-}F}$ = 3.6 Hz, CH), 124.2 (q, $J_{C\text{-}F}$ = 272.4 Hz, C), 123.4 (q, $J_{C\text{-}F}$ = 3.7 Hz, CH), 74.2 (C), 57.5 (CH_2), 50.0 (CH_2), 21.7 (CH_3).

^{19}F NMR (376 MHz, $CDCl_3$) δ –62.6 (s).

HRMS (ESI) Exact mass calculated for $[C_{31}H_{27}F_3NO_3S]^+$ $[M+H]^+$: 550.1645, found: 550.1658.

Enantiomeric excess was determined by HPLC using a Chiralpak IC column (90:10 *i*-hexane:*i*-PrOH, 0.5 mL/min, 254 nm, 25 °C); t_r (major) = 20.1 min, t_r (minor) = 22.3 min, 98% ee.



(*R*)-4,5-Diphenyl-3-(*o*-tolyl)-1-tosyl-1,2,3,6-tetrahydropyridin-3-ol (323c). Prepared according to General Procedure C, using alkynone **321c** (125 mg, 0.30 mmol) and phenylboronic acid (73.0 mg, 0.60 mmol) at 80 °C. ^{1}H NMR analysis of the crude material showed the ratio of

major:minor products was 10:1. Purification by column chromatography (80 to 90% CH_2Cl_2/petroleum ether) gave **323c** (107 mg, 72%) as an off-white solid.

R_f = 0.24 (90% CH_2Cl_2/petroleum ether).

m.p. 190–192°C ($CHCl_3$).

IR 3500 (OH), 3056, 2925, 1598, 1443, 1346, 1166, 1124, 1094, 1021 cm^{-1}.

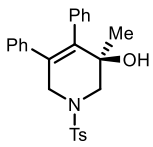
$[\alpha]_D^{25}$ +16.0 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (1H, s, Ar**H**), 7.67 (2H, d, *J* = 7.9 Hz, Ar**H**), 7.34 (2H, d, *J* = 7.9 Hz, Ar**H**), 7.20–7.03 (5H, m, Ar**H**), 7.04–6.80 (8H, m, Ar**H**), 4.37 (1H, d, *J* = 16.4 Hz, C**H**$_a$H$_b$C=), 3.78 (1H, d, *J* = 12.0 Hz, C**H**$_a$H$_b$COH), 3.69 (1H, d, *J* = 16.4 Hz, CH$_a$**H**$_b$C=), 3.26 (1H, d, *J* = 12.0 Hz, CH$_a$**H**$_b$COH), 3.15 (1H, br s, O**H**), 2.46 (3H, s, C**H**$_3$), 2.33 (3H, s, C**H**$_3$).

^{13}C NMR (101 MHz, DMSO-d_6) δ 143.3 (C), 140.1 (C), 139.3 (C), 137.6 (C), 137.1 (C), 133.8 (C), 132.8 (C), 132.5 (C), 131.2 (CH), 130.0 (2 × CH), 129.5 (2 × CH), 128.1 (2 × CH), 127.6 (2 × CH), 127.5 (CH), 127.2 (2 × CH), 126.5 (2 × CH peaks merged into one peak), 126.0 (2 × CH), 125.6 (CH), 124.8 (CH), 73.7 (C), 54.7 (CH_2), 49.0 (CH_2), 20.6 (CH_3), 20.6 (CH_3).

HRMS (ESI) Exact mass calculated for $[C_{31}H_{30}NO_3S]^+$ [M+H]$^+$: 496.1941, found: 496.1928.

Enantiomeric excess was determined by HPLC using a Chiralpak IC column (90:10 *i*-hexane:*i*-PrOH, 0.5 mL/min, 210 nm, 25 °C); t_r (major) = 47.3 min, t_r (minor) = 50.6 min, >99% ee.



(*R*)-3-Methyl-4,5-diphenyl-1-tosyl-1,2,3,6-tetrahydropyridin-3-ol (305). Prepared according to General Procedure C, using alkynone **300** (102 mg, 0.30 mmol) and phenylboronic acid (73.0 mg, 0.60 mmol) at 60 °C. ^{1}H NMR analysis of the crude material showed the ratio of major:minor products was 16:1. Purification by column chromatography (0.5% MeOH/CH_2Cl_2) followed by trituration with cold Et_2O gave **305** (88.0 mg, 70%) as a white solid.

R_f = 0.12 (0.5% MeOH/CH_2Cl_2).

m.p. 179–181 °C (Et_2O).

IR 3550 (OH), 2992, 2955, 1598, 1340, 1156, 1091, 1050, 963, 835 cm^{-1}.

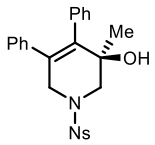
$[\alpha]_D^{25}$ +112.0 (*c* 1.00, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76–7.70 (2H, d, *J* = 8.0 Hz, Ar**H**), 7.38 (2H, d, *J* = 8.0 Hz, Ar**H**), 7.15–6.98 (8H, m, Ar**H**), 6.93–6.87 (2H, m, Ar**H**), 3.99 (1H, d, *J* = 16.2 Hz, C**H**$_a$H$_b$C=), 3.70 (1H, d, *J* = 16.2 Hz, CH$_a$**H**$_b$C=), 3.56 (1H, d, *J* = 11.4 Hz, C**H**$_a$H$_b$COH), 2.98 (1H, d, *J* = 11.4 Hz, CH$_a$**H**$_b$COH), 2.50 (1H, s, O**H**), 2.47 (3H, s, ArC**H**$_3$), 1.19 (3H, s, C**H**$_3$COH).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.2 (C), 140.1 (C), 138.7 (C), 137.0 (C), 133.0 (C), 132.7 (C), 130.5 (2 × CH), 130.1 (2 × CH), 128.7 (2 × CH), 128.08 (2 × CH), 128.05 (2 × CH), 127.7 (2 × CH), 127.2 (CH), 126.9 (CH), 69.6 (C), 56.2 (CH_2), 50.2 (CH_2), 24.9 (CH_3), 21.7 (CH_3).

HRMS (ESI) Exact mass calculated for $[C_{25}H_{25}NO_3SNa]^+$ [M+Na]$^+$: 442.1447, found: 442.1451.

Enantiomeric excess was determined by HPLC using a Chiralpak AD-H column (90:10 *i*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (minor) = 32.6 min, t_r (major) = 59.5 min, 99% ee.



(*R*)-3-Methyl-1-[(4-nitrophenyl)sulfonyl]-4,5-diphenyl-1,2,3,6-tetrahydropyridin-3-ol (323d). Prepared according to General Procedure C, using alkynone **321d** (112 mg, 0.30 mmol) and phenylboronic acid (73.0 mg, 0.60 mmol) at 80 °C. ^{1}H NMR analysis of the crude material showed the ratio of major:minor products was >19:1. Purification by column chromatography (5% EtOAc/$CHCl_3$) gave **323d** (113 mg, 86%) as an off-white solid.

R_f = 0.20 (5% EtOAc/$CHCl_3$).

m.p. 190–191 °C ($CHCl_3$).

IR 3563 (OH), 2923, 2853, 1529, 1347, 1255, 1165, 1046, 965, 884 cm^{-1}.

$[\alpha]_D^{25}$ +84.0 (*c* 1.00, $CHCl_3$).

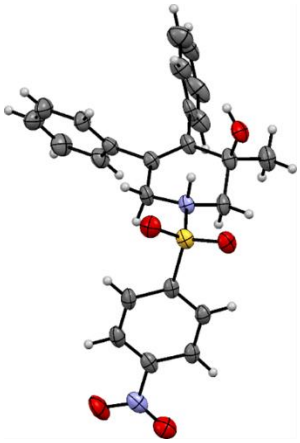
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47–8.39 (2H, m, Ar**H**), 8.07–8.00 (2H, m Ar**H**), 7.17–7.05 (6H, m Ar**H**), 7.05–6.97 (2H, m Ar**H**), 6.94–6.87 (2H, m Ar**H**), 4.00 (1H, d, *J* = 16.2 Hz, C**H**$_a$H$_b$C=C), 3.82 (1H, d, *J* = 16.2 Hz, CH$_a$**H**$_b$C=C), 3.57 (1H, d, *J* = 11.5 Hz, C**H**$_a$H$_b$COH), 3.15 (1H, d, *J* = 11.5 Hz, CH$_a$**H**$_b$COH), 2.41 (1H, s, O**H**), 1.24 (3H, s, C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.6 (C), 141.9 (C), 140.3 (C), 138.2 (C), 136.5 (C), 132.5 (C), 130.5 (2 × CH), 129.2 (2 × CH), 128.7 (2 × CH), 128.2 (2 × CH), 127.8 (2 × CH), 127.5 (CH), 127.1 (CH), 124.7 (2 × CH), 69.6 (C), 55.8 (CH_2), 49.9 (CH_2), 25.2 (CH_3).

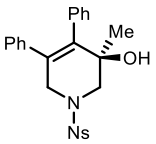
HRMS (ESI) Exact mass calculated for $[C_{24}H_{22}N_2O_5SNa]^+$ [M+Na]$^+$: 473.1142, found: 473.1139.

Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column (80:20 *i*-hexane:*i*-PrOH, mL/min, 254 nm, 25 °C); t_r (minor) = 34.5 min, t_r (major) = 42.7 min, 99% ee.

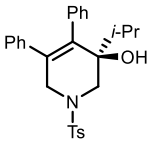
Slow diffusion of pentane into a solution of **321d** in CH_2Cl_2 gave crystals that were suitable for X-ray crystallography. Four molecules of **321d** are present in the P1 unit cell. Two different conformers are present in the cell; two molecules adopt each of the conformations (only one of the conformations is shown above, for clarity). The two conformations differ in the relative orientation of the tosyl group with respect to the hydroxyl groups.



ORTEP with ellipsoid probabilities at 50%



321d
CCDC 2040014
Flack parameter 0.031(12)



(*R*)-3-Isopropyl-4,5-diphenyl-1-tosyl-1,2,3,6-tetrahydropyridin-3-ol (323e). Prepared according to General Procedure C, using alkynone **321e** (111 mg, 0.30 mmol) and phenylboronic acid (73.0 mg, 0.60 mmol) at 80 °C. ^{1}H NMR analysis of the crude material showed the ratio of major:minor products was 12:1. Purification by column chromatography (1 to 2% EtOAc/$CHCl_3$) gave **323e** (107 mg, 80%) as a white solid.

R_f = 0.15 (1% EtOAc/$CHCl_3$).

m.p. 85–87 °C ($CHCl_3$).

IR 3519 (OH), 3053, 2964, 1598, 1493, 1442, 1347, 1248, 1167, 1092 cm^{-1}.

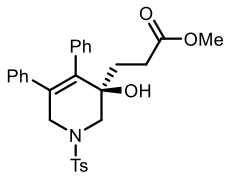
$[\alpha]_D^{25}$ +140.0 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75–7.69 (2H, m, Ar**H**), 7.43–7.35 (2H, m, Ar**H**), 7.14–7.04 (8H, m, Ar**H**), 6.90–6.82 (2H, m, Ar**H**), 3.92 (1H, d, *J* = 16.0 Hz, C**H**$_a$H$_b$C=), 3.69 (1H, d, *J* = 16.0 Hz, CH$_a$**H**$_b$C=), 3.48 (1H, d, *J* = 11.7 Hz, C**H**$_a$H$_b$COH), 3.09 (1H, d, *J* = 11.7 Hz, CH$_a$**H**$_b$COH), 2.48 (3H, s, ArC**H**$_3$), 2.43 (1H, s, O**H**), 1.83 (1H, app hept, *J* = 6.9 Hz, C**H**(CH$_3$)$_2$), 1.04 (3H, d, *J* = 6.9 Hz, CHC**H**$_3$), 0.84 (3H, d, *J* = 6.9 Hz, CHC**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.2 (C), 139.5 (C), 139.3 (C), 136.9 (C), 134.9 (C), 132.7 (C), 130.9 (2 × CH), 130.1 (2 × CH), 128.6 (2 × CH), 128.07 (2 × CH), 128.05 (2 × CH), 127.5 (2 × CH), 127.1 (CH), 126.8 (CH), 74.4 (C), 50.1 (CH_2), 49.8 (CH_2), 33.2 (CH), 21.8 (CH_3), 18.3 (CH_3), 16.1 (CH_3).

HRMS (ESI) Exact mass calculated for $[C_{27}H_{29}NO_3SNa]^+$ [M+Na]$^+$: 470.1761, found: 470.1761.

Enantiomeric excess was determined by HPLC using a Chiralpak IC column (80:20 *i*-hexane:*i*-PrOH, 1.0 mL/min, 210 nm, 25 °C); t_r (major) = 9.5 min, t_r (minor) = 10.8 min, 97% ee.



Methyl (*R*)-3-(3-hydroxy-4,5-diphenyl-1-tosyl-1,2,3,6-tetrahydropyridin-3-yl)propanoate (323f). Prepared according to General Procedure C, using alkynone **321f** (124 mg, 0.30 mmol) and phenylboronic acid (73.0 mg, 0.60 mmol) at 60 °C. ^{1}H NMR analysis of the crude material showed the ratio of major:minor products was 13:1. Purification by sequential column chromatography (15 to 20% EtOAc/petroleum ether) then (3 to 5 % EtOAc/CH_2Cl_2) gave **323f** (88.0 mg, 56%) as a white solid.

R_f = 0.40 (5% EtOAc/CH_2Cl_2).

m.p. 145–146 °C ($CHCl_3$).

IR 3503 (OH), 2952, 1632 (C=O), 1598, 1440, 1347, 1166, 1091, 1018, 976 cm^{-1}.

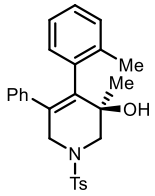
$[\alpha]_D^{25}$ +112.0 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74–7.64 (2H, m, Ar**H**), 7.40–7.32 (2H, m, Ar**H**), 7.16–7.05 (6H, m, Ar**H**), 7.05–6.98 (2H, m, Ar**H**), 6.94–6.86 (2H, m, Ar**H**), 3.99 (1H, d, *J* = 16.3 Hz, C**H**$_a$H$_b$C=), 3.68 (1H, d, *J* = 16.3 Hz, CH$_a$**H**$_b$C=), 3.61 (3H, s, OC**H**$_3$), 3.40 (1H, d, *J* = 11.5 Hz, C**H**$_a$H$_b$COH), 3.10 (1H, d, *J* = 11.5 Hz, CH$_a$**H**$_b$COH), 2.76 (1H, s, O**H**), 2.60–2.40 (2H, m, C**H**$_2$C=O), 2.45 (3H, s, ArC**H**$_3$), 2.08–1.86 (2H, m, C**H**$_2$CH$_2$C=O).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9 (C), 144.3 (C), 140.2 (C), 138.5 (C), 136.2 (C), 133.6 (C), 132.6 (C), 131.0 (2 × CH), 130.1 (2 × CH), 128.9 (2 × CH), 128.1 (2 × CH), 128.0 (2 × CH), 127.8 (2 × CH), 127.3 (CH), 127.1 (CH), 71.4 (C), 52.0 (CH_2), 52.1 (CH_3), 50.2 (CH_2), 32.0 (CH_2), 28.2 (CH_2), 21.7 (CH_3).

HRMS (ESI) Exact mass calculated for $[C_{28}H_{29}NO_5SNa]^+$ [M+Na]$^+$: 514.1659, found: 514.1663.

Enantiomeric excess was determined by HPLC using a Chiralpak AD-H column (90:10 *i*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (minor) = 35.2 min, t_r (major) = 50.8 min, 99% ee.



(*R*)-3-Methyl-5-phenyl-4-(*o*-tolyl)-1-tosyl-1,2,3,6-tetrahydropyridin-3-ol (323h). Prepared according to General Procedure C, using alkynone **321g** (107 mg, 0.3 mmol) and phenyl boronic acid (73.0 mg, 0.6 mmol) at 80 °C. ^{1}H NMR analysis of the crude material was unable to determine the ratio distal:proximal. Purification by column chromatography (3% EtOAc/$CHCl_3$) gave **323h** (100 mg, 77%) as an off-white solid as a 1.8:1 mixture of inseparable isomers.

R_f = 0.25 (4% EtOAc/$CHCl_3$).

m.p. = 78–81 °C ($CHCl_3$).

IR 3512 (OH), 2926, 1598, 1493, 1453, 1347, 1305, 1255, 1166, 1092 cm^{-1}.

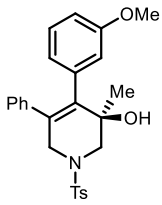
$[\alpha]_D^{25}$ +76.0 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): *combined aromatic signals*: 7.77–7.69 (5.3H, m, Ar**H**), 7.43–7.34 (7.4H, m, Ar**H**), 7.17–6.85 (23.7H, m, Ar**H**); *characteristic signals for the major isomer*: δ 3.91 (1H, d, *J* = 16.3 Hz, C**H**$_a$H$_b$C=), 3.87–3.80 (1H, d, *J* = 16.3 Hz, CH$_a$**H**$_b$C=), 3.53 (1H, d, *J* = 11.3 Hz, C**H**$_a$H$_b$C), 3.01 (1H, d, *J* = 11.3 Hz, CH$_a$**H**$_b$C), 2.51 (1H, s, O**H**), 2.47 (3H, s, ArC**H**$_3$), 1.80 (3H, s, CH, ArC**H**$_3$), 1.12 (3H, s, C**H**$_3$); *characteristic signals for the minor isomer*: 4.01 (1H, d, *J* = 16.3 Hz, C**H**$_a$H$_b$C=), 3.72 (1H, d, *J* = 16.3 Hz, CH$_a$**H**$_b$C=), 3.34 (1H, d, *J* = 11.2 Hz, C**H**$_a$H$_b$C), 3.24 (1H, d, *J* = 11.2 Hz, CH$_a$**H**$_b$C), 2.46 (3H, s, ArC**H**$_3$), 2.15 (1H, s, O**H**), 2.12 (3H, s, ArC**H**$_3$), 1.41 (3H, s, C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ *Combined aromatic/alkenyl signals*‡§*:* 144.3 (C), 144.2 (C), 139.2 (C), 138.7 (C), 138.4 (C), 138.3 (C), 137.5 (C), 135.8 (C), 135.2 (C), 135.4 (C), 133.1 (C), 132.9 (C), 132.8 (C), 132.7 (C), 131.6, 131.1, 130.3, 130.1, 130.0, 128.3, 128.2, 128.1, 128.0, 127.93, 127.89, 127.4, 125.1, 124.5; *characteristic signals for the major isomer*: 69.9 (C), 56.0 (CH_2), 49.8 (CH_2), 23.1 (CH_3), 21.8 (CH_3) 20.1 (CH_3); *characteristic signals for the minor isomer*: 70.6 (C), 55.8 (CH_2), 50.2 (CH_2), 26.0 (CH_3), 21.7 (CH_3), 20.8 (CH_3). ‡Lack of signals likely due to overlapped peaks. §Not all signals characterised due to ambiguity.

HRMS (ESI) exact mass calculated for $[C_{26}H_{27}NO_3SNa]^+$ [M+Na]$^+$: 456.1604, found: 456.1601.

Enantiomeric excess was determined by HPLC using a Chiralpak IC column (80:20 *i*-hexane:*i*-PrOH, 1.0 mL/min, 230 nm, 25 °C); *isomer a*: t_{ra} (minor) = 17.9 min, t_{ra} (major) = 19.7 min, 92% ee; *isomer b*: t_{rb} (minor) = 29.9 min, t_{rb} (major) = 35.6 min, 93% ee.



(*R*)-4-(3-Methoxyphenyl)-3-methyl-5-phenyl-1-tosyl-1,2,3,6-tetrahydropyridin-3-ol (323i). Prepared according to General Procedure C, using alkynone **321h** (111 mg, 0.30 mmol) and phenylboronic acid (73.0 mg, 0.60 mmol) at 60 °C. ^{1}H NMR analysis of the crude material showed the ratio of major:minor products was 14:1. Purification by column chromatography (0 to 2% EtOAc/CH_2Cl_2) gave **323i** (60.0 mg, 46%) as a white solid.

R_f = 0.19 (2% EtOAc/CH_2Cl_2).

m.p. 160–162 °C ($CHCl_3$).

IR 3543 (OH), 2974, 1597, 1491, 1450, 1344, 1317, 1257, 1223, 1156 cm^{-1}.

$[\alpha]_D^{25}$ +108.0 (*c* 1.00, $CHCl_3$).

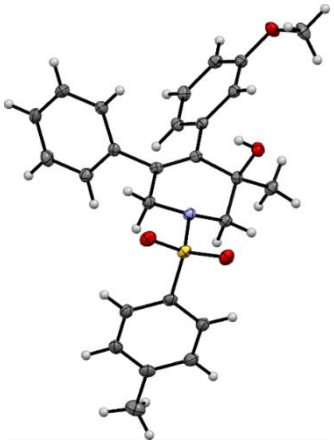
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75–7.68 (2H, m, Ar**H**), 7.37 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.13–7.07 (3H, m, Ar**H**), 7.02 (1H, t, *J* = 7.9 Hz, Ar**H**), 6.94–6.90 (2H, m, Ar**H**), 6.67–6.61 (2H, m, Ar**H**), 6.60–6.56 (1H, m, Ar**H**), 3.98 (1H, d, *J* = 16.2 Hz, C**H**$_a$H$_b$C=), 3.70 (1H, d, *J* = 16.2 Hz, CH$_a$**H**$_b$C=), 3.63 (3H, s, OC**H**$_3$), 3.55 (1H, d, *J* = 11.3 Hz, C**H**$_a$H$_b$COH), 2.98 (1H, d, *J* = 11.3 Hz, CH$_a$**H**$_b$COH), 2.55 (1H, s, O**H**), 2.46 (3H, s, ArC**H**$_3$), 1.20 (3H, s, C**H**$_3$COH).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.9 (C), 144.2 (C), 139.9 (C), 138.7 (C), 138.3 (C), 132.9 (C), 132.6 (C), 130.0 (2 × CH), 128.6 (2 × CH), 128.6 (CH), 128.1 (2 × CH), 128.0 (2 × CH), 127.2 (CH), 123.1 (CH), 116.2 (CH), 112.5 (CH), 69.6 (C), 56.2 (CH_2), 55.2 (CH_3), 50.1 (CH_2), 24.9 (CH_3), 21.7 (CH_3).

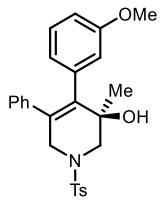
HRMS (ESI) Exact mass calculated for $[C_{26}H_{27}NO_4SNa]^+$ [M+Na]$^+$: 472.1553, found: 472.1553.

Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column (95:5 *i*-hexane:*i*-PrOH, mL/min, 230 nm, 25 °C); t_r (minor) = 20.4 min, t_r (major) = 23.8 min, 98% ee.

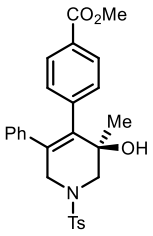
Slow diffusion of pentane into a solution of **323i** in CH_2Cl_2 gave crystals that were suitable for X-ray crystallography:



ORTEP with ellipsoid probabilities at 50%



323i
CCDC 2040015
Flack parameter –0.011(16)



Methyl (*R*)-4-(3-hydroxy-3-methyl-5-phenyl-1-tosyl-1,2,3,6-tetrahydropyridin-4-yl)benzoate (323j). Prepared according to General Procedure C, using alkynone **321i** (120 mg, 0.30 mmol) and phenylboronic acid (73.0 mg, 0.60 mmol) at 80 °C. ^{1}H NMR analysis of the crude material showed the ratio of major:minor products was 8:1. Purification by column chromatography (5% EtOAc/CH_2Cl_2) gave **323j** (63.0 mg, 44%) as a white solid.

R_f = 0.25 (5% EtOAc/CH_2Cl_2).

m.p. 190–192 °C ($CHCl_3$).

IR 3484 (OH), 2951, 1717 (C=O), 1608, 1493, 1436, 1403, 1339, 1276, 1164 cm^{-1}.

$[\alpha]_D^{25}$ +132.0 (*c* 1.00, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80–7.75 (2H, m, Ar**H**), 7.75–7.70 (2H, m, Ar**H**), 7.38 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.12 (2H, d, *J* = 7.8 Hz, Ar**H**), 7.12–7.05 (3H, m, Ar**H**), 6.91–6.84 (2H, m, Ar**H**), 4.04 (1H, d, *J* = 16.4 Hz, C**H**$_a$H$_b$C=), 3.84 (3H, s, OC**H**$_3$), 3.66 (1H, d, *J* = 16.4 Hz,

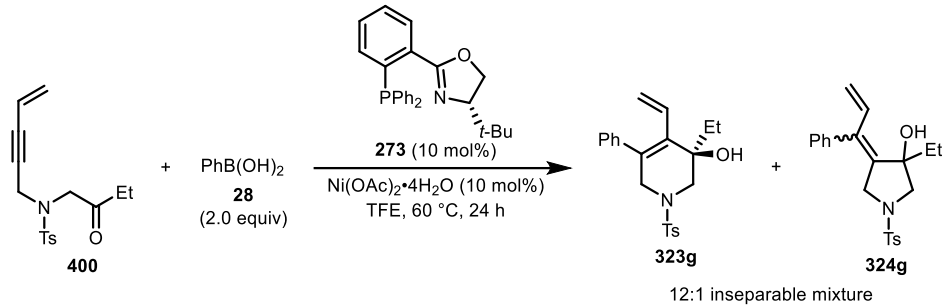
CH_aH_bC=), 3.64 (1H, d, *J* = 11.3 Hz, C**H**$_a$H$_b$COH), 2.91 (1H, d, *J* = 11.3 Hz, CH$_a$**H**$_b$COH), 2.64 (1H, s, O**H**), 2.47 (3H, s, ArC**H**$_3$), 1.13 (3H, s, C**H**$_3$COH).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.1 (C), 144.4 (C), 142.3 (C), 139.4 (C), 138.2 (C), 133.9 (C), 132.6 (C), 130.6 (2 × CH), 130.1 (2 × CH), 128.9 (2 × CH), 128.6 (C), 128.5 (2 × CH), 128.2 (2 × CH), 128.1 (2 × CH), 127.5 (CH), 69.4 (C), 56.3 (CH_2), 52.2 (CH_3), 50.1 (CH_2), 24.6 (CH_3), 21.7 (CH_3).

HRMS (ESI) Exact mass calculated for $[C_{27}H_{28}NO_5S]^+$ [M+H]$^+$: 478.1683, found: 478.1678.

Enantiomeric excess was determined by HPLC using a Chiralpak IC column (70:30 *i*-hexane:*i*-PrOH, 1.0 mL/min, 210 nm, 25 °C); t_r (minor) = 31.5 min, t_r (major) = 38.2 min, 98% ee.

(*R*)-3-Ethyl-5-phenyl-1-tosyl-4-vinyl-1,2,3,6-tetrahydropyridin-3-ol (323g) and 3-ethyl-4-(1-phenylallylidene)-1-tosylpyrrolidin-3-ol (324g)



Prepared according to General Procedure C, using alkynone **400** (92.0 mg, 0.30 mmol) and phenylboronic acid (73.0 mg, 0.60 mmol) at 60 °C. ^{1}H NMR analysis of the crude material showed the ratio of major:minor products was 12:1. Purification by column chromatography (5 to 10% EtOAc/pentane) gave a 12:1 inseparable mixture of **323g** and **324g**, respectively (103 mg, 90%), as a white solid.

R_f = 0.21 (20% EtOAc/pentane).

m.p. 43–45 °C ($CHCl_3$).

IR 3511 (OH), 2967, 2928, 1598, 1493, 1443, 1340, 1165, 1090, 971 cm^{-1}.

$[\alpha]_D^{25}$ +16.0 (*c* 1.00, $CHCl_3$).

HRMS (ESI) Exact mass calculated for $[C_{22}H_{26}NO_3S]^+$ [M+H]$^+$: 384.1628, found: 384.1630.

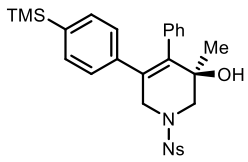
*Data for **323g**:*

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.64 (2H, m, Ar**H**), 7.40–7.28 (5H, m, Ar**H**), 7.15–7.07 (2H, m, Ar**H**), 6.08 (1H, dd, *J* = 18.0, 11.9 Hz, C**H**=CH$_2$), 5.42 (1H, dd, *J* = 18.0, 1.9 Hz, =C**H**$_a$H$_b$), 5.06 (1H, dd, *J* = 11.9, 1.9 Hz, =CH$_a$**H**$_b$), 3.76 (1H, d, *J* = 16.9 Hz, C**H**$_a$H$_b$C=), 3.66 (1H, d, *J* = 16.9 Hz, CH$_a$**H**$_b$C=), 3.25 (1H, d, *J* = 11.6 Hz, C**H**$_a$H$_b$COH), 3.06 (1H, d, *J* = 11.6 Hz, CH$_a$**H**$_b$COH), 2.44 (3H, s, ArC**H**$_3$), 2.24 (1H, s, O**H**), 2.03–1.89 (2H, m, C**H**$_2$CH$_3$), 0.94 (3H, t, *J* = 7.5 Hz, CH$_2$C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.1 (C), 138.8 (C), 136.0 (C), 135.3 (C), 132.7 (C), 131.7 (CH), 130.0 (2 × CH) 128.9 (2 × CH), 128.6 (2 × CH), 128.0 (2 × CH), 127.9 (CH), 119.0 (CH_2), 72.8 (C), 53.4 (CH_2), 50.7 (CH_2), 29.9 (CH_2), 21.7 (CH_3), 8.1 (CH_3).

Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column (90:10 *i*-hexane:*i*-PrOH, 1.5 mL/min, 254 nm, 25 °C); t_r (minor) = 6.0 min, t_r (major) = 7.1 min, 45% ee.

*Diagnostic ^{1}H NMR data for **324g**:* **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75–7.73 (1H, m, Ar**H**), 6.47 (1H, dd, *J* = 17.0, 10.5 Hz, C**H**=CH_2), 5.17 (1H, d, *J* = 10.2 Hz, =C**H**$_a$H$_b$), 4.59 (1H, d, *J* = 17.0 Hz, =CH_a**H**$_b$), 4.17–4.05 (2H, m, C**H**$_2$C=), 3.39 (1H, d, *J* = 9.5 Hz, C**H**$_a$H$_b$COH), 2.97 (1H, d, *J* = 9.5 Hz, CH_a**H**$_b$COH), 0.78 (3H, t, *J* = 7.4 Hz, CH_2C**H**$_3$).



(*R*)-3-Methyl-1-[(4-nitrophenyl)sulfonyl]-4-phenyl-5-[4-(trimethylsilyl)phenyl]-1,2,3,6-tetrahydropyridin-3-ol (373a). Prepared according to General Procedure C, using alkynone **321d** (112 mg, 0.30 mmol) and 4-(trimethylsilyl)phenylboronic acid (116 mg, 0.60 mmol) at 60 °C. ^{1}H NMR analysis of the crude material showed the ratio of major:minor products was >19:1. Purification by column chromatography (3 to 5% EtOAc/$CHCl_3$) gave **373a** (123 mg, 78%) as a white solid.

R_f = 0.29 (5% EtOAc/$CHCl_3$).

m.p. 180–182 °C ($CHCl_3$).

IR 3517 (OH), 2956, 1604, 1528, 1401, 1348, 1331, 1248, 1169, 1112 cm^{-1}.

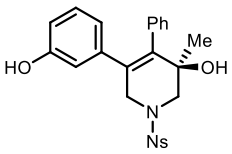
$[\alpha]_D^{25}$ +108.0 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46–8.39 (2H, m, Ar**H**), 8.07–7.99 (2H, m, Ar**H**), 7.28–7.21 (2H, m, Ar**H**), 7.19–7.08 (3H, m, Ar**H**), 7.07–7.00 (2H, m, Ar**H**), 6.92–6.84 (2H, m, Ar**H**), 3.98 (1H, d, *J* = 16.2 Hz, C**H**$_a$H$_b$C=), 3.81 (1H, d, *J* = 16.2 Hz, CH_a**H**$_b$C=), 3.57 (1H, d, *J* = 11.4 Hz, C**H**$_a$H$_b$COH), 3.14 (1H, d, *J* = 11.4 Hz, CH_a**H**$_b$COH), 2.39 (1H, s, O**H**), 1.23 (3H, s, C**H**$_3$COH), 0.17 (9H, s, Si(C**H**$_3$)$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.6 (C), 141.9 (C), 140.2 (C), 139.7 (C), 138.5 (C), 136.5 (C), 133.1 (2 × CH), 132.4 (C), 130.5 (2 × CH), 129.2 (2 × CH), 127.9 (2 × CH), 127.8 (2 × CH), 127.1 (CH), 124.7 (2 × CH), 69.6 (C), 55.8 (CH_2), 49.9 (CH_2), 25.2 (CH_3), –1.1 (3 × CH_3).

HRMS (ESI) Exact mass calculated for $[C_{27}H_{30}N_2O_5SSiNa]^+$ $[M+Na]^+$: 545.1537, found: 545.1532.

Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column (90:10 *i*-hexane:*i*-PrOH, 1.0 mL/min, 210 nm, 25 °C); t_r (minor) = 20.0 min, t_r (major) = 27.0 min, 99% ee.



(*R*)-5-(3-Hydroxyphenyl)-3-methyl-1-[(4-nitrophenyl)sulfonyl]-4-phenyl-1,2,3,6-tetrahydropyridin-3-ol (373b). Prepared according to General Procedure C, using alkynone **321d** (112 mg, 0.30 mmol) and 3-hydroxyphenylboronic acid (83.0 mg, 0.60 mmol) at 60 °C. ^{1}H NMR analysis of the crude material showed the ratio of major:minor products was 16:1. Purification by column chromatography (5 to 10% EtOAc/CH_2Cl_2) gave **373b** (94.0 mg, 67%) as a yellow solid.

R_f = 0.32 (10% EtOAc/CH_2Cl_2).

m.p. 117–119 °C ($CHCl_3$).

IR 3377 (OH), 3105, 1581, 1530, 1488, 1443, 1401, 1350, 1312, 1246 cm^{-1}.

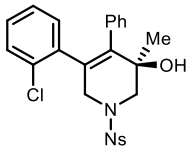
$[\alpha]_D^{25}$ +100.0 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, CD_3CN) δ 8.45–8.40 (2H, m, Ar**H**), 8.10–8.04 (2H, m, Ar**H**), 7.20–7.11 (3H, m, Ar**H**), 7.11–7.05 (2H, m, Ar**H**), 6.97 (1H, t, *J* = 7.9 Hz, Ar**H**), 6.77 (1H, br s, ArO**H**), 6.57–6.47 (2H, m, Ar**H**), 6.44 (1H, dd, *J* = 2.5, 1.6 Hz, Ar**H**), 3.93 (1H, d, *J* = 16.2 Hz, C**H**$_a$H$_b$C=), 3.72 (1H, d, *J* = 16.2 Hz, CH$_a$**H**$_b$C=), 3.54–3.49 (2H, m, C**H**$_a$H$_b$CO**H**), 3.06 (1H, d, *J* = 11.6 Hz, CH$_a$**H**$_b$COH), 1.09 (3H, s, C**H**$_3$COH).

^{13}C NMR (101 MHz, CD_3CN) δ 157.2 (C), 151.6 (C), 142.6 (C), 141.5 (C), 140.4 (C), 138.5 (C), 133.4 (C), 131.5 (2 × CH), 130.1 (2 × CH), 130.0 (CH), 128.1 (2 × CH), 127.4 (CH), 125.5 (2 × CH), 121.2 (CH), 116.7 (CH), 114.8 (CH), 69.8 (C), 56.6 (CH_2), 50.6 (CH_2), 25.1 (CH_3).

HRMS (ESI) Exact mass calculated for $[C_{24}H_{22}N_2O_6SNa]^+$ [M+Na]$^+$: 489.1091, found: 489.1086.

Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column (80:20 *i*-hexane:*i*-PrOH, 1.0 mL/min, 230 nm, 25 °C); t_r (minor) = 18.0 min, t_r (major) = 22.4 min, >99% ee.



(*R*)-5-(2-Chlorophenyl)-3-methyl-1-[(4-nitrophenyl)sulfonyl]-4-phenyl-1,2,3,6-tetrahydropyridin-3-ol (373c). Prepared according to General Procedure C, using alkynone **321d** (112 mg, 0.30 mmol) and (2-chlorophenyl)boronic acid (94.0 mg, 0.60 mmol) at 60 °C. ^{1}H NMR analysis of the crude material showed the ratio of major:minor products was 19:1. Purification by column chromatography (3 to 4% EtOAc/$CHCl_3$) gave **373c** (114 mg, 79%) as a white solid.

R_f = 0.17 (4% EtOAc/$CHCl_3$).

m.p. 129–131 °C ($CHCl_3$).

IR 3517 (OH), 2926, 1731, 1605, 1530, 1493, 1401, 1350, 1312, 1170 cm^{-1}.

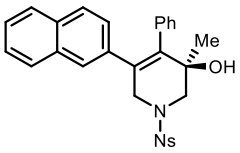
$[\alpha]_D^{25}$ +8.0 (*c* 1.00, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24–8.17 (2H, m, Ar**H**), 7.87–7.81 (1H, m, Ar**H**), 7.81–7.75 (2H, m, Ar**H**), 7.45 (1H, app td, *J* = 7.7, 1.5 Hz, Ar**H**), 7.41–7.34 (4H, m, Ar**H**), 7.28 (3H, dd, *J* = 7.8, 1.6 Hz, Ar**H**), 4.30 (1H, d, *J* = 12.3 Hz, C**H**$_a$H$_b$C=), 3.94 (1H, d, *J* = 12.3 Hz, C**H**$_a$H$_b$C=), 3.64 (1H, d, *J* = 15.4 Hz, C**H**$_a$H$_b$COH), 3.36 (1H, d, *J* = 15.4 Hz, CH$_a$**H**$_b$COH), 3.30 (1H, s, O**H**), 1.46 (3H, s, C**H**$_3$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.1 (C), 144.5 (C), 144.0 (C), 137.1 (C), 134.4 (C), 133.8 (C), 133.7 (C), 129.8 (CH), 129.7 (CH), 129.4 (CH), 128.9 (2 × CH), 128.8 (2 × CH), 128.2 (2 × CH), 128.0 (CH), 127.6 (CH), 124.5 (2 × CH), 76.4 (C), 57.1 (CH_2), 53.0 (CH_2), 29.8 (CH_3).

HRMS (ESI) Exact mass calculated for $[C_{24}H_{21}{}^{35}ClN_2O_5SNa]^+$ [M+Na]$^+$: 507.0752, found: 507.0752.

Enantiomeric excess was determined by HPLC using a Chiralpak AD-H column (80:20 *i*-hexane:*i*-PrOH, 1.0 mL/min, 210 nm, 25 °C); t_r (minor) = 12.4 min, t_r (major) = 21.0 min, >99% ee.



(*R*)-3-Methyl-5-(naphthalen-2-yl)-1-[(4-nitrophenyl)sulfonyl]-4-phenyl-1,2,3,6-tetrahydropyridin-3-ol (373d). Prepared according to General Procedure C, using alkynone **321d** (112 mg, 0.30 mmol) and naphthalen-2-ylboronic acid (103 mg, 0.60 mmol) at 60 °C. ^{1}H NMR analysis of the crude material showed the ratio of major:minor products was >19:1. Purification by column chromatography (3% EtOAc/$CHCl_3$) gave **373d** (77.0 mg, 51%) as a white solid.

R_f = 0.39 (5% EtOAc/$CHCl_3$).

m.p. 197–199 °C ($CHCl_3$).

IR 3523 (OH), 2928, 1605, 1529, 1451, 1401, 1348, 1312,1169, 1091 cm^{-1}.

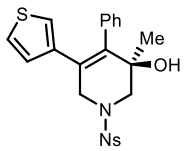
$[\alpha]_D^{25}$ +136.0 (*c* 1.00, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45–8.39 (2H, m, Ar**H**), 8.07–8.01 (2H, m, Ar**H**), 7.72–7.63 (2H, m, Ar**H**), 7.54 (1H, d, *J* = 8.5 Hz, Ar**H**), 7.45 (1H, s, Ar**H**), 7.44–7.37 (2H, m, Ar**H**), 7.15–7.03 (5H, m, Ar**H**), 6.97 (1H, dd, *J* = 8.5, 1.8 Hz, Ar**H**), 4.07 (1H, d, *J* = 16.3 Hz, C**H**$_a$H$_b$C=), 3.94 (1H, d, *J* = 16.3 Hz, CH$_a$**H**$_b$C=), 3.61 (1H, d, *J* = 11.5 Hz, C**H**$_a$H$_b$COH), 3.20 (1H, d, *J* = 11.5 Hz, CH$_a$**H**$_b$COH), 2.45 (1H, s, O**H**), 1.27 (3H, s, C**H**$_3$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.6 (C), 141.9 (C), 140.7 (C), 136.4 (C), 135.7 (C), 132.9 (C), 132.4 (C), 132.3 (C), 130.5 (2 × CH), 129.2 (2 × CH), 127.9 (2 × CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.5 (CH), 127.2 (CH), 126.8 (CH), 126.37 (CH), 126.35 (CH), 124.7 (2 × CH), 69.7 (C), 55.8 (CH_2), 50.0 (CH_2), 25.2 (CH_3).

HRMS (ESI) Exact mass calculated for $[C_{28}H_{24}N_2O_5SNa]^+$ [M+Na]$^+$: 523.1298, found: 523.1305.

Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column (80:20 *i*-hexane:*i*-PrOH, 1.0 mL/min, 210 nm, 25 °C); t_r (major) = 27.6 min, t_r (minor) = 34.7 min, >99% ee.



(*R*)-3-Methyl-1-[(4-nitrophenyl)sulfonyl]4-phenyl-5-(thiophen-3-yl)-1,2,3,6-tetrahydropyridin-3-ol (373e). Prepared according to General Procedure C, using alkynone **321d** (112 mg, 0.30 mmol) and 3-thienylboronic acid (77.0 mg, 0.60 mmol) at 60 °C. ^{1}H NMR analysis of the crude material showed the ratio of major:minor products was >19:1. Purification by column chromatography (4% EtOAc/$CHCl_3$) gave **373e** (87.0 mg, 64%) as a white solid.

R_f = 0.20 (3% EtOAc/$CHCl_3$).

m.p. 167–169 °C ($CHCl_3$).

IR 3521 (OH), 3104, 2927, 1605, 1530, 1454, 1401, 1350, 1169, 1091 cm^{-1}.

$[\alpha]_D^{25}$ +84.0 (*c* 1.00, $CHCl_3$).

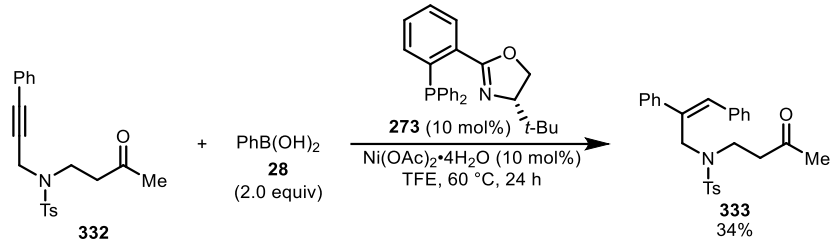
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48–8.39 (2H, m, Ar**H**), 8.10–8.02 (2H, m, Ar**H**), 7.26–7.22 (3H, m, Ar**H**), 7.12–7.04 (2H, m, Ar**H**), 7.01 (1H, dd, *J* = 5.1, 3.0 Hz, Ar**H**), 6.78 (1H, dd, *J* = 2.9, 1.4 Hz, Ar**H**), 6.47 (1H, dd, *J* = 5.0, 1.4 Hz, Ar**H**), 4.05 (1H, d, *J* = 15.9 Hz, C**H**$_a$H$_b$C=), 3.90 (1H, d, *J* = 15.9 Hz, CH$_a$**H**$_b$C=), 3.52 (1H, d, *J* = 11.5 Hz, C**H**$_a$H$_b$COH), 3.17 (1H, d, *J* = 11.5 Hz, CH$_a$**H**$_b$COH), 2.31 (1H, s, O**H**), 1.23 (3H, s, C**H**$_3$COH).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.6 (C), 142.0 (C), 140.1 (C), 138.0 (C), 137.1 (C), 130.2 (2 × CH), 129.2 (2 × CH), 128.3 (2 × CH), 127.7 (CH), 127.6 (CH), 126.7 (C), 125.0 (CH), 124.7 (2 × CH), 123.7 (CH), 69.7 (C), 55.6 (CH_2), 49.2 (CH_2), 25.2 (CH_3).

HRMS (ESI) Exact mass calculated for $[C_{22}H_{20}N_2O_5S_2Na]^+$ [M+Na]$^+$: 479.0706, found: 479.0705.

Enantiomeric excess was determined by HPLC using a Chiralpak IC column (80:20 *i*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (minor) = 23.7 min, t_r (major) = 36.4 min, 98% ee.

(*Z*)-*N*-(2,3-Diphenylallyl)-4-methyl-*N*-(3-oxobutyl)benzenesulfonamide (333)



Prepared according to General Procedure C, using alkynone **332** (107 mg, 0.30 mmol) and phenylboronic acid (73.0 mg, 0.60 mmol) at 60 °C. Purification by column chromatography (15% EtOAc/petroleum ether) gave (*Z*)-**333** (44.2 mg, 34%) as a colourless solid.

R_f = 0.32 (20% EtOAc/petroleum ether).

m.p. 65–67 °C ($CHCl_3$).

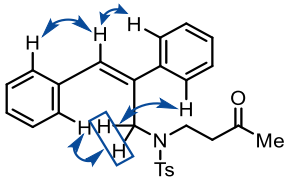
IR 3056, 2922, 1713 (C=O), 1598, 1495, 1343, 1305, 1154, 1104, 1020 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.44 (2H, m, Ar**H**), 7.41 (2H, d, *J* = 8.2 Hz, Ar**H**), 7.36–7.32 (5H, m, Ar**H**), 7.29 (1H, d, *J* = 7.3 Hz, Ar**H**), 7.22–7.17 (2H, m, Ar**H**), 7.16 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.01 (1H, s, =C**H**), 4.48 (2H, s, =CC**H**$_2$), 3.05–2.95 (2H, m, NC**H**$_2$CH$_2$), 2.38 (3H, s, ArC**H**$_3$), 2.25–2.17 (2H, m, C**H**$_2$C=O), 1.86 (3H, s, C**H**$_3$C=O).

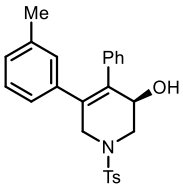
^{13}C NMR (101 MHz, $CDCl_3$) δ 207.0 (C), 143.4 (C), 140.0 (C), 137.0 (C), 136.5 (C), 135.3 (C), 133.7 (CH), 129.6 (2 × CH), 129.0 (2 × CH), 128.6 (2 × CH), 128.5 (2 × CH), 127.9 (CH), 127.54 (2 × CH), 127.45 (CH), 127.3 (2 × CH), 45.6 (CH_2), 42.0 (CH_2), 41.0 (CH_2), 30.0 (CH_3), 21.6 (CH_3).

HRMS (ESI) Exact mass calculated for $[C_{26}H_{27}NO_3SNa]^+$ [M+Na]$^+$: 456.1602, found: 456.1602.

Assignment of the alkene stereochemistry of (*Z*)-**10** was made based on the following NOE interactions observed in a series of 1D NOESY experiments:



(*Z*)-**10**



(*R*)-4-Phenyl-5-(*m*-tolyl)-1-tosyl-1,2,3,6-tetrahydropyridin-3-ol (336). Prepared according to General Procedure C, using alkynone **334** (98.0 mg, 0.30 mmol) and *m*-tolylboronic acid (82.0 mg, 0.60 mmol) at 60 °C. Unable to determine the ratio of distal:proximal by ^{1}H NMR of the

crude material. Purification by sequential column chromatography (15 to 20% EtOAc/petroleum ether) followed by (10% EtOAc/$CHCl_3$) to give **336** (46.0 mg, 37%) as a colourless solid.

R_f = 0.13 (10% EtOAc/$CHCl_3$).

m.p. 158–159 °C ($CHCl_3$).

IR 3489 (OH), 2980, 1598, 1493, 1344, 1238, 1166, 1092, 941, 857 cm^{-1}.

$[\alpha]_D^{25}$ +52.0 (*c* 1.00, $CHCl_3$).

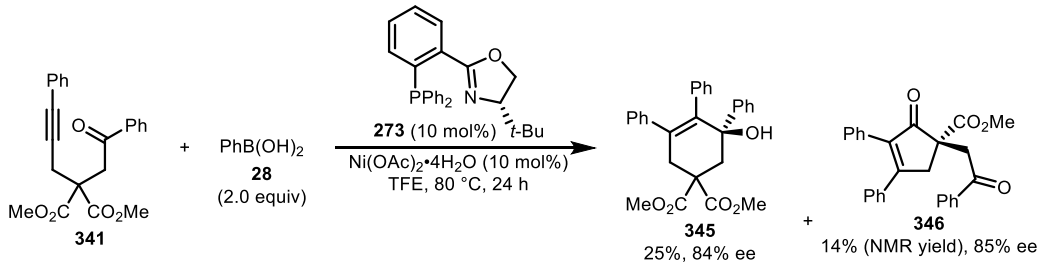
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76–7.71 (2H, m, Ar**H**), 7.39–7.32 (2H, m, Ar**H**), 7.18–7.08 (2H, m, Ar**H**), 7.05–6.93 (4H, m, Ar**H**), 6.86–6.82 (1H, m, Ar**H**), 6.75–6.70 (1H, m, Ar**H**), 4.58 (1H, app. d, C**H**OH), 4.34 (1H, d, *J* = 16.7, C**H**$_a$H$_b$C=C), 3.87 (1H, dd, *J* = 11.9, 3.2, C**H**$_a$H$_b$C(OH)), 3.40 (1H, d, *J* = 16.7, CH$_a$**H**$_b$C=C), 3.00 (1H, dd, *J* = 11.9, 3.1, C**H**$_a$H$_b$C(OH)), 2.44 (3H, s, ArC**H**$_3$), 2.20 (3H, s, ArC**H**$_3$), 2.16 (1H, d, *J* = 9.0, O**H**).

^{13}C NMR (101 MHz, $CDCl_3$): δ 144.0 (C), 138.6 (C), 138.0 (C), 137.8 (C), 135.7 (C), 134.4 (C), 132.7 (C), 129.9 (2 × CH), 129.6, 129.3 (2 × CH), 128.3 (CH), 128.1 (2 × CH), 128.0 (CH), 127.9 (2 × CH), 127.1 (CH), 126.3 (CH), 67.4 (CH), 50.7 (CH_2), 49.6 (CH_2), 21.6 (CH_3), 21.3 (CH_3).

HRMS (ESI) exact mass calculated for $[C_{25}H_{25}NO_3SNa]^+$ $[M+Na]^+$: 442.1447, found: 442.1440.

Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column (80:20 *i*-hexane:*i*-PrOH, 0.5 mL/min, 254 nm, 25 °C); t_r (minor) = 21.4 min, t_r (major) = 26.2 min, 41% ee.

Dimethyl (*R*)-2'-hydroxy-6'-phenyl-2',5'-dihydro-[1,1':2',1''-terphenyl]-4',4'(3'*H*)-dicarboxylate (345) and methyl (*S*)-2-oxo-1-(2-oxo-2-phenylethyl)-3,4-diphenylcyclopent-3-ene-1-carboxylate (346)



Prepared according to General Procedure C, using alkynone **341** (109 mg, 0.30 mmol) and phenylboronic acid (73.0 mg, 0.60 mmol) at 80 °C. Purification by column chromatography (85% $CHCl_3$/pentane to $CHCl_3$) gave **346** as a colourless oil (27.4 mg; additional inseparable, unidentified impurities were present, and therefore the yield was calculated by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard, *ca.* 65% purity. Calculated yield = 14%) followed by **345** (33.6 mg, 25%) as a colourless solid.

Data for **345**:

R_f = 0.44 (1% EtOAc/$CHCl_3$).

m.p. 50–52 °C ($CHCl_3$).

IR 3496 (OH), 3056, 2854, 1731 (C=O), 1559, 1491, 1441, 1256, 1212, 909 cm^{-1}.

$[\alpha]_D^{20}$ +36.0 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.44 (2H, m, Ar**H**), 7.33 (2H, t, *J* = 7.6 Hz, Ar**H**), 7.27–7.23 (1H, m, Ar**H**), 7.18–7.00 (5H, m, Ar**H**), 6.96–6.80 (3H, m, Ar**H**), 6.58–6.48 (2H, m, Ar**H**), 3.88 (3H, s, C**H**$_3$), 3.72 (3H, s, C**H**$_3$), 3.35 (1H, dd, *J* = 17.4, 2.6 Hz, C**H**$_a$H$_b$C=), 3.14 (1H, s, O**H**), 3.00 (1H, d, *J* = 17.4 Hz, CH$_a$**H**$_b$C=), 2.97 (1H, dd, *J* = 14.8, 2.6 Hz, C**H**$_a$H$_b$COH), 2.70 (1H, d, *J* = 14.8 Hz, CH$_a$**H**$_b$COH).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7 (C), 171.7 (C), 146.6 (C), 142.1 (C), 139.6 (C), 137.9 (C), 136.3 (C), 131.5 (2 × CH), 129.1 (2 × CH), 128.2 (2 × CH), 127.9 (2 × CH), 127.2 (2 × CH), 127.0 (CH), 126.7 (CH), 126.6 (CH), 126.1 (2 × CH), 75.0 (C), 53.3 (C), 53.07 (CH_3), 53.04 (CH_3), 46.1 (CH_2), 38.3 (CH_2).

HRMS (ESI) Exact mass calculated for $[C_{28}H_{26}O_5Na]^+$ [M+Na]$^+$: 465.1672, found: 465.1670.

Enantiomeric excess was determined by HPLC using a Chiralpak AD-H column (90:10 *i*-hexane:*i*-PrOH, 1.0 mL/min, 210 nm, 25 °C); t_r (minor) = 8.8 min, t_r (major) = 11.3 min, 84% ee.

Data for **346**:

R_f = 0.46 (1% EtOAc/$CHCl_3$).

IR 2924, 2854, 1737 (C=O), 1688 (C=O), 1597, 1447, 1403, 1353, 1202, 1153 cm^{-1}.

$[\alpha]_D^{20}$ +48.0 (*c* 1.00, $CHCl_3$).

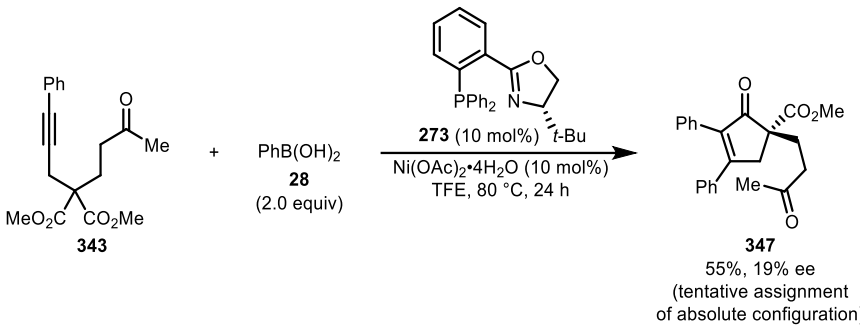
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06–7.95 (2H, m, Ar**H**), 7.60–7.56 (1H, m, Ar**H**), 7.48 (2H, t, *J* = 7.6 Hz, Ar**H**), 7.43–7.27 (10H, m, Ar**H**), 4.28 (1H, d, *J* = 18.3 Hz, C**H**$_a$H$_b$C=O), 4.10 (1H, d, *J* = 18.6 Hz, =CC**H**$_a$H$_b$), 3.73 (3H, s, C**H**$_3$), 3.33 (1H, d, *J* = 18.3 Hz, CH$_a$**H**$_b$C=O), 3.04 (1H, d, *J* = 18.6 Hz, =CCH$_a$**H**$_b$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.4 (C), 197.3 (C), 170.3 (C), 168.3 (C), 136.7 (C), 136.4 (C), 135.0 (C), 133.7 (CH), 132.0 (C), 130.6 (CH), 129.7 (2 × CH), 128.9 (2 × CH), 128.8 (CH), 128.7 (2 × CH), 128.61 (2 × CH), 128.59 (2 × CH), 128.3 (2 × CH), 56.7 (C), 53.2 (CH_3), 44.5 (CH_2), 41.7 (CH_2).

HRMS (ESI) Exact mass calculated for $[C_{27}H_{22}O_4Na]^+$ [M+Na]: 433.1410, found: 433.1410.

Enantiomeric excess was determined by HPLC using a Chiralpak AD-H column (90:10 *i*-hexane:*i*-PrOH, 1.0 mL/min, 210 nm, 25 °C); t_r (minor) = 6.5 min, t_r (major) = 7.9 min, 85% ee.

Methyl (*R*)-2-oxo-1-(3-oxobutyl)-3,4-diphenylcyclopent-3-ene-1-carboxylate (347)



Prepared according to General Procedure C, using alkynone **343** (94.9 mg, 0.30 mmol) and phenylboronic acid (73.0 mg, 0.60 mmol) at 80 °C. Purification by column chromatography (1 to 5% EtOAc/$CHCl_3$) gave **347** (59.8 mg, 55%) as an orange oil.

R_f = 0.22 (2% EtOAc/$CHCl_3$).

IR 3055, 2953, 1739 (C=O), 1698 (C=O), 1623, 1574, 1444, 1352, 1252, 1198 cm^{-1}.

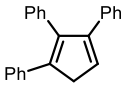
$[\alpha]_D^{20}$ –8.0 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.27 (8H, m, Ar**H**), 7.23–7.21 (2H, m, Ar**H**), 3.75 (3H, s, OC**H**$_3$), 3.59 (1H, d, *J* = 18.1 Hz, =CC**H**$_a$H$_b$), 2.92 (1H, d, *J* = 18.1 Hz, =CCH$_a$**H**$_b$), 2.74 (1H, ddd, *J* = 17.6, 9.7, 6.0 Hz, C**H**$_a$H$_b$C=O), 2.58 (1H, ddd, *J* = 17.6, 9.1, 6.0 Hz, CH$_a$**H**$_b$C=O), 2.42–2.20 (2H, m, C**H**$_2$CH$_2$C=O), 2.15 (3H, s, C**H**$_3$C=O).

^{13}C NMR (101 MHz, $CDCl_3$) δ 207.8 (C), 203.0 (C), 171.6 (C), 166.4 (C), 137.5 (C), 134.8 (C), 131.7 (C), 130.5 (CH), 129.6 (2 × CH), 128.63 (2 × CH), 128.60 (2 × CH), 128.34 (2 × CH), 128.29 (CH), 57.4 (C), 52.9 (CH_3), 41.3 (CH_2), 38.9 (CH_2), 30.1 (CH_3), 29.0 (CH_2).

HRMS (ESI) Exact mass calculated for $[C_{23}H_{22}O_4Na]^+$ [M+Na]$^+$: 385.1410, found: 385.1411.

Enantiomeric excess was determined by HPLC using a Chiralpak AD-H column (90:10 *i*-hexane:*i*-PrOH, 1.0 mL/min, 230 nm, 25 °C); t_r (minor) = 15.2 min, t_r (major) = 22.4 min, 19% ee.

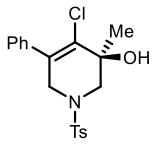


Cyclopenta-1,3-diene-1,2,3-triyltribenzene (355). Prepared according to General Procedure C, using alkynone **353** (70.0 mg, 0.30 mmol) and phenylboronic acid (73.0 mg, 0.60 mmol) at 80 °C. Purification by column chromatography (pentane) to give **355** (45.0 mg, 57%) as a colourless solid. The analytical data were consistent with those reported previously.[202]

R_f = 0.16 (pentane).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24–7.09 (10H, m, Ar**H**), 7.07–7.02 (4H, m, Ar**H**), 6.54 (1H, t, *J* = 1.8 Hz, C**H**), 3.63 (2H, d, *J* = 1.8 Hz, C**H**$_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 149.5 (C), 142.7 (C), 142.1 (C), 137.1 (C), 136.8 (C), 136.7 (C), 130.1 (2 × CH), 129.5 (CH), 128.4 (4 × CH), 128.22 (2 × CH), 128.18 (2 × CH), 127.9 (2 × CH), 126.94 (CH), 126.88 (CH), 126.5 (CH), 43.5 (CH_2).



(*S*)-4-Chloro-3-methyl-5-phenyl-1-tosyl-1,2,3,6-tetrahydropyridin-3-ol (364). Prepared according to General Procedure C, using alkynone **361** (89.8 mg, 0.30 mmol) and phenylboronic acid (73.0 mg, 0.60 mmol) at 60 °C. The ratio of major:minor products could not be determined by ^{1}H NMR analysis of the crude material. Purification by column chromatography (5% EtOAc/$CHCl_3$) gave **364** (13.1 mg, 12%) as a yellow solid.

R_f = 0.29 (5% EtOAc/$CHCl_3$).

m.p. 58–60 °C ($CHCl_3$).

IR 3480 (OH), 2928, 1598, 1536, 1493, 1350, 1308, 1253, 1166, 1092 cm^{-1}.

$[\alpha]_D^{20}$ –4.0 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.43–7.31 (5H, m, Ar**H**), 7.25–7.20 (2H, m, Ar**H**), 3.87 (1H, d, *J* = 16.2 Hz, C**H**$_a$H$_b$C=), 3.71 (1H, d, *J* = 16.2 Hz, CH$_a$**H**$_b$C=), 3.36 (1H, d, *J* = 11.6 Hz, C**H**$_a$H$_b$COH), 3.23 (1H, d, *J* = 11.6 Hz, CH$_a$**H**$_b$COH), 2.58 (1H, s, O**H**), 2.44 (3H, s, ArC**H**$_3$), 1.54 (3H, s, C**H**$_3$COH).

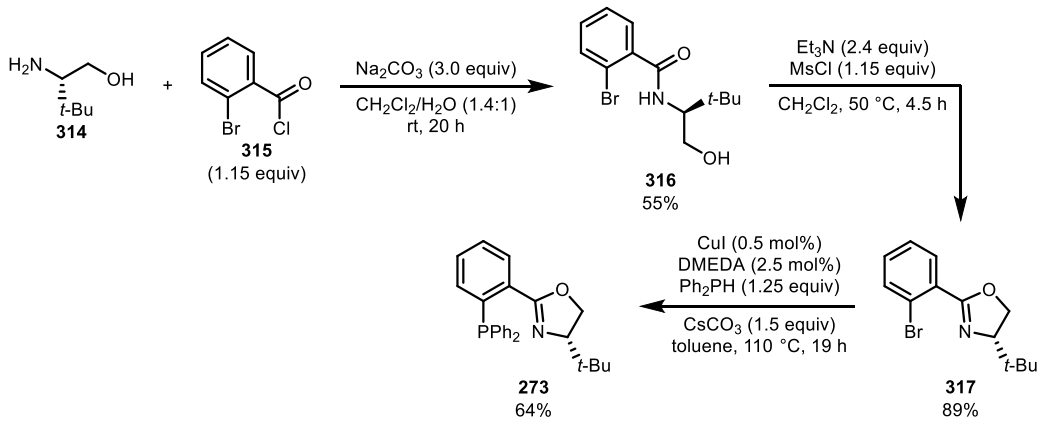
^{13}C NMR (101 MHz, $CDCl_3$) δ 144.4 (C), 136.4 (C), 133.2 (C), 132.7 (C), 132.4 (C), 130.1 (2 × CH), 128.7 (2 × CH), 128.6 (CH), 128.5 (2 × CH), 127.9 (2 × CH), 70.8 (C), 55.9 (CH_2), 51.1 (CH_2), 24.8 (CH_3), 21.7 (CH_3).

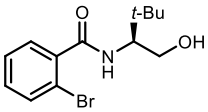
HRMS (ESI) Exact mass calculated for $[C_{19}H_{20}NO_3{}^{35}ClSNa]^+$ [M+Na]$^+$: 400.0745, found: 400.0751.

Enantiomeric excess was determined by HPLC using a Chiralpak AD-H column (90:10 *i*-hexane:*i*-PrOH, 1.0 mL/min, 210 nm, 25 °C); t_r (minor) = 28.3 min, t_r (major) = 31.8 min, 71% ee.

3.5 Ligand Synthesis

(*S*)-*t*-Bu-Phox (273)

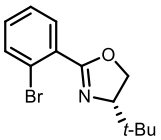




(*S*)-2-Bromo-*N*-(1-hydroxy-3,3-dimethylbutan-2-yl)benzamide (316). To a solution of (S)-2-amino-3,3-dimethylbutan-1-ol (1.33 mL, 10.2 mmol) in CH_2Cl_2 (35 mL) at room temperature was added a solution of Na_2CO_3 (3.26 g, 30.7 mmol) in H_2O (25 mL) and stirred vigorously. 2-Bromobenzoyl chloride (1.54 mL, 11.8 mmol) was added over 15 min and the resulting mixture stirred at room temperature for 20 h. The layers were separated, and the aqueous layer extracted with CH_2Cl_2 (4 × 15 mL). To the combined organic layers was added KOH (1 M in MeOH, 6 mL) and the mixture stirred for 30 min at room temperature and then neutralised with 1 M aqueous HCl. H_2O (10 mL) was added, and the mixture extracted with CH_2Cl_2 (4 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was recrystallised (acetone/hexane) to give **316** (1.69 g, 55%) as a colourless solid. The analytical data were consistent with those reported previously.[179]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63–7.56 (2H, m, Ar**H**), 7.38 (1H, td, *J* = 7.5, 1.2 Hz, Ar**H**), 7.29 (1H, ddd, *J* = 8.0, 7.4, 1.8 Hz, Ar**H**), 6.14 (1H, s, X**H**), 4.08 (1H, m, C**H**$_a$H$_b$), 3.97 (1H, m, CH$_a$**H**$_b$), 3.70 (1H, m, C**H**), 2.17 (1H, s, X**H**), 1.05 (9H, s, (C**H**$_3$)$_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.8 (C), 138.2 (CH), 133.2 (CH), 131.1 (CH), 129.6 (CH), 127.5 (CH), 119.1 (C), 62.5 (CH), 60.0 (CH_2), 34.0 (C), 27.1 (CH_3).

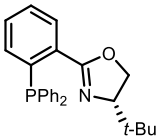


(*S*)-2-(2-Bromophenyl)-4-(*tert*-butyl)-4,5-dihydrooxazole (317). To a solution of alcohol **316** (1.69 g, 5.63 mmol), Et_3N (1.90 mL, 13.5 mmol) and CH_2Cl_2 (30 mL) under an argon atmosphere at 0 °C was added methanesulfonyl chloride (0.50 mL, 6.47 mmol) over 3 min and the resulting mixture was heated at 50 °C for 4.5 h. $NaHCO_3$ (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 6 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (10% EtOAc/petroleum ether) to give **317** (1.42 g, 89%) as a yellow oil. The analytical data were consistent with those reported previously.[179]

R_f = 0.34 (10% EtOAc/petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (1H, dd, *J* = 7.5, 1.9 Hz, Ar**H**), 7.62 (1H, dd, *J* = 8.0, 1.3 Hz, Ar**H**). 7.33 (1H, td, *J* = 7.5, 1.3 Hz, Ar**H**), 7.26 (1H, app td, *J* = 7.8, 1.9 Hz, Ar**H**), 4.38 (1H, dd, *J* = 10.2, 8.6 Hz, C**H$_a$**H$_b$), 4.25 (1H, dd, *J* = 8.6, 8.0 Hz, CH$_a$**H$_b$**), 4.10 (1H, dd, *J* = 10.2, 8.0 Hz, C**H**), 1.00 (9H, s, (C**H**$_3$)$_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 162.9 (C), 133.8 (CH), 131.6 (CH), 131.4 (CH), 130.4 (C), 127.2 (CH), 122.0 (C), 69.1 (CH_2), 34.1 (CH), 26.1 (CH_3).



(*S*)-*t*-Bu-Phox (273). A mixture of CuI (4.80 mg, 0.025 mmol), Ph_2PH (1.10 mL, 6.29 mmol), DMEDA (14.0 μL, 0.13 mmol) in toluene (5 mL) was stirred at room temperature for 20 min. $CsCO_3$ (2.66 g, 7.55 mmol) and a solution of the bromide **317** (1.42 g, 5.03 mmol) in toluene (5 mL) were added to the reaction mixture and the resulting suspension stirred at 110 °C for 19 h. The mixture was filtered through a celite plug (EtOAc) and the filtrate concentrated *in vacuo*. The residue was purified by column chromatography (24:1 petroleum ether/Et_2O then 9:1 CH_2Cl_2/Et_2O). The crude product was concentrated *in vacuo* and recrystallised with MeCN to give **273** (1.25 g, 64%) as a colourless solid. The analytical data were consistent with those reported previously.[179]

R_f = 0.5 (90% CH_2Cl_2/Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (1H, ddd, *J* = 7.7, 3.7, 1.5 Hz, Ar**H**), 7.36 (1H, app td, *J* = 7.5, 1.3 Hz, Ar**H**), 7.33–7.18 (10H, m, Ar**H**), 6.87 (1H, ddd, *J* = 7.8, 4.0, 1.3 Hz, Ar**H**), 4.08 (1H, dd, *J* = 10.2, 8.3 Hz, C**H$_a$**H$_b$), 4.01 (1H, dd, *J* = 8.3 Hz, CH$_a$**H$_b$**), 3.87 (1H, dd, *J* = 10.2, 8.3 Hz, C**H**), 0.73 (9H, s, (C**H**$_3$)$_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 162.8 (d, $^3J_{C\text{-}P}$ = 2.7 Hz, C), 138.9 (d, $^2J_{C\text{-}P}$ = 25.6 Hz, C), 138.7 (d, $^3J_{C\text{-}P}$ = 12.6 Hz, C), 138.4 (d, $^3J_{C\text{-}P}$ = 9.7 Hz, C), 134.5 (d, $^2J_{C\text{-}P}$ = 21.0 Hz, 2 × CH), 134.3 (CH), 133.7 (d, $^2J_{C\text{-}P}$ = 20.2 Hz, 2 × CH), 132.1 (d, $^2J_{C\text{-}P}$ = 19.8 Hz, C), 130.4 (CH), 130.0 (d, $^4J_{C\text{-}P}$ = 3.0 Hz, CH), 128.6 (d, $^3J_{C\text{-}P}$ = 9.4 Hz, 2 × CH), 128.5 (d, $^3J_{C\text{-}P}$ = 5.7 Hz, 2 × CH), 128.4, (CH), 128.2 (CH), 76.9 (CH), 68.4 (CH_2), 33.7 (C), 25.9 (3 × CH_3).

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Part II

Molecular Editing of Cyclic Ketones: C-to-N Atom Exchange

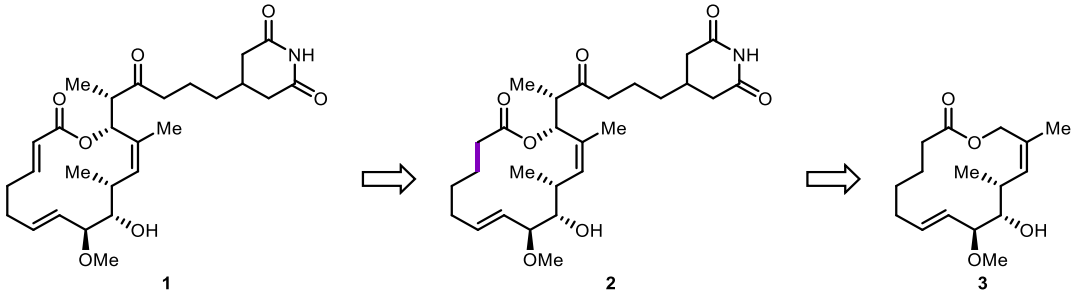
5 Introduction

5.1 Molecular Editing

The need to develop new drugs helps drive the discovery of novel synthetic methodologies, from new disconnections to the modification of advanced intermediates at a late stage.[1,2] Molecular editing as a concept is one that has been of great interest due to its ability to take a complex molecule and perform small, targeted edits. This can enable processes such as scaffold hopping, the computer-aided screening of different core structures of bioactive compounds, which can have profound effects on a candidates pharmacokinetic profile.[3]

5.1.1 History

In the early 2000s Danishefsky and co-workers were working on the total synthesis of a variety of natural products, one of which was of migrastatin (**1**), a potent inhibitor of tumour cell migration.[4–8] Once **1** was synthesised the group set to make analogues through post-synthetic modification. Specifically, they were interested in modification of the α,β-unsaturated ketone, as they postulated that it may be a biovulnerability due it its electrophilicity (Scheme 5.1). Reduction of alkene **1** to the 2,3-dihydro form **2** retained the bioactivity during in vitro testing but lacked significant improvement theorised the modification would have.

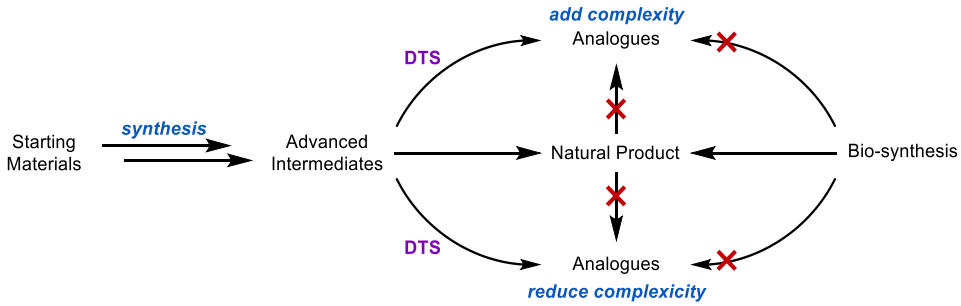


Scheme 5.1: *Molecular editing of migrastatin as a means to explore the SAR of migrastatin. IC_{50} calculated using a chamber cell migration assay with 4T1 tumor cells.*

Whilst they were not able to get the improvement they had hoped for they realised that the synthetic route to access **1** would allow for further exploration of SAR *via* manipulation of the intermediates, which led to the definition of diverted total synthesis (DTS) (Scheme 5.2).[9] Whilst manipulations of the natural product and the biosynthetic pathway to access analogues is possible, these options are often limited due to the complexity of the products being synthesised or the cost of the natural product/biosynthetic intermediates. On the other hand, total synthesis utilises simple starting materials to make the

natural product, proceeding through various advanced intermediates. It is from these intermediates that the total synthesis can be "diverted" to introduce new structural features that would not be possible through the alternative methods. Whilst this concept may not have been defined earlier, it was one that had shown previous success; for example in 1969 Corey reported the synthesis of prostaglandins $F_{2\alpha}$ and E_2 through the utilisation of a common advanced intermediate that would become to be known as the "Corey lactone".[10] The synthesis of various prostaglandins and their analogues using the Corey lactone was subsequently reported which allowed for the structure-activity relationship (SAR) of this class of compounds to be thoroughly explored.[11]

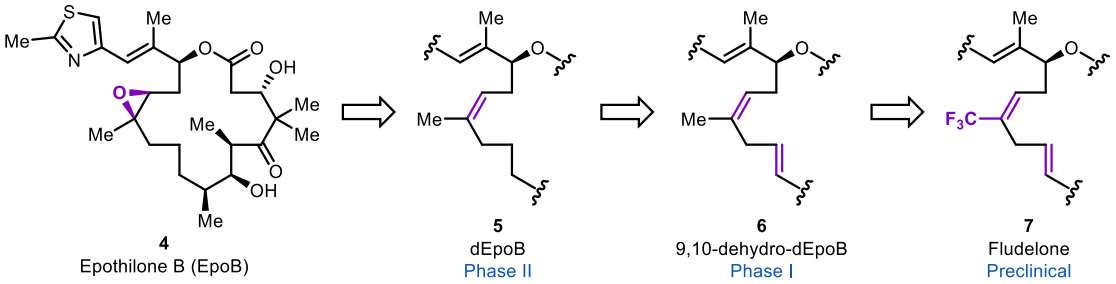
Employing a DTS approach Danishefsky and co-workers were able to further explore the SAR of **1**, which ultimately led them to discovering that macrocyclic core **3** afforded a thousand-fold improvement in potency compared to the natural product.[9] Finally, further derivatisation of the core, such as substituting the ester with an amide or a tertiary alcohol afforded several promising candidates which were all structurally simpler than the natural product.[12]



Scheme 5.2: *Definition of DTS compared to post-modification and biosynthesis.*

From this Danishefsky *et al* realised that a DTS approach allowed for the "molecular editing" of unnecessary or undesirable structural features from the natural product.[13,14] An example of this is the DTS of epothilone B **4** which was first synthesised by the Danishefsky in 1997 (Scheme 5.3).[15,16] Whilst **4** was highly cytotoxic and exhibited activity again multi-drug resistant cell lines preliminary in vivo studies showed that it was highly toxic in mice. This was postulated to be due to the presence of the reactive epoxide providing the compound with nonselective cytotoxicity. Based on this the desepoxy variant **5** was synthesised. Whilst **5** was less active it was better tolerated during in vivo studies, and ultimately made it to phase II trials for the treatment of breast cancer.[17,18] Work on the biosynthesis of **4** led to the discovery of **6** as a very minor impurity; Danishefsky and co-workers rapidly responded by developing an alternative route to synthesise **6** and provide material for testing.[19,20] Unfortunately the activity was not translated well into this analogue. Pharmacokinetic studies showed that the ester was

susceptible to esterases which was thought to be the cause of the drop in potency. Despite the previous poor result the authors envisaged that they could access **7** which substitutes a methyl group with a trifluoromethyl group which may have positive effects. Two years later they managed to access and test **7** which was found to be significantly more potent than **6** whilst also improving metabolic stability, ultimately leading it to preclinical trials.[21]

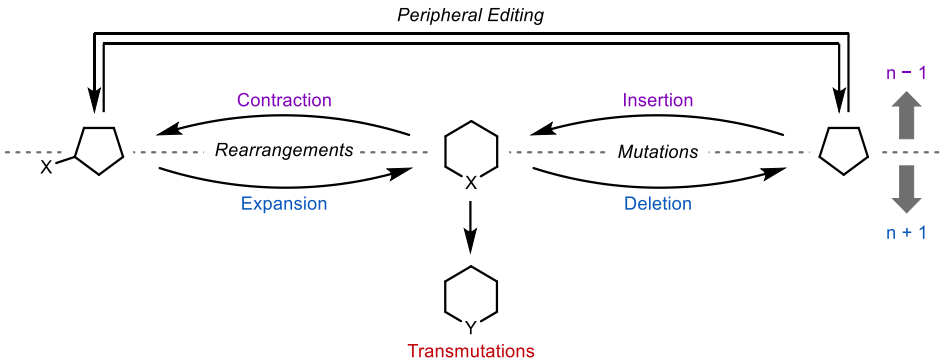


Scheme 5.3: *Molecular editing of* ***4*** *as a means to explore the SAR.*

Since Danishefsky conceptualised DTS and molecular editing various other groups have utilised this approach on a myriad of natural products; there are also various reviews of work, that encapsulate these concepts.[22–29]

5.1.2 Contemporary Approach

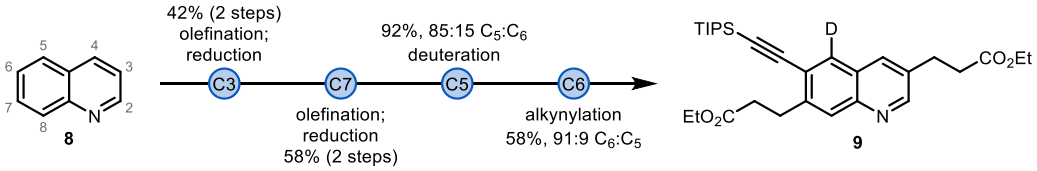
In recent years, the concept of molecular editing has evolved to be used more generally outside of the context of DTS. Both late-stage functionalisation and molecular editing have emerged to be desirable transformations for both general synthesis and drug discovery.[1,2] For example, in drug discovery, molecular editing could be used to effect very specific, small changes to lead compounds, such as atom insertions/deletions, allowing for analogues to be accessed that may typically require *de novo* synthesis. Levin *et al* have attempted to further define molecular editing into specific classes of reactions proposing that molecular editing is comprised of peripheral editing and skeletal editing (Scheme 5.4).[30]



Scheme 5.4: *Levin's proposed definition of molecular editing into different (sub)catagories of reactions.*

Peripheral editing has been well documented over recent years through C-H functionalisation; from transition-metal catalysed processes to photocatalysis, a wide range of C-H bonds can be targeted for derivatisation with many being possible at a late stage on complex molecules.[31–37] Such edits, like C-H methylation or C-H fluorination, can be very powerful in drug discovery due to the profound effects that such groups can have on parameters such as metabolic stability and potency.[38–40]

An example of current state-of-the-art C-H functionalisation is shown in Scheme 5.5.[41] Yu and co-workers developed the selective C-H functionalisation of quinolines through the use of bespoke templating ligands that allow for differentiation of adjacent reaction sites, such as C_6-H and C_7-H or geometrically similar targets with C_3-H and C_7-H. Through this process they were able to perform selective remote C-H functionalisation on a variety of compounds, including the anticancer natural product camptothecin. Furthermore, by utilising the sterics of the introduced groups they were able to perform four sequential directed functionalisations of quinoline (**8**) to form **9**.

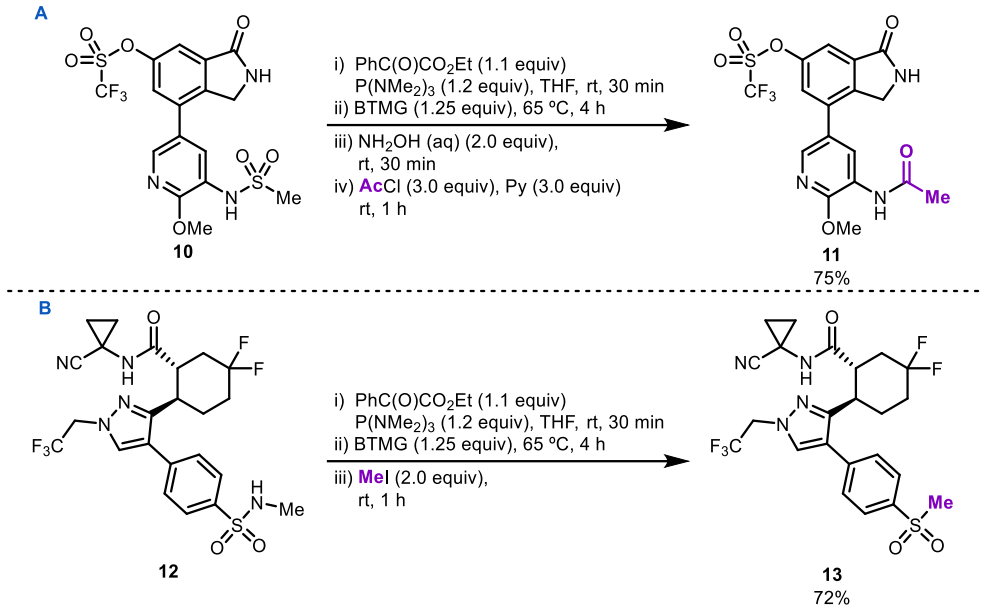


Scheme 5.5: *Yu's approach to the seqeuntial C-H functionalisation of* ***8****.*

On the other hand, the definition of skeletal editing is not as clear. Fundamentally it would involve the modification of the core structure, however then there is the question of "what is the core structure?", especially when heteroatoms are introduced. For example, would a tertiary amine be part of the core structure, or a peripheral site? The skeletal editing of rings is clearer and can be split into various categories (Scheme 5.4).[30] First off there are rearrangements and mutations, i.e. does the group added/removed from the ring remain in the final structure on the periphery. If the group remains, then this constitutes a rearrangement affording either a ring contraction or a ring expansion. If the group does not remain as part of the final structure, then this instead constitutes a mutation affording either an insertion or a deletion. Finally, there is also the possibility that the ring may remain the same size, but with an atom being modified, either through an isomerisation process or through an atom exchange process. These definitions are obvious in a cyclic system, however without further definition this leaves a grey area regarding the skeletal editing of acyclic systems.

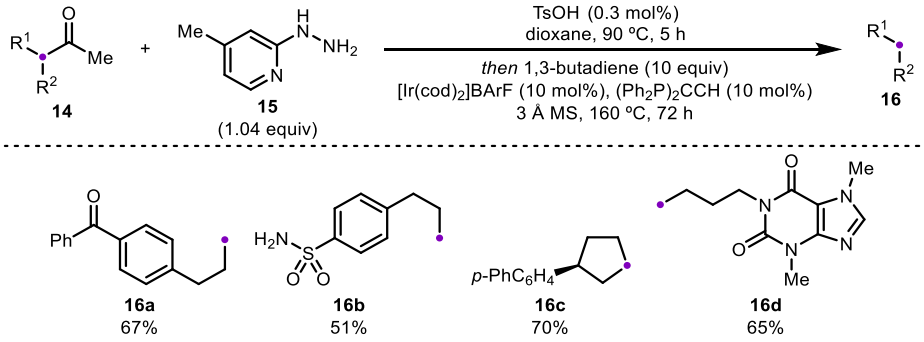
Maloney reported a process for the reductive cleavage of secondary sulfonamides which could then be used further to elicit atom deletions of both the sulfur (Scheme 5.6A) and

the nitrogen (Scheme 5.6B) atoms in several complex bioactive molecules (**10** and **12**).[42] In this example would the sulfonamide be considered as part of the periphery or the core structure hence is this considered peripheral or skeletal editing?



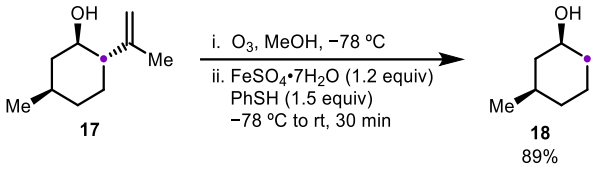
Scheme 5.6: *Maloney's approach for the deletion of sulfur and nitrogen atoms from sulfonamides* ***10*** *and* ***12****.*

C-C bond breaking and defunctionalisation reactions have received considerable attention over the last decade, as breaking typically unreactive C-C bonds can allow novel structures to be accessed and enable alternative retrosynthetic logic.[43,44] Dong reported the deacetylation of ketones **14** utilising iridium-catalysis to access the defunctionalised products **16** (Scheme 5.7).[45] They also showed that the alkyliridium intermediate could be further exploited and reacted with various dienes, allowing access to the one-carbon homologated ketones, among other products.



Scheme 5.7: *Iridium-catalysed deacylation of ketones* ***14****.*

Kwon *et al* described a dealkenylative process to fragment alkenes (**17**) to access valuable simplified terpenes (**18**, Scheme 5.8).[46] The reaction was tolerable to a wide range of substrates, including those containing amines, alcohols and epoxides. Likewise, the reaction could be scaled up to 100 mmol with ease such as the example shown below.



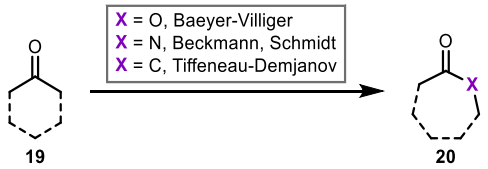
Scheme 5.8: *Dealkenylation of exocyclic alkene* ***17****.*

In the examples above C-C bonds are cleaved, which in the latter example is a typically unreactive bond. Thus, these examples may constitute as skeletal editing as typically the carbon backbone would be considered as the core structure, however without a definitive definition it is not clear. On the other hand, rings offer a clear dividing line whereby the ring is the skeleton with everything else being considered the periphery.

These transformations are of great interest, not only due to the under-development of this area, but it would also provide a new class of simple disconnections that could be made. Furthermore, if this chemistry could be applied on complex intermediates then it could accelerate the drug discovery process, as being able to perform scaffold hopping along with changing single atoms can have huge impacts on a compounds pharmacokinetics, all whilst avoiding *de novo* synthesis.[47–50] The remainder of this introduction will focus on the skeletal editing of cyclic substrates effecting small, often single atom, changes. However, it is possible in some circumstances to achieve medium/large edits of cyclic compounds.[51]

5.2 Atom Insertions

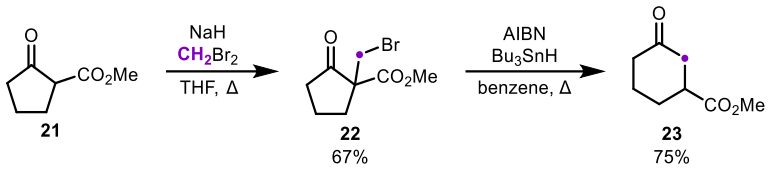
Of all the classes of skeletal editing reactions, the insertion of atoms into a ring is the most established, with ketones **19** often being exploited as a functional handle (Scheme 5.9). It is possible to introduce both heteroatoms (oxygen and nitrogen) and carbon atoms through classical rearrangements such as the Baeyer-Villiger rearrangement, Beckmann rearrangement, Schmidt rearrangement and the Tiffeneau-Demjanov rearrangement.[52,53,62–64,54–61] These rearrangements have seen extensive use in syntheses, from producing simple building blocks to applications in total synthesis. The Beckmann rearrangement is of particular importance as it is estimated that around 90% of all caprolactam, a feedstock for nylon 6, is made using this reaction.[65]



Scheme 5.9: *Name reactions involving an atom insertion into cyclic ketones* ***19****.*

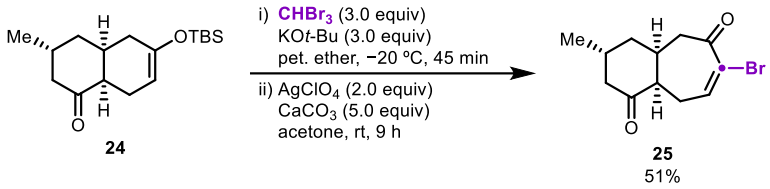
The insertion of a carbon atom into cyclic ketones such as **19** can also be achieved using diazo compounds *via* a Büchner-Curtius-Schlotterbeck reaction or a Roskamp reaction.[66–69] By using either diazomethane or a substituted diazo species, the insertion of a CH_2 or a substituted carbon can be achieved.

The Dowd-Beckwith reaction is a ring expansion of β-keto esters (**21**) in a two-step process (Scheme 5.10).[70–73] First substitution with a dihaloalkane, such as CH_2Br_2, affords **22**, which when subjected to a radical initiator expands to insert a carbon atom into the ring yielding **23**. This has been shown to work on 5-, 6-, and 7-membered rings along with various dihaloalkanes, such as 1,4-diiodobutane, to expand the ring by up to four carbons.



Scheme 5.10: *Single atom insertion of **21** via a Dowd-Beckwith reaction forming **23**.*

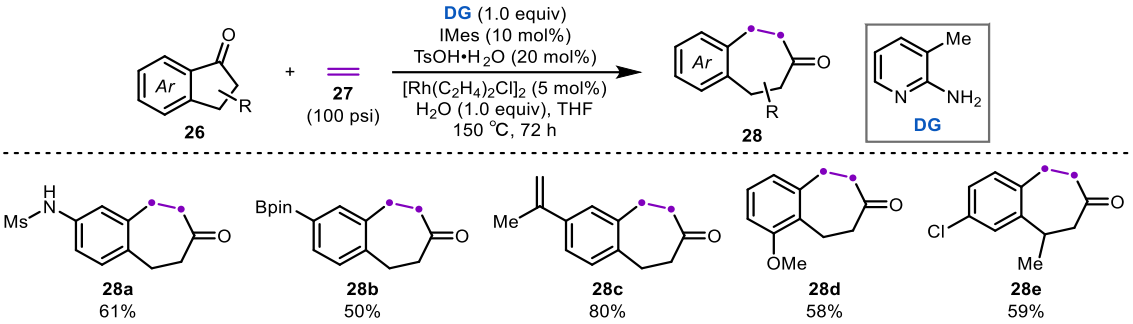
Conia developed the insertion of dibromocarbenes into silyl enol ethers, which has seen use in total synthesis, such as the synthesis of fastigiatine (Scheme 5.11).[74,75] The Diels-Alder adduct **24** was reacted with dibromocarbene (formed *in situ* between KO*t*-Bu and bromoform) to form a dibromocyclopropane, which under Lewis acidic conditions subsequently undergoes a bond migration to form the enone **26**. This reactivity has also been applied to enol ethers, enamines and enol acetates.[76–79]



Scheme 5.11: *Insertion of dibromocarbene into **24**.*

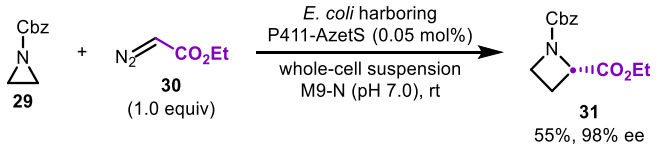
Whilst one-carbon homologations of cyclic ketones are well known, two-carbon homologations are not as well documented. Dong reported that by employing rhodium-catalysis indanones **26** could undergo a ring expansion through the insertion of ethene (**27**) to form the ring expanded products **28** (Scheme 5.12).[80] A "cut-and-sew" process was described where oxidative addition into the benzoylic C-C bond of **26** by rhodium, followed by insertion into **27** and finally reductive elimination formed **28**.[81] To facilitate the oxidative addition an aminopyridine directing group was utilised, as typically this reactivity is limited to strained rings. Functional groups such as an electron-deficient amines (**28a**), aryl boronates (**28b**) and vinyl groups (**28c**) as well as both electron rich (**28d**)

and electron poor substrates were well tolerated. This chemistry enabled the concise synthesis of various bioactive molecules and was also demonstrated on derivatised steroids.



Scheme 5.12: *Rhodium-catalysed insertion of ethene into indanones* ***26****.*

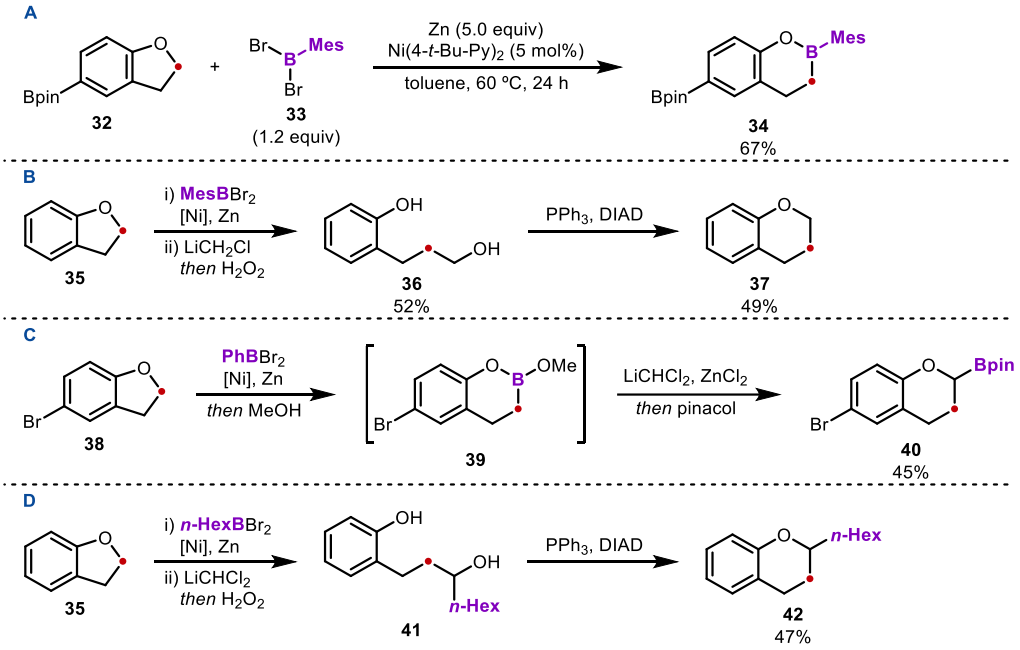
Arnold and co-workers described the one-carbon insertion into aziridines (**29**) employing an engineered "carbene transferase" enzyme to obtain enantioenriched azetidines (**31**) (Scheme 5.13).[82] The evolved variant of cytochrome $P450_{B53}$, P411-AzetS, not only enables excellent enantiocontrol, which is typically difficult to achieve due to the di-radical mechanism, but it is also selective for the [1,2]-Stevens rearrangement over extrusion of ethene.[83–85] Whilst the substrate scope was not extensive, it was able to tolerate a variety of substituted benzyl carbamates as well as isopropyl diazoacetate in moderate to good yields and enantioselectivities. The reaction could also be scaled up to 10 mmol, as shown in Scheme 5.13, to afford **31** in a good yield and excellent enantioselectivity.



Scheme 5.13: *Enzyme-mediated insertion of* ***29*** *into* ***30****.*

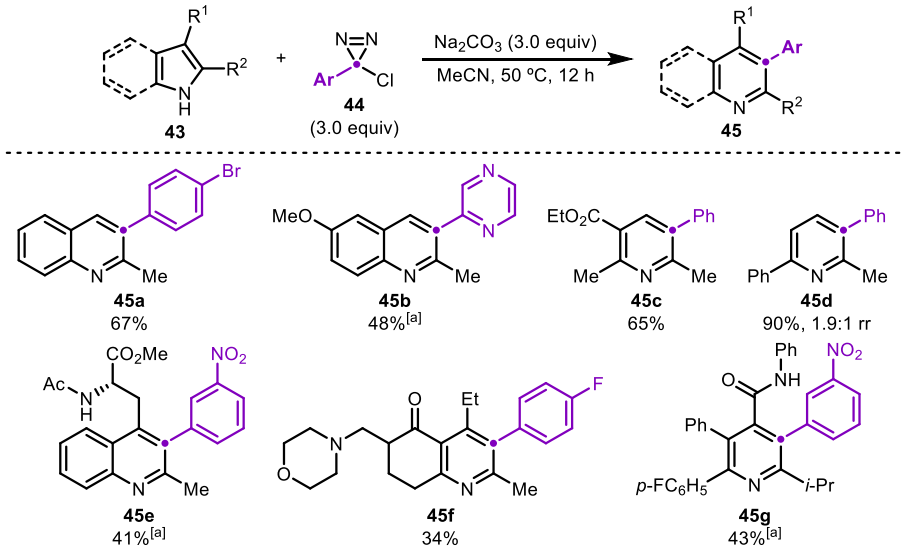
The cleavage of alkyl ethers typically requires harsh (Lewis) acidic conditions, however, Dong and co-workers developed a mild method for their cleavage allowing for the insertion of boron into the ring (Scheme 5.14).[86] Br_2BMes facilitates the cleavage of the ether **32**, which followed by a nickel-catalysed reductive cross coupling afforded **34** (Scheme 5.14A). The chemistry was tolerant of various functional groups, such as an aryl boronate as shown, along with different size rings. The products (**34**) could also be further manipulated, such as a one-carbon homologation/oxidation sequence followed by a Mitsunobu reaction to afford the ring-expanded product **37** (Scheme 5.14B). Similarly utilising $PhBBr_2$ for the boron insertion, followed by methanolysis intermediate **39** could be accessed. Subsequent homologation with $LiCHCl_2$ followed by intramolecular chloride displacement affords **40** which is amenable to further derivatisation (Scheme 5.14C).

Finally, by using $LiCHCl_2$ as the homologating reagent a double insertion could occur to also transfer the group on the boron reagent into the ring-expanded product **42**, allowing for a series of flavins to be synthesised (Scheme 5.14D).



Scheme 5.14: *A) The insertion of boron into benzofuran **32**. B–D) Manipulation of the boron-inserted product to form the ring-expanded products **37**, **40** and **42**.*

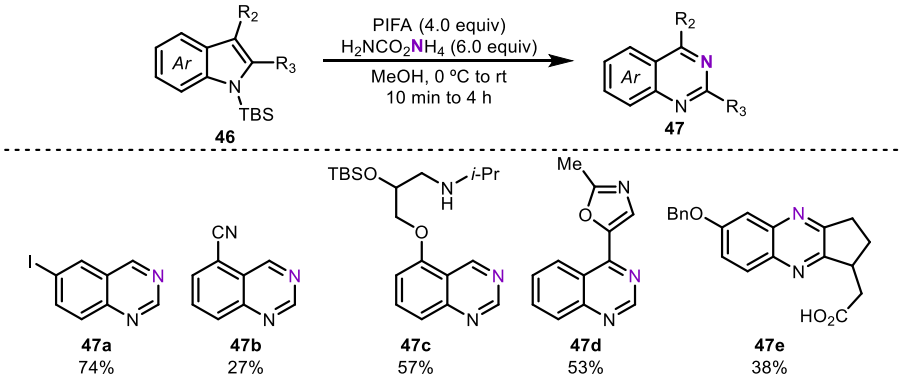
Classically the majority of ring expansions leverage a carbonyl, however, there are some exceptions, such as the Ciamician-Dennstedt rearrangement which utilises a haloform to achieve a one-carbon insertion into pyrroles.[87] Recently Levin reported the use of diazirines **44** as a substitute for haloforms. These diazirines **44** have the benefit of being able to transfer an aryl group whilst avoiding problematic Reimer-Tiemann formylation side-reactions (Scheme 5.15).[88,89]



Scheme 5.15: *Carbon insertion into pyrroles and indoles (**43**). [a]**44** (5.0 equiv).*

Under the developed reaction conditions a variety of 3-arylpyridines and 3-arylquinolines could be accessed from **43**, tolerating aryl bromides (**45a**) and pyrazines (**45b**). Several complex structures were also amenable to the atom insertion process, such as a tryptophan derivative (**45e**), Moban (**45f**) and a Lipitor derivative (**45g**). More recently Levin and co-workers have described the use of diazirines **44** to achieve carbon atom insertion into pyrroles forming pyrimidines.[90]

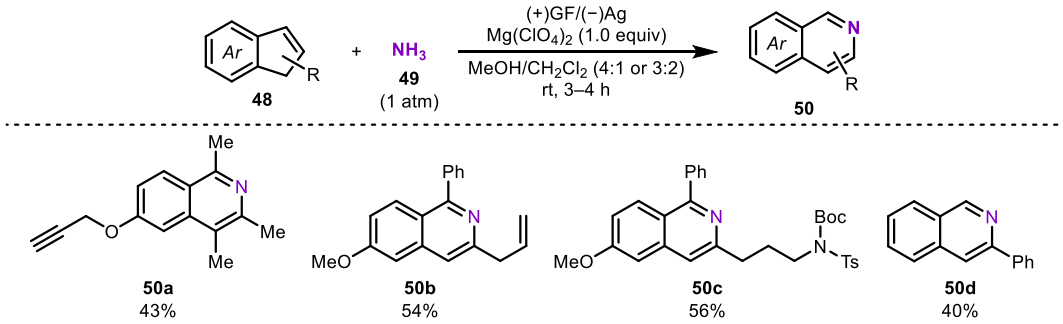
Morandi and co-workers have reported an analogous atom insertion for indoles enabling the insertion of a nitrogen atom affording quinazolines **47** (Scheme 5.16).[91] Ammonium carbamate was used as the nitrogen source, which in conjunction with PIFA forms an electrophilic iodonitrene *in situ*. The iodonitrene reacts with **46**, forming an aziridine that then eliminates iodobenzene/aromatises to form **47**; the use of TBS-indoles was required to avoid interactions between the iodonitrene and the indole nitrogen whilst also stabilising cationic intermediates.[92] The reaction conditions were mild which allowed aryl iodides (**47a**), nitriles (**47b**) and secondary amines (**47c**) among various other functional groups to be tolerated in moderate to good yields. This chemistry could also be used for the late-stage functionalisation of bioactive compounds such as Pindolol (**47d**) and Pimprinine (**47e**). Interestingly applying the chemistry to an advanced intermediate of APD334, which contains a fused cyclopentane ring, rearrangement instead forms a quinoxaline **47e**.



Scheme 5.16: *Nitrogen insertion into N-TBS protected indoles **46**.*

Cheng *et al* reported the insertion of nitrogen into indenes **48** affording a variety of isoquinolines **50** (Scheme 5.17).[93] The method developed was very economical, using NH_3 as the nitrogen source with H_2 being the only by-product. The use of electrochemistry allowed for the tolerance of functional groups such as alkynes (**50a**) and alkenes (**50b**) which may not be tolerated under classical oxidative cleavage methods. A protected amine (**50c**) worked well under the reaction conditions. It is believed that the reaction

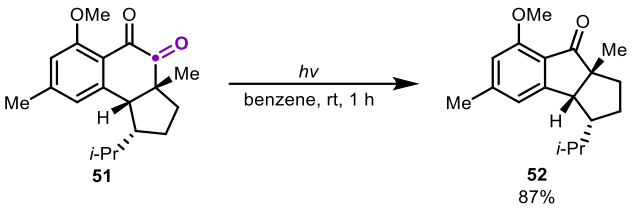
proceeds through an aziridine intermediate which undergoes a rearrangement to form the desired product **50**.



Scheme 5.17: *Nitrogen insertion into indenes to form **50**.*

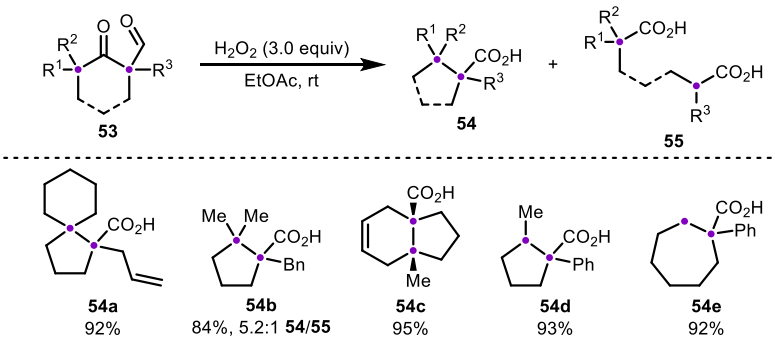
5.3 Atom Deletions

The deletion of a carbonyl carbon has been shown on the diketone **51** which was an intermediate in the total synthesis of hemigeran B (Scheme 5.18).[94] When Nicolaou and coworkers synthesised **51** they found that the product was not stable and rapidly underwent photomediated decarbonylation forming **52**. They proposed that the atom deletion occurs through a Norrish type-I fragmentation.



Scheme 5.18: *Photomediated decarbonylation of **51**.*

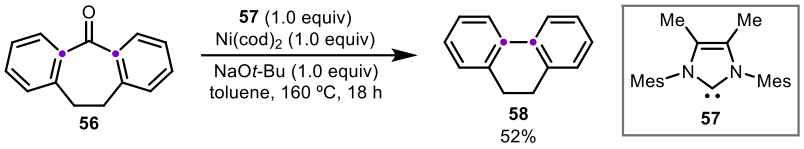
The carbon atom deletion of tetrasubstituted ketones has been described by Garcia-Garibay, however the reaction is limited to crystalline ketones due to it being performed in the solid state.[95–97] Xie *et al* sought to address this by using α-formyl cyclic ketones **53** which undergo deformylation under oxidative conditions to form the atom deleted product **54** (Scheme 5.19).[98]



Scheme 5.19: *Oxidative decarbonylation of α-formyl cyclic ketones **55***

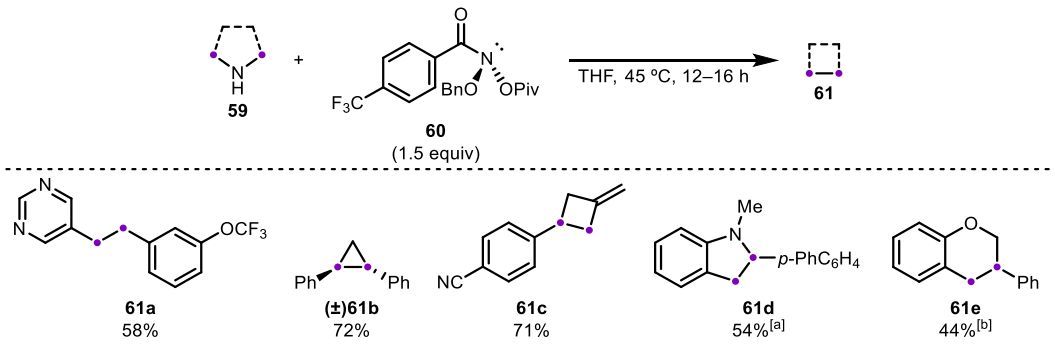
Under the developed conditions a variety of substituted ketones **54** underwent oxidative decarbonylation to form products such as spirocycles (**54a**) and fused ring systems (**54c**). Likewise, both tri- and di-substituted ketones (**54d** and **54e**) were tolerated.

As shown above, the decarbonylation of cyclic ketones is a challenging process due to having to cleave two C-C bonds, often requiring bespoke substrates. Ito reported a general rhodium-catalysed decarbonylation of simple cyclic ketones.[99,100] Whilst the process worked well on strained cyclic ketones stoichiometric rhodium was required on larger ring systems. Further development of rhodium-catalysed decarbonylations have been made, however, they are typically limited to acyclic ketones.[101,102] More recently ketones have also been shown to undergo decarbonylation *via* nickel-catalysis (Scheme 5.20).[103] This reaction is extremely challenging with stoichiometric nickel being required, however, nickel is significantly cheaper than rhodium making it still a viable process. A singular example was shown with a cyclic ketone **56** undergoing decarbonylation to form **57**.



Scheme 5.20: *Nickel-catalysed decarbonylation of **56**.*

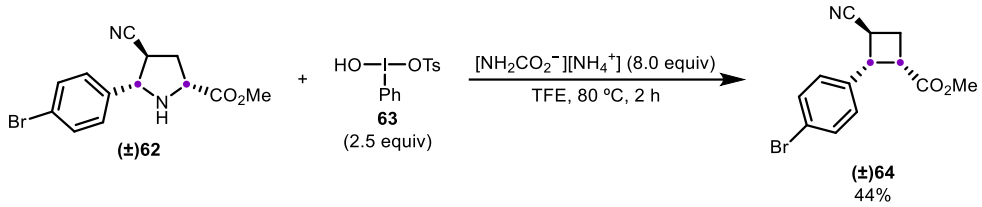
Levin *et al* reported the deletion of nitrogen from azacycles **59** through the use of the "anomeric amide" reagent **60** (Scheme 5.21).[104] The developed reaction conditions are simple and mild, as well as applicable to a variety of substrates to form cyclopropanes (**61b**), cyclobutanes (**61c**) along with heterocycles (**61a** and **61d**). Notably, **61c** is of interest as hydroamination of the alkene provides an intermediate of a H_3 receptor modulator.[105] One limitation of this chemistry is that the amine (**59**) must be activated, typically requiring at least one benzylic substituent. This chemistry is desirable as it provides alternative retrosynthetic logic as it turns accessible C-N bonds into surrogates for the formation of C-C bonds.



Scheme 5.21: *Nitrogen-atom deletion from cyclic secondary amines **59**. [a]Et_3N (1.0 equiv) added. [b]**60** (2.0 equiv).*

Similarly, Lu has also reported the deletion of nitrogen from azacycles. A large scope was demonstrated, with functional groups such as methoxy phenyls being tolerated, which were not seen under Levin's system, as well as nitrogen atom deletion from macrocycles.[106] However in their process they utilise $N_3SO_2N_3$, which despite the authors having described as safe in solution, it has been labelled as "exceedingly explosive" in previous reports.[107]

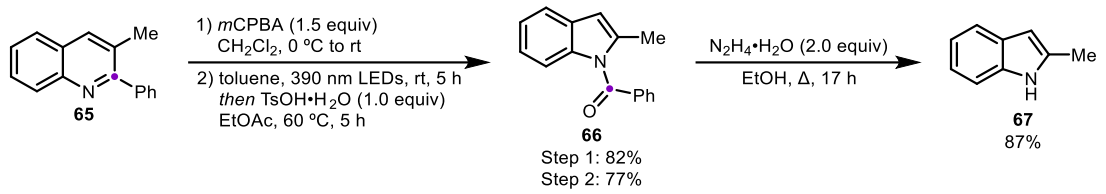
The stereoselective deletion of nitrogen from pyrrolidines (**62**) to form cyclobutanes (**64**) has been reported by Antonchick (Scheme 5.22).[92] Unlike previous reports of nitrogen atom deletion, they employed a similar system as Morandi (see Scheme 5.16) where an iodonitrene is formed from ammonium carbamate using the hypervalent iodine species **63**. In this case nitrene transfer occurs, reacting with the amine, and the subsequent diazene extrudes nitrogen followed by radical recombination.



Scheme 5.22: *Stereoselective nitrogen-atom deletion to form cyclubutanes **64**.*

Whilst the deletion of nitrogen from azacycles has been extensively reported in the last few years there is still no solution for the deletion of oxygen from oxacycles. The current state-of-the-art is the nickel-catalysed deoxygenation of acyclic diaryl ethers reported by Shi.[108]

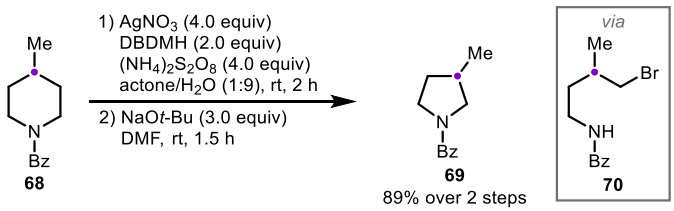
The reaction of quinoline-*N*-oxides under photochemical conditions is historically well documented. When employing a high energy mercury lamp a wide range of products, including **66**, were formed. Levin *et al* sought to take advantage of this reactivity with optimisation achieving the selective formation of **66** through strict control of the wavelength of light used (Scheme 5.23).[109] Under these conditions a wide range of quinoline-*N*-oxides were shown to undergo the ring contraction. The authors also demonstrated that starting with a quinoline **65** you could perform an oxidation followed by the rearrangement to obtain the acylated indole **66**, which could then be cleaved to form **67**, effectively achieving a carbon-deletion over three steps. This also highlights that often the context matters on whether the process is a ring contraction or an atom deletion; if only the first two steps were considered it would be a ring contraction, however together it would be considered an atom deletion process.



Scheme 5.23: *Carbon-atom deletion of* ***65*** *via* ***66****.*

Future work to allow for the atom deletion on other aromatic nitrogen heterocycles, such as pyridines, in a practical manner would be of great interest. Currently nitrogen atom deletion of pyridines can only be achieved using complex organometallic reagents.[110]

Sarpong *et al* reported the ring-opening of azacycles *via* silver-catalysis (Scheme 5.24).[111] Taking a piperidine derivative **68** and subjecting it to the developed conditions results in the ring-opened 1,5-amino acid, which then undergoes a Hunsdiecker reaction *in situ* utilising 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) forming **70**.[112] Finally, a base-mediated cyclisation of **70** affords the carbon-atom deleted product **69** in an 89% yield over two steps. Whilst it is possible to do the reaction as a one-pot procedure, lower yields were obtained.

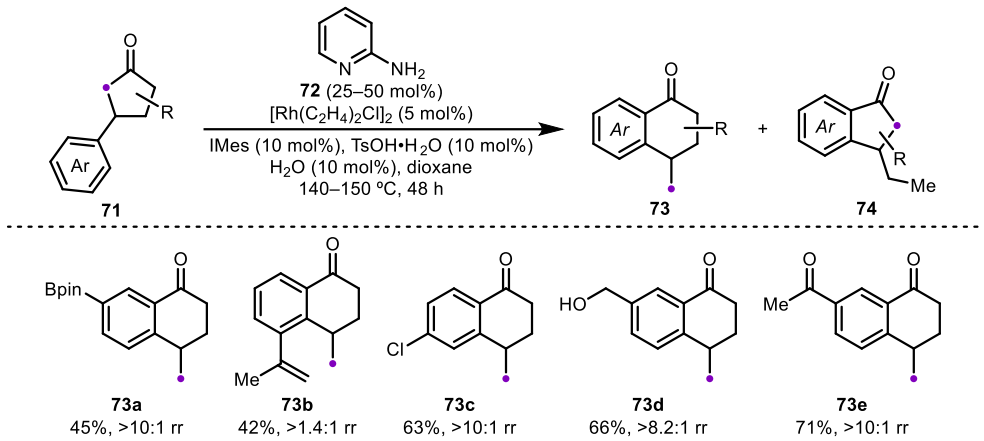


Scheme 5.24: *Carbon-atom deletion from azacycles such as* ***68****.*

5.4 Ring Expansions

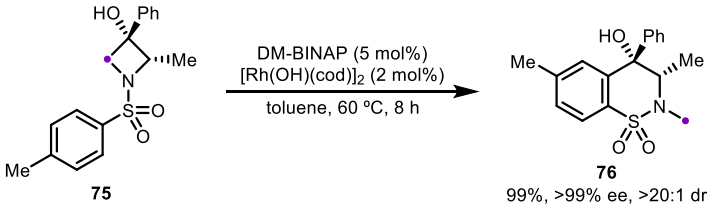
Ring expansions involving carbonyls have been well described such as the Dowd-Beckwith rearrangement and semipinacol rearrangements, however whether it is classed as a ring expansion, or an atom insertion depends on the starting point.[70,113,114] In the case of the Dowd-Beckwith rearrangement if you start with the β-ketoester then it may be considered an atom insertion, however, if you start from the α-halomethylated intermediate then it would be considered a ring expansion.

Dong showed that by employing a pyridine directing group (**72**), the imine formed from **71** facilitates C-C bond cleavage under Rhodium catalysis (Scheme 5.25).[115] The intermediate alkylrhodium then species undergoes a migration/cyclisation/reductive elimination sequence to form the rearranged product **73**. This chemistry is tolerant of a variety of functional group such as aryl boronates (**73a**), alkenes (**73b**), aryl chlorides (**73c**), alcohols (**73d**), and acyclic ketones (**73e**), typically forming the products in good yields and regioselectivity.



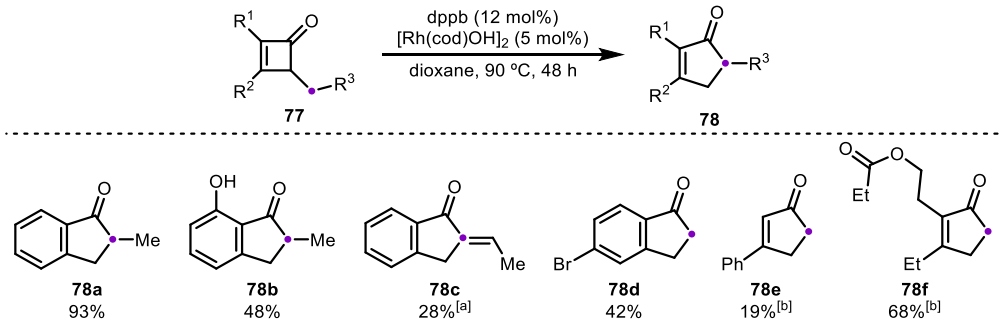
Scheme 5.25: *Rhodium-catalysed rearrangement/ring expansion of **71**.*

The insertion of rhodium into strained ring systems is a well understood process that can occur through various pathways. Murakami and co-workers exploited the ring-opening of cyclobutanols (**75**) followed by a 1,5-rhodium migration/cyclisation to afford the ring expanded products (**76**) (Scheme 5.26).[116] When employing a chiral ligand the reaction could be rendered enantioselective, however, the reaction was also stereoselective when using enantioenriched starting materials.



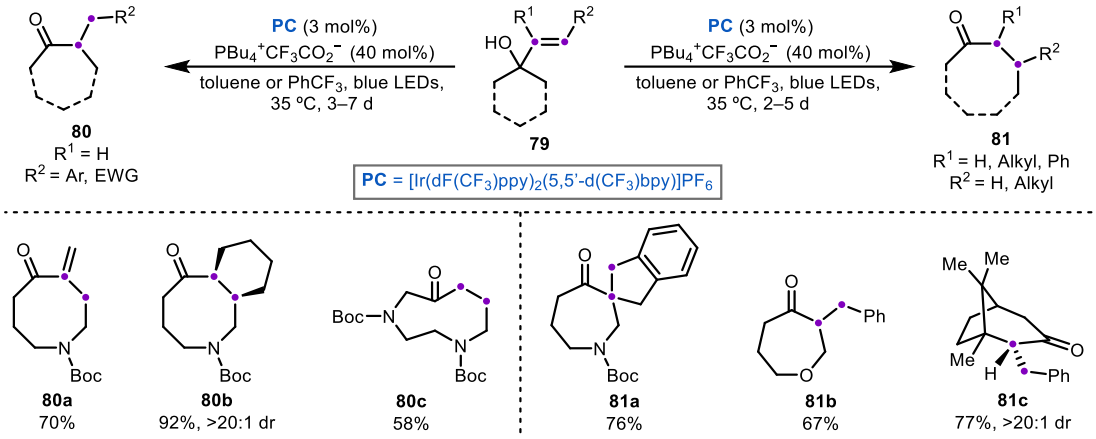
Scheme 5.26: *Stereoselective ring expansion of **75** to **76**.*

Dong *et al* developed a ring expansion of cyclobutenones **77** using rhodium-catalysis (Scheme 5.27).[117] The strained ring allows for insertion of rhodium, forming a 5-membered rhodacycle which then undergoes a β-hydride elimination/migratory insertion to form the less strained 6-membered rhodacycle. Finally reductive elimination affords the product **78**. Under these conditions a variety of benzocyclobutenones (**78a**–**78d**) were tolerated along with cyclobutenones (**78e** and **78f**).



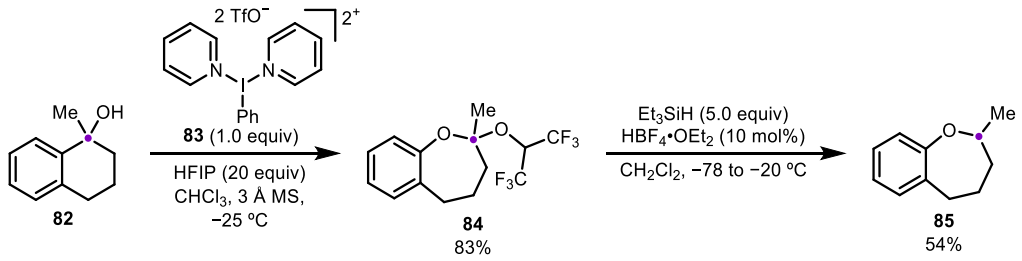
Scheme 5.27: *Rhodium-catalysed ring expansion of cyclobutenones **77**. [a]150 °C for 48 h. [b]PhEt as the solvent at 110 °C for 48 h*

Knowles and co-workers reported that cyclic alcohols could be ring-opened *via* proton-coupled electron transfer (PCET) to form acyclic ketones and aldehydes.[118–120] This was further expanded to vinyl alcohols **79**, which under PCET activation with a photocatalyst (PC) rearrange to afford the ring expanded products **80** or **81**, depending on the identity of R^2 (Scheme 5.28).[121] When R^2 is an aryl group, or an electron-withdrawing group, **79** rearranges to afford the one-carbon ring expanded product **80**. On the other hand, when R^2 is deactivated, being either a hydrogen or an alkyl group, **79** rearranges to form the two-carbon ring expansion product **81**. This chemistry is quite powerful as it allowed the synthesis of a variety of medium-sized (hetero)cycles including the formation of fused ring systems (**80b**), bridged ring systems (**81c**), and spirocycles (**81a**). Using an allene allows an α,β-unsaturated ketone (**80a**) to be accessed.



Scheme 5.28: *The regiodivergent ring expansion of* ***79****.*

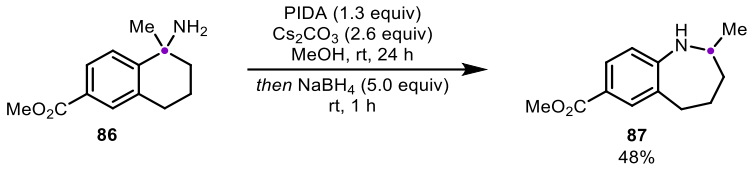
Wengryniuk reported the oxidative rearrangement of benzylic tertiary alcohols using the hypervalent iodine reagent **83** (Scheme 5.29).[122] Under the developed conditions a variety of alcohols underwent a ring expansion to form various medium-sized cyclic acetals (**84**). Of note is that after the ring expansion, **84** could be subjected to reductive conditions to afford the ring expanded cyclic ether **85**.



Scheme 5.29: *Ring expansion/reduction of* ***82*** *to the oxacycle* ***85****.*

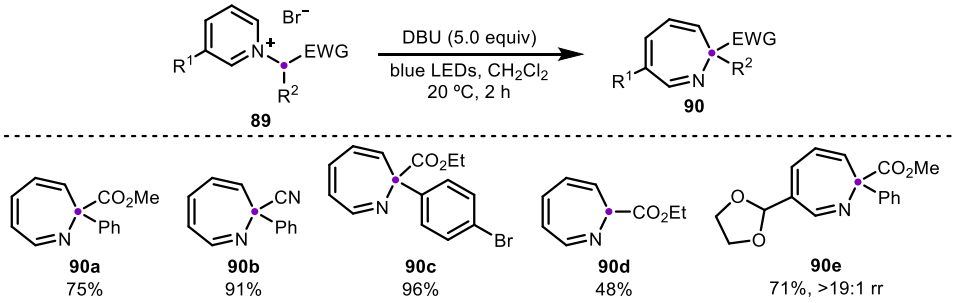
The nitrogen equivalent was later reported by Murai using a one-pot procedure allowing for cyclic amines (**86**) to be formed from tertiary benzylic amines (**87**) (Scheme 5.30).[123]

Similar ring expansions have also been achieved using spirocyclic aminals, with NBS as the oxidant, to afford cyclic amidines.[124]



Scheme 5.30: *Ring expansion/reduction of* ***86*** *to the azacycle* ***87****.*

The insertion of diazo compounds into arenes, such as the Buchner reaction, has seen use in the synthesis of both drugs and natural products.[67,125–127] More recently, Beeler and co-workers have developed a visible-light-mediated aza-Buchner reaction (Scheme 5.31).[128] Whilst initial attempts focussed on reacting pyridine directly with a diazo species, only poor yields were obtained, along with a large excess of pyridine being required. However, they found that deprotonation of the preformed pyridinium **89** afforded the desired products **90** in good yields. Other improvements included performing the reaction in flow, as it was hypothesised that this would improve photon flux and minimise aerobic oxidative to a ketoester which was the major observable side-product. Under the optimised conditions a variety of pyridinium salts were tolerated affording the azepine products **90** in good yields and regioselectivity. Whilst 3-substituted pyridiniums (**90e**) were tolerated, the regioselectivity was often poor. The reaction was also amenable to polycyclic salts.

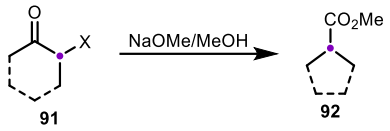


Scheme 5.31: *Visible-light-mediated aza-Buchner reaction of pyridiniums* ***89****.*

5.5 Ring Contractions

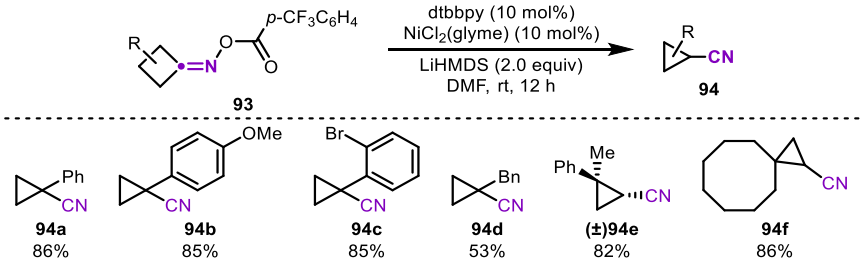
One of the most notable ring contractions of carbocycles is the Favorskii rearrangement, whereby a cyclic α-haloketone (**91**) reacts with base and subsequently rearranges forming a ring contracted ester (**92**) through a cyclopropyl intermediate (alternatively it can proceed through a quasi-Favorskii mechanism circumventing this step) (Scheme 5.32).[129,130] Due to its utility the Favorskii rearrangement has seen general use in numerous total syntheses along with enabling access to compounds such as cubane.[131–134] Other notable ring contractions include the pinacol rearrangement, a cationic equivalent of the quasi-Favorskii rearrangement, the Wolff rearrangement of α-diazo ketones, the benzilic

rearrangement of cyclic α-diketones, and various oxidative ring contractions (mediated by thallium, lead and hypervalent iodine species).[135–137]



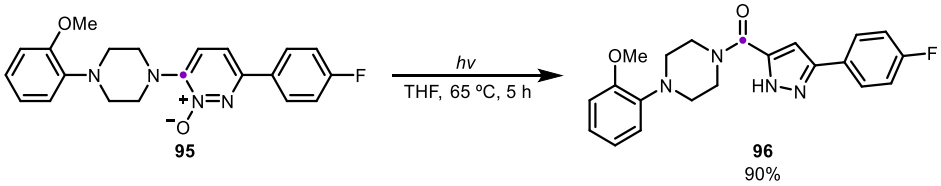
Scheme 5.32: *Favorskii rearrangement of* ***91*** *to* ***92****.*

Mei and co-workers reported a Favorskii-type rearrangement of cyclobutanimines **93** to form cyclopropanes **94** (Scheme 5.33).[138] Whilst a nickel catalyst was utilised control reactions showed that only a minor loss in yield was observed in the absence of the nickel catalyst. They proposed that the majority of **94** is formed through α-deprotonation of the imine, followed by a Favorskii-type rearrangement. Under the conditions shown arenes at the 2-position with various stereoelectronic properties were tolerated (**94a**–**94d**). Similarly, alkyl substituents at the 2- and 3-position were also tolerated to form **94e** as a single diastereomer, and the spirocycle **94f**.

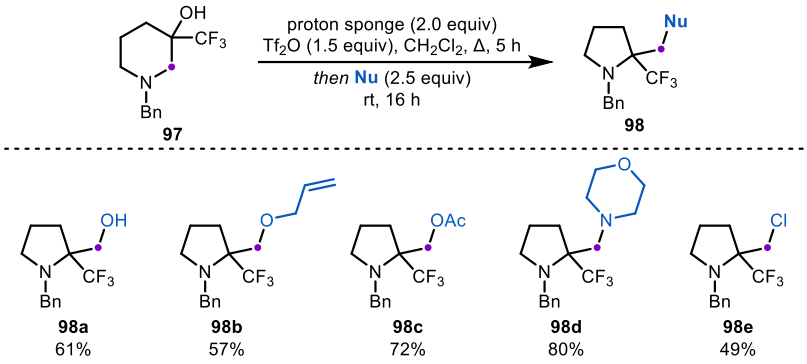


Scheme 5.33: *Favorksii-type rearrangement of* ***93****.*

Pyridazine *N*-oxides were shown to be susceptible to photoinduced rearrangements by Buchardt and co-workers, however, Frederich expanded upon this reactivity to allow for the general regioselective synthesis of pyrazoles (Scheme 5.34).[139–141] The authors described that the commercially available 3,6-dichloropyridazine could be oxidised to the *N*-oxide, which can undergo a regioselective Suzuki cross-coupling followed by an S_NAr reaction facilitating the modular synthesis of substrates such as **95**. Subjection of **95** to UV light promoted the ring contraction to pyrroles, such as the hNK_3 receptor antagonist **96** that was isolated on a multigram scale. The rearrangement reaction was generally very efficient and tolerated a broad range of heteroatoms and functional groups.

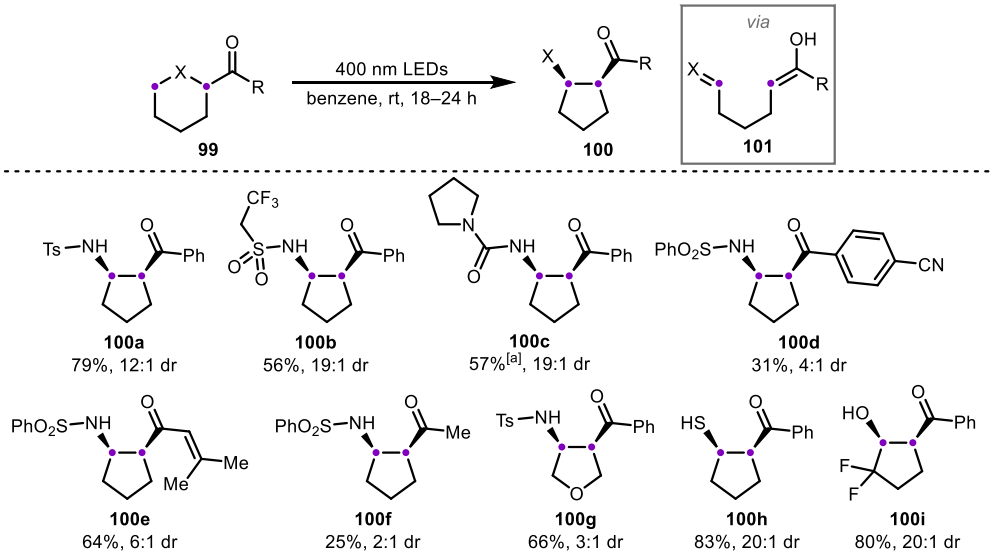


Scheme 5.34: *UV-mediated ring contraction of* ***95****.*



Scheme 5.35: *Nucleophilic addition/ring contraction of* ***97****.*

Based on Knight's report on the ring contraction of 3-oxygenated piperidines with BBr_3 Cossy *et al* reported the general ring contraction of piperidines **97** to pyrroles with a trifluoromethyl containing tertiary centre **98** (Scheme 5.35).[142,143] Tf_2O and proton sponge were used to activate the alcohol and form an aziridinium intermediate, which could then undergo ring opening when subjected to a variety of different nucleophiles, such as alcohols (**98a** and **98b**), carboxylates (**98c**), amines (**98d**) and halides (**98e**).



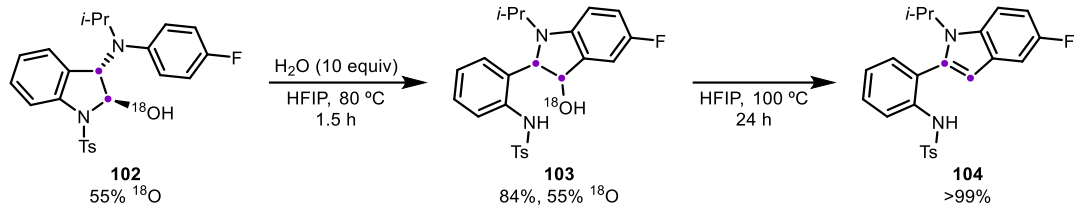
Scheme 5.36: *Ring contraction of 2-carbonyl heterocycles* ***99****. [a]Cyanoumbelliferone (30 mol%) added.*

Sarpong and co-workers described the general ring contraction of 2-carbonyl heterocycles **99** (Scheme 5.36).[144] It was found that simply subjecting the heterocycles **99** to the correct wavelength of light facilitates excitation of the carbonyl leading to a Norrish type II/fragmentation sequence forming **101**, which then undergoes a Mannich reaction to form the product **100**. The reaction was incredibly versatile with various piperidines (**100a**–**100f**) undergoing ring contraction as well as morpholines (**100g**), tetrahydrothiopyrans (**100h**)and tetrahydropyrans (**100i**). The chemistry was also applicable to various bioactive compounds, peptides, and sugars. Finally, it was also shown that addi-

tion of a chiral phosphoric acid rendered the Mannich reaction enantioselective with up to 90% ee being obtained in the ring-contracted products.

5.6 Transmutations

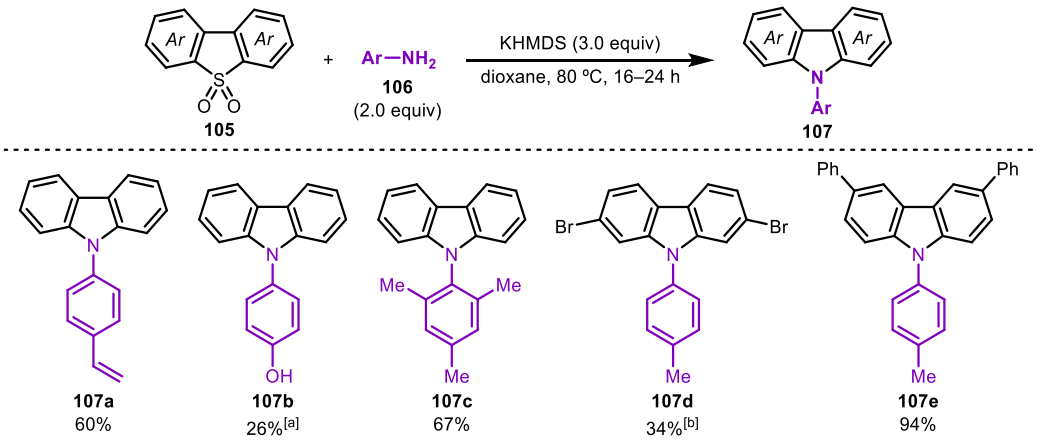
Finally, there are also transmutations of rings, an area less explored than the alternative classes of transformations. Transmutations consist of modifications of the ring, made through reactions such as isomerisations or atom exchanges, without affecting the ring size itself. Sawada described the rearrangement of **102** to the ring-switched product **104** (Scheme 5.37).[145] The authors showed that the reaction proceeds through the direct ring-switched product **103**, however, further heating promotes dehydration to form the indole **104**.



102 55% ^{18}O **103** 84%, 55% ^{18}O **104** >99%

Scheme 5.37: *Ring-switch of **102** to **104** via **103**.*

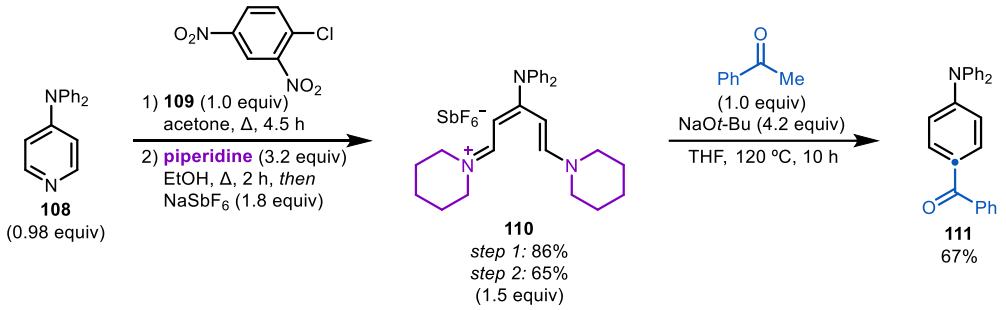
Yorimitsu *et al* reported that utilising sequential S_NAr reactions with anilines **106**, biaryl sulfones **105** could undergo a S-to-N atom exchange (or as they dubbed "an aromatic metamorphosis") (Scheme 5.38).[146] The reaction was simple and worked well for a variety of anilines (**107a–107c**) and sulfones (**107d** and **107e**). In the case of the aminoalcohol **107b**, a poor yield was obtained which may be due to competitive S_NAr reactions with the phenol. This group, along with others, have since expanded this manifold to various other nucleophiles such as arylphosphines, diarylmethanes, and benzylic nitriles to form a variety of S-to-X atom exchanged products.[147–149]



107a 60% **107b** 26%[a] **107c** 67% **107d** 34%[b] **107e** 94%

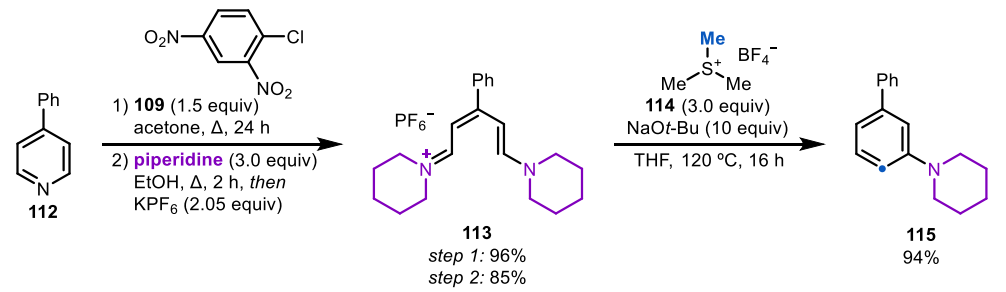
Scheme 5.38: *S-to-N atom exchange of **105** via sequential S_NAr reactions. [a]100 °C. [b]KHMDS (2.0 equiv).*

The transposition of the nitrogen atom in pyridines is possible through the Zincke reaction; formation of an activated Zincke salt (a pyridinium salt formed between a pyridine and **109**) followed by addition of a primary amine displaces the nitrogen, effectively forming a N-to-N atom exchanged product.[150,151] Kano and co-workers utilised the ANRORC (addition of the nucleophile, ring opening and ring closure) type mechanism of such Zincke salts to achieve a N-to-C atom exchange (Scheme 5.39).[152] By taking the pyridine **108**, forming the Zincke salt, and then reacting it with piperidine the intermediate **110** is formed; unlike the Zincke reaction cyclisation is not possible due to a secondary amine being used. Addition of a secondary nucleophile, in this case an enolate, allows for a [5+1] annulation with **110** to form the atom exchanged product **111**. A variety of acetophenones were accessed through this method, however, a relatively electron-rich pyridine is required to enable the S_NAr reaction of the pyridine with **109**.



Scheme 5.39: *N-to-C atom exhange of pyridines **108** via **110**.*

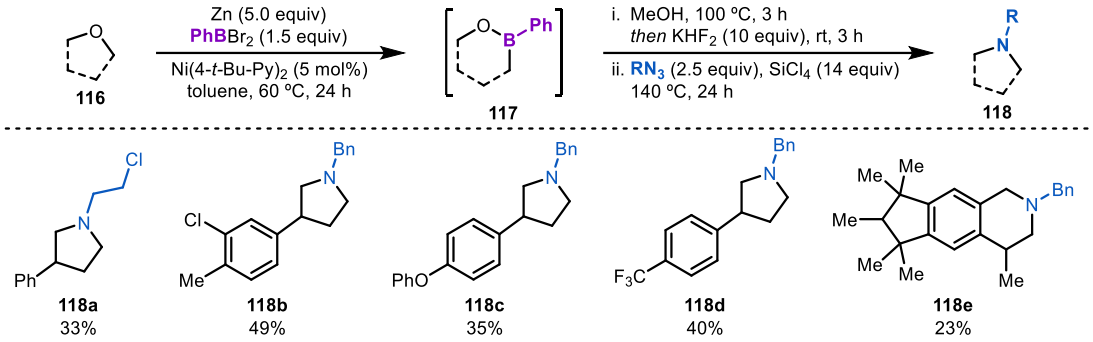
Kano further expanded this methodology by utilising sulfur ylids (formed from deprotonation of **114**) as a one-carbon unit to achieve the N-to-C atom exchange and form *m*-substituted anilines **115** (Scheme 5.40).[153] A variety of *p*-substituted pyridines and secondary amines were tolerated, including bioactive amines such as Fluoxetine. Attempts to use pyridines with electron withdrawing groups, or with *m*- or *o*-substitution, failed to form the pyridinium salt. Meanwhile primary amines failed to mediate ring opening of the Zincke salts.



Scheme 5.40: *N-to-C atom exhange of pyridines **112** via **113**.*

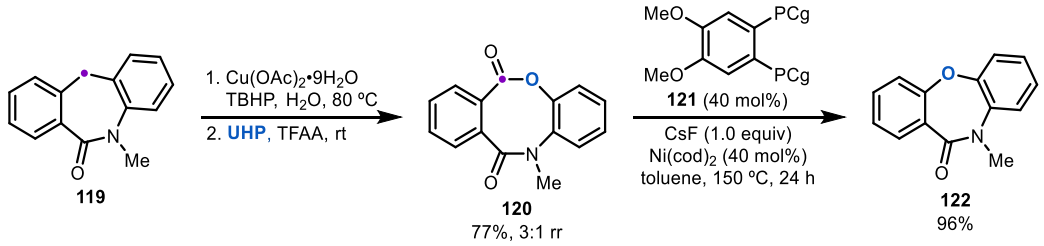
In Dong's report of the insertion of boron into oxacycles **116**, they showed that **117** could undergo further manipulation to achieve the O-to-N atom exchanged products **118**

(Scheme 5.41).[86] Conversion of **117** into the Molander salt followed by treatment with alkyl azides installs the amine moity, which after dehydration forms the azacycle **118**. This process was shown to tolerate primary alkyl chlorides (**118a**) along with a variety of substituted aromatics (**118b–118d**). This sequence was also applicable to galaxolide, a synthetic musk, to form the nitrogen analogue **118e**.



Scheme 5.41: *O-to-N atom exchange of oxacycles* ***116*** *affording azacycles* ***118****.*

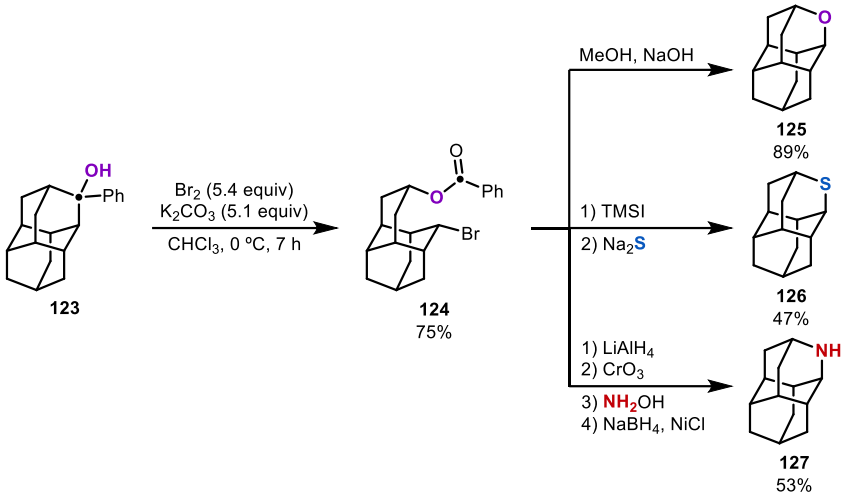
In 2016 Yamaguchi reported the synthesis of acyclic diaryl ethers through decarbonylation of esters however the scope was limited as non-heteroaryl substrates were not successful.[154] Li and co-workers realised that if they could optimise the decarbonylation of non-heteroaryl systems then they could ultimately take a substrate such as **119** and perform a C-to-O atom exchange (Scheme 5.42).[155] The key to getting the decarbonylation step to work was through use of a bulky electron-rich bisphosphine ligand (**121**) developed by the Stradiotto group which facilitated the challenging reductive elimination.[156] With the decarbonylation optimised, they highlighted its utility in the C-to-O atom exchange of substrates such as **119** in a multi-step process. By performing a benzylic oxidation and Baeyer-Villiger oxidation gave **120**, which after subjection to their decarbonylation conditions formed the C-to-O atom-exchanged product **122**.



Scheme 5.42: *C-to-O atom exhange of* ***119*** *via a nickel-catalysed decarbonylation.*

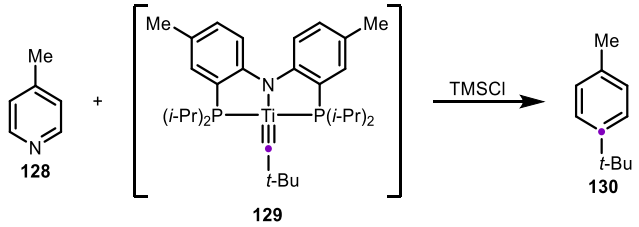
Schreiner *et al* utilised a molecular editing approach to synthesise heteroatom doped diamondoids (Scheme 5.43).[157] The easily accessible alcohol **123** undergoes an oxidative cleavage when subjected to Br_2 and K_2CO_3 to form **124** which can then be further manipulated to achieve various atom exchanged products. Menthanolysis of **124** followed by cyclisation affords the C-to-O atom exchanged product **125**. To form the C-to-S atom

exchanged product **126** the ester is first activated with TMSI to form the alkyl iodide, which upon treatment with Na_2S forms the desired product. Finally, the C-to-N atom exchange sequence begins with a reduction/oxidation of **124** forming a ketone, which after condensation with hydroxylamine gives an oxime. The oxime can then undergo a nickel-mediated reduction to reduce both the oxime and cleave the N-O bond to form an amine followed by an *in situ* cyclisations yielding the C-to-N atom exchanged product **127**.



Scheme 5.43: *A molecular editing approach to oxygen **125**, sulfur **126** and nitrogen **127** doped dimaondoids.*

The N-to-C atom exchange of pyridine **128** to **130** has been described by Mindiola (Scheme 5.44).[158] A complex organotitanium reagent **129** facilitates this transformation, which was shown to act as a catalyst with the overall cycle giving 18% yield with respect to titanium. Whilst this chemistry is not practical in its current state, it provides precedence for the development of new chemistry that could achieve similar transformations.

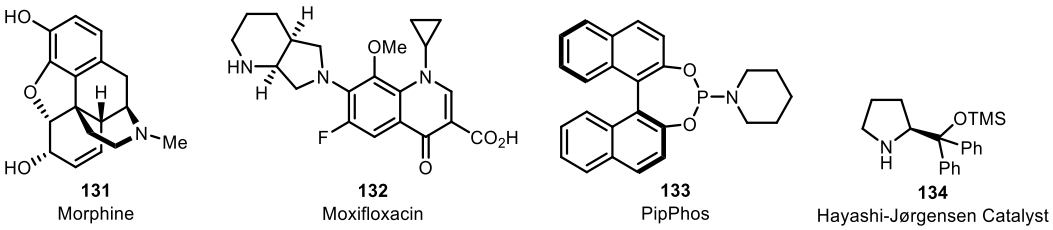


Scheme 5.44: *N-to-C atom exhange of pyridines (**128**) using **129**.*

5.7 Synthesis of Piperidines and Pyrrolidines

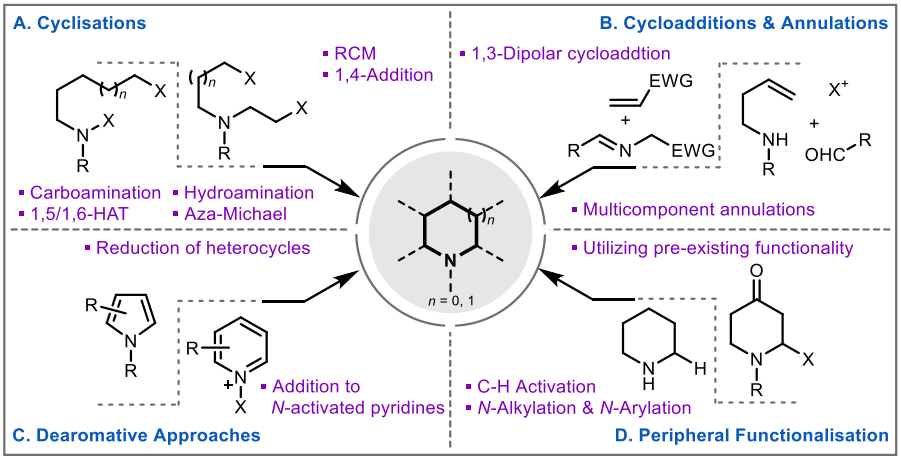
Piperidines and pyrrolidines, among other various saturated heterocycles, represent a privileged motif that is found in a variety of settings from natural products (**131**), to medicines (**132**), ligands (**133**), organocatalysts (**134**) and chiral auxiliaries (Scheme 5.45).[159–163] It is reported that piperidines and pyrrolidines both place within the top ten rings featured in FDA approved medicines.[162,164] The prevalence of these rings in a medicinal setting may be down to a number of reasons: from their potential bioactive

properties, to the addition of sp^3 character to drugs which can effect properties such as potency and solubility.[165–167]



Scheme 5.45: *Examples of notable compounds which contain a piperidine and/or a pyrrolidine.*

Due to the prevalence and importance of these scaffolds vast efforts have been made to develop new synthetic routes to access a variety of substituted cores, which can be utilised as fragments in drug discovery, or as building blocks for further derivatisation.[168–172] A variety of methods for the synthesis of piperidines and pyrrolidines is outlined in Scheme 5.46. The synthesis of these scaffolds can be broken down into four general categories: cyclisations, cycloadditions & annulations, dearomative approaches, and peripheral functionalisation.



Scheme 5.46: *A general overview of some of the possible synthetic routes to piperidines and pyrrolidines.*

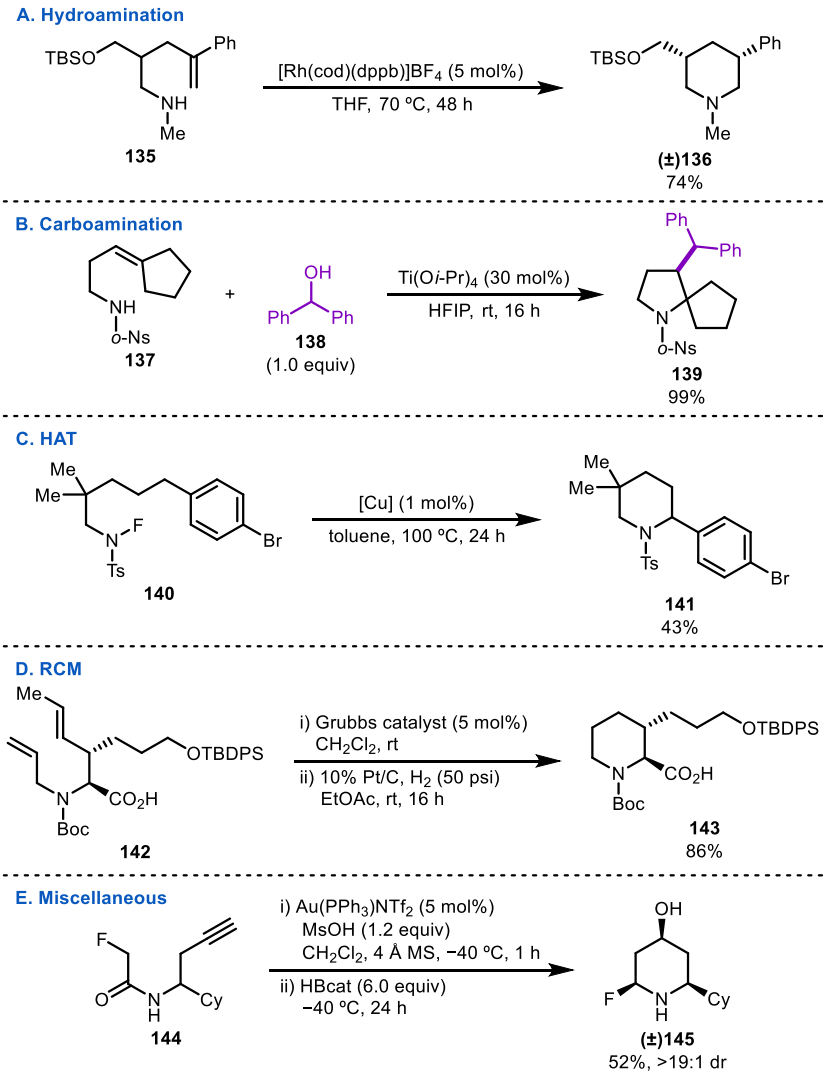
5.7.1 Cyclisations

Select examples for the syntheses of piperidines and pyrrolidines *via* cyclisations are shown in Scheme 5.47. One of the most prominent strategies for the formation of these saturated heterocycles is forming a C-N bond through cyclisation (Scheme 5.47A–C).[173] Whilst nucleophilic displacement of an electrophile by the nitrogen is possible, these substrates can often be difficult to access driving the need for alternative methods.

Buchwald described the rhodium-catalysed *anti*-Markovnikov hydroamination of alkenes (**135**) to form 3-arylpiperidines (**136**) (Scheme 5.47A).[174] Donohoe described 5- and 6-

endo-trig cyclisations to form an array of pyrrolidines (**139**) and piperidines; the use of both a Lewis acid and HFIP stabilises carbocations, allowing for activation of electrophilic alcohols (**138**) (Scheme 5.47B).[175] C-H amination methods are also of great interest, due to the avoidance of prefunctionalisation. Muniz described the copper-catalysed formation of both piperidines (**141**) and pyrrolidines utilising *N*-fluorosulfonamides (**140**) (Scheme 5.47C).[176] More recent advances utilise a dual C-H amination procedure to obtain enantioenriched pyrrolidines under rhodium-catalysis.[177]

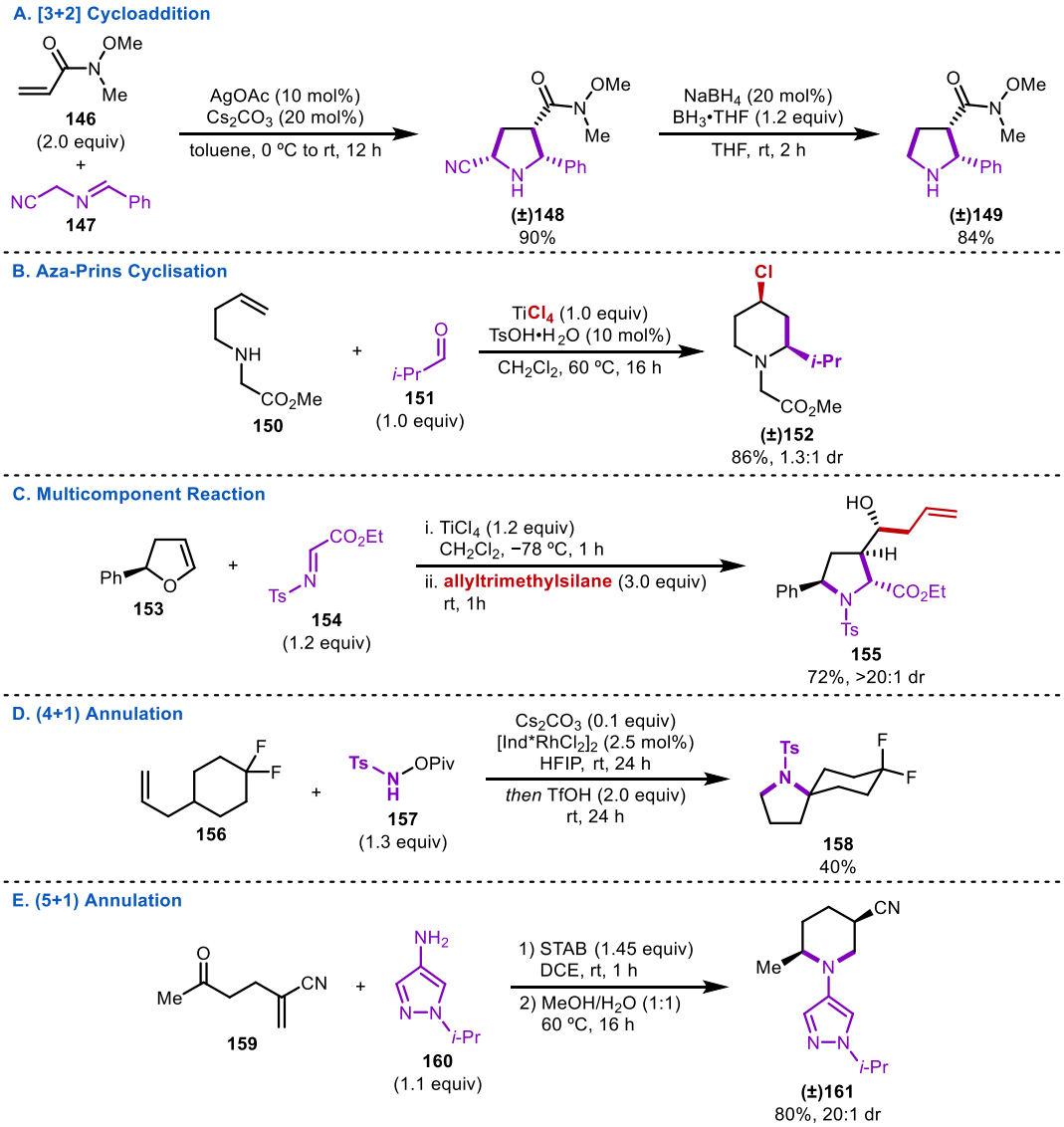
Cyclisation methods proceeding through C-C bond formation are also prevalent, such as RCM to afford pyrrolines and tetrahydropiperidines (**143**) whereby the alkene can be further functionalised or reduced (Scheme 5.47D).[178,179] More complex cyclisations are also possible, such as Zhang's gold-catalysed cyclisation of substrates, such as **144**, to form trisubstituted piperidines (**145**) with good diastereoselectivity (Scheme 5.47E).[180]



Scheme 5.47: *Methods for the synthesis of piperidines and pyrrolidines via intramolecular cyclisation.*

5.7.2 Cycloadditions & Annulations

Select examples for the synthesis of piperidines and pyrrolidines *via* cycloadditions & annulations are shown in Scheme 5.48. The use of [3+2] cycloadditions for the formation of pyrrolidines is an incredibly popular approach, such as the cycloaddition between azomethines (**147**) and alkenes (**146**).[181,182] The requirement of an electron-withdrawing group on the azomethine to stabilise the ylide typically means only 2,5-disubstituted pyrrolidines can be formed, such as **148**. Zhang reported the use of a nitriles as a transient stabilising group that once removed under reductive conditions afforded 2,3-disubstitued pyrrolidines (**149**) (Scheme 5.48A).[183] On the other hand, [4+2] aza-Diels-Alder reactions for the formation of piperidine derivatives are less common.[184,185]

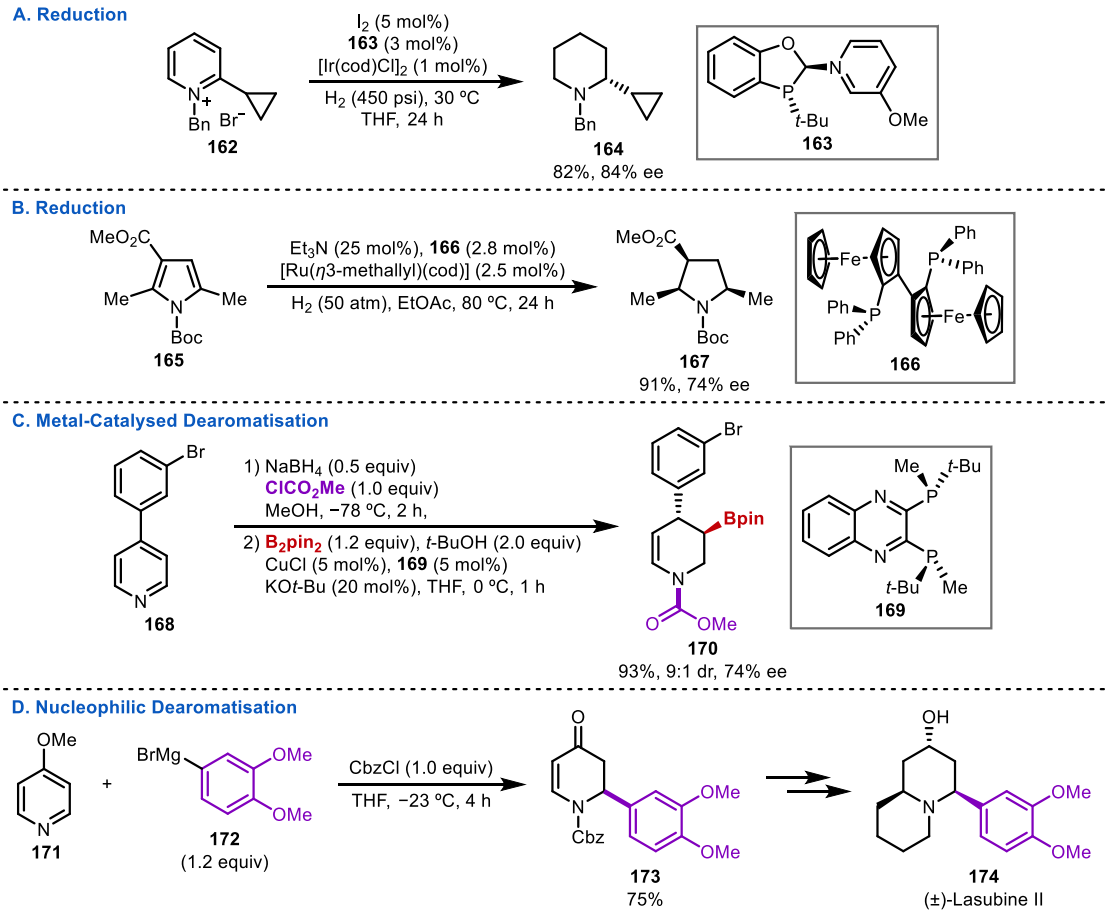


Scheme 5.48: *Methods for the synthesis of piperidines and pyrrolidines via cycloadditions & intermolecular annulations.*

Annulation approaches provide possibilities for the synthesis of these heterocycles, be it through utilising carbonyls, or employing elaborate catalysis methodology.[181] Weghe reported the use of an aza-Prins cyclisation between readily accessible starting materials forming piperidines containing an alkyl chloride (**152**) (Scheme 5.48B).[186] The synthesis of enantioenriched substituted pyrroles (**155**) through a multi-component reaction was reported by Fanwick (Scheme 5.48C).[187] The nitrene precursor **157** allowed for [4+1] annulations under rhodium-catalysis to form a variety of pyrroles (**158**) from simple alkene starting materials (**156**) (Scheme 5.48D).[188] Sather *et al* described a simple diastereoselective [5+1] annulation through a reductive amination/aza-Michael sequence forming *N*-(hetero)aryl piperidines (**161**) (Scheme 5.48E).[189]

5.7.3 Dearomative Approaches

Select examples for the synthesis of piperidines and pyrrolidines *via* dearomatisation are shown in Scheme 5.49. This approach is popular as the activation of pyridines allows for facile reductions or addition of various nucleophiles.[190] Additionally, multifunctionalised pyridines are easily accessed which in turn can afford multifunctionalised piperidines which are typically challenging to synthesise.

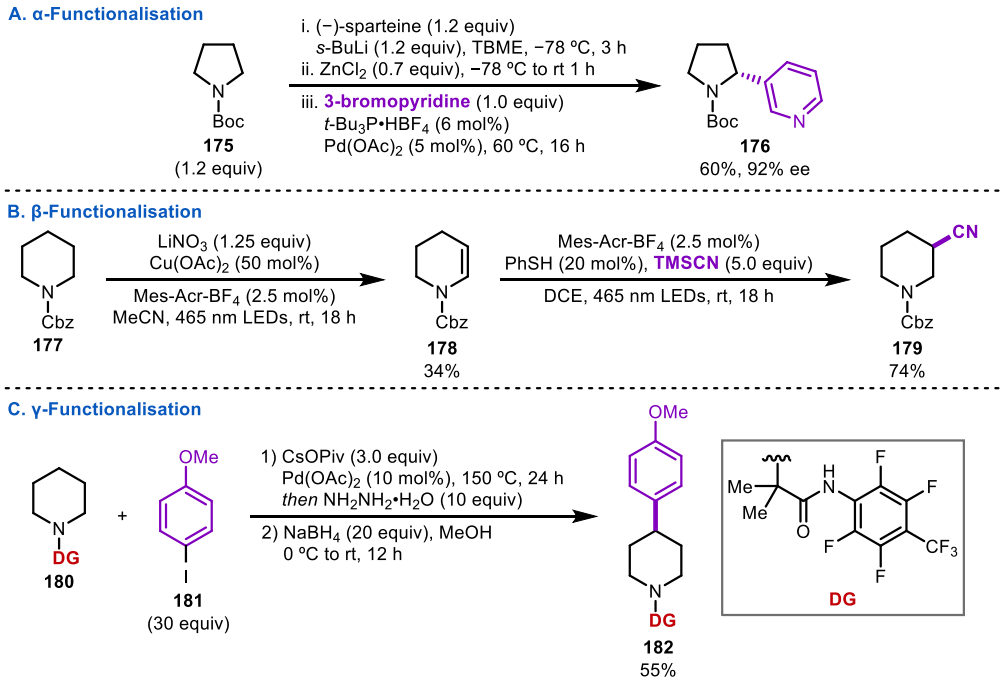


Scheme 5.49: *Methods for the synthesis of piperidines and pyrrolidines via dearomatisation approaches.*

The reduction of (activated) pyridines, and less commonly pyrrolidines, allows rapid access to their respective saturated heterocycles, often asymmetrically when employing a chiral ligand (Scheme 5.49A–B).[191–193] Ito and co-workers described the enantioselective copper-catalysed borylation of pyridiniums to afford functionally rich tetrahydropyridines (**170**) which could be further derivatised by methods such as carbamate hydrolysis, cross-coupling or oxidation of the boronate, and reduction of the alkene to form a piperidine (Scheme 5.49C).[194] Organometallics can also add into activated pyridines, such as the addition of **172** into a pyridinium; the resulting product **173** is synthetically useful as it can undergo enolate alkylations, 1,2- and 1,4-additions among other reactions, providing access to complex piperidines, such as Lasbubine II (**174**) (Scheme 5.49D).[195]

5.7.4 Peripheral Functionalisation

Finally pre-existing piperidines and pyrrolidines can be further functionalised, either through exploiting built in synthetic handles, or through C-H activation methods. Examples of typical synthetic handles that can be utilised are carbonyls or alkenes, however it is also possible to have access to alkyl halides (**152**) or alkyl boronates (**170**) which can enable diversification *via* cross-coupling reactions. The only limitation with this approach is that the desired starting scaffold may not be commercially available.



Scheme 5.50: *Methods for the synthesis of piperidines and pyrrolidines via C-H functionalisation.*

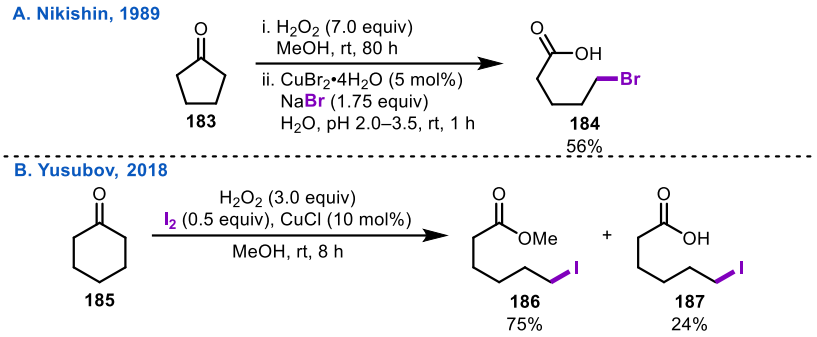
C-H functionalisation is an attractive option as it offers improved atom economy and rapid diversification of simple, accessible starting materials; owing to these benefits a wealth of chemistry has been reported on the C-H functionalisation of pyrrolidines and piperidines,

often guided by a directing group.[196,197] Select examples for the C-H functionalisation of piperidines and pyrrolidines are shown in Scheme 5.50.

α-Functionalisation is by far the most reported, as adjacency to the nitrogen provides benefits such as charge stabilisation as well being more readily targeted by directing groups installed on the nitrogen. Campos and co-workers reported the enantioselective α-arylation of pyrrolidines (**175**) *via* a directed enantioselective deprotonation, followed by a Negishi cross-coupling (Scheme 5.50A).[198] More recent reports by Seidel showed that deprotonation of the amine in pyrrolidines and piperidines can react with a hydride acceptor be oxidise to an imine. This imine can then be exploited, such as the addition of alkyl, alkenyl, alkynyl and aryl nucleophiles (albeit in a racemic fashion).[199,200] Nicewicz reported a methodology for the β-functionalisation of piperidines (**177**) with nucleophiles through a two-step process (Scheme 5.50B).[201] First photocatalytic oxidation forms the enamine (**178**), which then can react under another photocatalytic step to install a nucleophile, such as a cyanide to yield β-cyanopiperidines (**179**). Similar approaches have been taken using ruthenium-catalysis to allow for the β-alkylation of piperidines and pyrrolidines using aldehydes.[202] Currently, general methods for the β-functionalisation often employ a directing group at the α-position.[196] γ-Functionalisation is the hardest to achieve due to the remote nature of the hydrogen. Sanford *et al* described the transannular C-H arylation of piperidines (**180**) through the use of a bespoke directing group (Scheme 5.50C).[203] A later report showed that use of picolinic acid or quinolinic acid as a ligand helped aid the C-H activation step, allowing for milder conditions and improved scope.[204] Directing group free methods of γ-functionalisation of piperidines include a decatung-state/copper-mediated C-H trifluoromethylation reported by MacMillan.[205]

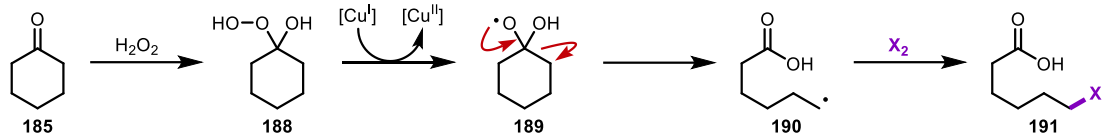
5.8 Oxidative Cleavage of Cyclic Ketones

Deconstructive functionalisations of ring systems is a powerful tool as it can generate remotely functionalised acyclic systems.[45,111,206] Classically, oxidative cleavage of ketones is possible through a Baeyer-Villiger oxidation, followed by either hydrolysis of the ester to form a distal alcohol, or alternatively under halogenating acidic conditions (e.g. H_2SO_4 and HBr) to form a distal halide.[207,208] In 1989 Nikishin reported the oxidative cleavage of cyclopentanone (**183**) with H_2O_2, to form an initial peroxyacetal species, followed by subjection to copper-catalysis which cleaved the ring, affording alkyl bromide **184** (Scheme 5.51A).[209] More recently Yusubov reported a streamlined methodology to achieve this transformation by simply combining the steps and using an alternative halide source (Scheme 5.51B).[210] I_2 could also be exchanged with other radical quenchers, such as TEMPO to form the TEMPO adduct.[211]



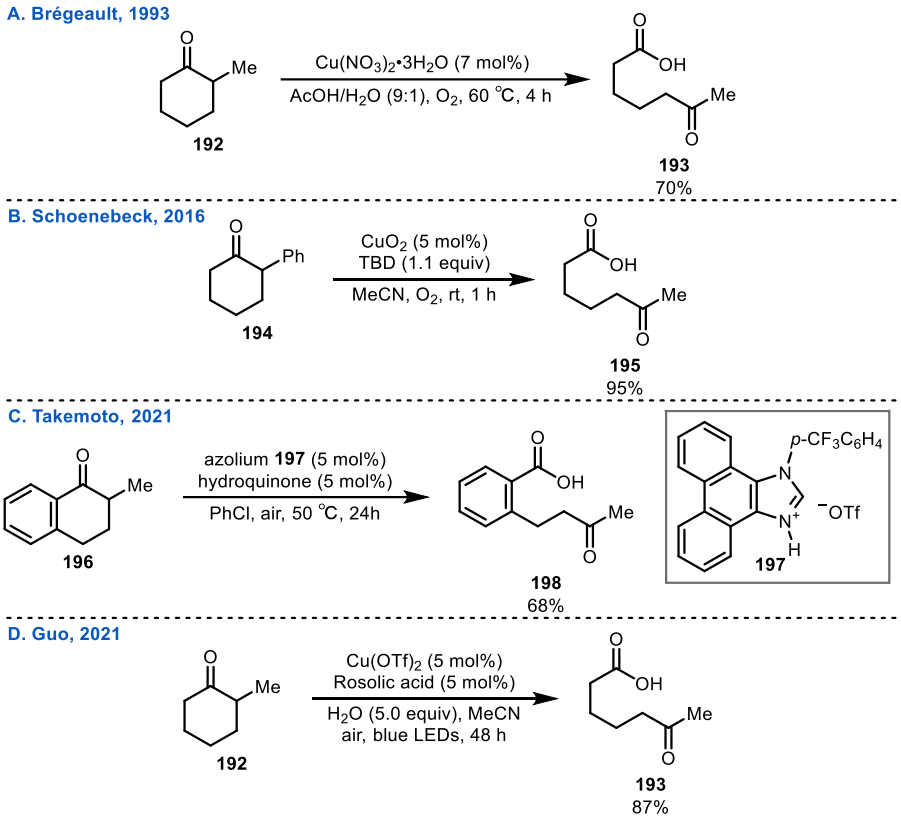
Scheme 5.51: *Oxidative cleavage of cyclic ketones to afford haloacids.*

A proposed mechanism for these transformations is shown in Scheme 5.52. First addition of hydrogen peroxide to the ketone **185** forms **188**, which then gets cleaved by the copper catalyst to give **189**. A ring opening forms the unstable radical **190**, which get trapped by a radical acceptor to form the distal functionalised acyclic product **191**.



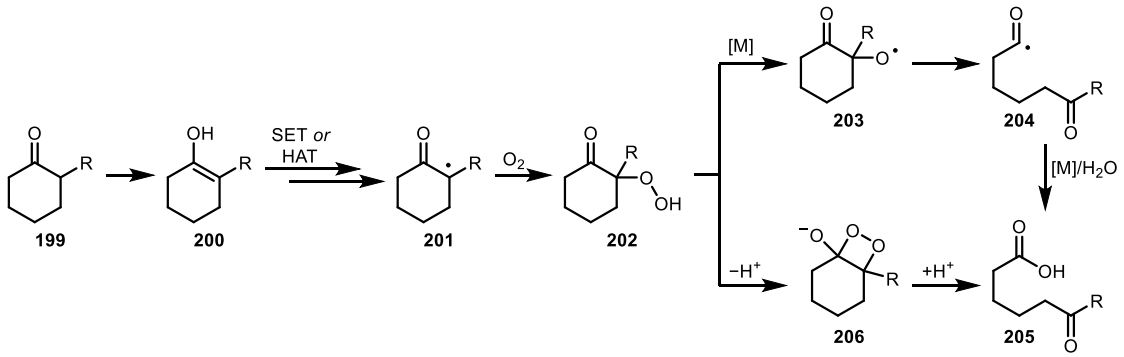
Scheme 5.52: *Proposed mechanism for the formation of acyclic acid **191**.*

Alternatively, there are a variety of methods that allow for the oxidative cleavage of α-substituted cyclic ketones into ketoacids (such as **192**) (Scheme 5.53). Typically this can be achieved under aerobic conditions with a catalyst, such as a copper/iron salt or even a polyoxometalate (Scheme 5.53A–B).[212–214] In 2016 Schoenebeck reported the oxidative cleavage of ketone **194** to **195** using CuO_2 as the catalyst, however they found that under slightly modified conditions α-hydroxylation of the ketone was favoured.[215] Alternative organo-radical co-catalysis can effect this transformation, using azolium **197** and hydroquinone (Scheme 5.53C).[216] Guo *et al* reported that the copper-catalysed oxidative cleavage can be enabled using a photosensitiser (rosolic acid) under visible light; either water could be used to obtain the ketoacid (**193**), or various alcohols could be used to access ketoesters (Scheme 5.53D).[217,218]



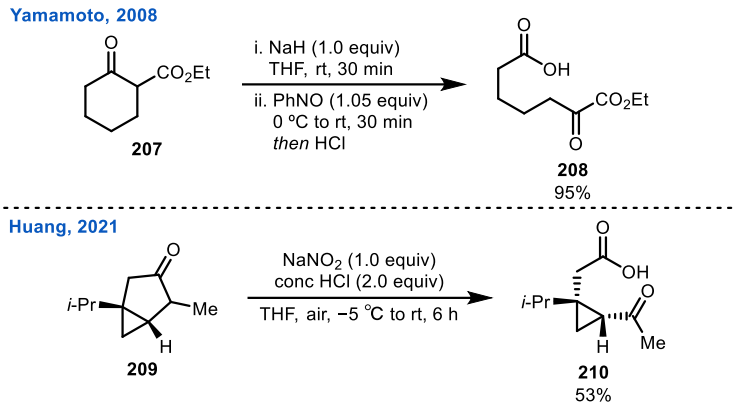
Scheme 5.53: *Oxidative cleavage of α-substituted ketones via a radical pathway.*

The reactions above are all thought to follow a similar mechanistic pathway, as shown in Scheme 5.54. First it is thought that **199** enolises to **200** which can then either undergo a SET or HAT process enabled by the catalyst to form **201**.[215,216,218] Trapping of the radical with oxygen then forms **202** (alternatively it may be possible for the ketone **199** to directly react with O_2, mediated by the catalyst, to form **202**). **202** is then thought to take one of two pathways: homolysis of the peroxide to form an oxy radical **203**, or base mediated formation of a 1,2-dioxetane **206**. If the oxy radical **203** is formed then ring opening, followed by radical quenching forms the product **205**.[215] Alternatively formation of the 1,2-dioxetane **206** can undergo a ring opening to form the product **205**.[216]



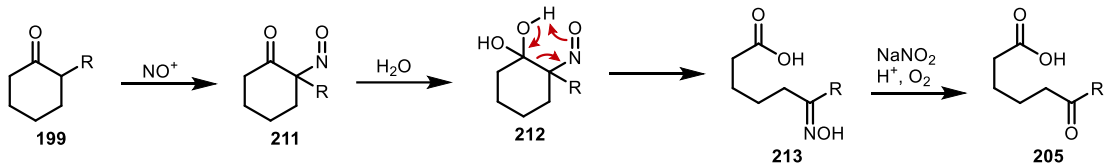
Scheme 5.54: *Proposed mechanism for the formation of **205** via the methods shown in Scheme 5.53.*

Finally, nitroso(niums) species can also be employed for the oxidative cleavage of α-substituted cyclic ketones. Yamamoto and co-workers took advantage of the acidity of cyclic β-ketoesters (**207**) by deprotonating them, followed by addition of nitrosobenzene which elicited the oxidative cleavage yielding ketoesters (**208**) (Scheme 5.55A).[219] More recently Huang showed that general α-substituted cyclic ketones (**209**) could be oxidatively cleaved using $NaNO_2$/HCl, which forms nitrosonium *in situ*, to access ketoacids (**210**) (Scheme 5.55B).[220]



Scheme 5.55: *Oxidative cleavage of α-substituted ketones via nitrosobenzene and nitrosonium.*

A proposed mechanism for Haung's methodology is shown in Scheme 5.56. First addition of the nitrosonium formed *in situ* to the ketone **199** affords **211**. Addition of water then forms **212** which can fragment to form the oxime **213**. Finally, deoximation forms the desired product **205**.[221] Yamamoto's methodology is thought to follow a similar pathway, utilising nitrosobenzene in place of a nitrosonium.

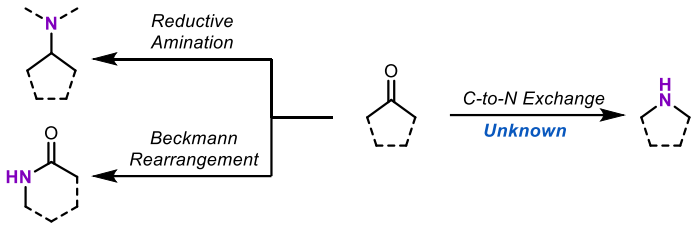


Scheme 5.56: *Proposed mechanism for the formation of **205** utilising Huang's conditions.*

6 Results and Discussions

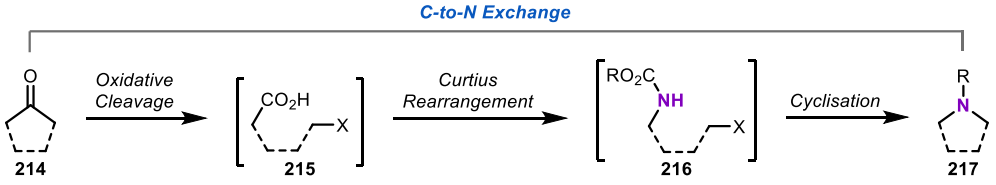
6.1 Project Aims

The C-to-N atom exchange of ketones is a process that is currently unknown, however it would be of great value as it would allow for the synthesis of numerous heterocycles, such as piperidines and pyrrolidines. These products are of significant importance due to their prevalence in pharmaceuticals, agrochemicals, and natural products. Likewise, the ubiquitous nature of ketones would make for a diversely applicable process, from late-stage skeletal editing of valuable scaffolds to diversification of commercially available materials.



Scheme 6.1: *Molecular editing of cyclic ketones.*

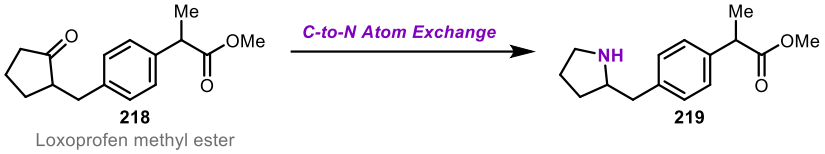
Ketones are an incredibly versatile functional group as complexity can be rapidly installed, from the addition into the carbonyl or Wittig reactions, to aldol reactions or α-arylations.[222,223,232,224–231] Due to these properties, along with numerous acyclic and cyclic ketones being commercially available, ketones are attractive targets for further research. The addition of nitrogen atoms to cyclic ketones through peripheral editing is also possible through reductive aminations, α-aminations and other methods.[233–237] However, the skeletal editing of cyclic ketones with respect to introducing nitrogen is underreported with limited examples existing, such as the Beckmann rearrangement which inserts a nitrogen atom forming an amide (Scheme 6.1).[238]



Scheme 6.2: *Proposed C-to-N atom exchange process.*

We envisioned that the C-to-N atom exchange of cyclic ketones could be achieved through a three-step process (Scheme 6.2). Yusubov and co-workers showed that cyclic ketones **214** could be ring-opened utilising copper-catalysis to afford haloacids **215**.[210] This provides the foundation for our atom exchange process as it sets up for a Curtius rearrangement to introduce the nitrogen as the carbamate **216**.[239–242] Finally, a cyclisation process, ideally performed in the same pot as the Curtius rearrangement, forms the

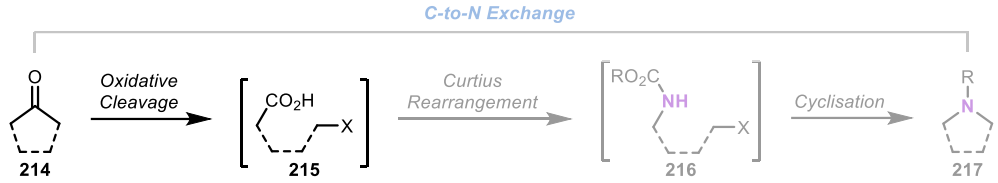
atom exchanged product **217**. Ideally the process would be general and functional group tolerant, enabling the late-stage functionalisation of complex molecules, such as Loxoprofen methyl ester (**218**), enabling a molecular editing approach for scaffold hopping (Scheme 6.3).



Scheme 6.3: *Theoretical application of the C-to-N atom exchange process to a loxoprofen derivative.*

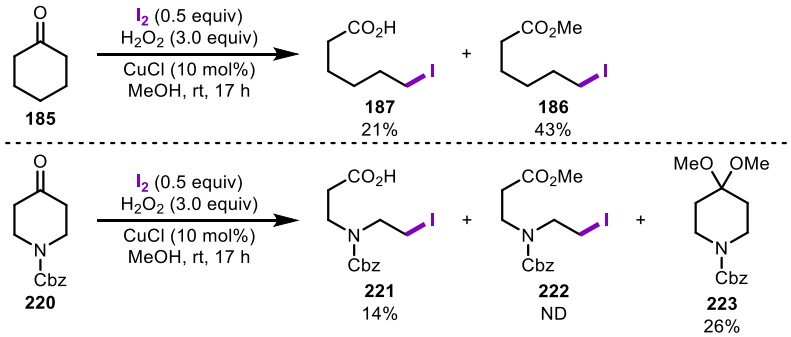
6.2 Haloacid Approach

6.2.1 Oxidative Cleavage



Scheme 6.4: *Outline of the proposed C-to-N atom exchange process.*

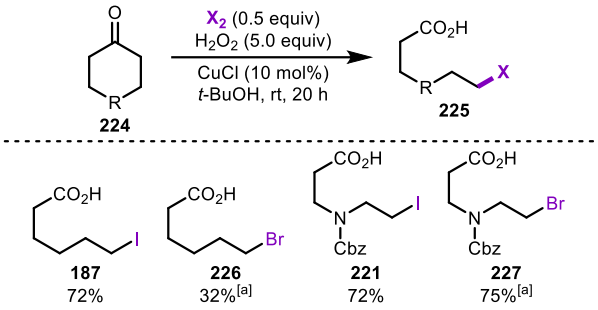
Starting with the first step of the process, the oxidative cleavage of ketones to haloacids, we set out to test Yusubov's reported conditions (Scheme 5.51B) on both the reported substrate cyclohexanone (**185**) and the piperidone **220** (Scheme 6.5).



Scheme 6.5: *Testing literature conditions for the oxidative cleavage of ketone **185** and **220**. Yields determined by ^{1}H NMR analysis using TMB as an internal standard.*

When using **185**, a 2.1:1 ratio of the methyl ester **186** to acid **187** was observed in an overall yield of 64% by NMR; this contrasts to the reported 3:1 mixture in an overall 99% yield.[210] In the case of the piperidone **220**, the acid **221** was observed in a 14% yield with none of the methyl ester **222** being detected, along with 26% of the dimethyl acetal **223**. From these preliminary results, optimisation was required to ensure the overall yield of the proposed multi-step process was practical.

A brief screen utilising **185** showed that the choice of solvent has a significant impact on the product distribution. Bulkier solvents such as *i*-PrOH and *t*-BuOH favoured the formation of the acid, which agrees with the literature results. The workup procedure was also investigated, investigating both an aqueous basic extraction and a silica plug. Both workup procedures gave similar NMR yields from the crude mixtures, however it was found that the aqueous basic extraction was capricious with small changes to the workup often leading to significant changes to the yield. Subjecting the test substrates **185** and **220** to the conditions shown, followed by filtration through a silica plug, afforded the results as shown in Scheme 6.6.

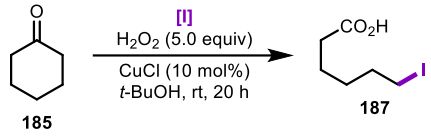


Scheme 6.6: *Oxidative cleavage of **185** and **220**. Yields determined by ^{1}H NMR analysis using TMB as an internal standard. [a]Average of 3 experiments.*

In the case of using I_2 as the halogen source the corresponding iodoacids (**187** and **221**) were formed in good yields. It was also postulated that I_2 could be switched with Br_2 to form the bromoacids which may or may not perform better in the later steps. When using cyclohexanone, the bromoacid **226** was obtained in a relatively poor yield, however the piperidone **220** gave comparable results as to when using I_2. It was interesting to note that when using Br_2 the reaction mixture was incredibly exothermic upon addition of H_2O_2, which was not the case when using I_2. This may have ramifications on scaled up reactions or industrial applications.

Further optimisation explored the source and equivalents of iodine was investigated (Table 6.1). Changes to the equivalents of I_2 had minimal impact (Entry 1 and 2). NIS (Entry 2) could be used as an alternative iodine source giving **187** in a 75% yield. Both TBAI and NaI (Entry 4 and 5) exhibited no reactivity. Despite NIS providing a minor increase in yield we decided to continue using I_2 due to it being more atom economical along with any unreacted iodine being easy to remove.

Table 6.1: *Investigation into the iodine source and equivalents.*

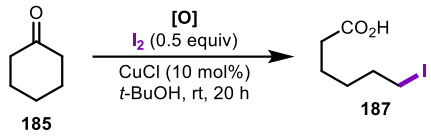


Entry	[I]	Equiv	187 (%)
1	I_2	0.5	72
2	I_2	1.0	69
3	NIS	1.0	75
4	TBAI	1.0	0
5	NaI	1.0	0

Yields determined by ^{1}H NMR analysis using TMB as an internal standard.

Next the source and equivalents of the oxidant was screened as shown in Table 6.2.

Table 6.2: *Investigation into the oxidant.*



Entry	[O]	Equiv	187 (%)
1	H_2O_2	1.5	37
2	H_2O_2	2.0	55
3	H_2O_2	3.0	61
4	H_2O_2	4.0	69
5	H_2O_2	5.0	72
6[a]	H_2O_2	5.0	76
7	H_2O_2	10	66
8[b]	H_2O_2	10	57
9	UHP	5.0	52
10[c]	UHP	10	69
11	$NaBO_3$	5.0	0
12	TBHP	5.0	0
13	Oxone	5.0	0

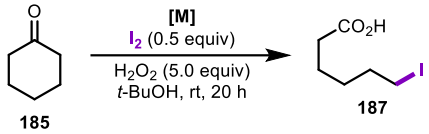
Yields determined by ^{1}H NMR analysis using TMB as an internal standard. [a]H_2O_2 was added over 5 hours. [b]I_2 (1.0 equiv). [c]MeCN used as the solvent.

Lowering the equivalents of H_2O_2 (Entries 1–4) led to progressively lower yields. Alternatively, when increasing the equivalents of H_2O_2 (Entry 7) only minor differences were observed compared to using 5.0 equivalents (Entry 5), however in the case of using 1.0

equivalent of I_2 with 10 equivalents of H_2O_2 (Entry 8) there was a slight drop in the yield. Little effect was observed between addition of H_2O_2 over 1 minute or slow addition over 5 hours (Entry 6). Alternative oxidants were also screened with UHP affording **187** in a slightly reduced yield (Entry 9). Improved results were obtained when using 10 equivalents of UHP in MeCN (Entry 10); the aim here was to try and reduce intermediate radicals being quenched with protons, however H_2O_2 remained the best option. $NaBO_3$, TBHP and Oxone provided no reactivity (Entries 11–13). The concentration of H_2O_2 was investigated with 30% w/w H_2O_2 being used, however 50% w/w H_2O_2 gave similar results.

Investigation into the metal catalyst was next undertook, as shown in Table 6.3.

Table 6.3: *Investigation into the catalyst.*



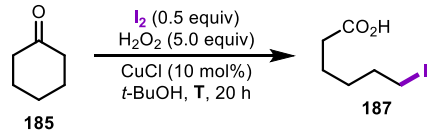
Entry	[M]	mol%	187 (%)
1	CuCl	1.0	45
2	CuCl	2.5	58
3	CuCl	5.0	59
4[a]	CuCl	10	65
5	CuCl	10	72
6	CuCl	20	55
7	CuCl	40	39
8	CuCl	100	0
9	$CuCl_2$	10	38
10	CuBr	10	0
11	CuI	10	5
12	CuTc	10	8
13	CuOAc	10	8
14	$Cu(OAc)_2$	10	12
15	$CoCl_2$	10	0
16	$NiCl_2$	10	0
17	$FeCl_2$	10	35
18	$ZnCl_2$	10	0

Yields determined by ^1H NMR analysis using TMB as an internal standard. [a]>99.99% purity CuCl was used.

The equivalents of CuCl (Entries 1–8) had a large impact on the reaction yield; both attempts to decrease and increase the equivalencies had a negative effect on the reaction with 0.1 equivalents being optimal. The purity of CuCl also had minor impact on the reaction (Entry 4 and 5). Alternative Cu(I) and Cu(II) salts were screened (Entries 9–14) with none affording results comparable to CuCl. Interestingly $CuCl_2$ (Entry 9) gave much lower yields than CuCl, given that the latter is likely oxidised under the reaction conditions. Alternative metal salts (Entries 15–18) were also screened, with only $FeCl_2$ showing any reactivity.

Next the temperature of the reaction was screened as shown in Table 6.4. Increasing the temperature from room temperature to 50 °C led to progressively worse yields (Entries 2–5). Reduced temperatures of 10 °C also had little effect on the yield, however *i*-PrOH had to be used as the reaction solvent to avoid the reaction from freezing which may have also influenced this result. Alternatively, adding H_2O_2 to the reaction at 0 °C followed by heating the reaction to room temperature gave similar results as peroxide addition at room temperature (Entry 2).

Table 6.4: *Investigation into the temperature.*



Entry	T (°C)	187 (%)
1[a]	10	69
2	rt	72
3	30	61
4	40	52
5	50	44

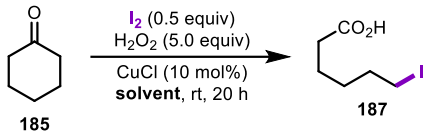
Yields determined by ^{1}H NMR analysis using TMB as an internal standard. [a]i-PrOH was used as the solvent.

Finally, the solvent and reaction concentration were screened as shown in Table 6.5. In all circumstances complete selectivity for the iodoacid **187** as observed, with none of the esterification product **186** being observed. Various alcohols were screened such as *i*-PrOH, *t*-AmylOH, *s*-BuOH and *t*-BuOH (Entries 1–3 and 6); both *s*-BuOH and *t*-BuOH performed similarly. A mixture of *t*-BuOH/H_2O (Entry 4) was assessed; however, this did not yield better results. When varying the concentration of *t*-BuOH (Entries 5–10) the yield increased as the concentration was increased, up to a concentration of 1.0 M. Entry 8 and

9 show that under these conditions the use of 5.0 equivalents of H_2O_2 was much more productive than the use of 3.0 equivalents.

The addition of acid additives, in the form of HCl and H_2SO_4, was also examined due to previous reports suggesting that a low pH is beneficial, however no improvement was observed.[209] Further inquiries into the workup were made utilising the optimised conditions (as shown in Scheme 6.7). When performing an aqueous basic extraction it was found that extracting with saturated aqueous $NaHCO_3$ afforded **187** in a 60% yield, however extracting with NH_4OH and 2 M NaOH gave a yield of 38% and 52% respectively. Alternatively, a silica plug (elution with petroleum ether then EtOAc) to remove residual iodine afforded better yields, however the material isolated was not as pure.

Table 6.5: *Investigation into the solvent.*

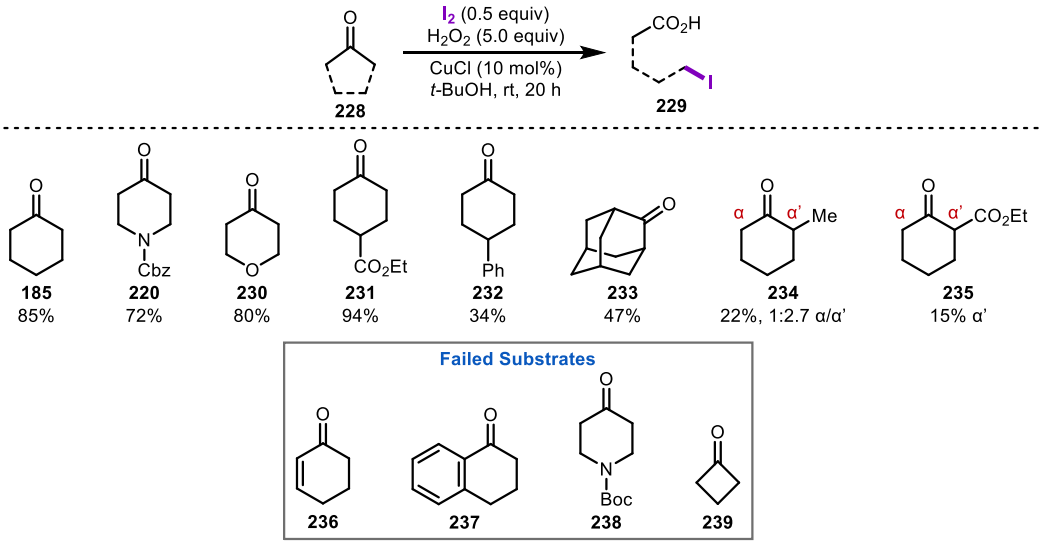


Entry	Solvent	Conc (M)	187 (%)
1[b]	*i*-PrOH	0.2	64
2[b]	*t*-AmylOH	0.2	59
3	*s*-BuOH	0.2	71
4	*t*-BuOH/H_2O (1:1)	0.2	44
5	*t*-BuOH	0.1	60
6	*t*-BuOH	0.2	72
7[a]	*t*-BuOH	0.5	81
8[a]	*t*-BuOH	1.0	85
9[b,c]	*t*-BuOH	1.0	59
10[a]	*t*-BuOH	1.5	78

Yields determined by ^{1}H NMR analysis using TMB as an internal standard. [a]Average of 3 runs. [b]Average of 2 runs. [c]H_2O_2 (3.0 equiv) was used.

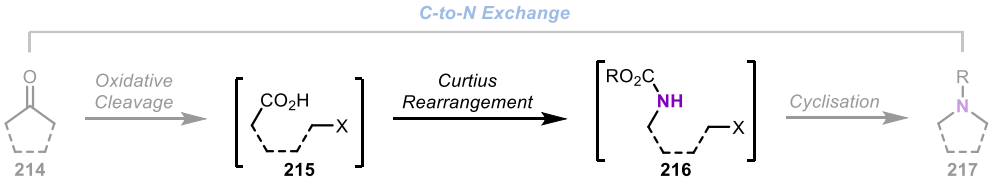
With the optimised conditions in hand and utilising a silica plug for the workup we set out to do an initial screen of substrates to see what would be tolerated. One big limitation that was envisioned of this atom exchange process was the harsh nature of the oxidative cleavage reaction. Scheme 6.7 shows that a variety of substrates were tolerated, such as heterocycles (**220** and **230**). γ-Substitution was also tolerated with functional groups such an ester (**231**) and an arene (**232**). Adamantanone (**233**) also underwent cleavage. Unfortunately, α-substituted cyclohexanones (**234** and **235**) gave poor yields.

Several substrates were unfortunately not compatible, such as a cyclohexenone (**236**), a benzylic ketone (**237**) and an acid-labile Boc amine (**238**), all forming a complex mixture. A separate reaction was done with cyclohexanone in the presence of 1.0 equivalent of *trans*-5-decene however, only 5% of the alkene remained at the end of the reaction, implying that alkenes are not compatible under these reaction conditions. In the case of cyclobutanone (**239**), exclusive formation of the Bayer-Villiger product was observed.



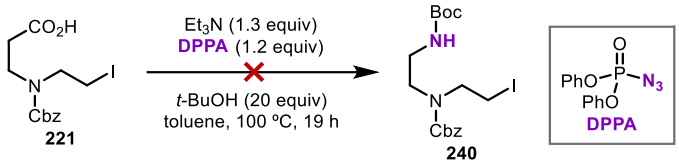
Scheme 6.7: *Yields determined by ^{1}H NMR analysis using TMB or DMT as an internal standard.*

6.2.2 Curtius Rearrangement



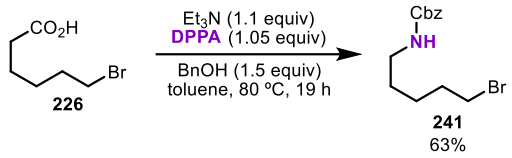
Scheme 6.8: *Outline of the proposed C-to-N atom exchange process.*

With the oxidative cleavage step optimised we next investigated the Curtius rearrangement. Initially we attempted the conditions shown in Scheme 6.9 to obtain the Boc protected amine **240**, unfortunately no product was observed. Variation of the equivalents of base used, along with the order of addition/heating all led to no formation of the desired product being observed. Further analysis of the reaction showed that addition of DPPA/Et_3N gave consumption of **221**, forming the acyl azide as indicated by NMR spectroscopy and mass spectrometry. Other nucleophiles were also evaluated, such as allyl alcohol and aqueous HCl, however these failed to form any of the desired product.



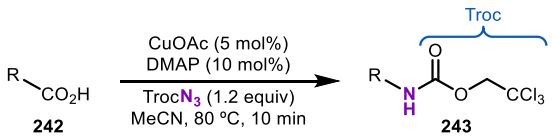
Scheme 6.9: *Initial attempted Curtius rearrangement of* ***221****.*

Given that the primary alkyl iodide **187** and **221** may be overreactive and unstable we investigated using the commercially available and stable bromoacid **226** instead to see if this had any appreciable benefits. Using *t*-BuOH and allyl alcohol with bromoacid **226** failed to afford any product, however when BnOH was utilised the reaction proceeded to give the Cbz carbamate **241** in a 63% yield (Scheme 6.10). Unfortunately, **241** was difficult to purify by column chromatography due to the formation of phosphate side products which coeluted with the desired product.



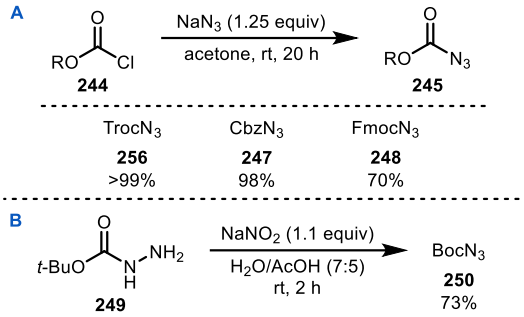
Scheme 6.10: *Curtius rearrangement of* ***226*** *using BnOH as the nucleophile.*

Whilst the reaction was shown to work it had multiple flaws: inconsistency across nucleophiles, mediocre yields and hard to remove impurities. Because of these flaws we searched for an alternative robust set of conditions for our atom exchange process. A recent report by Li described a Curtius rearrangement using a co-catalytic system of CuOAc and DMAP with an azidoformate as the nitrogen and nucleophile source (Scheme 6.11).[243] This looked to be an attractive option as they reported an average yield of 87% across 84 examples with numerous functional groups being tolerated. Additionally, by using the catalyst loadings as shown below the reactions were typically complete within 10 minutes which is desirable for a multi-step process. The reaction was also shown to work with catalyst loadings as a low as 0.1 mol%, but extended reaction times were required. Finally, due to the reaction being incredibly efficient with the only by-products being CO_2 and N_2 the authors demonstrated that the reaction could be scaled to gram scale, and the product isolated without need for column chromatography.



Scheme 6.11: *Li's reported work on a "contemporary" Curtius rearrangement.*

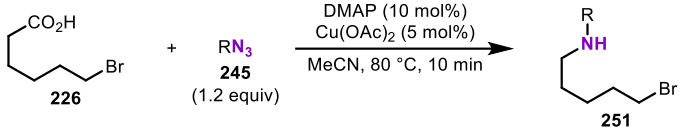
To begin a selection of azidoformates were synthesised. Either the chloroformate was substituted with NaN_3 yielding the azidoformates **256–248**, or the hydrazine was oxidised to the azidoformate **250**.



Scheme 6.12: *Synthesis of azidoformates **256–248** and **250**.*

Replication of Li's conditions with the bromoacid **226** afforded the desired Troc-protected product in a 98% NMR yield and an 85% isolated yield (Table 6.6, Entry 1). The alternative azidoformates (Entries 2–4) were also screened to see if any other protecting groups could be utilised, however only $CbzN_3$ was reactive, affording 80% of the Cbz-protected product (Entry 2). These results are in line with the authors observations that more electron-deficient azidoformates perform better under these conditions.

Table 6.6: *Applying Li's conditions to acid **226** with various azidoformates.*



Entry	R	251 (%)
1	Troc	98 (85)[a]
2	Cbz	80
3	Boc	0
4	Fmoc	0

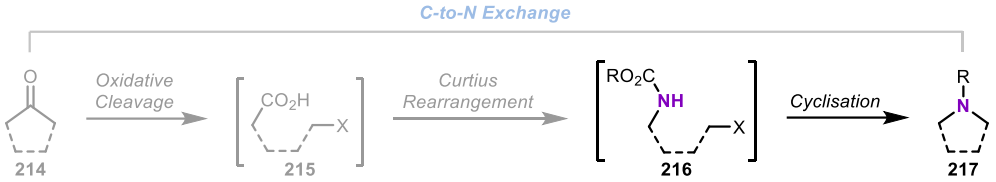
Yields determined by ^{1}H NMR analysis using DMT as an internal standard. [a]Isolated yield.

This reaction was briefly screened to gain a greater understanding. Reaction analysis with thin layer chromatography and ^{1}H NMR spectroscopy showed that full conversion was achieved within 10 minutes, as reported. However, longer reaction times were often employed for subsequent reactions to ensure complete conversion across a range of substrates. Increasing the temperature or the equivalents of the azidoformate had little impact on the yield. It was found that purity of the azidoformate was paramount, as small impurities between batches could negatively impact the yield by >10%. The easiest way to ensure that the azidoformate was pure was by utilising fresh, clean chloroformate

starting material (this also removes the need for purification *via* column chromatography). It was also found that the solvent had to be dry, as using non-anhydrous MeCN was detrimental to the yield.

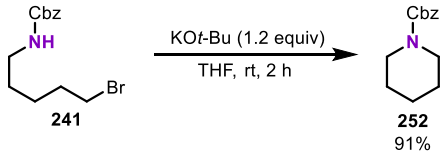
In conclusion a literature procedure was investigated and adapted to provide a robust procedure for the Curtius rearrangement of haloacids.

6.2.3 Cyclisation



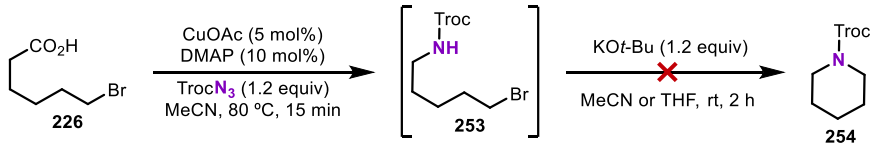
Scheme 6.13: *Outline of the proposed C-to-N atom exchange process.*

With the Curtius rearrangement resolved we next sought to address the cyclisation step. Preliminary results showed cyclisation of carbamate **241** by deprotonation with KO*t*-Bu in THF afforded the piperidine **252** in an excellent yield, providing an excellent starting point the cyclisation step. The reaction also gave similar results when using NaH in DMF, however the crude product was not as pure.



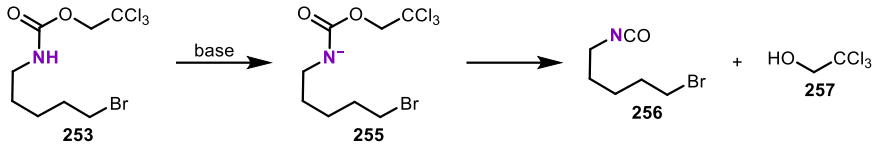
Scheme 6.14: *Initial attempted cyclisation of* ***241****.*

With the optimised Curtius rearrangement conditions readily affording the Troc-protected amine **253**, we next investigated the cyclisation conditions with this substrate. Given the Curtius rearrangement of bromoacid **241** was quick and clean, telescoping the carbamate into the cyclisation would improve the reactions economy (Scheme 6.15). Initial attempts to add KO*t*-Bu directly, or solvent swapping into THF, unfortunately provided trace amounts of **254**. Various conditions for the cyclisation were tested based on similar reaction conditions in the literature, such as utilising different bases (K_2CO_3, $CsCO_3$, KO*t*-Bu, NaH), solvents (DMF and THF) and temperatures. Unfortunately, none of these variations afforded the product in a high yield.



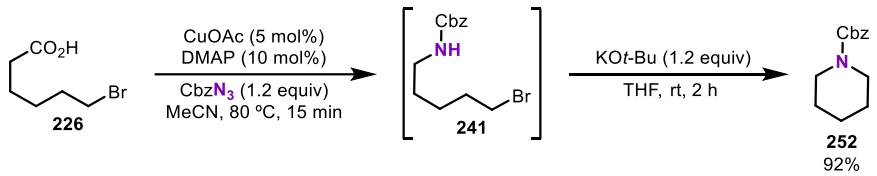
Scheme 6.15: *Attempted Curtius rearrangment/cyclisation sequence of* ***226*** *via the Troc carbamate* ***253****.*

The poor performance of the cyclisation of **253** is hypothesised to be due to the acidity of 2,2,2-trichloroethanol (Scheme 6.16). Upon deprotonation it is thought that the anion **255** eliminates the acidic 2,2,2-trichloroethanol (**257**) to form the isocyanate **256** (observed by mass spectrometry), rather than the desired reactivity of amine alkylation.



Scheme 6.16: *Hypothesised side-reaction upon subjection of **253** to basic conditions.*

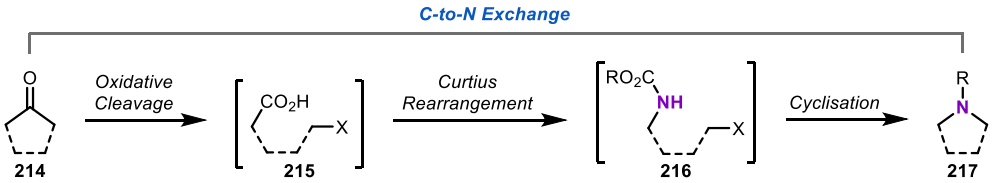
Given that the cyclisation of the Troc-protected amine **253** was unsuccessful we instead decided to use the Cbz-protected amine **241** given its earlier success. Fortunately, **241** can be accessed using these Curtius rearrangement conditions (as shown in Table 6.6), albeit with a small decrease in the yield. Attempts were made to telescope **241** by adding base directly to the reaction mixture, however this did not form any of the desired product **252**. However simply performing a solvent swap into THF after the first step afforded **252** in a 92% yield over 2 steps (Scheme 6.17).



Scheme 6.17: *Attempted Curtius rearrangment/cyclisation sequence of acid **226**. Yield determined by ^{1}H NMR analysis using TMB as an internal standard.*

With all the individual steps optimised, along with the latter two being shown that they can be telescoped, all that was left was to combine the steps together to make a general and reliable process for the C-to-N atom exchange of cyclic ketones.

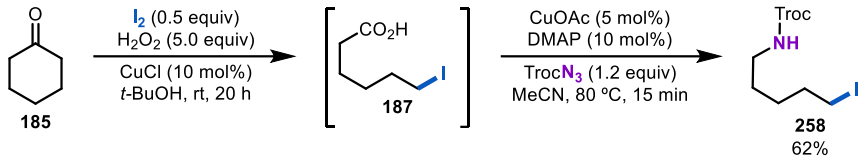
6.2.4 Telescoping Optimisation



Scheme 6.18: *Outline of the proposed C-to-N atom exchange process.*

To begin with we investigated telescoping the first two steps, the oxidative cleavage and the Curtius rearrangement. A solvent swap between the two reactions was attempted, however no product was observed after the second step, thus a workup was required. By utilising a silica plug after the first step, as previously described, a 62% NMR yield of

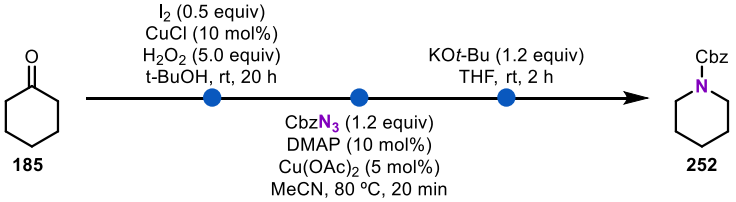
iodide **258** over the first two steps was observed (Scheme 6.19). Separate attempts of this process when using an aqueous wash yielded comparable results.



Scheme 6.19: *Attempt to telescope the first two steps using cyclohexanone (**185**). Yield determined by ^{1}H NMR analysis using TMB as an internal standard.*

From here we next examined combining all three steps together with an initial attempt giving a 24% yield over three steps (average yield 62%), leaving a lot of room for improvement. To begin, the workup procedures for the oxidative cleavage and Curtius rearrangement steps were probed to see its impact on the overall yield (Table 6.7).

Table 6.7: *C-to-N atom exchange process and optimisation of the intermediate workups.*



Entry	OC Workup	Curtius Workup	Yield (%)	
			Overall	Final 2 Steps
1	Plug	Swap	29 (66)	36 (60)
2	Wash	Swap	38 (72)	48 (69)
3	Plug	Wash	42 (75)	49 (70)
4	Wash	Wash	32 (68)	47 (69)
5	Plug	Column	39 (73)	46 (68)
6	Extraction	Swap	49 (79)	72 (85)
7[a]	–	Swap	–	70 (84)
8[a]	–	Extraction	–	73 (85)

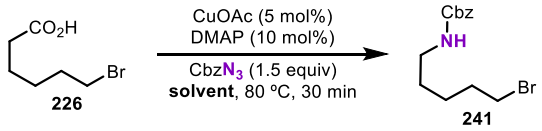
*Yields determined by ^{1}H NMR analysis using TMB as an internal standard. Oxidative cleavage (OC) yield was calculated beforehand. Yield in brackets refer to the average yield per step. Plug refers to a silica plug. Wash refers to aqueous acidic washes. Extraction refers to a base/acid workup. Swap refers to a solvent swap. Column refers to purification via column chromatography. [a]Commercial bromoacid **226** was used.*

A selection of workups were investigated: for the oxidative cleavage both an aqueous wash (quenched with $Na_2S_2O_3$, extracted with CH_2Cl_2 and the organics washed with 10% HCl) and a silica plug were tested. For the Curtius rearrangement both a solvent swap and an acid wash were examined. Various combinations of these workups were trialled (Entries 1–4), however there was no clear trend between the workup procedure and the

yields. Entry 5 shows that when the crude carbamate was subjected to column chromatography before undergoing cyclisation there was negligible impact on the yield of the final step. The lower yields could be due to two possibilities: impurities being carried through that inhibit subsequent reactions, or the cyclisation onto the alkyl iodide being worse than the alkyl bromide which was screened. To address this some oxidative cleavage product was worked up using an aqueous basic extraction procedure to access clean iodoacid **187**, which was then subjected to further reactions (Entry 6). The results of using clean iodoacid **187** was a much-improved yield of 49% over three steps (72% yield over the last two steps), implying that the purity of the haloacid is paramount for a high yielding process. To further confirm this commercial bromoacid **226** was utilised (Entry 7 and 8), which gave similar results to Entry 5. These results also show the choice of workup used after the Curtius step had minimal impact on the overall yield.

Knowing that clean haloacid material was required for good yields we investigated the purification of the oxidative cleavage product. Attempts were made to purify using an aqueous extraction with a basic solution, unfortunately, this method was temperamental on the test substrate **187**. Additionally, when this was attempted on other substrates the products failed to transfer into the aqueous layer. The less desirable option of performing column chromatography was also attempted, however these low molecular weight acids proved exceedingly difficult to purify by this method. Additionally, as we were trying to make a general, and ideally simple, three-step process, we would like to minimise the number of column chromatography steps required. Ultimately, we were unable to improve upon the original silica plug workup.

Table 6.8: *Investigation into the Curtius rearrangement solvent using acid* ***226****.*



Entry	Solvent	241 (%)
1	THF	0
2	DMF	80
3	DMSO	67
4	dioxane	0
5	toluene	0

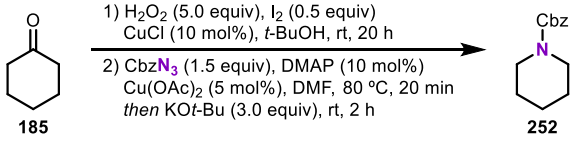
Yields determined by ^{1}H NMR analysis using TMB as an internal standard.

Another area of improvement would be to remove the workup following the Curtius rearrangement step given the as it is not imperative. Early attempts were made to add the

base directly after; however, it may be due to the acidic nature of MeCN that these reactions were unsuccessful. Based on this we investigated if the solvent of the Curtius rearrangement could instead be altered to one which is more tolerant of basic conditions (Table 6.8). Polar aprotic solvents (Entries 1–4) had mixed results: neither THF or dioxane afforded any product, however DMF and DMSO yielded **241** in 80% and 67% respectively. The use of toluene of the solvent (Entry 5) also led to no reaction.

Next, we set out to test the atom exchange sequence (a silica plug was employed for the oxidative cleavage workup) employing DMF as the solvent for both the Curtius rearrangement and the cyclisation (Table 6.9). Gratifyingly these results (Entries 1–4) were comparable to the solvent swap approach. Unfortunately, the use of clean bromoacid **226** (Entry 5) still afforded better results. With these conditions in hand, we set out to examine the potential scope for this process.

Table 6.9: *C-to-N atom exchange process.*



185 252

Entry	X	Curtius Workup	Yield (%)	
			Overall	Final 2 Steps
1	I	None	34 (58)	50 (71)
2	I	Extraction	40 (63)	59 (77)
3	Br	None	36 (60)	56 (75)
4	Br	Extraction	37 (61)	58 (76)
5[a]	Br	Extraction	–	77 (88)

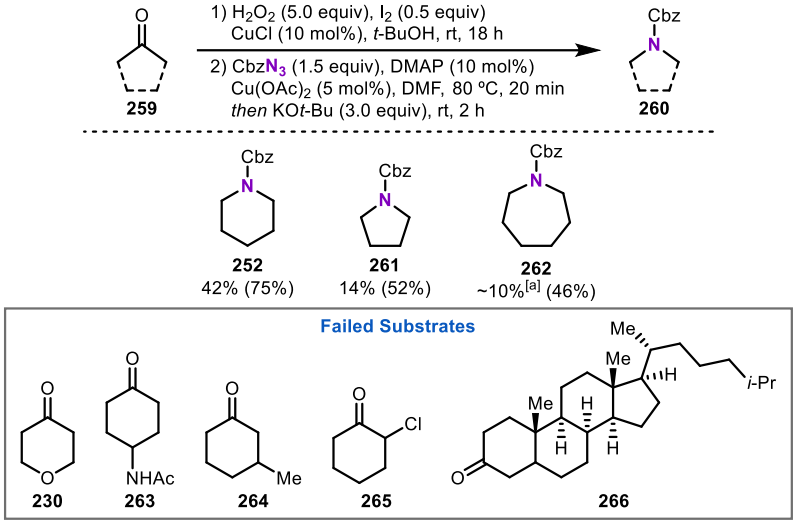
*Yields determined by ^{1}H NMR analysis using TMB as an internal standard. Oxidative cleavage yield was calculated beforehand. Yield in brackets refer to the average yield per step. [a]Commercial bromoacid **226** was used. Average of 2 experiments.*

6.2.5 Attempted Scope

The attempted scope for the atom exchange process is as shown in Table 6.10. Whilst with the test substrate cyclohexanone gave the isolated atom exchanged product **252** in a respectable 42% over 3 steps, attempts to translate this to other substrates were not as bountiful. Simple homologues **261** and **262** both performed poorly, with **262** being unable to be isolated due to coelution of other impurities. Other substrates were also tested, including a pyranone (**230**), 4-acetamide (**263**), 3-methyl (**264**), and 2-chloro (**265**), however these were all unsuccessful. A steroid (**266**) was also attempted however this also afforded no product. In the case of the pyranone **230** it did appear to have formed the

desired product at the end of the process, however, attempts to purify it using column chromatography were unsuccessful due to coelution of other impurities.

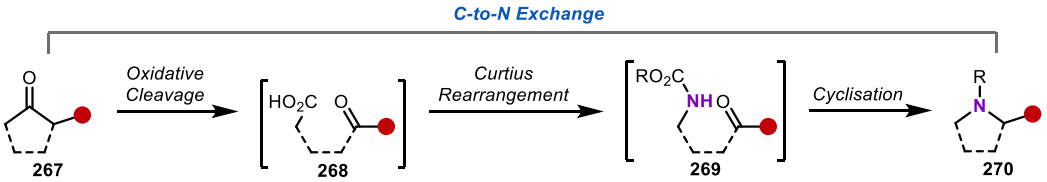
Table 6.10: *Attempted C-to-N atom exchange scope.*



[a]*Yield determined by* ^{1}*H NMR analysis using TMB as an internal standard. Cyclisation reaction time was also extended to 24 h.*

Based on these results it was clear that this approach was not worth pursuing further as the scope was going to be both limited and low yielding. From here we considered how we may be able to recoup some of our efforts and remodel the sequence to achieve the desired C-to-N atom exchange.

6.3 Ketoacid Approach

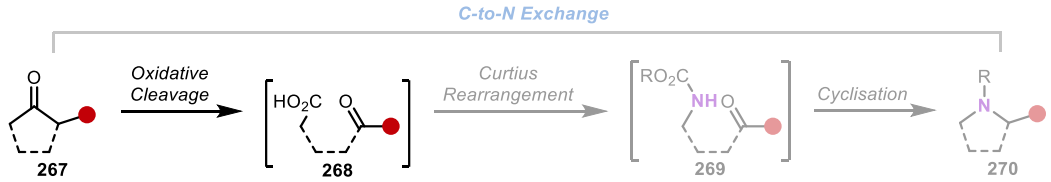


Scheme 6.20: *Proposed alternative C-to-N atom exchange process.*

To achieve our original goal for the skeletal editing of cyclic ketones we set out to re-examine our original proposed route to make it viable. It was clear that the oxidative cleavage step was the biggest handicap, from the lack of functional group tolerance to the issues when telescoping the product. Based on this we searched the literature for alternative methodologies that could be applied. What we found was there was multiple recent reports of oxidative cleavages of α-substituted cyclic ketones into ketoacids (see 5.8 Oxidative Cleavage of Cyclic Ketones). If we could apply this to ketone **267** to access the ketoacid **268**, then a subsequent Curtius rearrangement can once again be used to introduce the nitrogen, followed by a cyclisation to form the atom exchanged product **270** (Scheme 6.20). This route was attractive due to there being numerous reports of the oxi-

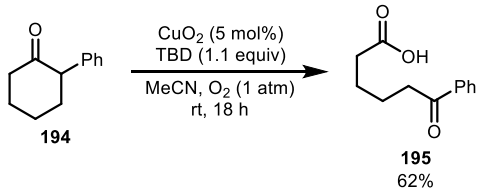
dative cleavage of **267** with good functional group compatibility. Ideally one of the reported methods could be used as reported without the need for further optimisation. The Curtius rearrangement step used in the previous method could also be applied, which would avoid the need for optimisation of this step too. This leaves the cyclisation step of a carbamate onto a ketone as the main step of interest. There are multiple possibilities in which this can be achieved, such as a deprotection/reductive amination sequence, which would ideally be developed to be a one-pot procedure.

6.3.1 Oxidative Cleavage



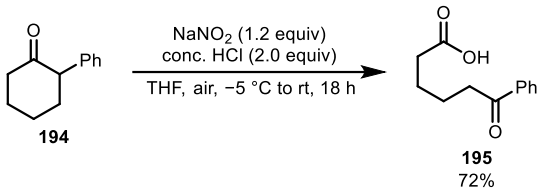
Scheme 6.21: *Outline of the proposed modified C-to-N atom exchange process.*

As mentioned, there are a variety of methods available for the cleavage of α-substituted ketones, so the first step was to test them to see which would work best in our atom exchange process. To begin with we repeated work reported by Schoenebeck to form the ketoacid **195** in a 62% yield (Scheme 6.5).[215] Whilst this afforded **195**, which allowed us to continue exploring the subsequent steps, this methodology was limited in substrate scope as the authors focussed on mainly accessing α-hydroxy ketones.



Scheme 6.22: *Oxidative cleavage of **194**.*

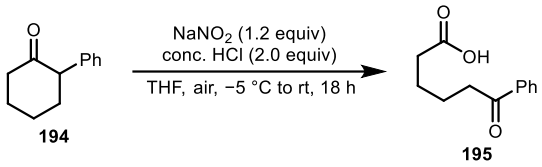
Applying Haung's conditions on ketone **194** afforded ketoacid **195** in a 72% yield; this looked like a promising start as the authors reported a broad scope. The authors performed their scope on a 0.20 mmol scale, however they observed decreases in the yields upwards of 20% when scaling up to gram-scale; this trend was unfortunately observed when performing this chemistry using ketone **194** on a 1.0 mmol scale. Reduced temperatures and extended cooling periods were investigated, however these had minimal impact on the outcome.

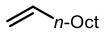
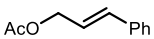
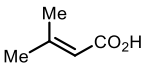


Scheme 6.23: *Oxidative cleavage of* ***194****. Yield determined by* ^{1}*H NMR analysis using DMT as an internal standard.*

Despite the shortcomings of this method a small robustness screen was performed with various alkenes to see if this type of methodology offered any improvements over the previous oxidative conditions (Table 6.11). Whilst vinyl groups and 1,1-disubstitued alkenes were not tolerated, internal alkenes were to some extent which was a significant improvement compared to the previously examined oxidative cleavage methodology.

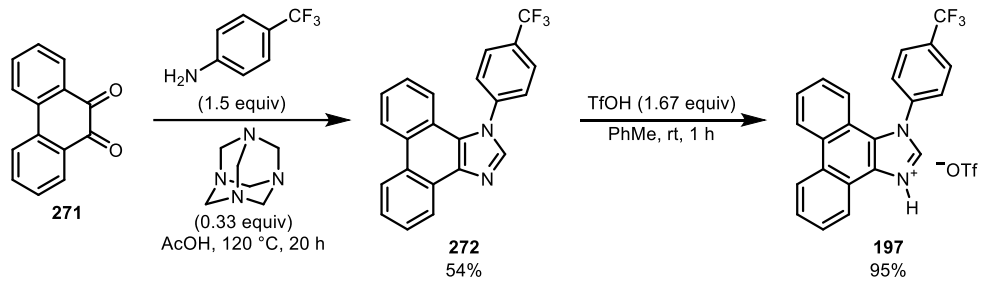
Table 6.11: *Robustness screen of alkenes.*



Entry	Additive	Recovery (%)	194 (%)
1		4	45
2		14	53
3		52	65
4		72	38

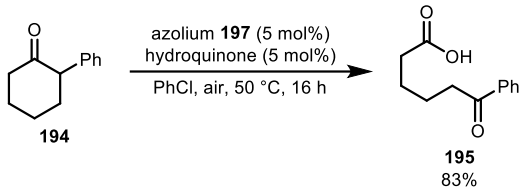
Yields determined by ^{1}*H NMR analysis using DMT as an internal standard.*

Takemoto's report on utilising an azolium catalyst **197** to effect this transformation was next examined. The synthesis of the catalyst was easily achieved through a multi-component condensation on **271**, followed by salt formation to afford **197** in a 51% overall yield.



Scheme 6.24: *Preparation of the azolium catalyst* ***197****.*

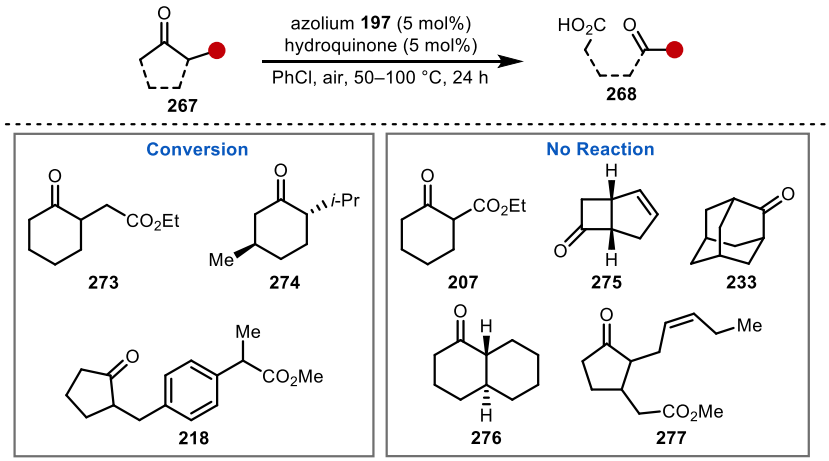
Application of their described conditions onto ketone **194** on a 0.25 mmol scale afforded ketoacid **195** in an 83% yield which was promising (Scheme 6.25). Upon scaling the reaction up to 1.0 mmol only 84% conversion was observed. It was found that increasing the temperature 60 °C gave full conversion and an 86% NMR yield/72% isolated yield. Further increases to the temperature were found to only have a detrimental effect on the yield. The reaction also did not appear to be rate-limited by oxygen transfer into the solution as leaving the reaction open to air *vs.* bubbling air through the reaction *vs.* using an atmosphere of O_2 all gave comparable results.



Scheme 6.25: *Oxidative cleavage of* ***194*** *(0.25 mmol). Yield determined by* ^{1}*H NMR analysis using DMT as an internal standard.*

As Takemoto and co-workers focussed more on the catalyst design and mechanism only a small number of substrates were reported, therefore we set out to do an initial screen of substrates (Table 6.12). Both loxoprofen methyl ester (**218**) and menthone (**274**) showed conversion under the reaction conditions. Unfortunately, there were also several substrates that showed no reactivity. Ketoester **207** was also not tolerated, which would be valuable to allow for the synthesis of amino acids. Decalin **276** and methyl jasmonate (**277**) were also unreactive. Strained ring systems such as cyclobutanes (**275**) and adamantanone (**233**) also afforded no product, which may suggest that the ketone requires an enolisable proton for the reaction to be successful (see Scheme 5.54).

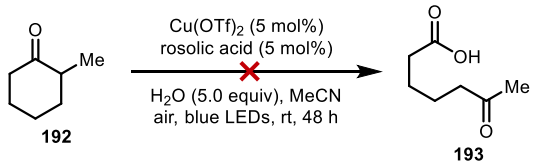
Table 6.12: *Initial screening of oxidative cleavage scope.*



Loxoprofen methyl ester (**218**) was investigated further as we ideally wanted to be able to perform our atom exchange process on drug-like molecules. At 60 °C no reaction was

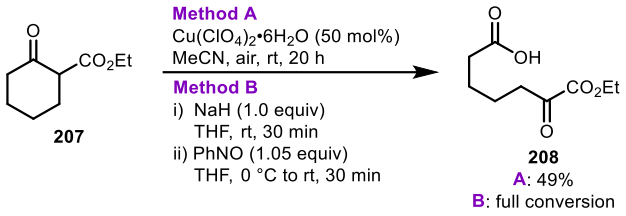
observed, however at 100 °C the starting material was slowly consumed. Unfortunately, no product was able to be isolated. Haung's conditions were tested, but also led to no reaction.[220] In the case of menthone (**274**) increasing the temperature was beneficial, as 24 hours at 60 °C gave a 63% NMR yield, while 24 hours at 80 °C gave a 73% NMR yield. Ketone **273**, whilst giving full conversion, only formed the product in a 15% NMR yield. In this the reaction was repeated at lower temperatures, but this gave no improvements.

Guo reported the oxidative cleavage of cyclic ketones utilising copper catalysis, which was aided by a photosensitiser and blue LEDs.[218] Their reported methodology was attractive as it had the largest reported scope all the oxidative cleavage methods. Additionally good yields were consistently obtained, even on alkyl-substituted ketones which often performed worse using other methods. Attempts to repeat this work using ketone **192** was unsuccessful with ketoacid **193** being unable to be isolated (Scheme 6.26). Brief attempts were made to get the reaction to work, such as varying the temperature, solvent, and substrate, however none of these changes were fruitful. The authors also demonstrated that upon scaling the reaction up that the reactions could take upwards of 96 hours. Based on the information above this methodology was not explored further.



Scheme 6.26: *Attempted oxidative cleavage of* ***192*** *using Guo's conditions.*

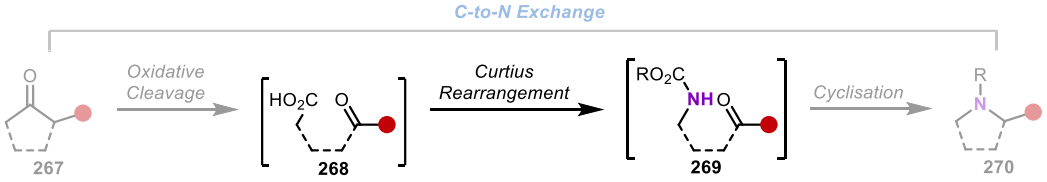
Several of the failed substrates were also examined in greater depth. Adamantanone (**233**) and methyl jasmonate (**277**) were tested using various other conditions such as Haung's conditions, Guo's conditions, along with the $Cu(ClO_4)_2$/$Cu(NO_3)$ mediated aerobic oxidative cleavage, however all of these methods exhibited no reactivity.[213,214] The Ketoester **207** was also investigated further as the products would be of high value. In this case there are several reports of the oxidative cleavage that specifically targets such substrates (Scheme 6.27). Method A utilised copper-catalysis and afforded **208** in a 49% yield.[244] Method B first deprotonates at the α-position which then reacts with nitrosobenzene to give full conversion of the starting material.[245] Both of these methods hold promise for the oxidative cleavage of **207** as part of the atom exchange process.



Scheme 6.27: *Oxidative cleavage of ketoester **207**.*

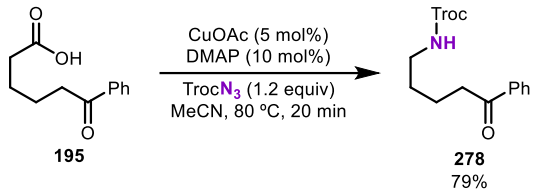
In summary Takemoto's methodology was promising for the oxidative cleavage of cyclic α-substituted ketones **267**. However, in the case of the cyclic β-ketoester **207** alternative methodologies can be employed to access the product **208**.

6.3.2 Curtius Rearrangement



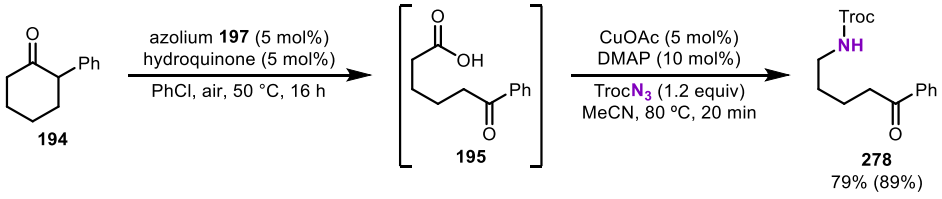
Scheme 6.28: *Outline of the proposed modified C-to-N atom exchange process.*

A Curtius rearrangement was again utilised as the method to introduce the nitrogen atom. Given that extensive work was done on this step in the previous attempted atom exchange process, the conditions were simply transplanted to the ketoacid **195** to affording the carbamate **278** in a 79% yield (Scheme 6.29).



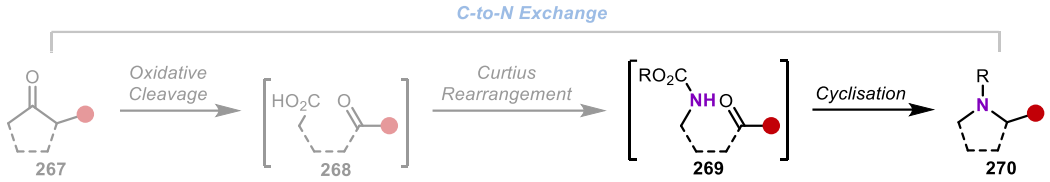
Scheme 6.29: *Curtius rearrangement of ketoacid **195**.*

With these results in hand an initial attempt to telescope the first two steps together formed **278** in a 79% yield over two steps, which was very promising. It was here where the simple conditions of the oxidative cleavage is exemplified, as only a simple solvent swap was required.



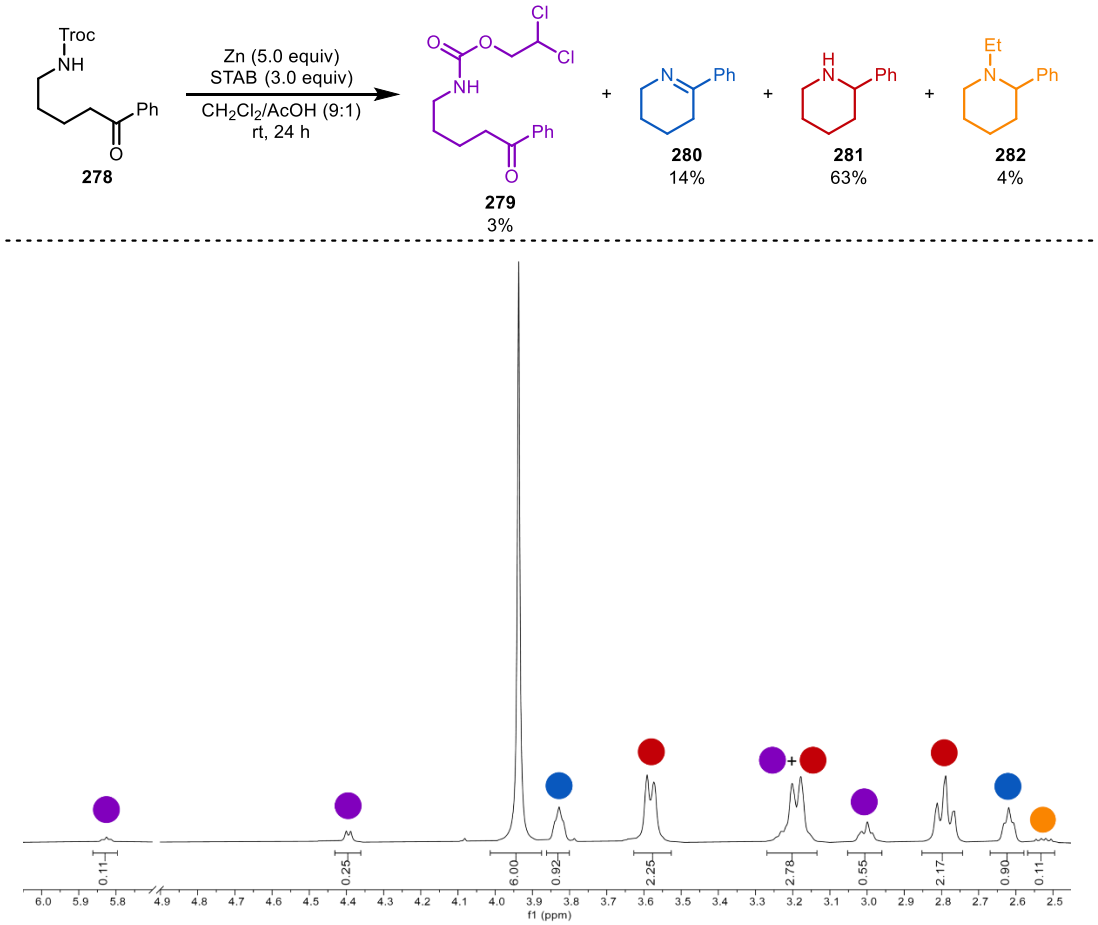
Scheme 6.30: *Telescoped procedure of converting **194** to **278**. Yield in brackets refer to average yield per step. Yield determined by ^{1}H NMR analysis using DMT as an internal standard.*

6.3.3 Cyclisation



Scheme 6.31: *Outline of the proposed modified C-to-N atom exchange process.*

Finally, the last step, a reductive cyclisation between the carbamate and the ketone was investigated. The most obvious method for this transformation is an initial deprotection followed by a reductive amination. Ideally this sequence would be done in a single pot; fortunately, Troc carbamates are conventionally deprotected under reductive conditions which helps facilitate this goal.[246] Our initial idea was that it may be possible to use conditions that would perform both steps in one pot, Zn/AcOH for the Troc deprotection and STAB for the reductive amination step (Scheme 6.32).



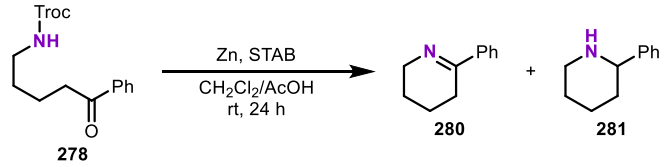
Scheme 6.32: *Yields determined by ^{1}H NMR analysis using DMT as an internal standard.*

Gratifyingly subjection of carbamate **278** under the conditions shown afforded 63% of the desired product **281**. Notably, there were several other species identified, such as 14% of the intermediate imine **280**. Later work eventually led to the identification of small

amounts of the *N*-ethylated product **282** and the protodechlorinated Troc group **279** from crude NMR spectra and mass spectrometry data. **282** is believed to be formed due to overreaction with STAB, which has been reported to be a possible side-reaction in the literature.[237] The protodechlorinated Troc group **279** is believed to be formed from quenching of the intermediate radical with a hydrogen atom. The absence of a Troc CH_2 peak at 4.72 ppm implies that all the starting material was consumed. Whilst the integrals of **279** at 5.83 ppm and 4.39 ppm corelate together the integral of the peak at 3.01 ppm is larger than expected. This suggests that there is another species present which we were unable to identify. Given the similarity in the chemical shifts between this impurity and the starting material it is likely they are structurally similar, with the impurity possibly being either the isocyanate or carbamic acid derivative.

As only the imine **280** had been identified at this point, initial optimisation focussed on maximising conversion to the product **281** (Table 6.13). Reducing the amount of AcOH to 3.0 equivalents (Entry 1) gave full conversion of **280**, but a lower yield of 51% compared to the initial result (Entry 2). Varying the ratio of the solvents (Entry 2 and 4) and extending the reaction time (Entry 3) appeared to have minor effects, with no clear correlation between these parameters and the yield. Increasing the equivalents of Zn (Entry 5 and 10) or using TFA (Entry 6) both had a detrimental effect on the yield of **281**. It was postulated that increasing the amount of STAB would push the reduction of the imine **280** to **281**, and whilst this can be seen in certain cases (Entries 4, 7 and 8), repeat reactions (Entry 9) break this trend which suggested that the reaction may be capricious. Additionally, there was no direct correlation with increasing the equivalents of STAB and the yield of **281**. In all examples retrospective analysis of the crude NMR data showed that the other impurities (**279** and **282**) accounted for ~13% of the mass balance, with no clear trends between the conditions and the impurity profile of the reaction. For the deprotection step an indium-mediated deprotection was tested affording the imine **280**, and a small amount of the piperidine **281**, resulting from *in situ* reduction.[247,248] However it is unlikely that these conditions would reduce a non-activated imine, therefore a reductive amination step would generally be required which in turn would require an intermediate workup due to the reaction conditions. Based on this, along with the price of In compared to Zn, this approach was not pursued further.

Table 6.13: *Initial screening for the deprotection/reductive amination of* ***278****.*

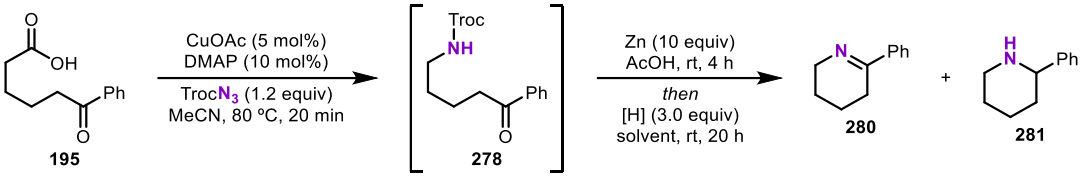


Entry	STAB (equiv)	Zn (equiv)	DCM/AcOH	280 (%)	281 (%)
1[a]	2.5	5.0	3.0 equiv	0	51
2	3.0	5.0	9:1	14	63
3[b]	3.0	5.0	9:1	17	52
4	3.0	5.0	4:1	12	52
5	3.0	10	4:1	20	45
6[c]	3.0	10	9:1	9	10
7	4.0	5.0	9:1	8	48
8	5.0	5.0	9:1	3	48
9	5.0	5.0	9:1	8	54
10	5.0	10	4:1	11	41

Yields determined by ^{1}H NMR analysis using DMT as an internal standard. [a]STAB was added after 5 hours. [b]48 h. [c]TFA was used.

Alternative reductants to STAB such as $NaBH_4$ and $NaCNBH_3$ were also tested, however, under the conditions above these gave poor results. Due little progress being made we subsequently investigated splitting the cyclisation into two parts, the deprotection and the reductive amination, with a solvent swap in-between. This would allow for more thorough investigation of the reduction conditions without the limitation on solvent. Additionally, in the case of $NaBH_4$ it would avoid the reduction of the ketone in **278**. For this set of screening, telescoping the Curtius rearrangement into the deprotection/reductive amination was also examined, utilising an aqueous workup in-between to remove any copper salts and DMAP (Table 6.14). Using STAB as the reductant in various solvents (Entries 1–4) did not lead to higher yields, however no intermediate imine **280** was remaining at the end of the reduction. $NaBH_4$ as the reductant showed promising results when used in MeOH (Entry 6) compared to AcOH (Entry 5). An attempt was also made to use $NaCNBH_3$ (Entry 7), though this gave poor results.

Table 6.14: *Optimisation of the deprotection/reductive amination of* ***195*** *via a Curtius rearrangement.*



Entry	[H]	Solvent	280 (%)	281 (%)
1	STAB	MeOH	0	36
2	STAB	MeCN	0	51
3	STAB	THF	0	52
4	STAB	DCE	0	33
5	$NaBH_4$	AcOH	26	29
6	$NaBH_4$	MeOH	0	64
7	$NaCNBH_3$	AcOH/DCM (4:1)	0	34

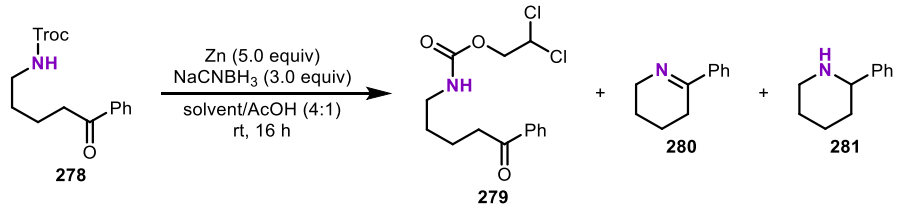
Yields determined by ^1H NMR analysis using DMT as an internal standard.

Simultaneously we also used this as an opportunity to exam methods of purification. The use of strong cation exchange resin (SCX) (either in the form of pre-packed cartridges or as Amberlyst-15 resin) was investigated for purification of amine **281**; this approach was found to be unreliable. However, the use of SCX provided valuable information in that it led to the identification of the *N*-ethylated product **282**. Similarly, it also showed that **282** and the imine **280** were isolated with the product **281** using this approach. Therefore, optimisation to ensure that there was no **282** and **280** at the end of the reaction would be required if we wanted to purify the product using this method or an acid/base extraction. When STAB was not utilized as the reductant (Entries 5–7) no *N*-ethylated product **282** was observed, therefore using an alternative reductant eliminates the formation of this impurity. Whilst $NaBH_4$ performed well we wanted to avoid this for several reasons: the possibility of forming STAB *in situ* and its potential to reduce any ketones present if the deprotection was not complete. Additionally, the use of $NaBH_4$ would require a solvent swap.

In an attempt to move away from $NaBH_4$, $NaCNBH_3$ was investigated further, screening various other solvents in the presence of AcOH (Table 6.15). THF, DCE and MeCN (Entries 1–3) all performed poorly with large amounts of the imine **280** being observed. MeOH as the solvent (Entry 4) showed very promising results with 71% of the product **281** being observed with only 4% of **280** remaining. When $NaCNBH_3$ was added after 3 hours (Entry 5) there was a surprising drop in the yield of the reaction. In all circumstances no *N*-ethylation of **282** was observed. In the last instance, due to its clean reaction profile, we

were able to identify **279**. Based on these results the amount of **279** formed was shown to be heavily dependent on the solvent used.

Table 6.15: *Solvent screen of the deprotection/reductive amination sequence using $NaCNBH_3$.*

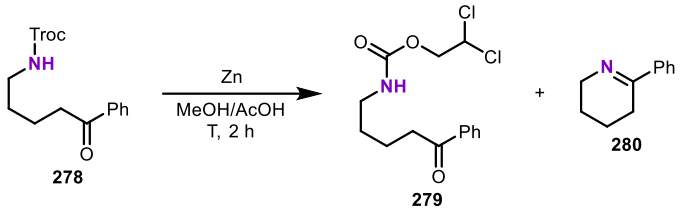


Entry	Solvent	279 (%)	280 (%)	281 (%)
1	THF	7	35	28
2	DCE	18	10	44
3	MeCN	7	25	31
4	MeOH	6	4	71
5[a]	MeOH	14	0	30
6	AcOH	20	0	46

Yields determined by ^{1}H NMR analysis using DMT as an internal standard. [a]$NaCNBH_3$ added after 2 hours.

The deprotection step was next studied to gain a better understanding of this step, and how to minimise the formation of the side product **279** (Table 6.16). The equivalents of Zn (Entry 1 and 2) as well as the purity of the Zn had little impact on the ratio of the products formed. The concentration of the reaction (Entry 7 and 8) and the temperature (Entry 1 and 2) also had negligible impact. The ratio of the solvents used had a substantial impact on the ratio of **279**/**280**; using a greater ratio of AcOH (Entries 2, 4, 5, 6 and 7) led to the almost selective formation of the imine **280**. However, the results in Table 6.16 does not align with previous results as when using MeOH/AcOH (4:1) as the solvent system (Table 6.15, Entry 4) only 6% of the side product **279** was observed, however when using solely AcOH (Table 6.15, Entry 6) 20% of **279** was observed. This would suggest that the inclusion of $NaCNBH_3$ in the deprotection step also have an impact the product distribution. To investigate this effect the deprotection/reductive amination was tested using various ratios of AcOH/MeOH (Table 6.17). Additionally, 5.0 equivalents of $NaCNBH_3$ were used to ensure full conversion of the imine **280**.

Table 6.16: *Optimisation of the deprotection step.*

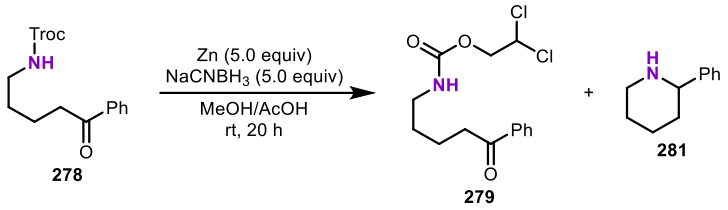


Entry	Zn (equiv)	AcOH/MeOH	Conc (M)	T (°C)	279/280
1	10	1:4	0.1	40	1:4.2
2	10	1:4	0.1	rt	1:5.0
3	20	1:4	0.1	rt	1:4.4
4	10	2:3	0.1	rt	1:7.1
5	5.0	3:2	0.1	rt	1:8.3
6	5.0	4:1	0.1	rt	1:10
7	5.0	5:0	0.05	rt	1:19
8	5.0	5:0	0.1	rt	1:19

*Ratio of **279/280** was determined from analysis of the crude ^{1}H NMR spectra.*

Formation of the product **281** was favoured when using a 2:3 ratio of AcOH/MeOH (Entry 2) compared to Entries 3 and 4, however the correlation observed between the amount of AcOH and **279** was less clear. To take advantage of the results in Table 6.16 reactions were screened where the deprotection in AcOH was stirred at room temperature for 4 hours and then diluted with MeOH and $NaCNBH_3$ added (Entries 5–7). The results from this were promising with the levels of **279** observed being low, and in the case of Entry 5, the yield of **281** was good. Even though comparable results had been obtained before (**Table 6.15**, Entry 4) this result was found to be more reliable, as well as having a very clean reaction profile which would enable purification *via* an acid/base extraction.

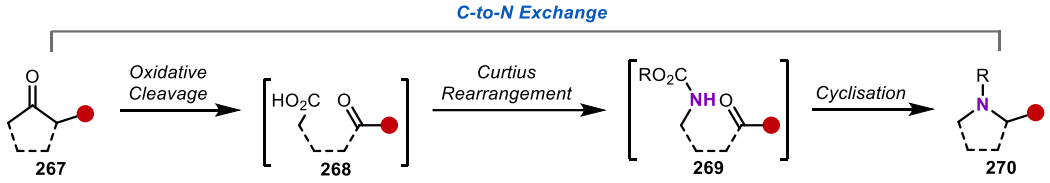
Table 6.17: *Solvent screen of the deprotection/reductive amination sequence using $NaCNBH_3$.*



Entry	AcOH/MeOH	279 (%)	281 (%)
1	AcOH	20	46
2	2:3	5	64
3	3:2	12	55
4	4:1	8	41
5[a]	1:2	3	70
6[a]	1:3	4	64
7[a]	1:4	4	63

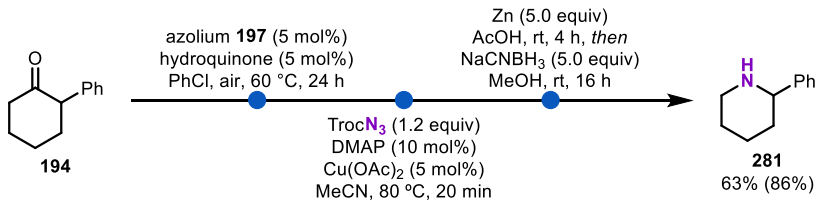
Yields determined by ^1H NMR analysis using DMT as an internal standard. [a]*Deprotection was done in AcOH for 4 hours, then MeOH/$NaCNBH_4$ was added and stirred for a further 16 hours.*

6.3.4 Telescoping Optimisation



Scheme 6.33: *Proposed alternative C-to-N atom exchange process.*

With all three steps optimised we next investigated stitching them together to make a general procedure for the C-to-N atom exchange of cyclic ketones **267**. Based on the results in the previous sections we arrived at the process as shown in Scheme 6.34 for the atom exchange of **194** into **281**.



Scheme 6.34: *C-to-N atom exchange of **194** into **281**. Yield in brackets refers to the average yield per step.*

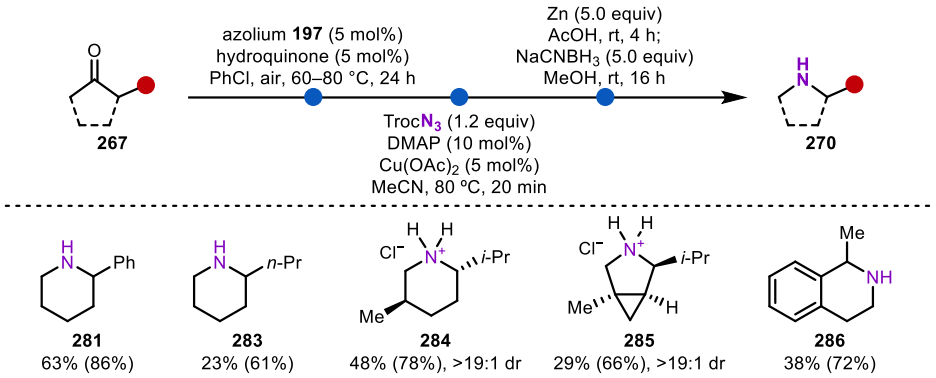
The procedure consisted of first subjecting the ketone **194** to the oxidative cleavage conditions followed by a solvent swap, and then performing the Curtius rearrangement. At this point an aqueous acidic wash was performed to remove any copper salts and DMAP which may hamper subsequent reactions and purifications. The crude carbamate was then subjected to the developed deprotection/reductive amination sequence. Finally,

purification by an acid/base workup affords pure **281** in a 62% yield over 3 steps without any column chromatography being required. It was observed that the azolium **197** carried through all three steps as it was not soluble in the aqueous acidic layer, however it was caught when using an acidic resin, ruling out purification *via* SCX resin.

6.3.5 Substrate Scope

The current scope for the process is as shown in Table 6.18. Piperidine **281** worked well, being isolated in a 63% yield over 3 steps, equating to an 86% average yield per step. Alkyl substituted ketones were also tolerated with the natural alkaloid **283** being formed in a 23% yield. Simple natural products could also be employed as starting materials, with the nitrogen containing analogues of menthone (**284**) and thujone (**285**) being afforded in good to moderate yields, along with excellent diastereoselectivity. Finally, this process has also been demonstrated to work on fused ring systems to form a tetrohydroisoquinoline **286**. We hope to explore this chemistry on a variety of other cyclic ketones, as discussed further in the future work section below.

Table 6.18: *Scope of the C-to-N atom exchange of cyclic ketones.*

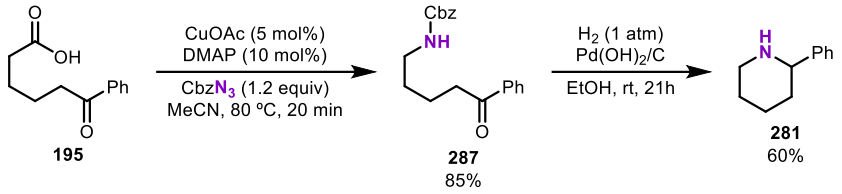


*Reactions employed 1.0 mmol of **267**. **284** and **285** were isolated as the HCl salt via addition of 2 M HCl in Et_2O to the organic solution after the workup.*

6.3.6 Alternative Cyclisation Methods Investigated

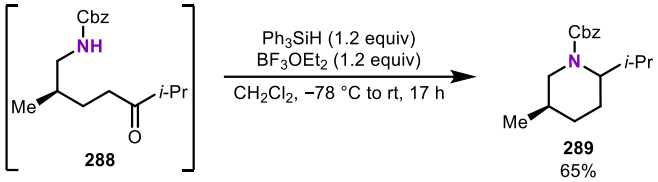
As we had shown that we could access Cbz-protected amines (**287**) in the Curtius rearrangement (Table 6.6) we also investigated these as cyclisation precursors. The first idea was that a hydrogenation step that would not only cleave the protecting group, but also reduce the imine formed *in situ*. Initial attempts using Pd/C as the hydrogenation catalyst unfortunately gave no reactivity, however switching over to $Pd(OH_2)/C$ afforded piperidine **281** in a 60% yield (Scheme 6.35). Attempts to translate this to other substrates, such as the menthone derivative **288**, were not compatible with the protecting group remaining intact and starting material recovered. Various conditions were attempted to

resolve this, such as using transfer hydrogenation conditions at elevated temperatures, however these all gave complex mixtures.



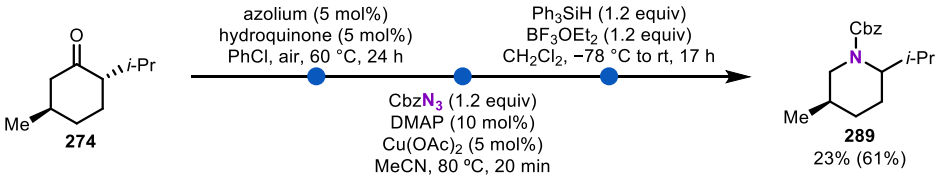
Scheme 6.35: *Curtius rearrangement of* ***195*** *followed by cyclisation under hydrogenation conditions. Yields determined by* ^{1}*H NMR analysis using DMT as an internal standard.*

Menthone derivative **288** was further examined due to its lack of reactivity under the hydrogenation conditions. The direct reductive cyclisation was attempted utilising a Lewis acid and a reductant which afforded the cyclic carbamate **289** (Scheme 6.36).



Scheme 6.36: *Reductive cyclisation of* ***288****. Yields determined by* ^{1}*H NMR analysis using DMT as an internal standard. Major diastereomer not determined.*

Unfortunately, when we attempted use this in conjunction with the other steps only a 23% yield was observed over three steps (Scheme 6.37).



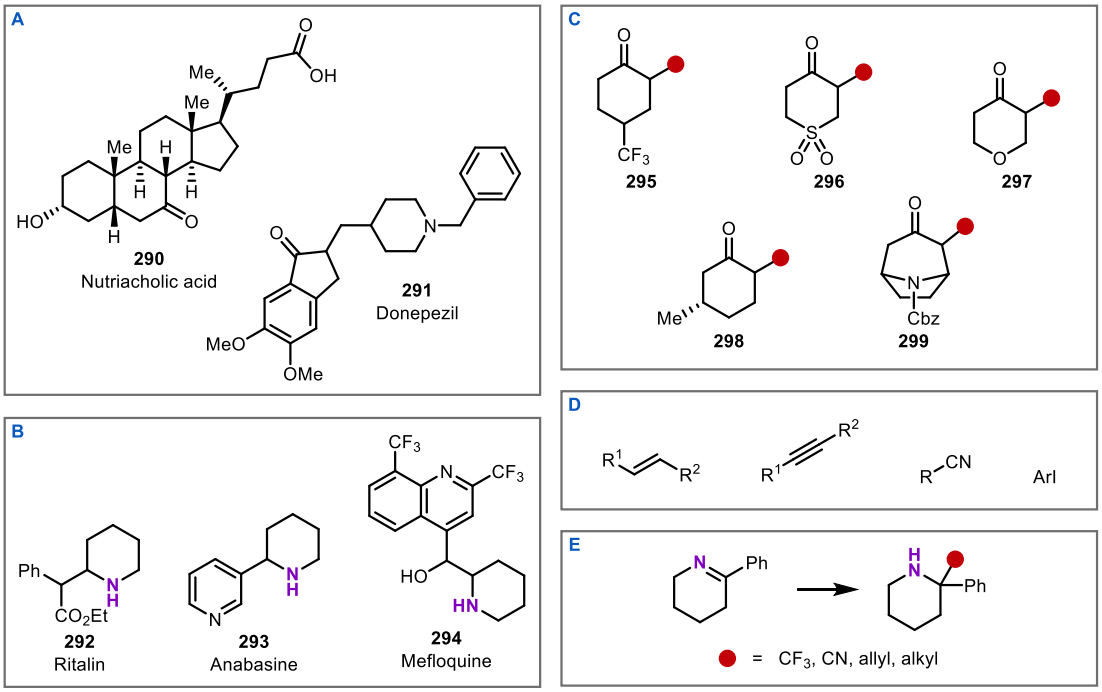
Scheme 6.37: *C-to-N atom exchange of* ***274****. Yields determined by* ^{1}*H NMR analysis using DMT as an internal standard. Major diastereomer not determined.*

6.3.7 Conclusions and Future Work

In conclusion we have developed a C-to-N atom exchange process to take α-substituted cyclic ketones, a versatile and readily available scaffold, and convert them into valuable heterocyclic products. The two-pot procedure is operationally simple and requires no column chromatography, utilising only two aqueous workups. The atom exchange process has been shown to work on several cyclic ketones, including terpene-based ketones such as menthone and thujone.

In the future we hope to apply this chemistry to various other substrates, such as the application to complex biologically relevant compounds (**290** and **291**) as a tool for late-stage functionalisation (Scheme 6.38A). Alternatively, this chemistry could also be used to

make biologically relevant compounds and natural products (**292–294**) (Scheme 6.38B). For the general substrate scope a diverse range of substrates could be explored, investigating the tolerated functional groups, ring sizes, and heterocycles (**296** and **297**) to make fragments that may be of interest to industry (Scheme 6.38C). Enantioenriched ketones (**298**) could also be used to access valuable enantioenriched heterocyclic products. This methodology would allow access to 2,5-disubstituted piperidines with *trans*-stereochemistry which is orthogonal to reductive processes from the parent pyridine where *cis*-stereochemistry is typically observed.[249] Given that the reduction of pyridines is a key pathway to accessing piperidines it would be good to explore reducible functional groups that may not be tolerated under hydrogenation conditions, but may be tolerated under Zn/AcOH, such as alkenes, alkynes, nitriles and aryl halides (Scheme 6.38D). Finally, the intermediate imine formed could potentially be further exploited by adding various nucleophiles to introduce new moieties such as a trifluoromethyl, nitrile, allyl, alkyl or aryl substituent, forming a quaternary centre (Scheme 6.38E).[250–252]



Scheme 6.38: *Future work. A) C-to-N exchange on biologically relevant compounds. B) C-to-N exchange to afford biologically relevant compounds or natural products. C) Application to synthetically valuable fragments. D) Reducible functional groups. E) Further derivatisation of the intermediate imine.*

Further investigations will also be done into improving the final workup, as currently it can be difficult to perform due to the emulsions that form (likely due to the excess of zinc salts present). To address this various basic aqueous solutions could be tested, such as NH_4OH, to see if these offer improvements, or addition of a chelator such as Rochelle's salt or EDTA. If those offer no improvement then it may be possible to separate the emulsion using a centrifuge to make the purification much easier, and more consistent.

7 EXPERIMENTAL

7.1 GENERAL INFORMATION

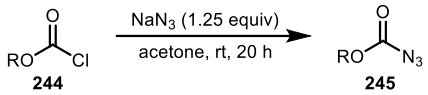
All air-sensitive reactions were carried out under an inert atmosphere using oven-dried apparatus. All commercially available reagents were used as received unless otherwise stated. Petroleum ether refers to Sigma-Aldrich product 24587 (petroleum ether boiling point 40–60 °C). Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien 60F254 0.2 mm precoated plates. Compounds were visualised by exposure to UV light or by dipping the plates into solutions of potassium permanganate or vanillin followed by gentle heating. Flash column chromatography was carried out using silica gel (Fisher Scientific 60 Å particle size 35-70 micron or Fluorochem 60 Å particle size 40-63 micron).

Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. The solvent of recrystallisation is reported in parentheses. Infrared (IR) spectra were recorded on Bruker platinum alpha FTIR spectrometer on the neat compound using the attenuated total reflectance technique. High resolution mass spectra were recorded using electrospray ionisation (ESI) techniques.

NMR spectra were acquired on Bruker Ascend 400 or Ascend 500 spectrometers. ^{1}H and ^{13}C NMR spectra were referenced to external tetramethylsilane *via* the residual protonated solvent (^{1}H) or the solvent itself (^{13}C). ^{19}F NMR spectra were referenced through the solvent lock (^{2}H) signal according to the IUPAC-recommended secondary referencing method following Bruker protocols. All chemical shifts are reported in parts per million (ppm). For $CDCl_3$, the shifts are referenced to 7.26 ppm for ^{1}H NMR spectroscopy and 77.16 ppm for ^{13}C NMR spectroscopy. Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. High resolution mass spectra were recorded using electrospray ionisation (ESI) techniques. Coupling constants are quoted in Hz (J). ^{1}H NMR splitting patterns were designated as singlet (s), doublet (d), triplet (t), quartet (q), pentet (p). Splitting patterns that could not be interpreted or easily visualised were designated as multiplet (m), apparent (app) or broad (br).

7.2 Preparation of Key Intermediates

General Procedure A: Azidoformate Synthesis



To a suspension of NaN_3 (1.25 equiv) in acetone (30 ml) at room temperature was added the chloroformate (1.0 equiv) dropwise over 10 minutes. The flask was then sealed, wrapped in foil, and stirred for 20 h at room temperature. The solution was filtered through celite (EtOAc), and the filtrate concentrated *in vacuo* to give the title compound. *Note: use of clean chloroformate afforded the product clean after a celite plug, otherwise column chromatography was necessary.*



2,2,2-Trichloroethyl carbonazidate (246). Prepared according to General Procedure A using NaN_3 (1.63 g, 25.0 mmol) and 2,2,2-trichloroethyl chloroformate (2.75 mL, 20.0 mmol). The azidoformate **246** was obtained as a colourless oil (4.36 g, >99%). The analytical data were consistent with those previously reported.[253]

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.82 (2H, s, C**H**$_2$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.8 (C), 93.9 (C), 76.7 (CH_2).



Benzyl carbonazidate (247). Prepared according to modification of General Procedure A using NaN_3 (1.63 g, 25.0 mmol) and benzyl chloroformate (2.86 mL, 20.0 mmol). The crude residue was purified by a silica plug (3% EtOAc/petroleum ether) to give the azidoformate **247** as a colourless oil (3.47 g, 98%). The analytical data were consistent with those previously reported.[254]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.35 (5H, m, Ar**H**), 5.24 (2H, s, C**H**$_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.6 (C), 134.5 (C), 129.0 (CH), 128.8 (2 × CH), 128.6 (2 × CH), 70.2 (CH_2).

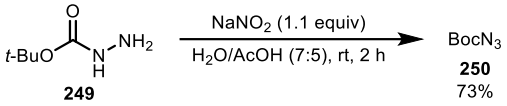


(9*H*-Fluoren-9-yl)methyl carbonazidate (248). Prepared according to modification of General Procedure A using NaN_3 (1.63 g, 25.0 mmol) and (9*H*-fluoren-9-yl)methyl chloroformate (4.53 g, 20.0 mmol). The crude residue was purified by column chromatography (0 to 5% EtOAc/petroleum ether) to give the azidoformate **248** as a colourless oil (3.25 g, 70%). The analytical data were consistent with those previously reported.[254]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (2H, dt, *J* = 7.5, 1.1 Hz, Ar**H**), 7.59 (2H, dd, *J* = 7.5, 0.9 Hz, Ar**H**), 7.43 (2H, tt, *J* = 7.5, 0.9 Hz, Ar**H**), 7.34 (2H, td, *J* = 7.5, 1.1 Hz, Ar**H**), 4.49 (2H, d, *J* = 7.3 Hz, C**H**$_2$), 4.27 (1H, t, *J* = 7.4 Hz, C**H**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7 (C), 143.1 (2 × C), 141.5 (2 × C), 128.2 (2 × CH), 127.4 (2 × CH), 125.2 (2 × CH), 120.3 (2 × CH), 70.4 (CH_2), 46.6 (CH).

tert-Butyl carbonazidate (250)

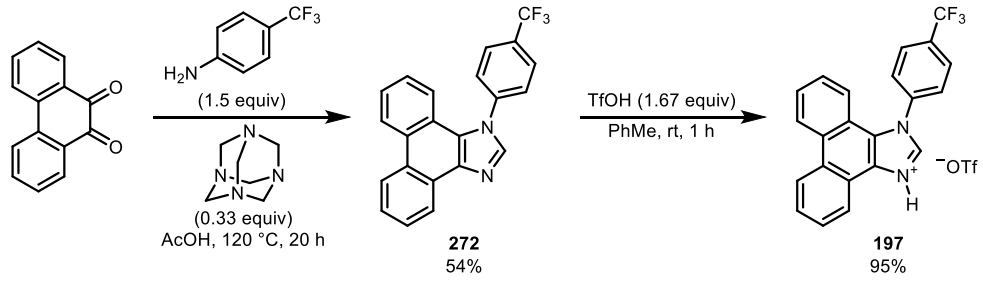


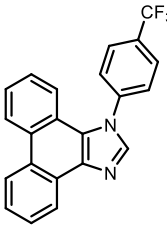
To a solution of hydrazine **249** (3.00 g, 22.7 mmol) in H_2O (7 mL) and AcOH (5 mL) at 0 °C was added $NaNO_2$ (1.72 g, 25.0 mmol) over 5 minutes and the resulting solution heated to room temperature and stirred for 2 h. The reaction was diluted with H_2O (20 mL) and the mixture was extracted with Et_2O (3 × 30 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ (2 × 30 mL), brine (30 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give azidoformate **250** (2.37 g, 73%) as a yellow liquid. The analytical data were consistent with those previously reported.[255]

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (9H, s, C(C**H**$_3$)$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9 (C), 84.8 (C), 27.8 (3 × CH_3).

1-[4-(Trifluoromethyl)phenyl]-1*H*-phenanthro[9,10-*d*]imidazol-3-ium trifluoromethanesulfonate (197)

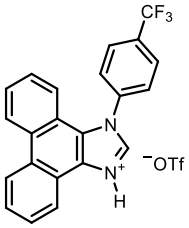




1-(4-(Trifluoromethyl)phenyl)-1*H*-phenanthro[9,10-*d*]imidazole (272). To a solution of phenanthrene-9,10-dione (2.08 g, 10.0 mmol) and hexamethylenetetramine (459 mg, 3.30 mmol) in AcOH (10 mL) at room temperature was added 4-(trifluoromethyl)aniline (1.88 mL, 15.0 mmol), and the resulting solution heated at 120 °C for 20 h. The reaction was diluted with H_2O (50 mL) and the solid filtered. The solid was then redissolved in toluene and then filtered to remove any trace solids/oily residue and the filtrate concentrated *in vacuo*. The residue was purified by recrystallisation from hot EtOH to give **272** (1.94 g, 54%) as brown flakes. The analytical data were consistent with those previously reported.[256]

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82–8.67 (3H, m, Ar**H**), 7.98 (1H, s, Ar**H**), 7.92 (2H, d, *J* = 8.3 Hz, Ar**H**), 7.78–7.71 (3H, m, Ar**H**), 7.68 (1H, ddd, *J* = 8.3, 7.0, 1.5 Hz, Ar**H**), 7.58 (1H, ddd, *J* = 8.3, 6.7, 1.6 Hz, Ar**H**), 7.43–7.34 (2H, m, Ar**H**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.7 (CH), 141.1 (C), 138.7 (C), 131.9 (q, *J* = 33.3 Hz, C), 129.5 (C), 128.6 (C), 127.70 (CH), 127.66 (2 × CH), 127.4 (q, *J* = 3.9 Hz, 2 × CH), 127.3 (C), 126.6 (CH), 126.2 (C), 126.1 (CH), 125.7 (CH), 124.5 (CH), 123.8 (q, *J* = 272 Hz, C), 123.3 (CH), 122.8 (CH), 122.5 (C), 121.2 (CH).

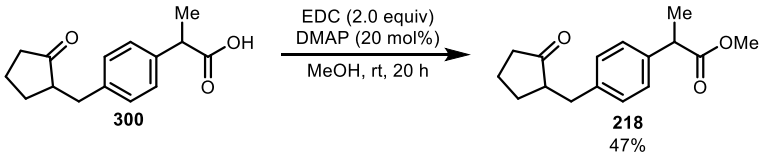


1-(4-(Trifluoromethyl)phenyl)-1*H*-phenanthro[9,10-*d*]imidazol-3-ium triflate (197). Amine **272** (1.94 g, 5.40 mmol) was dissolved in the minimum amount of toluene, and then to the stirred solution at room temperature TfOH (0.80 mL, 9.00 mmol) was added, and the mixture stirred for a further 1 h. The solid was filtered and washed with Et_2O, toluene and pentane to give **197** (2.55 g, 95%) as a beige solid. The analytical data were consistent with those previously reported.[257]

^{1}H NMR (500 MHz, $CDCl_3$) δ 15.89 (1H, s, N**H**), 9.17 (1H, s, Ar**H**), 8.84 (1H, d, *J* = 7.9 Hz, Ar**H**), 8.79–8.74 (1H, m, Ar**H**), 8.61–8.51 (1H, m, Ar**H**), 8.07 (2H, d, *J* = 8.3 Hz, Ar**H**), 7.89 (2H, d, *J* = 8.3 Hz, Ar**H**), 7.88–7.83 (2H, m, Ar**H**), 7.77 (1H, ddd, *J* = 8.4, 7.1, 1.3 Hz, Ar**H**), 7.49 (1H, ddd, *J* = 8.2, 7.1, 1.1 Hz, Ar**H**), 7.30 (1H, dd, *J* = 8.3, 1.2 Hz, Ar**H**).

^{13}C NMR (101 MHz, CD_2Cl_2) δ 138.4 (CH), 138.2 (C), 134.5 (q, *J* = 33.7 Hz, C), 130.9 (C), 130.2 (C), 129.6 (2 × CH peaks concealed as one), 128.8 (CH), 128.6 (q, *J* = 3.7 Hz, 2 × CH), 128.5 (CH), 128.3 (2 × CH), 128.0 (C), 126.1 (C), 125.2 (CH), 124.3 (CH), 123.7 (q, *J* = 270.2 Hz, C), 123.0 (CH), 121.7 (CH), 120.8 (q, *J* = 316.2 Hz, C), 120.5 (C), 120.5 (C).

Loxoprofen methyl ester (218)



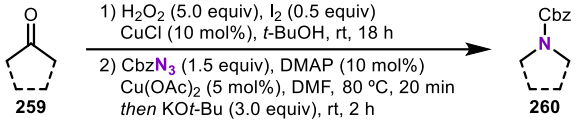
To a solution of loxoprofen (1.23 g, 5.00 mmol) and DMAP (122 mg, 1.00 mmol) in MeOH (30 mL) at 0 °C was added EDC (1.92 g, 10.0 mmol) and the resulting solution heated to room temperature and stirred for 20 h. The reaction was diluted with H_2O (50 mL) and then extracted with EtOAc (3 × 50 mL). The organics were washed with saturated aqueous ammonium chloride (50 mL), saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL), and then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography to give the product **218** (615 mg, 47%) as a colourless oil. The analytical data were consistent with those previously reported.[258]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (2H, d, *J* = 8.2 Hz, Ar**H**), 7.12 (2H, d, *J* = 8.2 Hz, Ar**H**), 3.69 (1H, q, *J* = 7.2 Hz, CHC**H**$_3$), 3.66 (3H, s, OC**H**$_3$), 3.12 (1H, dd, *J* = 13.9, 4.1 Hz, ArC**H**$_a$H$_b$), 2.50 (1H, dd, *J* = 13.9, 9.6 Hz, ArCH$_a$**H**$_b$), 2.40–2.27 (2H, m, C**H**C=O and C**H**$_a$H$_b$C=O), 2.17–2.04 (2H, m, CH$_a$**H**$_b$C=O and C**H**$_a$H$_b$), 2.02–1.91 (1H, m, CHC**H**$_a$H$_b$), 1.82–1.65 (1H, m, CHCH$_a$**H**$_b$), 1.59–1.50 (1H, m, CH$_a$**H**$_b$), 1.48 (3H, d, *J* = 7.2 Hz, CHC**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 220.3 (C), 175.2 (C), 139.0 (C), 138.5 (C), 129.3 (2 × CH), 127.6 (2 × CH), 52.2 (CH_3), 51.1 (CH), 45.1 (CH), 38.3 (CH_2), 35.3 (CH_2), 29.4 (CH_2), 20.7 (CH_2), 18.7 (CH_3).

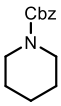
7.3 Atom Exchange via Halo-Acid

General Procedure B: C-to-N Atom Exchange of Cyclic Ketones



To a solution of the ketone (0.50 mmol) in *t*-BuOH (0.5 mL) at room temperature was added I_2 (63.4 mg, 0.25 mmol), CuCl (4.95 mg, 0.10 mmol) and H_2O_2 (30% w/w in H_2O, 3.0 mmol, 255 μL), and the resulting mixture was stirred for 18 h. The crude mixture was then filtered through a silica plug (h = 7 cm, d = 3 cm, washed with pentane [until the filtrate went from purple to colourless] and then eluting with Et_2O) and concentrated *in vacuo* to give the crude acid.

The crude material was redissolved in anhydrous DMF (2.0 mL) at room temperature and $CbzN_3$ (133 mg, 0.75 mmol), DMAP (6.11 mg, 0.050 mmol) and $Cu(OAc)_2$ (4.54 mg, 0.025 mmol) were added. The reaction mixture was heated at 80 °C for 10 minutes and then cooled back to room temperature. KO*t*-Bu (168 mg, 1.50 mmol) was added, the vessel rinsed with anhydrous DMF (0.5 mL), and the mixture stirred at room temperature for 2 hours. The reaction was quenched with 1 M HCl (10 mL) and separated. The organic layer was washed with brine (10 mL) and the organics dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was then purified by column chromatography to give the title compound.



Benzyl piperidine-1-carboxylate (252). Prepared according to General Procedure B using cyclohexanone (52 μL, 0.50 mmol). Purification by column chromatography (6% EtOAc/pentane) gave **252** as a colourless oil (46.4 mg, 42% over 3 steps). The analytical data were consistent with those previously reported.[259]

R_f = 0.25 (8% EtOAc/petrol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.27 (5H, m, Ar**H**), 5.13 (2H, s, C**H**$_2$Ar), 3.48–3.40 (4H, m, 2 × NC**H**$_2$), 1.64–1.47 (6H, m, 3 × C**H**$_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4 (C), 137.1 (C), 128.5 (2 × CH), 127.9 (CH), 127.8 (2 × CH), 66.9 (CH_2), 44.9 (CH_2), 25.7 (CH_2), 24.4 (CH_2).



Benzyl pyrrolidine-1-carboxylate (261). Prepared according to General Procedure B using cyclopentanone (44 µL, 0.50 mmol). Purification by column chromatography (0 to 4% EtOAc/CH_2Cl_2) gave **261** as a colourless oil (14.5 mg, 14% over 3 steps). The analytical data were consistent with those previously reported.[259]

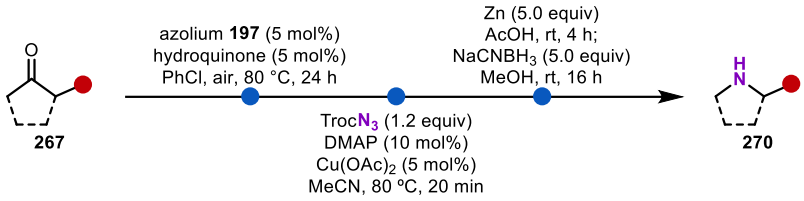
R_f = 0.45 (4% EtOAc/CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.27 (5H, m, Ar**H**), 5.14 (2H, s, C**H**$_2$Ar), 3.44–3.36 (4H, m, 2 × NC**H**$_2$), 1.89–1.83 (4H, m, 2 × C**H**$_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.1 (C), 137.3 (CH), 128.6 (2 × CH), 128.0 (2 × CH), 66.7 (CH_2), 46.2 (br, 2 × CH_2), 25.8 and 25.2 (2 × CH_2).

7.4 Atom Exchange via Keto-Acid

General Procedure C: C-to-N Atom Exchange of α-Substituted Cyclic Ketones

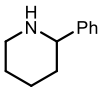


To a solution of the ketone (1.00 mmol) in chlorobenzene (5 mL) at room temperature was added hydroquinone (5.50 mg, 0.05 mmol) and azolium (**197**) (25.6 mg, 0.05 mmol), the mixture was then stirred at 80 °C for 24 h. The solvent was removed by blowing a stream of N_2 over the hot solution to give the crude acid.

The residue was re-dissolved in anhydrous MeCN (10 mL) at room temperature, and then $Cu(OAc)_2$ (9.10 mg, 0.05 mmol), DMAP (12.2 mg, 0.10 mmol) and $TrocN_3$ (262 mg, 1.20 mmol) were added followed by further anhydrous MeCN (10 mL). The mixture was then heated at 80 °C for 20 min. The reaction was diluted with 10% HCl (15 mL) and the mixture extracted with EtOAc (2 × 25 mL). The combined organics were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give the crude carbamate.

The residue was re-dissolved in AcOH (5 mL) at room temperature, and then Zn (327 mg, 5.00 mmol) was added, and the suspension stirred for 4 h at room temperature. To the reaction mixture was then added MeOH (10 mL) and $NaCNBH_3$ (314 mg, 5.00 mmol), and the suspension stirred for a further 16 h at room temperature. The MeOH was then removed *in vacuo* and the reaction diluted with H_2O (20 mL) and basified with 10 M

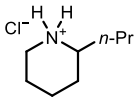
NaOH. The mixture was extracted with CH_2Cl_2 (4 × 10 mL), and then the combined organics were extracted with 10% HCl (3 × 10 mL). The combined aqueous layers were basified with 10 M NaOH and then extracted with CH_2Cl_2 (3 × 20 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give the pure amine product. *Note: If the amine product may be volatile, then 2 M HCl in Et_2O was added to the organics (after filtration of Na_2SO_4) to form the ammonium salt.*



2-Phenylpiperidine (281). Prepared according to General Procedure C using 2-phenylcyclohexan-1-one (174 mg, 1.0 mmol). Amine **281** (101 mg, 63% over 3 steps) was isolated as a yellow oil. The analytical data is consistent with that previously reported.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.33 (2H, m, Ar**H**), 7.33–7.29 (2H, m, Ar**H**), 7.25–7.21 (1H, m, Ar**H**), 3.59 (1H, dd, *J* = 10.4, 2.8 Hz, C**H**), 3.23–3.16 (1H, m, NC**H**$_a$H$_b$), 2.80 (1H, td, *J* = 11.6, 2.8 Hz, NCH$_a$**H**$_b$), 1.93–1.85 (1H, m, CHC**H**$_a$H$_b$), 1.84–1.73 (1H, m NCH$_2$C**H**$_a$H$_b$ and N**H**), 1.71–1.63 (1H, m, C**H**$_a$H$_b$), 1.61–1.46 (3H, m CHCH$_a$**H**$_b$ and NCH$_2$C**H**$_a$H$_b$ and C**H**$_a$H$_b$).

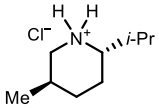
^{13}C NMR (126 MHz, $CDCl_3$) δ 145.7 (C), 128.5 (2 × CH), 127.1 (CH), 126.8 (2 × CH), 62.5 (CH), 48.0 (CH_2), 35.1 (CH_2), 26.1 (CH_2), 25.6 (CH_2).



Coniine hydrochloride (283). Prepared according to General Procedure C using 2-propylcyclohexan-1-one (140 mg, 1.00 mmol). Amine **283** (38.1 mg, 23% over 3 steps) was isolated as a colourless solid. The analytical data is consistent with that previously reported.[260]

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.47 (1H, s, N**H**), 9.17 (1H, s, N**H**), 3.45 (1H, d, *J* = 12.6 Hz, NC**H**$_a$H$_b$), 2.98–2.87 (1H, m, NC**H**), 2.87–2.75 (1H, m, NCH$_a$**H**$_b$), 2.02–1.87 (4H, m, C**H**$_a$H$_b$Et and CHC**H**$_a$H$_b$ and NCH$_2$**H**$_a$H$_b$ and NCH$_2$CH$_2$C**H**$_a$H$_b$), 1.85–1.78 (1H, m, NCH$_2$CH$_2$CH$_a$**H**$_b$), 1.76–1.59 (2H, m, CH$_a$**H**$_b$Et and NCH$_2$H$_a$**H**$_b$), 1.54–1.36 (3H, m, C**H**$_2$CH$_3$ and CHCH$_a$**H**$_b$), 0.94 (3H, t, *J* = 7.3 Hz, C**H**$_3$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 57.4 (CH), 44.9 (CH_2), 35.5 (CH_2), 28.4 (CH_2), 22.6 (CH_2), 22.4 (CH_2), 18.8 (CH_2), 13.9 (CH_3).



(2*R*,5*S*)-2-Isopropyl-5-methylpiperidin-1-ium chloride (284). Prepared according to General Procedure C using (+)-menthone (154 mg, 1.00 mmol). The crude amine salt was purified by trituration with Et_2O to give **284** (85.0 mg, 48% over 3 steps) as a colourless solid as a >19:1 mixture of diastereomers.

m.p. 206–208 °C ($CHCl_3$).

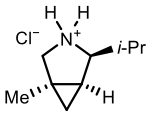
IR 3415, 3281, 2981, 2888, 1658, 1050, 1023, 1001, 823, 760 cm^{-1}.

$[\alpha]_D^{25}$ −16.0 (*c* 1.00, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.34 (1H, s, N**H**), 9.08 (1H, s, N**H**), 3.44 (1H, ddd, *J* = 12.5, 4.3, 2.2 Hz, NC**H**$_a$H$_b$), 2.66 (1H, tdt, *J* = 10.7, 4.9, 2.3 Hz, NC**H**), 2.44 (1H, tdd, *J* = 12.5, 10.6, 2.3 Hz, NCH$_a$**H**$_b$), 2.28–2.16 (1H, m, C**H**(CH$_3$)$_2$), 2.16–2.10 (1H, m, C**H**(CH$_3$)), 1.95–1.88 (1H, m, CHC**H**$_a$H$_b$), 1.88–1.82 (1H, m, NCHC**H**$_a$H$_b$), 1.70–1.58 (1H, m, NCHCH$_a$**H**$_b$), 1.11 (3H, d, *J* = 6.9 Hz, CHCHC**H**$_3$), 1.08 (4H, d, *J* = 6.9 Hz, CHCHC**H**$_3$ and CHCH$_a$**H**$_b$), 0.94 (3H, d, *J* = 6.6 Hz, C**H**$_3$).

^{13}C NMR (126 MHz, $CDCl_3$) δ *Major*: 63.0 (CH), 51.7 (CH_2), 31.7 (CH_2), 30.8 (CH), 28.4 (CH), 24.8 (CH_2), 20.0 (CH_3), 18.9 (CH_3), 18.0 (CH_3). *Minor*: 60.7(CH), 47.3(CH_2), 31.1 (CH_2), 27.4 (CH_2), 27.3 (CH), 22.4 (CH_2), 20.3 (CH_3), 19.1 (CH_3), 18.4 (CH_3).

HRMS (ESI) Exact mass calculated for $[C_9H_{20}N]^+$ [M+H]$^+$: 142.1590, found: 142.1584.



(1*S*,4*R*,5*S*)-1-Isopropyl-4-methyl-3-azabicyclo[3.1.0]hexan-3-ium chloride (185). Prepared according to General Procedure C using (−)-α-thujone (152 mg, 1.00 mmol). Amine **285** (51.1 mg, 29% over 3 steps) was isolated as a yellow oil as a >19:1 mixture of diastereomers.

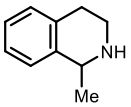
IR 3401, 2959, 2876, 2519, 2446, 1645, 1597, 1463, 1423, 1385 cm^{-1}.

$[\alpha]_D^{25}$ +28.0 (*c* 1.00, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.08 (1H, s, N**H**), 9.05 (1H, s, N**H**), 3.91 (1H, d, J = 9.9 Hz, NC**H**), 3.36 (1H, dd, J = 11.1, 6.0 Hz, NC**H**$_a$H$_b$), 3.26–3.16 (1H, m, NCH$_a$**H**$_b$), 1.62 (1H, p, J = 6.9 Hz, C**H**(CH$_3$)$_2$), 1.48 (3H, d, J = 6.4 Hz, NCHC**H**$_3$), 1.40 (1H, td, J = 8.0, 3.7 Hz, CC**H**), 1.08 (1H, dd, J = 6.7, 4.2 Hz, CC**H**$_a$H$_b$), 0.97 (3H, d, J = 6.8 Hz, C**H**$_3$), 0.89 (3H, d, J = 7.0 Hz, C**H**$_3$), 0.64 (1H, t, J = 7.5 Hz, CCH$_a$**H**$_b$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 57.2 (CH), 48.0 (CH_2), 32.5 (C), 30.2 (CH), 25.3 (CH), 20.0 (CH_3), 19.9 (CH_3), 16.1 (CH_3), 8.7 (CH_2).

HRMS (ESI) Exact mass calculated for $[C_9H_{18}N]^+$ [M+H]$^+$: 140.1434, found: 140.1422.



1-Methyl-1,2,3,4-tetrahydroisoquinoline (286). Prepared according to a modification of General Procedure C using 1-methyl-3,4-dihydronaphthalen-2(1*H*)-one (160 mg, 1.00 mmol). Stirred for 24 h at 60 °C for the ring opening step. Amine **286** (56.4 mg, 38% over 3 steps) was isolated as an orange oil. The analytical data is consistent with that previously reported.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18–7.10 (3H, m, Ar**H**), 7.10–7.06 (1H, m, Ar**H**), 4.11 (1H, q, J = 6.6 Hz, C**H**), 3.27 (1H, td, J = 12.6, 5.0 Hz, NC**H**$_a$H$_b$), 3.03 (1H, ddd, J = 12.6, 8.9 4.7 Hz, NCH$_a$**H**$_b$), 2.92–2.84 (1H, m, C**H**$_a$H$_b$), 2.74 (1H, td, J = 16.3, 4.6 Hz, CH$_a$**H**$_b$), 1.86 (1H, s, N**H**), 1.47 (3H, d, J = 6.7 Hz, C**H**$_3$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.6 (C), 134.9 (C), 129.3 (CH), 126.1 (CH), 126.01 (CH), 125.99 (CH), 51.7 (CH), 41.9 (CH_2), 30.2 (CH_2), 22.8 (CH_3).

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