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Enantioselective Nickel-Catalysed Arylative and Alkenylative Cyclisations onto Electron-Deficient Alkenes *via E*/*Z* Isomerisation

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

by

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Supervisor: Prof. Hon Wai Lam

February 2023

Declaration

I (Simone Gillbard) hereby declare that the work contained within this thesis is the original work of my own research and any collaboration is clearly referenced. 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 referenced where relevant. I confirm that appropriate credit has been given within the thesis to the work of others.

This thesis contains results reported in the following publication:

"Enantioselective Nickel-Catalyzed *Anti*-Arylmetallative Cyclizations onto Acyclic Electron-Deficient Alkenes" S. M. Gillbard, H. Green, S. P. Argent and H. W. Lam, *Chem. Commun.* **2021**, *57*, 4436–4439.

The following review was written as part of this PhD:

"Nickel-Catalyzed Arylative Cyclizations of Alkyne- and Allene-Tethered Electrophiles using Arylboron Reagents" S. M. Gillbard and H. W. Lam, *Chem. Eur. J.* **2022**, *28*, e202104230.

Acknowledgements

Firstly, I would like to thank Professor Hon W. Lam for accepting me into the group. You have been an excellent supervisor and I greatly appreciate all the advice I have received from you through the years as well as the support you provided through the global pandemic and my pregnancy, where working in the laboratory was not an option. I have thoroughly enjoyed my time in the Lam group.

Thank you to all past and present Lam group members who contributed to making the PhD experience so memorable. A special mention goes to Somnath. I will forever strive to be as hardworking as you. To Jash, Steve, Nhon, Sinem, Luke, Harley and Dmitry. I will remember all the laughs we have had in the lab, in the pub and everywhere else. A big thank you to Harley for carrying out corrections to my paper and Kieran and Johnny for taking the time to proofread various parts of this thesis.

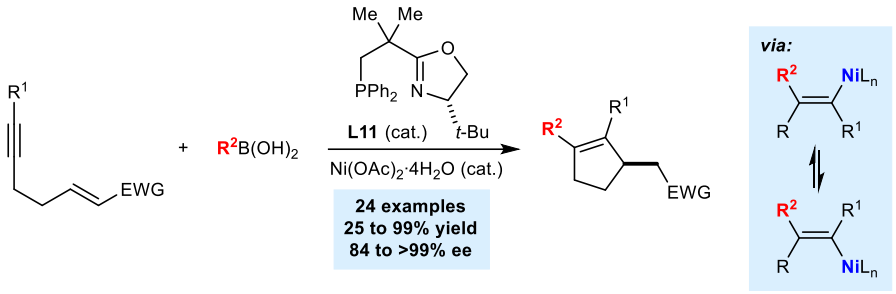
Not just Lam group members have helped making the PhD experience so memorable but also my dear friends Tom and Lizzie. The camping trips have definitely been a highlight of my time as a PhD student.

I would also like to say thank you to all the technical staff in the School of Chemistry for keeping everything running smoothly and for the running of crystal structures and the help with running special NMRs.

Lastly, to Sebastian and Margot, you helped me through the whole journey. I love you both very much. And to my family in Denmark, you have always made me believe that anything is achievable with a bit of hard work and determination.

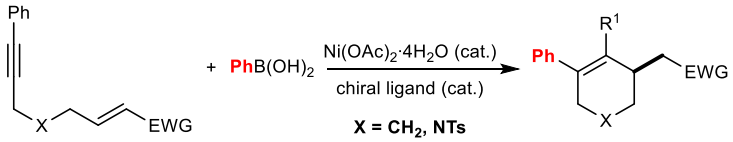
Abstract

Herein is presented a highly enantioselective nickel-catalysed *anti*-carbometallative-cyclisation reaction of substrates containing an alkyne tethered to an electron-deficient alkene. Enantioenriched cyclopentene products, that are otherwise difficult to synthesise, are obtained in up to 99% yield and >99% ee. The overall *anti*-carbometalation of the alkyne is enabled by the critical reversible *E*/*Z* isomerisation of alkenylnickel intermediates.



Investigation of the substrate scope revealed that alkyne substituents such as (hetero)aryl and alkenyl groups were compatible with the reaction and substrates containing electron-deficient alkenes such as α,β-unsaturated alkyl or (hetero)aryl ketones, nitroalkenes, α,β-unsaturated esters and alkenyl nitriles successfully participated in the reaction. Also, (hetero)arylboronic acid as well as alkenylboronic acids were tolerated in the reaction.

Efforts were made towards the synthesis of enantioenriched 6-membered carbo- and heterocyclic products by extending the tether between the alkyne and the electron-deficient alkene in the substrate.



Contents

Abbreviations

Å	ångströms
Ac	acyl
acac	acetylacetonate
aq.	aqueous
Ar	aryl
Bn	benzyl
boc	*t*-butyloxycarbonyl
Bs	4-bromobenzenesulfonyl
Bu	butyl
Bus	*tertiary*-butylsulfonyl
ca.	*circa*
cat.	catalytic
CDI	1,1'-carbonyldiimidazole
COD	1,5-cyclooctadiene
Coe	cyclooctene
Cp	cyclopentadienyl
Cy	cyclohexane
d	doublet
DEPT	distortionless enhancement by polarisation transfer
DMA	dimethylacetamide
DMC	dimethyl carbonate
DMEDA	dimethylethylenediamine
DMF	dimethylformamide
DMMS	dimethoxymethylsilane
DMSO	dimethylsulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
dppp	1,3-bis(diphenylphosphino)propane
d.r.	diastereomeric ratio
E	electrophile
ee	enantiomeric excess
Equiv	equivalents
Et	ethyl

EWG	electron withdrawing group
g	grams
glyme	1,2-dimethoxyethane
h	hour(s)
Hex	hexyl
HPLC	high performance liquid chromatography
HRMS	high-resolution mass spectrometry
Hz	hertz
i	*iso*
IPr	1,3-bis-(2,6-diisopropylphenyl)-imidazol-2-ylidene
IR	infrared
J	coupling constant
L_n	ligand (any number)
M	metal
M	molar
m	multiplet
MBS	4-methoxybenzenesulfonyl
Me	methyl
mg	milligram
MHz	mega hertz
min	minute(s)
mL	millilitres
mm	millimetre
mmol	millimole
m.p.	melting point
Ms	methanesulfonyl
n	*normal*
nm	nanometre
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
NOESY	nuclear overhauser effect spectroscopy
Ns	4-nitrobenzenesulfonyl
pet. ether	petroleum ether
PG	protecting group

Ph	phenyl
PhBpin	phenylboronic acid pinacol ester
ppm	parts per million
Pr	propyl
q	quartet
rac	racemic
RT	room temperature
s	singlet
s	*sec*
sat.	saturated
t	triplet
t	*tertiary*
t_r	retention time
t-AmOH	*tertiary*-amyl alcohol
TBS	*tertiary*-butyldimethylsilyl
temp.	temperature
Tf	triflyl
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
Ts	4-toluenesulfonyl
UV	ultraviolet

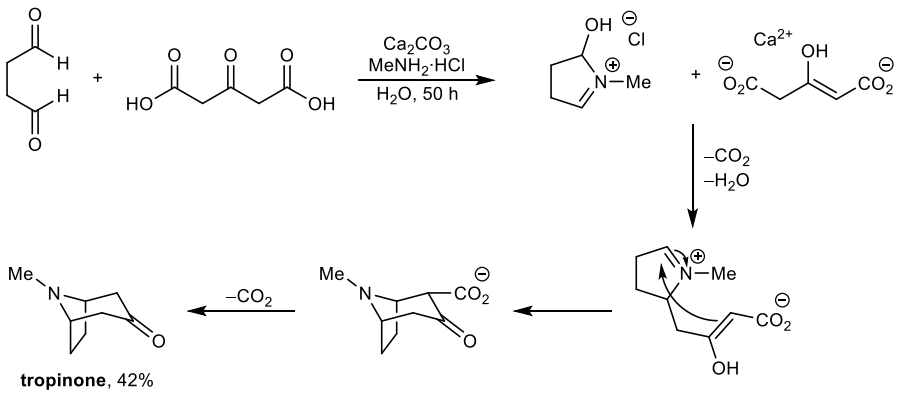
Throughout this work, the numbering of compounds has been divided into sections. Compounds are given a number prefaced with the letter **I** as it appears in the introduction and are numbered **I1, I2**, etc. Numbering in the results and discussion are not prefaced with a letter and are numbered **1**, **2**, etc. Compounds that were synthesised but do not appear in the main text are prefaced with the letter **S** and are numbered **S1**, **S2**, etc. when they appear in the experimental section. Compounds used as ligands are prefaced with the letter **L**.

1.0 Introduction

1.1 Domino Reactions

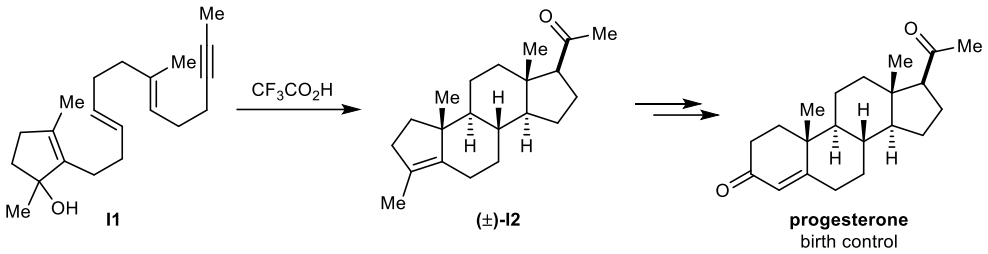
Domino reactions combine two or more bond-forming steps into a single process under one set of reaction conditions without the addition of further reagents or catalysts.[1–4] In these types of reactions, the subsequent step can take place as a result of the functionality formed in the previous step. Often high energy unisolable intermediates can be utilised in these reactions. The synthesis of complex molecules, in a step-economic manner, by combining several bond-formation steps into one process makes domino reactions a versatile tool in synthetic chemistry.[1–12]

One remarkable example of a domino reaction is Robinson's one-step synthesis of tropinone from 1917, reacting succindialdehyde and acetone dicarboxylic acid with methylamine hydrochloride under basic conditions (Scheme 1).[13–15] Tropinone was isolated for the first time in 1901 after a lengthy synthetic approach by Willstätter and the product was obtained in <1% overall yield.[16,17] During Robinson's one-step synthesis, tropinone was isolated in 42% yield.[18]



Scheme **1**: One-step synthesis of tropinone *via* a double Mannich reaction.

Numerous approaches employing domino reactions as the key step in total syntheses of complex molecules have been reported.[19–21] One example from 1971 is the total synthesis of progesterone where a monocyclic precursor **I1** undergoes acid-catalysed domino cyclisation to give a tetracyclic intermediate **I2**, which can be converted into progesterone (Scheme 2).[22]

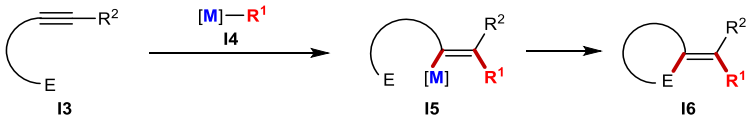


Scheme **2**: Key domino cyclisation step in total synthesis of progesterone from 1971.

These examples highlight the advantages of domino reactions with its efficient approach to bond-formation as well as economic and environmental benefits. Furthermore, Robinson's one-step synthesis of tropinone seen in Scheme 1 and the synthesis of progesterone seen in Scheme 2 are examples of domino reactions utilising unisolable intermediates. This introduction will focus on transition-metal-catalysed domino reactions of alkyne-tethered electrophiles.

1.2 Transition-Metal-Catalysed Carbometallative Cyclisation of Alkyne-Tethered Electrophiles using Organoboron Pronucleophiles

Due to their multiple reactive sites, alkyne-tethered electrophiles **I3** are excellent candidates for domino reactions and have been used in transition-metal catalysed arylative and alkylative reactions to synthesise a diverse range of carbo- and heterocycles (Scheme 3).[23–81]



Scheme **3**: Arylative and alkylative cyclisation of alkyne-tethered electrophiles by migratory insertion/cyclisation pathways.

In these reactions, a pronucleophile and a transition-metal catalyst undergo transmetalation to generate an organometallic species (**I4**). Migratory insertion of alkyne **I3** into the organometallic species **I4** gives alkenyl-metal species **I5**, which can subsequently add to the tethered electrophile in an intramolecular fashion. Overall, two new bonds are formed to give carbo- and heterocyclic compounds, typically of general structure **I6**. It should be mentioned that alternative transition-metal catalysed arylative

and alkylative cyclisation reactions of alkyne-tethered electrophiles, resulting in a similar product outcome have been reported; however, proceeding *via* oxidative cyclisation to form metallacyclic intermediates.[82–93] One example of this type of reaction utilising organoboron reagents as the pronucleophile will be discussed in Section 1.4.2.

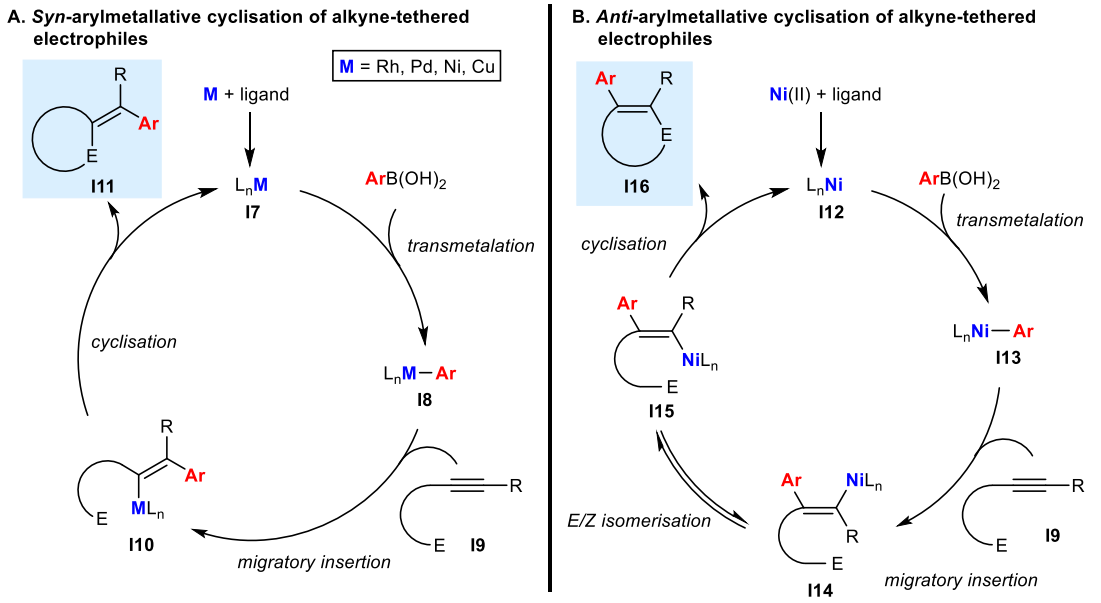
Organoboron compounds are, due to their chemical stability, low toxicity, and widespread availability commonly used as pronucleophiles in transition metal catalysed carbometalation-cyclisation reactions of alkyne-tethered electrophiles.[94] These types of reactions have been described using rhodium,[34–55] palladium, [56–66] copper,[67] and nickel catalysis.[68–81] By modifying the alkyne-tethered electrophile substrate a range of cyclic systems can be obtained, and by employing an enantioenriched metal catalyst enantioselective reactions can be achieved.

1.3 Mechanistic Insight

This section will discuss mechanistic aspects of transition-metal-catalysed carbometallative cyclisation of alkyne-tethered electrophiles using organoboron pronucleophiles. General catalytic cycles for the carbometallative cyclisation of alkyne-tethered electrophiles with arylboronic acid are seen in Scheme 4. Arylboronic acids are by far the most commonly used arylboron reagent in these types of reactions; however, the use of aryl pinacolboronates, aryl trifluoroboronates and arylboroxines have also been reported.[70,78] Two modes of migratory insertion of the alkyne to the arylmetal species are possible placing the metal either distal or proximal to the tethered electrophile and this provides regioisomers of the alkenylmetal intermediates (**I10** vs. **I14**) and consequently, differing products are obtained (**I11** and **I16**).

Catalytic cycle **A** starts with coordination of the ligand to the metal followed by transmetalation of arylboronic acid with the newly formed metal catalyst to give arylmetal species **I8** (Scheme 4A). Regioselective *syn*-stereospecific 1,2-addition of the arylmetal species (**I8**) across the alkyne in **I9** leads to alkenylmetal species **I10** with the metal placed proximal to the electrophile. Direct cyclisation of alkenylmetal species **I10** onto the tethered electrophile leads to cyclic products containing an exocyclic alkene (**I11**). Rhodium and palladium have been used extensively to catalyse *syn*-carbometallative cyclisation reactions of alkyne-tethered electrophiles with arylboron

reagents. Recently, the more abundant metals, copper and nickel have been uncovered as viable catalysts in these types of reaction as well. The proposed oxidation states of the active metal catalysts will be discussed in the relevant sections.



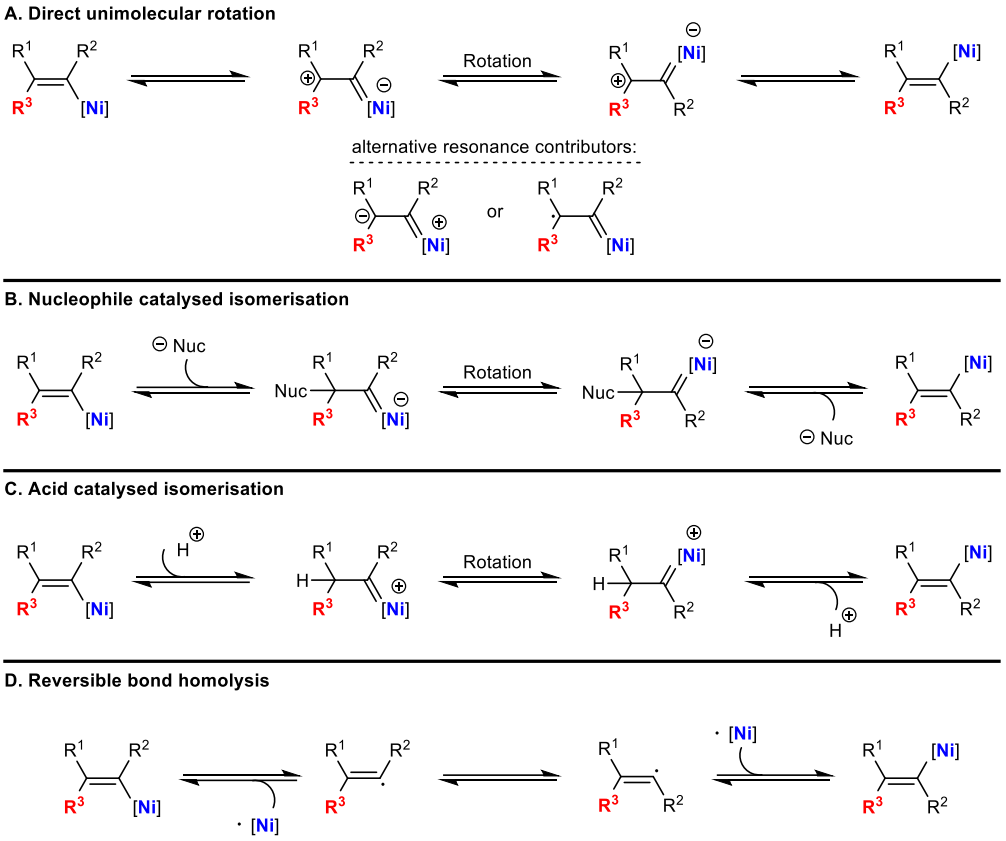
Scheme **4:** General Catalytic cycles for transition-metal-catalysed *syn*- and *anti*-carbometallative cyclisation reactions of alkyne-tethered electrophiles with organoboron reagents.

The initial steps of catalytic cycle **B** are identical to catalytic cycle **A** starting with coordination of the ligand to the nickel followed by transmetalation of arylboronic acid with the newly formed nickel catalyst to give arylnickel species **I12** (Scheme 4B). This time, regioselective *syn*-stereospecific 1,2-addition of **I12** across the alkyne in **I9** leads to alkenylnickel species **I14** with the metal placed distal to the electrophile. Direct cyclisation of the alkenylnickel species **I14** onto the tethered electrophile is not possible due to geometric constraints; however, nickel has been found to undergo reversible *E*/*Z* isomerisation providing alkenylnickel species **I15**. The isomerised alkenylnickel species **I15** is now able to cyclise onto the tethered electrophile and product **I16**, containing an endocyclic alkene, is formed. In this case, overall *anti*-carbometalation is observed.

The regioselectivity of the *syn*-stereospecific 1,2-addition of arylmetal species **I7** or **I12** across the alkyne in **I9** is the key step influencing the outcome of the reaction to obtain either exocyclic product **I11** or endocyclic product **I16**. Alkyne-tethered

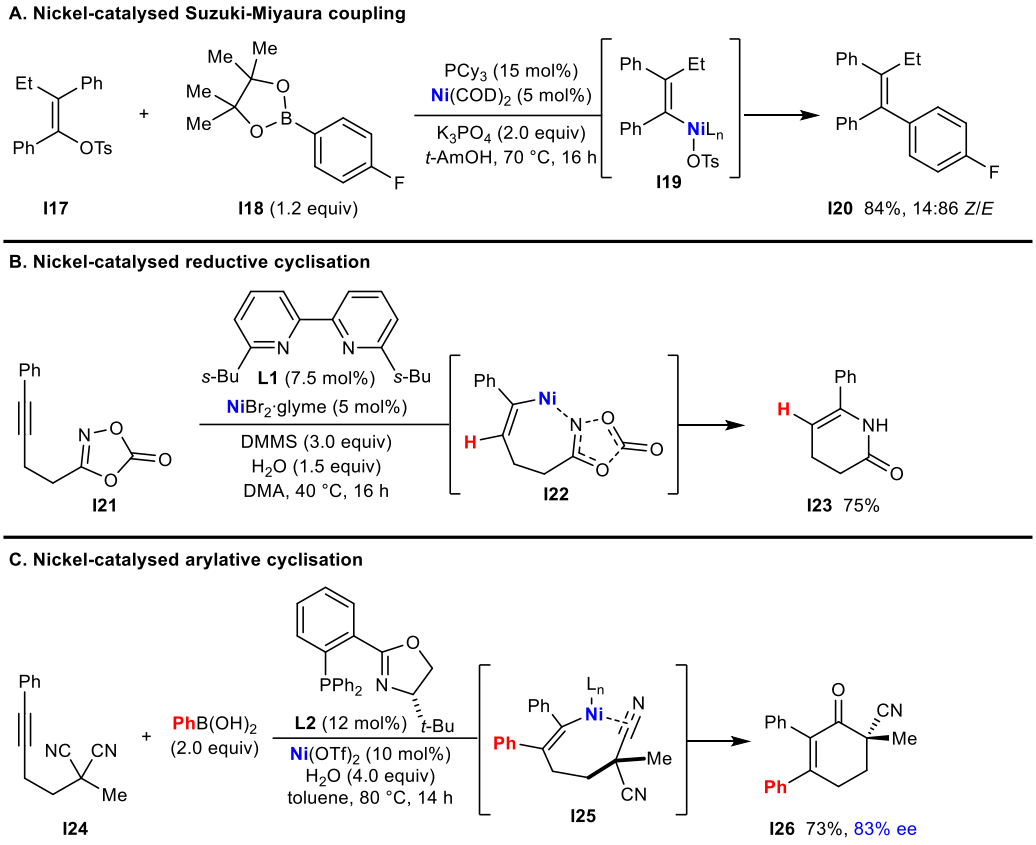
electrophiles with R = hetero(aryl) or alkenyl undergo migratory insertion with an organometallic species, commonly placing the metal distal to the electrophile providing alkenylmetal species **I14**, which subsequently leads to endocyclic products **I16** (see Scheme 4B). When R = alkyl, the metal is commonly placed proximal to the electrophile providing alkenylmetal species **I10**, which subsequently leads to exocyclic products **I11** (see Scheme 4A). sp^2-Hybridised groups have a greater electron-withdrawing effect by induction than sp^3-hybridised groups due to their higher s-character. This electron-withdrawing effect presumably biases alkynes, containing an sp^2-hybridised substituent, towards nucleophilic attack proximal to the electrophile and thus placing the metal distal to the electrophile. Additionally, alkenylmetal intermediate **I14** is presumably stabilised by the adjacent sp^2-hybridised group. The result is limitations to metal-catalysed carbometallative cyclisation reactions. *Anti*-carbometallative variants are restricted to R = hetero(aryl) or alkenyl and only few examples of R = alkyl are reported (see Section 1.5). Oppositely, *syn*-carbometallative variants are restricted to R = alkyl and only few examples of R = aryl are reported (see Section 1.4).

Several reviews have discussed 1,2-functionalisation of alkynes.[95–98] Regarding alkenylnickel isomerisation, one review on nickel-catalysed *anti*-selective alkyne functionalisation reactions was particularly thorough in describing the possible mechanism of the alkenylnickel isomerisation step (Scheme 5).[95] The considerations included direct unimolecular rotation (Scheme 5A), nucleophile-catalysed isomerisation (Scheme 5B), acid-catalysed isomerisation (Scheme 5C) and reversible bond homolysis (Scheme 5D). It is worth mentioning that *E*/*Z* isomerisation of alkenylnickel intermediates has been observed in reactions other than nickel catalysed *anti*-cabometallative cyclisation reactions of alkyne-tethered electrophiles with organoboron reagents and these reactions are described where relevant. [33,93,99–107]



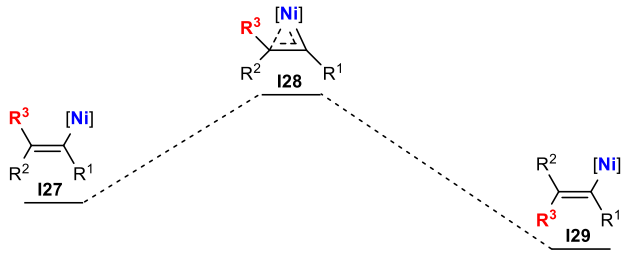
Scheme **5**: Theoretical mechanisms of alkenylnickel isomerisation.

Recently, computational investigations into the *E*/*Z* isomerisation of alkenylnickel intermediates have been reported (Scheme 6).[99,107,108] The reactions vary significantly with regards to the substrates, the reaction mechanisms, the pronucleophiles used and the oxidation state of the active nickel species; however, they have the all-important alkenylnickel isomerisation step in common. One report by Zell, Sigman and co-workers described the nickel(II)-catalysed Suzuki-Miyaura cross-coupling of enol tosylates with aryl pinacol boronates (Scheme 6A).[107] Another report by Seo, Chang and co-workers described the intramolecular hydroamidation of alkyne-tethered dioxazolones with a nickel(I)-hydride species (Scheme 6B),[99] and a third report by Liu, Yu and co-workers described a DFT study on the already known nickel(II)-catalysed *anti*-carbometallative desymmetrising cyclisation of alkyne-tethered malononitriles with arylboronic acids (Scheme 6C).[78,108] All three reports include a computational study of the reaction mechanism and importantly, computational rational for the alkenylnickel isomerisation step.



Scheme **6**: Reports that include computational calculations of alkenylnickel isomerisation.

Although the three alkenylnickel intermediates seen in Scheme 6 vary significantly (**I19**, **I122** and **I25**), the energetically most favourable isomerisation process of the alkenylnickel species were calculated to be the same in all cases. It is proposed that the alkenylnickel isomerisation goes *via* a η^1- to η^2-vinyl-like transition state (Scheme 7). The electron-rich nickel(I)-catalysed reaction seen in Scheme 6B, is proposed to occur by electron donation from the nickel to the Ni–C bond weakening the double bond character of the C–C bond and promoting back-donation to the nickel centre. In the nickel(II)-catalysed reactions (Scheme 6A and 6C) the formation of a η^2-vinyl-like transition state is not commented on. Additionally, all three reports agreed that the isomerised alkenylnickel intermediate was more stable than the starting alkenylnickel intermediate.

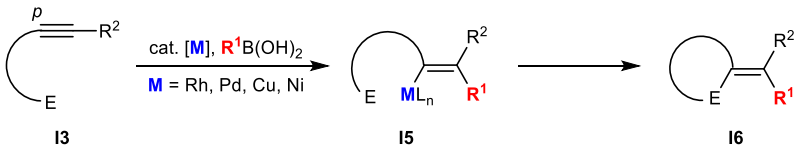


Scheme **7**: Alkenylnickel isomerisation.

In the report by Seo, Chang and co-workers (see Scheme 6B),[99] other possible mechanisms for the alkenylnickel isomerisation step were explored using computational chemistry. Intermediates resulting from nucleophile catalysed isomerisation, electrophile catalysed isomerisation and reversible bond homolysis were all investigated. However, the intermediates all had higher energies than the activation barrier for the η^1- to η^2-vinyl-like transition state.

1.4 Transition-Metal-Catalysed *syn*-Carbometallative Cyclisation of Alkyne-Tethered Electrophiles using Organoboron Pronucleophiles

This section describes transition-metal-catalysed *syn*-selective arylative cyclisation reactions of alkyne-tethered electrophiles with organoboron reagents (Scheme 8). In these types of reactions, the alkyne inserts into the arylmetal species placing the metal proximal to the electrophile allowing for direct cyclisation. Transition metals known to catalyse these types of reactions are rhodium, palladium, copper and nickel and this section is arranged accordingly.



Scheme **8**: Metal-catalysed *syn*-carbometallative cyclisation reactions.

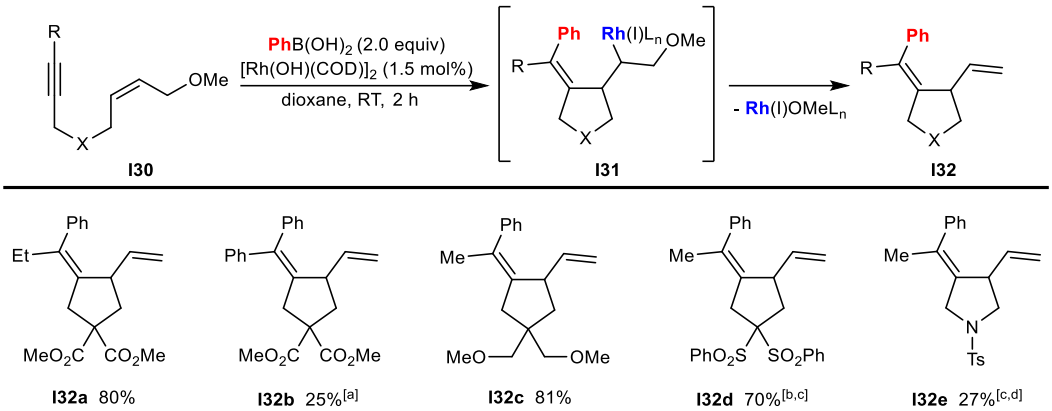
1.4.1 Rhodium Catalysis

Organorhodium species are known to undergo insertion with alkynes,[109] and are therefore excellent candidates for domino reactions of alkyne-tethered electrophiles. Rhodium-catalysed carbometallative cyclisation of alkyne-tethered electrophiles with organoboron reagents have been researched extensively with substrates containing electrophiles such as carbonyls,[34–36,40,48,49] nitriles,[37] isocyanates,[41] imines,[50] hydrazones,[52] allenes,[42] alkenes[43] and alkynes[45]; however, this section will only discuss the use of alkyne-tethered electron-deficient alkenes. The proposed mechanisms of these reactions follow the general catalytic cycle shown in Scheme 4A, and it is widely believed that rhodium is of oxidation state +1 throughout the catalytic cycle.

In 2005, Murakami and co-workers reported the rhodium-catalysed addition-cyclisation-elimination reaction of 1,6-enynes with boronic acids (Table 1).[38] 1,6-Enynes **I30** were treated with phenylboronic acid (2.0 equiv) and $[Rh(OH)(COD)]_2$ (1.5 mol%) in dioxane at room temperature for 2 h under a nitrogen atmosphere to give cyclopentane and pyrrolidine products **I32**. The reaction of substrate **I30a**, containing an ethyl-substituted alkyne, led to the desired product **I32a** in 80% yield; however, the reaction of substrate **I30b**, containing a phenyl-substituted alkyne, required elevated temperatures (50 °C) to give product **I32b** in 25% yield. The lower yield observed is likely due to lower regioselectivity of migratory insertion of aryl-alkyne **I30b** into the arylrhodium species in comparison with alkyl-alkynes as discussed in Section 1.3. The reaction tolerated substrates containing a range of functional groups in the tether between the alkyne and the electron-deficient alkene, such as dimethyl malonate (**I32a** and **I32b**), 1,1-bis(methoxymethyl) (**I32c**) and (1,1-disulfonyl)dibenzene (**I32d**). Also, the reaction of aza-1,6-enyne **I30e**, bearing a sulfonamide group in the tether provided the desired product **I32e**; however, in a reduced yield of 27%.

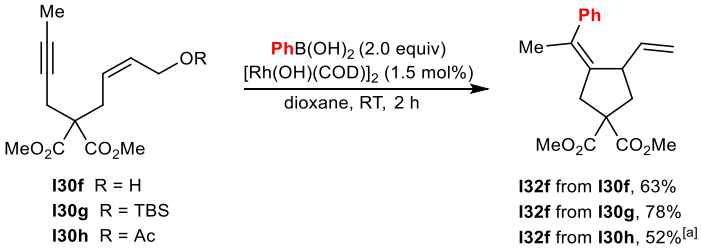
The proposed mechanism follows the general catalytic cycle shown in Scheme 4A; however, an additional β-methoxy elimination step of intermediate **I31** is required to liberate product **I32** and regenerate the active rhodium(I) species (Table 1).

Table **1**: Rhodium-catalysed arylmetallative cyclisation onto allyl methyl ethers.



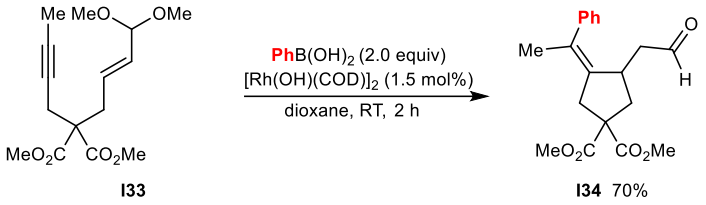
[a] Reaction carried out at 50 °C. [b] 16 h reaction time. [c] Reaction carried out using $PhB(OH)_2$ (4 equiv) and $[Rh(OH)(COD)]_2$ (3 mol%). [d] 12 h reaction time.

Allylic alcohol **I30f** and allylic silyl ether **I30g** were transformed into the corresponding product **132f** in good yields under the standard reaction conditions; however, allylic acetate **I30h** required the use of 4.0 equivalents of phenylboronic acid, 3 mol% $[Rh(OH)(COD)]_2$ and 24 hour reaction time to give **I32f** in 52% yield and starting material remained (Scheme 9).



Scheme **9**: Rhodium-catalysed arylmetallative cyclisation onto allyl alcohol, allyl *t*-butyldimethylsilyloxy and allyl acetate. [a] Reaction carried out using $PhB(OH)_2$ (4 equiv), $[Rh(OH)(COD)]_2$ (3 mol%) and 24 h reaction time.

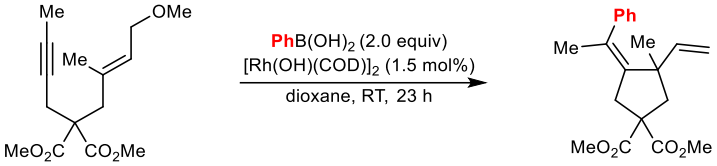
Next, α,β-unsaturated dimethyl acetal **I33**, bearing the alkene with (*E*)-configuration, was exposed to the reaction conditions and aldehyde **I34** was obtained after acidic hydrolysis in 70% yield (Scheme 10).



I33 **I34** 70%

Scheme **10**: Rhodium-catalysed arylmetallative cyclisation onto α,β-unsaturated dimethyl acetal.

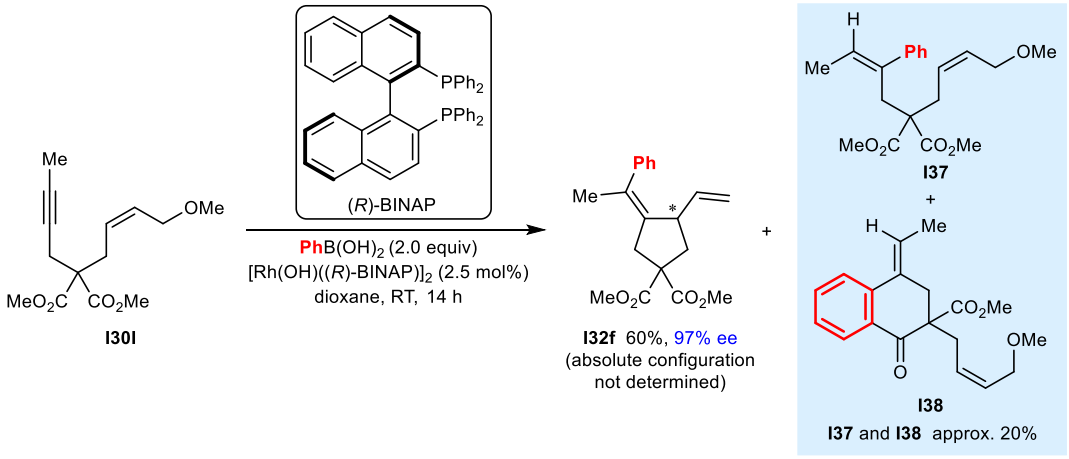
Pleasingly, having a sterically hindered trisubstituted alkene in the substrate was compatible with the reaction and product **I36**, containing a quaternary centre, was obtained in 61% yield (Scheme 11).



I35 *E/Z* (9:1) **I36** 61%

Scheme **11**: Rhodium-catalysed arylmetallative cyclisation onto sterically hindered allyl methyl ether.

An enantioselective variant of the reaction was achieved by exposing enyne **I30l** to phenylboronic acid (2.0 equiv) and [Rh(OH)((*R*)-BINAP)]$_2$ (2.5 mol%) in dioxane at room temperature to give product **I32f** in 60% yield and 97% ee (Scheme 12). Side-products **I37** and **I38** were also isolated in approximately 20% combined yield. The equivalent non-enantioselective variant using [Rh(OH)(COD)]$_2$ led to products **I32f**, **I37** and **I38** in a >95:5 ratio of **I32f**:(**I37** and **I38**). It was postulated that the more sterically demanding character of (*R*)-BINAP compared with COD influenced the lower regioselectivity observed in the enantioselective variant.



Scheme **12**: Enantioselective rhodium-catalysed arylmetallative cyclisation onto allyl methyl ether.

Side-products **I37** and **I38** were a result of phenylrhodium addition across the alkyne being of opposite regioselectivity to that required to obtain the desired product, placing the metal distal to the electrophile (Figure 1). The newly formed alkenylrhodium species **I39** can undergo protoderhodation to give **I37**. Alternatively, the alkenylrhodium species **I39** can undergo 1,4-migration of rhodium to give an arylrhodium species which can subsequently cyclise onto one of the ester groups to give **I38**. Arylative cyclisation reactions of alkyne-tethered electrophiles involving 1,4-migration of the metal have been reported using rhodium,[23–30] iridium[31] and cobalt catalysis.[32]

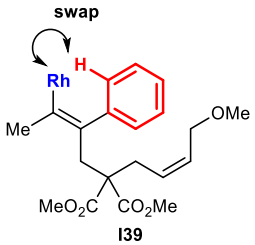
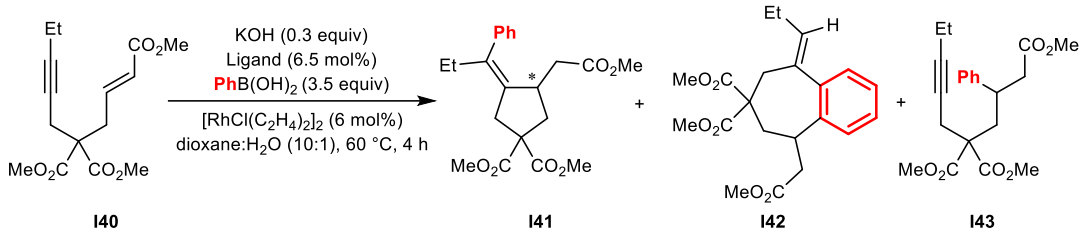


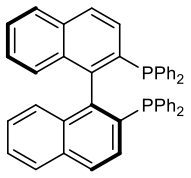
Figure **1**: 1,4-Migration of rhodium.

Hayashi and co-workers reported the rhodium-catalysed arylative cyclisation reaction onto electron-deficient alkenes using a chiral diene ligand (Table 2).[39] The reaction of 1,6-enyne **I40** with phenylboronic acid (3.5 equiv), $[RhCl(C_2H_4)_2]_2$ (6.0 mol%), KOH (0.3 equiv) and (*S*)-BINAP (6.5 mol%) in dioxane:H_2O (10:1) at 60 °C was carried out and led to a mixture of products. The desired cyclopentane product **I41**

was obtained in 23% yield and 95% ee as well as product **I42** in 22% yield and product **I43** in 45% yield. Product **I42** was a result of alkyne insertion into the phenylrhodium species occurring with opposite regioselectivity followed by 1,4-migration of rhodium and subsequent nucleophilic attack of the electron-deficient alkene. Product **I43** resulted from the phenylrhodium species adding directly to the electron-deficient alkene. These results highlight the challenges associated with designing domino processes that involve multiple reactive sites and intermediates. Interestingly, the reaction showed far greater selectivity towards the formation of the desired product when using chiral diene ligand **L3** providing **I41** in 83% yield and 99% ee and only small amounts of side-products **I42** and **I43** were observed.

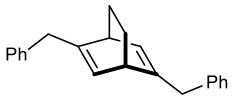
Table **2**: Enantioselective rhodium-catalysed arylmetallative cyclisation onto α,β-unsaturated ester – chiral ligand effect. Absolute configuration of **I41** not determined.





(*S*)-BINAP

I41 23%, 95% ee
I42 22%
I43 45%

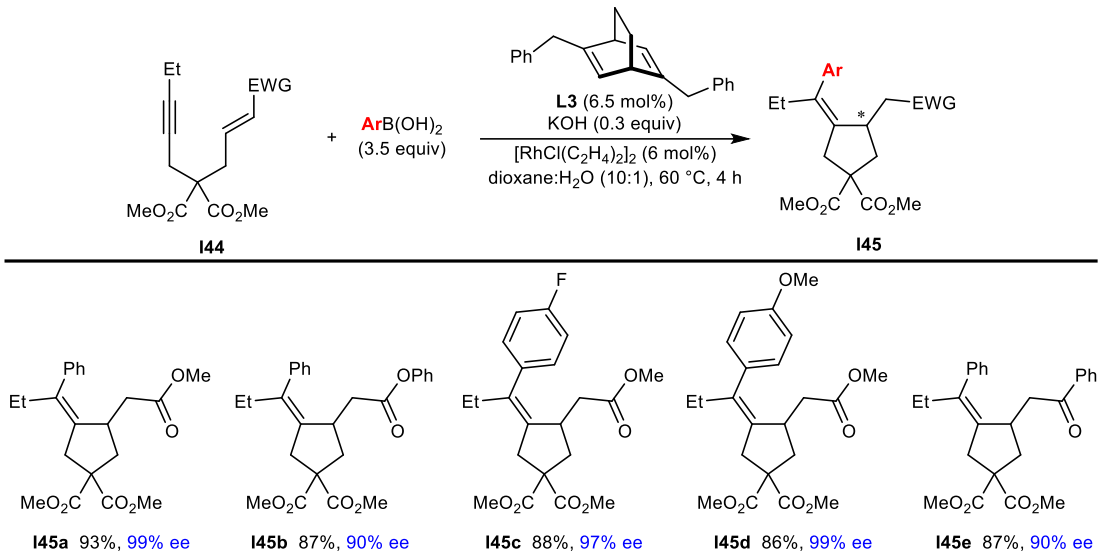


L3

I41 83%, 99% ee
I42 5%
I43 5%

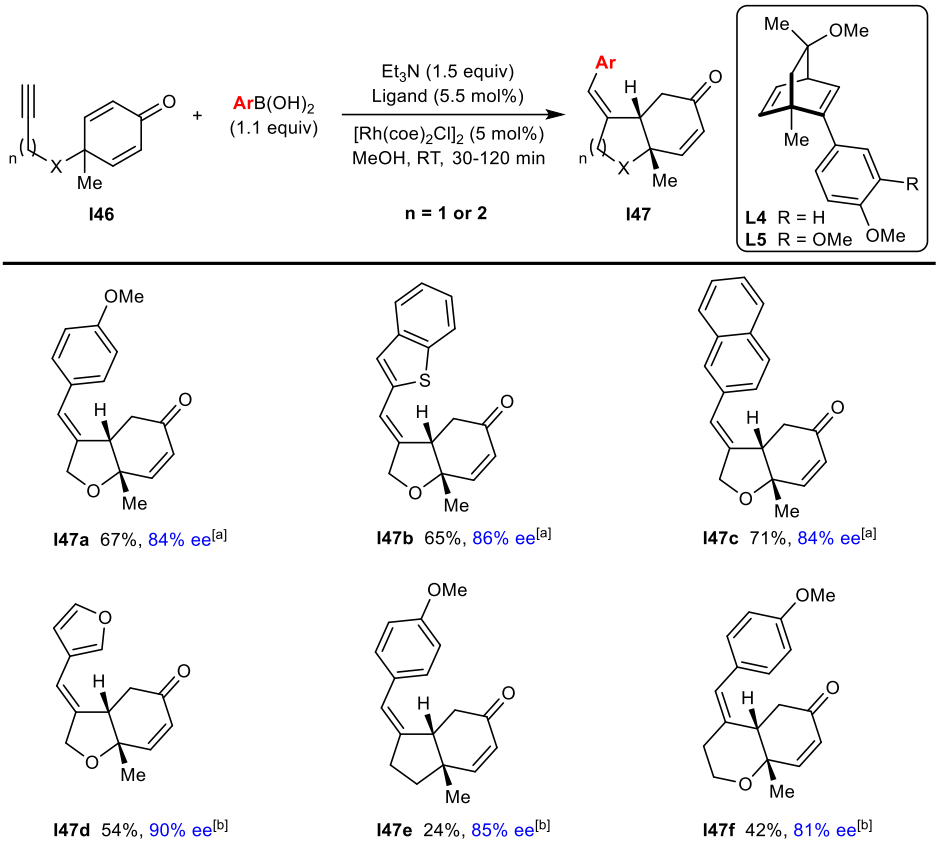
The reaction of alkyne-tethered α,β-unsaturated methyl ester demonstrated great yields and excellent enantioselectivity when using phenylboronic acid (**I45a**) as well as 4-methoxyphenylboronic acid (**I45c**) or 4-fluorophenylboronic acid (**I45d**, Table 3). The use of alkyne-tethered α,β-unsaturated phenyl ester led to a slight decrease in enantiomeric excess (**I45b**, 90% ee). Also, cyclisation onto an α,β-unsaturated phenyl ketone was compatible with the reaction (**I45e**).

Table **3**: Enantioselective rhodium-catalysed arylmetallative cyclisation onto α,β-unsaturated esters and ketones. Absolute configuration of **I45** not determined.



In 2013, Lautens and co-workers, converted cyclohexadienone-tethered terminal alkynes into tetrahydrobenzofuranone products using rhodium catalysis (Table 4).[46] Cyclohexadienone-tethered terminal alkynes **I46** were exposed to (hetero)arylboronic acid (1.1 equiv), $[Rh(coe)_2Cl]_2$ (5.0 mol%), Et_3N (1.5 equiv) and ligand **L4** or **L5** (5.5 mol%) in MeOH at room temperature to give the desired products **I47** in moderate yields and enantioselectivities. Various heteroarylboronic acids (**I47b** and **I47d**) and arylboronic acids (**I47a**¸ **I47c**, **I47e** and **I47f**) were compatible with the reaction. Changing from a substrate containing an oxygen in the tether between the alkyne and the cyclohexadienone (**I47a-d**) to an all-carbon-containing tether led to a decrease in the yield to 24% (**I47e**). Extending the tether by one carbon also resulted in a reduced yield (**I47f**, 42%).

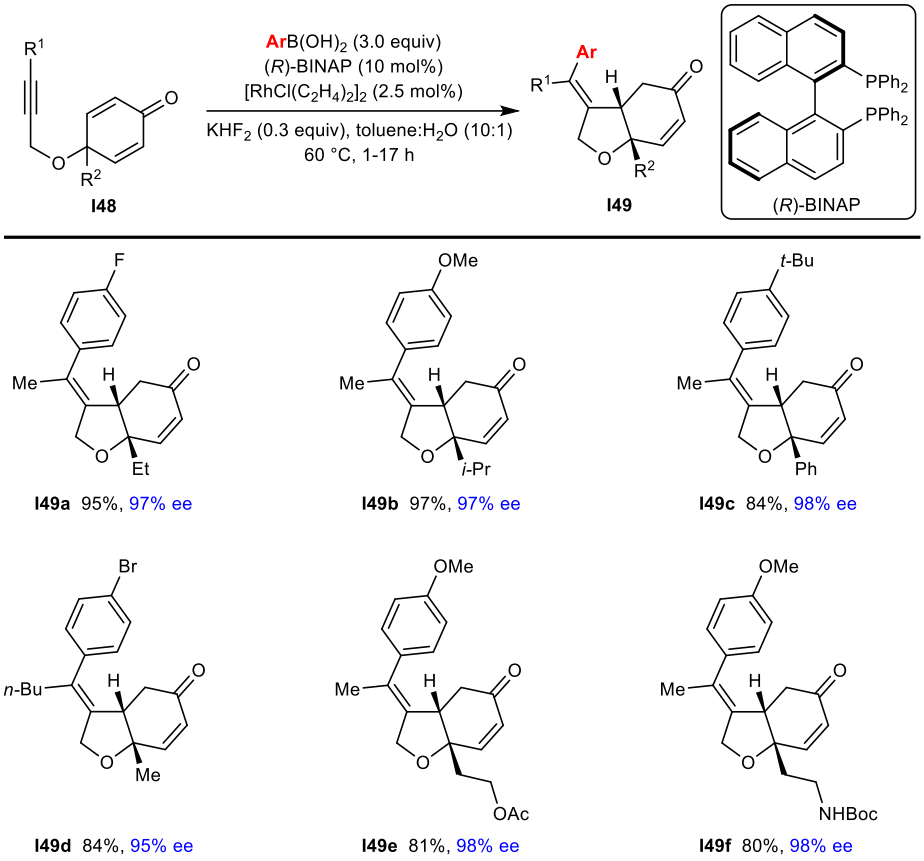
Table **4**: Enantioselective rhodium-catalysed arylmetallative cyclisation onto cyclohexadienone – using a chiral diene ligand.



[a] Reaction carried out using ligand **L5**, [b] Reaction carried out using ligand **L4**.

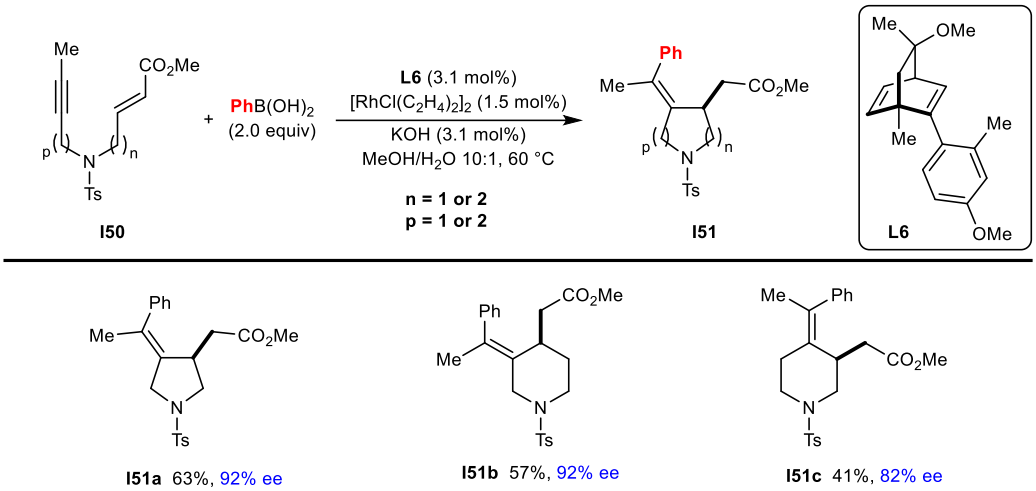
In 2013, Tian, Lin and co-workers reported a similar study to the rhodium-catalysed arylative cyclisation of cyclohexadienone-tethered alkynes by Lautens and co-workers seen in Table 4.[47] Alkyne-tethered cyclohexadienones **I48** were exposed to arylboronic acid (3.0 equiv), $[RhCl(C_2H_4)_2]_2$ (2.5 mol%), (*R*)-BINAP (10 mol%) and KHF_2 (0.3 equiv) in a 10:1 mixture of toluene:H_2O at 60 °C to give the desired tetrahydrobenzofuranone products **I49** (Table 5). In contrast to the previous report, it was possible to have a substituent on the alkyne (R^1) and vary the group at the quaternary centre (R^2). Furthermore, the reaction showed excellent yields up to 99% and enantiomeric excesses up to 99%. The reaction tolerated methyl (**I49d**), ethyl (**I49a**), *i*-propyl (**I49b**) and phenyl (**I49c**) substituents at the R^2-position as well as an acetoxyethyl (**I49e**) and a Boc-protected aminoethyl group (**I49f**). As well as having a substrate containing a methyl substituent on the alkyne (**I49a-c**, **I49e** and **149f**), also an *n*-butyl substituent was tolerated (**I49d**). A range of 4-substituted phenylboronic acids were successful in the reaction with substituents such as methoxy (**I49b**, **I49e** and **I49f**), fluoro (**I491**), *t*-butyl (**I49c**) and bromo (**I49d**).

Table **5**: Enantioselective rhodium-catalysed arylmetallative cyclisation onto cyclohexadienone – using a chiral bisphosphine ligand.



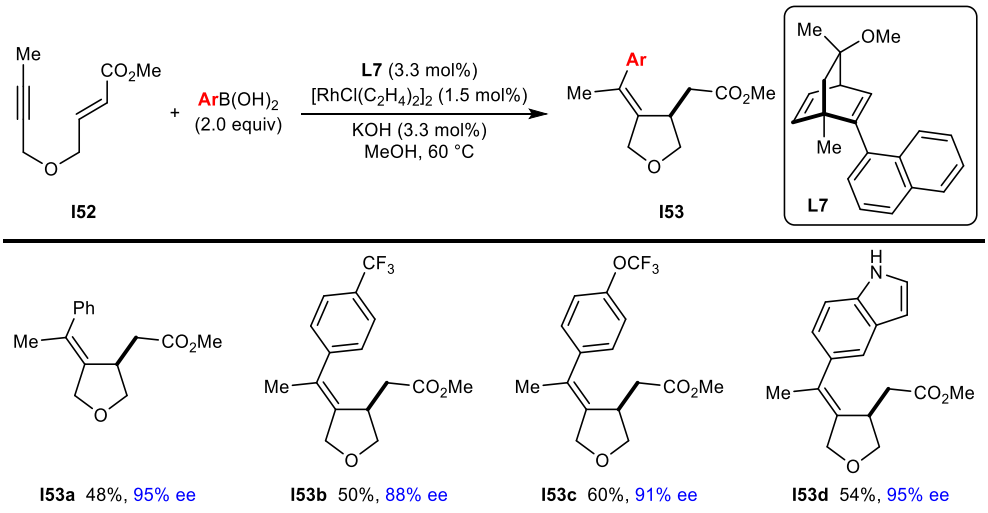
In 2015, the synthesis of chiral pyrrolidines and piperidines was achieved *via* enantioselective rhodium-catalysed arylative cyclisation of alkyne-tethered α,β-unsaturated esters containing a nitrogen in the tether (Table 6).[51] Exposing 1,6-enyne **I50a** to phenylboronic acid (2.0 equiv), $[RhCl(C_2H_4)_2]_2$ (1.5 mol%), KOH (3.1 mol%) and chiral diene ligand **L6** (3.1 mol%) in a 10:1 mixture of MeOH:H_2O at 60 °C led to pyrrolidine **I51a** in 63% yield and 92% ee. Extending the tether between the alkyne and the α,β-unsaturated ester by one carbon on either side of the nitrogen provided piperidines **I51b** and **I51c**, containing exocyclic alkenes at the 3-position and 4-position, respectively.

Table **6**: Enantioselective rhodium-catalysed arylmetallative cyclisation onto α,β-unsaturated esters.



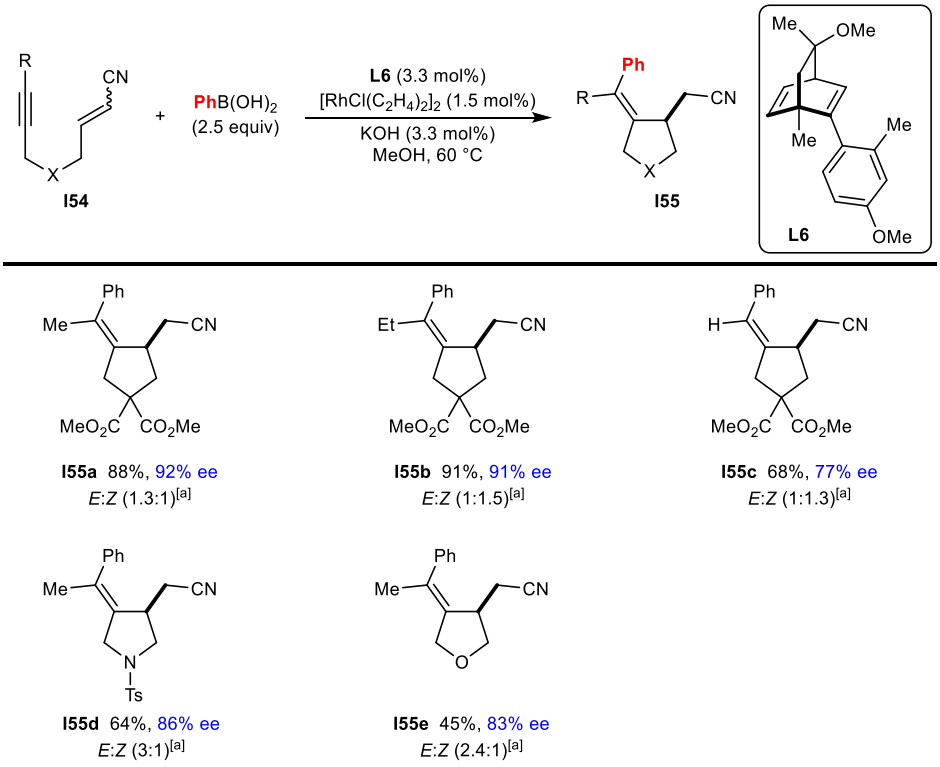
In 2019, Darses and co-workers reported the rhodium-catalysed arylative cyclisation of 1,6-enynes **I52** containing an oxygen in the tether between the alkyne and the α,β-unsaturated ester (Table 7).[53] They reacted substrate **I52** with (hetero)arylboronic acid (2.0 equiv), $[RhCl(C_2H_4)_2]_2$ (1.5 mol%), KOH (3.3 mol%) and chiral diene ligand **L7** (3.3 mol%) in MeOH at 60 °C to obtain enantioenriched tetrahydrofurans **I53**. The reaction was tolerant of phenylboronic acid (**I53a**), 4-(trifluoromethyl)phenylboronic acid (**I53b**), 4-(trifluoromethoxy)phenylboronic acid (**I53c**) and 5-indolylboronic acid (**I53d**).

Table **7**: Enantioselective rhodium-catalysed arylmetallative cyclisation onto α,β-unsaturated esters.



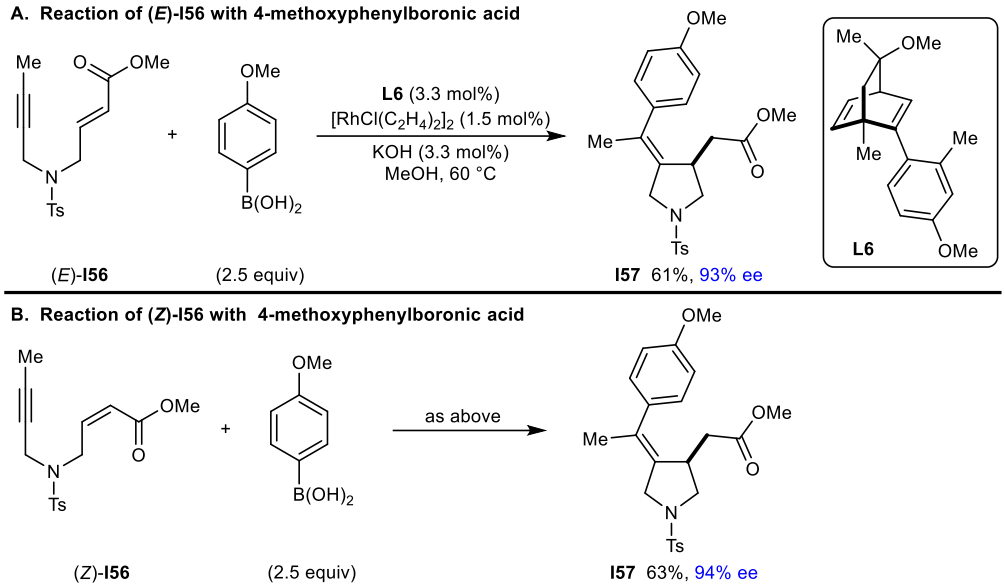
Further, in 2019, Darses and co-workers reported the enantioselective rhodium-catalysed arylative cyclisation of alkyne-tethered α,β-unsaturated nitriles, containing mixtures of *E*/*Z* stereoisomers (Table 8).[54] The reaction of **I54** with phenylboronic acid led to cyclopentane, pyrrolidine and tetrahydrofuran products **I55** in moderate to good yields (45-91%) and enantiomeric excesses (77-92%). Substrates containing a methyl- (**I55a**) or ethyl-group (**I55b**) on the alkyne were tolerated in the reaction as well as a terminal alkyne (**I55c**); however, with decreased enantioselectivity. All-carbon-tethered substrates (**I55a-c**) appeared to perform better than substrates containing a nitrogen (**I55d**) or oxygen (**I55e**) in the tether between the alkyne and the α,β-unsaturated nitrile.

Table **8**: Enantioselective rhodium-catalysed arylmetallative cyclisation onto α,β-unsaturated nitriles.



[a] Refers to the *E*:*Z* ratios of the starting material **I54**.

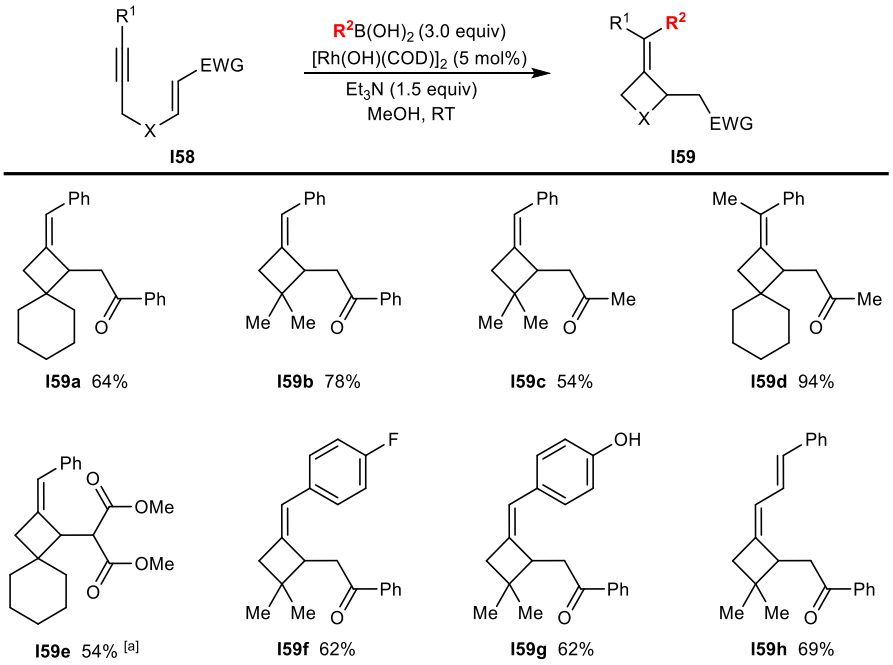
The reaction conditions seen in Table 8 were applied to the reaction of alkyne-tethered α,β-unsaturated esters (*E*)-**I56** and (*Z*)-**I56**; however using 4-methoxyphenylboronic acid (Scheme 13). The stereoisomeric substrates (*E*)-**I56** and (*Z*)-**I56** were subjected separately to the reaction conditions, and interestingly, the outcomes from the reactions were the same (Scheme 13A and 13B).



Scheme **13**: Comparing rhodium-catalysed arylmetallative cyclisation reactions of stereoisomeric substrates.

In 2022, Lee and co-workers reported the rhodium-catalysed arylative cyclisation of 1,5-enynes leading to alkylidene cyclobutanes (Table 9).[55] 1,5-Enyne **I58** was reacted with boronic acid (3.0 equiv), $[Rh(OH)(COD)]_2$ (5 mol%) and Et_3N (1.5 equiv) in MeOH at room temperature to get products **I59**. The use of substrates containing terminal alkynes worked well in the reaction (**I59a-c** and **I59e-h**), as well as substrates with methyl-substituted alkynes (**I59d**). Substrates containing electrophiles such as α,β-unsaturated phenyl ketones (**I59a**, **I59b** and **I59f-h**) and methyl ketones (**I59c** and **I59d**) were compatible with the reaction, as well as an α,β-unsaturated malonate (**I59e**). Having either a *gem*-dimethyl group (**I59b**, **I59c** and **I59f-h**) or a cyclohexyl group (**I59a**, **I59d** and **I59e**) in the tether between the alkyne and the electron-deficient alkene was tolerated. Lastly, it was found that both arylboronic acids (**I59a-g**) and alkenylboronic acids (**I59h**) worked in the reaction.

Table **9**: Rhodium-catalysed carbometallative cyclisation onto α,β-unsaturated ketones and malonates.



[a] Reaction carried out at 50 °C.

In summary, this section describes *syn*-selective rhodium-catalysed carbometallative cyclisation reactions of alkyne-tethered electron-deficient alkenes using organoboron pronucleophiles.

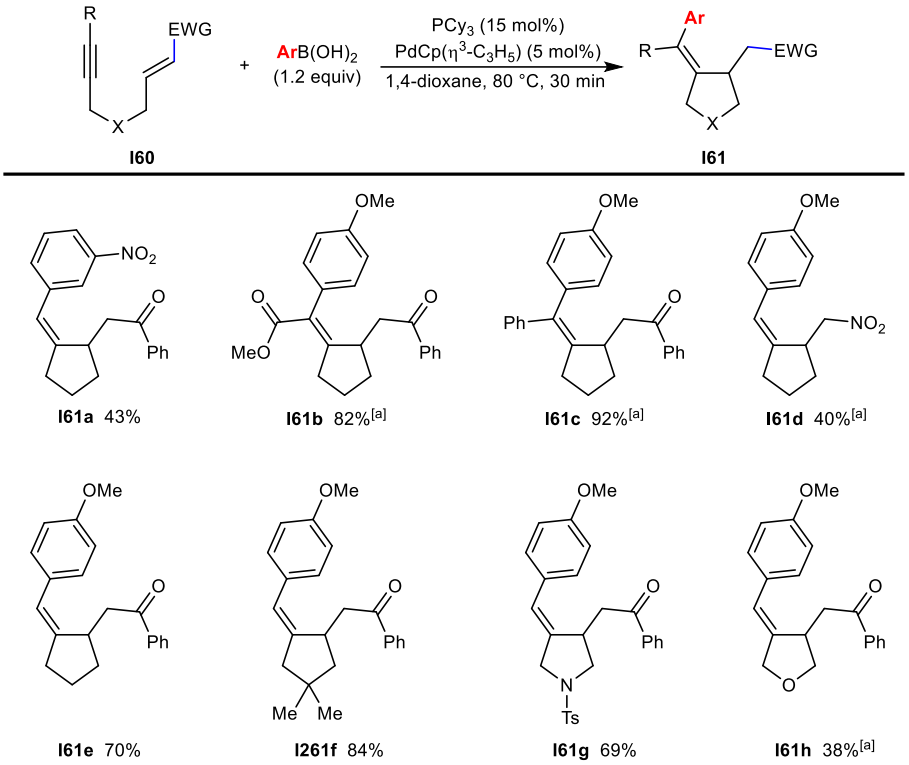
1.4.2 Palladium Catalysis

This section will focus on palladium-catalysed arylative cyclisation reactions of alkyne-tethered electron-deficient alkenes with organoboron reagents[62,65,85]; however, this type of reaction has also been reported using alkyne-tethered ketones.[57,60,61,64] Palladium-catalysed arylative cyclisation reactions have been reported to proceed *via* differing reaction mechanisms. Palladium(0)-catalysed reactions are believed to proceed *via* an oxidative palladium(0)/palladium(II) catalytic cycle.[85] Palladium(II)-catalysed reactions are thought to be redox-neutral and these reaction generally use a cationic palladium(II) catalyst;[57,61,62,64,65] however, neutral palladium(II) catalysts have also been employed.[60,63] This difference in oxidation state of the active metal catalyst could lead to a difference in reactivity. Examples of palladium(0)- and

palladium(II)-catalysed reactions will be discussed in this section, although the palladium(0)-catalysed variant does not follow the catalytic cycle seen in Scheme 4A.

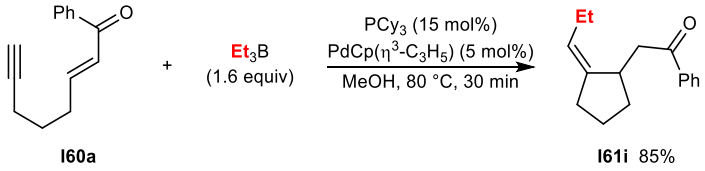
In 2008, Tsukamoto and co-workers reported the arylative cyclisation reaction of alkyne-tethered electron-deficient alkenes with arylboronic acids utilising a palladium(0) catalyst (Table 10).[85] They exposed 1,6-enyne **I60** to arylboronic acid (1.2 equiv), $PdCp(\eta^3\text{-}C_3H_5)$ (5 mol%) and PCy_3 (15 mol%) in 1,4-dioxane at 80 °C to get cyclohexane, pyrrolidine and tetrahydrofuran products **I61**. Electron-rich phenylboronic acids performed better in the reaction (**I61e**, 70%) than electron-poor phenylboronic acids (**I61a**, 43%). The installation of an ester (**I61b**) or a phenyl group (**I61c**) on the alkyne was compatible with the reaction, when carried out in methanol in place of 1,4-dioxane, and led to great yields of 82% and 92%, respectively. Arylative cyclisation of an alkyne-tethered nitroalkene was tolerated and provided product **I61d** in 40% yield. Variation of the tether between the alkyne and the electron-deficient alkene was investigated. Having a *gem*-dimethyl group (**I61f**) or a tosyl-protected nitrogen (**I61g**) in place of the methylene group (**I61a-e**) was compatible with the reaction; however, the installation of an oxygen in the tether led to product **I61h** in a moderate yield (38%).

Table **10**: Palladium-catalysed arylative cyclisation of alkyne-tethered α,β-unsaturated ketones and nitroalkenes.



[a] Reaction carried out in methanol.

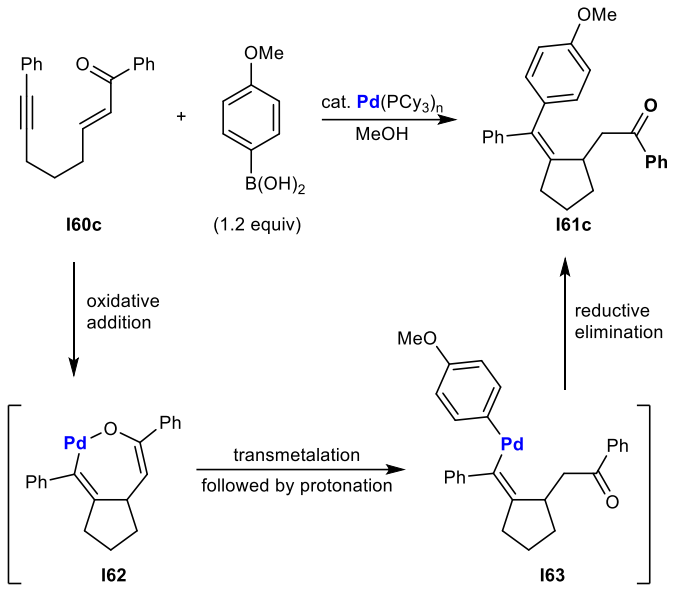
Interestingly, changing the organoboron species from an arylboronic acid to triethylborane was compatible with the reaction, when carried out in methanol, and led to product **I61i** in 85% yield (Scheme 14). When the reaction was carried out in 1,4-dioxane, no product was observed by TLC.



Scheme **14**: Palladium-catalysed alkylative cyclisation of alkyne-tethered α,β-unsaturated ketone.

The overall outcome of the palladium(0)-catalysed reaction is equivalent to the outcome seen in the general catalytic cycle shown in Scheme 4A; however, the reaction mechanism is different and can be seen in Scheme 15. Oxidative addition of alkyne-tethered enone to palladium(0) results in the formation of palladacycle **I62**. Transmetalation of the boronic acid with species **I62** followed by protonation and

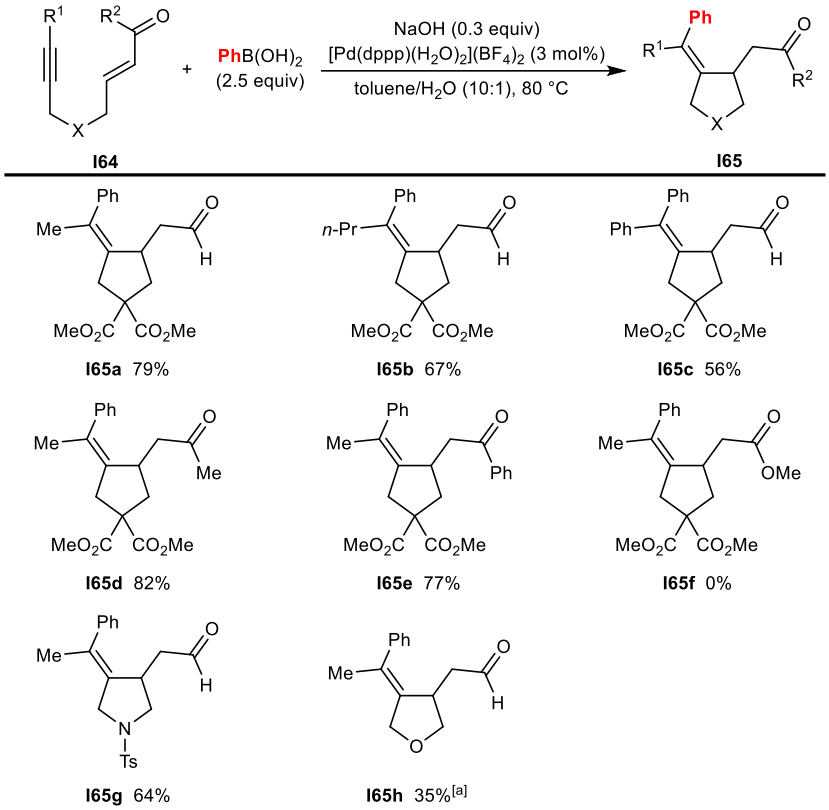
subsequent reductive elimination lead to the product **I61c** and regeneration of the palladium(0) species.



Scheme **15**: Proposed mechanistic cycle.

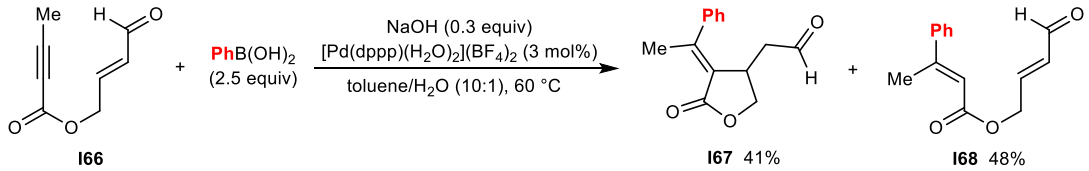
In 2012, Han, Lu and co-workers reported an arylative cyclisation reaction of 1,6-enynes **I64** with arylboronic acids and a cationic palladium(II) catalyst to give cyclopentane, pyrrolidine and tetrahydrofuran products **I65** (Table 11).[62] Enynes **I64** were reacted with phenylboronic acid (2.5 equiv), NaOH (0.3 equiv) and $[Pd(dppp)(H_2O)_2](BF_4)_2$ (3 mol%) in a 10:1 mixture of toluene:H_2O at 80 °C to give the desired products **I65**. Substrates containing a methyl (**I65a** and **I65d-h**) or *n*-propyl substituent (**I65b**) on the alkyne were tolerated in the reaction, as well as a phenyl substituent (**I65c**); however, this led to a decreased yield. Variation of the all-carbon tether (**I65a-f**) to a nitrogen- or oxygen-containing tether was compatible with the reaction (**I65g** and **I65h**); however, in the latter case a lower yield was observed. Changing the electrophile from an α,β-unsaturated aldehyde to an α,β-unsaturated ketone was tolerated (**I65d** and **I65e**); however, having an α,β-unsaturated ester was detrimental to the reaction (**I65f**).

Table **11**: Palladium-catalysed arylmetallative cyclisation onto α,β-unsaturated aldehydes and ketones.



[a] Reaction carried out at 60 °C.

The palladium-catalysed arylative cyclisation reaction of allylic alkynoate **I66** led to butyrolactone **I67** in 41% yield along with uncyclised product **I68** in 48% yield (Scheme 16).

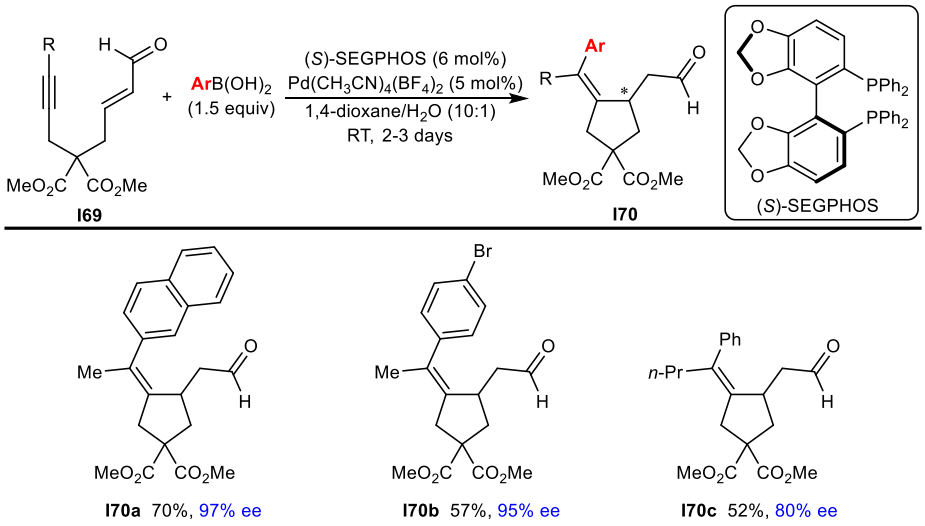


Scheme **16**: Palladium-catalysed arylmetallative cyclisation onto α,β-unsaturated aldehyde.

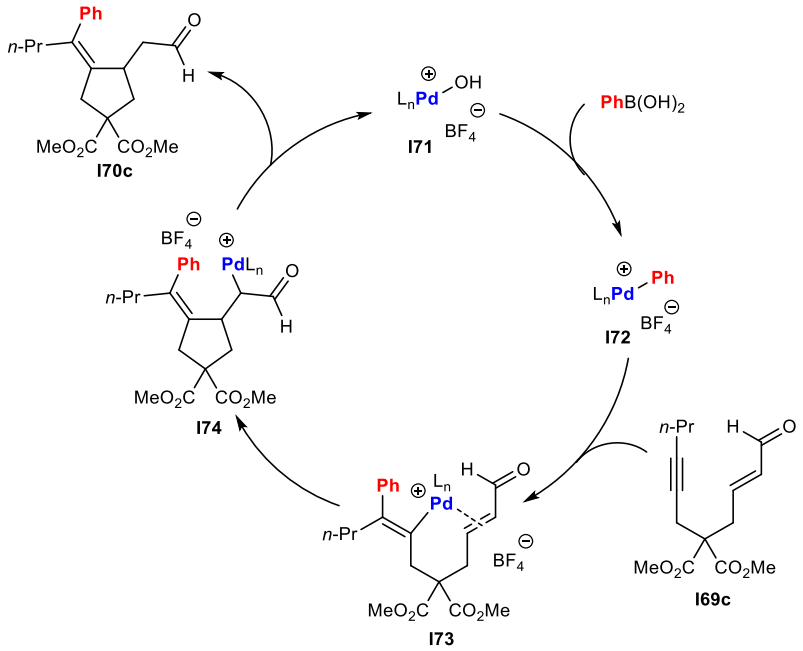
Chiral bisphosphine ligand, (*S*)-SEGPHOS, was found to induce enantioselectivity in the reaction (Table 12). The optimised enantioselective reaction conditions were modified compared with the non-enantioselective reaction conditions. 1,6-Enynes **I69** were reacted with arylboronic acid (1.5 equiv), $Pd(CH_3CN)_4(BF_4)_2$ (5 mol%) and (*S*)-SEGPHOS (6 mol%) in 1,4-dioxane:H_2O (10:1) at room temperature

for 2-3 days to get products **I70** in up to 97% ee. Changing the substituent on the alkyne from a methyl group (**I70a** and **I70b**) to an *n*-propyl group (**I70c**) was tolerated; however, providing the corresponding product with decreased enantioselectivity (86% ee).

Table **12**: Enantioselective palladium-catalysed arylmetallative cyclisation onto α,β-unsaturated aldehydes. Absolute configuration of **I70** not determined.



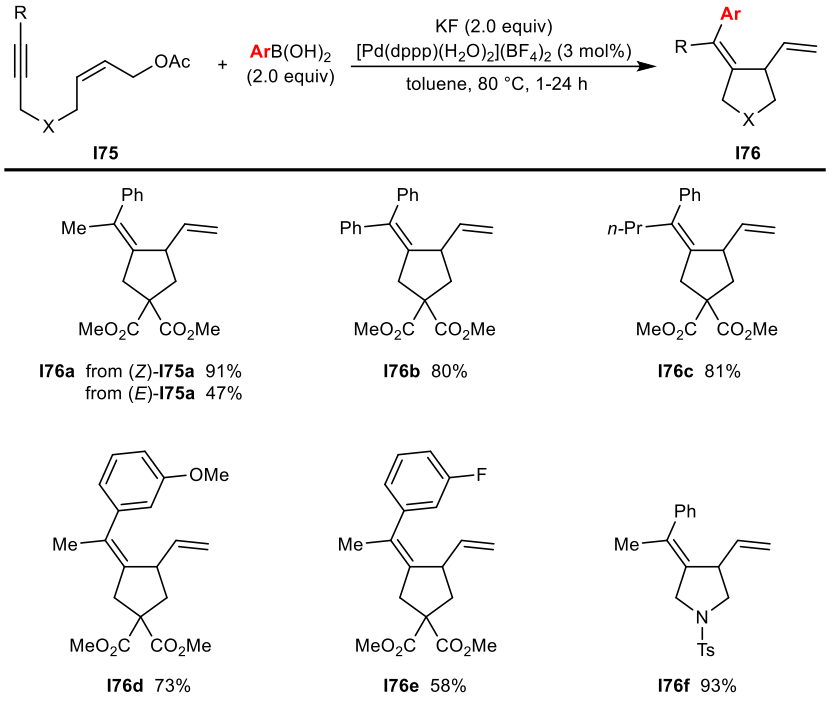
The proposed reaction mechanism for the palladium(II)-catalysed arylative cyclisation reaction follows the general catalytic cycle shown in Scheme 4A; however, with the active metal catalyst being of cationic nature (Scheme 17). Initially, transmetalation of palladium species **I71** with phenylboronic acid provides phenylpalladium species **I72** which adds across the alkyne in enyne **I69c** to give alkenylpalladium species **I73**. Cyclisation onto the tethered electrophile followed by protodepalladation releases product **I70c** and regenerates the active palladium species. It is proposed that the palladium species is of oxidation state +2 throughout the catalytic cycle rather than following a palladium(II)/palladium(0) catalytic cycle as seen in Scheme 15. The suggestion of a +2 oxidation state is based on the fact that halogen-substituted phenylboronic acids are compatible with the reaction and they would presumably undergo oxidative addition in the presence of palladium(0) (see Table 12).



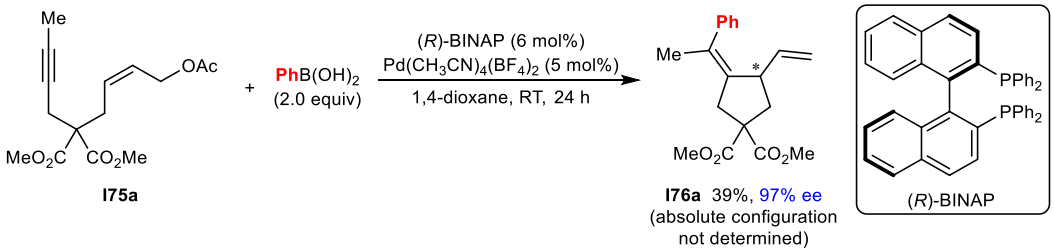
Scheme **17**: Proposed mechanistic cycle.

In 2017, Han, Lu and co-workers reported the arylative cyclisation reaction of 1,6-enynes **I75** with a subsequent β-heteroatom elimination leading to carbo- and heterocycles containing an allylic group (**I76**, Table 13).[65] The outcome of the reaction was very dependent on the stereochemistry of the alkene in 1,6-enyne **I75**. The (*Z*)-isomer led to an excellent yield (**I76a**, 91%); however, the (*E*)-isomer led to a poor yield (**I76a**, 47%). Substrates containing a phenyl- or *n*-propyl-substituted alkyne were tolerated in the reaction (**I76b** and **I76c**). Substituted phenylboronic acids, with substituents such as 3-methoxy (**I76d**) or 3-fluoro (**I76e**), were compatible with the reaction. Changing the all-carbon tether (**I76a-e**) in the substrate to a nitrogen-containing tether led to pyrrolidine **I76f** in 93% yield.

Table **13**: Palladium-catalysed arylmetallative cyclisation onto allyl acetate.



The enantioselective reaction of **I75a** was carried out using (*R*)-BINAP and the enantioenriched product **I76a** was obtained in 39% yield and 97% ee (Scheme 18).



Scheme **18**: Enantioselective palladium-catalysed arylmetallative cyclisation onto allyl acetate.

In summary, this section describes *syn*-selective palladium-catalysed domino reactions of alkyne-tethered electron-deficient alkenes with organoboron pronucleophiles. Different reaction mechanisms have been discussed that result in the same reaction outcomes.

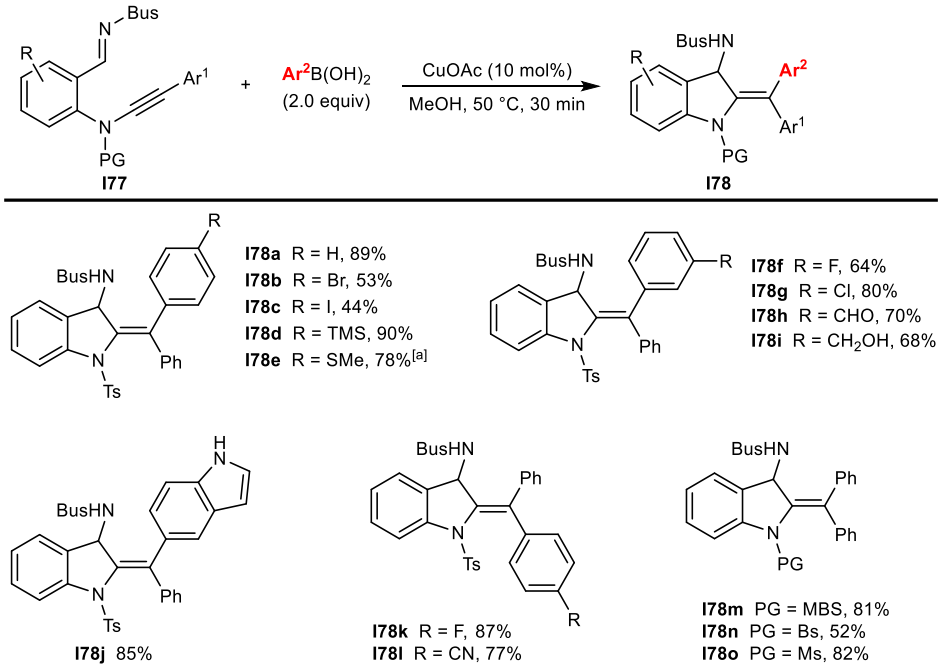
1.4.3 Copper Catalysis

In the presence of copper, arylboronic acids are known to undergo carbocupration with alkynes, making copper a viable metal for carbometallative cyclisation reactions.[110–113] The use of cheaper and more earth-abundant first-row transition-metals in these types of reactions is an attractive addition to the field.

In 2020, Qian, Ye and co-workers reported a *syn*-carbometallative cyclisation reaction involving a copper-catalyst (Table 14).[67] They reacted ynamide-tethered imines **I77** with (hetero)arylboronic acid (2.0 equiv) and CuOAc (10 mol%) in MeOH at 50 °C to get 2,3-disubstituted indolines **I78**. Commonly, nucleophilic addition of arylboronic acids to ynamides occur at the α-position.[114,115] However, reversal of this regioselectivity, as seen in this copper-catalysed carbometalation/cyclisation reaction, has also been reported.[116]

A range of substituted phenylboronic acids were tolerated in the reaction with substituents such as fluoro (**I78f**), chloro (**I78g**), bromo (**I78b**) and iodo (**I78c**), as well as a TMS (**I78d**), a thiomethyl (**I78e**), a formyl (**I78h**) and a hydroxymethyl substituent (**I78i**). Also, 5-indolylboronic acid was compatible with the reaction (**I78j**). As well as phenyl-alkyne containing substrates (**I78a**-**j**), substituted aryl-alkynes were also successful in providing the corresponding products **I78k** and **I78l**; however, alkyl-substituted alkynes and terminal alkynes only provided the desired products in low yields (<30%). Variation of the ynamide protecting group from a tosyl group (**I78a-l**) to a 4-methoxybenzenesulfonyl (**I78m**) or mesyl group (**I78o**) had little effect on the yields; however, the 4-bromobenzenesulfonyl protecting group led to a decrease in the yield (**I78n**, 52%).

Table **14**: Copper-catalysed arylmetallative cyclisation onto imines.



[a] 1 h reaction time.

The proposed mechanism for the copper-catalysed arylative cyclisation reaction follows the general catalytic cycle shown in Scheme 4A with the active metal catalyst being of oxidation state +1.

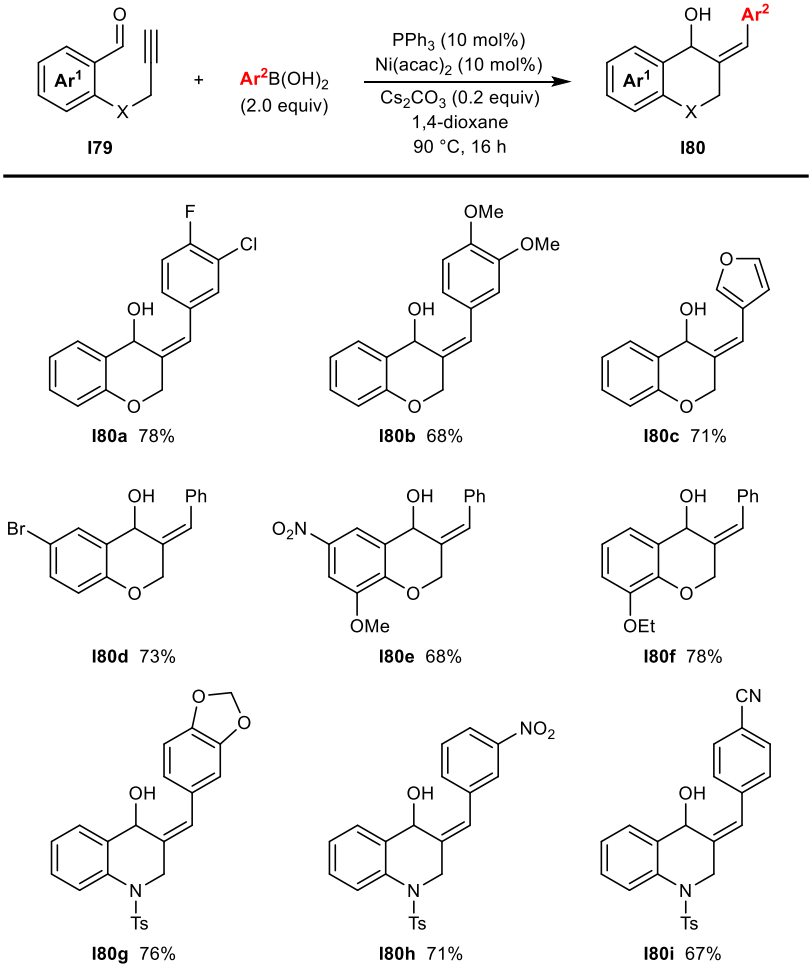
1.4.4 Nickel Catalysis

Similarly to copper, nickel is an abundant first-row transition-metal and therefore the use of nickel as a catalyst in carbometallative cyclisation reactions is an attractive alternative to using precious metals such as palladium and rhodium. As well as the advantages of being an abundant first-row transitions-metal, exploration of alternative catalytic systems, based on the metal, are of interest due to the potential discovery of new reactivity. Arylboronic acids are known to undergo insertion with alkynes in the presence of a nickel-catalyst,[117,118] and this makes nickel a potential candidate for catalysing domino reactions of alkyne-tethered electrophiles where the organonickel species undergoes insertion with the alkyne and the generated alkenylnickel intermediate is trapped by the tethered electrophile. The proposed mechanisms of these reactions follow the general catalytic cycle shown in Scheme 4A. The oxidation state of nickel in these reactions is unclear and some believe it to be +1

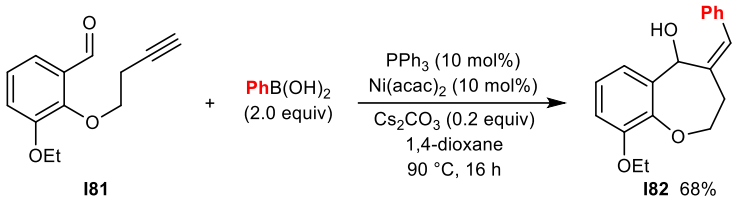
while others believe it to be +2. Further discussion on this topic can be found in Schemes 21, 27 and 30.

In 2018, Reddy and co-workers reported the first example of a *syn*-selective nickel-catalysed carbometalation/cyclisation reaction of alkyne-tethered electrophiles with boronic acids.[68] Terminal alkyne-tethered ketones **I79** were treated with (hetero)arylboronic acid (2.0 equiv), $Ni(acac)_2$ (10 mol%), PPh_3 (10 mol%), and Cs_2CO_3 (0.2 equiv) in 1,4-dioxane at 90 °C to afford chromane and tetrahydroquinoline products **I80** (Table 15). Disubstituted phenylboronic acids bearing electron-withdrawing (**I80a**) or electron-donating groups (**I80b**) were tolerated, as well as 3-furylboronic acid (**I80c**); however, alkenylboronic acids were found to be unsuitable in the reaction. Substitution on the aryl moiety of the 2-propargyloxy benzaldehyde was also explored and substituents such as bromo (**I80d**), nitro (**I80e**), and alkoxy groups (**I80e** and **I80f**) were tolerated. The scope of the arylboronic acid in reactions of 2-propargylamino benzaldehydes was investigated. 1,3-Benzodioxole-5-boronic acid (**I80g**), 3-nitrophenylboronic acid, (**I80h**) and 4-cyanophenylboronic acid (**I80i**) were all successful in the reaction.

Table **15**: Nickel-catalysed arylmetallative cyclisation onto aldehydes.



The reaction of substrate **I81** with the tether between the alkyne and the ether extended by one carbon, provided the 7-membered benzoxepine product **I82** in 68% yield (Scheme 19).

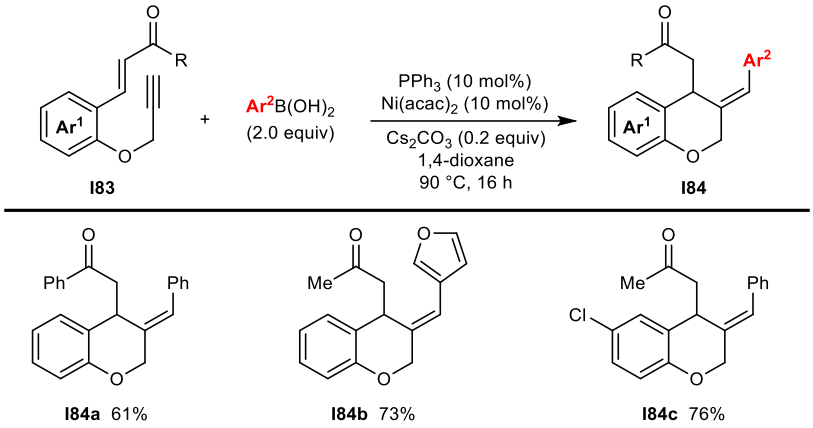


Scheme **19**: Nickel-catalysed arylmetallative cyclisation onto aldehyde.

To further extend the scope, the electrophile was changed from an aldehyde to an enone (Table 16). Cyclisation onto methyl- (**I84b** and **I84c**) and phenyl-substituted enones (**I84a**) were tolerated. A substrate containing a chloro substituent on the aryl

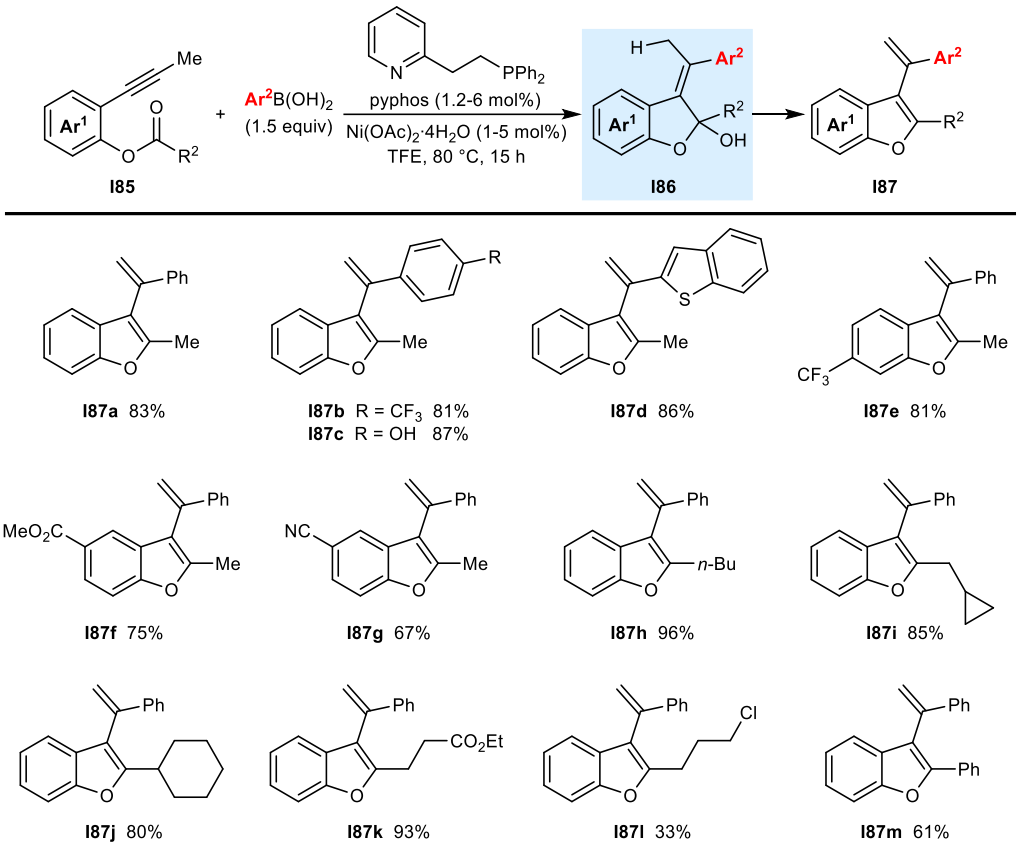
moiety was also compatible with the reaction (**I84c**). Phenylboronic acid (**I84a** and **I84c**) and 3-furylboronic acids (**I84b**) were successful in providing the desired products.

Table **16**: Nickel-catalysed arylmetallative cyclisation onto α,β-unsaturated ketones.



In 2019, Cho and co-workers reported the nickel-catalysed *syn*-carbometallative cyclisation reaction of alkyne-tethered esters **I85** to give multifunctionalised benzofurans **I87** (Table 17).[69] They reacted substrates **I85** with (hetero)arylboronic acid (1.5 equiv), $Ni(OAc)_2 \cdot 4H_2O$ (1-5 mol%) and pyphos (1.2-6 mol%) in TFE at 80 °C to obtain the desired products **I87**. As well as phenylboronic acid (**I87a** and **I87e-m**), also 4-(trifluoromethyl)phenylboronic acid (**I87b**) and 4-hydroxyphenylboronic acid (**I87c**) were tolerated in the reaction, as was benzothiophen-2-ylboronic acid (**I87d**).

Table **17**: Nickel-catalysed arylmetallative cyclisation onto esters.

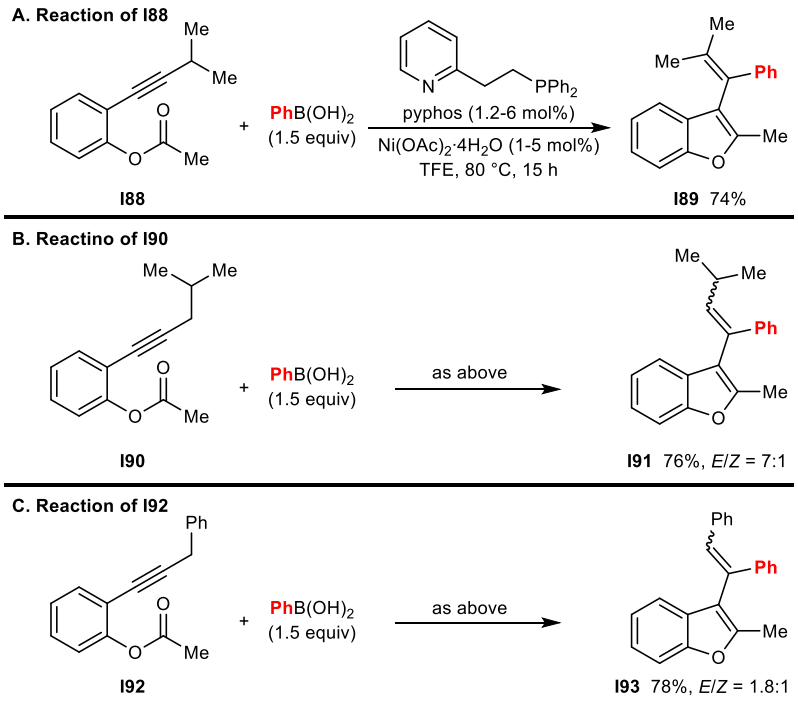


Electron-withdrawing groups, such as trifluoromethyl (**I87e**), ester (**I87f**) or nitrile (**I87g**) were tolerated as substituents on the aryl moiety of the substrate. A range of substituents at the R^2-position were compatible with the reactions, such as methyl (**I87a-g**), *n*-butyl (**I87h**), cyclopropylmethyl (**I87i**), cyclohexyl (**I87j**) and phenyl (**I87m**). Substrates containing alkyl chains at the R^2-position with an ester (**I87k**) or chloro group (**I87l**) were successful in providing the desired products; however, in the latter case a lower yield of 33% was observed.

The proposed mechanism follows the general catalytic cycle shown in Scheme 4A; however, the cyclisation step is followed by protonation of the intermediate nickel alkoxide and subsequent dehydration of intermediate **I86** leads to the desired products **I87**.

Next, an investigation of the alkyne substituent was carried out (Scheme 20). *i*-Propyl-substituted substrate **I88** was subjected to the reaction conditions and the corresponding tetra-substituted alkene product **I89** was obtained in 74% yield (Scheme 20A). Substrate **I90** and **I92**, containing a methylene group directly connected to the

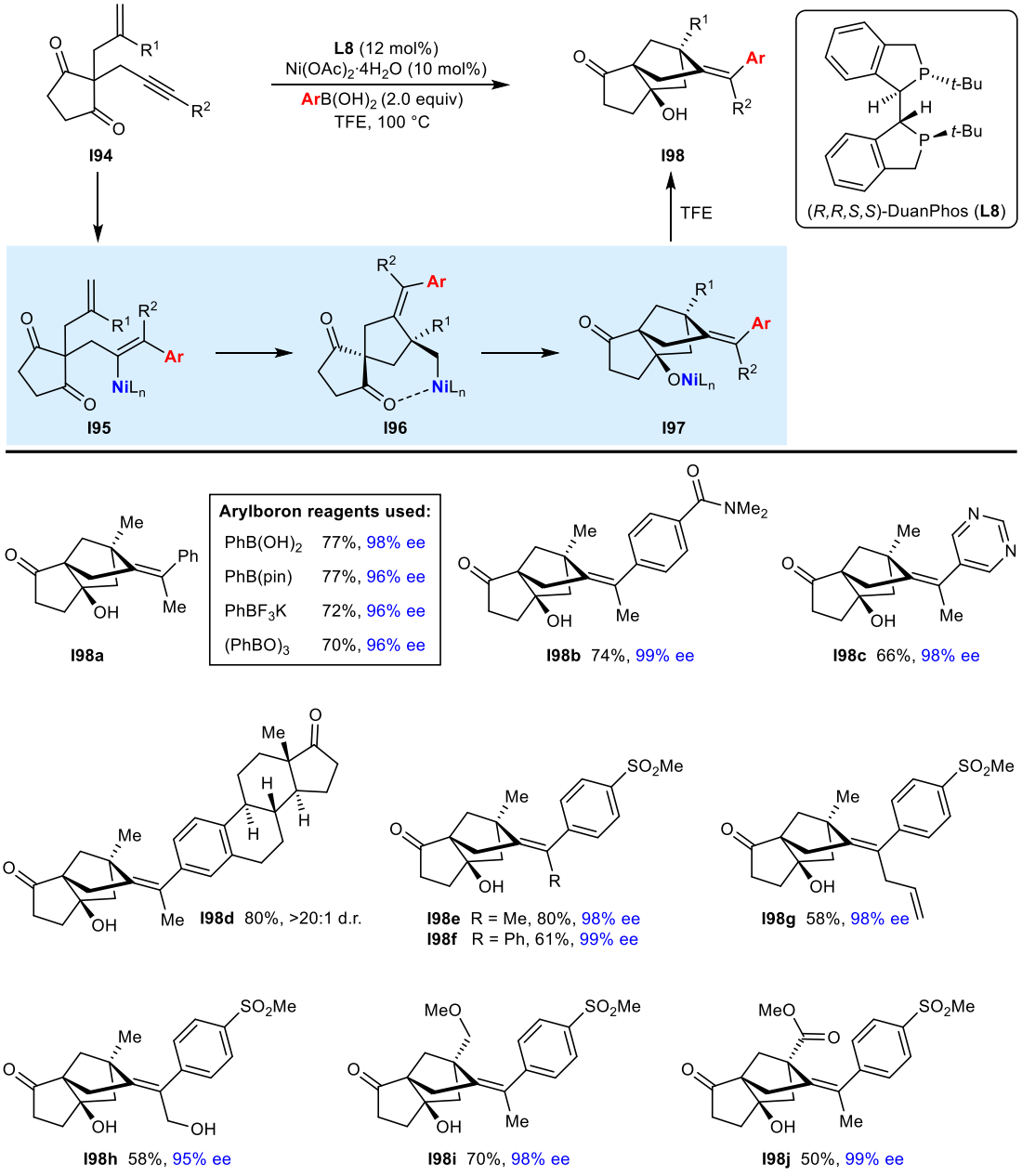
alkyne were separately exposed to the reaction conditions. Both substrates led to the corresponding tri-substituted alkene products (**I91** and **I93**) in good yields; however, both were isolated as mixtures of *E*/*Z* isomers (Scheme 20B and 20C).



Scheme **20**: Nickel-catalysed arylmetallative cyclisation onto esters.

In 2020, Kong and co-workers reported a process where nickel-catalysed difunctionalisation of alkynes was incorporated into more complex domino reactions of substrates containing 3 reactive sites including an alkyne, an unactivated alkene and a 1,3-diketone (Table 18).[70] The sequential domino cyclisation led to the synthesis of complex bridged tricyclo[5.2.1.$0^{1,5}$]decanes **I98** containing 3 new carbon-carbon bonds in high regio- and enantioselectivities. The reaction of enynones **I94** was carried out in the presence of (hetero)arylboronic acid (2.0 equiv), $Ni(OAc)_2 \cdot 4H_2O$ (10 mol%) and (*R*,*R*,*S*,*S*)-DuanPhos (**L8**, 12 mol%) in TFE at 100 °C. Interestingly, various arylboron reagents were compatible with the reaction such as $PhB(OH)_2$, PhBpin, $PhBF_3K$ and $(PhBO)_3$, and they all led to somewhat similar results (**I98a**).

Table **18**: Enantioselective nickel-catalysed arylative sequential domino cyclisation.



Firstly, an investigation of the scope of the boronic acid revealed that amide-substituted phenylboronic acid worked well in the reaction (**I98b**) as well as pyrimidine-5-boronic acid (**I98c**) and both reactions showed excellent enantioselectivity. Remarkably, an estrone-derived boronic acid was tolerated in the reaction and afforded the corresponding product **I98d** in 80% yield and >20:1 diastereomeric ratio. 4-(Methylsulfonyl)phenylboronic acid was also compatible with the reaction (**I98e-j**); however, neither alkyl- nor alkenylboronic acids provided the desired products.

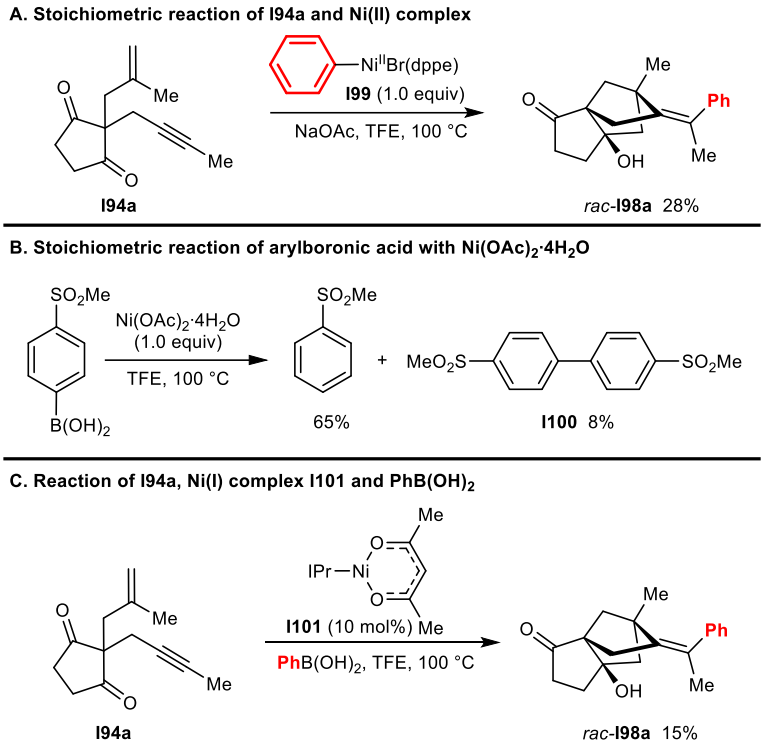
Secondly, the scope of the alkyne substituent was investigated. In addition to the methyl group (**I98a-e**, **I98i** and **I98j**), allyl (**I98g**) and hydroxymethyl (**I98h**) groups were also compatible with the reaction. Interestingly, a phenyl-alkyne was also successful in providing the desired product in a moderate yield (**I98f**, 61%). It is reasonable to think that the electronic bias imposed on the alkyne by the phenyl group, which is opposite to that of an alkyl group, is the cause for the decrease in yield and, taking this into account, a yield of 61% is surprisingly good. Terminal alkynes were not tolerated in the reaction and provided only complex mixtures of unidentified products.

Thirdly the scope of the alkene substituent was investigated. Substrate **I94i** bearing a methoxymethyl substituent at the R^1-position performed well in the reaction leading to the desired product **I98i** in 70% yield and 98% ee. Also, substrate **I94j** containing an ester group performed well in the reaction (**I98j**).

The proposed mechanistic cycle follows the general mechanism seen in Scheme 4A; however, additional steps take place. Transmetalation of arylboronic acid with the nickel catalyst is followed by addition of the resultant arylnickel species across the alkyne to give alkenylnickel species **I95**. From here two sequential cyclisation steps take place. The first cyclisation is an intramolecular migratory insertion of the alkenylnickel species **I95** into the unactivated double bond giving alkyl-nickel species **I96**, which undergoes subsequent nucleophilic cyclisation onto the cyclic 1,3-diketone providing nickel alkoxide species **I97** followed by protonation to release the complex bridged tricyclo[5.2.1.$0^{1,5}$]decanes **I98** and regenerate the active nickel catalyst.

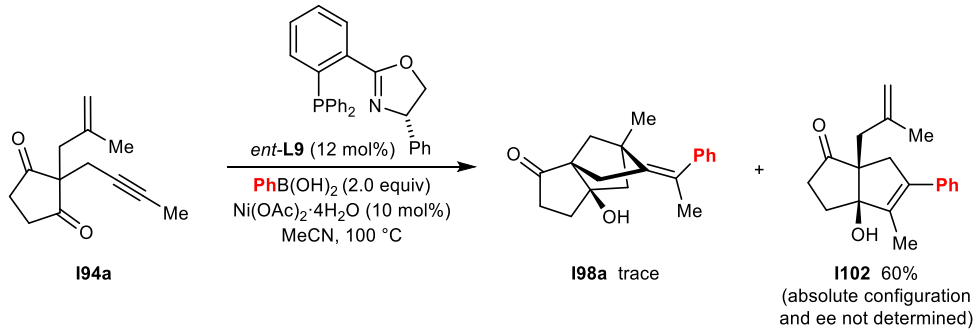
To gain insight into the oxidation state of the active nickel catalyst, mechanistic studies were carried out (Scheme 21). The stoichiometric reaction of enynone **I94a** with Ni(II) complex **I99** led to formation of product *rac*-**I98a** in 28% yield suggesting that a nickel(II) species is involved in the catalytic cycle (Scheme 21A). However, a second stoichiometric reaction of 4-(methylsulfonyl)phenylboronic acid with $Ni(OAc)_2 \cdot 4H_2O$ led to the formation of deboronated (methylsulfonyl)benzene in 65% yield and biaryl product **I100** in 8% yield (Scheme 21B). The formation of a biaryl product suggests that the formation of a nickel(I) species is possible. The biaryl product is obtained by reductive elimination of a diarylnickel(II) species which also releases a nickel(0) species. A comproportionation reaction between nickel(II) and nickel(0) could then provide nickel(I) species. Therefore, the reaction of enynone **I94a** with nickel(I) species

I101 was performed providing *rac*-**I98a** in 15% yield suggesting that a catalytic cycle involving an arylnickel(I) species is also viable (Scheme 21C).



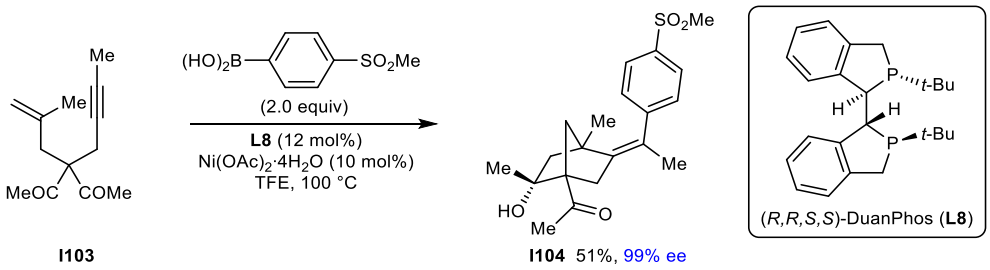
Scheme **21**: Mechanistic studies.

The reaction of enynone **I94a** under the standard reaction conditions; however, using (*S*)-PhPHOX (*ent*-**L9**) in place of (*R*,*R*,*S*,*S*)-DuanPhos (**L8**) led to only a trace amount of the desired product **I98a**. (Scheme 22). Product **I102**, which is the result of alkyne insertion into the arylnickel species occurring with opposite regioselectivity, was obtained in 60% yield. Following alkyne insertion, *E*/*Z* isomerisation of the resulting alkenylnickel species occurs and subsequent nucleophilic attack of the cyclic 1,3-diketone. This is an example of an *anti*-carbometallative cyclisation reaction (see Section 1.5). In these types of reactions, alkyl-substituted alkynes generally lead to decomposition of the substrate[72,74,75,77,79] or significantly reduced yields (see Table 20, 28 and 31 and Scheme 34) and therefore this result is notable. The outcome of the reaction appears to be highly dependent on the chiral ligand used, either (*R*,*R*,*S*,*S*)-DuanPhos (**L8**) or (*S*)-PhPHOX (*ent*-**L9**) (see Table 18 vs. Scheme 22).



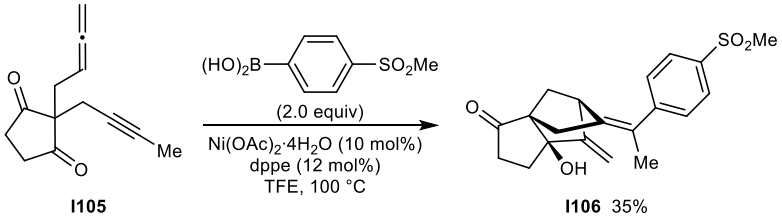
Scheme **22**: Nickel-catalysed arylmetallative cyclisation onto cyclic 1,3-diketone.

Substrate **I103** containing an acyclic 1,3-diketone was subjected to the reaction conditions and highly functionalised bicyclo[2,2,1]heptane derivative **I104** was obtained in 51% yield and 99% ee (Scheme 23).



Scheme **23**: Enantioselective nickel-catalysed arylative sequential domino cyclisation.

Substrate **I105**, containing an allene instead of an alkene, was successful in providing the desired arylative cyclisation product **I106** in 35% yield under racemic reaction conditions using dppe as a ligand (Scheme 24).

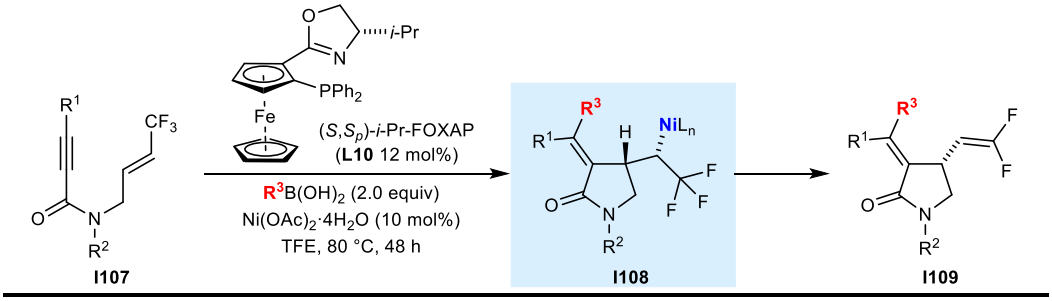


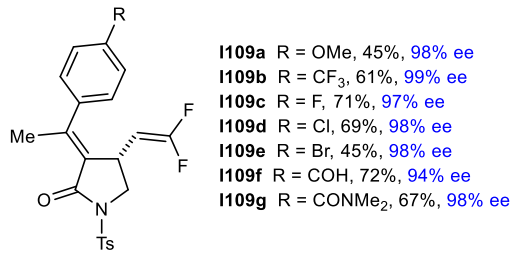
Scheme **24**: Nickel-catalysed arylative sequential domino cyclisation.

In 2022, Kong and co-workers reported the enantioselective nickel-catalysed carbometallative cyclisation onto trifluoromethyl alkenes followed by β-fluoride elimination (Table 19).[71] Alkyne-tethered trifluoromethyl alkenes **I107**, containing an

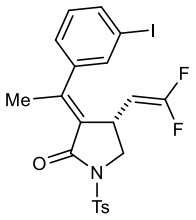
amide in the tether, were reacted with boronic acid (2.0 equiv), $Ni(OAc)_2 \cdot 4H_2O$ (10 mol%) and (S,S_p)-*i*-Pr-FOXAP (**L10**, 12 mol%) in TFE at 80 °C for 48 hours to obtain the corresponding 4-*gem*-difluorovinyl-substituted 2-pyrrolidones **I109**.

Table **19**: Enantioselective nickel-catalysed carbometallative cyclisation onto trifluoromethyl alkenes.

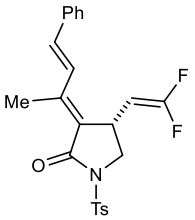




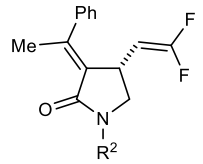
I109a R = OMe, 45%, 98% ee
I109b R = CF_3, 61%, 99% ee
I109c R = F, 71%, 97% ee
I109d R = Cl, 69%, 98% ee
I109e R = Br, 45%, 98% ee
I109f R = COH, 72%, 94% ee
I109g R = $CONMe_2$, 67%, 98% ee



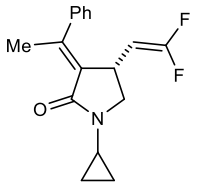
I109h 41%, 99% ee



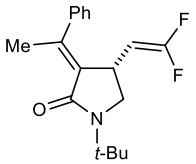
I109i 52%, 96% ee



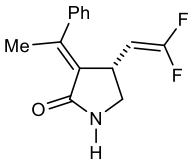
I109j R^2 = Ph, 57%, 97% ee
I109k R^2 = Bn, 62%, 98% ee



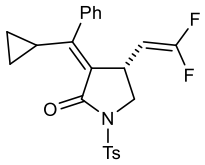
I109l 57%, 98% ee



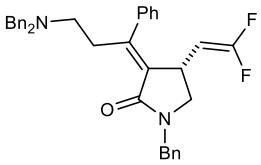
I109m 55%, 83% ee



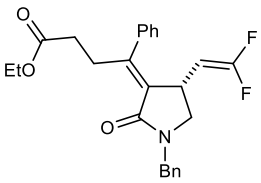
I109n 32%, 98% ee



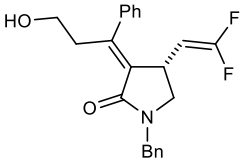
I109o 50%, 98% ee



I109p 59%, 97% ee



I109q 60%, 98% ee

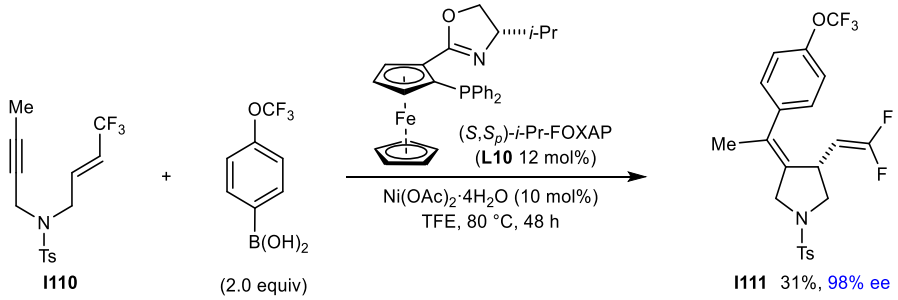


I109r 62%, 97% ee

The scope of substituted phenylboronic acids was examined extensively and overall good yields and excellent enantioselectivities were observed. Electron-rich phenylboronic acids, such as 4-methoxyphenylboronic acid (**I109a**) was tolerated and electron-poor phenylboronic acids, such as 4-(trifluoromethyl)phenylboronic acid (**I109b**), 4-formylphenylboronic acid (**I109f**) and 4-(dimethylcarbamoyl)phenylboronic acid (**I109g**) were also tolerated. Halogen-substituted phenylboronic acids were examined in the reaction and 4-fluoro- (**I109c**),

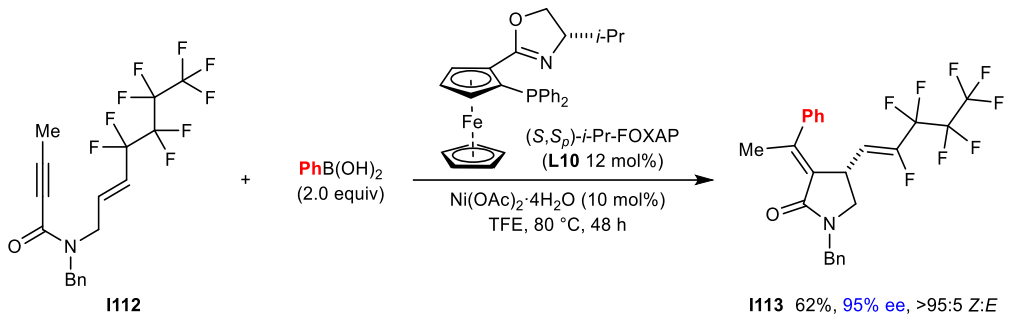
4-chloro- (**I109d**), 4-bromo- (**I109e**) and 3-iodophenylboronic acid (**I109h**) were all compatible. Interestingly, (*E*)-styreneboronic acid participated in the reaction and provided product **I109i** in 52% yield and 96% ee. Next, variation of the amide protecting group was investigated. As well as tosyl (**I109a-i** and **I109o**), also phenyl (**I109j**), benzyl (**I109k** and **I109p-r**) and cyclopropyl protecting groups (**I109l**) were well-tolerated; however, having a *t*-butyl-protected amide led to a decrease in the enantioselectivity of the reaction (**I109m**). Notably, the unprotected amide **I107n** was also successful in providing 2-pyrrolidone **I109n** in 32% yield and 98% ee. In addition to having a methyl substituent on the alkyne (**I109a-n**), a substrate containing a cyclopropyl substituent was also tolerated in the reaction (**I109o**). Substrates with ester- (**I109q**) or amine-containing alkyl chains (**I109p**) on the alkyne were successful in the reaction and substrate **I107r**, containing a TBS-protected hydroxy alkyl chain on the alkyne, provided the direct deprotected product **I109r** in 62% yield and 97% ee.

1,6-Enyne **I110**, containing an *N*-tosyl-protected amine in place of an *N*-tosyl-protected amide in the tether, was subjected to the standard reaction conditions; however, using 4-(trifluoromethoxy)phenylboronic acid (Scheme 25). 4-*gem*-Difluorovinyl-substituted pyrrolidine **I111** was obtained in 31% yield and 98% ee.



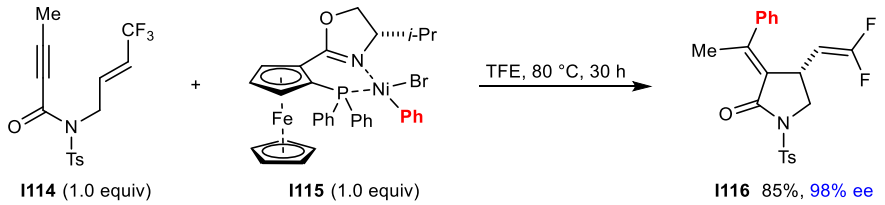
Scheme **25**: Enantioselective nickel-catalysed arylmetallative cyclisation onto trifluoromethyl alkenes.

Employing 1,6-enyne **I112** with a perfluoroalkyl substituent on the alkene was tolerated under the standard reaction conditions and the desired product **I113** was obtained in 62% yield, 95% ee and *Z*:*E* selectivity of more than 95:5 (Scheme 26).



Scheme **26**: Enantioselective nickel-catalysed arylmetallative cyclisation onto a perfluoroalkyl-substituted alkene.

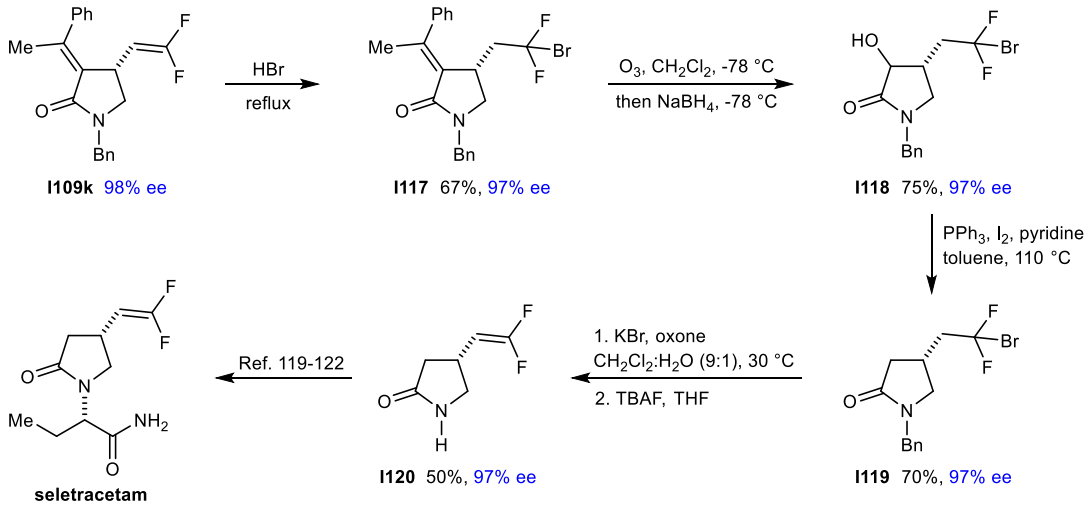
For mechanistic studies, phenylnickel(II) complex **I115** was isolated and used in a stoichiometric reaction with 1,6-enyne **I114** (Scheme 27). The reaction provided the desired product **I116** in 85% yield and 98% ee.



Scheme **27**: Mechanistic study.

The proposed mechanism follows the general catalytic cycle shown in Scheme 4A; however, an additional step is required to close the cycle. Cyclisation of the alkenylnickel intermediate onto the trifluoromethyl alkene provides alkylnickel intermediate **I108** (Table 19) which can undergo β-fluoride elimination to release the product (**I109**). A mechanistic pathway involving a nickel(0) species undergoing oxidative cyclisation with the 1,6-enyne was also considered; however, there are two reasons that the carbometalation/cyclisation/elimination reaction was thought to be more feasible. Firstly, the result seen in Scheme 27 suggest that a phenylnickel(II) species is involved in the mechanistic cycle. Secondly, during optimisation of the reaction, hydroarylation products were observed that were a result of carbometalation of the alkyne followed by protonation of the resultant alkenylnickel intermediate. In nickel(0)-catalysed reactions the cyclisation step is believed to precede arylation and therefore arylated, uncyclised products are unlikely to result from a nickel(0)-catalysed mechanistic pathway.

4-*gem*-Difluorovinyl-substituted 2-pyrrolidone **I109k** was used in the enantioselective synthesis of antiepileptic drug seletracetam, which until now relied heavily on the resolution of racemates (Scheme 28).[119–121] First protection of the *gem*-difluorovinyl group in **I109k** with HBr gave **I117**, which underwent ozonolysis of the alkene to give a diketone and subsequent reduction gave alcohol **I118** in high diastereoselectivity while maintaining high enantioselectivity (97%). Deoxygenation to give **I119** followed by oxidative debenzylation and elimination of hydrogen bromide gave pyrrolidone **I120**. Finally, seletracetam can be prepared by nucleophilic substitution of pyrrolidone **I120** with (*R*)-2-bromobutyric acid followed by amidation of the carboxylic acid.[119–122]

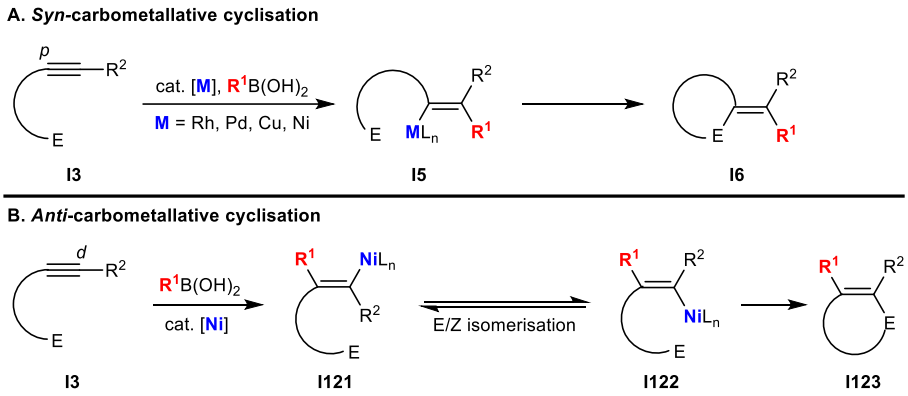


Scheme **28**: Synthesis of seletracetam from **I109k**.

In summary, this section describes nickel-catalysed *syn*-carbometallative cyclisation reactions of alkyne-tethered electrophiles using organoboron pronucleophiles. Variation of the tether and/or the electrophile gives access to a diverse range of carbo- and heterocyclic products such as chromanes, tetrahydroquinolines, benzoxepines, benzofurans, pyrrolidines and 2-pyrrolidones. Also, tricyclo[5.2.1.$0^{1,5}$]decanes and bicyclo[2.2.1]heptanes are obtained in more complex domino sequences.

1.5 Nickel-Catalysed *anti*-Carbometallative Cyclisation of Alkyne-Tethered Electrophiles using Organoboron Pronucleophiles

Section 1.4 described how alkyne-tethered electrophiles can undergo arylative cyclisation with an organoboron species in the presence of metals catalysts such as rhodium, palladium, copper and nickel to give cyclised products containing an exocyclic alkene (Scheme 29A). In these reactions the organometallic species adds across the alkyne placing the metal proximal to the electrophile, and with the overall 1,2-addition being *syn*-stereospecific the following cyclisation can occur directly. Migratory insertion of alkynes with organonickel species have been reported to give alkene products with mixtures of (*E*)- and (*Z*)-isomers.[100] The ability of alkenylnickel species undergoing *E*/*Z* isomerisation has led to a different mode of cyclisation reactions where the overall 1,2-addition is *anti*-stereospecific (Scheme 29B). 1,2-Addition of an organonickel species across the alkyne placing nickel distal to the electrophile leads to alkenylnickel species **I121** which cannot directly cyclise onto the tethered electrophile due to geometric constraints; however, alkenylnickel isomerisation allow for the cyclisation to occur and cyclic products containing an endocyclic alkene are obtained (**I123**).



Scheme **29**: Transition-metal-catalysed *syn*- and *anti*-carbometallative cyclisation reactions.

It should be mentioned that other alkenylmetal species have also been reported to undergo *E*/*Z* isomerisation and include alkenylcobalt,[123] alkenylruthenium,[124] alkenylrhodium[125–130] and alkenylpalladium species.[131–136] Further, palladium has been reported to catalyse *anti*-selective addition/cyclisation reactions of alkyne-tethered electrophiles with organoboron reagents to give cyclic products containing

endocyclic alkenes.[56,58,59,66] However, the proposed mechanisms for the palladium(0)-catalysed reactions involve an *anti*-Wacker type oxidative addition and will not be discussed further in this thesis.

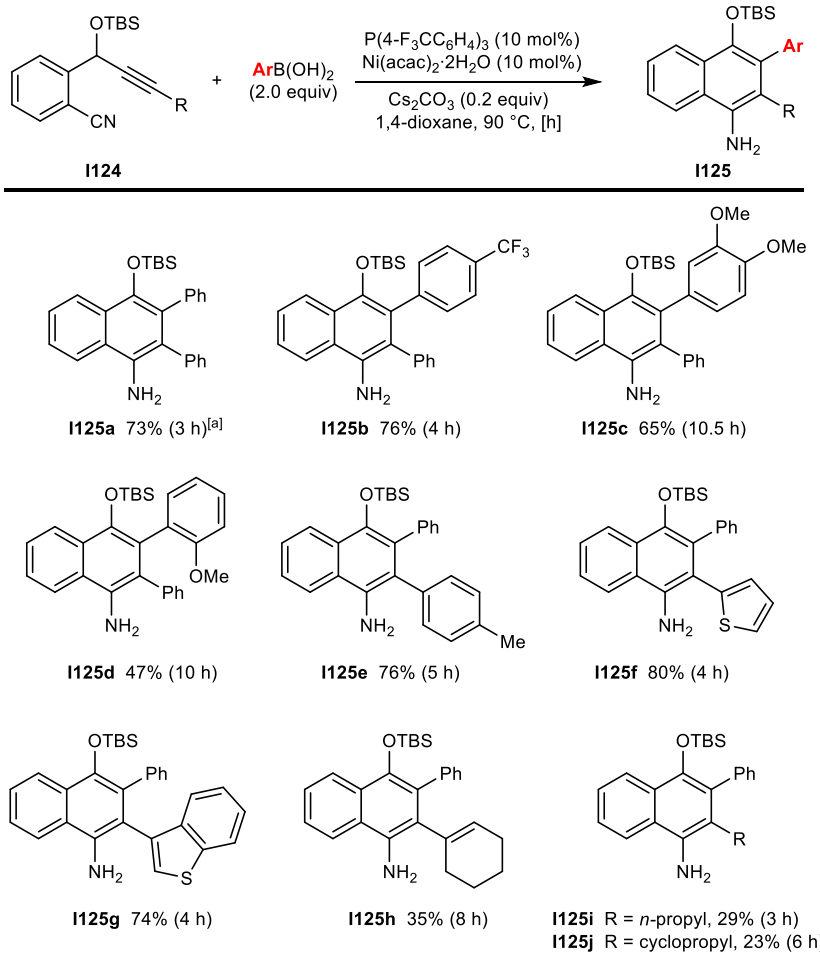
This section will focus on nickel-catalysed *anti*-carbometallative cyclisation reactions of alkyne-tethered electrophiles using organoboron pronucleophiles and is separated into non-enantioselective variants (Section 1.5.1) and enantioselective variants (Section 1.5.2).

1.5.1 Non-Enantioselective Variants

Non-enantioselective variants includes nickel-catalysed arylative cyclisation onto nitriles, azides, *N*-tosyl amides, ketones and α,β-unsaturated ketones to give either achiral products or racemic products.

In 2016, the seminal report of nickel-catalysed arylative cyclisation reactions of alkyne-tethered electrophiles with arylboronic acids involving an *anti*-carbometalation step was reported by Liu and co-workers (Table 20).[73] 2-(Cyano)phenyl propargyl ethers **I124** were exposed to arylboronic acid (2.0 equiv), $Ni(acac)_2 \cdot H_2O$ (10 mol%), $P(4\text{-}F_3CC_6H_4)_3$ (10 mol%) and Cs_2CO_3 (0.2 equiv) in 1,4-dioxane at 90 °C to give highly functionalised 1-naphthylamines **I125**. The reaction tolerated phenylboronic acids with electron-withdrawing (**I125b**) and electron-donating groups (**I125c** and **I125d**). However, alkylboronic acids such as *n*-butylboronic acid were found to be unsuitable in the reaction. Aryl-substituted alkynes were successful in the reaction (**I125a-e**) as well as heteroaryl-substituted alkynes, such as 2-thienyl alkyne (**I125f**) and 3-benzothienyl alkyne (**I125g**). Further, substrates containing cyclohexenyl (**I125h**, 35%), *n*-propyl (**I125i**, 29%) and cyclopropyl (**I125j**, 23%) substituents on the alkyne were compatible with the reaction; however, in lower yields. The latter two results are rare examples of alkyl-substituted alkynes being tolerated in *anti*-selective arylative cyclisation reactions. As discussed in Section 1.3, (hetero)aryl substituents or alkenyl substituents are generally required on the alkyne to obtain the desired regioselectivity of migratory insertion and the lower yields observed in these cases may be attributed to the lower regioselectivities.

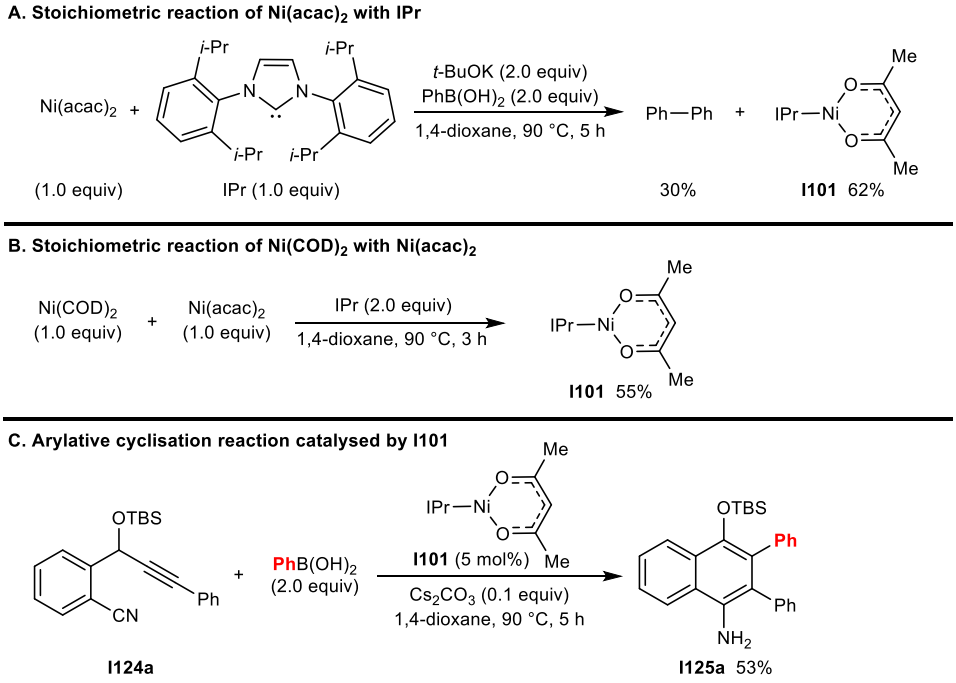
Table **20**: Nickel-catalysed *anti*-carbometallative cyclisation onto nitriles.



[a] Reaction carried out using $Ni(acac)_2 \cdot 2H_2O$ (5 mol%), $P(4\text{-}F_3CC_6H_4)_3$ (5 mol%) and Cs_2CO_3 (0.1 equiv).

To gain insight into the oxidation state of the active nickel species, mechanistic investigations were carried out (Scheme 30). The stoichiometric reaction of $Ni(acac)_2$ with 1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene (IPr), which during optimisation was found to be effective in the reaction, in the presence of two equivalents each of *t*-BuOK and phenylboronic acid led to biphenyl in 30% yield and three-coordinate distorted T-shaped nickel(I) complex **I101** in 62% yield (Scheme 30A). The nickel(I) complex was identified by X-ray crystallography. As previously mentioned, the observation of a biaryl product in the reaction of a nickel(II) species with arylboronic acid could suggest the formation of a nickel(I) species *via* a comproportionation reaction between a nickel(II) species and a newly formed nickel(0) species. Indeed, the stoichiometric reaction of $Ni(COD)_2$ and $Ni(acac)_2$ in the presence of IPr (2.0 equiv) provided nickel(I) species **I101** in 55% yield (Scheme 30B). Next, nickel(I) complex **I101** was found to catalyse the arylative cyclisation reaction of 2-(cyano)phenyl propargyl ether **I124a** with phenylboronic acid giving the desired

product **I125a** in 53% yield, suggesting that a nickel(I) species is involved in the catalytic cycle (Scheme 30C). The proposed mechanism follows the general catalytic cycle shown in Scheme 4B with the active nickel species being of oxidation state +1. It is worth noting that nickel(I) species are also known to undergo disproportionation reaction which would result in a nickel(0) and a nickel(II) species being formed.[137]

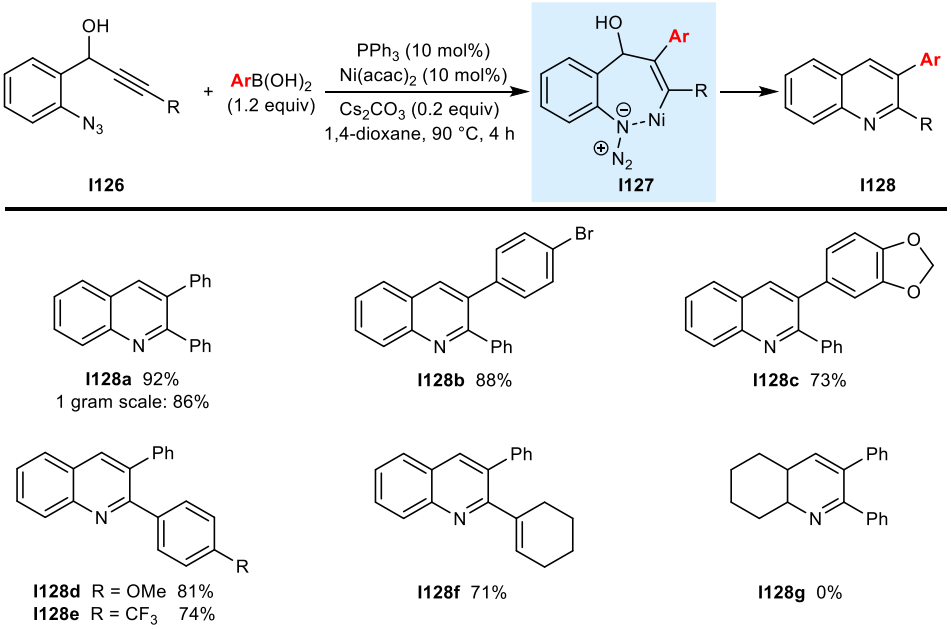


Scheme **30**: Mechanistic studies.

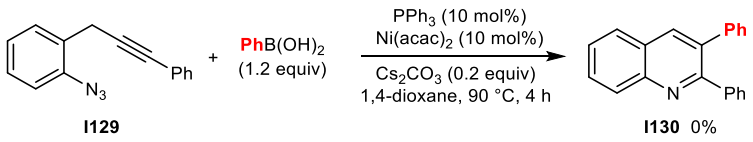
In 2018, Reddy and co-workers reported the synthesis of 2,3-diarylquinolines *via* a nickel-catalysed *anti*-carbometallative cyclisation of azidophenyl propargyl alcohol **I126** (Table 21).[75] In this reaction, the alkenylmetal species is trapped with a non-carbon centred electrophile (**I127**). Substrate **I126** was reacted with arylboronic acids (1.2 equiv), $Ni(acac)_2$ (10 mol%), PPh_3 (10 mol%) and Cs_2CO_3 (0.2 equiv) in 1,4-dioxane at 90 °C for 4 h to give 2,3-diarylquinolines (**I128**). The reaction tolerated phenylboronic acid (**I128a** and **I128d-f**) as well as 4-bromophenylboronic acid (**I128b**) and 1,3-benzodioxole boronic acid (**I128c**). The reaction worked well with both electron-donating (**I128d**) and electron-withdrawing groups (**I128e**) on the aryl-alkyne and a 71% yield was obtained when having a cyclohexenyl-substituted alkyne (**I127f**). Non-aromatic azido alkynol substrate **I126g** did not participate in the reaction (**I128g**). Additionally, substrates containing an alkyl-substituted alkyne were detrimental to the reaction. The proposed mechanism follows the general catalytic cycle shown in Scheme

4B; however, in contrast with the previous example by Liu and co-workers it is suggested that the nickel species is of oxidation state +2.

Table **21**: Nickel-catalysed *anti*-carbometallative cyclisation onto azides.



The presence of a propargylic hydroxyl group in substrate **I126** was important to the success of the reaction as substrate **I129**, without this functionality, led to slow decomposition of the starting material under the standard reaction conditions (Scheme 31).

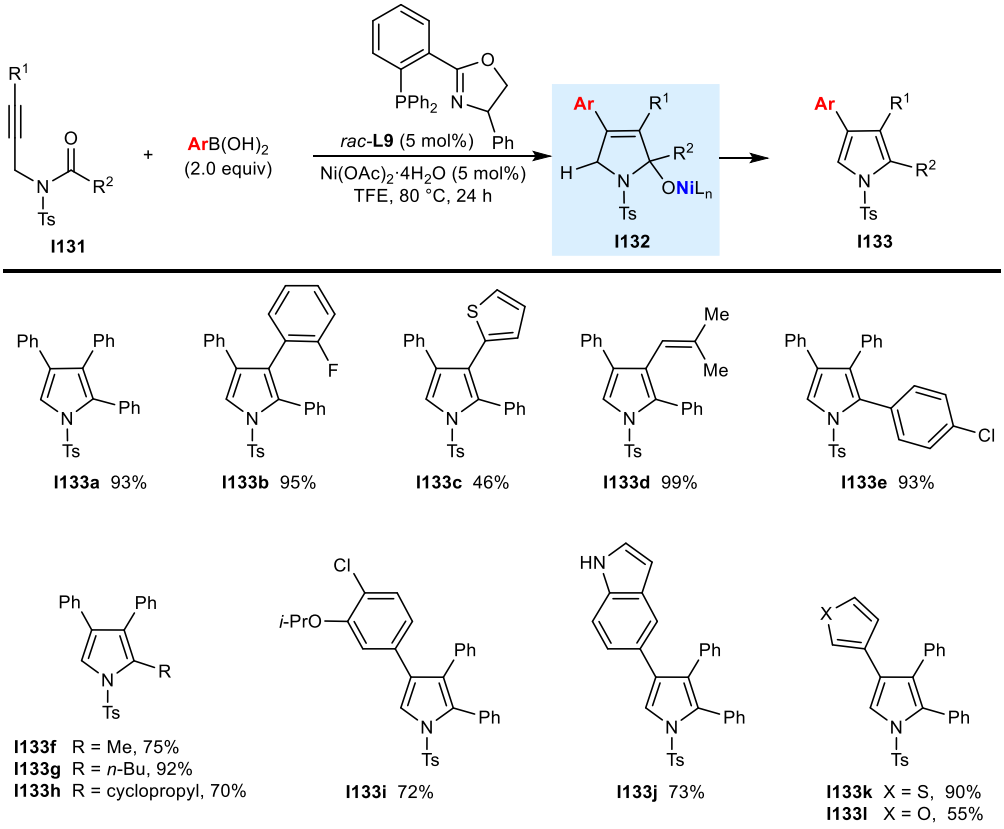


Scheme **31**: Nickel-catalysed *anti*-carbometallative cyclisation onto an azide.

In 2018, the Lam group reported the nickel-catalysed *anti*-carbometallative cyclisation reaction of *N*-tosyl alkynamides **I131** with (hetero)arylboronic acids (2.0 equiv) to give substituted pyrroles **I133** (Table 22).[77] The use of $Ni(OAc)_2 \cdot 4H_2O$ (5 mol%) and racemic Ph-PHOX (*rac*-**L9**, 5 mol%) in TFE at 80 °C facilitated the reaction. Substrates containing substituents on the alkyne such as 2-fluorophenyl (**I133b**), 2-thienyl (**I133c**) and alkenyl (**I133d**) were tolerated in the reaction; however,

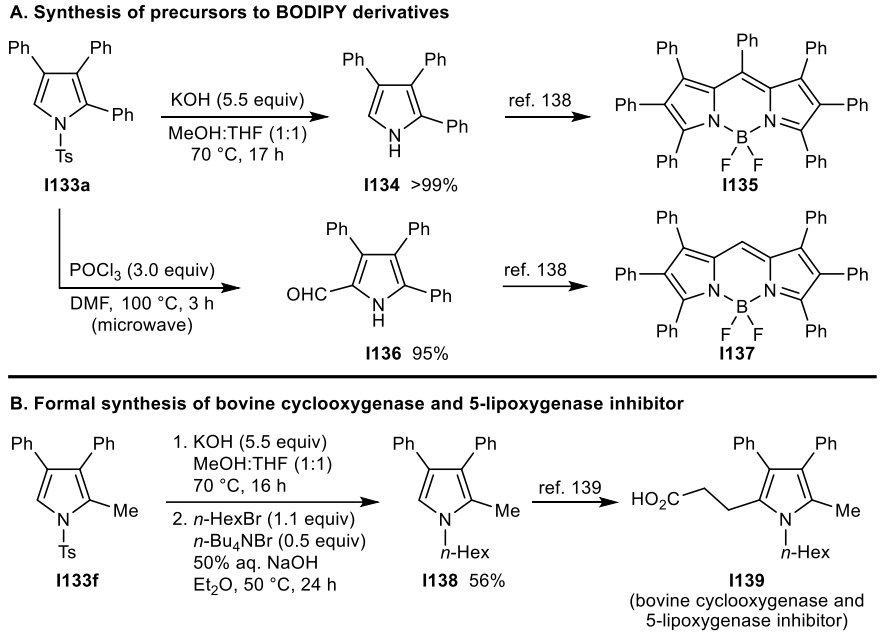
having a methyl substituent on the alkyne led to a complex mixture of products. Excellent yields were observed with various aryl groups (**I133a-e** and **I133i-l**) or alkyl groups (**I133f-h**) on the *N*-tosyl amide. Substituted phenylboronic acids were tolerated in the reaction (**I133i**) as well as a variety of heteroarylboronic acids such as 5-indolyl (**I133j**), 3-thienyl (**I133k**) and 3-furylboronic acid (**I133l**); however, 4-pyridinylboronic acid was not compatible with the reaction, nor was methyl or cyclopropylboronic acid. The proposed mechanism follows the general catalytic cycle shown in Scheme 4B. Protonation of the nickel-alkoxide **I132** and elimination of water is required to obtain the desired pyrrole products.

Table **22**: Nickel-catalysed *anti*-carbometallative cyclisation onto amides.



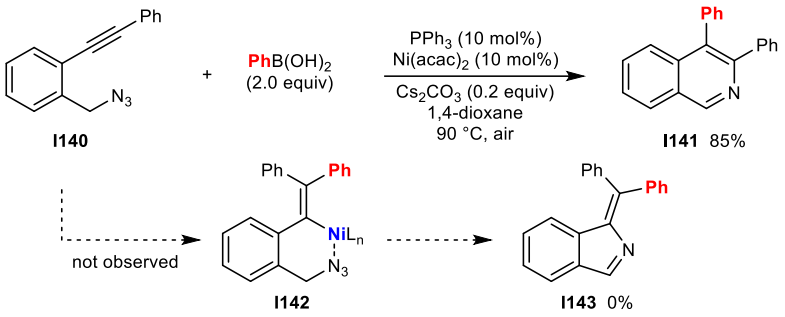
The utility of the described process is seen in Scheme 32 in the synthesis of pyrroles that have been used in the preparation of 4,4-difluoro-4-bora-3*a*,4*a*-diaza-*s*-indacene (BODIPY) derivatives (Scheme 32A)[138] and bovine cyclooxygenase and 5-lipoxygenase inhibitor **I139** (Scheme 32B).[139] Tosyl-deprotection of pyrrole **I133a** was achieved using KOH in MeOH:THF (1:1) at 70 °C to obtain pyrrole **I134**, a precursor to BODIPY derivative **I135**. Additionally, the reaction of **I133a** with $POCl_3$

in DMF at 100 °C in a microwave reactor led to formylation with concomitant tosyl-deprotection to give pyrrole **I136**, a precursor to BODIPY derivative **I137**. A further application of the methodology was described in the synthesis of pyrrole **I138**, a precursor to **I139**, through a tosyl-deprotection of **I133f** followed by *N*-alkylation using *n*-hexyl bromide.



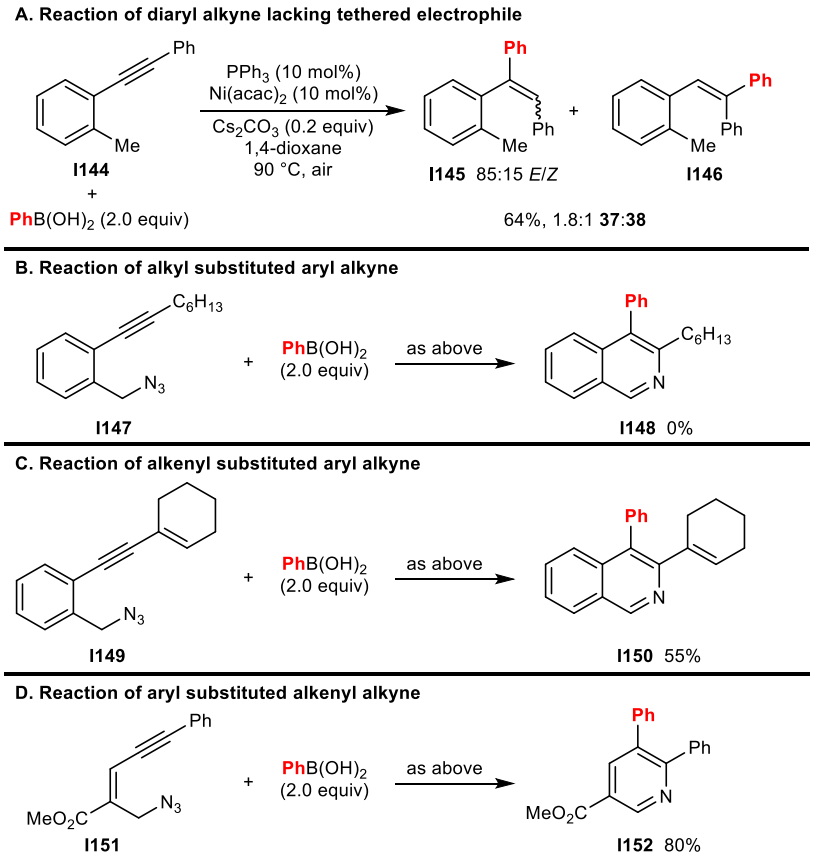
Scheme **32**: Synthetic application of pyrroles **I133a** and **I133f**.

In 2020, Reddy and co-workers reported the nickel-catalysed arylative cyclisation of sterically and electronically unbiased diaryl alkynes leading to the synthesis of pyridine and indene derivatives (Scheme 33).[79] The process was proposed to proceed *via* electrophile-driven regioselective arylnickelation. Diaryl alkyne **I140** was reacted with phenylboronic acid (2.0 equiv), $Ni(acac)_2$ (10 mol%), PPh_3 (10 mol%) and Cs_2CO_3 (0.2 equiv) in 1,4-dioxane under air at 90 °C. The desired isoquinoline **I141** was observed in 85% yield. This result was surprising, since one might have expected the formation of product **I143**, resulting from the alkyne undergoing migratory insertion with the phenylnickel species with opposite regioselectivity. Indeed, nickel-catalysed hydroarylation of diaryl alkyne **I144**, which lacks the azido group, led to a mixture of stereo- and regioisomers (**I145** and **I146**, Scheme 34A). This emphasises the importance of the polarising electrophile group in controlling the regioselectivity of migratory insertion.



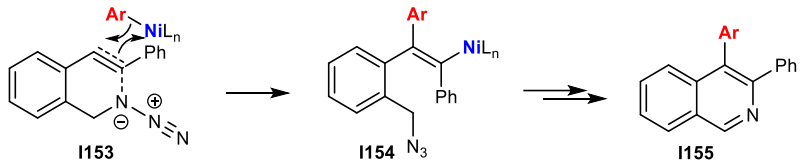
Scheme **33**: Nickel-catalysed *anti*-carbometallative cyclisation of 2-functionalised diarylalkynes.

Alkyl-substituted aryl alkyne **I147** did not participate in the reaction, highlighting the importance of extended conjugation (Scheme 34B). Substrates **I149** or **I151**, both bearing an aryl group and an alkenyl group on the alkyne; however, with alternative connectivities of the two groups on the alkyne, were both successful in providing the desired products (Scheme 34C and 34D). This further highlights the importance of the polarising electrophile in this arylative cyclisation of seemingly electronically unbiased alkynes.



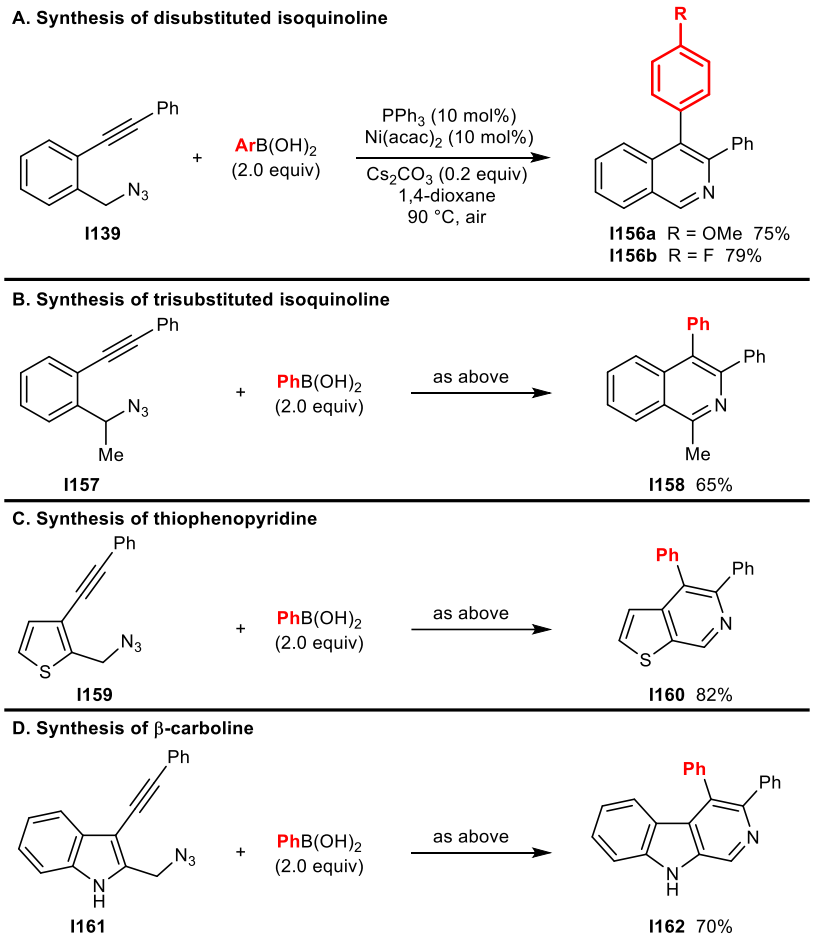
Scheme **34**: Regioselectivity studies of migratory insertion.

The authors suggest two possible reaction pathways. The first pathway is closely related to the mechanistic cycle seen in Scheme 4B. However, it is proposed that the regioselectivity of migratory insertion of the alkyne into the arylnickel species is controlled by the polarising effect of the tethered electrophile as opposed to steric and electronic effect of the alkyne substituents (Scheme 35). Migratory insertion provides alkenylnickel species **I154** which can undergo analogous steps to the ones seen in Scheme 4B. The second suggested mechanism involves an initial "*anti*-Wacker type" addition.[56,58,59,66]



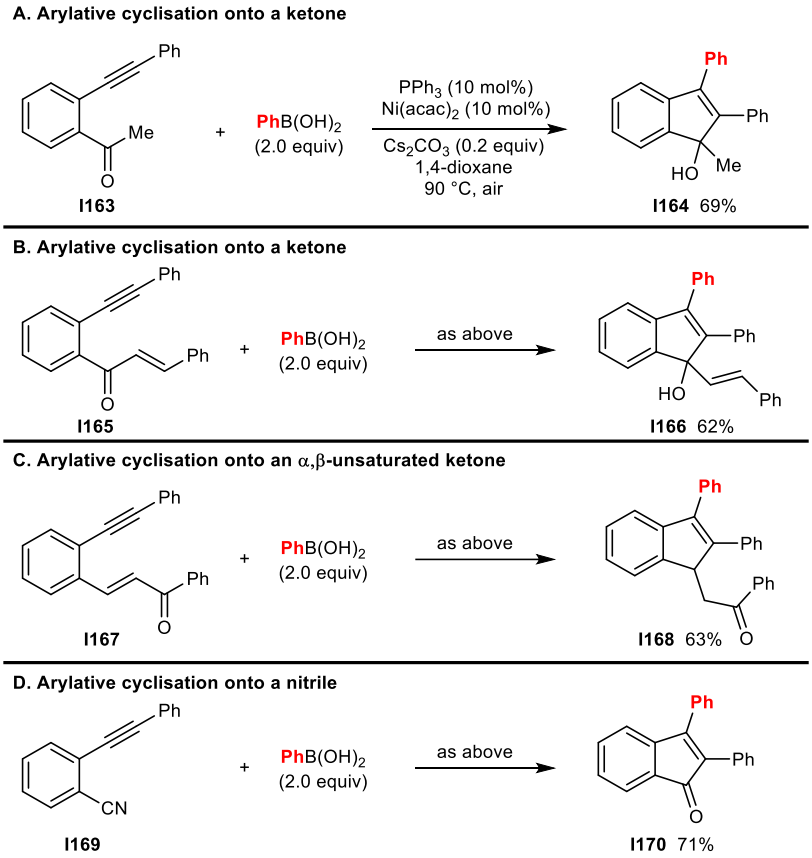
Scheme **35**: Proposed electrophile-driven migratory insertion.

The scope of the process is shown in Schemes 36 and 37. 4-Substituted phenylboronic acids bearing either a methoxy- (**I156a**) or fluoro-group (**I156b**) were compatible in the arylative cyclisation reaction of 2-substituted diaryl alkynes (Scheme 36A). A substrate containing an alkyl group alpha to the azide led to the trisubstituted isoquinoline **I158** in 65% yield (Scheme 36B). Thiophenopyridine **I160** (Scheme 36C) and β-carboline **I162** (Scheme 36D) were successfully prepared by subjecting thiophene- and indole-containing substrates to the reaction conditions, respectively.



Scheme **36**: Nickel-catalysed *anti*-carbometallative cyclisation onto an azide.

Next, diaryl alkyne substrates containing alternative electrophiles to the azide group were investigated (Scheme 37). Arylative cyclisation onto ketones (Scheme 37A) and conjugated enones (Scheme 37B and 37C) led to racemic indene products **I164**, **I166** and **I168**. The synthesis of indenone **I170** was achieved by subjecting 2-cyano-substituted diaryl alkyne **I169** to the reaction conditions (Scheme 37D).



Scheme **37**: Nickel-catalysed *anti*-carbometallative cyclisation onto ketones, conjugated ketones and nitrile.

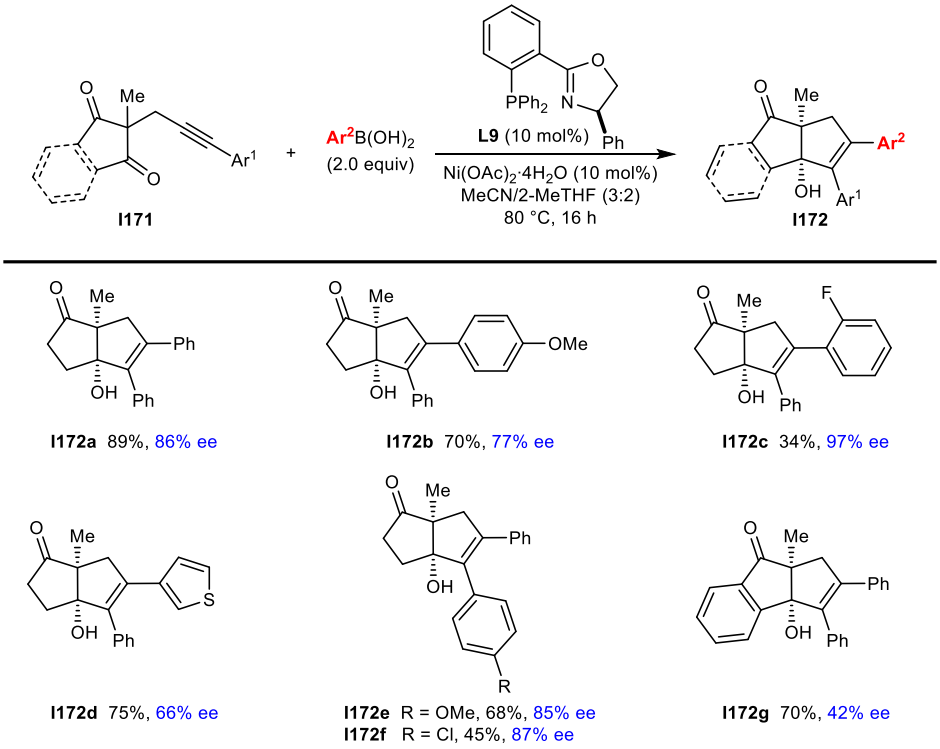
In summary, this section describes non-enantioselective nickel-catalysed *anti*-carbometallative cyclisation reaction with organoboron pronucleophiles. Variation of the tether and/or the electrophile gives access to a diverse range of carbo- and heterocyclic products such as 1-naphthylamines, quinolines, pyrroles, β-carbolines, thiophenopyridines, indenes and indenones.

1.5.2 Enantioselective Variants

Enantioenriched phosphine-oxazoline ligands have been employed in nickel-catalysed *anti*-carbometallative cyclisation reactions of alkyne-tethered electrophiles and this has led to enantioselective variants of this process. Electrophiles that have been explored include ketones, electron-deficient alkenes, malonate esters, malononitriles and allylic phosphates. The variety of substrates employed in these reactions has led to a diverse range of carbo- and heterocyclic products containing enantioenriched tertiary or quaternary centres.

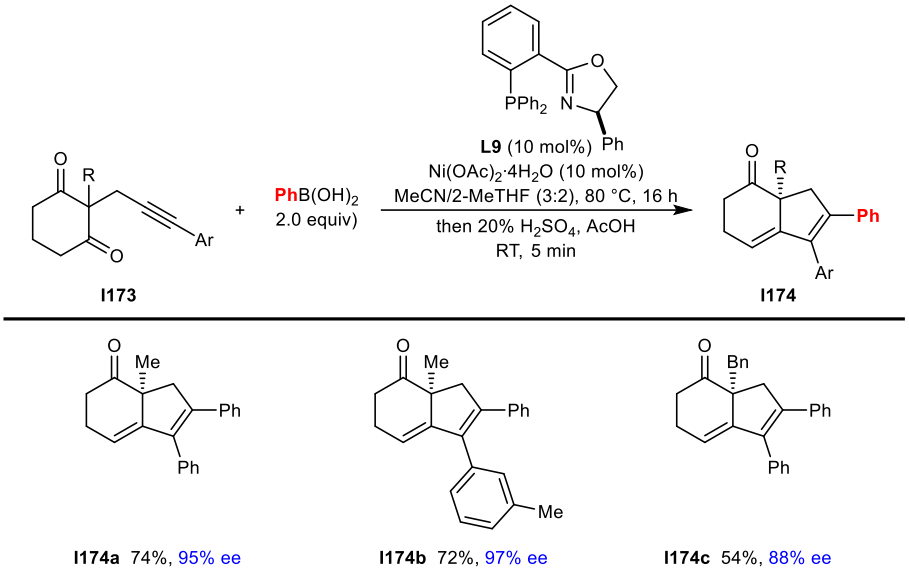
In 2016, the Lam group reported the first example of enantioselective arylative cyclisation of alkyne-tethered electrophiles involving reversible alkenylnickel *E*/*Z* isomerisation (Table 23).[72] Substrates containing an aryl alkyne tethered to a cyclic 1,3-diketone were reacted with (hetero)arylboronic acid (2.0 equiv), $Ni(OAc)_2 \cdot 4H_2O$ (10 mol%) and (*R*)-PhPHOX (**L9**, 10 mol%) in a 3:2 mixture of MeCN and 2-MeTHF at 80 °C to give fused bicyclic products **I172**. Phenylboronic acids with substituents at the 4-position (**I172b**) and 2-position (**I172c**) were tolerated in the reaction; however, the latter led to a lower yield but increased enantioselectivity. 3-Thienylboronic acid was also effective but a decrease in enantioselectivity was observed (**I172d**). The use of alkenylboronic acids in this transformation did not provide any of the desired product. Methoxy- or chloro-substituted aryl alkyne substrates were successful in the reaction (**I172e** and **I172f**). None of the desired products were obtained when using a terminal alkyne, methyl alkyne or trimethyl silyl-substituted alkyne; however, in the latter two cases some products were observed when using achiral ligand pyphos in place of (*R*)-PhPHOX (**L9**). Arylative cyclisation onto indan-1,3-dione **I171g** led to tricyclic product **I172g** in 70% yield and 42% ee. The proposed mechanism follows the general catalytic cycle shown in Scheme 4B with nickel being in oxidation state +2 throughout the catalytic cycle; however, an alternative mechanism involving a Nickel(I) species is not ruled out.

Table **23**: Enantioselective nickel-catalysed *anti*-carbometallative cyclisation onto five-membered cyclic 1,3-diketones.



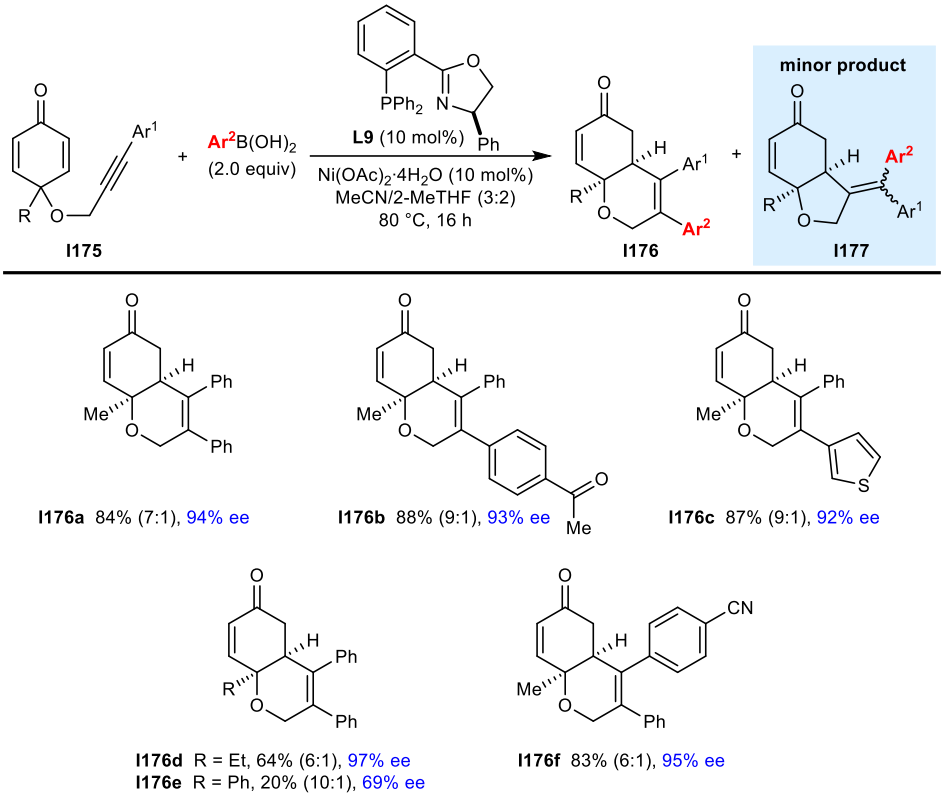
Next, the work was extended to alkyne-tethered six-membered cyclic 1,3-diketones (Table 24). Under the standard reaction conditions, mixtures of tertiary-alcohol-containing cyclisation product and dehydration products **I174** were obtained. Therefore, 20% H_2SO_4 in AcOH was added after cyclisation had occurred to drive the dehydration reaction to completion. It appeared that the enantioselectivity of the arylative cyclisation onto six-membered cyclic 1,3-diketones was improved in comparison with five-membered cyclic 1,3-diketone. Substrates containing both methyl groups (**I174a** and **I174b**) and a benzyl group (**I174c**) at the quaternary centre were successful in providing the corresponding products.

Table **24**: Enantioselective nickel-catalysed *anti*-carbometallative cyclisation onto six-membered cyclic 1,3-diketones.

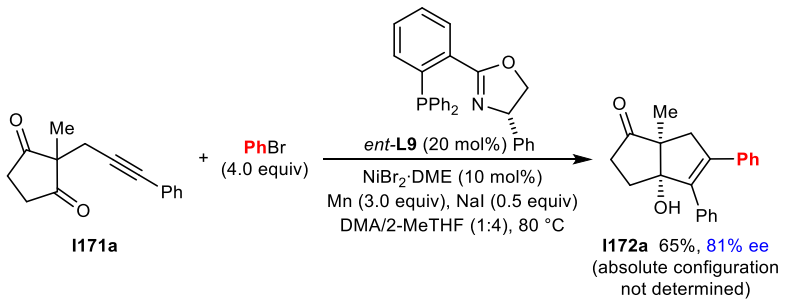


Arylative cyclisation of substrates containing alkyne-tethered cyclohexa-1,3-dienones to give fused bicyclic products **I176** was investigated (Table 25). In these reactions a minor product (**I177**) was observed which was the result of migratory insertion of the alkyne to the arylnickel species taking place with opposite regioselectivity. As well as phenylboronic acid (**I176a**¸ **I176d-f**), 4-acetylphenylboronic acid (**I176b**) and 3-thienylboronic acid (**I176c**) were well-tolerated. Variation of the substituent at the quaternary centre in **I175** was explored and both methyl groups (**I176a-c** and **I176f**) and an ethyl group (**I176d**) were compatible with the reaction; however, a phenyl group led to a decrease in yield and enantioselectivity (**I176e**, 20%, 69% ee). Substrate **I175f**, containing a 4-cyanophenyl group on the alkyne, was also successful in the reaction (**I176f**).

Table **25**: Enantioselective nickel-catalysed *anti*-carbometallative cyclisation onto cyclohexa-2,5-dienones.



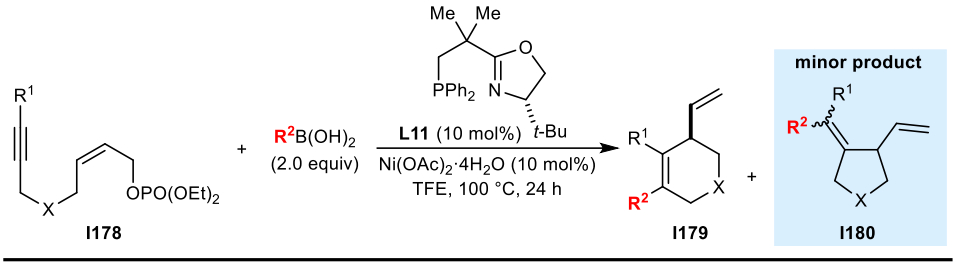
In 2020, Kong and co-workers reported a similar transformation to the nickel-catalysed arylative cyclisation reaction of alkyne-tethered cyclic diketones seen in Table 23; however, employing alternative reaction conditions (Scheme 38).[33] Aryl bromides were used instead of arylboronic acids in this reductive cyclisation process along with manganese as a stoichiometric reductant. One enantioselective example was reported, employing (*S*)-PhPHOX (*ent*-**L9**), to give **I172a** in 65% yield and 81% ee.



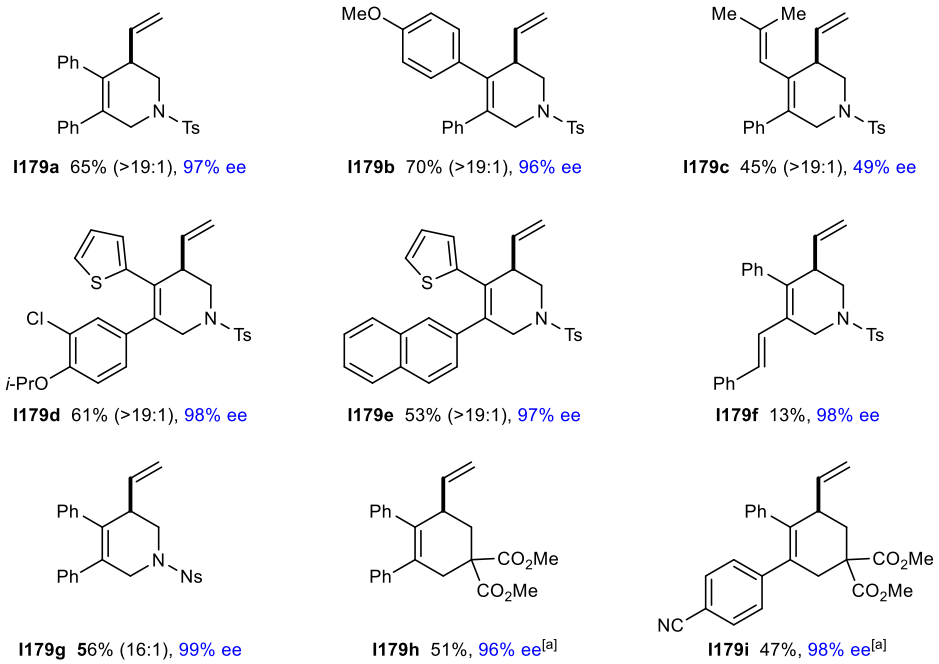
Scheme **38**: Nickel-catalysed reductive *anti*-carbometallative cyclisation.

In 2017, the Lam group reported enantioselective nickel-catalysed arylative allylic alkenylations where the intermediate alkenylnickel species cyclises onto a tethered (*Z*)-allylic phosphate generating enantioenriched 1,4-diene-containing carbo- and heterocyclic products (Table 26).[74] Substrates **I178** were reacted with boronic acid (2.0 equiv), $Ni(OAc)_2 \cdot 4H_2O$ (10 mol%) and (*S*)-*t*-Bu-NeoPHOX (**L11**, 10 mol%) in TFE at 100 °C to give products **I179** and excellent enantioselectivities were observed. Minor products **I180**, that were a result of opposite regioselectivity of migratory insertion of alkynes with arylnickel species, were observed in most reactions. Substrates containing aryl- (**I179a**, **I179b** and **I179f-i**), heteroaryl- (**I179d and I179e**) and alkenyl-substituted alkynes (**I179c**) were successful in the reaction; however, the alkenyl-substituted alkyne led to a decrease in yield and enantioselectivity (45%, 49% ee). The use of a substrate containing a methyl substituent on the alkyne led to a complex mixture of products, as it is often observed in nickel-catalysed *anti*-carbometallative cyclisation reactions of alkyl-substituted alkyne-tethered electrophiles.[72,74,75,77,79] A disubstituted phenylboronic acid worked in the reaction (**I179d**), as well as 2-naphthylboronic acid (**I179e**). Interestingly, an alkenylboronic acid was tolerated in the reaction; however, a lower yield was observed (**I179f**, 13%), which is likely due to competing protodeboronation of the alkenylboronic acid. Alkylative cyclisation using methylboronic acid was attempted but no reactivity was observed. Next, an investigation of the tether was carried out and it was found that the presence of a 4-nitrophenylsulfonamide in the tether was compatible with the reaction (**I179g**). Having an all-carbon tether led to the successful formation of carbocyclic products (**I179h** and **I179i**).

Table **26**: Enantioselective nickel-catalysed *anti*-carbometallative cyclisation onto (*Z*)-allylic phosphates.



I178 **I179** **I180**



I179a 65% (>19:1), 97% ee

I179b 70% (>19:1), 96% ee

I179c 45% (>19:1), 49% ee

I179d 61% (>19:1), 98% ee

I179e 53% (>19:1), 97% ee

I179f 13%, 98% ee

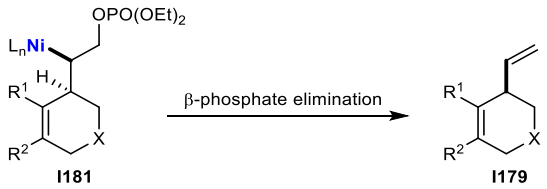
I179g 56% (16:1), 99% ee

I179h 51%, 96% ee[a]

I179i 47%, 98% ee[a]

[a] The product contained trace quantities of inseparable, unidentified impurities, and the ratio of **I179**:**I180** could not be determined.

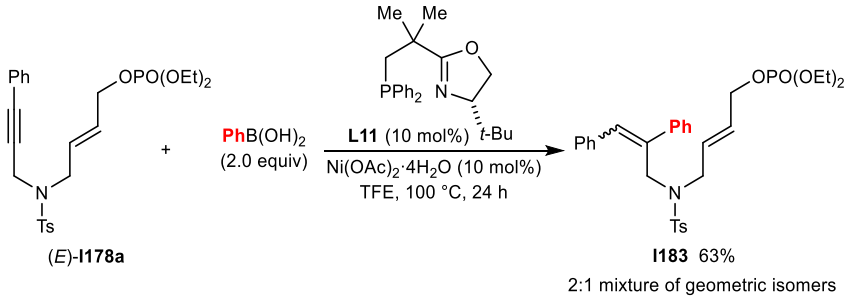
The proposed mechanism follows the general catalytic cycle shown in Scheme 4B with nickel in the +2 oxidation state; however, an additional β-phosphate elimination step of the cyclised intermediate **I181** is required to liberate the desired product **I179** and regenerate the active nickel(II) species (Scheme 39).



I181 **I179**

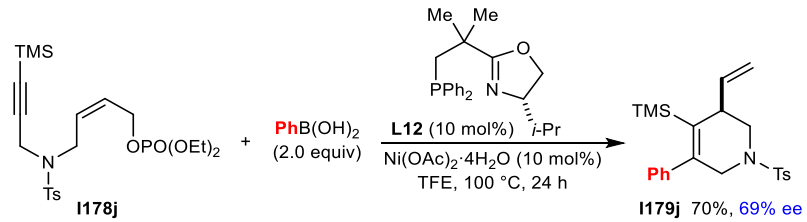
Scheme **39**: β-Phosphate elimination of intermediate **I181**.

Substrate (*E*)-**I178a**, containing an (*E*)-allylic phosphate, was subjected to the reaction conditions; however, only hydroarylation product **I183** was observed in a 2:1 mixture of geometric isomers (Scheme 40). This result suggests that the (*Z*)-stereochemistry of the allylic phosphate is crucial for cyclisation to occur, perhaps because steric and/or electronic requirements are better accommodated by the (*Z*)-allylic phosphate. Albeit, in other reports successful cyclisation onto Michael acceptors containing an (*E*)-alkene have been described (see Scheme 37 and Table 16, 19 and 31).[68,71,79,81]



Scheme **40**: Enantioselective nickel-catalysed *anti*-carbometallative cyclisation onto (*E*)-allylic phosphate.

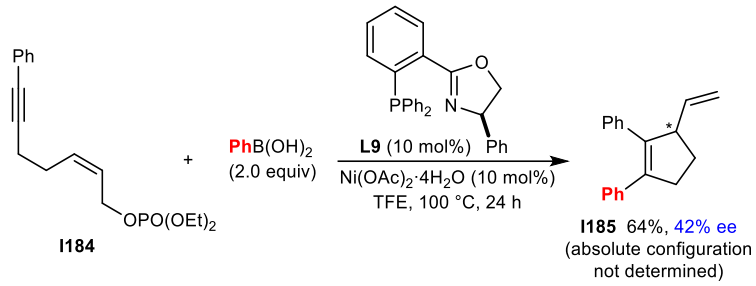
Substrate **I178j**, containing a trimethylsilyl-substituted alkyne, was successful in the reaction when using (*S*)-*i*-Pr-NeoPHOX (**L12**) instead of (*S*)-*t*-Bu-NeoPHOX (**L11**) and gave the desired product **I179j** in 70% yield and 69% ee (Scheme 41). This result was welcome since previous reports had observed less success when using trimethylsilyl-substituted alkyne substrates.[72]



Scheme **41**: Enantioselective nickel-catalysed *anti*-carbometallative cyclisation onto (*Z*)-allylic phosphate.

1,5-Enyne **I184** was subjected to the reaction conditions, using (*R*)-PhPHOX (**L9**) in place of (*S*)-*t*-Bu-NeoPHOX (**L11**), to obtain the five-membered cyclic product

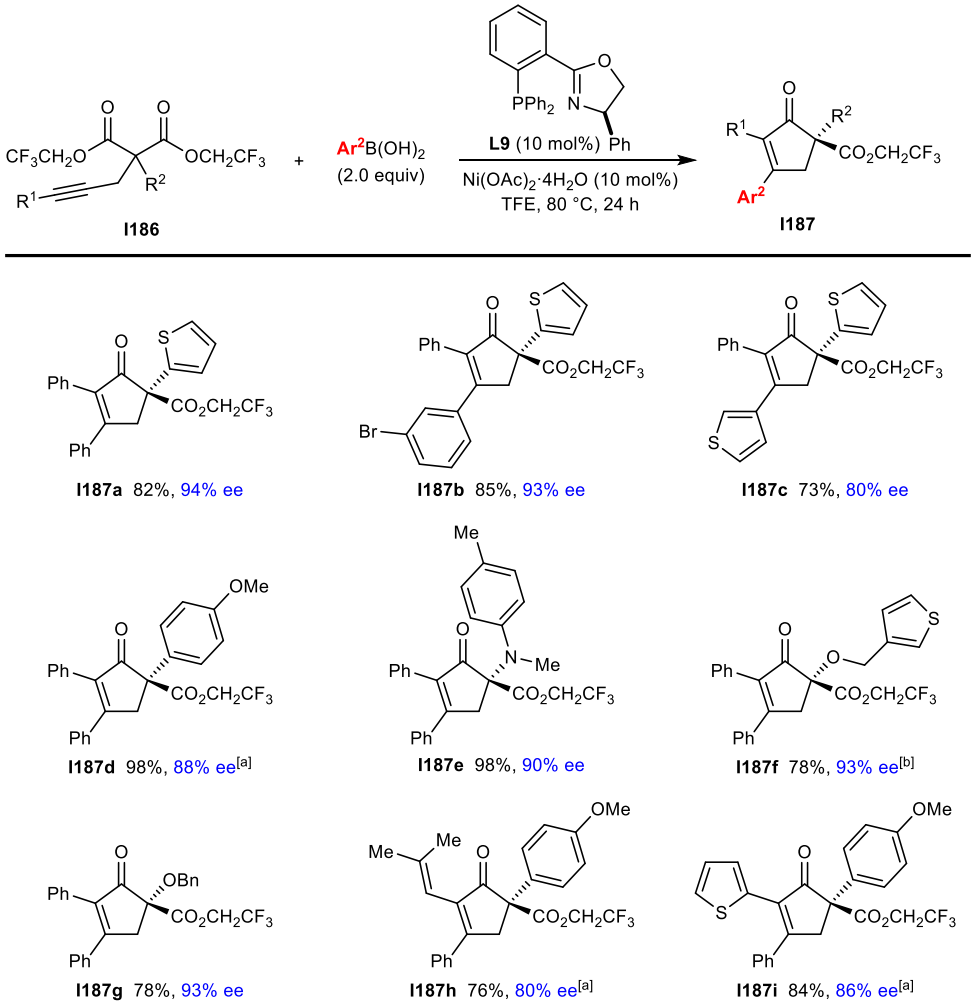
I185 (Scheme 42). The formation of product **I185** was achieved in 64% yield; however, only 42% ee.



Scheme **42**: Enantioselective nickel-catalysed *anti*-carbometallative cyclisation onto (*Z*)-allylic phosphate.

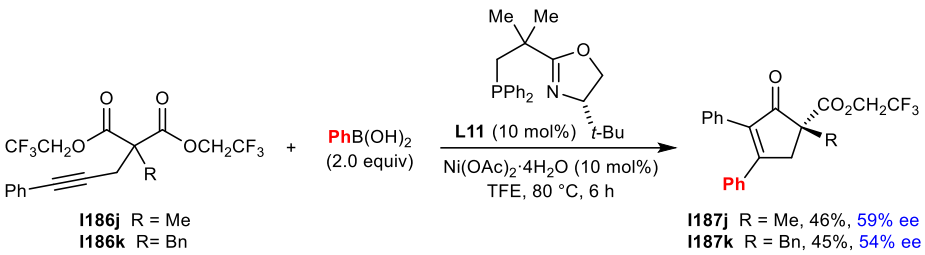
In 2018, the Lam group reported the synthesis of chiral cyclopent-2-enones by the enantioselective nickel-catalysed arylative desymmetrisation of alkyne-tethered malonate esters (Table 27). [76] Substrates **I186** were reacted with (hetero)arylboronic acid (2.0 equiv), $Ni(OAc)_2 \cdot 4H_2O$ (10 mol%) and (*R*)-PhPHOX (**L9**, 10 mol%) in TFE at 80 °C to obtain the desired products **I187** in generally good yield and enantioselectivities. Having a 2-thienyl substituent at the quaternary centre was tolerated in the reaction (**I187a-c**). Other substituents at this position were also successful such as 4-methoxy phenyl (**I187d**, **I187h** and **I187i**), anilino (**I187e**), 3-thienylmethoxy (**I187f**) and benzyloxy (**I187g**). As well as phenylboronic acid (**I187a** and **I187d-i**), substituted phenylboronic acids (**I187b**) and 3-thienylboronic acid (**I187c**) were also successful in the reaction. Variation of the alkyne substituent found phenyl (**I187a-g**), alkenyl (**I187h**) and 2-thienyl groups (**I187i**) to be compatible with the reaction.

Table **27**: Enantioselective nickel-catalysed *anti*-carbometallative cyclisation onto malonate esters.



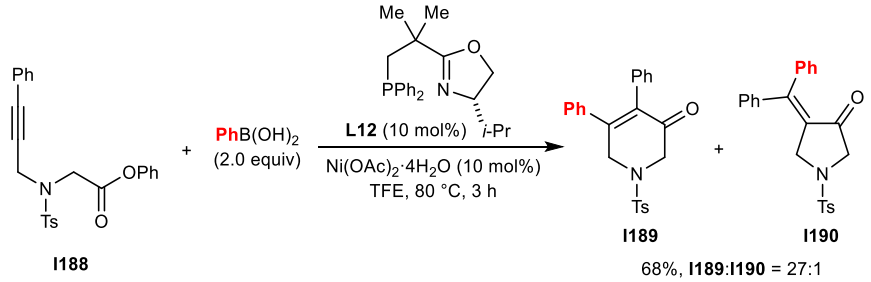
[a] Reaction carried out at 100°C. [b] Reaction carried out using $Ni(OAc)_2 \cdot 4H_2O$ (20 mol%) and **L9** (20 mol%).

The reaction of substrate **I186j** or **I186k** containing either a methyl or benzyl substituent, respectively, at the quaternary centre led to moderate yields and poor enantioselectivities when using (*R*)-PhPHOX (**L9**) as the ligand; however, changing the ligand to (*S*)-*t*-Bu-NeoPHOX (**L11**) led to improved but still modest enantioselectivities (Scheme 43).



Scheme **43**: Enantioselective nickel-catalysed *anti*-carbometallative cyclisation onto malonate esters.

The arylative cyclisation reaction of substrate **I188**, containing an alkyne tethered to a phenyl ester was also described using (*S*)-*i*-Pr-NeoPHOX (**L12**) as a ligand, and this led to a 27:1 inseparable mixture of the desired product **I189** and minor product **I190** in 68% yield (Scheme 44).



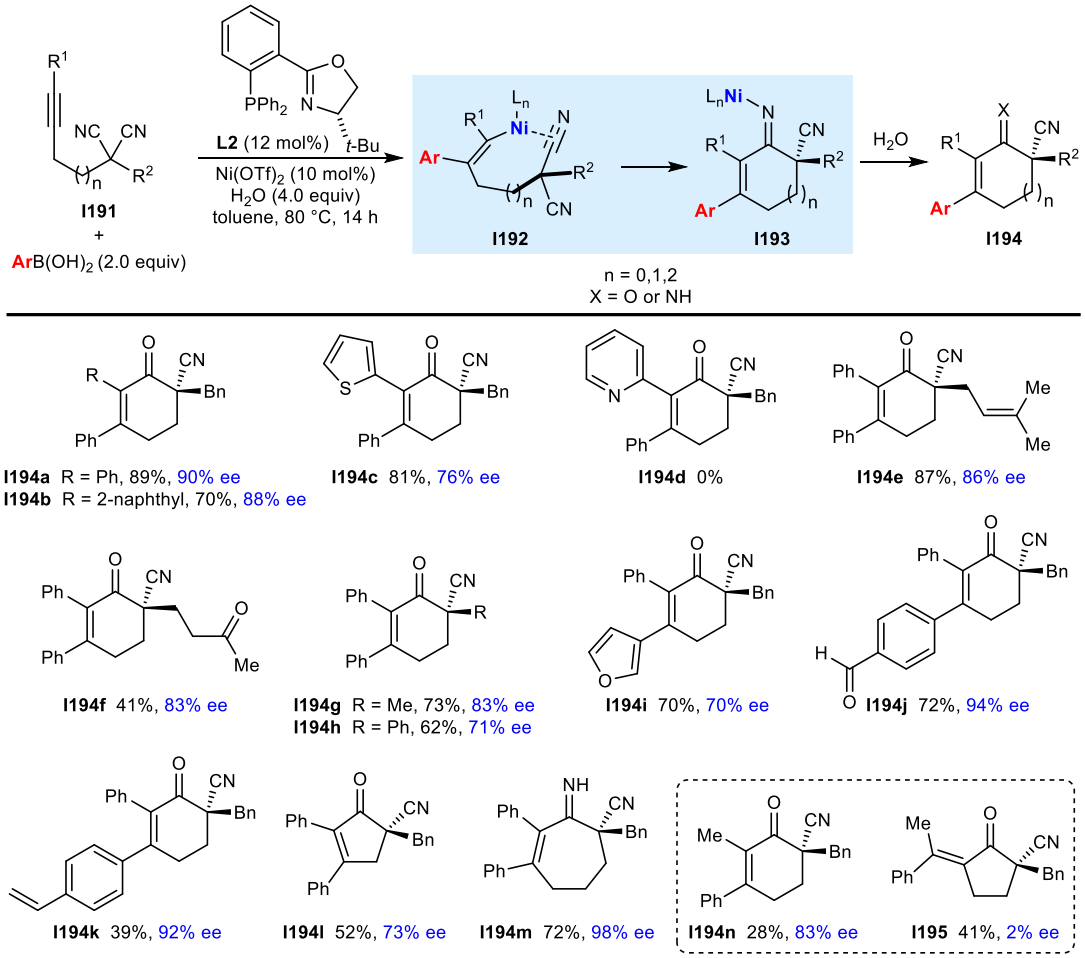
Scheme **44**: Enantioselective nickel-catalysed *anti*-carbometallative cyclisation onto a phenyl ester.

In 2020, Liu and co-workers reported the enantioselective nickel-catalysed *anti*-carbometallative desymmetrisation of malononitriles to give cycloenones with a nitrile-containing all-carbon quaternary centre (Table 28).[78] Malononitriles **I191** were subjected to (hetero)arylboronic acid (2.0 equiv), $Ni(OTf)_2$ (10 mol%), (*S*)-*t*-BuPHOX (**L2**, 12 mol%) and H_2O (4.0 equiv) in toluene at 80 °C to give the corresponding products **I194**. Substrates containing a phenyl (**I194a** and **I194e-m**) or naphthyl group (**I194b**) on the alkyne were tolerated, as was substrate **I191c** containing a 2-thienyl group on the alkyne; however, having a 2-pyridyl substituent on the alkyne was not compatible with the reaction (**I194d**). Methyl-substituted alkyne **I191n** led to the desired product **I194n** in 28% yield along with product **I195** in 41% yield, which was formed as a result of opposite regioselectivity of migratory insertion of the alkyne into the phenylnickel species. Changing the substituent at the α-position of the malononitrile from a benzyl group (**I194a-c** and **I194i-m**) to an allylic group (**I194e**), a 3-oxobutyl

(**I194f**), a methyl (**I194g**) or a phenyl (**I194h**) was tolerated. Various boronic acids were compatible with the reaction, such as phenylboronic acid (**I194a-h** and **I194l-n**), 3-furylboronic acid (**I194i**), 4-formylphenylboronic acids (**I194j**) and 4-vinylphenylboronic acids (**I194k**). Boronic acids that were investigated that did not provide the desired desymmetrisation product were 4-carboxyphenylboronic acid, 4-aminocarbonylphenylboronic acid, 3-pyridylboronic acid, 5-indolylboronic acid, 2-methoxycarbonylphenylboronic acid and (*E*)-styreneboronic acid. Cyclopentenone **I194l** and 7-membered imine **I194m** were obtained by shortening or extending the carbon-tether of the substrate, respectively. The 7-membered imine **I194m** could be readily hydrolysed to the corresponding ketone by treatment with 3 M HCl at 0 °C.

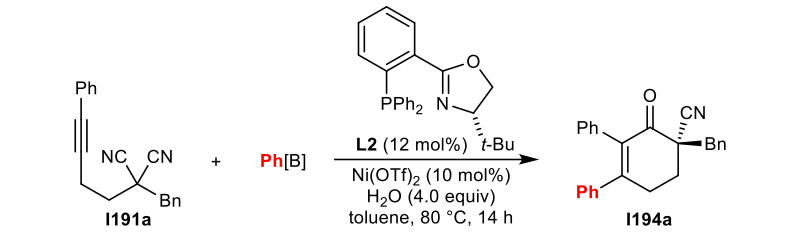
The proposed mechanism follows the general catalytic cycle shown in Scheme 4B. The isomerised alkenyl-nickel species **I192** cyclises onto one of the two tethered nitrile groups to give intermediate **I193** (Table 28). Protonation of **I193** initially gives the imine which, with the exception of seven-membered imine **I194m**, is hydrolysed to the ketone *in situ*. Competition experiments revealed that electron-rich arylboronic acids react slightly faster than electron-poor arylboronic acids. Also, electron-rich aryl alkynes react significantly faster than electron-poor aryl alkynes. ^{13}C Kinetic isotopic effect (KIE) experiments of a substrate at natural abundance revealed a significant ^{13}C KIE for the nitrile carbon, suggesting that the addition to the nitrile is likely the rate-determining step (RDS); however, the transmetalation step cannot be ruled out as the RDS. Finally, ^{31}P NMR spectroscopy studies suggested that water aids the transmetalation step. This is in accordance with other reports.[140–142]

Table **28**: Enantioselective nickel-catalysed *anti*-carbometallative cyclisation onto malononitriles.



Various phenylboron sources were investigated in the reaction of alkyne-tethered malononitrile **I191a**, and it was found that triphenylboroxin and potassium phenyltrifluoroborate performed comparably to phenylboronic acid regarding the yield and enantioselectivity (Table 29). Phenylboronic acid pinacol ester was unsuccessful in providing the desired product, perhaps due to slow transmetalation under base-free conditions.

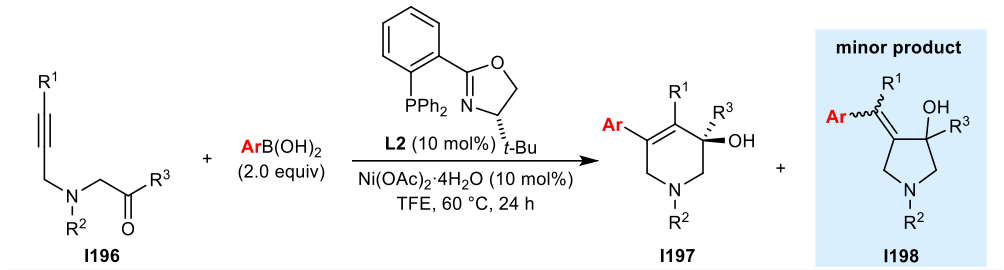
Table **29**: Investigation of phenylboron reagents.

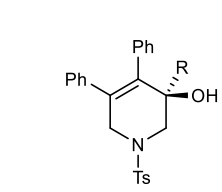


PhB(OH)$_2$ (2.0 equiv)	(PhBO)$_3$ (0.7 equiv)	PhBF$_3$K (2.0 equiv)	PhB(pin) (2.0 equiv)
89%, 90% ee	91%, 90% ee	87%, 89% ee	N.R. (at 100 °C)

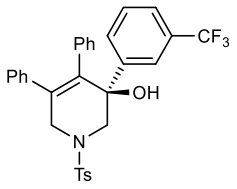
In 2021, the Lam group reported the enantioselective nickel-catalysed arylative cyclisation of alkyne-tethered ketones **I196** with (hetero)arylboronic acid (2.0 equiv), Ni(OAc)$_2$·4H$_2$O (10 mol%) and (*S*)-*t*-BuPHOX (**L2**, 10 mol%) in TFE at 60 °C to give products **I197** (Table 30).[80] Minor products **I198** were observed in most reactions, which were the result of the arylnickel species adding across the alkyne with opposite regioselectivity. Substrates containing methyl (**I197a**¸ **I197e** and **I197h-j**), ethyl (**I197f**), *i*-propyl (**I197b**), 3-(trifluoromethyl)phenyl (**I197c**) and 3-methoxy-3-oxopropyl ketones (**I197d**) were compatible with the reaction. As well as a phenyl substituent on the alkyne (**I197a-d** and **I197h-j**), also 4-carbomethoxyphenyl (**I197e**) and vinyl (**I197f**) substituents were tolerated in the reaction; however, the enantioselectivity decreased in the latter case. Interestingly, substrate **I196g** containing a chloroalkyne successfully provided the corresponding product **I197g** in 12% yield and 71% ee. A substrate containing a 4-nitrophenylsulfonyl group on the amine was used in the investigation of the boronic acid scope. 4-(Trimethylsilyl)phenylboronic acid (**I197h**), 3-hydroxyphenylboronic acid (**I197i**) and 3-thienylboronic acid (**I197j**) were all effective and good yields and enantioselectivities were observed.

Table **30**: Enantioselective nickel-catalysed *anti*-carbometallative cyclisation onto ketones.

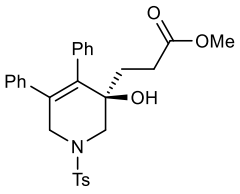




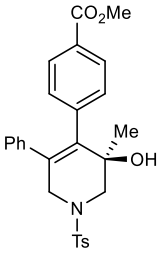
I197a R = Me, 70% (16:1), 99% ee
I197b R = *i*-Pr, 80% (12:1), 97% ee[a]



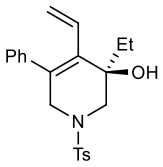
I197c 76% (16:1), 98% ee[a]



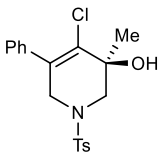
I197d 56% (13:1), 99% ee



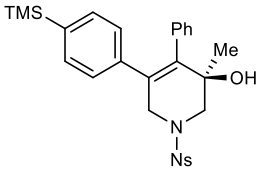
I197e 44% (8:1), 98% ee[a]



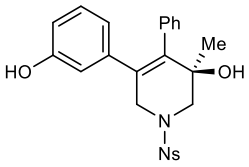
I197f 90% (12:1), 45% ee[b]



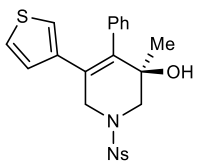
I197g 12%, 71% ee



I197h 78% (>19:1), 99% ee



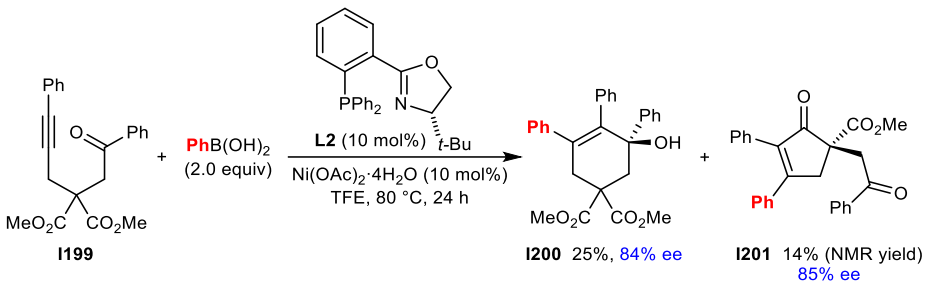
I197i 67% (16:1), >99% ee



I197j 64% (>19:1), 98% ee

[a] Reaction carried out at 80 °C. [b] Product **I197f** was obtained as an inseparable 12:1 mixture together with the minor product **I198f** in 90% combined yield.

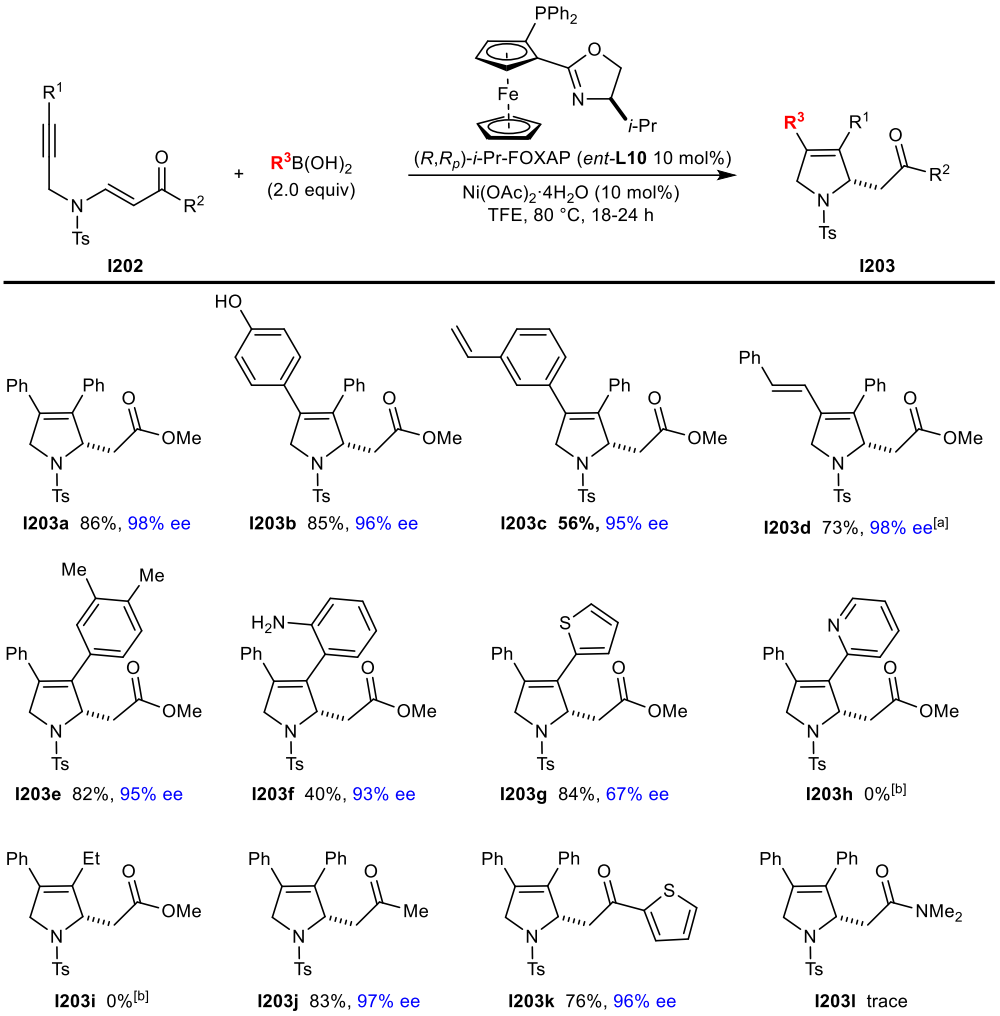
To prepare carbocyclic product **I200**, the reaction of alkyne-tethered ketone **I199** was carried out and the desired product **I200** was obtained in 25% yield with 84% ee (Scheme 45). A second product **I201** was obtained in 14% yield and 85% ee which was a result of the intermediate alkenylnickel species undergoing desymmetrising cyclisation onto one of the ester groups. Attempts at shortening and extending the tether to obtain five- or seven-membered products were unsuccessful.



Scheme **45**: Enantioselective nickel-catalysed *anti*-carbometallative cyclisation onto a ketone.

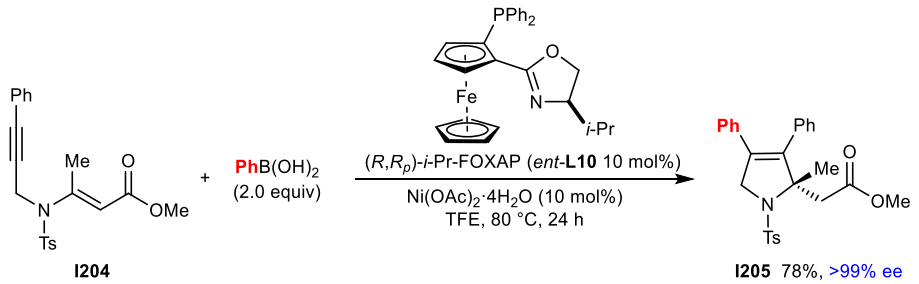
In 2022, after the publication of the work presented in this thesis, Iqbal, Cho and co-workers reported the enantioselective nickel-catalysed arylative cyclisation reaction of alkyne-tethered aminoacrylates **I202** to give 2,3,4-trisubstituted 3-pyrrolines **I203** (Table 31).[81] As well as phenylboronic acid (**I203a** and **I203e-k**), 4-hydroxyphenylboronic acid (**I203b**) and 3-vinylphenylboronic acid (**I203c**) were also tolerated and pleasingly, (*E*)-styrylboronic acid was successful in the reaction, providing the corresponding product **I203d** in 73% yield and 98% ee. Next, variation of the alkyne substituent was investigated. Phenyl groups (**I203a-d**, **I203j** and **I203k**) and disubstituted phenyl groups (**I203e**) were compatible in the reaction. Having a 2-amino-substituted phenyl alkyne led to the corresponding product **I203f** in a lower yield but the enantioselectivity remained good (40% yield and 95% ee) where having a 2-thienyl-substituted alkyne led to the desired product **I203g** in a good yield but decreased enantioselectivity (84% yield and 67% ee). 2-Pyridyl-substituted alkyne **I202h** and ethyl alkyne **I202i** did not participate in the arylative cyclisation reaction and only hydroarylation products were observed. As well as alkyne-tethered α,β-unsaturated methyl esters (**I202a-i**), an α,β-unsaturated methylketone (**I202j**) and an α,β-unsaturated 2-thienylketone (**I202k**) were also tolerated; however, α,β-unsaturated dimethylamide **I202l** was not. Extending of the tether by one carbon between the alkyne and the aminoacrylate was attempted; however, only hydroarylation of the alkyne was observed.

Table **31**: Enantioselective nickel-catalysed *anti*-carbometallative cyclisation onto aminoacrylates.



[a] Reaction carried out using $Ni(OAc)_2 \cdot 4H_2O$ (15 mol%) and (R,R_p)-i-Pr-FOXAP (**Lx**, 15 mol%) and 48 h reaction time. [b] Hydroarylation products were observed.

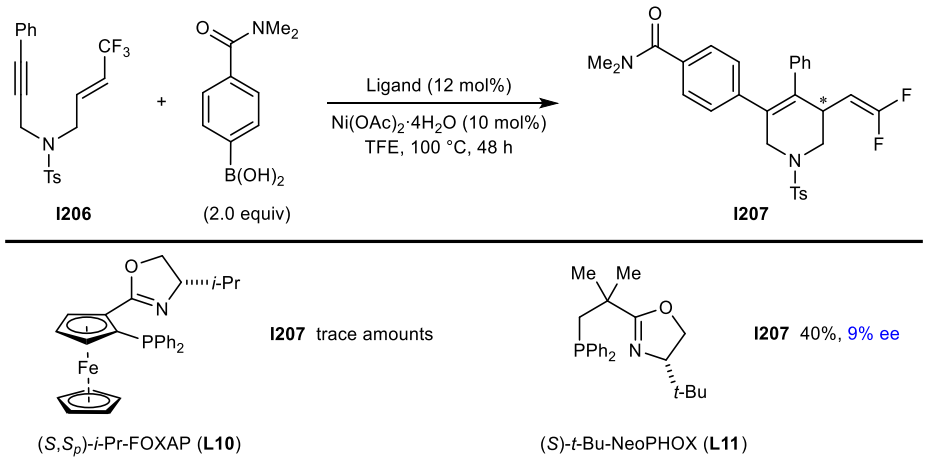
Substrate **I204** containing a sterically hindered aminoacrylate was subjected to the standard reaction conditions and successfully provided the desired product **I205** in 78% yield and >99% ee (Scheme 46).



Scheme **46**: Enantioselective nickel-catalysed *anti*-carbometallative cyclisation onto a sterically hindered aminoacrylate.

In 2022, Kong and co-workers reported the enantioselective nickel-catalysed carbometallative cyclisation of alkyne-tethered trifluoromethyl alkenes followed by β-fluoride elimination (see Table 19).[71] In an attempt to achieve *anti*-carbometallative cyclisation, substrate **I206** containing a phenyl-substituted alkyne was prepared (Table 32). Under their standard conditions, using (S,S_p)-*i*-Pr-FOXAP (**L10**), the reaction of **I206** led to trace amounts of the desired product **I207**; however, using (*S*)-*t*-Bu-NeoPHOX (**L11**) instead led to product **I207** in 40% yield and 9% ee.

Table **32**: Enantioselective nickel-catalysed *anti*-carbometallative cyclisation onto trifluoromethyl alkenes.



In summary, this section describes enantioselective nickel-catalysed *anti*-carbometallative cyclisation reaction with organoboron pronucleophiles to give a range of enantioenriched carbo- and heterocyclic products.

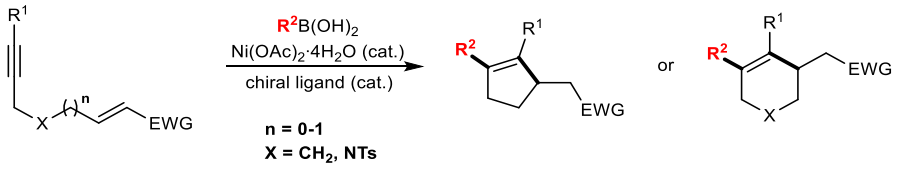
In conclusion, transition-metal-catalysed domino reactions of alkyne-tethered electrophiles involving carbometalation of the alkyne followed by cyclisation of the resulting alkenylmetal species onto the tethered electrophile enables the formation of complex cyclic structures in an efficient manner. By modification of the substrate or transition-metal catalyst a range of carbo- and heterocyclic products can be obtained. *Syn*-carbometallative cyclisation reactions leading to carbo- and heterocyclic products containing an exocyclic alkene are well established using rhodium and palladium catalysts. More recently, copper and nickel have also emerged as useful catalysts in *syn*-carbometallative cyclisation reactions. Nickel has also been identified as a catalyst for *anti*-carbometallative cyclisation reactions where the intermediate alkenylnickel intermediate undergoes *E*/*Z* isomerisation before cyclising onto the tethered

electrophile. This class of reactions lead to carbo- and heterocyclic products containing an endocyclic alkene. The regioselectivity of migratory insertion of the alkyne to the arylmetal species is the key step influencing the outcome of the reaction to obtain either exocyclic products or endocyclic products.

2.0 Results and Discussion

2.1 Aims and Objectives

The Lam group and others have previously reported examples of asymmetric nickel-catalysed *anti*-carbometallative cyclisation reactions of alkyne-tethered electrophiles affording enantioenriched carbo- and heterocycles; however, this area of research offers further potential for expanding scope. Reported reactions include arylative desymmetrising cyclisation onto cyclic 1,3-diketones or cyclohexa-2,5-dienones to give highly diastereo- and enantioselective fused bicyclic products. The synthesis of less complex, non-fused molecules could be achieved using acyclic electrophiles in non-desymmetrising cyclisations. In this regard, non-desymmetrising cyclisations are achievable using (*Z*)-allylic phosphates as the electrophile in allylic substitutions; however, the use of acyclic, conjugated, electron-deficient alkenes would complement the applicability of the *anti*-carbometallative cyclisation of alkyne-tethered electrophiles greatly (Scheme 47). Organonickel species are known to undergo addition to electron-deficient alkenes.[143–145] Therefore it was postulated that alkyne-tethered electron-deficient alkenes could be used as substrates in nickel-catalysed *anti*-carbometallative cyclisation reactions.



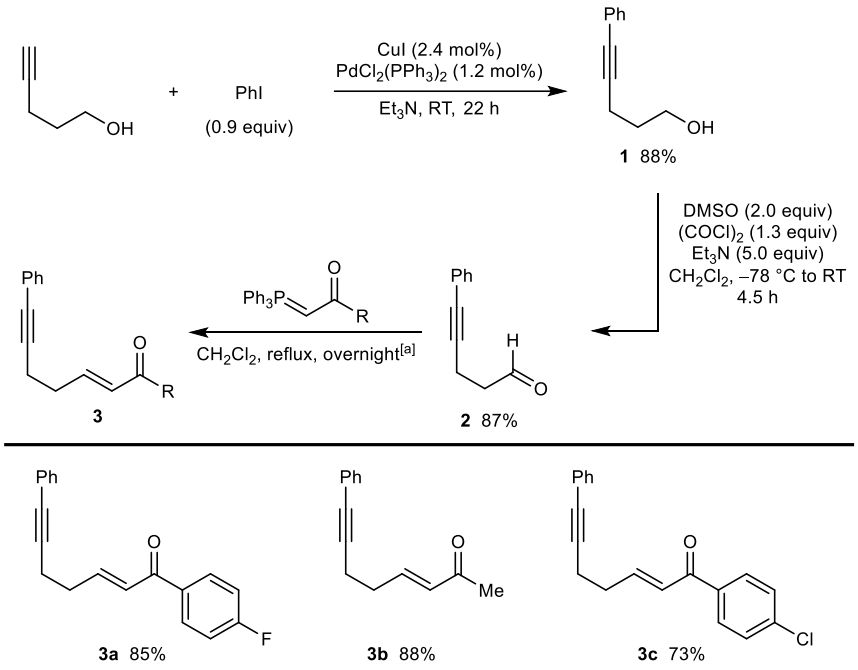
Scheme **47**: Nickel-catalysed *anti*-carbometallative cyclisation of alkyne-tethered electron-deficient alkenes.

2.2 Carbometallative Cyclisation Providing Five-Membered Carbocyclic Products

2.2.1 Optimisation

Before proceeding with reaction investigation, the synthesis of substrates **3a-3c** was carried out (Table 33). A Sonogashira cross-coupling of 4-pentyn-1-ol with phenyl iodide afforded phenyl alkyne **1**, which was transformed into aldehyde **2** *via* a Swern oxidation. Next, aldehyde **2** was exposed to various triphenylphosphoranylidenes in Wittig olefinations to give (*E*)-selective enones **3**. The stereochemistry of the major stereoisomer obtained from the reaction was determined by the coupling constant between the two alkenyl hydrogen atoms.

Table **33**: Synthesis of substrates **3a-3c**.



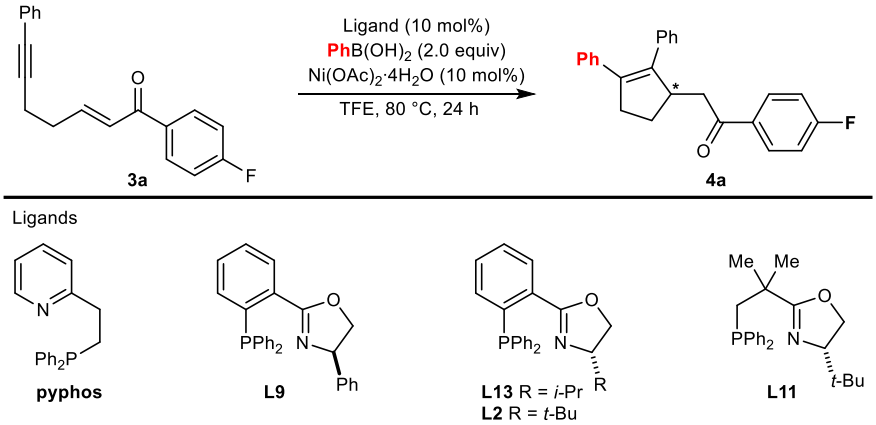
[a] See Section 3.5 for detailed reaction conditions.

An investigation of nickel-catalysed *anti*-carbometallative cyclisation of alkyne-tethered electron-deficient alkenes was carried out (Table 34). Reaction conditions similar to ones previously reported by the Lam group were considered,[72,74] with the initial reaction utilising pyphos, an achiral P,N-ligand. 1,5-Enyne **3a** was reacted with phenylboronic acid (2.0 equiv), $Ni(OAc)_2 \cdot 4H_2O$ (10 mol%), pyphos (10

mol%) in TFE at 80 °C for 24 hours (entry 1). Pleasingly, the desired product **4a** was obtained in 44% yield.

The use of enantioenriched phosphine-oxazoline ligands in nickel-catalysed *anti*-carbometallative cyclisation reactions of alkyne-tethered electrophiles has been reported to be highly enantioselective.[72,74,76,78,80,81] Therefore, phosphine-oxazoline ligands were the starting point for the exploration of an enantioselective reaction (Table 34, entries 2-5). The use of (*R*)-PhPHOX (**L9**) led to the desired product **4a** in 67% yield and 84% ee and the use of (*S*)-*i*-PrPHOX (**L13**) resulted in 22% yield and 70% ee (entries 2 and 3). Pleasingly, it was found that (*S*)-*t*-Bu-NeoPHOX (**L11**) performed excellently in the reaction providing cyclopentene **4a** in 86% yield and >99% ee (entry 5). Also, (*S*)-*t*-BuPHOX (**L2**) performed well in the reaction giving **4a** in 66% yield and 96% ee (entry 4). (*S*)-*t*-BuPHOX (**L2**) and (*S*)-*t*-Bu-NeoPHOX (**L11**) were carried forward for further optimisation.

Table **34**: Ligand screen using enyne **3a**.

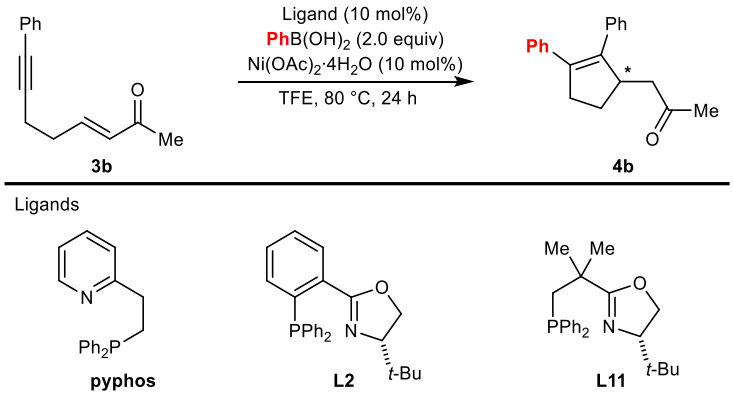


Entry[a]	Ligand	Recovery of 3a [%]	Yield of 4a [%]	ee of 4a
1[b]	pyphos	-	44	-
2[b]	L9	-	67	–84
3	L13	35	22	70
4	L2	-	66	96
5[b]	L11	-	86	>99

[a] Reactions were carried out using 0.05 mmol of **3a** in TFE (0.5 mL). Yields were determined by ^{1}H NMR spectroscopic analysis using 1,3,5-trimethoxybenzene as an internal standard. [b] 20 h reaction time.

The two most successful phosphine-oxazoline ligands, (*S*)-*t*-BuPHOX (**L2**) and (*S*)-*t*-Bu-NeoPHOX (**L11**), were used in the arylative cyclisation reaction of 1,5-enyne **3b**, containing an α,β-unsaturated methyl ketone as the electrophile (Table 35). Similarly to the reaction of **3a** seen in Table 34, the *anti*-carbometallative cyclisation reaction of enyne **3b** was found to perform better when using (*S*)-*t*-Bu-NeoPHOX, (**L11**), leading to cyclopentene **4b** in 99% yield and 99% ee (entry 3), in comparison to the 71% yield and 91% ee observed when using (*S*)-*t*-BuPHOX, (**L2**, entry 2).

Table **35**: Ligand screen using enyne **3b**.

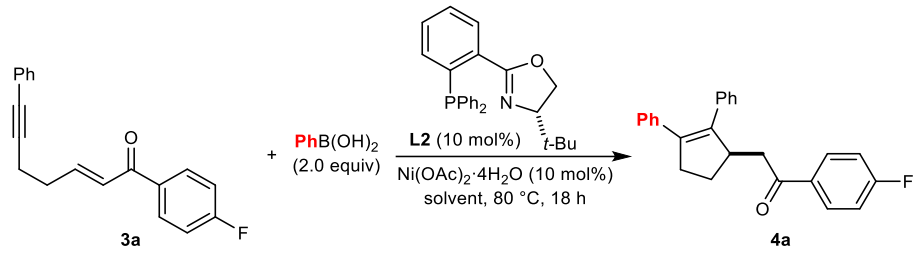


Entry[a]	Ligand	Yield of 4b [%]	ee of 4b
1	pyphos	51	-
2	L2	71	91
3[b]	L11	99	99

[a] Reactions were carried out using 0.05 mmol of **3b** in TFE (0.5 mL). Yields were determined by ^{1}H NMR spectroscopic analysis using 1,3,5-trimethoxybenzene as an internal standard. [b] 20 h reaction.

Screening of solvents was carried out using substrate **3a** with either ligand **L2** or ligand **L11** (Table 36 and Table 37, respectively). Assignment of the absolute configuration of products **4** is discussed in Section 2.2.9. MeCN performed similarly to TFE in the reaction of **3a** with phenylboronic acid (2.0 equiv) in the presence of $Ni(OAc)_2{\cdot}4H_2O$ (10 mol%) and (*S*)-*t*-BuPHOX (**L2**, 10 mol%) providing the desired product **4a** in 70% yield and 94% ee (Table 36, entry 3). The use of THF led to a large decrease in yield; however, the enantioselectivity remained excellent and using DMC as the solvent led only to recovery of starting material (entries 2 and 4).

Table **36**: Solvent screen using enyne **3a** and ligand **L2**.

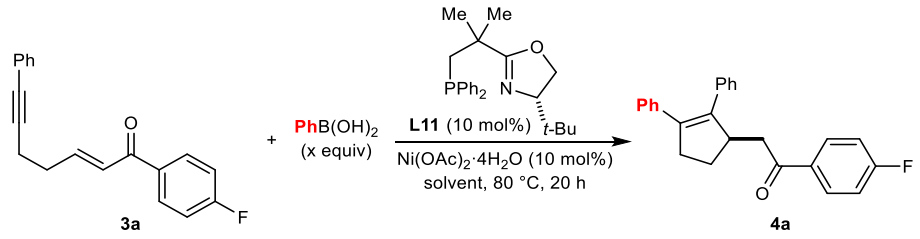


Entry[a]	Solvent	Recovery of 3a [%]	Yield of 4a [%]	ee of 4a
1[b]	TFE	-	66	96
2	THF	40	25	98
3	MeCN	-	70	94
4	DMC	65	-	-

[a] Reactions were carried out using 0.05 mmol of **3a** in solvent (0.5 mL). Yields were determined by ^{1}H NMR spectroscopic analysis using 1,3,5-trimethoxybenzene as an internal standard. [b] 24 h reaction time.

Next, solvent screening was carried out using substrate **3a** and ligand **L11** (Table 37). Replacing TFE with THF appeared to have minimal effect on the enantioselectivity of the reaction; however, the yield decreased significantly (entry 2). When MeCN was used in place of TFE, both the yield and enantioselectivity decreased (entry 3). It was decided to continue optimisation of the reaction using ligand **L11** and TFE as the solvent. Lowering the equivalents of phenylboronic acid to 1.5 or stoichiometric amounts had no effect on the outcome of the reaction (entries 1, 4 and 5).

Table **37**: Solvent and equivalents of $PhB(OH)_2$ screen using enyne **3a** and ligand **L11**.

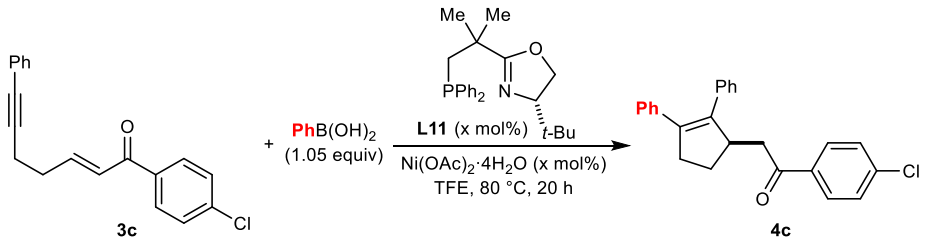


Entry[a]	Solvent	x [equiv]	Recovery of 3a [%]	Yield of 4a [%]	ee of 4a
1	TFE	2.0	-	86	>99
2	THF	2.0	49	42	98
3	MeCN	2.0	14	69	46
4	TFE	1.5	-	86	>99
5	TFE	1.0	-	85	>99

[a] Reactions were carried out using 0.05 mmol of **3a** in solvent (0.5 mL). Yields were determined by ^{1}H NMR spectroscopic analysis using 1,3,5-trimethoxybenzene as an internal standard.

Enyne **3c** was used on an increased scale (0.20 mmol) when investigating the equivalents of catalyst required in the reaction (Table 38). The increase in reaction scale was done to counteract the decreased amount of catalyst required and aid with weighing out of the catalyst. The enantioselectivity of the reaction was not affected by the amount of catalyst added; however, the yield decreased when using 2 mol% catalyst (entry 3) but was within experimental error when using 5 mol% catalyst in comparison to 10 mol% (entry 2).

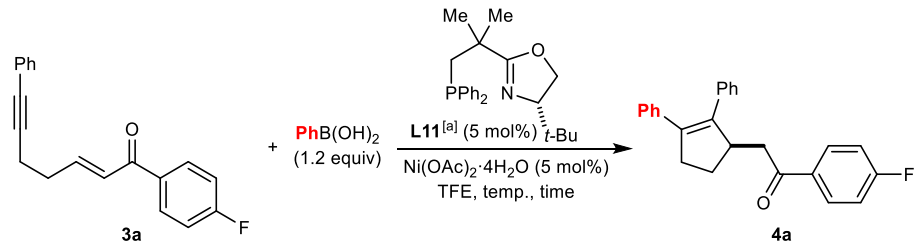
Table **38**: Catalyst equivalent screen using enyne **3c**.



Entry[a]	Catalyst [mol%]	Recovery of 3c [%]	Yield of 4c [%]	ee of 4c
1	10	-	74	>99
2	5	-	69	>99
3	2	15	55	>99

[a] Reactions were carried out using 0.20 mmol of **3c** in TFE (2.0 mL). Yields were determined by ^{1}H NMR spectroscopic analysis using 1,3,5-trimethoxybenzene as an internal standard.

Frequently, starting material remained, as observed by TLC, when carrying out arylative cyclisation reactions on 0.30 mmol scale at 80 °C (Scheme 48). Therefore, all subsequent reactions were initially carried out at 100 °C.

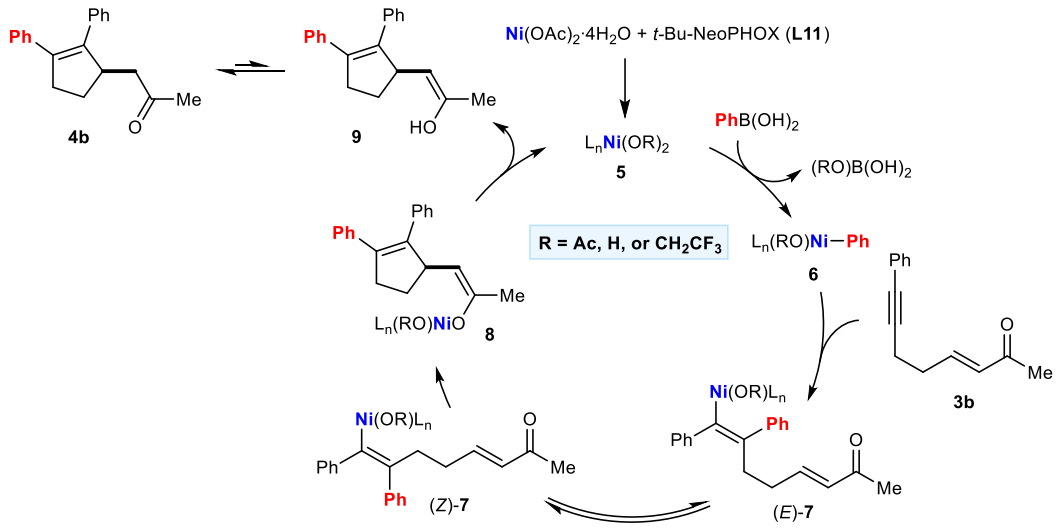


Scheme **48**: Temperature effect on reaction. Reactions were carried out using 0.30 mmol of **3a** in TFE (3.0 mL). [a] Synthesis of (*S*)-*t*-Bu-NeoPHOX (**L11**) was performed by Dr. Connor Yap.

Following investigation of the reaction parameters, optimised reaction conditions were obtained. Heating a mixture of enyne (**3**), phenylboronic acid (1.2 equiv), and 5 mol% each of $Ni(OAc)_2 \cdot 4H_2O$ and (*S*)-*t*-Bu-NeoPHOX (**L11**) in TFE at 100 °C successfully gave cyclopentene products **4** in generally good yields and high enantiomeric excess.

2.2.2 Proposed Mechanistic Cycle

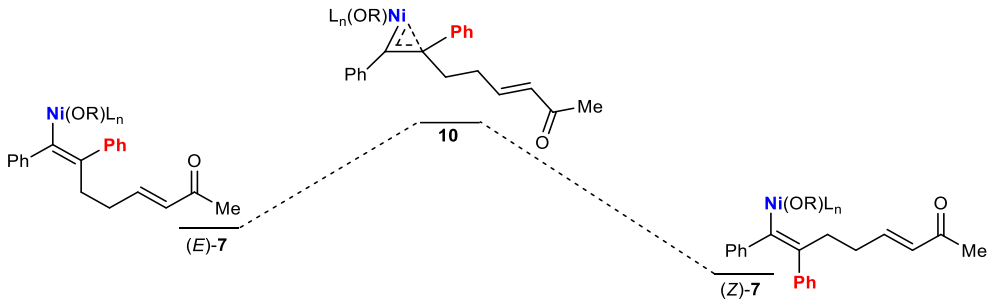
The proposed mechanistic cycle follows the one reported in the introductory section (Scheme 4B) starting with coordination of the ligand to nickel(II) acetate followed by transmetalation of the catalyst with phenylboronic acid leading to phenylnickel species **6** (Scheme 49). Subsequent addition of the phenylnickel species across the alkyne in a *syn*-fashion gives alkenylnickel species (*E*)-**7**. The (*Z*)-alkenylnickel species (*Z*)-**7** is accessed through a vital *E/Z* isomerisation step which enables cyclisation onto the tethered electron-deficient alkene leading to alkoxynickel species **8**. Protodenickelation provides enol **9** and the active catalyst is regenerated. Lastly, keto-enol tautomerisation provides product **4b**.



Scheme **49**: Proposed mechanistic cycle.

As commented on in Section 1.3, various computational investigations of the important alkenylnickel isomerisation step have recently been reported and they have all located the η^1- to η^2-vinyl-like transition state to have the lowest energy

barrier.[99,107,108] In light of these reports, it is proposed that the alkenylnickel isomerisation between (*E*)-**7** and (*Z*)-**7** goes *via* a similar transition state (Scheme 50).

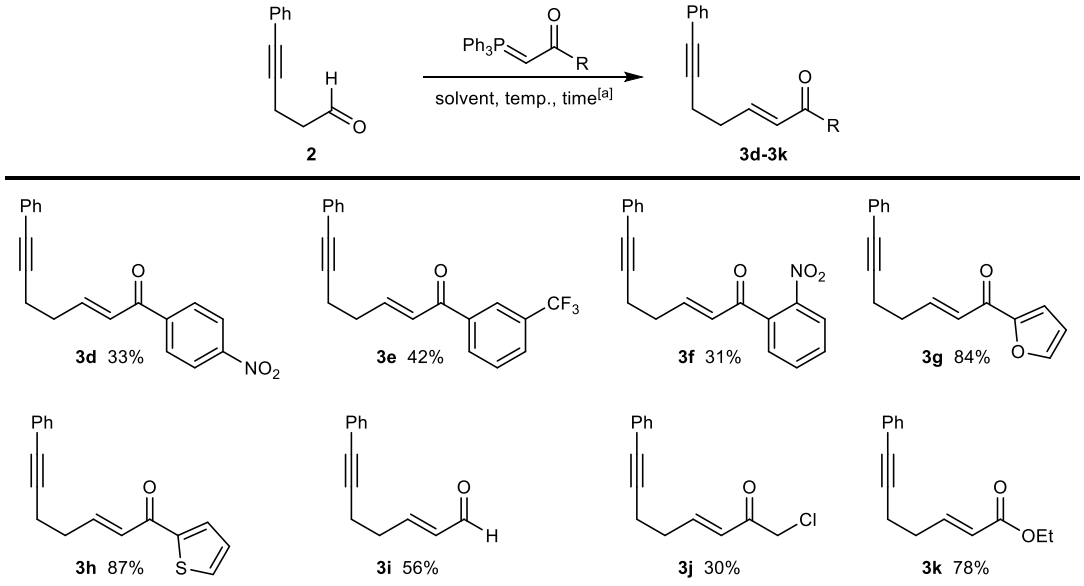


Scheme **50**: Alkenylnickel isomerisation.

2.2.3 Scope of the Electron-Deficient Alkene

Prior to carrying out an investigation of the scope of the reaction regarding the electron-deficient alkene, the synthesis of substrates **3d-3k** was completed (Table 39). Aldehyde, **2** was exposed to various triphenylphosphoranylidenes in Wittig olefinations to give enones **3d-3k**.

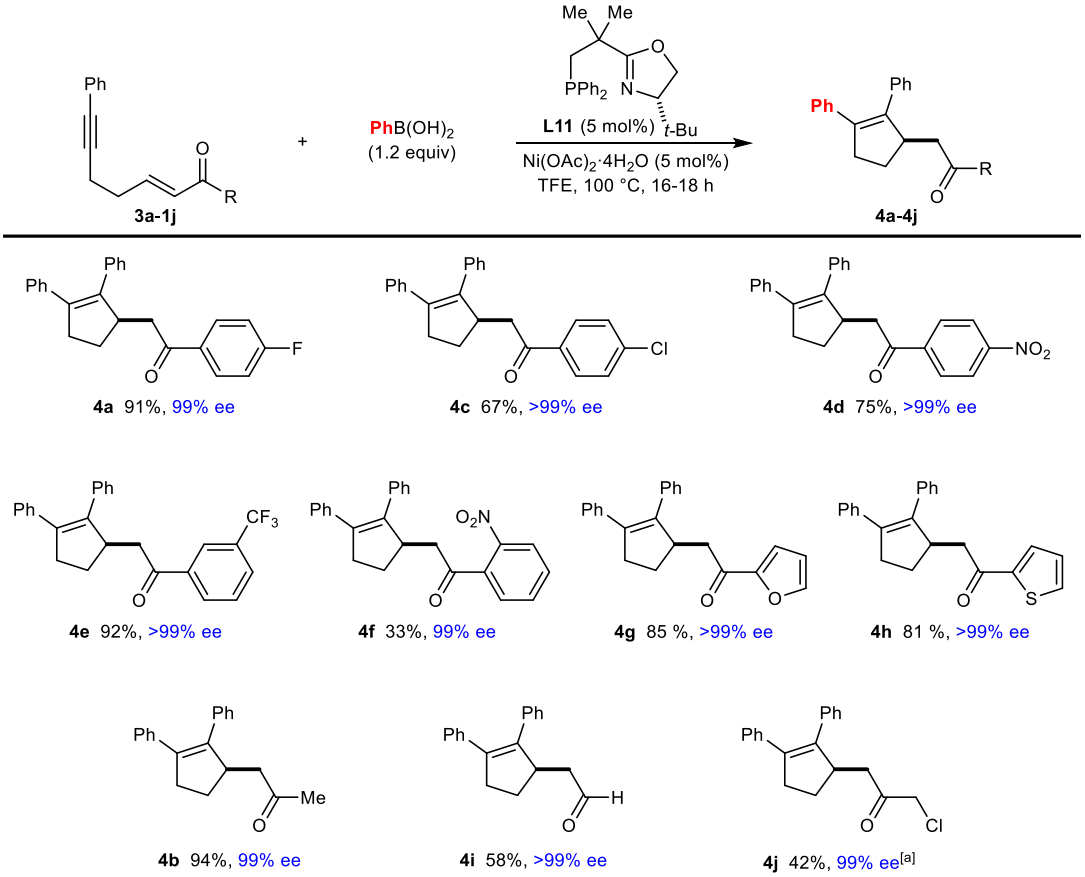
Table **39**: Synthesis of substrates **3d-3k**.



[a] See Section 3.5 for detailed reaction conditions.

An evaluation of the reaction scope was carried out for 1,5-enynes containing a phenyl alkyne and an alkene conjugated to an (hetero)aryl or alkyl carbonyl group (Table 40). The arylative cyclisation reaction was compatible with 4- (**4a**, **4c** and **4d**), 3- (**4e**), and 2-substituted α,β-unsaturated phenyl ketones (**4f**) containing substituents such as halogens (**4a** and **4c**), a nitro group (**4d** and **4f**) or a trifluoromethyl group (**4e**). Generally good yields and excellent enantiomeric excesses were observed (33-94%, ≥99% ee). Having a nitro-group *ortho* to the ketone led to a diminished yield; however, the enantiomeric excess was unaffected (**4f**, 33%, 99% ee). Analysis by TLC revealed the formation of a second species; however, when isolated a mixture of unidentified products was observed. Heteroaromatic α,β-unsaturated ketones, namely 2-furanyl-ketone and 2-thienyl-ketone, were suitable substrates in the formation of cyclopentene **4g** (85%) and **4h** (81%), respectively, both in >99% ee.

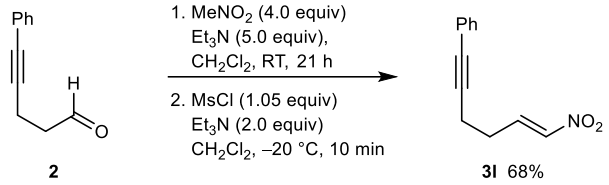
Table **40**: Electron-deficient alkene scope – α,β-unsaturated ketone.



Reactions were carried out using 0.30 mmol of **3a-3j** in TFE (3 mL). Yields are of isolated products obtained after purification by column chromatography. [a] Reaction carried out using $PhB(OH)_2$ (2.0 equiv), $Ni(OAc)_2 \cdot 4H_2O$ (20 mol%) and **L11** (20 mol%).

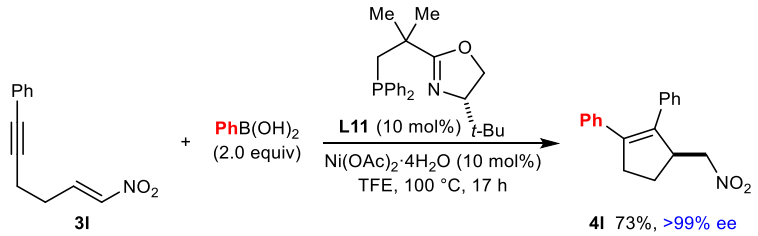
The scope of α,β-unsaturated alkyl ketones was investigated. The reaction tolerated α,β-unsaturated methyl ketone (**4b**, 94%, 99% ee) and α,β-unsaturated aldehyde (**4i**, 58%, >99% ee). Furthermore, an alkyne-tethered α,β-unsaturated chloromethyl ketone was successfully transformed into cyclopentene **4j**; however, modified reaction conditions using 2.0 equivalents of phenylboronic acid and 20 mol% each of $Ni(OAc)_2 \cdot 4H_2O$ and (*S*)-*t*-Bu-NeoPHOX (**L11**) were required to get a modest yield (42%, 99% ee). Under the standard reaction conditions <20% product was observed.

Next, nitroalkene **3l** was synthesised *via* a Henry reaction of aldehyde **2** with nitromethane followed by mesylation of the resulting alcohol and subsequent elimination of the mesylate group (Scheme 51).



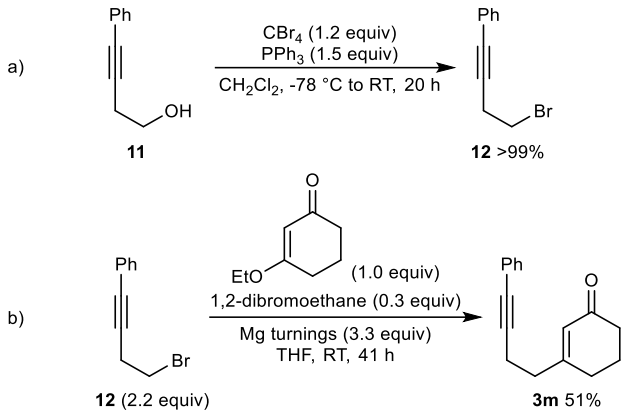
Scheme **51**: Synthesis of substrate **3l**.

Pleasingly, reacting nitroalkene substrate **3l** with phenylboronic acid (2.0 equiv) in the presence of $Ni(OAc)_2 \cdot 4H_2O$ (10 mol%) and (*S*)-*t*-Bu-NeoPHOX (**L11**, 10 mol%) in TFE at 100 °C gave cyclopentene **4l** in 73% yield and >99% ee (Scheme 52). These elevated reaction conditions were required when using the nitroalkene substrate **3l** to ensure the reaction went to completion.



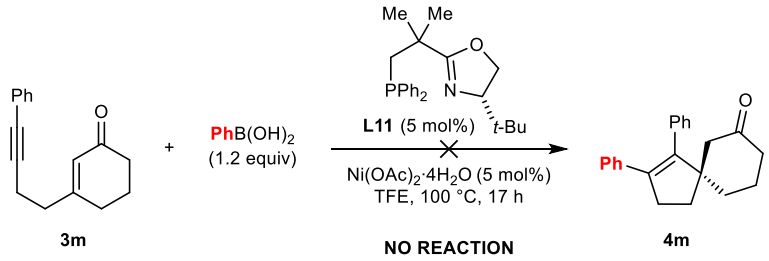
Scheme **52**: Electron-deficient alkene scope – nitroalkene. Reaction was carried out using 0.30 mmol of **3l** in TFE (3 mL). Yield is of isolated product obtained after purification by column chromatography.

The synthesis of substrate **3m** was achieved by transforming alcohol **11** into bromide **12** *via* an Appel reaction followed by formation of the corresponding Grignard reagent and subsequent addition to 3-ethoxy-2-cyclohexenone (Scheme 53).



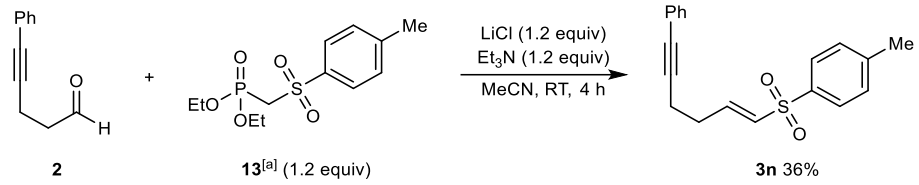
Scheme **53**: Synthesis of substrate **3m**.

Unfortunately, subjecting cyclic α,β-unsaturated ketone **3m** to the reaction conditions in an attempt to obtain spirocycle **4m** led to the recovery of starting material (Scheme 54). Presumably, the lack of reactivity is due to the steric hindrance around the α,β-unsaturated ketone.



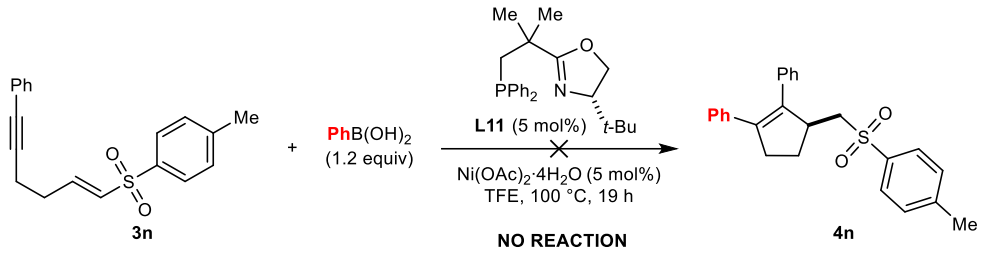
Scheme **54**: Electron-deficient alkene scope – cyclic α,β-unsaturated ketone. Reaction was carried out using 0.30 mmol of **3m** in TFE (3 mL).

α,β-Unsaturated sulfone **3n** was synthesised by the Horner-Wadsworth-Emmons reaction by reacting aldehyde **2** with phophonate **13** under basic conditions **3n** (Scheme 55).



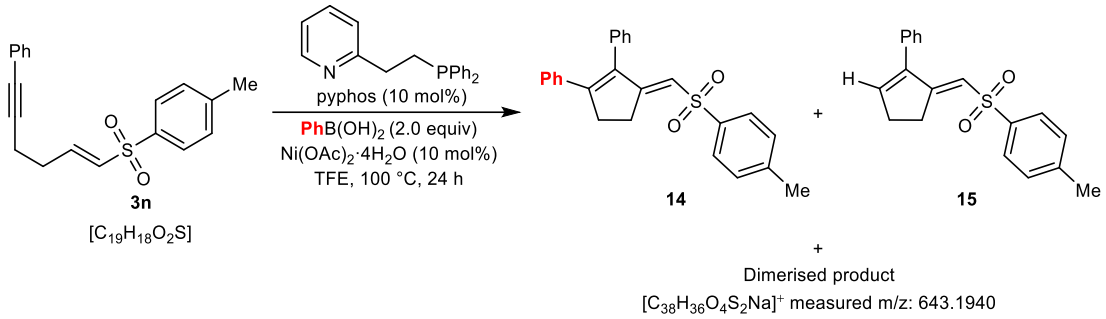
Scheme **55**: Synthesis of substrate **3n**. [a] See Section 3.4 for synthesis of **13**.

Arylative cyclisation of enyne **3n** was unsuccessful in providing product **4n** and only recovery of starting material was observed (Scheme 56).



Scheme **56**: Electron-deficient alkene scope – α,β-unsaturated sulfone. Reaction was carried out using 0.30 mmol of **3n** in TFE (3 mL).

Interestingly, when pyphos was used in place of (*S*)-*t*-Bu-NeoPHOX (**L11**) a complex mixture of products was observed (Scheme 57). Dienes **14** and **15** were identified as a minor component, with a significant portion being assigned to an unidentified compound with mass 643.1940 m/z suggesting dimerisation of **3n**. Alternative solvents were trialled (THF and MeCN); however, no improvement was observed, therefore further optimisation was not pursued. The formation of dienes was also observed when exposing an alkyne-tethered α,β-unsaturated ester to the reaction conditions and the rationale behind the formation of dienes will be discussed in Section 2.2.7.

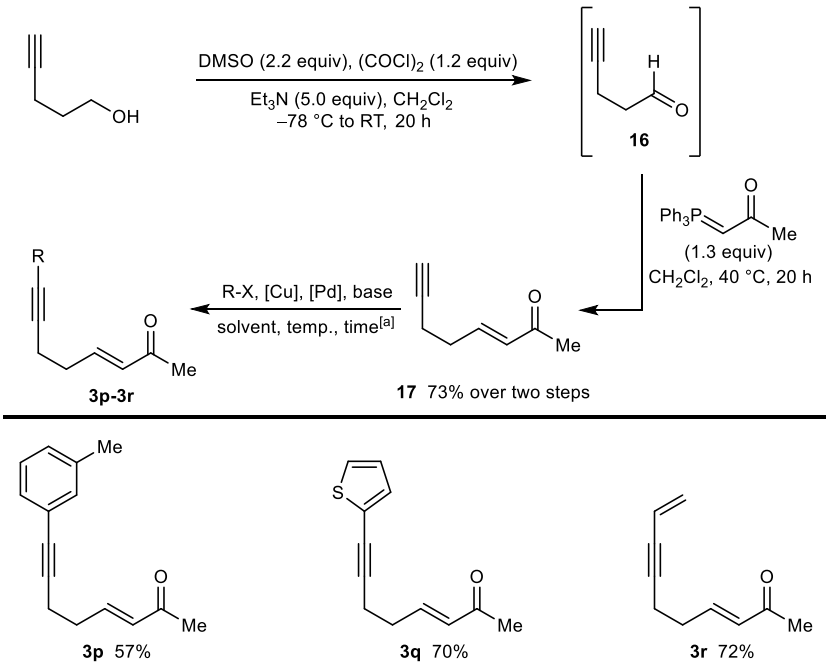


Scheme **57**: Reaction of **3n** using achiral P,N-ligand pyphos. Reaction was carried out using 0.30 mmol of **3n** in TFE (3 mL).

2.2.4 Scope of the Alkyne Substituent

Variation of the alkyne substituent was next investigated. First, the syntheses of substrates **3p-3r** were carried out (Table 41). A Swern oxidation of 4-pentyn-1-ol gave aldehyde **16** *in situ* which was then treated with 1-(triphenylphosphoranylidene)-2-propanone to give common intermediate **17**. From this common intermediate, one step was required to obtain the desired substrates **3p-3r**. Sonogashira cross-couplings of alkyne **17** with aryl-, heteroaryl- or alkenyl-halides led to substrates **3p**, **3q** and **3r**, respectively.

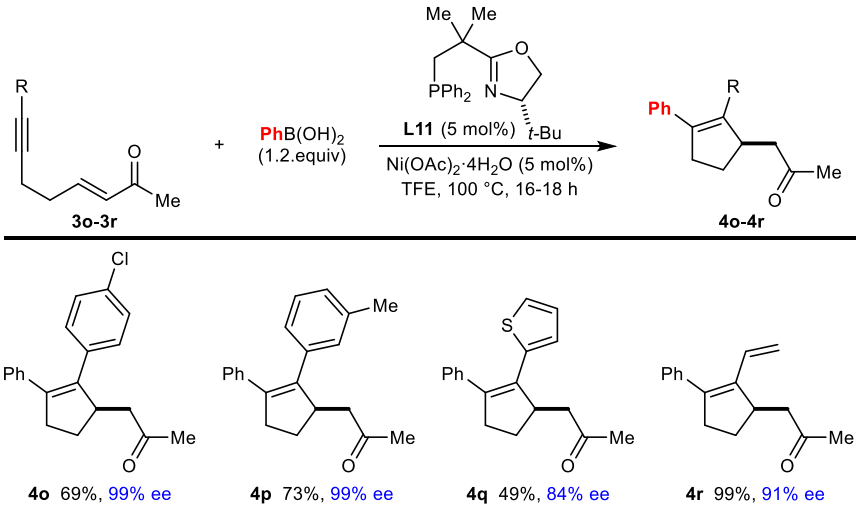
Table **41**: Synthesis of substrates **3p-3r**.



[a] See Section 3.5 for detailed reaction conditions.

The substituted alkynes **3o-3r** were exposed to the nickel-catalysed arylative cyclisation conditions (Table 42). The reaction proceeded efficiently with both 4-chloro- (**4o**) and 3-methyl-substituted phenyl groups (**4p**) and gave good yields and excellent enantiomeric excesses. It became apparent that the substituent on the alkyne was important in controlling the enantioselectivity of the reaction. A decrease in the enantioselectivities was observed for the reactions of 2-thienyl-substituted enyne (**3q**) and vinyl-substituted enyne (**3r**) giving products **4q** (49%, 84% ee) and **4r** (99%, 91% ee), respectively. In Section 2.2.6, a speculative stereochemical model describing the enantioinduction observed in the reaction of alkyne-tethered α,β-unsaturated *t*-butyl-ketone with 2-fluorophenylboronic acid is shown. It appears that a steric interaction between the alkyne substituent and the *t*-butyl group on the ligand is key to the enantioinduction. This corresponds well with the decrease in enantioselectivity observed for substrates containing a smaller alkyne substituent with less steric effect such as a 2-thienyl group (**3q**) or vinyl group (**3r**) as well as a methyl group as seen in Scheme 58.

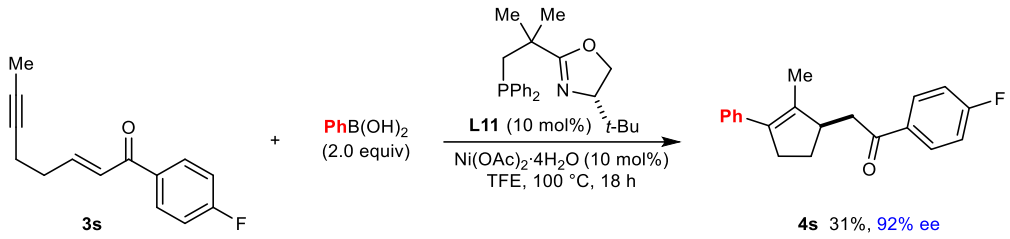
Table **42**: Alkyne substituent scope.



Reactions were carried out using 0.30 mmol of **3o-3r** in TFE (3 mL). Yields are of isolated products obtained after purification by column chromatography. Synthesis of substrate **3o** was performed by Dr. R. E. Ruscoe.

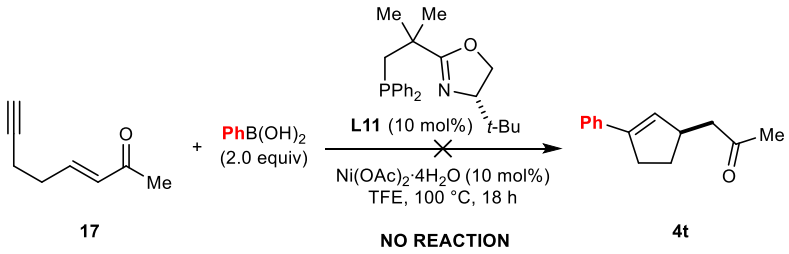
Surprisingly, reacting methyl-substituted alkyne **3s** with phenylboronic acid (2.0 equiv) in the presence of $Ni(OAc)_2 \cdot 4H_2O$ (10 mol%) and (*S*)-*t*-Bu-NeoPHOX (**L11**, 10 mol%) in TFE at 100 °C gave cyclopentene **4s** in 31% yield and >92% ee

(Scheme 58). As noted in the introduction, alkyl-substituted alkynes are not generally compatible with or lead to modest yields in nickel-catalysed *anti*-carbometallative cyclisation chemistry, making this a very welcomed result.



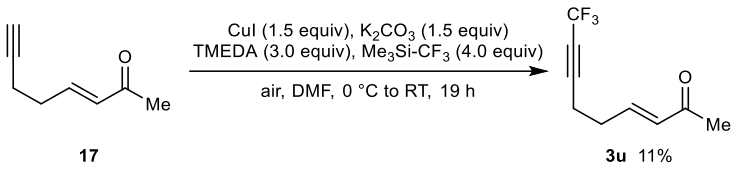
Scheme **58**: Alkyne substituent scope. Reaction was carried out using 0.30 mmol of **3s** in TFE (3 mL). Synthesis of substrate **3s** and entry reaction performed by Dr. H. Green.

The reaction of terminal enyne **17** with phenylboronic acid (2.0 equiv), $Ni(OAc)_2{\cdot}4H_2O$ (10 mol%) and (*S*)-*t*-Bu-NeoPHOX (**L11**, 10 mol%) in TFE at 100 °C led to recovery of starting material (Scheme 59). The use of terminal alkynes have previously been reported to be detrimental to nickel-catalysed *anti*-carbometallative cyclisation reactions.[72]



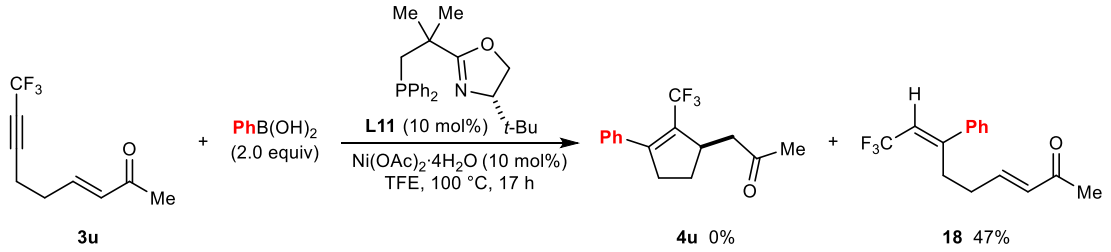
Scheme **59**: Alkyne substituent scope. Reaction was carried out using 0.30 mmol of **17** in TFE (3 mL).

As discussed in the introduction, the electron-donating effect of alkyl substituents on alkynes is unfavourable in nickel-catalysed *anti*-carbometallative cyclisation chemistry. It was hypothesised that having an electron-withdrawing alkyl substituent on the alkyne could allow for *anti*-carbometallative cyclisation to take place. Trifluoromethyl-substituted alkyne **3u** was prepared in an 11% yield *via* an oxidative trifluoromethylation reaction using terminal alkyne **17** and the Ruppert-Prakash reagent, Me_3SiCF_3, a source of nucleophilic trifluoromethyl anion (Scheme 60).



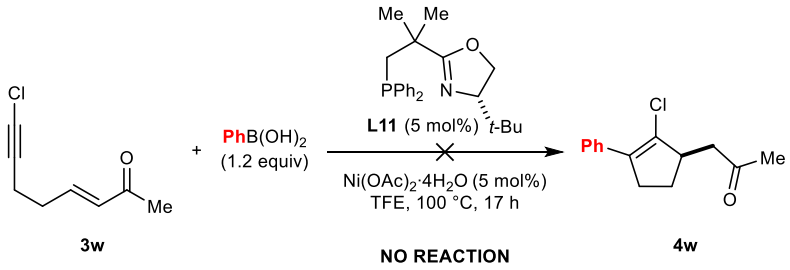
Scheme **60**: Synthesis of substrate **3u**.

Unfortunately, the arylative cyclisation reaction of trifluoromethyl alkyne **3u** was unsuccessful in providing the desired product **4u** (Scheme 61). However, alkyne hydroarylation product **18** was isolated in 47% yield. Trifluoromethyl-substituted alkene **18** was only observed as the (*E*)-isomer, suggesting that the *E*/*Z* isomerisation step was disfavoured in comparison with protodenickelation.



Scheme **61**: Alkyne substituent scope – trifluoromethylalkyne. Reaction was carried out using 0.05 mmol of **3u** in TFE (0.5 mL). Yield is of isolated product obtained after purification by column chromatography.

It was hypothesised that chloroalkyne **3w** could undergo arylative cyclisation. However, subjecting chloroalkyne **3w** to the standard reaction conditions to obtain chloro-substituted cyclopentene **4w** resulted in the recovery of starting material (Scheme 62).

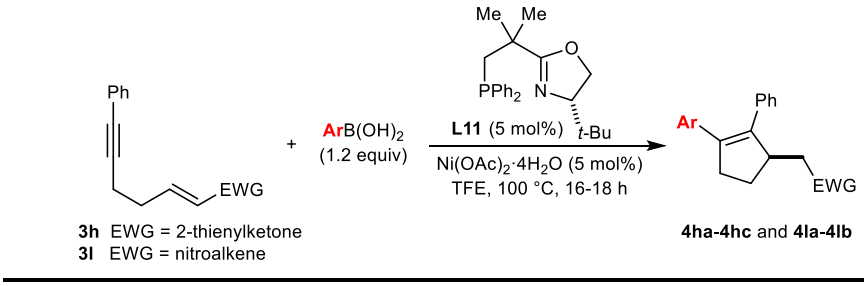


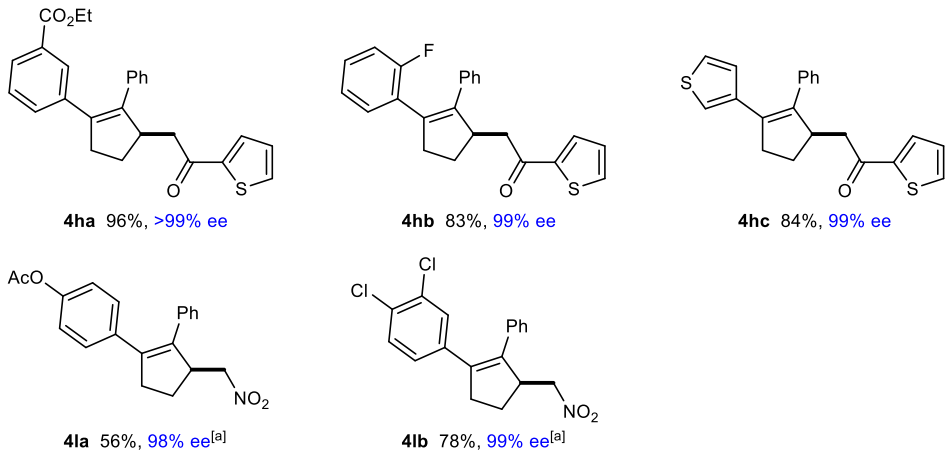
Scheme **62**: Alkyne substituent scope – chloroalkyne. Reaction was carried out using 0.30 mmol of **3w** in TFE (3 mL). Synthesis of substrate **3w** performed by Dr. H. Green.

2.2.5 Scope of the Boronic acid

An investigation of the scope of the boronic acid in the reaction using substrates **3h** and **3l** was carried out (Table 43). Various 4- (**4la**), 3- (**4ha**) and 2-substituted phenylboronic acids (**4hb**) were compatible with the reaction leading to modest to high yields and excellent enantiomeric excesses. 3,4-Disubstituted phenylboronic acid (**4lb**) and 3-thienylboronic acid (**4hc**) were also tolerated.

Table **43**: (Hetero)arylboronic acid scope.



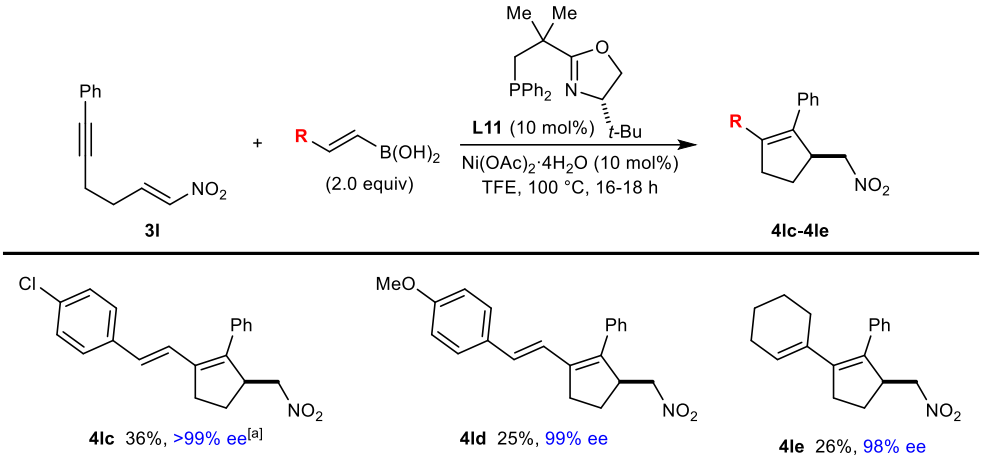


Reactions were carried out using 0.30 mmol of **3h** or **3l** in TFE (3 mL). Yields are of isolated products obtained after purification by column chromatography. [a] Reaction carried out using $PhB(OH)_2$ (2.0 equiv), $Ni(OAc)_2 \cdot 4H_2O$ (10 mol%) and **L11** (10 mol%).

Interestingly, alkenylboronic acids were also compatible with the reaction (Table 44). *trans*-2-(4-Chlorophenyl)vinylboronic acids (**4lc**) and *trans*-2-(4-methoxyphenyl)vinylboronic acid (**4ld**) were both successful in providing the desired products; however, in low yields of 36% and 25%, respectively. Exposing substrate **3l** to cyclohexene-1-boronic acid led to the desired product in 26% yield (**4le**). Across all three examples the enantioselectivity of the reaction was excellent. The lower yields

observed are presumably a result of competitive protodeboronation of the alkenylboronic acids.

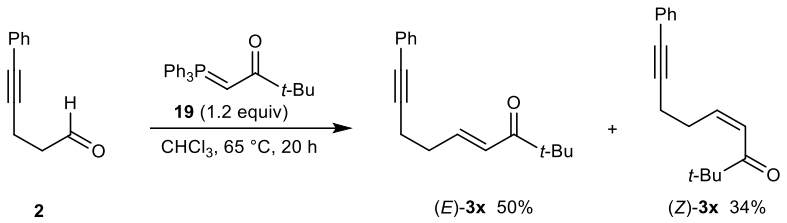
Table **44**: Alkenylboronic acid scope.



Reactions were carried out using 0.30 mmol of **3l** in TFE (3 mL). Yields are of isolated products obtained after purification by column chromatography. Entries **4ld** and **4le** were performed by Dr. H. Green. [a] Unreacted starting material **3l** was observed by ^{1}H NMR spectroscopy in approximately 1:1 ratio with product **4lc**.

2.2.6 Cyclisation onto an α,β-Unsaturated *t*-Butyl Ketone

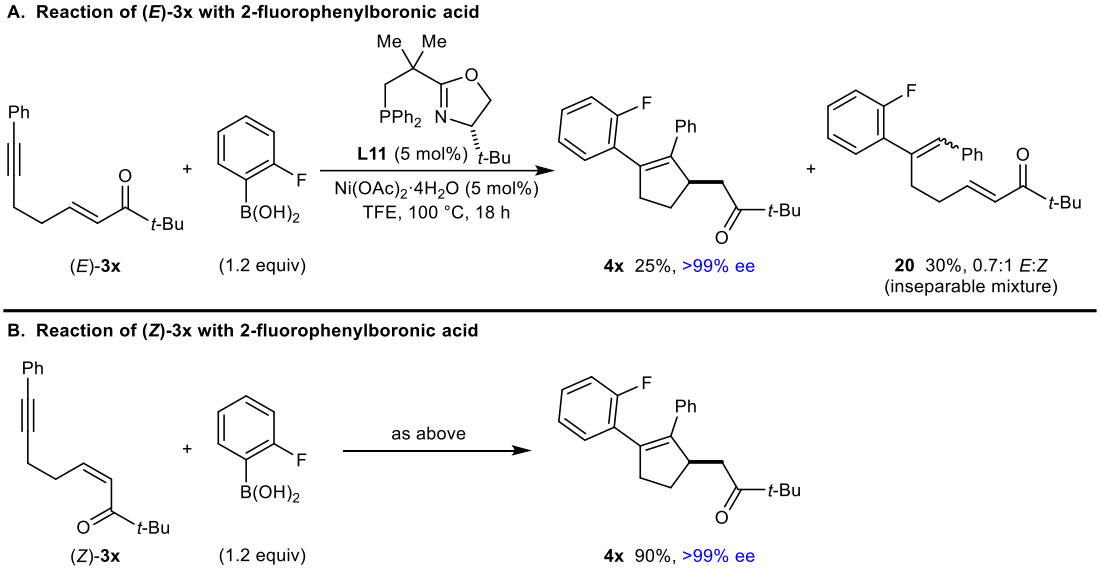
The 1,5-enyne substrate consisting of a phenyl alkyne tethered to an α,β-unsaturated *t*-butyl ketone was isolated in the form of the (*E*)- and (*Z*)-isomer in 50% and 34% yield, respectively (Scheme 63).



Scheme **63**: Synthesis of substrates (*E*)-**3x** and (*Z*)-**3x**.

The (*E*)- and (*Z*)-isomers were individually subjected to the arylative cyclisation reaction conditions using 2-fluorophenylboronic acid (Scheme 64). The reaction of the (*E*)-isomer (*E*)-**3x** gave the desired product **4x** in 25% yield and >99% ee as well as an inseparable mixture of (*E*)- and (*Z*)-isomers of hydroarylation product **20** in 30% yield

(Scheme 64A). Subjecting the (*Z*)-isomer (*Z*)-**3x** to the reaction conditions led to the desired product **4x** in 90% yield and >99% ee (Scheme 64B).



Scheme **64**: Comparing arylmetallative cyclisation of stereoisomeric substrates containing an α,β-unsaturated *t*-butyl ketone. Reactions were carried out using 0.30 mmol of (*E*)-**3x** or (*Z*)-**3x** in TFE (3 mL). Yields are of isolated products obtained after purification by column chromatography.

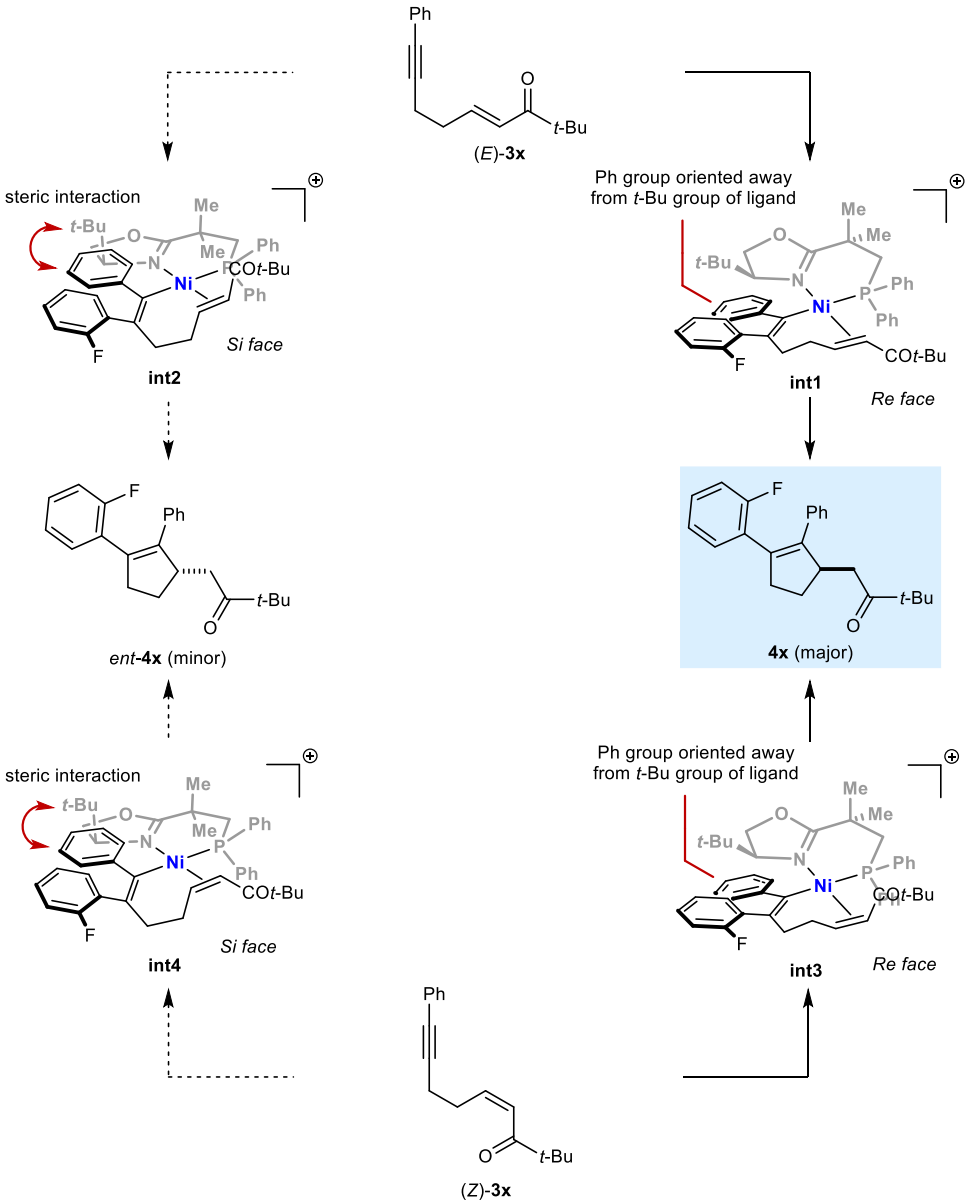
It is encouraging that using the stereoisomeric substrate of (*E*)-**3x** leads to a significant increase in the yield. Conceivably, other low yielding reactions could benefit from applying the (*Z*)-isomer substrate rather than the (*E*)-isomer substrate, although electron-deficient (*Z*)-alkenes are often more difficult to synthesise. In fact, similar results were observed when individually applying the arylative cyclisation reaction conditions to substrates containing either the (*E*)- or (*Z*)-alkenyl nitrile which is discussed in Section 2.2.8.

The observation of (*Z*)-alkenes performing significantly better than (*E*)-alkenes in the arylative cyclisation reaction is in accordance with previously reported work by the Lam group which found that in enantioselective nickel-catalysed intramolecular allylic alkenylations, the (*Z*)-allylic phosphates gave arylated cyclisation products but the corresponding (*E*)-isomers did not.[74] It is unclear why differing results are obtained from the arylative cyclisation reaction of (*E*)-**3x** and (*Z*)-**3x**, though, it is plausible that

the lower thermodynamic stability of (*Z*)-**3x** leads to greater reactivity toward nucleophilic attack, and/or the steric hinderance is less prevalent in (*Z*)-**3x**.

Additionally, it was confirmed by HPLC that the major enantiomer of product **4x** was the same whether starting from the (*E*)- or (*Z*)-isomer (Scheme 64). These results contrast with various examples of enantioselective 1,4-additions of carbon nucleophiles to electron-deficient alkenes where substrates containing (*E*)- and (*Z*)-isomers lead to opposite enantiomers.[146–149] However, reactions of (*E*)- and (*Z*)-isomers leading to the same major enantiomer of 1,4-addition products have also been reported.[54,150]

A speculative stereochemical model describing the enantioinduction observed in the reactions of (*E*)-**3x** or (*Z*)-**3x** with 2-fluorophenylboronic acid is shown in Scheme 65. The reaction of the square planar aryl-nickel species with (*E*)-**3x** or (*Z*)-**3x** will lead to a square planar alkenylnickel complex (**int1-4**). Phosphine, being a better π-acceptor than the oxazoline, will be trans to the electron-rich phenyl group and subsequently the alkenyl group. The labile α,β-unsaturated *t*-butyl ketone is prochiral and can coordinate to the nickel *via* the *re* or *si* face. When nickel is coordinating to the *re* face of the alkene, as seen in **int1** and **int3**, the phenyl group is pointing away from the *t*-butyl group on the oxazoline. However, when nickel coordinates to the *si* face of the alkene as seen in **int2** and **int4** there is a steric interaction between the phenyl group and the *t*-butyl group on the oxazoline making this pathway less favourable. As a result, whether the α,β-unsaturated *t*-butyl ketone is the (*E*)- or (*Z*)-isomer, migratory insertion of the alkene into the alkenylnickel bond is more favourable *via* the *re* face leading to the major enantiomer **4x**.

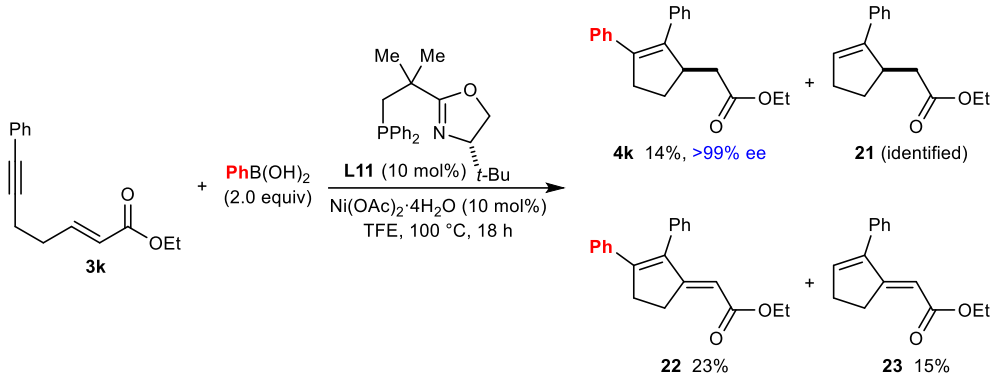


Scheme **65**: Speculative stereochemical model of the reactions of (*Z*)-**3x** and (*E*)-**3x** with 2-fluorophenylboronic acid.

2.2.7 Cyclisation onto an α,β-Unsaturated Ester

Substrate **3k** containing an α,β-unsaturated ester was subjected to phenylboronic acid (2.0 equiv), in the presence of $Ni(OAc)_2 \cdot 4H_2O$ (10 mol%) and (*S*)-*t*-Bu-NeoPHOX (**L11**, 10 mol%) in TFE at 100 °C which led to the isolation of three products and identification of a fourth product (Scheme 66). The desired cyclisation product **4k** was isolated in 14% yield and >99% ee, as well as the conjugated dienes **22** and **23**, in 23% and 15% yield, respectively. The diene containing products were the

result of a Heck-type cyclisation. Lastly, the reductive cyclisation product **21** was identified; however, complete purification of the compound proved challenging and therefore an accurate mass was not obtained (see Section 3.6 for further information).

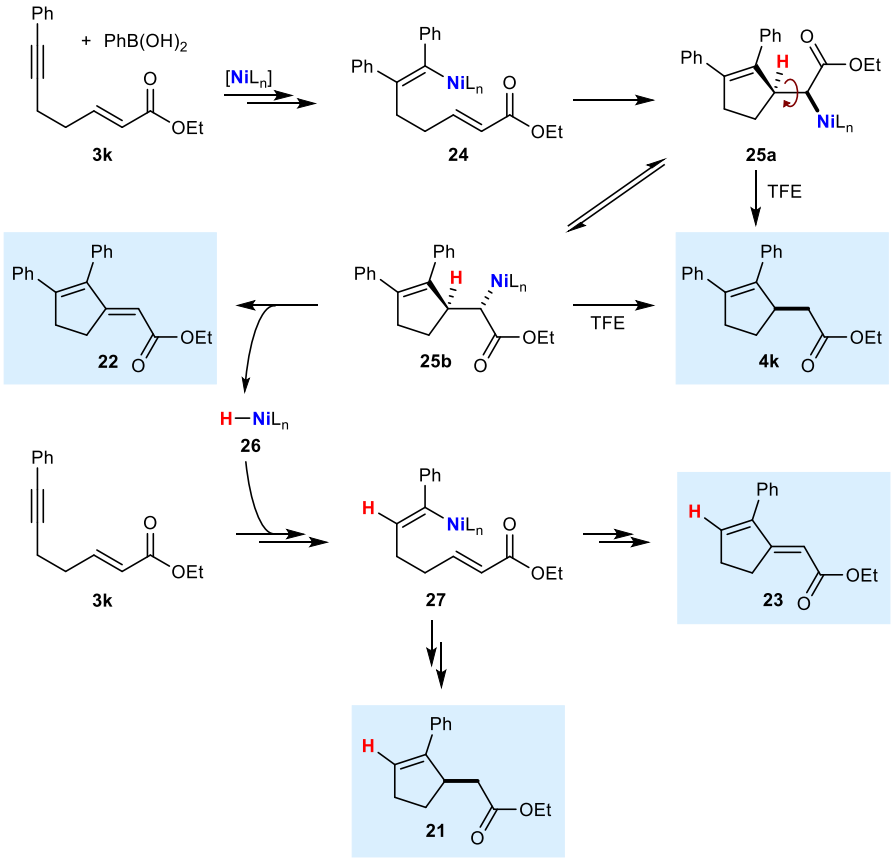


Scheme **66**: Electron-deficient alkene scope – α,β-unsaturated ester. Reaction was carried out using 0.30 mmol of **3k** in TFE (3 mL). Yields are of isolated products obtained after purification by column chromatography.

Rationale for the formation of the four cyclisation products is seen in Scheme 67. Initially, addition of a phenylnickel species across the alkyne followed by *E*/*Z* isomerisation gives alkenylnickel species **24**, which is in accordance with the previously described mechanistic cycle (see Schemes 4B and 49). It is proposed that migratory insertion of the alkene to the alkenylnickel species which occurs in a concerted manner leads to *C*-bound nickel enolate **25a**, which contrasts with the previously proposed mechanistic cycle where an *O*-bound nickel enolate is obtained. The nickel enolate **25a** can undergo protodenickelation to give the desired product **4k** (14%, >99% ee); however, the low yield suggests that this step is slow in comparison with substrates containing ketones, aldehyde or nitro groups (see Table 40 and Scheme 52). A possible reason for this is that protodenickelation is faster *via* the *O*-bound, rather than the *C*-bound nickel enolate, and ester-derived nickel enolates are more likely to exist as the *C*-bound variant compared with ketone-derived nickel enolates and nickel nitronates.

A competing reaction to protodenickelation can occur where the nickel-enolate **25a** can undergo rotation around the C–C bond leading to intermediate **25b** followed by *syn*-stereospecific β-hydride elimination giving product **22** and nickel hydride **26**. This type of reactivity has previously been observed in the nickel-catalysed addition of

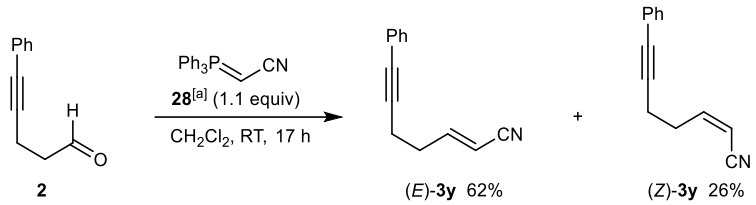
arylboronic acids to α,β-unsaturated alkenes leading to either the Mizoroki-Heck- or Michael-type addition by fine-tuning of the ligand.[143] The eliminated nickel hydride species **26** can undergo alkyne hydronickelation with substrate **3k** followed by *E*/*Z* isomerisation giving alkenylnickel species **27** and from here the mechanism proceed *via* a series of analogous steps to the example mentioned above forming the reductive cyclisation product **21** and conjugated diene **23**. Since the publication of the work presented in this thesis, a reductive cyclisation reaction of alkyne-tethered dioxazolones with nickel(I)-hydride species proceeding *via* alkenylnickel isomerisation has been reported (See Scheme 6B).[99]



Scheme **67**: Mechanistic rationale of the formation of products **4k**, **21**, **22** and **23**.

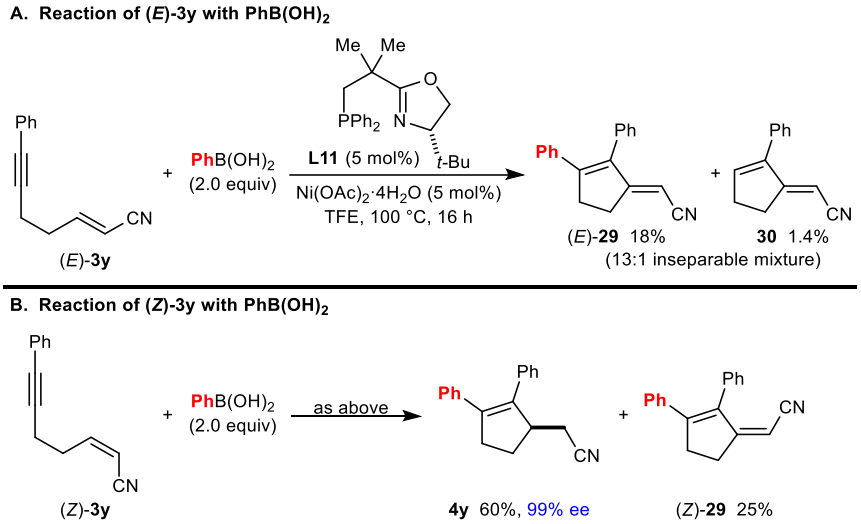
2.2.8 Cyclisation onto an α,β-Unsaturated Nitrile

The 1,5-enyne substrate consisting of a phenyl alkyne tethered to an α,β-unsaturated nitrile was isolated as the (*E*)-isomer ((*E*)-**3y**) and the (*Z*)-isomer ((*Z*)-**3y**) in 62% and 26% yield, respectively (Scheme 68).



Scheme **68**: Synthesis of substrates (*E*)-**3y** and (*Z*)-**3y**. [a] See Section 3.4 for the synthesis of **28**.

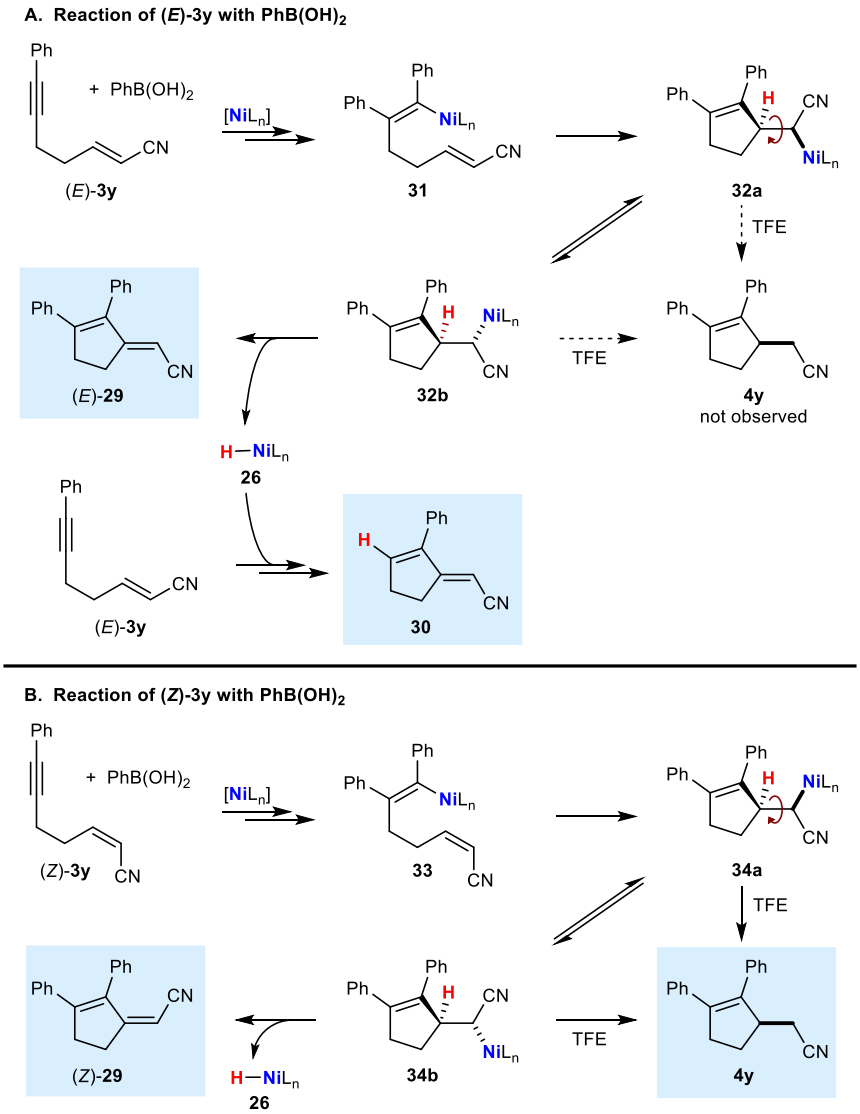
The isomers were individually subjected to the arylative cyclisation reaction conditions (Scheme 69). The reaction of (*E*)-**3y** gave an inseparable mixture of conjugated dienes (*E*)-**29** and **30** in 18% and 1% yield respectively, and none of the desired arylative cyclisation product **4y** was observed. To account for the mass balance, a second fraction, which was visible by TLC, was isolated by column chromatography. However, a mixture of unidentified products was observed. Subjecting the (*Z*)-isomer (*Z*)-**3y** to the reaction conditions gave the desired arylative cyclisation product **4y** in 60% yield and 99% ee and conjugated enyne (*Z*)-**29** in 25% yield. As previously observed, the (*Z*)-isomer substrate is more successful at providing the desired arylative cyclisation product compared with the (*E*)-isomer substrate.



Scheme **69**: Comparing arylmetallative cyclisation of stereoisomeric substrates containing an alkenyl nitrile. Reactions were carried out using 0.30 mmol of (*E*)-**3y** or (*Z*)-**3y** in TFE (3 mL). Yields are of isolated products obtained after purification by column chromatography.

A proposed mechanism for the formation of (*E*)-**29**, **30**, **4y** and (*Z*)-**29** utilising substrates (*E*)-**3y** and (*Z*)-**3y** is seen in Scheme 70. It is notable that the conjugated dienes (*E*)-**29** and (*Z*)-**29** obtained from substrates (*E*)-**3y** and (*Z*)-**3y**, respectively, are of opposite stereochemistry. This can be explained by examining the proposed mechanism of the nickel-catalysed *anti*-carbometallative addition-cyclisation-elimination reactions. Initially, addition of a phenylnickel species across the alkyne of substrate (*E*)-**3y** followed by *E*/*Z* isomerisation gives alkenylnickel species **31** (Scheme 70A). It is proposed that migratory insertion of the alkene to the alkenylnickel species which occurs in a concerted manner leads to α-cyano alkylnickel species **32a**. The α-cyano alkylnickel species **32a** can undergo protodenickelation to give the desired product **4y**; however, this product is not detected which suggests that the protodenickelation step is slow, and rotation around the C–C bond followed by *syn*-stereospecific β-hydride elimination to give product (*E*)-**29** is more favourable. The small amount of **30** observed can be explained by the nickel hydride species **26** undergoing alkyne hydronickelation with substrate (*E*)-**3y** and **30** is formed *via* analogous steps to the above.

The reaction of alkenyl nitrile (*Z*)-**3y** with phenylboronic acid succeeds *via* a similar reaction mechanism as described above (Scheme 70B). However, in this case the opposite diastereoisomer of cyclised α-cyano alkylnickel intermediate is obtained (**34a** rather than **32a**), which after rotation of the C–C bond followed by *syn*-stereospecific β-hydride elimination leads to conjugated diene (*Z*)-**29**, with opposite stereochemistry, in 25% yield. More significantly, protodenickelation of either intermediate **34a** or **34b** is more favourable than β-hydride elimination when starting from alkenyl nitrile (*Z*)-**3y** which is evident from the 60% yield observed of the desired product **4y**. It is proposed that the different tendencies of **32a** and **34a** to undergo protodenickelation is subject to the different absolute configurations of the stereocenter bearing the carbon nickel bond.



Scheme **70**: Mechanistic rationale for the formation of products (*E*)-**29** and **30** from enyne (*Z*)-**3y** and products (*Z*)-**29** and **4y** from (*E*)-**3y**.

2.2.9 Absolute Configuration

The absolute configurations of products **4a**, **4hb**, **4hc** and **4x** were determined by X-ray crystallography to be of (*R*)-configuration, and those of the remaining products were assigned by analogy (Figure 2). Conformational disorder is observed in the fluorophenyl moiety in product **4hb** and **4x**, as well as in the thiophene group attached directly to the cyclopentene ring in product **4hc**.

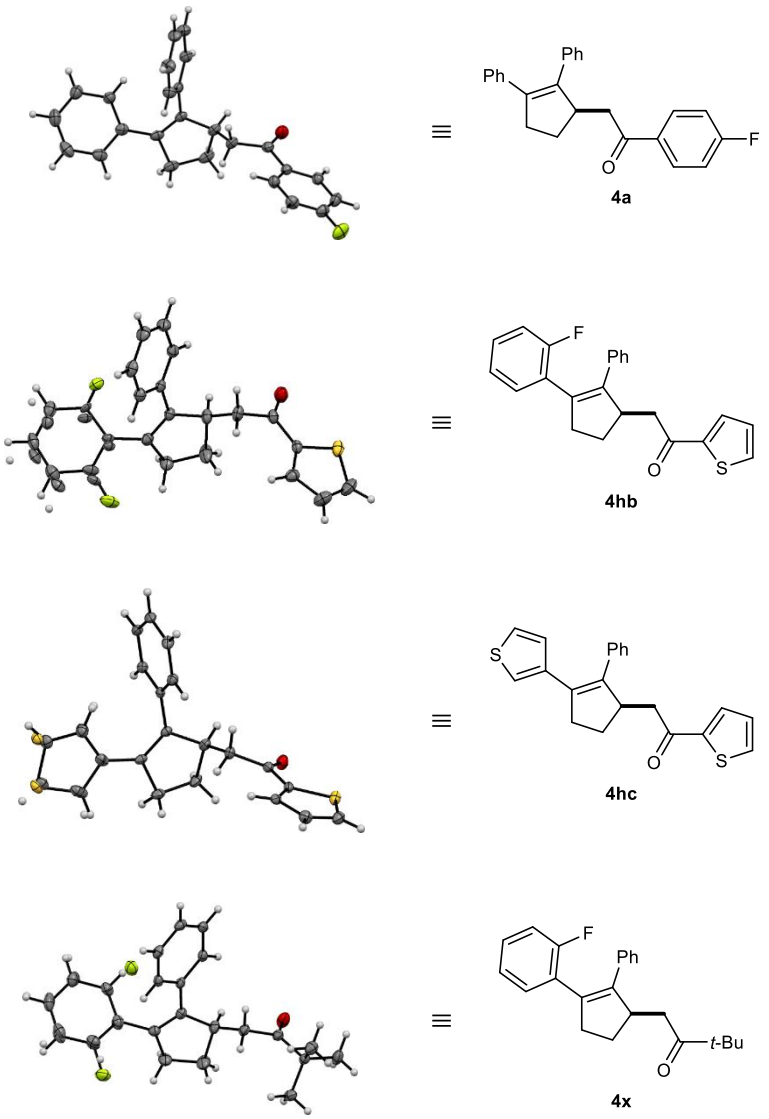


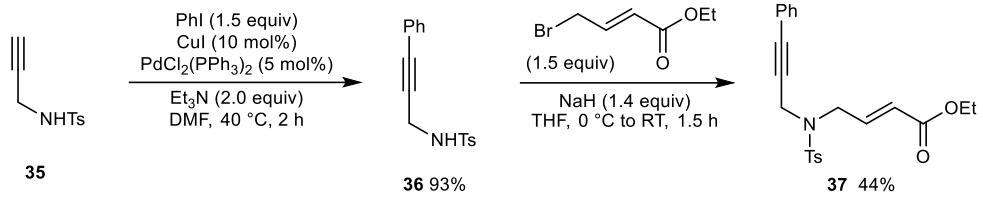
Figure **2**: X-Ray crystallography Structures of **4a**, **4hb**, **4hc** and **4x**. The crystals were run, solved and refined by Dr Stephen Argent.

2.3 Arylative Cyclisation Providing Six-Membered Hetero- and Carbocyclic Products

2.3.1 Optimisation

Optimisation of the arylative cyclisation reaction of alkyne-tethered electron-deficient alkenes leading to six-membered carbo- and heterocycles was carried out simultaneously with optimisation of the arylative cyclisation reaction to give five-membered carbocycles (see Section 2.2.1). Firstly, the synthesis of substrate **37** was completed (Scheme 71). A Sonogashira cross-coupling of tosylated propargylamine

with phenyl iodide provided phenyl-alkyne **36** which was exposed to ethyl-4-bromo crotonate in a nucleophilic substitution reaction to give substrate **37**.



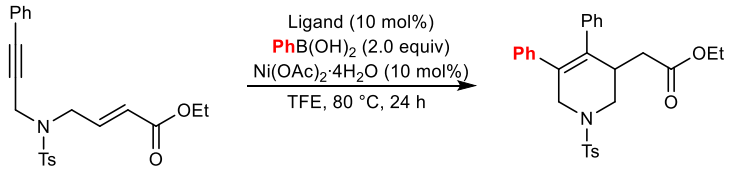
Scheme **71**: Synthesis of substrate **37**.

The initial reaction of alkyne **37** with phenylboronic acid (2.0 equiv) in the presence of $Ni(OAc)_2 \cdot 4H_2O$ (10 mol%) and pyphos (10 mol%) in TFE at 80 °C provided the arylative cyclisation product **38** in 53% yield as observed by ^1H NMR spectroscopy using an internal standard (Table 45, entry 1). A series of chiral phosphine-oxazoline ligands (entries 2-7) were next investigated. The use of (*S*)-*t*-Bu-NeoPHOX (**L11**), that was used for the five-membered scope, resulted in recovery of starting material (entry 6) while the use of less sterically hindered (*S*)-*i*-Pr-NeoPHOX (**L12**) led to the desired product in 49% yield and 48% ee (entry 5). An increase in the enantioselectivity of the reaction was observed when using (*R*)-PhPHOX (**L9**), giving **38** in 41% yield and 76% ee (entry 2). A further increase in enantioselectivity was observed when using ligands (*S*)-*i*-PrPHOX (**L13**) or (*S*)-*t*-BuPHOX (**L2**) showing 88% ee and 86% ee, respectively (entries 3 and 4). The 2-tolyl-substituted phosphine-oxazoline ligand **L14** was trialled with no reactivity being observed (entry 7).

Notably, β-hydride elimination leading to Heck-style cyclisation products was not observed for the arylative cyclisation reaction of α,β-unsaturated ester **37** as it was seen for α,β-unsaturated ester **3k** (see Scheme 66).

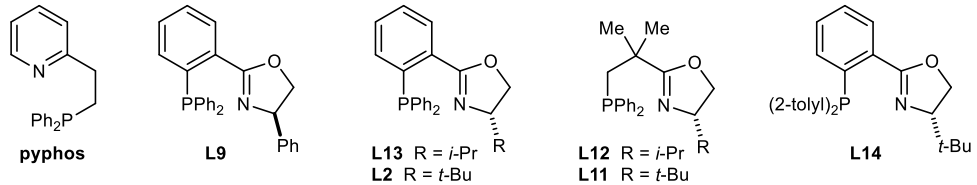
Efforts to improve the enantioselectivity of the reaction were made. Bisphosphine ligands **L15** and **L16** (entries 8 and 9) as well as nitrogen bidentate ligand **L17** (entry 10) and nitrogen tridentate ligand **L18** (entry 11) were investigated. Largely, no reactivity was observed; however, the bisphosphine ligand (*R*)-HexaPHEMP (**L16**) did provide the desired product in 18% yield and 57% ee (entry 9).

Table **45**: Ligand screen using enyne **37**.

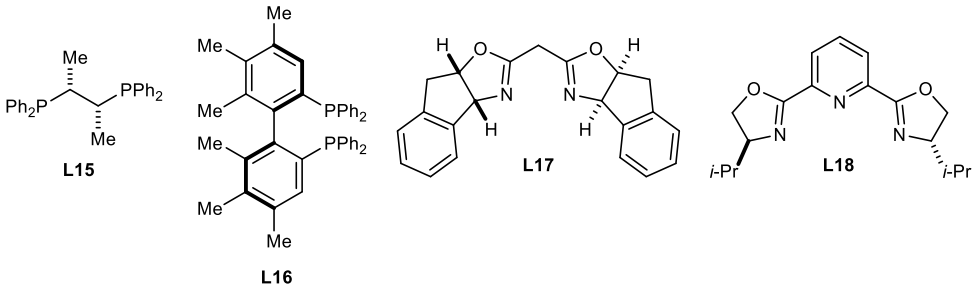


37 **38**

Ligands



pyphos **L9** **L13** R = *i*-Pr, **L2** R = *t*-Bu; **L12** R = *i*-Pr, **L11** R = *t*-Bu; **L14**



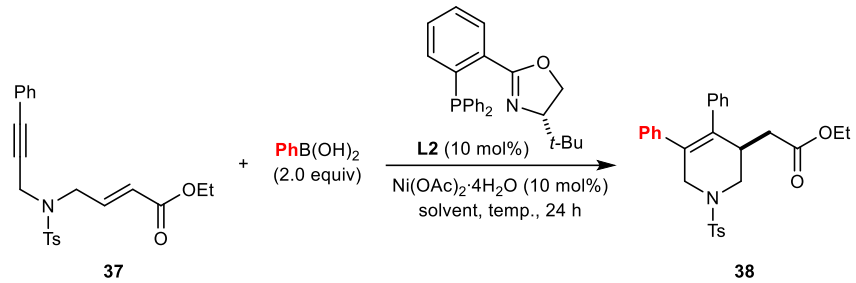
L15 **L16** **L17** **L18**

Entry[a]	Ligand	Recovery of 37 [%]	Yield of 38 [%]	ee of 38 [%]
1	pyphos	-	53	0
2	L9	-	41	–76
3	L13	5	35	88
4	L2	-	42	86
5	L12	-	49	–48
6	L11	77	-	-
7	L14	51	-	-
8	L15	78	-	-
9	L16	43	18	57
10	L17	81	-	-
11	L18	79	-	-

[a] Reactions were carried out using 0.05 mmol of **37** in TFE (0.5 mL). Yields were determined by ^{1}H NMR spectroscopic analysis using 1,3,5-trimethoxybenzene as an internal standard.

The simultaneous investigation of the arylative cyclisation reaction of 1,5- and 1,6-enynes identified (*S*)-*t*-BuPHOX (**L2**) as a common ligand in successfully providing the desired products in adequate yields and enantioselectivity. Therefore, **L2** was chosen as the ligand to carry across for further optimisation. *Note: the idea of using a common ligand was later abandoned and therefore the final optimised reaction conditions for 1,5-enynes utilise (S)-t-Bu-NeoPHOX (**L11**).*

Table **46**: Solvent and temperature screen using enyne **37**.



37 **38**

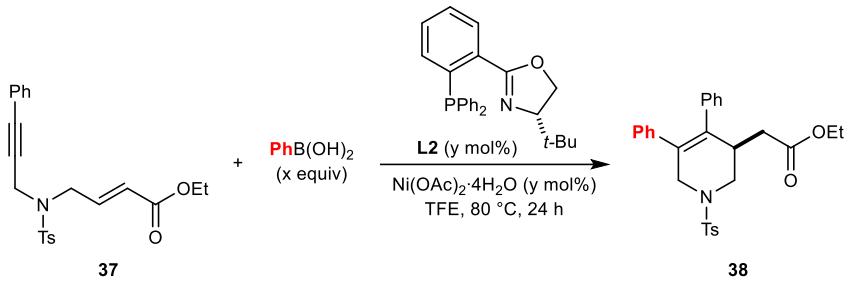
Entry[a]	**Solvent**	**Temperature [°C]**	**Recovery of 37 [%]**	**Yield of 38 [%]**	**ee of 38 [%]**
1	TFE	80	-	42	86
2	THF	80	42	22	66
3	MeCN	80	64	Trace	-
4	DMC	80	80	-	-
5	TFE	60	-	37	87
6	THF	60	-	50	66

[a] Reactions were carried out using 0.05 mmol of **37** in solvent (0.5 mL). Yields were determined by ^{1}H NMR spectroscopic analysis using 1,3,5-trimethoxybenzene as an internal standard.

An evaluation of solvents for the arylative cyclisation reaction of **37** revealed that in comparison to TFE, THF led to a decrease in yield and enantiomeric excess (Table 46, entry 2), MeCN led to only traces of the product (entry 3) and DMC gave no product (entry 4). It was found that a decrease in temperature had no effect on the enantioselectivity of the reaction and at the lower temperature the yield decreased in the presence of TFE (entry 5) and increased in the presence of THF (entry 6).

Decreasing the amount of phenylboronic acid and catalyst appeared to have no effect on the arylative cyclisation reaction on a 0.05 mmol scale (Table 47); however, due to inconsistent results when scaling up, it was decided to use the elevated reaction conditions with 2.0 equivalents of phenylboronic acid and 10 mol% catalyst.

Table **47**: Equivalents screen using enyne **37**.



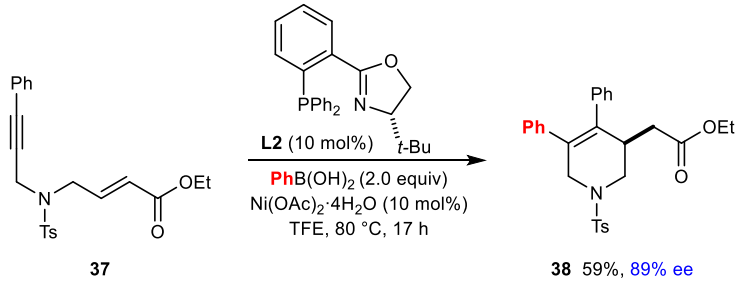
37 **38**

Entry[a]	PhB(OH)2 [equiv]	Catalyst [mol%]	Yield of 38 [%]	ee of 38 [%]
1	2.0	10	42	86
2	2.0	5	46	84
3	1.2	5	44	87

[a] Reactions were carried out using 0.05 mmol of **37** in TFE (0.5 mL). Yields were determined by ^{1}H NMR spectroscopic analysis using 1,3,5-trimethoxybenzene as an internal standard.

2.3.2 Scope

The optimised reaction conditions were applied to substrate **37** on a 0.30 mmol scale, reacting alkyne **37** with phenylboronic acid (2.0 equiv) in the presence of $Ni(OAc)_2{\cdot}4H_2O$ (10 mol%) and (*S*)-*t*-BuPHOX (**L2**, 10 mol%) in TFE at 80 °C (Scheme 72). The desired product **38** was obtained in 59% yield and 89% ee. The mass balance of the reaction was an inseparable mixture of stereoisomeric alkyne hydroarylation products containing an unidentified impurity.

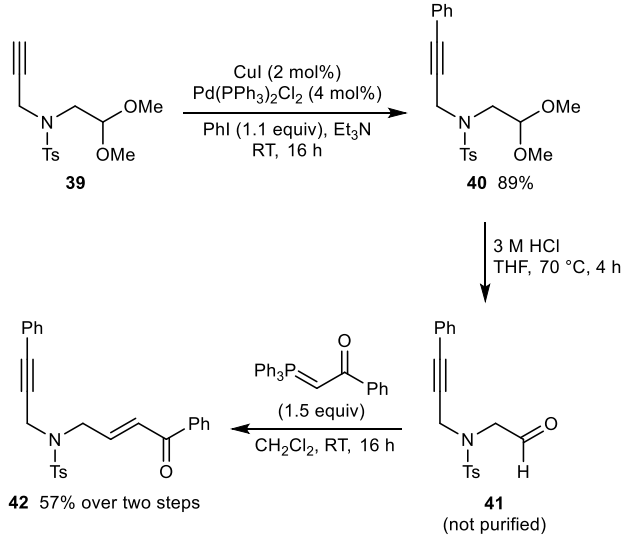


37 **38** 59%, 89% ee

Scheme **72**: Arylmetallative cyclisation reaction of enyne **37**. Reaction was carried out using 0.30 mmol of **37** in TFE (3 mL). Yield is of isolated product obtained after purification by column chromatography.

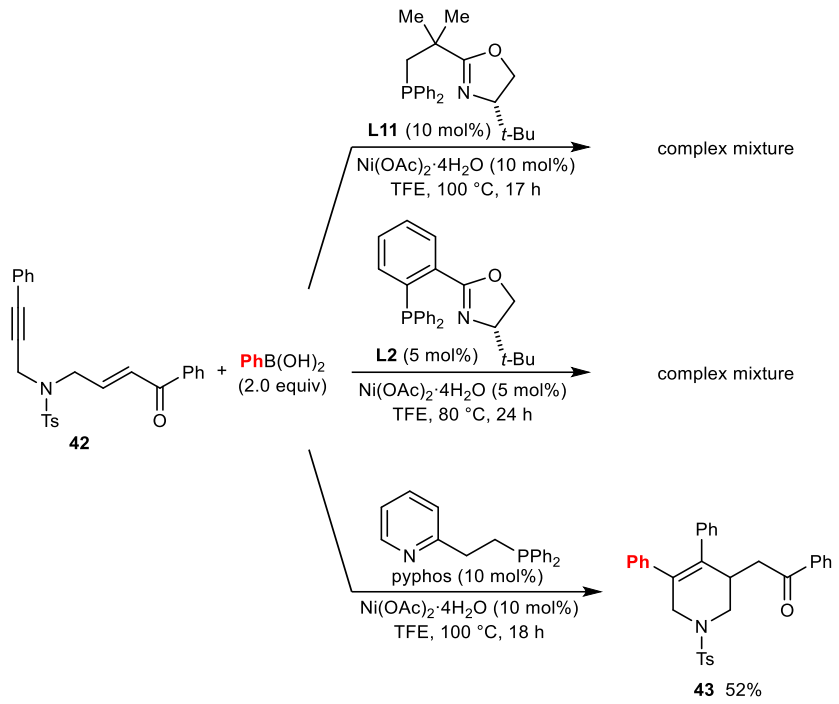
Next, the synthesis of substrate **42** was carried out. A Sonogashira cross-coupling of intermediate **39** with phenyl iodide gave phenyl-alkyne **40** (Scheme 73). An acid-catalysed acetal deprotection of **40** led to aldehyde **41**, which after an aqueous

workup was used without further purification in the subsequent Wittig olefination to give enyne **42** in 57% yield over two steps.



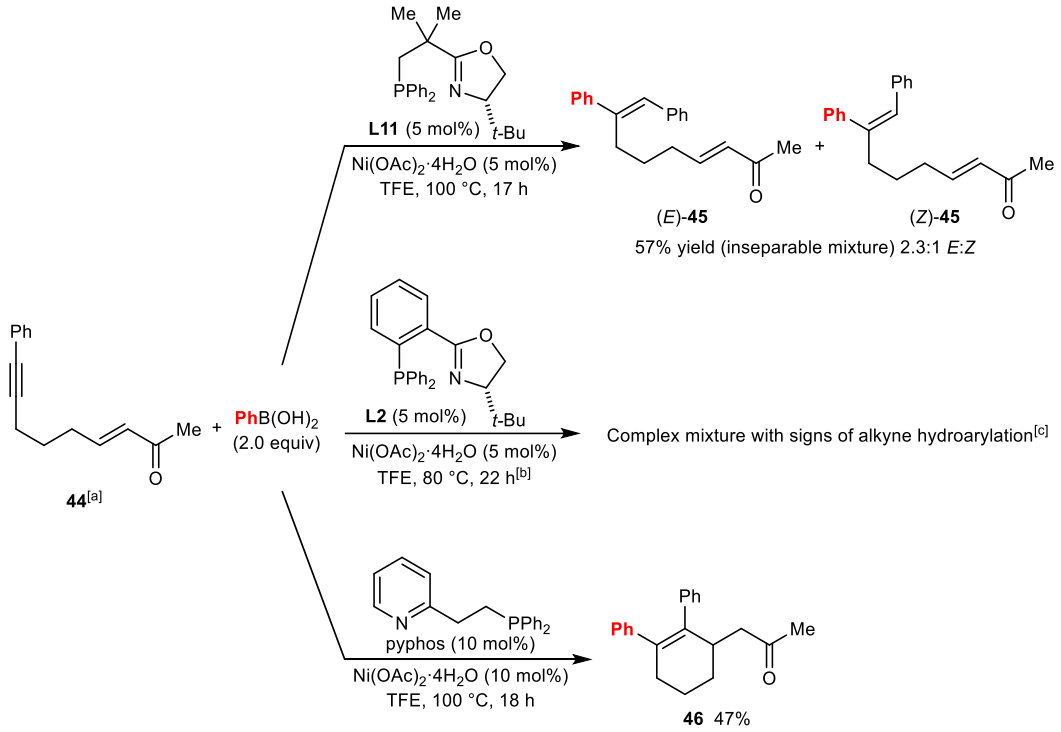
Scheme **73**: Synthesis of substrate **42**.

It was assumed that the lower electrophilicity and therefore reactivity of an α,β-unsaturated ester in comparison with an α,β-unsaturated ketone would mean that phenyl ketone **42** would be compatible in arylative cyclisation reaction when exposed to the optimised conditions (Scheme 74). However, the reaction of **42** with phenylboronic acid using either the optimised conditions for 1,5-enynes using (*S*)-*t*-Bu-NeoPHOX (**L11**) or the optimised conditions for 1,6-enynes using (*S*)-*t*-BuPHOX (**L2**) led to complex mixtures of side-products with no evidence of the desired product. Interestingly, utilising the achiral ligand pyphos in the arylative cyclisation reaction led to the desired product **43** in 52% yield.



Scheme **74**: Arylmetallative cyclisation reactions of enyne **42**. Reactions were carried out using 0.30 mmol of **42** in TFE (3 mL). Yields are of isolated product obtained after purification by column chromatography.

The carbon-tethered enyne **44** was next investigated in the arylative cyclisation reaction (Scheme 75). The synthesis of substrate **44** was achieved *via* the same route as the synthesis of **3b**; however, utilising 5-hexyn-1-ol in place of 4-pentyn-1-ol. The reaction of **44** with phenylboronic acid (2.0 equiv) in the presence of $Ni(OAc)_2{\cdot}4H_2O$ (5 mol%) and (*S*)-*t*-Bu-NeoPHOX (**L11**, 5 mol%) in TFE at 100 °C gave a 2.3:1 mixture of inseparable stereoisomeric alkyne hydroarylation products (*E*)-**45** and (*Z*)-**45**, respectively, in 57% yield and the desired product was undetected. Next, the reaction of **44** with phenylboronic acid (1.2 equiv) in the presence of $Ni(OAc)_2{\cdot}4H_2O$ (5 mol%) and (*S*)-*t*-BuPHOX (**L2**, 5 mol%) in TFE at 80 °C led to a complex mixture of products with signs of alkyne hydroarylation products in the crude ^1H NMR spectrum and the desired product was undetected. Other phosphine-oxazoline ligands, (*R*)-PhPHOX (**L9**) and (*S*)-*i*-PrPHOX (**L13**), were also attempted; however, without improvement to the reaction outcome. Interestingly, as observed with substrate **42** (see Scheme 74), utilising the achiral ligand pyphos in the arylative cyclisation reaction of substrate **44** was successful in providing the desired product **46** in 47% yield.



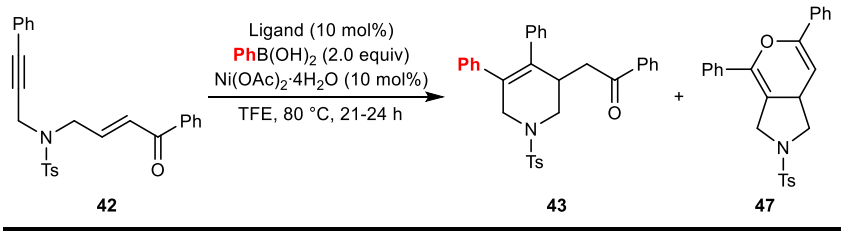
Scheme **75**: Arylmetallative cyclisation reactions of enyne **44**. Reactions were carried out using 0.30 mmol of **44** in TFE (3 mL). Yields are of isolated products obtained after purification by column chromatography. [a] See Section 3.5 for the synthesis of **44**. [b] The reaction was carried out with 1.2 equivalents of $PhB(OH)_2$. [c] The alkyne hydroarylation product was not isolated.

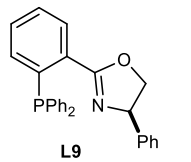
2.3.3 Further Optimisation

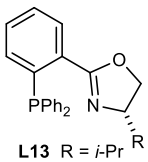
It was puzzling that chiral phosphine-oxazoline ligands were not able to provide the desired products in the arylative cyclisation reactions of 1,6-enynes **42** and **44**; however, both substrates provided the racemic products when utilising pyphos as the ligand. An expanded ligand screen was carried out using substrate **42** and phenylboronic acid (2.0 equiv) in the presence of $Ni(OAc)_2{\cdot}4H_2O$ (10 mol%) and various chiral ligands (10 mol%) in TFE at 80 °C (Table 48). Initially, chiral phosphine-oxazoline ligands were tested. (*R*)-PhPHOX **L9** failed to provide the desired product and instead, led to 14% recovery of starting material along with pyran **47** in 20% yield (entry 1), using (*S*)-*i*-PrPHOX **L13** gave a complex mixture of unidentified products (entry 2) and employing (*S*)-*t*-BuPHOX **L2** in THF rather than TFE led to 42% recovery of starting material as well as pyran **47** in 24% yield (entry 3). Pyran **47** was expected to be formed *via* a thermally promoted hetero-Diels-Alder reaction.[151–153] A control reaction exposing enyne **42** in toluene to heat (100 °C) for 23 hours led to pyran **47** in 56% yield and thereby confirmed the hypothesis (Scheme 76).

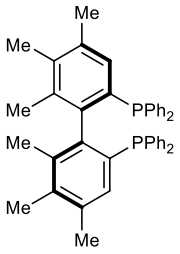
Previously, it was demonstrated that bisphosphine ligand **L16** was successful in the arylative cyclisation reaction of **37** (see Table 45), and therefore this ligand was applied to the arylative cyclisation reaction of alkyne **42**; however, a complex mixture of products was observed with no sign of the desired product (Table 48, entry 4). Next, pyphos resembling chiral P,N-ligands were tried. (*R*)-Quinap (**L19**) provided pyran **47** in 30% yield along with starting material recovery (entry 5). However, the use of P,N-ligand **L20** in the arylative cyclisation reaction led to a trace amount of the desired product as well as recovery of some stating material and pyran **47** (entry 6).

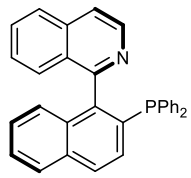
Table **48**: Ligand screen using enyne **42**.

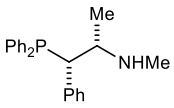



L9


L13 R = *i*-Pr
L2 R = *t*-Bu


L16


L19

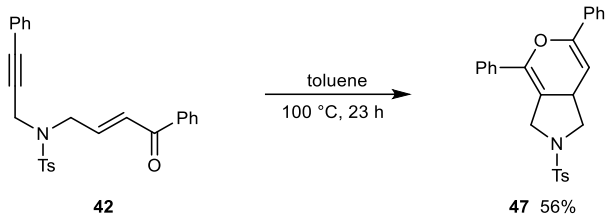

L20

Entry[a]	Ligand	Recovery of 42 [%]	Yield of 43 [%]	ee of 43 [%]	Yield of 47 [%]
1	L9	14	-	-	20
2[b]	L13	-	-	-	trace
3[c]	L2	42	-	-	24
4[b]	L16	-	-	-	-
5	L19	17	-	-	30
6	L20	12	>10	-	22
7[d]	L20	trace	51	68	>10

[a] Reactions were carried out using 0.05 mmol of **42** in TFE (0.5 mL). Yields were determined by ^{1}H NMR spectroscopic analysis using 1,3,5-trimethoxybenzene as an internal standard. [b] Complex mixtures observed. [c] Reaction carried out in THF. [d] Reaction carried out using Cs_2CO_3 (0.2 equiv).

It has been reported for nickel-catalysed *anti*-carbometallative cyclisation reactions, that increased yields were obtained when adding a sub-stoichiometric amount

of Cs_2CO_3.[68,73,75,79] Therefore, the reaction was repeated but Cs_2CO_3 (0.2 equiv) added and this resulted in an increase in the yield of the desired product to 51% and only traces of starting material and pyran **47** were observed (entry 7). The enantiomeric excess of the desired product was 68%.

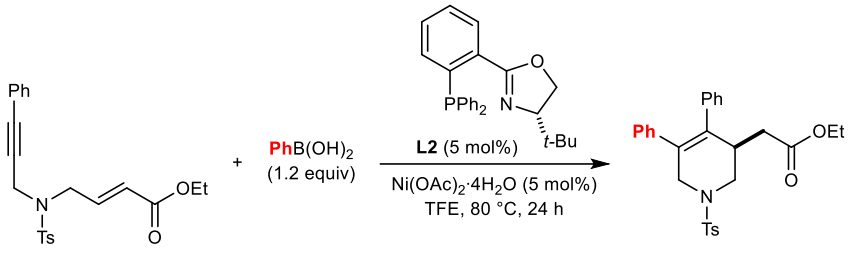


42 **47** 56%

Scheme **76**: Hetero-Diels-Alder side-product. Reaction was carried out using 0.05 mmol of **42** in TFE (0.5 mL). Yield was determined by ^{1}H NMR spectroscopic analysis using 1,3,5-trimethoxybenzene as an internal standard.

The benefits of using Cs_2CO_3 in arylative cyclisation reactions is not ubiquitous. During optimisation, Cs_2CO_3 was considered as an additive in the arylative cyclisation reaction of alkyne-tethered α,β-unsaturated ester **37** (Table 49). The reaction led to an increase in yield from 44 to 56%; however, a decrease in enantioselectivity from 87 to 84% ee, and it was decided at that time not to further pursue the use of Cs_2CO_3 as an additive.

Table **49**: Effect of Cs_2CO_3 using enyne **37**.



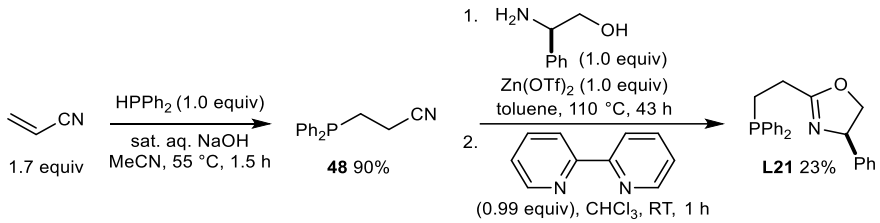
37 **38**

Entry[a]	**Cs_2CO_3 [mol%]**	**Yield of 38 [%]**	**ee of 38 [%]**
1	-	44	87
2	10	56	84

[a] Reactions were carried out using 0.05 mmol of **37** in TFE (0.5 mL). Yields were determined by ^{1}H NMR spectroscopic analysis using 1,3,5-trimethoxybenzene as an internal standard.

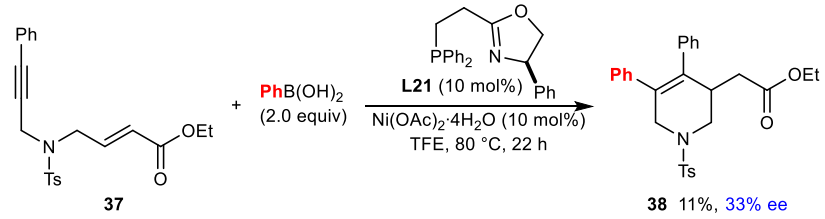
Next, chiral phosphine-oxazoline ligand **L21** was synthesised (Scheme 77). The flexibility of the tether between the phosphine and the oxazoline resembles that of

pyphos. Since pyphos had previously proven to perform well in the arylative cyclisation reaction of 1,6-enynes (see Scheme 74 and 75), it was thought ligand **L21** could perform similarly. The synthesis of phosphine-oxazoline **L21** started with a base catalysed hydrophosphination reaction of acrylonitrile with diphenylphosphine to give phosphine-nitrile intermediate **48**. A condensation reaction of **48** with a chiral β-amino alcohol gave phosphine-oxazoline ligand **L21** as the zinc-complex. Stirring the zinc-complex with 2,2'-bipyridine at room temperature for an hour was required to release the ligand.[154]



Scheme **77**: Synthesis of ligand **L21**.

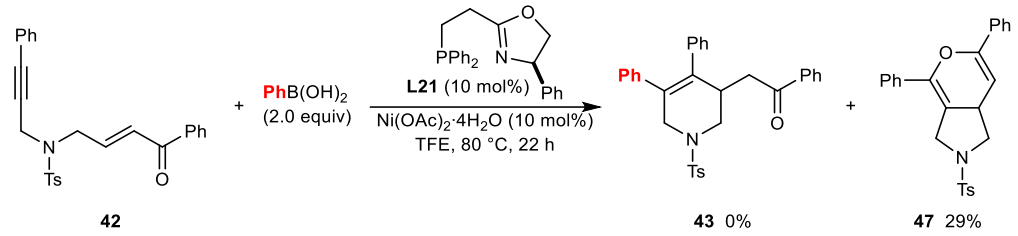
Substrate **37**, which had previously been successful in the arylative cyclisation reaction using chiral phosphine-oxazoline ligands, was exposed to the arylative cyclisation reaction conditions using **L21** (Scheme 78). The reaction of **37** with phenylboronic acid (2.0 equiv) in the presence of $Ni(OAc)_2 \cdot 4H_2O$ (10 mol%) and ligand **L21** (10 mol%) in TFE at 80 °C led to the formation of the desired product **38** in 11% isolated yield with 33% ee. The mass balance was unreacted starting material.



Scheme **78**: Arylmetallative cyclisation reaction of **37** using ligand **L21**. Reaction was carried out using 0.05 mmol of **37** in TFE (0.5 mL). Yield is of isolated product obtained after purification by column chromatography.

Secondly, substrate **42**, which had previously demonstrated limited success in the enantioselective arylative cyclisation reaction (see Scheme 74 and Table 48), was

exposed to phosphine-oxazoline **L21** (Scheme 79). Unfortunately, the reaction of **42** with phenylboronic acid (2.0 equiv) in the presence of $Ni(OAc)_2 \cdot 4H_2O$ (10 mol%) and ligand **L21** (10 mol%) in TFE at 80 °C did not provide the desired product and instead led to the formation of side-product **47** in 29% yield as well as 24% starting material recovery.

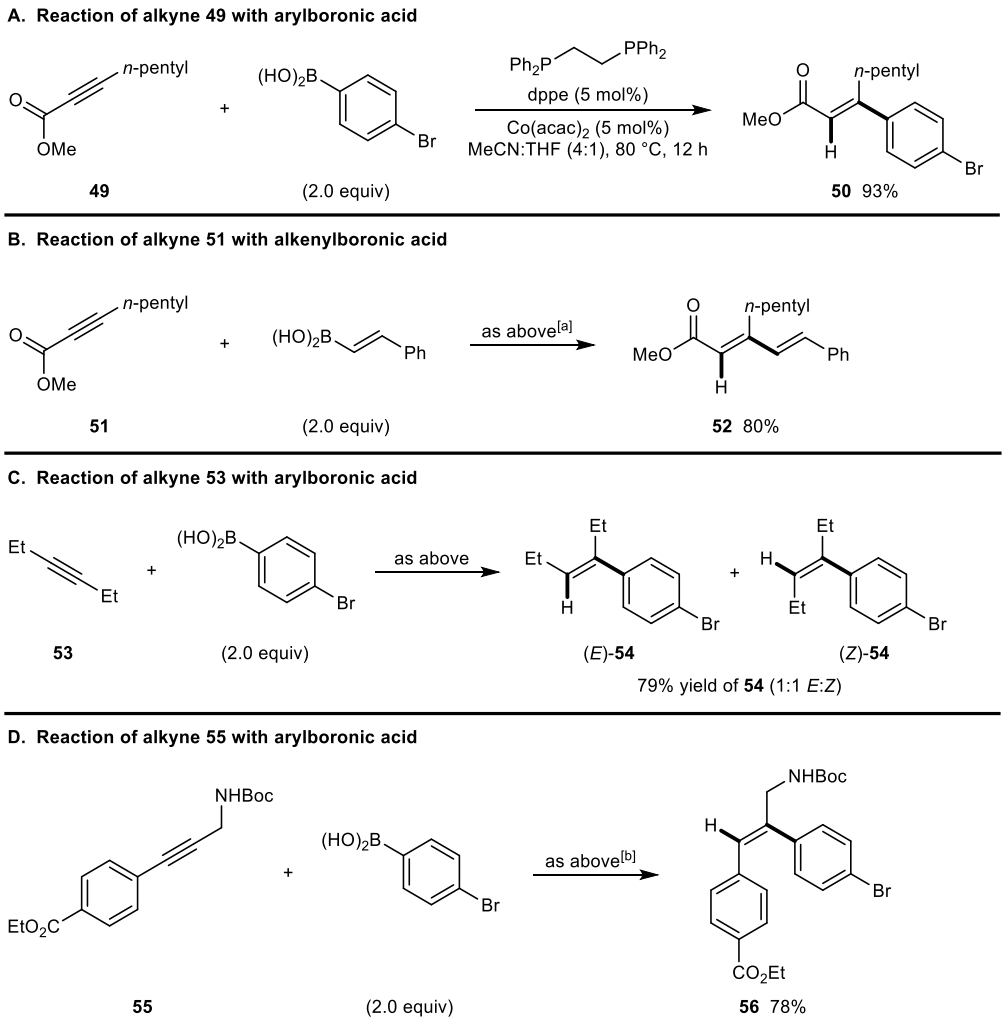


Scheme **79**: Arylmetallative cyclisation reaction of **42** using ligand **L21**. Reaction was carried out using 0.05 mmol of **42** in TFE (0.5 mL). Yield is of isolated product obtained after purification by preparative TLC.

2.4 Cobalt-Catalysed *anti*-Carbometallative Cyclisation

Employing an alternative metal to nickel in *anti*-carbometallative cyclisation reactions could lead to new reactivities. Further, changing the metal could be the key to overcoming some of the limitations that are known for nickel-catalysed *anti*-carbometallative cyclisation reactions. Such reactions are generally limited to the use of (hetero)arylboronic acid and the use of (hetero)aryl- or alkenyl-substituted alkynes.

In 2008 cobalt was reported to catalyse the hydroarylation reaction of alkynes with boronic acids (Scheme 80).[123] The reaction of alkyne **49** with 4-bromophenylboronic acid (2.0 equiv), $Co(acac)_2$ (5 mol%) and dppe (5 mol%) in MeCN:THF (4:1) at 80 °C gave hydroarylation product **50** in 93% yield (Scheme 80A). Interestingly, (*E*)-styrylboronic acids could also be applied in the reaction giving diene product **52** in 80% yield (Scheme 80B). The use of 3-hexyne in the reaction led to a 1:1 mixture of stereoisomeric alkyne hydroarylation products (*E*)-**54** and (*Z*)-**54** in 79% yield (Scheme 80C). Lastly, the reaction of aryl-substituted propargyl carbamate **55** with 4-bromophenylboronic acid led to the *E*/*Z* isomerised hydroarylation product **56**, exclusively, in 78% yield (Scheme 80D).

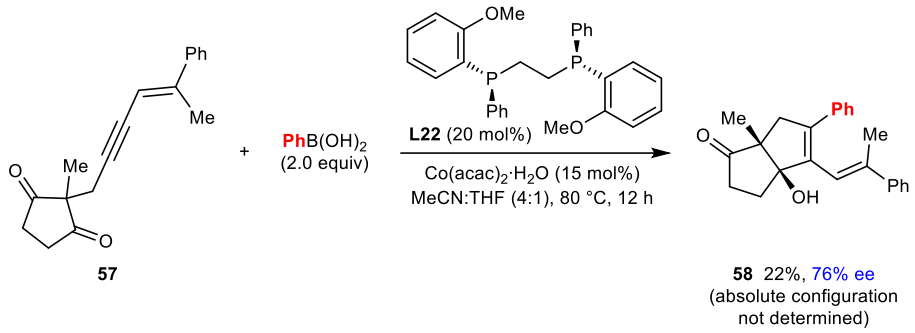


Scheme **80**: Cobalt-catalysed hydroarylation reactions.[123] [a] Reaction carried out in MeCN:THF (3:1). [b] 24 h reaction time.

With the ability of cobalt to catalyse hydroarylation reactions of alkynes with boronic acids as well as the ability to undergo alkenylcobalt isomerisation, it is conceivable that cobalt could be successful in catalysing the *anti*-carbometallative cyclisation reaction of an alkyne-tethered electrophile. Further, cobalt could be used in these reactions to address some of the limitations that are known for nickel-catalysed *anti*-carbometallative cyclisation reactions such as the limited success observed when using alkenylboronic acids.

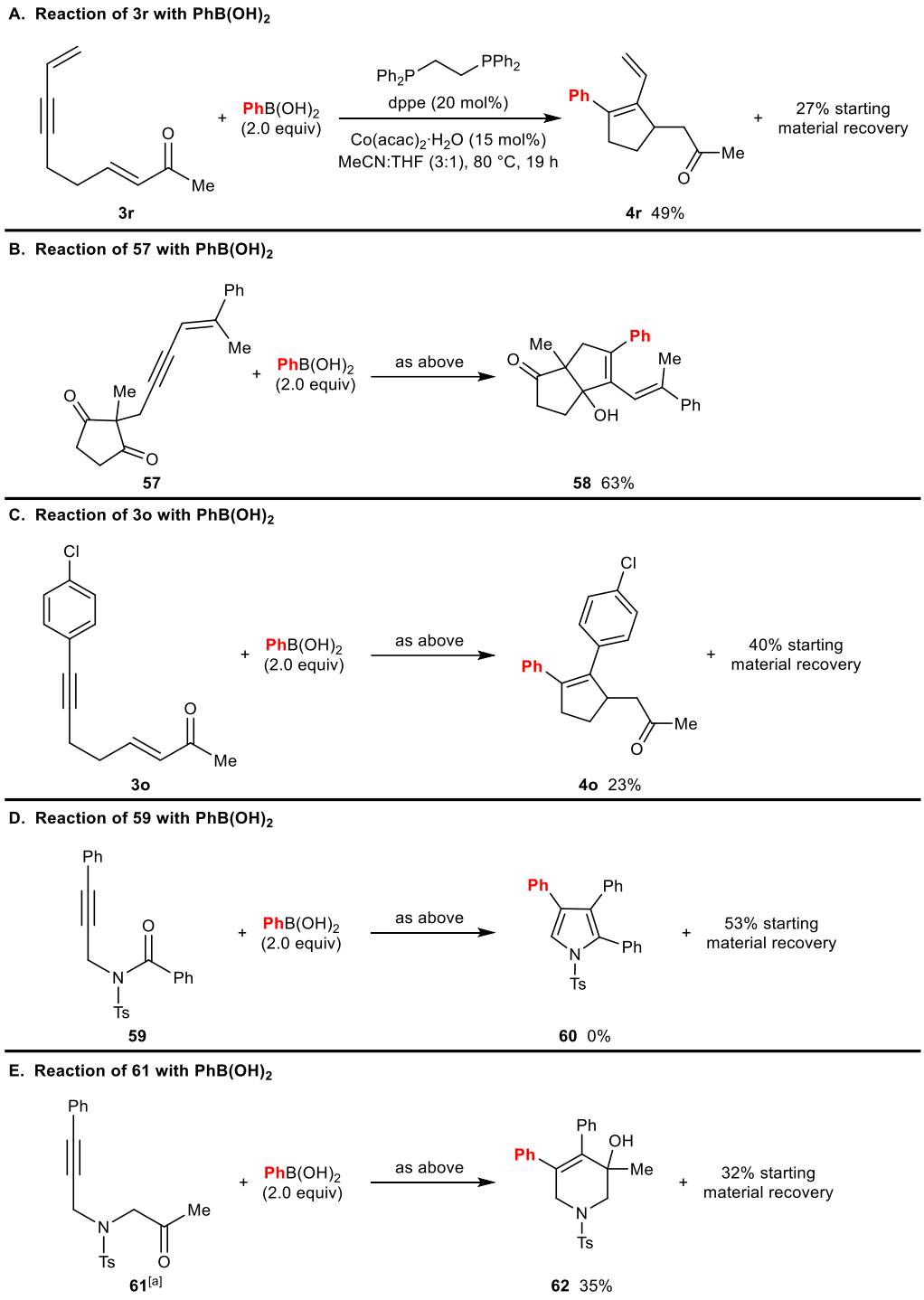
2.4.1 Exploring Cobalt as a Catalyst for *anti*-Carbometallative Cyclisation

Previous work within the Lam group demonstrated a proof of concept reaction by subjecting alkyne tethered cyclic diketone **57** to phenylboronic acid (2.0 equiv) in the presence of $Co(acac)_2 \cdot H_2O$ (15 mol%) and (S,S)-DIPAMP **L22** (20 mol%) in MeCN:THF (4:1) at 80 °C (Scheme 81). The desired product **58** was isolated in 22% yield and 76% ee indicating that enantioselectivity is achievable for cobalt-catalysed *anti*-carbometallative cyclisation reactions.



Scheme **81**: Cobalt-catalysed *anti*-carbometallative cyclisation reaction. Reaction performed by a previous member of the Lam group.

Given the success of the described reaction, an initial investigation of cobalt-catalysed *anti*-carbometallative cyclisation reactions was carried out using substrates that have previously been used in corresponding nickel-catalysed reactions (Scheme 82).

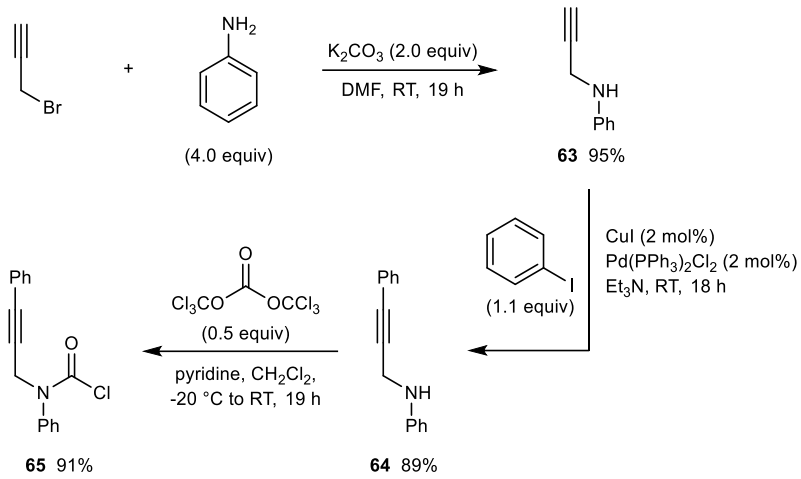


Scheme **82**: Cobalt-catalysed *anti*-carbometallative cyclisation reactions. Reactions were carried out using 0.10 mmol of **3r**, **57**, **3o**, **59** or **61** in MeCN (0.3 mL) and THF (0.1 mL). Yields were determined by ^{1}H NMR spectroscopic analysis using 1,3,5-trimethoxybenzene as an internal standard. Synthesis of substrate **57** was performed by a previous member of the Lam group and synthesis of substrate **3o** was performed by Dr. R. E. Ruscoe. Synthesis of substrate **59** was performed by the author during her masters project. [a] See Section 3.7 for the synthesis of **61**.

Subjecting enyne-tethered electron-deficient alkene **3r** to phenylboronic acid (2.0 equiv), $Co(acac)_2 \cdot H_2O$ (15 mol%) and dppe (20 mol%) in MeCN:THF (3:1) at 80 °C provided the desired product **4r** in 49% yield and 27% unreacted starting material (Scheme 82A). Less successful was the reaction of aryl-alkyne-tethered electron-deficient alkene **3o** under the same reaction conditions leading to the desired product **4o** in 23% yield and the remainder being unreacted starting material (Scheme 82C). The reaction of enyne-tethered cyclic diketone **57** provided the desired product **58** in 63% yield (Scheme 82B). Next, *N*-tosyl alkynamide **59** was exposed to the reaction conditions; however, the desired pyrrole product **60** was not observed and only starting material remained (Scheme 82D). Lastly, alkyne-tethered ketone **61** provided the desired *anti*-carbometallative cyclisation product **62** in 35% yield along with 32% unreacted starting material under the cobalt-catalysed reaction conditions (Scheme 82E). Overall, substrates containing an alkenyl-substituted alkyne are more successful in the reaction than substrates containing an aryl-substituted alkyne. Pleasingly, cobalt was found to be suitable for catalysing known *anti*-carbometallative cyclisation reactions.

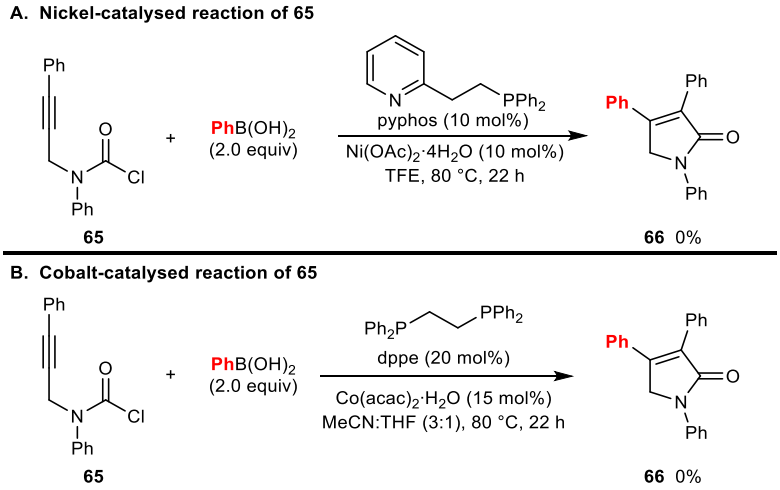
2.4.2 Investigating Alternative Substrates

With cobalt catalysed *anti*-carbometallative cyclisation reactions showing promise, a search for new reactivity began. The synthesis of carbamoyl chloride **65** started with a nucleophilic substitution reaction of propargyl bromide with aniline leading to propargyl amine **63** which was subjected to Sonogashira cross-coupling giving phenyl-alkyne **64** (Scheme 83). Next, the formation of carbamoyl chloride **65** was achieved *via* an amidation reaction of **64** with triphosgene. It was thought that carbamoyl chloride **65** could participate in either nickel- or cobalt catalysed arylative cyclisation to obtain dihydropyrrolones **66**.



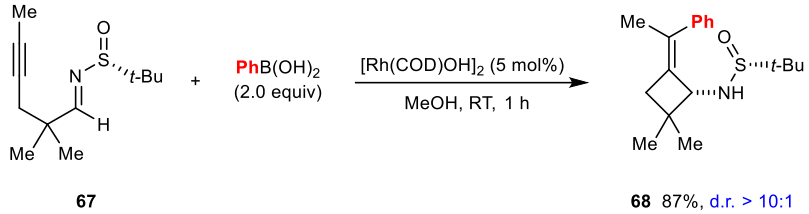
Scheme **83**: Synthesis of substrate **65**.

Alkyne-tethered carbamoyl chloride **65** was reacted with phenylboronic acid using either nickel- or cobalt-catalysed *anti*-carbometallative cyclisation conditions (Scheme 84). The nickel-catalysed reaction conditions used $Ni(OAc)_2 \cdot 4H_2O$ (10 mol%) and pyphos (10 mol%) in TFE at 80 °C while the cobalt-catalysed reaction conditions used $Co(acac)_2 \cdot H_2O$ (15 mol%) and dppe (20 mol%) in MeCN:THF (3:1) at 80 °C. The ^{1}H NMR spectrum of the unpurified reaction mixture was compared with that of known compound **66**.[155] Unfortunately, the desired product **66** was not observed for either of the reactions and following isolation of side-products, only mixtures of unidentified products were obtained.



Scheme **84**: Metal-catalysed *anti*-carbometallative cyclisation reaction of **65**. Reaction was carried out using 0.05 mmol of **65** in TFE (0.5 mL) (A). Reaction was carried out using 0.10 mmol of **65** in MeCN (0.3 mL) and THF (0.1 mL) (B).

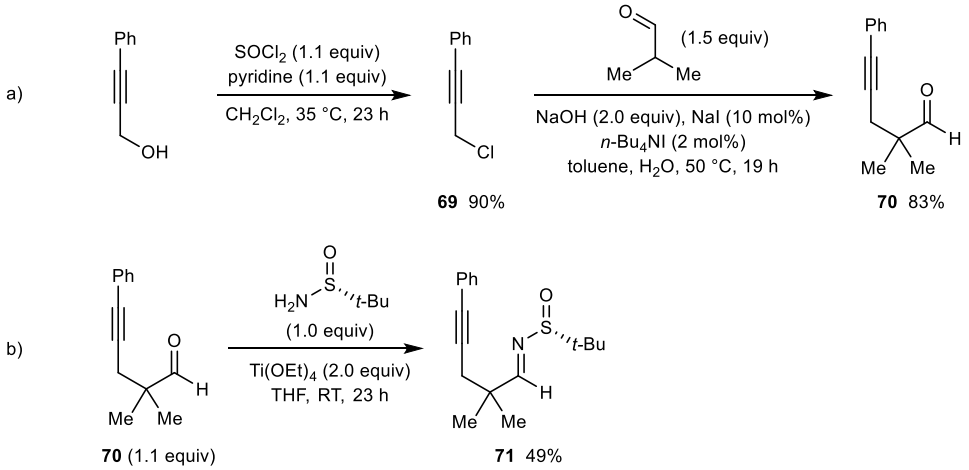
In 2015, the rhodium-catalysed addition-cyclisation reaction of alkyne-tethered imines was reported (Scheme 85).[50] Exposing sulfinimine **67** to phenylboronic acid and $[Rh(COD)OH]_2$ in MeOH at room temperature led to product **68** in 87% yield and >10:1 d.r. It was thought that a substrate similar to **67** could undergo nickel- or cobalt-catalysed *anti*-carbometallative cyclisation reaction; however, based on previous results, changing the methyl-alkyne to a phenyl-alkyne.



67 **68** 87%, d.r. > 10:1

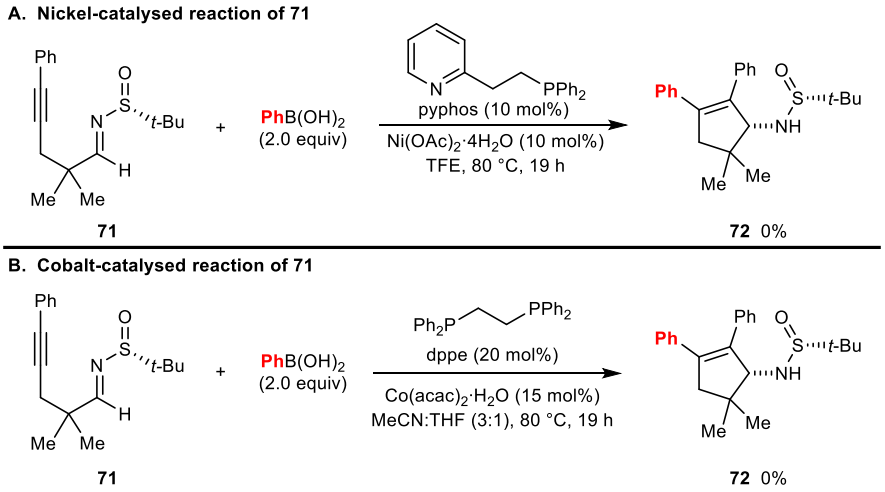
Scheme **85**: Rhodium-catalysed carbometallative cyclisation reaction of **67**.[50]

Thus, sulfinimine **71** was synthesised (Scheme 86). 3-Phenyl-2-propyn-1-ol was converted into the corresponding alkyl chloride **69** using thionyl chloride and pyridine. A nucleophilic substitution reaction of alkyl chloride **69** with isobutyraldehyde provided aldehyde **70** which was converted into sulfinimine **71** *via* imine formation with chiral *t*-butylsulfinamide as the limiting reagent.



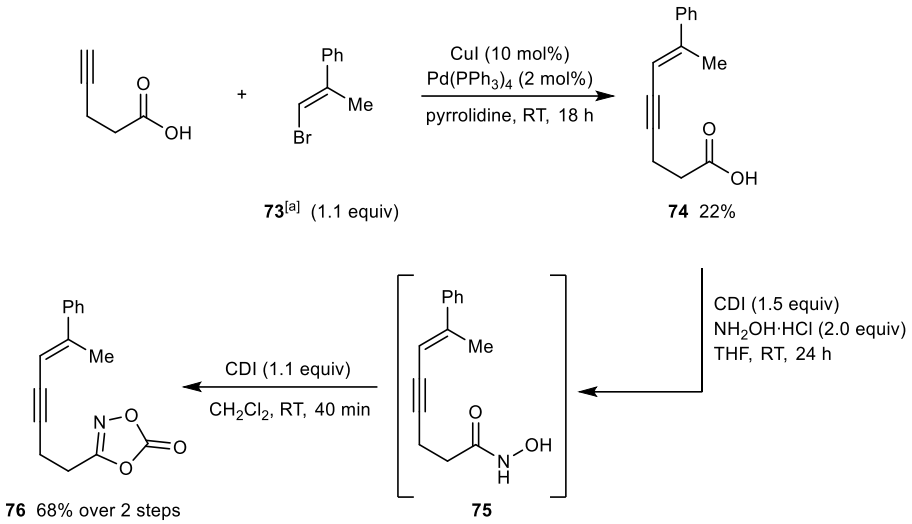
Scheme **86**: Synthesis of substrate **71**.

Alkyne-tethered sulfinimine **71** was reacted with phenylboronic acid and either nickel- or cobalt-catalysed *anti*-carbometallative cyclisation conditions (Scheme 87). Starting material recovery was observed by ^{1}H NMR spectroscopy in both metal-catalysed reactions. Analysis of the nickel-catalysed reaction indicated the presence of trace products; however, other than starting material, none of these materials were present in sufficient quantities for isolation.



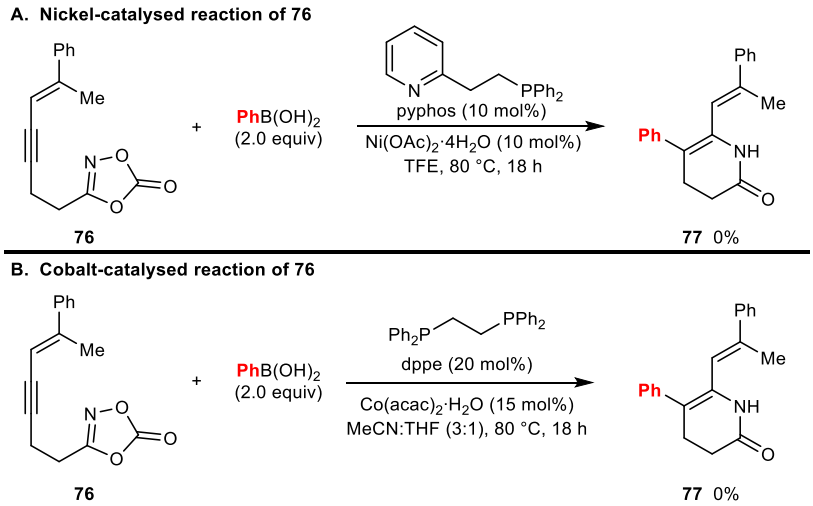
Scheme **87**: Metal-catalysed *anti*-carbometallative cyclisation reaction of **71**. Reaction was carried out using 0.05 mmol of **71** in TFE (0.5 mL) (A). Reaction was carried out using 0.10 mmol of **71** in MeCN (0.3 mL) and THF (0.1 mL) (B).

As mentioned in the introduction, alkyne-tethered dioxazolones can undergo intramolecular hydroamidation under nickel-catalysed reaction conditions (see Scheme 6B).[99] It was thought that similar substrates could participate in cobalt- or nickel-catalysed *anti*-carbometallative cyclisation reactions. Alkyne-tethered dioxazolone **76** containing an alkenyl-substituted alkyne was synthesised (Scheme 88). A Sonogashira cross-coupling of 4-pentynoic acid and alkenyl bromide **73** provided carboxylic acid **74** which was transformed into the hydroxamic acid **75**. After a simple workup **75** was used directly in the following reaction providing the dioxazolone **76**.



Scheme **88**: Synthesis of substrate **76**. [a] See Section 3.7 for the synthesis of **73**.

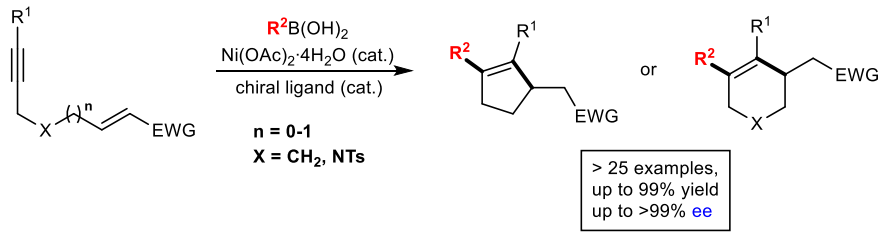
Alkyne-tethered dioxazolone **76** was reacted with phenylboronic acid under either nickel- or cobalt-catalysed *anti*-carbometallative cyclisation conditions (Scheme 89). Analysis of the metal-catalysed reactions by ^{1}H NMR spectroscopy indicated the consumption of starting material; however, isolation of various fractions revealed only unidentified products and no sign of the desired product.



Scheme **89**: Metal-catalysed *anti*-carbometallative cyclisation reaction of **76**. Reactions were carried out using 0.05 mmol of **76** in TFE (0.5 mL) (A) or MeCN (0.15 mL) and THF (0.05 mL) (B).

2.5 Conclusion and Future Work

In conclusion, an enantioselective nickel-catalysed arylative cyclisation reaction of alkyne-tethered electron-deficient alkenes proceeding *via* alkenylnickel isomerisation was successfully developed (Scheme 90). Variation of the electron-deficient alkene was successful with acyclic enones, nitroalkenes and α,β-unsaturated esters and nitriles. As well as arylboronic acids, alkenylboronic acids also showed encouraging results. The broad scope of enantioenriched cyclopentene products, that are otherwise hard to synthesise, were obtained in good yields and excellent enantioselectivities, often >99% ee. Interesting results were observed when comparing arylative cyclisation onto (*E*)- vs (*Z*)-alkenes. Further, products resulting from β-hydride elimination and reductive cyclisation were isolated.



Scheme **90**: Nickel-catalysed *anti*-carbometallative cyclisation of alkyne-tethered electron-deficient alkenes.

An investigation into extending of the tether in the substrate, from 1,5-enynes to 1,6-enynes, was conducted; however, with limited success regarding the enantioselectivity of this reaction. Finally, an investigation using cobalt as the catalyst for the *anti*-carbometallative cyclisation reaction of alkyne-tethered electrophiles was carried out. Preliminary results showed promising reactivity; however, cobalt-catalysed arylative cyclisation to obtain novel carbo- and heterocyclic products was not identified.

As previously mentioned, alkyl substituents on the alkyne are either reported to be detrimental in *anti*-carbometallative cyclisation reactions or lead to very modest yields. In this body of work, trifluoromethyl-substituted alkynes were reported to undergo alkyne hydroarylation suggesting that the substrate is somewhat compatible

with these conditions; however, protodenickelation occurs preferentially to cyclisation onto the tethered electrophile. An investigation of the *anti*-carbometallative cyclisation reaction of substrates containing an alkyl substituent on the alkyne with varying electron-withdrawing capability would be of interest (Figure 3). In this regard, a substituent that is less electron-withdrawing than the trifluoromethyl group could be achieved by reducing the number of fluorine substituents in the substrate (**78** and **79**) or by substituting the fluorine substituents with less electronegative halogens, such as the trichloride substrate **80**.

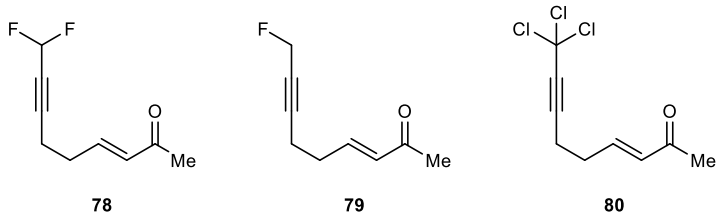


Figure **3**: Investigation of the importance of the electronics of the alkyne by variation of the alkyne substituent.

In this body of work, it was found that the nickel-catalysed *anti*-carbometallative cyclisation reaction of 1,6-enynes worked well when using the racemic P,N-ligand, pyphos; however, when using chiral ligands the reactivity was shut down. There are a few conceivable ways in which improvement to the reaction of 1,6-enynes could be achieved.

Firstly, it was found that Cs_2CO_3 had a positive effect on the yield of the reaction of **42** when using chiral P,N-ligand **L21** (see Table 48); however, the enantioselectivity was 68% ee. Further optimisation of the reaction of 1,6-enynes by repeating chiral screening reactions; however, with the addition of Cs_2CO_3 could lead to satisfactory reaction outcomes.

Secondly, the success of pyphos in the reaction compared with chiral ligands suggests that a pyphos-resembling chiral ligands could be the key to accessing an extended scope with good yields and enantioselectivities. Examples of chiral ligands containing characteristics of pyphos are seen in Figure 4. The first example is chiral P,N-ligand **L23** which was synthesised by Knochel and co-workers for asymmetric iridium-catalysed reactions.[156] The second example is chiral P,N-ligand **L24** which

was synthesised by Terada and co-workers as a derivatisation of products obtained in the enantioselective hydrophosphinylation of 1,1-vinyl quinoline *N*-oxides with diarylphosphine oxides.[157] The third example is chiral P,N-ligand **L25** which was synthesised by Andersson and co-workers as an iridium catalyst for the asymmetric hydrogenation of olefins.[158] These ligands contain either a pyridyl entity, which is also present in pyphos (**L23** and **L25**), or a quinolyl entity (**L24**). All three examples also contain a chiral framework and the diphenylphosphanyl group, another shared feature with pyphos. Any of these chiral P,N-ligands may possess the advantageous properties of pyphos with regard to the yield of the reaction and at the same time promote high levels of enantioselectivity.

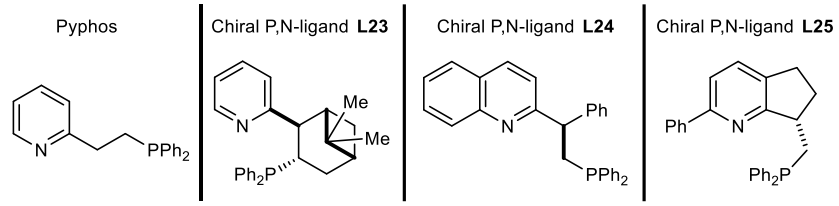
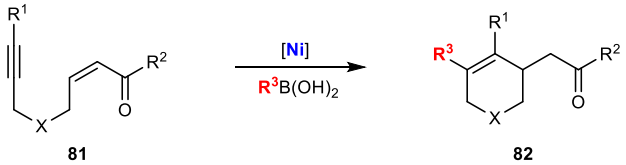


Figure **4**: Chiral P,N-ligands.

Thirdly, as it was observed during this work for 1,5-enynes, utilising the stereoisomeric substrate in the nickel-catalysed *anti*-carbometallative cyclisation reaction leads to a significant increase in yields (see Schemes 64 and 69). This method could be applied to 1,6-enynes in an effort to obtain the desired cyclohexene products in good yields (Scheme 91).



Scheme **91**: Using stereoisomeric 1,6-enyne.

Lastly, to probe the Thorpe-Ingold effect, substrates **83**, **84** and **85** containing a *gem*-dimethyl, cyclohexyl or *gem*-diester, respectively, in the tether between the alkyne and the electron-deficient alkene could be investigated (Figure 5).

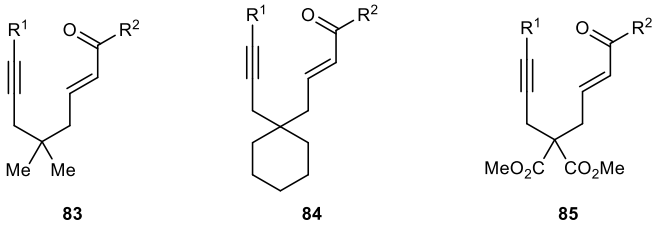
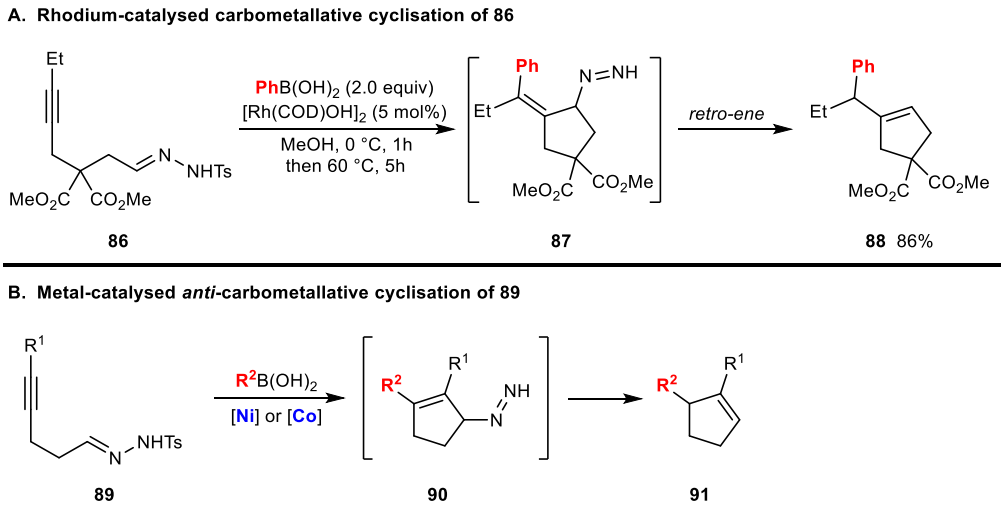


Figure **5**: Thorpe-Ingold effect.

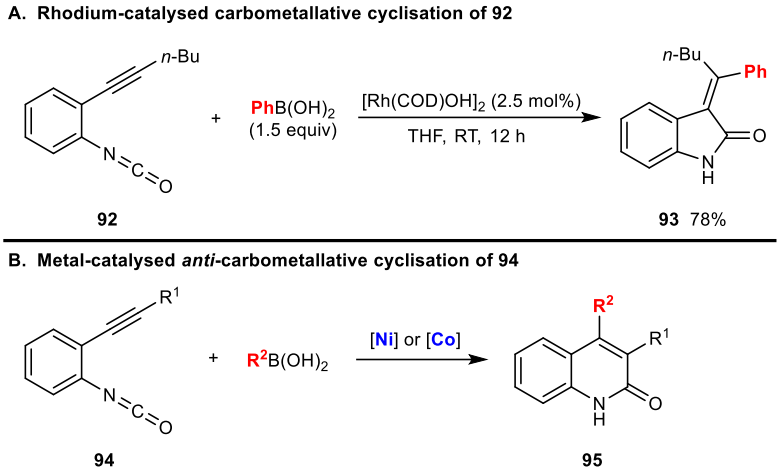
Further investigation into cobalt-catalysed *anti*-carbometallative cyclisation reactions using substrates seen in Section 2.4.2 could be carried out, for example by changing the cobalt source, ligand or using additives such as Cs_2CO_3. Other substrate classes, such as the ones described below, could be investigated for the synthesis of alternative carbo- and heterocycles.

In 2018 a rhodium-catalysed carbometallative cyclisation of alkyne-tethered hydrazones **86** with arylboronic acids was reported (Scheme 92A).[52] The cyclisation step is followed by a 1,5-sigmatropic rearrangement which eliminates dinitrogen to give product **88**. It is possible that this class of substrate could engage with nickel- or cobalt-catalysed reaction conditions leading to the *anti*-carbometallative cyclisation-rearrangement product (Scheme 92B).



Scheme **92**: Metal-catalysed addition-cyclisation reaction of alkyne-tethered imine.

Murakami and co-workers reported the rhodium-catalysed carbometallative cyclisation reaction of 2-alkynylaryl isocyanates **92** with arylboronic acids (Scheme 93A).[41] Potentially, nickel or cobalt could be used to catalyse the *anti*-carbometallative variant of this reaction to obtain 2-quinolinone products **95** (Scheme 93B).



Scheme **93**: Metal-catalysed addition-cyclisation reaction of alkyne-tethered isocyanate.

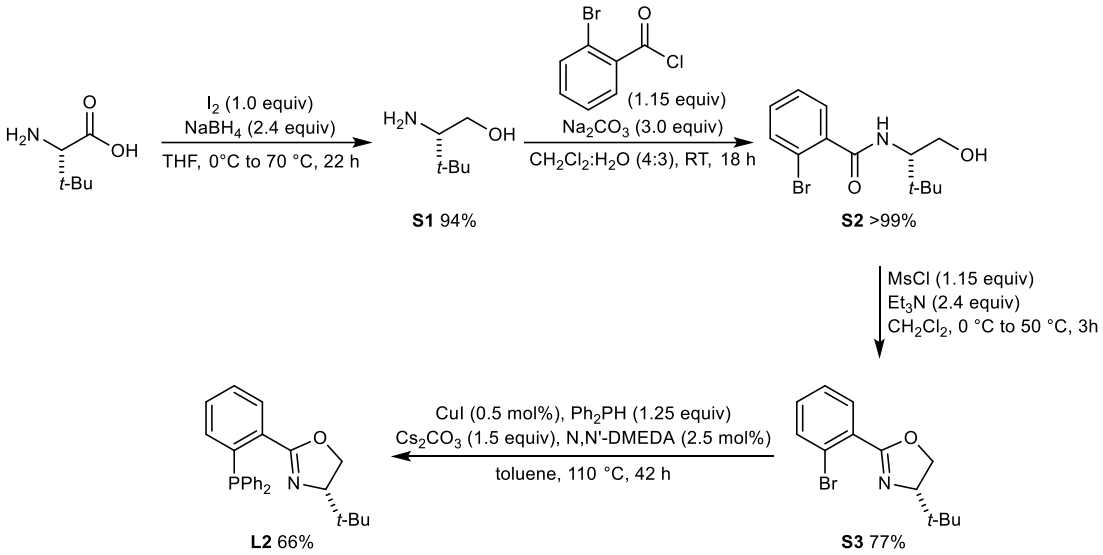
3.0 Experimental

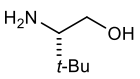
3.1 General Information

All air-sensitive reactions were carried out under an inert atmosphere (argon) 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). 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). Automated column chromatography was carried out on an Interchim PuriFlash system using normal phase column (silica STD, 50μm). 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. 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. X-ray diffraction data were collected at 120 K on an Agilent SuperNova diffractometer using CuKα radiation. Solvents (THF, toluene, MeCN, DMF and Et_3N) were freshly degassed using a stream of argon (20 min). 2-[2-(Diphenylphosphino)ethyl]pyridine (pyphos) or racemic Ph-PHOX[77] were used as achiral ligands to prepare authentic racemic products for obtaining chiral HPLC assays.

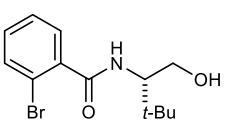
3.2 Preparation of Ligands

(*S*)-4-(*t*-Butyl)-2-(2-(diphenylphosphaneyl)phenyl)-4,5-dihydrooxazole (L2).



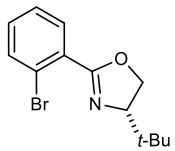


(*S*)-*t*-Leucinol (S1). The title compound was prepared according to a previously reported procedure.[159] To a solution of (*L*)-*t*-leucine (5.00 g, 38.1 mmol) in THF (100 mL) under an argon atmosphere at 0 °C was added $NaBH_4$ (3.46 g, 91.5 mmol) followed by slow addition of I_2 (9.67 g, 38.1 mmol) over 30 min. The reaction was heated to 70 °C and stirred for 22 h. The solution was cooled to room temperature, methanol (100 mL) was added slowly and the solution was stirred for 30 min. Additional methanol (100 mL) was added and the volatiles were removed *in vacuo*. The resulting slurry was diluted with aqueous KOH solution (20% w/w, 75 mL) and stirred for 5 h. The aqueous layer was extracted with CH_2Cl_2 (6 × 60 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give alcohol **S1** (4.34 g, 94%) as a colourless oil. The analytical data were consistent with those reported previously.[159] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (1H, dd, *J* = 10.3, 3.8 Hz, C**H**$_2$), 3.20 (1H, app t, *J* = 10.3 Hz, C**H**$_2$), 2.50 (1H, dd, *J* = 10.3, 3.8 Hz, C**H**), 2.10 (3H, app s, N**H**$_2$ and O**H**), 0.89 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 62.4 (CH_2), 61.9 (CH), 33.4 (C), 26.4 (3 × CH_3).



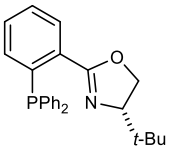
(*S*)-2-Bromo-*N*-(1-hydroxy-3,3-dimethylbutan-2-yl)benzamide (S2). The title compound was prepared according to a previously reported procedure.[159] To a vigorously stirred solution of (*S*)-*t*-leucinol **S1** (4.34 g, 37.0 mmol) in CH_2Cl_2 (120 mL) was added a

solution of Na_2CO_3 (11.8 g, 111 mmol) in H_2O (90 mL). 2-Bromobenzoyl chloride (5.6 mL, 42.6 mmol) was added dropwise over 15 min under an argon atmosphere and the resulting mixture was stirred at room temperature for 18 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic layers were stirred with 1 M KOH solution in MeOH (19 mL) for 30 min. The resulting solution was neutralised to pH ≈ 7 using 1 M aqueous HCl followed by the addition of H_2O (25 mL). The aqueous layer was extracted with CH_2Cl_2 (4 × 35 mL) then the combined organic layers were washed with brine (75 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Recrystallisation from acetone and petroleum ether gave amide **S2** (11.1 g, >99%) as a colourless solid. The analytical data were consistent with those reported previously.[159] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.53 (2H, m, Ar**H**), 7.37-7.32 (1H, m, Ar**H**), 7.29-7.23 (1H, m, Ar**H**), 6.23 (1H, d, *J* = 9.4 Hz, N**H**), 4.06 (1H, ddd, *J* = 9.4, 7.5, 3.5 Hz, C**H**), 3.94 (1H, dd, *J* = 11.4, 3.5 Hz, C**H**$_2$), 3.67 (1H, dd, *J* = 11.4, 7.5 Hz, C**H**$_2$), 2.90 (1H, s, O**H**), 1.03 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8 (C), 138.1 (C), 133.5 (CH), 131.4 (CH), 129.9 (CH), 127.8 (CH), 119.2 (C), 63.1 (CH_2), 60.4 (CH), 33.9 (C), 27.2 (3 × CH_3).



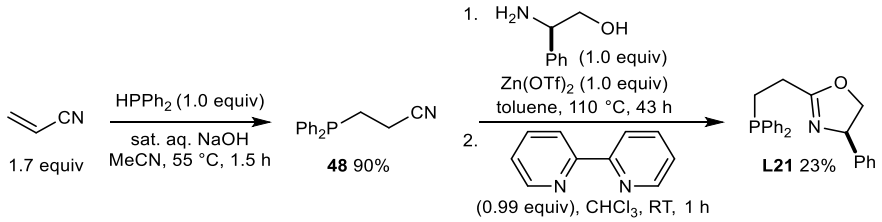
(*S*)-2-(2-Bromophenyl)-4-(*t*-butyl)-4,5-dihydrooxazole (S3). The title compound was prepared according to a previously reported procedure.[159] To a solution of (*S*)-2-bromo-*N*-(1-hydroxy-3,3-dimethylbutan-2-yl)benzamide **S2** (4.80 g, 16.0 mmol) and Et_3N (5.4 mL, 38.4 mmol) in CH_2Cl_2 (78 mL) under an argon atmosphere at 0 °C was added MsCl (1.4 mL, 18.4 mmol) dropwise over 3 min and the reaction was stirred at 50 °C for 3 h. The reaction was cooled to room temperature and saturated aqueous $NaHCO_3$ (30 mL) was added and the reaction stirred vigorously for 5 min. The layers were separated, then the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc/pentane) to give dihydro-oxazole **S3** (3.50 g, 77%) as an off-white solid. The analytical data were consistent with those reported previously.[159] R_f = 0.35 (20% EtOAc/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.60 (2H, m, Ar**H**), 7.36-7.30 (1H, m, Ar**H**), 7.29-7.24 (1H, m, Ar**H**), 4.38 (1H, dd, *J* = 10.2, 8.3 Hz, C**H**$_2$), 4.26 (1H, app t, *J* = 8.3 Hz, C**H**$_2$), 4.10 (1H, dd, *J* = 10.2, 8.3 Hz, C**H**), 1.00 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (101 MHz,

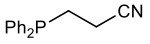
$CDCl_3$) δ 162.9 (C), 133.8 (CH), 131.6 (CH), 131.4 (CH), 130.4 (C), 127.2 (CH), 122.0 (C), 76.8 (CH), 69.1 (CH_2), 34.1 (C), 26.1 (3 × CH_3).



(*S*)-4-(*t*-Butyl)-2-[2-(diphenylphosphaneyl)phenyl]-4,5-dihydrooxazole (L2). The title compound was prepared according to a previously reported procedure.[159] A solution of CuI (6.7 mg, 0.04 mmol), Ph_2PH (1.5 mL, 8.75 mmol) and *N*,*N*'-DMEDA (20 μL, 0.18 mmol) in toluene (7 mL) under an argon atmosphere at room temperature was stirred for 20 min. To the solution was added under an argon atmosphere the dihydro-oxazole **S3** (1.98 g, 7.00 mmol), Cs_2CO_3 (3.42 g, 10.5 mmol) and toluene (7 mL) and the reaction was stirred at 110 °C for 42 h. The reaction was filtered through a pad of celite (CH_2Cl_2) and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (4% Et_2O/pentane until excess $HPPh_2$ was eluted, then 10% Et_2O/CH_2Cl_2). The pale yellow oil was layered with MeCN (5 mL) to facilitate crystallisation and the volatiles were removed *in vacuo* to give (*S*)-*t*-BuPHOX **L2** (1.79 g, 66%) as a colourless solid. The analytical data were consistent with those reported previously.[159] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96-7.91 (1H, m, Ar**H**), 7.39-7.33 (1H, m, Ar**H**), 7.33-7.26 (9H, m, Ar**H**), 7.26-7.21 (2H, m, Ar**H**), 6.90-6.84 (1H, m, Ar**H**), 4.08 (1H, dd, *J* = 10.2, 8.3 Hz, C**H**$_2$), 4.01 (1H, app t, *J* = 8.3 Hz, C**H**$_2$), 3.88 (1H, dd, *J* = 10.2, 8.3 Hz, C**H**), 0.73 (9H, s, C(C**H**$_3$)$_3$); HRMS (ESI) Exact mass calculated for $[C_{25}H_{27}NOP]^+$ $[M+H]^+$: 388.1825, found: 388.1824.

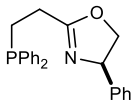
(*R*)-2-[2-(Diphenylphosphaneyl)ethyl]-4-phenyl-4,5-dihydrooxazole (L21).





3-(Diphenylphosphaneyl)propanenitrile (48) The title compound was prepared according to a previously reported procedure.[160] To a stirred solution of diphenylphosphine (2.3 mL, 13.4 mmol) in saturated aqueous NaOH solution (50%, 0.1 mL) and MeCN (5 mL) was added acrylonitrile (1.5 mL, 22.6 mmol) over 5 min.

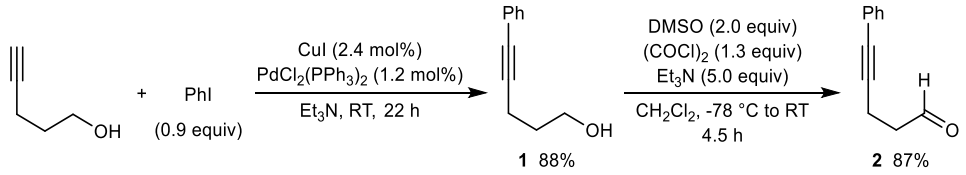
The solution was heated to 55 °C and the reaction was stirred for 1.5 h. The reaction was washed with brine (3 × 7 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was recrystallised from pentane to give diphenylphosphine-nitrile **48** (2.88 g, 90%) as an off-white solid. The analytical data were consistent with those reported previously.[161] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.36 (10H, m, Ar**H**), 2.41-2.35 (4H, m, C**H**$_2$C**H**$_2$); HRMS (ESI) Exact mass calculated for $[C_{15}H_{14}NNaP]^+$ $[M+Na]^+$: 262.0756, found: 262.0755.

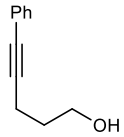


(*R*)-2-[2-(Diphenylphosphaneyl)ethyl]-4-phenyl-4,5-dihydrooxazole (L21). The title compound was prepared according to a previously reported procedure.[162] A solution of diphenylphosphine-nitrile **48** (150 mg, 0.63 mmol) and $Zn(OTf)_2$ (228 mg, 0.63 mmol) in dry toluene (4 mL) was stirred for 5 min. A solution of (*R*)-2-phenylglycinol (86.0 mg, 0.63 mmol) in dry toluene (2 mL) was added to the reaction followed by stirring at 110 °C for 43 h. The reaction was washed with brine (3 × 8 mL) and saturated aqueous $NaHCO_3$ (3 × 7 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (4.7 mL) under an argon atmosphere and 2,2-bipyridine (97.0 mg, 0.62 mmol) was added to the reaction which was stirred at room temperature for 1 h.[154] The reaction was filtered through a pad of silica ($CHCl_3$) and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (5 to 20% EtOAc/pet. ether) to give phosphine-oxazoline **L21** (51.8 mg, 23%) as a colourless oil. R_f = 0.51 (40% EtOAc/pet. ether); IR 3052, 3028, 2899, 1663 (C=N), 1480, 1433, 1376, 1221, 1159, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.41 (4H, m, Ar**H**), 7.38-7.26 (9H, m, Ar**H**), 7.26-7.21 (2H, m, Ar**H**), 5.14 (1H, dd, *J* = 10.2, 8.3 Hz, C**H**), 4.56 (1H, dd, *J* = 10.2, 8.3 Hz, C**H**$_a$H$_b$), 4.05 (1H, app t, *J* = 8.3 Hz, CH$_a$**H**$_b$), 2.59-2.40 (4H, m, C**H**$_2$C**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7 (d, $^3J_{C\text{-}P}$ = 14.5 Hz, C), 142.5 (C), 138.0 (d, $^1J_{C\text{-}P}$ = 12.6 Hz, 2 × C), 133.0 (d, $^2J_{C\text{-}P}$ = 5.8 Hz, 2 × CH), 132.8 (d, $^2J_{C\text{-}P}$ = 5.8 Hz, 2 × CH), 128.92 (CH), 128.90 (CH), 128.8 (2 × CH), 128.7 (2 × CH), 128.6 (2 × CH), 127.7 (CH), 126.8 (2 × CH), 74.8 (CH_2), 69.8 (CH), 24.9 (d, $^1J_{C\text{-}P}$ = 20.1 Hz, CH_2), 24.5 (d, $^2J_{C\text{-}P}$ = 12.5 Hz, CH_2); ^{31}P NMR (162 MHz, $CDCl_3$) δ –15.4 (s); HRMS (ESI) Exact mass calculated for $[C_{23}H_{22}NNaOP]^+$ $[M+Na]^+$: 382.1331, found: 382.1333.

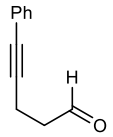
3.3 Preparation of Key Intermediates

5-Phenylpent-4-ynal (2)





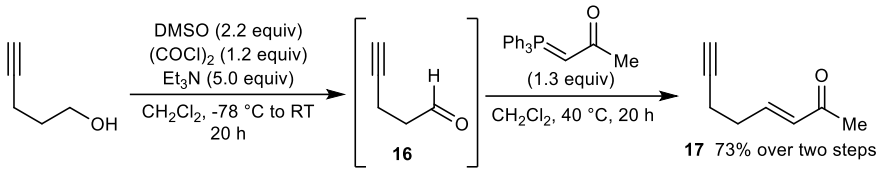
5-Phenylpent-4-yn-1-ol (1). The title compound was prepared according to a previously reported procedure.[163] To a solution of iodobenzene (5.4 mL, 48.0 mmol) in Et_3N (80 mL) under an argon atmosphere at room temperature was added $PdCl_2(PPh_3)_2$ (337 mg, 0.480 mmol) and CuI (183 mg, 0.960 mmol) and the mixture was stirred for 5 min. To the solution was added 4-pentyn-1-ol (3.7 mL, 40.0 mmol) slowly and the reaction was stirred at room temperature for 22 h. The volatiles were removed *in vacuo* and saturated aqueous $NaHCO_3$ (150 mL) was added to the resulting slurry. The mixture was extracted with EtOAc (3 × 100 mL) and the combined organic layers were washed with brine (150 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (70% Et_2O/pet. ether) to give the alkyne **1** (5.61 g, 88%) as a brown oil. The analytical data were consistent with those reported previously.[163] R_f = 0.23 (70% Et_2O/pentane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.33 (2H, m, Ar**H**), 7.31-7.21 (3H, m, Ar**H**), 3.82 (2H, t, *J* = 5.9 Hz, C**H**$_2$), 2.54 (2H, t, *J* = 6.9 Hz, C**H**$_2$), 1.93-1.81 (2H, m, C**H**$_2$), 1.63 (1H, s, O**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.6 (2 × CH), 128.3 (2 × CH), 127.8 (CH), 123.8 (C), 89.4 (C), 81.3 (C), 62.0 (CH_2), 31.5 (CH_2), 16.1 (CH_2).



5-Phenylpent-4-ynal (2). The title compound was prepared using a modification of a previously reported procedure.[164] To a solution of $(COCl)_2$ (1.4 mL, 16.2 mmol) in CH_2Cl_2 (40 mL) at −78 °C was added DMSO (1.8 mL, 25.0 mmol) dropwise over 4 min and the solution was stirred at this temperature for 30 min. A solution of 5-phenylpent-4-yn-1-ol **1** (2.00 g, 12.5 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 5 min and the mixture was stirred at −78 °C for 2 h. Et_3N (8.7 mL, 62.4 mmol) was added and the mixture was warmed to room temperature and stirred for 2 h. The reaction was diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with 2 M aqueous HCl (30 mL), saturated aqueous $NaHCO_3$ (30 mL) and brine (30 mL), dried ($MgSO_4$), filtered,

and concentrated *in vacuo*. The residue was purified by column chromatography (30% EtOAc/pet. ether) to give the aldehyde **2** (1.72 g, 87%) as an orange oil. The analytical data were consistent with those reported previously.[165] R_f = 0.49 (40% EtOAc/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.85 (1H, s, CO**H**), 7.42-7.34 (2H, m, Ar**H**), 7.31-7.26 (3H, m Ar**H**), 2.84-2.65 (4H, m, 2 × C**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.6 (C), 131.7 (2 × CH), 128.4 (2 × CH), 128.0 (CH), 123.5 (C), 87.9 (C), 81.6 (C), 42.9 (CH_2), 12.8 (CH_2).

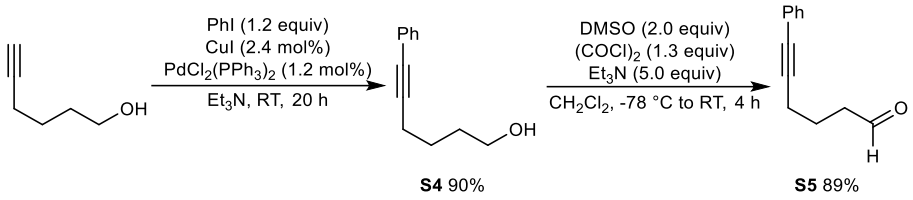
(*E*)-Oct-3-en-7-yn-2-one (17)



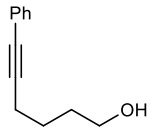
To a solution of $(COCl)_2$ (2.9 mL, 34.5 mmol) in CH_2Cl_2 (65 mL) at −78 °C was added a solution of DMSO (4.6 mL, 65.4 mmol) in CH_2Cl_2 (15 mL) dropwise over 8 min and the solution was stirred at −78 °C for 30 min. A solution of 4-pentyn-1-ol (2.50 g, 29.7 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 5 min and the mixture was stirred at −78 °C for 1 h. Et_3N (20.7 mL, 149 mmol) was added and the mixture was warmed to room temperature and stirred for 20 h. The reaction was diluted with H_2O (15 mL) and the two layers were separated. The aqueous layer was acidified with 1 M aqueous HCl and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were washed with 1% aqueous HCl solution saturated with NaCl (50 mL), 5% aqueous $NaHCO_3$ (50 mL), H_2O (75 mL) and brine (50 mL), dried ($MgSO_4$), filtered, and gently concentrated *in vacuo* until *ca.* 5 mL of intermediate **16** remained. The residue was diluted in CH_2Cl_2 (40 mL) and 1-(triphenylphosphoranylidene)-2-propanone (12.3 g, 38.6 mmol) was added and the reaction was stirred at 40 °C for 20 h. The volatiles were removed *in vacuo* and the residue was purified by column chromatography (20% EtOAc/pet. ether) to give the enone **17** (2.66 g, 73% over two steps) as an orange oil. The analytical data were consistent with those reported previously.[166] R_f = 0.43 (30% EtOAc/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (1H, dt, *J* = 16.0, 6.6 Hz, CH_2C**H**=), 6.13 (1H, dt, *J* = 16.0, 1.5 Hz, CH_2CH=C**H**), 2.50-2.41 (2H, m, C**H**$_2$), 2.41-2.33 (2H, m, C**H**$_2$), 2.26

(3H, s, C**H**$_3$), 2.01 (1H, t, *J* = 2.6 Hz, ≡C**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.5 (C), 145.4 (CH), 132.3 (CH), 82.7 (C), 69.7 (≡CH), 31.3 (CH_2), 27.1 (CH_3), 17.6 (CH_2).

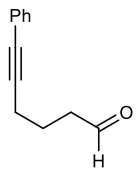
6-Phenylhex-5-ynal (S5)



S4 90% **S5** 89%



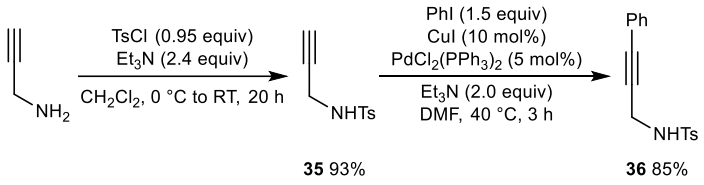
6-Phenylhex-5-yn-1-ol (S4). The title compound was prepared according to a previously reported procedure.[167] To a solution of iodobenzene (3.4 mL, 30.6 mmol) in Et_3N (60 mL) under an argon atmosphere at room temperature was added $PdCl_2(PPh_3)_2$ (215 mg, 0.306 mmol) and CuI (116 mg, 0.611 mmol) and the mixture was stirred for 5 min. To the solution was added 5-hexyn-1-ol (2.8 mL, 25.5 mmol) slowly and the reaction was stirred at room temperature for 20 h. The volatiles were removed *in vacuo* and saturated aqueous $NaHCO_3$ (150 mL) was added to the resulting slurry. The mixture was extracted with EtOAc (3 × 100 mL) and the combined organic layers were washed with brine (150 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (20 to 40% EtOAc/pet. ether) to give phenyl-alkyne **S4** (4.00 g, 90%) as a red oil. The analytical data were consistent with those reported previously.[168] R_f = 0.23 (70% Et_2O/pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.35 (2H, m, Ar**H**), 7.29-7.23 (3H, m, Ar**H**), 3.71 (2H, t, *J* = 6.1 Hz, C**H**$_2$), 2.46 (2H, t, *J* = 6.6 Hz, C**H**$_2$), 1.80-1.64 (4H, m, 2 × C**H**$_2$) 1.44 (1H, s, O**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.7 (2 × CH), 128.3 (2 × CH), 127.7 (CH), 124.0 (C), 90.0 (C), 81.1 (C), 62.6 (CH_2), 32.0 (CH_2), 25.2 (CH_2), 19.3 (CH_2).



6-Phenylhex-5-ynal (S5). The title compound was prepared according to a previously reported procedure.[164] To a solution of $(COCl)_2$ (1.3 mL, 14.9 mmol) in CH_2Cl_2 (40 mL) at –78 °C was added DMSO (1.6 mL, 23.0 mmol) dropwise over 1 min and the solution was stirred at this temperature for 30 min. A solution of 6-phenylhex-5-yn-1-ol **S4** (2.00 g, 11.5 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 3 min and the mixture was stirred at –78 °C for 2 h. Et_3N

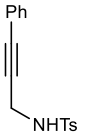
(8.0 mL, 57.4 mmol) was added and the mixture was warmed to room temperature and stirred for 1.5 h. The reaction was diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with 2M aqueous HCl (40 mL), saturated aqueous $NaHCO_3$ (40 mL) and brine (40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc/pet. ether) to give aldehyde **S5** (1.75 g, 89%) as a yellow oil. The analytical data were consistent with those reported previously.[164] R_f = 0.62 (40% EtOAc/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.85 (1H, t, *J* = 1.4 Hz, CO**H**), 7.44-7.34 (2H, m, Ar**H**), 7.32-7.27 (3H, m, Ar**H**), 2.66 (2H, td, *J* = 7.2, 1.4 Hz, C**H**$_2$), 2.50 (2H, t, *J* = 6.9 Hz, C**H**$_2$), 2.00-1.90 (2H, m, C**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.1 (C), 131.7 (2 × CH), 128.4 (2 × CH), 127.9 (CH), 123.7 (C), 88.9 (C), 81.8 (C), 42.9 (CH_2), 21.3 (CH_2), 19.0 (CH_2).

4-Methyl-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (36)



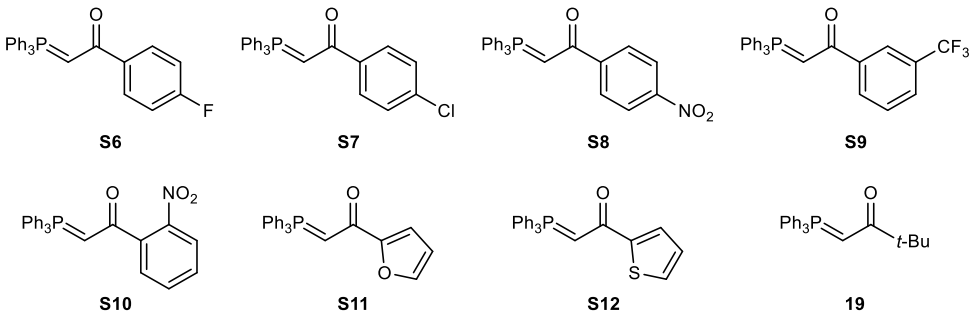
4-Methyl-N-(prop-2-yn-1-yl)benzenesulfonamide (35). The title compound was prepared according to a previously reported procedure.[169] To a solution of propargyl amine (5.00 g, 90.7 mmol) in CH_2Cl_2 (120 mL) at 0 °C under an argon atmosphere was added 4-toluenesulfonyl chloride (16.4 g, 86.2 mmol) and the mixture was stirred for 10 min. To the reaction at 0 °C was added slowly Et_3N (30.4 mL, 218 mmol) and the resulting solution was warmed to room temperature and stirred for 20 h. The reaction was diluted with Et_2O (500 mL), washed with 10% aqueous HCl solution (300 mL) and brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give *N*-tosyl-propargylamine **35** (16.8 g, 93%) as an off-white solid. The analytical data were consistent with those reported previously.[170] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.69 (2H, m, Ar**H**), 7.36-7.26 (2H, m, Ar**H**), 4.86 (1H, t, *J* = 6.1 Hz, N**H**), 3.82 (2H, dd, *J* = 6.1, 2.5 Hz, C**H**$_2$), 2.42 (3H, s, C**H**$_3$), 2.10 (1H, t, *J* = 2.5 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).



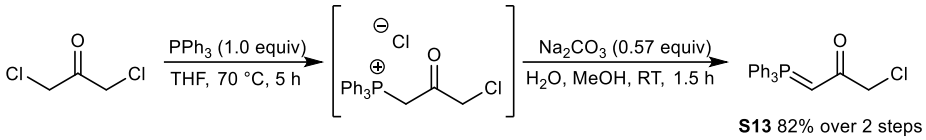
4-Methyl-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (36). The title compound was prepared according to a previously reported procedure.[171] To a stirred solution of $PdCl_2(PPh_3)_2$ (670 mg, 0.96 mmol) and CuI (364 mg, 1.91 mmol) in DMF (24 mL) under a nitrogen atmosphere was added freshly degassed Et_3N (5.3 mL, 38.2 mmol) and iodobenzene (3.2 mL, 28.7 mmol). A solution of *N*-tosyl-propargylamine **35** (4.00 g, 19.1 mmol) in DMF (16 mL) was added to the reaction and the resulting solution was stirred at 40 °C for 3 h. The reaction was quenched with 50% brine (300 mL) and the aqueous layer was extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 × 300 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (10 to 40% EtOAc/pet. ether) to give phenyl-alkyne **36** (4.62 g, 85%) as a brown solid. The analytical data were consistent with those reported previously.[171] R_f = 0.50 (3 × 30% EtOAc/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.77 (2H, m, Ar**H**), 7.34-7.20 (5H, m, Ar**H**), 7.18-7.10 (2H, m, Ar**H**), 4.61 (1H, t, *J* = 6.2 Hz, N**H**), 4.08 (2H, d, *J* = 6.2 Hz, C**H**$_2$), 2.36 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9 (C), 137.0 (C), 131.7 (2 × CH), 129.9 (2 × CH), 128.7 (CH), 128.3 (2 × CH), 127.6 (2 × CH), 122.2 (C), 84.9 (C), 83.3 (C), 34.0 (CH_2), 21.6 (CH_3).

3.4 Preparation of Triphenylphosphoranylidenes and Phosphonates



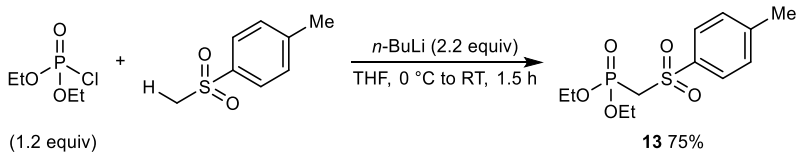
Syntheses of phosphoranes **S6** to **S12** and **19** were performed by previous members of the Lam group.

1-Chloro-3-(triphenyl-λ^5-phosphaneylidene)propan-2-one (S13).



To a solution of dichloroacetone (3.00 g, 23.6 mmol) in THF (12 mL) at room temperature under an argon atmosphere was added triphenylphosphine (6.20 g, 23.6 mmol) and the mixture was stirred at 70 °C for 5 h. The reaction was cooled to room temperature and the precipitate was collected by filtration. The phosphonium salt was dissolved in MeOH (12 mL) and the solution was heated to 65 °C followed by the addition of EtOAc (4 mL) and stirring for 18 h. The solution was cooled to room temperature and Et_2O (100 mL) was added. The phosphonium salt was collected by filtration and dried at 80 °C for 48 h. The phosphonium salt was dissolved in MeOH (6 mL) at room temperature and a solution of Na_2CO_3 (1.43 g, 13.5 mmol) in H_2O (24 mL) was added. The reaction was diluted with H_2O (20 mL) and stirred for 1.5 h. The solid was collected by filtration and dried under reduced pressure for 4 h to give phosphorane **S13** (6.81 g, 82%) as a colourless solid. The analytical data were consistent with those reported previously.[172] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75-7.62 (6H, m, Ar**H**), 7.61-7.53 (3H, m, Ar**H**), 7.52-7.42 (6H, m, Ar**H**), 4.28 (1H, d, *J* = 24.1 Hz, =C**H**), 4.01 (2H, s, C**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.3 (d, $^2J_{C\text{-}P}$ = 4.6 Hz, C), 133.2 (d, $^3J_{C\text{-}P}$ = 10.3 Hz, 6 × CH), 132.4 (d, $^4J_{C\text{-}P}$ = 2.9 Hz, 3 × CH), 129.1 (d, $^2J_{C\text{-}P}$ = 12.4 Hz, 6 × CH), 126.4 (d, $^1J_{C\text{-}P}$ = 91.3 Hz, 3 × C), 51.4 (d, $^1J_{C\text{-}P}$ = 110.0 Hz, =CH), 47.5 (d, $^3J_{C\text{-}P}$ = 16.5 Hz, CH_2).

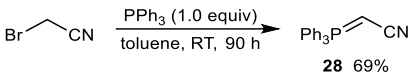
Diethyl (tosylmethyl)phosphonate (13).



The title compound was prepared according to a previously reported procedure.[173] To a solution of 4-(methylsulfonyl)toluene (2.50 g, 14.7 mmol) in THF (14 mL) at 0 °C under an argon atmosphere was added *n*-BuLi (1.8 M in hexanes, 17.5 mL, 32.3 mmol)

slowly over 4 min and the solution was stirred for 30 min. To the reaction at 0 °C was added slowly over 6 min diethyl chlorophosphate (2.6 mL, 17.6 mmol) and the resulting solution was stirred for 1 h. The reaction was quenched with saturated aqueous NH_4Cl (5 mL), extracted with CH_2Cl_2 (2 × 30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (80% EtOAc/pet. ether) to give phosphonate **13** (3.37 g, 75%) as an off-white solid. The analytical data were consistent with those reported previously.[173] R_f = 0.06 (40% EtOAc/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95-7.77 (2H, m, Ar**H**), 7.42-7.30 (2H, m, Ar**H**), 4.19-4.10 (4H, m, C**H**$_2$), 3.73 (2H, d, *J* = 16.8 Hz, C**H**$_2$), 2.44 (3H, s, ArC**H**$_3$), 1.29 (6H, t, *J* = 7.1 Hz, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.3 (C), 137.2 (C), 129.8 (2 × CH), 128.5 (2 × CH), 63.5 (d, $^2J_{C\text{-}P}$ = 6.5 Hz, 2 × CH_2), 54.0 (d, $^1J_{C\text{-}P}$ = 137.6 Hz, CH_2), 21.8 (CH_3), 16.3 (d, $^3J_{C\text{-}P}$ = 6.4 Hz, 2 × CH_3).

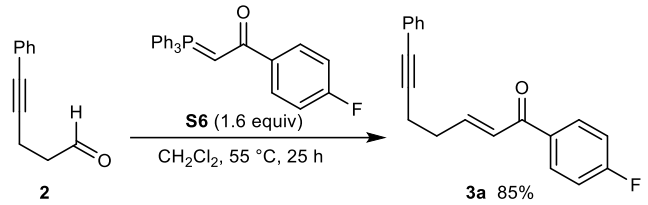
2-(Triphenyl-λ^5-phosphaneylidene)acetonitrile (28).



The title compound was prepared according to a previously reported procedure.[174] To a solution of bromoacetonitrile (2.00 g, 16.7 mmol) in toluene (30 mL) at room temperature was added a solution of triphenylphosphine (4.37 g, 16.7 mmol) in toluene (10 mL) and the reaction was stirred for 90 h. The solid was collected by filtration and washed with toluene (2 × 5 mL) and pentane (3 × 5 mL). The phosphonium salt was dissolved in CH_2Cl_2 (100 mL) and 2 M aqueous KOH (100 mL) was added. The mixture was vigorously shaken before the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give phosphorane **28** (3.46 g, 69%) as an off-white solid. The analytical data were consistent with those reported previously.[174] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65-7.58 (9H, m, Ar**H**), 7.55-7.45 (7H, m, 6 × Ar**H** and =C**H**); HRMS (ESI) Exact mass calculated for $[C_{20}H_{16}NNaP]^+$ $[M+Na]^+$: 324.0913, found 324.0911.

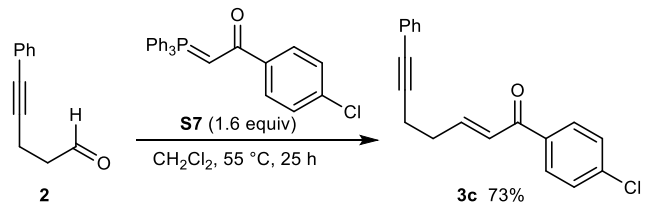
3.5 Preparation of Final Carbometallative Cyclisation Precursors

(*E*)-1-(4-Fluorophenyl)-7-phenylhept-2-en-6-yn-1-one (3a)



To a solution of aldehyde **2** (500 mg, 3.16 mmol) in CH_2Cl_2 (15 mL) under an argon atmosphere at reflux was added the phosphorane **S6** (2.02 g, 5.06 mmol) and the reaction was stirred at reflux for 25 h. The volatiles were removed *in vacuo* and the residue was purified by column chromatography (10% EtOAc/pet. ether) to give the enone **3a** (744 mg, 85%) as a yellow solid. R_f = 0.69 (40% EtOAc/pet. ether); m.p. 58−59 °C (Et_2O); IR 3062, 2912, 1670 (C=O), 1621, 1596, 1505, 1489, 1227, 1155, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03-7.93 (2H, m, Ar**H**), 7.42-7.34 (2H, m, Ar**H**), 7.31-7.26 (3H, m, Ar**H**), 7.15-7.06 (3H, m, 2 × Ar**H** and CH_2C**H**=), 6.98 (1H, d, *J* = 15.4 Hz, CH_2CH=C**H**), 2.69-2.59 (4H, m, C**H**$_2$C**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.3 (C), 165.7 (d, $J_{C\text{-}F}$ = 254.0 Hz, C), 147.2 (CH), 134.3 (d, $J_{C\text{-}F}$ = 2.9 Hz, C), 131.7 (2 × CH), 131.3 (d, $J_{C\text{-}F}$ = 9.5 Hz, 2 × CH), 128.4 (2 × CH), 128.0 (CH), 126.9 (CH), 123.6 (C), 115.8 (d, $J_{C\text{-}F}$ = 21.9 Hz, 2 × CH), 88.5 (C), 82.0 (C), 32.0 (CH_2), 18.7 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –105.7 (s); HRMS (ESI) Exact mass calculated for $[C_{19}H_{15}FNaO]^+$ $[M+Na]^+$: 301.0999, found 301.0994.

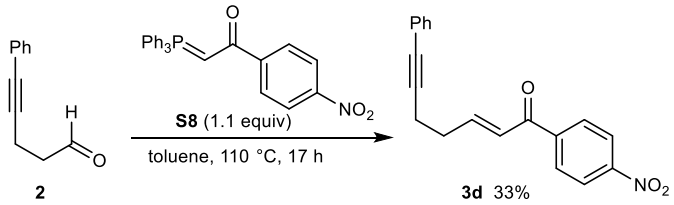
(*E*)-1-(4-Chlorophenyl)-7-phenylhept-2-en-6-yn-1-one (3c)



To a solution of aldehyde **2** (500 mg, 3.16 mmol) in CH_2Cl_2 (15 mL) under an argon atmosphere at reflux was added the phosphorane **S7** (2.10 g, 5.06 mmol) and the reaction was stirred at reflux for 25 h. The volatiles were removed *in vacuo* and the

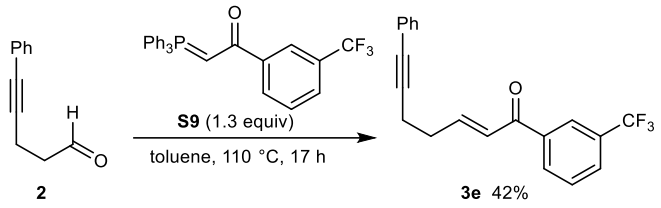
residue was purified by column chromatography (10% EtOAc/pet. ether) to give the enone **3c** (682 mg, 73%) as an orange solid. R_f = 0.69 (40% EtOAc/pet. ether); m.p. 68−69 °C (Et_2O); IR 3056, 2924, 1666 (C=O), 1615, 1586, 1488, 1090, 818, 754, 690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.98-7.79 (2H, m, Ar**H**), 7.52-7.31 (4H, m, Ar**H**), 7.31-7.26 (3H, m, Ar**H**), 7.12 (1H, dt, *J* = 15.5, 6.4 Hz, CH_2C**H**=), 6.96 (1H, dt, *J* = 15.5, 1.3 Hz, CH_2CH=C**H**), 2.72-2.56 (4H, m, C**H**$_2$C**H**$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.6 (C), 147.6 (CH), 139.3 (C), 136.2 (C), 131.7 (2 × CH), 130.2 (2 × CH), 129.0 (2 × CH), 128.4 (2 × CH), 128.0 (CH), 126.9 (CH), 123.6 (C), 88.4 (C), 82.1 (C), 32.0 (CH_2), 18.7 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{19}H_{15}{}^{35}ClNaO]^+$ $[M+Na]^+$: 317.0704, found 317.0704.

(*E*)-1-(4-Nitrophenyl)-7-phenylhept-2-en-6-yn-1-one (3d)



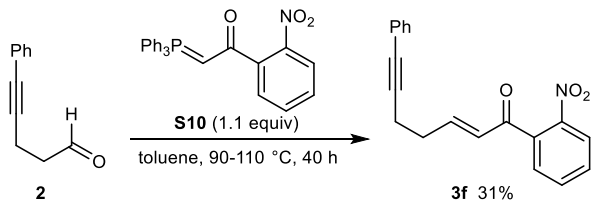
To a mixture of aldehyde **2** (273 mg, 1.72 mmol) and the phosphorane **S8** (807 mg, 1.90 mmol) under an argon atmosphere was added toluene (17 mL) and the reaction was stirred at 110 °C for 17 h. The volatiles were removed *in vacuo* and the residue was purified by column chromatography (15% EtOAc/pentane) to give the enone **3d** (173 mg, 33%) as an orange solid. R_f = 0.53 (30% EtOAc/pet. ether); m.p. 84–85 °C (Et_2O); IR 3083, 2912, 1670 (C=O), 1615, 1599, 1517, 1489, 1347, 1268, 1212 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.32-8.21 (2H, m, Ar**H**), 8.09-8.02 (2H, m, Ar**H**), 7.41-7.35 (2H, m, Ar**H**), 7.33-7.27 (3H, m, Ar**H**), 7.21-7.12 (1H, m, CH_2C**H**=), 6.97 (1H, d, *J* = 15.5 Hz, CH_2CH=C**H**), 2.74-2.59 (4H, m, C**H**$_2$C**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.5 (C), 150.2 (C), 149.5 (CH), 142.8 (C), 131.7 (2 × CH), 129.7 (2 × CH), 128.5 (2 × CH), 128.1 (CH), 127.0 (CH), 123.9 (2 × CH), 123.5 (C), 88.2 (C), 82.3 (C), 32.0 (CH_2), 18.6 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{19}H_{15}NNaO_3]^+$ $[M+Na]^+$: 328.0944, found: 328.0959.

(*E*)-7-Phenyl-1-[3-(trifluoromethyl)phenyl]hept-2-en-6-yn-1-one (3e)



To a mixture of aldehyde **2** (233 mg, 1.47 mmol) and the phosphorane **S9** (857 mg, 1.91 mmol) under an argon atmosphere was added toluene (10 mL) and the reaction was stirred at 110 °C for 17 h. The volatiles were removed *in vacuo* and the residue was purified by column chromatography (7% EtOAc/pet. ether) followed by a second purification by column chromatography (40% CH_2Cl_2/pet. ether) to give the enone **3e** (204 mg, 42%) as a yellow oil. R_f = 0.59 (30% EtOAc/pet. ether); IR 3065, 2918, 1674 (C=O), 1624, 1490, 1330, 1165, 1123, 1070, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.19 (1H, s, Ar**H**), 8.11 (1H, app dt, *J* = 7.8, 1.4, Hz, Ar**H**), 7.81 (1H, dd, *J* = 7.8, 1.7 Hz, Ar**H**), 7.58 (1H, app t, *J* = 7.8 Hz, Ar**H**), 7.43-7.34 (2H, m, Ar**H**), 7.31-7.26 (3H, m, Ar**H**), 7.21-7.13 (1H, m, CH_2C**H**=), 7.04-6.96 (1H, m, CH_2CH=C**H**), 2.74-2.60 (4H, m, C**H**$_2$C**H**$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.4 (C), 148.6 (CH), 138.5 (C), 131.9 (CH), 131.7 (2 × CH), 131.3 (q, J_{C-F} = 33.1 Hz, C), 129.34 (CH), 129.27 (q, J_{C-F} = 3.6 Hz, CH), 128.4 (2 × CH), 128.0 (CH), 126.6 (CH), 125.5 (q, J_{C-F} = 3.7 Hz, CH), 123.9 (q, J_{C-F} = 272.5 Hz, C), 123.6 (C), 88.3 (C), 82.1 (C), 32.1 (CH_2), 18.6 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.8 (s, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{20}H_{15}F_3NaO]^+$ $[M+Na]^+$: 351.0967, found 351.0969.

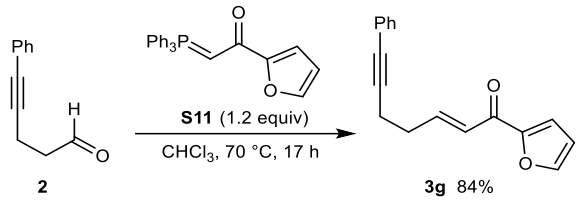
(*E*)-1-(2-Nitrophenyl)-7-phenylhept-2-en-6-yn-1-one (3f)



To a mixture of aldehyde **2** (300 mg, 1.90 mmol) and the phosphorane **S10** (887 mg, 2.09 mmol) under an argon atmosphere was added toluene (10 mL) and the reaction was stirred at 90 °C for 16 h and then at 110 °C for 24 h. The volatiles were removed

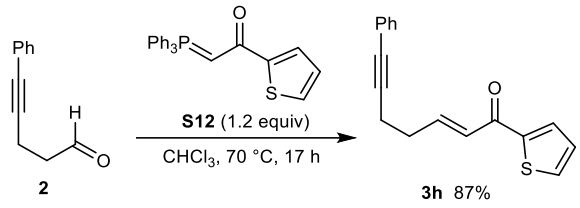
in vacuo and the residue was purified by column chromatography (15 to 20% EtOAc/pet. ether) to give the enone **3f** (178 mg, 31%) as a red oil. R_f = 0.19 (20% EtOAc/pet. ether); IR 3034, 2924, 1664 (C=O), 1625, 1528, 1489, 1347, 1286, 757, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (1H, d, *J* = 8.2 Hz, Ar**H**), 7.69 (1H, app t, *J* = 7.5 Hz, Ar**H**), 7.60 (1H, app t, *J* = 7.8 Hz, Ar**H**), 7.43 (1H, d, *J* = 7.5 Hz, Ar**H**), 7.39-7.31 (2H, m, Ar**H**), 7.31-7.26 (3H, m, Ar**H**), 6.71-6.39 (2H, m, C**H**=C**H**), 2.65-2.46 (4H, m, C$\mathbf{H}_2$C$\mathbf{H}_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.0 (C), 149.2 (CH), 146.9 (C), 136.3 (C), 134.0 (CH), 131.7 (2 × CH), 131.5 (CH), 130.6 (CH), 129.0 (CH), 128.4 (2 × CH), 128.0 (CH), 124.5 (CH), 123.5 (C), 87.9 (C), 82.1 (C), 31.7 (CH_2), 18.5 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{19}H_{15}NNaO_3]^+$ $[M+Na]^+$: 328.0944, found 328.0945.

(*E*)-1-(Furan-2-yl)-7-phenylhept-2-en-6-yn-1-one (3g)



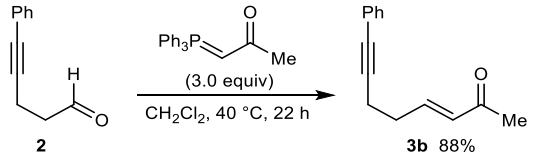
A solution of aldehyde **2** (300 mg, 1.90 mmol) and the phosphorane **S11** (843 mg, 2.28 mmol) in $CHCl_3$ (7 mL) under an argon atmosphere at 70 °C was stirred for 17 h. The volatiles were removed *in vacuo* and the residue was purified by column chromatography (15% EtOAc/pet. ether) to give the enone **3g** (401 mg, 84%) as a brown solid. R_f = 0.35 (30% EtOAc/pet. ether); m.p. 50−51 °C (Et_2O); IR 3120, 2897, 2220 (C≡C), 1654 (C=O), 1615, 1603, 1556, 1463, 1396, 1274 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (1H, d, *J* = 1.7 Hz, Ar**H**), 7.42-7.34 (2H, m, Ar**H**), 7.30-7.25 (3H, m, Ar**H**), 7.25-7.17 (2H, m, CH_2C**H**= and Ar**H**), 6.92 (1H, dt, *J* = 15.6, 1.5 Hz, CH_2CH=C**H**), 6.55 (1H, dd, *J* = 3.6, 1.7 Hz, Ar**H**), 2.68-2.57 (4H, m, C$\mathbf{H}_2$C$\mathbf{H}_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.1 (C), 153.4 (C), 146.7 (CH), 146.5 (CH), 131.7 (2 × CH), 128.3 (2 × CH), 127.9 (CH), 126.1 (CH), 123.7 (C), 117.8 (CH), 112.5 (CH), 88.5 (C), 81.9 (C), 32.0 (CH_2), 18.7 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{17}H_{14}NaO_2]^+$ $[M+Na]^+$: 273.0886, found: 273.0886.

(*E*)-7-Phenyl-1-(thiophen-2-yl)hept-2-en-6-yn-1-one (3h)



A solution of aldehyde **2** (400 mg, 2.53 mmol) and the phosphorane **S12** (1.17 g, 3.03 mmol) in $CHCl_3$ (9 mL) under an argon atmosphere at 70 °C was stirred for 17 h. The volatiles were removed *in vacuo* and the residue was purified by column chromatography (15% EtOAc/pet. ether) to give the enone **3h** (586 mg, 87%) as an orange solid. R_f = 0.50 (30% EtOAc/pet. ether); m.p. 65−66 °C (Et_2O); IR 3074, 2923, 1654 (C=O), 1598, 1512, 1489, 1414, 1354, 1234, 969 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (1H, d, *J* = 3.7 Hz, Ar**H**), 7.65 (1H, d, *J* = 4.9 Hz, Ar**H**), 7.43-7.34 (2H, m, Ar**H**), 7.29-7.25 (3H, m, Ar**H**), 7.22-7.09 (2H, m, Ar**H** and CH_2C**H**=), 6.92 (1H, d, *J* = 15.3 Hz, CH_2CH=C**H**), 2.70-2.57 (4H, m, C**H**$_2$C**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.3 (C), 146.4 (CH), 145.2 (C), 134.0 (CH), 132.2 (CH), 131.7 (2 × CH), 128.4 (2 × CH), 128.3 (CH), 127.9 (CH), 126.6 (CH), 123.7 (C), 88.5 (C), 81.9 (C), 31.9 (CH_2), 18.7 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{17}H_{14}NaOS]^+$ $[M+Na]^+$: 289.0658, found: 289.0659.

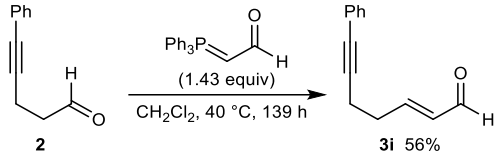
(*E*)-8-Phenyloct-3-en-7-yn-2-one (3b)



To a solution of aldehyde **2** (500 mg, 3.16 mmol) in CH_2Cl_2 (10 mL) under an argon atmosphere at 40 °C was added 1-(triphenylphosphoranylidene)-2-propanone (3.02 g, 9.48 mmol) and the reaction was stirred at 40 °C for 22 h. The volatiles were removed *in vacuo* and the residue was purified by column chromatography (15% EtOAc/pet. ether) to give the enone **3b** (549 mg, 88%) as a yellow oil. R_f = 0.46 (40% EtOAc/pet. ether); IR 3047, 2924, 2237 (C≡C), 1671 (C=O), 1627, 1490, 1359, 1159, 971, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.34 (2H, m, Ar**H**), 7.31-7.25 (3H, m, Ar**H**), 6.87

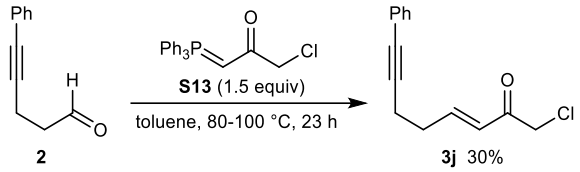
(1H, dt, *J* = 16.1, 6.5 Hz, $CH_2C\mathbf{H}$=), 6.17 (1H, dt, *J* = 16.1, 1.4 Hz, CH_2CH=C**H**), 2.62-2.56 (2H, m, $C\mathbf{H}_2$), 2.56-2.49 (2H, m, $C\mathbf{H}_2$), 2.27 (3H, s, $C\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.5 (C), 145.8 (CH), 132.3 (CH), 131.7 (2 × CH), 128.4 (2 × CH), 128.0 (CH), 123.6 (C), 88.2 (C), 81.9 (C), 31.7 (CH_2), 27.1 (CH_3), 18.6 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{14}H_{14}NaO]^+$ $[M+Na]^+$: 221.0937, found: 221.0937.

(*E*)-7-Phenylhept-2-en-6-ynal (3i)



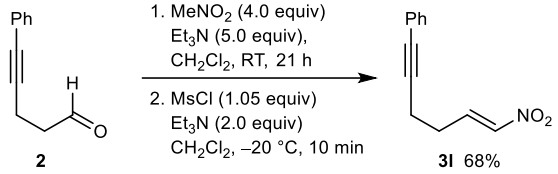
To a solution of aldehyde **2** (500 mg, 3.16 mmol) in CH_2Cl_2 (5 mL) under an argon atmosphere at 40 °C was added a solution of (triphenylphosphoranylidene)acetaldehyde (1.09 g, 3.57 mmol) in CH_2Cl_2 (6 mL) in 6 portions over 50 min and the reaction was stirred at 40 °C for 70 h. An additional portion of the phosphorane (289 mg, 0.948 mmol) in CH_2Cl_2 (3 mL) was added to the reaction and stirring was continued at 40 °C for 69 h. The volatiles were removed *in vacuo* and the residue was purified by column chromatography (10% EtOAc/pet. ether) to give the enal **3i** (326 mg, 56%) as a yellow oil. R_f = 0.44 (30% EtOAc/pet. ether); IR 3034, 2912, 2817, 2742, 1684 (C=O), 1489, 1123, 1012, 755, 691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (1H, d, *J* = 7.8 Hz, C**H**=O), 7.41-7.36 (2H, m, Ar**H**), 7.31-7.27 (3H, m, Ar**H**), 7.00-6.85 (1H, m, $CH_2C\mathbf{H}$=), 6.23 (1H, dd, *J* = 15.6, 7.8 Hz, CH_2CH=C**H**), 2.69-2.59 (4H, m, $C\mathbf{H}_2C\mathbf{H}_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.9 (C), 156.0 (CH), 133.9 (CH), 131.7 (2 × CH), 128.4 (2 × CH), 128.1 (CH), 123.4 (C), 87.8 (C), 82.1 (C), 31.9 (CH_2), 18.4 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{13}H_{12}NaO]^+$ $[M+Na]^+$: 207.0780, found 207.0781.

(*E*)-1-Chloro-8-phenyloct-3-en-7-yn-2-one (3j)



To a mixture of aldehyde **2** (500 mg, 3.16 mmol) and 1-chloro-3-(triphenyl-λ5-phosphanylidene)propan-2-one **S13** (1.67 g, 4.74 mmol) under an argon atmosphere was added toluene (15 mL) and the reaction was stirred at 80 °C for 1 h and at 100 °C for 22 h. The volatiles were removed *in vacuo* and the residue was purified by column chromatography (10% EtOAc/pentane) to give the enone **3j** (223 mg, 30%) as a brown oil. R_f = 0.17 (10% EtOAc/pet. ether); IR 3019, 2928, 1694 (C=O), 1626, 1598, 1489, 1441, 1398, 1192, 968 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41-7.35 (2H, m, Ar**H**), 7.30-7.27 (3H, m, Ar**H**), 7.08 (1H, dt, *J* = 15.9, 6.4 Hz, CH_2C**H**=), 6.44 (1H, dt, *J* = 15.9, 1.5 Hz, CH_2CH=C**H**), 4.22 (2H, s, C**H**$_2$Cl), 2.64-2.55 (4H, m, C**H**$_2$C**H**$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.1 (C), 148.0 (CH), 131.7 (2 × CH), 128.4 (2 × CH), 128.1 (CH), 127.2 (CH), 123.5 (C), 88.0 (C), 82.1 (C), 47.2 (CH_2), 31.9 (CH_2), 18.4 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{14}H_{13}{}^{35}ClNaO]^+$ $[M+Na]^+$: 255.0547, found: 255.0548.

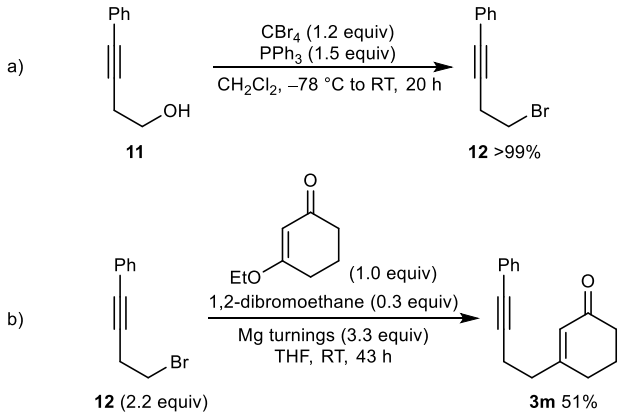
(*E*)-(6-Nitrohex-5-en-1-yn-1-yl)benzene (3l)



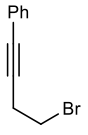
To a solution of aldehyde **2** (633 mg, 4.00 mmol) and $MeNO_2$ (0.87 mL, 16.0 mmol) in CH_2Cl_2 (4.0 mL) under an argon atmosphere at room temperature was added Et_3N (2.8 mL, 20.0 mmol) and the reaction was stirred for 21 h. The volatiles were removed *in vacuo* and the resulting solid was dissolved in CH_2Cl_2 (12 mL). To the mixture at −20 °C was added slowly MsCl (0.33 mL, 4.20 mmol) followed by Et_3N (1.1 mL, 8.00 mmol) and the reaction was stirred for 10 min. The reaction was diluted with 1 M aqueous HCl (30 mL) and extracted with CH_2Cl_2 (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 (15% EtOAc/pentane) to give the nitroalkene **3l** (548 mg, 68%) as a yellow oil. R_f = 0.54 (30% EtOAc/pet. ether); IR 3103, 2914, 1650, 1521, 1489, 1441, 1348, 946, 755, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.28 (6H, m, 5 × Ar**H** and CH_2C**H**=), 7.11 (1H, d, *J* = 13.4 Hz, CH_2CH=C**H**), 2.66 (2H, t, *J* = 7.0 Hz, ≡CC**H**$_2$), 2.62-2.52 (2H, m, C**H**$_2$CH=CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.6 (CH), 140.4 (CH), 131.7 (2 × CH), 128.5 (2 × CH), 128.3 (CH), 123.2 (C), 87.0 (C), 82.7 (C), 27.8 (CH_2), 18.4 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{12}H_{11}NNaO_2]^+$ $[M+Na]^+$: 224.0682, found: 224.0678.

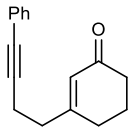
3-(4-Phenylbut-3-yn-1-yl)cyclohex-2-en-1-one (3m).



*Synthesis of substrate **11** performed by previous member of the Lam group.*

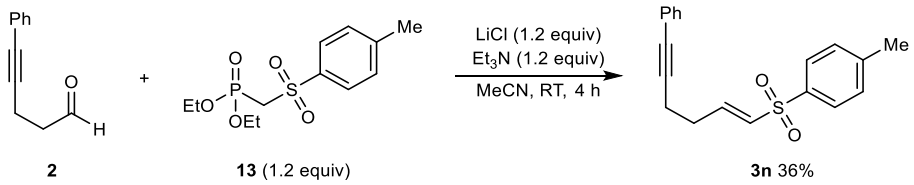


(4-Bromobut-1-yn-1-yl)benzene (12). To a solution of alcohol **11** (1.00 g, 6.84 mmol) and CBr_4 (2.72 g, 8.21 mmol) in CH_2Cl_2 (120 mL) under an argon atmosphere at –78 °C was added slowly over 7 min a solution of PPh_3 (2.69 g, 10.3 mmol) in CH_2Cl_2 (50 mL). The reaction was stirred at –78 °C for 30 min followed by stirring at room temperature for 20 h. The reaction was filtered through a pad of silica (EtOAc) and concentrated *in vacuo* to give bromide **12** (1.41 g, >99%) as a colourless oil. The analytical data were consistent with those reported previously.[24] ^1H NMR (400 MHz, $CDCl_3$) δ 7.47-7.39 (2H, m, Ar**H**), 7.35-7.26 (3H, m, Ar**H**), 3.53 (2H, t, *J* = 7.4 Hz, C**H**$_2$), 2.98 (2H, t, *J* = 7.4 Hz, C**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.8 (2 × CH), 128.4 (2 × CH), 128.2 (CH), 123.2 (C), 86.7 (C), 82.6 (C), 29.7 (CH_2), 24.0 (CH_2).



3-(4-Phenylbut-3-yn-1-yl)cyclohex-2-en-1-one (3m). To a solution of magnesium turning (123 mg, 5.07 mmol) in THF (0.5 mL) under an argon atmosphere at room temperature was added 1,2-dibromoethane (37 μL, 0.46 mmol) until bubbles were observed. A solution of alkyne **12** (700 mg, 3.38 mmol) in THF (4 mL) was added dropwise over 3 min and the resulting solution was stirred for 2 h. The reaction was cooled to 0 °C and 3-ethoxy-2-cyclohexen-1-one (0.22 mL, 1.54 mmol) was added dropwise over 3 min followed by stirring at room temperature for 41 h. The reaction was quenched at 0 °C with 1 M aqueous HCl (10 mL), extracted with Et_2O (3 × 20 mL), washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (5 to 25% EtOAc/pet. ether) to give enone **3m** (177 mg, 51%) as a pale yellow solid. The analytical data were consistent with those reported previously.[24] R_f = 0.24 (30% EtOAc/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.32 (2H, m, Ar**H**), 7.31-7.24 (3H, m, Ar**H**), 5.98 (1H, t, *J* = 1.5 Hz, =C**H**), 2.63 (2H, t, *J* = 6.8 Hz, C$\mathbf{H}_2$), 2.52 (2H, t, *J* = 7.2 Hz, C$\mathbf{H}_2$), 2.43-2.32 (4H, m, 2 × C$\mathbf{H}_2$), 2.07-1.97 (2H, m, C$\mathbf{H}_2$); HRMS (ESI) Exact mass calculated for $[C_{16}H_{16}NaO]^+$ $[M+Na]^+$: 247.1093, found: 247.1090.

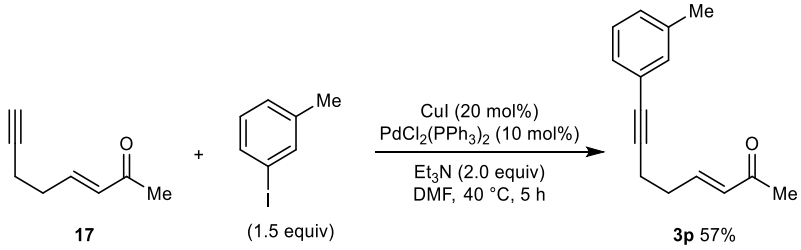
(*E*)-1-Methyl-4-[(7-phenylhept-1-en-6-yn-1-yl)sulfonyl]benzene (3n).



Et_3N (0.53 mL, 3.79 mmol) was added to a solution of aldehyde **2** (500 mg, 3.16 mmol), sulfone **13** (1.16 g, 3.79 mmol) and LiCl (161 mg, 3.79 mmol) in MeCN (12 mL) and the reaction was stirred at room temperature for 4 h. The reaction was diluted with saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc/pet. ether) to give α,β-unsaturated sulfone **3n** (349 mg, 36%) as an off-white solid. R_f = 0.51 (40% EtOAc/pet. ether); m.p. 92–93 °C (Et_2O); IR 3047, 2918, 2239 (C≡C), 1637, 1595, 1488, 1302, 1141, 1086, 762 cm^{-1}; ^{1}H NMR

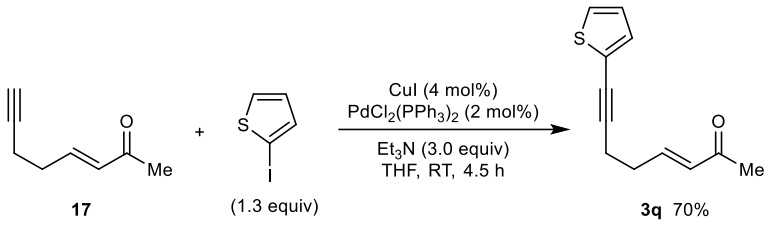
(400 MHz, $CDCl_3$) δ 7.84-7.71 (2H, m, Ar**H**), 7.35-7.20 (7H, m, Ar**H**), 7.04 (1H, dt, *J* = 15.1, 6.5 Hz, CH_2C**H**=), 6.47 (1H, dt, *J* = 15.1, 1.5 Hz, CH_2CH=C**H**), 2.64-2.57 (2H, m, C**H**$_2$), 2.57-2.49 (2H, m, C**H**$_2$), 2.40 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.3 (C), 144.0 (CH), 137.6 (C), 132.1 (CH), 131.6 (2 × CH), 129.9 (2 × CH), 128.3 (2 × CH), 128.0 (CH), 127.7 (2 × CH), 123.3 (C), 87.5 (C), 82.3 (C), 30.6 (CH_2), 21.7 (CH_3), 18.1 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{19}H_{18}NaO_2S]^+$ $[M+Na]^+$: 333.0920, found: 333.0922.

(*E*)-8-(*m*-Tolyl)oct-3-en-7-yn-2-one (3p)



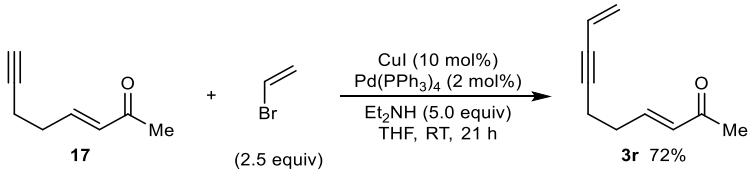
To a solution of $PdCl_2(PPh_3)_2$ (173 mg, 0.246 mmol) and CuI (93.7 mg, 0.492 mmol) in DMF (3 mL) under an argon atmosphere at room temperature was added Et_3N (0.68 mL, 4.91 mmol) and 3-iodotoluene (0.47 mL, 3.68 mmol). A solution of alkyne **17** (300 mg, 2.46 mmol) in DMF (2 mL) was added and the reaction was stirred at 40 °C for 5 h. The reaction was diluted with 50% brine (50 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 × 50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc/pet. ether) and further purified by dissolving the residue in Et_2O and filtering off the solid to give the enone **3p** (297 mg, 57%) as an orange oil. R_f = 0.32 (20% EtOAc/pet. ether); IR 3033, 2919, 1697, 1672 (C=O), 1626, 1358, 1252, 971, 783, 691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.14 (3H, m, Ar**H**), 7.13-7.06 (1H, m, Ar**H**), 6.88 (1H, dt, *J* = 15.9, 6.5 Hz, CH_2C**H**=), 6.18 (1H, d, *J* = 15.9 Hz, CH_2CH=C**H**), 2.62-2.50 (4H, m, C**H**$_2$C**H**$_2$), 2.32 (3H, s, C**H**$_3$), 2.28 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.6 (C), 145.9 (CH), 138.1 (C), 132.32 (CH), 132.30 (CH), 128.9 (CH), 128.7 (CH), 128.3 (CH), 123.4 (C), 87.9 (C), 82.1 (C), 31.7 (CH_2), 27.1 (CH_3), 21.4 (CH_3), 18.6 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{15}H_{16}NaO]^+$ $[M+Na]^+$: 235.1093, found: 235.1087.

(*E*)-8-(Thiophen-2-yl)oct-3-en-7-yn-2-one (3q)



To a solution of $PdCl_2(PPh_3)_2$ (28.7 mg, 0.041 mmol), CuI (15.6 mg, 0.082 mmol) and alkyne **17** (250 mg, 2.05 mmol) in THF (5 mL) under an argon atmosphere at room temperature was added Et_3N (0.86 mL, 6.14 mmol) and 2-iodothiophene (559 mg, 2.66 mmol) and the reaction was stirred for 4.5 h. The reaction was filtered through celite (EtOAc) and concentrated *in vacuo*. The residue was purified by column chromatography (20% EtOAc/pet. ether) to give the enone **3q** (293 mg, 70%) as a red oil. R_f = 0.32 (20% EtOAc/pet. ether); IR 3105, 2849, 1671 (C=O), 1626, 1426, 1358, 1253, 1190, 971, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (1H, d, *J* = 5.2 Hz, Ar**H**), 7.12 (1H, d, *J* = 3.6 Hz, Ar**H**), 6.94 (1H, dd, *J* = 5.2, 3.6 Hz, Ar**H**), 6.85 (1H, dt, *J* = 16.1, 6.6 Hz, CH_2C**H**=), 6.16 (1H, d, *J* = 16.1 Hz, CH_2CH=C**H**), 2.65-2.57 (2H, m, C$\mathbf{H}_2$), 2.56-2.49 (2H, m, C$\mathbf{H}_2$), 2.27 (3H, s, C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.5 (C), 145.6 (CH), 132.4 (CH), 131.4 (CH), 127.0 (CH), 126.5 (CH), 123.6 (C), 92.3 (C), 75.1 (C), 31.5 (CH_2), 27.1 (CH_3), 18.9 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{12}H_{12}NaOS]^+$ $[M+Na]^+$: 227.0501, found: 227.0500.

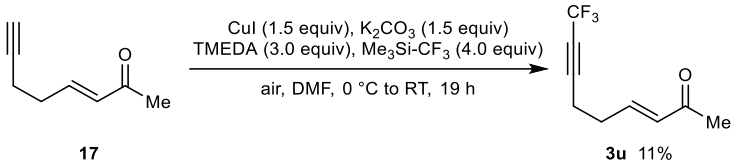
(*E*)-Deca-3,9-dien-7-yn-2-one (3r)



To a mixture of $Pd(PPh_3)_4$ (56.7 mg, 0.049 mmol) and CuI (46.9 mg, 0.246 mmol) under an argon atmosphere at room temperature was added vinyl bromide (1 M in THF, 6.1 mL, 6.10 mmol) and Et_2NH (1.3 mL, 12.3 mmol) and the resulting mixture was stirred for 5 min. A solution of alkyne **17** (300 mg, 2.46 mmol) in THF (1.3 mL) was added dropwise and the reaction was stirred at room temperature for 21 h. The reaction

was filtered through celite (Et_2O) and concentrated *in vacuo*. The residue was purified by column chromatography (10% EtOAc/pet. ether) to give the enone **3r** (261 mg, 72%) as an orange oil. R_f = 0.37 (20% EtOAc/pet. ether); IR 3009, 2913, 2848, 2225 (C≡C), 1698, 1672 (C=O), 1627, 1359, 1252, 971 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.82 (1H, dt, *J* = 16.2, 6.4 Hz, $CH_2C\mathbf{H}$=), 6.13 (1H, dt, *J* = 16.2, 1.4 Hz, CH_2CH=C**H**), 5.76 (1H, ddt, *J* = 17.6, 11.0, 1.8 Hz, C**H**=CH_2), 5.56 (1H, dd, *J* = 17.6, 2.1 Hz, =C**H**$_a$H$_b$), 5.40 (1H, dd, *J* = 11.0, 2.1 Hz, =CH$_a$**H**$_b$), 2.52-2.42 (4H, m, C**H**$_2$C**H**$_2$), 2.26 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.6 (C), 145.8 (CH), 132.3 (CH), 126.4 (CH_2), 117.4 (CH), 89.0 (C), 80.6 (C), 31.6 (CH_2), 27.1 (CH_3), 18.5 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{10}H_{13}O]^+$ $[M+H]^+$: 149.0961, found: 149.0965.

(*E*)-9,9,9-Trifluoronon-3-en-7-yn-2-one (3u)

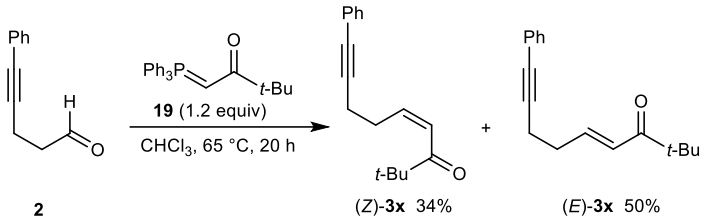


17 **3u** 11%

CuI (701 mg, 3.68 mmol), K_2CO_3 (509 mg, 3.68 mmol), TMEDA (1.1 mL, 7.37 mmol) and DMF (11 mL) were added to a flask and stirred vigorously open to air for 15 min. The flask was sealed and flushed with argon. $Me_3Si–CF_3$ (0.73 mL, 4.91 mmol) was added and the reaction was stirred for 5 min and then cooled to 0 °C. A solution of alkyne **17** (300 mg, 2.46 mmol) and $Me_3Si–CF_3$ (0.73 mL, 4.91 mmol) in DMF (11 mL) was added to the reaction and the resulting solution was stirred at 0 °C for 30 min followed by stirring at room temperature for 19 h. The reaction was diluted with H_2O (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with H_2O (3 × 20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (30% EtOAc/pentane) to give the trifluoromethyl-alkyne **3u** (50.4 mg, 11%) as a yellow oil. R_f = 0.20 (30% EtOAc/pet. ether); IR 2928, 2263 (C≡C), 1700, 1677 (C=O), 1632, 1362, 1282, 1254, 1125, 1021 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.79-6.71 (1H, m, $CH_2C\mathbf{H}$=), 6.15 (1H, d, *J* = 15.9 Hz, CH_2CH=C**H**), 2.58-2.43 (4H, m, C**H**$_2$C**H**$_2$), 2.27 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.1 (C), 143.5 (CH), 132.7 (CH), 114.1 (q, $^1J_{C\text{-}F}$ = 256.5 Hz, CF_3), 87.2 (q, $^3J_{C\text{-}F}$ = 6.3 Hz, C), 69.59 (q, $^2J_{C\text{-}F}$ = 52.2 Hz, C), 29.9

(d, $^{5}J_{C\text{-}F}$ = 1.7 Hz, CH_2), 27.3 (CH_3), 17.3 (d, $^{4}J_{C\text{-}F}$ = 1.8 Hz, CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –49.8 (s); HRMS (ESI) Exact mass calculated for $[C_9H_9F_3NaO]^+$ $[M+Na]^+$: 213.0498, found 213.0499.

(*Z*)-2,2-Dimethyl-9-phenylnon-4-en-8-yn-3-one [(*Z*)-(3x)] and (*E*)-2,2-dimethyl-9-phenylnon-4-clen-8-yn-3-one [(*E*)-(3x)]



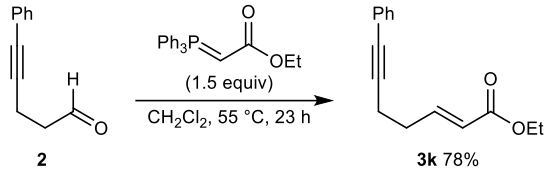
To a mixture of aldehyde **2** (400 mg, 2.53 mmol) and the phosphorane **19** (1.09 g, 3.03 mmol) under an argon atmosphere was added $CHCl_3$ (9 mL) and the reaction was stirred at 65 °C for 20 h. The volatiles were removed *in vacuo* and the residue was purified by column chromatography (1 to 3% EtOAc/pet. ether) followed by a second purification by column chromatography (1% EtOAc/pentane) to give the enone (*Z*)-**3x** (206 mg, 34%) as a yellow oil followed by the enone (*E*)-**3x** (305 mg, 50%) as an off-white solid.

Data for (Z)-**3x**: R_f = 0.66 (30% EtOAc/pet. ether); IR 3032, 2967, 2869, 1683 (C=O), 1614, 1490, 1476, 1074, 755, 691 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.35 (2H, m, Ar**H**), 7.29-7.24 (3H, m, Ar**H**), 6.49 (1H, dt, *J* = 11.6, 1.8 Hz, CH_2CH=C**H**), 6.29 (1H, dt, *J* = 11.6, 7.1 Hz, CH_2C**H**=), 2.91-2.83 (2H, m, C**H**$_2$C=), 2.54 (2H, t, *J* = 7.0 Hz, C**H**$_2CH_2$C=), 1.15 (9H, s, C(C**H**$_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.8 (C), 146.4 (CH), 131.7 (2 × CH), 128.3 (2 × CH), 127.8 (CH), 124.1 (CH), 123.9 (C), 89.3 (C), 81.4 (C), 43.8 (C), 28.8 (CH_2), 26.4 (3 × CH_3), 19.4 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{17}H_{20}NaO]^+$ $[M+Na]^+$: 263.1406, found: 263.1405.

Data for (E)-**3x**: R_f = 0.61 (30% EtOAc/pet. ether); m.p. 38–40 °C (Et_2O); IR 3051, 2969, 2869, 1685 (C=O), 1623, 1490, 1475, 1099, 1070, 754 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.34 (2H, m, Ar**H**), 7.28-7.25 (3H, m, Ar**H**), 6.99 (1H, dt, *J* = 15.3, 6.6 Hz, CH_2C**H**=), 6.62 (1H, dt, *J* = 15.3, 1.5 Hz, CH_2CH=C**H**), 2.58 (2H, td, *J* = 6.6, 1.5 Hz, C**H**$_2CH_2$C=), 2.54-2.49 (2H, m, C**H**$_2$C=), 1.15 (9H, s, C(C**H**$_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.3 (C), 144.9 (CH), 131.7 (2 × CH), 128.3 (2 × CH), 127.9 (CH),

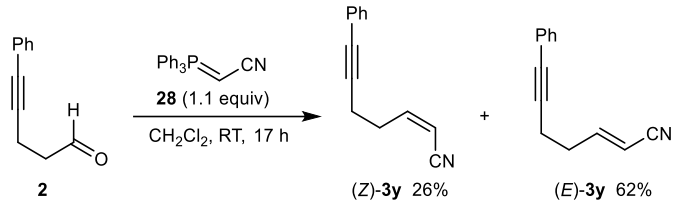
125.4 (CH), 123.7 (C), 88.6 (C), 81.7 (C), 43.1 (C), 31.8 (CH_2), 26.3 (3 × CH_3), 18.7 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{17}H_{20}NaO]^+$ $[M+Na]^+$: 263.1406, found: 263.1407.

Ethyl (*E*)-7-phenylhept-2-en-6-ynoate (3k)



To a solution of aldehyde **2** (500 mg, 3.16 mmol) in CH_2Cl_2 (15 mL) under an argon atmosphere at reflux was added (carbethoxymethylene)triphenylphosphorane (1.65 g, 4.74 mmol) and the reaction was stirred at reflux for 23 h. The volatiles were removed *in vacuo* and the residue was purified by column chromatography (5 to 10% EtOAc/pet. ether) to give the enone **3k** (562 mg, 78%) as a yellow oil. The analytical data were consistent with those reported previously.[175] R_f = 0.60 (40% EtOAc/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.35 (2H, m, Ar**H**), 7.32-7.26 (3H, m, Ar**H**), 7.04 (1H, dt, *J* = 15.6, 6.5 Hz, CH_2C**H**=), 5.93 (1H, dt, *J* = 15.6, 1.5 Hz, CH_2CH=C**H**), 4.20 (2H, q, *J* = 7.1 Hz, C**H**$_2CH_3$), 2.61-2.55 (2H, m, C**H**$_2$), 2.55-2.48 (2H, m, C**H**$_2$), 1.30 (3H, t, *J* = 7.1 Hz, CH_2C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6 (C), 146.8 (CH), 131.8 (2 × CH), 128.4 (2 × CH), 127.9 (CH), 123.7 (C), 122.7 (CH), 88.4 (C), 81.8 (C), 60.4 (CH_2), 31.5 (CH_2), 18.6 (CH_2), 14.4 (CH_3).

(*Z*)-7-Phenylhept-2-en-6-ynenitrile [(*Z*)-3y] and (*E*)-7-phenylhept-2-en-6-ynenitrile [(*E*)-3y]

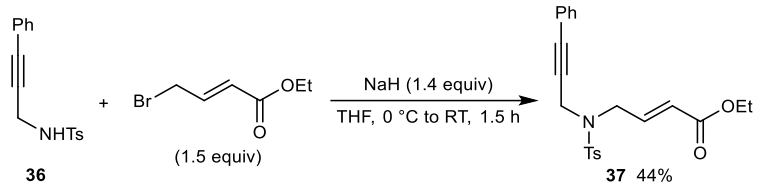


To a solution of aldehyde **2** (500 mg, 3.16 mmol) in CH_2Cl_2 (25 mL) under an argon atmosphere at room temperature was added (triphenylphosphoranylidene)acetonitrile **28** (1.05 g, 3.48 mmol) and the reaction was stirred at room temperature for 17 h. The volatiles were removed *in vacuo* and the residue was purified by column chromatography (1 to 4% Et_2O/pentane) to give the α,β-unsaturated nitrile (*Z*)-**3y** (148 mg, 26%) as a yellow oil followed by the α,β-unsaturated nitrile (*E*)-**3y** (353 mg, 62%) as a yellow oil.

Data for (Z)-**3y**: R_f = 0.27 (2% Et_2O/pentane, 4 elutions); IR 3061, 2910, 2220 (C≡N), 1598, 1490, 1441, 1330, 1128, 1069, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.37 (2H, m, Ar**H**), 7.34-7.26 (3H, m, Ar**H**), 6.73-6.53 (1H, m, CH_2C**H**=), 5.43 (1H, d, *J* = 10.9 Hz, CH_2CH=C**H**), 2.73 (2H, app q, *J* = 6.9 Hz, C**H**$_2$C=), 2.61 (2H, t, *J* = 6.9 Hz, C**H**$_2CH_2$=); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.8 (CH), 131.7 (2 × CH), 128.4 (2 × CH), 128.1 (CH), 123.4 (C), 115.9 (C), 101.1 (CH), 87.5 (C), 82.3 (C), 30.9 (CH_2), 18.7 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{13}H_{11}NNa]^+$ $[M+Na]^+$: 204.0784, found: 204.0783.

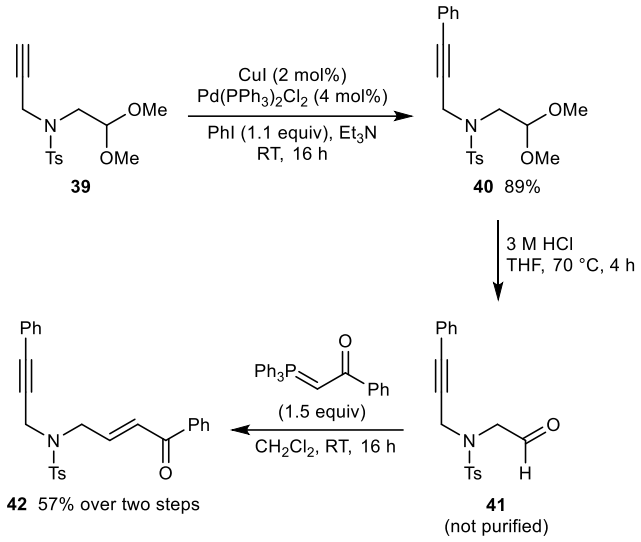
Data for (E)-**3y**: R_f = 0.19 (2% Et_2O/pentane, 4 elutions); IR 3054, 2912, 2223 (C≡N), 1634, 1598, 1489, 1441, 1344, 1070, 958 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.35 (2H, m, Ar**H**), 7.34-7.27 (3H, m, Ar**H**), 6.82 (1H, dt, *J* = 16.4, 6.6 Hz, CH_2C**H**=), 5.48 (1H, dt, *J* = 16.4, 1.6 Hz, CH_2CH=C**H**), 2.62-2.57 (2H, m, C**H**$_2$), 2.56-2.49 (2H, m, C**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.6 (CH), 131.7 (2 × CH), 128.4 (2 × CH), 128.2 (CH), 123.3 (C), 117.3 (C), 101.3 (CH), 87.3 (C), 82.5 (C), 32.4 (CH_2), 18.3 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{13}H_{11}NNa]^+$ $[M+Na]^+$: 204.0784, found: 204.0781.

Ethyl (*E*)-4-{[4-methyl-*N*-(3-phenylprop-2-yn-1-yl)phenyl]sulfonamido}but-2-enoate (37)

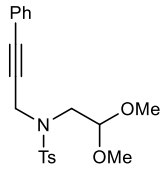


A solution of the *N*-tosyl propargyl amine **36** (3.00 g, 10.5 mmol) in THF (5 mL) was added dropwise to an ice-cooled suspension of NaH (60% dispersion in mineral oil, 588 mg, 14.7 mmol) in THF (25 mL). The resulting solution was warmed to room temperature and stirred for 45 min. Ethyl-4-bromo crotonate (75% purity, 2.9 mL, 15.8 mmol) was added slowly and the resulting solution was stirred at room temperature for 1.5 h. The reaction was quenched with H_2O (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with H_2O (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered, and concentrated in *vacuo*. The residue was purified by column chromatography (20 to 30% Et_2O/pet. ether) to give the enone **37** (1.84 g, 44%) as a yellow solid. The analytical data were consistent with those reported previously.[176] R_f = 0.26 (40% Et_2O/pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (2H, d, *J* = 7.9 Hz, Ar**H**), 7.30-7.23 (5H, m, Ar**H**), 7.07 (2H, d, *J* = 7.2 Hz, Ar**H**), 6.86 (1H, dt, *J* = 15.7, 5.8 Hz, CH_2C**H**=), 6.08 (1H, d, *J* = 15.7 Hz, CH_2CH=C**H**), 4.31 (2H, s, C**H**$_2$), 4.19 (2H, q, *J* = 7.1 Hz, C**H**$_2$), 4.04 (2H, dd, *J* = 5.8, 1.6 Hz, C**H**$_2$), 2.35 (3H, s, ArC**H**$_3$), 1.28 (3H, t, *J* = 7.1 Hz, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7 (C), 144.0 (C), 141.6 (CH), 135.9 (C), 131.7 (2 × CH), 129.8 (2 × CH), 128.7 (CH), 128.3 (2 × CH), 127.9 (2 × CH), 124.7 (CH), 122.1 (C), 86.3 (C), 81.4 (C), 60.8 (CH_2), 47.6 (CH_2), 37.8 (CH_2), 21.6 (CH_3), 14.3 (CH_3).

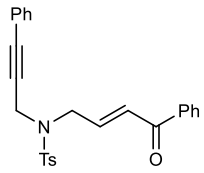
(*E*)-4-Methyl-*N*-(4-oxo-4-phenylbut-2-en-1-yl)-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (42)



*Synthesis of substrate **39** was performed by a previous member of the Lam group*

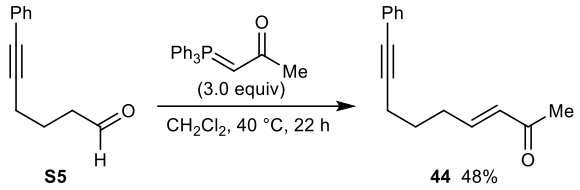


***N*-(2,2-Dimethoxyethyl)-4-methyl-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (40)**. To a solution of $PdCl_2(PPh_3)_2$ (421 mg, 0.60 mmol), CuI (57.1 mg, 0.30 mmol), and alkyne **39** (4.46 g, 15.0 mmol) in Et_3N (60 mL) under an argon atmosphere at room temperature was added iodobenzene (1.9 mL, 16.5 mmol), and the reaction was stirred for 23 h. The reaction was diluted with EtOAc (100 mL), washed with 10% aqueous HCl solution (100 mL), 50% brine (3 × 100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (30% EtOAc/pet. ether) to give the alkyne **40** (5.01 g, 89%) as a brown solid. R_f = 0.18 (20% EtOAc/pet. ether); m.p. 63–65 °C (Et_2O); IR 2998, 2833, 1595, 1489, 1436, 1331, 1306, 1262, 1159, 1131 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85-7.73 (2H, m, Ar**H**), 7.27-7.20 (5H, m, Ar**H**), 7.10-6.98 (2H, m, Ar**H**), 4.61 (1H, t, *J* = 5.5 Hz, C**H**$(OCH_3)_2$), 4.47 (2H, s, ≡CC**H**$_2$), 3.44 (6H, s, C(OC**H**$_3)_2$), 3.34 (2H, d, *J* = 5.5 Hz, C**H**$_2$CH), 2.33 (3H, s, ArC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.7 (C), 136.2 (C), 131.6 (2 × CH), 129.7 (2 × CH), 128.5 (CH), 128.2 (2 × CH), 127.9 (2 × CH), 122.4 (C), 104.6 (CH), 85.6 (C), 82.4 (C), 54.9 (2 × CH_3), 47.9 (CH_2), 39.3 (CH_2), 21.6 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{20}H_{23}NNaO_4S]^+$ $[M+Na]^+$: 396.1240, found: 396.1245.



(*E*)-4-Methyl-*N*-(4-oxo-4-phenylbut-2-en-1-yl)-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (42). A solution of alkyne **40** (1.00 g, 2.68 mmol) in a mixture of 3 M aqueous HCl (6.3 mL) and THF (8 mL) was stirred at 70 °C for 4 h. The volatiles were removed *in vacuo* and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with H_2O (20 mL), brine (20 mL), dried ($MgSO_4$), filtered, and concentrated in *vacuo* to leave aldehyde **41** that was used immediately in the next step without further purification. To a solution of aldehyde **41** (877 mg, 2.68 mmol) in CH_2Cl_2 (20 mL) under an argon atmosphere at room temperature was added 1-phenyl-2-(triphenyl-λ-5-phosphanylidene)ethan-1-one (1.53 g, 4.02 mmol) and the reaction was stirred at room temperature for 16 h. The volatiles were removed *in vacuo* and the residue was purified by column chromatography (20% EtOAc/pentane) to give the enone **42** (656 mg, 57% over two steps) as an orange solid. R_f = 0.44 (40% EtOAc/pet. ether); m.p. 82–84 °C (Et_2O); IR 3027, 1722, 1673 (C=O), 1625, 1579, 1490, 1346, 1158, 1091, 754 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.94-7.89 (2H, m, Ar**H**), 7.84-7.79 (2H, m, Ar**H**), 7.59-7.55 (1H, m, Ar**H**), 7.45 (2H, t, *J* = 7.7 Hz, Ar**H**), 7.31-7.27 (3H, m, Ar**H**), 7.26-7.21 (2H, m, Ar**H**), 7.14 (1H, dt, *J* = 15.5, 1.7 Hz, CH_2CH=C**H**), 7.12-7.06 (2H, m, Ar**H**), 6.93 (1H, dt, *J* = 15.5, 5.5 Hz, CH_2C**H**=), 4.37 (2H, s, ≡CC**H**$_2$), 4.18 (2H, dd, *J* = 5.5, 1.7 Hz, C**H**$_2$C=), 2.35 (3H, s, C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.1 (C), 144.1 (C), 141.6 (CH), 137.4 (C), 135.9 (C), 133.3 (CH), 131.7 (2 × CH), 129.9 (2 × CH), 128.81 (2 × CH), 128.80 (2 × CH), 128.75 (CH), 128.4 (CH), 128.3 (2 × CH), 128.0 (2 × CH), 122.1 (C), 86.4 (C), 81.5 (C), 48.2 (CH_2), 38.1 (CH_2), 21.6 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{26}H_{23}NNaO_3S]^+$ $[M+Na]^+$: 452.1291, found: 452.1293.

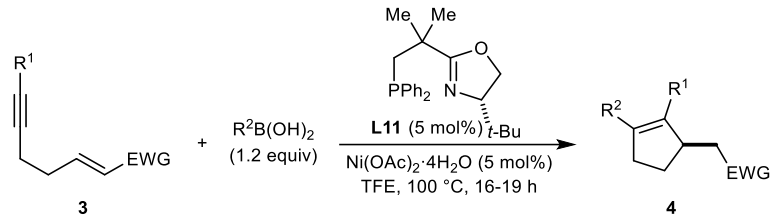
(*E*)-9-Phenylnon-3-en-8-yn-2-one (44)



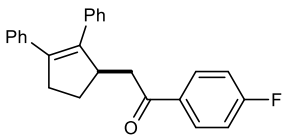
To a solution of aldehyde **S5** (500 mg, 2.90 mmol) in CH_2Cl_2 (10 mL) under an argon atmosphere at 40 °C was added 1-(triphenylphosphoranylidene)-2-propanone (2.77 g, 8.70 mmol) and the reaction was stirred at 40 °C for 22 h. The volatiles were removed *in vacuo* and the residue was purified by column chromatography (10% EtOAc/pet. ether) to give the enone **44** (298 mg, 48%) as a yellow oil. The analytical data were consistent with those reported previously.[177] R_f = 0.37 (20% EtOAc/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.36 (2H, m, Ar**H**), 7.31-7.26 (3H, m, Ar**H**), 6.83 (1H, dt, *J* = 15.9, 6.9 Hz, CH_2C**H**=), 6.14 (1H, dt, *J* = 15.9, 1.5 Hz, CH_2CH=C**H**), 2.49-2.39 (4H, m, 2 × C**H**$_2$), 2.25 (3H, s, C**H**$_3$), 1.85-1.74 (2H, m, C**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.5 (C), 147.2 (CH), 131.8 (CH), 131.5 (2 × CH), 128.2 (2 × CH), 127.7 (CH), 123.7 (C), 89.0 (C), 81.5 (C), 31.5 (CH_2), 27.1 (CH_2), 27.0 (CH_3), 19.0 (CH_2).

3.6 Enantioselective Nickel-Catalysed *anti*-Carbometallative Cyclisations onto Electron-Deficient Alkenes

General Procedure A



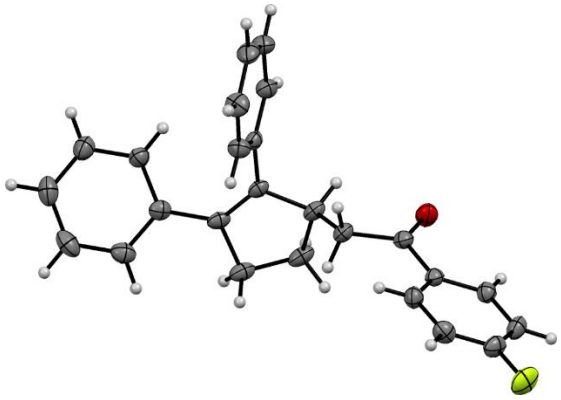
An oven-dried microwave vial fitted with a magnetic stirrer bar was charged with the appropriate substrate **3** (0.30 mmol), boronic acid (0.36 mmol), $Ni(OAc)_2{\cdot}4H_2O$ (3.7 mg, 0.015 mmol) and (*S*)-*t*-Bu-NeoPHOX (**L11**, 5.5 mg, 0.015 mmol). The vial was capped with a crimp cap seal and flushed with argon (5 min). Freshly degassed TFE (3 mL, using a stream of argon for 20 min) was added, the cap was sealed with PTFE tape, and the contents were stirred at room temperature for 10 min and then transferred to a pre-heated oil bath and stirred at 100 °C for 16–19 h. The reaction was cooled to room temperature, diluted with 50% brine (10 mL), and 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 to give the arylative cyclisation product **4**.

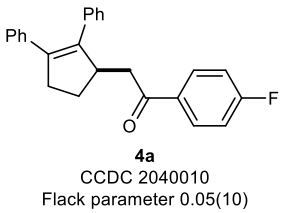


(*R*)-2-(2,3-Diphenylcyclopent-2-en-1-yl)-1-(4-fluorophenyl)ethan-1-one (4a). Prepared according to General Procedure A, using enyne **3a** (83.5 mg, 0.30 mmol) and phenylboronic acid (43.9 mg, 0.36 mmol) and stirring for 16 h. Purification by column chromatography (3% EtOAc/pet. ether) gave **4a** (97.6 mg, 91%) as an off-white solid. R_f = 0.69 (40% EtOAc/pet. ether); m.p. 82−83 °C (Et_2O); IR 3050, 2946, 1804, 1674 (C=O), 1594, 1411, 1359, 1273, 1233, 1153 cm^{-1}; $[\alpha]_D^{25}$ −116.0 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.92-7.83 (2H, m, Ar**H**), 7.30-7.11 (10H, m, Ar**H**), 7.10-7.03 (2H, m, Ar**H**), 3.94-3.77 (1H, m, C**H**CH_2), 3.11 (1H, dddd, *J* = 15.9, 9.2, 6.6, 2.7 Hz, C**H**$_a$H$_b$C=), 3.01 (1H, dd, *J* = 16.6, 3.3 Hz, C**H**$_a$H$_b$C=O), 2.90 (1H, dd, *J* = 16.6, 10.5 Hz, CH$_a$**H**$_b$C=O), 2.73 (1H, dddd, *J* = 15.9, 9.3, 4.8, 1.3 Hz, CH$_a$**H**$_b$C=), 2.42 (1H,

app dtd, J = 13.3, 8.9, 6.6 Hz, $CH_2C\mathbf{H}_aH_bCH$), 1.76 (1H, app ddt, J = 13.3, 9.2, 4.7 Hz, $CH_2CH_a\mathbf{H}_bCH$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.5 (C), 165.8 (d, $J_{C\text{-}F}$ = 254.5 Hz, C), 140.8 (C), 138.2 (C), 137.8 (C), 137.5 (C), 133.7 (d, $J_{C\text{-}F}$ = 3.4 Hz, C), 130.8 (d, $J_{C\text{-}F}$ = 9.4 Hz, 2 × CH), 129.0 (2 × CH), 128.6 (2 × CH), 128.2 (2 × CH), 128.1 (2 × CH), 127.1 (CH), 126.8 (CH), 115.7 (d, $J_{C\text{-}F}$ = 21.9 Hz, 2 × CH), 46.8 (CH), 42.6 (CH_2), 36.6 (CH_2), 29.1 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –105.6 (s); HRMS (ESI) Exact mass calculated for $[C_{25}H_{21}FNaO]^+$ $[M+Na]^+$: 379.1469, found 379.1461; Enantiomeric excess was determined by HPLC using a Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH, 0.5 mL/min, 280 nm, 25 °C); t_r (minor) = 10.2 min, t_r (major) = 11.5 min, 99% ee.

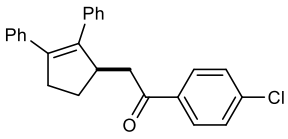
Slow diffusion of pentane into a solution of **4a** in Et_2O gave crystals that were suitable for X-ray crystallography:





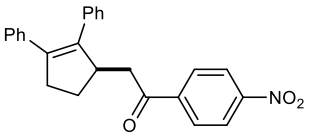
4a
CCDC 2040010
Flack parameter 0.05(10)

ORTEP with ellipsoid probabilities at 50%

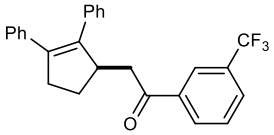


(*R*)-1-(4-Chlorophenyl)-2-(2,3-diphenylcyclopent-2-en-1-yl)ethan-1-one (4c). Prepared according to General Procedure A, using enyne **3c** (88.4 mg, 0.30 mmol) and phenylboronic acid (43.9 mg, 0.36 mmol) and stirring for 18 h. Purification by column chromatography (5% EtOAc/pet. ether) gave **4c** (75.3 mg, 67%) as an off-white solid. R_f = 0.65 (30% EtOAc/pet. ether); m.p. 37−39 °C (Et_2O); IR 3052, 2946, 1680 (C=O), 1587, 1487, 1399, 1356, 1271, 1092, 757 cm^{-1}; $[\alpha]_D^{25}$ −108.0 (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.82-7.75 (2H, m, Ar**H**), 7.41-7.35 (2H, m, Ar**H**), 7.28-7.26 (1H, m, Ar**H**), 7.26-7.11 (9H, m, Ar**H**), 3.90-3.80 (1H, m, C**H**CH_2), 3.11 (1H, dddd, J =

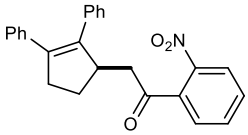
15.9, 9.2, 6.6, 2.8 Hz, C**H**$_a$H$_b$C=), 3.00 (1H, dd, *J* = 16.6, 3.2 Hz, C**H**$_a$H$_b$C=O), 2.89 (1H, dd, *J* = 16.6, 10.6 Hz, CH$_a$**H**$_b$C=O), 2.72 (1H, dddd, *J* = 15.9, 9.2, 4.8, 1.4 Hz, CH$_a$**H**$_b$C=), 2.42 (1H, app dtd, *J* = 13.3, 9.0, 6.7 Hz, CH$_2$C**H**$_a$H$_b$CH), 1.75 (1H, app ddt, *J* = 13.3, 9.1, 4.6 Hz, CH$_2$CH$_a$**H**$_b$CH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.9 (C), 140.7 (C), 139.5 (C), 138.2 (C), 137.7 (C), 137.5 (C), 135.6 (C), 129.6 (2 × CH), 129.0 (2 × CH), 128.9 (2 × CH), 128.6 (2 × CH), 128.2 (2 × CH), 128.1 (2 × CH), 127.1 (CH), 126.9 (CH), 46.8 (CH), 42.7 (CH_2), 36.6 (CH_2), 29.1 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{25}H_{21}{}^{35}ClNaO]^+$ $[M+Na]^+$: 395.1173, found: 395.1167; Enantiomeric excess was determined by HPLC using a Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH, 0.5 mL/min, 280 nm, 25 °C); t_r (minor) = 11.0 min, t_r (major) = 13.1 min, >99% ee.



(*R*)-2-(2,3-Diphenylcyclopent-2-en-1-yl)-1-(4-nitrophenyl)ethan-1-one (4d). Prepared according to General Procedure A, using enyne **3d** (91.6 mg, 0.30 mmol) and phenylboronic acid (43.9 mg, 0.36 mmol) and stirring for 19 h. Purification by column chromatography (10% EtOAc/pentane) gave **4d** (86.6 mg, 75%) as a yellow oil. R_f = 0.44 (20% EtOAc/pet. ether); IR 3077, 2944, 1692 (C=O), 1602, 1525, 1345, 1318, 1273, 761, 698 cm^{-1}; $[\alpha]_D^{20}$ −144.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32-8.15 (2H, m, Ar**H**), 8.04-7.89 (2H, m, Ar**H**), 7.29-7.26 (1H, m, Ar**H**), 7.26-7.09 (9H, m, Ar**H**), 3.93-3.81 (1H, m, C**H**CH$_2$), 3.18-3.04 (2H, m, C**H**$_a$H$_b$C= and C**H**$_a$H$_b$C=O), 2.96 (1H, dd, *J* = 16.9, 10.2 Hz, CH$_a$**H**$_b$C=O), 2.74 (1H, dddd, *J* = 15.9, 9.2, 4.9, 1.4 Hz, CH$_a$**H**$_b$C=), 2.45 (1H, app dtd, *J* = 13.3, 8.9, 6.5 Hz, CH$_2$C**H**$_a$H$_b$CH), 1.76 (1H, app ddt, *J* = 13.3, 9.2, 4.7 Hz, CH$_2$CH$_a$**H**$_b$CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.6 (C), 150.3 (C), 141.6 (C), 140.3 (C), 138.5 (C), 137.5 (C), 137.3 (C), 129.2 (2 × CH), 129.0 (2 × CH), 128.7 (2 × CH), 128.2 (2 × CH), 128.1 (2 × CH), 127.2 (CH), 127.0 (CH), 123.9 (2 × CH), 46.7 (CH), 43.4 (CH_2), 36.6 (CH_2), 29.1 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{25}H_{21}O_3NNa]^+$ $[M+Na]^+$: 406.1414, found: 406.1414; Enantiomeric excess was determined by HPLC using a Chiralpak AS-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 280 nm, 25 °C); t_r (minor) = 11.1 min, t_r (major) = 13.1 min, >99% ee.

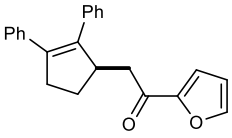


(*R*)-2-(2,3-Diphenylcyclopent-2-en-1-yl)-1-[3-(trifluoromethyl)phenyl]ethan-1-one (4e). Prepared according to General Procedure A, using enyne **3e** (98.5 mg, 0.30 mmol) and phenylboronic acid (43.9 mg, 0.36 mmol) and stirring for 17 h. Purification by column chromatography (4% EtOAc/pet. ether) gave **4e** (112 mg, 92%) as a light yellow oil. R_f = 0.58 (20% EtOAc/pet. ether); IR 3055, 2927, 1690 (C=O), 1611, 1495, 1440, 1331, 1168, 1128, 695 cm^{-1}; $[\alpha]_D^{25}$ −100.0 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (1H, s, Ar**H**), 8.02 (1H, d, *J* = 7.9 Hz, Ar**H**), 7.78 (1H, d, *J* = 7.9 Hz, Ar**H**), 7.55 (1H, app t, *J* = 7.9 Hz, Ar**H**), 7.28-7.11 (10H, m, Ar**H**), 3.96-3.79 (1H, m, C**H**CH_2), 3.13 (1H, dddd, *J* = 15.9, 9.2, 6.6, 2.8 Hz, C$\mathbf{H}_a$$H_b$C=), 3.07 (1H, dd, *J* = 16.6, 3.3 Hz, C$\mathbf{H}_a$$H_b$C=O), 2.93 (1H, dd, *J* = 16.6, 10.4 Hz, $CH_a$$\mathbf{H}_b$C=O), 2.73 (1H, dddd, *J* = 15.9, 9.4, 4.8, 1.4 Hz, $CH_a$$\mathbf{H}_b$C=), 2.42 (1H, app dtd, *J* = 13.3, 8.9, 6.7 Hz, CH_2C$\mathbf{H}_a$$H_b$CH), 1.77 (1H, app ddt, *J* = 13.3, 9.1, 4.6 Hz, $CH_2CH_a$$\mathbf{H}_b$CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.8 (C), 140.5 (C), 138.3 (C), 137.7 (C), 137.3 (C), 131.4 (CH), 131.3 (q, $^2J_{C\text{-}F}$ = 33.0 Hz, C), 129.4 (q, $^3J_{C\text{-}F}$ = 3.7 Hz, CH), 129.3 (CH), 129.0 (2 × CH), 128.7 (2 × CH), 128.2 (2 × CH), 128.1 (2 × CH), 127.2 (CH), 126.9 (CH), 125.1 (q, $^3J_{C\text{-}F}$ = 3.7 Hz, CH), 123.8 (q, $^1J_{C\text{-}F}$ = 272.5 Hz, C), 46.9 (CH), 42.9 (CH_2), 36.6 (CH_2), 29.1 (CH_2) (one quaternary carbon signal was not identified); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.8 (s, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{26}H_{21}F_3NaO]^+$ $[M+Na]^+$: 429.1437, found: 429.1438; Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column (99:1 *iso*-hexane:*i*-PrOH, 0.3 mL/min, 280 nm, 25 °C); t_r (major) = 23.0 min, t_r (minor) = 24.5 min, >99% ee.

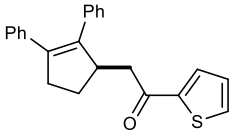


(*R*)-2-(2,3-Diphenylcyclopent-2-en-1-yl)-1-(2-nitrophenyl)ethan-1-one (4f). Prepared according to General Procedure A, using enyne **3f** (91.6 mg, 0.30 mmol) and phenylboronic acid (43.9 mg, 0.36 mmol) and stirring for 17 h. Purification by column chromatography (10% EtOAc/pet. ether) gave **4f** (37.6 mg, 33%) as an orange solid. R_f = 0.44 (30% EtOAc/pet. ether); m.p. 79−80 °C (Et_2O); IR 3045, 2924, 1706 (C=O), 1598, 1573, 1525, 1439, 1347, 1198, 757 cm^{-1}; $[\alpha]_D^{25}$ −88.0 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.11-8.00 (1H, m, Ar**H**), 7.66-7.60 (1H, m, Ar**H**), 7.58-7.52 (1H, m, Ar**H**), 7.26-7.16 (5H, m, Ar**H**), 7.16-7.07 (6H, m, Ar**H**), 3.94-3.83 (1H, m, C**H**CH_2),

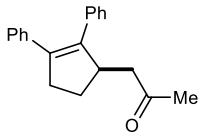
3.13 (1H, dddd, *J* = 15.6, 9.0, 6.2, 2.7 Hz, C**H**$_a$H$_b$C=), 2.89 (1H, dd, *J* = 17.9, 3.1 Hz, C**H**$_a$H$_b$C=O), 2.82-2.69 (2H, m, CH$_a$**H**$_b$C=O and CH$_a$**H**$_b$C=), 2.53 (1H, app dtd, *J* = 13.1, 8.9, 6.2 Hz, CH$_2$C**H**$_a$H$_b$CH), 2.03-1.97 (1H, m, CH$_2$CH$_a$**H**$_b$CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.1 (C), 145.8 (C), 140.1 (C), 138.6 (C), 138.2 (C), 137.7 (C), 137.3 (C), 134.2 (CH), 130.5 (CH), 129.0 (2 × CH), 128.6 (2 × CH), 128.2 (2 × CH), 128.1 (2 × CH), 127.6 (CH), 127.1 (CH), 126.8 (CH), 124.5 (CH), 46.9 (CH_2), 46.0 (CH), 36.8 (CH_2), 28.8 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{25}H_{21}NNaO_3]^+$ $[M+Na]^+$: 406.1414, found: 406.1416; Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column (90:10 *iso*-hexane:*i*-PrOH, 0.5 mL/min, 280 nm, 25 °C); t_r (minor) = 21.1 min, t_r (major) = 22.2 min, 99% ee.



(*R*)-2-(2,3-Diphenylcyclopent-2-en-1-yl)-1-(furan-2-yl)ethan-1-one (4g). Prepared according to General Procedure A, using enyne **3g** (75.1 mg, 0.30 mmol) and phenylboronic acid (43.9 mg, 0.36 mmol) and stirring for 17 h. Purification by column chromatography (5 to 10% EtOAc/pet. ether) gave **4g** (83.5 mg, 85%) as an off-white solid. R_f = 0.51 (30% EtOAc/pet. ether); m.p. 99−101 °C (Et_2O); IR 3116, 3094, 2944, 1664 (C=O), 1562, 1469, 1397, 1160, 911, 757 cm^{-1}; $[\alpha]_D^{25}$ −132.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (1H, d, *J* = 1.7 Hz, Ar**H**), 7.26-7.23 (2H, m, Ar**H**), 7.22-7.10 (8H, m, Ar**H**), 7.07 (1H, d, *J* = 3.6 Hz, Ar**H**), 6.48 (1H, dd, *J* = 3.6, 1.7 Hz, Ar**H**), 3.89-3.78 (1H, m, C**H**CH$_2$), 3.11 (1H, dddd, *J* = 15.9, 9.1, 6.5, 2.7 Hz, C**H**$_a$H$_b$C=), 2.88 (1H, dd, *J* = 15.9, 3.6 Hz, C**H**$_a$H$_b$C=O), 2.79 (1H, dd, *J* = 15.9, 10.6 Hz, CH$_a$**H**$_b$C=O), 2.72 (1H, dddd, *J* = 15.9, 9.2, 5.0, 1.4 Hz, CH$_a$**H**$_b$C=), 2.44-2.27 (1H, m, CH$_2$C**H**$_a$H$_b$CH), 1.79 (1H, app ddt, *J* = 13.5, 9.2, 4.8 Hz, CH$_2$CH$_a$**H**$_b$CH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.3 (C), 153.1 (C), 146.3 (CH), 140.8 (C), 138.2 (C), 137.8 (C), 137.4 (C), 129.0 (2 × CH), 128.5 (2 × CH), 128.2 (2 × CH), 128.1 (2 × CH), 127.0 (CH), 126.8 (CH), 117.1 (CH), 112.2 (CH), 46.9 (CH), 42.6 (CH_2), 36.6 (CH_2), 28.9 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{23}H_{20}NaO_2]^+$ $[M+Na]^+$: 351.1361, found: 351.1353; Enantiomeric excess was determined by HPLC using a Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH, 0.5 mL/min, 280 nm, 25 °C); t_r (minor) = 10.8 min, t_r (major) = 12.8 min, >99% ee.

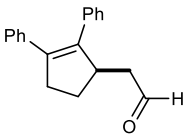


(*R*)-2-(2,3-Diphenylcyclopent-2-en-1-yl)-1-(thiophen-2-yl)ethan-1-one (4h). Prepared according to General Procedure A, using enyne **3h** (79.9 mg, 0.30 mmol) and phenylboronic acid (43.9 mg, 0.36 mmol) and stirring for 18 h. Purification by column chromatography (5% EtOAc/pet. ether) gave **4h** (83.5 mg, 81%) as an off-white solid. R_f = 0.57 (30% EtOAc/pet. ether); m.p. 130−131 °C (Et_2O); IR 3098, 2925, 1645 (C=O), 1518, 1493, 1412, 1277, 1232, 856, 695 cm^{-1}; $[\alpha]_D^{25}$ −128.0 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (1H, d, *J* = 5.0 Hz, Ar**H**), 7.56 (1H, d, *J* = 3.8 Hz, Ar**H**) 7.28-7.12 (10H, m, Ar**H**), 7.07 (1H, app t, *J* = 4.4 Hz, Ar**H**), 3.92-3.79 (1H, m, C**H**CH_2), 3.12 (1H, dddd, *J* = 15.9, 9.1, 6.6, 2.7 Hz, C**H**$_a$H$_b$C=), 2.97 (1H, dd, *J* = 15.8, 3.3 Hz, C**H**$_a$H$_b$C=O), 2.84 (1H, dd, *J* = 15.8, 10.7 Hz, CH$_a$**H**$_b$C=O), 2.72 (1H, dddd, *J* = 15.9, 9.3, 4.9, 1.4 Hz, CH$_a$**H**$_b$C=), 2.39 (1H, app dtd, *J* = 13.3, 8.9, 6.5 Hz, CH_2C**H**$_a$H$_b$CH), 1.82 (1H, app ddt, *J* = 13.3, 9.2, 4.7 Hz, CH_2CH$_a$**H**$_b$CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.1 (C), 144.8 (C), 140.7 (C), 138.2 (C), 137.8 (C), 137.4 (C), 133.6 (CH), 132.0 (CH), 129.0 (2 × CH), 128.6 (2 × CH), 128.2 (2 × CH), 128.11 (CH), 128.06 (2 × CH), 127.1 (CH), 126.8 (CH), 47.3 (CH), 43.4 (CH_2), 36.6 (CH_2), 28.9 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{23}H_{20}NaOS]^+$ $[M+Na]^+$: 367.1127, found: 367.1149; Enantiomeric excess was determined by HPLC using a Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH, 0.5 mL/min, 280 nm, 25 °C); t_r (minor) = 10.9 min, t_r (major) = 13.1 min, >99% ee.

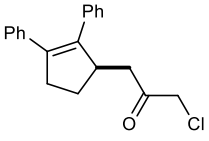


(*R*)-1-(2,3-Diphenylcyclopent-2-en-1-yl)propan-2-one (4b). Prepared according to General Procedure A, using enyne **3b** (59.5 mg, 0.30 mmol) and phenylboronic acid (43.9 mg, 0.36 mmol) and stirring for 16 h. Purification by column chromatography (5% EtOAc/pet. ether) gave **4b** (78.2 mg, 94%) as an off-white solid. R_f = 0.59 (40% EtOAc/pet. ether); m.p. 55−57 °C (Et_2O); IR 3021, 2941, 1704 (C=O), 1597, 1488, 1441, 1360, 1158, 769, 694 cm^{-1}; $[\alpha]_D^{25}$ −172.0 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.26-7.20 (3H, m, Ar**H**), 7.20-7.06 (7H, m, Ar**H**), 3.76-3.59 (1H, m, C**H**CH_2), 3.06 (1H, dddd, *J* = 15.8, 9.0, 6.3, 2.7 Hz, C**H**$_a$H$_b$C=), 2.70 (1H, dddd, *J* = 15.8, 9.2, 5.2, 1.5 Hz, CH$_a$**H**$_b$C=), 2.53 (1H, dd, *J* = 16.9, 3.5 Hz, C**H**$_a$H$_b$C=O), 2.44-2.33 (2H, m, CH$_a$**H**$_b$C=O and CH_2C**H**$_a$H$_b$CH), 2.05 (3H, s, C**H**$_3$), 1.67 (1H, app ddt, *J* = 13.8, 9.1, 5.0 Hz, CH_2CH$_a$**H**$_b$CH); ^{13}C NMR

(101 MHz, $CDCl_3$) δ 208.8 (C), 140.7 (C), 138.0 (C), 137.7 (C), 137.5 (C), 129.0 (2 × CH), 128.6 (2 × CH), 128.2 (2 × CH), 128.0 (2 × CH), 127.0 (CH), 126.8 (CH), 47.9 (CH_2), 46.4 (CH), 36.5 (CH_2), 30.5 (CH_3), 29.1 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{20}H_{20}NaO]^+$ $[M+Na]^+$: 299.1406, found: 299.1405; Enantiomeric excess was determined by HPLC using a Chiralpak AS-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 280 nm, 25 °C); t_r (minor) = 6.3 min, t_r (major) = 7.7 min, 99% ee.

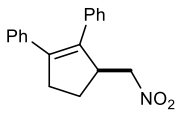


(*R*)-2-(2,3-Diphenylcyclopent-2-en-1-yl)acetaldehyde (4i). Prepared according to General Procedure A, using enyne **3i** (55.3 mg, 0.30 mmol) and phenylboronic acid (43.9 mg, 0.36 mmol) and stirring for 17 h. Purification by column chromatography (5% EtOAc/pet. ether) gave **4i** (45.5 mg, 58%) as an off-white solid. R_f = 0.59 (30% EtOAc/pet. ether); m.p. 56−57 °C (Et_2O); IR 3077, 3022, 2919, 2839, 2732, 1712 (C=O), 1597, 1489, 1442, 761 cm^{-1}; $[\alpha]_D^{25}$ −180.0 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 9.72 (1H, app t, *J* = 2.0 Hz, O=C**H**), 7.30-7.26 (1H, m, Ar**H**), 7.25-7.19 (2H, m, Ar**H**), 7.18-7.07 (7H, m, Ar**H**), 3.77-3.67 (1H, m, C**H**CH_2), 3.09 (1H, dddd, *J* = 15.9, 9.0, 6.3, 2.7 Hz, C**H**$_a$H$_b$C=), 2.75 (1H, dddd, *J* = 15.9, 9.2, 5.1, 1.4 Hz, CH$_a$**H**$_b$C=), 2.55 (1H, ddd, *J* = 16.6, 3.8, 1.5 Hz, C**H**$_a$H$_b$C=O), 2.47-2.35 (2H, m, CH$_a$**H**$_b$C=O and CH_2C**H**$_a$H$_b$CH), 1.76 (1H, app ddt, *J* = 13.7, 9.5, 5.0 Hz, CH_2CH$_a$**H**$_b$CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.6 (CH), 140.1 (C), 138.3 (C), 137.5 (C), 137.3 (C), 128.9 (2 × CH), 128.7 (2 × CH), 128.2 (2 × CH), 128.1 (2 × CH), 127.2 (CH), 126.9 (CH), 48.1 (CH_2), 45.4 (CH), 36.6 (CH_2), 28.9 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{19}H_{18}NaO]^+$ $[M+Na]^+$: 285.1250, found: 285.1254; Enantiomeric excess was determined by HPLC using a Chiralpak IC column (95:5 *iso*-hexane:*i*-PrOH, 0.4 mL/min, 230 nm, 25 °C); t_r (major) = 17.7 min, t_r (minor) = 18.4 min, >99% ee.



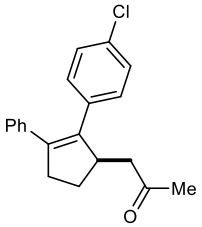
(*R*)-1-Chloro-3-(2,3-diphenylcyclopent-2-en-1-yl)propan-2-one (4j). Prepared according to a modification of General Procedure A, using enyne **3j** (69.8 mg, 0.30 mmol), phenylboronic acid (73.2 mg, 0.60 mmol), $Ni(OAc)_2 \cdot 4H_2O$ (14.9 mg, 0.06 mmol) and (*S*)-*t*-Bu-NeoPHOX (**L11**, 22.0 mg, 0.06 mmol) and stirring for 18 h. Purification by column chromatography (3

to 4% EtOAc/pentane) gave **4j** (39.1 mg, 42%) as a yellow solid. R_f = 0.56 (20% EtOAc/pet. ether); m.p. 48–49 °C (Et_2O); IR 3021, 2931, 1731 (C=O), 1717, 1598, 1490, 1442, 1397, 1069, 1030 cm^{-1}; $[\alpha]_D^{20}$ −148.0 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.26 (1H, m, Ar**H**), 7.26-7.08 (9H, m, Ar**H**), 4.04-3.83 (2H, m, C**H**$_2$Cl), 3.82-3.70 (1H, m, C**H**CH_2), 3.08 (1H, dddd, *J* = 15.9, 8.9, 6.1, 2.7 Hz, C**H**$_a$H$_b$C=), 2.72 (1H, dddd, *J* = 15.9, 9.2, 5.3, 1.6 Hz, CH$_A$**H**$_B$C=), 2.64 (1H, dd, *J* = 17.1, 4.1 Hz, C**H**$_a$H$_b$C=O), 2.56 (1H, dd, *J* = 17.1, 9.7 Hz, CH$_a$**H**$_b$C=O), 2.41 (1H, app dtd, *J* = 13.0, 8.8, 6.1 Hz, CH$_2$C**H**$_a$H$_b$CH), 1.69 (1H, app ddt, *J* = 13.0, 9.0, 5.2 Hz, CH$_2$CH$_a$**H**$_b$CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.3 (C), 140.2 (C), 138.4 (C), 137.5 (C), 137.2 (C), 129.0 (2 × CH), 128.7 (2 × CH), 128.2 (2 × CH), 128.1 (2 × CH), 127.2 (CH), 126.9 (CH), 48.6 (CH_2), 46.4 (CH), 44.1 (CH_2), 36.5 (CH_2), 29.1 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{20}H_{19}{}^{35}ClNaO]^+$ $[M+Na]^+$: 333.1017, found: 333.1019; Enantiomeric excess was determined by HPLC using a Chiralpak AS-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 280 nm, 25 °C); t_r (minor) = 8.3 min, t_r (major) = 11.2 min, 99% ee.

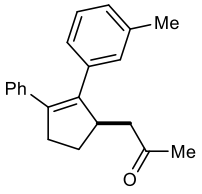


(*S*)-[3-(Nitromethyl)cyclopent-1-ene-1,2-diyl]dibenzene (4l). Prepared according to a modification of General Procedure A, using enyne **3l** (60.4 mg, 0.30 mmol), phenylboronic acid (73.2 mg, 0.60 mmol), $Ni(OAc)_2{\cdot}4H_2O$ (7.5 mg, 0.03 mmol) and (*S*)-*t*-Bu-NeoPHOX (**L11**, 11.0 mg, 0.03 mmol) and stirring for 17 h. Purification by column chromatography (5% EtOAc/pentane) gave **4l** (61.4 mg, 73%) as a yellow solid. R_f = 0.46 (10% EtOAc/pet. ether); m.p. 49−50 °C (Et_2O); IR 3077, 3056, 2919, 2846, 1546, 1490, 1442, 1380, 762, 692 cm^{-1}; $[\alpha]_D^{25}$ −128.0 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.24 (3H, m, Ar**H**), 7.24-7.06 (7H, m, Ar**H**), 4.37 (1H, dd, *J* = 12.1, 3.8 Hz, C**H**$_a$H$_b$NO$_2$), 4.25 (1H, dd, *J* = 12.1, 10.3 Hz, CH$_a$**H**$_b$NO$_2$), 4.11-3.96 (1H, m, C**H**CH_2), 3.17 (1H, dddd, *J* = 16.3, 9.2, 6.8, 2.7 Hz, C**H**$_a$H$_b$C=), 2.78 (1H, dddd, *J* = 16.3, 9.4, 4.5, 1.3 Hz, CH$_a$**H**$_b$C=), 2.39 (1H, app dtd, *J* = 13.5, 9.1, 6.9 Hz, CH$_2$C**H**$_a$H$_b$CH), 2.02 (1H, ddt, *J* = 13.5, 8.8, 4.1 Hz, CH$_2$CH$_a$**H**$_b$CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.8 (C), 136.9 (C), 136.02 (C), 135.98 (C), 128.9 (2 × CH), 128.7 (2 × CH), 128.2 (2 × CH), 128.1 (2 × CH), 127.7 (CH), 127.4 (CH), 78.4 (CH_2), 49.9 (CH), 36.4 (CH_2), 26.7 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{18}H_{17}NNaO_2]^+$ $[M+Na]^+$: 302.1151, found:

302.1149; Enantiomeric excess was determined by HPLC using a Chiralpak IC column (99.5:0.5 *iso*-hexane:*i*-PrOH, 0.3 mL/min, 280 nm, 25 °C); t_r (minor) = 38.0 min, t_r (major) = 39.3 min, >99% ee.

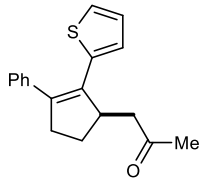


(*R*)-1-[2-(4-Chlorophenyl)-3-phenylcyclopent-2-en-1-yl]propan-2-one (4o). Prepared according to General Procedure A, using enyne **3o** (69.8 mg, 0.30 mmol) and phenylboronic acid (43.9 mg, 0.36 mmol) and stirring for 16 h. Purification by column chromatography (5% EtOAc/pet. ether) gave **4o** (64.6 mg, 69%) as an off-white solid. R_f = 0.58 (30% EtOAc/pet. ether); m.p. 84−85 °C (Et_2O); IR 3052, 2928, 1704 (C=O), 1486, 1361, 1157, 1088, 1010, 821, 763 cm^{-1}; $[\alpha]_D^{25}$ −184.0 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.24-7.12 (5H, m, Ar**H**), 7.11-7.02 (4H, m, Ar**H**), 3.71-3.61 (1H, m, C**H**CH_2), 3.05 (1H, dddd, *J* = 16.0, 9.1, 6.4, 2.7 Hz, C**H**$_a$H$_b$C=), 2.69 (1H, dddd, *J* = 16.0, 9.3, 5.2, 1.4 Hz, CH$_a$**H**$_b$C=), 2.49 (1H, dd, *J* = 17.0, 3.5 Hz, C**H**$_a$H$_b$C=O), 2.44-2.33 (2H, m, CH$_a$**H**$_b$C=O and CH$_2$C**H**$_a$H$_b$CH), 2.07 (3H, s, C**H**$_3$), 1.66 (1H, app ddt, *J* = 13.7, 9.4, 5.0 Hz, CH$_2$CH$_a$**H**$_b$CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.5 (C), 139.3 (C), 139.0 (C), 137.4 (C), 135.9 (C), 132.7 (C), 130.3 (2 × CH), 128.8 (2 × CH), 128.2 (2 × CH), 128.1 (2 × CH), 127.0 (CH), 47.8 (CH_2), 46.1 (CH), 36.7 (CH_2), 30.5 (CH_3), 29.1 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{20}H_{19}{}^{35}ClNaO]^+$ $[M+Na]^+$: 333.1017, found: 333.1029; Enantiomeric excess was determined by HPLC using a Chiralpak AS-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 280 nm, 25 °C); t_r (minor) = 5.9 min, t_r (major) = 6.7 min, 99% ee.

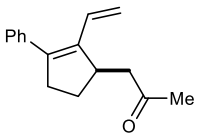


(*R*)-1-[3-Phenyl-2-(m-tolyl)cyclopent-2-en-1-yl]propan-2-one (4p). Prepared according to General Procedure A, using enyne **3p** (63.7 mg, 0.30 mmol) and phenylboronic acid (43.9 mg, 0.36 mmol) and stirring for 17 h. Purification by column chromatography (6% EtOAc/pet. ether) gave **4p** (63.4 mg, 73%) as a colourless oil. R_f = 0.51 (20% EtOAc/pet. ether); IR 3053, 2924, 1714 (C=O), 1600, 1493, 1443, 1360, 1159, 761, 697 cm^{-1}; $[\alpha]_D^{25}$ −136.0 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.19-7.08 (6H, m, Ar**H**), 7.05-7.00 (1H, m, Ar**H**), 6.96-6.93 (1H, m, Ar**H**), 6.92-6.86 (1H, m, Ar**H**),

3.71-3.60 (1H, m, C**H**CH_2), 3.05 (1H, dddd, *J* = 15.9, 9.0, 6.3, 2.5 Hz, C**H**$_a$H$_b$C=), 2.70 (1H, dddd, *J* = 15.9, 9.4, 5.1, 1.4 Hz, CH_a**H**$_b$C=), 2.53 (1H, dd, *J* = 16.9, 3.4 Hz, C**H**$_a$H$_b$C=O), 2.43-2.32 (2H, m, CH_a**H**$_b$C=O and CH_2C**H**$_a$H$_b$CH), 2.27 (3H, s, C**H**$_3$), 2.06 (3H, s, C**H**$_3$), 1.66 (1H, app ddt, *J* = 13.7, 9.4, 5.0 Hz, CH_2CH_a**H**$_b$CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.9 (C), 140.9 (C), 138.1 (C), 137.7 (C), 137.6 (C), 137.5 (C), 129.4 (CH), 128.4 (CH), 128.1 (2 × CH), 128.0 (2 × CH), 127.8 (CH), 126.7 (CH), 126.1 (CH), 47.9 (CH), 46.5 (CH_2), 36.5 (CH_3), 30.5 (CH_2), 29.1 (CH_3), 21.6 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{21}H_{22}NaO]^+$ $[M+Na]^+$: 313.1563, found: 313.1559; Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column (99:1 *iso*-hexane:*i*-PrOH, 0.3 mL/min, 280 nm, 25 °C); t_r (major) = 23.6 min, t_r (minor) = 25.6 min, 99% ee.

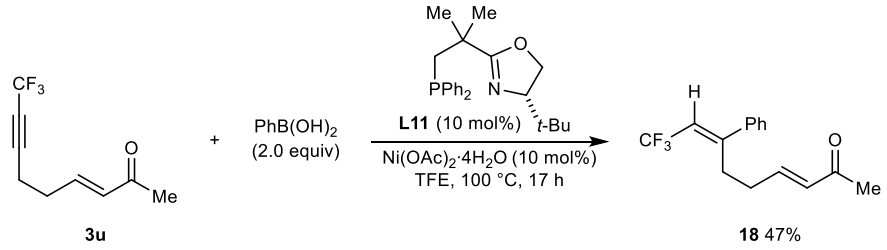


(*R*)-1-[3-Phenyl-2-(thiophen-2-yl)cyclopent-2-en-1-yl]propan-2-one (4q). Prepared according to General Procedure A, using enyne **3q** (61.3 mg, 0.30 mmol) and phenylboronic acid (43.9 mg, 0.36 mmol) and stirring for 17 h. Purification by column chromatography (8% EtOAc/pet. ether) gave **4q** (41.7 mg, 49%) as an off-white solid. R_f = 0.42 (30% EtOAc/pet. ether); m.p. 68−70 °C (Et_2O); IR 3074, 2925, 2843, 1713 (C=O), 1598, 1491, 1360, 1159, 761, 670 cm^{-1}; $[\alpha]_D^{25}$ −36.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.27 (2H, m, Ar**H**), 7.26-7.21 (3H, m, Ar**H**), 7.12 (1H, dd, *J* = 5.1, 1.1 Hz, Ar**H**), 6.90 (1H, dd, *J* = 5.1, 3.6 Hz, Ar**H**), 6.80 (1H, dd, *J* = 3.6, 1.1 Hz, Ar**H**), 3.71-3.56 (1H, m, C**H**CH_2), 2.98 (1H, app dtd, *J* = 16.8, 8.4, 2.6 Hz, C**H**$_a$H$_b$C=), 2.75 (1H, dd, *J* = 16.9, 3.0 Hz, C**H**$_a$H$_b$C=O), 2.71-2.62 (1H, m, CH_a**H**$_b$C=), 2.53 (1H, dd, *J* = 16.9, 10.7 Hz, CH_a**H**$_b$C=O), 2.41-2.26 (1H, m, CH_2C**H**$_a$H$_b$CH), 2.14 (3H, s, C**H**$_3$), 1.71 (1H, app ddt, *J* = 13.1, 8.5, 3.2 Hz, CH_2CH_a**H**$_b$CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.7 (C), 140.0 (C), 139.0 (C), 138.2 (C), 133.4 (C), 128.5 (2 × CH), 128.2 (2 × CH), 127.4 (CH), 126.9 (CH), 126.1 (CH), 125.1 (CH), 47.6 (CH_2), 46.2 (CH), 37.7 (CH_2), 30.5 (CH_3), 29.1 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{18}H_{18}NaOS]^+$ $[M+Na]^+$: 305.0971, found: 305.0971; Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column (95:5 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 280 nm, 25 °C); t_r (major) = 6.2 min, t_r (minor) = 6.7 min, 84% ee.



(*R*)-1-(3-Phenyl-2-vinylcyclopent-2-en-1-yl)propan-2-one (4r). Prepared according to General Procedure A, using enyne **3r** (44.5 mg, 0.30 mmol) and phenylboronic acid (43.9 mg, 0.36 mmol) and stirring for 17 h. Purification by column chromatography (20% EtOAc/cyclohexane) gave **4r** (67.4 mg, 99%) as a yellow oil. R_f = 0.50 (30% EtOAc/pet. ether); IR 3083, 2928, 1712 (C=O), 1600, 1492, 1358, 1158, 900, 763, 698 cm^{-1}; $[\alpha]_D^{25}$ +20.0 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.32 (2H, m, Ar**H**), 7.30-7.25 (3H, m, Ar**H**), 6.64 (1H, dd, *J* = 17.7, 11.0 Hz, C**H**=), 5.24-5.13 (2H, m, =C$\mathbf{H}_2$), 3.56 (1H, app t, *J* = 9.4 Hz, C**H**CH_2), 2.94 (1H, app dt, *J* = 17.5, 8.8 Hz, C$\mathbf{H}_a$$H_b$C=), 2.78 (1H, dd, *J* = 16.9, 2.5 Hz, C$\mathbf{H}_a$$H_b$C=O), 2.64 (1H, app dd, *J* = 17.5, 9.4 Hz, $CH_a$$\mathbf{H}_b$C=), 2.47 (1H, dd, *J* = 16.9, 10.8 Hz, $CH_a$$\mathbf{H}_b$C=O), 2.22-2.11 (1H, m, CH_2C$\mathbf{H}_a$$H_b$CH), 2.18 (3H, s, C$\mathbf{H}_3$), 1.69 (1H, app ddt, *J* = 11.4, 8.1, 1.7 Hz, $CH_2CH_a$$\mathbf{H}_b$CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.0 (C), 141.8 (C), 138.8 (C), 137.7 (C), 131.0 (CH), 128.34 (2 × CH), 128.27 (2 × CH), 127.3 (CH), 115.5 (CH_2), 46.8 (CH_2), 40.9 (CH), 36.1 (CH_2), 30.6 (CH_3), 28.8 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{16}H_{18}NaO]^+$ $[M+Na]^+$: 249.1250, found: 249.1241; Enantiomeric excess was determined by HPLC using a Chiralpak AS-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 280 nm, 25 °C); t_r (minor) = 5.4 min, t_r (major) = 6.2 min, 91% ee.

(3*E*,7*E*)-9,9,9-Trifluoro-7-phenylnona-3,7-dien-2-one (18)

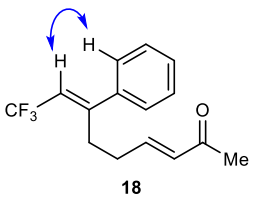


An oven-dried microwave vial fitted with a magnetic stirrer bar was charged with enyne **3u** (9.5 mg, 0.05 mmol), phenylboronic acid (12.2 mg, 0.10 mmol), $Ni(OAc)_2·4H_2O$ (1.2 mg, 0.005 mmol) and (*S*)-*t*-Bu-NeoPHOX **L11** (1.8 mg, 0.005 mmol). The vial was capped with a crimp cap seal and flushed with argon (5 min). Freshly degassed TFE (0.5 mL, using a stream of argon for 20 min) was added, the cap was sealed with PTFE tape, and the contents were stirred at room temperature for 10 min and then at

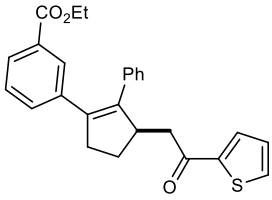
100 °C for 17 h. The reaction was cooled to room temperature and filtered through a pad of silica (EtOAc) twice to give **18** (6.3 mg, 47%) as a colourless oil. R_f = 0.56 (30% EtOAc/pet. ether); IR 2955, 2854, 1699, 1676 (C=O), 1650, 1629, 1359, 1260, 1110, 975 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43-7.32 (5H, m, Ar**H**), 6.67 (1H, dt, *J* = 15.9, 7.0 Hz, CH_2C**H**=), 5.95 (1H, d, *J* = 15.9 Hz, CH_2CH=C**H**), 5.82 (1H, q, *J* = 8.6 Hz, C=C**H**(CF_3)), 2.90 (2H, t, *J* = 7.3 Hz, C**H**$_2CH_2C$=), 2.29 (2H, app q, *J* = 7.3, 6.7 Hz, CH_2C**H**$_2$C=), 2.19 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.6 (C), 146.1 (CH), 139.3 (C), 132.2 (CH), 129.4 (CH), 129.0 (2 × CH), 126.8 (2 × CH), 117.5 (q, $^2J_{C\text{-}F}$ = 33.5 Hz, CH), 31.1 (CH_2), 29.7 (CH_2), 26.8 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –56.5 (d, *J* = 8.6 Hz); HRMS (ESI) Exact mass calculated for $[C_{15}H_{15}F_3NaO]^+$ $[M+Na]^+$: 291.0967, found: 291.0968. (2 × quaternary carbons (**C**F_3 and =**C**Ph), expected to be split by fluorine, were not seen due to the carbon NMR being too weak).

Assignment of the alkene stereochemistry of **18** was made based on the following NOE interactions observed in the 2D NOESY spectrum between the alkenyl proton at 5.82 ppm and the aromatic protons at 7.43-7.32 ppm:

Key NOE interaction:

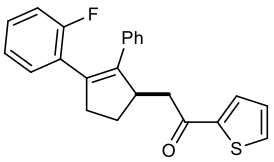


18



Ethyl (*R*)-3-{3-[2-oxo-2-(thiophen-2-yl)ethyl]-2-phenylcyclopent-1-en-1-yl}benzoate (4ha). Prepared according to General Procedure A, using enyne **3h** (79.9 mg, 0.30 mmol) and 3-ethoxycarbonylphenylboronic acid (69.8 mg, 0.36 mmol) and stirring for 18 h. Purification by column chromatography (10% EtOAc/pet. ether) gave **4ha** (120 mg, 96%) as a yellow solid. R_f = 0.48 (20% EtOAc/pet. ether); m.p. 83−84 °C (Et_2O); IR 3079, 2929, 1716 (C=O), 1660, 1441, 1280, 1222, 1109, 756, 699 cm^{-1}; $[\alpha]_D^{25}$ −96.0 (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.86 (1H, app t, *J* = 1.7 Hz, Ar**H**), 7.82 (1H, app dt, *J* = 7.6, 1.6 Hz, Ar**H**), 7.60 (1H, dd, *J* = 4.9, 1.1 Hz, Ar**H**), 7.57 (1H, dd, *J* = 3.8, 1.2 Hz, Ar**H**), 7.26-7.17 (5H, m, Ar**H**), 7.17-7.12 (2H, m, Ar**H**), 7.07 (1H, dd, *J* = 5.0, 3.8 Hz, Ar**H**), 4.31 (2H, app

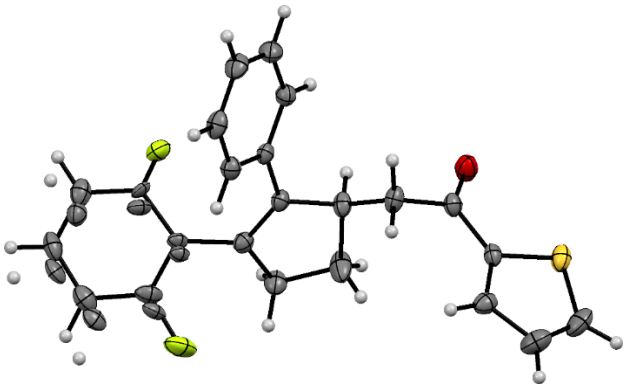
qd, *J* = 7.1, 1.9 Hz, OC**H**$_2$), 3.93-3.80 (1H, m, C**H**CH$_2$), 3.15 (1H, dddd, *J* = 15.8, 9.1, 6.4, 2.8 Hz, C**H**$_a$H$_b$C=), 2.97 (1H, dd, *J* = 15.9, 3.3 Hz, C**H**$_a$H$_b$C=O), 2.86 (1H, dd, *J* = 15.9, 10.7 Hz, CH$_a$**H**$_b$C=O), 2.74 (1H, dddd, *J* = 15.8, 9.2, 4.9, 1.4 Hz, CH$_a$**H**$_b$C=), 2.41 (1H, app dtd, *J* = 13.4, 9.0, 6.5 Hz, CH$_2$C**H**$_a$H$_b$CH), 1.84 (1H, app ddt, *J* = 13.4, 9.3, 4.8 Hz, CH$_2$CH$_a$**H**$_b$CH), 1.34 (3H, t, *J* = 7.1 Hz, C**H**$_3$); ^{13}C NMR (126 MHz, CDCl$_3$) δ 192.9 (C), 166.7 (C), 144.8 (C), 142.1 (C), 138.0 (C), 137.3 (C), 137.1 (C), 133.7 (CH), 132.7 (CH), 132.0 (CH), 130.4 (C), 129.1 (CH), 128.9 (2 × CH), 128.7 (2 × CH), 128.14 (CH), 128.05 (CH), 127.9 (CH), 127.3 (CH), 61.0 (CH$_2$), 47.3 (CH), 43.3 (CH$_2$), 36.5 (CH$_2$), 29.0 (CH$_2$), 14.4 (CH$_3$); HRMS (ESI) Exact mass calculated for [C$_{26}$H$_{24}$NaO$_3$S]$^+$ [M+Na]$^+$: 439.1338, found: 439.1331; Enantiomeric excess was determined by HPLC using a Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 280 nm, 25 °C); t$_r$ (minor) = 7.5 min, t$_r$ (major) = 9.3 min, >99% ee.

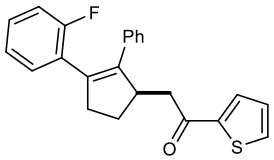


(*R*)-2-[3-(2-Fluorophenyl)-2-phenylcyclopent-2-en-1-yl]-1-(thiophen-2-yl)ethan-1-one (4hb). Prepared according to General Procedure A, using enyne **3h** (79.9 mg, 0.30 mmol) and 2-fluorophenylboronic acid (50.4 mg, 0.36 mmol) and stirring for 18 h. Purification by column chromatography (5% EtOAc/pet. ether) gave **4hb** (89.8 mg, 83%) as an off-white solid. R$_f$ = 0.73 (30% EtOAc/pet. ether); m.p. 129−131 °C (Et$_2$O); IR 3079, 2930, 2850, 1657 (C=O), 1484, 1446, 1414, 1204, 755, 698 cm^{-1}; $[\alpha]_D^{25}$ −172.0 (*c* 1.00, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.64-7.55 (2H, m, Ar**H**), 7.24-7.10 (6H, m, Ar**H**), 7.10-7.05 (3H, m, Ar**H**), 7.04-6.91 (1H, m, Ar**H**), 3.99-3.90 (1H, m, C**H**CH$_2$), 3.19-3.07 (1H, m, C**H**$_a$H$_b$C=), 3.01 (1H, dd, *J* = 16.1, 3.3 Hz, C**H**$_a$H$_b$C=O), 2.90 (1H, dd, *J* = 16.1, 10.7 Hz, CH$_a$**H**$_b$C=O), 2.65 (1H, dddd, *J* = 16.2, 9.3, 5.0, 1.5 Hz, CH$_a$**H**$_b$C=), 2.43 (1H, app dtd, *J* = 13.3, 8.9, 6.5 Hz, CH$_2$C**H**$_a$H$_b$CH), 1.84 (1H, app ddt, *J* = 13.3, 9.2, 4.8 Hz, CH$_2$CH$_a$**H**$_b$CH); ^{13}C NMR (126 MHz, CDCl$_3$) δ 193.0 (C), 160.3 (d, *J*$_{C-F}$ = 247.1 Hz, C), 144.8 (C), 143.0 (C), 136.4 (C), 134.3 (C), 133.6 (CH), 132.0 (CH), 131.0 (d, *J*$_{C-F}$ = 4.5 Hz, CH), 128.6 (d, *J*$_{C-F}$ = 8.1 Hz, CH), 128.5 (2 × CH), 128.3 (2 × CH), 128.1 (CH), 127.1 (CH), 126.3 (d, *J*$_{C-F}$ = 15.5 Hz, C), 123.9 (d, *J*$_{C-F}$ = 3.6 Hz, CH), 115.8 (d, *J*$_{C-F}$ = 22.6 Hz, CH), 45.6 (CH), 43.6 (CH$_2$), 37.1 (d, *J*$_{C-F}$ = 2.8 Hz, CH$_2$), 29.4 (CH$_2$); ^{19}F NMR (376 MHz, CDCl$_3$) δ –113.2 (s); HRMS (ESI) Exact mass calculated for [C$_{23}$H$_{19}$FNaOS]$^+$ [M+Na]$^+$: 385.1033, found: 385.1037; Enantiomeric

excess was determined by HPLC using a Chiralcel OD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 280 nm, 25 °C); t_r (major) = 5.9 min, t_r (minor) = 8.2 min, 99% ee.

Slow evaporation of a solution of **4hb** in pentane gave crystals that were suitable for X-ray crystallography:

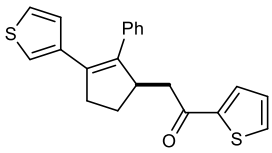




4hb
CCDC 2040011
Flack parameter -0.001(6)

ORTEP with ellipsoid probabilities at 50%

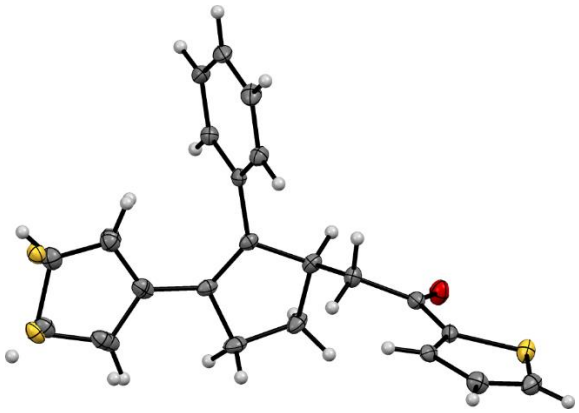
Note: There is conformational disorder in the fluorophenyl ring moiety. Occupancies of the two disorder components were refined and constrained to sum to unity. The geometries of the two disorder components were restrained to be similar (SAME). Rigid bond and similarity restraints were applied to the anisoptropic displacement parameters of the disordered atoms (RIGU, SIMU). Carbon atoms C20 and C20a were constrained to have identical anisotropic displacement parameters (see .cif file for details).

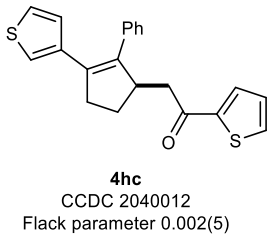


(*R*)-2-[2-Phenyl-3-(thiophen-3-yl)cyclopent-2-en-1-yl]-1-(thiophen-2-yl)ethan-1-one (4hc). Prepared according to General Procedure A, using enyne **3h** (79.9 mg, 0.30 mmol) and 3-thienylboronic acid (46.1 mg, 0.36 mmol) and stirring for 18 h. Purification by column chromatography (5% EtOAc/pet. ether) gave **4hc** (88.0 mg, 84%) as a yellow solid. R_f = 0.56 (20% EtOAc/pet. ether); m.p. 117−118 °C (Et_2O); IR 3102, 2926, 2847, 1659 (C=O), 1517, 1415, 1310, 1234, 849, 701 cm^{-1}; $[\alpha]_D^{25}$ −56.0 (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.59 (1H, dd, *J* = 4.9, 1.1 Hz, Ar**H**), 7.55 (1H, dd, *J* = 3.8, 1.1 Hz, Ar**H**), 7.38-7.32 (2H, m, Ar**H**), 7.30-7.26 (1H, m, Ar**H**), 7.25-7.20 (2H, m,

Ar**H**), 7.06 (2H, dt, *J* = 5.0, 3.1 Hz, Ar**H**), 7.01 (1H, dd, *J* = 3.1, 1.3 Hz, Ar**H**), 6.67 (1H, dd, *J* = 5.0, 1.3 Hz, Ar**H**), 3.84-3.67 (1H, m, C**H**CH_2), 3.08-2.93 (2H, m, C$\mathbf{H}_a$$H_b$C= and C$\mathbf{H}_a$$H_b$C=O), 2.86-2.74 (2H, m, $CH_a$$\mathbf{H}_b$C=O and $CH_a$$\mathbf{H}_b$C=), 2.40 (1H, app dtd, *J* = 13.2, 8.9, 5.7 Hz, CH_2C$\mathbf{H}_a$$H_b$CH), 1.78 (1H, app ddt, *J* = 13.2, 9.1, 5.6 Hz, $CH_2CH_a$$\mathbf{H}_b$CH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.9 (C), 144.8 (C), 140.3 (C), 138.4 (C), 138.2 (C), 133.6 (CH), 132.8 (C), 131.9 (CH), 129.0 (2 × CH), 128.8 (2 × CH), 128.1 (CH), 127.4 (CH), 127.3 (CH), 124.7 (CH), 122.6 (CH), 47.9 (CH), 43.8 (CH_2), 36.0 (CH_2), 29.1 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{21}H_{18}NaOS_2]^+$ $[M+Na]^+$: 373.0691, found: 373.0692; Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column (90:10 *iso*-hexane:*i*-PrOH, 0.5 mL/min, 280 nm, 25 °C); t_r (major) = 15.0 min, t_r (minor) = 19.4 min, 99% ee.

Slow evaporation of a solution of **4hc** in pentane gave crystals that were suitable for X-ray crystallography:



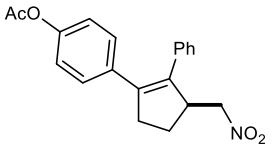


4hc
CCDC 2040012
Flack parameter 0.002(5)

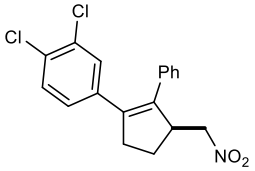
ORTEP with ellipsoid probabilities at 50%

Note: Conformational disorder is observed for the thiophene group attached directly to the cyclopentene ring. The occupancies of the two disorder components were refined and constrained to sum unity, resulting in values of 0.66(1) and 0.34(1) respectively. The geometries of the two disorder components were restrained to be similar (SADI), planar (FLAT) and have 1,2 and 1,3 bond distances set a target values generated by the FragmentDB function in the Software Olex2 v1.3 (DFIX, DANG). Rigid bond and similarity restraints (RIGU, SIMU) were applied to the anisotropic displacement parameters of all atoms in the disordered moieties. The three pairs of overlapping atoms in the disordered moieties were constrained to have identical anisotropic displacement

parameters (EADP). All hydrogen atoms in the structure were observed in the electron density map before being geometrically placed and refined using a riding model (see .cif file for details).

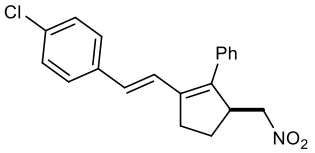


(*S*)-4-[3-(Nitromethyl)-2-phenylcyclopent-1-en-1-yl]phenyl acetate (4la). Prepared according to a modification of General Procedure A, using enyne **3l** (60.4 mg, 0.30 mmol), 4-acetoxyphenylboronic acid (108 mg, 0.60 mmol), $Ni(OAc)_2{\cdot}4H_2O$ (7.5 mg, 0.03 mmol) and (*S*)-*t*-Bu-NeoPHOX (**L11**, 11.0 mg, 0.03 mmol) and stirring for 18 h. Purification by column chromatography (5% EtOAc/pentane) gave **4la** (57.0 mg, 56%) as a colourless oil. R_f = 0.26 (10% EtOAc/pet. ether); IR 3063, 2918, 2858, 1756 (C=O), 1543, 1506, 1369, 1185, 1172, 1010 cm^{-1}; $[\alpha]_D^{25}$ −108.0 (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.32-7.27 (2H, m, Ar**H**), 7.26-7.23 (1H, m, Ar**H**), 7.18-7.07 (4H, m, Ar**H**), 6.94-6.87 (2H, m, Ar**H**), 4.36 (1H, dd, *J* = 12.2, 3.8 Hz, C**H**$_a$H$_b$NO$_2$), 4.23 (1H, dd, *J* = 12.2, 10.3 Hz, CH$_a$**H**$_b$NO$_2$), 4.04-3.97 (1H, m, C**H**CH$_2$), 3.13 (1H, dddd, *J* = 16.3, 9.3, 6.7, 2.9 Hz, C**H**$_a$H$_b$C=), 2.76 (1H, dddd, *J* = 16.3, 9.5, 4.6, 1.3 Hz, CH$_a$**H**$_b$C=), 2.38 (1H, app dtd, *J* = 13.4, 9.1, 6.8 Hz, CH$_2$C**H**$_a$H$_b$CH), 2.26 (3H, s, C**H**$_3$), 2.01 (1H, app ddt, *J* = 13.4, 8.8, 4.4 Hz, CH$_2$CH$_a$**H**$_b$CH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.5 (C), 149.8 (C), 139.7 (C), 136.4 (C), 135.9 (C), 134.4 (C), 129.2 (2 × CH), 129.0 (2 × CH), 128.7 (2 × CH), 127.8 (CH), 121.3 (2 × CH), 78.4 (CH_2), 50.0 (CH), 36.4 (CH_2), 26.6 (CH_2), 21.3 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{20}H_{19}NNaO_4]^+$ $[M+Na]^+$: 360.1206, found: 360.1203; Enantiomeric excess was determined by HPLC using a Chiralpak IC column (90:10 *iso*-hexane:*i*-PrOH, 0.5 mL/min, 280 nm, 25 °C); t_r (major) = 32.3 min, t_r (minor) = 35.3 min, 98% ee.



(*S*)-1,2-Dichloro-4-[3-(nitromethyl)-2-phenylcyclopent-1-en-1-yl]benzene (4lb). Prepared according to a modification of General Procedure A, using enyne **3l** (60.4 mg, 0.30 mmol), 3,4-dichlorophenylboronic acid (115 mg, 0.60 mmol), $Ni(OAc)_2{\cdot}4H_2O$ (7.5 mg, 0.03 mmol) and (*S*)-*t*-Bu-NeoPHOX (**L11**, 11.0 mg, 0.03 mmol) and stirring for 18 h. Purification by column chromatography (10%

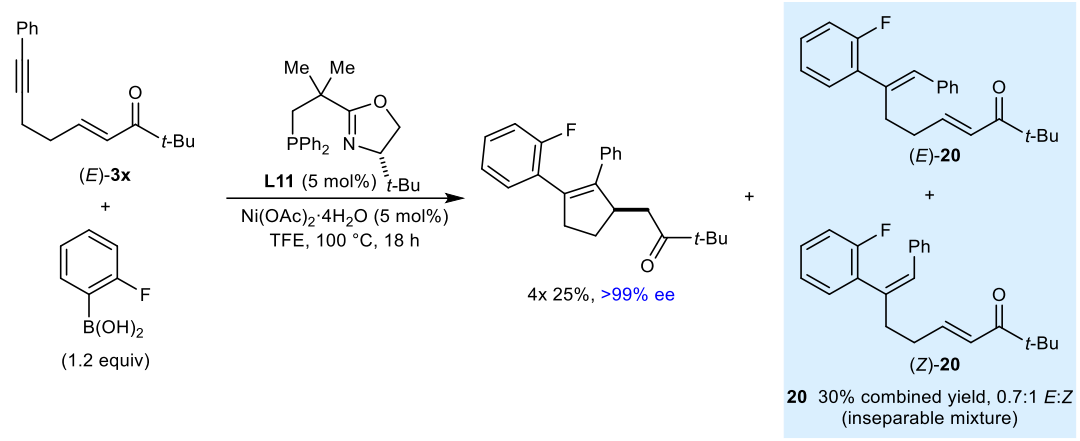
EtOAc/pentane) gave **4lb** (81.2 mg, 78%) as an orange oil. R_f = 0.50 (20% EtOAc/pet. ether); IR 3023, 2924, 2850, 1545, 1469, 1376, 1135, 1028, 762, 698 cm^{-1}; $[\alpha]_D^{25}$ −144.0 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.26 (3H, m, Ar**H**), 7.24-7.16 (2H, m, Ar**H**), 7.15-7.09 (2H, m, Ar**H**), 6.88 (1H, dd, *J* = 8.4, 2.0 Hz, Ar**H**), 4.36 (1H, dd, *J* = 12.2, 3.9 Hz, C**H**$_a$H$_b$NO$_2$), 4.23 (1H, dd, *J* = 12.2, 10.0 Hz, CH$_a$**H**$_b$NO$_2$), 4.09-3.88 (1H, m, C**H**CH$_2$), 3.10 (1H, dddd, *J* = 16.1, 9.3, 6.7, 2.8 Hz, C**H**$_a$H$_b$C=), 2.83-2.76 (1H, m, CH$_a$**H**$_b$C=), 2.40 (1H, app dtd, *J* = 13.6, 8.9, 6.6 Hz, CH$_2$C**H**$_a$H$_b$CH), 2.03 (1H, app ddt, *J* = 13.6, 9.5, 4.5 Hz, CH$_2$CH$_a$**H**$_b$CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.3 (2 × C), 136.8 (C), 135.3 (C), 132.4 (C), 131.2 (C), 130.1 (CH), 129.9 (CH), 129.2 (2 × CH), 128.6 (2 × CH), 128.3 (CH), 127.6 (CH), 78.2 (CH$_2$), 50.0 (CH), 36.2 (CH$_2$), 26.6 (CH$_2$); HRMS (ESI) Exact mass calculated for $[C_{18}H_{15}{}^{35}Cl_2NNaO_2]^+$ $[M+Na]^+$: 370.0372, found: 370.0.374; Enantiomeric excess was determined by HPLC using a Chiralpak IC column (90:10 *iso*-hexane:*i*-PrOH, 0.5 mL/min, 280 nm, 25 °C); t_r (major) = 14.6 min, t_r (minor) = 15.3 min, 99% ee.



(*S*,*E*)-1-Chloro-4-{2-[3-(nitromethyl)-2-phenylcyclopent-1-en-1-yl]vinyl}benzene (4lc). Prepared according to a modification of General Procedure A, using enyne **3l** (60.4 mg, 0.30 mmol), *trans*-2-(4-chlorophenyl)vinylboronic acid (109 mg, 0.60 mmol), Ni(OAc)$_2$·4H$_2$O (7.5 mg, 0.03 mmol) and (*S*)-*t*-Bu-NeoPHOX (**L11**, 11.0 mg, 0.03 mmol) and stirring for 16 h. Purification by column chromatography (5% EtOAc/pentane) gave **4lc** (37.1 mg, 36%) as a yellow oil. R_f = 0.67 (30% EtOAc/pet. ether); IR 3025, 2924, 2851, 1545, 1489, 1376, 1090, 961, 810, 700 cm^{-1}; $[\alpha]_D^{25}$ −224.0 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.47-7.25 (9H, m, Ar**H**), 6.98 (1H, d, *J* = 16.1 Hz, =C**H**), 6.56 (1H, d, *J* = 16.1 Hz, =C**H**), 4.39 (1H, dd, *J* = 12.1, 3.7 Hz, C**H**$_a$H$_b$NO$_2$), 4.17 (1H, dd, *J* = 12.1, 10.2 Hz, CH$_a$**H**$_b$NO$_2$), 4.12-3.99 (1H, m, C**H**CH$_2$), 2.94 (1H, dddd, *J* = 11.8, 8.9, 6.0, 2.2 Hz, C**H**$_a$H$_b$C=), 2.81-2.73 (1H, m, CH$_a$**H**$_b$C=), 2.40 (1H, app dtd, *J* = 14.4, 8.8, 5.9 Hz, CH$_2$C**H**$_a$H$_b$CH), 2.02-1.89 (1H, m, CH$_2$CH$_a$**H**$_b$CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.8 (C), 139.2 (C), 135.9 (C), 135.4 (C), 133.5 (C), 131.0 (CH), 129.0 (2 × CH), 128.9 (2 × CH), 128.8 (2 × CH), 128.1 (CH), 127.9 (2 × CH), 124.0 (CH), 78.8 (CH$_2$), 49.0 (CH), 32.1 (CH$_2$), 26.7 (CH$_2$); HRMS (ESI) Exact mass calculated for $[C_{20}H_{18}{}^{35}ClNNaO_2]^+$ $[M+Na]^+$: 362.0918,

found: 362.0916; Enantiomeric excess was determined by HPLC using a Chiralpak AS-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 280 nm, 25 °C); t_r (major) = 9.5 min, t_r (minor) = 10.7 min, >99% ee.

(*R*)-1-[-(2-Fluorophenyl)-2-phenylcyclopent-2-en-1-yl]-3,3-dimethylbutan-2-one (4x), (4*E*,8*E*)-8-(2-fluorophenyl)-2,2-dimethyl-9-phenylnona-4,8-dien-3-one [(*E*)-20], and (4*E*,8*Z*)-8-(2-fluorophenyl)-2,2-dimethyl-9-phenylnona-4,8-dien-3-one [(*Z*)-20]

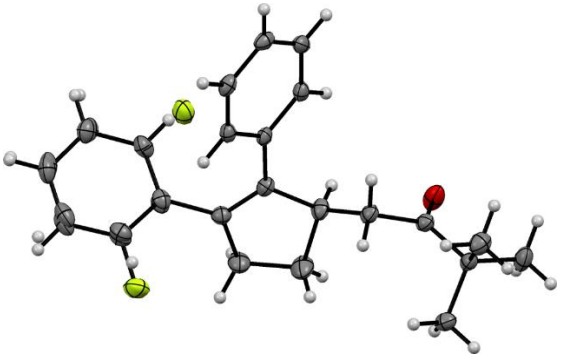


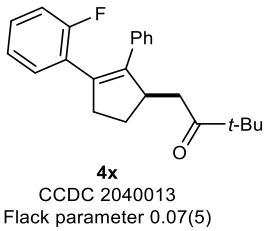
Prepared according to General Procedure A, using enyne (*E*)-**3x** (79.9 mg, 0.30 mmol) and 2-fluorophenylboronic acid (50.4 mg, 0.36 mmol) and stirring for 18 h. Purification by column chromatography (2% EtOAc/pentane) gave **4x** (25.0 mg, 25%) as a colourless solid followed by a 0.7:1 mixture of inseparable alkyne hydroarylation products (*E*)-**20** and (*Z*)-**20**, respectively, (30.6 mg, 30%) as a colourless oil.

Data for **4x**: R_f = 0.29 (3% EtOAc/pet. ether); m.p. 103–105 °C (Et_2O); IR 3057, 2964, 2868, 1703 (C=O), 1483, 1446, 1365, 1206, 1057, 754 cm^{-1}; $[\alpha]_D^{20}$ −156.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21-7.11 (4H, m, Ar**H**), 7.09-7.03 (2H, m, Ar**H**), 7.02-6.89 (3H, m, Ar**H**), 3.83 (1H, app tdd, *J* = 7.8, 5.5, 3.3 Hz, C**H**CH_2), 3.11-2.99 (1H, m, C**H**$_a$H$_b$C=), 2.67-2.54 (2H, m, CH$_a$**H**$_b$C= and C**H**$_a$H$_b$C=O), 2.49 (1H, dd, *J* = 17.7, 3.4 Hz, CH$_a$**H**$_b$C=O), 2.40 (1H, app dtd, *J* = 12.9, 8.8, 6.2 Hz, CH_2C**H**$_a$H$_b$CH), 1.63-1.55 (1H, m, CH_2CH$_a$**H**$_b$CH), 1.06 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.7 (C), 160.4 (d, J_{C-F} = 246.9 Hz, C), 143.5 (C), 136.6 (C), 133.9 (C), 131.1 (d, J_{C-F} = 4.6 Hz, CH), 128.6 (CH), 128.5 (2 × CH), 128.3 (2 × CH), 127.0 (CH), 126.5 (d,

$J_{C\text{-}F}$ = 15.6 Hz, C), 123.9 (d, $J_{C\text{-}F}$ = 3.4 Hz, CH), 115.8 (d, $J_{C\text{-}F}$ = 22.3 Hz, CH), 44.4 (CH), 44.3 (C), 41.0 (CH_2), 37.1 (d, $J_{C\text{-}F}$ = 2.9 Hz, CH_2), 29.9 (CH_2), 26.4 (3 ×CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –113.3 (s); HRMS (ESI) Exact mass calculated for $[C_{23}H_{25}FNaO]^+$ $[M+Na]^+$: 359.1782, found 359.1785; Enantiomeric excess was determined by HPLC using a Chiralpak IC column (90:10 *iso*-hexane:*i*-PrOH, 0.5 mL/min, 280 nm, 25 °C); t_r (minor) = 8.0 min, t_r (major) = 9.3 min, >99% ee.

Slow evaporation of a solution of **4x** in pentane gave crystals that were suitable for X-ray crystallography:





4x
CCDC 2040013
Flack parameter 0.07(5)

ORTEP with ellipsoid probabilities at 50%

Note: Conformational disorder is observed in the fluorophenyl moiety. The occupancies of the coplanar disorder components were refined and restrained to sum to unity, having values of 0.92(1) and 0.08(1) each. The geometries of the two components are restrained to be similar (SAME). The anisotropic displacement parameters of the coincident atoms are contrained to be identical (EADP). A rigid bond and similarity restraint was applied to all atoms in the disordered moieties. All hydrogen atoms were observed in the electron density map before being geometrically placed and refined with a riding model (see .cif file for details).

Data for the mixture of (*E*)-**20** and (*Z*)-**20**: R_f = 0.20 (3% EtOAc/pet. ether); IR 3028, 2971, 2929, 1687 (C=O), 1620, 1487, 1475, 1448, 1218, 1106 cm^{-1}; HRMS (ESI) Exact mass calculated for $[C_{23}H_{25}FNaO]^+$ $[M+Na]^+$: 359.1782, found: 359.1788.

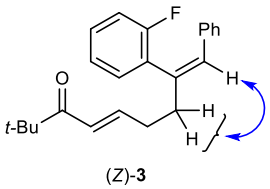
Overlapping NMR signals (integrals refer to the sum of the integrals for each isomer): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.36 (2H, m, Ar**H**), 7.34-7.27 (5H, m, Ar**H**), 7.17-7.05 (8H, m, Ar**H**), 7.00-6.90 (4H, m, 3 × Ar**H** and CH_2C**H**= (from (*Z*)-**20**)).

Characteristic NMR signals signals for (E)-**20**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (1H, dt, *J* = 15.2, 6.8 Hz, $CH_2C\mathbf{H}$=), 6.64 (1H, s, C=C**H**Ph), 6.36 (1H, dt, *J* = 15.2, 1.6 Hz, C**H**C=O), 2.89 (2H, t, *J* = 7.7 Hz, $C\mathbf{H}_2CH_2CH$=), 2.29-2.21 (2H, m, $C\mathbf{H}_2CH$=), 1.10 (9H, s, $C(C\mathbf{H}_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.2 (C), 160.1 (d, $J_{C\text{-}F}$ = 246.8 Hz, C), 146.28 (CH), 137.7 (C), 137.3 (C), 132.0 (d, $J_{C\text{-}F}$ = 1.5 Hz, CH), 130.6 (d, $J_{C\text{-}F}$ = 4.3 Hz, CH), 129.1 (d, $J_{C\text{-}F}$ = 8.2 Hz, CH), 129.0 (2 × CH), 128.5 (2 × CH), 127.1 (CH), 124.6 (CH), 124.3 (d, $J_{C\text{-}F}$ = 3.4 Hz, CH), 116.2 (CH), 42.9 (C), 31.2 (CH_2), 29.6 (d, $J_{C\text{-}F}$ = 3.4 Hz, CH_2), 26.28 (3 × CH_3) (one quaternary carbon signal was not identified); ^{19}F NMR (376 MHz, $CDCl_3$) δ –114.6 (s).

Characteristic NMR signals signals for (Z)-**20**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.59 (1H, s, C=C**H**Ph), 6.50 (1H, dt, *J* = 15.3, 1.6 Hz, =C**H**C=O), 2.69 (1H, t, *J* = 7.0 Hz, $C\mathbf{H}_2CH_2CH$=), 2.37-2.30 (2H, m, $C\mathbf{H}_2CH$=), 1.14 (9H, s, $C(C\mathbf{H}_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.3 (C), 160.0 (d, $J_{C\text{-}F}$ = 245.9 Hz, C), 146.31 (CH), 136.9 (C), 135.8 (C), 131.2 (d, $J_{C\text{-}F}$ = 4.3 Hz, CH), 129.7 (CH), 129.3 (d, $J_{C\text{-}F}$ = 8.0 Hz, CH), 128.7 (2 × CH), 128.1 (2 × CH), 126.8 (CH), 124.8 (CH), 124.5 (d, $J_{C\text{-}F}$ = 3.5 Hz, CH), 116.0 (CH), 43.0 (C), 38.3 (d, $J_{C\text{-}F}$ = 1.7 Hz, CH_2), 30.9 (CH_2), 26.31 (3 × CH_3) (one quaternary carbon signal was not identified); ^{19}F NMR (376 MHz, $CDCl_3$) δ –115.1 (s)

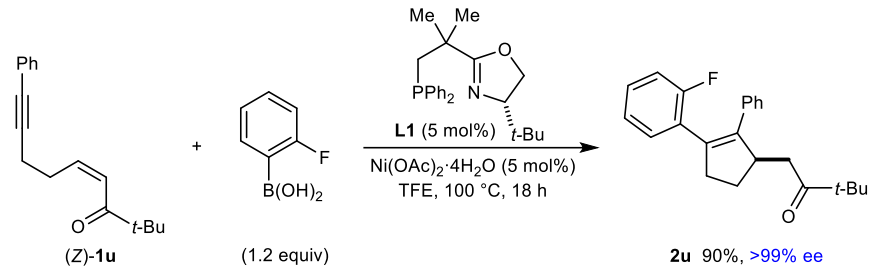
Assignment of the alkenyl stereochemistries of (*E*)-**20** and (*Z*)-**20** was made based on the following NOE interaction observed in the 2D NOESY spectrum of the mixture, between the alkenyl proton at 6.59 ppm and the methylene protons at 2.69 ppm, which correspond to those (*Z*)-**20**:

Key NOE interaction:



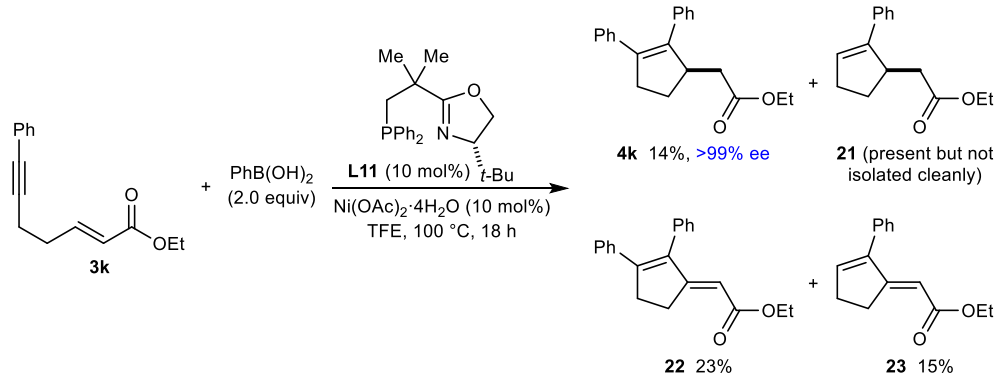
(*Z*)-**3**

(*R*)-1-[-(2-Fluorophenyl)-2-phenylcyclopent-2-en-1-yl]-3,3-dimethylbutan-2-one (4x)



Prepared according to General Procedure A, using enyne (*Z*)-**3x** (79.9 mg, 0.30 mmol) and 2-fluorophenylboronic acid (50.4 mg, 0.36 mmol) and stirring for 18 h. Purification by column chromatography (3% EtOAc/pentane) gave **4x** (90.8 mg, 90%) as a colourless solid. For the characterisation data, see above. Enantiomeric excess was determined by HPLC using a Chiralpak IC column (90:10 *iso*-hexane:*i*-PrOH, 0.5 mL/min, 280 nm, 25 °C); t_r (minor) = 7.8 min, t_r (major) = 9.2 min, >99% ee.

Ethyl (*R*)-2-(2,3-diphenylcyclopent-2-en-1-yl)acetate (4k), ethyl (*R*)-2-(2-phenylcyclopent-2-en-1-yl)acetate (21), ethyl (*E*)-2-(2,3-diphenylcyclopent-2-en-1-ylidene)acetate (22), and ethyl (*E*)-2-(2-phenylcyclopent-2-en-1-ylidene)acetate (23)

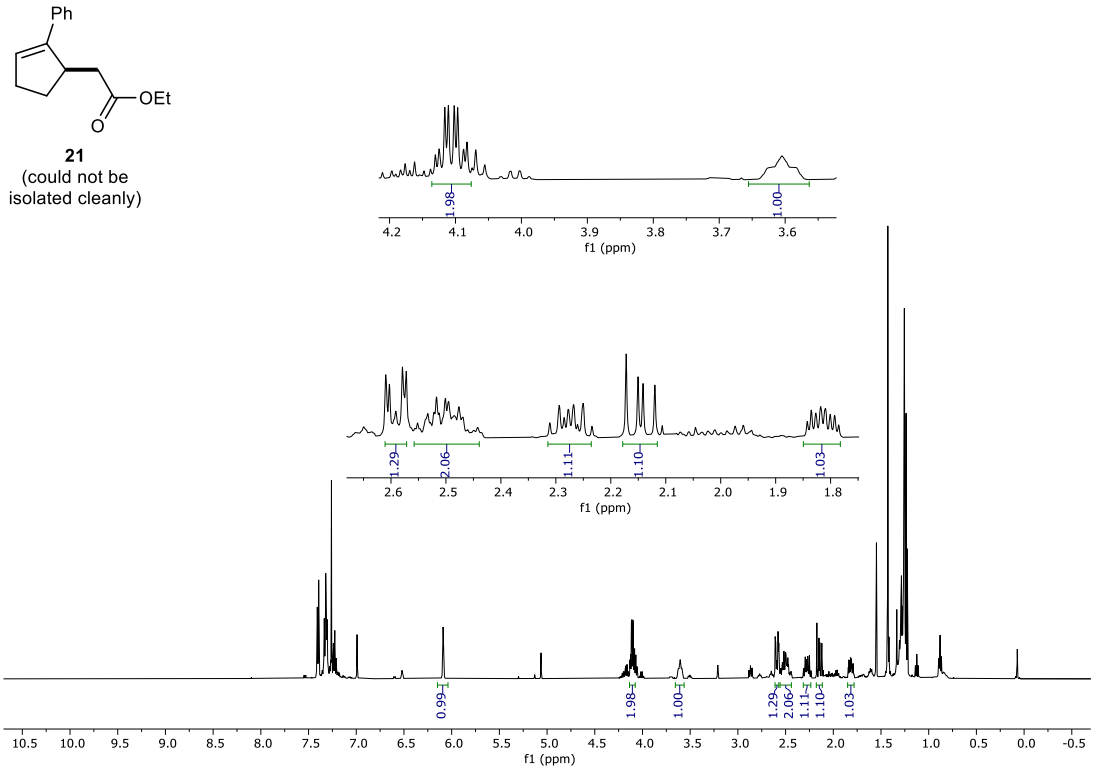


An oven-dried microwave vial fitted with a magnetic stirrer bar was charged with the enyne **3k** (0.30 mmol), phenylboronic acid (73.2 mg, 0.60 mmol), $Ni(OAc)_2 \cdot 4H_2O$ (7.5 mg, 0.03 mmol) and (*S*)-*t*-Bu-NeoPHOX (**L11**, 11.6 mg, 0.03 mmol). The vial was capped with a crimp cap seal and flushed with argon (5 min). Freshly degassed TFE (3 mL, using a stream of argon for 20 min) was added, the cap was sealed with PTFE tape,

and the contents were stirred at room temperature for 10 min and then at 100 °C for 18 h. The reaction was cooled to room temperature, diluted with 50% brine (10 mL), and 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 (0.5 to 2% EtOAc/pentane) to give a mixture of **4k** and **23** (23.9 mg) followed by **22** (20.7 mg, 23%) as a colourless solid. A second purification of the mixture of **4k** and **23** by column chromatography (0.5% MeOH/CH_2Cl_2) gave **4k** (13.2 mg, 14%) as a colourless oil, followed by **23** (10.4 mg, 15%) as a colourless solid. The reductive cyclisation product **21** was present in the reaction but could not be isolated cleanly (8.8 mg of very impure material was obtained).

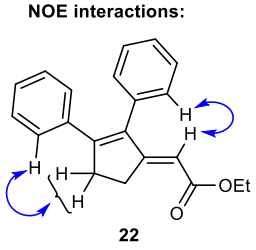
Data for **4k**: R_f = 0.55 (20% EtOAc/pet. ether) and 0.55 (0.5% MeOH/CH_2Cl_2); IR 3054, 2979, 2936, 1729 (C=O), 1599, 1493, 1443, 1370, 1270, 1170 cm^{-1}; $[\alpha]_D^{25}$ −128.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.19 (3H, m, Ar**H**), 7.19-7.08 (7H, m, Ar**H**), 4.05 (2H, q, *J* = 7.1 Hz, C**H**$_2$CH$_3$), 3.69-3.60 (1H, m, C**H**CH$_2$), 3.09 (1H, dddd, *J* = 15.8, 9.1, 6.4, 2.7 Hz, C**H**$_a$H$_b$C=), 2.71 (1H, dddd, *J* = 15.8, 9.1, 5.0, 1.5 Hz, CH$_a$**H**$_b$C=), 2.44 (1H, dd, *J* = 15.4, 4.1 Hz, C**H**$_a$H$_b$C=O), 2.40-2.34 (1H, m, CH$_2$C**H**$_a$H$_b$CH), 2.21 (1H, dd, *J* = 15.4, 10.5 Hz, CH$_a$**H**$_b$C=O), 1.82 (1H, app ddt, *J* = 13.6, 9.3, 4.9 Hz, CH$_2$CH$_a$**H**$_b$CH), 1.21 (3H, t, *J* = 7.1 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3 (C), 140.7 (C), 138.1 (C), 137.7 (C), 137.5 (C), 129.0 (2 × CH), 128.5 (2 × CH), 128.2 (2 × CH), 128.0 (2 × CH), 127.0 (CH), 126.8 (CH), 60.4 (CH_2), 47.5 (CH), 38.8 (CH_2), 36.4 (CH_2), 28.8 (CH_2), 14.4 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{21}H_{22}NaO_2]^+$ $[M+Na]^+$: 329.1512, found: 329.1512; Enantiomeric excess was determined by HPLC using a Chiralpak IC column (99:1 *iso*-hexane:*i*-PrOH, 0.5 mL/min, 280 nm, 25 °C); t_r (minor) = 12.7 min, t_r (major) = 13.1 min, >99% ee.

Diagnostic data for **21**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.15-6.04 (1H, m, **H**C=), 4.11 (2H, app qd, *J* = 7.1, 2.8 Hz, C**H**$_2$CH$_3$), 3.66-3.56 (1H, m, C**H**CH$_2$C=O), 2.59 (1H, dd, *J* = 15.3, 3.3 Hz, C**H**$_a$H$_b$C=O), 2.56-2.44 (2H, m, C**H**$_2$C=), 2.31-2.24 (1H, m, CH$_2$C**H**$_a$H$_b$CH), 2.15 (1H, dd, *J* = 15.3, 10.8 Hz, CH$_a$**H**$_b$C=O), 1.87-1.77 (1H, m, CH$_2$CH$_a$**H**$_b$CH); HRMS (ESI) Exact mass calculated for $[C_{15}H_{18}NaO_2]^+$ $[M+Na]^+$: 253.1199, found: 253.1196.



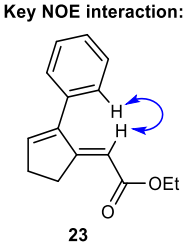
Data for **22**: R_f = 0.50 (20% EtOAc/pet. ether); m.p. 147–149 °C (Et_2O); IR 2971, 2923, 1688 (C=O), 1617, 1605, 1579, 1438, 1371, 1179, 1135 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40-7.31 (3H, m, Ar**H**), 7.21-7.11 (7H, m, Ar**H**), 5.47 (1H, t, *J* = 2.6 Hz, =C**H**C=O), 4.15 (2H, q, *J* = 7.1 Hz, C**H**$_2$CH$_3$), 3.32 (2H, dt, *J* = 7.8, 2.6 Hz, C**H**$_2$C=CH), 3.15-3.10 (2H, m, C**H**$_2$CH$_2$C=CH), 1.26 (3H, t, *J* = 7.1 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.9 (C), 168.2 (C), 153.8 (C), 141.6 (C), 136.0 (C), 135.6 (C), 129.7 (2 × CH), 129.1 (2 × CH), 128.5 (2 × CH), 128.4 (CH), 128.2 (2 × CH), 127.7 (CH), 109.0 (CH), 59.6 (CH_2), 35.3 (CH_2), 30.1 (CH_2), 14.6 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{21}H_{20}NaO_2]^+$ $[M+Na]^+$: 327.1356, found: 327.1352.

Assignment of the alkene stereochemistry of **22** was made based on the following NOE interactions observed in a series of 1D NOESY experiments between the alkenyl proton at 5.47 ppm and the aromatic protons at 7.21-7.11 ppm and between the methylene protons at 3.15-3.10 ppm and the aromatic protons at 7.21-7.11 ppm:

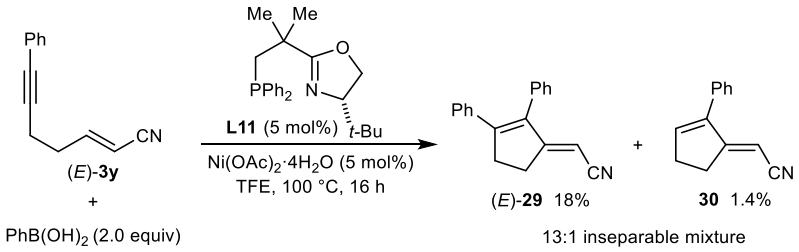


Data for **23**: R_f = 0.55 (20% EtOAc/pet. ether) and 0.45 (0.5% MeOH/CH_2Cl_2); m.p. 49–51 °C (Et_2O); IR 2975, 2904, 1694 (C=O), 1617, 1589, 1490, 1367, 1290, 1172, 1112 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42-7.27 (5H, m, Ar**H**), 6.59 (1H, t, *J* = 2.8 Hz, CH_2C**H**=), 5.79-5.76 (1H, m, =C**H**C=O), 4.16 (2H, q, *J* = 7.1 Hz, C**H**$_2CH_3$), 3.25 (2H, dt, *J* = 7.6, 2.4 Hz, C**H**$_2$C=CH), 2.69 (2H, dt, *J* = 7.6, 2.8 Hz, C**H**$_2CH_2$C=CH), 1.26 (3H, t, *J* = 7.1 Hz, CH_2C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1 (C), 166.6 (C), 146.9 (C), 146.1 (CH), 135.2 (C), 128.6 (2 × CH), 128.5 (2 × CH), 127.9 (CH), 108.8 (CH), 59.7 (CH_2), 32.1 (CH_2), 31.5 (CH_2), 14.6 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{15}H_{16}NaO_2]^+$ $[M+Na]^+$: 251.1043, found: 251.1046.

Assignment of the alkene stereochemistry of **23** was made based on the following NOE interaction observed in the 2D NOESY spectrum between the alkenyl proton at 5.79-5.76 ppm and the aromatic protons at 7.42-7.27 ppm:



(*E*)-2-(2,3-Diphenylcyclopent-2-en-1-ylidene)acetonitrile [(*E*)-29] and (*E*)-2-(2-phenylcyclopent-2-en-1-ylidene)acetonitrile (30)



Prepared according to a modification of General Procedure A, using enyne (*E*)-**3y** (54.4 mg, 0.30 mmol), phenylboronic acid (73.2 mg, 0.60 mmol), $Ni(OAc)_2·4H_2O$ (7.5 mg, 0.03 mmol), and (*S*)-*t*-Bu-NeoPHOX (**L11**, 11.0 mg, 0.03 mmol) and stirring for 16 h. Purification by column chromatography (5% EtOAc/pentane) followed by a second purification by column chromatography (100% CH_2Cl_2) gave an inseparable 13:1

mixture of (*E*)-**29** and **30** (14.9 mg) as a colourless solid. The calculated yields of (*E*)-**29** and **30** are 18% and 1.4%, respectively.

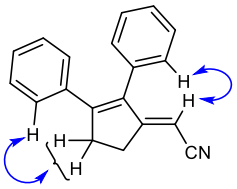
R_f = 0.51 (100% CH_2Cl_2); IR 3059, 2918, 2197 (C≡N), 1600, 1561, 1486, 1438, 1364, 1261, 922 cm^{-1}.

NMR and HRMS data for (*E*)-**29**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.35 (3H, m, Ar**H**), 7.26-7.14 (5H, m, Ar**H**), 7.14-7.09 (2H, m, Ar**H**), 4.93-4.81 (1H, m, =C**H**CN), 3.18-3.14 (2H, m, C**H**$_2$CH$_2$C=CH), 3.14-3.10 (2H, m, C**H**$_2$C=CH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.4 (C), 154.9 (C), 140.0 (C), 135.3 (C), 134.3 (C), 129.5 (2 × CH), 129.3 (2 × CH), 129.0 (CH), 128.5 (2 × CH), 128.32 (2 × CH), 128.25 (CH), 119.1 (C), 86.1 (CH), 34.4 (CH_2), 29.7 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{19}H_{16}N]^+$ $[M+H]^+$: 258.1277, found: 258.1277.

Diagnostic NMR and HRMS data for **30**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.62 (1H, t, *J* = 2.9 Hz, **H**C=CPh), 5.20 (1H, t, *J* = 2.7 Hz, =C**H**CN), 3.07 (2H, dt, *J* = 7.8, 2.7 Hz, C**H**$_2$C=CHCN), 2.74 (2H, dt, *J* = 7.8, 2.9 Hz, C**H**$_2$C=CPh); HRMS (ESI) Exact mass calculated for $[C_{13}H_{11}NNa]^+$ $[M+Na]^+$: 204.0784, found: 204.0782.

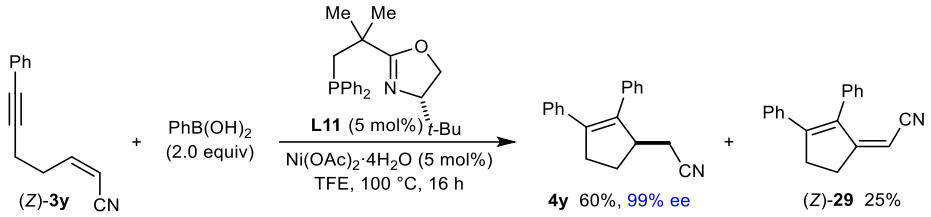
Assignment of the alkene stereochemistry of (*E*)-**29** was made based on the following NOE interactions observed in the 2D NOESY spectrum between the alkenyl proton at 4.93-4.81 ppm and the aromatic protons at 7.26-7.14 ppm and between the methylene protons at 3.18-3.14 ppm and the aromatic protons at 7.26-7.14 ppm:

Key NOE interactions:



(*E*)-**29**

(*R*)-2-(2,3-Diphenylcyclopent-2-en-1-yl)acetonitrile (4y) and (*Z*)-2-(2,3-diphenylcyclopent-2-en-1-ylidene)acetonitrile [(*Z*)-29]



A modification of General Procedure A was followed, using enyne (*Z*)-**3y** (54.4 mg, 0.30 mmol), phenylboronic acid (73.2 mg, 0.60 mmol), $Ni(OAc)_2 \cdot 4H_2O$ (7.5 mg, 0.03 mmol), and (*S*)-*t*-Bu-NeoPHOX (**L11**, 11.0 mg, 0.03 mmol) and stirring for 16 h. Purification by column chromatography (5% EtOAc/pentane) gave **4y** (46.8 mg, 60%) as a yellow solid followed by (*Z*)-**29** (19.6 mg, 25%) as an off-white solid.

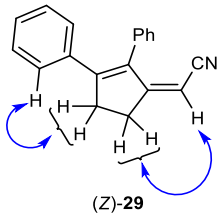
Data for **4y**: R_f = 0.35 (15% EtOAc/pet. ether); m.p. 66–69 °C (Et_2O); IR 3027, 2954, 2849, 2238 (C≡N), 1598, 1489, 1454, 1442, 1414, 759 cm^{-1}; $[\alpha]_D^{20}$ −128.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.26 (3H, m, Ar**H**), 7.26-7.21 (1H, m, Ar**H**), 7.19-7.10 (6H, m, Ar**H**), 3.59-3.50 (1H, m, C**H**CH_2), 3.22 (1H, dddd, *J* = 16.0, 9.0, 6.1, 2.8 Hz, C**H**$_a$H$_b$C=), 2.78 (1H, dddd, *J* = 16.0, 9.3, 5.1, 1.5 Hz, CH_a**H**$_b$C=), 2.54-2.38 (2H, m, CH_2C**H**$_a$H$_b$CH and C**H**$_a$H$_b$CN), 2.28 (1H, dd, *J* = 16.8, 7.9 Hz, CH_a**H**$_b$CN), 2.02 (1H, app ddt, *J* = 13.9, 9.5, 5.0 Hz, CH_2CH_a**H**$_b$CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.1 (C), 138.1 (C), 137.0 (C), 136.5 (C), 128.9 (2 × CH), 128.8 (2 × CH), 128.2 (2 × CH), 128.1 (2 × CH), 127.5 (CH), 127.3 (CH), 119.1 (C), 47.5 (CH), 36.5 (CH_2), 28.1 (CH_2), 22.1 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{19}H_{17}NNa]^+$ $[M+Na]^+$: 282.1253, found: 282.1250; Enantiomeric excess was determined by HPLC using a Chiralpak AS-H column (98:2 *iso*-hexane:*i*-PrOH, 0.4 mL/min, 280 nm, 25 °C); t_r (minor) = 52.7 min, t_r (major) = 56.4 min, 99% ee.

Data for (*Z*)-**29**: R_f = 0.20 (15% EtOAc/pet. ether); m.p. 135–136 °C (Et_2O); IR 3045, 2964, 2197 (C≡N), 1600, 1583, 1561, 1487, 1442, 1375, 765 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46-7.39 (3H, m, Ar**H**), 7.26-7.15 (7H, m, Ar**H**), 5.22-5.06 (1H, m, =C**H**CN), 3.12-3.06 (2H, m, C**H**$_2$CH$_2$C=CH), 2.98-2.92 (2H, m, C**H**$_2$C=CH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4 (C), 155.4 (C), 140.0 (C), 135.4 (C), 134.6 (C), 130.0 (2 × CH), 129.04 (2 × CH), 128.96 (CH), 128.7 (CH), 128.4 (2 × CH), 128.3 (2 × CH), 116.1

(C), 85.3 (CH), 34.1 (CH_2), 31.7 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{19}H_{15}NNa]^+$ $[M+Na]^+$: 280.1097, found: 280.1094.

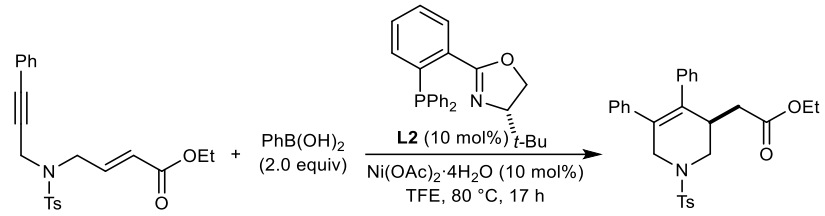
Assignment of the alkene stereochemistry of (*Z*)-**29** was made based on the following NOE interactions observed in the 2D NOESY spectrum between the alkenyl proton at 5.22-5.06 ppm and the methylene protons at 2.98-2.92 ppm and between the methylene protons at 3.12-3.06 ppm and the aromatic protons at 7.26-7.15 ppm:

Key NOE interactions:



(*Z*)-**29**

Ethyl (*R*)-2-(4,5-diphenyl-1-tosyl-1,2,3,6-tetrahydropyridin-3-yl)acetate (38)

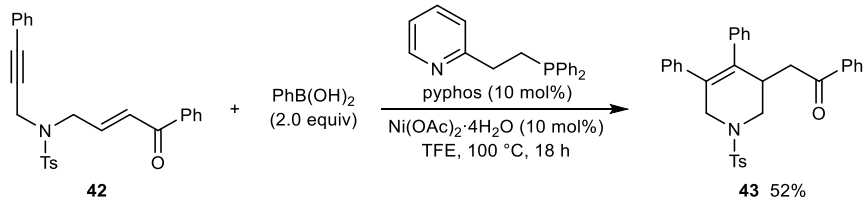


37 **38** 59%, 89% ee

An oven-dried microwave vial fitted with a stirrer bar was charged with the enyne **37** (119 mg, 0.30 mmol), phenylboronic acid (73.2 mg, 0.60 mmol), $Ni(OAc)_2{\cdot}4H_2O$ (7.5 mg, 0.03 mmol), and (*S*)-*t*-BuPHOX (**L2**, 11.6 mg, 0.03 mmol). The vial was capped with a crimp cap seal and flushed with argon. TFE (3 mL) which had been freshly degassed (using a stream of argon for 20 min) was added, the cap was sealed with PTFE tape, and the contents were stirred at room temperature for 10 min and then at 80 °C for 17 h. The reaction was cooled to room temperature, quenched with 50% brine (10 mL), and 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 (10% EtOAc/pentane) to give **38** (84.1 mg, 59%) as a colourless solid. R_f = 0.55 (40% EtOAc/pet. ether); m.p. 138–139 °C (Et_2O); IR 2923, 2854, 1729 (C=O), 1705, 1597, 1346, 1163, 1090, 702, 669 cm^{-1}; $[\alpha]_D^{25}$ +128.0 (*c* 1.00, $CHCl_3$); ^1H

NMR (500 MHz, $CDCl_3$) δ 7.76-7.62 (2H, m, Ar**H**), 7.31 (2H, d, *J* = 8.0 Hz, Ar**H**), 7.15-7.05 (6H, m, Ar**H**), 7.01-6.95 (2H, m, Ar**H**), 6.95-6.89 (2H, m, Ar**H**), 4.47 (1H, d, *J* = 16.3 Hz, C**H**$_a$H$_b$C=) 4.13-4.02 (2H, m, C**H**$_2$CH$_3$), 3.97-3.88 (1H, m, NC**H**$_a$H$_b$CH), 3.32-3.17 (2H, m, CH$_a$**H**$_b$C= and C**H**CH$_2$), 2.81 (1H, ddd, *J* = 11.8, 3.6, 1.5 Hz, NCH$_a$**H**$_b$CH), 2.72 (1H, dd, *J* = 17.2, 10.4 Hz, C**H**$_a$H$_b$C=O), 2.42 (3H, s, ArC**H**$_3$), 2.27 (1H, ddd, *J* = 17.2, 2.9, 1.5 Hz, CH$_a$**H**$_b$C=O), 1.22 (3H, t, *J* = 7.1 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6 (C), 143.9 (C), 139.5 (C), 138.8 (C), 136.7 (C), 132.9 (C), 132.7 (C), 129.9 (2 × CH), 129.6 (4 × CH, two peaks merged into one peak), 128.18 (2 × CH), 128.16 (2 × CH), 128.0 (2 × CH), 127.3 (CH), 127.1 (CH), 60.7 (CH_2), 49.7 (CH_2), 47.2 (CH_2), 37.3 (CH), 35.4 (CH_2), 21.7 (CH_3), 14.3 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{28}H_{29}NNaO_4S]^+$ $[M+Na]^+$: 498.1710, found: 498.1710; Enantiomeric excess was determined by HPLC using a Chiralcel AD-H column (90:10 *iso*-hexane:*i*-PrOH, 0.5 mL/min, 254 nm, 25 °C); t_r (major) = 21.7 min, t_r (minor) = 24.4 min, 89% ee.

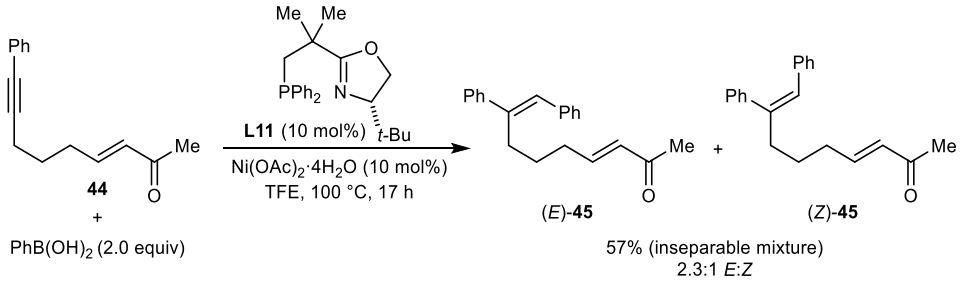
2-(4,5-Diphenyl-1-tosyl-1,2,3,6-tetrahydropyridin-3-yl)-1-phenylethan-1-one (43)



An oven-dried microwave vial fitted with a stirrer bar was charged with the enyne **42** (129 mg, 0.30 mmol), phenylboronic acid (73.2 mg, 0.60 mmol), $Ni(OAc)_2{\cdot}4H_2O$ (7.5 mg, 0.03 mmol), and pyphos (8.7 mg, 0.03 mmol). The vial was capped with a crimp cap seal and flushed with argon. TFE (3 mL) which had been freshly degassed (using a stream of argon for 20 min) was added, the cap was sealed with PTFE tape, and the contents were stirred at room temperature for 10 min and then at 100 °C for 18 h. The reaction was cooled to room temperature, quenched with 50% brine (10 mL), and 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 (10 to 20% EtOAc/pentane) to give **43** (77.7 mg, 52%) as a colourless solid. R_f = 0.59 (40% EtOAc/pet. ether); m.p. 85–88 °C (Et_2O); IR 3056, 2855, 1681

(C=O), 1597, 1493, 1445, 1342, 1162, 995, 760 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.94-7.84 (2H, m, Ar**H**), 7.69-7.64 (2H, m, Ar**H**), 7.55-7.50 (1H, m, Ar**H**), 7.44-7.39 (2H, m, Ar**H**), 7.30-7.27 (2H, m, Ar**H**), 7.16-7.01 (8H, m, Ar**H**), 7.00-6.95 (2H, m, Ar**H**), 4.56 (1H, d, *J* = 16.5 Hz, C**H**$_a$H$_b$C=), 3.88 (1H, dt, *J* = 11.8, 1.4 Hz, NC**H**$_a$H$_b$CH), 3.62-3.53 (2H, m, C**H**$_a$H$_b$C=O and C**H**CH$_2$), 3.25 (1H, dd, *J* = 16.5, 1.9 Hz, CH$_a$**H**$_b$C=), 2.85-2.80 (1H, m, NCH$_a$**H**$_b$CH), 2.76-2.69 (1H, m, CH$_a$**H**$_b$C=O), 2.38 (3H, s, ArC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.1 (C), 143.8 (C), 139.6 (C), 138.9 (C), 137.2 (C), 137.0 (C), 133.3 (CH), 133.0 (C), 132.7 (C), 129.8 (2 × CH), 129.74 (2 × CH), 129.68 (2 × CH), 128.6 (2 × CH), 128.24 (4 × CH, two peaks merged into one peak), 128.20 (2 × CH), 127.9 (2 × CH), 127.3 (CH), 127.1 (CH), 49.7 (CH_2), 47.4 (CH_2), 39.7 (CH_2), 36.1 (CH), 21.6 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{32}H_{29}NNaO_3S]^+$ $[M+Na]^+$: 530.1760, found: 530.1750.

(3*E*,8*E*)-8,9-Diphenylnona-3,8-dien-2-one [(*E*)-45] and (3*E*,8*Z*)-8,9-diphenylnona-3,8-dien-2-one [(*Z*)-45]



An oven-dried microwave vial fitted with a stirrer bar was charged with the enyne **44** (63.7 mg, 0.30 mmol), phenylboronic acid (73.2 mg, 0.60 mmol), $Ni(OAc)_2·4H_2O$ (7.5 mg, 0.03 mmol), and (*S*)-*t*-Bu-NeoPHOX (**L11**, 11.0 mg, 0.03 mmol). The vial was capped with a crimp cap seal and flushed with argon. TFE (3 mL) which had been freshly degassed (using a stream of argon for 20 min) was added, the cap was sealed with PTFE tape, and the contents were stirred at room temperature for 10 min and then at 100 °C for 17 h. The reaction was cooled to room temperature, quenched with 50% brine (10 mL), and 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 (10% EtOAc/pentane) to give a 2.3:1 mixture of inseparable

alkyne hydroarylation products (*E*)-**45** and (*Z*)-**45**, respectively (50.0 mg, 57%), as a yellow oil.

R_f = 0.41 (20% EtOAc/pet. ether); IR 3021, 2929, 1696, 1672 (C=O), 1625, 1493, 1443, 1359, 1252, 976 cm^{-1}; HRMS (ESI) Exact mass calculated for $[C_{21}H_{22}NaO]^+$ $[M+Na]^+$: 313.1563, found: 313.1562.

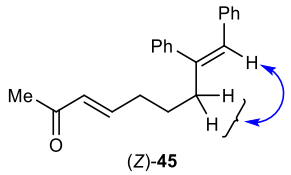
Overlapping NMR signals (integrals refer to the sum of the integrals for each isomer): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48-7.43 (3H, m, Ar**H**), 7.41-7.27 (12H, m, Ar**H**), 7.26-6.90 (5H, m, Ar**H**), 1.62-1.56 (4H, m, $CH_2C\mathbf{H}_2CH_2C$=).

Characteristic NMR signals for major stereoisomer (*E*)-**45**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 (1H, s, =C**H**Ph), 6.67 (1H, dt, *J* = 16.0, 6.9 Hz, $CH_2C\mathbf{H}$=CH), 5.96 (1H, dt, *J* = 16.0, 1.6 Hz, CH_2CH=C**H**), 2.80-2.72 (2H, m, $C\mathbf{H}_2CH_2CH_2C$=), 2.21-2.16 (2H, m, $CH_2CH_2C\mathbf{H}_2C$=), 2.16 (3H, s, $C\mathbf{H}_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.7 (C), 147.8 (CH), 142.7 (C), 142.4 (C, overlapped with minor stereoisomer (*Z*)-**18**), 138.2 (C), 131.8 (CH), 129.13 (CH), 128.9 (2 × CH), 128.8 (CH), 128.7 (CH), 128.6 (2 × CH), 128.5 (2 × CH), 126.7 (2 × CH), 32.2 (CH_2), 29.5 (CH_2), 27.2 (CH_2), 26.9 (CH_3).

Characteristic NMR signals for minor stereoisomer (*Z*)-**45**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81-6.75 (1H, m, $CH_2C\mathbf{H}$=CH), 6.45 (1H, s, =C**H**Ph), 6.07 (1H, dt, *J* = 16.0, 1.6 Hz, CH_2CH=C**H**), 2.57-2.52 (2H, m, $C\mathbf{H}_2CH_2CH_2C$=), 2.30-2.24 (2H, m, $CH_2CH_2C\mathbf{H}_2C$=), 2.23 (1H, s, $C\mathbf{H}_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.8 (C), 148.1 (CH), 142.4 (C, overlapped with major stereoisomer (*E*)-**18**), 140.9 (C), 137.3 (C), 131.7 (CH), 129.07 (2 × CH), 128.0 (2 × CH), 127.5 (2 × CH), 127.2 (CH), 127.1 (CH), 126.9 (2 × CH), 126.4 (CH), 40.2 (CH_2), 32.0 (CH_2), 27.0 (CH_3), 26.4 (CH_2).

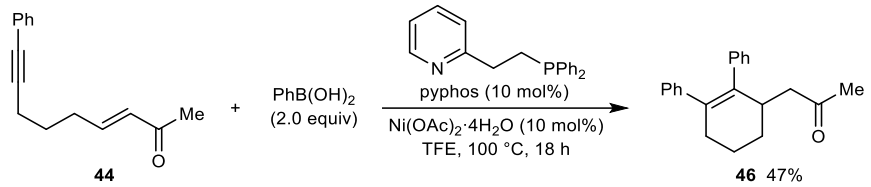
Assignment of the alkenyl stereochemistries of (*E*)-**45** and (*Z*)-**45** was made based on the following NOE interaction observed in the 2D NOESY spectrum of the mixture, between the alkenyl proton at 6.45 ppm and the methylene protons at 2.57-2.52 ppm, which correspond to those (*Z*)-**45**:

Key NOE interaction:



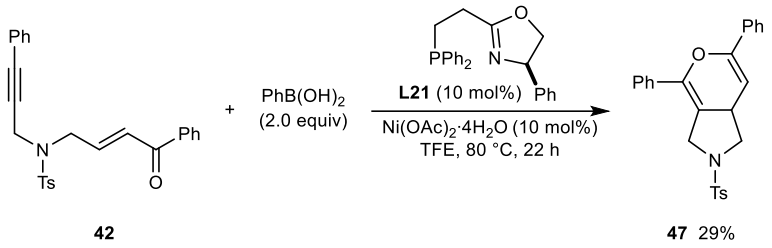
(*Z*)-**45**

1-[3',4',5',6'-Tetrahydro-(1,1':2',1''-terphenyl)-3'-yl]propan-2-one (46)



An oven-dried microwave vial fitted with a stirrer bar was charged with the enyne **44** (63.7 mg, 0.30 mmol), phenylboronic acid (73.2 mg, 0.60 mmol), $Ni(Oac)_2 \cdot 4H_2O$ (7.5 mg, 0.03 mmol), and pyphos (8.7 mg, 0.03 mmol). The vial was capped with a crimp cap seal and flushed with argon. TFE (3 mL) which had been freshly degassed (using a stream of argon for 20 min) was added, the cap was sealed with PTFE tape, and the contents were stirred at room temperature for 10 min and then at 100 °C for 18 h. The reaction was cooled to room temperature, quenched with 50% brine (10 mL), and 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 (5% EtOAc/pentane) to give **46** (47.1 mg) as a colourless oil containing a small amount of unidentified, inseparable impurities. By using 1,3,5-trimethoxybenzene as the internal standard, the purity of **46** was determined by ^{1}H NMR analysis to be 87% (by weight) and the yield was calculated to be 47%. R_f = 0.49 (20% EtOAc/pet. ether); IR 3019, 2928, 1713 (C=O), 1598, 1490, 1442, 1357, 1158, 1069, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17-7.01 (6H, m, Ar**H**), 7.01-6.90 (4H, m, Ar**H**), 3.34-3.20 (1H, m, C**H**CH_2), 2.65-2.57 (1H, m, =CC**H**$_a$H$_b$), 2.43 (1H, dd, *J* = 16.8, 10.3 Hz, C**H**$_a$H$_b$C=O), 2.33-2.20 (2H, m, CH$_a$**H**$_b$C=O and =CCH$_a$**H**$_b$), 1.97 (3H, s, C**H**$_3$), 1.92 (1H, ddd, *J* = 13.1, 5.7, 3.6 Hz, =CCH$_2$CH$_2$C**H**$_a$H$_b$), 1.83-1.77 (2H, m, =CCH$_2$C**H**$_2$), 1.73-1.66 (1H, m, =CCH$_2$CH$_2$CH$_a$**H**$_b$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.6 (C), 143.7 (C), 141.9 (C), 137.9 (C), 137.1 (C), 129.9 (2 × CH), 129.2 (2 × CH), 127.8 (2 × CH), 127.7 (2 × CH), 126.1 (CH), 125.9 (CH), 47.4 (CH_2), 35.2 (CH), 32.4 (CH_2), 30.4 (CH_3), 27.9 (CH_2), 19.6 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{21}H_{22}NaO]^+$ $[M+Na]^+$: 313.1563, found: 313.1567.

4,6-Diphenyl-2-tosyl-1,2,3,7a-tetrahydropyrano[3,4-c]pyrrole (47).

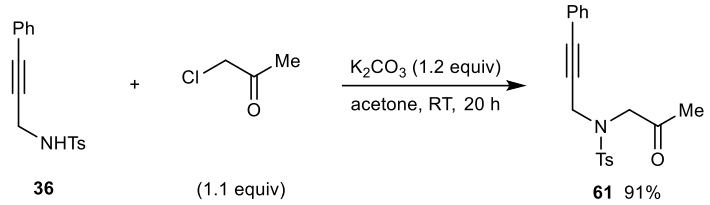


42 **47** 29%

An oven-dried microwave vial fitted with a magnetic stirrer bar was charged with enyne **42** (21.4 mg, 0.05 mmol), phenylboronic acid (12.2 mg, 0.10 mmol), $Ni(OAc)_2 \cdot 4H_2O$ (1.2 mg, 0.005 mmol), and ligand **L21** (1.1 mg, 0.005 mmol). The vial was capped with a crimp cap seal and flushed with argon. Freshly degassed TFE (0.5 mL, using a stream of argon for 20 min) was added, the cap was sealed with PTFE tape, and the contents were stirred at room temperature for 10 min and then at 80 °C for 22 h. The reaction was filtered through a pad of silica (EtOAc) and purified by preparative TLC (20% EtOAc/pet. ether) to give pyran **47** (6.3 mg, 29%) as a yellow solid and recovery of starting material **42** (5.2 mg, 24%). R_f = 0.38 (20% EtOAc/pet. ether); m.p. 63−65 °C (Et_2O); IR 3062, 2923, 2852, 1597, 1493, 1446, 1342, 1156, 1092, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69-7.61 (4H, m, Ar**H**), 7.45-7.34 (8H, m, Ar**H**), 7.26-7.23 (2H, m, Ar**H**), 5.37 (1H, d, *J* = 2.3 Hz, =C**H**), 4.41 (1H, dd, *J* = 13.5, 1.9 Hz, =CC**H**$_a$H$_b$), 4.02 (1H, dd, *J* = 13.5, 1.8 Hz, =CCH$_a$**H**$_b$), 3.93 (1H, dd, *J* = 9.0, 7.6 Hz, CHC**H**$_a$H$_b$), 3.62 (1H, ddd, *J* = 10.1, 7.8, 2.0 Hz, =CHC**H**), 2.87 (1H, dd, *J* = 10.1, 9.0 Hz, CHCH$_a$**H**$_b$), 2.36 (3H, s, ArC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.8 (C), 134.1 (C), 133.7 (C), 133.4 (C), 129.9 (2 × CH), 129.8 (C), 129.2 (CH), 129.0 (CH), 128.6 (4 × CH, 2 peaks merged into one peak), 128.4 (C), 127.6 (2 × CH), 127.2 (2 × CH), 124.8 (2 × CH), 109.0 (C), 96.0 (CH), 53.8 (CH_2), 49.6 (CH_2), 36.3 (CH), 21.6 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{26}H_{24}NO_3S]^+$ $[M+H]^+$: 430.1471, found: 430.1473.

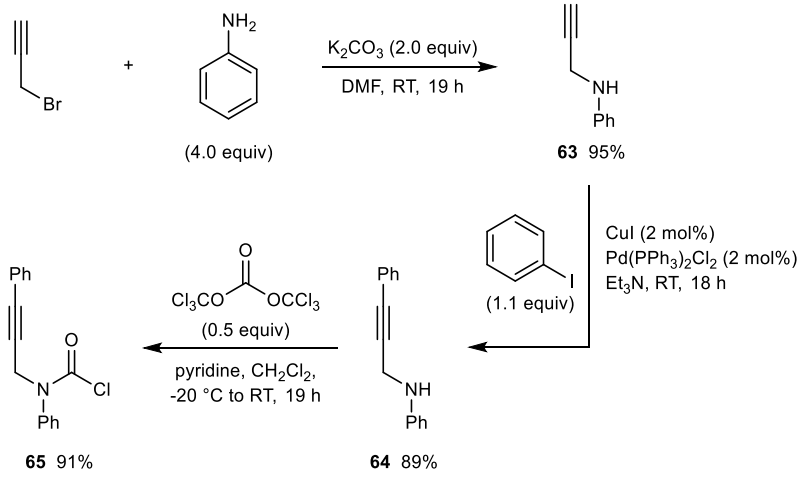
3.7 Cobalt-Catalysed *anti*-Carbometallative Cyclisation

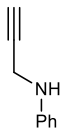
4-Methyl-*N*-(2-oxopropyl)-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (61)



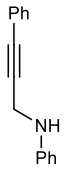
The title compound was prepared according to a previously reported procedure.[178] To a solution of the *N*-tosyl propargyl amine **36** (999 mg, 3.50 mmol) and K_2CO_3 (581 mg, 4.20 mmol) in acetone (10 mL) was added chloroacetone (0.31 mL, 3.85 mmol) and the resulting solution was stirred at room temperature for 20 h. The reaction was filtered through celite (EtOAc) and concentrated in *vacuo*. The residue was purified by column chromatography (20 to 30% EtOAc/pet. ether) to give the ketone **61** (1.09 g, 91%) as a yellow solid. The analytical data were consistent with those reported previously.[80] R_f = 0.41 (40% EtOAc/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.66 (2H, m, Ar**H**), 7.30-7.26 (2H, m, Ar**H**), 7.26-7.20 (3H, m, Ar**H**), 7.14-7.08 (2H, m, Ar**H**), 4.37 (2H, s, ≡CC**H**$_2$), 4.03 (2H, s, C**H**$_2$C=O), 2.35 (3H, s, C**H**$_3$), 2.24 (3H, s, ArC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.6 (C), 144.1 (C), 135.5 (C), 131.7 (2 × CH), 129.9 (2 × CH), 128.8 (CH), 128.3 (2 × CH), 127.8 (2 × CH), 121.9 (C), 86.4 (C), 81.4 (C), 55.8 (CH_2), 39.1 (CH_2), 27.3 (CH_3), 21.6 (CH_3).

Phenyl(3-phenylprop-2-yn-1-yl)carbamic chloride (65)

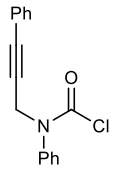




***N*-(Prop-2-yn-1-yl)aniline (63)**. The title compound was prepared according to a previously reported procedure.[179] To a stirred solution of aniline (18.4 mL, 202 mmol) in DMF (45 mL) was added K_2CO_3 (13.9 g, 101 mmol) under an argon atmosphere. The solution was stirred for 5 min at room temperature and a solution of propargyl bromide (80 wt% in toluene, 5.4 mL, 50.5 mmol) in DMF (15 mL) was added dropwise and then the reaction was stirred at room temperature for 19 h. The reaction was diluted with H_2O (300 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (100 mL) and 5% aqueous LiCl solution (50 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (5 to 10% EtOAc/cyclohexane) to give propargyl amine **63** (6.28 g, 95%) as an orange oil. The analytical data were consistent with those reported previously.[180] R_f = 0.46 (20% EtOAc/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.15 (2H, m, Ar**H**), 6.88-6.79 (1H, m, Ar**H**), 6.75-6.69 (2H, m, Ar**H**), 3.96 (2H, d, *J* = 2.5 Hz, C**H**$_2$), 3.89 (1H, s, N**H**), 2.37-2.13 (1H, m, ≡C**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.0 (C), 129.3 (2 × CH), 118.7 (CH), 113.6 (2 × CH), 81.1 (C), 71.4 (CH), 33.7 (CH_2).

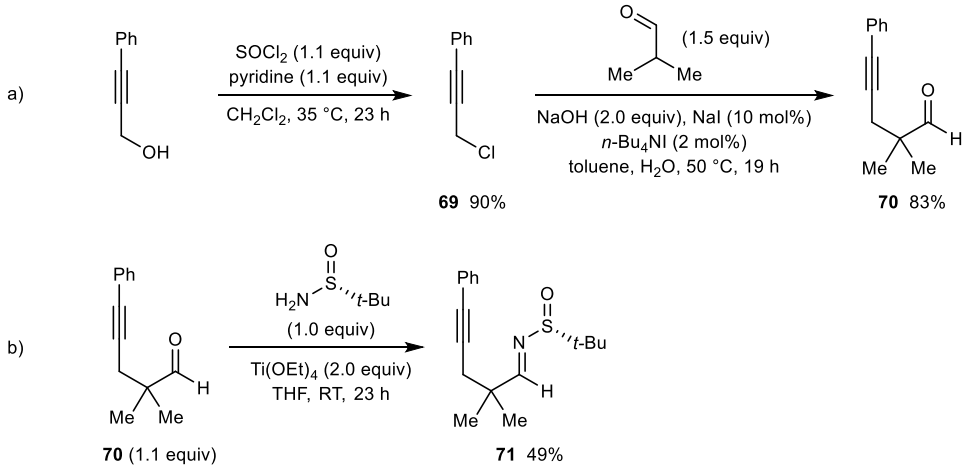


***N*-(3-Phenylprop-2-yn-1-yl)aniline (64)**. The title compound was prepared according to a previously reported procedure.[179] To a solution of iodobenzene (0.98 mL, 8.80 mmol) and alkyne **63** (1.05 g, 8.00 mmol) in Et_3N (80 mL) under an argon atmosphere at room temperature was added $PdCl_2(PPh_3)_2$ (112 mg, 0.16 mmol) and CuI (30.5 mg, 0.16 mmol) and the mixture was stirred at room temperature for 18 h. The volatiles were removed in *vacuo* and H_2O (50 mL) was added to the resulting slurry. The mixture was extracted with EtOAc (3 × 50 mL) and 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 (10% EtOAc/pet. ether) to give alkyne **64** (1.48 g, 89%) as a brown oil. The analytical data were consistent with those reported previously.[181] R_f = 0.29 (10% EtOAc/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.37 (2H, m, Ar**H**), 7.37-7.29 (3H, m, Ar**H**), 7.29-7.23 (2H, m, Ar**H**), 6.82 (1H, app t, *J* = 7.3 Hz, Ar**H**), 6.79-6.73 (2H, m, Ar**H**), 4.18 (2H, s, C**H**$_2$), 3.98 (1H, s, N**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.3 (C), 131.8 (2 × CH), 129.4 (2 × CH), 128.38 (2 × CH), 128.35 (CH), 123.0 (C), 118.6 (CH), 113.7 (2 × CH), 86.5 (C), 83.4 (C), 34.7 (CH_2).



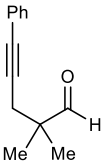
Phenyl(3-phenylprop-2-yn-1-yl)carbamic chloride (65). TAKE EXTRA CARE WHEN CARRYING OUT THIS REACTION! To a solution of triphosgene (371 mg, 1.25 mmol) in dry CH_2Cl_2 (6 mL) under an argon atmosphere at –20 °C was slowly added pyridine (0.8 mL) and the mixture was stirred for 20 min. A solution of amine **64** (518 mg, 2.50 mmol) in dry CH_2Cl_2 (2 mL) was added slowly and the reaction was stirred at room temperature for 19 h. The reaction was quenched with 1 M aqueous HCl (10 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated in *vacuo* to give carbamoyl chloride **65** (616 mg, 91%) as a brown oil. R_f = 0.37 (10% EtOAc/pet. ether); IR 3061, 2246 (C≡C), 1729 (C=O), 1594, 1491, 1371, 1229, 1203, 954, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52-7.42 (3H, m, Ar**H**), 7.42-7.34 (4H, m, Ar**H**), 7.34-7.27 (3H, m, Ar**H**), 4.71 (2H, s, C**H**$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.5 (C), 141.3 (C), 131.9 (2 × CH), 129.7 (2 × CH), 129.2 (CH), 128.8 (CH), 128.6 (2 × CH), 128.5 (2 × CH), 122.3 (C), 85.9 (C), 82.6 (C), 42.9 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{16}H_{12}{}^{35}ClNNaO]^+$ $[M+Na]^+$: 292.0500, found: 292.0496.

(*R*,*E*)-*N*-(2,2-Dimethyl-5-phenylpent-4-yn-1-ylidene)-2-methylpropane-2-sulfinamide (71).

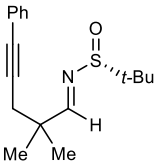


(3-Chloroprop-1-yn-1-yl)benzene (69). To a stirred solution of 3-phenyl-2-propyn-1-ol (2.5 mL, 20.0 mmol) in dry CH_2Cl_2 (40 mL) was added pyridine (1.8 mL, 22.0 mmol) under an argon atmosphere. The resulting solution was cooled

to 0 °C and $SOCl_2$ (1.6 mL, 22 mmol) was added. The mixture was heated to 35 °C and stirred for 23 h. The reaction was diluted with H_2O (80 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (10% EtOAc/pet. ether) to give propargyl chloride **69** (2.71 g, 90%) as a brown oil. The analytical data were consistent with those reported previously.[182] R_f = 0.66 (30% EtOAc/pet. ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52-7.42 (2H, m, Ar**H**), 7.40-7.29 (3H, m, Ar**H**), 4.39 (2H, s, C**H**$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 132.0 (2 × CH), 129.0 (CH), 128.5 (2 × CH), 122.2 (C), 86.5 (C), 83.9 (C), 31.3 (CH_2).



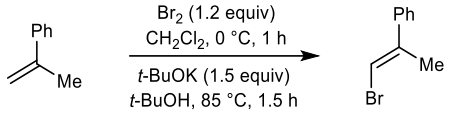
2,2-Dimethyl-5-phenylpent-4-ynal (70). The title compound was prepared according to a previously reported procedure.[183] To a vigorously stirred solution of NaOH (560 mg, 14 mmol), NaI (105 mg, 0.70 mmol), *n*-Bu_4NI (51.7 mg, 0.14 mmol) in H_2O (1.0 mL) and toluene (1.0 mL) at 50 °C was added dropwise over 15 min a solution of propargyl chloride **69** (1.05 g, 7.00 mmol) and isobutyraldehyde (0.96 mL, 10.5 mmol) in toluene (3.0 mL). The mixture was stirred for 19 h. The reaction was diluted with H_2O (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (0.5% to 1% EtOAc/pet. ether) to give aldehyde **70** (1.08 g, 83%) as a yellow oil. The analytical data were consistent with those reported previously.[183] R_f = 0.49 (15% EtOAc/pet. ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.61 (1H, s, CO**H**), 7.44-7.36 (2H, m, Ar**H**), 7.32-7.27 (3H, m, Ar**H**), 2.57 (2H, s, C**H**$_2$), 1.23 (6H, s, C(C**H**$_3$)$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.9 (C), 131.7 (2 × CH), 128.4 (2 × CH), 128.0 (CH), 123.5 (C), 85.7 (C), 83.4 (C), 46.0 (C), 27.8 (CH_2), 21.5 (2 × CH_3).



(*R*,*E*)-*N*-(2,2-Dimethyl-5-phenylpent-4-yn-1-ylidene)-2-methylpropane-2-sulfinamide (71). To a solution of aldehyde **70** (512 mg, 2.75 mmol) in THF (5 mL) was added $Ti(OEt)_4$ (1.14 g, 5.00 mmol) and (*R*)-*t*-butylsulfinamide (303 mg, 2.50 mmol) and the resulting solution was stirred at room temperature for 23 h. The reaction was treated with MeOH and a few drops of saturated aqueous $NaHCO_3$ until precipitation formed. The solution was dried (Na_2SO_4), filtered, and concentrated in *vacuo*. The residue was purified by column chromatography (5 to 8% EtOAc/pet. ether) to give sulfinimine **71** (353 mg,

49%) as a colourless oil. R_f = 0.46 (10% EtOAc/pet. ether); IR 3964, 2927, 2903, 2207 (C≡C), 1621 (C=N), 1490, 1364, 1185, 1087 (S=O), 757 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (1H, s, **H**C=N), 7.39-7.33 (2H, m, Ar**H**), 7.29-7.24 (3H, m, Ar**H**), 2.70-2.55 (2H, m, C**H**$_2$), 1.29 (6H, d, *J* = 3.8 Hz, C(C**H**$_3$)$_2$), 1.18 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9 (CH), 131.7 (2 × CH), 128.3 (2 × CH), 127.9 (CH), 123.7 (C), 86.6 (C), 83.1 (C), 56.8 (C), 41.4 (C), 30.4 (CH_2), 24.72 (CH_3), 24.66 (CH_3), 22.4 (3 × CH_3); HRMS (ESI) Exact mass calculated for $[C_{17}H_{23}NNaOS]^+$ $[M+Na]^+$: 312.1393, found: 312.1391.

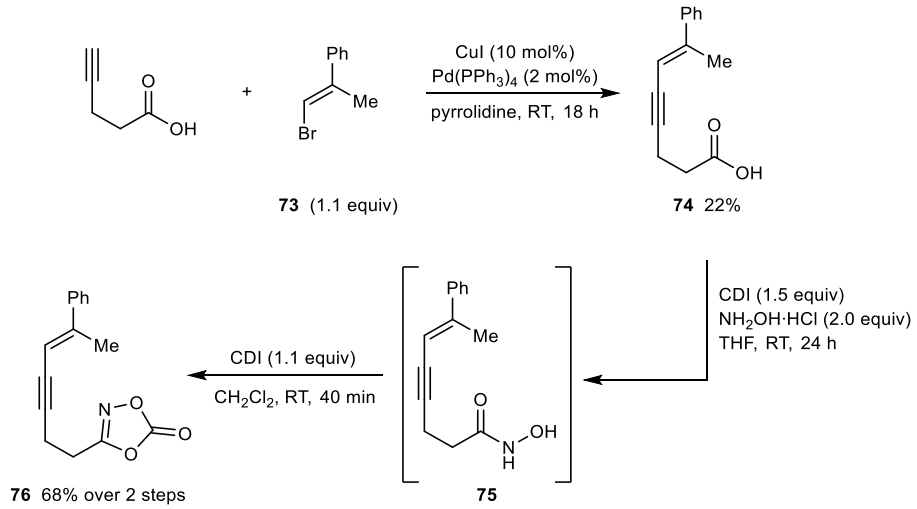
(*E*)-(1-Bromoprop-1-en-2-yl)benzene (73).

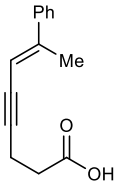


73 89%

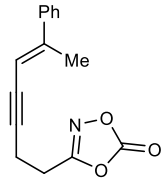
The title compound was prepared according to a previously reported procedure.[184] To a degassed round bottom flask (argon) was added styrene (2.6 mL, 20.0 mmol) and CH_2Cl_2 (30 mL) and the mixture was cooled to 0 °C before bromine (1.2 mL, 24.0 mmol) was added dropwise. The reaction was stirred at room temperature for 1 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ and the organic layer was collected, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. To the crude residue was added *t*-BuOH (100 mL) followed by *t*-BuOK (3.37 g, 30.0 mmol) and the mixture was stirred at 85 °C for 1.5 h. The reaction was diluted with H_2O (50 mL) and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (2% EtOAc/pet. ether) to give alkenyl bromide **73** (3.51 g, 89%) as a colourless oil. The analytical data were consistent with those reported previously.[184] R_f = 0.69 (10% EtOAc/pet. ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.28 (5H, m, Ar**H**), 6.45 (1H, q, *J* = 1.4 Hz, C**H**), 2.23 (3H, d, *J* = 1.3 Hz, C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.7 (C), 141.1 (C), 128.7 (2 × CH), 128.0 (CH), 126.1 (2 × CH), 105.5 (CH), 19.8 (CH_3).

(*E*)-3-(6-Phenylhept-5-en-3-yn-1-yl)-1,4,2-dioxazol-5-one (76).



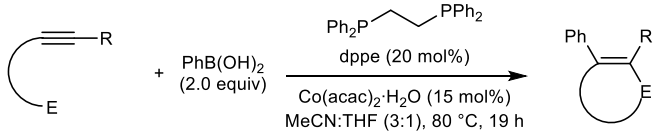


(*E*)-7-Phenyloct-6-en-4-ynoic acid (74). To a solution of alkenyl bromide **73** (1.08 g, 5.50 mmol), $Pd(PPh_3)_4$ (116 mg, 0.10 mmol) and CuI (95.2 mg, 0.50 mmol) in pyrrolidine (20 mL) under an argon atmosphere at room temperature was added 4-pentynoic acid (491 mg, 5.00 mmol) and the mixture was stirred at room temperature for 18 h. The reaction was diluted with H_2O (50 mL) and washed with EtOAc (4 × 50 mL). The aqueous layer was acidified with 2 M aqueous HCl until pH ≈ 1–2 and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in *vacuo*. The residue was purified by column chromatography (40% EtOAc/pet. ether) to give carboxylic acid **74** (235 mg, 22%) as an off-white solid. R_f = 0.35 (70% EtOAc/pet. ether); m.p. 100–102 °C (Et_2O); IR 3055 (OH), 3034, 2925, 2212 (C≡C), 1698 (C=O), 1495, 1432, 1300, 1206, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.74 (1H, s, COO**H**), 7.45-7.38 (2H, m, Ar**H**), 7.36-7.27 (3H, m, Ar**H**), 5.85 (1H, s, =C**H**), 2.82-2.73 (2H, m, ≡CC$\mathbf{H}_2$), 2.73-2.62 (2H, m, C$\mathbf{H}_2$COOH), 2.28 (3H, s, C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.7 (C), 147.9 (C), 141.1 (C), 128.5 (2 × CH), 128.1 (CH), 125.5 (2 × CH), 106.7 (CH), 93.5 (C), 80.0 (C), 33.7 (CH_2), 18.6 (CH_3), 15.7 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{14}H_{14}NaO_2]^+$ $[M+Na]^+$: 237.0886, found: 237.0888.



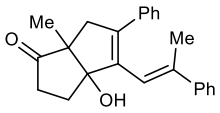
(*E*)-3-(6-Phenylhept-5-en-3-yn-1-yl)-1,4,2-dioxazol-5-one (75). To a solution of carboxylic acid **74** (107 mg, 0.50 mmol) in dry THF (2 mL) under an argon atmosphere was added 1,1'-carbonyldiimadazole (122 mg, 0.75 mmol) and the resulting solution was stirred at room temperature for 1 h. Powdered $NH_2OH{\cdot}HCl$ (42 μL, 1.00 mmol) was added, and the mixture was stirred at room temperature for 23 h. The reaction was diluted with 0.5 M aqueous HCl (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude hydroxamic acid **75** was dissolved in CH_2Cl_2 (5 mL) and 1,1'-carbonyldiimadazole (89.2 mg, 0.55 mmol) was added under an argon atmosphere. The solution was stirred at room temperature for 40 min. The reaction was diluted with 1 M aqueous HCl (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in *vacuo*. The residue was filtered through a pad of silica (CH_2Cl_2) and the filtrate was concentrated in *vacuo* to give dioxazolone **76** (87.1 mg, 68%) as an orange solid. R_f = 0.75 (70% EtOAc/pet. ether); m.p. 59–61 °C (Et_2O); IR 2921, 2854, 1866, 1825, 1639, 1494, 1376, 1146, 982, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47-7.39 (2H, m, Ar**H**), 7.37-7.27 (3H, m, Ar**H**), 5.84 (1H, s, =C**H**), 2.98-2.91 (2H, m, ≡$CCH_2C\mathbf{H}_2$), 2.91-2.83 (2H, m, ≡$CC\mathbf{H}_2$), 2.28 (3H, s, $C\mathbf{H}_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.3 (C), 154.1 (C), 148.9 (C), 140.8 (C), 128.6 (2 × CH), 128.3 (CH), 125.5 (2 × CH), 106.1 (CH), 90.7 (C), 81.7 (C), 25.1 (CH_2), 18.6 (CH_3), 16.1 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{16}H_{17}NNaO_4]^+$ $[M+MeOH+Na]^+$: 310.1055, found: 310.1055. $[M+Na]^+$ was not detected by HRMS.

General procedure B: cobalt-catalysed *anti*-carbometallative cyclisation reactions

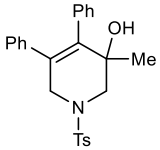


An oven-dried microwave vial fitted with a magnetic stirrer bar was charged with the appropriate substrate (0.10 mmol), phenylboronic acid (24.4 mg, 0.20 mmol), $Co(acac)_2{\cdot}H_2O$ (4.4 mg, 15.0 μmol) and dppe (8.0 mg, 20.0 μmol). The vial was capped with a crimp cap seal and flushed with argon (5 min). Freshly degassed MeCN (0.3 mL,

using a stream of argon for 20 min) and THF (0.1 mL, using a stream of argon for 20 min) were added, the cap was sealed with PTFE tape, and the contents were stirred at room temperature for 10 min and then transferred to a pre-heated oil bath and stirred at 80 °C for 19 h. The reaction was cooled to room temperature, diluted with brine (2 mL), and extracted with EtOAc (3 × 2 mL). The combined organic layers were filtered through a syringe plug layered with cotton wool, Na_2SO_4 and silica (EtOAc), and concentrated *in vacuo*. To the residue was added 0.7 mL of internal standard (5 mg/mL 1,3,5-trimethoxybenzene in $CDCl_3$).



(*E*)-3a-Hydroxy-6a-methyl-5-phenyl-4-(2-phenylprop-1-en-1-yl)-3,3a,6,6a-tetrahydropentalen-1(2*H*)-one (58). Prepared according to General Procedure B, using diketone **57** (26.6 mg, 0.10 mmol). Purification by preparative TLC (10% EtOAc/pet. ether) gave **58** as a colourless solid containing a small amount of unidentified, inseparable impurities. R_f = 0.18 (10% EtOAc/pet. ether); IR 3437 (OH), 2960, 2928, 1729 (C=O), 1494, 1445, 1137, 1070, 762, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46-7.27 (8H, m, Ar**H**), 7.25-7.18 (2H, m, Ar**H**), 6.52 (1H, s, =C**H**), 3.23 (1H, dd, *J* = 17.1, 1.7 Hz, =CC**H**$_a$H$_b$), 2.73 (1H, dd, *J* = 17.1, 2.9 Hz, =CCH$_a$**H**$_b$), 2.55-2.36 (2H, m, C**H**$_a$H$_b$C=O and C**H**$_a$H$_b$COH), 2.15-1.95 (2H, m, CH$_a$**H**$_b$C=O and CH$_a$**H**$_b$COH), 1.76 (1H, s, O**H**), 1.55 (3H, s, =CC**H**$_3$), 1.21 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 221.8 (C), 141.9 (C), 140.7 (C), 137.7 (C), 136.8 (C), 128.52 (2 × CH), 128.47 (2 × CH), 128.3 (C), 128.0 (CH), 127.74 (2 × CH), 127.66 (CH), 125.9 (2 × CH), 119.8 (CH), 92.9 (C), 56.0 (C), 45.1 (CH_2), 36.8 (CH_2), 30.0 (CH_2), 17.7 (CH_3), 15.7 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{24}H_{24}NaO_2]^+$ $[M+Na]^+$: 367.1667, found 367.1669. (Melting point was not obtained)



3-Methyl-4,5-diphenyl-1-tosyl-1,2,3,6-tetrahydropyridin-3-ol (62). Arylative cyclisation product **62** was not isolated; however, data for this compound was available in the group and these data were used to determine the yield by ^1H NMR.[80]

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5.0 Appendix: Publication

This thesis contains results reported in the following publication:

ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2021, **57**, 4436

Received 3rd March 2021,
Accepted 23rd March 2021

DOI: 10.1039/d1cc01166a

rsc.li/chemcomm

Enantioselective nickel-catalyzed *anti*-arylmetallative cyclizations onto acyclic electron-deficient alkenes†

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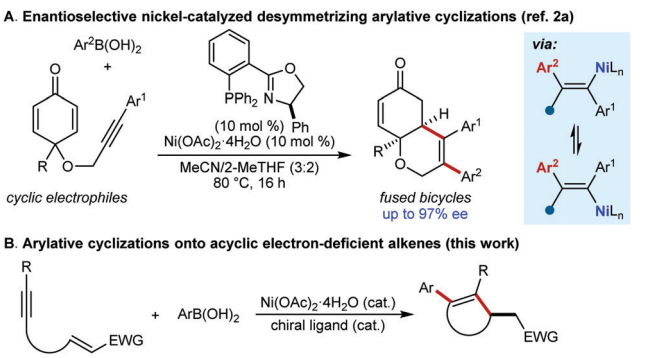
Enantioselective nickel-catalyzed reactions of (hetero)arylboronic acids or alkenylboronic acids with substrates containing an alkyne tethered to various acyclic electron-deficient alkenes are described.

The metal-catalyzed addition of an arylboron reagent to an alkyne, followed by enantioselective intramolecular nucleophilic addition of the resulting alkenylmetal species onto a tethered electrophile, is a versatile domino reaction sequence for the synthesis of diverse chiral carbo- and heterocycles.[1] We[2] and others[3] have recently described nickel-catalyzed variants of these reactions in which reversible *E*/*Z* isomerization of the intermediate alkenylnickel species enables enantioselective arylative cyclizations to proceed that would otherwise be impossible because of geometric constraints. Variants of these reactions that give achiral products,[4] and several related processes,[5–7] have also been described.

We have previously described enantioselective desymmetrizing nickel-catalyzed arylative cyclizations onto cyclohexa-2,5-dienones, which give fused bicyclic products with high diastereo- and enantioselectivities (Scheme 1A).[2a] However, the use of a broader range of acyclic electron-deficient, conjugated alkenes in cyclizations would be valuable in providing less complex, non-fused products, and would substantially increase the synthetic utility of this methodology. Herein, we demonstrate that acyclic enones, nitroalkenes, α,β-unsaturated esters, and α,β-unsaturated nitriles can be used as electrophiles in the enantioselective preparation of various non-fused chiral carbo- and heterocycles (Scheme 1B). Collectively, these results represent a substantial increase in the scope of nickel-catalyzed *anti*-carbometallative cyclizations.

This study began with the reactions of $PhB(OH)_2$ with substrates **1a–1p** (Table 1). An evaluation of conditions[8] led to the finding that heating the substrate **1**, $PhB(OH)_2$ (1.2 equiv.), and 5 mol% each of $Ni(OAc)_2{\cdot}4H_2O$ and (*S*)-*t*-Bu-NeoPHOX (**L1**)[2b,9] in TFE at 100 °C for 16–19 h gave the desired products **2** in generally good yields and high enantioselectivities.[10] In some cases (**2j**, **2o**, and **2p**), using 2.0 equivalents of $PhB(OH)_2$ and increasing the catalyst loading were required for acceptable yields. Aromatic ketones with halide (**2a** and **2b**), nitro (**2c** and **2e**), or trifluoromethyl (**2d**) substituents at various positions of the benzene are tolerated, as are 2-furyl (**2f**), 2-thienyl (**2g**), and methyl ketones (**2h** and **2k–2n**). Notably, an α,β-unsaturated aldehyde underwent arylative cyclization to give **2i** in 58% yield and >99% ee. An α-chloroketone, containing a potentially labile carbon–chlorine bond, is also tolerated (**2j**). The alkynyl group can be changed from phenyl (**2a–2j**) to 4-chlorophenyl (**2k**), 3-methylphenyl (**2l**), 2-thienyl (**2m**), and vinyl (**2n**), although **2m** was formed in lower yield and enantioselectivity. Aryl- and alkenyl-substituted alkynes are usually required for high regioselectivities in the initial arylnickelation step, presumably because the resulting alkenylnickel intermediates are better stabilized by an adjacent sp^2-hybridized group. Therefore, it was of interest to evaluate the reaction of methyl-substituted alkyne **1o**,



Scheme 1 Enantioselective nickel-catalyzed arylative cyclizations onto electron-deficient alkenes.

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† Electronic supplementary information (ESI) available: Experimental procedures, full spectroscopic data for new compounds, and crystallographic data for **2a**, **2r**, **2s**, and **2y**. CCDC 2040010–2040013. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1cc01166a

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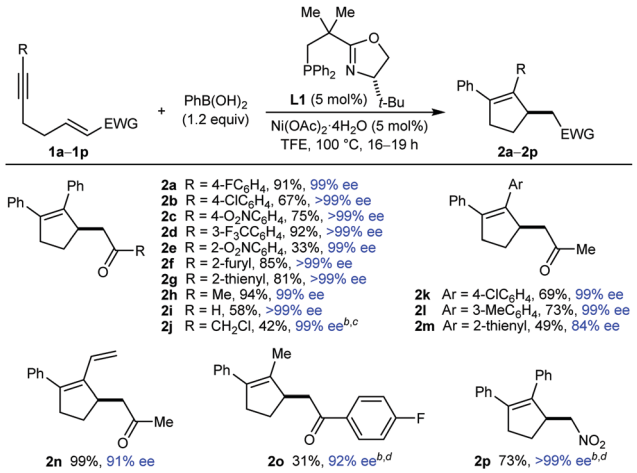
Table 1 Scope of alkynes tethered to electron-deficient alkenes[a]

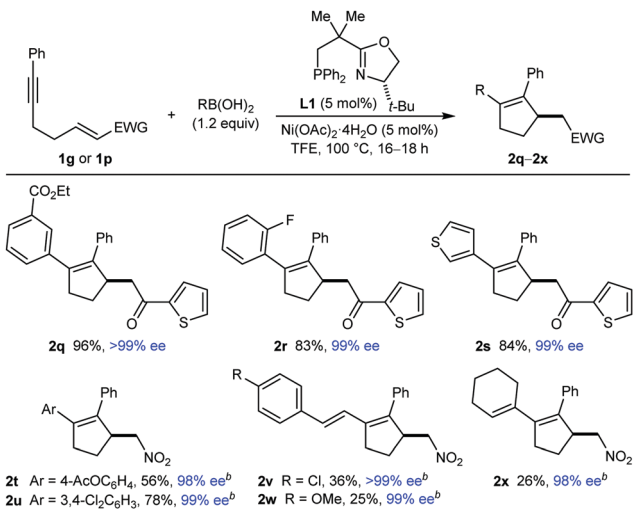


[a] Reactions were conducted using 0.30 mmol of **1** in TFE (3 mL). Yields are of isolated products. Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase. [b] Using 2.0 equivalents of $PhB(OH)_2$. [c] Using 20 mol% each of $Ni(OAc)_2{\cdot}4H_2O$ and **L1**. [d] Using 10 mol% each of $Ni(OAc)_2{\cdot}4H_2O$ and **L1**.

which gave **2o** in 31% yield and 92% ee. This reaction also gave a mixture of other unidentified products, presumably because of low regioselectivity in the initial arylnickelation. A nitroalkene can also be used as the electrophile (**2p**).

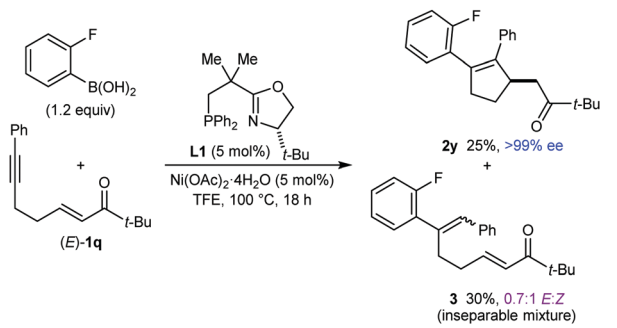
The results of evaluating different boronic acids in reactions with substrates **1g** or **1p** are shown in Table 2. Substituted phenylboronic acids with various groups at the *para* (**2t**), *meta* (**2q**), or *ortho* (**2r**) positions successfully underwent the reaction to give products with reasonable to high yields and high enantioselectivities, as did 3,4-dichlorophenylboronic acid (**2u**) and 3-thienylboronic acid (**2s**). Various alkenylboronic acids also reacted with **1p** to give products **2v–2x** in >99% ee but in low yields because of competitive protodeboronation.

Table 2 Scope of boronic acids[a]

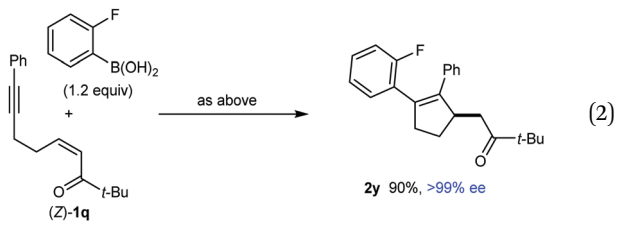


[a] See footnote *a* of Table 1. [b] Using 2.0 equivalents of boronic acid and 10 mol% each of $Ni(OAc)_2{\cdot}4H_2O$ and **L1**.

Further investigations into the scope of these reactions revealed some interesting findings. For example, the reaction of 2-fluorophenylboronic acid with substrate (*E*)-**1q**, which contains an α,β-unsaturated *t*-butyl ketone, gave the arylative cyclization product **2y** in only 25% yield but in >99% ee (eqn (1)). This reaction also gave the alkyne hydroarylation products **3** in 30% yield, which were isolated as a 0.7 : 1 mixture of inseparable *E*- and *Z*-isomers, respectively. Evidently, the steric hindrance imparted by the *t*-butyl group had a negative effect on the efficiency of arylative cyclization. Interestingly, however, the analogous reaction with the stereoisomeric substrate (*Z*)-**1q** gave **2y** in 90% yield and >99% ee (eqn (2)). The markedly different propensity of (*E*)-**1q** and (*Z*)-**1q** to undergo the desired reaction is reminiscent of our prior work in enantioselective nickel-catalyzed intramolecular allylic alkenylations, where *Z*-allylic phosphates gave arylative cyclization products but the corresponding *E*-isomers did not.[2b] The reasons for the differing results obtained from (*E*)-**1q** and (*Z*)-**1q** are not clear, but perhaps the lower thermodynamic stability of (*Z*)-**1q** is manifested in greater reactivity toward nucleophilic attack, and/or the steric requirements of the reaction are better accommodated by (*Z*)-**1q**. Moreover, the major enantiomer of **2y** is identical for both reactions (see the ESI† for tentative stereochemical models). These results contrast with several other examples of enantioselective 1,4-additions of carbon nucleophiles to electron-deficient alkenes where *E*- and *Z*-isomers of the substrates give opposite enantiomers of the products.[11] However, reactions where *E*- and *Z*-isomers give the same major enantiomers of 1,4-addition products are also known.[1j,11b]



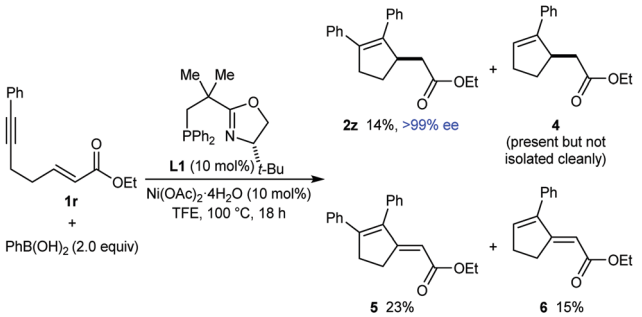
(1)



(2)

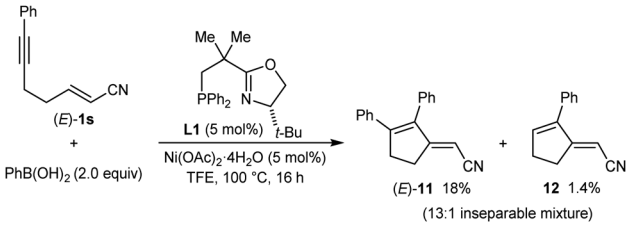
Thus far, only enones or nitroalkenes had been used as electrophiles. Interestingly, use of an α,β-unsatured ester gave other types of products (eqn (3)). Substrate **1r** reacted with $PhB(OH)_2$ (2.0 equiv.) in the presence of 10 mol% each of $Ni(OAc)_2{\cdot}4H_2O$ and (*S*)-*t*-Bu-NeoPHOX (**L1**) to give the arylative cyclization product **2z** (14%, >99% ee), conjugated dienes **5** (23% yield) and **6** (15% yield) resulting from Heck-type cyclizations,[12,13] and what appeared to be the reductive cyclization product **4**, which could not be isolated cleanly. These results can be

explained by considering the mechanism of nickel-catalyzed *anti*-carbometallative cyclizations that we have proposed previously (Scheme 2).[2,4c] Reaction of **1r** and $PhB(OH)_2$ would, after arylnickelation and reversible *E*/*Z* isomerization,[2,4c] lead to alkenylnickel species **7**. A *syn*-stereospecific migratory insertion of the alkene[2b] would then give the *C*-bound nickel enolate **8**. Protodenickelation of **8** by TFE gives the arylative cyclization product **2z**. However, the low yield of **2z** suggests that this step is slow compared with substrates containing ketones or nitro groups (Tables 1 and 2).[14] In competition with protodenickelation of **8**, bond rotation to give **8′** and stereospecific *syn*-β-hydride elimination gives diene **5** and a nickel hydride species **9**. The nickel hydride **9** can then enter analogous reaction pathways with substrate **1r** but *via* alkyne hydronickelation to give **10** and eventually, the reductive cyclization product **4** and diene **6**.

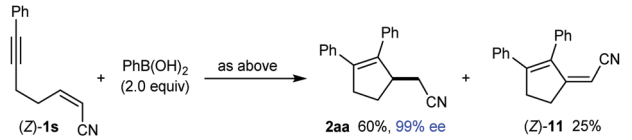


(3)

Conjugate dienes were also obtained from substrates containing an α,β-unsaturated nitrile (eqn (4) and (5)). The reaction of $PhB(OH)_2$ with (*E*)-**1s** gave an inseparable 13 : 1 mixture of dienes (*E*)-**11** (18% yield) and **12** (1.4% yield), and the remainder of the material was a mixture of unidentified products (eqn (4)). None of the desired product **2aa** was detected. In contrast, the stereoisomeric substrate (*Z*)-**1s** gave **2aa** in 60% yield and 99% ee, along with diene (*Z*)-**11** in 25% yield (eqn (5)). The observation that the *Z*-isomer of the substrate is more effective in providing the product **2aa** is similar to the results shown in eqn (1) and (2). For a mechanistic rationale of the production of different stereoisomers of dienes (*E*)-**11** and (*Z*)-**11** from (*E*)-**1s** and (*Z*)-**1s**, respectively, see the ESI.†



(4)

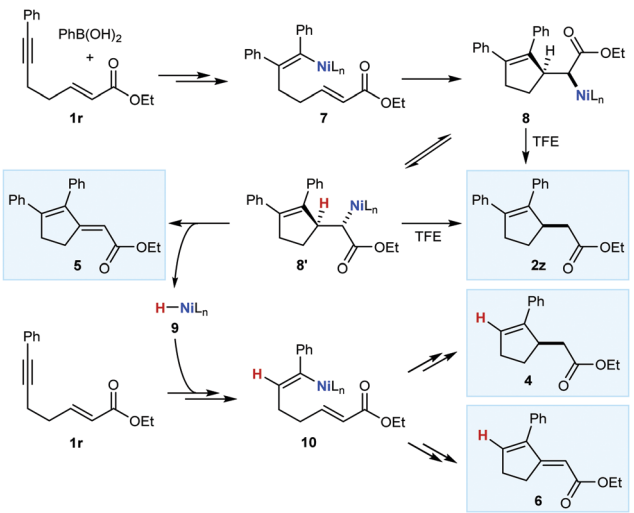


(5)

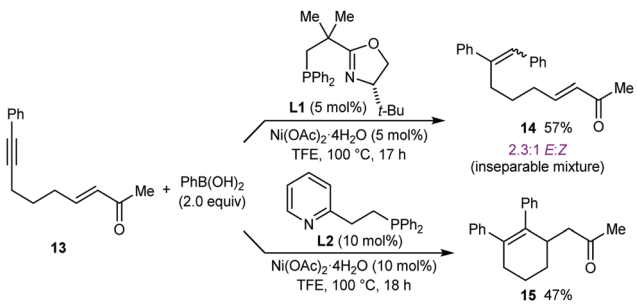
Next, the formation of six-membered rings was attempted. However, reaction of **13** (a higher homologue of substrate **1h** that successfully gave product **2h** (see Table 1)) with $PhB(OH)_2$ (2.0 equiv.) in the presence of 10 mol% each of $Ni(OAc)_2{\cdot}4H_2O$ and (*S*)-*t*-Bu-NeoPHOX (**L1**) failed to provide the desired six-membered arylative cyclization product. Instead, a 2.3 : 1 mixture of inseparable stereoisomeric alkyne hydroarylation products (*E*)-**14** and (*Z*)-**14**, respectively, was obtained in 57% yield (Scheme 3). Replacing (*S*)-*t*-Bu-NeoPHOX (**L1**) with other chiral phosphine–oxazoline ligands did not lead to any improvement.[8] However, use of the achiral ligand pyphos (**L2**) gave racemic **15** in 47% yield (Scheme 3).[15]

The reaction of $PhB(OH)_2$ with substrate **16a**, which contains a *para*-toluenesulfonamide group, gave only a complex mixture of unidentified products (Scheme 4). As with **13**, improved results were not obtained with other chiral phosphine–oxazoline ligands[8] but use of pyphos (**L2**) gave the racemic arylative cyclization product **17** in 52% yield.

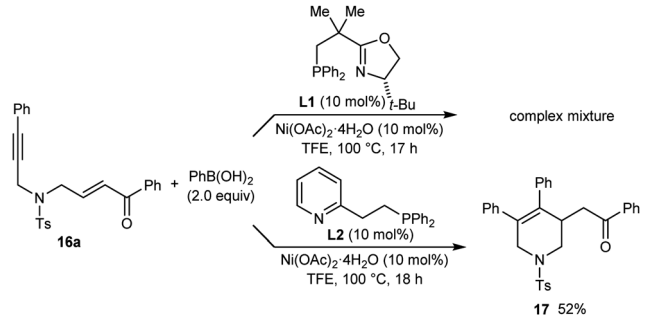
Given the results shown in Schemes 3 and 4, it was not surprising that substrate **16b** (see eqn (6)), which contains an α,β-unsaturated ester rather than an α,β-unsaturated ketone, did not provide the desired arylative cyclization product when it was reacted with $PhB(OH)_2$ using **L1** as the chiral ligand. However, unlike for substrates **13** and **16a**, it was interesting to observe that (*S*)-*t*-Bu-PHOX (**L3**) was an effective chiral ligand in the arylative cyclization of **16b**, which reacted smoothly with $PhB(OH)_2$ (2.0 equiv.) in the presence of 10 mol% each of $Ni(OAc)_2{\cdot}4H_2O$ and **L3** to give tetrahydropyridine



Scheme 2 Mechanistic rationale of the formation of **2z** and **4**–**6**.

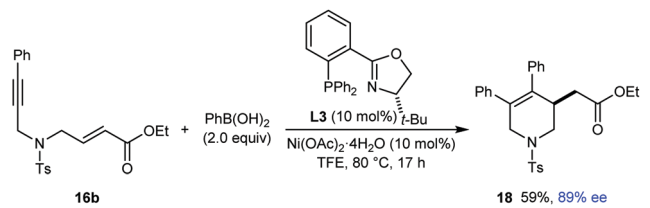


Scheme 3



Scheme 4

18 in 59% yield and 89% ee (eqn (6)).



(6)

In summary, we have reported enantioselective nickel-catalyzed *anti*-carbometallative cyclizations of (hetero)arylboronic acids and alkenylboronic acids with acyclic substrates containing an alkyne tethered to an enone, nitroalkene, α,β-unsaturated ester, or α,β-unsaturated nitrile. The products are various non-fused chiral carbo- and heterocycles, and the enantioselectivities are excellent in most cases (often ≥99% ee). These results represent a substantial increase in the scope over our previous work.[2] Interesting findings comparing the efficiencies of *E*/*Z* stereoisomers of certain substrates, and the isolation of products resulting from β-hydride eliminations and reductive cyclizations have also been described (eqn (1)–(5)).[16]

This work was supported by the Engineering and Physical Sciences Research Council and AstraZeneca [Industrial CASE Studentship, grant number EP/S513854/1]; the University of Nottingham; and GlaxoSmithKline.

Conflicts of interest

There are no conflicts to declare.

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14 A possible reason is that protodenickelation proceeds faster via the *O*-bound, rather than the *C*-bound nickel enolate, and ketone-derived enolates are more likely to exist as the *O*-bound form compared with ester-derived enolates. Similarly, protodenickelation of nickel nitronates is likely to be more rapid than ester-derived nickel enolates because of a higher ratio of *O*- *vs.* *C*-bound forms.

15 Product **15** contained an inseparable impurity and therefore the yield was calculated by ^{1}H NMR analysis using an internal standard.

16 The research data associated with this publication can be found at:http://dx.doi.org/10.17639/nott.7109.