Nickel-Catalysed Enantioselective Arylative Cyclisations

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Declaration

I hereby declare that, except where specific reference is made to other sources, the work contained within this thesis is the original work of my own research since the registration of the PhD degree in October 2014, and any collaboration is clearly indicated. This thesis has been composed by myself and has not been submitted, in whole or part, for any other degree, diploma or other qualification. The candidate confirms that the work submitted is his own, except where work which has formed part of jointly-authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

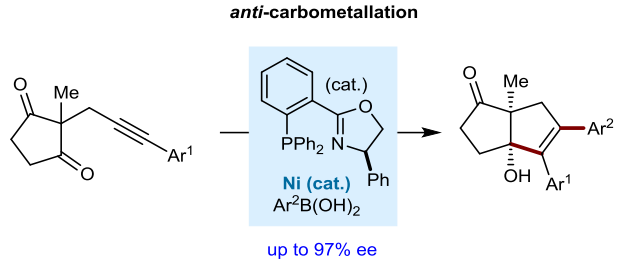
The following thesis contains results reported in the following publication:

Enantioselective Nickel-Catalyzed anti-Carbometallative Cyclizations of Alkynyl Electrophiles Enabled by Reversible Alkenylnickel E/Z Isomerization, C. Clarke, C. A. Incerti-Pradillos, H. W. Lam, *J. Am. Chem. Soc*. **2016**, 138, 8068–8071

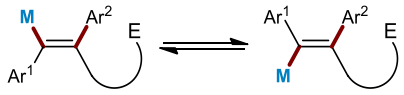
Abstract

Enantioselective Nickel-catalysed *anti*-Carbometallative Cyclisations of Alkynyl Electrophiles Enabled by Reversible Alkenylnickel *E/Z* Isomerisation

Highly enantioselective *anti*-carbometallations of alkynes bearing tethered ketones is described using a Ni(II) salt and a commercially available chiral phosphinooxazoline ligand.

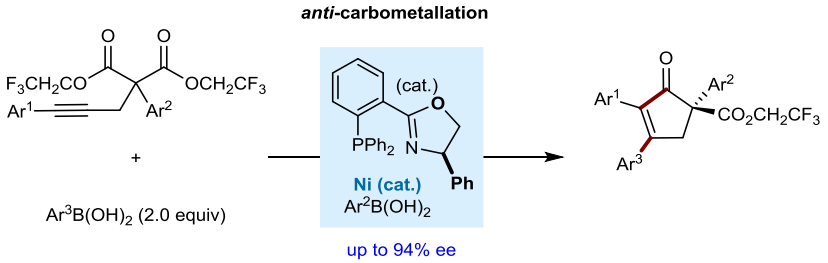


Due to the *syn*-selective nature of alkyne-migratory insertion, many examples of carbometallative processes giving the cyclised *syn*-products have been reported, however, *anti*-carbometallative processes are rare. The mechanism of this *anti*-carbometallation is thought to occur *via* an alkenylnickel *E/Z*-isomerisation of the organometallic species formed after initial alkyne migratory insertion.



Although a number of examples of such isomerisaions have been reported, the utilisation of the phenomina in ring-forming reactions to give *anti*-carbometallation products is much less well explored.

Further reaction development for the nickel-catalysed *anti*-carbometallative cyclisations of alkynyl electrophiles has allowed for the synthesis of enantioenriched cyclopentenones.



The use of the trifloroethanol leaving group is important for efficient reactivity and allows the previously unreactive ester electrophile to be used. However, inorder to obtain high enantioselectivities and aryl group at the quaternaty centre of the substrate is required.

Acknowledgments

Thank you to my supervisor Prof. Hon Wai Lam, for giving me the opportunity to work in his group and for his support and assistance throughout my PhD. Thanks to all members of the Lam group past and present, with special thanks to those who I have worked with on projects both successful and not.

Contents

Abbreviations

Ac	acetyl
acac	acetylacetonate
app	apparent
aq.	aqueous
Ar	aryl
atm	atmosphere
BINAP	(2,2'-*bis*(diphenylphosphino)-1,1'-binaphthyl)
Bn	benzyl
Boc	*t*-butyloxycarbonyl
br	broad
Bu	butyl
cat.	catalyst
cod	1,5-cyclooctadiene
Conv.	conversion
Cy	cyclohexane
d	doublet
DBA	dibenzylideneacetone
DME	dimethoxyethane
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
EDG	electron-donating group
ee	enantiomeric excess(es)
equiv.	equivalent
Et	ethyl
EWG	electron-withdrawing group
Hex	hexyl
HPLC	high performance liquid chromatography
HRMS	high-resolution mass spectrometry
i	*iso*
IR	infrared
IPA	*iso*-propanol
LG	leaving group

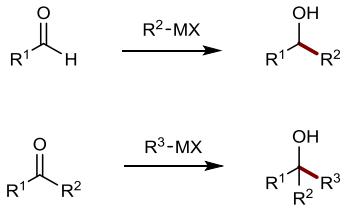
m	multiplet
Me	methyl
mg	milligram
MHz	megahertz
min	minute(s)
mL	millilitre
mmol	millimol
m.p.	melting point
MS	molecular sieves
m/z	mass to charge ratio
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
Np	naphthyl
N.R.	no reaction
Nu	nucleophile
PMP	*para*-Methoxyphenyl
Rt	room temperature
t	triplet
TBAT	tetrabutylammonium difluorotriphenylsilicate
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
t	tert(iary)
Ts	4-toluenesulfonyl

Throughout this work, “wedges” have been used to indicate stereochemistry at quaternary centres and “blocks” have been used to indicate stereochemistry at tertiary centres. Compounds are given a number prefaced with the letter I as it appears in the introduction, with numbering starting again in the results and discussion for clarity. Compounds that were synthesised but do not appear in the main text are prefaced with the letter S when they appear in the experimental section. Compounds used as ligands on metal centres are prefaced with the letter L.

1.0 Chapter 1: Introduction

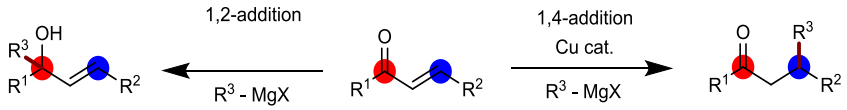
1.1 Transition-metal-catalysed-1,2- and 1,4-additions of organometallics

The nucleophilic additions of organometallics such as Grignard reagents and organolithium species to carbonyls have been well-studied. Additions of these organometallic species to aldehydes or ketones gives the secondary or tertiary alcohol, a transformation that is widely used in synthesis (scheme 1).



Scheme 1: Addition of organometallics to carbonyl groups.

α,β-Unsaturated carbonyl compounds have also been well-studied as electrophiles. Interestingly, these electrophiles can either undergo 1,2-additions, if the nucleophile adds into the carbonyl (highlighted in red) or 1,4-additions if the β-carbon is attacked (highlighted in blue) (scheme 2). When organometallics such as Grignard reagents react with α,β-unsaturated carbonyls, the ionic nature of the carbon-magnesium bond means that the reaction is electrostatically driven and 1,2-addition products are formed. However, the presence of a catalytic copper salt forms organometallics with more a covalent nature and therefore 1,4-additions are preferred as the LUMO of the α,β-unsaturated carbonyl has the largest coefficient at the β-carbon (scheme 2).



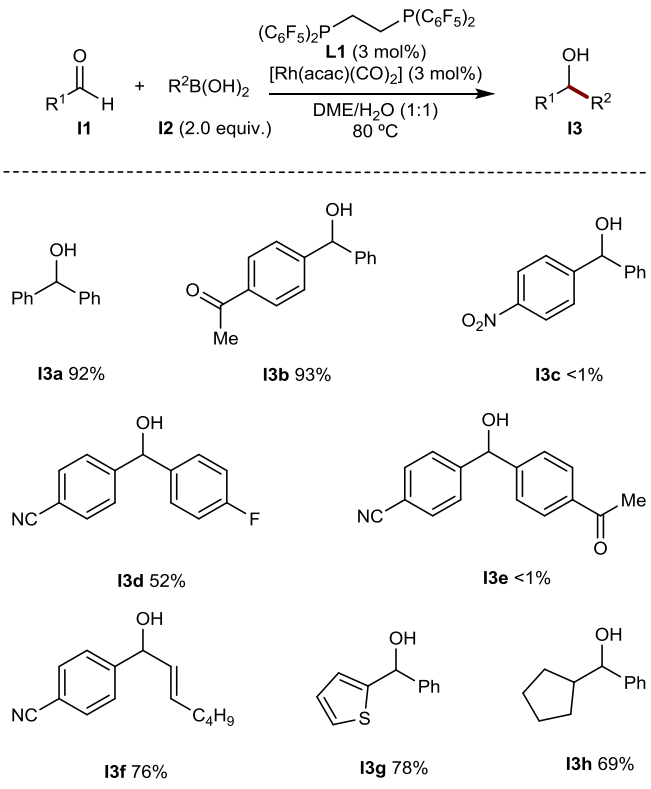
Scheme 2: Nucleophilic additions of organometallics to α,β-unsaturated ketones.

Both of these transformations are invaluable; however, the use of these basic and highly reactive nucleophiles means that the functional group tolerance in such transformations is low. As a result the use of a transition metal catalyst to add milder and air/moisture stable nucleophiles, such as boronic acids has attracted much attention.

The field of transition-metal-catalysed additions of organometallics is vast, with the state of the art ever advancing. The following section therefore describes only representative examples, concentrating on the pioneering publications that have inspired many iterations and variations. However, it is this wide variety of additions that makes this field so powerful to the synthetic chemist.

1.1.1 Rhodium-catalysed additions of organometallics to carbonyls

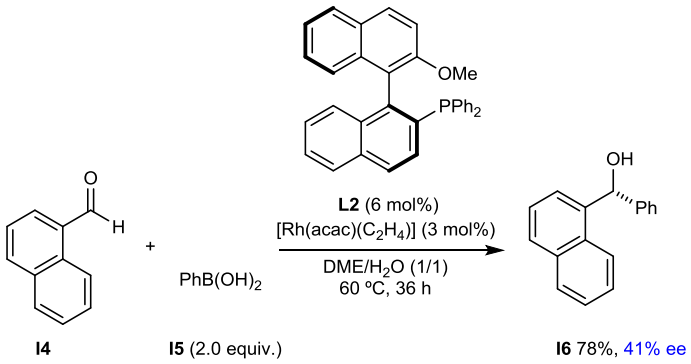
The first examples of rhodium-catalysed-1,2-additions of organoboron species were reported by Miyaura and co-workers.[1] They carried out the 1,2-addition of arylboronic acids to aldehydes forming secondary alcohols. They postulated that a large P-Rh-P angle present in the catalyst was important in the carbonyl insertion and therefore only bisphosphine ligands were efficient. They also found that the addition of water as a co-solvent was important for the reactivity. Rh catalysed additions of a range of aryl- and alkenylboronic acids to both aromatic and aliphatic aldehydes were reported (scheme 3).



Scheme 3: Rhodium-catalysed arylation of aldehydes.

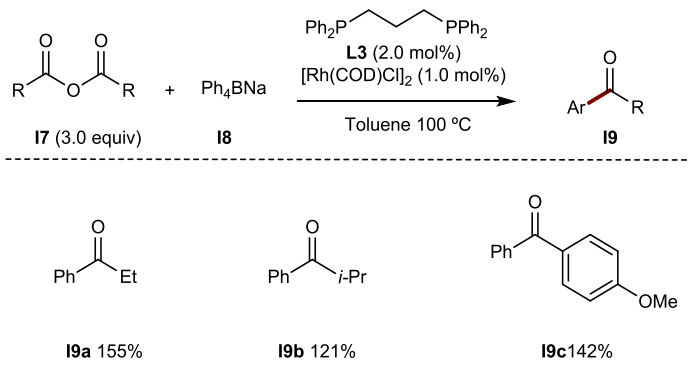
Nitrogroups on the aldehyde were detrimental to the efficiency of the reaction and 4-nitrophenylboronic acid was ineffective **I3c**. The catalytic system was also able to selectively add into the aldehyde in preference of a ketone **I3b**. Alkenyl boronic acids were also effective giving allylic alcohol **I3f**. Heteroaryl and aliphatic aldehydes were also well tolerated **13g** and **I3h**.

Employing chiral monodentate ligand (*S*)-2-(diphenylphosphanyl)-2'-methoxy-1,1'binaphthyl (**L2**) enantioenriched product **I6** was formed in good yield. However, only a moderate enantioselectivity was observed (scheme 4).



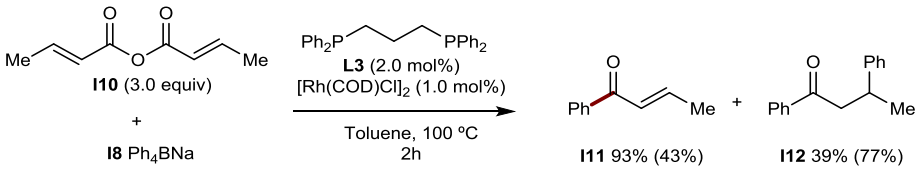
Scheme 4: Entioselective rhodium-catalysed arylation of 2-napthaldehyde.

Miura and co-workers reported the rhodium catalysed addition of organoboron reagents to the carbonyl group of acid anhydrides (scheme 5).[2]



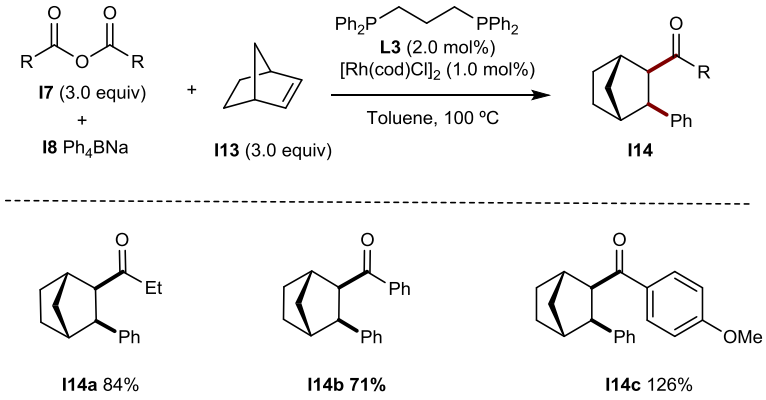
Scheme 5: Rhodium-catalysed arylation of acid anhydrides. Yield =(mmol **I9**/ mmol **I8**) × 100.

Rhodium is able to catalyse the addition of sodium to a number of different aliphatic and aromatic acid anhydrides with good yields. However, when alkenylacid anhydride **I10** was used, the rhodium-phenyl species performed a conjugate addition with the product **I11** to give side product **I12** (scheme 6)



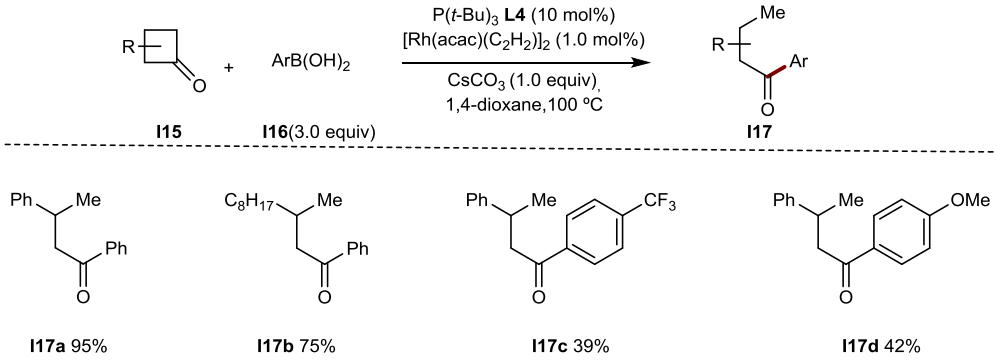
Scheme 6: Rhodium catalysed phenylation of alkenylacid anhydride. Yield in parenthesis is that after a prolonged reaction time of 24h.

Miura and co-workers also reported a rhodium catalysed three-component coupling of sodium tetraphenylborate, norbornene and an acid anhydride (scheme 7).



Scheme 7: Rhodium-catalysed three-component coupling.

In 2004, Murakami and co-workers demonstrated the rhodium catalysed, direct arylation of strained ketones.[3] The additions to cyclobutanones were followed by a ring-opening reaction to give arylketones **I17** (scheme 8).



Scheme 8: Rhodium-catalysed addition/ring opening of arylboronic acids with cyclobutanones.

The use of D_2O as a co-solvent showed deuterium incorporation at the α-position and assisted in the elucidation of the proposed mechanism figure 1.

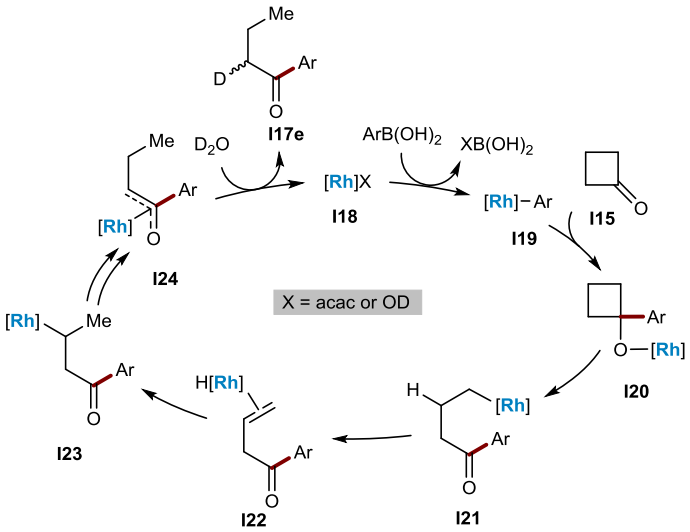
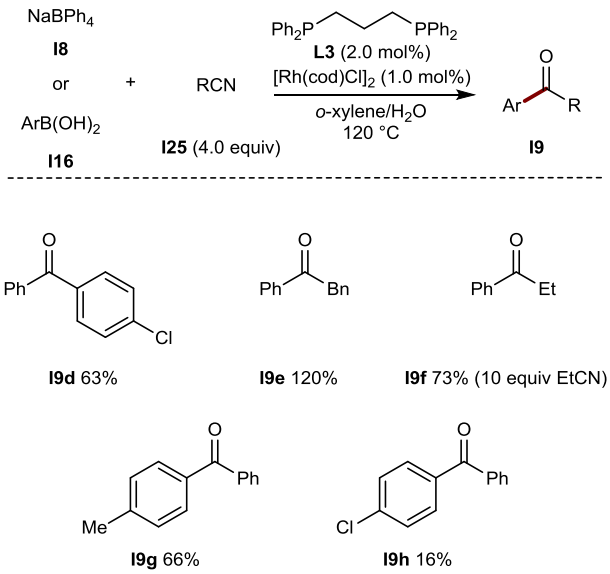


Figure 1: Proposed catalytic cycle

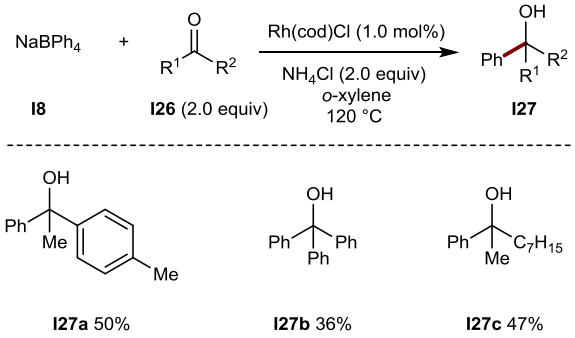
Arylrhodium species **I19** is formed by transmetallation with the arylboronic acid. This then undergoes a 1,2-addition of the carbonyl to give rhodium-alkoxide **I20**. This species then fragments to give rhodium-alkyl **I21**. This intermediate then undergoes β-hydride elimination and reinsertion to give **I22** and **I23** respectively. A series of β-hydride eliminations and reinsertions leads to rhodium enolate **I24** that undergoes protonolysis to give product **I17e**.

In 2005, Miura and co-workers reported the utility of a rhodium catalyst in the addition of arylboron reagents to nitriles (scheme 9).[4]



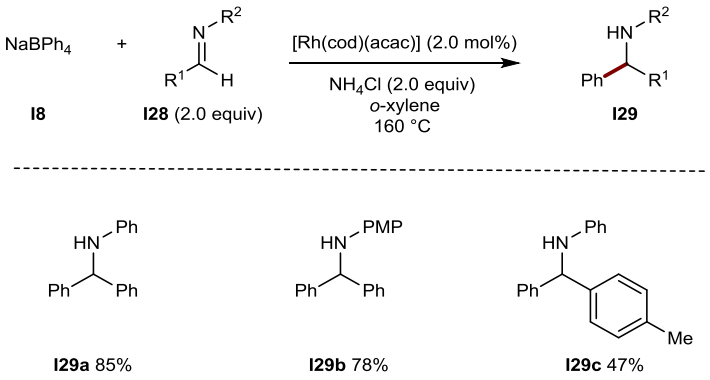
Scheme 9: Rhodium-catalysed addition of arylboron reagents to nitriles. Yield = (mmol **I9** / mmol **I8** or **I16**)×100

The following year they extended this methodology to include imines and ketones.[5] The arylation of ketones was previously thought to be very challenging, however Miura and co-workers were able to use this same catalytic system to give phenylation of acetophenone in moderate yield (47%) and after optimisation they were able to access a range of tertiary alcohols in moderate yields (scheme 10).



Scheme 10: Rhodium-catalysed arylation of ketones.

Both aromatic and aliphatic ketones were successful substrates under the reaction conditions. They also reported the rhodium catalysed arylation of imines (scheme 11).

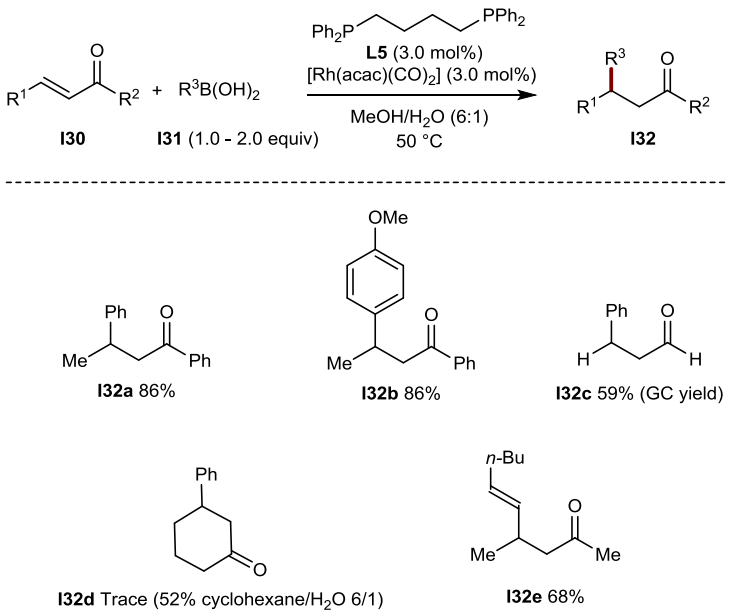


Scheme 11: Rhodium-catalysed additions of sodium tetraphenyl borane to imines.

These pioneering publications have demonstrated the efficiency of rhodium as a catalyst for the nucleophilic additions of organoboron reagents to a number of different electrophilic coupling partners and have pathed the way for the cutting edge in modern catalysis. There are also many examples of these basic principles being deployed with chiral rhodium complexes to give rise to enantioenriched products.[6]

1.1.2 Rhodium-catalysed-1,4-additions of boronic acids

Rhodium as a catalyst for the conjugate addition of organoboron reagents to α,β-unsaturated systems has also been extensively studied. The pioneering publication in this area is work by Miyaura and co-workers reported in 1997. Here they use a rhodium(I) catalyst with dppb **L5** as a bidentate ligand in DMF, cyclohexane or methanol with water as a co-solvent (Scheme 12).[7]



Scheme 12: Rhodium-catalysed-1,4-additions of boronic acids.

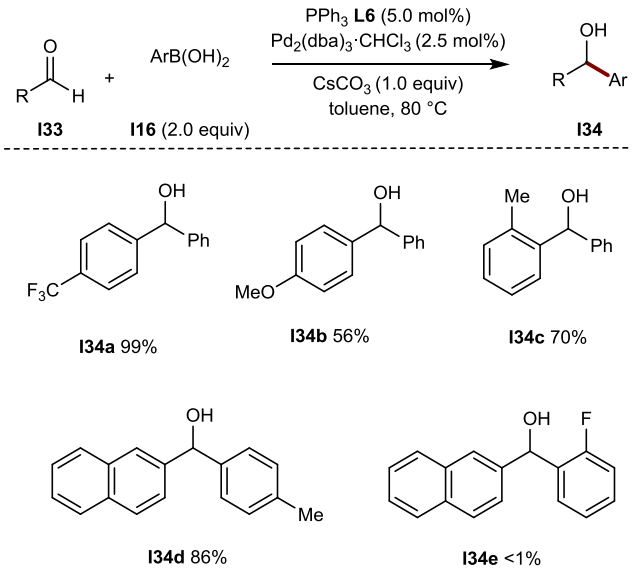
The electronics of the boronic acid did not affect the efficiency of the reaction. For cyclohexanone substrate only trace product was formed in the methanol/water mixture but moderate yields were achieved in cyclohexane/water **I32d**. This process was not limited to aryl boronic acids, alkenyl boronic acids were also successfully deployed **I32e**.

As with 1,2 additions, rhodium has been extensively studied for enantioselective conjugate additions to a wide variety of electron deficient alkenes, all of which is underpinned by this pioneering work.[6]

1.1.3 Palladium-catalysed additions of organoboron reagents

Palladium catalysts have also successfully been used in the nucleophilic additions of organoboron reagents to carbonyls. In 2005, Ohta and co-workers reported the first

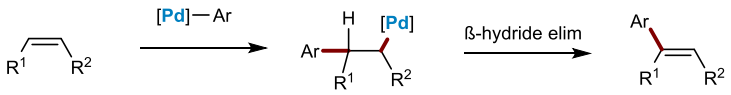
example of such reactivity in the palladium catalysed addition of arylboronic acids to aldehydes (scheme 13).[8]



Scheme 13: Palladium-catalysed additions of arylboronic acids to aldehydes.

Whilst optimising this chemistry, it was determined that a catalytic amount of $CHCl_3$ was essential to the reaction, the $CHCl_3$ adduct of the palladium catalyst could be replaced by the addition of a catalytic amount of $CHCl_3$ and then other palladium precatalysts could be used efficiently. The reaction was tolerant of a number of different arylboronic acids and arylaldehydes, however having an electron withdrawing fluorine group at the 2-position of the boronic acid proved detrimental.

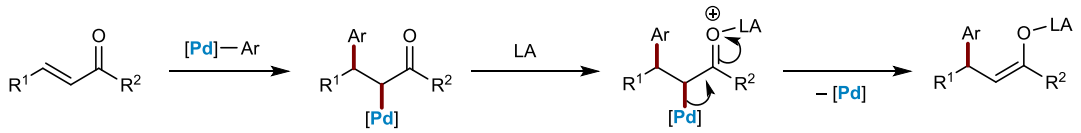
Palladium has been used extensively in cross coupling chemistry, the success of which resulted in the 2005 Nobel Prize in chemistry for Suzuki, Negishi and Heck. One of the reactions that contributed to the award of the Nobel Prize was the so called 'Mizoroki–Heck' reaction, where an aryl halide is coupled with an alkene. A key step of which is a β-hydride elimination to give the corresponding substituted alkenyl products (scheme 14).



Scheme 14: Key β-hydride elimination step in the 'Mizoroki–Heck' reaction.

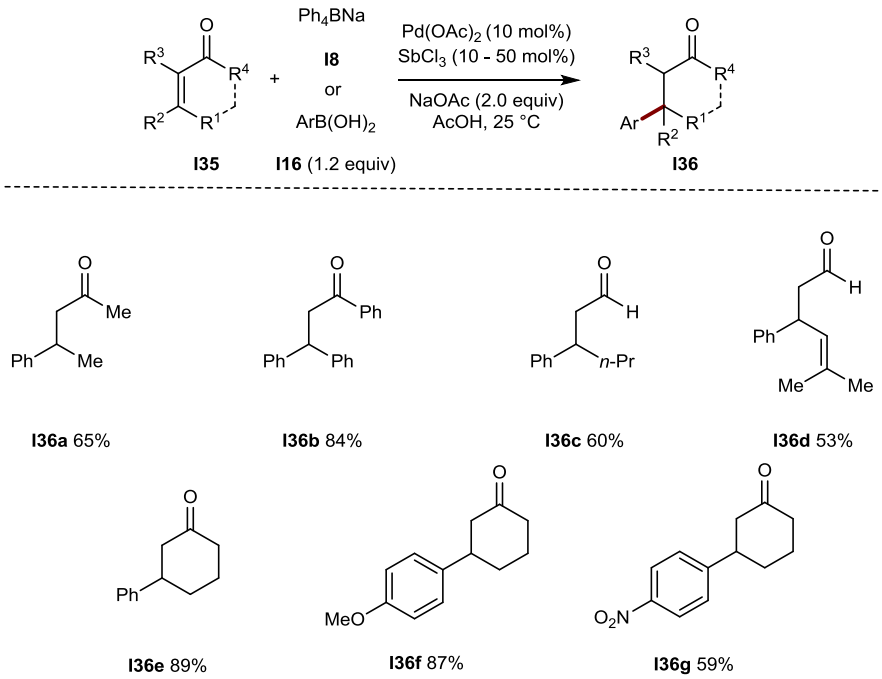
Because of the facile nature of β-hydride elimination palladium-catalysed-1,4-additions are challenging. One of the first examples of palladium-catalysed-1,4-

additions of arylboron reagents reported by Uemura and co-workers utilised a Lewis acid co-catalyst.[9] They propose that the Lewis acid is able to intercept the palladium enolate before β-hydride elimination. Leading to a metal enolate that can be subsequently protonated to generate the 1,4-addition products (scheme 15).



Scheme 15: Proposed mechanism for the palladium-catalysed-1,4-addition products formed in the presence of a Lewis acid co-catalyst. LA = lewis acid.

Various Lewis acids were successful, but antimony chloride proved the most generally effective additive (scheme 16).



Scheme 16: Palladium/antimony-catalysed-1,4-additions of organoboron reagents.

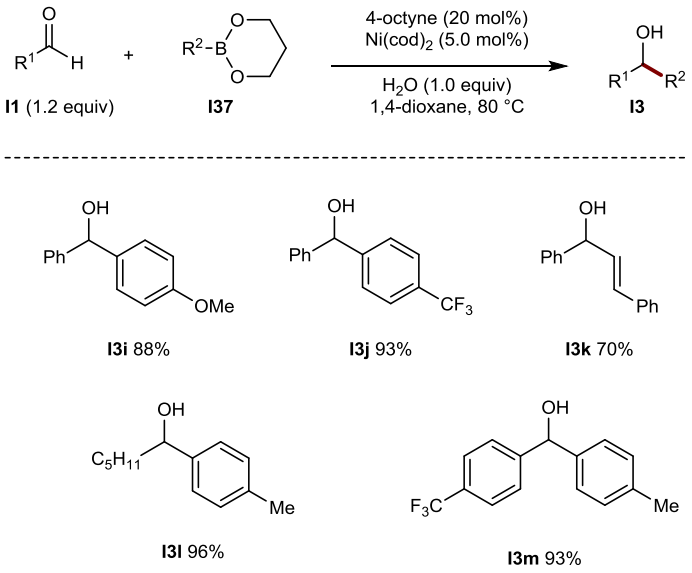
Enones and enals are both tolerated in the reaction, the substrates can bear other alkene moieties as in **I36d** which is unaffected and the reactivity is tolerant of varying electronics of the boronic acids.

These 1,2- and 1,4-additions of organoboron reagents catalysed by palladium have also been extensively studied for many different electrophilic components, and by

utilising chiral auxiliaries or chiral ligands on palladium they have also been rendered stereoselective.[10]

1.1.4 Nickel-catalysed nucleophilic additions of organoboron reagents

The first row transition metals have also been utilised in the addition of organoboron reagents to electrophiles. An early example using nickel to catalyse the addition of boronic esters to aldehydes was reported by Shirakawa and co-workers in 2005. A catalytic amount of an alkyne was used with a Ni(0) catalyst (scheme 17). [11]

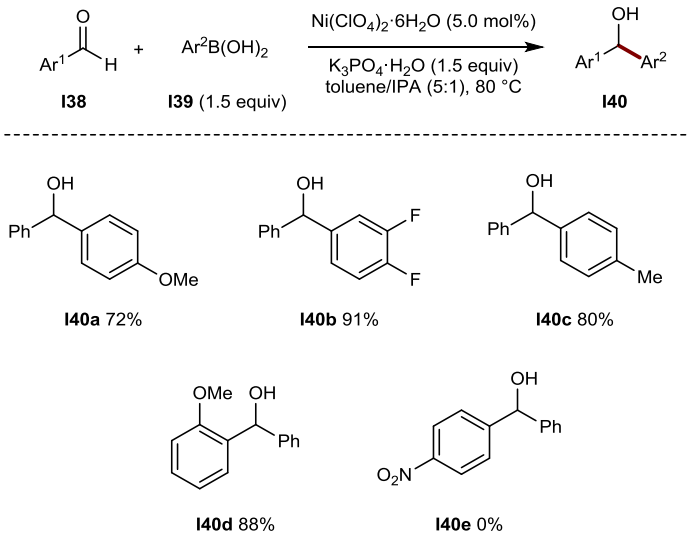


Scheme 17: Nickel-catalysed additions of arylboron reagents to aldehydes.

This chemistry is not limited to arylboronic acids, as an alkenyl boronic acid is tolerated in **I3k** and also the aldehyde can be aliphatic or aromatic. Interestingly in this reaction no side products of addition of the organoboron across the alkyne were observed. In 2007, a variation of this reaction was reported by Aoyama and co-workers that utilised a phosphine ligand as opposed to an alkyne, this gave way to the potential for this chemistry to be performed asymmetrically.[12]

These previous reports relied on a Ni(0) precatalyst that is expensive and hard to handle, in 2008 Bao and co-workers reported the first nickel salt catalysed aldehyde arylation.[13] Importantly this reaction was also the first example of such nickel catalysed reactions being carried out using boronic acids and not esters, with many

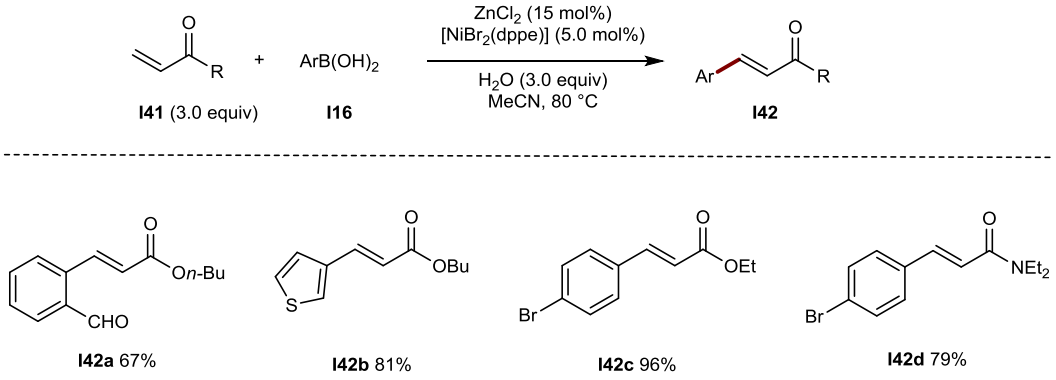
more boronic acids being commercially available this is also an important improvement to this methodology (scheme 18).



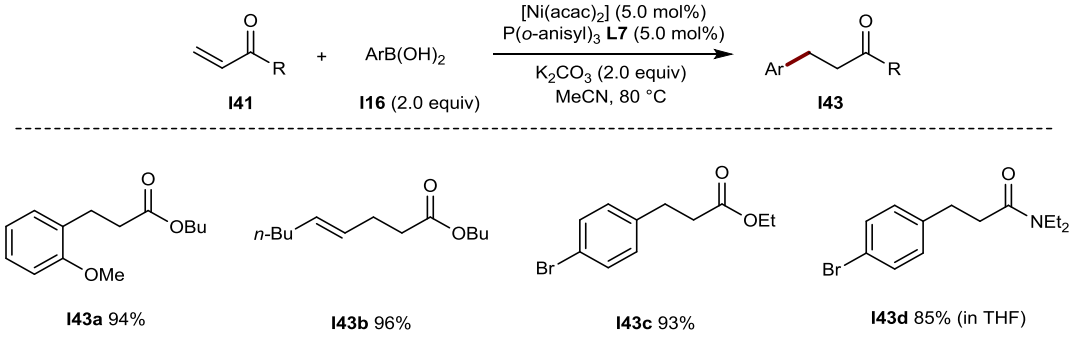
Scheme 18: Nickel-catalysed additions of arylboronic acids to aromatic aldehydes.

The boronic acid can be varied with little effect on the reaction efficiency. However, none of the desired product was formed when 4-nitrobenzaldehyde was used (**I40e**).

Similarly to rhodium and palladium, the intermediate arylnickel species formed after transmetallation with an organoboron reagent can perform 1,4-additions to electron deficient alkenes. As with palladium the resulting nickel enolate has the potential to either perform a β-hydride elimination to give the 'Mizoroki–Heck' products, alternatively protonolysis can occur to give the 1,4-addition products. In 2007, Cheng and co-workers presented the use of a simple nickel(II) catalytic system that selectively gave either the 'Mizoroki–Heck' or '1,4-addition' products by adjusting the environment about the nickel centre (schemes 19 and 20).[14]



Scheme 19: Nickel catalysed 'Mizoroki-Heck type' coupling of enones and arylboronic acids.



Scheme 20: Nickel-catalysed-1,4-additions of arylboronic acids to enones.

Interestingly the proposed mechanisms involve a common intermediate **I44**, that can either β-hydride eliminate to give products of type **I43e** or isomerise to an O-bound nickel-enolate that can readily be protonated to give products **I42e** (figure 2).

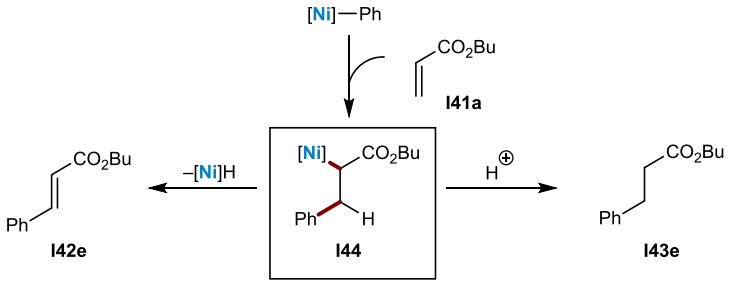
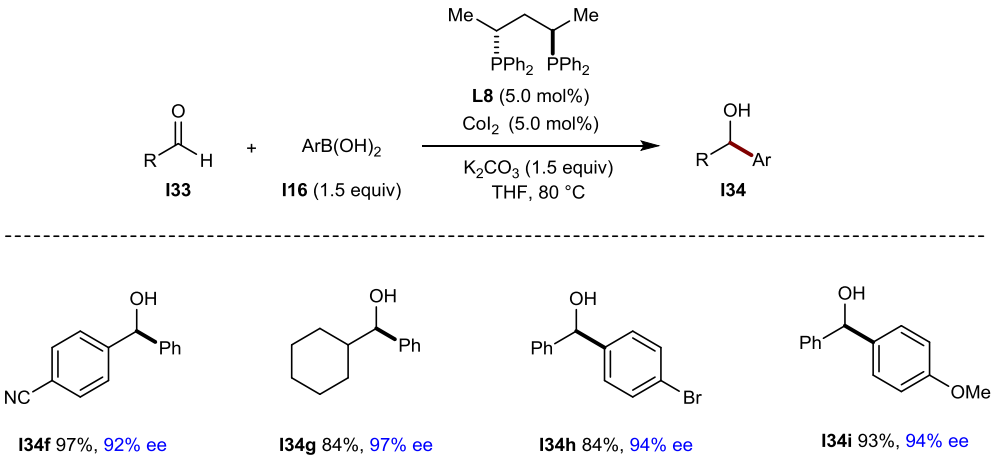


Figure 2: Point of divergence in the Mizoroki–Heck vs 1,4-addition in the nickel catalysed enone arylation.

The difference in reactivity is suggested to be due to the steric bulk about the Ni centre, with bulky monophosphine ligands being more crowded that the Ni(dppe)Br_2 complex that has readily accessible vacant sites for β-hydride elimination.

1.1.5 Cobalt-catalysed nucleophilic additions of organoboron reagents

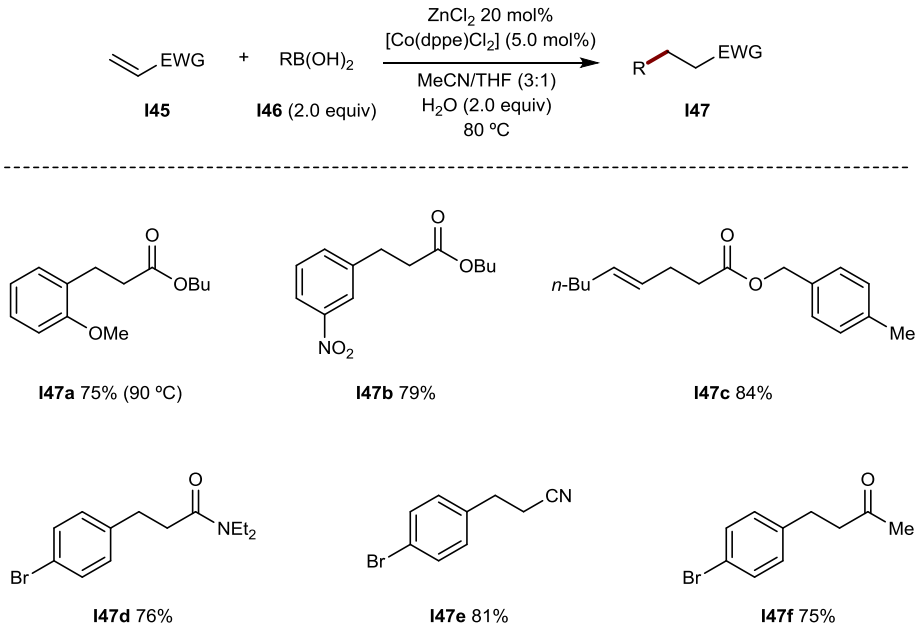
Cheng and co-workers have also carried out pioneering work using cobalt as a cheap abundant catalyst for these addition reactions of organoboron regents to π-electrophiles. In 2010, they reported the use of a cobalt(II) salt as a catalyst for the addition of boronic acids to aldehydes, and in the same publication demonstrated the use of a commercially available chiral bisphosphine ligand to render the process enantioselective (scheme 21).[15]



Scheme 21: Cobalt-catalysed enantioselective aldehyde arylation.

The reaction is very tolerant of varying electronics on the boronic acid, and the aldehyde can be either aromatic or aliphatic.

In 2012, Cheng and co-workers also reported the use of a related cobalt catalyst system in the 1,4-addition of organoboron reagents to electron deficient alkenes (scheme 22). [16]

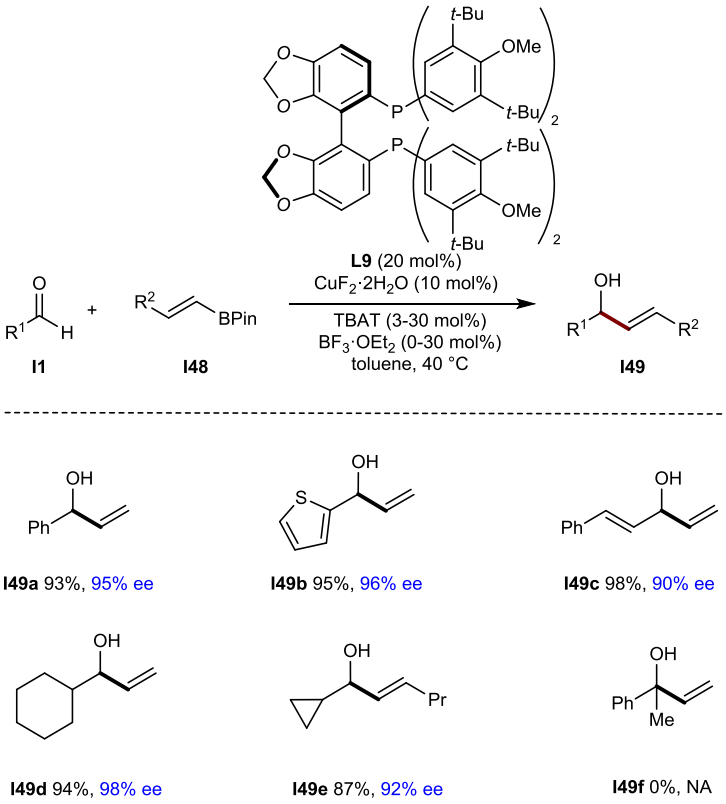


Scheme 22: Cobalt-catalysed conjugate addition of boronic acids.

The reaction was very efficient for a range of aryl- and alkenylboronic acids with the more sterically encumbered 2-methoxyphenyl boronic acid requiring a slight elevation of temperature **I47a**. The system was also compatible with alkenes with a number of different electron-withdrawing groups (**147d**, **147e** and **147f**).

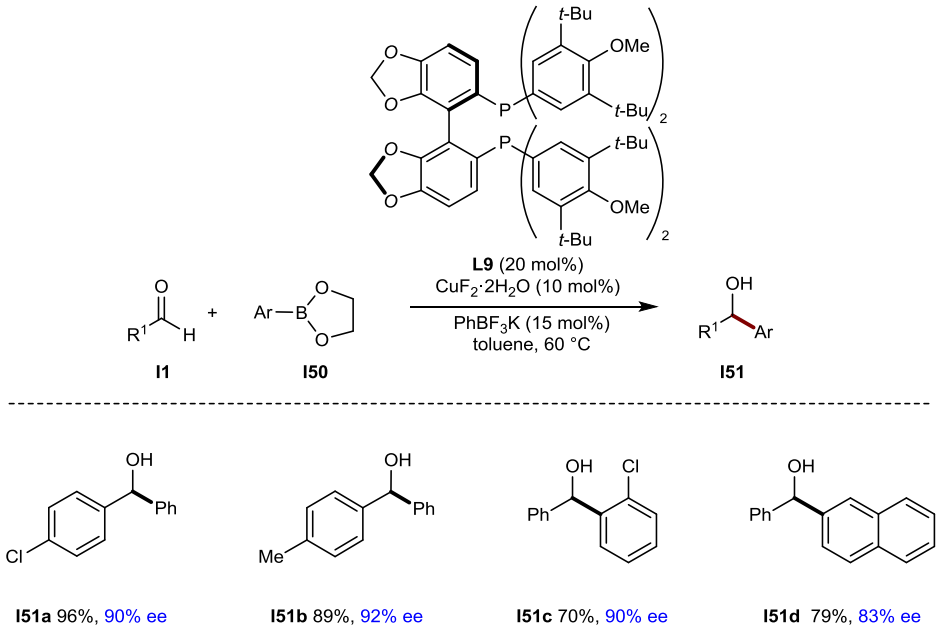
1.1.6 Copper-catalysed nucleophilic additions of organoboron reagents

Copper has also been utilised in the 1,2-additions of organoboron reagents. In 2006, Shibasaki and co-workers reported the copper-catalysed enantioselective alkenylation and arylation of aldehydes using boronic esters. The primary investigation of the publication was into the alkenylation of aldehydes. A commercial copper(II) salt was used with commercially available chiral bisphosphine (*R*)-DTBM-segphos (**L9**) using alkenyl boronic esters (scheme 23). [17]



Scheme 23: Copper-catalysed alkenylation of aldehydes.

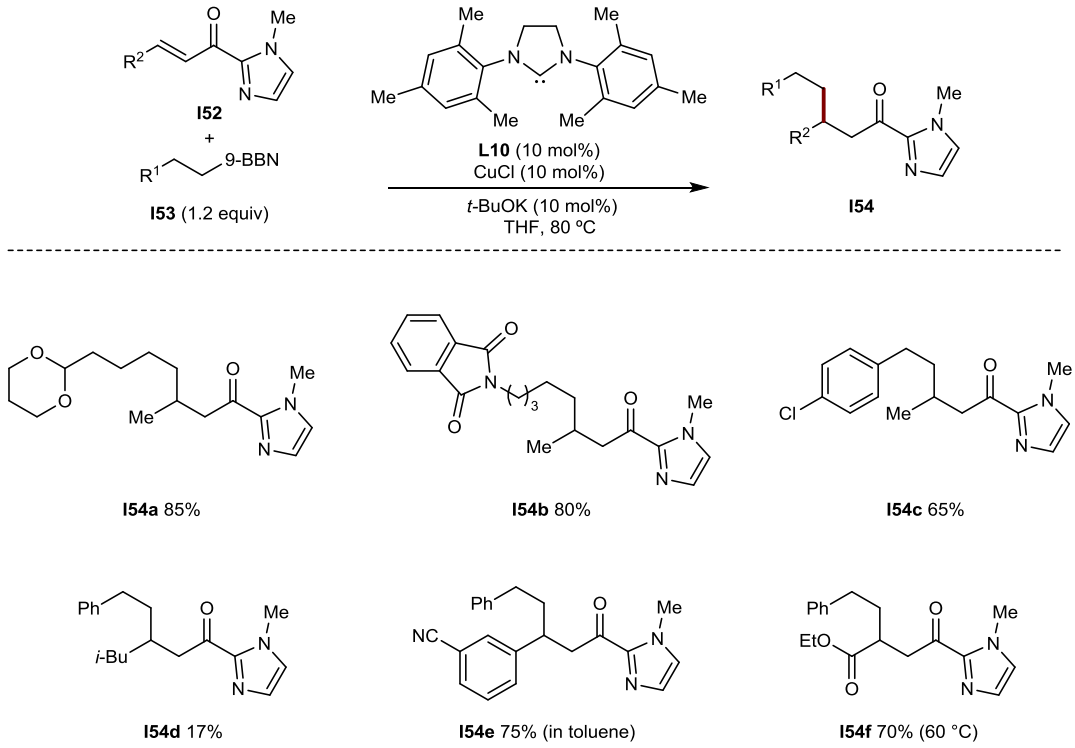
The scope of this reaction with respect to the aldehyde was broad with both aromatic and aliphatic aldehydes giving chiral allylic alcohol products in excellent yields and enantioselectivities. Ketones were not suitable substrates, and none of the tertiary allylic alcohol **I49f** was formed. This methodology was also extended to arylboronic esters (scheme 24).



Scheme 24: Copper-catalysed arylation of aldehydes

Examples of enantioselective aldehyde arylation were limited to aromatic aldehydes; however, varying electronics and sterics on both the aldehyde and boronic ester were well tolerated.

Copper-catalysed-1,4-additions of organoboron reagents were not reported until 2010, by Sawamura and co-workers.[18] Although as early as 1976, Suzuki and co-workers reported organoboron 1,4-additions utilising a stoichiometric amount of copper. Sawamura and co-workers utilised a Cu(I) catalyst with a NHC ligand **L10** in the conjugate addition of alkyl-9-BBN reagents (formed *in situ)* to α,β-unsaturated ketones (scheme 25).



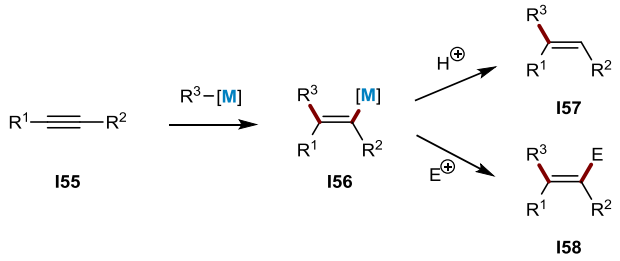
Scheme 25: Copper-catalysed-1,4-additions of organoboron reagents.

The reaction is tolerant to a number of alkylboron reagents and substituents at the β-position of the enone. The yield is reduced by the *i*-Bu group in **I54d**, and when the enone contains an aryl group, toluene is required as a solvent **54e**. Interestingly the regioselectivity of the 1,4-addition is not effected when the β-position bears an ester group, and **I54f** is the only observed product.

Whilst the additions of these organometallic reagents to π-electrophiles was emerging as an exciting and valuable field, naturally the nature of the coupling partner was also explored. Therefore the additions of organometallics to other π-unsaturated systems were also of interest.

1.2 Transition-metal-catalysed carbometallations of alkynes

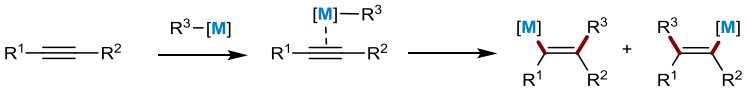
The additions of organometallics to alkynes results in the formation of highly substituted alkenes.[19] Commonly, the organometallic will react with the alkyne in a *syn*-selective migratory insertion reaction; where the two new bonds are formed on the same side of the resulting alkene (scheme 26).



Scheme 26: Additions of organometallics across alkynes.

The alkenylmetal intermediate formed after migratory insertion **I56** can undergo protonolysis leading to sterically defined tri-substituted alkenes **I57**. In addition to this **I56** has the potential to react further with an electrophile to increase the complexity of the transformation leading to tetra-substituted alkenes **I58**. This is an exciting contrast to the 1,2-additions previously discussed where generally the catalyst turnover step was the protonolysis of a metal-alkoxide. As in 1,4-additions, the metal enolate is also turned over by protonation, but this species has also been shown to react further with other electrophiles.[20,21,22,23]

Controlling the regioselectivity of this initial migratory insertion is important, otherwise additions across unsymmetrical alkynes lead to undesirable mixtures of products (scheme 27).

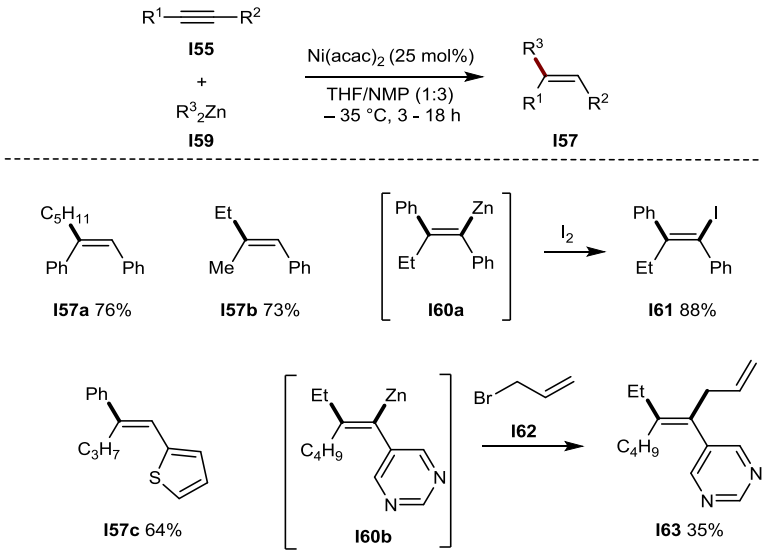


Scheme 27: mixtures of products formed when regioselectivity is not controlled.

Traditional methods of carrying out these transformations employ a stoichiometric organometallic reagent (Mg, Li or Al).[19] The basic and nucleophilic nature of these reagents means that functional group tolerance of these transformations is limited. This area of chemistry has been vastly explored and therefore the preliminary examples of this class of transformations will be represented, concentrating as much as possible on demonstrating the breadth of this field.

1.2.1 Nickel-catalysed additions of organozinc and –magnesium reagents to alkynes

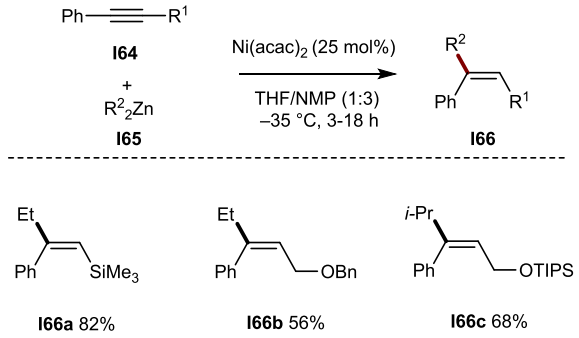
To control the regio- and stereoselectivities of carbometallation reactions of alkynes, Knochel and co-workers used a nickel catalyst to effect the addition of dialkyl- and diarylzinc reagents across various alkynes (scheme 28). [24]



Scheme 28: Nickel-catalysed additions of alkyl-zinc reagents.

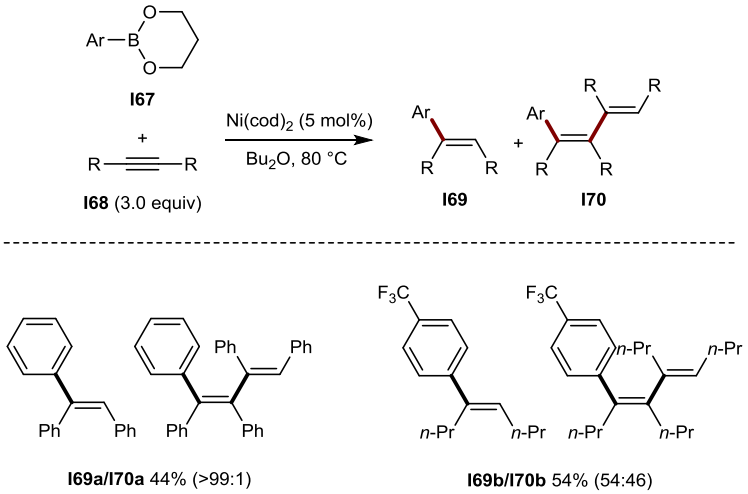
A range of aliphatic and aromatic organozinc reagents were successfully added across a wide range of alkynes. When 1-phenylprop-1-yne was used the regiocontrol was excellent with the metal adding α to the phenyl ring. The alkenylmetal intermediates of this process are also trapped with iodine leading to alkenyliodides **I61**. Heterocyclic alkenes were also synthesised from a range of heterocyclic acetylenes, the alkenylzinc intermediates of which can be intercepted with a range of electrophiles such as allylbromide to give tetrasubstituted alkene **I63**.

The regioselectivity was reversed when silylated phenyl acetylenes were used, with the metal being situated α to the silicon after migratory insertion. They were also able to effect this transformation on a range of propargylic ethers which also had a directing effect on the regioselectivity of the process (scheme 29).



Scheme 29: Nickel-catalysed additions of alkylzinc reagents to unsymmetrical alkynes.

Arylboronic acids were utilised with a nickel catalyst by Shirakawa and co-workers in the hydroarylations of alkynes (scheme 30).[25]



Scheme 30: Nickel-catalysed additions of arylboron reagents to alkynes.

Mixtures of products are observed, **I69** from the hydroarylation of the alkyne, and **I70** from the alkenylnickel intermediate of migratory insertion reacting with another alkyne moiety. They propose a Ni(0)/(II) redox cycle (figure 3).

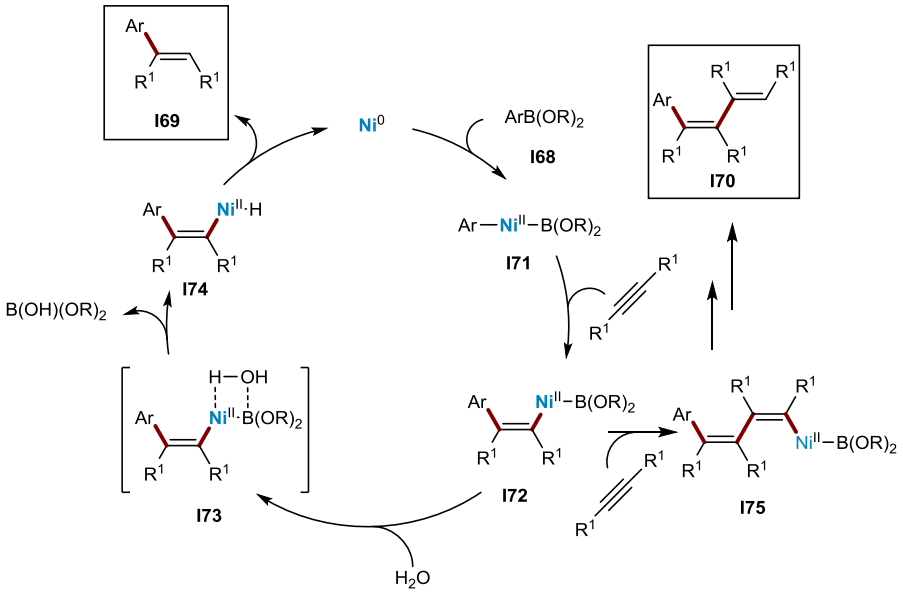
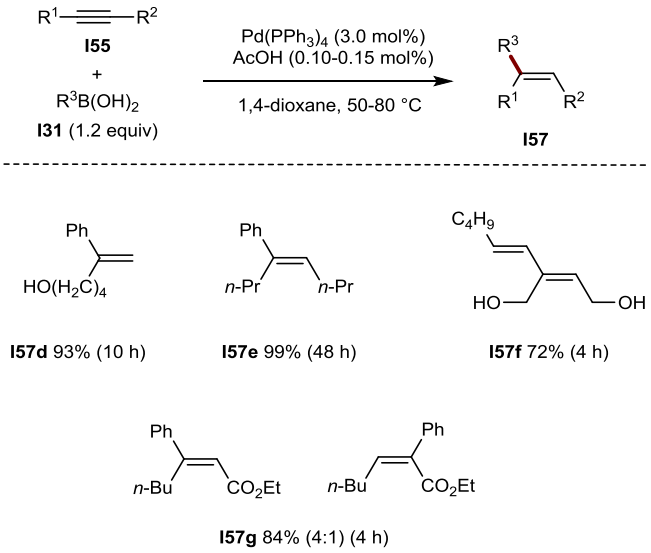


Figure 3: Proposed catalytic cycle for nickel-catalysed additions of arylboron reagents across alkynes.

Nickel(0) oxidatively adds into the arylboronic acid to generate arylnickel species **I71**, this undergoes migratory insertion across the alkyne to give alkenylnickel species **I72**. This species can add across another molecule of alkyne to give dimerisation products **I70**. However, if water coordinates to the nickel **I73**, σ-bond metathesis gives nickel hydride species **I74**. Nickel hydride reductively eliminates to give hydroarylation product **I69** and regenerate the active nickel(0) catalyst.

1.2.2 Palladium-catalysed arylation of alkynes

The use of a palladium catalyst with organoboron compounds was reported by Oh and co-workers in 2003.[26] A Pd(0) catalyst, with an acid co-catalyst was utilised to add a range of aryl- and alkenylboronic acids across a number of terminal and internal alkynes (scheme 31).



Scheme 31: Palladium-catalysed additions of organoboron reagents to alkynes.

The reaction is efficient for a range of terminal alkynes with longer reaction times being required for internal dialkyl alkynes **I57e**. When the alkyne is activated with an electron withdrawing group the reaction is facile, but with a loss of regioselectivity **I57g**. They propose the catalytic cycle in figure 4.

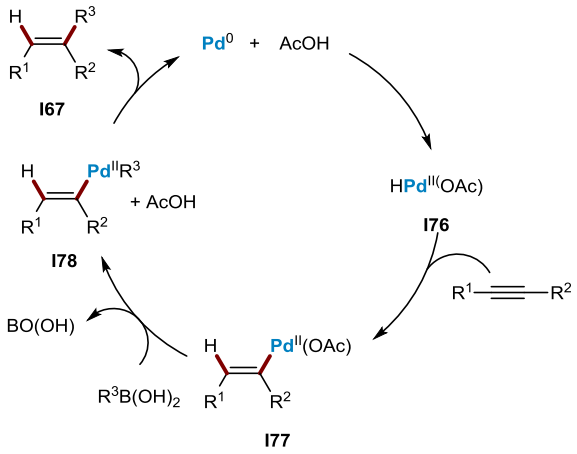
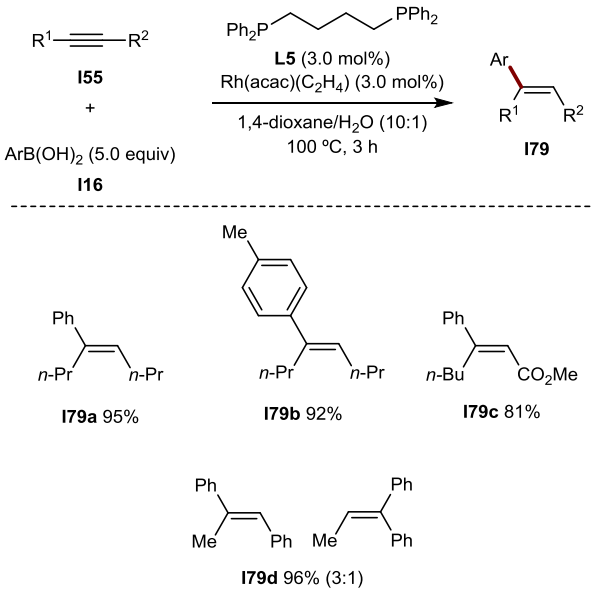


Figure 4: Proposed catalytic cycle for the palladium-catalysed hydroarylation of alkynes using arylboron reagents.

Pd(0) under goes oxidative addition with the acid co-catalyst to form palladium hydride **I76** that reacts with the alkyne to give vinyl-Pd(II) intermediate **I77**. This species can undergo facile transmetallation with the boronic acid to give intermediate **I78** and regenerate the acid co-catalyst. Reductive elimination of this species gives the product **I67** and oxidative addition of the Pd(0) species with the reformed acid co-catalyst regenerates the Pd-H.

1.2.3 Rhodium-catalysed arylation of alkynes

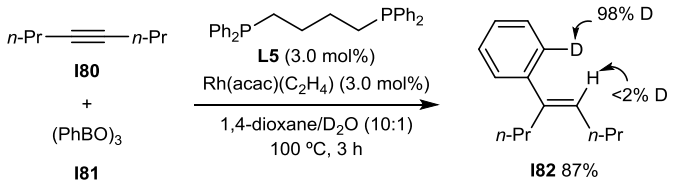
Whilst pursuing their groups interest in the addition of arylboronic acids into unsaturated systems, Hayashi and co-workers reported the first examples of rhodium catalysed hydroarylation of alkynes in 2001 (scheme 32).[27] By utilising arylboronic acids as the organometallic, the functional group tolerance of this process is greatly improved.



Scheme 32: Rhodium-catalysed hydroarylation of alkynes

The yields of this transformation are high and substrates containing electrophilic moieties such as **I79c** are tolerated in this transformation. When an unsymmetrical alkyne is used products **I79d** are obtained in a high combined yield but as a 3:1 mixture, with preference for the initial addition placing the rhodium adjacent to the phenyl group.

Interestingly, whilst carrying out the reaction in the presence of D_2O, deuterium incorporation was exclusively on the *ortho*-position of the aryl-group (scheme 33).



Scheme 33: Deuterium labelling experiment.

It is proposed that this occurs as a result of the alkenylrhodium intermediate moving to the *ortho*-aryl position *via* a 1,4-migration **I83** to **I84** (figure 5).

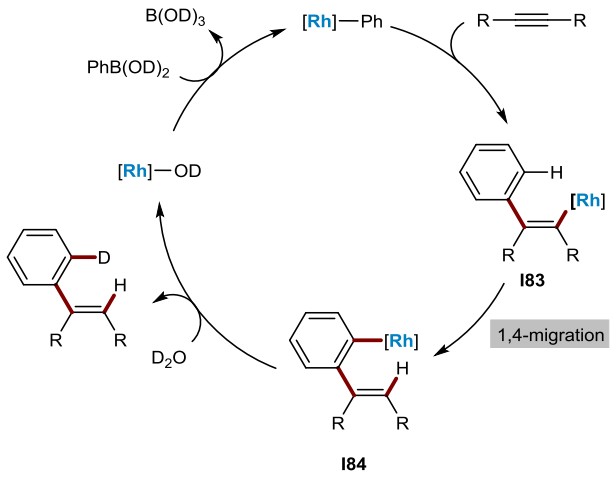
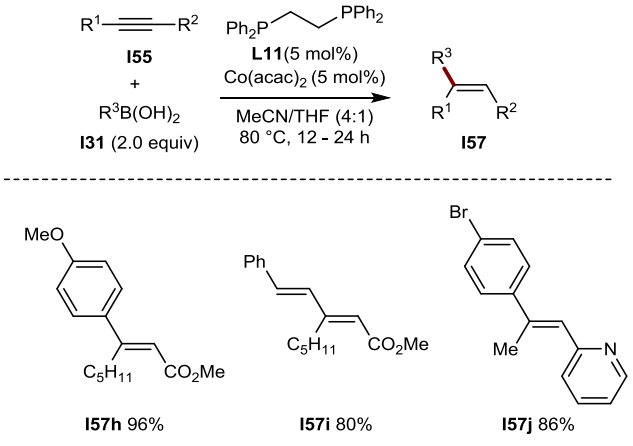


Figure 5: Proposed catalytic cycle.

1.2.4 Cobalt-catalysed arylation of alkynes using boronic acids

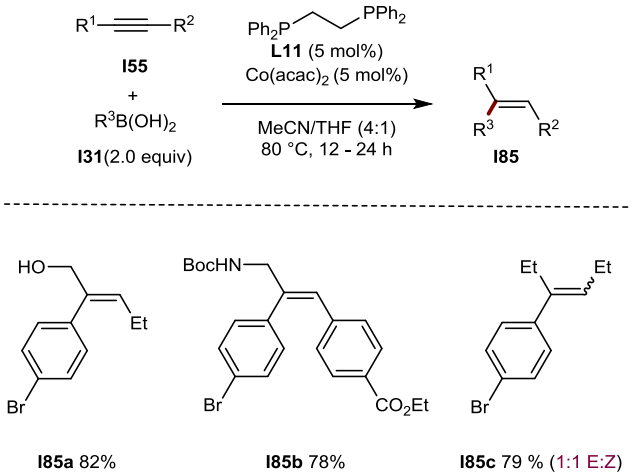
In 2008, Cheng and co-workers reported the use of a cobalt catalyst in the hydroarylation of alkynes with boronic acids (scheme 34).[28]



Scheme 34: Cobalt-catalysed alkyne arylation.

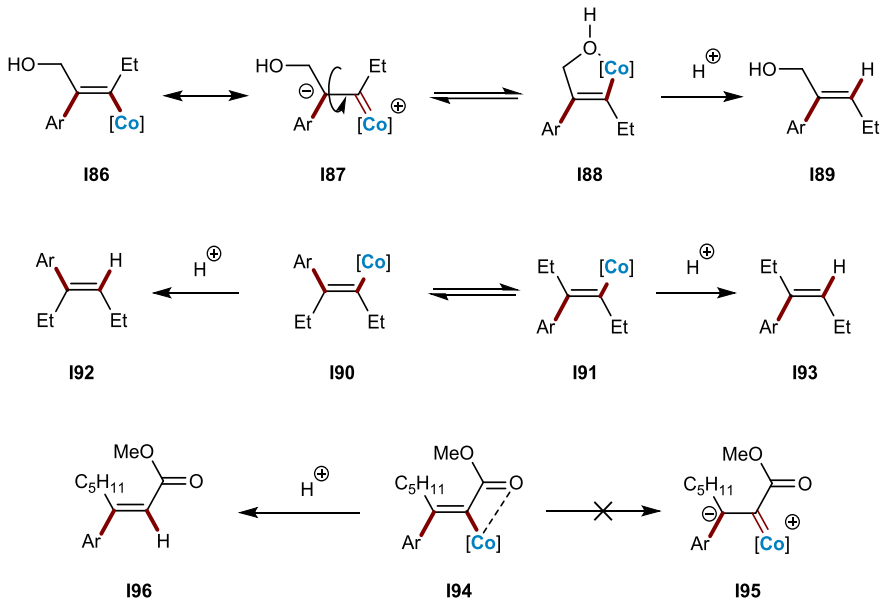
The reaction was efficient for varying electronics on the arylboronic acid, and alkenylboronic acids were also compatible **I57i**. Heteroaromatics on the alkyne **I57j** are also tolerated. Interestingly, the hydroarylation of propargyl alcohols and

carbamates gave *trans*-hydroarylation product **I85** in good yield. Additionally, when the unactivated alkyne 3-hexyne was used, it gave **I85** as a 1:1 mixture of *E*/*Z* isomers (scheme 35).



Scheme 35: Stereoselectivity of the cobalt-catalysed alkyne arylation

The rationale for the observed stereochemistry of the products was due to the coordinating ability of the substituents on the alkyne (scheme 36).

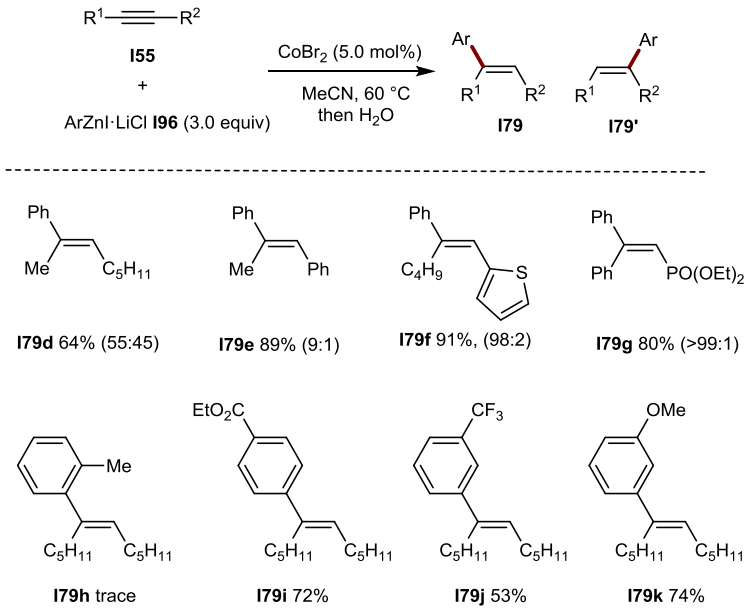


Scheme 36: Mechanistic explanations of the observed stereochemistry.

After the initial *syn*-selective migratory insertion across the alkyne, the nature of the substituents on the alkyne have an influence on the alkenylcobalt intermediate

formed. If the cobalt centre is able to push electrons into the alkene double bond to form an intermediate such as **I87** then the alkene C-C bond would be able to freely rotate. The presence of the coordinating alcohol may stabilise *anti*-carbometallation intermediate **I88** and therefore result in the *anti*-hydroarylation product **I89** being the major product. However, for 3-hexyne there is no coordinating group present so there is no preference for either isomer. In the case of activated alkynes such as in **I94**, the carbonyl group may initially coordinate to the cobalt making the mechanism of isomerisation unfavourable as it breaks this stabilising interaction. Therefore exclusively *syn*-hydroarylation products are observed for activated alkynes.

Cobalt has also been used in the hydroarylation of alkynes with arylzinc transmetallating agents. Oshima and co-workers report the use of $CoBr_2$ as a catalyst for the additions of arylzinc reagents across alkynes (scheme 37).[29]



Scheme 37: Cobalt-catalysed hydroarylation of alkynes**. I79**:**I79'** ratio in parenthesis.

The regioselectivity of the addition is generally well controlled when the two groups on the alkyne are electronically distinguishable. However, when both groups are alkyl as in **I79d**, the regioselectivity is poor. Good yields are observed for varying electronics of the arylzinc reagent; however, sterically encumbered arylzinc reagents were ineffective **I79h**.

Yoshikai and co-workers reported a similar process in 2012 (figure 6).[30] Interestingly however, in their case the alkenylcobalt intermediate **I97** formed after migratory insertion is thought to undergo a 1,4-migration onto the *ortho*-position of the adjacent aryl group to form this aryl-cobalt intermediate **I98**. This transmetallates with another arylzincate to give orthoarylzincate **I99** that can be trapped by a number of electrophiles such as I_2 or D_2O (figure 6).

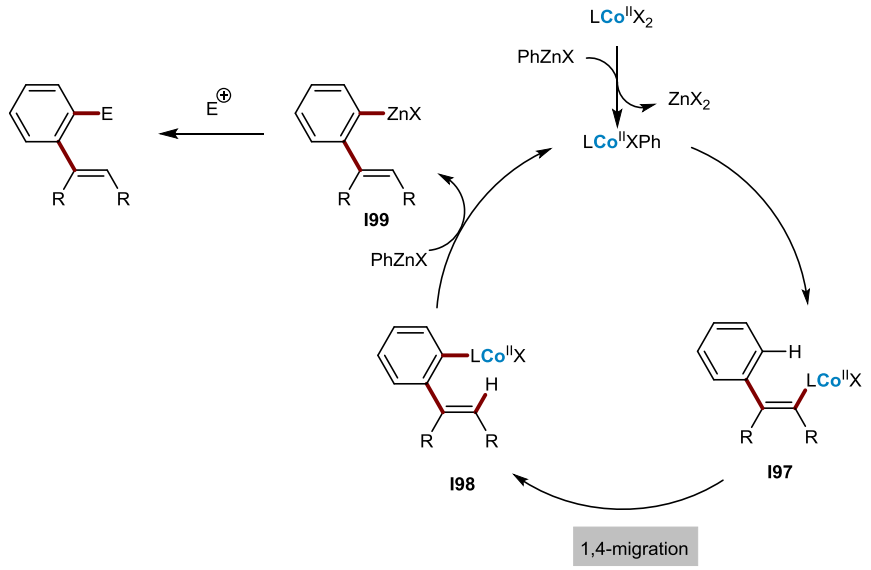
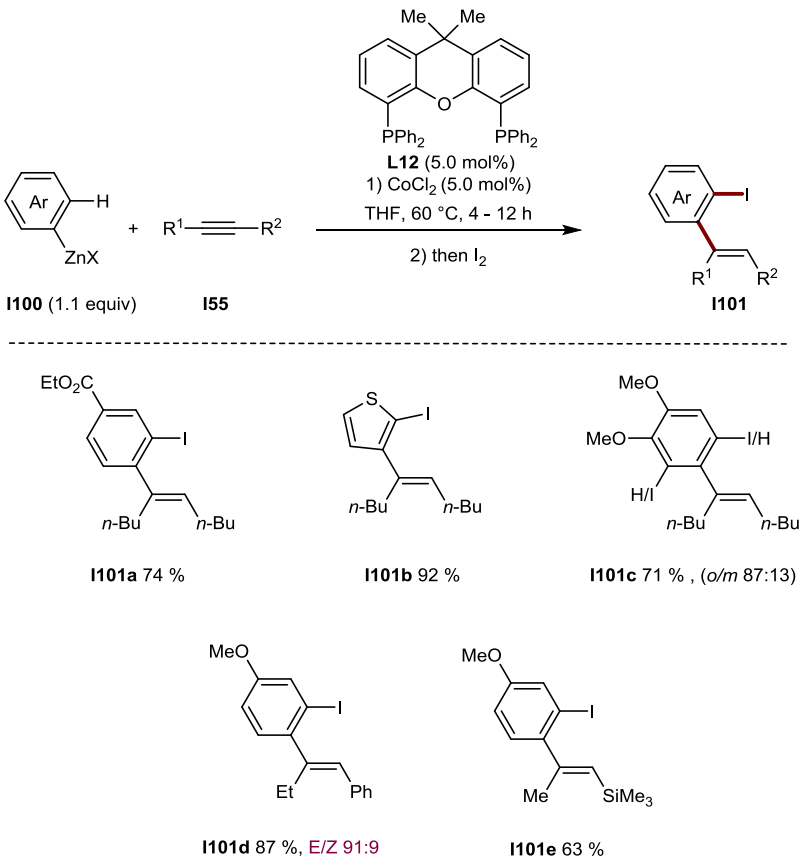


Figure 6: Catalytic cycle for the cobalt-catalysed addition of arylzincates to alkynes involving a 1,4-cobalt migration.

To explore the scope of the reaction Yoshikai and co-workers tested a range of arylzinc reagents and alkynes trapping with I_2 (scheme 38).

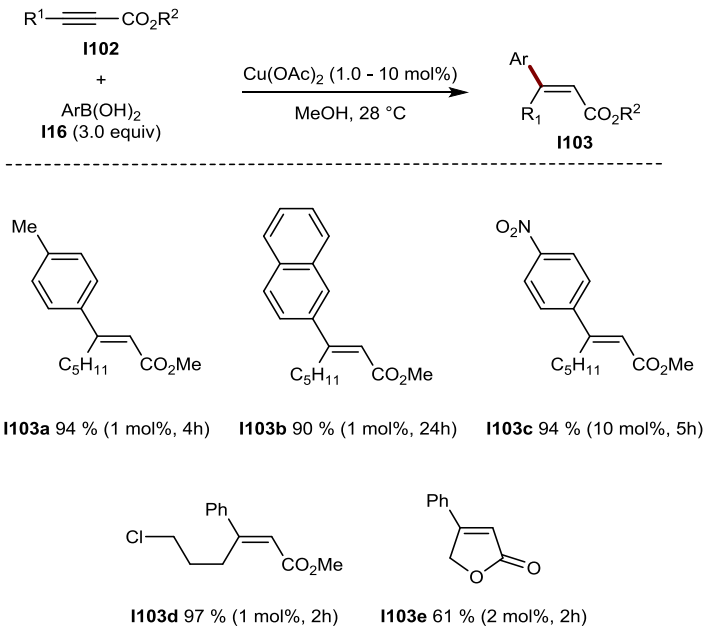


Scheme 38: Cobalt-catalysed addition of arylzincates to alkynes involving a 1,4-cobalt migration.

The arylzinc reagents can contain electrophiles such as esters in **I101a** and heteroaromatics are also tolerated. When the arylzinc reagent is unsymmetrical as in **I101c**, mixtures of isomers are observed with the least hindered arylzinc being formed preferentially. Unsymmetrical alkynes give good selectivity when one of the substituents is aryl or silyl **I101d** and **I101e** respectively, as the metal is directed to be adjacent to this group after attack of the alkyne.

1.2.5 Copper-catalysed hydroarylation of alkynes

Cu(II) salts have also been investigated as catalysts for the hydroarylation of alkynes by Yamamoto and co-workers.[31] They investigated a range of transition metal catalysts bearing oxygen containing counter ions, as this is thought to promote transmetallation with oxophilic boron reagents. $Cu(OAc)_2$ was found to be a proficient catalyst, giving good yields of the *syn*-hydroarylation products with low catalyst loadings and at ambient temperature (scheme 39).

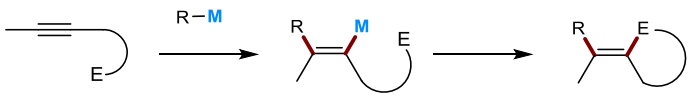


Scheme 39: Copper-catalysed hydroaylations of alkynes.

Reactions involving sterically encumbering boronic acids such as 2-napthylboronic acid required longer reaction times **I103b**. Electron poor arylboronic acids required higher catalyst loadings to affect the hydroarylation efficiently. The methodology is tolerant to electrophiles on the alkyne **I101d**, and when the alkyne contained an alcohol group, lactone products **I101e** were formed *in situ*. This hydroarylation/lactonization methodology was explored further by the same group.[32]

1.3 Transition-metal-catalysed carbometallative cyclisations

The ability of these transition metal catalysts to effect additions of organometallics to electrophiles, such as carbonyls and electron deficient alkenes, as well as performing migratory insertions across alkynes has led to the emergence of so called 'domino' processes (scheme 40).



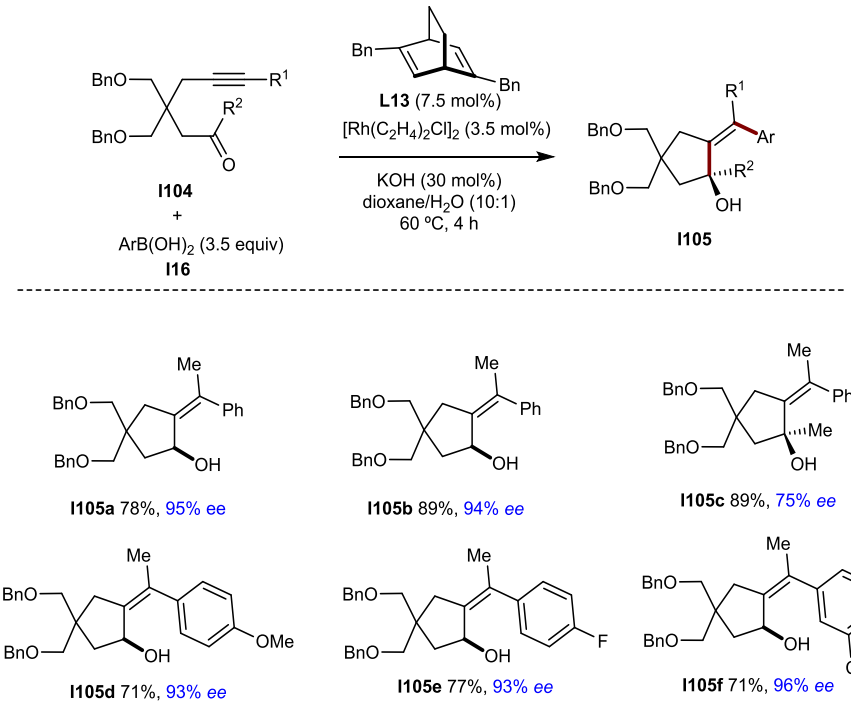
Scheme 40: Carbometallative cyclisation of alkynyl-electrophile.

By tethering the electrophile to the alkyne the alkenylmetal species formed after migratory insertion can cyclise onto the electrophile. However, the effectiveness of

these catalysts to perform direct additions of organometallics to these electrophiles also presents a challenge when trying to carry out such domino reactions.

1.3.1 Rhodium-catalysed arylative cyclisations of alkynyl electrophiles

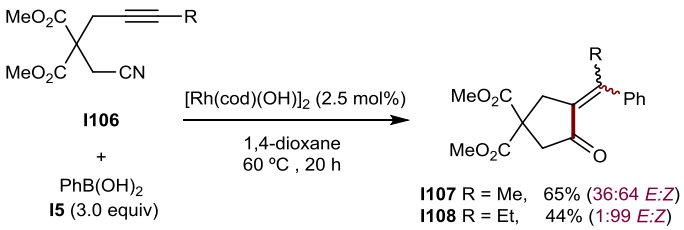
In 2005, Hayashi and co-workers reported an early example of this methodology, in the rhodium catalysed arylative cyclisation of alkynes with tethered aldehydes and ketones (scheme 41). [33]



Scheme 41: Rhodium-catalysed arylative cyclisation of alkynones.

A chiral diene ligand **L13** is employed with a rhodium catalyst to achieve the arylative cyclisation products in good yields and enantiomeric excess.

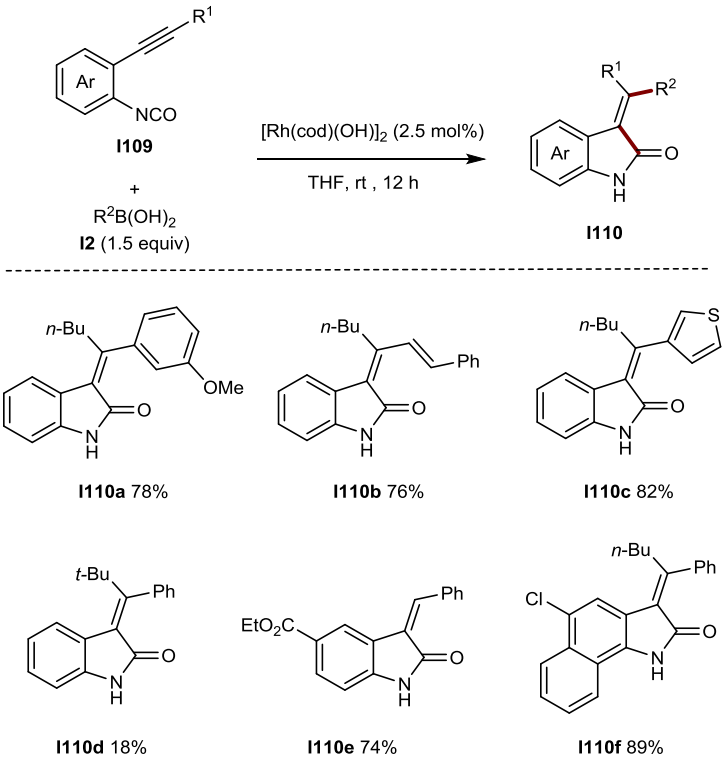
The electrophilic partner for this chemistry is not restricted to carbonyl compounds. Murakami and co-workers also demonstrated the arylative cyclisation of alkynes bearing tethered nitriles (scheme 42).[34]



Scheme 42: Rhodium-catalysed arylative cyclisation of alkyne-tethered nitriles.

This was the first example of nucleophilic attack by an organorhodium species to a nitrile. Interestingly, this reaction produced mixtures of *E*/*Z* isomers about the double bond.

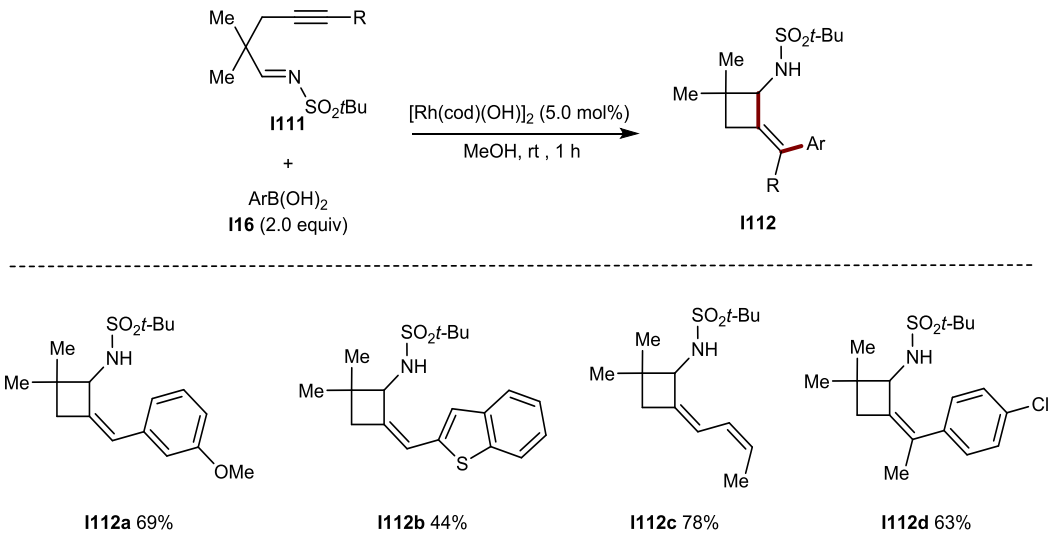
In 2007, Murakami and co-workers were also able demonstrate the use of isocyanates as the tethered electrophile for this process.[35] Using this methodology a large number of 3-alkylindeneoxindoles were synthesised (scheme 43).



Scheme 43: Rhodium-catalysed tandem arylative cyclisation of alkynyl-isocyanates.

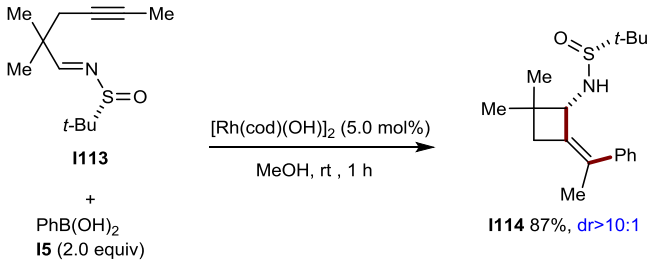
A range of aryl- and alkenylboronic acids are successful in this arylative cyclisation. However, a bulky alkyl group on the alkyne lead to a depreciation in the yield of the reaction **I110d**.

In 2015, Lee and co-workers used tethered imines as the electrophile (scheme 44). [36]



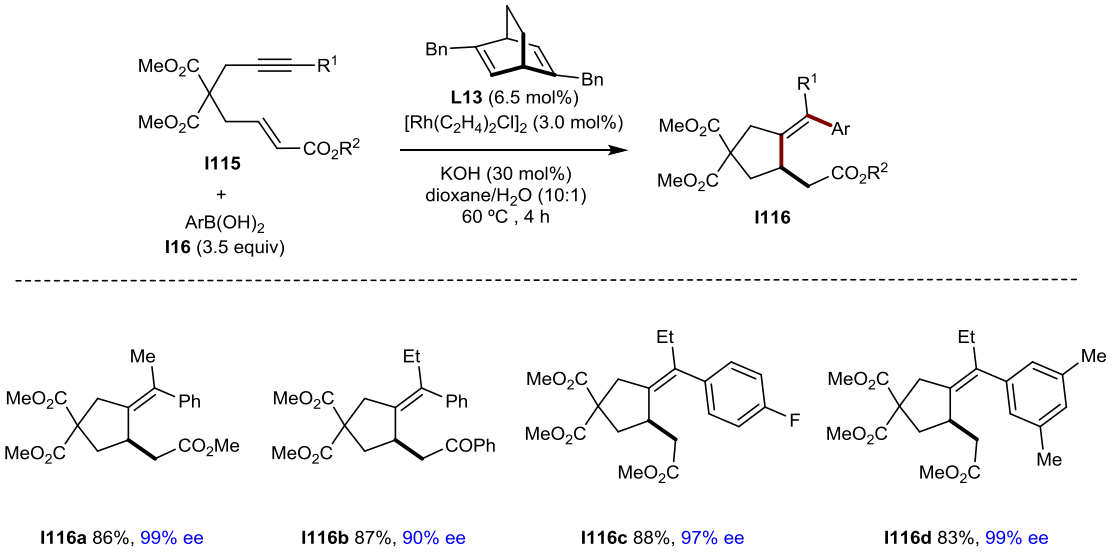
Scheme 44: Rhodium-catalysed arylative cyclisations of alkyne-tethered imines.

By employing a chiral sulfinylimines in the substrate, the diastereoselectivity of the imine addition was controlled (scheme 45).



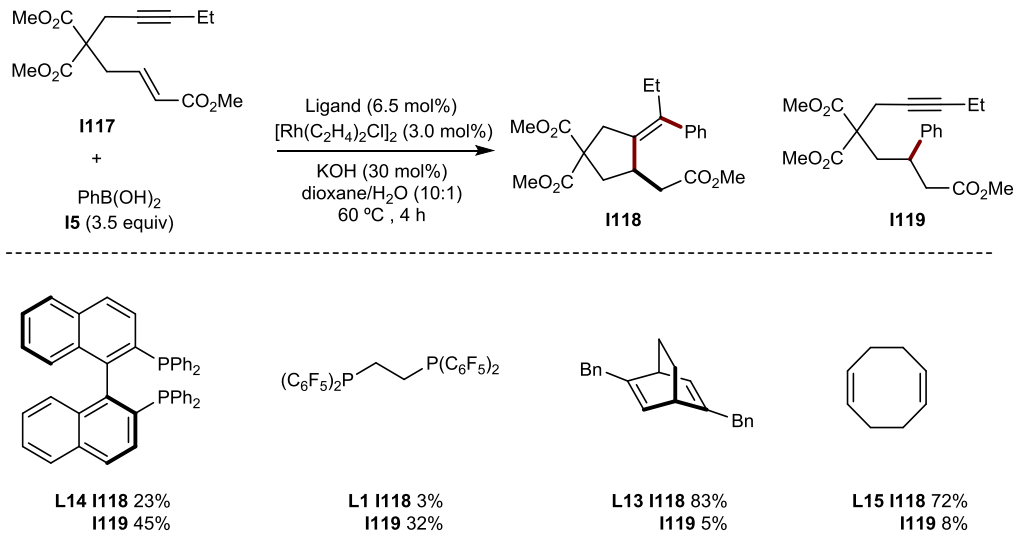
Scheme 45: Diastereoselective arylative cyclisation of alkyne tethered imine **I113**.

Organorhodium complexes readily perform conjugate additions to electron deficient alkenes.[7] Therefore by using an electron deficient alkene as the tethered electrophile the intermediate alkenylrhodium species formed after migratory insertion of the alkyne can go on to cyclise. Hayashi and co-workers demonstrated this in 2005 by tethering α,β-enoates to alkynes.[37] Using a rhodium(I) precatalyst with a chiral diene ligand **L13** cyclic products **I116** were formed in high yield and enantiomeric excess (scheme 46).



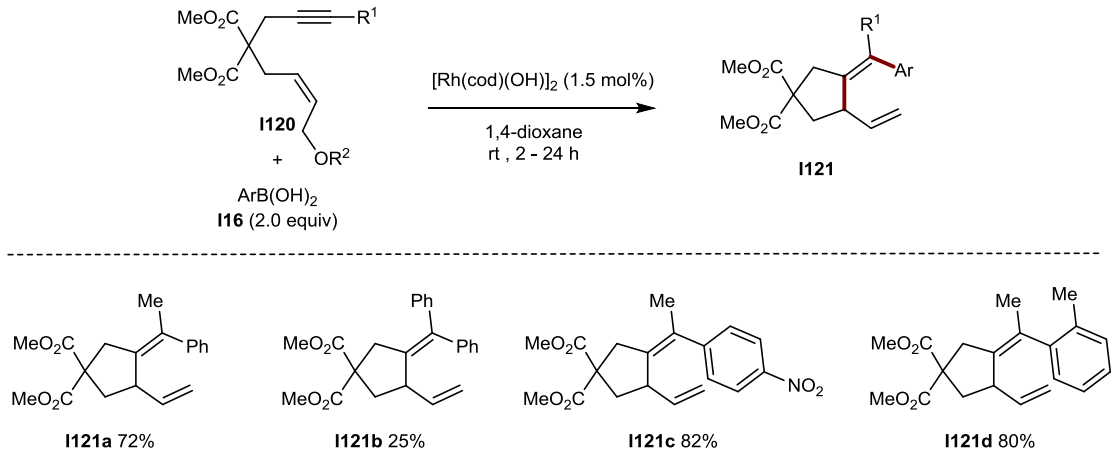
Scheme 46: Rhodium-catalysed enantioselective arylative cyclisations of alkynones.

Interestingly in this reaction, when a bis-phosphine ligand **L14** was used, the major product of the reaction became the direct 1,4-addition to the α,β-enoate; demonstrating the difficulty of such tandem processes that contain many potentially reactive intermediates (scheme 47).



Scheme 47: Ligand effect on the rhodium-catalysed arylative cyclisation of alkyne-tethered α,β-enoates.

When the tethered alkene contains an allylic leaving group the alkenylrhodium intermediate can cyclise onto this to give allylic alkenylation products **I121** (scheme 48).[38]



Scheme 48: Rhodium-catalysed arylative cyclisation of 1,6-eneynes bearing an allylic leaving group.

It was proposed that the alkenylrhodium intermediate formed after alkyne migratory insertion was able to perform a migratory insertion into the alkene followed by β-alkoxy elimination to regenerate the active catalyst (figure 7).

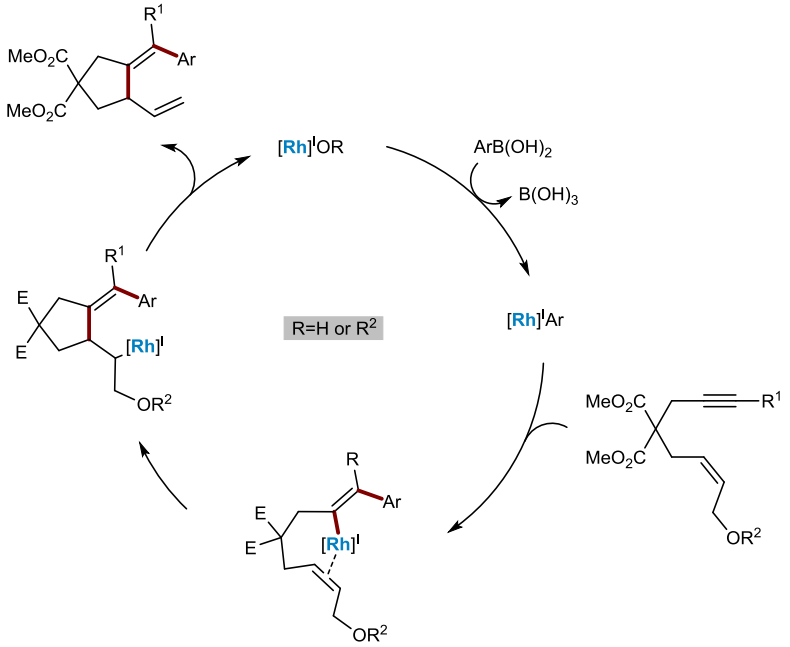
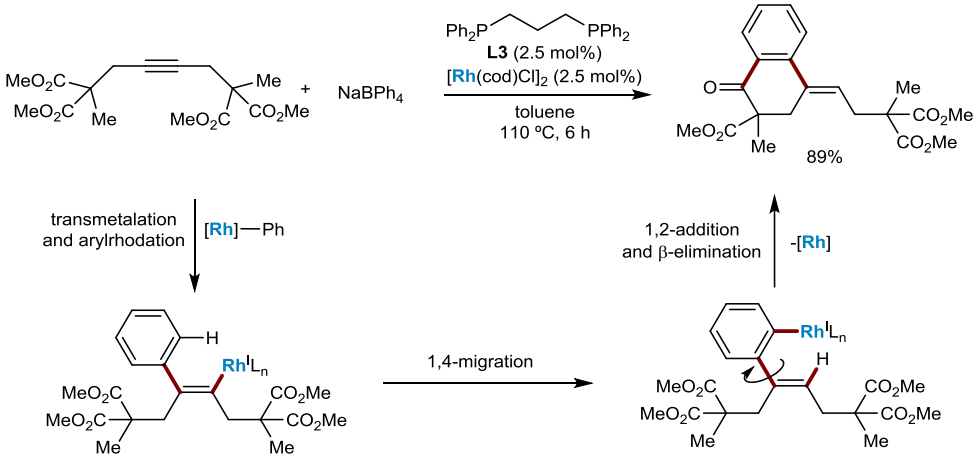


Figure 7: Proposed catalytic cycle for the rhodium-catalysed arylative cyclisation of 1,6-eneynes bearing an allylic leaving group.

All of the examples shown demonstrate the use of a rhodium(I) pre-catalyst combined with a ligand to initially perform an arylation reaction of a triple bond. The intermediate formed as a result of this initial reaction is then trapped by a wide variety of tethered electrophiles, a number of the preliminary examples of the

utilisation of this methodology are discussed; however, since the publication of these pioneering examples many variations of these reactions have been developed, many giving rise to the formation of synthetically useful products. [39,40]

Work by Murakami and co-workers in 2005 found interesting reactivity of the alkenylrhodium species formed after the initial migratory insertion (scheme 49).[41]

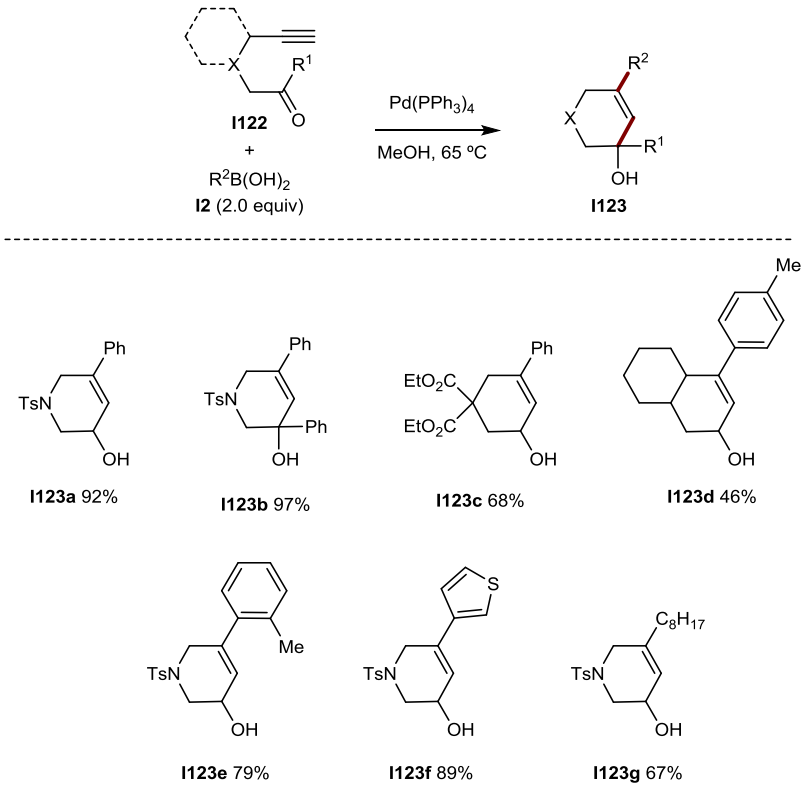


Scheme 49: Arylative cyclisation of alkynyl-malonates involving an 1,4-rhodium migration

When organoboron reagents were added across an alkyne with tethered ester groups, it was found that the alkenylrhodium species underwent a 1,4-migration with the *ortho*-hydrogen on the newly added aryl group. This allowed the newly formed arylmetal species to cyclise onto the distal electrophile with respect to the initial insertion products (scheme 49).

1.3.2 Palladium-catalysed carbometallative cyclisations

Arylative cyclisations of alkynes with tethered electrophiles under palladium catalysis has also been well studied. Interestingly under palladium(0) catalysis, using boronic acids, in a process analogous to those reported for rhodium, Tsukamoto and co-workers have found that *anti*-carbometallative products are formed (scheme 50).[42]



Scheme 50: Palladium-catalysed *anti*-carbometallative cyclisation.

Using a simple commercially available palladium catalyst, they are able to form the *anti*-carbometallation products **I123** in good yields. Aryl-, alkyl- and heteroaryl boronic acids work well in this process.

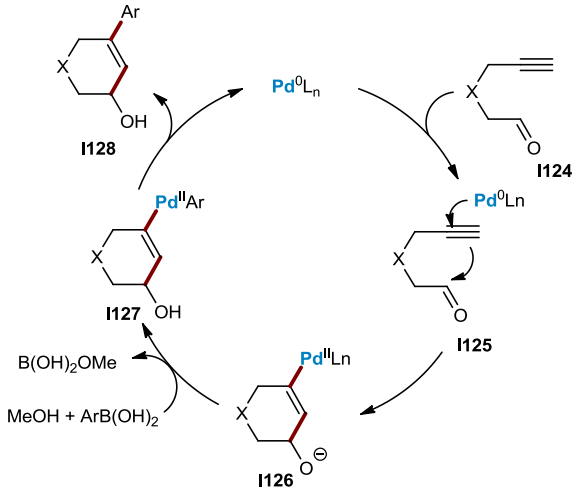
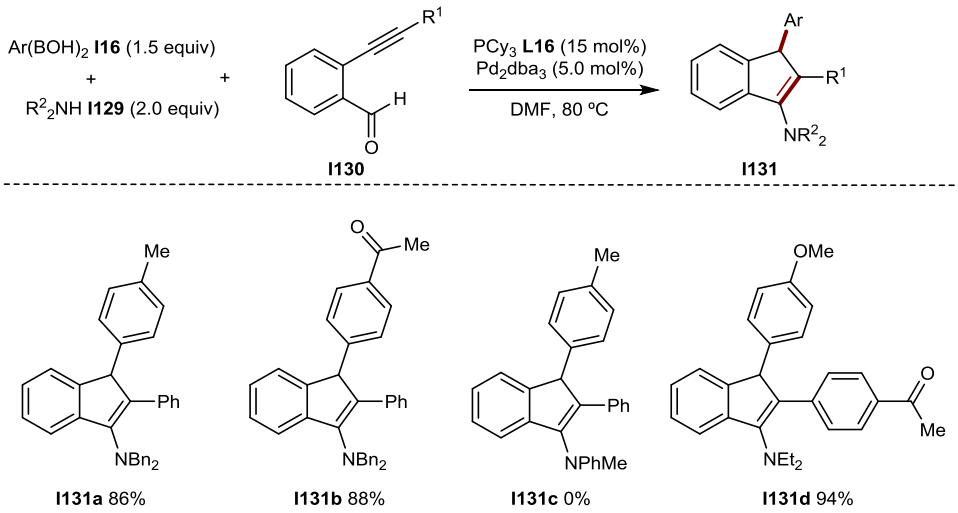


Figure 8: Proposed catalytic cycle for palladium-catalysed *anti*-carbometallative cyclisation.

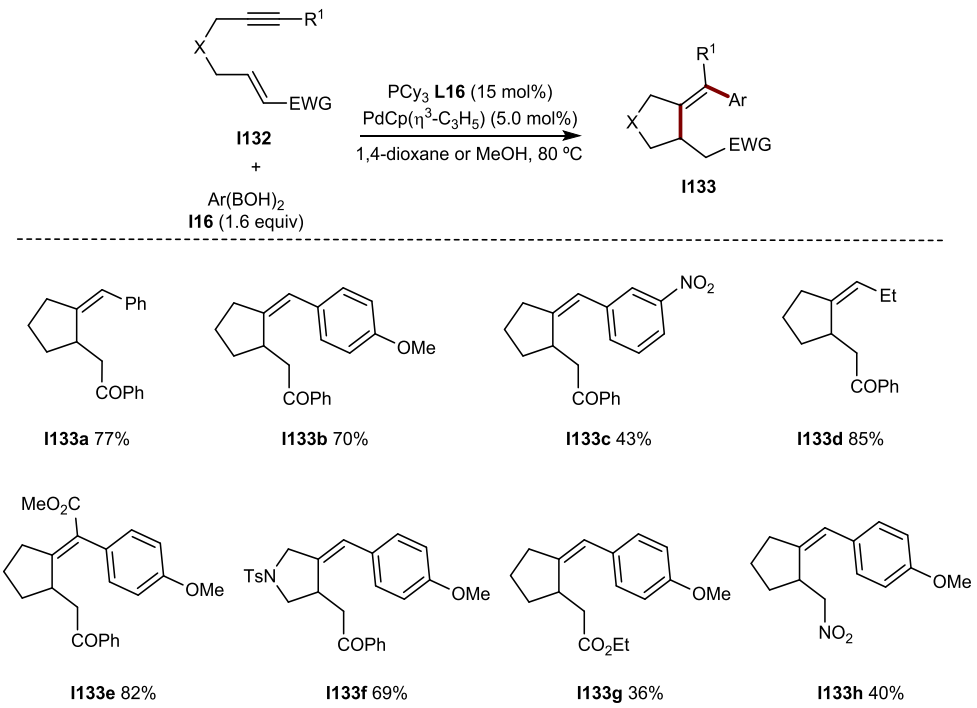
This mechanism involves an initial '*anti*-Wacker' type oxidative addition where palladium(0) first attacks the alkyne **I124**. The adjacent carbon atom then attacks the tethered electrophile **I125**. Solvolysis with methanol to form a methoxypalladium(II) intermediate is followed by transmetallation with the boronic acid to give **I127**. This arylpalladium(II) species reductively eliminates to give the product **I128** and regenerate the active Pd(0) catalyst. Interestingly, there have been no examples of this palladium(0) *anti*-carbometallative cyclisation methodology being successfully deployed in an enantioselective process.

Tsukamoto and co-workers extended this methodology to include tethered imines formed *in situ* in a three component coupling (scheme 51). [43]



Scheme 51: Palladium-catalysed arylative cyclisation of alkynyl-imines.

Interestingly, in 2008 Tsukamoto and co-workers found that when this same catalytic system was applied to alkynyl-enones **I132** *syn*-carbometallation products are formed (scheme 52).[44]



Scheme 52: Palladium-catalysed arylative cyclisation of alkynyl-enones.

A metallacycle forming oxidative addition, leading to intermediate **I135** is proposed to be the cause of the observed change in reactivity (figure 9). This intermediate then transmetallates with the arylboronic acid and undergoes reductive elimination as seen previously (figure 8).

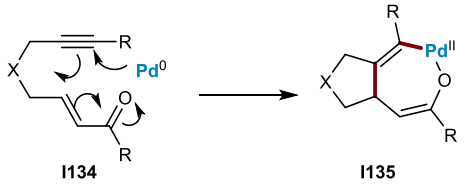
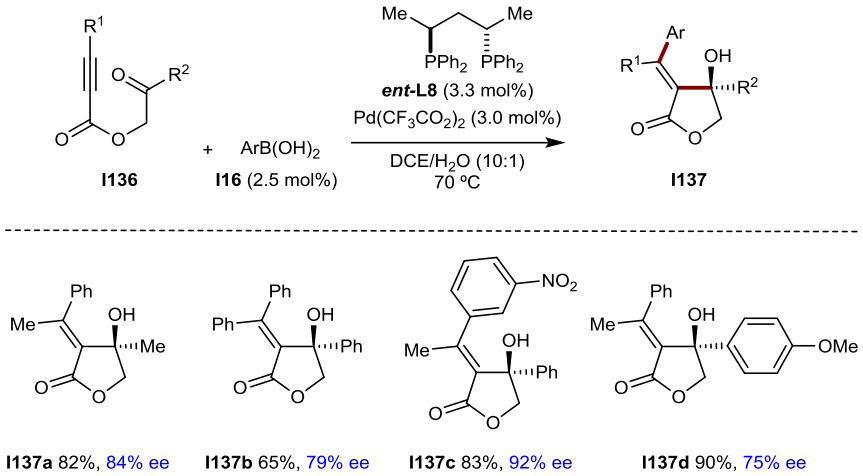


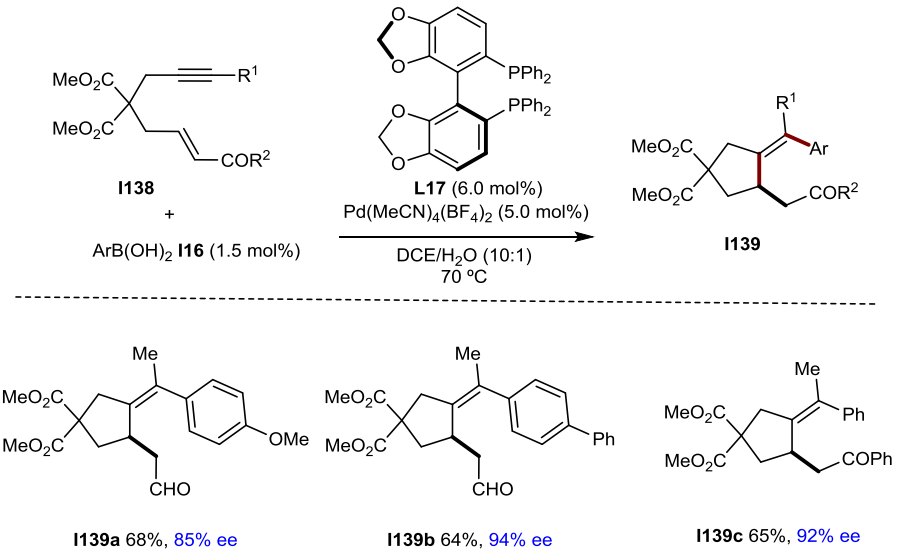
Figure 9: Metallacycle formation leading to *syn*-carbometallation.

Cationic palladium(II) complexes have been used to render these arylative cyclisation processes enantioselective. In 2007, Lu and co-workers reported the arylative cyclisation of arylmethyl-2-alkynoates **I136** with arylboronic acids (scheme 53). They propose a redox neutral Pd(II) cycle where the first step is migratory insertion across the alkyne followed by nucleophilic attack of the palladium-vinyl species in an analogous reaction to that seen by Hayashi and co-workers in 2005 for their rhodium catalysed process (scheme 46).[45]



Scheme 53: Palladium-catalysed enantioselective arylative cyclisation of alkynones.

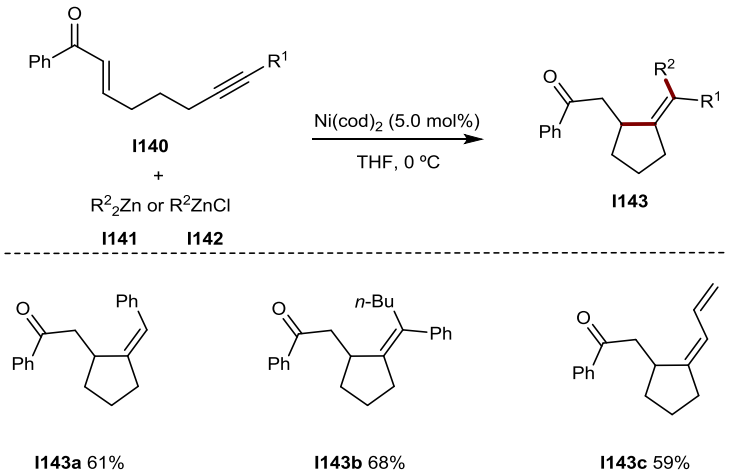
And in 2012, Lu and co-workers extended this methodology to perform enantioselective palladium catalysed arylative cyclisations on alkynones and alkynals (scheme 54).[46]



Scheme 54: Palladium-catalysed enantioselective arylative cyclisations of alkynyl-enones.

1.3.3 Nickel-catalysed carbometallative and reductive cyclisations

In 1996, Montgomery and co-workers were able to demonstrate the use of a nickel(0) catalyst with alkyl- and arylzinc reagents in the alkylative cyclisations of alkynyl-enones (scheme 55). [47]



Scheme 55: Nickel-catalysed carbometallative cyclisations of alkynyl-enones.

The proposed mechanism of this cyclisation involves an initial cyclisation of the alkynone to give metallacycle **I144**. Transmetallation of the organozinc reagent can give intermediate **I145**, reductive elimination regenerates the active nickel(0) species and gives the cyclisation product **I143** (figure 10).

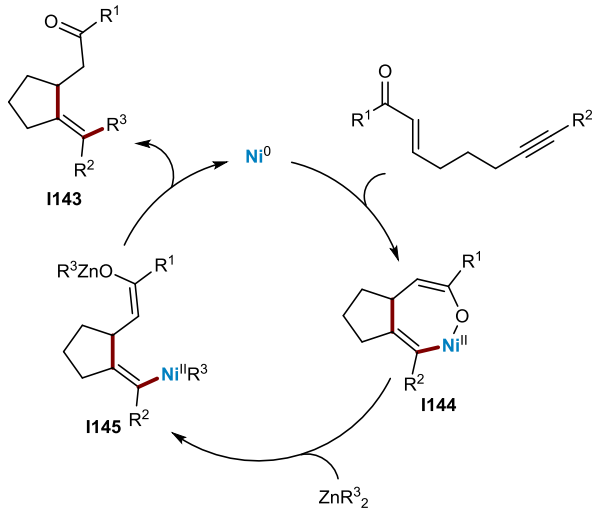
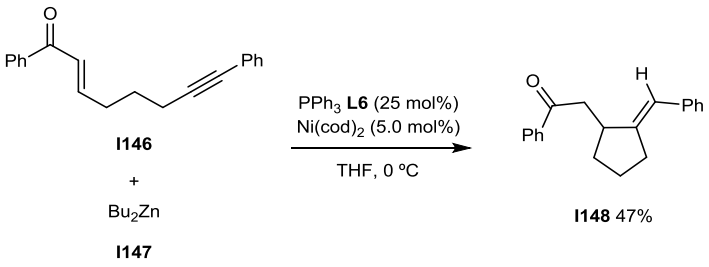


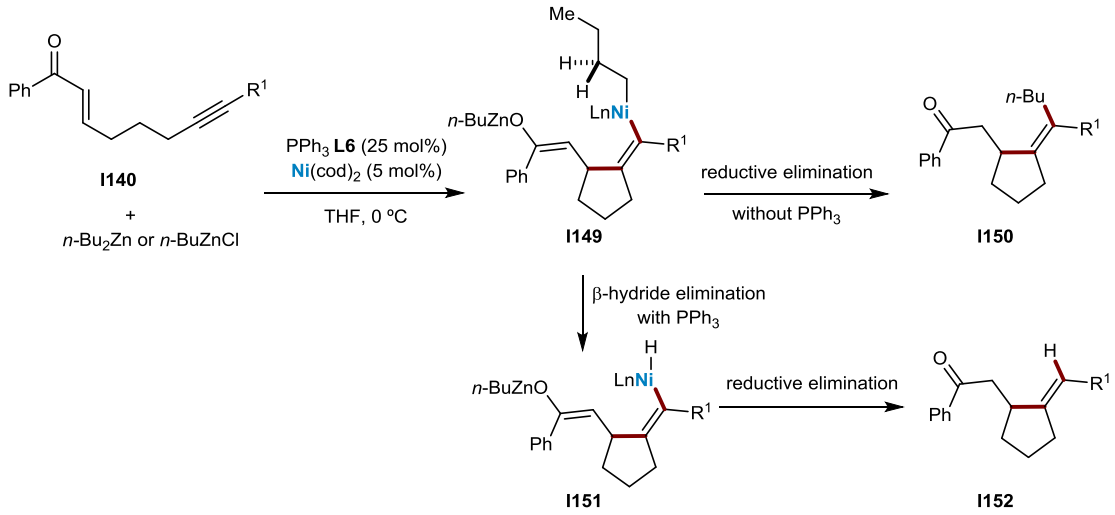
Figure 10: Proposed catalytic cycle for the nickel-catalysed cyclisation.

Interestingly, using the similar reaction conditions but pre-treating $Ni(cod)_2$ with triphenylphosphine (5.0 equiv) resulted in the formation of reductive cyclisation products **I148** (scheme 56).



Scheme 56: Conditions leading to reductive cyclisation products.

Montgomery and co-workers proposed, that the ligated triphenylphosphine (**L6)** promoted β-hydride elimination of intermediate **I149** leading to reduced products **I152** (scheme 57).

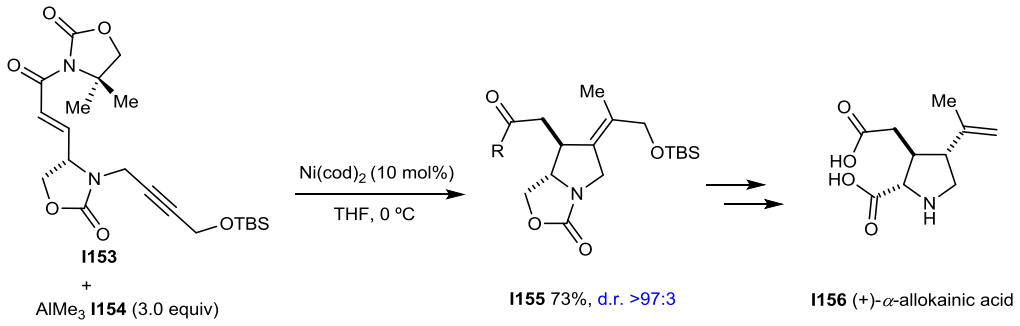


Scheme 57: Proposed pathways resulting in either alkylative or reductive cyclisations.

A number of potential causes of this diversion from common intermediate **I149** are proposed. It is suggested that the coordination of unreacted substrate **I140** may remove electron density from the Ni centre due to the electron difficency of the alkene making it a good π-acceptor. This removal of electron density may make reductive elimination more favourable. However, the coordination of basic triphenylphosphine ligands could result in a more electron rich metal centre, in turn making a reductive process less favorable facilitating non-reductive β-hydride elimination. They also propose that the presence of coordinating triphenylphosine ligands may alter the geometry about Ni in intermediate **I149** forcing the alkyl- and alkenyl-groups *trans* to one another, hindering reductive elimination. Another possibility that Montgomery and co-workers do not discuss is that the increased

steric bulk about the metal centre may promote β-hydride elimination as the product **I151** is considerably less sterically encumbered.

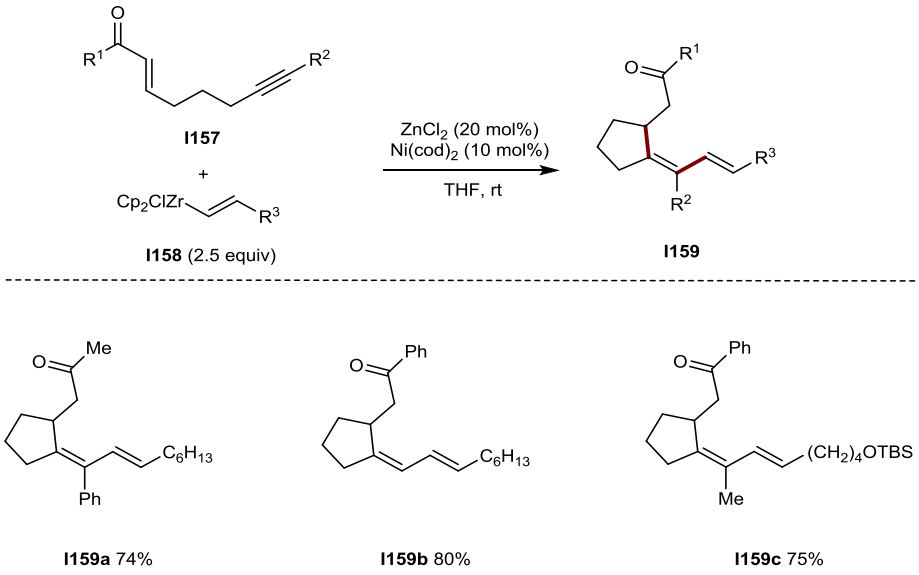
Montgomery and co-workers were also able to use this methodology with trimethylaluminium in the enantioselective synthesis of (+)-α-allokainic acid (**I156)** (scheme 58).



Scheme 58: Nickel-catalysed alkylative cyclisation step in synthesis of (+)-α-allokainic acid.

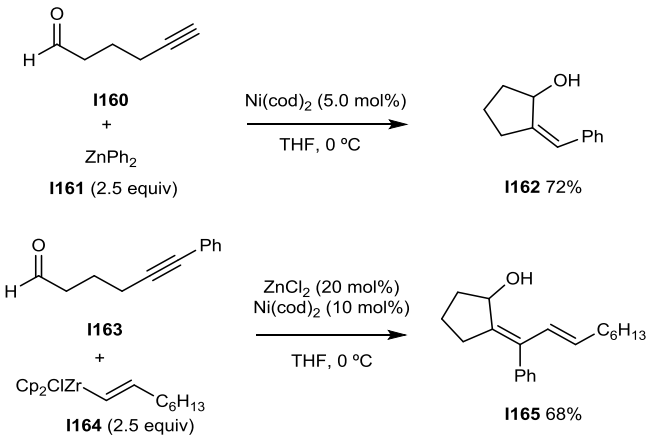
Dimethyl zinc reagents were first tested in this reaction in line with the previously reported work, however it was found that commercially available trimethyl aluminium gave the desired product in good yield.

To expand the scope to alkenyl-organometallics, Montgomery and co-workers also used organozirconium reagents. These were produced from the corresponding alkyne and Schwartz reagent (scheme 59).[48]



Scheme 59: Nickel-catalysed cyclisations of alkynyl-enones with organozirconium reagents.

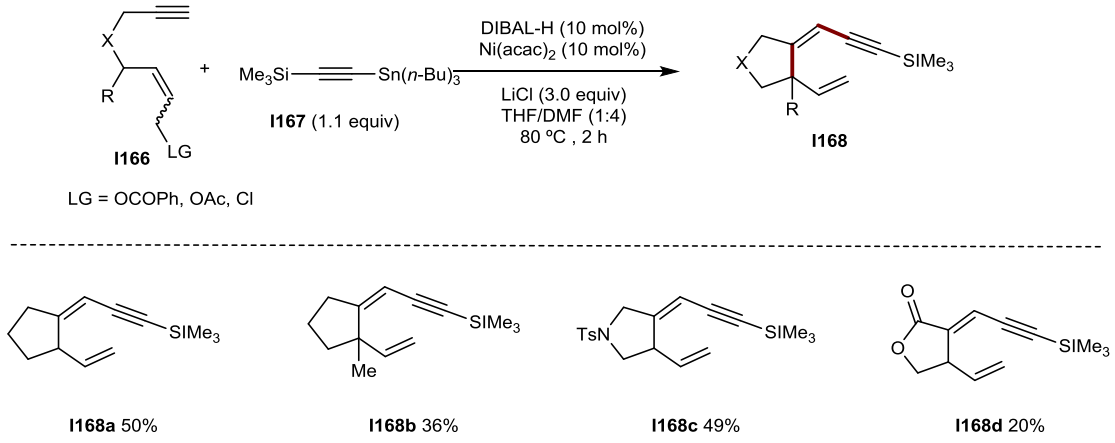
The electrophilic component of the substrate is not limited to electron deficient alkenes, Montgomery and co-workers also reported the nickel-catalysed carbometallative cyclisations of alkynals, using both organozinc and organozirconium partners (scheme 60). [48,49]



Scheme 60: Nickel-catalysed cyclisations of alkynals.

The presence of a phosphine ligand results in the formation of reductive cyclisation products for alkylzinc groups with β-hydrogens.

The use of Ni(0) catalysis, combined with organotin reagents has also been developed for the carbometallative cyclisation of alkynes bearing tethered allylic leaving groups by Ikeda and co-workers (scheme 61). [50]



Scheme 61: Nickel-catalysed cyclisation of 1,6-eneynes bearing allylic leaving groups.

In this process an air-stable nickel(II) pre-catalyst is used in the presence of DIBAL-H as a reductant to form Ni(0) *in situ*. Ikeda and co-workers also demonstrated the use of organozinc and organoaluminium species for this cyclisation.[51]

1.4 *anti*-Carbometallations of alkynes

As discussed in section 1.3.2, the addition of organometallics across alkynes leads to sterically well-defined products. These reactions give predictable products due to the *syn*-selective nature of migratory insertion. Because of this, the scope of much of this chemistry results in the two new bonds being formed on the same side of the alkene with *anti*-additions across alkynes being much less common (Figure 11).

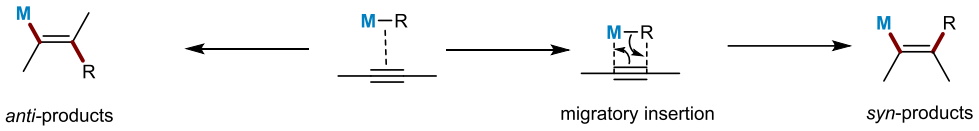
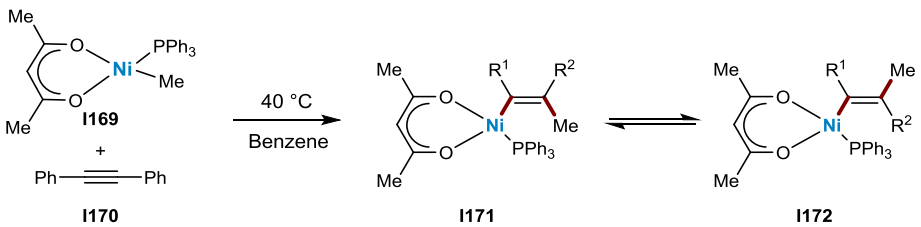


Figure 11: Stereoselectivity of additions across alkynes.

In section 1.2.2 the *anti*-carbometallative cyclisations of alkynones utilising a Pd(0) catalyst was discussed, however the mechanism of this reaction relies on the initial '*anti*-wacker' type cyclisation of the alkynones to the *anti*-carbometallation products, followed by transmetallation with the organometallic. Therefore, the formal *anti*-additions of organometallics across alkynes are much less well explored with a few select examples.

1.4.1 Reports of alkyne anti-carbometallation

An early example of *anti*-addition products being observed was reported by Bergman and co-workers (scheme 62).[52]



Scheme 62: Isomerisation of alkenylnickel complex **I169**.

They observed that when alkylnickel complex **I169** was treated with alkyne **I170**, **I171** was the initial sole product of the reaction. This initial migratory insertion was extremely facile with full conversion occurring in around 30 minutes. When a solution of **I171** was left at room temperature for several days they observed isomerisation to **I172**. It was proposed that the presence of free triphenylphosphine in the reaction medium is able to help promote this isomerisation by adding in to the alkenylnickel intermediate and breaking the double bond allowing free rotation (figure 12).

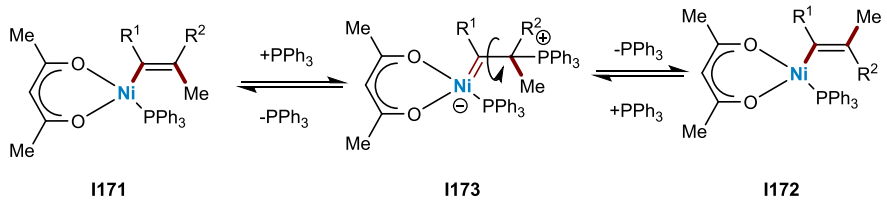
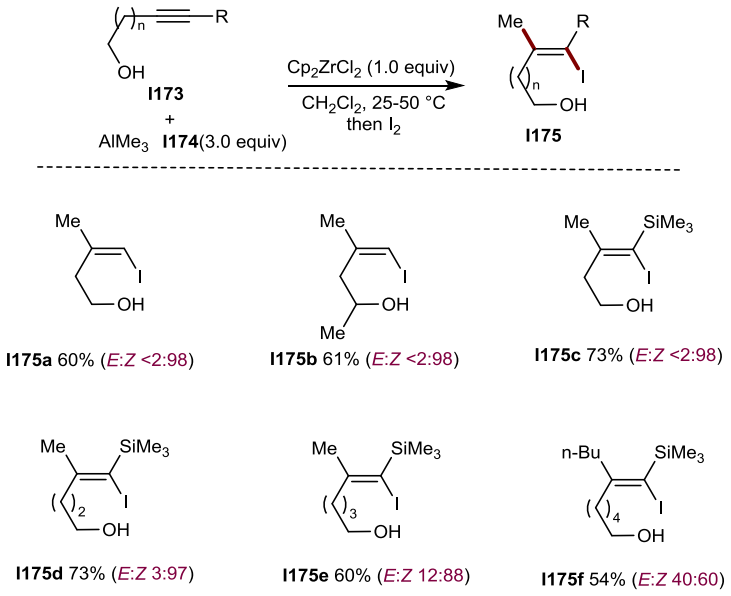


Figure 12: Proposed mechanism of alkenylnickel isomerisation.

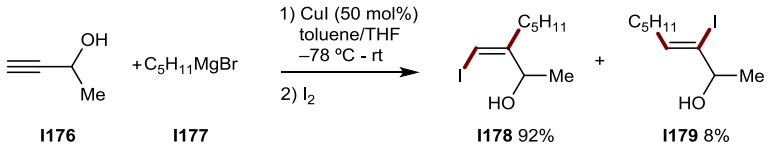
When the alkynes contain tethered heteroatoms, in a number of cases, *anti*-carbometallation products were observed by Negishi and co-workers. They propose that initial *syn*-selective carbometallation occurs and then coordination of the heteroatom drives isomerisation of the initial alkenylmetal species to give the *anti*-addition products (scheme 63).[53]



Scheme 63: *anti*-carbometallations of heteroatom tethered alkynes.

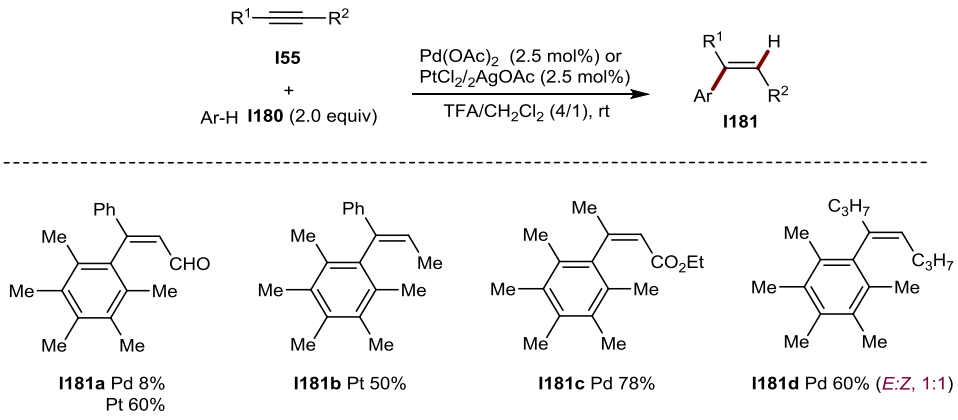
syn-Products are formed when the alcohol is not present. This proposal is also supported by the observed reactivity in the cobalt catalysed hydroarylation of alkynes with arylboronic acids reported by Cheng and co-workers and discussed previously (scheme 35). When the alkyne has a tethered heteroatom that is able to coordinate to the alkenylmetal species, this drives the possible *E/Z*-isomerisation to give *anti*-products in this case also.

A similar reactivity was reported by Ma and co-workers in 2006, for a Cu(I) catalysed process (Scheme 64).[54]



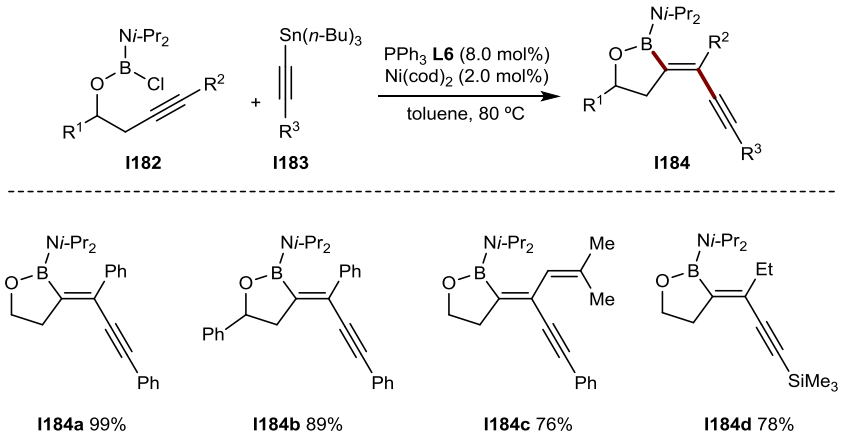
Scheme 64: *anti*-Additions observed in additions of alkyl-copper reagents across alkynes.

In 2000, palladium and platinum complexes were demonstrated by Fujiwara and co-workers to give *anti*-addition products. However, they suggest that it is not an initial *syn*-addition followed by isomerisation but in fact an initial *anti*-addition (scheme 65). [55]



Scheme 65: *anti*-Carbometallation products in Pd/Pt-catalysed arylation of alkynes.

The ability of these vinyl metal species to isomerise freely has been proposed by Suginome and co-workers in the nickel catalysed *trans*-alkynylboration of alkynes (scheme 66).[56,57]



Scheme 66: Nickel-catalysed alkynylboration of alkynes.

In this work, they propose the alkenylnickel species is driven to the *trans*-geometry by the steric clash with the *i*-Pr groups on the nitrogen (figure 13).

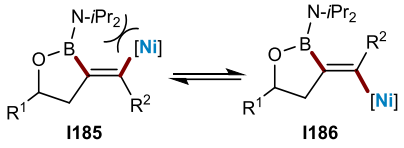
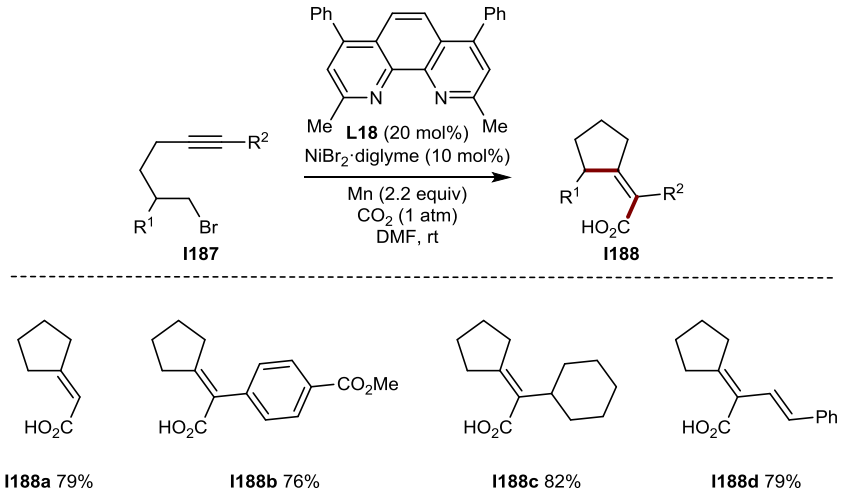
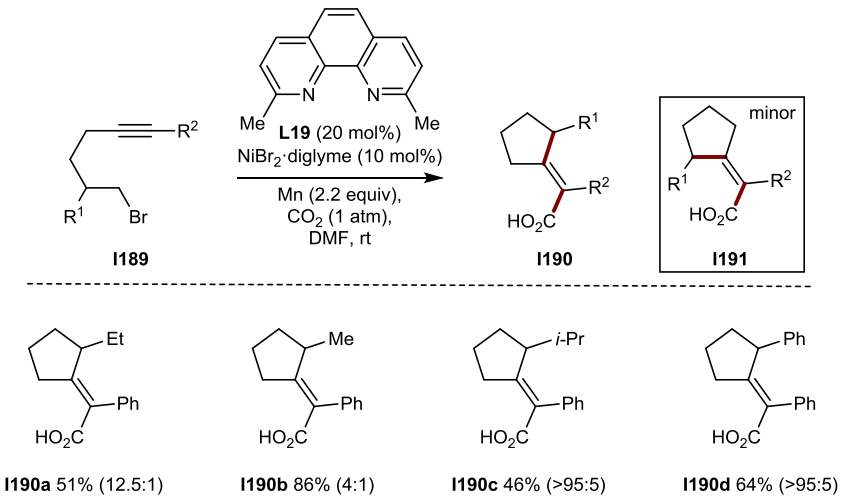


Figure 13: Proposed driving force of alkenylnickel *E*/*Z*-isomerisation.

Martin and co-workers have proposed a similar *E*/*Z*-isomerisation of a alkenylnickel species.[58] In their work from 2015, they report a nickel-catalysed carboxylative cyclisation; they propose that the observed *E*/*Z*-isomerisation is controlled by the steric bulk present in the substrate allowing either the *syn*- and the *anti*-addition products to be formed exclusively (scheme 67).

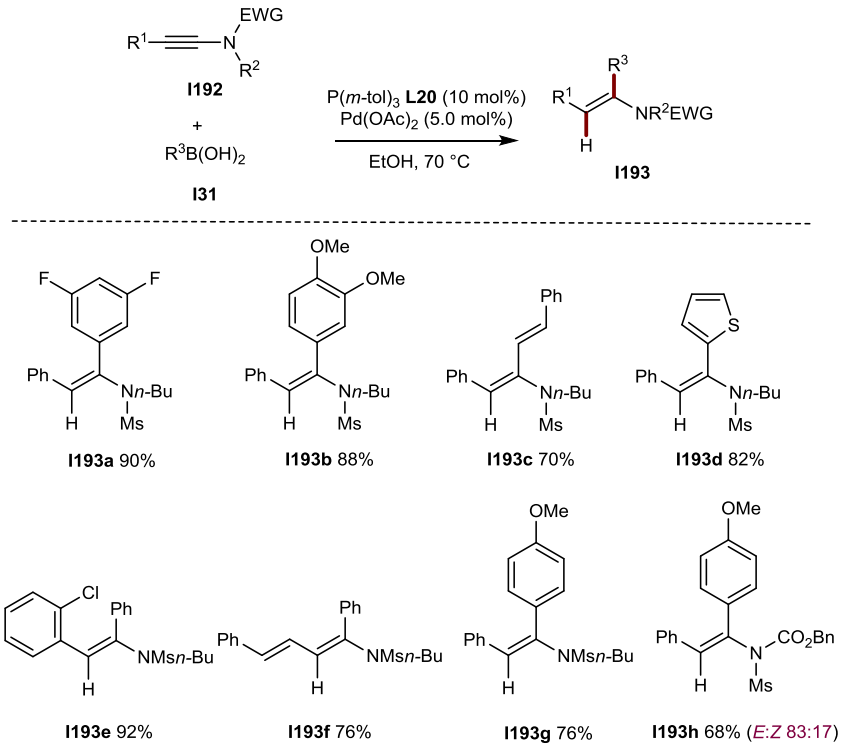




Scheme 67: Scheme 66: *syn*-Carbometallation products of nickel-catalysed carboxylative cyclisation (top). *anti*-Carbometallation products of nickel-catalysed carboxylative cyclisation (bottom).

It is proposed that after the initial carbometallation step, the R^1 group in the substrate drives the reversible *E*/*Z*-isomerisation to give the *anti*-addition products as the major product.

Ynamides have been shown to facilitate an *E*/*Z*-isomerisation in the palladium-catalysed hydroarylation reaction as reported by Zhu and co-workers (scheme 68).[59]



Scheme 68: Palladium-catalaysed *anti*-carbometallation of ynamides.

It is proposed that the lone pair of the nitrogen is able to reversibly break the double bond to allow free rotation (figure 14).

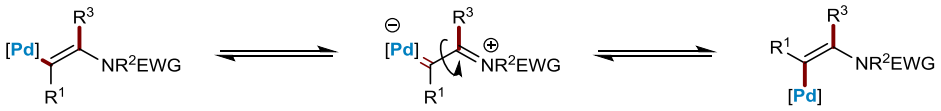
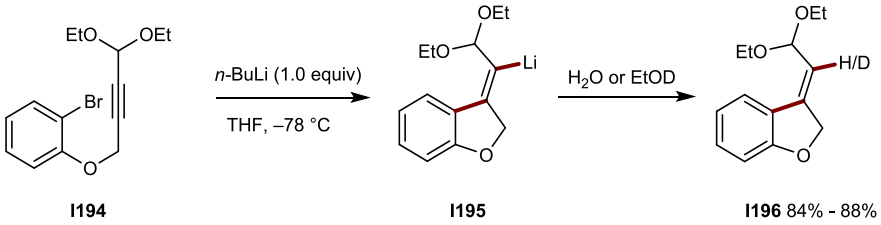


Figure 14: Proposed mechanism facilitating alkenylpalladium *E*/*Z*-isomerisation.

1.4.2 Radical/single electron processes

Many of the *trans*-addition processes discussed thus far, are thought to be carried out under redox neutral conditions or involve two electron redox cycles. However, a number of single electron processes also lead to the formation of *anti*-carbometallation products.

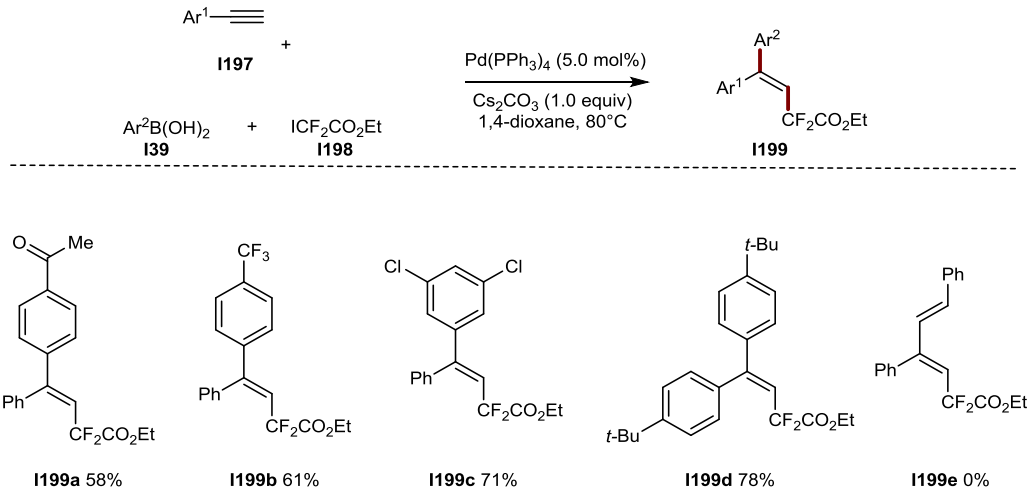
In 2008, Fressigne and co-workers carried out studies on the *anti*-carbolithiation of an alkyne **I194** (scheme 69).[60]



Scheme 69: *anti*-carbolithiation of alkyne **I194**.

By monitoring the reaction using NMR spectroscopy, they were able to observe that the addition occurs solely in an *anti*-manner, and they were able to support this observation by carrying out computational modelling.

anti-Addition products are also observed in the palladium-catalysed intermolecular aryldifluoroalkylation of alkynes as reported by Liang and co-workers (Scheme 70).[61]



Scheme 70: Palladium-catalysed intermolecular aryldifluoroalkylation of alkynes.

Their proposed catalytic cycle is shown in figure 15.

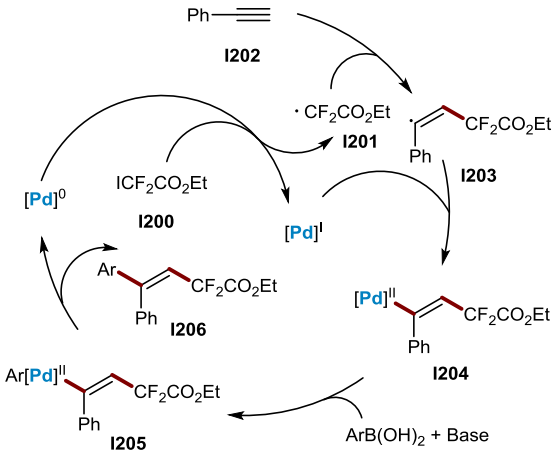
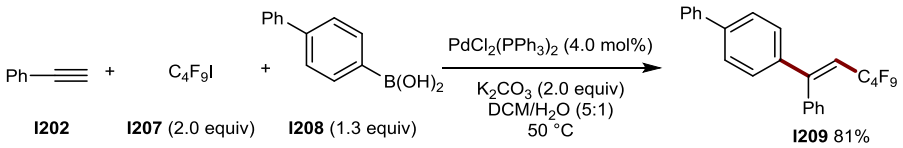


Figure 15: Proposed catalytic cycle for palladium-catalysed intermolecular aryldifluoroalkylation of alkynes.

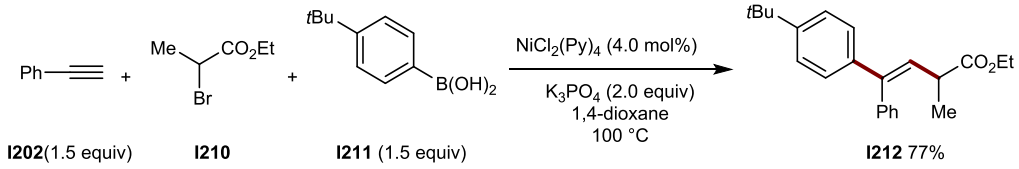
Pd(0) reacts with alkylhalide **I200** to give alkyl radical **I201** and a Pd(I) species. The alkyl radical combines with the alkyne **I202**, which on recombination with the Pd(I) species gives alkenyl-Pd(II) **I204**. It is this Pd-C bond formation that places the palladium on the least hindered face of the resulting alkene leading to the observed *E*-geometry. **I204** then transmetallates with arylboronic acid to give intermediate **I205** that, after reductive elimination gives product **I206** and regenerates the active Pd(0) catalyst.

A similar mechanism is proposed by Nevado and co-workers for the palladium catalysed stereoselective carboperfluoroalkylation of alkynes (scheme 71).[62]



Scheme 71: *anti*-Carbometallation products formed in the palladium-catalysed carboperfluoroalkylation of alkynes.

Similar reactivity is also reported by Nevado and co-workers using a nickel catalyst in the stereoselective dicarbofunctionalisation of alkynes (scheme 72).[63]



Scheme 72: *anti*-Carbometalation products formed under nickel catalysis.

Hu and co-workers reported the *Z*-selective olefin synthesis *via* iron-catalysed reductive coupling of alkyl halides with terminal arylalkynes also relying on the initial radical addition to the alkyne followed by combination with the transition metal *trans* to the newly formed C-C bond (scheme 73).[64]

Scheme 73: *anti*-Carbometalation products formed under iron catalysis.

These interesting transformations resulting in *anti*-carbometallations offer powerful complimentary methodologies to the many examples *syn*-selective transition metal catalysed additions across alkynes, many of which have been outlined here.

1.5 Objectives

Given the wide variety of carbometallative cyclisations of alkyne tethered electrophiles discussed in section 1.3 utilising precious metals such as palladium, rhodium and iridium, the initial aim of this work is to explore such reactions utilising the more abundant first-row transitions metals.

The use of first-row transitions metals for such processes would both offer industrally attractive catalyst alternatives for these reactions, due to the lower cost of these metals. Additionally, as is discussed at length throughout this introduction, for many of the reactions highlighted, the first-row transition metals often give varying products to their precious metal counterparts.

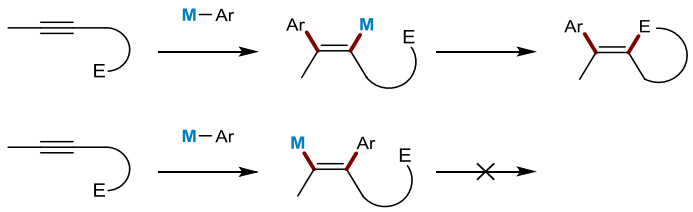
Therefore, initial investigations will be carried out using substrates that have been utilised in established carbometallative cyclisation reactions, however it is also hoped that the utilisation of first-row transition metals may also allow for the discovery of new reactivity rather than merely a cheaper alternative to exsisting catalysts.

2.0 Chapter 2: Results and Discussion

2.1 Nickel Catalysed *anti*-Carbometallative Cyclisations of Alkyne-Tethered Ketones

2.1.1 Aims and objectives

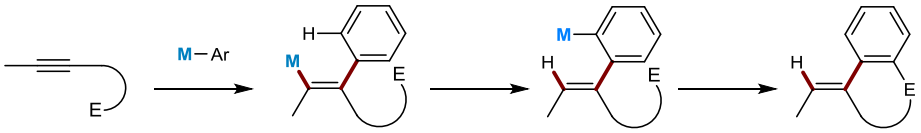
Arylative cyclisations, as discussed previously, rely on controlling the regioselectivity of the initial migratory insertion across the alkyne so that the resulting alkenyl metal species is proximal to the tethered electrophile and thus able to cyclise (scheme 74).



Scheme 74: The effect of the regioselectivity of migratory insertion on arylative cyclisation reactions.

Hayashi and co-workers, as discussed previously (scheme 49), were able to cyclise onto the distal electrophile due to the ability of the alkenylrhodium species to undergo a 1,4-migration.

The aim of this work was to investigate the arylative cyclisations of alkynyl-electrophiles enabled by a alkenyl-to-aryl 1,4-metal migration, utilising first row transition metals as catalysts.

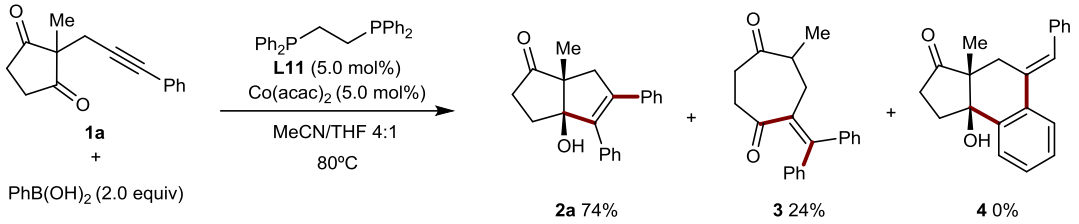


Scheme 75: Cyclisation onto the distal electrophile enabled by a 1,4-migration. M = first row transition metal.

The first row transitions metals are of interest in catalysis due to their much greater natural abundance making them a cheaper and more sustainable alternative to the precious metal catalysts which dominate much of this chemistry.

2.1.2 Cobalt-catalysed arylative cyclisations of alkynones

As discussed previously (1.2.4) cobalt has been used to successfully catalyse the additions of organometallics to alkynes (schemes 34 and 35) and a range of electrophiles (schemes 21 and 22) and undergo 1,4-metal migrations (scheme 38). Therefore, reported reaction conditions were tested on substrate **1a** with most giving little to no conversion of starting material. The conditions used by Cheng and co-workers in the addition of arylboronic acids to alkynes [28] (scheme 21) however gave good conversion of starting material (scheme 76).



Scheme 76: Initial result for the cobalt-catalysed arylative cyclisation of alkynone **1a**.

The minor product of the reaction **3** was a known product[65] resulting from addition across the alkyne followed by direct cyclisation onto the tethered ketone and ring expansion (figure 16).

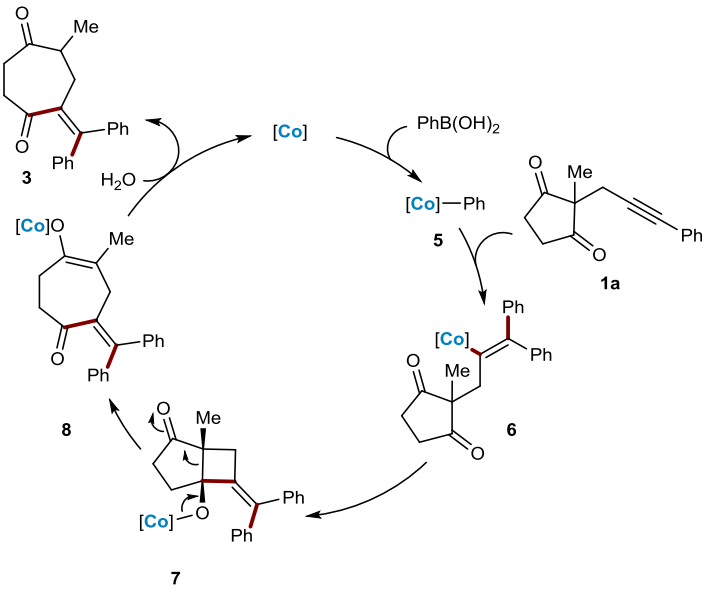


Figure 16: Proposed mechanism for the formation of product **3**.

The cobalt catalyst transmetallates with phenylboronic acid to give cobalt-aryl species **5**. Migratory insertion across the alkyne with the regioselectivity that places

that cobalt proximal to the tethered electrophile gives intermediate **6**. This alkenyl-cobalt species is then able to cyclise onto the tethered electrophile. The resulting 5,4-bicycle **7** then undergoes a retro-aldol type reaction/ring expansion leading to cycloheptadione product **8**. This reactivity has been observed in a number of rhodium-catalysed transformations.[65,66]

The structure of the major product **2a** was verified by single crystal X-ray crystallography.

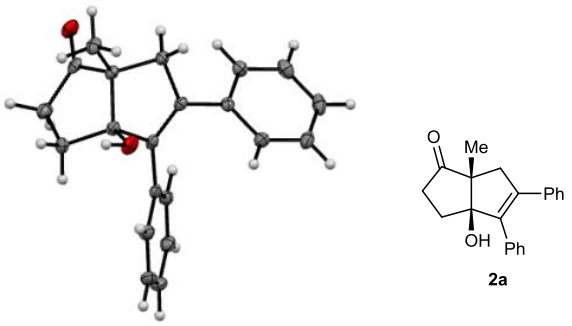


Figure 17: X-ray crystal structure of **2**. X-ray crystallography carried out by Dr W. Lewis.

This unexpected novel product **2a** was highly interesting, as it is the product of a formal *anti*-addition across the alkyne followed by cyclisation onto the diketone (figure 18).

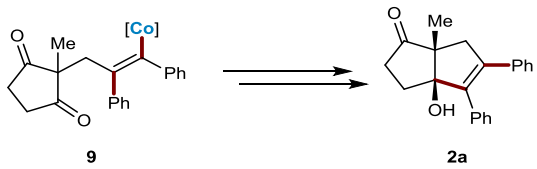


Figure 18: Formation of **8a** from the corresponding *anti*-carbometallation product **9**.

anti-Carbometallation products are observed by Cheng and co-workers in their hydroarylation work when the alkyne contains a heteroatom (scheme 36).[28]

Cheng and co-workers suggest that the alkenyl-cobalt species formed after the initial *syn*-selective migratory insertion of aryl-cobalt, intermediate **11** can readily isomerise via a 'cobalt carbene' type species **12**. They propose that electrons from cobalt are able to push back into the alkenyl π-system breaking the double bond and allowing free rotation. When a heteroatom is tethered to the alkyne this reversible

isomerisation is driven towards the *anti*-carbometallation product **13** by the coordinating ability of the heteroatom, making this isomer more favourable.

Based on their proposed mechanism the corresponding proposed catalytic cycle for our *anti*-carbometallative cyclisation is shown in figure 19.

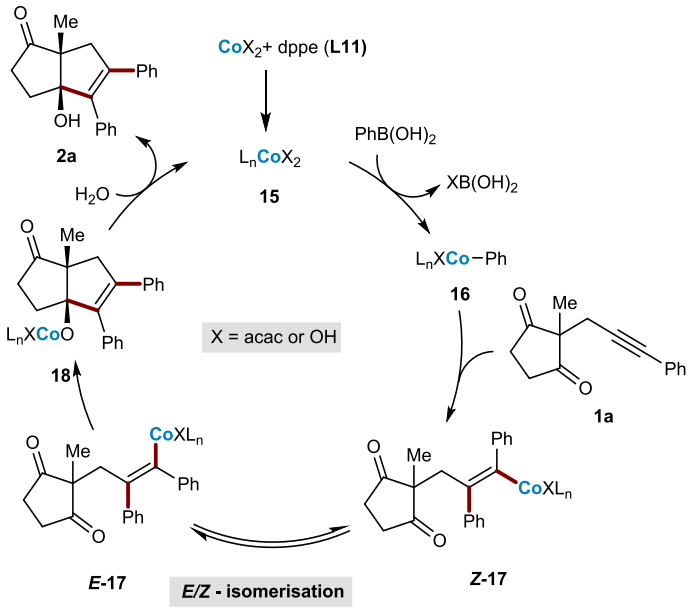


Figure 19: Proposed catalytic cycle for the cobalt-catalysed *anti*-carbometallative cyclisation of alkynone **1a**.

Initial formation of the active cobalt catalyst by combination with the ligand **L11** gives **15** which can transmetallate with phenylboronic acid to give arylcobalt species **16**. *Syn*-selective migratory insertion of **16** across the alkyne of **1a** would then give alkenylcobalt intermediate **17**. If this species is able to readily isomerise as proposed by Cheng[28], then *E*/*Z* isomerisation would be driven towards the *E*-isomer by the ability of this isomer to cyclise onto the tethered electrophile. Protonolysis of the cobalt-alkoxide **18** by water in the reaction mixture would give **2a** and regenerate the active catalyst.

Disappointingly, this result was difficult to reproduce and yields varying from 12-34% were obtained when repeating the reaction. To try and improve the reproducibility, a number of different solvents were tested. However, in almost all other solvent systems tried, the reaction was completely shut down. In MeCN or THF individually, only trace products were observed. This is in keeping with the

observations of Cheng and co-workers as they propose MeCN is important to facilitate the reaction, but the addition of THF is necessary to assist in solubilising the boronic acid.[28]

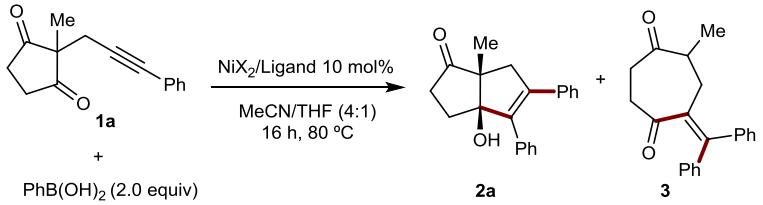
A number of different inorganic bases were tested along with a range of cobalt salts containing different counterions. Different batches of $Co(acac)_2$ were also tested in case salt purity was the issue. However the addition of base was detrimental to the reaction and no improvement was observed with various other Co salts.

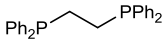
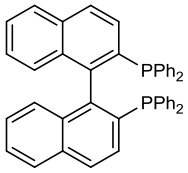
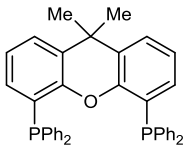
Therefore, whilst continuing to investigate the reasons behind this issue of reproducibility other first row transition metals were investigated.

2.1.3 Nickel as a catalyst for *anti*-carbometallative cyclisations

As previously discussed, Bao and co-workers reported nickel-catalysed additions of arylboronic acids to aldehydes, in an analogous fashion to the cobalt catalysed additions reported by the same group (scheme 18).[13] Due to the similarity in the reactivity of these two first-row transition metal salts in the nucleophilic additions of arylboronic acids, nickel (II) salts with a small selection of ligands (table 1) were tested in the reaction.

Table 1: Initial screen of nickel catalysts for the *anti*-carbometallative cyclisations of alkynone **1a**. Yield determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.



	Ligand	Conversion % (**2a**:**3**)	
		$Ni(acac)_2$	$Ni(OAc)_2$•$4H_2O$
L11		80% (1:1)	78% (4:3)
L6	PPh_3	64% (>20:1)	42% (>20:1)
L21	PCy_2Ph	31% (>20:1)	69% (5:2)
L14		46% (>20:1)	43% (>20:1)
L12		44% (>20:1)	41% (>20:1)

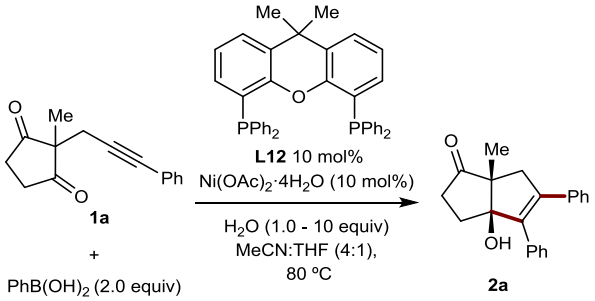
Pleasingly, nickel was also able to catalyse this reaction with both the 5,5-bicycle **2a** and the ring expansion product **3** being observed. To try and improve the efficiency of this reaction and the ratio of desired product **2a** to side product **3** various solvents, nickel salts and bases were tested in the reaction. However in all cases, deviating from the conditions used in table 1 was detrimental to the reaction. As both $Ni(OAc)_2 \cdot 4H_2O$ and $Ni(acac)_2$ gave very similar results, $Ni(OAc)_2 \cdot 4H_2O$ was arbitrarily chosen for subsequent investigations.

In all cases starting material remained in the mixture, implying that the reaction had halted. After working up the reaction an appreciable amount of the anhydride trimer of phenylboronic acid (phenyl boroxine) was observed in the ^{1}H NMR spectrum. This side product is the result of three molecules of boronic acid undergoing a condensation reaction. Although it was not clear whether this was formed during the work up or during the reaction, an investigation was carried out to see if this side product could be used in place of the boronic acid without affecting the yield of the

reaction. When phenyl boroxine was used in place of the boronic acid, little conversion to the desired product was observed and therefore the importance of water in the reaction was investigated.

A number of reactions were carried out where varying quantities of water were added to the reaction mixture (Table 2).

Table 2: Effect of added water to the yield of the reaction. Yield determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

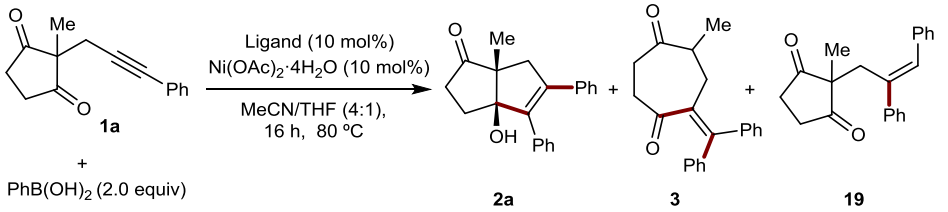


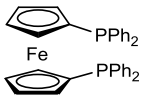
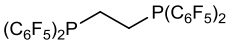
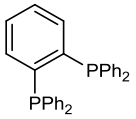
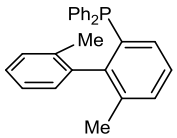
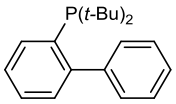
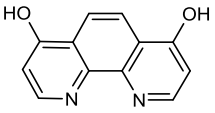
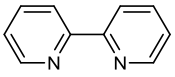
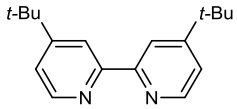
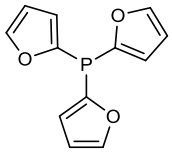
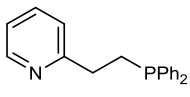
Entry	Equiv. H_2O	Yield (%)
1	0.0	41
2	1.0	19
3	3.0	24
4	5.0	25
5	7.0	8
6	10.0	0

However, the addition of water into the reaction mixture was detrimental to the reaction with all results being lower than those observed for the reaction with no added water (entry 1).

The effect of a wide variety of mono- and bidentate ligands were then screened to see if the conversion could be increased (Table 3).

Table 3: Screen of ligands with $Ni(OAc)\cdot 4H_2O$. Ratio of **2a**:**3**:**19** shown in parenthesis. [a] Reactions carried out by Dr C. A. Incerti-Pradillos. Yield determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.



No Ligand			$P(2\text{-Naphth})_3$
34% (0:0:1)	**L22** 38% (1:0:0)	**L1** 34% (1:0:0)	**L23** N.R
$P(4\text{-}FC_6H_4)_3$	$P(3,5\text{-}CF_3C_6H_3)_3$		$P(o\text{-tolyl})_3$
L24 53% (1:0:0)[a]	**L25** 35%(1:0:0)[a]	**L26** 88% (5:4:0)	**L27** 25% (1:0:0)
			
L28 N.R	**L29** N.R	**L30** 21% (0:0:1)[a]	**L31** 15% (0:0:1)[a]
			
L32 31% (0:0:1)[a]	**L33** 42% (1:0:0)[a]	**L34** >95% (13:1:0)	

Interestingly, $Ni(OAc)_2\cdot 4H_2O$ was able to catalyse the reaction without a ligand, phosphine ligands gave good conversions to the desired product **2a**, but with bulkier ligands were detrimental to the reaction. The bipyridine ligands **L30** – **L32** gave only product **19**. This product is the result of the alkenyl-metal species formed after migratory insertion undergoing protonolysis prior to isomerisation/cyclisation.

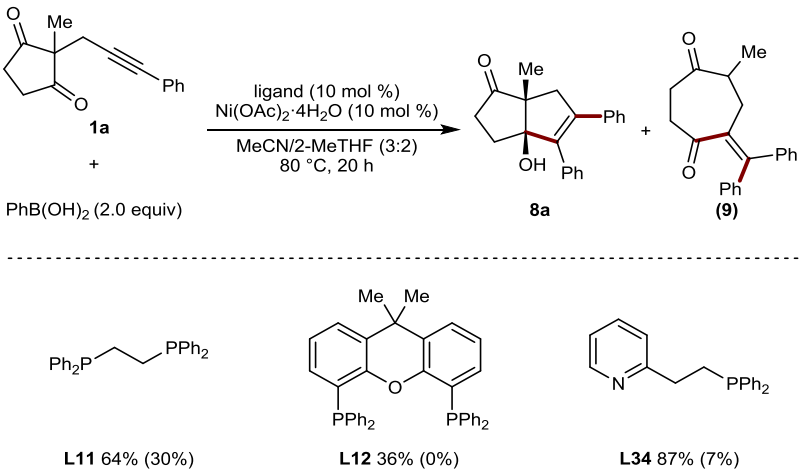
Pleasingly, P-N ligand pyphos (**L34**) gave full conversion of starting material, with desired product **2a** being formed with little side product observed. Encouraged by this excellent result, an attempted to lower the catalyst loading of the reaction was

carried out; however, with loadings less than 10%, an appreciable loss of yield was observed.

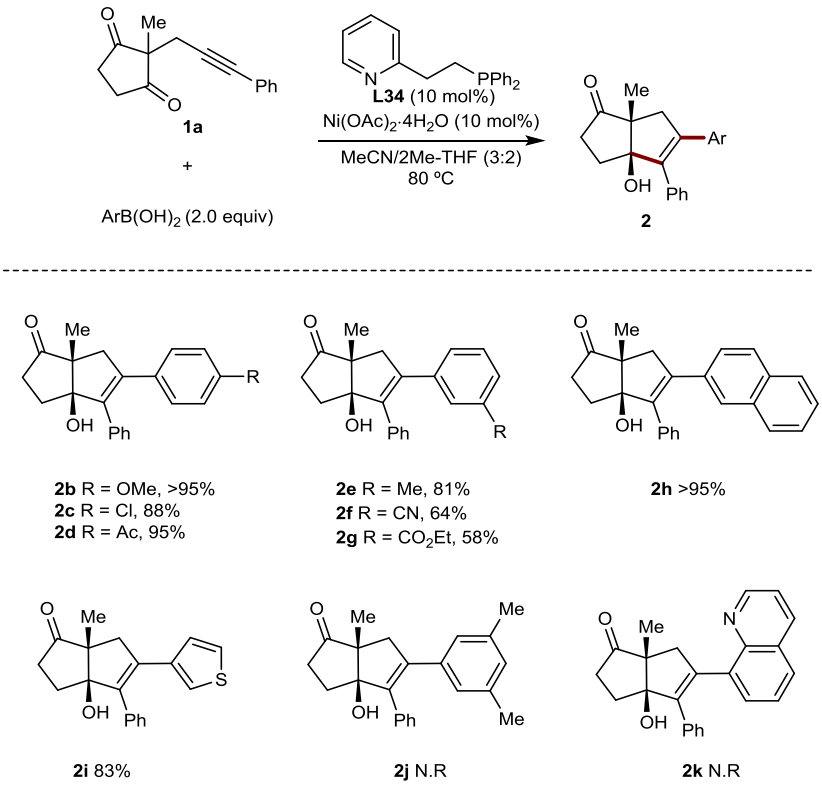
With these conditions in hand the scope of this chemistry was investigated. When the scope of the reaction with respect to the boronic acids was investigated it was observed that the solubility of the boronic acid was often an issue even at reaction temperatures of 80 °C. Because of this a 3:2 mixture of MeCN/2-MeTHF was used as this increased boronic acid solubility.

A small number of the successful ligands were re-screened under these new conditions, and pleasingly pyphos **L34** still gave **2a** in excellent yield (Table 4).

Table 4: Screen of successful ligands under new solvent conditions. Yield determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.



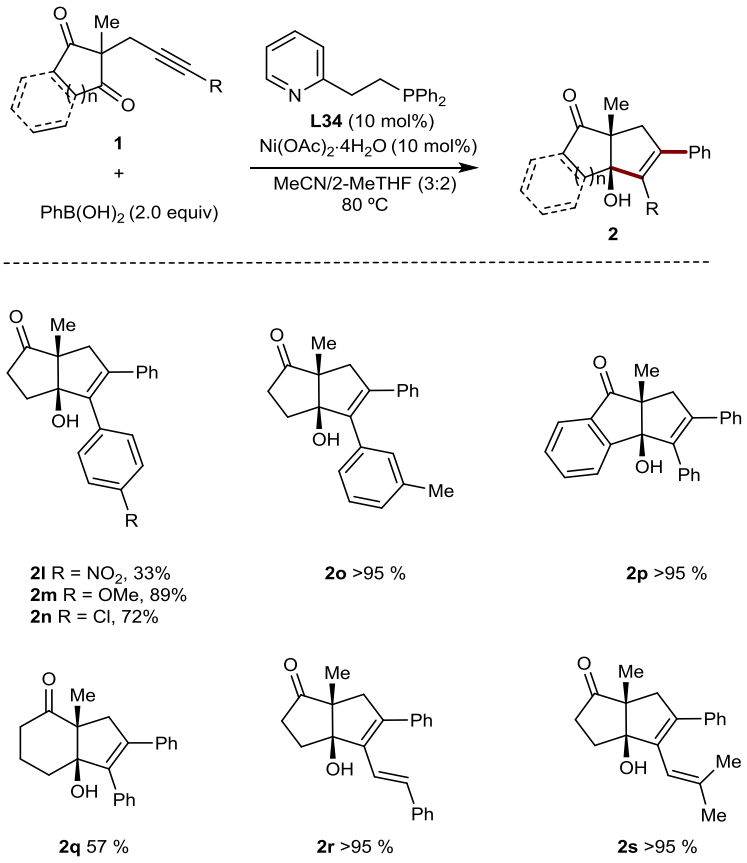
Initially the boronic acid scope in the reaction was investigated (scheme 77).



Scheme 77: Scope of arylboronic acids in the nickel-catalysed *anti*-carbometallative cyclisations of alkynone **1a**. Yield determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Para-substituents are tolerated well in the reaction with both electron-donating groups **2c**, and electron-withdrawing groups **2b** and **2d** giving high yields. *meta*-Substitution is also well tolerated with electron-withdrawing groups giving a slight decrease in the yield **2g**. Naphthylboronic acid was well tolerated in the case of **2h**; however, more sterically encumbered 3,5-dimethylphenylboronic acid was ineffective in the reaction. Pleasingly, heteroaryl boronic acids were also tolerated in the reaction with 3-thienylboronic acid giving **2i** in high yield. 8-Quinolinylboronic acid was also ineffective in this transformation. However, even in the MeCN/2-MeTHF solvent system this boronic acid was poorly soluble.

The scope of the diketone substrate was then investigated (scheme 78).



Scheme 78: Substrate scope for the arylative cyclisations of alkynones with phenylboronic acid. Yield determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

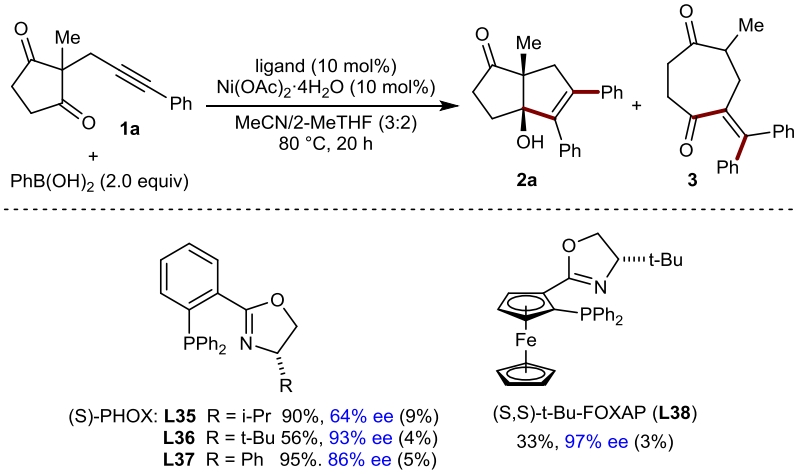
Substitution at the *para*-position of the aryl group was well-tolerated. However, a nitro group was detrimental to the yield **2l** but *meta*-substitution was well tolerated **2o**. Pleasingly, the electrophile could be altered with an indanedione also being suitable, leading to **2p** in excellent yield. The size of the diketone ring could be altered with cyclohexane-1,3-diones also being suitable leading to 6,5-bicycle **2q** in moderate yield. The substrates also were not limited to aryl-substituted alkynes with enynes also making excellent substrates for this reaction leading to diene products **2r** and **2s** in excellent yields.

2.1.4 Enantioselective variant

Encouraged by the success of this nickel-catalysed *anti*-carbometallative cyclisation, the possibility rendering it enantioselective was considered. By selectively adding into one of the ketones present in the substrate the electrophile is desymmetrised and thus enantioenriched alcohol products are formed. In order to control this addition, it

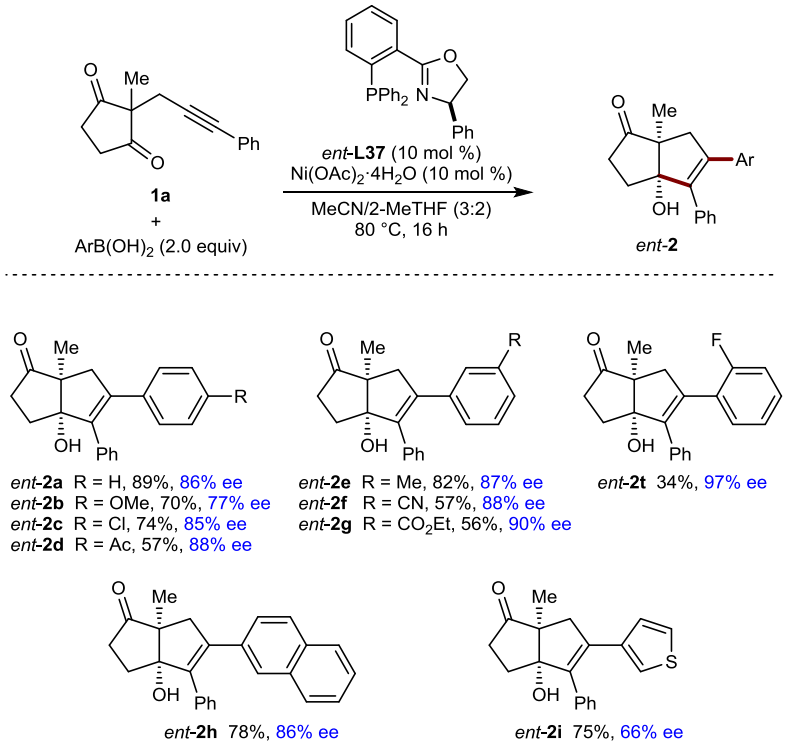
was envisioned that the use of the commercially available chiral phosphinooxazoline ligands with $Ni(OAc)_2 \cdot 4H_2O$ may give a similar reactivity to that observed with the achiral P-N ligand pyphos **L34** (Table 5).

Table 5: Screen of commercially available chiral phosphinooxazoline ligands. Yield determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.



To our delight, all of the commercially available chiral oxazoline ligands initially tested exhibited a similar activity and regioselectivity to that observed with pyphos. Pleasingly, high yields and enantioselectivities were obtained. **L37** was used for subsequent reaction evaluation as it gave the best balance of enantioselectivity and yield.

With these conditions in hand the scope of the enantioselective *anti*-carbometallative cyclisation of alkynones was explored. Again, a range of boronic acids in the reaction was initially investigated (scheme 79).



Scheme 79: Scope of arylboronic acids in the enantioselective *anti*-carbometallative cyclisation of alkynone **1a**.

As was observed for the achiral ligand system (scheme 77) the scope of arylboronic acids was broad. *para*-Substituted phenylboronic acids gave good yields and enantioselectivities. However, a slight drop in enantioselectivity was observed for the electron-rich boronic acid in *ent*-**2b**. *meta*-Substituents are also well tolerated giving good to excellent yields and good enantioselectivities. *ortho*-Substituents are well-tolerated, the yield of the reaction was moderate but the enantioselectivity of this transformation was excellent. Naphthylboronic acid was well-tolerated and pleasingly, heteroaryl 3-thienylboronic acid also reacted well but resulted in significantly lower enantioselectivity.

By growing single crystals of the enantioenriched products that were suitable for X-ray analysis the absolute stereochemistry of the products was determined (figure 20).

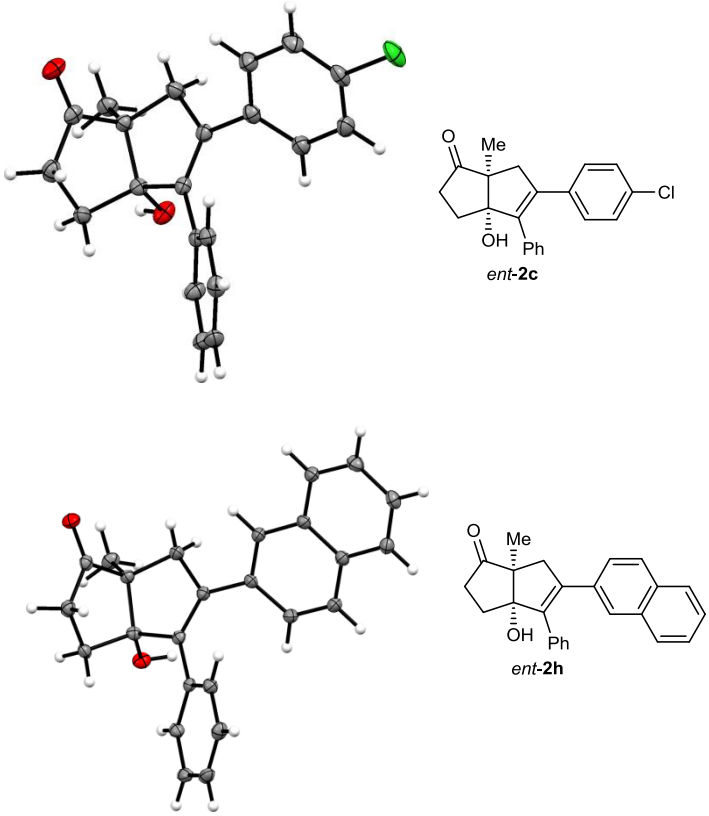
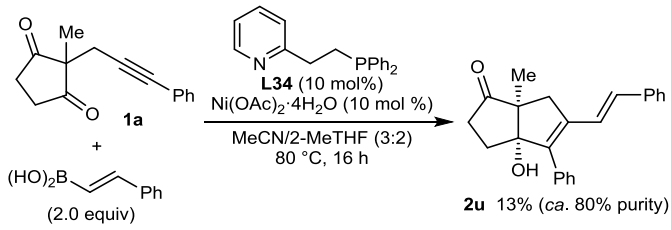


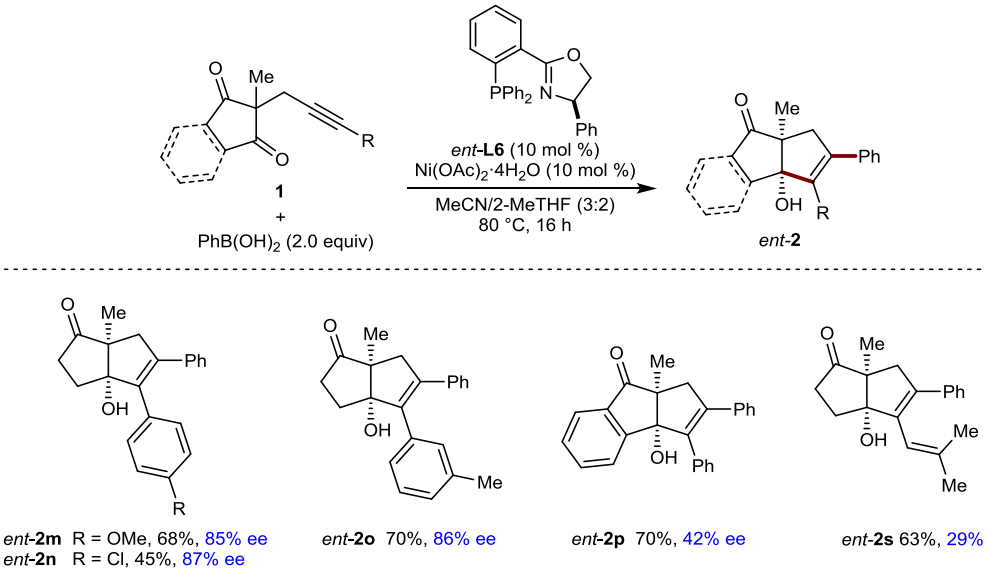
Figure 20: X-ray structures of enantioenriched products *ent*-**2c** and *ent*-**2h**. X-ray crystallography carried out by Dr W. Lewis.

The range of boronic acids sucessful in the reaction was broad, although, so far the boronic acids tested had been limited to arylboronic acids. Therefore, an alkenylboronic acid was investigated. With (*R*)-PhPhox ligand **L37**, no product was observed with only starting material recovered. However, using pyphos (**L34**) as the ligand the *anti*-carbometallative cyclisation product was isolated successfully, albeit in poor yield (scheme 80).



Scheme 80: *anti*-Carbometallative cyclisation of alkynone **1a** with alkenylboronic acid.

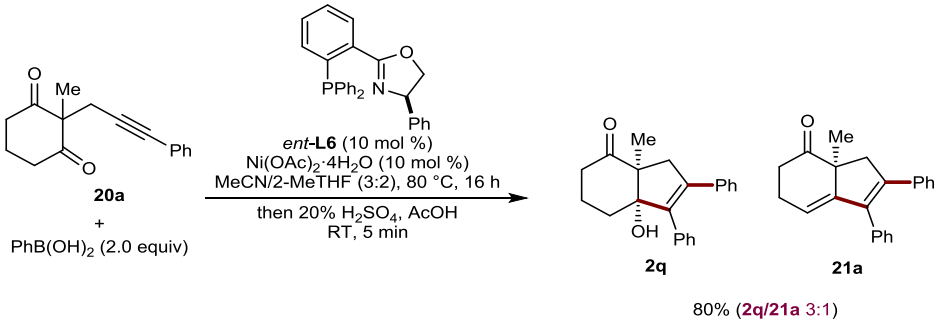
The scope of the diketone substrate was then investigated (scheme 81).



Scheme 81: Scope of alkynone in the enantioselective *anti*-carbometallative cyclisation with phenyl boronic acid.

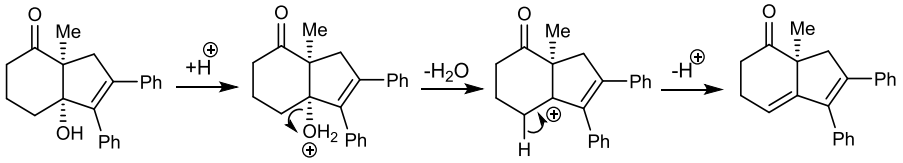
As with the Ni/pyphos system, substituents on the arylgroup on the alkyne were generally well-tolerated with moderate to good yields and good enantioselectivities being obtained. An indanedione substrate worked well giving *ent*-**2p** in good yield, but the enantioselectivity of this transformation was poor. Pleasingly enynes were also tolerated in this process giving *ent*-**2s** in good yield but poor enantioselecivity.

To investigate the scope of this chemistry further cyclohexa-1,3-dione substrate **20a** was tested. The conversion of this reaction was good, but the isolated product was a 3:1 mixture of **2q** and **21a** (scheme 82).



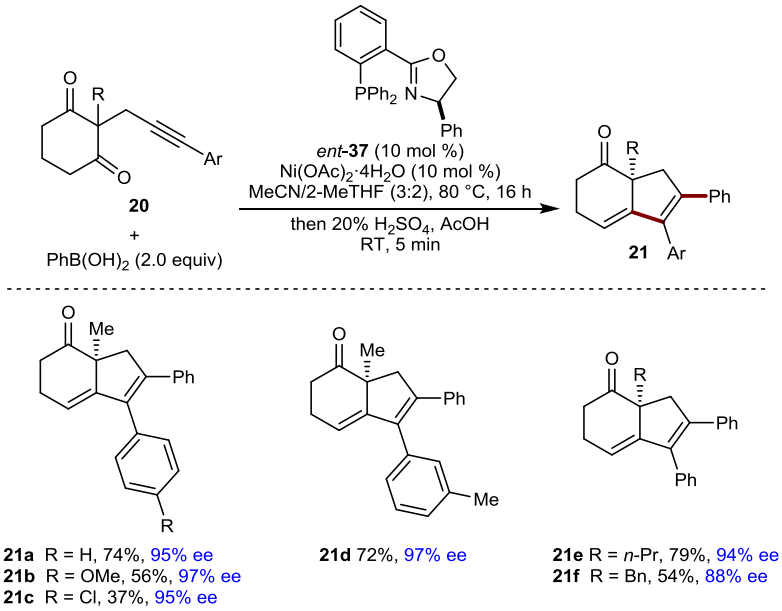
Scheme 82: *anti*-Carbometallative cyclisation of alkynyl-cyclohexa-1,3-dione **21a**. Yield based on molecular weight of alcohol **2q**.

Product **21** is the result of the cyclised product **2q** undergoing dehydration under the reactions conditions (scheme 83).



Scheme 83: Proposed mechanism for the partial dehydration of **2q** during the course of the reaction.

Due to this dehydration only happening partially, the crude reaction mixture was treated with 20% H_2SO_4/AcOH to drive the process to completion and give enantioenriched diene products **21** (scheme 84).

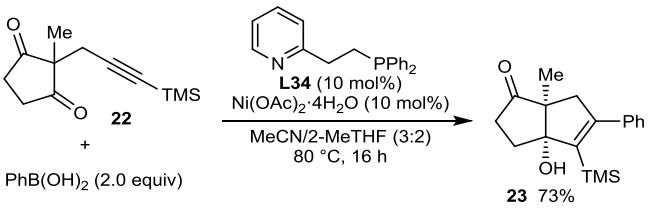


Scheme 84: Scope of alkynyl-cyclohexa-1,3-diones

The scope of the cyclohexanone substrates was good with respect to the aryl group on the alkyne, with good yields and excellent enantioselectivities obtained. When the substituent at the quaternary centre was altered to *n*-propyl **21e**, this was well-tolerated with good yield and excellent enantioselectivity. However, when this group was the sterically more encumbering benzyl group, the yield and enantioselectivity of the reaction dropped (**21f**).

2.1.5 Non-aryl substituted alkynes

Whilst exploring the scope of this chemistry the alkyne moiety of the substrate has been internal, and with an aryl or alkenyl group attached. Therefore substrate **22** was tested, which contains a silylalkyne (scheme 85).

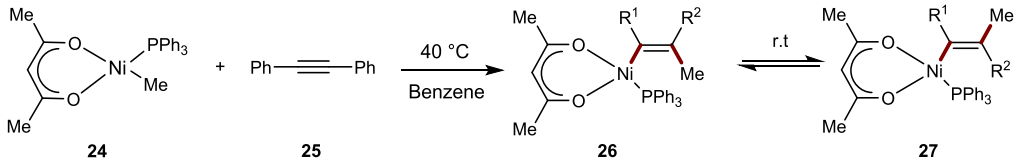


Scheme 85: Arylative cyclisation of silicon terminated alkynone **22**.

This substrate sucessfully gave cyclised product **23** when achiral conditions previously deployed were used, however none of the desired product was observed when ligand *ent*-**L37** was used. Potentially the increased steric demands of ligand *ent*-**L37** was incompatable with the bulky TMS group making the initial alkyne migratory insertion unfavourable.

2.1.6 Mechanistic insight

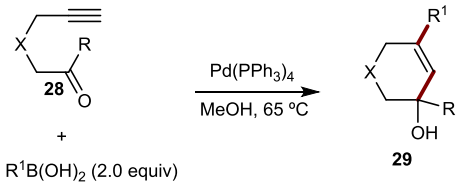
In 1981, Bergman and co-workers described that when an organo-nickel complex **24** adds across an alkyne **25**, the initial product formed is the *syn*-carbometallation product **26**.[52] This product is then able to isomerise to the *anti*-carbometallation products **27** at ambient temperature (scheme 86).



Scheme 86: Literature example of isomerisation of an alkenyl-nickel species.

This isomerisation is similar to the mechanism proposed by Cheng and co-workers for the *anti*-carbometallation products observed in their cobalt-catalysed hydroarylations discussed previously (scheme 36).[28]

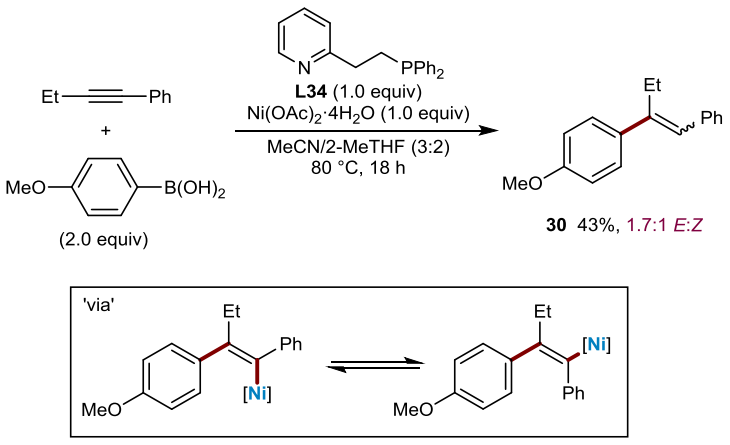
Palladium has also been used in *anti*-carbometallative cyclisations of alkynones **28** (scheme 87).[42]



Scheme 87: Palladium-catalysed *anti*-carbometallative cyclisations.

It is proposed that *anti*-carbometallation is achieved by an initial '*anti*-Wacker-type' addition of Pd(0) to the alkyne, followed by cross-coupling of the resulting alkenyl palladium species with the boronic acid (figure 8).

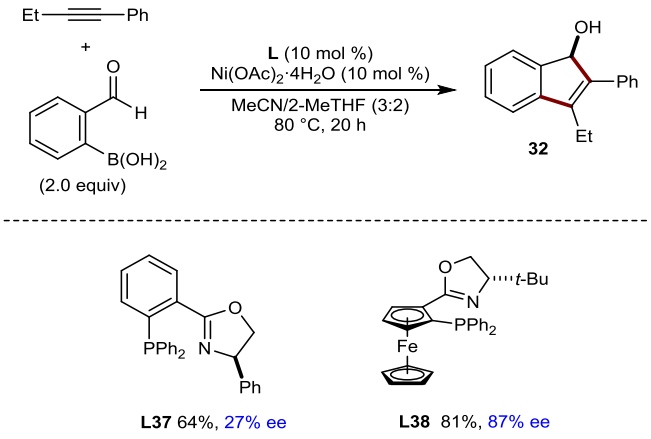
To investigate the mechanism of this nickel-catalysed process, Dr C. A. Incerti-Pradillos reacted internal alkyne 1-phenyl-1-butyne with 4-methoxyphenylboronic acid and a stoichiometric quantity of achiral nickel catalyst (scheme 88). Importantly 1-phenyl-1-butyne does not bear any potentially co-ordination heteroatom that may promote formation of the *anti*-carbometallation products as described by Cheng and co-workers (scheme 36).[28]



Scheme 88: Hydroarylation of internal alkyne. Reaction carried out by Dr C. A. Incerti-Pradillos.

The hydroarylation product **30** was isolated in moderate yield as a 1.7:1 mixture of *E/Z* isomers. The result of this reaction suggests that the alkenyl-metal species formed after initial addition across the alkyne is able to isomerise as observed by Bergman and co-workers and that a tethered electrophile is not required to gain *anti*-carbometallation products.[52]

Based on these results, it was hypothesised that this catalytic system may also be suitable for *syn*-carbometallative cyclisations of arylboronic acids bearing an *ortho*-electrophile such as 2-formylboronic acid, with internal alkynes such as 1-phenyl-1-butyne (scheme 89).



Scheme 89: Nickel-catalysed enantioselective *syn*-carbometallative cyclisation of 1-phenyl-1-butyne.

Pleasingly, with chiral oxazoline ligands, this reaction was successfully rendered enantioselective, demonstrating the power of this methodology to catalyse both *syn*- or *anti*-carbometallative cyclisations.

The results of these experiments show that the alkenyl-nickel species is able to give both *syn*- or *anti*-carbometallation products through a facile *E*/*Z*-isomerisation. Therefore the mechanism is more likely to be like that shown in figure 21, rather than one involving an '*anti*-Wacker type' addition (figure 8).

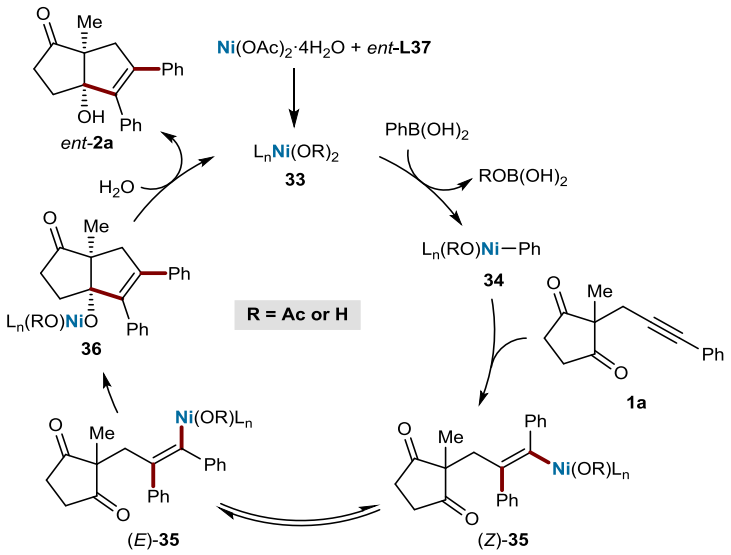
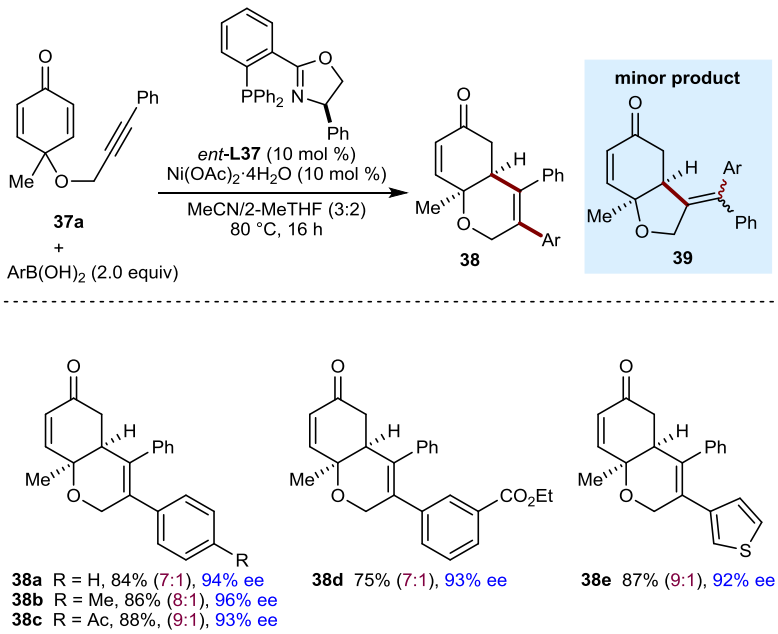


Figure 21: Proposed catalytic cycle.

Initially, the ligand chelates to the nickel salt to form the active complex **33**. This complex is able to transmetallate with $PhB(OH)_2$ to give arylnickel species **34**. *syn*-Selective migratory insertion of the alkyne of substrate **1a** gives alkenyl-nickel species (*Z*)-**35**, which undergoes reversible *E/Z*-isomerisation with alkenyl-nickel (*E*)-**35**. Cyclisation of this species onto the tethered ketone gives nickel-alkoxide **36** that, after protonolysis gives product *ent*-**2a** and regenerates the active nickel species. Presumably it is the cyclisation that drives the equilibrium of this reversible *E/Z*-isomerisation towards the *E*-isomer. Presumably the cycle for the alkynylcyclohexa-2,5-dienones is comparable, with protonation of the nickel enolate formed after cyclisation being the likely catalyst turnover step.

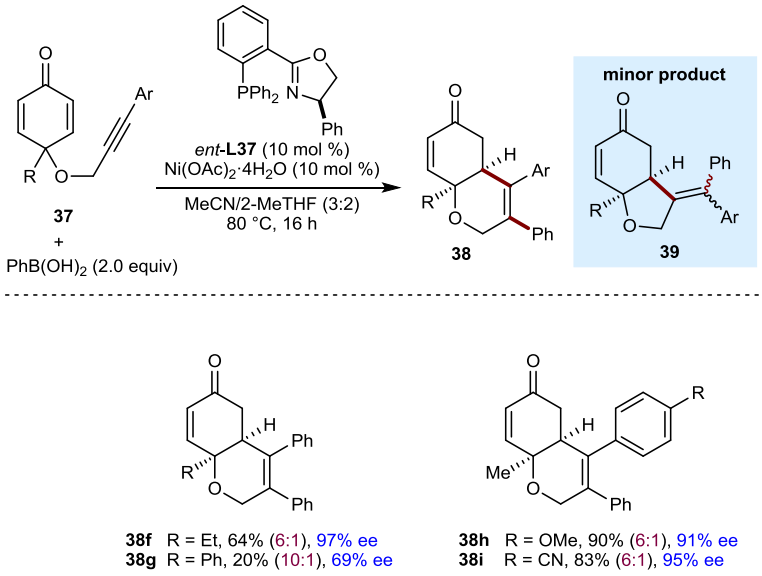
2.2 Further Development of Nickel-Catalysed *anti*-Carbometallative Cyclisations Carried out by Other Members of the Lam group

Driven by the success of this nickel-catalysed *anti*-carbometallative cyclisation process, work on expanding the scope of this chemistry was persued. The Lam group was successfully able to use the developed catalytic system to catalyse the *anti*-carbometallative cyclisations of alkynyl-dienones[68] (scheme 90).



Scheme 90: Scope of arylboronic acids in the *anti*-carbometallative cyclisation of alknylcyclohexa-2,5-dienone **37a.** Reactions carried out by Dr C. A. Incerti-Pradillos.

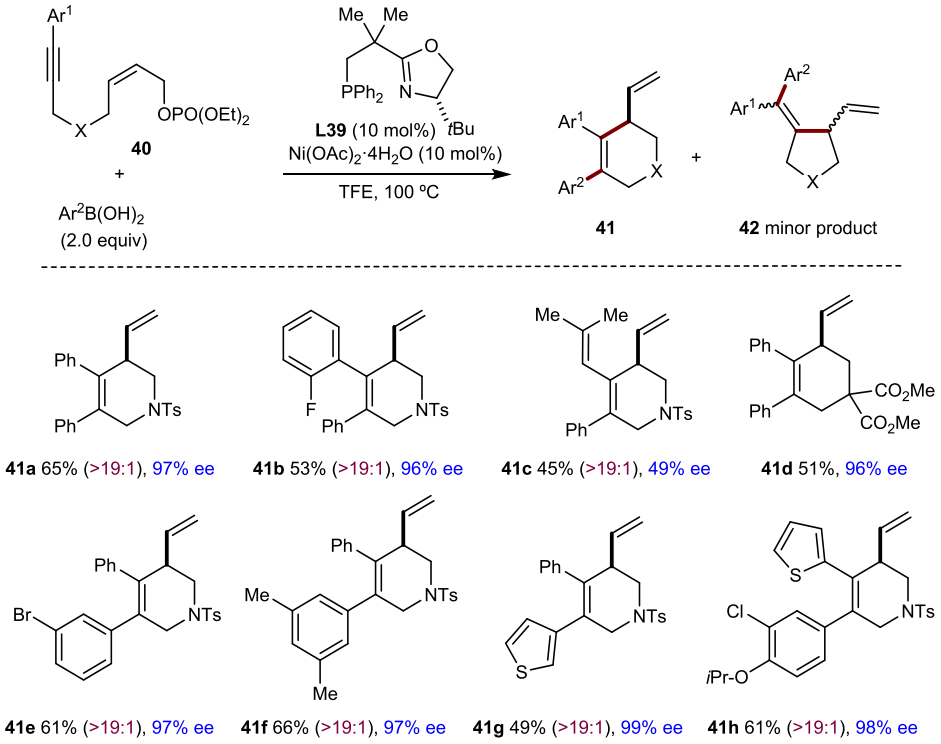
As with the diketone substrates the scope of this process with respect to the boronic acid component was broad giving the 5,5-bicycle product **33** in good yield and excellent enantioselectivity. The products were isolated as mixtures containing minor amounts of a side product formed when the boronic acid addition takes place with the opposite regioselectivity (**39**).



Scheme 91: Scope of alknylcyclohexa-2,5-dienones in the *anti*-carbometallative cyclisation with phenyl boronic acid. Reactions carried out by Dr C. A. Incerti-Pradillos.

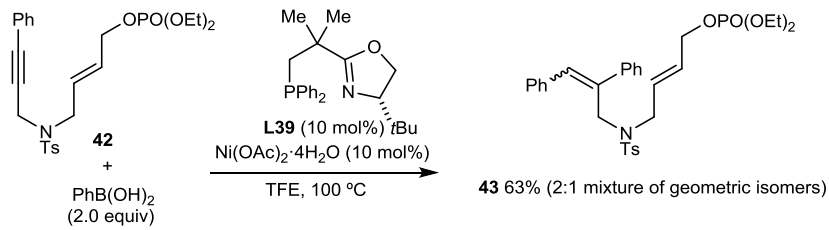
Electron rich and poor aryl-groups are well tolerated on the alkyne, however altering the group at the quaternary center to a phenyl group has an adverse effect on both the yield and enentioselectivity of the reaction.

Work within the Lam group extending the scope of this chemistry has also been carried out. By using 1,6-enynes bearing allylic leaving groups **40**, the nickel-catalysed *anti*-carbometallative cyclisations of these species was carried out (scheme 92).[67]



Scheme 92: Nickel-catalysed *anti*-carbometallative cyclisation of 1,6-enynes. Reactions carried out by C. Yap, Dr G. M. J. Lenagh-Snow and Dr. S. N. Karad

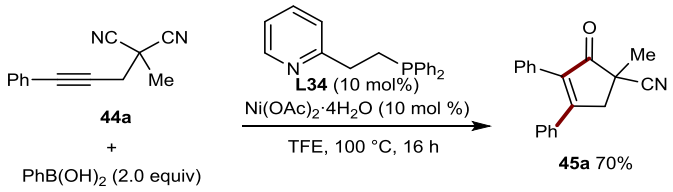
This reaction showed a similar tolerance to both substituents on the arylboronic acid and the alkyne as was observed in the *anti*-carbometallative cyclisations of alkyne-tethered diketones (schemes 80 and 82). Additionally, it was also observed that although alkenyl substituents on the alkyne were tolerated in place of an aryl group, this was detrimental to the enantioselectivity of the transformation. The geometry and nature of the allylic leaving group were also important for the efficiency of this process, when the *E*-allylic phosphate (**42)** is used no cyclisation products are observed (scheme 93).



Scheme 93: Reactivity of *E*-allylic phosphate. Reactions carried out by C. Yap, Dr G. M. J. Lenagh-Snow and Dr. S. N. Karad

2.3 Synthesis of Cyclopentanones *via* Nickel-Catalysed *anti*-Carbometallative Cyclisations

It was hypothesised that an alkyne with a tethered malononitrile moiety **44a** may be a suitable substrate for this chemistry. The feasibility of this reaction was studied using conditions employed in the *anti*-carbometallative vinylation of allylic phosphates (scheme 92),[67] where the use of TFE as a solvent was crucial for efficient reactivity (scheme 94).[67]



Scheme 94: Nickel-catalysed *anti*-carbometallative cyclisation of alkyne-tethered malononitrile. Reaction carried out by Dr S. N. Karad.

Pleasingly, this reaction worked efficiently to give cyclopentanone product **45a** in good yield. The proposed mechanism is shown in figure 23, and is based on those proposed for previous *anti*-carbometallative cyclisations (figure 21 and schemes 90, 91 and 92).[67,68]

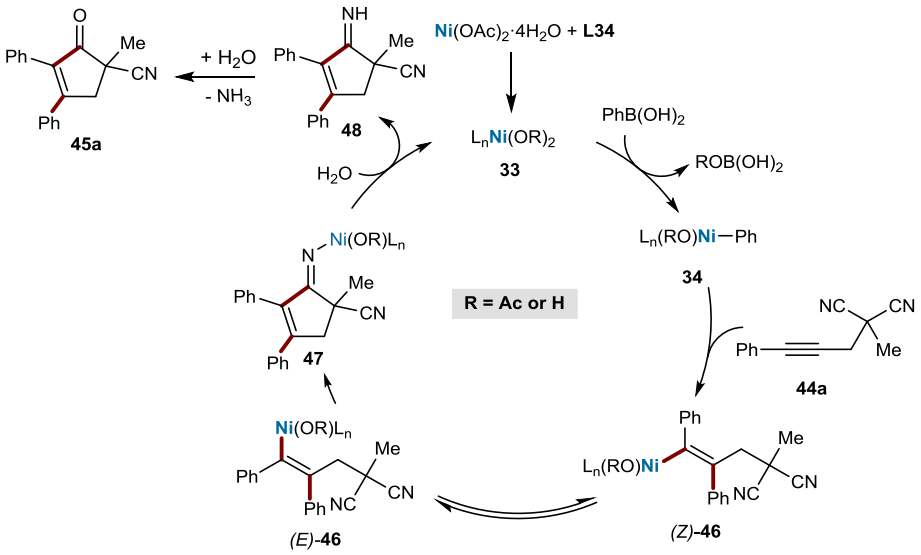


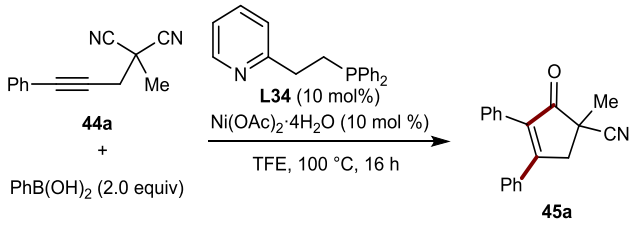
Figure 23: Proposed catalytic cycle.

Complexation of $Ni(OAc)_2 \cdot 4H_2O$ with the ligand gives active nickel catalyst **33**, which is able to transmetallate with phenylboronic acid to give arylnickel species **34**. *Syn*-selective migratory insertion across the alkyne of **44a** gives alkenylnickel species (*Z*)-**46**. The key step is the proposed reversible *E*/*Z* isomerisation of this species to give vinyl-nickel species (*E*)-**46** that is able to cyclise onto the tethered nitrile. The resulting imine released by protodemetallation by water in the reaction mixture regenerating the active nickel catalyst. Imine **48** is then hydrolysed to cyclopentanone **45a** during the course of the reaction and acidic workup.

2.3.1 Reaction Development

To check the necessity of the fluorinated solvent TFE, a screen of solvents was carried out (table 6).

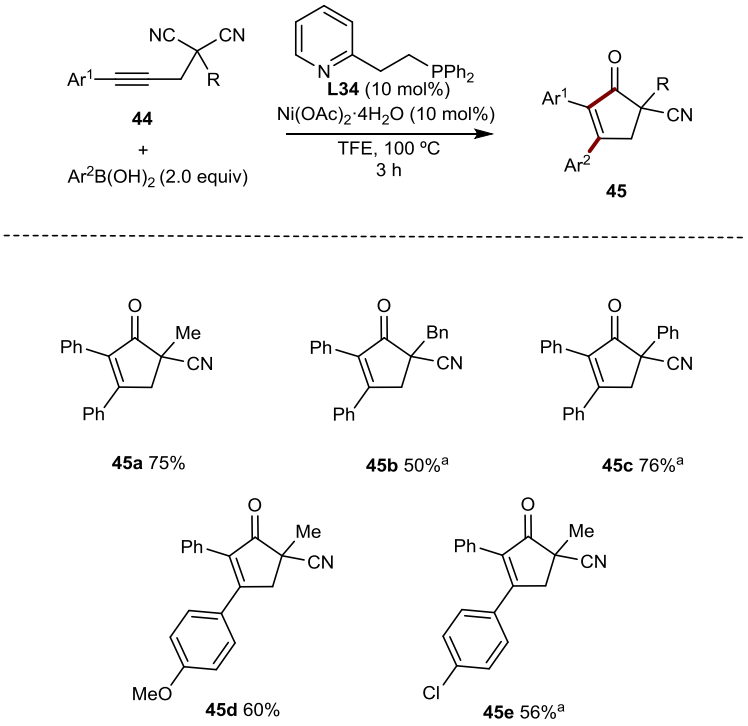
Table 6: Screen of solvents. [a] Reactions carried out by Dr S. N. Karad. Yield determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.



Entry	Solvent(s)	Yield (%)
1[a]	TFE	70
2[a]	THF	43
3[a]	1,4-Dioxane	trace
4	CH_3CN	17
5	2-MeTHF	18
6[a]	1,4-Dioxane/CH_3CN (2:3)	16
7	2-MeTHF/CH_3CN (2:3)	24

As with the *anti*-carbometallative alkenylation of allylic phosphates chemistry carried out in the group (scheme 91),[67] TFE was superior for this transformation with previously successful solvents mixtures used in this nickel chemistry giving the desired product only in poor yield.

These reaction conditions were then used on a small range of substrates to examine the scope of this racemic *anti*-carbometallative cyclisation (scheme 95).

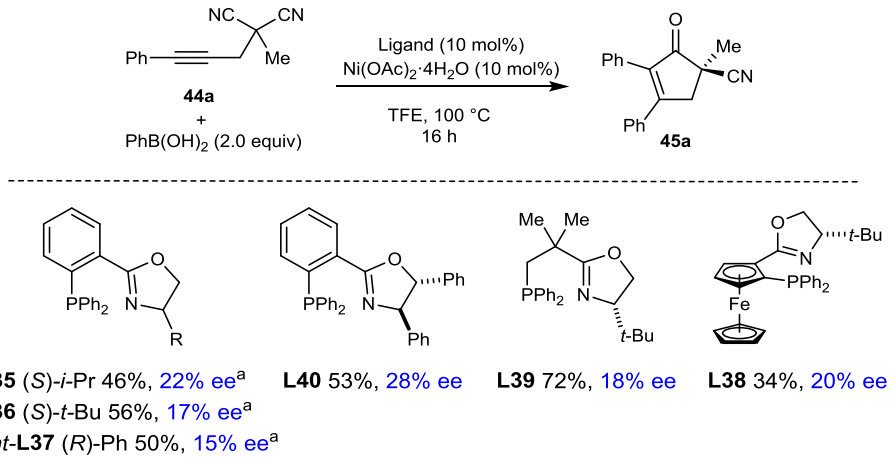


Scheme 95: Scope of *anti*-carbometallative cyclisation of alkyn-tethered malononitriles. [a] Approx. 90% purity.

Altering the quaternary centre of the substrate to bulkier phenyl and benzyl groups was tolerated to give cyclopentanones **45b** and **45c**. Electron-donating and electron-withdrawing groups were also well tolerated on the boronic acids **45d** and **45e**. However, in the case of **45b**, **45c** and **45e**, approx. 10% of an impurity was isolated alongside the desired product. This impurity appears to be the result of another arylation occurring to the product **45**; however, the structure of this impurity is unconfirmed.

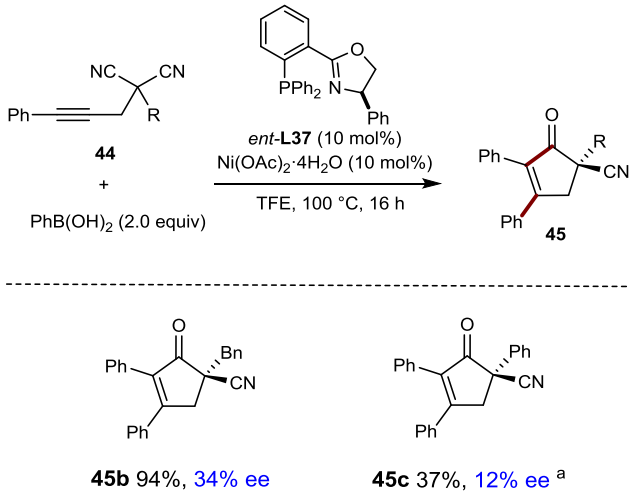
Pleased that the preliminary scope of this process appeared to be sufficiently general, attention turned to rendering the transformation enantioselective (table 7).

Table 7: Screen of chiral phosphinooxazoline ligands. [a] Reactions carried out by Dr S. N. Karad. Yield determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. Absolute stereochemistry not determined.



L35 (*S*)-*i*-Pr 46%, 22% ee[a] **L40** 53%, 28% ee **L39** 72%, 18% ee **L38** 34%, 20% ee
L36 (*S*)-*t*-Bu 56%, 17% ee[a]
ent-**L37** (*R*)-Ph 50%, 15% ee[a]

Testing a range of *P,N* ligands known to be the most efficient for the catalysis of these types of *anti*-carbometallative cyclisations (Table 5 and scheme 92) gave moderate to good yields for all those tested; however, in all cases the enantioselectivity was poor. Lowering the temperature had no effect on the enantioselectivity but was detrimental to the yield. It was hoped that increasing the steric bulk at the quaternary centre of the substrate may improve the enantioselectivity of the reaction (scheme 96). Unfortunately, there was little improvement for these substrates.



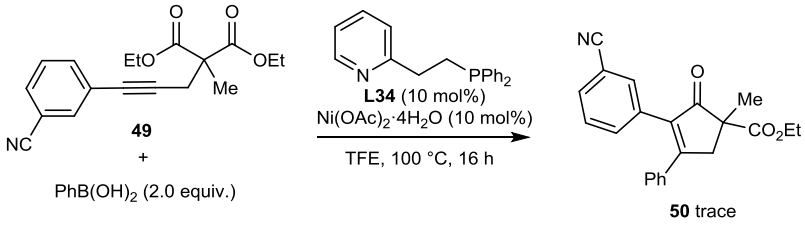
45b 94%, 34% ee **45c** 37%, 12% ee [a]

Scheme 96: Effect of quaternary centre. [a] Reaction carried out by Dr. S. N. Karad. Yield determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. Absolute stereochemistry not determined.

2.3.2 Alkynyl-Tethered Malonate Substrates for the Synthesis of Enantioenriched Cyclopentanones

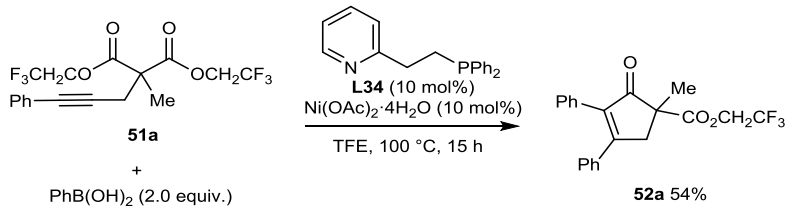
It was hypothesised that similar cyclopentanone products could be formed if the electrophile was replaced by a malonate. Due to the success of enantioselective additions to ketones in discussed in chapter 1 (schemes 80 and 82) it was hoped these substrates may give cyclopentenone products in increased enantioselectivities.

Substrate **49** had been previously prepared in the group by Dr. B. Partridge and therefore was chosen to test this hypothesis (scheme 97).



Scheme 97: Test of malonate substrate. Reaction carried out by Dr S. N. Karad.

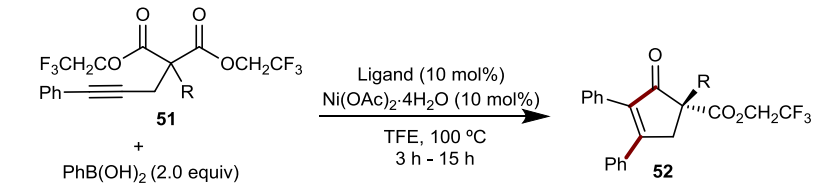
Although a trace amount of product was detectable by the presence of characteristic peaks in the ^{1}H NMR spectrum, it was not successfully isolated. It was postulated that the trifluoroethanol ester may be more electrophilic due to the electron-withdrawing nature of the CF_3 group and therefore malonate **51a** was tested in the reaction (scheme 98).

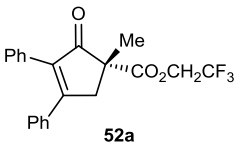
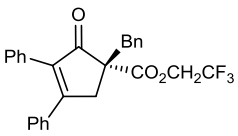
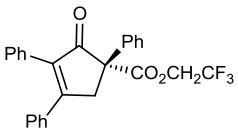


Scheme 98. Nickel-catalysed *anti*-carbometallative cyclisation of alkynyl-malonate. Reaction carried out by Dr. S. N. Karad. Yield determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

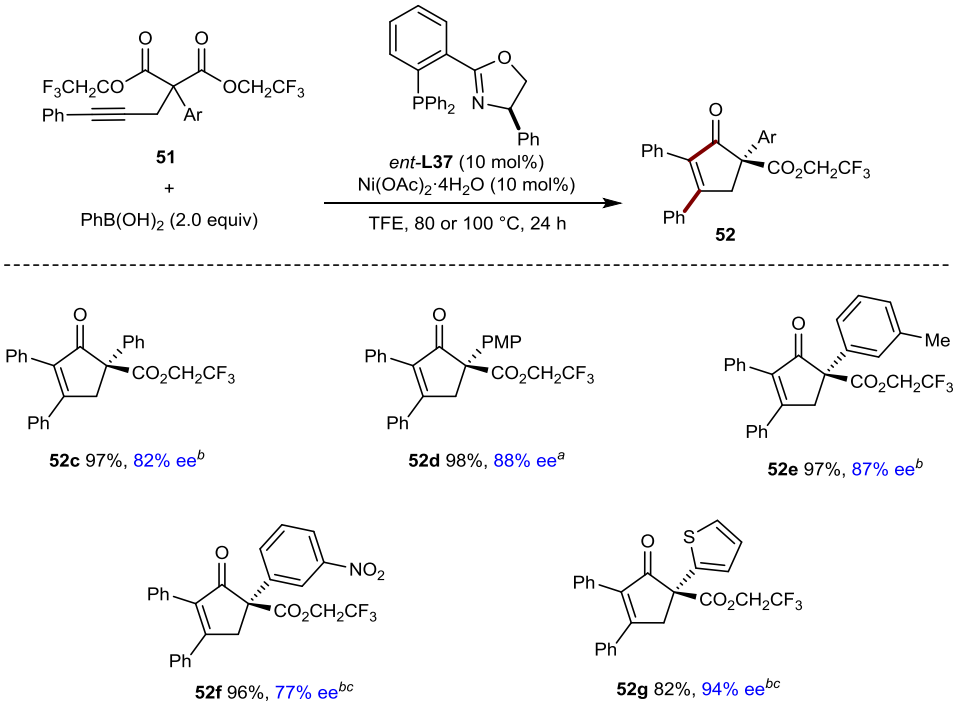
Pleasingly the reaction using achiral ligand pyphos worked well to give the desired product **52a**, a number of chiral *P*,*N* ligands were tested. The most successful ligands are shown in table 8. The effect of varying the substituent at the alpha-position on the substrate was also tested (table 8).

Table 8: Substrate and ligand screen. [a] Reaction carried out by Dr S. N. Karad. [b] Reaction carried out for 3 h. Yield determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. Absolute stereochemistry not determined.



	ent-**L37**	**L36**	**L39**
 **52a**	99%, 29% ee [ab]	59%, 10% ee [ab]	38%, 58% ee [ab]
 **52b**	88%, 0% ee	73%, 19% ee	50%, 53% ee
 **52c**	99%, 80% ee [ab]	87%, 65% ee [ab]	49%, 64% ee [ab]

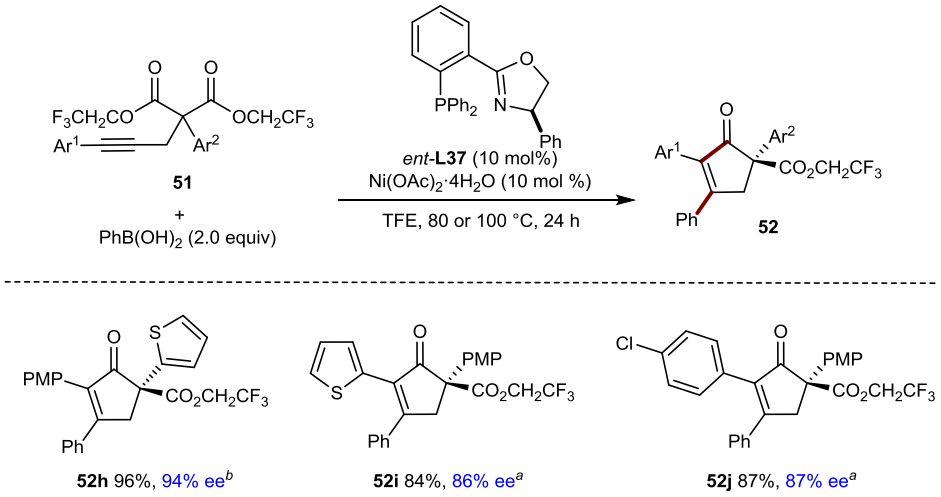
When the substituent at the alpha-position is alkyl **52a** and **52b**, **L40** gave the highest enantioselectivity, although yields are modest. When the alpha-position bears an aromatic group however, cyclopentenone **52c** was formed in quantitative yield and satisfactory enantioselectivity, using commercially available ligand *ent*-**L37**. Encouraged by this result, the scope of this process with varying aromatic substituents at the alpha-position was examined (scheme 99).



Scheme 99: Scope of aryl substituent at the alpha-position. [a] Reaction at 100 °C, [b] Reaction at 80 °C, [c] Reaction carried out by Dr S. N. Karad. Absolute stereochemistry not determined.

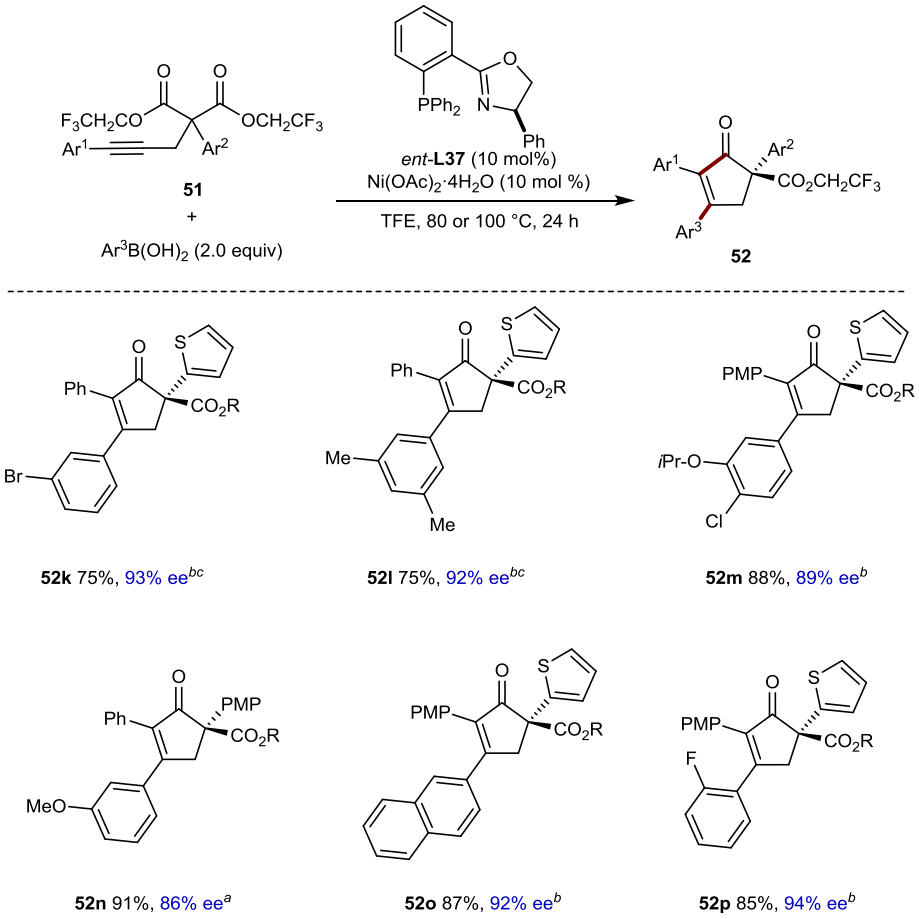
Pleasingly the reaction was tolerant to a number of different aryl groups at the alpha-position. The more electron-rich *para*-methoxyphenyl (PMP), group gave an increase in enantioselectivity as did the more sterically encumbered 3-methylphenyl group (**52d** and **52e** respectively). The electron-poor 3-nitrophenyl group gave a notable loss of enantiometric excess but the yield remained high. Pleasingly, heteroaryl groups were also tolerated and 2-thienyl at the alpha-position gave cyclopentenone **52g** in good yield and high enantiomeric excess. The reason for the considerable increase in enantiomeric excess for the thiophene containing substrate is currently unknown; however, the coordinating ability of the sulfur may play a role.

The scope of this process with respect to the substituent on the alkyne was then explored (scheme 100).



Scheme 100: Scope of alkyne on substrate. [a] Reaction at 100 °C, [b] Reaction at 80 °C. Absolute stereochemistry not determined.

Both electron-rich and electron-poor aryl groups are well-tolerated on the alkyne (**52h** and **52j** respectively). Pleasingly, the alkyne can also bear a heteroaromatic substituent **52i**. With the scope of this process appearing to be tolerant to different aryl groups on the alkyne, a range of boronic acids were also investigated (scheme 101).



Scheme 101: Scope of arylboronic acids. [a] Reaction at 100 °C, [b] Reaction at 80 °C, [c] Reaction carried out by Dr S. N. Karad. Absolute stereochemistry not determined.

Pleasingly, the process was broadly tolerant of all arylboronic acids tested giving the cyclopentenone products in very high yields and good enantiomeric excesses.

Based on our previous work in this area of *anti*-carbometallative cyclisations (figure 21) the proposed catalytic cycle is shown in figure 24.

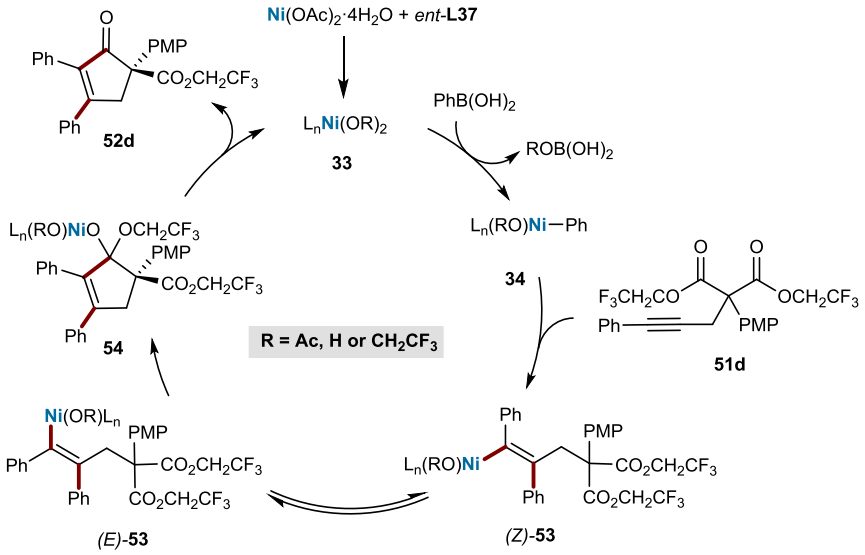
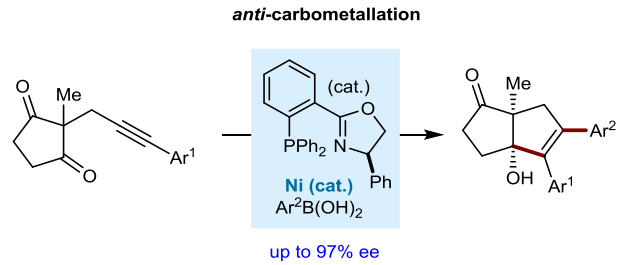


Figure 24: Proposed catalytic cycle.

Substrate **51d** is used as a representative example. The catalytically active nickel complex is formed *in situ* by the combination of the nickel salt and chiral ligand *ent*-**L37**. This species is able to transmetallate with phenylboronic acid to give arylnickel intermediate **34**. *Syn*-carbometallation of the alkyne to give (*Z*)-**53** is followed by reversible *E*/*Z*-isomerisation to the intermediate (*E*)-**53**. This alkenylnickel intermediate can cyclise onto the tethered ester. Intermediate **54** then collapses to give product **52d** and regenerate the active catalytic species.

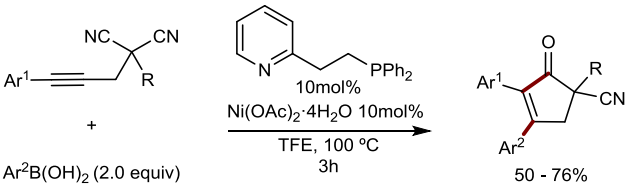
2.4 Conclusions and Future Work

The enantioselective *anti*-carbometallative cyclisations of alkyne-tethered electrophiles has been described, giving chiral bicycles in good yields and enantioselectivities (scheme 102).



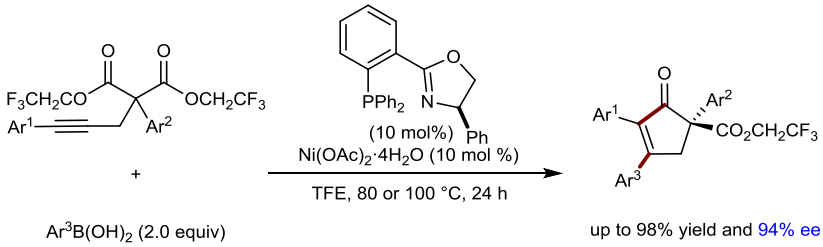
Scheme 102: Summary of nickel-catalysed *anti*-carbometallative cyclisations of alkyne-tethered diketones

The formation of cyclopentenone products by utilising the nickel-catalysed *anti*-carbometallative cyclisations of alkynes tethered to malononitriles is described (scheme 103). The process gives the desired products in good yields; however, an enantioselective variant of this reaction proved difficult to achieve.



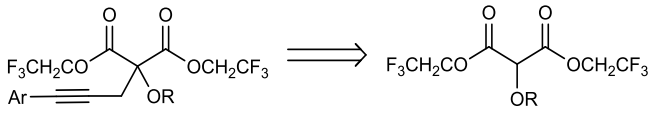
Scheme 103: Nickel-catalysed *anti*-carbometallative cyclisation of alkynyl-malononitriles.

The formation of related products by using malonate tethered alkynes is also described. Pleasingly, this related process gives cyclopentenone products in excellent yields and high enantiomeric excess (scheme 104).



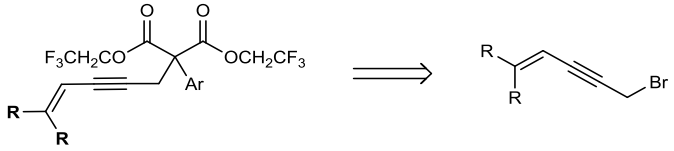
Scheme 104: Nickel-catalysed enantioselective *anti*-carbometallative cyclisation of alkynyl-malonates.

Currently the process is limited to aryl-rich substrates. The aim is to overcome some of these limitations by changing the nature of the alpha-substituent (scheme 105).



Scheme 105: Possible substrate to overcome the need for an aryl group at the alpha position.

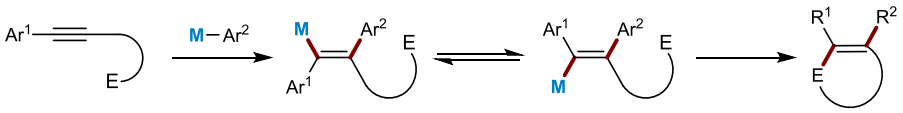
By having a heteroatom at the α-position it is hoped that this may interact with the catalyst and affect the enantioselectivity of the nucleophilic addition. Expanding the substrate scope by synthesising substrates with substituents on the alkyne other than aryl groups is also an aim (scheme 106).



Scheme 106: Possible substrate to overcome the need for an aryl group on the alkyne.

By trying to utilise alkyl- and alkenylboronic acids it is hoped the scope of this process can be improved.

The novel *anti*-carbometallation products are proposed to arise through a reversible *E*/*Z*-isomerisation of the alkenylnickel species formed after an initial *syn*-selective migratory insertion, the reversible isomerisation is proposed to be driven towards the *E*-isomer by the ability this isomer to cyclise onto the tethered electrophile (scheme 107).

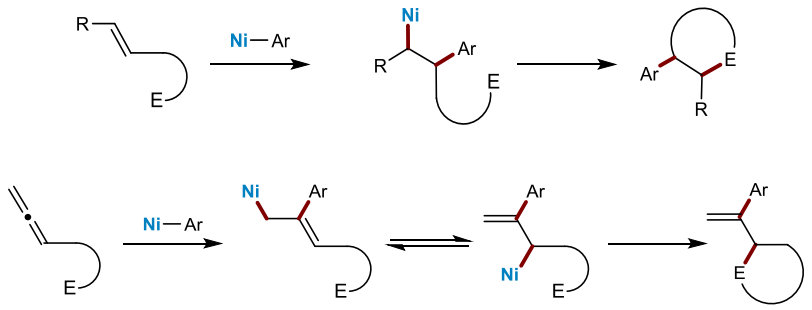


Scheme 107: General reaction motif for *anti*-carbometallative cyclisations.

Therefore, varying the nature of the tethered electrophile to further expand the scope of this chemistry would be of great interest. When compared to the wide scope that is demonstrated for rhodium- and palladium-catalysed *syn*-selective carbometallative cyclisations the potential of this methodology becomes apparent.

Whilst the electrophilic component could be altered, changing the π-unsaturated component tethered to the electrophile could also give some interesting reactivity.

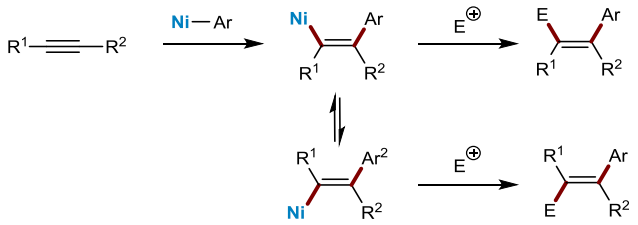
Alkenes and allenes as coupling partners may also give rise to some interesting carbometallative cyclisation products (scheme 108).



Scheme 108: Possible arylative cyclisations of alkenyl- and allenyl-electrophiles.

The nickel-catalysed *syn*-selective arylative cyclisation of 2-formylphenyl boronic acid was also demonstrated (scheme 89). These types of annulation reactions have been reported for a number of the precious metals; however, further development of a first row transition metal catalysed variant offers a valuable more-sustainable alternative.

In addition to exploring the scope of these intramolecular tandem processes, the development of an intermolecular variant where the alkyne and the electrophile are not tethered would also be of interest (scheme 109).



Scheme 109: Nickel-catalysed intermolecular three-component coupling outlining the challenge faced due to the facile *E*/*Z*-isomerisation.

The challenge of such a reaction would be controlling the geometry of the alkenylnickel intermediate prior to electrophilic attack. It is however clear that further development of this inexpensive air-stable nickel catalyst could lead to some interesting and novel reactivity, to complement the existing methodologies of the precious metals.

Chapter 3: Experimental

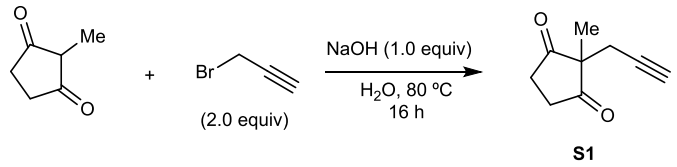
3.1 General Information

All air-sensitive reactions were carried out under a nitrogen atmosphere using oven-dried apparatus. Anhydrous THF was dried and purified by passage through activated alumina columns using a solvent purification system. Anhydrous MeCN and 2-MeTHF were purchased and used as received from Acros Organics. All commercially available reagents were used as received unless otherwise stated. Arylboronic acids were used as received unless the sample contained >10% boroxine as determined by ^{1}H NMR analysis. In this case, the boronic acid was stirred in a mixture of Et_2O and water for 30 min. The organic phase was separated, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give the corresponding boronic acid which was used without further purification. Pet. ether refers to petroleum ether boiling point 40-60 °C. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien $60F_{254}$ 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. Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. The solvent of recrystallization is reported in parentheses. Infra-red (IR) spectra were recorded on eithera Shimadzu IRAffinity-1, Nicolet Avatar 360 or a Bruker alpha FT instrument on the neat compound. NMR spectra were acquired on Bruker AV500, Bruker AV400, Bruker AV(III)400HD, Bruker DPX400, Bruker DPX300, Bruker Ascent500 or Bruker Ascent400 spectrometer. ^{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). All chemical shifts are reported in parts per million (ppm). For $CDCl_3$, the shifts are referenced to 7.27 ppm for ^{1}H NMR spectroscopy and 77.0 ppm for ^{13}C NMR spectroscopy. Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q (quartet), app (apparent), br (broad) and m (multiplet). 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). X-ray diffraction data were collected at 120 K on an Agilent SuperNova diffractometer using CuKα radiation. Chiral HPLC analysis was performed on an Agilent 1290

series or Agilent 1260 series instrument using 4.6 × 250 mm columns. References after compound title correspond to those previously reported in the literature.

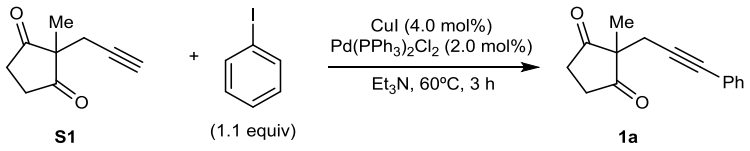
3.2 Synthesis of Substrates

2-Methyl-2-(prop-2-yn-1-yl)cyclopentane-1,3-dione (S1)[65]



A 2M solution of sodium hydroxide (45mL, 90.0 mmol) was added to a suspension of 2-methyl-1,3-dicyclopentadiene (10.1 g, 90.0 mmol) in water (45 mL). Propargyl bromide (21.4 g, 180.0 mmol) was then added and the solution was stirred at 80 °C for 16 h. The reaction was cooled to room temperature, and the mixture extracted with EtOAc (2 × 30 mL), washed with water (20 mL) and brine (20 mL). The combined organic layers were then dried ($MgSO_4$) and concentrated under reduced pressure. The residue was then purified by column chromatography (20% EtOAc/pet. ether) to give alkyndione **S1** (10.0 g, 74%) as a white solid. m.p. 60-62°C (Et_2O) R_f = 0.33 (30% EtOAc/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.82-2.66 (4H, m, C**H**$_2$C**H**$_2$), 2.39 (2H, d, *J* = 2.7 Hz, C**H**$_2$C≡CH), 1.94 (1H, t, *J* = 2.7 Hz, CH$_2$C≡C**H**), 1.06 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.1 (2 × C), 78.8 (C), 70.7 (CH), 55.3 (C), 35.8 (2 × CH_2), 24.3 (CH_2), 19.3 (CH_3).

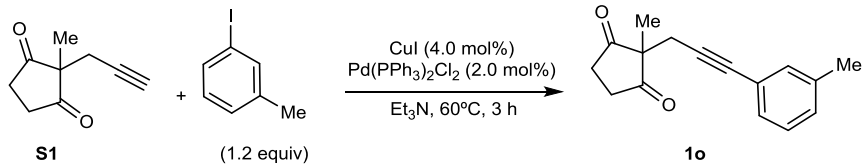
2-Methyl-2-(3-phenylprop-2-yn-1-yl)cyclopentane-1,3-dione (1a)[65]



2-Methyl-2-propargyl-1,3-cyclopentanedione **S1** (1.0 g, 6.66 mmol) was added to a solution of $Pd(PPh_3)_2Cl_2$ (93.0 mg, 0.133 mmol) and CuI (50.7 mg, 0.266 mmol) in Et_3N (33 mL). Iodobenzene (1.63 g, 7.99 mmol) was added and the mixture was stirred at 60 °C for 2 h. The reaction was cooled to room temperature, water (20 mL) and saturated aqueous NH_4Cl (5 mL) were added, and the mixture was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (40 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography (0-20% EtOAc/pet. ether) to give alkyndione **1a**

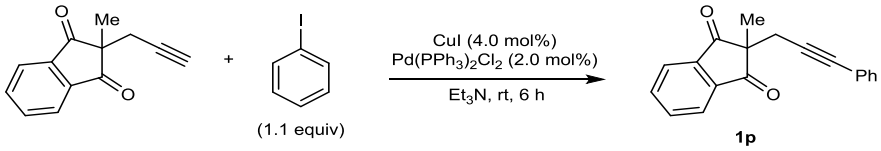
(0.99g, 66%) as a pale yellow solid m.p. 63-66 °C (Et_2O). R_f = 0.35 (30% EtOAc/pet. ether), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.27 (5H, m, Ar**H**), 2.85 (4H, s, C**H**$_2$C**H**$_2$), 2.7 (2H, s, C**H**$_2$C≡C), 1.19 (3H, s, C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.6 (2 × C), 131.6 (2 × CH), 128.31 (CH), 128.28 (2 × CH), 122.5 (C), 84.0 (C), 82.9 (C), 55.5 (C), 36.0 (2 × CH_2), 26.0 (CH_2), 18.9 (CH_3).

2-Methyl-2-[3-(3-methylphenyl)prop-2-yn-1-yl]cyclopentane-1,3-dione (1o)[65]



2-Methyl-2-propargyl-1,3-cyclopentanedione **S1** (1.50 g, 10.0 mmol) was added to a solution of $Pd(PPh_3)_2Cl_2$ (140 mg, 0.199 mmol), CuI (75.8 mg, 0.398 mmol), and Et_3N (2.4 mL, 17.2 mmol) in DMSO (20 mL). A solution of 3-bromotoluene (1.33 mL, 11.0 mmol) in DMSO (10 mL) was added and the mixture was stirred at 90 °C for 2 h. The reaction was cooled to room temperature, water (50 mL) was added, and the mixture was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with 10% aqueous HCl (3 × 20 mL), dried (Na_2SO_4) and concentrated *under reduced pressure*. The residue was purified by column chromatography (10% EtOAc/pet. ether) to give alkyndione **1o** (0.851g, 35%) as a brown oil. R_f = 0.48 (30% EtOAc/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16-7.09 (4H, m, Ar**H**), 2.90-2.77 (4H, s, C**H**$_2$C**H**$_2$), 2.66 (2H, s, C**H**$_2$C≡C), 2.28 (3H, s, ArC**H**$_3$), 1.15 (3H, s, CH_2C(C**H**$_3$)CO); ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.6 (2 × C), 138.0 (C), 132.2 (CH), 129.2 (CH), 128.7 (CH), 128.2 (CH), 122.3 (C), 83.5 (C), 83.0 (C), 55.5 (C), 36.0 (2 × CH_2), 26.0 (CH_3), 21.1 (CH_2), 18.9 (CH_3).

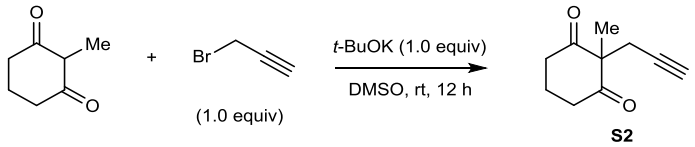
2-Methyl-2-(3-phenylprop-2-yn-1-yl)-2,3-dihydro-1H-indene-1,3-dione (1p)[65]



2-Methyl-2-propynyl-1,3-indandione (401 mg, 2.02 mmol) was added to a solution of $Pd(PPh_3)_2Cl_2$ (28.4 mg, 0.04 mmol) and CuI (15.2 mg, 0.08 mmol) in Et_3N (10

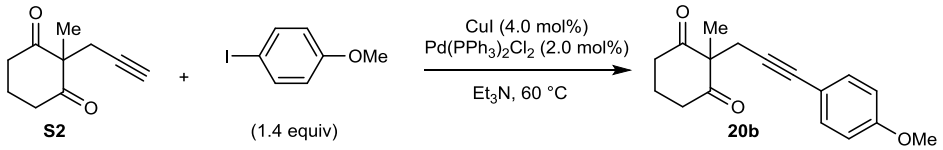
mL). Iodobenzene (490 mg, 7.99 mmol) was added and the mixture was stirred at 60 °C for 6 h. The reaction was cooled to room temperature, water (10 mL) and saturated aqueous NH_4Cl (5 mL) were added, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography (10% EtOAc/pet. ether) to give alkynone **1p** (385 mg, 70%) as a pale yellow solid. R_f = 0.2 (20% EtOAc/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06-8.01 (2H, m, Ar**H**), 7.90-7.86 (2H, m, Ar**H**), 7.17- 7.09 (3H, m, Ar**H**), 6.91-6.88 (2H, m, Ar**H**), 2.90 (2H, s, C**H**$_2$), 1.37 (3H, s, C**H**$_3$); HRMS (ESI) Exact mass calculated for $[C_{19}H_{14}NaO_2]^+$ $[M+Na]^+$: 297.0886, found: 297.0879.

2-Methyl-2-(prop-2-yn-1-yl)cyclohexane-1,3-dione (S2) [69]



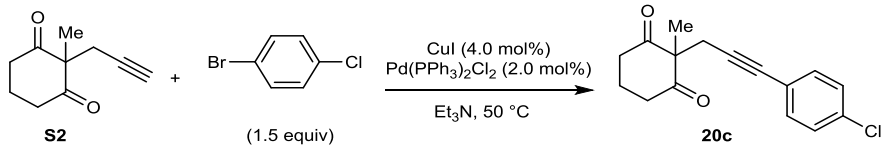
Under an inert atmosphere, propargyl bromide (4.8 g, 40.0 mmol) was added to a solution of *t*-BuOK (4.5 g, 40.0 mmol) and 2-methylcyclohexa-1,3-diketone (5.0 g, 40.0 mmol) in DMSO (100 mL) at 0 °C. The solution was then allowed to warm to room temperature and stirred for 12 h. A solution of saturated aqueous NH_4Cl (100 mL) was then added and the mixture extracted with EtOAc (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography (20% EtOAc/pet. ether) to give alkyndione **S2** (4.85 g, 85%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.81 – 2.54 (6H, m, C**H**$_2$CH$_2$C**H**$_2$ and C**H**$_2$C≡C**),** 2.09 – 1.84 (3H, m, CH$_2$C**H**$_2$CH$_2$ and C≡C**H**), 1.30 (3H, s, C**H**$_3$); HRMS (ESI) Exact mass calculated for $[C_{15}H_{14}NaO_2]^+$ $[M+Na]^+$: 249.0886, found: 249.0883.

2-[3-(4-Methoxyphenyl)prop-2-yn-1-yl]-2-methylcyclohexane-1,3-dione (20b)[65]



Alkynyl 1,3-diketone **S1** (660 mg, 4.00 mmol), CuI (30.4 mg, 0.16 mmol) and $Pd(PPh_3)_2Cl_2$ (56.1 mg, 0.08 mmol) were added to a flask which was then sealed and purged with N_2. Degassed Et_3N (20 mL) was then added followed by 4-iodoanisole (1.31 mL, 5.60 mmol) and the mixture was stirred at 60 °C for 2 h. The reaction was cooled to room temperature, water (50 mL) was added, and the mixture extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (10% EtOAc/pet. ether) to give *alkynone* **20b** (890 mg, 82%) as a yellow oil. ^{1}H NMR (300 MHz,$CDCl_3$) δ 7.32-7.20 (2H, m, Ar**H**), 6.83-6.73 (2H, m, Ar**H**), 3.78 (3H, s, OC**H**$_3$), 2.83 (2H, s, C**H**$_2$C≡C), 2.72 (4H, t, J = 6.8 Hz, C**H**$_2$CH$_2$C**H**$_2$), 2.09-1.89 (2H, m, CH$_2$C**H**$_2$CH$_2$), 1.33 (3H, s, C**H**$_3$). ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.4 (2 × C), 159.3 (C), 132.9 (2 × CH), 115.1 (C), 113.8 (2 × CH), 83.9 (C), 82.8 (C), 64.0 (C), 55.2 (CH_3), 38.5 (2 × CH_2) , 26.7 (CH_2), 21.4 (CH_2), 17.2 (CH_3).

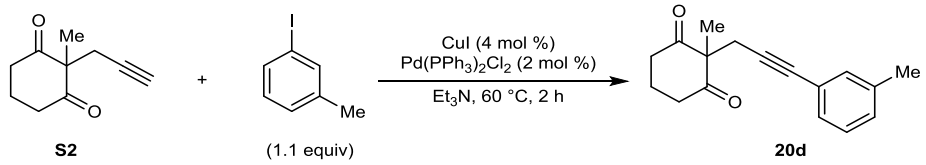
2-[3-(4-Chlorophenyl)prop-2-yn-1-yl]-2-methylcyclohexane-1,3-dione (20c)[65]



Alkynyl 1,3-diketone **S1** (660 mg, 4.00 mmol), CuI (30.4 mg, 0.16 mmol) and $Pd(PPh_3)_2Cl_2$ (56.1 mg, 0.08 mmol) were added to a flask which was then sealed and purged with N_2. Degassed Et_3N (20 mL) was then added followed by 4-chlorobromobenzene (1.15 g, 6.00 mmol) and the mixture was stirred at 50 °C for 12 h. The reaction was cooled to room temperature, water (50 mL) was added, and the mixture extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (10% EtOAc/pet. ether) to give *alkynone* **20c** (561 mg, 51%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.18 (4H, m, Ar**H**), 2.86

(2H, s, C**H**$_2$C≡C), 2.80-2.62 (4H, m, C**H**$_2$CH$_2$C**H**$_2$)), 2.09-1.92 (2H, m, CH$_2$C**H**$_2$CH$_2$), 1.37 (3H s, C**H**$_3$); ^{13}C NMR (75 MHz, CDCl$_3$) δ 209.1 (2 × C), 134.0 (C), 132.8 (2 × CH), 128.5 (2 × CH), 121.6 (C), 86.8 (C), 81.7 (C), 64.1 (C), 38.3 (2 × CH$_2$), 25.9 (CH$_2$), 22.0 (CH$_2$), 17.3 CH$_3$).

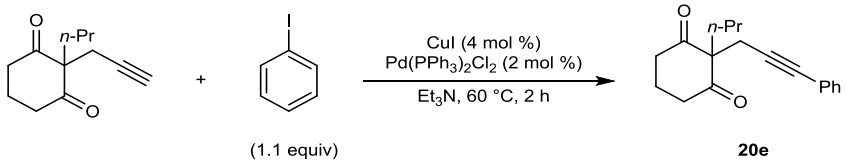
2-Methyl-2-[3-(*m*-tolyl)prop-2-yn-1-yl]cyclohexane-1,3-dione (20d)



S2 (1.1 equiv) **20d**

Alkynyl 1,3-diketone **S2** (660 mg, 4.00 mmol), CuI (30.4 mg, 0.16 mmol) and Pd(PPh$_3$)$_2$Cl$_2$ (56.1 mg, 0.08 mmol) were added to a flask which was then sealed and purged with N$_2$. Degassed Et$_3$N (20 mL) was then added followed by 3-iodotoluene (0.60 mL, 4.40 mmol) and the mixture was stirred at 60 °C for 2 h. The reaction was cooled to room temperature, water (50 mL) was added, and the mixture extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na$_2$SO$_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (10% EtOAc/pet. ether) to give *alkynone* **20d** (1.01g, 99%) as an orange oil. R$_f$ = 0.3 (20% EtOAc/pet. ether); IR 3009, 2964, 1730, 1699 (C=O), 1602, 1455, 1319, 1240, 1130, 1026 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.21-7.02 (4H, m, Ar**H**), 2.84 (2H, s, C**H**$_2$C≡C), 2.80-2.62 (4H, m, C**H**$_2$CH$_2$C**H**$_2$), 2.28 (3H, s, ArC**H**$_3$), 2.07-1.88 (2H, m, CH$_2$C**H**$_2$CH$_2$), 1.34 (3H, s, O=CCC**H**$_3$); ^{13}C NMR (75 MHz, CDCl$_3$) δ 209.2 (2 × C), 137.8 (C), 132.1 (CH), 128.8 (CH), 128.5 (CH), 128.0 (CH), 122.7 (C), 85.1 (C), 83.0 (C), 63.9 (C), 38.4 (2 × CH$_2$), 26.4 (CH$_2$), 21.5 (CH$_2$), 21.1 (CH$_2$), 17.2 (CH$_3$); HRMS (ESI) Exact mass calculated for [C$_{17}$H$_{18}$NaO$_2$]$^+$ [M+Na]$^+$: 277.1199, found: 277.1214.

2-(3-Phenylprop-2-yn-1-yl)-2-propylcyclohexane-1,3-dione (20e)

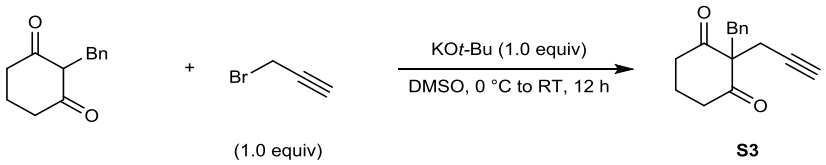


(1.1 equiv) **20e**

Alkynyl 1,3-diketone (225 mg, 1.17 mmol), CuI (8.9 mg, 47 μmol) and Pd(PPh$_3$)$_2$Cl$_2$ (16.1 mg, 23 μmol) were added to a flask which was then sealed and purged with N$_2$.

Degassed Et_3N (15 mL) was then added followed by iodobenzene (0.14 mL, 1.29 mmol) and the mixture stirred at 60 °C for 2 h. The reaction was cooled to room temperature, water (50 mL) was added, and the mixture extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (10% EtOAc/pet. ether) to give *alkynone* **20e** (265 mg, 84%) as an orange oil. R_f = 0.3 (20% EtOAc/pet. ether); IR 3043, 2965, 2877, 1725, 1697 (C=O), 1602, 1491, 1418, 1324, 1240 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.30 (2H, m, Ar**H**), 7.29-7.25 (3H, m, Ar**H**), 2.82 (2H, s, C**H**$_2$C≡C), 2.70 (4H, t, *J* = 6.8 Hz, C**H**$_2$CH$_2$C**H**$_2$), 2.05-2.00 (2H, m, CH$_2$C**H**$_2$CH$_2$), 1.86-1.76 (2H, m, C**H**$_2$CH$_2$CH$_3$), 1.22-1.07 (2H, m, CH$_2$C**H**$_2$CH$_3$), 0.88 (3H, t, *J* = 7.2 Hz, CH$_2$CH$_2$C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.2 (2 × C), 131.6 (2 × CH), 128.2 (2 × CH), 128.0 (CH), 123.1 (C), 86.0 (C), 82.8 (C), 67.7 (C), 39.9 (2 × CH_2), 39.6 (CH_2), 26.1 (CH_2), 18.5 (CH_2), 16.8 (CH_2), 14.4 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{18}H_{20}NaO_2]^+$ $[M+Na]^+$: 291.1356, found: 291.1372.

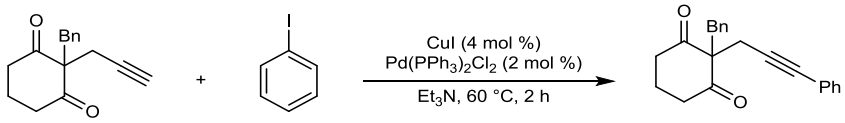
2-Benzyl-2-(prop-2-yn-1-yl)cyclohexane-1,3-dione (S3)



2-Benzylcyclohexane-1,3-dione (3.28 g, 16.2 mmol) was added to a solution of KO*t*-Bu (1.82 g, 16.2 mmol) in DMSO (50 mL). The solution was then cooled to 0 °C and propargyl bromide (80% in toluene, 1.75 mL, 16.2 mmol) was added. The mixture was then allowed to warm to room temperature and stirred for 12 h. Saturated aqueous NH_4Cl solution (50 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (10% EtOAc/pet. ether) to give *alkynone* **S3** (1.57 g, 40%) as an amorphous yellow solid. R_f = 0.4 (20% EtOAc/pet. ether); IR 3308, 3006, 2960, 1722, 1698 (C=O), 1604, 1342, 1259, 1083, 1014 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26-7.20 (3H, m, Ar**H**), 7.03-6.96 (2H, m, Ar**H**), 3.04 (2H, s, C**H**$_2$Ph), 2.72 (2H, d, *J* = 2.7 Hz, C**H**$_2$C≡C), 2.50 (2H, ddd, *J* = 17.2, 8.5, 4.8 Hz, C**H**$_2$CH$_2$C**H**$_2$), 2.15

(ddd, *J* = 17.2, 8.5, 4.8 Hz, C**H**$_2$CH$_2$C**H**$_2$), 1.97 (1H, t, *J* = 2.7 Hz, ≡C**H**), 1.76 (1H, dtt, *J* = 13.5, 9.0, 4.8 Hz, CH$_2$C**H**$_2$CH$_2$), 1.30-1.14 (1H, m, CH$_2$C**H**$_2$CH$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.9 (2 × C), 135.4 (C), 129.7 (2 × CH), 128.6 (2 × CH), 127.4 (CH), 80.1 (C), 70.9 (CH), 68.0 (C), 44.4 (CH_2), 40.9 (2 × CH_2), 26.4 (CH_2), 15.4 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{16}H_{16}NaO_2]^+$ $[M+Na]^+$: 263.1043, found: 263.1046.

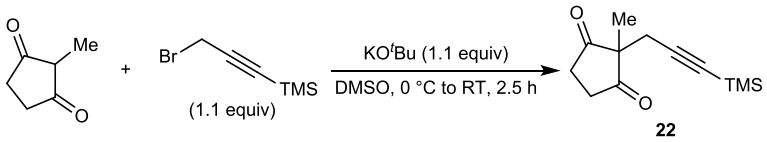
2-Benzyl-2-(3-phenylprop-2-yn-1-yl)cyclohexane-1,3-dione (20f)



S3 (1.1 equiv) **20f**

Alkynyl 1,3-diketone **S3** (500 mg, 2.08 mmol), CuI (15.8 mg, 0.08 mmol) and $Pd(PPh_3)_2Cl_2$ (28.1 mg, 0.04 mmol) were added to a flask which was then sealed and purged with N_2. Degassed Et_3N (20 mL) was then added followed by iodobenzene (0.26 mL, 2.29 mmol) and the mixture stirred at 60 °C for 2 h. The reaction was cooled to room temperature, water (50 mL) was added, and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (10% EtOAc/pet. ether) to give *alkynone* **20f** (594 mg, 90%) as an orange solid. R_f = 0.3 (10% EtOAc/pet. ether); m.p. 73-76 °C (Et_2O); IR 2960, 1722, 1698 (C=O), 1602, 1491, 1456, 1342, 1240, 1083, 1014 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.22 (8H, m, Ar**H**), 7.09-6.97 (2H, m, Ar**H**), 3.12 (2H, s, C**H**$_2$Ph), 2.96 (2H, s, C**H**$_2$CC), 2.54 (2H, ddd, *J* = 17.2, 8.5, 4.8 Hz, C**H**$_2$CH$_2$C**H**$_2$), 2.15 (2H, ddd, *J* = 17.2, 8.5, 4.8 Hz, C**H**$_2$CH$_2$C**H**$_2$), 1.79 (1H, dtt, *J* = 13.3, 8.8, 4.8 Hz, CH$_2$C**H**$_2$CH$_2$), 1.21 (1H, dtt, *J* = 13.3, 9.2, 4.8 Hz, CH$_2$C**H**$_2$CH$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.4 (2 × C), 135.8 (C), 131.5 (2 × CH), 129.8 (2 × CH), 128.7 (2 × CH), 128.2 (2 × CH), 128.1 (CH), 127.3 (CH), 122.8 (C), 85.4 (C), 83.1 (C), 68.0 (C), 44.2 (CH_2), 41.1 (2 × CH_2), 28.1 (CH_2), 15.5 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{22}H_{20}NaO_2]^+$ $[M+Na]^+$: 339.1356, found: 339.1364.

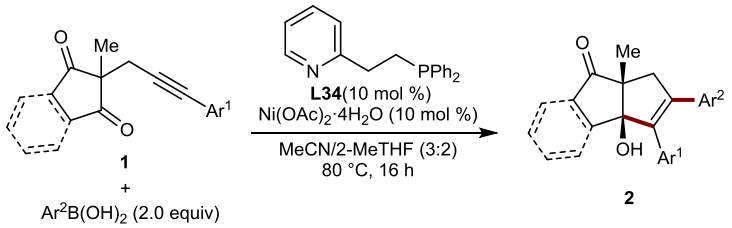
2-Methyl-2-[3-(*m*-tolyl)prop-2-yn-1-yl]cyclohexane-1,3-dione (22)



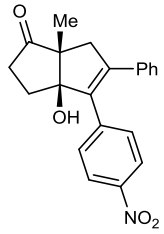
An oven-dried flask was charged with 2-methyl-1,3-cyclopentanedione (500 mg, 4.46 mmol), KO*t*-Bu (550 mg, 4.87 mmol), and a stirrer bar. The flask was sealed with a septum, and the vessel was purged with N_2 for 10 min. Anhydrous DMSO (15 mL) was added and the mixture was stirred at room temperature for 15 min. The mixture was cooled to 0 °C, 3-bromo-1-(trimethylsilyl)-1-propyne (0.82 mL, 4.82 mmol) was added dropwise, and the reaction was stirred at room temperature for 2.5 h. The reaction was diluted with EtOAc (30 mL), washed with brine (2 × 40 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (20% EtOAc/pet. ether) to give *alkynone* **22** as a pale yellow solid (654 mg, 66%). R_f = 0.5 (20% EtOAc/pet. ether); m.p. 34-38 °C (Et_2O); IR 2962, 2904, 2256, 2178, 1769, 1730 (C=O), 1453, 1417, 1373, 1316, 1251, 1074, 1045, 913, 845, 735, 645 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.79 (4H, s, C**H**$_2$C**H**$_2$), 2.47 (2H, s, C**H**$_2$C≡C), 1.10 (3H, s, CC**H**$_3$), 0.11 (9H, s, Si(C**H**$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.5 (2 × C), 100.8 (C), 87.7 (C), 55.5 (C), 36.1 (2 × CH_2), 26.7 (CH_2), 18.7 (CH_3), –0.2 (3 × CH_3); HRMS (ESI) Exact mass calculated for $C_{12}H_{18}NaO_2Si$ $[M + Na]^+$: 245.0968, found: 245.0971.

3.3 Non-enantioselective entries

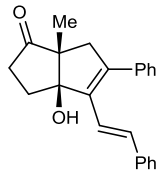
General procedure A



An oven-dried microwave vial fitted with a stirrer bar was charged with alkynyl electrophile **1** (0.10 mmol) the arylboronic acid (0.20 mmol), $Ni(OAc)_2•4H_2O$ (2.5 mg, 0.01 mmol) and pyphos (2.9 mg, 0.01 mmol). The vial was capped with a crimp cap PTFE seal and purged with a stream of N_2. Deoxygenated MeCN (0.6 mL) and 2-MeTHF (0.4 mL) were added and the mixture was stirred at 80 °C for 16 h. The reaction was cooled to room temperature, diluted with CH_2Cl_2 (5 mL) and washed with a 1:1 mixture of H_2O and saturated aqueous NH_4Cl solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure the NMR yields quoted were calculated using ^1H NMR of the crude reaction mixtures and 1,3,5-trimethoxybenzene as an internal standard. In order to obtain NMR spectra the residue was purified by preparative TLC to give the title compound.



(±)-3a-Hydroxy-6a-methyl-4-(4-nitrophenyl)-5-phenyl-1,2,3,3a,6,6a-hexahydropentalen-1-one (2l). The title compound was prepared according to General Procedure A using alkynyl electrophile **1l** (27.1 mg, 0.10 mmol) and phenylboronic acid (24.4 mg, 0.20 mmol), and purified by preparative TLC (10% EtOAc/CH_2Cl_2). 33% NMR yield. IR 3425 (OH), 2925, 1735 (C=O), 1593, 1515 (NO), 1345 (NO), 1071, 1027, 851, 736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.17-8.10 (2H, m, Ar**H**), 7.51-7.45 (2H, m, Ar**H**), 7.27-7.17 (3H, m, Ar**H**), 7.12-7.05 (2H, m, Ar**H**), 3.33 (1H, d, *J* = 17.7 Hz, C**H**$_2$C=C), 2.73 (1H, d, *J* = 17.7 Hz, C**H**$_2$C=C), 2.56-2.40 (1H, m, C**H**$_2$COH), 2.18-1.92 (4H, m, C**H**$_2$C**H**$_2$C=O and O**H**), 1.24 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 220.7 (C), 147.0 (C), 146.4 (C), 142.9 (C), 137.9 (C), 134.8 (C), 129.9 (2 × CH), 128.6 (3 × CH), 128.5 (2 × CH), 123.7 (2 × CH), 92.9 (C), 56.6 (C), 45.3 (CH_2), 36.3 (CH_2), 29.1 (CH_2), 15.3 (CH_3); HRMS (ESI) Exact mass calculated for: $C_{21}H_{20}NO_4$ $[M+H]^+$: 372.1206 , found: 372.1203.

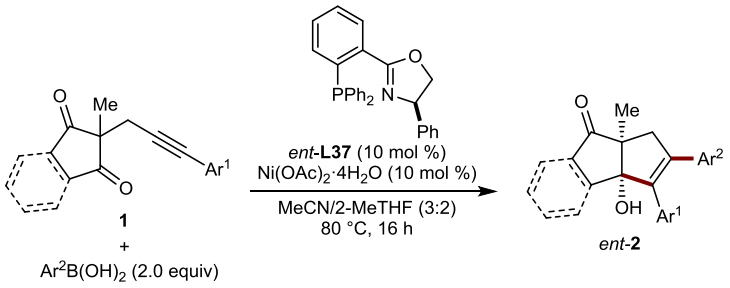


(±)-3a-Hydroxy-6a-methyl-5-phenyl-4-[(E)-2-phenylethenyl]-1,2,3,3a,6,6a-hexahydropentalen-1-one (2r). The title compound was prepared according to General Procedure A using alkynyl electrophile **1r** (25.2 mg, 0.10 mmol) and phenylboronic acid (24.4 mg, 0.20 mmol), and purified by preparative TLC (10% EtOAc/CH_2Cl_2). >95%

NMR yield. IR 3424 (OH), 2924, 2853, 1729 (C=O), 1493, 1446, 1133, 1071, 910, 698, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47-7.20 (11H, m, Ar**H** and CH=C**H**Ph), 6.90 (1H, d, J = 16.8Hz, C**H**=CHPh), 3.16 (1H, d, *J* = 18.0 Hz, C**H**$_2$C=C), 2.92-2.78 (1H, m, C**H**$_2$COH), 2.69 (1H, d, *J* = 18.0 Hz, C**H**$_2$C=C), 2.59-1.43 (1H, m, C**H**$_2$COH) 2.27-2.09 (1H, m, CH_2C**H**$_2$C=O), 1.99 (1H, br s, OH), 1.24 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 221,7 (C), 114.0 (C), 137.4 (C), 137.0 (C), 136.2 (C), 131.2 (CH) 128.7 (4 × CH), 128.4 (2 × CH), 128.2 (CH), 127.7 (CH), 126.4 (2 × CH), 121.0 (CH), 92.2 (C), 56.6 (C), 45.7 (CH_2), 36.7 (CH_2), 29.7 (CH_2), 16.1 (CH_3); HRMS (ESI) Exact mass calculated for Chemical Formula: $C_{23}H_{22}NaO_2$ $[M+Na]^+$: 353.1512, found: 353.1509.

3.4 Enantioselective Nickel-Catalysed Cyclisation of Alkynyl Electrophiles

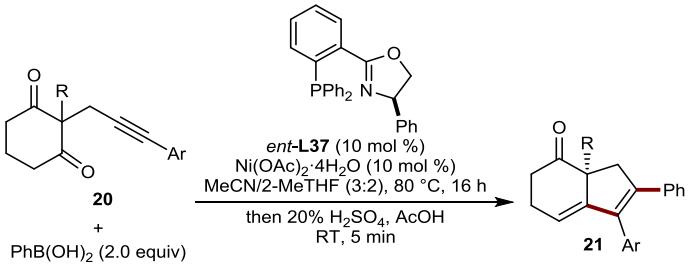
General Procedure B



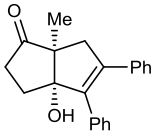
An oven-dried microwave vial fitted with a stirrer bar was charged with $Ni(OAc)_2$•$4H_2O$ (7.5 mg, 0.03 mmol) and (*R*)-Ph-PHOX (*ent*-**L37**, 12.2 mg, 0.03 mmol). The vial was capped with a crimp cap PTFE seal and purged with a stream of N_2. Deoxygenated MeCN (0.9 mL) and 2-MeTHF (0.6 mL) were added and the mixture was stirred at 80 °C for 20 min. In a separate vial, the alkynyl electrophile **1** (0.30 mmol) and the arylboronic acid (0.60 mmol) were weighed out and the vial was purged with a stream of N_2. Deoxygenated MeCN (0.9 mL) and 2-MeTHF (0.6 mL) were added. The resulting solution was then transferred to the first microwave vial *via* syringe and the reaction was stirred at 80 °C for 16 h. The reaction was cooled to room temperature, diluted with CH_2Cl_2 (15 mL) and washed with a 1:1 mixture of H_2O and saturated aqueous NH_4Cl solution (25 mL). The aqueous layer was extracted with CH_2Cl_2 (15 mL). The combined organic layers were dried

(Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography to give the title compound.

General Procedure C

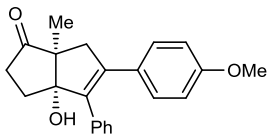


An oven-dried microwave vial fitted with a stirrer bar was charged with $Ni(OAc)_2$•$4H_2O$ (7.5 mg, 0.03 mmol), (*R*)-Ph-PHOX (*ent*-**L37**, 12.2 mg, 0.03 mmol). The vial was capped with a crimp cap PTFE seal and purged with a stream of N_2. Deoxygenated MeCN (0.9 mL) and 2-MeTHF (0.6 mL) were added the mixture was stirred at 80 °C for 20 min. In a separate vial, alkynyl electrophile **20** (0.30 mmol) and the corresponding phenylboronic acid (0.60 mmol) were weighed out and the vial was purged with a stream of N_2. Deoxygenated MeCN (0.9 mL) and 2-MeTHF (0.6 mL) were added. The resulting solution was then transferred to the first microwave vial *via* syringe and the reaction was stirred at 80 °C for 16 h. The reaction was cooled to room temperature and 20% H_2SO_4 in AcOH (2 mL) was added. The mixture was stirred at room temperature for 15 min, diluted with CH_2Cl_2 (15 mL) and carefully washed with saturated aqueous $NaHCO_3$ solution (25 mL). The aqueous layer was extracted with CH_2Cl_2 (15 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography to give the title compound.



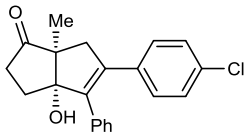
(3a*S*,6a*S*)-3a-Hydroxy-6a-methyl-4,5-diphenyl-3,3a,6,6a-tetrahydropentalen-1(2*H*)-one (*ent*-2a). The title compound was prepared according to General Procedure B using alkynyl electrophile **1a** (67.9 mg, 0.30 mmol) and phenylboronic acid (73.1 mg, 0.60 mmol), and purified by column chromatography (10% EtOAc/CH_2Cl_2) to give a colourless solid (81.1

mg, 89%). R_f = 0.4 (10% EtOAc/CH_2Cl_2); m.p. 114-116 °C (Et_2O); $[\alpha]_D^{23}$ –24.4 (*c* 0.62, $CHCl_3$); IR 3588 (OH), 3009, 2968, 2930, 1736 (C=O), 1602, 1458, 1240, 1060, 1045 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.24 (5H, m, Ar**H**), 7.18-7.11 (5H, m, Ar**H)**, 3.26 (1H, d, *J* = 17.1 Hz, C**H**$_2$C=C), 2.73 (1H, d, *J* = 17.1 Hz, C**H**$_2$C=C), 2.45 (1H, ddd, *J* = 18.4, 8.8, 1.2 Hz, C**H**$_2$C=O), 2.21-2.00 (2H, m, C**H**$_2$CH$_2$C=O, and C**H**$_2$C=O), 2.00-1.90 (2H, m, C**H**$_2$C=O and O**H**), 1.25 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 221.7 (C), 142.5 (C), 140.1 (C), 135.7 (C), 135.6 (C), 129.0 (2 × CH), 128.6 (4 × CH), 128.1 (2 × CH), 127.8 (CH), 127.5 (CH), 92.8 (C), 56.3 (C), 44.8 (CH_2), 36.6 (CH_2), 29.1 (CH_2), 15.5 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{21}H_{20}NaO_2]^+$ $[M+Na]^+$: 327.1356, found: 327.1346. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (80:20 *iso*-hexane:*i*-PrOH, 1.5 mL/min, 254 nm, 25 °C); t_r (minor) = 3.6 min, t_r (major) = 4.3 min, 86% ee.



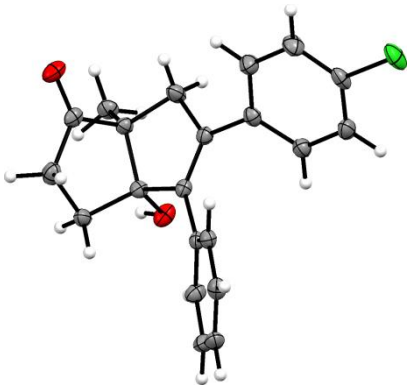
(3a*S*,6a*S*)-3a-Hydroxy-5-(4-methoxyphenyl)-6a-methyl-4-phenyl-3,3a,6,6a-tetrahydropentalen-1(2*H*)-one (*ent*-2b). The title compound was prepared according to General Procedure B using alkynyl electrophile **1a** (67.9 mg, 0.30 mmol) and 4-methoxyphenylboronic acid (91.2 mg, 0.60 mmol), and purified by column chromatography (10% EtOAc/CH_2Cl_2) to give a colourless amorphous solid (70.0 mg, 70%). R_f = 0.4 (10% EtOAc/CH_2Cl_2); $[\alpha]_D^{23}$ –32.8 (*c* 0.74,$CHCl_3$); IR 3588 (OH), 2965, 2932, 1735 (C=O), 1607, 1514, 1297, 1252, 1181, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.23, (5H, m, Ar**H**), 7.10-7.03 (2H, m, Ar**H**), 6.72-6.65 (2H, m, Ar**H**), 3.75 (3H, s, OC**H**$_3$), 3.24 (1H, d, *J* = 17.0 Hz, C**H**$_2$C=C), 2.70 (1H, d, *J* = 17.0 Hz, C**H**$_2$C=C), 2.53-2.35 (1H, m, C**H**$_2$C=O), 2.19-1.82 (4H, m, C**H**$_2$C**H**$_2$C=O and O**H**), 1.23 (3H, s, CC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 221.9 (C), 159.1 (C), 141.9 (C), 138.4 (C), 136.2 (C), 129.9 (2 × CH), 129.0 (2 × CH), 128.6 (2 × CH), 127.9 (C), 127.4 (CH), 113.4 (2 × CH), 92.8 (C), 56.2 (C), 55.1 (CH_3), 44.6 (CH_2), 36.5 (CH_2), 29.0 (CH_2), 15.5 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{22}H_{22}NaO_3]^+$ $[M+Na]^+$: 357.1461, found: 357.1460. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (80:20 *iso*-

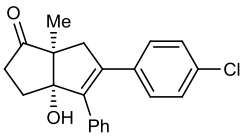
hexane:*i*-PrOH, 1.5 mL/min, 280 nm, 25 °C); t_r (major) = 4.6 min, t_r (minor) = 5.9 min, 77% ee.



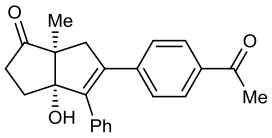
(3a*S*,6a*S*)-5-(4-Chlorophenyl)-3a-hydroxy-6a-methyl-4-phenyl-3,3a,6,6a-tetrahydropentalen-1(2*H*)-one (*ent*-2c). The title compound was prepared according to General Procedure B using alkynyl electrophile **1a** (67.9 mg, 0.30 mmol) and 4-chlorophenylboronic acid (93.8 mg, 0.60 mmol), and purified by column chromatography (10% EtOAc/CH_2Cl_2) to give a colourless solid (74.8 mg, 74%). R_f = 0.75 (10% EtOAc/CH_2Cl_2); m.p. 118-120 °C (Et_2O); $[\alpha]_D^{23}$ –19.7 (*c* 0.72, $CHCl_3$); IR 3588, 3009, 2968, 2930, 1736 (C=O), 1601, 1496, 1336, 1240, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.29 (3H, m, Ar**H**), 7.26-7.22 (2H, m, Ar**H**), 7.15-7.10 (2H, m, Ar**H**), 7.06-7.01 (2H, m, Ar**H**), 3.22 (1H, d, *J* = 17.0 Hz, C**H**$_2$C=C), 2.71 (1H, d, *J* = 17.0 Hz, C**H**$_2$C=C), 2.51-2.41 (1H, m, C**H**$_2$C=O), 2.21-1.89 (4H, m, C**H**$_2$C**H**$_2$C=O and O**H**), 1.23 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 221.5 (C), 141.2 (C), 140.8 (C), 135.4 (C), 134.0 (C), 133.6 (C), 129.8 (2 × CH), 128.9 (2 × CH), 128.7 (2 × CH), 128.3 (2 × CH), 127.7 (CH), 92.7 (C), 56.3 (C), 44.6 (CH_2), 36.5 (CH_2), 29.2 (CH_2), 15.4 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{21}H_{19}ClNaO_2]^+$ $[M+Na]^+$: 361.0966, found: 361.0968. Enantiomeric excess was determined by HPLC with Chiralcel OD-H column (80:20 *iso*-hexane:*i*-PrOH, 1.5 mL/min, 280 nm, 25 °C); t_r (minor) = 3.2 min, t_r (major) = 3.6 min, 85% ee.

Slow diffusion of petroleum ether into a solution of *ent*-**2c** in EtOAc gave crystals that were suitable for X-ray crystallography:

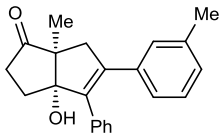




ent-**2c**
CCDC 1449254
Flack parameter = 0.005(11)

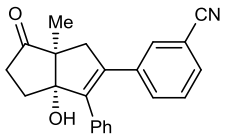


(3a*S*,6a*S*)-5-(3-Acetylphenyl)-3a-hydroxy-6a-methyl-4-phenyl-3,3a,6,6a-tetrahydropentalen-1(2*H*)-one (*ent*-2d). The title compound was prepared according to General Procedure B using alkynyl electrophile **1a** (67.9 mg, 0.30 mmol) and 4-acetylphenylboronic acid (98.4 mg, 0.60 mmol), and purified by column chromatography (10% EtOAc/CH_2Cl_2) to give a colourless solid (58.9 mg, 57%). R_f = 0.2 (10% EtOAc/CH_2Cl_2); m.p. 51-55 °C (Et_2O); $[\alpha]_D^{23}$ –98.0 (*c* 0.56, $CHCl_3$); IR 3587 (OH), 3009, 1739 (C=O), 1683 (C=O), 1606, 1406, 1360, 1270, 1240, 1059 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86-7.69 (2H, m, Ar**H**), 7.36-7.32 (3H, m, Ar**H**), 7.27-7.23 (2H, m, Ar**H**), 7.23-7.19 (2H, m, Ar**H**), 3.28 (1H, d, *J* = 17.0 Hz, C**H**$_2$C=C), 2.77 (1H, d, *J* = 17.0 Hz, C**H**$_2$C=C), 2.54 (3H, s, C**H**$_3$C=O), 2.49 (1H, ddd, *J* = 18.4, 8.8, 1.4 Hz, C**H**$_2$C=O), 2.25-1.92 (4H, m, C**H**$_2$C**H**$_2$C=O and O**H**), 1.26 (3H, s, O=CCC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 221.3 (C), 197.5 (C), 142.5 (C), 141.4 (C), 140.5 (C), 136.0 (C), 135.2 (C), 128.9 (2 × CH), 128.8 (2 × CH), 128.7 (2 × CH), 128.1 (2 × CH), 127.9 (CH), 92.7 (C), 56.4 (C), 44.6 (CH_2), 36.6 (CH_2), 29.3 (CH_2), 26.6 (CH_3), 15.4 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{22}H_{22}NaO_3]^+$ $[M+Na]^+$: 357.1461, found: 357.1460. Enantiomeric excess was determined by HPLC with a Chiralpak IC-3 column (80:20 *iso*-hexane:*i*-PrOH, 1.5 mL/min, 280 nm, 25 °C); t_r (major) = 8.1 min, t_r (minor) = 9.6 min, 88% ee.

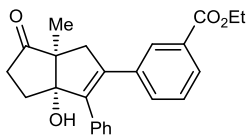


(3a*S*,6a*S*)-3a-Hydroxy-6a-methyl-4-phenyl-5-(*m*-tolyl)-3,3a,6,6a-tetrahydropentalen-1(2*H*)-one (*ent*-2e). The title compound was prepared according to General Procedure B using alkynyl electrophile **1a** (67.9 mg, 0.30 mmol) and 3-methylphenylboronic acid (81.6 mg, 0.60 mmol), and purified by column chromatography (10% EtOAc/CH_2Cl_2) to give a colourless solid (78.0 mg, 82%). R_f = 0.6 (10% EtOAc/CH_2Cl_2); m.p. 108-114 °C (Et_2O); $[\alpha]_D^{23}$ +23.5 (*c* 0.74, $CHCl_3$); IR 3687 (OH), 3010, 2986, 1736 (C=O), 1602, 1442, 1336, 1240, 1117, 1059 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.22 (5H, m, Ar**H**), 7.05-6.95 (3H, m, Ar**H**), 6.88 (1H, d, *J* = 7.3 Hz, Ar**H**), 3.25 (1H, d, *J* = 17.1 Hz, C**H**$_2$C=C), 2.72 (1H, d, *J* = 17.1 Hz, C**H**$_2$C=C), 2.45 (1H, ddd, *J* = 18.3,

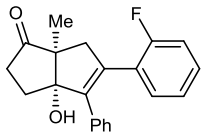
8.8, 1.3 Hz, C**H**$_2$C=O), 2.22-2.15 (4H, m, C**H**$_2$CH$_2$C=O and ArC**H**$_3$), 2.13-2.02 (2H, m, C**H**$_2$C**H**$_2$C=O), 1.94 (1H, app td, *J* = 11.7, 8.8 Hz, C**H**$_2$C=O) 1.23 (3H, s, O=CCC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 221.9 (C), 142.6 (C), 139.9 (C), 137.6 (C), 135.8 (C), 135.5 (C), 129.2 (CH), 129.0 (2 × CH), 128.53 (CH), 128.45 (2 × CH), 127.9 (CH), 127.4 (CH), 125.7 (CH), 92.7 (C), 56.3 (C), 44.8 (CH_2), 36.6 (CH_2), 29.1 (CH_2), 21.3 (CH_3), 15.5 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{22}H_{22}NaO_2]^+$ $[M+Na]^+$: 341.1512, found: 341.1516. Enantiomeric excess was determined by HPLC with Chiralpak AD-H column (80:20 *iso*-hexane:*i*-PrOH, 1.5 mL/min, 280 nm, 25 °C); t_r (minor) = 3.2 min, t_r (major) = 4.8 min, 87% ee.



3-[(3a*S*,6a*S*)-3a-Hydroxy-6a-methyl-6-oxo-3-phenyl-1,3a,4,5,6,6a-hexahydropentalen-2-yl]benzonitrile (*ent*-2f). The title compound was prepared according to General Procedure B using alkynyl electrophile **1a** (67.9 mg, 0.30 mmol) and 3-cyanophenylboronic acid (88.2 mg, 0.60 mmol), and purified by column chromatography (10% EtOAc/CH_2Cl_2) to give a colourless solid (56.0 mg, 57%). R_f = 0.4 (10% EtOAc/CH_2Cl_2); m.p. 49-55 °C (Et_2O); $[\alpha]_D^{23}$ +22.0 (*c* 0.52, $CHCl_3$); IR 3588 (OH), 3009, 2969, 2931, 2233 (C≡N), 1739 (C=O), 1601, 1459, 1373, 1060 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45, (1H, dt, *J* = 7.5, 1.4 Hz, Ar**H**), 7.39 (1H, t, *J* = 1.4 Hz, Ar**H**) 7.37-7.31 (4H, m, Ar**H**), 7.23-7.19 (4H, m, Ar**H**), 3.22 (1H, d, *J* = 17.0 Hz, C**H**$_2$C=C), 2.74 (1H, d, *J* = 17.0 Hz, C**H**$_2$C=C), 2.50 (1H, ddd, *J* = 18.6, 8.9, 1.4 Hz, C**H**$_2$C=O), 2.22-2.04 (2H, m, C**H**$_2$C=O and C**H**$_2$CH$_2$C=O), 2.00-1.92 (2H, m, C**H**$_2$CH$_2$C=O and O**H**), 1.25 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 221.0 (C), 142.7 (C), 140.0 (C), 137.0 (C), 134.7 (C), 132.8 (CH), 132.0 (CH), 131.1 (CH), 128.93 (2 × CH) 128.91 (CH), 128.7 (2 × CH), 128.2 (CH), 118.4 (C), 112.4 (C), 92.6 (C), 56.4 (C), 44.4 (CH_2), 36.5 (CH_2), 29.3 (CH_2), 15.4 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{22}H_{19}NNaO_2]^+$ $[M+Na]^+$: 352.1308, found: 352.1311. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.5 mL/min, 280 nm, 25 °C); t_r (minor) = 8.5 min, t_r (major) = 10.0 min, 88% ee.

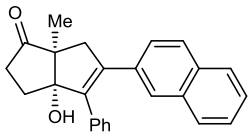


Ethyl 3-[(3a*S*,6a*S*)-3a-hydroxy-6a-methyl-6-oxo-3-phenyl-1,3a,4,5,6,6a-hexahydropentalen-2-yl]benzoate (*ent*-2g). The title compound was prepared according to General Procedure B using alkynyl electrophile **1a** (67.9 mg, 0.30 mmol) and 3-ethoxycarbonylphenylboronic acid (116.4 mg, 0.60 mmol), and purified by column chromatography (10% EtOAc/CH_2Cl_2) to give a colourless amorphous solid (62.7 mg, 56%). R_f = 0.4 (10% EtOAc/CH_2Cl_2); $[\alpha]_D^{23}$ +24.0 (*c* 0.69, $CHCl_3$); IR 3589 (OH), 3009, 2982, 1736 (C=O), 1715 (C=O), 1602, 1443, 1370, 1335, 1278, 1112 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.80 (2H, m, Ar**H**), 7.33-7.29 (3H, m, Ar**H**), 7.29-7.16 (4H, m, Ar**H**), 4.29 (q, *J* = 7.1 Hz, C**H**$_2$CH$_3$), 3.29 (1H, d, *J* = 17.1 Hz, C**H**$_2$C=C), 2.76 (1H, d, *J* = 17.1 Hz, C**H**$_2$C=C), 2.54-2.41 (1H, m, C**H**$_2$C=O), 2.23-2.03 (3H, m, C**H**$_2$C**H**$_2$C=O and O**H**), 1.95 (1H, app td, *J* = 11.5, 8.8 Hz, C**H**$_2$CH$_2$C=O), 1.32 (3H, t, *J* = 7.1 Hz, CH$_2$C**H**$_3$), 1.25 (3H, s, O=CCC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 221.5 (C), 166.2 (C), 141.34 (C), 141.29 (C), 135.8 (C), 135.4 (C), 132.8 (CH), 130.4 (C), 129.5 (CH), 128.90 (2 × CH), 128.86 (CH), 128.68 (2 × CH), 128.1 (CH), 127.7 (CH), 92.7 (C), 61.0 (CH_2), 56.3 (C), 44.6 (CH_2), 36.6 (CH_2), 29.2 (CH_2), 15.5 (CH_3), 14.3 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{24}H_{24}NaO_4]^+$ $[M+Na]^+$: 399.1567, found: 399.1587. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (80:20 *iso*-hexane:*i*-PrOH, 1.5 mL/min, 280 nm, 25 °C); t_r (major) = 4.2 min, t_r (minor) = 6.5 min, 90% ee.



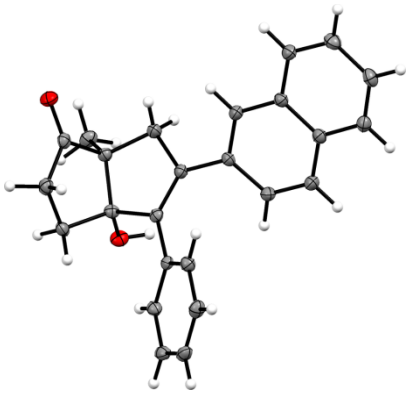
(3a*S*,6a*S*)-5-(2-Fluorophenyl)-3a-hydroxy-6a-methyl-4-phenyl-3,3a,6,6a-tetrahydropentalen-1(2*H*)-one (*ent*-2t). The title compound was prepared according to General Procedure B using alkynyl electrophile **1a** (67.9 mg, 0.30 mmol) and 2-fluorophenylboronic acid (83.9 mg, 0.60 mmol), and purified by column chromatography (10% EtOAc/CH_2Cl_2) to give a colourless oil (35.5 mg, 34%). R_f = 0.3 (5% EtOAc/CH_2Cl_2); $[\alpha]_D^{23}$ −11.6 (*c* 0.13, $CHCl_3$); IR 3442 (OH), 1728 (C=O), 1486, 1447, 1235, 1119, 1074, 758, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.15 (6H, m, Ar**H**), 7.05-6.91 (3H, m, Ar**H**), 3.20 (1H, d, *J* = 17.3 Hz, C**H**$_2$C=C), 2.71 (1H, d, *J* = 17.3 Hz, C**H**$_2$C=C), 2.50-2.43

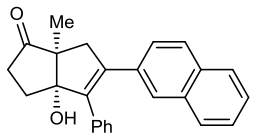
(1H, m, C**H**$_2$C=O), 2.29-2.21 (1H, m, C**H**$_2$C=O), 2.14-1.97 (2H, m, C**H**$_2$CH$_2$C=O), 1.23 (3H, s, C**H**$_3$), the O**H** signal appears as broad singlet in the region from 2.60 to 1.90 ppm overlapping with the alkyl protons; ^{13}C NMR (101 MHz, $CDCl_3$) δ 221.5 (C), 159.8 (d, $^1J_{C\text{-}F}$ = 248.4 Hz, C), 143.0 (C), 138.3 (C), 134.9 (C), 130.7 (d, $^4J_{C\text{-}F}$ =3.8 Hz, CH), 129.4 (d, $^3J_{C\text{-}F}$ = 8.4 Hz, CH), 128.5 (2 × CH), 128.2 (2 × CH), 127.5 (CH), 124.4 (d, $^2J_{C\text{-}F}$ = 14.6 Hz, C), 123.8 (d, $^4J_{C\text{-}F}$ = 3.1 Hz, CH), 115.8 (d, $^2J_{C\text{-}F}$ = 22.2 Hz, CH), 92.2 (C), 56.9 (C), 45.6 (d, $^4J_{C\text{-}F}$ = 3.1 Hz, CH_2), 36.6 (CH_2), 29.3 (CH_2), 15.4 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{21}H_{19}FNaO_2]^+$ $[M+Na]^+$: 345.1261, found: 345.1260. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (80:20 *iso*-hexane:*i*-PrOH, 1.5 mL/min, 230 nm, 25 °C); t_r (minor) = 3.3 min, t_r (major) = 3.6 min, 97% ee.



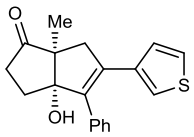
(3a*S*,6a*S*)-3a-Hydroxy-6a-methyl-5-(naphthalen-2-yl)-4-phenyl-3,3a,6,6a-tetrahydropentalen-1(2*H*)-one (*ent*-2h). The title compound was prepared according to General Procedure B using alkynyl electrophile **1a** (67.9 mg, 0.30 mmol) and 2-naphthylboronic acid (103.2 mg, 0.60 mmol), and purified by column chromatography (10% EtOAc/CH_2Cl_2) to give a colourless solid (83.1 mg, 78%). R_f = 0.4 (10% EtOAc/CH_2Cl_2); m.p. 102-105 °C (Et_2O); $[\alpha]_D^{23}$ –227.1 (*c* 0.58, $CHCl_3$); IR 3588 (OH), 3009, 1738 (C=O), 1601, 1459, 1333, 1240, 1117, 1059, 1045 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76-7.65 (3H, m, Ar**H**), 7.55 (1H, d, *J* = 8.7 Hz, Ar**H**), 7.48-7.41 (2H, m, Ar**H**), 7.30 (5H, s, Ar**H**), 7.13 (1H, dd, *J* = 8.7, 1.7 Hz, Ar**H**), 3.42 (1H, d, *J* = 17.1 Hz, C**H**$_2$C=C), 2.82 (1H, d, *J* = 17.1 Hz, C**H**$_2$C=C), 2.56-2.42 (1H, m, C**H**$_2$C=O), 2.29-1.92 (4H, m, C**H**$_2$C**H**$_2$C=O and O**H**), 1.27 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 221.8 (C), 142.5 (C), 140.5 (C), 135.7 (C), 133.2 (C), 133.0 (C), 132.7 (C), 129.1 (2 × CH), 128.6 (2 × CH), 128.2 (CH), 128.0 (CH), 127.6 (CH), 127.5 (CH), 127.3 (CH), 126.5 (CH), 126.3 (CH), 126.1 (CH), 92.9 (C), 56.4 (C), 44.9 (CH_2), 36.6 (CH_2), 29.2 (CH_2), 15.5 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{25}H_{22}NaO_2]^+$ $[M+Na]^+$: 377.1512, found: 377.1512. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (80:20 *iso*-hexane:*i*-PrOH, 1.5 mL/min, 280 nm, 25 °C); t_r (major) = 4.6 min, t_r (minor) = 5.4 min, 86% ee.

Slow diffusion of petroleum ether into a solution of *ent*-**2h** in EtOAc gave crystals that were suitable for X-ray crystallography:

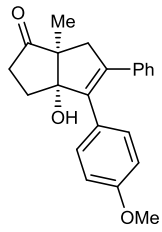




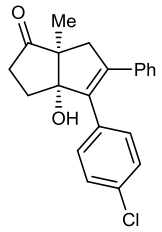
ent-**2h**
CCDC 1449255
Flack parameter = 0.09(9)



(3a*S*,6a*S*)-3a-Hydroxy-6a-methyl-4-phenyl-5-(thiophen-3-yl)-3,3a,6,6a-tetrahydropentalen-1(2*H*)-one (*ent*-2i). The title compound was prepared according to General Procedure B using alkynyl electrophile **1a** (67.9 mg, 0.30 mmol) and 3-thienylboronic acid (76.8 mg, 0.60 mmol), and purified by column chromatography (10% EtOAc/CH_2Cl_2) to give a pale yellow solid (69.7 mg, 75%). R_f = 0.5 (10% EtOAc/CH_2Cl_2); m.p. 98-102°C (Et_2O); $[\alpha]_D^{23}$ +116.3 (*c* 0.63, $CHCl_3$); IR 3588 (OH), 3009, 2967, 1738 (C=O), 1602, 1321, 1264, 1240, 1072, 1045 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.35 (3H, m, Ar**H**), 7.31-7.25 (2H, m, Ar**H**), 7.09-7.03 (2H, m, Ar**H**), 6.60 (1H, dd, *J* = 5.0, 1.4 Hz, Ar**H**), 3.20 (1H, d, *J* = 16.7 Hz, C$\mathbf{H}_2$C=C), 2.78 (1H, d, *J* = 16.7 Hz, C$\mathbf{H}_2$C=C), 2.52-2.37 (1H, m, C$\mathbf{H}_2$C=O), 2.19-2.03 (2H, m, C$\mathbf{H}_2$C=O and C$\mathbf{H}_2$C$\mathbf{H}_2$C=O), 1.98-1.89 (2H, m, C$\mathbf{H}_2$CH_2C=O and O**H**), 1.23 (3H, s, C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 221.6 (C), 139.0 (C), 136.8 (C), 136.6 (C), 136.2 (C), 129.0 (2 × CH), 128.8 (2 × CH), 127.8 (CH), 127.1 (CH), 125.0 (CH), 124.7 (CH), 92.7 (C), 56.1 (C), 44.4 (CH_2), 36.5 (CH_2), 29.2 (CH_2), 15.6 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{19}H_{18}NaO_2S]^+$ $[M+Na]^+$: 333.0920, found: 333.0927. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (80:20 *iso*-hexane:*i*-PrOH, 1.5 mL/min, 280 nm, 25 °C); t_r (minor) = 4.3 min, t_r (major) = 5.4 min, 66% ee.

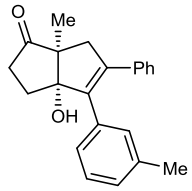


(3a*S*,6a*S*)-3a-Hydroxy-4-(4-methoxyphenyl)-6a-methyl-5-phenyl-3,3a,6,6a-tetrahydropentalen-1(2*H*)-one (*ent*-2m). The title compound was prepared according to General Procedure B using alkynyl electrophile **1m** (76.9 mg, 0.30 mmol) and phenylboronic acid (73.1 mg, 0.60 mmol), and purified by column chromatography (10% EtOAc/CH_2Cl_2) to give a pale yellow solid (68.2 mg, 68%). R_f = 0.2 (5% EtOAc/CH_2Cl_2); m.p. 114-116 °C (Et_2O); $[\alpha]_D^{23}$ +10.8 (*c* 0.16, $CHCl_3$); IR 3431 (OH), 2927, 1730 (C=O), 1606, 1509, 1287, 1246, 1177, 1034, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24-7.09 (7H, m Ar**H**), 6.89-6.78 (2H, m, Ar**H**), 3.81 (3H, s, OC**H**$_3$), 3.24 (1H, d, *J* = 17.1 Hz, C**H**$_2$C=C), 2.70 (1H, d, *J* = 17.1 Hz, C**H**$_2$C=C), 2.43 (1H, dd, *J* = 19.5, 9.0 Hz, C**H**$_2$C=O), 2.32 (1H, br s, O**H**) 2.25-2.15 (1H, m, C**H**$_2$C=O), 2.10-1.95 (2H, m, C**H**$_2$CH$_2$C=O), 1.23 (3H, s, CC**H**$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 222.2 (C), 158.8 (C), 141.6 (C), 139.6 (C), 135.8 (C), 130.1 (2 × CH), 128.5 (2 × CH), 128.0 (2 × CH), 127.8 (C), 127.7 (CH), 113.9 (2 × CH), 92.7 (C), 56.2 (C), 55.1 (CH_3), 44.7 (CH_2), 36.5 (CH_2), 28.9 (CH_2), 15.5 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{22}H_{22}NaO_3]^+$ $[M+Na]^+$: 357.1461, found: 357.1454. Enantiomeric excess was determined by HPLC with a Chiralpak IC-3 column (90:10 *iso*-hexane:*i*-PrOH, 0.8 mL/min, 254 nm, 25 °C); t_r (major) = 9.0 min, t_r (minor) = 10.3 min, 85% ee.

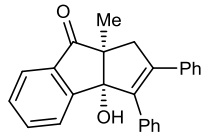


(3a*S*,6a*S*)-4-(4-Chlorophenyl)-3a-hydroxy-6a-methyl-5-phenyl-3,3a,6,6a-tetrahydropentalen-1(2*H*)-one (*ent*-2n). The title compound was prepared according to General Procedure B using alkynyl electrophile **1n** (78.2 mg, 0.30 mmol) and phenylboronic acid (73.1 mg, 0.60 mmol), and purified by column chromatography (10% EtOAc/CH_2Cl_2) to give a colourless solid (46.0 mg, 45%). R_f = 0.5 (10% EtOAc/CH_2Cl_2); m.p. 120-125 °C (Et_2O); $[\alpha]_D^{23}$ –73.9 (*c* 0.56, $CHCl_3$); IR 3586 (OH), 3009, 2969, 1737 (C=O), 1601, 1488, 1337, 1092, 1059, 1016 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.25 (3H, m, Ar**H**), 7.24-7.17 (4H, m, 4**H**), 7.14-7.08 (2H, m, Ar**H**), 3.27 (1H, d, *J* = 17.3 Hz, C**H**$_2$C=C), 2.70 (1H, d, *J* = 17.3 Hz, C**H**$_2$C=C), 2.53-2.38 (1H, m, C**H**$_2$C=O), 2.22-2.12 (1H, m, C**H**$_2$C=O), 2.10-1.89 (3H, m, C**H**$_2$CH$_2$C=O and O**H**), 1.23 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 221.4 (C),

143.5 (C), 138.8 (C), 135.3 (C), 134.1 (C), 133.4 (C), 130.4 (2 × CH), 128.8 (2 × CH), 128.6 (2 × CH), 128.2 (2 × CH), 128.1 (CH), 92.8 (C), 56.4 (C), 44.9 (CH_2), 36.4 (CH_2), 29.0 (CH_2), 15.4 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{21}H_{19}ClNaO_2]^+$ $[M+Na]^+$: 361.0966, found: 361.0964. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (80:20 *iso*-hexane:*i*-PrOH, 1 mL/min, 280 nm, 25 °C); t_r (minor) = 3.5 min, t_r (major) = 4.3 min, 87% ee.

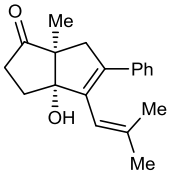


(3a*S*,6a*S*)-3a-Hydroxy-6a-methyl-5-phenyl-4-(*m*-tolyl)-3,3a,6,6a-tetrahydropentalen-1(2*H*)-one (*ent*-2o). The title compound was prepared according to General Procedure B using alkynyl electrophile **1o** (72.1 mg, 0.30 mmol) and phenylboronic acid (73.1 mg, 0.60 mmol), and purified by column chromatography (10% EtOAc/CH_2Cl_2) to give a colourless oil (66.8 mg, 70%). R_f = 0.3 (5% EtOAc/CH_2Cl_2); $[\alpha]_D^{23}$ +14.8 (*c* 0.18, $CHCl_3$); IR 3422 (OH), 2925, 1731 (C=O), 1457, 1247, 1072, 789, 761, 734, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24-7.05 (8H, m, Ar**H**), 7.01 (1H, d, *J* = 7.4 Hz, Ar**H**), 3.25 (1H, d, *J* = 17.0 Hz, C**H**$_2$C=C), 2.73 (1H, d, *J* = 17.0 Hz, C**H**$_2$C=C), 2.44 (1H, dd, *J* = 18.4, 8.5 Hz, C**H**$_2$C=O), 2.31 (3H, s, ArC**H**$_3$), 2.25 (1H, br s, O**H**), 2.20-2.16 (1H, m, C**H**$_2$C=O), 2.12-2.04 (1H, m, C**H**$_2$CH$_2$C=O) 1.97-1.90 (1H, m, CH$_2$C**H**$_2$C=O), 1.23 (3H, s, O=CCC**H**$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 222.1 (C), 142.0 (C), 140.2 (C), 138.1 (C), 135.7 (C), 135.6 (C), 129.3 (CH), 128.5 (2 × CH), 128.4 (CH), 128.2 (CH), 128.0 (2 × CH), 127.7 (CH), 126.1 (CH), 92.7 (C), 56.2 (C), 44.6 (CH_2), 36.6 (CH_2), 29.0 (CH_2), 21.5 (CH_3), 15.5 (CH_3); HRMS (ESI) Exact mass calculated for $C_{22}H_{22}NaO_2$ $[M+Na]^+$: 341.1512, found: 341.1493. Enantiomeric excess was determined by HPLC Chiralcel with OD-H column (80:20 *iso*-hexane:*i*-PrOH, 1.5 mL/min, 254 nm, 25 °C); t_r (minor) = 3.3 min, t_r (major) = 3.8 min, 86% ee.



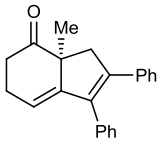
(3a*S*,8a*S*)-3a-Hydroxy-8a-methyl-2,3-diphenyl-3a,8a-dihydrocyclopenta[*a*]inden-8(1*H*)-one (*ent*-2p). The title compound was prepared according to General Procedure B using alkynyl electrophile **1p** (82.3 mg, 0.30 mmol) and phenylboronic acid (73.1 mg, 0.60

mmol), and purified by column chromatography (10% EtOAc/CH_2Cl_2) to give a colourless solid (74.5 mg, 70%). R_f = 0.8 (10% EtOAc/CH_2Cl_2); m.p. 124-129 °C (Et_2O); $[\alpha]_D^{23}$ +43.2 (*c* 0.83, $CHCl_3$); IR 3586 (OH) 3060, 3009, 1714 (C=O), 1603, 1444, 1340, 1292, 1116, 1052, 989 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83-7.75 (1H, m, Ar**H**), 7.44-7.40 (2H, m, Ar**H**), 7.33-7.24 (3H, m, Ar**H**), 7.15-7.04 (7H, m, Ar**H**), 7.03-6.98 (1H, m, Ar**H**), 3.49 (1H, d, *J* = 17.4 Hz, C**H**$_2$C=C), 2.87 (1H, d, *J* = 17.4 Hz, C**H**$_2$C=C), 2.46 (1H, s, O**H**), 1.47 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.4 (C), 154.6 (C), 140.4 (C), 140.0 (C), 135.9 (C), 135.6 (C), 134.6 (2 × CH), 130.0 (2 × CH), 129.2 (CH), 128.3 (2 × CH), 128.2 (2 × CH), 127.9 (2 × CH), 127.6 (CH), 127.4 (CH), 125.2 (CH), 123.9 (CH), 92.8 (C), 58.5 (C), 43.6 (CH_2), 19.0 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{25}H_{20}NaO_2]^+$ $[M+Na]^+$: 375.1356, found: 375.1380. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (95:5 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 280 nm, 25 °C); t_r (minor) = 18.9 min, t_r (major) = 26.0 min, 42% ee.

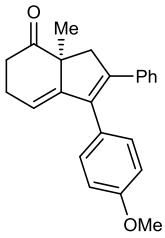


(3aS,6aS)-3a-Hydroxy-6a-methyl-4-(2-methylprop-1-en-1-yl)-5-phenyl-1,2,3,3a,6,6a-hexahydropentalen-1-one (*ent*-2s). The title compound was prepared according to General Procedure B using alkynyl electrophile **1s** (61.3 mg, 0.30 mmol) and phenylboronic acid (73.1 mg, 0.60 mmol), and purified by column chromatography (10% EtOAc/CH_2Cl_2) to give a colourless solid (53.0 mg, 63%). R_f = 0.5 (10% EtOAc/CH_2Cl_2); $[\alpha]_D^{25}$ +4.7 (*c* 0.85, $CHCl_3$); IR 3444 (OH), 2966, 2898, 1721 (C=O), 1492, 1443, 1347, 1062, 853, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.37 (2H, m, Ar**H**), 7.30– 7.17 (3H, m, Ar**H**), 5.87 (1H, dq, *J* = 2.9, 1.6 Hz, C**H**=C(Me)$_2$), 3.12 (1H, dd, *J* = 16.9, 1.6 Hz, C**H**$_2$C=C), 2.69 (1H, dd, *J* = 16.9, 2.9 Hz, C**H**$_2$C=C), 2.51 – 2.29 (2H, m, C**H**$_2$C=O), 2.12 – 1.89 (2H, m, C**H**$_2$CH$_2$C=O), 1.79 (3H, d, *J* = 1.4 Hz, C(C**H**$_3$)(CH$_3$)), 1.18 (3H, s, O=CCC**H**$_3$), 1.16 (3H, d, *J* = 1.4 Hz, C(CH$_3$)(C**H**$_3$)). ^{13}C NMR (101 MHz, $CDCl_3$) δ 222.0 (C), 140.4 (C), 139.2 (C), 137.5 (C), 136.9 (C), 128.1 (2 × CH), 127.5 (2 × CH), 127.4 (CH), 117.0 (CH), 92.4 (C), 55.5 (C), 44.8 (CH_2), 36.6 (CH_2), 29.6 (CH_2), 25.8 (CH_3), 19.8 (CH_3), 15.6 (CH_3). HRMS (ESI) Exact mass calculated for $C_{19}H_{22}NaO_2$ $[M+Na]^+$: 305.1512, found: 305.1515. Enantiomeric excess was

determined by HPLC Chiralcel with OD-H column (80:20 *iso*-hexane:*i*-PrOH, 1.5 mL/min, 254 nm, 25 °C); t_r (major) = 3.1 min, t_r (minor) = 3.8 min, 29% ee.

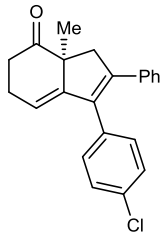


(*S*)-3a-Methyl-1,2-diphenyl-3,3a,5,6-tetrahydro-4*H*-inden-4-one (21a). The title compound was prepared according to General Procedure C using substrate **20a** (72.1 mg, 0.30 mmol) and phenylboronic acid (73.1 mg, 0.60 mmol), and purified by column chromatography (10% EtOAc/pet. ether) to give a pale yellow oil (67.0 mg, 74%). R_f = 0.3 (10% EtOAc/pet. ether); $[\alpha]_D^{23}$ +58.2 (*c* 0.71, $CHCl_3$); IR 3009, 2930, 2854, 1703 (C=O), 1601, 1490, 1444, 1240, 1098, 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.30 (3H, m, Ar**H**), 7.23-7.17 (2H, m, Ar**H**), 7.16 (5H, s, Ar**H**), 5.78-5.39 (1H, m, =C**H**), 3.62 (1H, d, *J* = 16.8 Hz, $CH_3CC\mathbf{H}_2C$=C), 2.79-2.65 (2H, m, $C\mathbf{H}_2C$=O), 2.60 (1H, d, *J* = 16.8 Hz, $CH_3CC\mathbf{H}_2C$=C), 2.52-2.24 (2H, m, $C\mathbf{H}_2CH_2C$=O), 1.45 (3H, s, $C\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.1 (C), 153.7 (C), 139.7 (C), 136.6 (C), 136.5 (C), 135.7 (C), 129.5 (2 × CH), 128.6 (2 × CH), 127.9 (4 × CH), 127.4 (CH), 127.3 (CH), 116.5 (CH), 53.5 (C), 44.1 (CH_2), 35.9 (CH_2), 24.2 (CH_3), 23.2 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{22}H_{20}NaO]^+$ $[M+Na]^+$: 323.1406, found: 323.1422. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (80:20 *iso*-hexane:*i*-PrOH, 1.5 mL/min, 280 nm, 25 °C); t_r (major) = 3.4 min, t_r (minor) = 4.4 min, 95% ee.

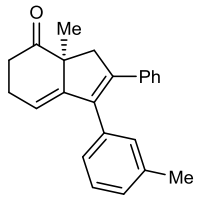


(*S*)-1-(4-Methoxyphenyl)-3a-methyl-2-phenyl-3,3a,5,6-tetrahydro-4*H*-inden-4-one (21b). The title compound was prepared according to General Procedure C using substrate **20b** (81.1 mg, 0.30 mmol) and phenylboronic acid (73.1 mg, 0.60 mmol), and purified by column chromatography (5% EtOAc/pet. ether) to give a pale yellow oil (55.1 mg, 56%). R_f = 0.5 (20% EtOAc/pet. ether); $[\alpha]_D^{23}$ +13.6 (*c* 0.54, $CHCl_3$); IR 3008, 2961, 2930, 1707 (C=O), 1604, 1511, 1462, 1246, 1177, 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.19-7.11 (7H, m, Ar**H**), 6.91-6.87 (2H, m, Ar**H**), 5.61 (1H, dd, *J* =

6.7, 2.6 Hz, =C**H**), 3.84 (3H, s, OC**H**$_3$), 3.60 (1H, d, *J* = 16.7 Hz, $CH_3CC\mathbf{H}_2C$=C), 2.84-2.65 (2H, m, C**H**$_2$C=O), 2.57 (1H, d, *J* = 16.7 Hz, $CH_3CC\mathbf{H}_2C$=C), 2.51-2.27 (2H, m, C**H**$_2$CH$_2$C=O), 1.44 (s, 1H, CC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.2 (C), 158.8 (C), 153.8 (C), 139.3 (C), 136.7 (C), 136.1 (C), 130.7 (2 × CH), 127.9 (4 × CH), 127.8 (C), 127.2 (CH), 116.3 (CH), 114.0 (2 × CH), 55.2 (CH_3), 53.4 (C), 44.1 (CH_2), 35.9 (CH_2), 24.2 (CH_3), 23.2 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{23}H_{22}NaO_2]^+$ $[M+Na]^+$: 353.1512, found: 353.1514. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (80:20 *iso*-hexane:*i*-PrOH, 1.5 mL/min, 280 nm, 25 °C); t_r (major) = 4.8 min, t_r (minor) = 5.5 min, 97% ee.

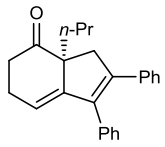


(*S*)-1-(4-Chlorophenyl)-3a-methyl-2-phenyl-3,3a,5,6-tetrahydro-4*H*-inden-4-one (21c). The title compound was prepared according to General Procedure C using substrate **20c** (82.4 mg, 0.30 mmol) and phenylboronic acid (73.1 mg, 0.60 mmol), and purified by column chromatography (5% EtOAc/pet. ether) to give a pale yellow oil (37.7 mg, 37%). R_f = 0.3 (10% EtOAc/pet. ether); $[\alpha]_D^{23}$ –29.2 (*c* 0.56, $CHCl_3$); IR 1713 (C=O), 1488, 1287, 1090, 835, 764, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.30 (2H, m, Ar**H**), 7.22-7.11 (7H, m, Ar**H**), 5.58 (1H, dd, *J* = 7.0, 2.7 Hz, =C**H**), 3.62 (1H, d, *J* = 16.9 Hz, $CH_3CC\mathbf{H}_2C$=C), 2.82-2.68 (2H, m, C**H**$_2$C=O), 2.59 (1H, d, *J* = 16.9 Hz, $CH_3CC\mathbf{H}_2C$=C), 2.53-2.31 (2H, m, C**H**$_2$CH$_2$C=O), 1.44 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.8 (C), 153.3 (C), 140.5 (C), 136.2 (C), 135.3 (C), 134.1 (C), 133.2 (C), 131.0 (2 × CH), 128.9 (2 × CH), 128.1 (2 × CH), 127.9 (2 × CH), 127.5 (CH), 116.6 (CH), 53.5 (C), 44.2 (CH_2), 35.8 (CH_2), 24.2 (CH_3), 23.2 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{22}H_{19}ClNaO_2]^+$ $[M+Na]^+$: 357.1017, found: 357.1002. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (80:20 *iso*-hexane:*i*-PrOH, 1.5 mL/min, 280 nm, 25 °C); t_r (major) = 3.5 min, t_r (minor) = 4.5 min, 95% ee.



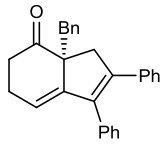
(*S*)-3a-Methyl-2-phenyl-1-(*m*-tolyl)-3,3a,5,6-tetrahydro-4*H*-inden-4-one (21d). The title compound was prepared according to General Procedure C using substrate **20d** (76.3 mg, 0.30 mmol) and

phenylboronic acid (73.1 mg, 0.60 mmol), and purified by column chromatography (5% EtOAc/pet. ether) to give a pale yellow oil (68.2 mg, 72%). R_f = 0.6 (20% EtOAc/pet. ether) $[\alpha]_D^{23}$ +75.1 (*c* 0.34, $CHCl_3$); IR 3008, 2929, 2855, 1704 (C=O), 1601, 1494, 1445, 1360, 1240, 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (1H, m, Ar**H**), 7.16 (5H, s, Ar**H**), 7.15-7.10 (1H, m, Ar**H**), 7.04-7.01 (1H, m, Ar**H**), 7.0-6.95 (1H, m, Ar**H**) 5.58 (1H, ddd, *J* = 7.0, 3.0, 0.9 Hz, =C**H**), 3.61 (1H, d, *J* = 16.7 Hz, $CH_3CC\mathbf{H}_2C$=C), 2.84-2.67 (2H, m, $C\mathbf{H}_2C$=O), 2.60 (1H, d, *J* = 16.7 Hz, $CH_3CC\mathbf{H}_2C$=C), 2.51-2.35 (2H, m, $C\mathbf{H}_2CH_2C$=O), 2.33 (3H, s, $ArC\mathbf{H}_3$), 1.44 (3H, s, O=$CCC\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.2 (C), 153.8 (C), 139.4 (C), 138.2 (C), 136.7 (C), 136.6 (C), 135.7 (C), 130.0 (CH), 128.5 (CH), 128.1 (CH), 127.93 (2 × CH), 127.90 (2 × CH), 127.3 (CH), 126.5 (CH), 116.5 (CH), 53.4 (C), 44.1 (CH_2), 35.9 (CH_2), 24.2 (CH_3), 23.2 (CH_2), 21.4 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{23}H_{22}NaO]^+$ $[M+Na]^+$: 337.1563, found: 337.1576. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (80:20 *iso*-hexane:*i*-PrOH, 1.5 mL/min, 280 nm, 25 °C); t_r (major) = 3.1 min, t_r (minor) = 3.7 min, 97% ee.



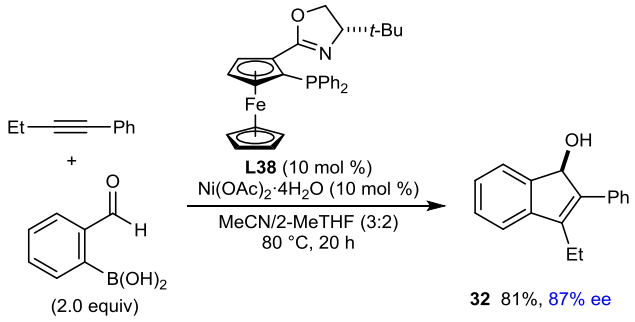
(*S*)-1,2-Diphenyl-3a-propyl-3,3a,5,6-tetrahydro-4*H*-inden-4-one (21e). The title compound was prepared according to General Procedure C using substrate **20e** (94.9 mg, 0.30 mmol) and phenylboronic acid (73.1 mg, 0.60 mmol), and purified by column chromatography (5% EtOAc/pet. ether) to give a pale yellow oil (78.3 mg, 79%). R_f = 0.6 (20% EtOAc/pet. ether); $[\alpha]_D^{23}$ –35.4 (*c* 0.73, $CHCl_3$); IR 3009, 2963, 1708 (C=O), 1601, 1491, 1445, 1240, 1102, 1074, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.30 (3H, m, Ar**H**), 7.24-7.14 (7H, m, Ar**H**), 5.59 (1H, ddd, *J* = 6.8, 3.1, 0.9 Hz, =C**H**), 3.62 (1H, d, *J* = 17.0 Hz, $CH_3CC\mathbf{H}_2C$=C), 2.89-2.59 (3H, m, $C\mathbf{H}_2C$=O and $CH_3CC\mathbf{H}_2C$=C), 2.55-2.27 (2H, m, $C\mathbf{H}_2CH_2C$=O), 1.87 (1H, td, *J* = 12.8, 4.5 Hz, $C\mathbf{H}_2CH_2CH_3$), 1.69 (1H, td, *J* = 12.8, 4.5 Hz, $C\mathbf{H}_2CH_2CH_3$), 1.54-1.41 (1H, m, $CH_2C\mathbf{H}_2CH_3$), 1.40-1.21 (1H, m, $CH_2C\mathbf{H}_2CH_3$), 0.93 (3H, t, *J* = 7.3 Hz, $CH_2CH_2C\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.3 (C), 152.9 (C), 140.2 (C), 137.5 (C), 136.4 (C), 135.8 (C), 129.5 (2 × CH), 128.6 (2 × CH), 128.0 (2 × CH), 127.9 (2 × CH), 127.4 (CH), 127.3 (CH), 116.8 (CH), 58.0 (CH), 41.4 (CH_2), 39.1 (CH_2), 35.7 (CH_2), 23.4 (CH_2), 17.8 (CH_2), 14.5 (CH_3); HRMS (ESI) Exact mass calculated

for $[C_{24}H_{24}NaO]^+$ $[M+Na]^+$: 351.1719, found: 357.1727. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (80:20 *iso*-hexane:*i*-PrOH, 1.5 mL/min, 280 nm, 25 °C); t_r (minor) = 3.5 min, t_r (major) = 5.0 min, 94% ee.



(*S*)-3a-Benzyl-1,2-diphenyl-3,3a,5,6-tetrahydro-4*H*-inden-4-one (21f). The title compound was prepared according to General Procedure C using substrate **20f** (94.9 mg, 0.30 mmol) and phenylboronic acid (73.1 mg, 0.60 mmol), and purified by column chromatography (10% EtOAc/pet. ether) to give a pale yellow oil (61.5 mg, 54%). R_f = 0.5 (10% EtOAc/pet. ether); $[\alpha]_D^{23}$ –43.6 (*c* 0.73, $CHCl_3$); IR 3009, 2929, 2854, 1704 (C=O), 1602, 1496, 1445, 1261, 1246, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32-7.28 (2H, m, Ar**H**), 7.26-7.18 (6H, m, Ar**H**), 7.17-7.08 (3H, m, Ar**H**), 7.06-7.03 (2H, m, Ar**H**), 6.99-6.95 (2H, m, Ar**H**), 5.70 (1H, dd, *J* = 6.7, 3.0 Hz, =C**H**), 3.50 (1H, d, *J* = 16.9 Hz, $CH_3CC\mathbf{H}_2C$=C), 3.22 (1H, d, *J* = 13.1 Hz, C$\mathbf{H}_2$Ph), 2.92 (1H, d, *J* = 13.1 Hz, C$\mathbf{H}_2$Ph), 2.85 (1H, d, *J* = 16.9 Hz, $CH_3CC\mathbf{H}_2C$=C), 2.69-2.58 (1H, m, C$\mathbf{H}_2$C=O), 2.43-2.24 (3H, m, C$\mathbf{H}_2$C$\mathbf{H}_2$C=O); ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.0 (C), 151.0 (C), 140.1 (C), 137.6 (C), 136.4 (2 × C), 135.4 (C), 130.1 (2 × CH), 129.5 (2 × CH), 128.4 (2 × CH), 127.94 (2 × CH) 127.83 (2 × CH), 127.82 (2 × CH), 127.3 (CH), 127.2 (CH), 126.9 (CH), 118.1 (CH), 58.8 (C), 42.81 (CH_2), 42.76 (CH_2), 36.9 (CH_2), 22.8 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{28}H_{24}NaO]^+$ $[M+Na]^+$: 399.1719 found: 399.1726. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (80:20 *iso*-hexane:*i*-PrOH, 1.5 mL/min, 280 nm, 25 °C); t_r (minor) = 4.7 min, t_r (major) = 7.4 min, 88% ee.

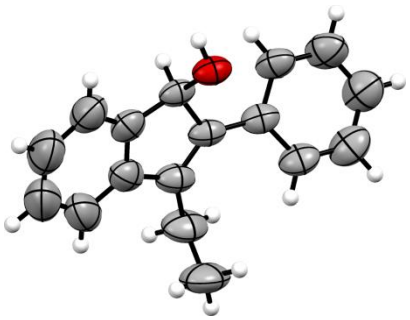
(*R*)-3-Ethyl-2-phenyl-1*H*-inden-1-ol (42)

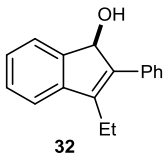


An oven-dried microwave vial fitted with a stirrer bar was charged with $Ni(OAc)_2$•$4H_2O$ (7.5 mg, 0.03 mmol) and (*S*,*S*)-*t*-Bu-FOXAP (**L38**, 14.9 mg, 0.03 mmol). The vial was capped with a crimp cap PTFE seal and purged with a stream of N_2. Deoxygenated MeCN (0.9 mL) and 2-MeTHF (0.6 mL) were added and the mixture was stirred at 80 °C for 20 min. In a separate vial, 1-phenyl-1-butyne (39.1 mg, 0.30 mmol) and 2-formylphenylboronic acid (90.0 mg, 0.60 mmol) were weighed out and the vial was purged with a stream of N_2. Deoxygenated MeCN (0.9 mL) and 2-MeTHF (0.6 mL) were added. The resulting solution was then transferred to the first microwave vial *via* syringe and the reaction was stirred at 80 °C for 16 h. The reaction was cooled to room temperature, diluted with CH_2Cl_2 (15 mL) and washed with a 1:1 mixture of H_2O and saturated aqueous NH_4Cl solution (25 mL). The aqueous layer was extracted with CH_2Cl_2 (15 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% EtOAc/pet. ether) to give *indenol* **10** (57.8 mg, 81%) as a colourless solid. R_f = 0.4 (20% EtOAc/pet. ether); m.p. 109-111°C (EtOAc/pet. ether); $[\alpha]_D^{23}$ +241.3 (*c* 0.62, $CHCl_3$); IR 3120 (OH), 2965, 1601 (C=O), 1494, 1465, 1298, 768, 746, 693, 501 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (1H, d, *J* = 7.2 Hz, Ar**H**), 7.54-7.43 (4H, m, Ar**H**), 7.43-7.31 (3H, m, Ar**H**), 7.27 (1H, td, *J* = 7.2, 1.5 Hz, Ar**H**), 5.54 (1H, d, *J* = 8.2 Hz, C**H**OH), 2.70 (2H, qd, *J* = 7.6, 1.7 Hz, C$\mathbf{H}_2$), 1.71 (1H, d, *J* = 8.2 Hz, O**H**), 1.33 (3H, t, *J* = 7.6 Hz, C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.6 (C), 143.5 (C), 142.8 (C), 141.3 (C), 135.0 (C), 128.8 (2 × CH), 128.6, (3 × CH), 127.2 (CH), 126.0 (CH), 123.4 (CH), 119.6 (CH), 77.5 (CH), 19.2 (CH_2), 13.32 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{17}H_{16}NaO]^+$ $[M+Na]^+$: 259.1093, found: 259.1099. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (80:20 *iso*-

hexane:*i*-PrOH, 1.5 mL/min, 280 nm, 25 °C); t_r (major) = 4.5 min, t_r (minor) = 5.8 min, 87% ee.

Slow diffusion of petroleum ether into a solution of **32** in EtOAc gave crystals that were suitable for X-ray crystallography:

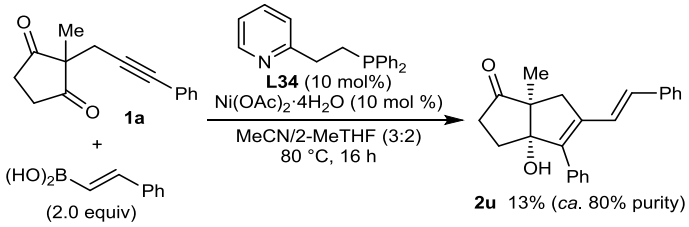




32
CCDC 1469146
Flack parameter = –0.16(11)

3.5 Further Exploration of Substrate Scope

(±)-3a-Hydroxy-6a-methyl-4-phenyl-5-[(*E*)-styryl)-3,3a,6,6a-tetrahydropentalen-1(2*H*)-one (S10)

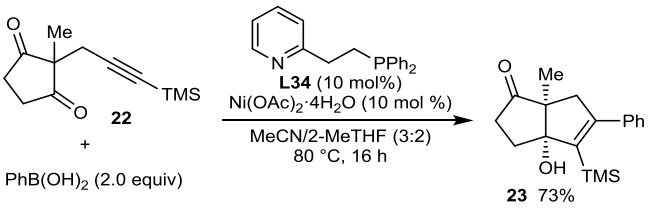


2u 13% (*ca.* 80% purity)

An oven-dried microwave vial fitted with a stirrer bar was charged with $Ni(OAc)_2$•$4H_2O$ (7.5 mg, 0.03 mmol) and pyphos (**L34**, 8.7 mg, 0.03 mmol). The vial was capped with a crimp cap PTFE seal and purged with a stream of N_2. Deoxygenated MeCN (0.9 mL) and 2-MeTHF (0.6 mL) were added and the mixture was stirred at 80 °C for 20 min. In a separate vial, the alkynyl electrophile **1a** (67.9 mg, 0.30 mmol) and *trans*-2-phenylvinylboronic acid (88.8 mg, 0.60 mmol) were weighed out and the vial was purged with a stream of N_2. Deoxygenated MeCN (0.9 mL) and 2-MeTHF (0.6 mL) were added. The resulting solution was then transferred to the first microwave vial *via* syringe and the reaction was stirred at 80 °C for 16 h. The reaction was cooled to room temperature, diluted with CH_2Cl_2 (15 mL) and washed with a 1:1 mixture of H_2O and saturated aqueous NH_4Cl solution (25 mL).

The aqueous layer was extracted with CH_2Cl_2 (15 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (5% EtOAc/CH_2Cl_2) to give **2u** as a colourless solid (12.4 mg, 13%) which also contained *ca.* 20% of unidentified impurities. R_f = 0.3 (5% EtOAc/CH_2Cl_2); IR 3436 (OH), 2931, 1717 (C=O), 1492, 1353, 1242, 1070, 1044, 753, 693 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53-7.28 (8H, m, Ar**H**), 7.26-7.12 (2H, m, Ar**H**), 6.94 (1H, d, *J* = 16.2 Hz, C**H**=C**H**Ph), 6.69 (1H, d, *J* = 16.2 Hz, C**H**=C**H**Ph), 3.16 (1H, d, *J* = 16.6 Hz, C**H**$_2$C=C), 2.65 (1H, d, *J* = 16.6 Hz, C**H**$_2$C=C), 2.53-2.33 (1H, m, C**H**$_2$C=O), 2.28-1.93 (3H, m, C**H**$_2$C**H**$_2$), 1.89 (1H, br s, O**H**), 1.25 (3H, s, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 221.5 (C), 142.5 (C), 141.0 (C), 136.9 (C), 134.9 (C), 133.8 (CH), 129.2 (2 × CH), 128.6 (2 × CH), 128.5 (2 × CH), 128.1 (CH), 127.8 (CH), 126.7 (2 × CH), 123.1 (CH), 92.4 (C), 56.3 (C), 41.0 (CH_2), 36.5 (CH_2), 29.2 (CH_2), 15.6 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{23}H_{22}NaO_2]^+$ $[M+Na]^+$: 353.1512, found: 353.1517.

(±)-3a-Hydroxy-6a-methyl-5-phenyl-4-(trimethylsilyl)-3,3a,6,6a-tetrahydropentalen-1(2*H*)-one (23)

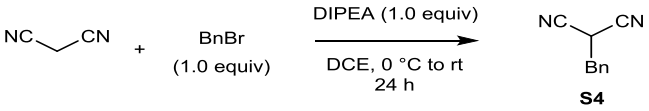


An oven-dried microwave vial fitted with a stirrer bar was charged with $Ni(OAc)_2$•$4H_2O$ (7.5 mg, 0.03 mmol) and pyphos (**L34**, 8.7 mg, 0.03 mmol). The vial was capped with a crimp cap PTFE seal and purged with a stream of N_2. Deoxygenated MeCN (0.9 mL) and 2-MeTHF (0.6 mL) were added and the mixture was stirred at 80 °C for 20 min. In a separate vial, the alkynyl electrophile **22** (66.7 mg, 0.30 mmol) and phenylboronic acid (73.1 mg, 0.60 mmol) were weighed out and the vial was purged with a stream of N_2. Deoxygenated MeCN (0.9 mL) and 2-MeTHF (0.6 mL) were added. The resulting solution was then transferred to the first microwave vial *via* syringe and the reaction was stirred at 80 °C for 16 h. The reaction was cooled to room temperature, diluted with CH_2Cl_2 (15 mL) and washed with a 1:1 mixture of H_2O and saturated aqueous NH_4Cl solution (25 mL). The aqueous layer was extracted with CH_2Cl_2 (15 mL). The combined organic layers

were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (20% EtOAc/pet. ether) to give *alcohol* **23** as a colourless solid (66.2 mg, 73%). R_f = 0.4 (20% EtOAc/pet. ether); m.p. 55-57 °C ($CHCl_3$); IR 3448 (OH), 2956, 2250, 1730 (C=O), 1586, 1461, 1251, 1123, 1062, 911 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.26 (3H, m, Ar**H**), 7.11-7.06 (2H, m, Ar**H**), 2.85 (1H, d, *J* = 17.2 Hz, C**H**$_2$C=C), 2.74 (1H, d, *J* = 17.2 Hz, C**H**$_2$C=C), 2.59-2.44 (2H, m, C**H**$_2$C=O), 2.27-2.08 (m, C**H**$_2$CH$_2$C=O), 1.74 (1H, s, O**H**), 1.15 (3H, s, CC**H**$_3$), 0.01 (9H, s, Si(C**H**$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 221.7 (C), 158.8 (C), 142.0 (C), 139.5 (C), 127.9 (2 × CH), 127.6 (CH), 127.1 (2 × CH), 95.7 (C), 58.0 (C), 49.8 (CH_2), 37.0 (CH_2), 31.9 (CH_2), 15.6 (CH_3), 0.8 (3 × CH_3); HRMS (ESI) Exact mass calculated for $[C_{18}H_{24}NaO_2Si]^+$ $[M+Na]^+$: 323.1438, found: 323.1441.

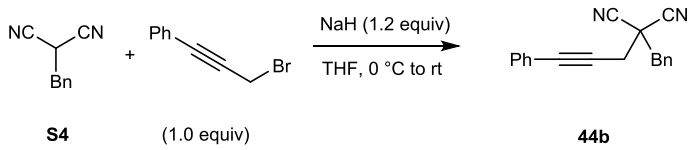
3.6 Synthesis of alkynylmalononitrile substrates

2-Benzylpropanedinitrile (S4)[70]



N,*N*-Diisopropylethylamine (23.7 mL, 136 mmol) was added dropwise to a stirred solution of malononitrile (9.0 g, 136 mmol) in DCE (270 mL) at 0 °C. Benzyl bromide (16.2 mL, 136 mmol) was then added dropwise and the solution allowed to-warm to room temperature. After 24 h the reaction was quenched with H_2O (300 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were then dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (0 – 20% EtOAc/pet. ether) to give benzylated malononitrile S4 as a colourless solid (7.8 g, 37%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.39 (3H, m, Ar**H**), 7.36-7.31 (2H, m, Ar**H**), 3.93 (1H, t, *J* = 7.0 Hz, (CN)$_2$C**H**), 3.29 (2H, d, *J* = 7.0 Hz, C**H**$_2$Ph). ^{13}C NMR (101 MHz, $CDCl_3$) δ 130.2 (C), 129.2 (2 × CH), 129.1 (2 × CH), 128.7 (CH), 112.2 (2 × C), 36.6 (CH), 24.9 (CH_2).

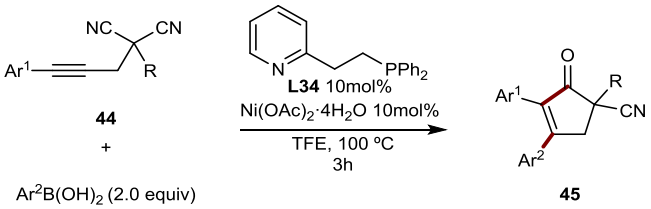
2-Benzyl-2-(3-phenylprop-2-yn-1-yl)propanedinitrile (44b)



2-Benzylpropanedinitrile **S4** (1.0g, 6.4 mmol) in THF (5 mL) was added to a suspension of NaH (0.18 g, 7.7 mmol) in THF (30 mL) at 0 °C. This was allowed to warm to room temperature and stirred for 30 min. Phenyl propargyl bromide (1.25 g, 6.4 mmol) was added dropwise and the resulting solution was stirred at room temperature for 2 h. The reaction was then quenched with a saturated aqueous NH_4Cl solution (50 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers were then dried (Na_2SO_4) and concentrated under reduced pressure. The residue was then purified by column chromatography (0 – 5% EtOAc/pet. ether) to give alkynyl-malanonitrile **44b** as a colourless solid (1.12 g, 65%). IR 3031, 2936, 2249 (CN), 1598, 1490, 1441, 1088, 759, 649, 474 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.51 (2H, m, Ar**H**), 7.47-7.35 (8H, m, Ar**H**), 3.43 (2H, s, C**H**$_2$Ph), 3.12 (2H, s, C**H**$_2$C≡C); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.9 (2 × CH), 131.4 (C), 130.28 (2 × CH), 130.25 (CH), 129.1 (CH), 129.0 (2 × CH), 128.8 (C), 128.4 (2 × CH), 114.5 (2 × C), 87.4 (C), 79.7 (C), 43.4 (C), 41.7 (CH_2), 28.5 (CH_2). HRMS (ESI) Exact mass calculated for $[C_{19}H_{14}N_2Na]^+$ $[M+Na]^+$: 293.1049, found: 293.1048.

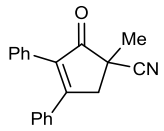
3.7 Arylative cyclisations of alkynylmalanonitriles

General procedure D

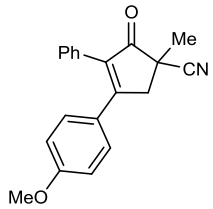


An oven-dried microwave vial fitted with a stirrer bar was charged with alkynyl electrophile **44** (0.30 mmol), the arylboronic acid (0.60 mmol), $Ni(OAc)_2$•$4H_2O$ (7.5 mg, 0.03 mmol) and pyphos (**L34**, 8.7 mg, 0.03 mmol). The vial was capped with a crimp cap PTFE seal and purged with a stream of N_2. Deoxygenated TFE (3.0 mL)

was added and the mixture was stirred at 100 °C for 3 h. The reaction was cooled to room temperature, diluted with EtOAc (5 mL) and washed with an aqueous solution of HCl (5%, 10 mL). The aqueous layer was extracted with EtOAc (5 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography to give the title compound.



1-Methyl-2-oxo-3,4-diphenylcyclopent-3-ene-1-carbonitrile (45a). The title compound was prepared according to General Procedure D using alkynyl-electrophile **44a** (58.3 mg, 0.30 mmol) and 2-phenylboronic acid (73.2 mg, 0.60 mmol), and purified by column chromatography (10% EtOAc/pet. ether) to give **45a** (61.5 mg, 75%) as a colourless oil. IR 3031, 2936, 2249 (CN), 1598, 1490, 1441, 1088, 759, 649, 474 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47-7.30 (8H, m, Ar**H**), 7.29-7.22 (2H, m, Ar**H**), 3.69 (1H, d, *J* = 18.2 Hz, C**H**$_2$), 3.12 (1H, d, *J* = 18.2 Hz, C**H**$_2$), 1.75 (2H, s, C**H**$_3$); 13C NMR (101 MHz, $CDCl_3$) δ 199.0 (C), 164.9 (C), 136.1 (C), 134.0 (C), 130.9 (CH), 130.8 (C), 129.4 (2 × CH), 128.72 (2 × CH), 128.66 (2 × CH), 128.6 (CH), 128.2 (2 × CH), 120.3 (C), 43.2 (CH_2), 41.1 (C), 23.7 (CH_3); HRMS (ESI) exact mass calculated for $[C_{19}H_{15}NONa]^+$ $[M+Na]^+$: 296.1046, found: 296.1053.

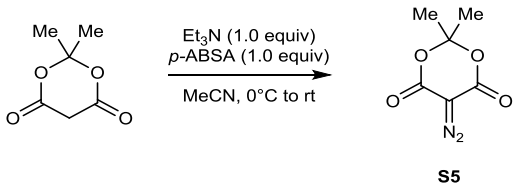


4-(4-Methoxyphenyl)-1-methyl-2-oxo-3-phenylcyclopent-3-ene-1-carbonitrile (45d). The title compound was prepared according to General Procedure D using alkynyl-electrophile **44a** (58.3 mg, 0.30 mmol) and 4-methoxyphenylboronic acid (91.2 mg, 0.60 mmol), and purified by column chromatography (10% EtOAc/pet. ether) to give **45d** (54.6 mg, 60%) as a yellow oil. IR 2934, 2841, 2238 (CN), 1707 (C=O), 1600, 1513, 1352, 1257, 1178, 728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 -7.35 (3H, m, Ar**H**), 7.34-7.29 (2H, m, Ar**H**), 7.28-7.23 (2H, m, Ar**H**), 6.84-6.79 (2H, m, Ar**H**), 3.82 (3H, s, OC**H**$_3$), 3.66 (1H, d, *J* = 17.9 Hz, C**H**$_2$), 3.10 (1H, d, *J* = 17.9 Hz, C**H**$_2$), 1.73 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.8 (C), 164.1 (C), 161.9 (C), 134.5 (C), 131.6 (C), 130.2 (2 × CH), 129.4 (2 × CH), 128.8 (2 × CH), 128.4

(CH), 126.1 (C), 120.5 (C), 114.1 (2 × CH), 55.4 (CH_3), 42.9 (CH_2), 41.0 (C), 23.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{20}H_{17}NO_2Na]^+$ $[M+Na]^+$: 326.1151, found: 326.1159.

3.8 Synthesis of alkynylmalonate substrates

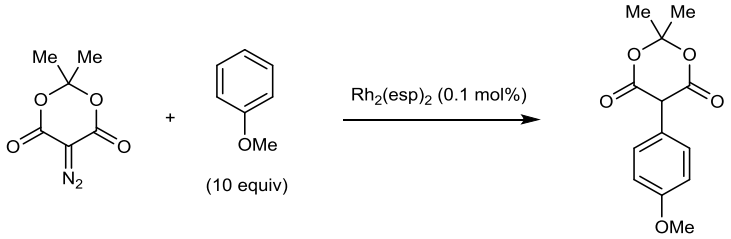
2,2-Dimethyl-4,6-dioxo-1,3-dioxane-5-diazonium (S5)[71]



S5

Meldrum's acid (10.0 g, 69.4 mmol) and 4-acetamidobenzenesulfonyl azide (16.7 g, 69.4 mmol) in MeCN (250mL) was cooled to 0 °C. Et_3N (9.7 mL, 69.4 mmol) was added and the solution was allowed to warm to room temperature and stirred for 2 h. The solution was then diluted with Et_2O (100 mL), filtered and concentrated under reduced pressure. The residue was then suspended in a mixture of CH_2Cl_2 and pet. ether (50mL, 1:1) and stirred at room temperature for 10 min. The suspension was then filtered and concentrated under reduced pressure to give to title compound **S5** (8.67 g, 73%) which was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.80 (6H, s, 2 × C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.3 (2 C), 107.1 (C), 26.8 (2 × CH_3).

5-(4-Methoxyphenyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (S6)[71]

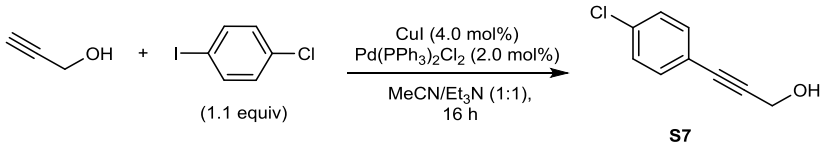


S5 **S6**

Diazo compound **S5** (3.0 g, 17.6 mmol) and $Rh_2(esp)_2$ (13.3 mg, 0.018 mmol) was added to a round bottom flask that was then sealed with a rubber septa and purged with a stream of N_2. Deoxygenated anisole (19 mL, 176.3 mmol) was then added and the solution stirred overnight at room temperature. The resulting suspension was

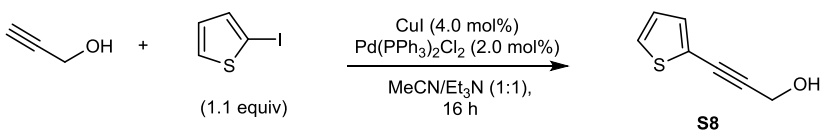
diluted with pet. ether (100 mL) and filtered and washed with cold pet. ether and dried under vacuum filtration to give the title compound **S6** (3.71 g, 84%) which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.19 (2H, m, Ar**H**), 6.97 – 6.92 (2H, m, Ar**H**), 4.73 (1H, s, C**H**$(C{=}O)_2$), 3.83 (3H, s, OC$\mathbf{H}_3$), 1.88 (3H,d, *J* = 0.8 Hz, C$\mathbf{H}_3$), 1.76 (3H, d, *J* = 0.8 Hz, C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.0 (2 C), 159.8 (C), 130.2 (2 × CH), 122.3 (C), 114.6 (2 × CH), 105.6 (C), 55.3 (CH), 52.1 (CH_3), 28.5 (CH_3), 27.5 (CH_3).

3-(4-Chlorophenyl)prop-2-yn-1-ol (S7)[72]



1-Chloro-4-iodobenzene (3.93 g, 16.5 mmol), $Pd(PPh_3)_2Cl_2$ (210 mg, 0.3 mmol), CuI (114 mg, 0.6 mmol) was added to a round bottom flask that was then sealed with a rubber septa and purged with a stream of N_2. Deoxygenated MeCN (10 mL) and Et_3N (10 mL) was then added followed by propargyl alcohol (0.89 mL 15.0 mmol). The solution was then stirred at room temperature overnight. A saturated aqueous solution of NH_4Cl (10 mL) was then added and the solution was then extracted with EtOAc (3 × 30 mL). The combined organic layers were then dried (Na_2SO_4) filtered and concentrated under reduced pressure. The residue was purified by column chromatography (20% EtOAc/pet. ether) to give the title compound **S7** (2.83 g, quant.) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.35 (2H, m, Ar**H**), 7.32-7.28 (2H, m, Ar**H**), 4.50 (2H, d, *J* = 6.1 Hz, C$\mathbf{H}_2$OH), 1.71 (1H, t, *J* = 6.1 Hz, CH_2O**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.7 (C), 132.9 (2 × CH), 128.7 (2 × CH), 121.0 (C), 88.1 (C), 84.6 (C), 51.6 (CH_2).

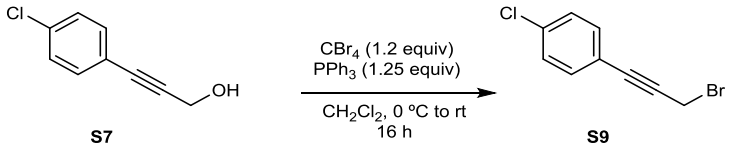
3-(Thiophen-2-yl)prop-2-yn-1-ol (S8)[73]



2-Iodothiophene (1.8 mL, 16.5 mmol), $Pd(PPh_3)_2Cl_2$ (210 mg, 0.3 mmol), CuI (114 mg, 0.6 mmol) was added to a round bottom flask that was then sealed with a rubber septa and purged with a stream of N_2. Deoxygenated MeCN (10 mL) and Et_3N (10

mL) was then added followed by propargyl alcohol (0.89 mL 15.0 mmol). The solution was then stirred at room temperature overnight. A saturated aqueous solution of NH_4Cl (10 mL) was then added and the solution was then extracted with EtOAc (3 × 30 mL). The combined organic layers were then dried (Na_2SO_4) filtered and concentrated under reduced pressure. The residue was purified by column chromatography (20% EtOAc/pet. ether) to give the title compound **S8** (1.6 g, 77%) as a yellow oil.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (1H, dd, *J* = 5.2, 1.2 Hz, Ar**H**), 7.23 (1H, dd, *J* = 3.6, 1.2 Hz, Ar**H**), 6.98 (1H, dd, *J* = 5.2, 3.6 Hz, Ar**H**), 4.52 (2H, d, *J* = 6.1 Hz, C**H**$_2$OH), 1.79-1.71 (1H, m, CH_2O**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.4 (CH), 127.4 (CH), 127.0 (CH), 122.4 (C), 91.1 (C), 79.1 (C), 51.7 (CH_2).

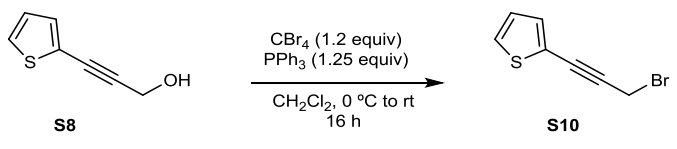
1-(3-Bromoprop-1-yn-1-yl)-4-chlorobenzene (S9)[72]



S7 **S9**

Triphenylphosphine (2.46 g, 9.4 mmol) was added to a solution of alcohol **S7** (1.25 g 7.5 mmol) and carbon tetrabromide (2.99 g, 9.0 mmol) in CH_2Cl_2 (25 mL) at 0 °C. The resulting solution was allowed to warm to room temperature and stirred overnight. EtOH (5 mL) was then added and the solution stirred for 30 min. The mixture was then concentrated under reduced pressure and the residue purified by column chromatography to give the title compound **S9** (1.71 g, quant.) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (2H, d, *J* = 8.4 Hz, Ar**H**), 7.33 (2H, d, *J* = 8.4 Hz, Ar**H**), 4.18 (2H, s, C**H**$_2$Br); ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.9 (C), 133.0 (2 × CH), 128.6 (2 × CH), 120.5 (C), 85.5 (C), 85.2 (C), 14.9 (CH_2).

2-(3-Bromoprop-1-yn-1-yl)thiophene (S10)[74]

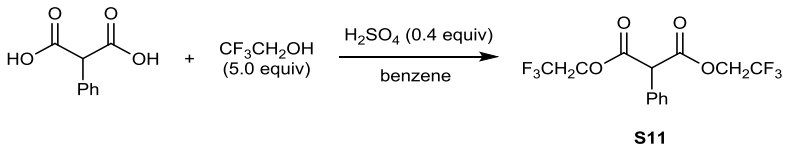


S8 **S10**

Triphenylphosphine (2.46 g, 9.4 mmol) was added to a solution of alcohol **S8** (1.04 g 7.5 mmol) and carbon tetrabromide (2.99 g, 9.0 mmol) in CH_2Cl_2 (25 mL) at 0 °C. The resulting solution was allowed to warm to room temperature and stirred overnight. EtOH (5 mL) was then added and the solution stirred for 30 min. The

mixture was then concentrated under reduced pressure and the residue purified by column chromatography to give the title compound **S10** (1.18 g, 78%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.27 (2H, m, Ar**H**), 7.02 (1H, dd, *J* = 5.2, 3.7 Hz, Ar**H**), 4.21 (2H, s, C**H**$_2$Br); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.9 (CH), 128.0 (CH), 127.0 (C), 125.2 (C), 88.1 (C), 80.1 (C), 15.2 (CH_2).

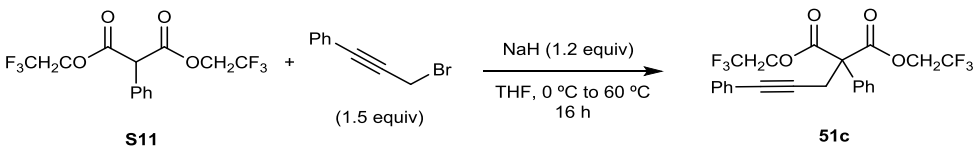
1,3-Bis(2,2,2-trifluoroethyl)-2-phenylpropanedioate (S11)



S11

A round bottom flask equipped with a reflux condenser was charged with phenylmalonic acid (4.0 g, 22.2 mmol), trifluroethanol (7.98 mL, 111.0 mmol), conc. H_2SO_4 (0.5 mL), benzene (20 mL) and a stirrer bar. The mixture was then heated at reflux overnight. The solution was then allowed to cool to room temperature and was diluted with benzene (50 mL). The solution was then washed with an aqueous solution of Na_2CO_3 (10% w/w, 3 × 40 mL), water (40 mL) and brine (40 mL). The organic layer was then dried (Na_2SO_4), filtered and concentrated under reduced pressure to give the title compound **S11** (2.56 g, 35%) as a yellow oil. IR 2980, 1755 (C=O), 1410, 1275, 1158, 1129, 1056, 979, 727, 547 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (5H, s, Ar**H**), 4.83 (1H, s, C**H**Ph), 4.64-4.46 (4H, m, 2 × C**H**$_2$CF$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.9 (2 × C), 130.6 (C), 129.2 (2 × CH), 129.1 (CH), 129.0 (2 × CH), 122.5 (q, $^{1}J_{C\text{-}F}$ = 277.3 Hz, C), 61.3 (q, $^{2}J_{C\text{-}F}$ = 37.2 Hz, 2 × CH_2), 56.7 (CH); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.81 (6F, t, *J* = 8.2 Hz); HRMS (ESI) exact mass calculated for $[C_{13}H_{10}F_6O_4Na]^+$ [M+Na]$^+$: 367.0375, found: 367.0362.

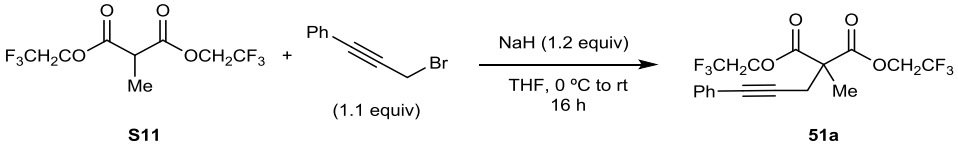
1,3-Bis(2,2,2-trifluoroethyl)-2-phenyl-2-(3-phenylprop-2-yn-1-yl)propanedioate (51c)



S11 **51c**

A solution of malonate **S11** (1.0 g, 3.0 mmol) in THF (5 mL) was added to an ice cooled suspension of NaH (0.14 g, 3.6 mmol) in THF (10 mL). The resulting solution was allowed to warm to room temperature and was stirred for ca. 30 min. Alkynylbromide (0.88 g, 4.5 mmol) was then added dropwise and the resulting solution was heated at 60 °C and stirred overnight. The solution was then cooled to room temperature and quenched with a saturated aqueous solution of NH_4Cl (50 mL). This solution was extracted with EtOAc (3 × 20 mL) and the combined organics dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was then purified by column chromatography (2% EtOAc/pet. ether) to give the title compound **51c** (0.49 g, 36%) as a yellow oil. IR 2976, 1754 (C=O), 1599, 1409, 1154, 1075, 973, 727, 691, 528 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.50 (2H, m, Ar**H**), 7.45 – 7.37 (3H, m, Ar**H**), 7.33 – 7.23 (5H, m, Ar**H**), 4.60 (4H, qd, *J* = 8.2, 2.2 Hz, C**H**$_2$CF$_3$), 3.52 (2H, s, C**H**$_2$C≡C); 13C NMR (101 MHz, Chloroform-d) δ 167.4 (2 × C), 133.9 (C), 131.6 (2 × CH), 128.7 (CH), 128.5 (2 × CH), 128.2 (CH), 128.2 (2 × CH), 127.7 (2 × CH), 123.9 (C), 121.9 (d, $^1J_{C\text{-}F}$ = 162.8 Hz, 2 × C), 84.6 (C), 83.2 (C), 62.3 (C), 61.4 (q, J = 37.3 Hz 2 × CH_2), 26.9 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.63 (6F, t, *J* = 8.2 Hz). HRMS (ESI) exact mass calculated for $[C_{22}H_{16}F_6O_4Na]^+$ $[M+Na]^+$: 481.0845, found 481.0856.

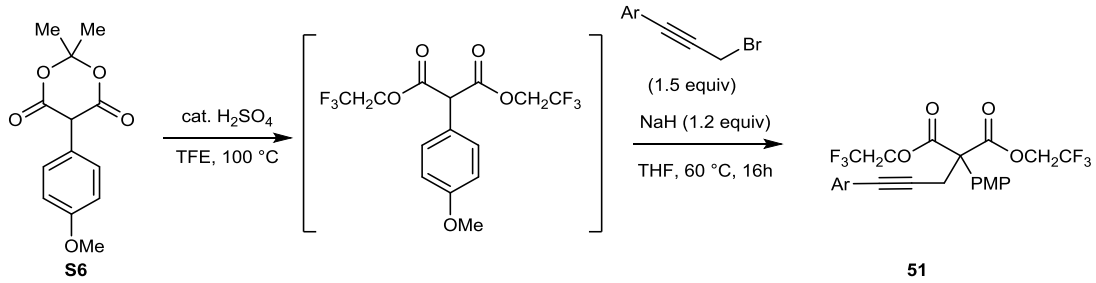
1,3-Bis(2,2,2-trifluoroethyl) 2-methyl-2-(3-phenylprop-2-yn-1-yl)propanedioate (51a)



A solution of malonate **S11** (1.0 g, 3.5 mmol) in THF (5 mL) was added to an ice cooled suspension of NaH (0.10 g, 4.2 mmol) in THF (10 mL). The resulting solution was allowed to warm to room temperature and was stirred for ca. 30 min. Alkynylbromide (0.76 g, 3.9 mmol) was then added dropwise and the resulting solution was then stirred overnight. The solution was then quenched with a saturated aqueous solution of NH_4Cl (50 mL). This solution was extracted with EtOAc (3 × 20 mL) and the combined organics dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was then purified by column chromatography (0 to 5% EtOAc/pet. ether) to give the title compound **54a** (0.76 g, 55%) as a yellow oil. IR

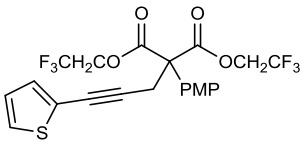
2978, 1755 (C=O), 1492, 1279, 1158, 1102, 975, 757, 691, 664 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.35 (2H, m, Ar**H**), 7.32-7.28 (3H, m, Ar**H**), 4.57 (4H, q, *J* = 8.2 Hz, 2 × C**H**CF_3), 3.09 (2H, s, C**H**$_2$C≡C), 1.56 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7 (2 × C), 131.6 (2 × CH), 128.2 (2 × CH), 123.9 (C), 122.7 (C), 121.1 (C), 84.2 (C), 82.8 (C), 61.2 (q, $^{2}J_{C\text{-}F}$ = 37.2 Hz, CH_2), 53.6 (C), 26.7 (CH_2), 19.8 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.94 (6F, t, *J* = 8.2 Hz). HRMS (ESI) exact mass calculated for $[C_{17}H_{14}F_6O_4Na]^+$ [M+Na]$^+$: 419.0688, found 419.0684.

General procedure E

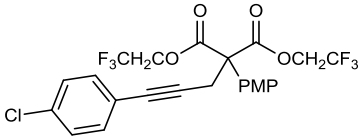


A microwave vial fitted with a stirrer bar was charged with methoxyphenylmeldrum's acid **S6** (0.5 g, 2.0 mmol), trifluoroethanol (10 mL) and a catalytic amount of H_2SO_4. The vial was then capped with a crimp capped PTFE seal and heated at 100 °C for 2 h. The solution was then allowed to cool to room temperature and diluted with a mixture of Et_2O/pet. ether (3:7, 100 mL). The solution was then washed with an aqueous solution of Na_2CO_3 (3 × 100 mL) and brine (50 mL). The organic layer was then dried (Na_2SO_4) and concentrated under reduced pressure. Residual solvent was removed under high vacuum and the crude mixture was used in the alkylation without further purification. A solution of methoxyphenylmalonic ester (0.44g, 1.18 mmol) in THF (5 mL) was added to an ice cooled suspension of NaH (34 mg, 1.42 mmol) in THF (10 mL). The resulting solution was allowed to warm to room temperature and was stirred for ca. 30 min. The appropriate alkynylbromide (1.76 mmol) was then added dropwise and the resulting solution was then warmed to 60 °C and stirred overnight. The solution was then cooled to room temperature and quenched with a saturated aqueous solution of NH_4Cl (50 mL). This solution was extracted with EtOAc (3 × 20 mL) and the combined organics dried (Na_2SO_4), filtered and concentrated under reduced pressure.

The residue was then purified by column chromatography to give the title compound.



1,3-Bis(2,2,2-trifluoroethyl)-2-(4-methoxyphenyl)-2-[3-(thiophen-2-yl)prop-2-yn-1-yl]propanedioate (51i). The title compound was prepared according to General Procedure E using methoxyphenylmeldrum's acid **S6** (0.50 g, 2.0 mmol) and 2-thionylpropargyl bromide **S10** (0.35 g, 1.76 mmol), and purified by column chromatography (10% EtOAc/pet. ether) to give **54i** (467.0 mg, 47% 2 steps) as a yellow oil. R_f 0.4 (10% EtOAc/pet. ether); IR 2968, 1753 (C=O), 1611, 1514, 1282, 1155, 1079, 976, 828, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47-7.39 (2H, m, Ar**H**), 7.20 (1H, dd, *J* = 5.1, 1.2 Hz, Ar**H**), 7.09 (1H, dd, *J* = 3.6, 1.1 Hz, Ar**H**), 6.97-6.89 (3H, m, Ar**H**), 4.60 (4H, q, *J* = 8.2 Hz, 2 × C**H**$_2$CF3), 3.83 (3H, s, ArOC**H**$_3$), 3.52 (2H, s, C**H**$_2$C≡C); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5(2 × C), 159.7 (C), 131.9 (CH), 129.0 (2 × CH), 126.84 (CH), 126.78 (CH), 125.7 (C), 122.7 (C), 122.5 (q, $^1J_{C\text{-}F}$ = 277.9 Hz, 2 × C), 113.9 (2 × CH), 87.3 (C), 77.7 (C), 61.6 (C), 61.4 (q, *J* = 37.0 Hz, 2 × CH_2), 55.3 (CH_3), 27.2 (CH_2). ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.62 (6F, t, *J* = 8.2 Hz); HRMS (ESI) exact mass calculated for $[C_{21}H_{16}F_6O_5SNa]^+$ $[M+Na]^+$: 517.0515, found 517.0507.

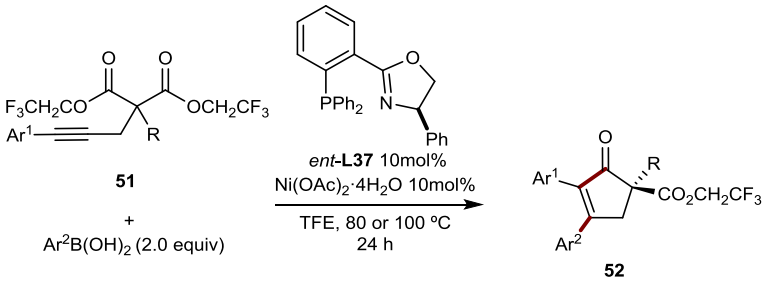


1,3-Bis(2,2,2-trifluoroethyl)-2-[3-(4-chlorophenyl)prop-2-yn-1-yl]-2-(4-methoxyphenyl)propanedioate (51j). The title compound was prepared according to General Procedure E using methoxyphenylmeldrum's acid **S6** (0.50 g, 2.0 mmol) and 4-chlorophenylpropargyl bromide **S9** (0.54 g, 1.76 mmol), and purified by column chromatography (10% EtOAc/pet. ether) to give **54j** (310 mg, 30 % 2 steps) as a yellow oil. R_f 0.5 (10% EtOAc/pet. ether); IR 2974, 1753 (C=O), 1515, 1490, 1282, 1157, 1087, 974, 827, 526 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46-7.41 (2H, m, Ar**H**), 7.25-7.20 (4H, m, Ar**H**), 6.96-6.90 (2H, m, Ar**H**), 4.65-4.53 (4H, m, 2 × C**H**$_2$CF3), 3.83 (3H, s, ArOC**H**$_3$), 3.49 (2H, s, C**H**$_2$C≡C); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6 (C), 159.7 (C), 134.3 (C), 132.8 (2 × CH), 129.0 (2 × CH), 128.5 (2 × CH), 125.6 (C), 122.5 (q, $^1J_{C\text{-}F}$ = 277.5 Hz, 2 × C), 121.2 (C), 113.9 (2 × CH), 84.4

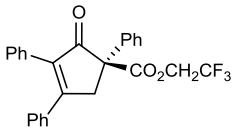
(C), 83.5 (C), 61.5 (C), 61.4 (q, $^{2}J_{C\text{-}F}$ = 37.4 Hz, 2 × CH_2), 55.3 (CH_3), 26.7 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.63 (6F, t, *J* = 8.2 Hz); HRMS (ESI) exact mass calculated for $[C_{23}H_{17}ClF_6O_5Na]^+$ $[M+Na]^+$: 545.0561, found: 545.0565.

3.9 Enantioselective arylative cyclisations of alkynylmalonates

General procedure F

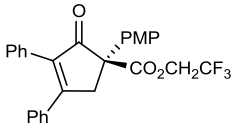


An oven-dried microwave vial fitted with a stirrer bar was charged with alkynyl electrophile **51** (0.30 mmol), the arylboronic acid (0.60 mmol), $Ni(OAc)_2$•$4H_2O$ (7.5 mg, 0.03 mmol) and (*R*)-PhPhox (*ent*-**L37** 12.2 mg, 0.03 mmol). The vial was capped with a crimp cap PTFE seal and evacuated and back filled with Ar (× 5). Deoxygenated TFE (3.0 mL) was added and the mixture was stirred 80 or 100 °C for 24 h. The reaction was cooled to room temperature, diluted with EtOAc (5 mL) and washed with brine (10 mL). The aqueous layer was extracted with EtOAc (5 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography to give the title compound.

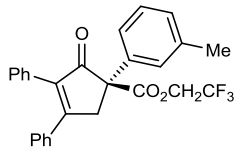


2,2,2-Trifluoroethyl-2-oxo-1,3,4-triphenylcyclopent-3-ene-1-carboxylate (52c). The title compound was prepared according to General Procedure F using alkynyl-electrophile **51c** (137.5 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol), and purified by column chromatography (10% EtOAc/pet. ether) to give **51c** (127.2 mg, 97%) as a yellow oil. R_f 0.3 (10% EtOAc/*n*-pentane);); $[\alpha]_D^{20}$ –92.3 (*c* 0.52, $CHCl_3$); IR 3058, 1763 (C=O), 1700 (C=O), 1445, 1407, 1281, 1153, 908, 731, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.46 (2H, m, Ar**H**), 7.45-7.25 (13H, m, Ar**H**), 4.59 (2H, qd, *J* = 8.3, 1.8 Hz, C**H**$_2$$CF_3$), 4.16 (1H, d, *J* = 18.1 Hz, C=CC**H**$_2$), 3.54 (1H, d, *J* = 18.1 Hz, C=CC**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.7 (C), 169.2 (C), 165.9 (C),

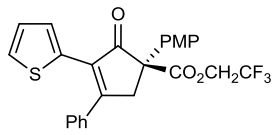
137.9 (C), 137.4 (C), 134.5 (C), 131.5 (C), 130.5 (CH), 129.6 (2 × CH), 128.8 (2 × CH), 128.6 (4 × CH) , 128.3 (CH), 128.3 (2 × CH), 127.9 (CH), 127.4 (2 × CH), 122.6 (q, $^{1}J_{C\text{-}F}$ = 277.6 Hz, C), 63.1 (C), 61.2 (q, $^{2}J_{C\text{-}F}$ = 36.8 Hz, CH_2), 43.7 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.58 (t, *J* = 8.3 Hz); HRMS (ESI) exact mass calculated for $[C_{26}H_{19}F_3O_3Na]^+$ $[M+Na]^+$: 459.1178, found: 459.1171. Enantiomeric excess was determined by HPLC with Chiralpak AD-H column (95:05 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (major) = 22.4 min, t_r (minor) = 46.5 min, 82% ee.



2,2,2-Trifluoroethyl-1-(4-methoxyphenyl)-2-oxo-3,4-diphenylcyclopent-3-ene-1-carboxylate (52d). The title compound was prepared according to General Procedure F using alkynyl-electrophile **51d** (146.5 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol), and purified by column chromatography (10% EtOAc/pet. ether) to give **52d** (137.7 mg, 98%) as a yellow oil. R_f 0.5 (20% EtOAc/pet. ether); $[\alpha]_D^{23}$ −71.03 (*c* 0.62, $CHCl_3$); IR 2933, 1762 (C=O), 1699 (C=O), 1611, 1512, 1282, 1252, 1152, 1031, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.43 (2H, m, Ar**H**), 7.42-7.30 (7H, m, Ar**H**), 7.29-7.25 (2H, m, Ar**H**), 6.97 – 6.91 (2H, m, Ar**H**), 4.58 (2H, qd, *J* = 8.3, 1.7 Hz, C**H**$_2$CF$_3$), 4.11 (1H, d, *J* = 18.1 Hz, C=CC**H**$_2$), 3.82 (3H, s, ArOC**H**$_3$), 3.54 (1H, d, *J* = 18.1 Hz, C=CC**H**$_2$); ^{13}C NMR (101 MHz, Chloroform-d) δ 200.1 (C), 169.5 (C), 165.8 (C), 159.2 (C), 137.4 (C), 134.56 (C), 131.6 (C), 130.5 (CH), 129.7 (C), 129.6 (2 × CH), 128.7 (2 × CH), 128.59 (2 × CH), 128.58 (2 × CH), 128.32 (CH), 128.27 (2 × CH), 122.7 (q, $^{1}J_{C\text{-}F}$ = 277.7 Hz, C), 114.2 (2 × CH), 62.3 (C), 61.2 (q, $^{2}J_{C\text{-}F}$ = 36.7 Hz, CH_2), 55.3 (CH_3), 43.7 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.57 (3F, td, *J* = 8.3, 2.3 Hz); HRMS (ESI) exact mass calculated for $[C_{27}H_{21}F_3O_4Na]^+$ $[M+Na]^+$: 489.1284, found: 489.1282. Enantiomeric excess was determined by HPLC with Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (minor) = 28.8 min, t_r (major) = 30.7 min, 88% ee.

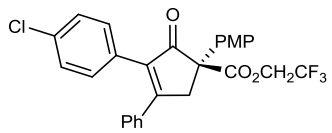


2,2,2-Trifluoroethyl-1-(3-methylphenyl)-2-oxo-3,4-diphenylcyclopent-3-ene-1-carboxylate (52e). The title compound was prepared according to General Procedure F using alkynyl-electrophile **51e** (141.7 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol), and purified by column chromatography (10% EtOAc/pet. ether) to give **52e** (129.7 mg, 97%) as a yellow oil. R_f 0.3 (10% EtOAc/pet. ether); $[\alpha]_D^{23}$ –90.5 (*c* 0.84, $CHCl_3$); IR 3057, 1762 (C=O), 1700 (C=O), 1623, 1351, 1282, 1157, 887, 729, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.25 (13H, Hm, Ar**H**), 7.20-7.12 (1H, m, Ar**H**), 4.60 (2H, qd, *J* = 8.3, 3.8 Hz, C**H**$_2$CF$_3$), 4.15 (1H, d, *J* = 18.2 Hz, C=CC**H**$_2$), 3.53 (1H, d, *J* = 18.2 Hz, C=CC**H**$_2$), 2.38 (3H, s, ArC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.8 (C), 169.3 (C), 165.8 (C), 138.5 (C), 137.9 (C), 137.4 (C), 134.5 (C), 131.5 (C), 130.5 (CH), 129.6 (2 × CH), 128.6 (2 × CH), 128.5 (4 × CH), 128.29 (CH), 128.26 (2 × CH), 128.1 (CH), 124.4 (CH), 122.6 (q, $^1J_{C\text{-}F}$ = 277.8 Hz, C), 63.1 (C), 61.1 (q, $^2J_{C\text{-}F}$ = 36.8 Hz, CH_2), 43.8 (CH_2), 21.5 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.55 (3F, t, *J* = 8.3 Hz); HRMS (ESI) exact mass calculated for $[C_{27}H_{21}F_3O_3Na]^+$ $[M+Na]^+$: 473.1335, found: 473.1348. Enantiomeric excess was determined by HPLC with Chiralpak AD-H column (98:02 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (minor) = 31.8 min, t_r (major) = 36.0 min, 87% ee.

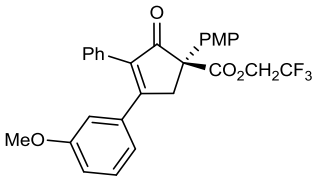


2,2,2-Trifluoroethyl-1-(4-methoxyphenyl)-2-oxo-4-phenyl-3-(thiophen-2-yl)cyclopent-3-ene-1-carboxylate (52i). The title compound was prepared according to General Procedure F using alkynyl-electrophile **51i** (148.3 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol), and purified by column chromatography (10% EtOAc/*n*-pentane) to give **52i** (118.5mg, 84%) as a yellow oil. R_f 0.4 (20% EtOAc/pet. ether); $[\alpha]_D^{20}$ –78.0 (*c* 0.82, $CHCl_3$); IR 2934, 1762 (C=O), 1706 (C=O), 1610, 1512, 1282, 1252, 1153, 1032, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50-7.38 (7H, m, Ar**H**), 7.33 (1H, dd, *J* = 5.1, 1.2 Hz, Ar**H**), 7.30 (1H, dd, *J* = 3.7, 1.2 Hz, Ar**H**), 7.00 (1H, dd, *J* = 5.1, 3.7 Hz, Ar**H**), 6.93 (2H, d, *J* = 8.9 Hz, Ar**H**), 4.58 (2H, qd, *J* = 8.3, 4.8 Hz, C**H**$_2$CF$_3$), 4.02 (1H, d, *J* = 18.7 Hz, C=CC**H**$_2$), 3.82 (3H, s, ArOC**H**$_3$), 3.48 (1H, d, *J* = 18.7 Hz, C=CC**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.0 (C), 169.2 (C), 165.7 (C), 159.2 (C), 135.3 (C), 131.5 (C), 130.6 (C), 130.3 (CH), 129.3 (C), 128.8

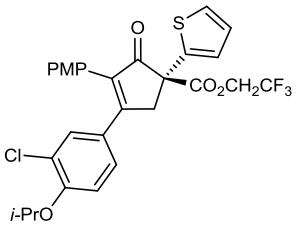
(2 × CH), 128.6 (2 × CH), 128.3 (CH), 127.6 (2 × CH), 127.0 (CH), 126.7 (CH), 122.6 (q, $^{1}J_{C\text{-}F}$ = 277.6 Hz, C), 114.1 (2 × CH), 62.2 (C), 61.2 (CH_2 q, $^{2}J_{C\text{-}F}$ = 36.7 Hz), 55.3 (CH_3), 44.9 (CH_2); ^{19}F NMR (376 MHz,$CDCl_3$) δ −73.58 (3F, t, *J* = 8.3 Hz); HRMS (ESI) exact mass calculated for $[C_{25}H_{19}F_3O_4SNa]^+$ $[M+Na]^+$: 495.0848, found: 495.0849. Enantiomeric excess was determined by HPLC with Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (minor) = 24.4 min, t_r (major) = 29.1 min, 86% ee.



2,2,2-Trifluoroethyl-3-(4-chlorophenyl)-1-(4-methoxyphenyl)-2-oxo-4-phenylcyclopent-3-ene-1-carboxylate (52j). The title compound was prepared according to General Procedure F using alkynyl-electrophile **51j** (156.8 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol), and purified by column chromatography (10% EtOAc/*n*-pentane) to give **52j** (123.3 mg, 87%) as a yellow oil. R_f 0.4 (20% EtOAc/pet. ether); $[\alpha]_D^{21}$ –66.7 (*c* 0.48, $CHCl_3$); IR 2934, 1761 (C=O), 1702 (C=O), 1512, 1282, 1253, 1155, 1089, 1032, 730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.31 (7H, m, Ar**H**), 7.24-7.19 (2H, m, Ar**H**), 6.96-6.90 (2H, m, Ar**H**), 4.57 (2H, qd, *J* = 8.3, 1.5 Hz, C**H**$_2$CF$_3$), 4.09 (1H, d, *J* = 18.2 Hz, C=CC**H**$_2$), 3.82 (3H, s, ArOC**H**$_3$), 3.54 (1H, d, *J* = 18.2 Hz, C=CC**H**$_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.7 (C), 169.3 (C), 166.4 (C), 159.2 (C), 136.0 (C), 134.30 (C), 134.26 (C), 131.0 (2 × CH), 130.7 (CH), 129.9 (C), 129.4 (C), 128.8 (2 × CH), 128.7 (2 × CH), 128.6 (2 × CH), 128.1(2 × CH), 122.6 (q, $^{1}J_{C\text{-}F}$ = 277.8 Hz, C), 114.1 (2 × CH), 62.3 (C), 61.2 (q, $^{2}J_{C\text{-}F}$ = 36.7 Hz, CH_2), 55.3 (CH_3), 43.7 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.60 (3F, t, *J* = 8.3 Hz); HRMS (ESI) exact mass calculated for $[C_{27}H_{20}ClF_3O_4Na]^+$ $[M+Na]^+$: 523.0894, found: 523.0898. Enantiomeric excess was determined by HPLC with Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (minor) = 34.1 min, t_r (major) = 54.4 min, 87% ee.

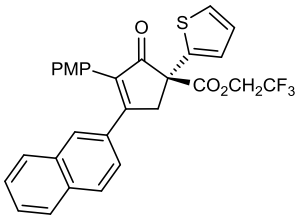


2,2,2-Trifluoroethyl-4-(3-methoxyphenyl)-1-(4-methoxyphenyl)-2-oxo-3-phenylcyclopent-3-ene-1-carboxylate (52n). The title compound was prepared according to General Procedure F using alkynyl-electrophile **51d** (146.5 mg, 0.30 mmol) and 3-methoxyphenylboronic acid (91.2 mg, 0.60 mmol), and purified by column chromatography (10% EtOAc/*n*-pentane) to give **52n** (136.1mg, 91%) as a yellow oil. R_f 0.1 (10% EtOAc/pet. ether); $[\alpha]_D^{20}$ −104.3 (*c* 0.46, $CHCl_3$); IR 2936, 1762 (C=O), 1702 (C=O), 1597, 1513, 1284, 1253, 1153, 1033, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47-7.42 (2H, m, Ar**H**), 7.40-7.33 (3H, m, Ar**H**), 7.30-7.21 (3H, m, Ar**H**), 7.00 (1H, ddd, J = 7.7, 1.7, 1.0 Hz, Ar**H**), 6.96-6.89 (3H, m, Ar**H**), 6.85 (1H, dd, J = 2.6, 1.7 Hz, Ar**H**), 4.58 (2H, qd, *J* = 8.3, 1.3 Hz, C$\mathbf{H}_2CF_3$), 4.09 (1H, d, *J* = 18.1 Hz, C=CC$\mathbf{H}_2$), 3.82 (3H, s, ArOC$\mathbf{H}_3$), 3.58 (3H, s, ArOC$\mathbf{H}_3$), 3.53 (d, *J* = 18.1 Hz, C=CC$\mathbf{H}_2$);^{13}C NMR (101 MHz, $CDCl_3$) δ 200.0 (C), 169.5 (C), 165.5 (C), 159.3 (C), 159.1 (C), 137.6 (C), 135.6 (C), 131.7 (C), 129.63 (C), 129.61 (CH), 129.55 (2 × CH), 128.7 (2 × CH), 128.6 (2 × CH), 128.3 (CH), 122.7 (q, $^1J_{C\text{-}F}$ = 277.8 Hz, C), 120.5 (CH), 116.8 (CH), 114.1 (2 × CH), 113.3 (CH), 62.3 (C), 61.1 (q, $^2J_{C\text{-}F}$ = 36.7 Hz, CH_2), 55.3 (CH_3), 55.0 (CH_3), 43.6 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.58 (3F, t, *J* = 8.3 Hz); HRMS (ESI) exact mass calculated for $[C_{28}H_{23}F_3O_5Na]^+$ $[M+Na]^+$: 519.1390, found: 519.1399. Enantiomeric excess was determined by HPLC with Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (minor) = 33.9 min, t_r (major) = 37.4 min, 86% ee.



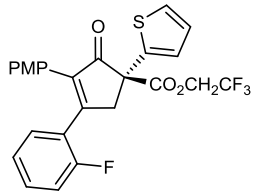
2,2,2-Trifluoroethyl-4-(3-chloro-4-isopropoxyphenyl)-3-(4-methoxyphenyl)-2-oxo-1-(thiophen-2-yl)cyclopent-3-ene-1-carboxylate (52m). The title compound was prepared according to General Procedure F using alkynyl-electrophile **51d** (148.3 mg, 0.30 mmol) and 3-chloro-4-isopropoxyphenylboronic acid (128.7 mg, 0.60 mmol), and purified by column chromatography (10% EtOAc/*n*-pentane) to give **52m** (149.3 mg, 88%) as a yellow oil. R_f 0.1 (10% EtOAc/pet. ether); $[\alpha]_D^{21}$ −45.5 (*c* 0.44, $CHCl_3$); IR 2978, 1764

(C=O), 1703 (C=O), 1594, 1511, 1494, 1278, 1248, 1158, 730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (1H, d, *J* = 2.3 Hz, Ar**H**), 7.32 (1H, dd, *J* = 5.2, 1.2 Hz, Ar**H**), 7.29 (1H, dd, *J* = 3.7, 1.2 Hz, Ar**H**), 7.26 (1H, dd, *J* = 8.8, 2.3 Hz, Ar**H**), 7.23-7.19 (2H, m, Ar**H**), 7.04 (1H, dd, *J* = 5.2, 3.7 Hz, Ar**H**), 6.94-6.89 (2H, m, Ar**H**), 6.83 (1H, d, *J* = 8.8 Hz, Ar**H**), 4.67-4.46 (3H, m, C**H**$(CH_3)_2$ and C**H**$_2CF_3$), 4.03 (1H, d, *J* = 17.8 Hz, C=CC**H**$_2$), 3.84 (3H, s, ArOC**H**$_3$), 3.60 (1H, d, *J* = 17.8 Hz, C=CC**H**$_2$), 1.40 (6H, d, *J* = 6.0 Hz, CH(C**H**$_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.7 (C), 168.4 (C), 162.9 (C), 159.7 (C), 155.4 (C), 139.1 (C), 135.1 (C), 130.7 (2 × CH), 130.2 (CH), 128.3 (CH), 127.2 (C), 126.7 (CH), 126.6 (CH), 125.7 (C), 123.9 (C), 123.5 (C), 122.6 (q, $^{1}J_{C\text{-}F}$ = 277.7 Hz, C), 114.2 (2 × CH), 114.1 (CH), 71.9 (CH), 61.4 (q, $^{2}J_{C\text{-}F}$ = 37.0 Hz, CH_2), 59.5 (C), 55.2 (CH_3), 43.8 (CH_2), 21.9 (2 × CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.63 (3F, t, *J* = 8.3 Hz); HRMS (ESI) exact mass calculated for $[C_{28}H_{24}ClF_3O_5SNa]^+$ $[M+Na]^+$: 587.0877, found 587.0880. Enantiomeric excess was determined by HPLC with Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (minor) = 19.7 min, t_r (major) = 22.9 min, 89% ee.



2,2,2-Trifluoroethyl-3-(4-methoxyphenyl)-4-(naphthalen-2-yl)-2-oxo-1-(thiophen-2-yl)cyclopent-3-ene-1-carboxylate (52o). The title compound was prepared according to General Procedure F using alkynyl-electrophile **51d** (148.3 mg, 0.30 mmol) and 2-napthyleneboronic acid (103.2 mg, 0.60 mmol), and purified by column chromatography (10% EtOAc/*n*-pentane) to give **52o** (136.8 mg, 87%) as a yellow oil. R_f 0.4 (20% EtOAc/pet. ether); $[\alpha]_D^{21}$ −7.4 (*c* 0.54, $CHCl_3$); IR 2963, 1764 (C=O), 1702 (C=O), 1602, 1509, 1283, 1248, 1159, 820, 730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (1H, d, *J* = 1.8 Hz, Ar**H**), 7.87-7.80 (2H, m, Ar**H**), 7.72 (1H, d, *J* = 8.7 Hz, Ar**H**), 7.59-7.50 (2H, m, Ar**H**), 7.38 (1H, dd, *J* = 8.7, 1.8 Hz, Ar**H**), 7.35 (2H, d, *J* = 4.4 Hz, Ar**H**), 7.28-7.23 (2H, m, Ar**H**), 7.09-7.03 (1H, m, Ar**H**), 6.91-6.85 (2H, m, Ar**H**), 4.69-4.49 (2H, m, C**H**$_2CF_3$), 4.21 (1H, d, *J* = 17.9 Hz, C=CC**H**$_2$), 3.83 (3H, s, ArOC**H**$_3$), 3.79 (1H, d, *J* = 17.9 Hz, C=CC**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.0 (C), 168.5 (C), 164.8 (C), 159.7 (C), 139.1 (C), 136.1 (C), 134.0 (C), 132.9 (C), 132.3 (C), 131.0 (2 × CH), 128.7 (CH), 128.1 (CH), 128.0 (CH), 127.71

(CH), 127.66 (C), 126.8 (CH), 126.73 (CH), 126.68 (CH), 125.7 (CH), 125.3 (CH), 123.4 (C), 122.6 (q, $^{1}J_{C\text{-}F}$ = 277.9 Hz, C), 114.0 (2 × CH), 61.4 (q, $^{2}J_{C\text{-}F}$ = 36.9 Hz, CH_2), 59.7 (C), 55.2 (CH_3), 44.2 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.61 (3F, t, *J* = 8.2 Hz); HRMS (ESI) exact mass calculated for $[C_{21}H_{29}F_3O_4SNa]^+$ $[M+Na]^+$: 545.1005, found: 545.1009. Enantiomeric excess was determined by HPLC with Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (minor) = 25.6 min, t_r (major) = 31.9 min, 92% ee.



2,2,2-Trifluoroethyl-4-(2-fluorophenyl)-3-(4-methoxyphenyl)-2-oxo-1-(thiophen-2-yl)cyclopent-3-ene-1-carboxylate (52p). The title compound was prepared according to General Procedure F using alkynyl-electrophile **51d** (148.3 mg, 0.30 mmol) and 2-fluorophenylboronic acid (84.0 mg, 0.60 mmol), and purified by column chromatography (10% EtOAc/*n*-pentane) to give **52p** (125.5 mg, 85%) as a yellow oil. R_f 0.4 (20% EtOAc/pet. ether); $[\alpha]_D^{22}$ −19.0 (*c* 0.42, $CHCl_3$); IR 2960, 1765 (C=O), 1708 (C=O), 1603, 1575, 1512, 1283, 1249, 1158, 759 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.36 (1H, m, Ar**H**), 7.34 (1H, dd, *J* = 5.2, 1.2 Hz, Ar**H**), 7.31 (1H, dd, *J* = 3.7, 1.2 Hz, Ar**H**), 7.22-7.07 (5H, m, Ar**H**), 7.05 (1H, dd, *J* = 5.2, 3.7 Hz, Ar**H**), 6.86-6.78 (2H, m, Ar**H**), 4.57 (2H, ddq, *J* = 50.3, 12.6, 8.2 Hz, C**H**$_2$CF$_3$), 4.04 (1H, dd, *J* = 18.5, 0.9 Hz, C=CC**H**$_2$), 3.79 (3H, s, ArOC**H**$_3$), 3.71 (1H, dd, *J* = 18.5, 0.9 Hz, C=CC**H**$_2$); ^{13}C NMR (101 MHz, Chloroform-d) δ 198.8 (C), 168.3 (C), 161.5 (C), 159.8 (d, $^{1}J_{C\text{-}F}$ = 251.7 Hz, C), 159.7 (C), 138.6 (C), 137.7 (C), 131.6 (d, $^{3}J_{C\text{-}F}$ = 8.2 Hz, CH), 130.5 (2 × CH), 130.0 (d, $^{3}J_{C\text{-}F}$ = 3.5 Hz, CH), 126.8 (CH), 126.7 (CH), 125.8 (CH), 124.4 (d, $^{4}J_{C\text{-}F}$ = 2.9 Hz, CH), 123.3 (d, $^{2}J_{C\text{-}F}$ = 14.5 Hz, C), 122.8 (C), 122.6 (q, $^{1}J_{C\text{-}F}$ = 277.9 Hz, C), 116.5 (d, $^{2}J_{C\text{-}F}$ = 21.8 Hz, CH), 113.8 (2 × CH), 61.4 (q, $^{2}J_{C\text{-}F}$ = 36.8 Hz, CH_2), 59.9 (C), 55.2 (CH_3), 44.7 (d, $^{4}J_{C\text{-}F}$ = 4.9 Hz, CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.71 (3F, t, *J* = 8.2 Hz), −110.68 (1F, dt, *J* = 11.5, 6.1 Hz); HRMS (ESI) exact mass calculated for $[C_{25}H_{18}F_4O_4SNa]^+$ $[M+Na]^+$: 513.0754, found: 513.0750. Enantiomeric excess was determined by HPLC with Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (minor) = 17.8 min, t_r (major) = 28.2 min, 94% ee.

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