Stereoselective Nickel-Catalysed Arylative Cyclisation Reactions

Thesis Submitted in Accordance with the Requirement of the University of Nottingham for the Degree of Doctor of Philosophy

By

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"Happiness can be found,

even in the darkest of times,

if one only remembers to turn on the light."

- J. K. Rowling

Declaration

I hereby declare that, except where specific reference is made to other sources, the work contained within this thesis is my original work since registration of the PhD degree in October 2015. This thesis has been composed by myself and has not been submitted, in whole or part, for any other degree, diploma or other qualification. I confirm that the work submitted is my own, except where the work has formed part of a jointly-authored publication. The contribution of the other authors is explicitly indicated where relevant. The appropriate credit within the thesis, by caption and/or citation has been given within the thesis where relevant. The publications covered in this thesis are mentioned below.

Part of the results presented in Chapter 1 are reported in the following publication:

Nickel-Catalysed, Ligand-Free, Diastereoselective Synthesis of 3-Methyleneindan-1-ols, Panchal, H., Clarke, C., Bell, C., Karad, S. N., Lewis, W., and Lam, H. W., *Chem. Commun*, **2018**, *54*, 12389-12392.

Part of the results presented in Chapter 2 are reported in the following publication:

Enantioselective Synthesis of Chiral Cyclopent-2-enones by Nickel-Catalyzed Desymmetrization of Malonate Esters, Karad, S. N.; Panchal, H.; Clarke, C.; Lewis, W.; Lam, H. W. *Angew. Chem., Int. Ed.* **2018**, *57*, 9122-9125.

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My friends have been an incredible support system for me when times were tough. Fredrik Karlsson, Lorna Day and Julia Hahn, you are all amazing people and I couldn't ask for better friends. For making me laugh, the support, the visits, the encouragement, and your time: thank you.

And finally, to Jordan Thompson. I can't think of a single time you weren't there for me. You've always believed in me, even when I didn't believe in myself. There will never be enough words to tell you how grateful I am.

Abbreviations

2-MeTHF	2-Methyltetrahydrofuran
Ac_2O	Acetic anhydride
acac	Acetic acetonate
AcCl	Acetyl chloride
AcOH	Acetic acid
Ar	Aryl
atm	Atmosphere
BINAP	1,1′-Binaphthalene-2,2′-diyl)bis(diphenylphosphine
BIPHEP	Bis(diphenylphosphino)-6,6′-dimethoxy-1,1′-biphenyl
Bn	Benzyl
BOC	Tertiary butyloxycarbonyl
BQ	Benzoquinone
Cat.	Catalytic
cod	Cyclooctadiene
coe	Cyclooctene
Cp	Cyclopentyl
CPME	Cyclopentylmethylether
Cy	Cyclohexyl
Cymene	Isopropylmethylbenzene
dba	Dibenylideneacetone
DCE	Dichloroethane
DIPEA	Diisopropylethylamine
DMEDA	Dimethyl ethylenediamine
DMF	Dimethyl Formamide
DMP	Dess-Martin Periodinane
DPEPhos	(Oxydi-2,1-phenylene)bis(diphenylphosphine)
DPPE	Diphenylphosphinoethane
DPPF	Diphenylphosphinoferrocene
DPPP	Diphenylphosphinopropane
DTBM	Ditertiary butyl methyl
equiv	Equivalents
ESI	Electrospray Ionisation
Et	Ethyl
EtOH	Ethanol

EWG	Electron Withdrawing Group
h	Hours
^{i}Pr	*Iso*-Propyl
m-CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
MeCN	Acetonitrile
MeO	Methoxy
MeOH	Methanol
min	Minutes
MsCl	Methanesulfonyl chloride
N,*N*'-DMEDA	*N*,*N*'-Dimethylethylenediamine
^{n}Bu	Butyl
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
OAc	Acetate
p-ABSA	4-Acetamidobenzenesulfonyl azide
Ph	Phenyl
PhMe	Toluene
PhPHOX	2-[2-(Diphenylphosphino)phenyl]-4-phenyl-2-oxazoline
Pin	Pinacol
Pr	Propyl
Py	Pyridine
Pyphos	2-(Diphenylphosphino)pyridine
R_f	Retention Fraction
RT	Room Temperature
TBME	Tertiary butyl methyl ether
Tert	Tertiary
Tf	Triflate
TFE	Trifluoroethanol
THF	Tetrahydrofuran
TMEDA	Tetramethylethylene diamine
TMS	Trimethylsilyl
Ts	Toluenesulfonyl
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

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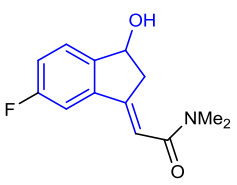
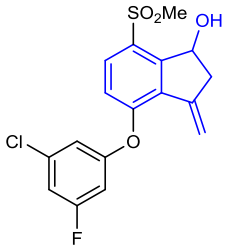
Abstract: Synthesis of 3-Methyleneindan-1-ols

Indanes and their derivatives are a common unit in a range of biologically active scaffolds.

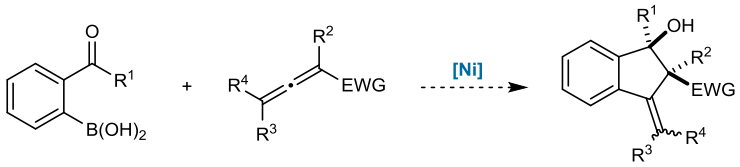


Enhancement of Calcium Activated Potassium Channel Activity



(HIF)-1α Inhibitor

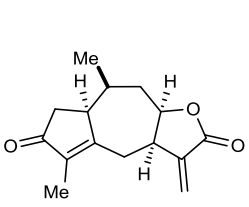
Numerous approaches have been reported for the synthesis of these scaffolds. Annulation reactions between *ortho*-functionalised aryl aldehydes or ketones with various unsaturated reaction partners provide a useful approach towards indenols.



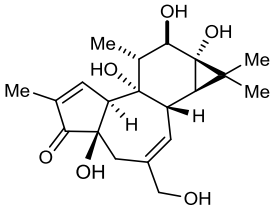
Herein, the synthesis of 3-methyleneindan-1-ols using nickel catalysis is reported. The reaction between activated allenes and 2-acylarylboronic acids generates the products in generally good yields and excellent diastereoselectivities. This methodology allows access to products with fully substituted olefins, and adjacent quaternary centres. The reaction can be effectively scaled up, the catalyst loading decreased, and enantioselectivity can be induced *via* the addition of a chiral ligand.

Abstract: Synthesis of Chiral Cyclopent-2-enones

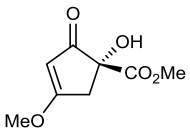
Cyclopentenones appear in a number of biologically active compounds, agrochemicals, and natural products. As a result, numerous methods have been developed for their synthesis, with the Pauson-Khand and Nazarov reactions being perhaps the most well known. Each method presents its own set of unique advantages and challenges, and with the scaffold present in a diverse range of compound classes, new strategies for their synthesis remain valuable.



(+)-achalensolide

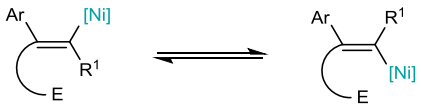


phorbol

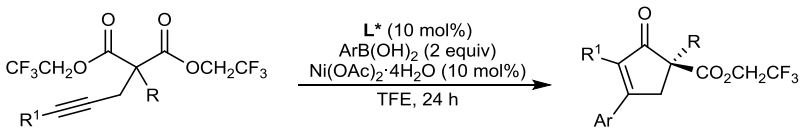


(–)-kjellmanianone

Herein, the synthesis of chiral cyclopent-2-enones *via* the enantioselective desymmetrisation of malonate esters by arylative cyclisations is reported. This allows for the generation of highly substituted cyclopent-2-enones with an α-quaternary centre. The cyclisation reactions proceed efficiently with a nickel-catalyst and chiral phosphinooxazoline ligand, enabled by the reversible *E*/*Z* isomerisation of the alkenylnickel species.



A range of substituents at the α-position, alkyne, and on the boronic acids are well tolerated, affording chiral cyclopent-2-enones in excellent yields and enantioselectivities. The reaction can be effectively scaled up, and the products manipulated to generate amides and alcohols.



1. Synthesis of 3-Methyleneindan-1-ols: Introduction

1.1. Indanols in Nature

Indanols and their derivatives represent an important structural motif, being present in a number of biologically active molecules and known to demonstrate analgesic and insecticidal properties.[1,2]

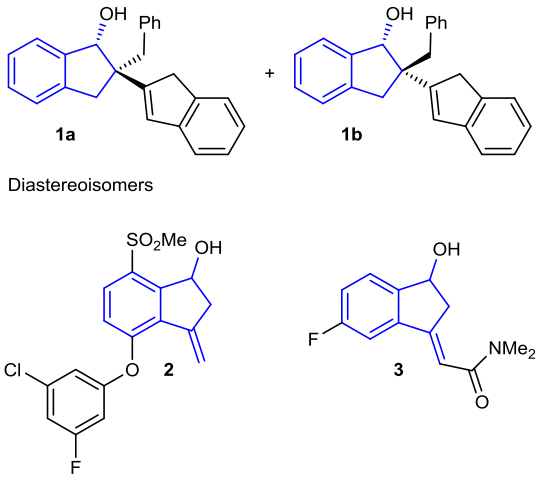


Figure 1

This section briefly introduces biologically active indanols and their derivatives. Indanol-dimers (diastereoisomers **1a** and **1b**, Figure 1) have demonstrated significant anti-inflammatory activity.[3] Compounds with both external and internal olefins have been used to treat a variety of disorders. Indan-1-ols, with an exocyclic olefin, are an important unit in the pharmaceutical industry (Figure 1). For example, **2** was patented in 2002 as a (HIF)-2α inhibitor,[4] and indanol **3** was patented in 2016 for the treatment of glioblastoma.[5,6]

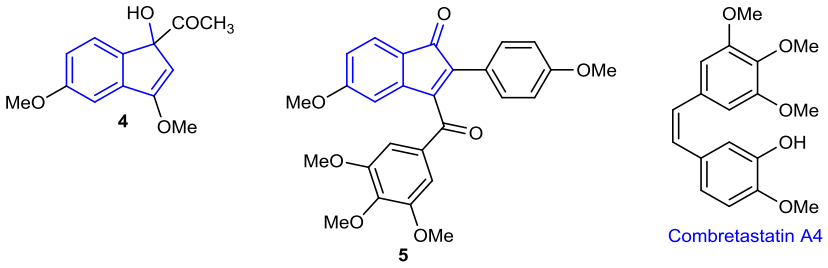


Figure 2

Indenols, with an internal olefin (Figure 2) have also demonstrated biological activity. Indenol **4**, which was isolated from etiolated seedlings of Adlay was

shown to be active against bacteria.[7] Indenol **5** was synthesised from combretastatin A4, which demonstrates anti-cancer properties.[8]

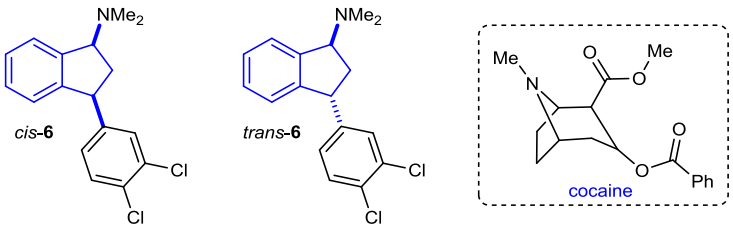


Figure 3

Indan-1-amines like those shown in Figure 3 (**6**) have the potential to be used as medication to treat cocaine abuse.[9] There are few, if any, effective pharmacological methods for aiding cocaine-abusers in stopping, so this represented a useful area of research.

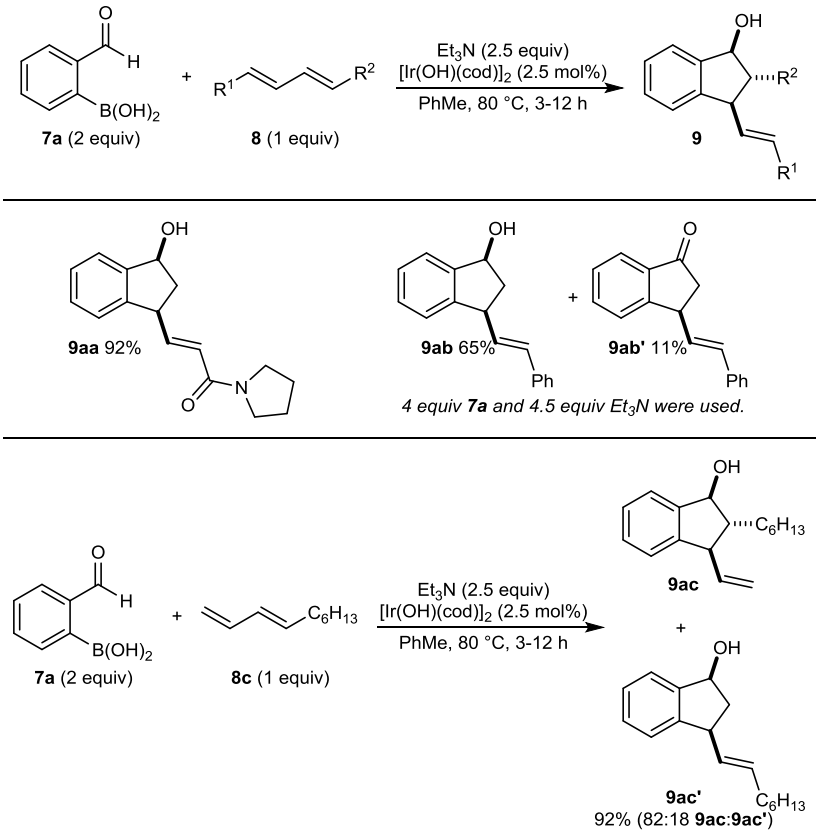
With indanols and related derivatives present in important biologically active compounds, the development of a range of synthetic methods to access them remain necessary.

1.2. Synthesis of Indanols and Derivatives

Indanols and their derivatives are prevalent in a range of compound classes. This section discusses the various routes used to access these compounds from a range of precursors.

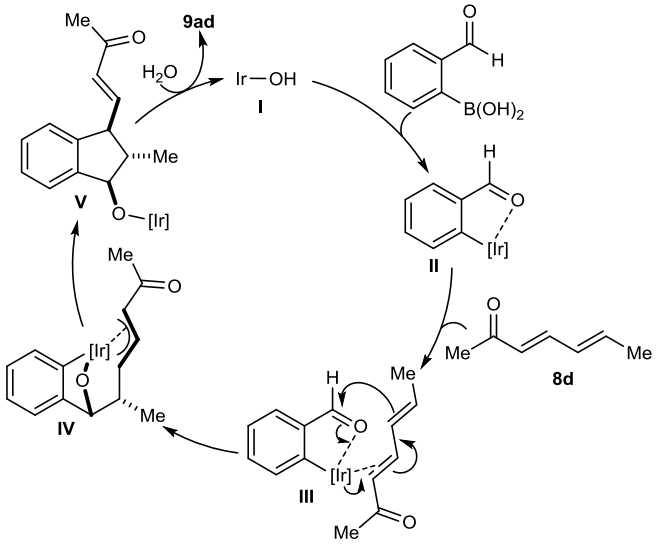
A common approach is an annulation reaction between *ortho*-functionalised aromatic aldehydes, ketones, esters or imines with unsaturated coupling partners. This method allows for the synthesis of indanols and their derivatives often *via* the formation of two new carbon-carbon bonds. This section discusses the intra- and intermolecular approaches towards the indane, indanol and indanone family of compounds.

1.2.1. Intermolecular Approaches to the Synthesis of Indanols and Derivatives



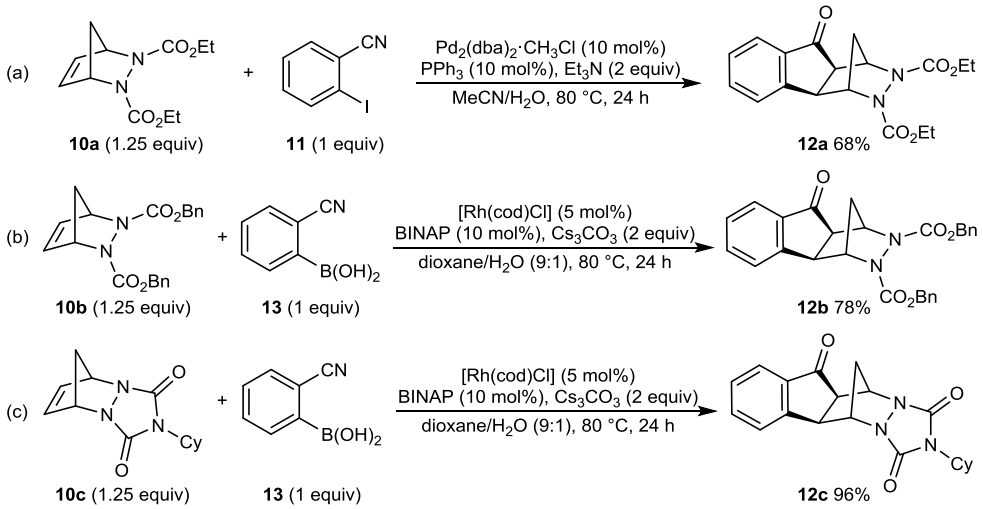
Scheme 1

In 2007, Hayashi and co-workers reported an iridium-catalysed annulation reaction between 1,3-dienes and 2-formylphenylboronic acid (Scheme 1).[10] The reaction was tolerant to both electron-donating and electron-withdrawing groups on the diene. The more electron-rich bond participates in the reaction. When a phenyl group was present on the diene, a minor quantity of indenone **9ab'** was also formed. With diene **8c**, a mixture of regioisomers in the ratio 82:18 was obtained.



Scheme 2

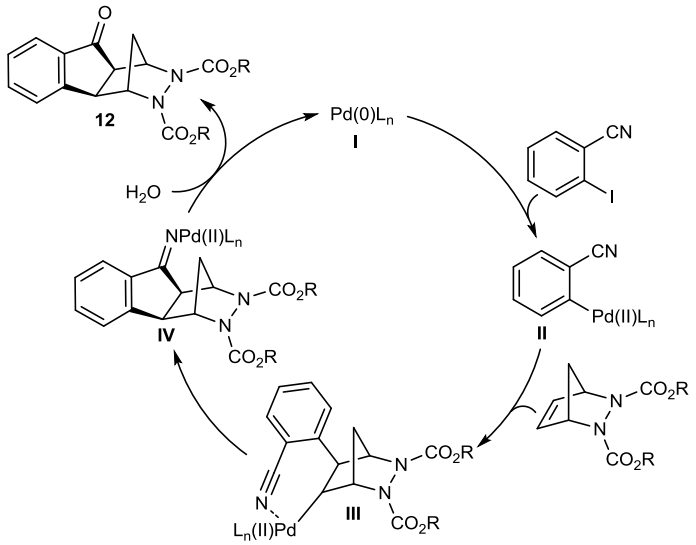
A catalytic cycle for the transformation was proposed (Scheme 2).[10] Transmetallation of the boronic acid onto the iridium catalyst gives complex **II**. Nucleophilic attack of the electron-rich alkene of the diene onto the carbonyl (**III**), is aided by coordination of the electron-poor alkene to the iridium, giving complex **IV**. Reductive elimination gives alkoxyiridium **V**, which undergoes hydrolysis to regenerate the active catalytic species and gives **9ad**.



Scheme 3

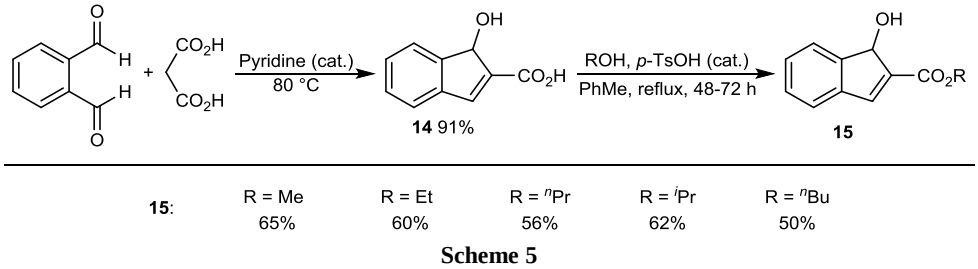
In 2011, a palladium and rhodium-catalysed approach to the synthesis of indanones was reported, from *ortho*-functionalised nitriles and diazabicyclic alkenes.[11] Treatment of alkene **10a** with 2-iodobenzonitrile **11** using a palladium catalyst afforded indenone **12a** in 68% yield (Scheme 3, (a)). The same product could be obtained using rhodium catalysis, and by using *ortho*-

cyanophenylboronic acid **13** instead of the iodide, in 78% isolated yield (Scheme 3, (b)). The same reaction was also carried out on alkene **10c**, and indanone **12c** was obtained in excellent 96% yield (Scheme 3, (c)).



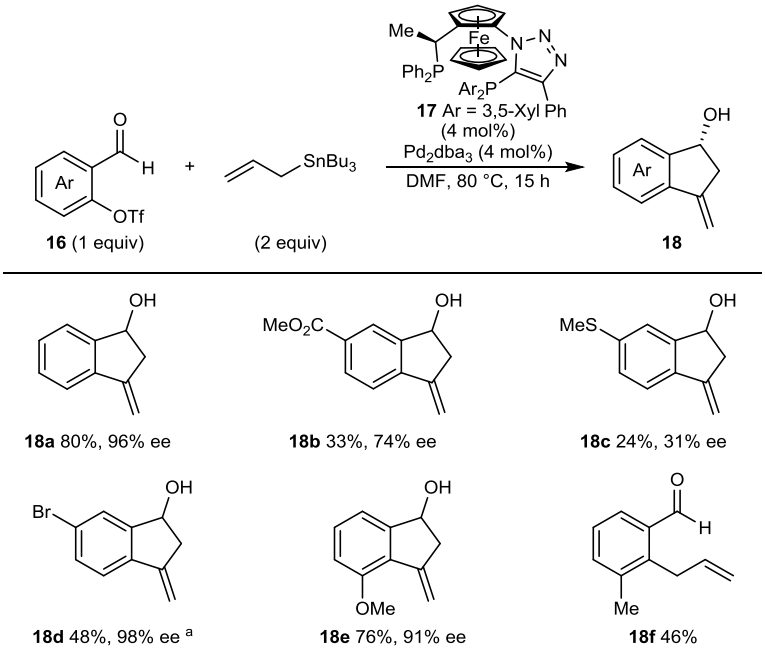
Scheme 4

A catalytic cycle was proposed (Scheme 4).[11] Oxidative addition of the aryl iodide gives intermediate **II**. Coordination and subsequent carbopalladation gives intermediate **IV**. Hydration then gave **12** and regenerated the palladium catalyst.



Scheme 5

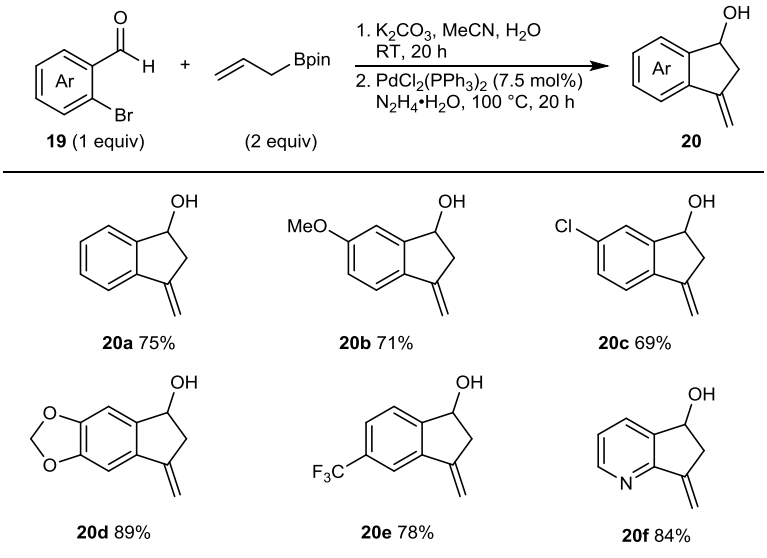
In 2014, Amri and co-workers reported a synthesis of indenols from phthalaldehyde and malonic acid (Scheme 5).[2] The reaction progressed in the presence of catalytic pyridine to give indenol **14**, which was then reacted with the relevant alcohol in the presence of catalytic *para*-toluenesulonic acid. The indenols **15** were investigated for their biological properties and demonstrated potent anti-oxidant activity and strong antibacterial properties against some pathogenic strains.



[a] *1 equiv of allyl stannane used*

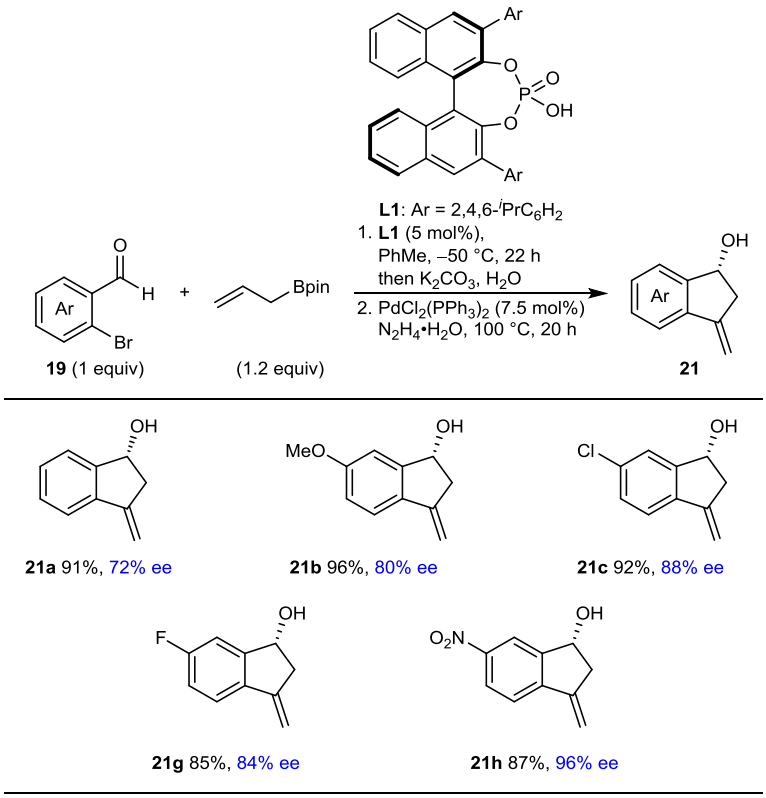
Scheme 6

In the same year, Fukuzawa and co-workers reported the synthesis of 3-methyleneindan-1-ols from allylstannanes and *ortho*-formylaryl triflates (Scheme 6).[12] The research describes the use of novel ClickFerrophos ligands which were effective in inducing excellent ee's. A range of substituted aryl-aldehydes were well-tolerated, offering modest to excellent yields (**18a**-**18e**). With electron-withdrawing groups, yields and enantioselectivities were considerably lower. A methyl-group *ortho*- to the triflate inhibits cyclisation, and the Stille product **18f** was isolated exclusively in 46% yield.



Scheme 7

In 2015, Sutherland and co-workers reported a one-pot, two-step allylboration-Heck reaction of 2-bromobenzaldehydes **19** with allylboronic acid, pinacol ester (Scheme 7).[13] The homoallylic alcohol generated in the first step underwent a Heck-cyclisation to give the 3-methyleneindan-1-ol **20**. Addition of all the reagents in one go gave only the homoallylic alcohol, so a step-wise addition procedure was developed. A range of electron-rich and electron-poor 2-bromobenzaldehydes underwent the one-pot allylation-Heck reaction to give 3-methyleneindan-1-ols **20a**-**20f** in moderate to excellent yields. An enantioselective approach was then sought.

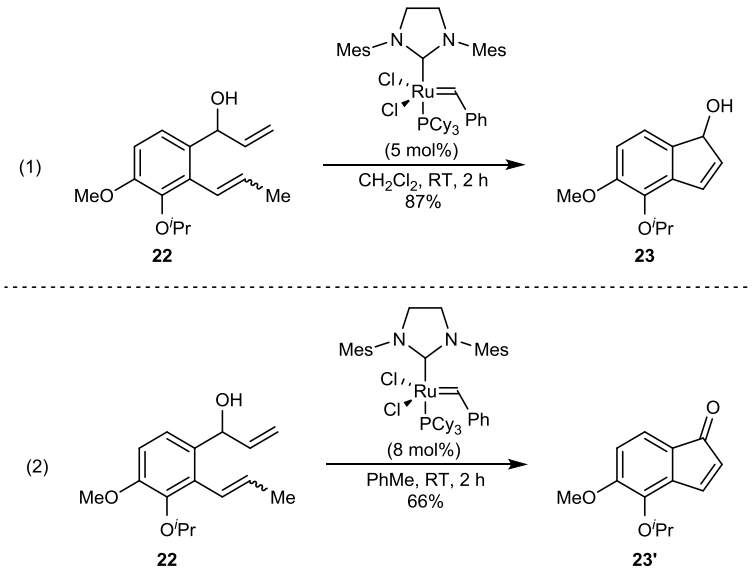


Scheme 8

A number of binaphthyl-derived chiral phosphoric acids were screened (Scheme 8).[13] To limit the background homoallylation reaction, the temperature for the first step was decreased, which led to an improved enantiomeric excess. Following modifications of the reaction conditions, a range of 3-methyleneindan-1-ols **21a**-**21h** were obtained in excellent yields and good enantioselectivities.

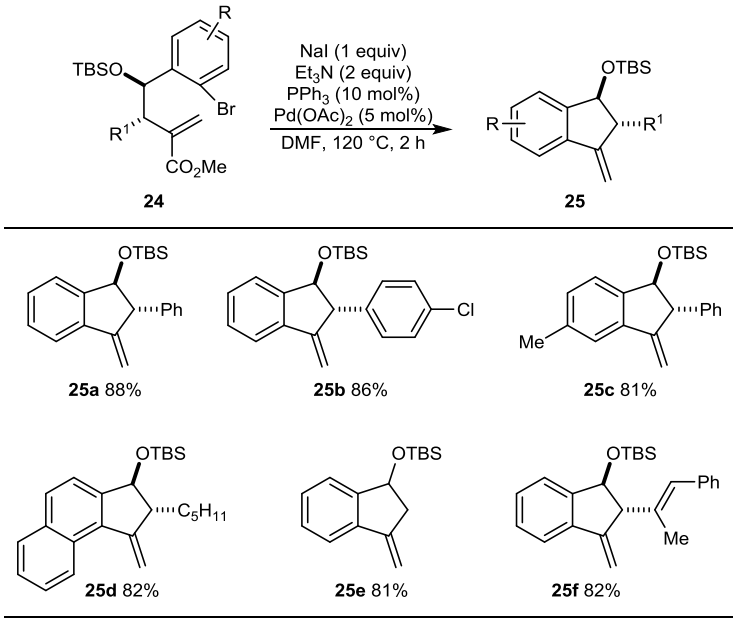
1.2.2. Intramolecular Approaches to the Synthesis of Indanols and Derivatives

Intramolecular processes to synthesise indanols and their derivatives have also been reported. However, this often requires longer synthetic routes to give specialised substrates to undergo the cyclisation.



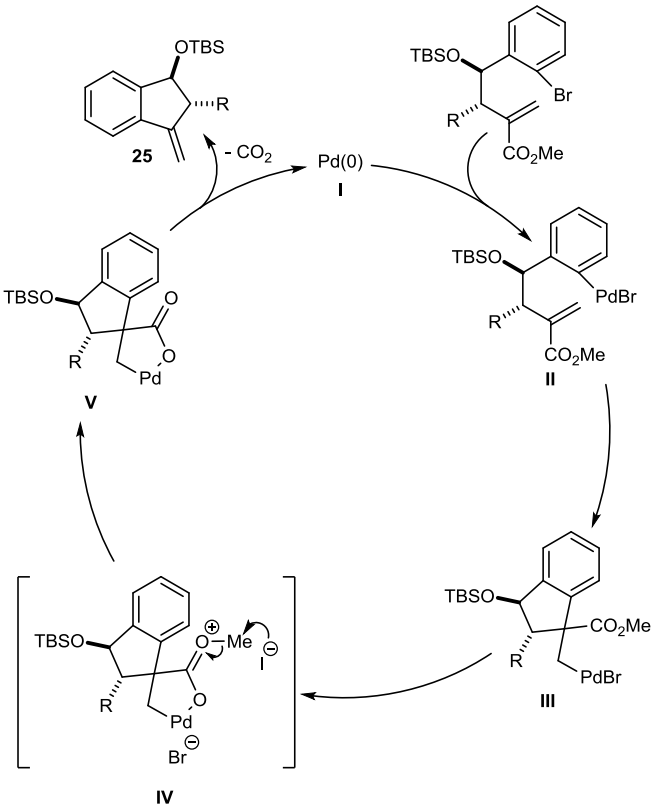
Scheme 9

A ring-closing-metathesis approach to indenols and indenones was reported by Fernandes and co-workers in 2004 (Scheme 9).[14] Grubbs second generation catalyst was used to access indenols and indenones in modest to good yields. Two examples are shown in Scheme 9.



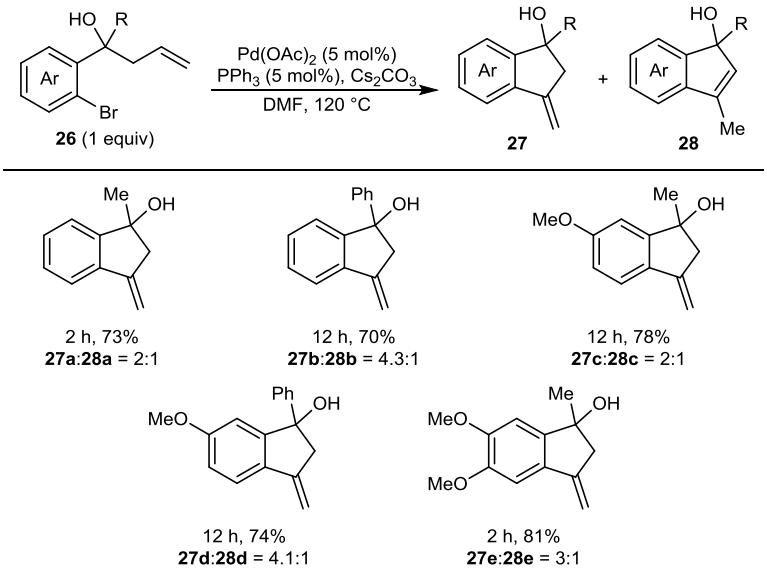
Scheme 10

In 2011, Kim and co-workers reported an iodide assisted synthesis of 3-methyleneinden-1-ols (Scheme 10).[15] Substrates **24** were subjected to a palladium catalyst in the presence of sodium iodide and triethylamine, and indenols **25a**-**25f** were obtained as the sole products. Various substituted aromatics at R^1 were well-tolerated (**25b**), and susbtrates with alkyl (**25d**) and alkenyl (**25f**) groups also reacted successfully. The reaction when R^1 was H also gave the corresponding 3-methyleneindan-1-ol **25e** in excellent yield.



Scheme 11

A catalytic cycle for this reaction was proposed (Scheme 11).[15] Oxidative addition into the carbon-bromine bond gives intermediate **II**. Subsequent 5-*exo*-*trig*-carbopalladation gives **III**. Nucleophilic iodide could facilitate the transformation of **III** to palladacycle **IV** *via* attack on the methyl group on the oxonium, which then gives **V**. Elimination of carbon dioxide gives the product **25** and regenerates the palladium catalyst.



Scheme 12

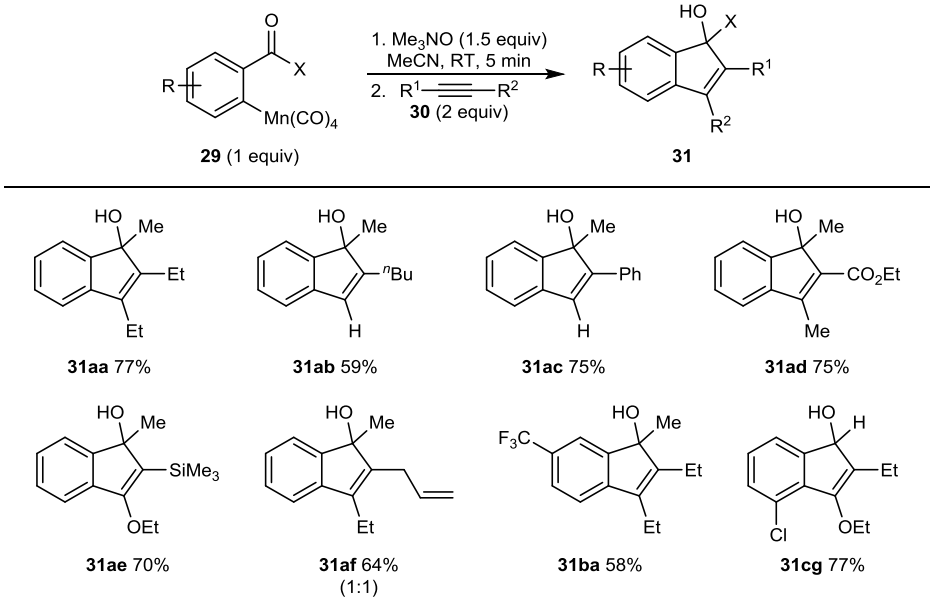
Another intramolecular example was reported in 2014 by Satyanarayana and co-workers (Scheme 12).[16] This methodology describes the synthesis of chromenes, with **27** and **28** as unexpected products when homoallylic alcohols were used, *via* an intramolecular Heck reaction. Products **27a**-**27e** were obtained in good yields and modest ratios.

1.3. Indenols and Derivatives from Alkynes

As discussed in section 1.2, annulation reactions are a useful tool for accessing indenols. Annulation chemistry with alkynes in the presence of transition metal catalysts is well-developed, and a range of carbocyclic and heterocyclic compounds can be obtained simply by varying the tethered electrophile. This section will focus on the annulation reactions of *ortho*-functionalised aromatic aldehydes, ketones, esters, imines and nitriles with alkynes as reaction partners.

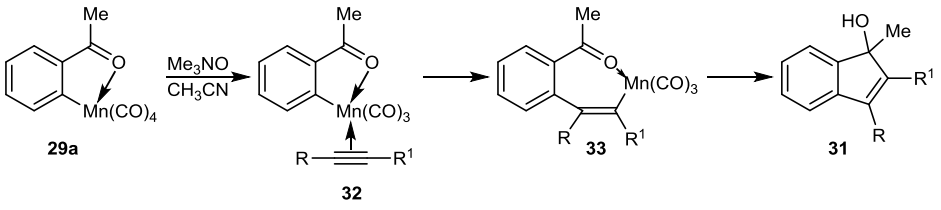
1.3.1. Addition to Carbonyl Groups

Ortho-acyl groups are common electrophilic traps for annulation reactions. Several examples using rhodium, palladium, or cobalt-catalysis have been reported, using either C-H activation approaches, 2-acylaryl halides or 2-acylarylboronic acids or esters with alkynes. This section will discuss the annulation reactions with aldehydes or ketones as the electrophilic trap.



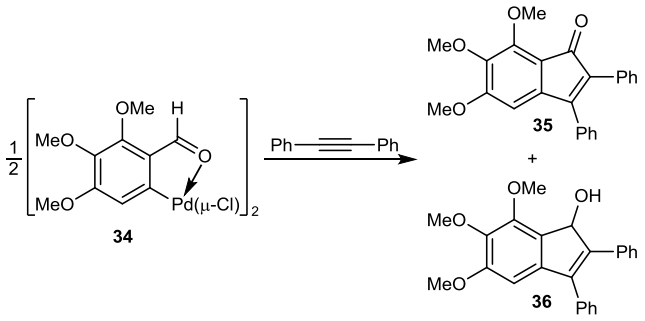
Scheme 13

A cyclisation reaction between *ortho*-manganated species **29** and alkynes **30** to generate the corresponding indenols was reported in 1988 by McCallum and co-workers (Scheme 13).[17] Aryl ketones were reacted with manganese reagents to provide the *ortho*-manganated derivatives. Reaction of these complexes with alkynes provided the indenols **31** in generally good yields and regioselectivities. The reaction was tolerant to terminal (**31ab** and **31ac**), internal (**31aa**, **31ad-31cg**), and both electron-rich and electron-poor alkynes. Halogen (**29c**) substitution and -CF_3 (**29b**) groups on the ketone were also tolerated. The reaction was proposed to be governed by sterics, with the bulkier group placed furthest from the aromatic ring.



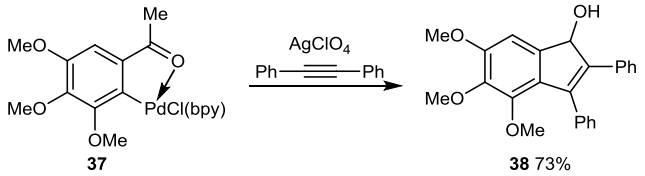
Scheme 14

The reaction was proposed to go *via* a two-step process. Decarboxylation, mediated by Me_3NO in acetonitrile generated the manganated intermediate **32** (Scheme 14).[17] Coordination of the alkyne to the now unsaturated manganese complex, followed by a regioselective migratory insertion across the alkyne gives the alkenylmanganese complex **33**. Cyclisation then gives indenol **31**.



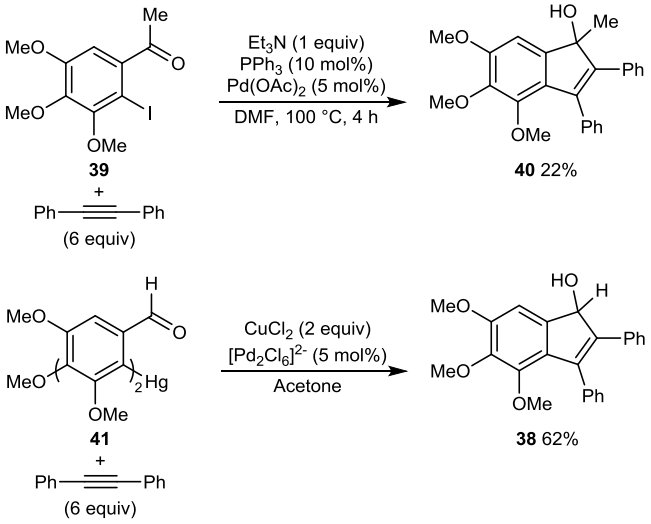
Scheme 15: Yield not given

In 1996, Gil-Rubio and co-workers reported the synthesis of indenols and indenones from palladium complex **34** (Scheme 15).[18] The reaction gave a 1:1 mixture of the corresponding indenone and indenol **35** and **36**.



Scheme 16

When the reaction was carried out in the presence of silver chloride, indenol **38** could be obtained in 73% yield from complex **37** (Scheme 16).[18] This methodology required stoichiometric palladium to generate the arylpalladium precursor.

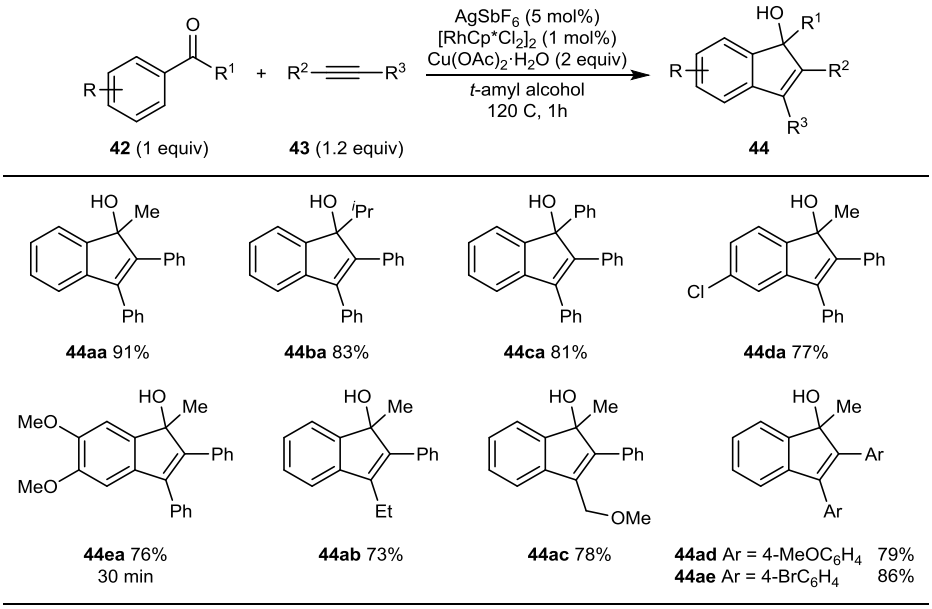


Scheme 17

The reaction was also attempted catalytically (Scheme 18).[18] The reaction with iodoarene **39** gave indenol **38** in 22% yield. With the mercury complex however, indenol **41** could be obtained in 62% yield. Similar chemistry was reported in 2002 by Martínez-Viviente, where the product obtained (indenols

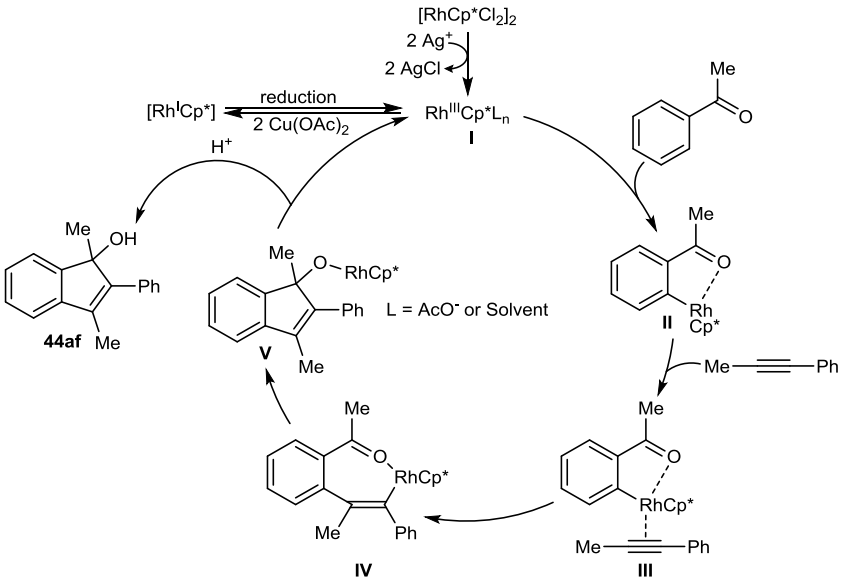
or indenones) could be varied by changing the charge on the arylpalladium complex.[19]

Catalytic C-H activation approaches provide a major advantage over the above approaches. These reactions do not require pre-functionalisation of the C-H bond, or stoichiometric quantities of precious metals like palladium.



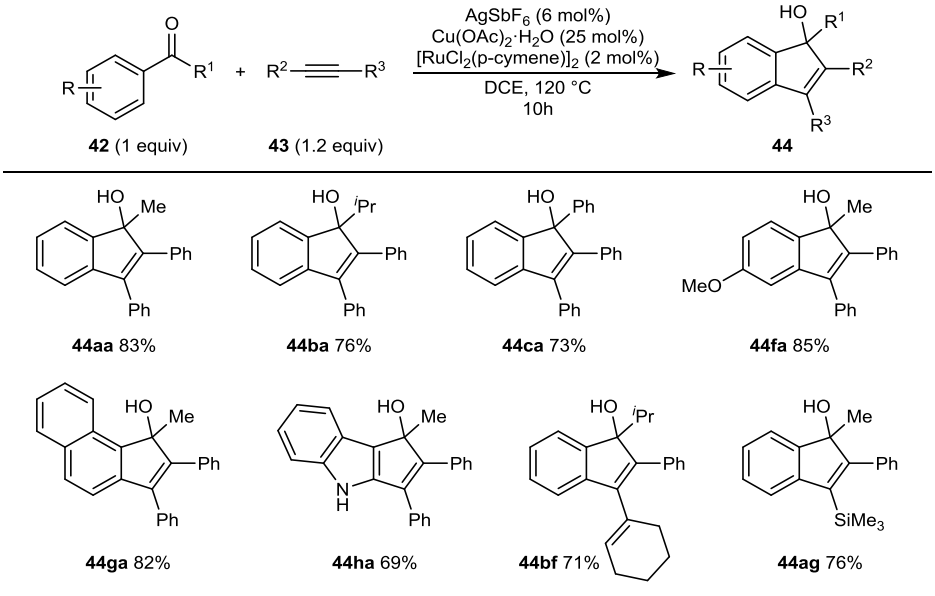
Scheme 18

Cheng *et al*. reported a rhodium-catalysed annulation reaction between arylketones and alkynes to generate indenols in 2011, *via* C-H activation (Scheme 18).[20] A range of substitution patterns were well-tolerated at both the ketone and the alkyne. Aryl-alkyl ketones (**42a**, **42b**, **42d** and **42e**) and aryl-aryl ketones (**42c**) reacted successfully, and indenols **44aa**-**44ea** were obtained in excellent yields. Halogen substitution (**44da**) and electron rich groups (**44ea**) on the aromatic ring of the ketone were also well-tolerated, giving the corresponding indenols in good yields. Unsymmetrical internal alkynes reacted successfully, with both alkyl and aryl substituents, to give indenols **44ab**-**44ae** in excellent regioselectivities.



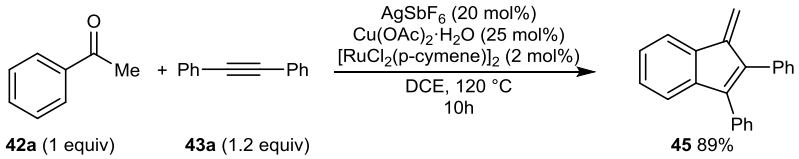
Scheme 19

A catalytic cycle was proposed for this reaction (Scheme 19).[20] The active Rh(III) species is generated *via* abstraction of chloride by silver cations. Coordination with the ketone and *ortho*-C-H bond activation gives the rhodacycle **II**. Coordination to the alkyne (**III**) and subsequent regioselective migratory insertion generates the alkenylrhodium species **IV**. Cyclisation (**V**) and protonation gives the indenol and regenerates the Rh(III) catalyst. The Rh(III) species is thought to be reduced by either the substrate or the solvent, so the $Cu(OAc)_2$ likely oxidises the reduced rhodium species back to the active catalytic species.



Scheme 20

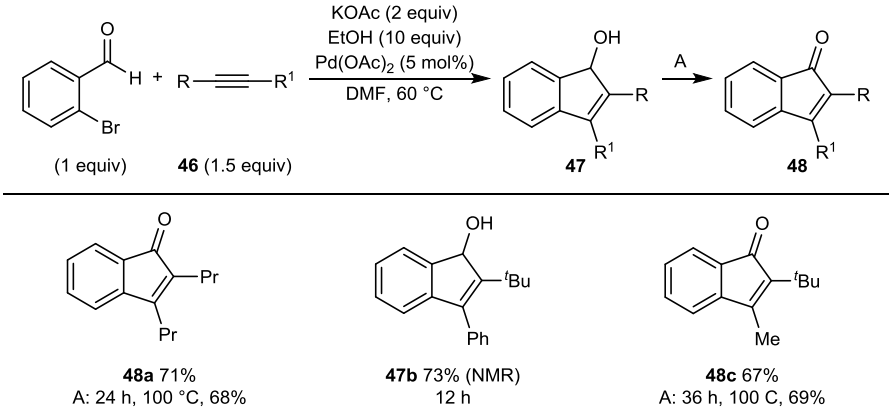
Relative to rhodium, ruthenium-catalysed approaches are under-explored. In 2012, Jeganmohan and co-workers reported the ruthenium-catalysed, C-H-activation approach to the synthesis of indenols, from aryl ketones and alkynes (Scheme 20).[21] This chemistry was also reported by Woodgate in 1999, as an unexpected result from a coupling reaction between substituted carbonyls and alkynes.[22] A range of substitution patterns on the ketone were well-tolerated, with both alkyl-aryl and aryl-aryl ketones giving the corresponding indenols **44** in excellent yields. Naphthyl tethered (**42g**) and indole tethered (**42h**) ketones also reacted successfully, giving the corresponding tricyclic ring systems **44ga** and **44ha** in good to excellent yields. Unsymmetrical alkynes (**43f** and **43g**) reacted successfully, giving the products in excellent observed regioselectivities.



Scheme 21

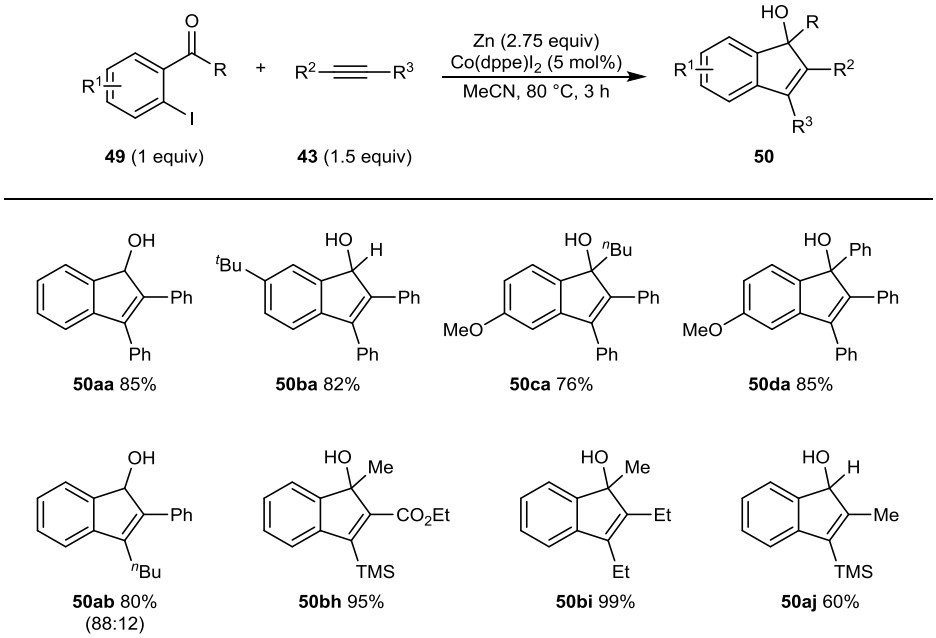
By altering the quantity of silver salt, benzofulvenes **45** could be accessed from the same starting materials, *via* dehydration of the corresponding indenols (Scheme 21).[21] This occurred when the amount of silver salt exceeded 8 mol% relative to the 2 mol% ruthenium used.

C-H activation approaches come with its own set of challenges. Regioselectivities for unsymmetrial starting materials can be poor, and often, directing groups are required to enhance the selectivity of one C-H bond over another. Furthermore, unless this directing group is incorporated into the product, they can be difficult to remove. Prior functionalisation can offer a solution. Halogens and boronic acids are commonly used to direct transition metal-catalysed reactions, ensuring activation only takes place at the pre-functionalised position.



Scheme 22

In 1999, a palladium catalysed synthesis of indenols and indenones was reported by Yamamoto and co-workers (Scheme 22).[23] The reaction between *ortho*-bromobenzaldehyde and **46** gave the corresponding indenol **47** in modest to good yields. In a couple of cases, heating this reaction further led to oxidation, and the corresponding indenones (**48a** and **48c**) could also be accessed.

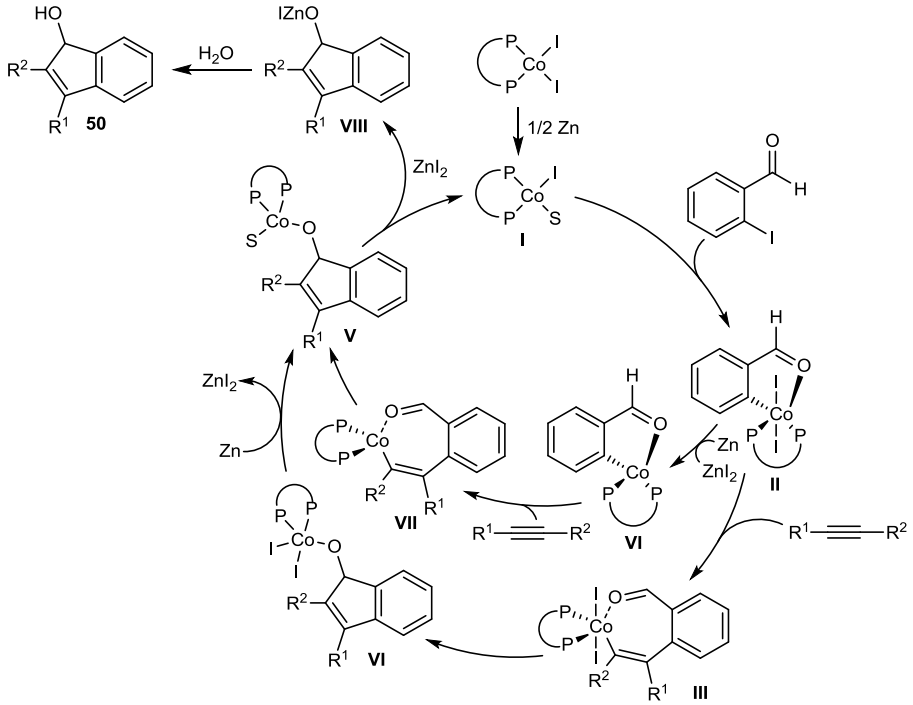


Regioisomeric ratios shown in parentheses

Scheme 23

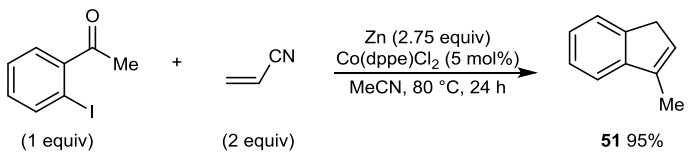
In 2003, a regioselective annulation between *ortho*-iodobenzaldehydes or *ortho*-iodo phenyl ketones and alkynes was reported by Cheng and co-workers using cobalt catalysis (Scheme 23).[1] A wide range of substitution patterns (bulky: **50aa**, electron-rich: **50ba**, **50da**; or silyl groups: **50bh**, **50aj**) on both

the aromatic ring, the keto-group, or the alkyne were well-tolerated, offering moderate to excellent yields and regioselectivities. This was the first reported example of the synthesis of indenols using cobalt-phosphine catalysis.



Scheme 24

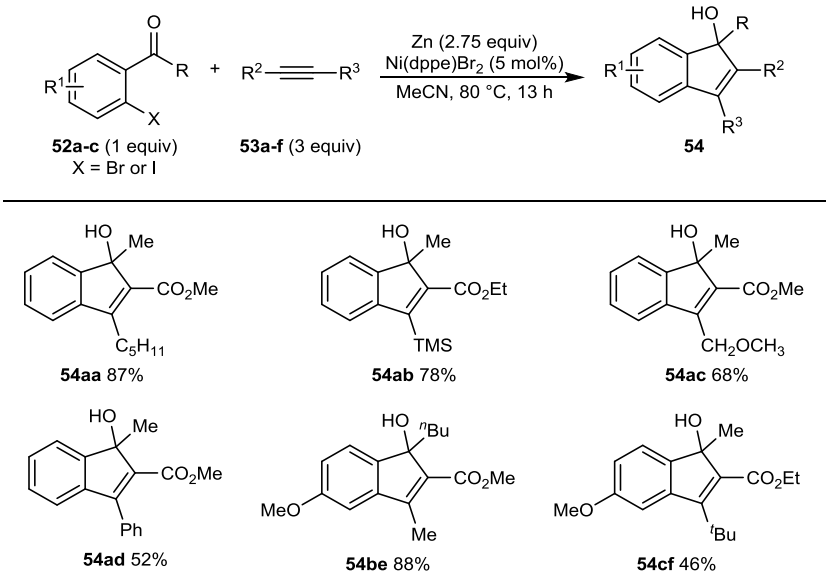
A catalytic cycle was proposed for the transformation (Scheme 24).[1,24] Reduction of Co (II) by zinc dust to Co(I) initiates the catalytic cycle. Oxidative addition to *ortho*-iodobenzaldehyde gives complex **II**. Insertion across the alkyne generates the seven-membered cobaltacycle **III**. Cyclisation and subsequent reduction of the Co(III) to Co(I) gives complex **V**. Transmetallation with zinc iodide gives the zinc alkoxide **VIII** and regenerates the active catalytic species. An alternative pathway, whereby complex **II** is reduced by zinc before undergoing insertion to give seven-membered cobaltacycle **VII** was also proposed.



Scheme 25

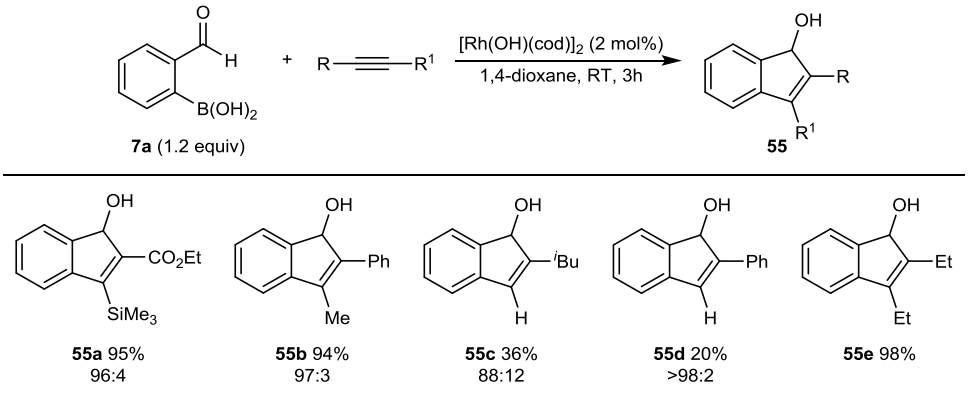
A year later, similar research was published by the same group, extending the methodology to acrylates and acrylonitriles, giving access to indenes.[24] When acrylonitrile was used, indene **51** was obtained in 95% yield, with no cyano

group present in the product (Scheme 25). In this case, it appears the acrylonitrile was acting as a 'masked' ethylene group, though the mechanism is currently unknown.



Scheme 26

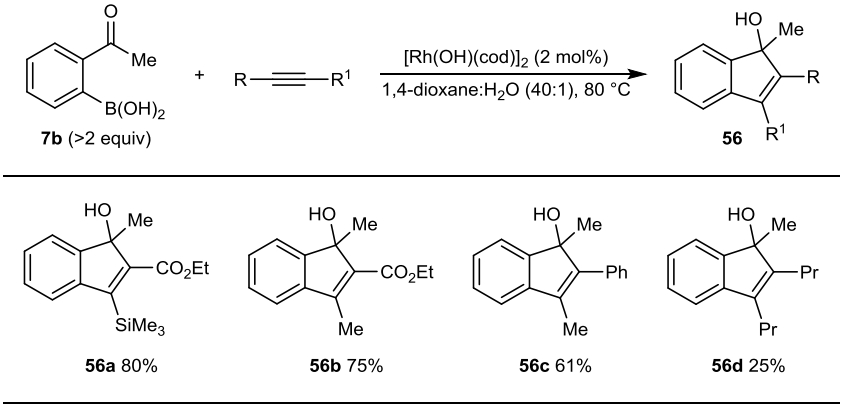
In the same year, Cheng *et al*. also reported a nickel-catalysed synthesis of indenols **54** from *ortho*-haloarylcarbonyls **52a-c** and alkynes **53a-f** (Scheme 26).[25] A range of alkynyl esters reacted successfully to give the corresponding indenols in moderate to excellent yields. Alkyl groups, silyl groups and aromatic groups on the alkyne were all tolerated. Bulkier groups gave lower yields (**54cf**). Electron-rich *ortho*-haloarylcarbonyls **54b** and **54c** also reacted successfully to give **54be** and **54cf** in good yields.



Scheme 27

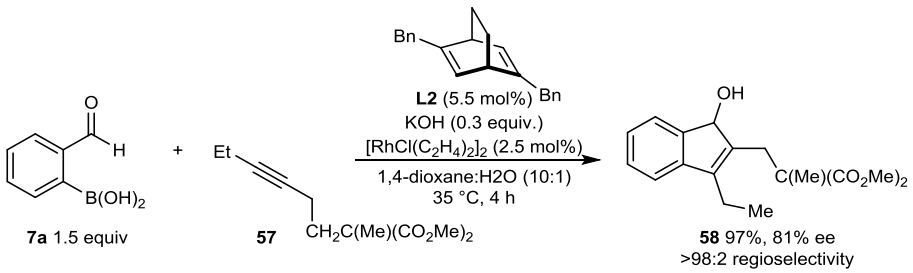
In 2005, the synthesis of inden-1-ols was reported by Murakami and co-workers using rhodium catalysis, from alkynes and *ortho*-formylphenylboronic

acid **7a** (Scheme 27).[26] Both symmetrical and unsymmetrical alkynes were well-tolerated. Terminal alkynes (**55c** and **55d**) offered lower yields than internal alkynes, and all reactions gave generally excellent regioselectivities.



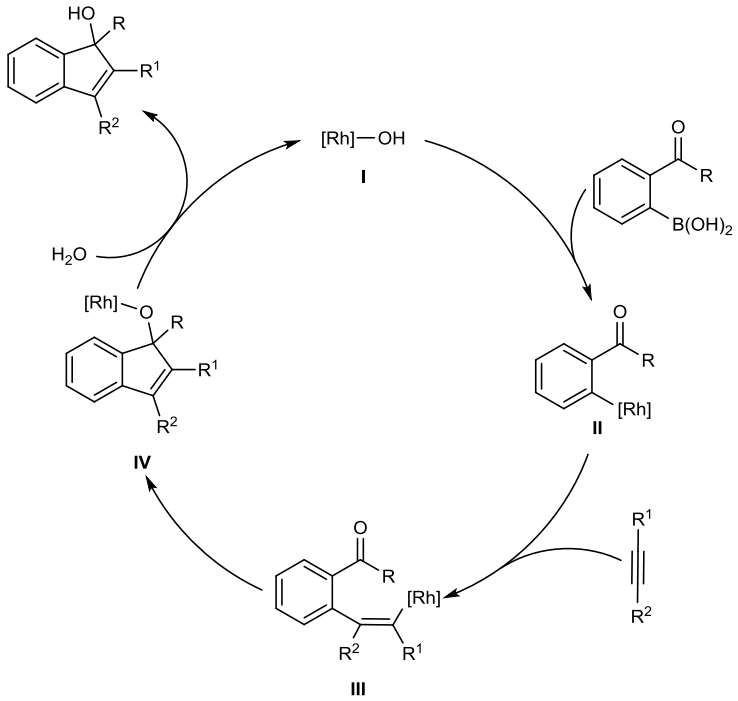
Scheme 28

The methodology was also applied to *ortho*-acetylphenylboronic acid **7b** and symmetrical and unsymmetrical alkynes. This reaction required more forcing conditions, namely, greater than 2 equivalents of the boronic acid, and an elevated temperature. Inden-1-ols **56** were isolated in modest yields and excellent regioselectivites (Scheme 28).[26] Similar research was published by Hayashi in 2005, where a range of substituted alkynes gave the corresponding indenols in moderate to excellent yields and regioselectivites. [27]



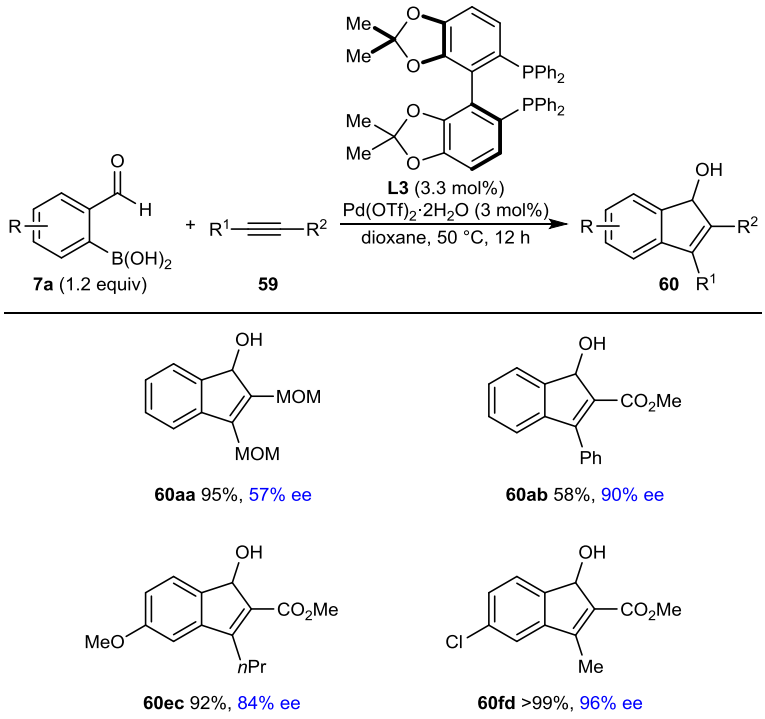
Scheme 29

Hayashi and co-workers also reported an enantioselective variant. Implementation of chiral diene ligand **L2** and 0.3 equivalents of potassium hydroxide gave indenol **58** in excellent yield and regioselectivity and 81% ee (Scheme 29).[27]



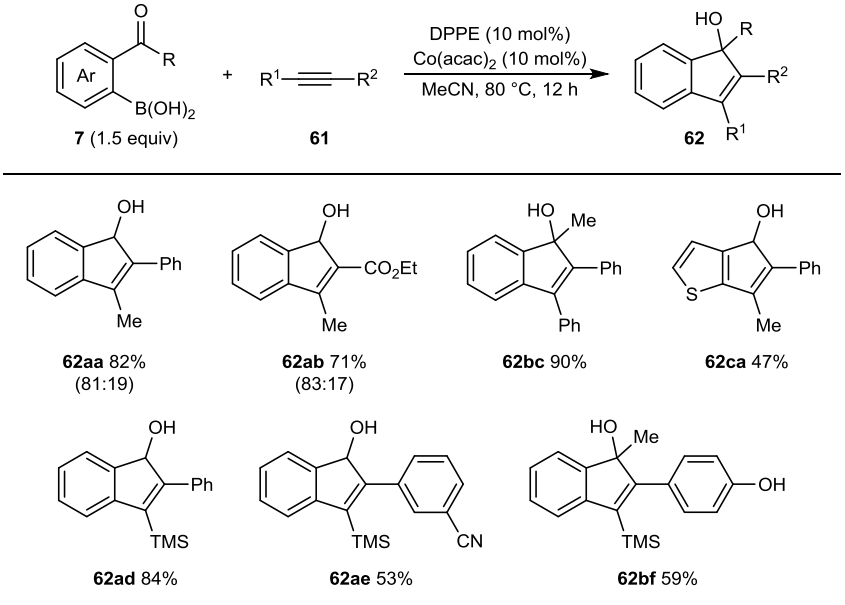
Scheme 30

Both processes (Scheme 27-Scheme 29) were proposed to proceed *via* a similar catalytic cycle.[26,27] Transmetallation of the rhodium complex gives arylrhodium species **II**. Coordination and migratory insertion gives the alkenylrhodium complex, which undergoes cyclisation to give alkoxyrhodium complex **IV**. Protonolysis regenerates the rhodium catalyst and the indenol (Scheme 30).



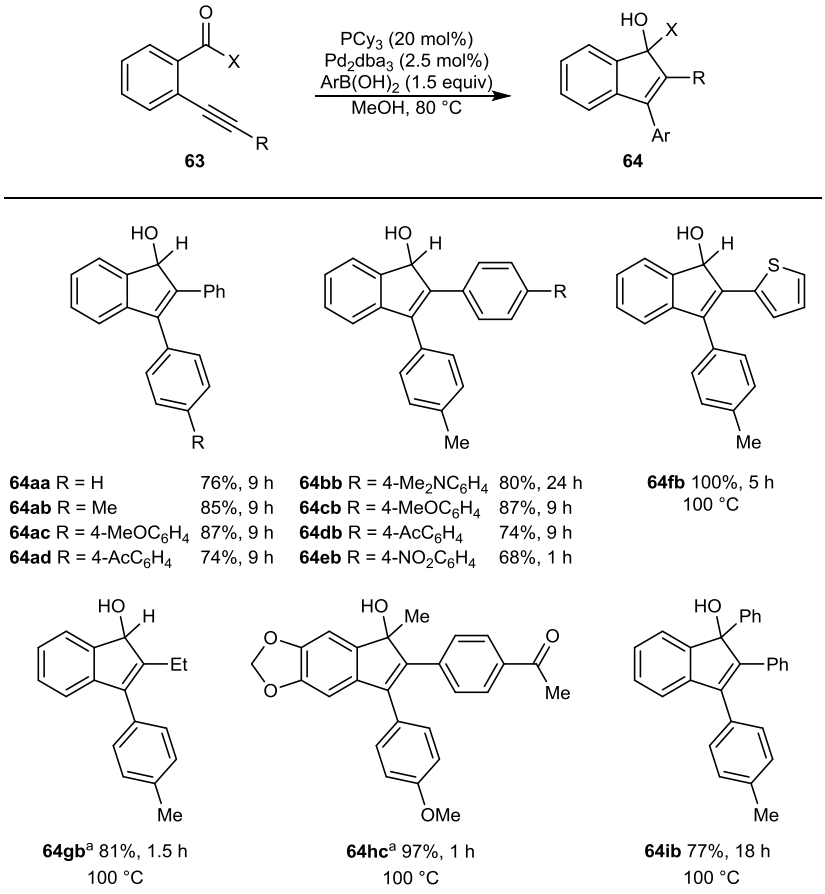
Scheme 31

In 2007, Lu and co-workers reported the enantioselective synthesis of indenols from *ortho*-formylarylboronic acids and alkynes catalysed by cationic palladium (Scheme 31).[28] This reaction tolerated electron-rich and halogen substituted *ortho*-formylarylboronic acids, giving indenols **60** in excellent yields and enantioselectivities. With alkyne **59b**, the yield of **60ab** was lower, but the excellent enantioselectivity was maintained. When an alkyne without an ester group (**59a**) was used, the ee of the product **60aa** was lower.



Scheme 32

In 2017, Ryu and co-workers reported a cobalt-catalysed synthesis of indenols from alkynes and *ortho*-carbonylarylboronic acids (Scheme 32).[29] Both symmetrical and unsymmetrical alkynes reacted successfully, giving the corresponding indenols **62** in generally excellent regioselectivities and good yields. Heteroarylboronic acid **7c** also reacted successfully to give indenol **62ca** in 47% yield. Alkyl, electron-rich aryl, electron-poor aryl, and silyl groups were also well-tolerated on the alkyne, and reactions with 2-acetylphenylboronic acid were also successful. The corresponding indenols **62bc** and **62bf** were obtained in modest to excellent yields.



[a] *(η^3–Allyl)-PdCp was used for this reaction.*

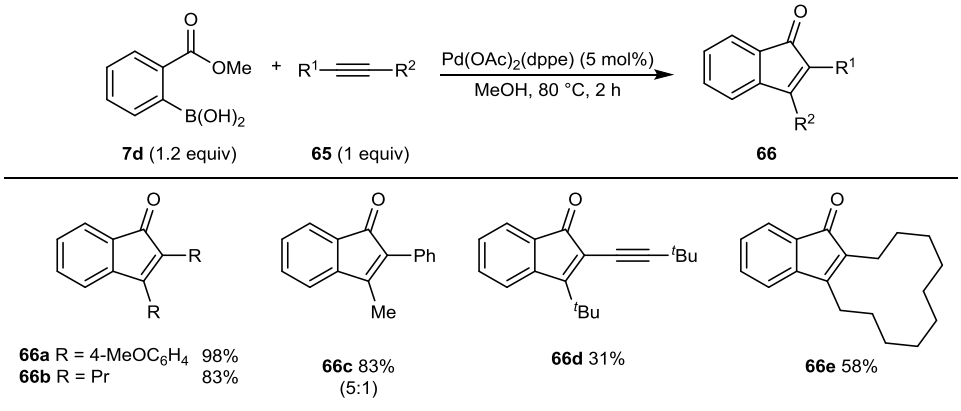
Scheme 33

In 2007, Kondo and co-workers reported an intramolecular palladium-catalysed approach to the synthesis of tri-substituted indenols **64** (Scheme 33).[30] Various *para*-substituted arylboronic acids gave the corresponding indenols in moderate to good yields (**64aa**-**64ad**). Various *para*-substituted aryl groups at the alkyne also worked well, as did heterocycles and alkyl

groups (**64aa-64hc**). Phenyl ketones worked equally well, albeit requiring a higher temperature, and **64ib** was obtained in 77% yield.

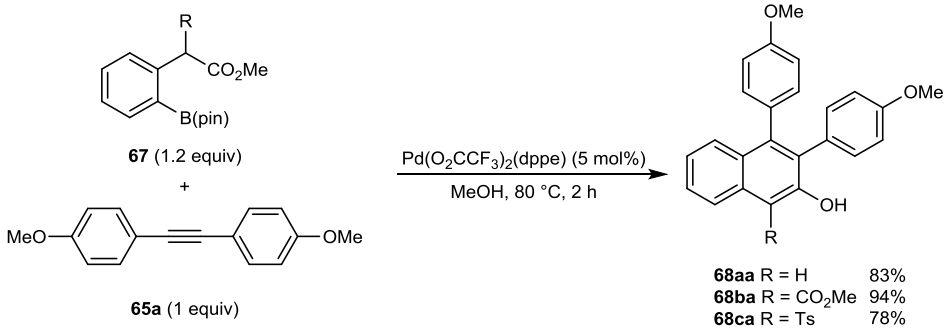
1.3.2. Addition to Esters

This section explores the synthesis of substituted indenone derivatives from alkynes and ester-containing compounds.



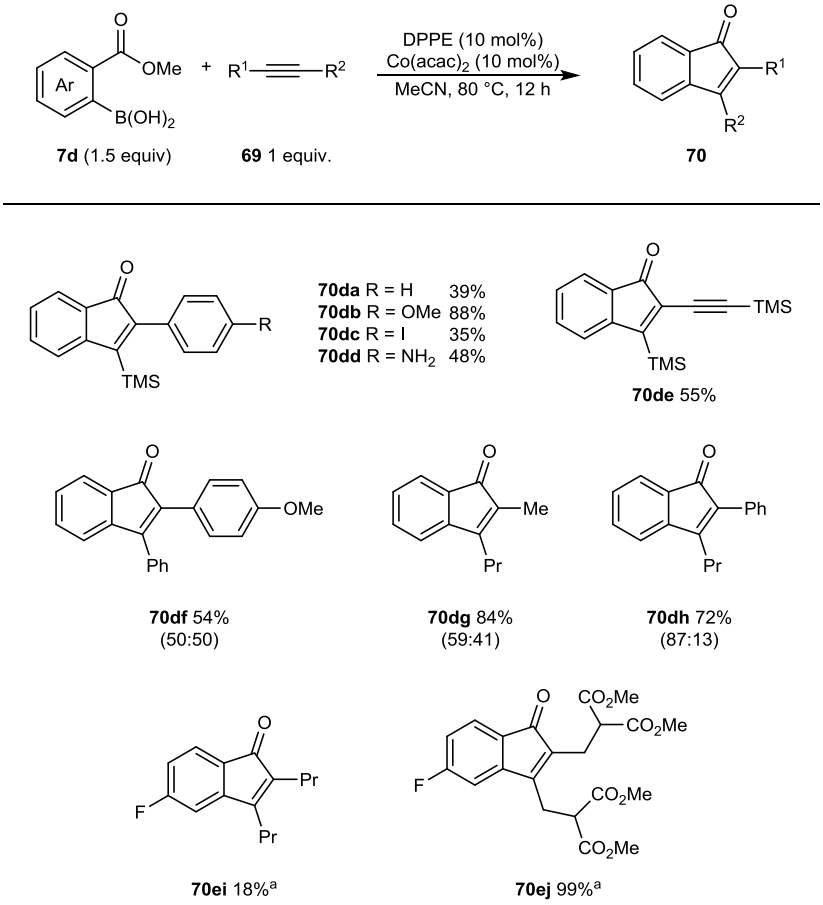
Scheme 34

In 2007, Kondo and co-workers reported a palladium catalysed synthesis of substituted indenones from internal alkynes and *ortho*-(methoxycarbonyl)phenylboronic acid **7d** (Scheme 34).[31] The reaction tolerated a range of alkynes, from alkyl (**66b**), to aryl (**66a**), and unsummetrical alkynes offering the corresponding indenones **66** in moderate to excellent yields and generally good regioselectivities. Reactions with terminal alkynes, alkynyl esters and trimethylsilyl alkynes were unsuccessful. The indenone could also be obtained in excellent yields in from the corresponding boronic acid pinacol ester, from various *ortho*-ester groups, and from *ortho*-cyanophenylboronic acid.



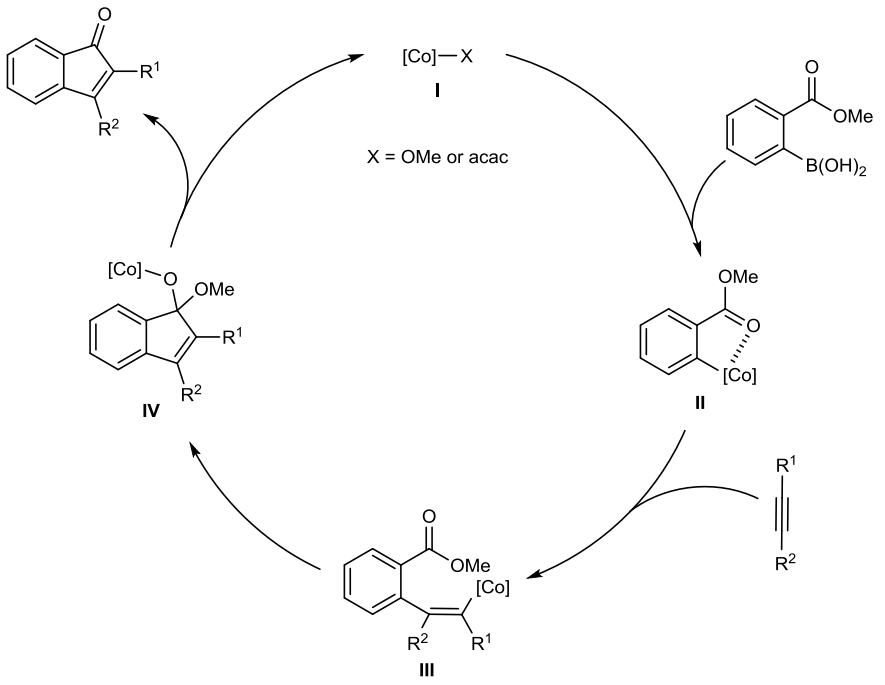
Scheme 35

This methodology was also applied to boronic acids **67**, with a -CHR moiety between the phenyl ring and the ester group (Scheme 35).[31] This gave access to a range of substituted naphthols in excellent yields.



Scheme 36

In 2016, Ryu and co-workers reported a cobalt-catalysed synthesis of indenones from *ortho*-(methoxycarbonyl)phenylboronic acid **7d** and a range of internal alkynes (Scheme 36).[32] Electron-rich and electron-poor substituted aromatics at the alkyne were well tolerated, offering moderate to excellent yields. Unsymmetrical alkynes gave generally good regioselectivities, except where the groups were similar (**70df** and **70dh**). Indenone **70df** was isolated as a 1:1 mixture of regioisomers, and indenone **70dg**, with a methyl- or propyl-group at the alkyne offered a lower regioisomeric ratio. The catalyst loading could also be lowered to 2 mol%.

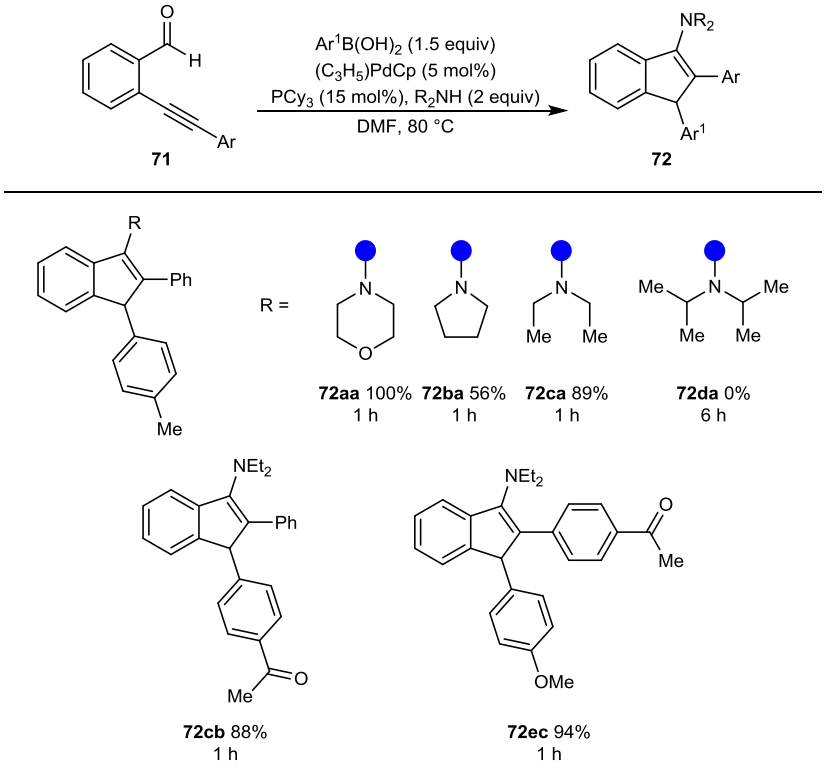


Scheme 37

A catalytic cycle was proposed (Scheme 37).[32] Transmetallation of the arylboronic acid generates aryl-cobalt complex **II**. Migratory insertion across the alkyne gives the alkenylcobalt intermediate **III**, which then undergoes cyclisation, generating the cobalt alkoxide **IV**. Collapse of the alkoxide gave the indenone and regenerated the cobalt catalyst.

1.4. Addition to Imines & Nitriles

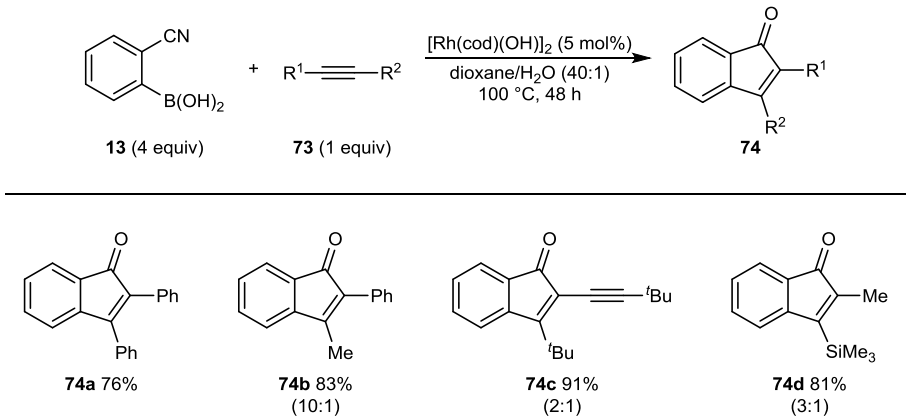
Reactions between alkynes and imines or nitriles are also well reported in the literature. These reactions lead to the synthesis of a range of substituted indenamines and indenones using two component couplings. C-H activation approaches and three-component coupling reactions are also discussed.



Scheme 38

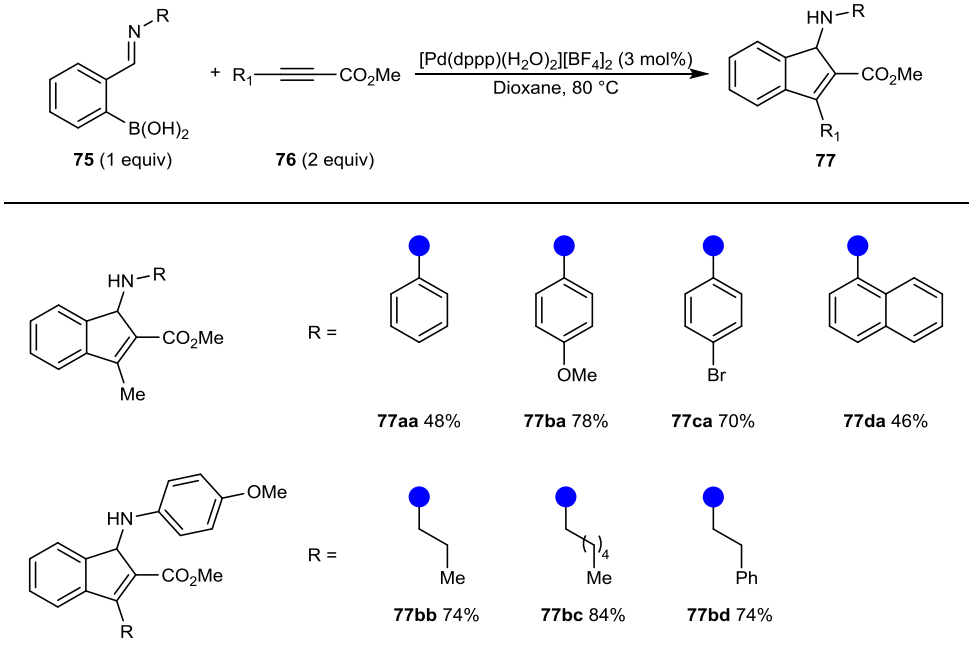
The palladium-catalysed intramolecular synthesis of indenols research (Scheme 33) was published alongside examples of indenamines by Kondo and co-workers in 2007 (Scheme 38).[30] Addition of excess of the secondary amine led to the formation of the imine *in situ*, which underwent cyclisation. The product then isomerised to give the corresponding indenamine product **72** in moderate to excellent yields. A range of amines worked well, ranging from morpholine (**72aa**) and pyrrolidine (**72ba**) to diethylamine (**72ca**). Sterically demanding amines like diisopropylamine did not give the desired product.

Intermolecular approaches are also popular. *Ortho*-functionalised arylboronic acids are commonly used in annulation reactions.



Scheme 39

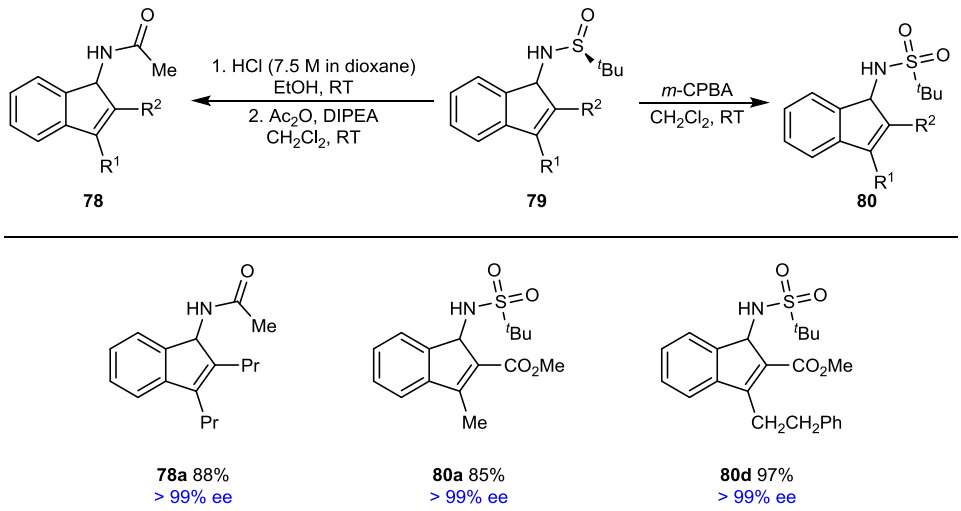
In 2005, Murakami and co-workers reported an annulation reaction between 2-cyanophenylboronic acid **13** and a range of substituted alkynes to generate the corresponding indenones (Scheme 39).[33] Symmetrical and unsymmetrical alkynes reacted successfully, offering modest regioselectivities and good to excellent yields.



Scheme 40

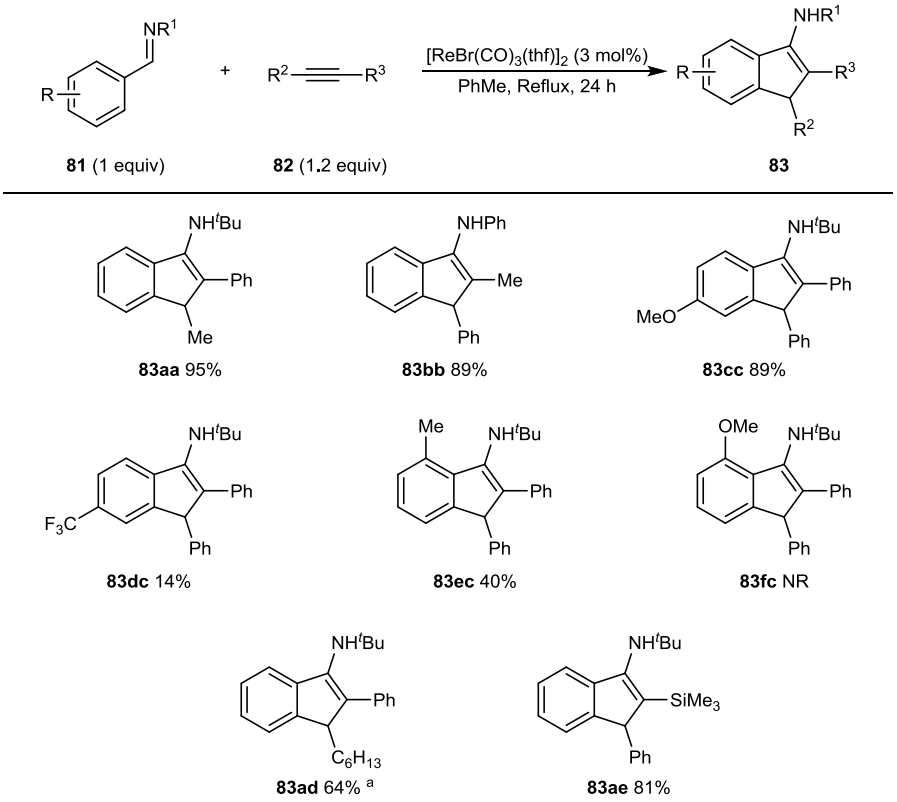
In 2011, the reaction between *ortho*-imine substituted arylboronic acids and alkynes was reported, generating a range of indenamines in moderate to excellent yields (Scheme 40).[34] A range of substituted aromatic groups on the amine worked well, with both bulky substituents like 1-naphthyl (**75d**) and electron-rich groups such as *para*-methoxy (**75b**) giving the corresponding

products in good to excellent yields. Unsymmetrical alkynes reacted to give the relevant indenamines in excellent yields and regioselectivities.



Scheme 41

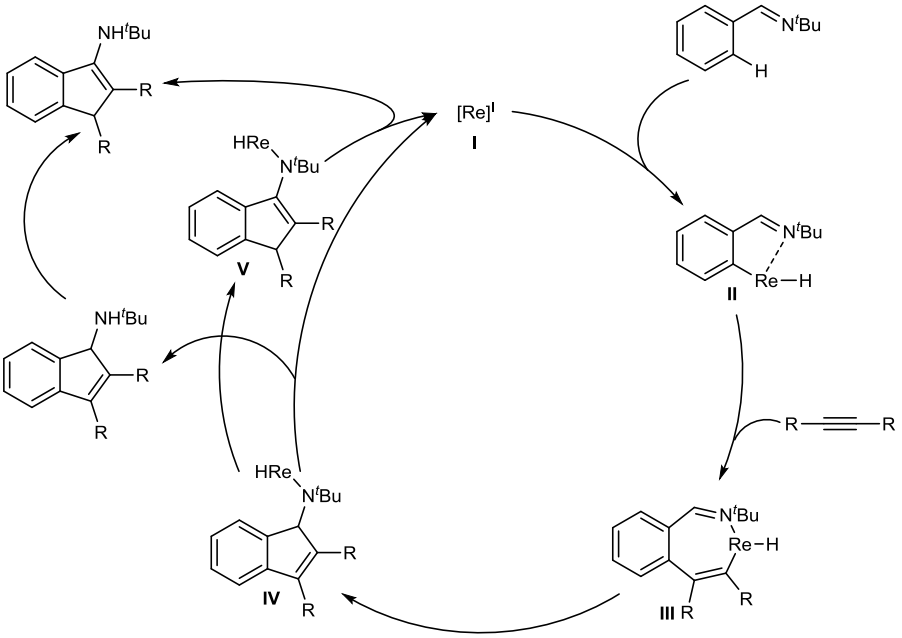
In order to induce enantioselectivity, a range of chiral ligands was screened (Scheme 41).[34] Unfortunately, this offered no success, so chiral sulfonimines were implemented instead. These offered the corresponding enantioenriched indenamine compounds in excellent yields and relatively modest diastereoselectivities. Treatment of the products with either acid, followed by acetic anhydride (**78**) or oxidation in the presence of *m*-CPBA (**80**) gave the indenamines with excellent ee.



[a] *135 °C*

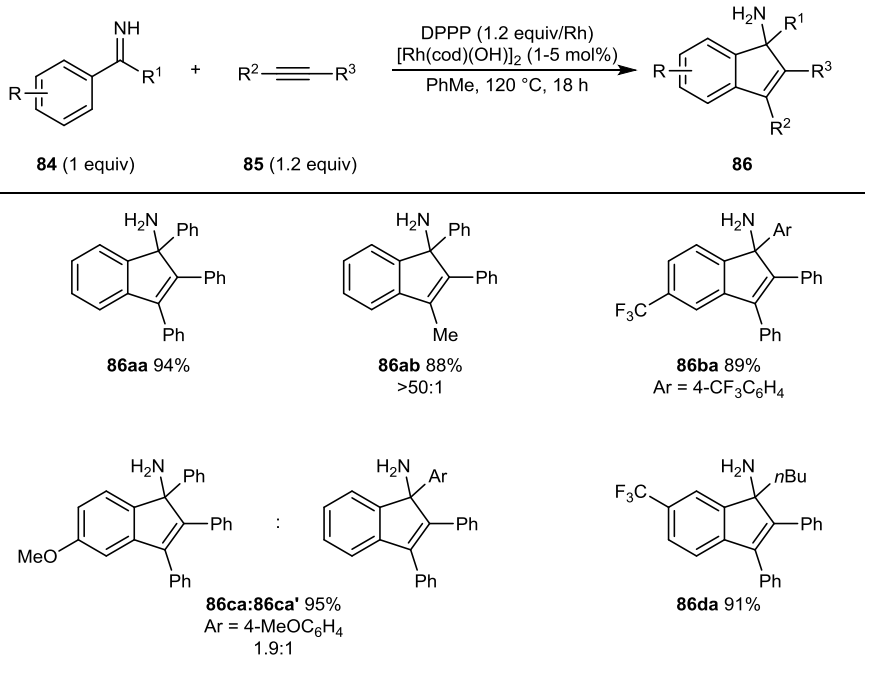
Scheme 42

A CH-activation approach to the synthesis of indenamines was first reported by Takai and co-workers in 2005 (Scheme 42).[35] This methodology reacted aldimines with alkynes in the presence of a rhenium catalyst to give the corresponding products in moderate to excellent yields. Electron-rich substituents on the aldimine were tolerated better than electron poor substituents (**83cc** 89% and **83dc** 14%). Substitution *ortho*- to the imine was tolerated only when a methyl group was used. Unsymmetrical alkynes also reacted successfully, offering the corresponding products as single observable regioisomers in excellent yield.



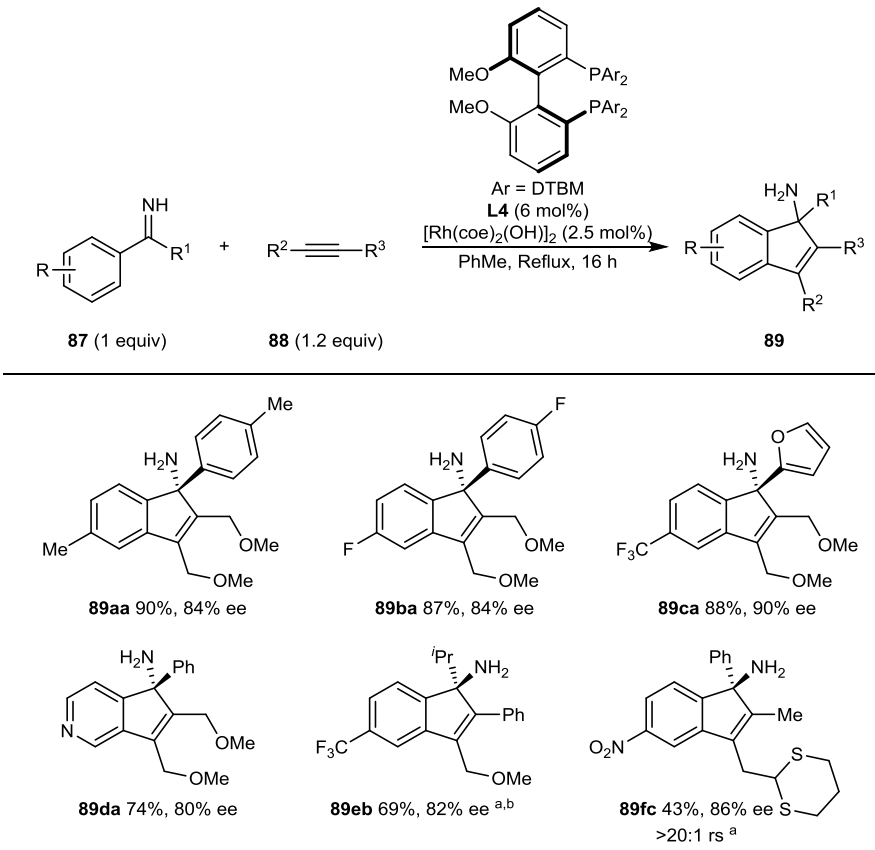
Scheme 43

A catalytic cycle was proposed (Scheme 43).[35] Coordination of the nitrogen atom to the rhenium centre, followed by C-H activation gives intermediate **II**. Insertion to the alkyne gives seven-membered metallocycle **III**. Intramolecular nucleophilic attack on the imine group gives intermediate **IV**. Here, intermediate **IV** could reductively eliminate to give **V**, and regenerate the catalyst. Intermediate **V** would then undergo a 1,3-rearrangemnet of hydrogen atoms to give **83**. Alternatively, **IV** could undergo a 1,3-rearrangement of hydrogen atoms to give **VI**, which would then reductively eliminate to give the product and regenerate the catalyst.



Scheme 44

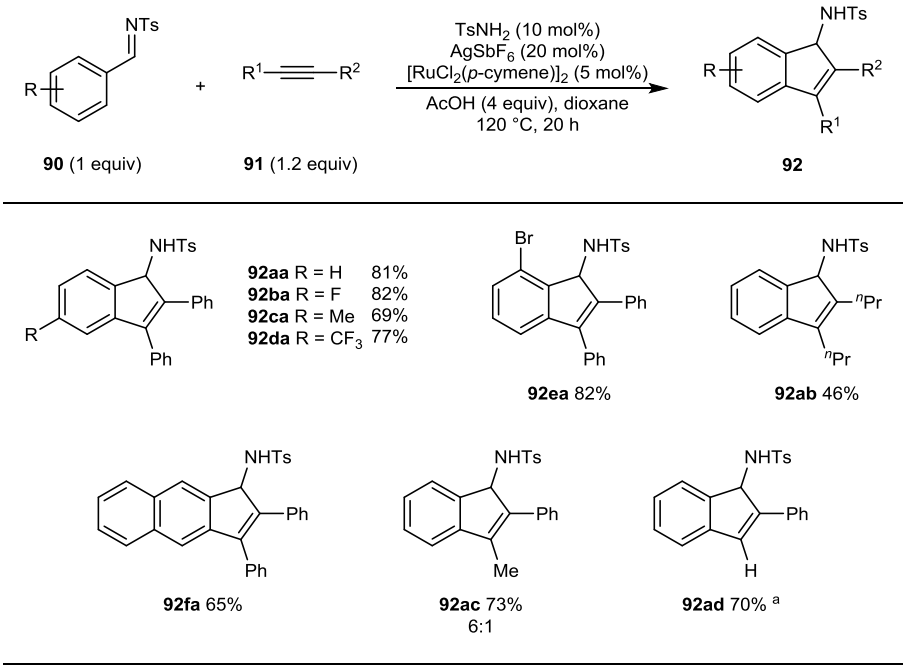
A rhodium variant of the C-H activation approach was also reported in 2010 by Zhao and co-workers (Scheme 44).[36] This chemistry used a range of both symmetrical and unsymmetrical ketimines to generate the corresponding indenamines. In the presence of an unsymmetrical ketimine **84c**, a mixture of products were obtained, where C-H activation had occurred at the 2-position on either aromatic ring, giving a ratio of 1.9:1 of each product (**86ca** and **86ca'**, 95%). Alkyl groups at the ketimine were also well tolerated, as were unsymmetrical alkynes, offering indenamine **86da** in excellent yields and regioselectivities.



rs = regioselectivity. [a] *5 mol% [Rh], 12 mol% **L**.* [b] *The opposite enantiomer of LX was used.*

Scheme 45

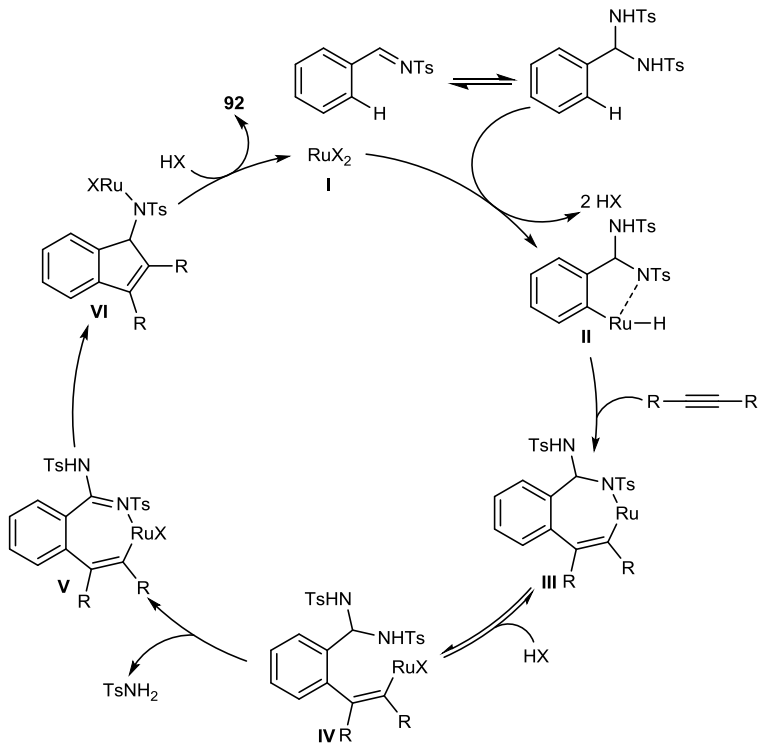
An enantioselective approach using rhodium catalysis was reported by Cramer *et al*. in 2011 (Scheme 45).[37] In the presence of a chiral BIPHEP ligand **L4**, moderate to excellent enantioselectivities could be achieved. A range of substitution patterns at both the ketimine and the alkyne were well tolerated, ranging from aromatic and heteroaromatic to alkyl groups. Unsymmetrical alkynes also reacted moderately well with both aromatic, aliphatic, and alicyclic systems reacting successfully, offering the corresponding products in moderate to excellent regioselectivities.



[a] *1-Phenyl-2-trimethylsilylacetylene was used.*

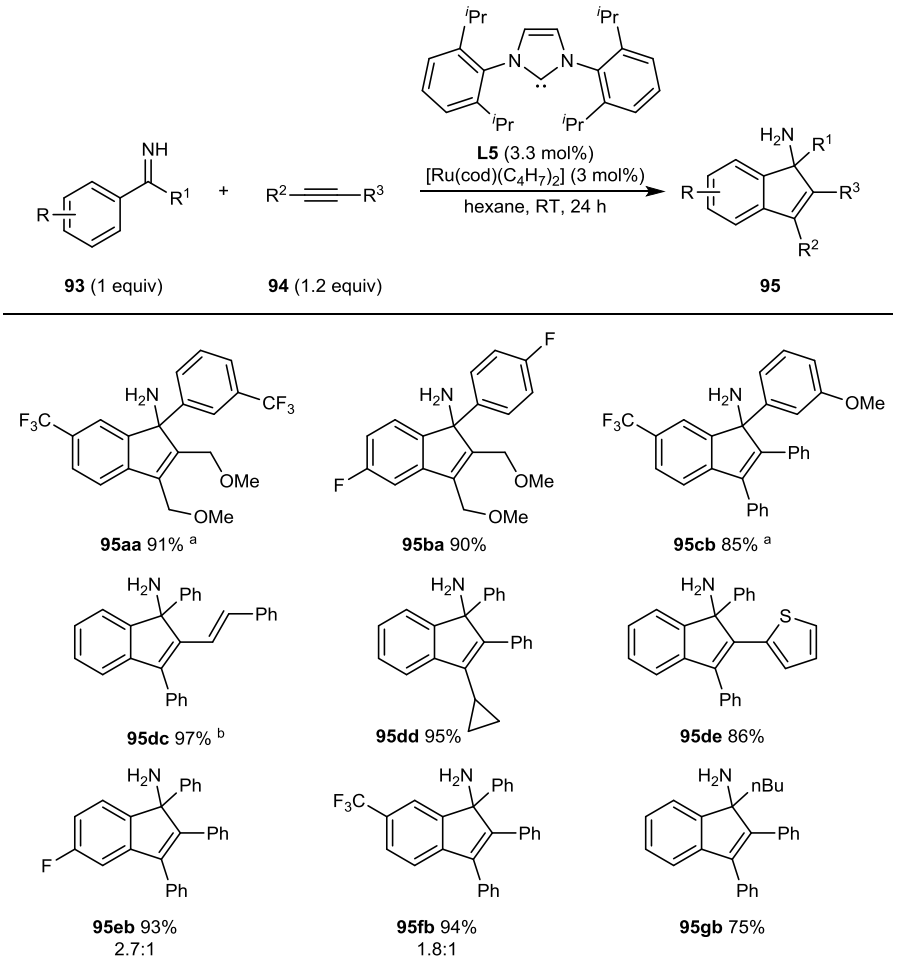
Scheme 46

In 2012, Li and co-workers reported the first example of C-H-activation of *N*-sulfonyl imines to give indenamines, *via* addition to an alkyne (Scheme 46).[38] The reaction was tolerant to a range of substituents on the aromatic ring, ranging from electron-poor trifluoromethyl groups (**90d**), to halogens (**90e**) and naphthyl groups (**90f**), giving the corresponding indenamines in good to excellent yields. Unsymmetrical alkynes gave a mixture of regioisomers. Indenamine **92ac** was obtained as a 6:1 mixture of regioisomers. Silylated alkynes afforded the corresponding indenamine **92ad** with complete desilylation under the reaction conditions. Similar chemistry was also reported by Cheng in 2014. This chemistry also tolerated enynes and a range of sulfonamides, to give the corresponding indenamines in modest to excellent yields and moderate regioselectivitites.[39]



Scheme 47

A catalytic cycle for this transformation was proposed (Scheme 47).[38] Nucleophilic addition of *p*-toluenesulfonamide to the imine, followed by deprotonation and cyclometallation gives intermediate **II**. Insertion across the alkyne generates the seven-membered rhodacycle **III**, which is able to undergo reversible protonolysis to give **IV**. Elimination of *p*-toluenesulfonamide then gives intermediate **V**, which undergoes cyclisation to give **VI**. Protonolysis then releases the product and regenerates the catalyst.



*a 60 °C. b IMes **L*** used instead.*

Scheme 48

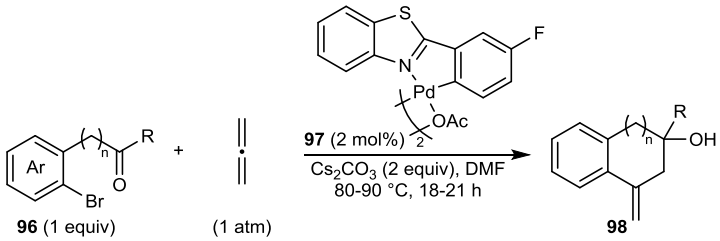
The reaction between ketimines and alkynes to generate substituted indenamines furnished with a quaternary centre was reported by Zhao and co-workers in 2013, catalysed by ruthenium (Scheme 48).[40] A range of symmetrical and unsymmetrical alkynes reacted successfully offering the corresponding indenamines **95** in modest to excellent yields and regioselectivities. Unsymmetrical ketimines, with only slight differences in structure offered a mixture of products (**95eb**-**95fb**). Unactivated, and unprotected ketimine **93g** also reacted successfully, affording **95gb** in 75% yield.

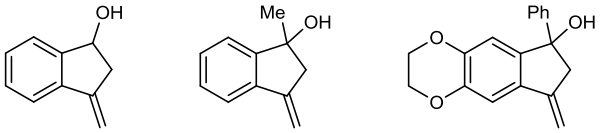
1.5. Indanols & Derivatives from Allenes

Compared to alkynes and alkenes, allenes in annulations to give indanes and their derivatives are relatively under-reported. This section will focus on the

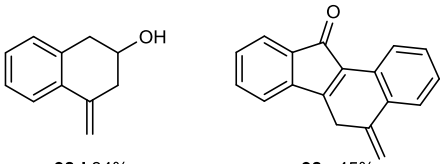
examples of the synthesis of 3-methyleneindan-1-ols and related compounds with allenes as reaction partners.

1.5.1. Addition to Carbonyls





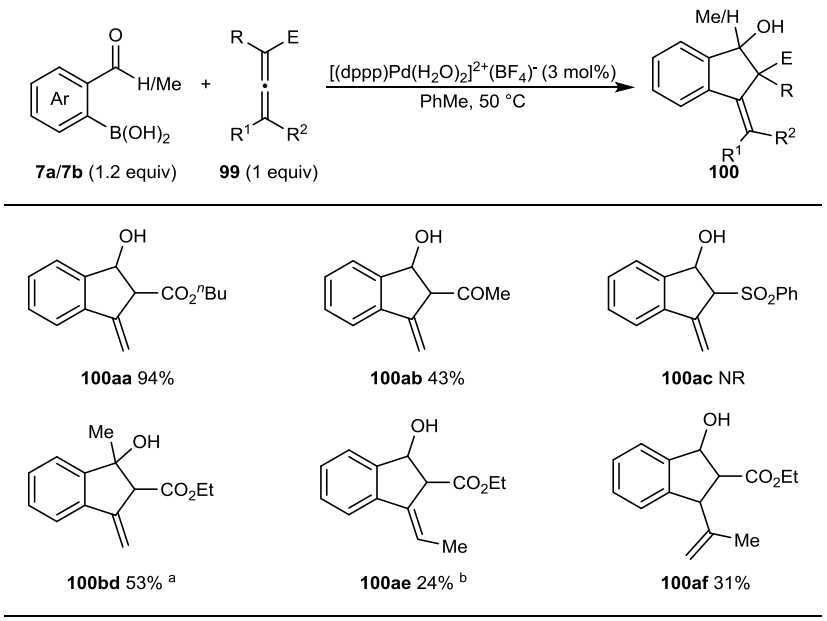
98a 90% **98b** 70% **98c** 70%



98d 34% **98e** 45%

Table 1

In 2000, Muir *et al*. reported a synthesis of indenols with aryl aldehydes and ketones under an atmosphere of allene in the presence of a palladium catalyst (Table 1).[41] Substitution at the aromatic ring was well-tolerated, and dioxole-substituted **98c** was obtained in a 70% yield. An extra -CH_2 group between the carbonyl and the aryl ring gave the 6-membered ring **98d** in 34% yield. When 2-(2-bromophenyl)indane-1,3-dione was reacted, the dehydration product **98e** was observed in modest 45% yield.



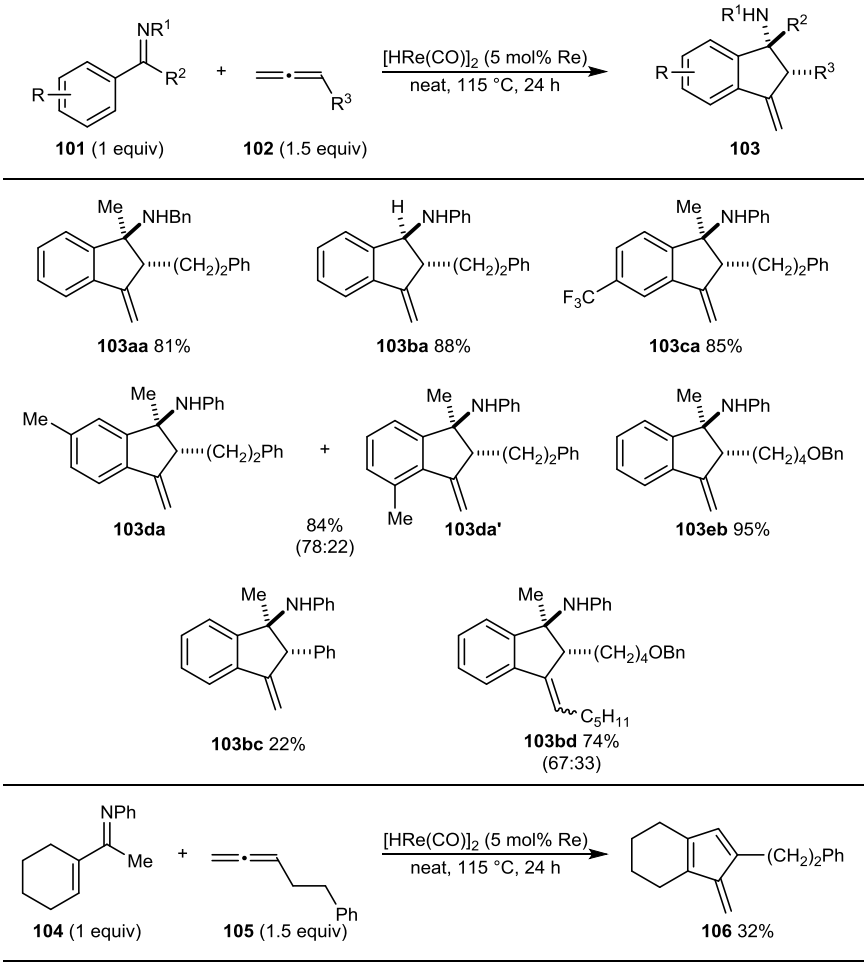
[a] *This reaction was carried out at 80 °C.* [b] *This reaction was carried out at 25 °C.*

Table 2

In 2009, Lu *et al*. reported the synthesis of 3-methyleneindan-1-ols **100** from allenoates and *ortho*-acylarylboronic acids (Table 2).[42] This reaction gave generally excellent yields, and a range of ester groups were well-tolerated. Yields dropped when allenone **99b** was used (**100ab**, 43%), or when 2-acetylphenylboronic acid was used (**100bd**, 53%). Substitution at the 3-position on the allene also diminished the yields, with **100ae** obtained in a 24% yield. When 3,3-dimethyl substituted allene was used, **100af** was obtained in a 31% yield. Reactions with electron-rich allenes, 1,1-disubstituted allenes, or sulfone-substituted allenes were unsuccessful.

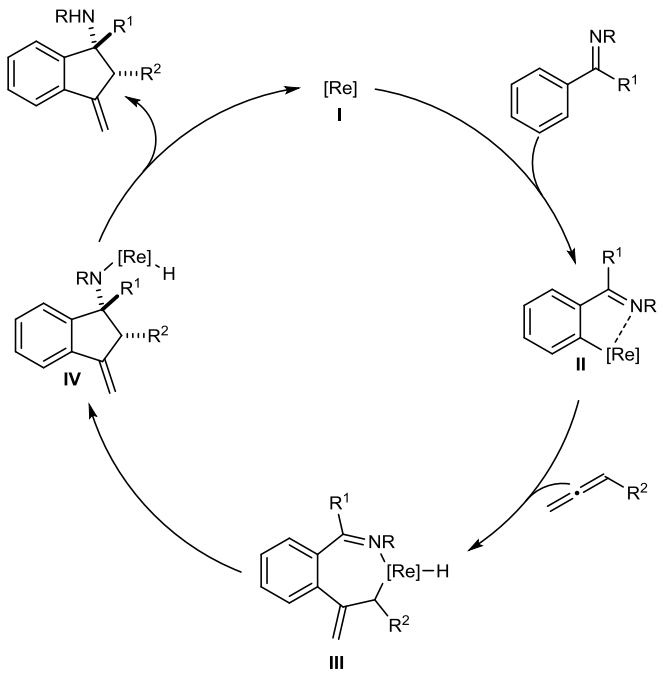
1.5.2. Addition to Imines

Two examples of reactions between aryl imines and allenes to give 3-methyleneindan-1-amines have been reported. These examples are presented in this section.



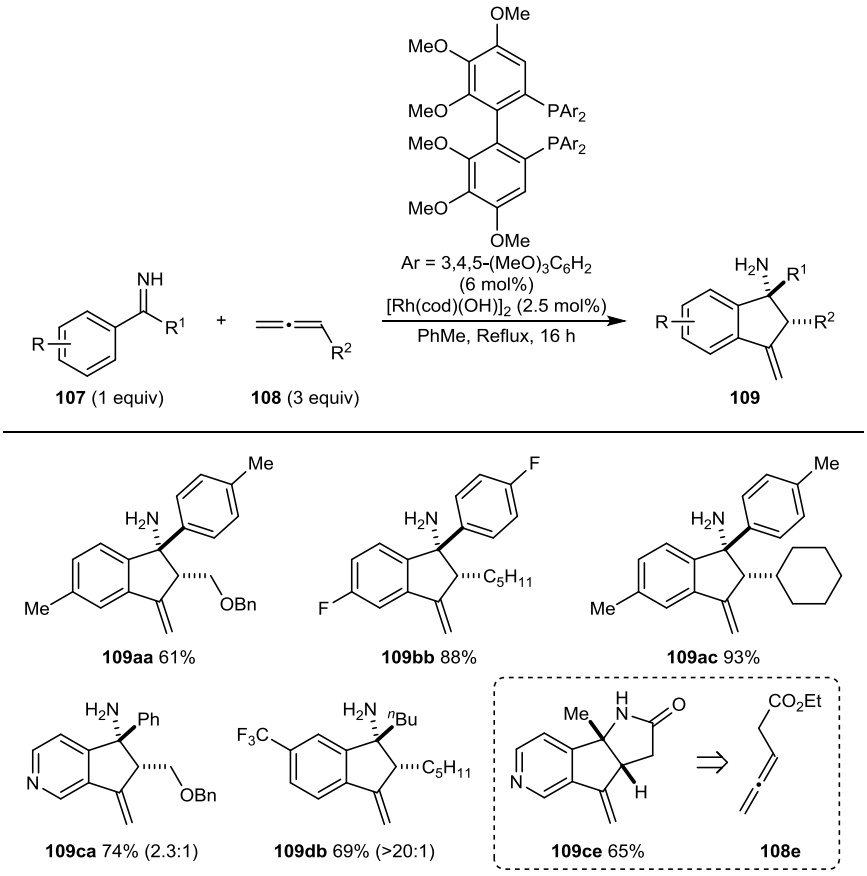
Scheme 49

In 2010, Takai and co-workers reported a highly diastereoselective annulation reaction between allenes and ketimines (Scheme 49).[43] Both aldimines and ketimines were well-tolerated, and **103aa** and **103ba** were obtained in excellent yields. Ketimine **101c** with the electron-poor -CF_3 group also reacted successfully and **103ca** was obtained in 85% yield. With ketimine **103d**, a mixture of regioisomers were obtained in a modest ratio of 78:22, in 84% yield. Aliphatic allenes reacted successfully (**102b**), however, a considerably lower yield was obtained when phenyl allene was used (**103bc**). With ketimine **104**, methylenecyclopentadiene **106** was obtained in 32% yield.



Scheme 50

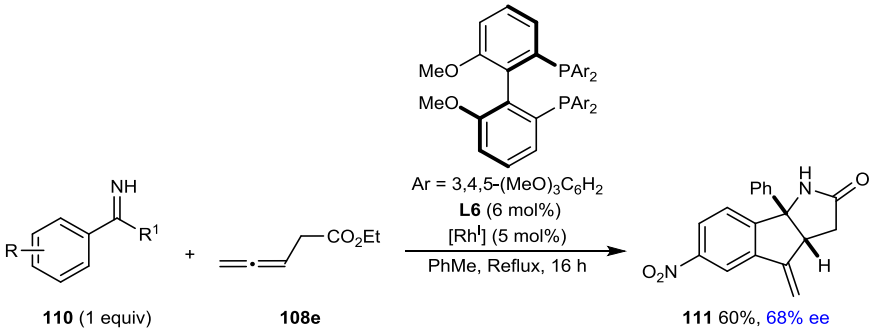
A catalytic cycle was proposed. Rhenium-catalysed C-H activation *ortho*- to the imine gives intermediate **II** (Scheme 50).[43] Regioselective insertion gives complex **III**, which then undergoes intermolecular nucleophilic cyclisation to give the corresponding product. The steric repulsion between the R^1 and R^2 groups is said to govern the *trans*-selectivity.



isomeric ratios shown in parentheses

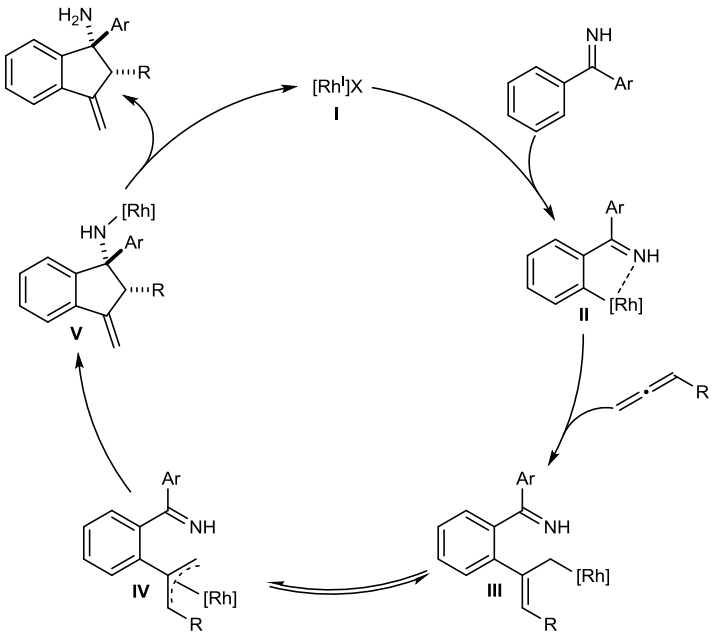
Scheme 51

Prior to his research on the couplings between imines and alkynes (Scheme 45),[37] Cramer and co-workers published a *syn*-selective allylation of ketimines *via* directed C-H activation (Scheme 51).[44] Aliphatic and alicyclic allenes reacted successfully to give indanamines **109** in modest to excellent yields, and generally good diastereoselectivity. Symmetrical ketimines **107a** and **107b** reacted successfully with allenes **108a**, **108b** and **108c** to give the corresponding indanamines **109aa**-**109ac** in good to excellent yields and diastereoselectivities. When allene **108e** was used, the primary amine was captured to give the corresponding lactam **109ce** exclusively, in 65% yield.



Scheme 52

An enantioselective variant was also reported (Scheme 52).[44] Using ligand **L6**, fused lactam **111** could be obtained in a modest 60% yield and 68% ee.



Scheme 53

The catalytic cycle was proposed to proceed *via* cyclometallation of the imine with a rhodium I complex, *via* either an oxidative addition-reductive elimination process, or a σ-bond metathesis to give **II** (Scheme 53).[44] Carborhodation of the allene gave intermediate **III**, which could exist as either the η^1- or the η^3-rhodium complex **IV**. Allylation then gives intermediate **V**, which releases the product and regenerates the catalyst.

Whilst a range of methods exist to synthesise indanols and related compounds, there is still room to improve the scope. Few examples using allenes as reaction partners have been reported. Furthermore, precious metals like rhodium, iridium and palladium are often required. Accessing these compounds using nickel-catalysis could therefore prove advantageous.

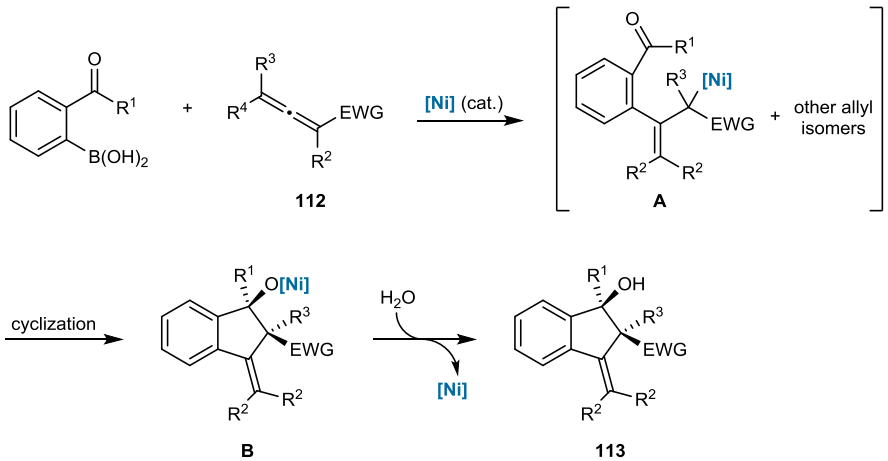
Herein, the development of a mild nickel-catalysed, highly diastereoselective approach to the synthesis of 3-methyleneindan-1-ols is described. The reaction between 2-formylarylboronic acids and 2-acetylphenylboronic acid and a range of activated allenes proceeded efficiently to give the corresponding products as single observable diastereoisomers.

2. Synthesis of 3-Methyleneindan-1-ols: Results & Discussion

2.1. Aims and Objectives

As discussed in the previous section, there are numerous methods to access indanols and their derivatives. Prior research carried out by Lu and co-workers demonstrated that 3-methyleneindan-1-ols can be accessed from allenoates and 2-formylphenylboronic acid in the presence of a cationic palladium catalyst.[42] There are areas where this research could be improved however, as the activating groups are currently limited to esters or ketones, and 1,1-disubstituted allenes were unreactive.

Recently, the Lam group has demonstrated that arylboronic acids add across alkynes,[45,46] and allenes,[47] in the presence of a nickel catalyst and suitable *P*,*N*-ligand. Building on this research, a nickel-catalysed reaction between *ortho*-acylarylboronic acids and activated allenes was envisaged. The aim of the project was to expand the scope of the reaction between activated allenes and *ortho*-acylphenylboronic acids, using nickel catalysis.

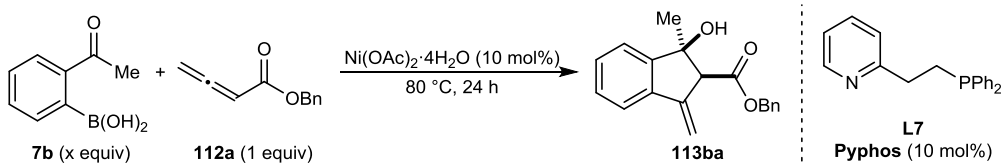


Scheme 54

The methodology envisaged is described in Scheme 54. Here, transmetallation of the 2-acylarylboronic acid and subsequent migratory insertion could give allyl-nickel intermediate **A**, and other isomers. Cyclisation (**B**) and subsequent

protonolysis would give 3-methyleneindan-1-ol **113** and release the nickel catalyst.

2.2. Control Reactions & Optimisation



7b (x equiv) **112a** (1 equiv) **113ba** **L7** **Pyphos** (10 mol%)

Entry	x	Ligand	Solvent	Yield (%)
1	2	PyPhos	MeCN:1,4-dioxane (3:2)	62
2[a]	2	-	MeCN:1,4-dioxane (3:2)	-
3[a]	2	PyPhos	MeCN:1,4-dioxane (3:2)	-
4	2	-	MeCN:1,4-dioxane (3:2)	53
5	2	PyPhos	1,4-dioxane	57
6	2	-	1,4-dioxane	87
7	1.5	-	1,4-dioxane	78
8	1.1	-	1,4-dioxane	54
9[b]	2	-	1,4-dioxane	82
10[b]	2	-	MeCN	41
11[b]	2	-	MeCN:1,4-dioxane (3:2)	97

Table 3: Yields were calculated from ^{1}H NMR spectra using 1,3,5-trimethoxybenzene as an internal standard. [a] These reactions were carried out without a catalyst. [b] These reactions were carried out at RT.

The investigation began by reacting 2-acetylphenylboronic acid **7b** and allene **112a** at 80 °C with nickel acetate and pyphos **L7** in a 3:2 mixture of acetonitrile:1,4-dioxane. 3-Methyleneindan-1-ol **113ba** was obtained in 62% yield (Table 3, Entry 1). Control reactions to determine suitable conditions and to improve the yield were then undertaken. Reactions in the absence of the nickel-catalyst were unsuccessful (Table 3, Entries 2 and 3). The addition of the ligand pyphos in either the mixture of acetonitrile:1,4-dioxane (3:2) or in 1,4-dioxane only did not improve the yield (Table 3, Entries 3-6). Lowering the number of equivalents of boronic acid was detrimental to the yield (Table 3, Entries 7 and 8). Pleasingly, the reaction was also successful at room temperature. In a solvent mixture of acetonitrile:1,4-dioxane (3:2), 3-methyleneindan-1-ol **113ba** was obtained in a 97% NMR yield. Carrying out

the reaction in just acetonitrile or 1,4-dioxane gave lower yields of **113ba** (Table 3, Entries 9-11).

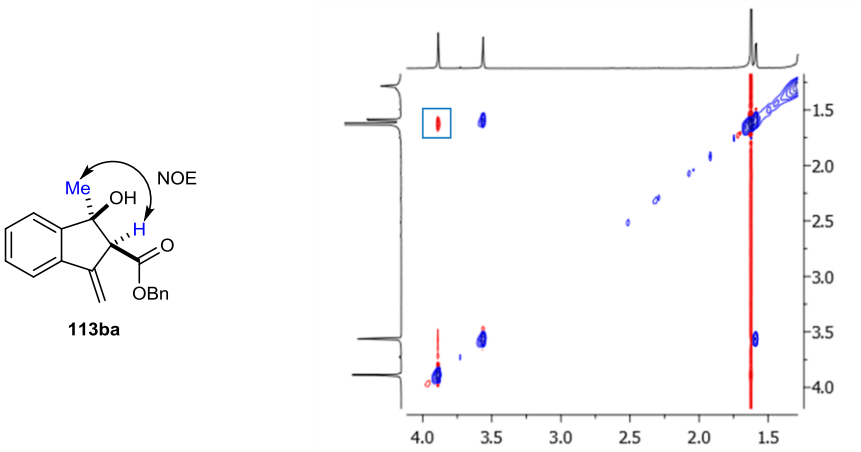


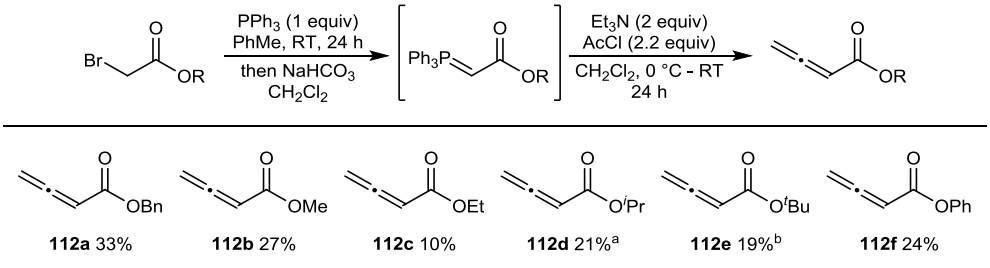
Figure 4

By ^{1}H NMR spectroscopy of the crude mixture, only one diastereoisomer was observed. The relative stereochemistry of the purified product **113ba** was tentatively assigned by NOE spectroscopy (Figure 4), and confirmed by X-ray crystallography of 3-methyleneindan-1-ols **113bp**, **113bk**, and **113bj**.

2.3. Allene Scope

With suitable conditions in hand, a range of activated allenes were synthesised and the reaction with 2-acetylphenylboronic acid **7b** was investigated.

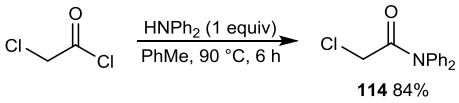
2.3.1. Synthesis of Allenes



Scheme 55: [a] Synthesised by Dr. C. I. A. Pradillos. [b] Synthesised by Dr. C. Clarke.

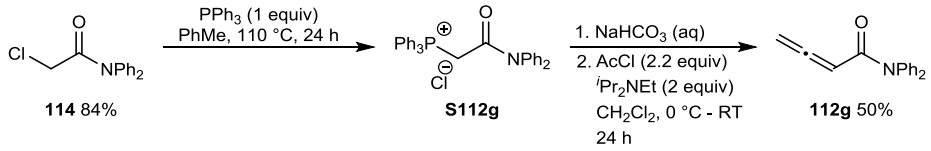
Ester substituted allenes **112a-112f** were synthesised from the corresponding commercially available bromoacetates. The reaction with triphenylphosphine yielded the phosphonium salt, which was deprotonated *via* a basic workup giving the ylide (Scheme 55). The subsequent Wittig reaction with acetyl chloride in the presence of triethylamine gave the corresponding allenoates

112a-112f. These compounds were isolated in low yields, ranging from 10-33%.



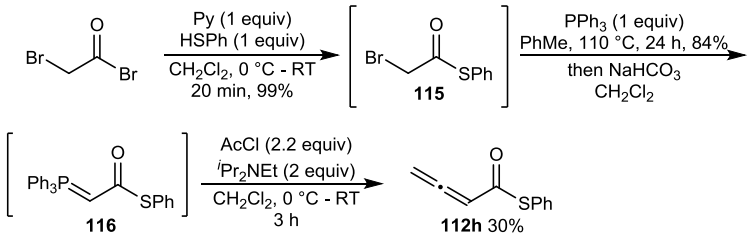
Scheme 56

To synthesise the amide-substituted allene **112g**, diphenylamine was acetylated with chloroacetyl chloride to give **114** (Scheme 56).



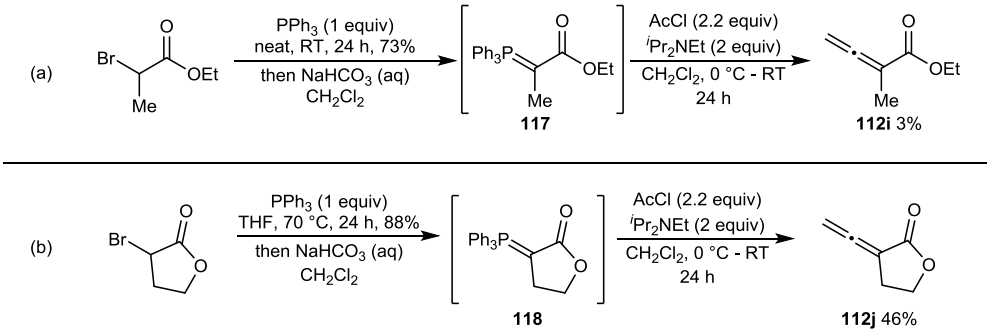
Scheme 57

Reacting **114** with triphenylphosphine gave the corresponding phosphonium salt **S112g**, which gave the relevant ylide after a basic workup. A subsequent Wittig reaction in the presence of *N*,*N*-diisopropylethylamine afforded the desired allene **112g** in a 50% isolated yield (Scheme 57).



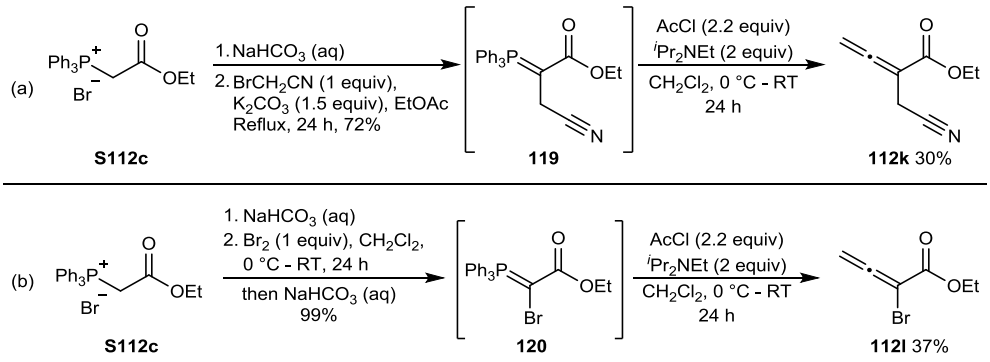
Scheme 58

Thioester-substituted allene **112h** was synthesised in an analogous manner to **112g**. Bromoacetyl bromide was reacted with thiophenol to give the corresponding thioester **115** in quantitative yield (Scheme 58). This was then directly subjected to a reaction with triphenylphosphine, and a basic workup gave the desired ylide **116**. A Wittig reaction with acetyl chloride in the presence of *N*,*N*-diisopropylamine gave allene **112h** in a modest 30% yield.



Scheme 59

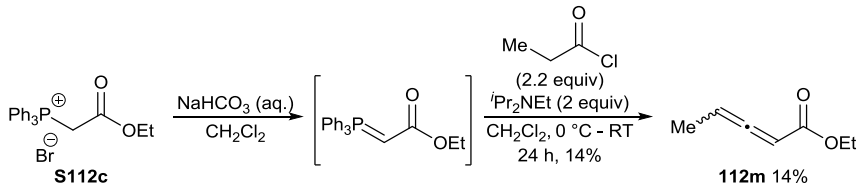
1,1-Disubstituted allenes were also synthesised using the Wittig reaction. Allene **112i**, with a methyl group at the 1-position was also synthesised in an analogous fashion to allenes **112a-112h**, from commercially available ethyl 2-bromopropionate. Allene **112i** was obtained in 3% yield (Scheme 59, (a)). For allene **112j**, α-bromo-γ-butyrolactone was reacted with triphenylphosphine to give the corresponding phosphonium salt. Treatment with sodium hydrogen carbonate gave ylide **118**, and the subsequent reaction with acetyl chloride in the presence of *N*,*N*-diisopropylamine gave allene **112j** in 46% isolated yield (Scheme 59, (b)).



Scheme 60

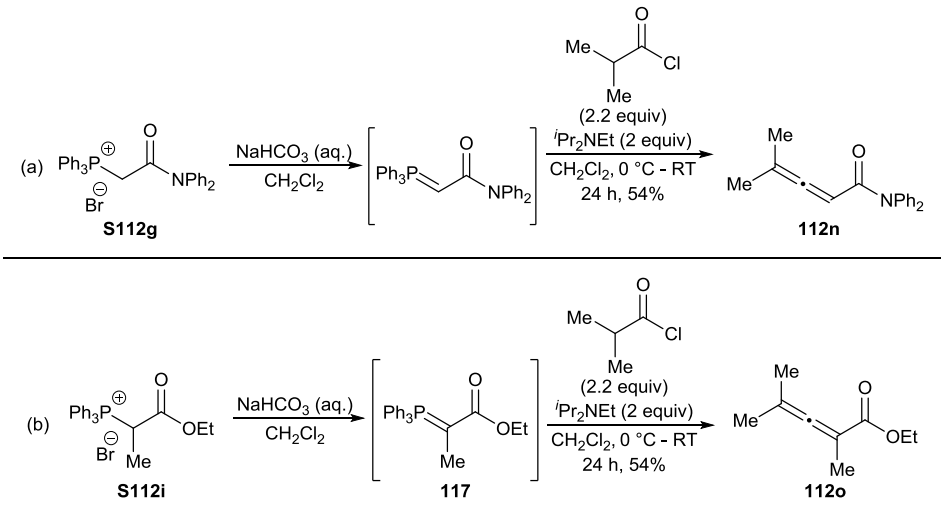
Allenes **112k** and **112l** were both synthesised from phosphonium salt **S112c**, which was accessed from the commercially available ethyl bromoacetate and triphenylphosphine, as for the synthesis of allene **112c**. For **112k**, the phosphonium salt **S112c** was treated with aqueous sodium hydrogen carbonate solution then reacted with bromoacetonitrile in the presence of potassium carbonate. Filtration and concentration gave ylide **119**, which was reacted directly with acetyl chloride and *N*,*N*-diisopropylamine to yield allene **112k** in 30% yield (Scheme 60, (a)).

For bromo-substituted allene **112l**, treatment of the phosphonium salt **S112c** with aqueous sodium hydrogen carbonate, followed by a reaction with bromine and a basic aqueous workup gave the bromo-substituted ylide **120**. This was then reacted directly with acetyl chloride in the presence of *N*,*N*-diisopropylamine to give allene **112l** in 37% isolated yield (Scheme 60, (b)).



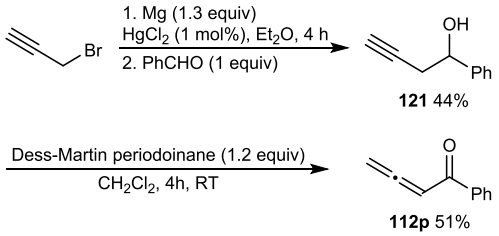
Scheme 61

Allene **112m** was also synthesised *via* Wittig reaction. Phosphonium salt **S112c** was treated with sodium hydrogen carbonate solution in an aqueous work up to give the ylide (Scheme 61). Reaction with propionyl chloride in the presence of *N*,*N*-diisopropylamine gave racemic allene **112m** in 14% yield.



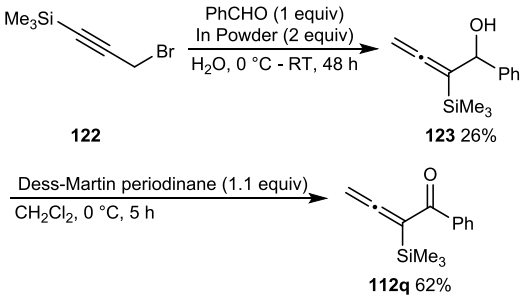
Scheme 62

3,3-Disubstituted allenes were also synthesised following a similar protocol. Allenes **112n** and **112o** were synthesised from phosphonium salts **S112g** and **S112i** respectively. Following the aqueous basic work up, a reaction with isobutyryl chloride in the presence of *N*,*N*-diisopropylethylamine to give allene **112n** in 54% isolated yield and allene **112o** in 62% yield (Scheme 62).



Scheme 63

Allene **112p** was synthesised from propargyl bromide following a literature procedure.[48] Propargylmagnesium bromide was formed in a reaction between propargyl bromide and magnesium in the presence of mercury dichloride, then reacted with benzaldehyde to give the homopropargyl alcohol **121** in 44% yield (Scheme 63). A Dess-Martin periodinane-mediated oxidation then gave allene **112p** in 51% yield.

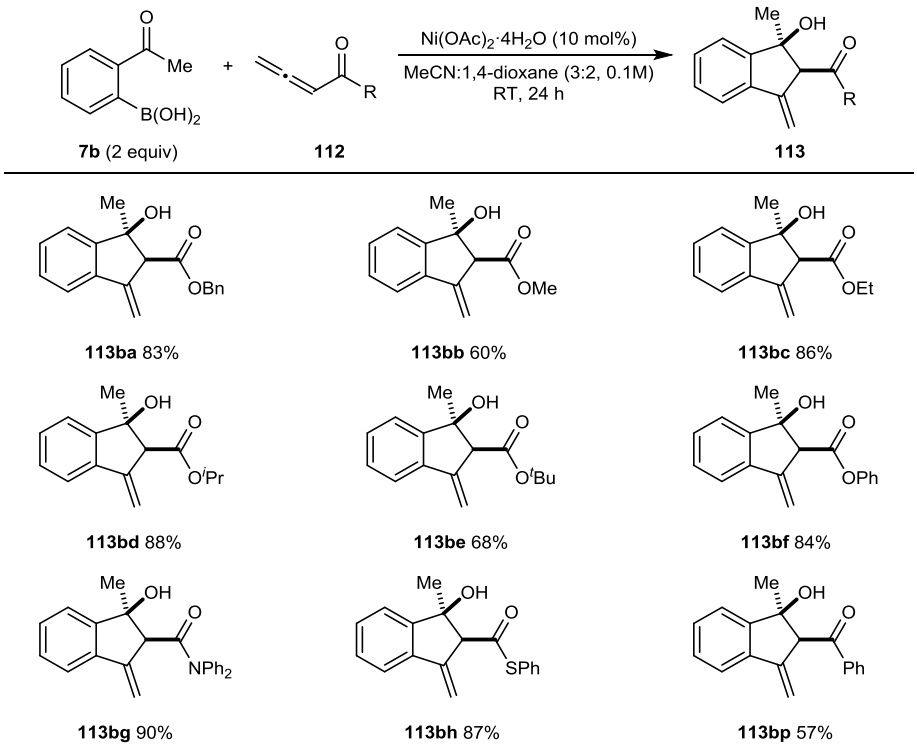


Scheme 64: These reactions were carried out by Dr. S. N. Karad

A silyl substituted allene **112q** was also synthesised following a similar procedure. Allenyl alcohol **123** was accessed *via* a Barbier-type reaction from benzaldehyde and (3-bromoprop-1-yn-1-yl)trimethylsilane **122** in the presence of indium powder (Scheme 64). Allene **112q** was then obtained *via* a Dess-Martin periodinane mediated oxidation reaction in 62% yield.

2.3.2. Reactions with 2-Acetylphenylboronic Acid

With a series of allenes in hand, the scope of the annulation reaction between activated allenes and 2-acetylphenylboronic acid **7b** was investigated.



Scheme 65

First, the scope with respect to monosubstituted allenes and 2-acetylphenylboronic acid **7b** was investigated. Pleasingly, both alkyl and aryl esters were well-tolerated, and 3-methyleneindan-1-ols **113ba-113bf**, bearing an ester functionality at the 2-position were isolated in 60-88% yield (Scheme 65). The reaction was also tolerant to amides, thioesters, and ketones, giving 3-methyleneindan-1-ols **113bg-113bp** in moderate to excellent yields.

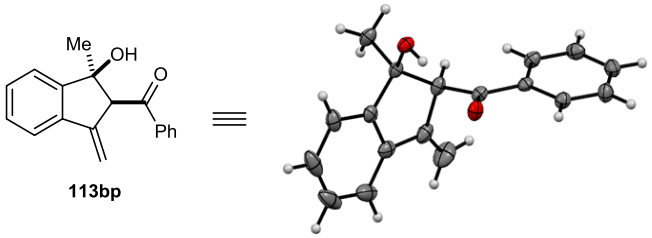
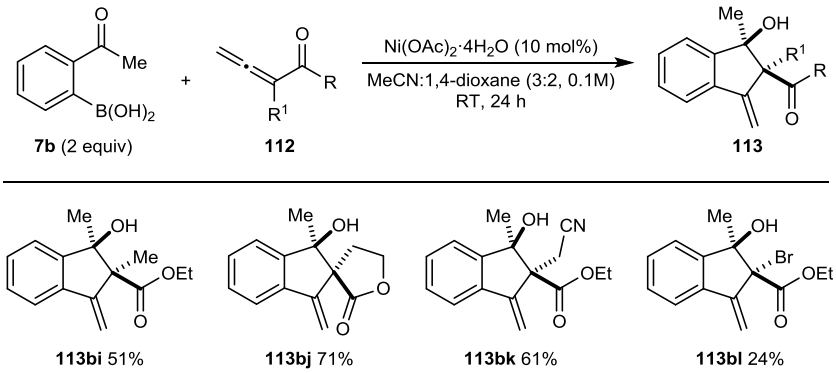


Figure 5

The relative stereochemistry of the purified 3-methyleneindan-1-ols was confirmed primarily by NOE spectroscopy, and for **113bp**, X-ray crystallography (Figure 5).



Scheme 66

Successful reactions between 1,1-disubstituted allenes and 2-acylarylboronic acids are unprecedented in the literature. Noteably, under the conditions reported by Lu and co-workers, the reaction was unsuccessful.[42] Pleasingly, this methodology tolerated a range of 1,1-disubstituted allenes (Scheme 66). Methyl-substituted 3-methyleneindan-1-ol **113bi** was obtained in 51% yield. Halogens and cyanomethyl groups were also well-tolerated, with **113bk** and **113bl** obtained as single observable diastereoisomers, in modest to good yields. Of interest is **113bj**, as this methodology enables access to spiro-3-methyleneindan-1-ols.

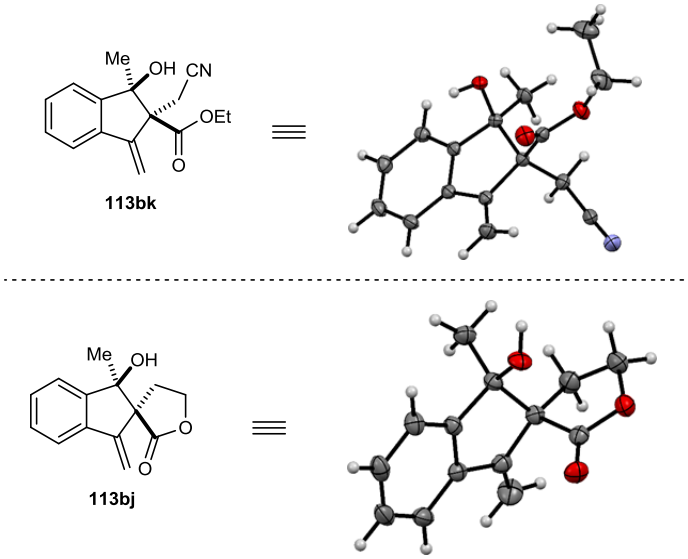
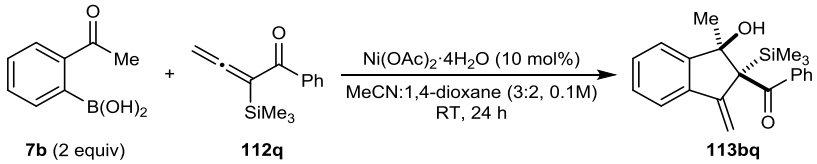


Figure 6

Pleasingly, indanols **113bk** and **113bj** were obtained as solids. Analysis by X-ray crystallography confirmed the relative stereochemistry observed by NOE spectroscopy (Figure 6).



Scheme 67

With a silyl group at the 1-position, the reaction between the allene **112q** and 2-acetylphenylboronic acid **7b** did not progress to completion (Scheme 67). However, the distinguishable methylene peaks were visible by ^{1}H NMR spectroscopy of the crude mixture.

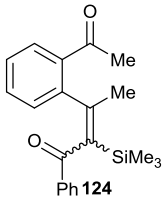
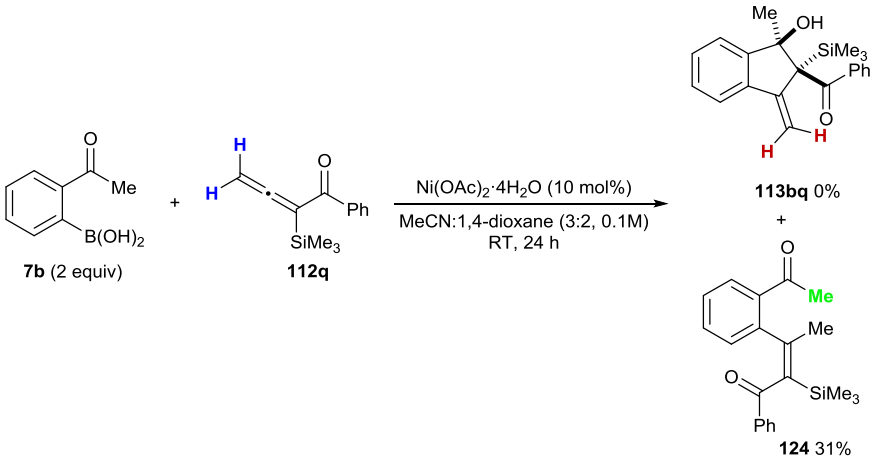


Figure 7

After purification by column chromatography, the only product isolated was uncyclised, isomerised product **124**, in place of the expected 3-methyleneindan-1-ol **113bq** (Scheme 68).



Scheme 68

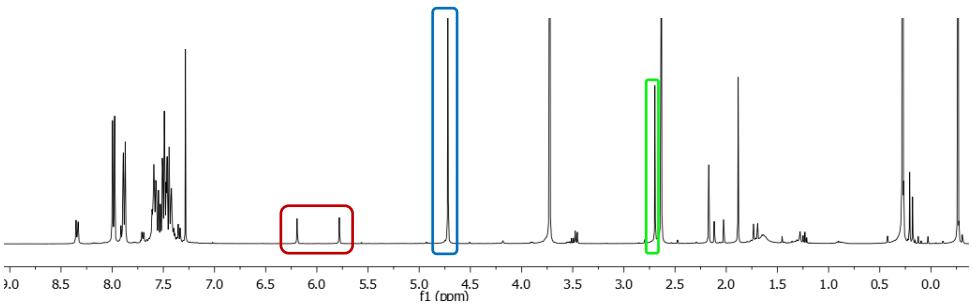
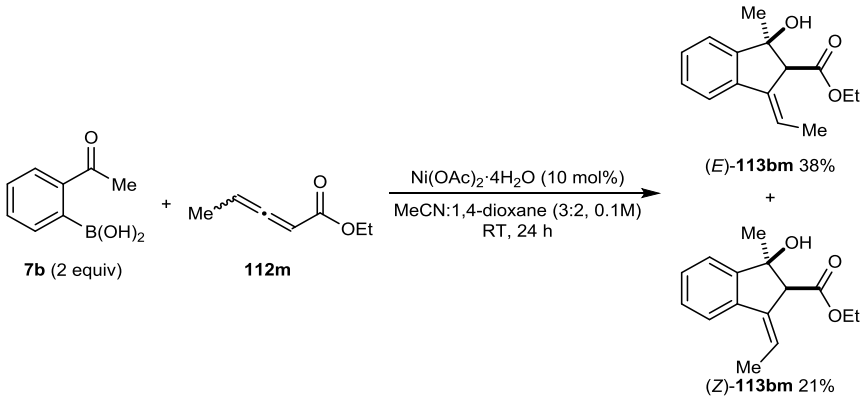


Figure 8

The reaction was repeated (Scheme 68), and full analysis of the crude mixture was obtained. By ^{1}H and ^{13}C NMR spectroscopy, the allene **112q** (blue), the cyclised indanol **113bq** (red) and the isomerised product **124** (green) were observed (Figure 8). However, after column chromatography, only **124** was obtained in 31% yield (Scheme 68).



Scheme 69

The reaction was attempted with racemic allenes **112m** and **112r**. By ^{1}H NMR spectroscopy of the crude mixture, a mixture of products was observed. Following purification, (*E*)-**113bm** was obtained in 38% yield, and (*Z*)-**113bm** in 21% yield (Scheme 69).

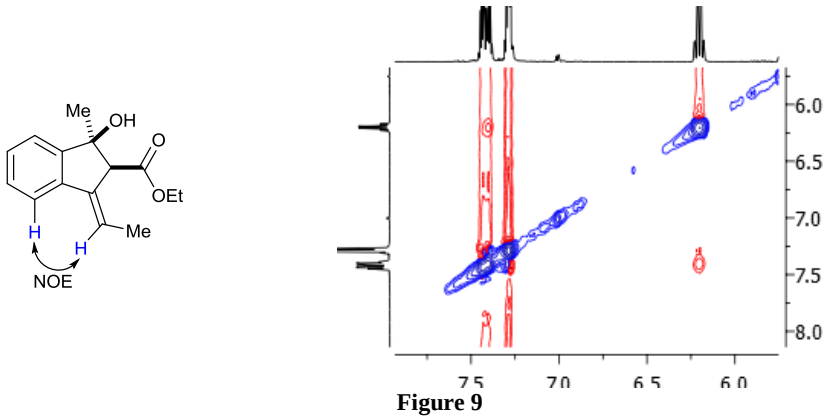


Figure 9

The NOE spectrum obtained for (*E*)-**113bm** is given in Figure 9. An NOE between the methylene proton and aromatic proton highlighted was observed, confirming the stereochemistry of the double bond.

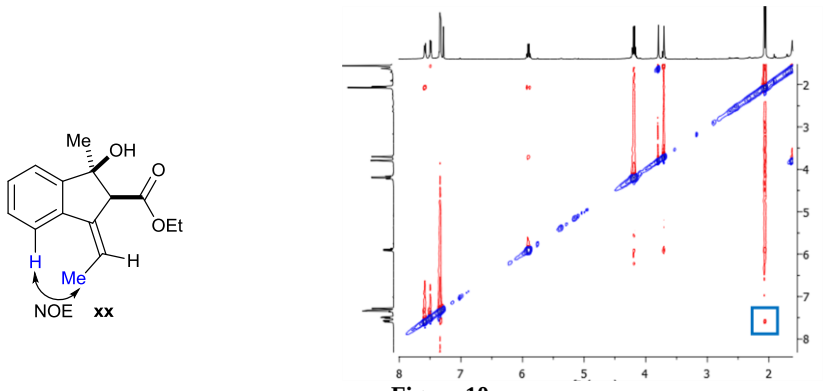
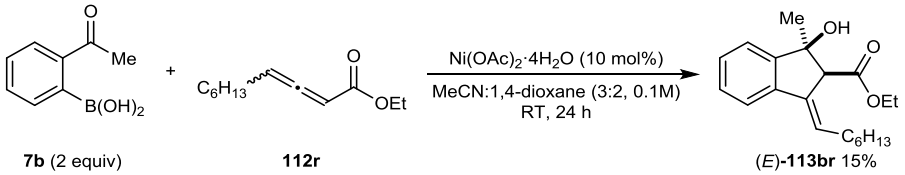


Figure 10

The NOE spectrum obtained for (*Z*)-**113bm** is given in Figure 10. An NOE between the methylene methyl group and aromatic proton highlighted was observed, confirming the stereochemistry of the double bond.



Scheme 70

Allene **112r** was also reacted with 2-acetylphenylboronic acid **7b**, and indanol (*E*)-**113br** was obtained in 15% yield. A mixture of products were observed by ^{1}H NMR spectroscopy of the crude mixture, but only (*E*)-**113br** was isolated (Scheme 70).

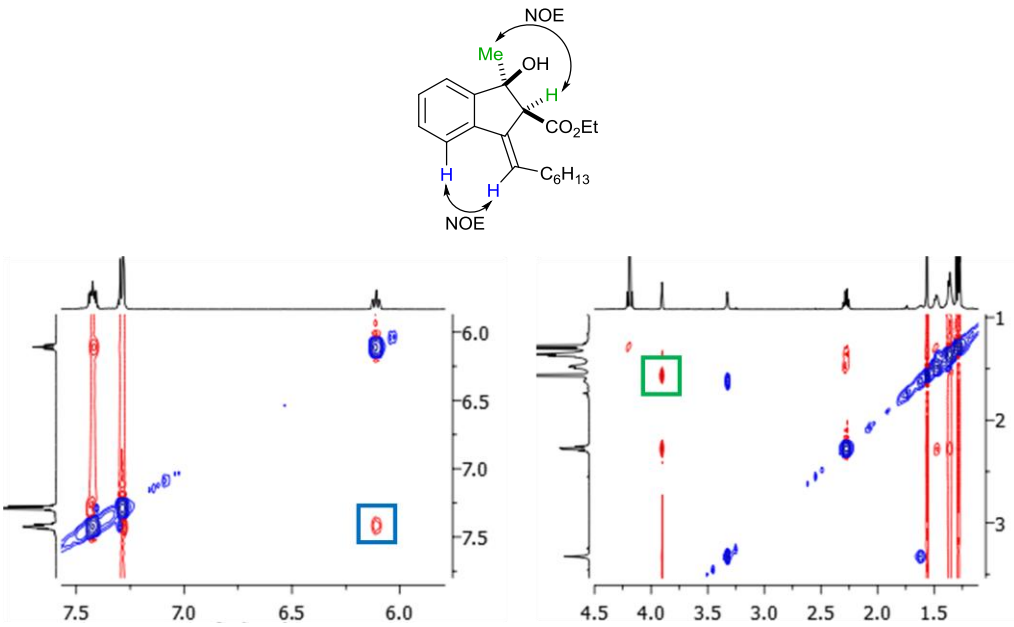
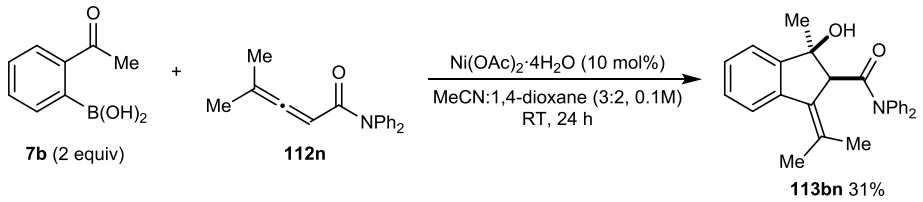


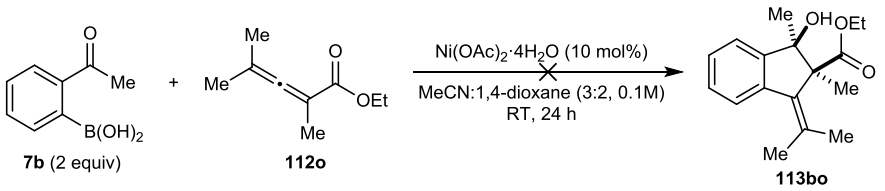
Figure 11

The spectra of the purified 3-methyleneindan-1-ol shows a positive NOE between the methylene proton and an aromatic proton (blue), and the methyl-group at the 1-position and the proton at the 2-position (green), confirming the stereochemistry of (*E*)-**113br** (Figure 11).



Scheme 71

The reaction was also attempted with 1,3,3-trisubstituted allene **112n** (Scheme 78). This reaction did not go to completion, but 3-methyleneindan-1-ol **113bn** was obtained in a 31% yield.

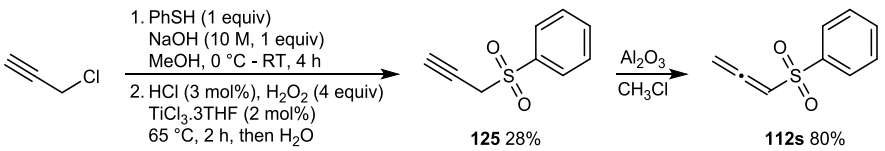


Scheme 72

The reaction with fully substituted allene **112o** was also carried out (Scheme 72). Unfortunately, the reaction was unsuccessful and only starting material was recovered.

2.3.3. Further Allene Scope

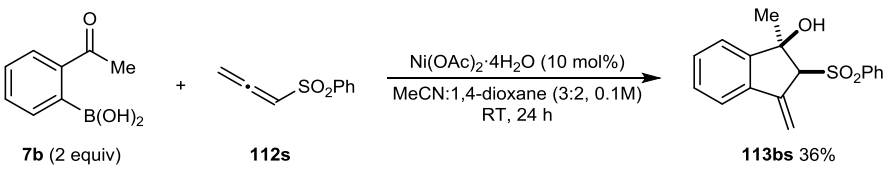
Following the success of the annulation reactions between 2-acetylphenylboronic acids **7b** and allenes **112a-112o**, the scope with respect to non-carbonyl substituted allenes was investigated.



Scheme 73

Allene **112s** was synthesised in a one-pot, two-step process from propargyl chloride (Scheme 73). Propargyl sulfone **125** was obtained from a reaction between propargyl chloride and thiophenol. After stirring for four hours, the suspension was treated with hydrogen peroxide and titanium trichloride in the

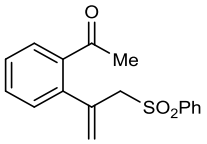
presence of acid. Filtration and recrystallisation gave the sulfone **125**, which was treated with alumina to give allene **112s**.



7b (2 equiv) **112s** **113bs** 36%

Scheme 74

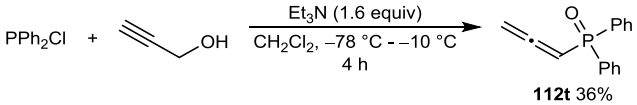
Successful reactions with sulfone-substituted allenes and *ortho*-acylarylboronic acids are unprecedented in the literature, and Lu reported that under their reaction conditions, sulfone-allene **112s** was unreactive.[42] Pleasingly, using nickel-catalysis, this reaction progressed to completion. However, issues with the purification of 3-methylenindan-1-ol **113bs** led to a low yield (Scheme 74, 36%). This product was also obtained as a single observable diastereoisomer, and the relative stereochemistry of the purified product was confirmed by NOE spectroscopy.



126 52%

Figure 12

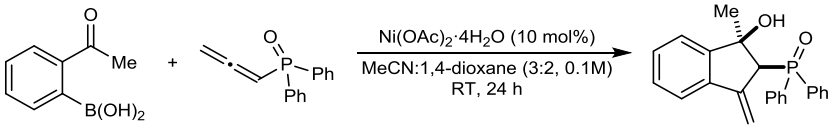
Two sets of methylene $=CH_2$ peaks were observed by ^1H NMR spectroscopy of the crude mixture, and a second, closely-eluting spot by thin layer chromatography. The second spot was confirmed to be coupled but un-cyclised material **126** (Figure 12).



112t 36%

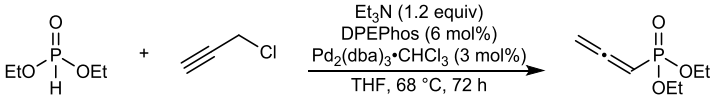
Scheme 75

A phosphine oxide-tethered allene was also synthesised. Propargyl alcohol was treated with chlorodiphenyl phosphine in the presence of triethylamine. The product was obtained after recrystallisation to give allene **112t** in 36% yield (Scheme 75).



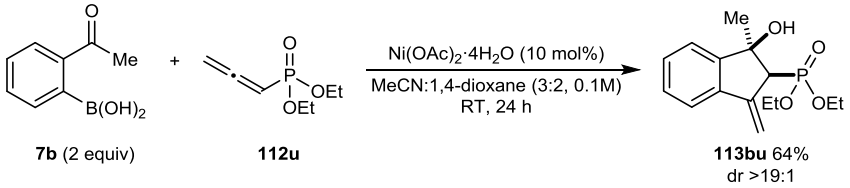
Scheme 76

Pleasingly, the reaction between allene **112t** and 2-acetylphenylboronic acid **7b** was successful, and the corresponding 3-methyleneindan-1-ol **113bt** was isolated in 70% yield, as a single observable diasteroisomer. The relative stereochemistry of the purified product was confirmed by NOE spectroscopy (Scheme 76).



Scheme 77: Synthesised by C. Bell

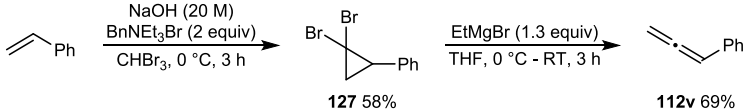
Following the success of the reaction of allene **112t** with 2-acetylphenylboronic acid, a phosphonate ester-allene **112u** was also synthesised. Diethylphosphite was reacted with propargyl chloride in a palladium catalysed coupling reaction. Allene **112u** was obtained in a 64% yield (Scheme 77).



Scheme 78

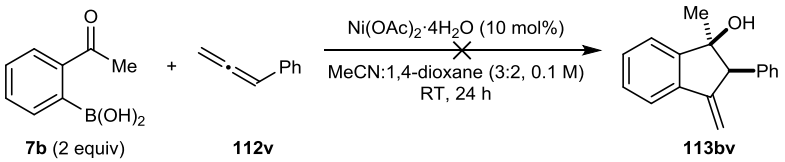
Allene **112u** was reacted with 2-acetylphenylboronic acid **7b**. 3-Methyleneindan-1-ol **113bu** was isolated as a single observable diastereoisomer, in 64% isolated yield (Scheme 78). NOE spectroscopy was used on the purified product to confirm the stereochemistry.

Attention was then turned to allenes bearing aromatic groups, amides, or ethers.



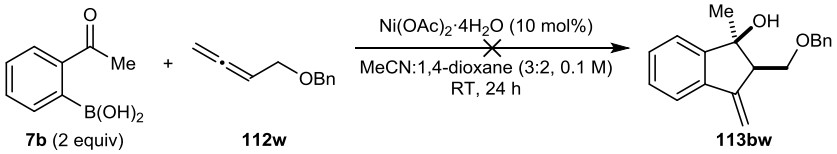
Scheme 79

Phenyl allene **112v** was synthesised following a literature procedure from styrene.[49] The reaction between styrene and bromoform in the presence of concentrated sodium hydroxide gave dibromocyclopropane **127** in 58% isolated yield (Scheme 79). This was then treated with ethylmagnesium bromide, which initiated a Skattebøl rearrangement to give phenyl allene **112v** in a modest 69% yield.



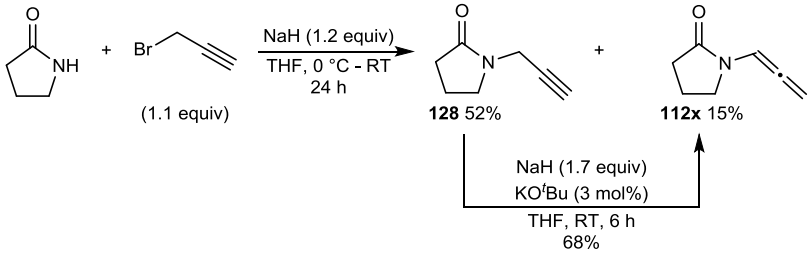
Scheme 80

Phenyl allene **112v** was then reacted with 2-acetylphenylboronic acid 7**b** under the established reaction conditions (Scheme 80). Unfortunately, this reaction was unsuccessful. No allene remained in the reaction mixture, but no product could be distinguished either, and the terminal methylene protons were not observed in the ^{1}H NMR spectrum of the crude reaction mixture. The reaction gave only a complex mixture of unidentifiable products.



Scheme 81

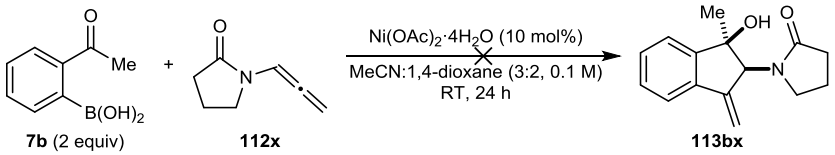
The reaction was attempted with allene **112w**. Unfortunately, this reaction was also unsuccessful (Scheme 86). By ^{1}H NMR spectroscopy of the crude mixture, allene **112w** was still visible, but the spectrum showed only a complex mixture of products, which were diffuclt to separate and identify.



Scheme 82

An allene directly connected to a lactam was then synthesised. Commercially available pyrrolidinone was reacted with propargyl bromide to give a mixture

of the propargylamide **128** and allene **112x**, which could be separated by column chromatography (Scheme 82). Treatment of the propargyl amide **128** with sodium hydride and potassium *tert*-butoxide gave the corresponding allene **112x** in 68% yield.

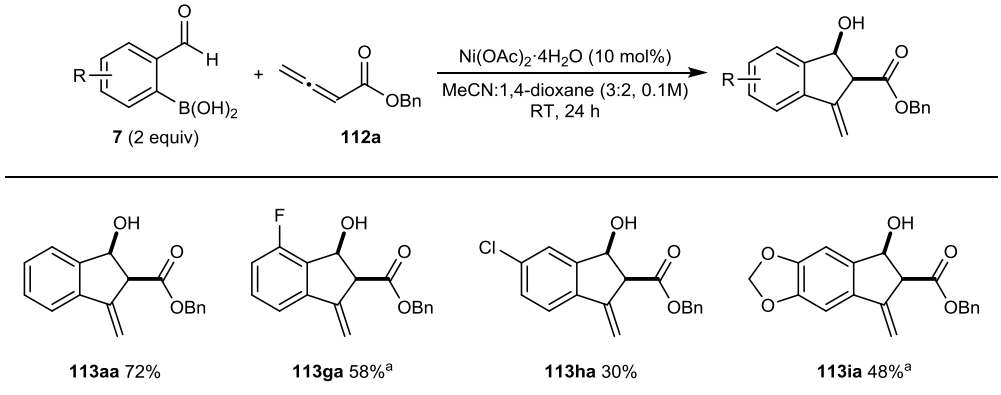


Scheme 83

The reaction between 2-acetylphenylboronic acid **7b** and allene **112x** was then attempted. By ^{1}H NMR spectroscopy of the crude mixture, complete consumption of the allene was observed. However, no single product could be clearly identified, and the distinguishable $=CH_2$ methylene peaks were not observed. Purification of the crude mixture was also problematic, and no significant quantity of any fraction was obtained. The reaction was deemed unsuccessful (Scheme 83).

2.4. Boronic Acid Scope

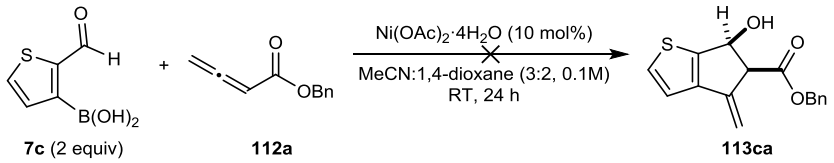
Following an exploration of the allene scope, the scope with respect to commercially available *ortho*-acylarylboronic acids was investigated with allene **112a**.



Scheme 84: [a] These reactions were carried out by Dr. C. Clarke

Commercially available boronic acids **7a-7i** were reacted with allene **112a**. 2-Formylphenylboronic acid **7a** afforded 3-methyleneindan-1-ol **113aa** in a modest 72% yield (Scheme 84). Halo-substituents on the aromatic ring were also tolerated, with 3-methyleneindan-1-ols **113ga** and **113ha** obtained in

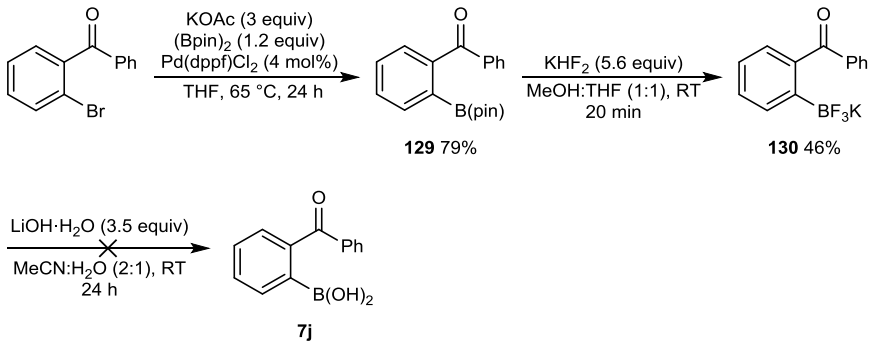
modest 58% and 30% yields respectively. Dioxane-substituted boronic acid **7i** afforded the corresponding 3-methyleneindan-1-ol **113ia** in moderate 48% yield



Scheme 85

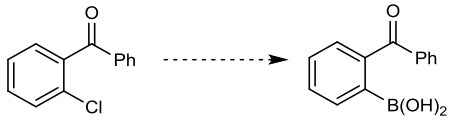
The reaction was also attempted with heteroarylboronic acid **7c** and allene **112a**, however, this was unsuccessful, and only starting material was recovered (Scheme 85).

To widen the boronic acid scope further, the synthesis of 2-(benzoylphenyl)boronic acid **7j** was undertaken.



Scheme 86

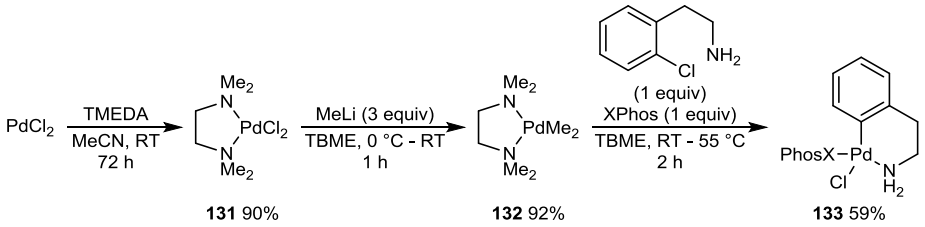
Following conditions described by Tang *et al*., commercially available 2-bromobenzophenone was treated with $(Bpin)_2$ in a Miyaura borylation reaction to give pinacol ester **129** in 79% yield (Scheme 86).[50] The pinacol ester was converted to the corresponding trifluoroborate **130** *via* a reaction with potassium hydrogen difluoride. Recrystallisation from acetone and diethyl ether afforded the pure trifluoroborate salt in 46% yield.[50] The final step involved hydrolysis of the trifluoroborate salt in the presence of lithium hydroxide. Unfortunately, this reaction was unsuccessful due to issues with purification. No product was obtained, and another route was sought.



Scheme 87

From research developed by Dreher *et al.*, a direct palladium-catalysed coupling between tetrahydroxydiboron and 2-chlorobenzophenone could yield the desired boronic acid in a single step (Scheme 87).[51]

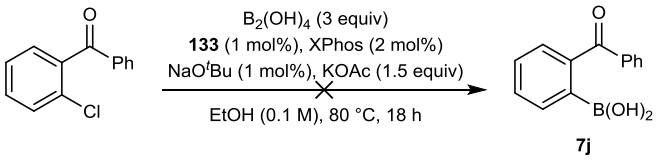
This particular transformation required the use of Buchwald's preformed XPhos catalyst, which was synthesised from commercially available palladium dichloride ($PdCl_2$).[52]



131 90% **132** 92% **133** 59%

Scheme 88

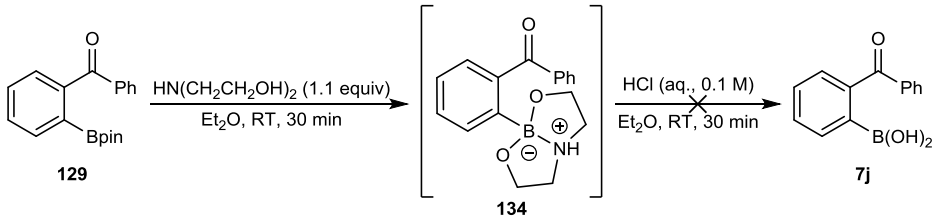
Palladium dichloride was first treated with tetramethylethylenediamine (TMEDA) in acetonitrile (Scheme 88). The complex **131** was isolated by filtration in 90% yield, and then treated with methyllithium solution to give palladium dimethyl complex **132** in excellent 92% yield. This complex was then reacted with 2-chlorophenethylamine and XPhos in TBME to give the second-generation Buchwald precatalyst **133** as a 1:1 complex with *tert*-butyl methyl ether. The complex was dissolved in dichloromethane and re-precipitated with *n*-hexanes to remove the *tert*-butyl methyl ether, giving the free catalyst in moderate 59% yield.



7j

Scheme 89

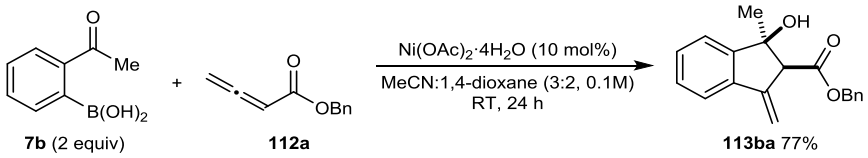
The reaction to access **7j** was then attempted from 2-chlorobenzophenone, using the Buchwald precatalyst **133**. Unfortunately, this reaction was also unsuccessful. By ^{11}B NMR spectroscopy, there was no product detected, and only starting material and de-halogenated starting material was observed by mass spectrometry.



Scheme 90

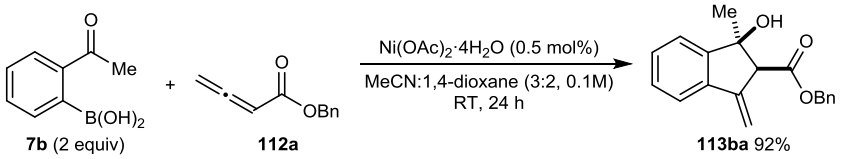
A final attempt to synthesise **7j** was attempted *via* an alternative hydrolysis of the pinacol ester. A diethanolamine mediated deprotection was reported by Santos *et al*. in 2011.[53] Pinacol ester **129** was treated with diethanolamine in diethyl ether, and the corresponding salt **134** precipitated out of solution, which was then isolated by filtration (Scheme 90). The salt was subsequently suspended in diethyl ether and treated with an aqueous solution of 0.1 M hydrochloric acid. Unfortunately, this reaction was also unsuccessful. A mixture of products was observed by ^{11}B NMR spectroscopy, and issues with purification led to no product being obtained.

Due to the lack of success, the synthesis of **7j** was abandoned. The sensitivity and scalability of the reaction was then investigated.



Scheme 91: Carried out under an air atmosphere.

The reaction was tested under an atmosphere of air. This reaction used commercially available acetonitrile and 1,4-dioxane, with no drying of either reagent, and no de-gassing. Fortunately, the reaction was still successful and 3-methyleneindan-1-ol **113ba** was obtained in 77% isolated yield (Scheme 91).



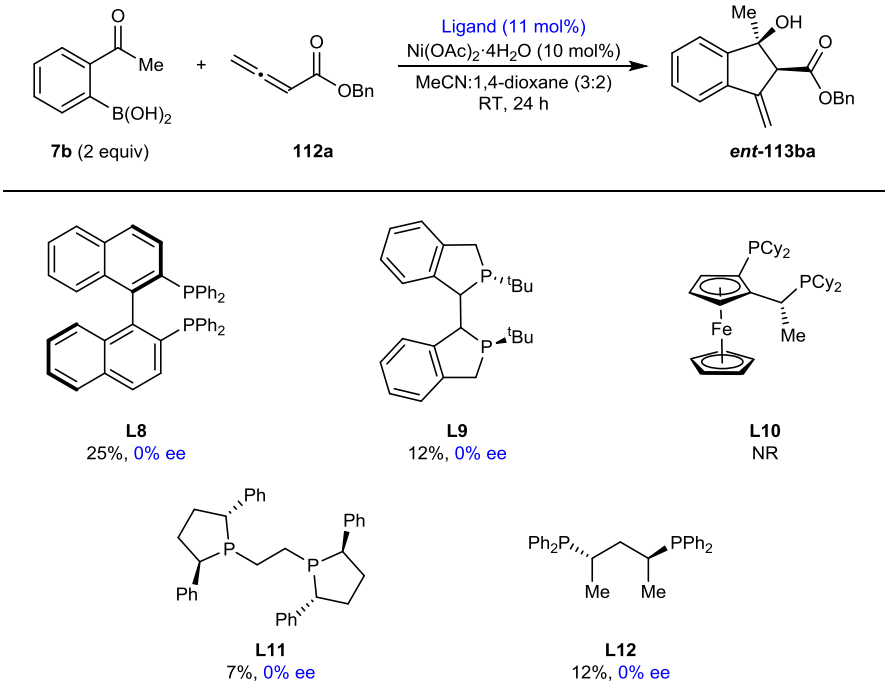
Scheme 92: Carried out using 3 mmol of **112a**.

The scalability and potential for a lower catalyst loading was also investigated. Pleasingly, when the reaction was scaled up to 3 mmol, the catalyst loading could be decreased to 0.5 mol%. There was no decrease to the yield and 3-

methyleneindan-1-ol **113ba** was obtained in an excellent 92% yield, as a single observable diastereoisomer (Scheme 92).

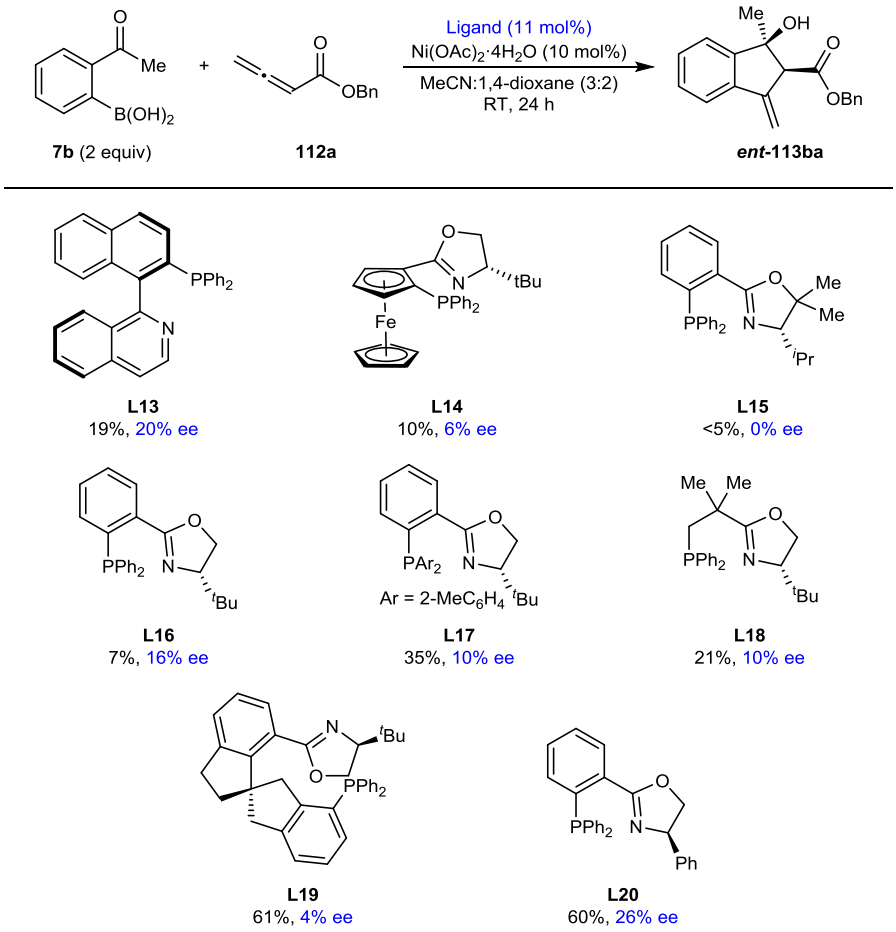
2.5. Development of an Enantioselective Variant of the Reaction

Following the success of the ligand-free synthesis of 3-methyleneindan-1-ols **113**, an investigation into the potential for enantioselectivity was undertaken. Firstly, a range of bis-phosphine type ligands were screened.



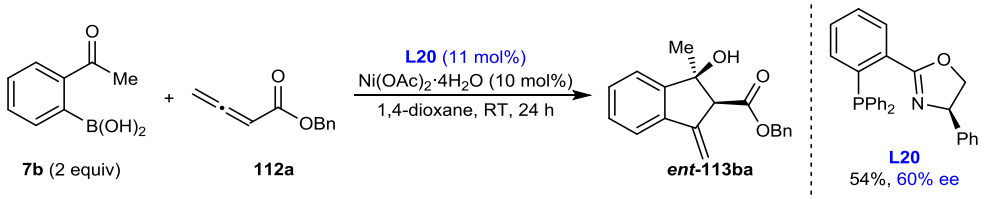
Scheme 93: Absolute configuration not determined

Unfortunately, reactions with bis-phosphine ligands gave generally poor yields (Scheme 93). Ligands **L8**-**L12** all gave 3-methyleneindan-1-ol **113ba** in poor yields, and no enantioselectivity was observed. With JOSIPHOS ligand **L10**, the reaction was unsuccessful.



Scheme 94: Absolute configuration not determined

The Lam group has had success with nickel-catalysts and phosphinooxazoline type ligands,[45,46] so a range of *P*,*N*-ligands were examined. QUINAP-based ligand **L8** offered some hope despite the low yield, giving 3-methyleneindan-1-ol ***ent*-113ba** in 20% ee (Scheme 94). Ligands **L9**-**L14** also offered lower yields and ee's. The yield was improved somewhat to 61% when **L14** was used, but the ee was still poor. (*R*)-PhPhox **L15** gave the best result so far, with 3-methyleneindan-1-ol ***ent*-113ba** obtained in 60% yield and 26% ee.



Scheme 95: Absolute configuration not determined

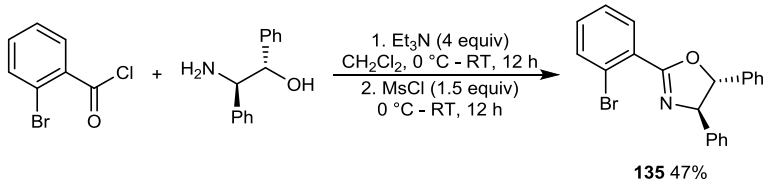
With only moderate success following the ligand screen, attention was then turned to the solvent in use. A range of solvents and solvent mixtures were tested, but only 1,4-dioxane gave an improved result. The yield was still

moderate at 54%, but 3-methyleneindan-1-ol ***ent*-113ba** could now be obtained in 60% ee (Scheme 95).

With this result in hand, ligands based on (*R*)-PhPhox **L20** were synthesised in an attempt to improve the enantioselectivity further. Ligands with bulkier scaffolds and varied electronics were synthesised.

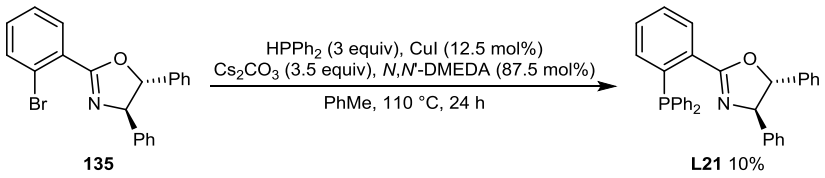
2.5.1. Ligand Synthesis

The ligands synthesised were based on the (*R*)-PhPhox **L20** scaffold, as this ligand had given the most promising results. They were synthesised from commercially available, enantiopure building blocks.



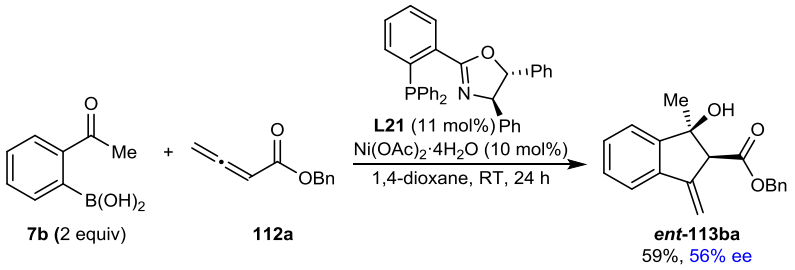
Scheme 96

Ligands with more substitution on the oxazoline ring were synthesised. First, a 1,2-bisphenyl substituted oxazoline was synthesised from the commercially available (1*S*,2*R*)-2-amino-1,2-diphenylethan-1-ol and 2-bromobenzoyl chloride (Scheme 96). The amide formed *in situ* was treated with methanesulfonyl chloride to generate the corresponding bromo-oxazoline compound **135** in 47% isolated yield.



Scheme 97

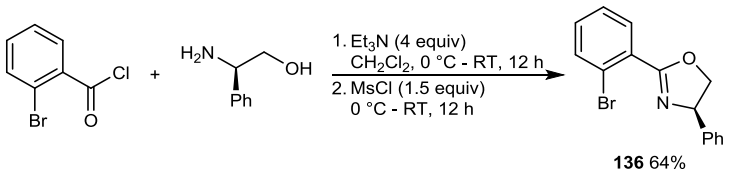
Diphenylphosphine and **135** were coupled in a copper mediated reaction. Purification followed by recrystallisation gave the corresponding ligand **L21** in 10% yield (Scheme 97).



Scheme 98: Absolute configuration not determined

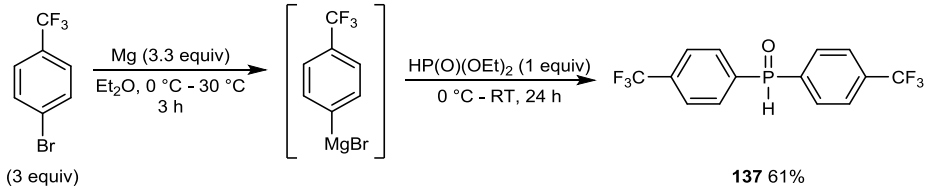
The ligand was then used in the enantioselective variant of the reaction. With the bulkier scaffold, however, there was no marked improvement in either the yield or the enantioselectivity (Scheme 98).

With this result in hand, electronic effects on the enantioselectivity were investigated.



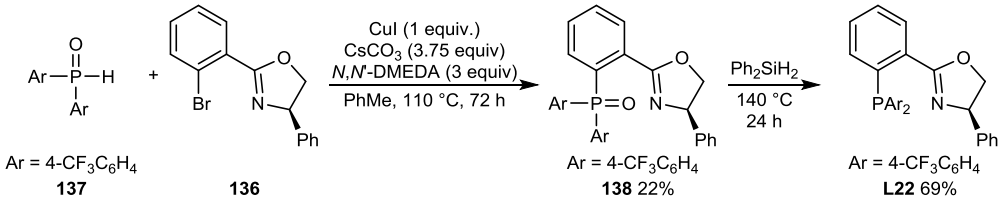
Scheme 99

To begin, the oxazoline **136** was synthesised from commercially available 2-bromobenzoyl chloride and (*R*)-2-amino-2-phenylethan-1-ol in a one-pot, two-step reaction. A solution of the aminoalcohol was treated with triethylamine and 2-bromobenzoyl chloride in dichloromethane (Scheme 99). After complete consumption of the aminoalcohol (12 h), cyclisation was induced *via* the addition of methanesulfonyl chloride. The corresponding ligand precursor **136** was isolated in 64% yield.



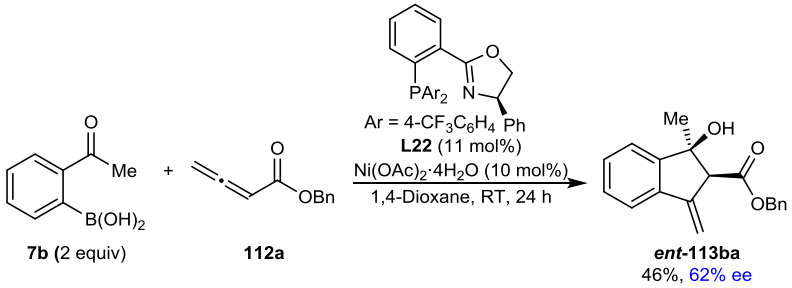
Scheme 100

The electronics were varied on the phosphine group of the ligand. This moiety was synthesised *via* a Grignard reaction. 4-Bromobenzotrifluoride was treated with magnesium, to generate the corresponding Grignard reagent (Scheme 100). Diethylphosphite was added and the corresponding aryl phosphine oxide **137** was obtained in 61% yield.



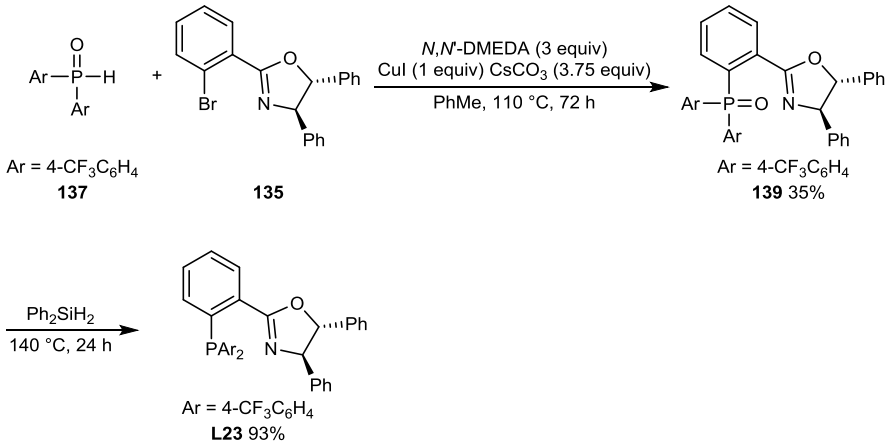
Scheme 101

The ligand was then synthesised *via* an Ullmann type coupling between the aryl phosphine oxide **137** and the bromo-oxazoline **136**, to give **138** in 22% yield (Scheme 101). The phosphine oxide product **138** was then reduced in neat diphenylsilane to give **L22** in 69% isolated yield.



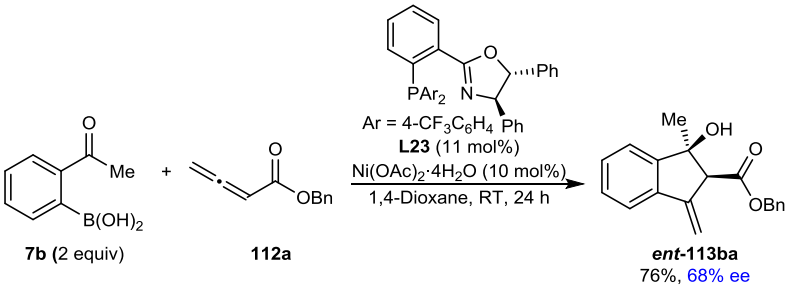
Scheme 102: Absolute configuration not determined

The reaction was then attempted with **L22** Pleasingly, 3-methyleneindan-1-ol ***ent*-113ba** was obtained in a modest 46% yield with an improved ee of 62% (Scheme 102).



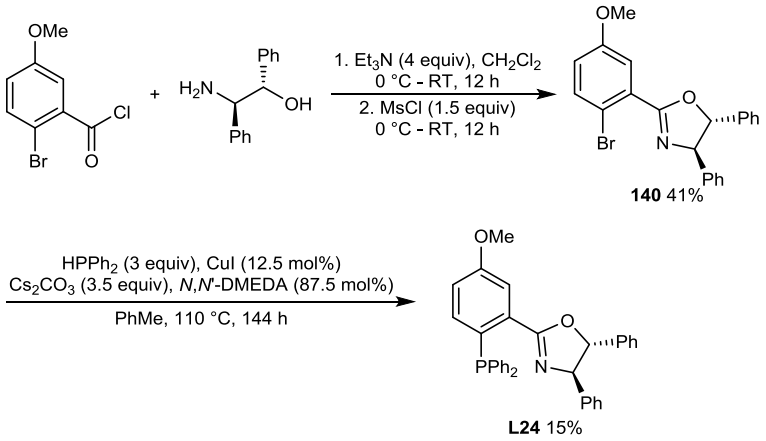
Scheme 103

A ligand combining both the steric and electronic changes was also synthesised. Phosphine oxide **137** and oxazoline **135** were reacted in a copper mediated coupling reaction to generate the ligand precursor **139** in 35% yield (Scheme 103). A reduction reaction with diphenylsilane gave the corresponding ligand **L23** in 93% yield.



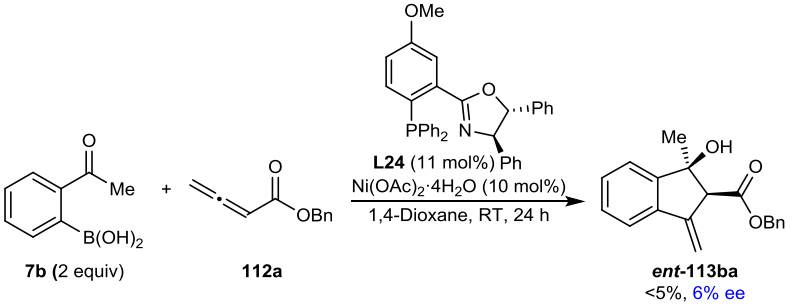
Scheme 104: Absolute configuration not determined

L23 was used in the enantioselective variant of the annulation reaction. Pleasingly, a slight improvement in both the yield and enantioselectivity of the product was observed. Indanol ***ent*-113ba** was obtained in 76% yield and 68% ee (Scheme 104).



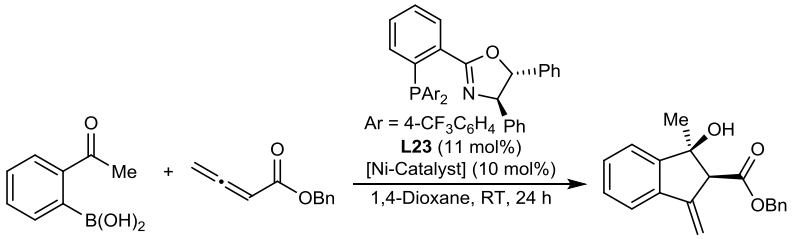
Scheme 105: Final reaction carried out by C. Bell

A ligand with an electron-donating group was also synthesised. The commercially available 2-bromo-5-methoxybenzoyl chloride was reacted with (1*S*,2*R*)-2-amino-1,2-diphenylethan-1-ol to form the amide, which was then treated with mesyl chloride to generate the methoxy-substituted oxazoline **140** in one-pot, in 41% yield. A copper mediated coupling with diphenylphosphine gives the corresponding ligand **L24** in 15% yield (Scheme 105).



Scheme 106: Absolute configuration not determined

The electron rich ligand **L24** was also trialled in the annulation reaction. Unfortunately, only a trace amount of product was obtained, with a significant decrease in the enantioselectivity (Scheme 106).



7b (2 equiv) **112a** ***ent*-113ba**

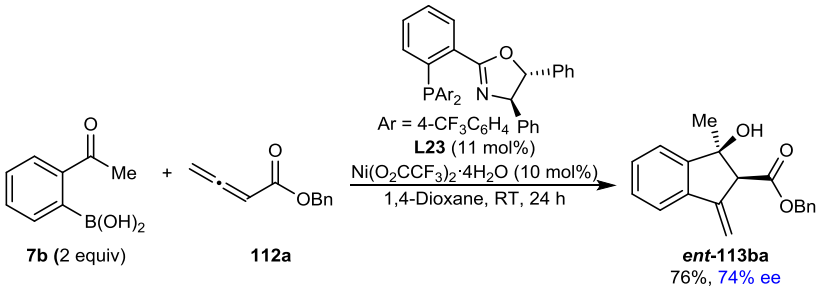
Entry	Catalyst	NMR Yield (%)	ee (%)
1	$Ni(OAc)_2 \cdot 4H_2O$	76	68
2	$Ni(OTf)_2$	80	64
3	$Ni(O_2CCF_3)_2 \cdot 4H_2O$	73	74
4	$Ni(acac)_2$	79	10
5	$NiCl_2 \cdot 6H_2O$	71	22
6	$Ni(NO_3)_2 \cdot 6H_2O$	83	66
7	$NiBr_2 \cdot DME$	62	70
8	$[Ni(\mu\text{-}OH_2)(O_2CCMe_3)_4(HO_2CCMe_3)_4]_2$*	68	66

Table 4: Absolute configuration not determined. * Synthesised according to a literature procedure.

With a promising result obtained with ligand **L23**, the effect on the enantioselectivity with various nickel salts was investigated. All nickel salts used gave generally good to excellent yields of 3-methyleneindan-1-ol ***ent*-113ba**. With $Ni(acac)_2$ and $NiCl_2 \cdot 6H_2O$, the ee was significantly lower than when $Ni(OAc)_2 \cdot 4H_2O$ was used (Table 4, Entries 4 & 5). Using $Ni(OTf)_2$, $Ni(NO_3)_2 \cdot 6H_2O$ or $NiBr_2 \cdot DME$ offered comparable yields and ee's to when $Ni(OAc)_2 \cdot 4H_2O$ was used (Table 4, Entries 2, 6 & 7). A nickel pivalate salt, synthesised from commercially available nickel hydroxide, was also employed.[54] 3-Methyleneindan-1-ol ***ent*-113ba** was obtained in a modest 68% yield and 66% ee (Table 4, Entry 8). The most promising result came when $Ni(O_2CCF_3)_2 \cdot 4H_2O$ (nickel trifluoroacetate) was used. 3-Methyleneindan-1-ol ***ent*-113ba** was obtained in 73% yield and 74% ee (Table 4, Entry 3). This nickel salt was therefore used for subsequent enantioselective variants of the reaction.

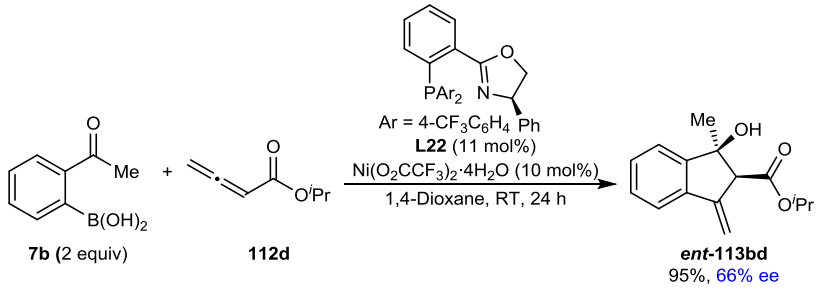
2.5.2. Enantioselective Nickel-Catalysed Annulation Reaction

With promising conditions in hand, two examples were carried out to demonstrate the potential for enantiocontrol.



Scheme 107: Absolute configuration not determined

The reaction was scaled up to 0.30 mmol scale, and carried out with **L23** and nickel trifluoroacetate. Indanol ***ent*-113ba** was obtained in 76% yield and 74% ee (Scheme 107). As the product obtained was an oil, the absolute configuration was not determined.

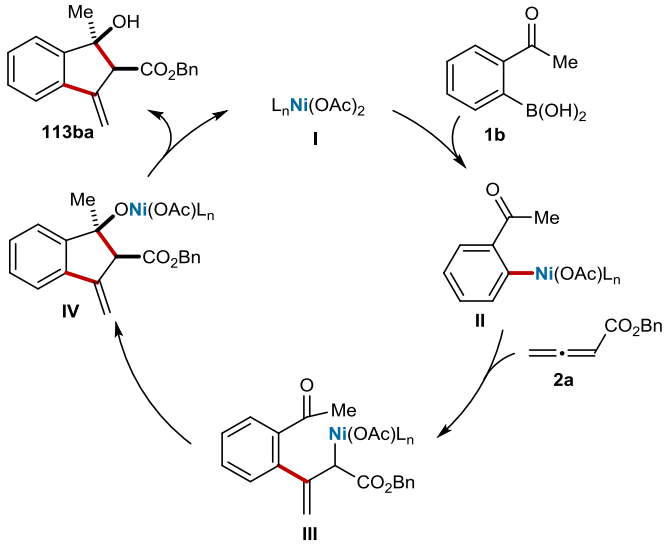


Scheme 108: Absolute configuration not determined

Due to the difficulties in preparing the ligands, the enantioselective reaction was also attempted with **L22**, allene **112d** and nickel trifluoroacetate. 3-methyleneindan-1-ol ***ent*-113bd** was obtained in 95% yield and 66% ee (Scheme 108).

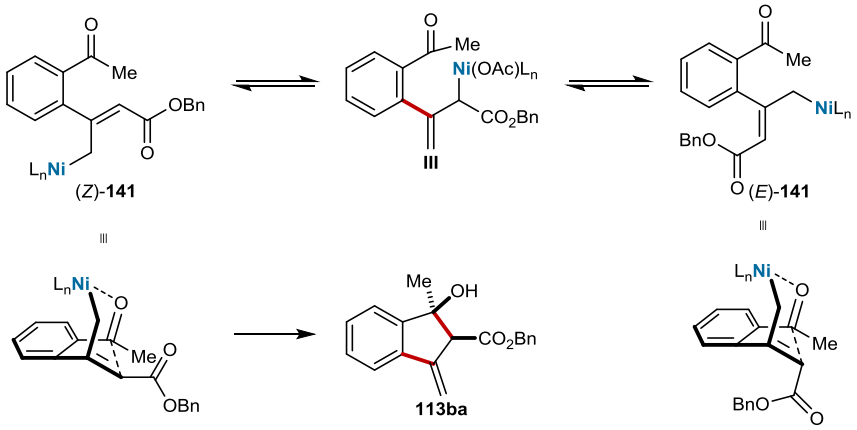
Crystals of ***ent*-113bd** were grown to obtain an absolute configuration. However, analysis of the crystals by HPLC showed they were racemic. Therefore, the absolute configurations were not determined.

2.6. Mechanistic Insights



Scheme 109

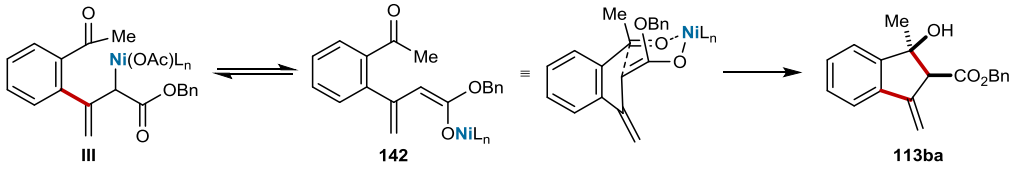
Based on prior research within the group,[45,46] and literature precedent,[42] a catalytic cycle is proposed (Scheme 109). Transmetallation of the active nickel species onto the boronic acid gives arylnickel species **II**. A regioselective migratory insertion into the allene is then proposed, giving the η^1-allylnickel complex **III**. Diastereoselective cyclisation then generates the nickel alkoxide complex **IV**, which undergoes protonolysis to give the desired 3-methyleneindan-1-ol **113ba** and regenerates the active nickel catalyst.



Scheme 110

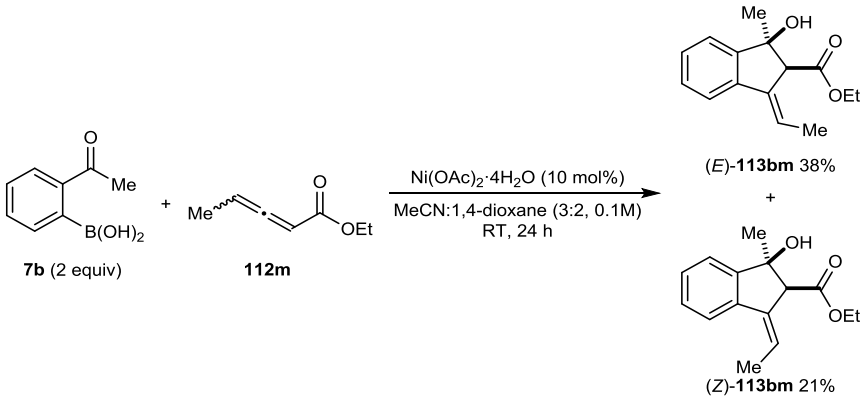
Interconversion between the η^1-allylnickel species and η^3-allylnickel species could give either the (*E*)-**141** or the (*Z*)-**141** species (Scheme 110). The (*E*)-allylnickel species **141** possesses unfavourable interactions between the ketone

group and the ester. Allylation of the ketone from (*Z*)-**141** could proceed *via* a six-membered transition state to give **141**.



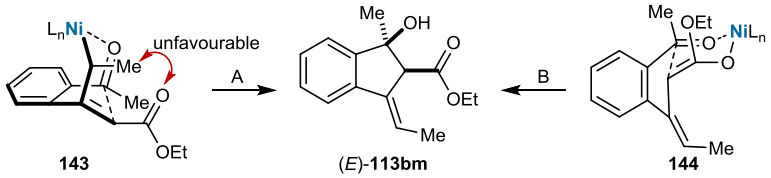
Scheme 111

The reaction could also proceed *via* an enolisation of the ester carbonyl group (Scheme 111). An aldol-type condensation with the ketone would then generate 3-methyleneindan-1-ol **113ba**.



Scheme 112

An insight into which whether the reaction proceeds *via* an allylation or an aldol-type mechanism can be gleaned from the reaction of 2-acetylphenylboronic acid **7b** and allene **112m** (Scheme 112). In this reaction, both isomers of the product were formed.



Scheme 113

Considering the intramolecular allylation pathway A, the six-membered transition state **143** could give rise to an unfavourable 1,3-allylic interaction between the terminal methyl group and the ester (Scheme 113, pathway A). This suggests that this mechanism proceeds *via* an aldol-type condensation (Scheme 113, pathway B). Whilst this mechanism is plausible for allenes bearing ester functionality, it is unclear as to whether this mechanism is

applicable to phosphorus-based or sulfur-based groups. Further investigations into the mechanism of this reaction are required.

3. Conclusions and Future Work

3.1. Conclusions

The development of a nickel-catalysed annulation reaction between activated allenes and *o*-carbonylarylboronic acids is reported. The scope is broadened to include allenes bearing 1,1-, 1,3- and 1,3,3- substitution patterns. This metholodogy also gives access to products with phosphorus and sulfur-based groups at the 2-position. All 3-methyleneindan-1-ols can be accessed as single observable diastereoisomers in excellent yields.

The potential for scaling up the reaction was demonstrated, and the catalyst loading could be decreased to 0.5 mol%. Furthermore, the reaction is tolerant to both air and moisture.

Enantiocontrol can be induced *via* the addition of a chiral ligand. Ligands based on chiral oxazoline (*R*)-PhPhox were synthesised and up to 74% ee was obtained.

3.2. Future Work

Research into the potential for accessing derivatives with aromatic rings, alkyl groups, or electron-rich groups at the 2-position should be undertaken. Further investigation into the reaction conditions and optimisation could lead to a process that gives access to a wider range of functionality.

Further research into the mechanism could provide a better understanding of how the reaction progresses. Reaction monitoring by ^{1}H NMR spectroscopy for example could provide valuable kinetic information. Furthermore, synthesis of enantiopure allenes could lead to a better understanding of the reaction mechanism.

4. Introduction: Synthesis of Chiral Cyclopent-2-enones

4.1. Cyclopent-2-enones in Nature

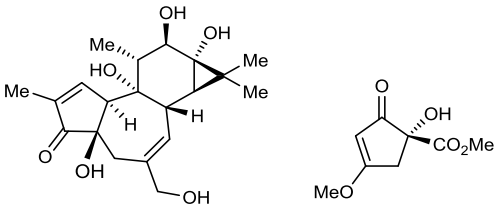


Figure 13

Cyclopent-2-enones are present in a number of biologically active compounds and natural products such as phorbol,[55] and (−)-kjellmanianone (Figure 13).[56,57] With such an important scaffold, novel approaches to their syntheses remain important.

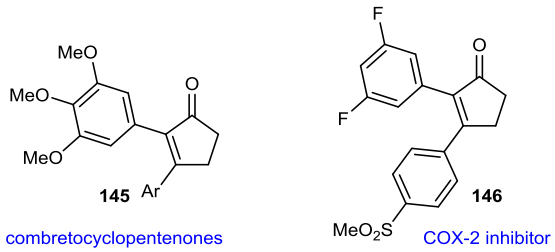


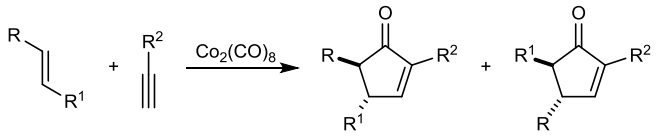
Figure 14

Cyclopent-2-enones with 2,3-diaryl substitution patterns have also demonstrated biological activity (Figure 14). This unit can be found in the potent COX-2 inhibitor,[58] as well as combretocyclopent-2-enones, which are known to exhibit anti-tumour activity.[59,60]

To date, numerous methods for the synthesis of cyclopent-2-enones have been reported. Perhaps the most well-known are the Pauson-Khand reaction: between alkynes, alkenes and carbon monoxide, and the Nazarov cyclisation: an intramolecular acid-mediated reaction of dienones. This chapter discusses selected examples of the Pauson-Khand reaction, Nazarov cyclisation, and other methods of synthesising cyclopent-2-enones with an α-quaternary centre, and/or 2,3-disubstitution.

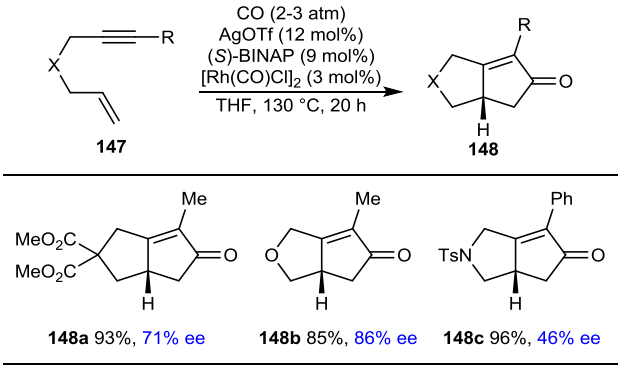
4.2. Pauson-Khand Reaction

The Pauson-Khand reaction is well reported in the literature. The reaction uses alkynes, alkenes, and traditionally carbon monoxide as the carbonyl source to access cyclopent-2-enones.[61]



Scheme 114

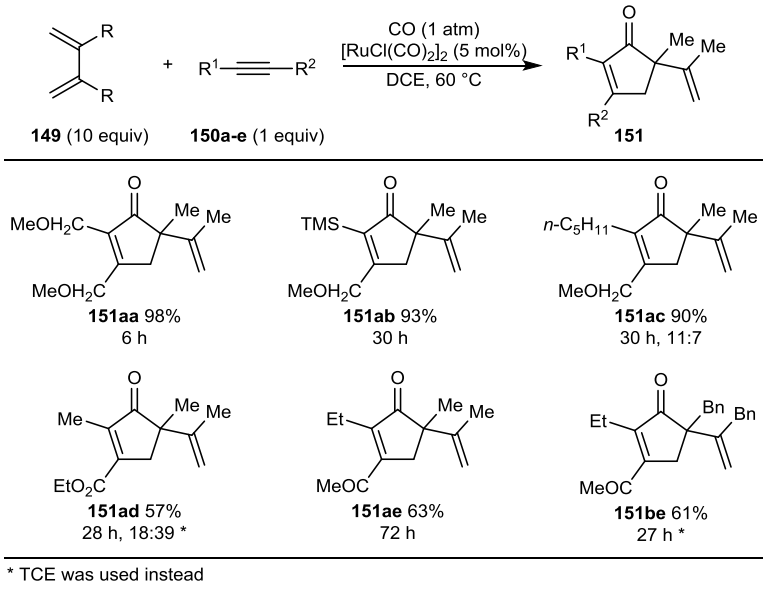
First reported in the 1970's, the Pauson-Khand reaction (Scheme 114) provided a useful tool towards cyclopent-2-enones.[61] A clear drawback however was the need for stoichiometric cobalt, high pressures of carbon monoxide, and generally harsh reaction conditions. Furthermore, unsymmetrical starting materials tended to give a mixture of regioisomers, which was difficult to control.[62] The stoichiometric Pauson-Khand reaction has been extensively reported in the literature, but more recently, catalytic and enantioselective examples have been developed.



Scheme 115

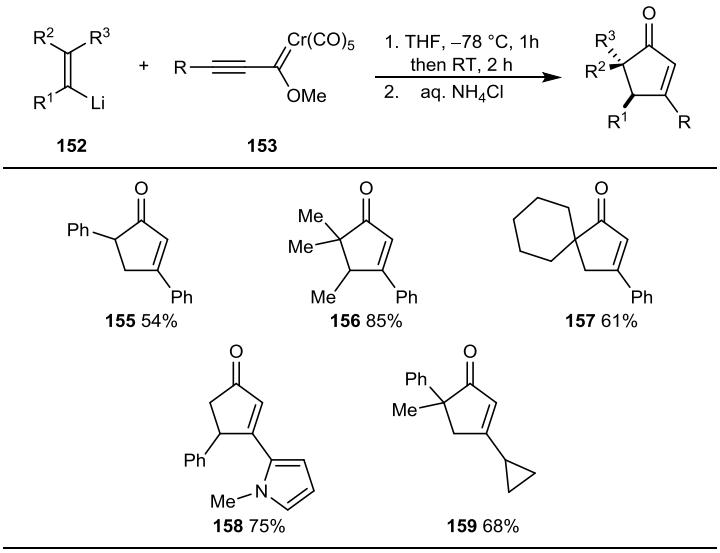
A rhodium-catalysed enantioselective synthesis of cyclopent-2-enones from enynes and carbon monoxide was reported by Choi and co-workers in 2000 (Scheme 115).[63] Enynes with carbon, oxygen, and nitrogen tethers reacted successfully to give **148a**-**148c** in excellent yields, and modest to good enantioselectivities. Alkyl and aromatic substituents at the alkyne were also well-tolerated. Since this report, numerous transition metal-catalysed iterations ranging from cobalt[64] to titanium,[65] and iridium[66] have been reported.[67] Due to the sheer quantity of reactions reported, this section will only discuss recent advances in the catalytic Pauson-Khand reaction, towards the synthesis of

cyclopent-2-enones with an α-quaternary centre, and/or a 2,3-disubstituted motif.



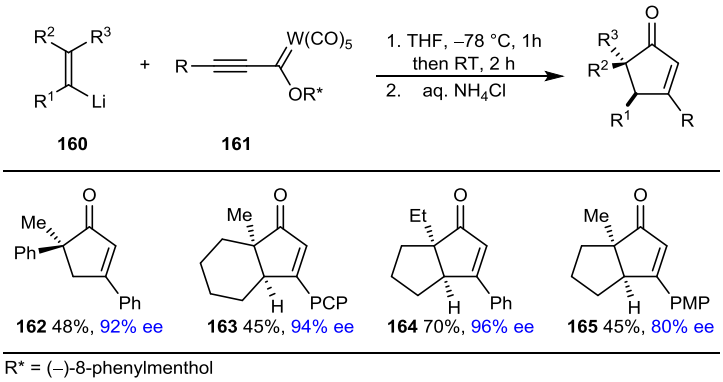
Scheme 116

In 2004, Williams and co-workers reported the first example of an intermolecular dienyl Pauson-Khand reaction, using alkynes, dienes and carbon monoxide (Scheme 116).[68] Cyclopent-2-enones with an α-quaternary centre could be accessed using rhodium catalysis, and just one atmosphere of carbon monoxide. Reactions with both symmetrical and unsymmetrical alkynes worked well, and cyclopent-2-enones **151** were obtained in excellent yields and generally good regioselectivities. Benzyl diene **149b** also reacted successfully to give **151be** in 61% yield.



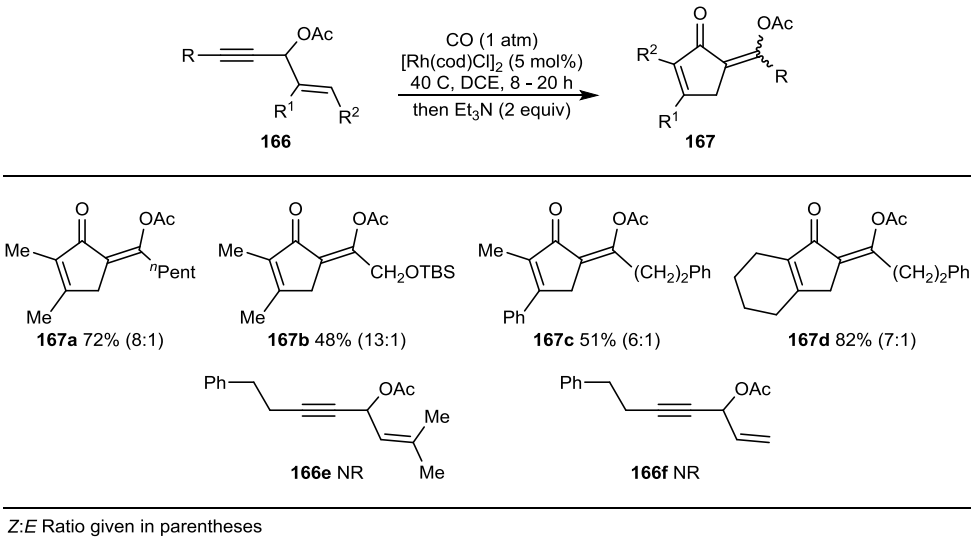
Scheme 117

In 2012, Tomas and co-workers reported an intramolecular Pauson-Khand type reaction which used a recyclable metal-carbonyl complex as the source of carbon monoxide (Scheme 117). The reaction between the metal complex, the bromoalkene and an alkyne gives the corresponding cyclopent-2-enone. The bromoalkenes were treated with *tert*-butyllithium solution to generate the alkenyllithium species **152**, which then reacts with the chromium-alkynylcarbene **153**, which was generated from a terminal alkyne and $[Cr(CO)_6]$. Both alkyl- and aryl- substituted alkenes reacted successfully, and the cyclopent-2-enones were obtained in excellent regioselectivities. Aryl, heteroaryl and alkyl substituted alkynes also reacted successfully, and cyclopent-2-enones **155-159** were obtained in good yields.[69]



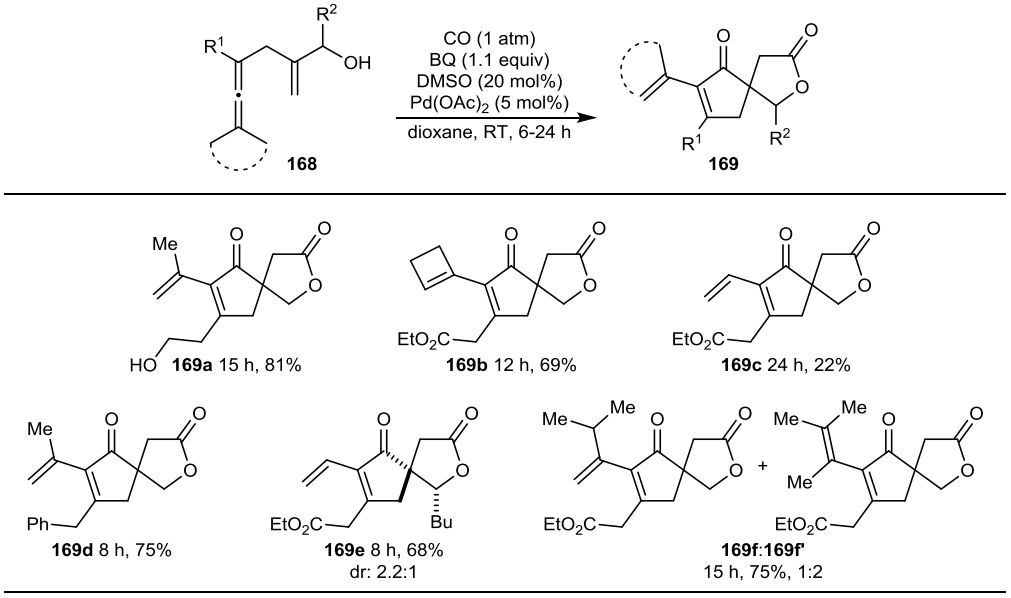
Scheme 118

With tungsten carbene **161**, derived from (−)-8-phenylmenthol, enantioenriched cyclopent-2-enones could also be accessed (Scheme 118).[69] Fused ring systems were also accessible, and the cyclopent-2-enones **162-165** were obtained in modest yields and good to excellent enantioselectivities.



Scheme 119

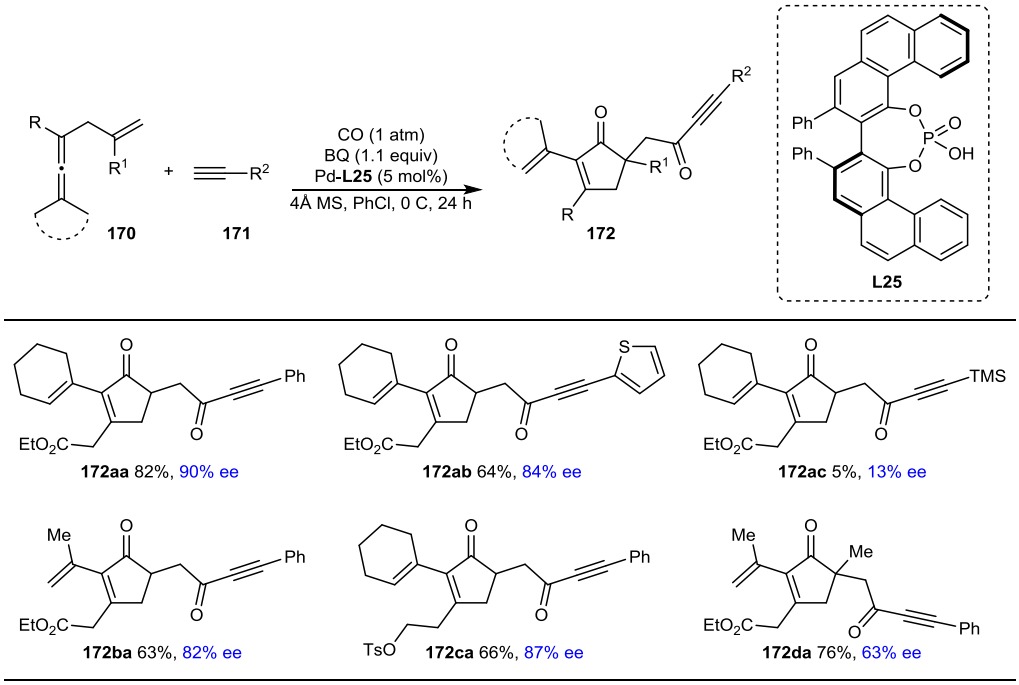
In 2012, Tang and co-workers reported a rhodium-catalysed carbonylation of enynes to give cyclopent-2-enones (Scheme 119).[70] A range of alkyl groups at the alkyne were well tolerated, and cyclopent-2-enones **167a-167d** were obtained in modest to good yields and modest *E*/*Z* selectivity. Alkyl and aryl groups at the alkene also reacted successfully to give **167** in moderate yields. Enyne **166d** with an internal alkene gave bicyclic **167d** in 82% yield. Enynes **166e** and **166f** did not react.



Scheme 120

An intramolecular palladium-catalysed synthesis of cyclopent-2-enones was reported by Backväll and co-workers in 2017, using allenes as the reaction partner instead of alkynes (Scheme 120).[71] This methodology also used just

one atmosphere of carbon monoxide, and gave cyclopent-2-enones with a spiro-centre at the α-position. Alkyl, cycloalkyl, and aryl groups at the allene were well-tolerated, with giving the corresponding products **169a**, **169b** and **169d** in good yields. The yield was considerably lower when a terminal allene **168c** was used (**169c**), and a butyl- group at R^2 gave **169e** in modest yield and diastereoselectivity. Unsymmetrical starting material **168f** gave a mixture of products in 75% combined yield, and a ratio of 1:2 **168f**:**168f'**.

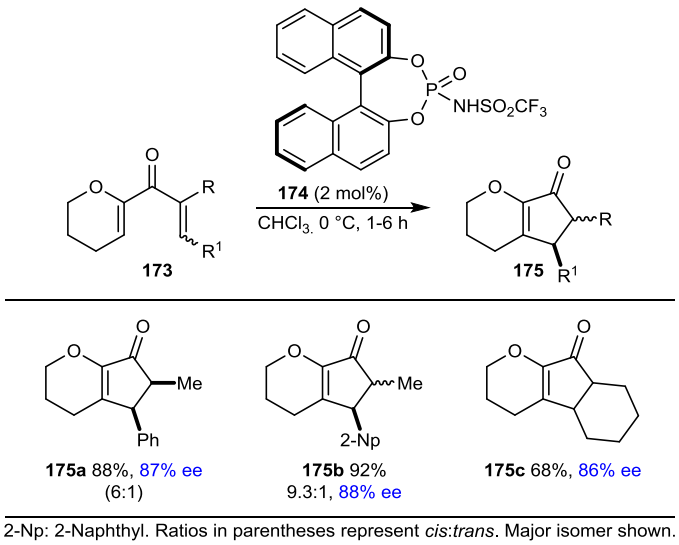


Scheme 121

An enantioselective palladium-catalysed carbonylative of enallenes was also reported by Backväll and co-workers in the same year (Scheme 121).[72] Both internal and external olefins reacted successfully. Aryl and heteroaryl groups at the alkyne were also well-tolerated (**172aa** and **172ab**), but the yield and ee was lower when TMS substrate **171c** was used. Ester and alkoxy-alkyl groups also reacted successfully to give cyclopent-2-enones **172ba-172da** in good yields and ee's.

4.3. Nazarov Cyclisation

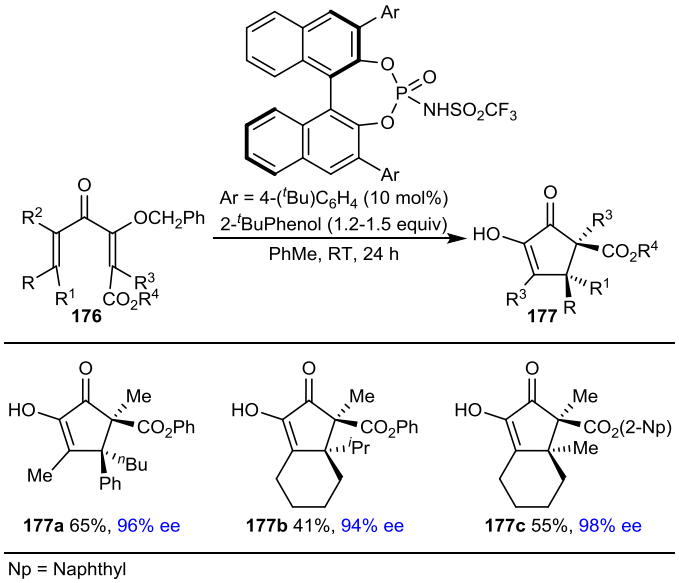
The Nazarov cyclisation is another common method to synthesise cyclopent-2-enones. This section will focus on the recent catalytic syntheses of cyclopent-2-enones with an α-quaternary centre, and/or a 2,3-disubstitution pattern.



2-Np: 2-Naphthyl. Ratios in parentheses represent *cis*:*trans*. Major isomer shown.

Scheme 122

In 2007, Nachtsheim and co-workers reported an electrocyclic, organocatalytic Nazarov cyclisation (Scheme 122).[73] The cyclopent-2-enones were obtained in good yields and enantioselectivities. Alkyl-, aryl- and dialkyl- substituted dienones reacted successfully to give **175** in good to excellent yields and enantioselectivities. The products were obtained as a mixture of *cis*- and *trans*-isomers, except for **175c**. This represented the first example of an enantioselective Brønsted acid catalysed Nazarov cyclisation.

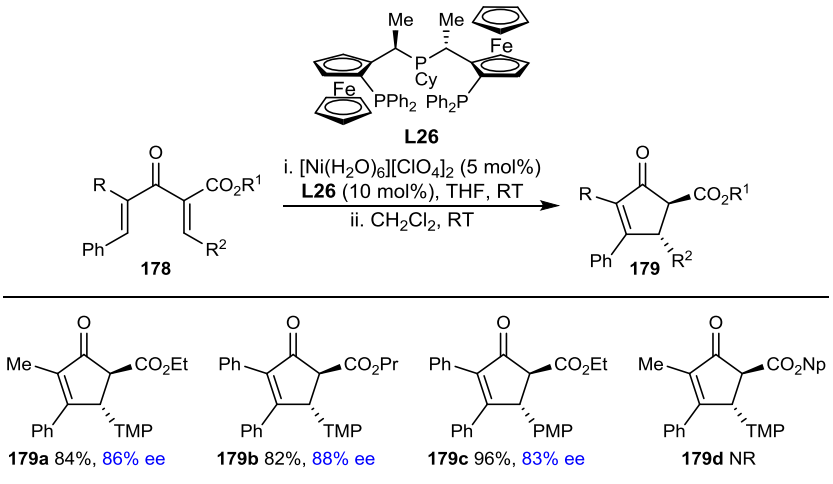


Np = Naphthyl

Scheme 123

Similar research was reported by Tius *et al*. in 2014, and selected examples are shown in Scheme 123.[74] Aliphatic, aromatic and alicyclic substituents were

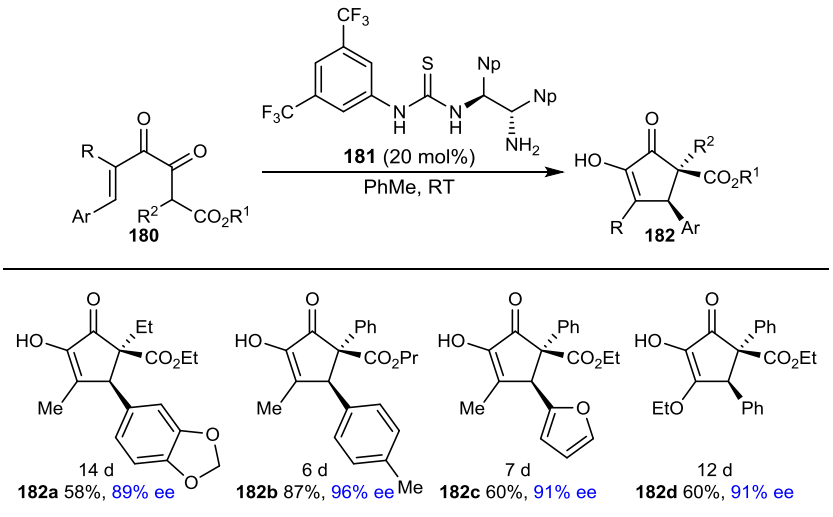
well-tolerated, and the cyclopent-2-enones **177** were obtained in modest yields and excellent enantioselectivities.



TMP = 2,4,6-trimethoxyphenyl. Np = 1-naphthyl.
Reaction time: 6-8 days for R^2 = TMP. 9-15 days for R^2 = PMP.

Scheme 124

In 2008, Togni and co-workers reported a nickel-catalysed Nazarov-cyclisation (Scheme 124).[75] The substrates required an electron-rich trimethoxyphenyl or *para*-methoxyphenyl groups at the 3-position, and took between 6-15 days to progress to completion. The reactions were tolerant to alkyl- and aryl-substituents, and the corresponding cyclopent-2-enones **178** were obtained in good yields and ee's. When a naphthtyl ester was used, however, no product was obtained.

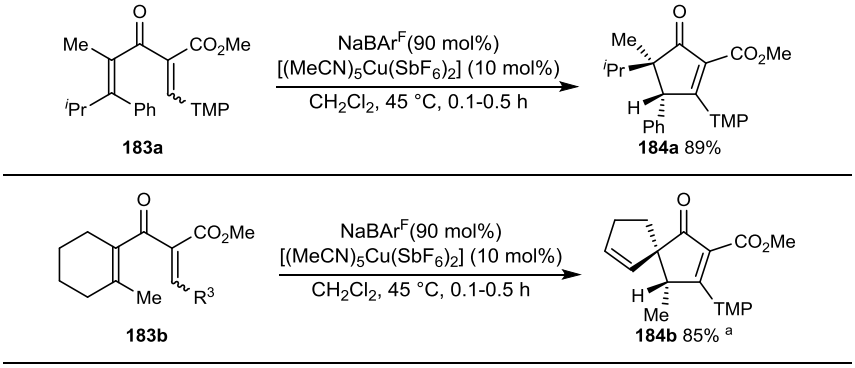


Np = 1-Naphthyl

Scheme 125

In 2010, Tius *et al.* also reported an organocatalysed Nazarov-cyclisation (Scheme 125).[76] Highly substituted cyclopent-2-enones with 2-hydroxy groups

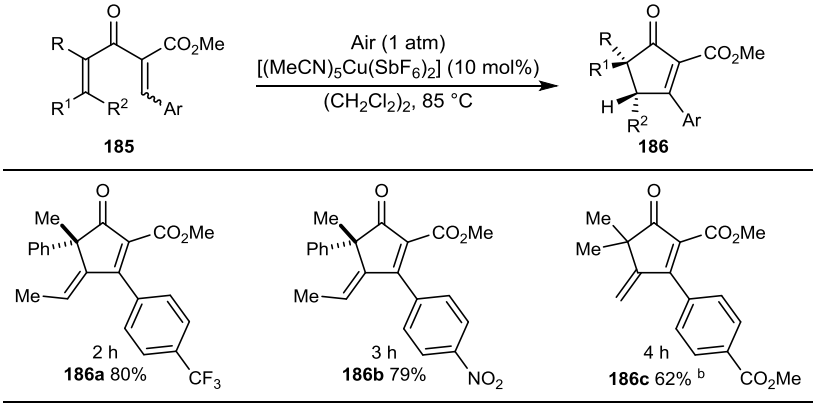
182 were obtained from substrates **180** in good yields and excellent enantioselectivities. A range of aryl groups were well-tolerated at the 4-position. Alkyl- and alkoxy- groups at the 3-position were also well-tolerated to give **181**. Both alkyl- and aryl- groups at R^2 also reacted successfully. These reactions however also required several days.



TMP = 2,4,6-trimethoxyphenyl. [a] This reaction was carried out at RT.

Scheme 126

In 2011, Frontier and co-workers reported a copper-catalysed cyclisation reaction that encompassed a Wagner-Meerwein rearrangement, offering a stereoselective approach to functionalised cyclopent-2-enones (Scheme 126).[77] Chemoselective 1,2-migration of the R^1 group led to cyclopent-2-enones with adjacent stereocentres, two examples are shown above. Cyclopent-2-enones **184b** with a spiro-centre at the α-position could also be obtained in excellent yield.



[b] [(tBuBOX)Cu(SbF6)2] was used instead

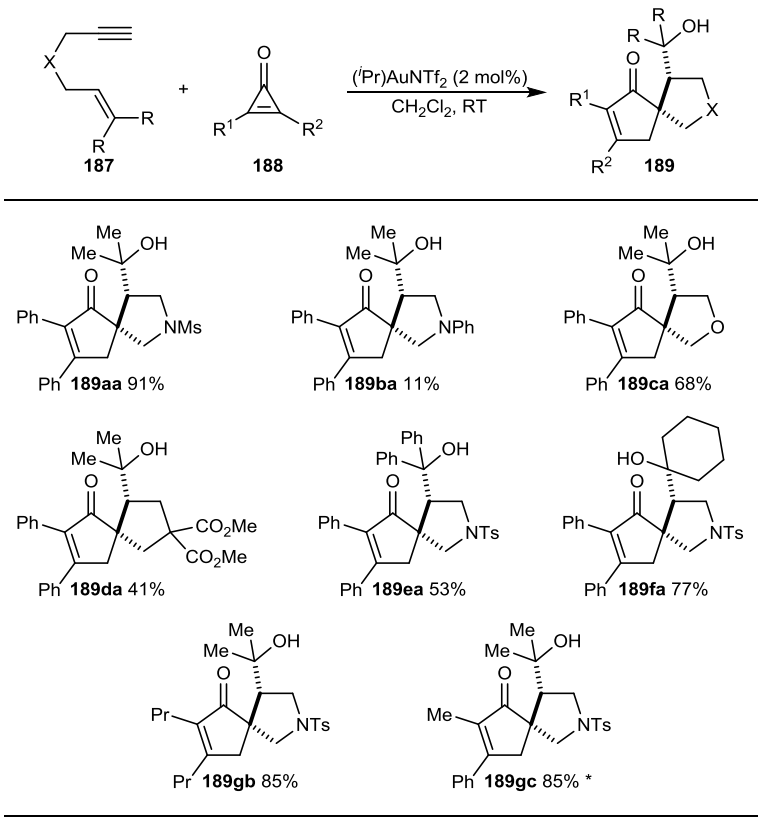
Scheme 127

In 2013, Frontier and co-workers also reported a similar transformation where electron-poor groups were also tolerated (Scheme 127).[78] The cyclisation-rearrangement-oxidation sequence gives cyclopent-2-enones with a methylene

at the 4-position. *Para*-CF_3, -NO_2, and ester groups all reacted successfully to give **186a-186c** in good yields.

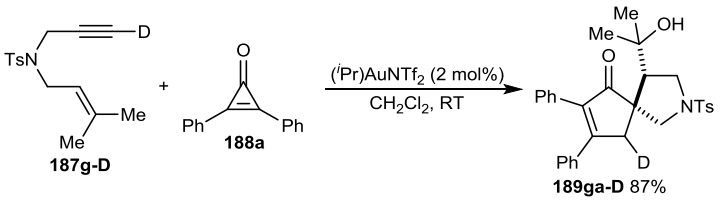
4.4. Micellaneous Methods towards Cyclopent-2-enones

Cyclopent-2-enones can also be accessed using other methods. This section focuses on recent catalytic examples of the synthesis of cyclopent-2-enones with an α-quaternary centre and/or a 2,3-disubstituted scaffold.



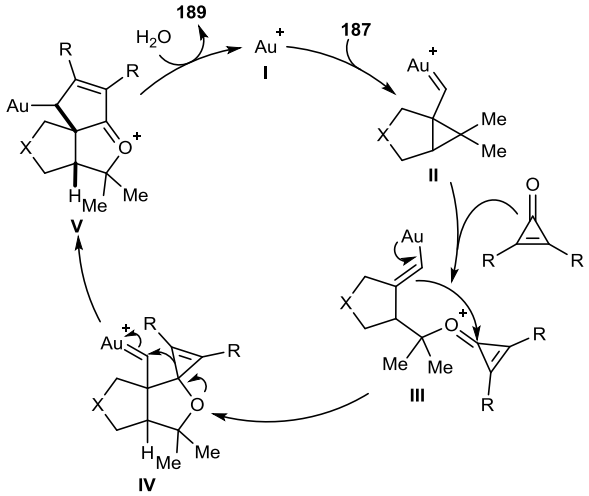
Scheme 128: This reaction was carried out at 0 °C.

In 2014, Sakurai and co-workers reported a gold-catalysed synthesis of cyclopent-2-enones from enynes and cyclopropenones (Scheme 128),[79] building on their research into palladium-catalysed ring-opening alkynylation of cyclopropenones.[80] Enynes with different *N*-protecting groups reacted successfully. With enyne **187b**, a lower yield of the cyclopent-2-enone **189ba** was obtained. Oxygen and carbon tethered enynes also reacted successfully, and **189ca** and **189da** were obtained in modest to good yields. Aryl-, alkyl-, and cyclic alkenes also reacted successfully, to give **189aa-189fa** in good yields. Aryl- and alkyl- substituted cyclopropenones also reacted successfully to give the corresponding cyclopent-2-enones in good yields.



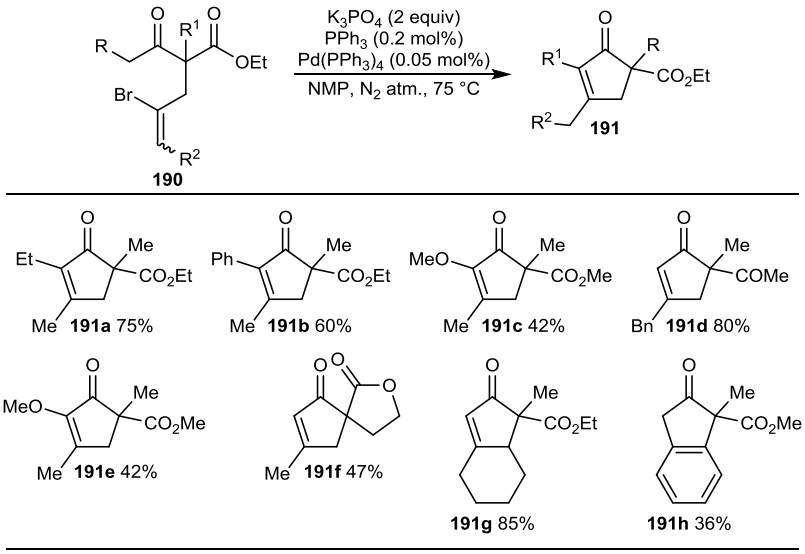
Scheme 129

The reaction with a deuterium atom at the alkyne also reacted successfully. Cyclopent-2-enone **188ga-D** was obtained as a single diastereoisomer (Scheme 129).[79]



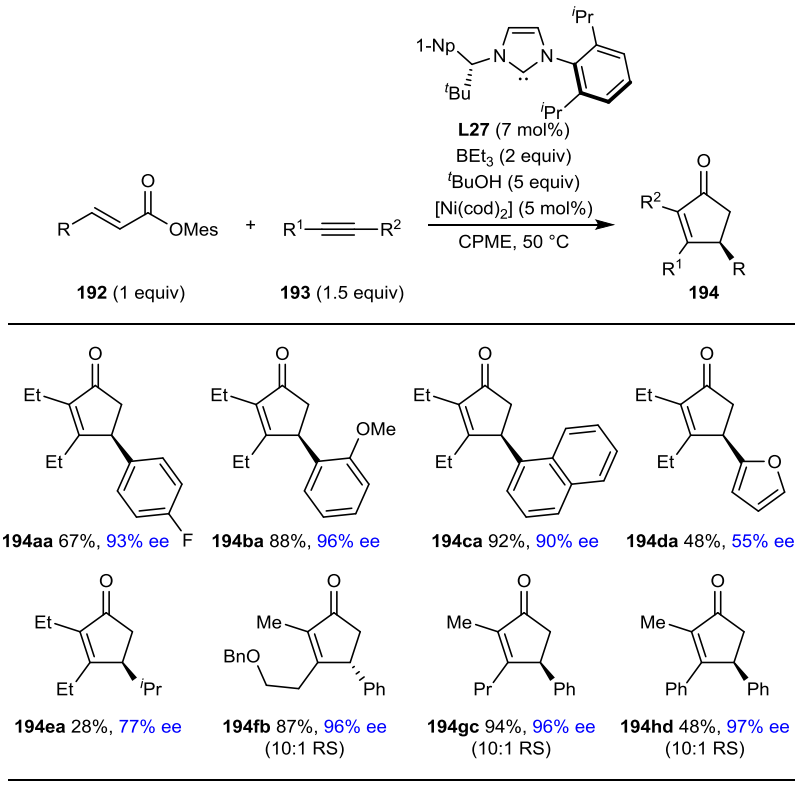
Scheme 130

A catalytic cycle was proposed (Scheme 130).[79]. The reaction of **187** with the gold catalyst generates carbene gold species **II**. The cyclopropane ring is opened followed by attack on the carbonyl (**III**) which gives intermediate **IV**. **V** is formed *via* a [3+2] annulation of the vinylgold with the cyclopropene *via* **IV**. Finally, hydrolysis regenerates the catalyst and releases the product **189**.



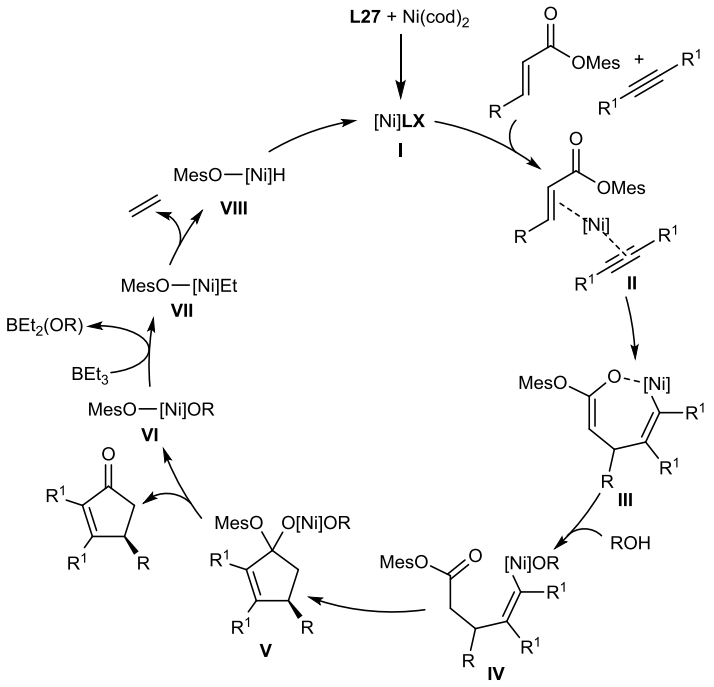
Scheme 131

In 2014, Chang and co-workers reported a palladium-catalysed synthesis of cyclopent-2-enones *via* an intramolecular carbonyl alkenylation reaction (Scheme 131).[81] The reaction was tolerant to various groups at the R position. Alkyl-, aryl-, and alkoxy- groups all gave the corresponding cyclopent-2-enones **191** in good yields. Lactone **190f** gave the cyclopent-2-enone **191f** with a spiro-centre at the 5-position in good yield. Cyclopent-2-enones **191g** and **191f** tethered to a cyclohexyl ring or a benzene ring were also obtained in modest to good yields.



Scheme 132

In the same year, Cramer and co-workers reported a nickel-catalysed enantioselective synthesis of cyclopent-2-enones *via* an annulation between arylenoates and alkynes (Scheme 132).[82] The reaction was tolerant to a range of substituted aryl groups on the alkene. Electron-poor and electron-rich groups reacted successfully to give **194aa** and **194ba** in good yields and ee's. Bulkier groups like 1-naphthyl (**194ca**) and heteroaryl groups like 2-furyl also reacted successfully to give **194da** in modest yield and ee. Alkyl groups were also tolerated, and **194ea** was obtained in a lower 28% yield and modest ee. Unsymmetrical alkynes gave the corresponding cyclopent-2-enones as a mixture of regioisomrs. Alkyl-alkyl and alkyl-aryl alkynes reacted to give **194fb**-**194hd** in moderate to good yields and excellent ee's, with a good regioisomeric ratio.



Scheme 133

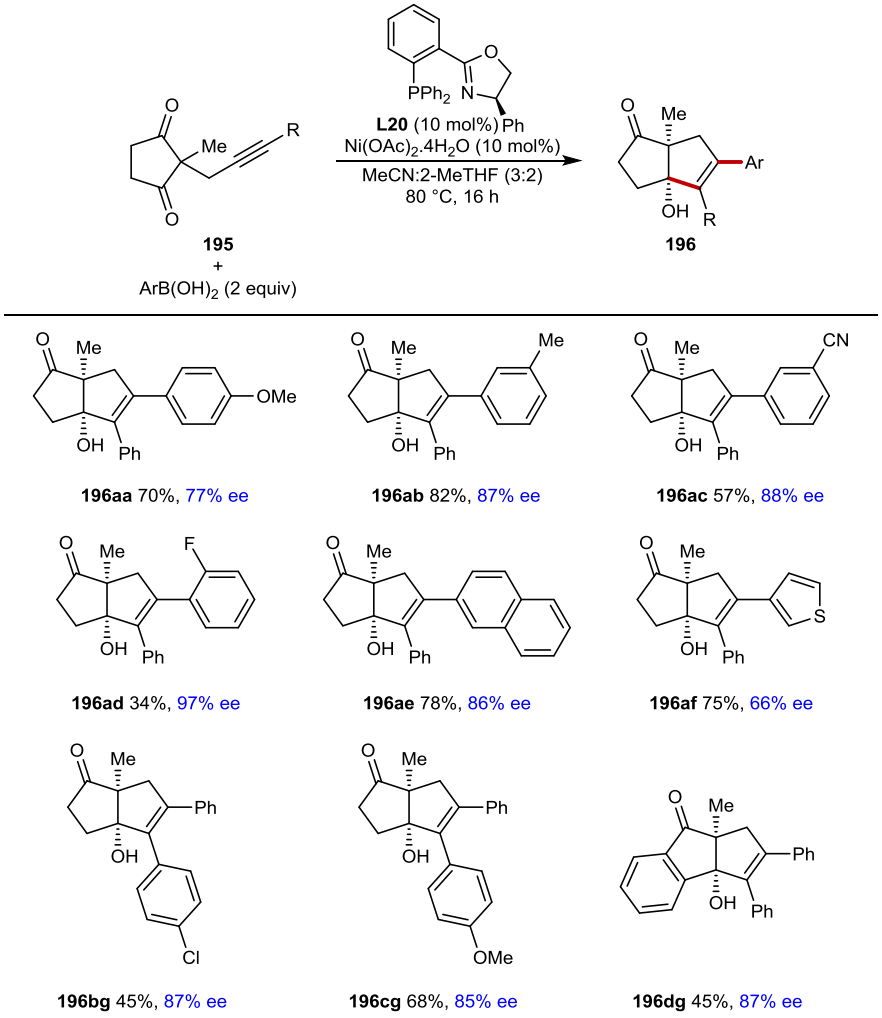
A catalytic cycle was proposed (Scheme 133).[82] Coordination of the enoate and the alkyne to the active nickel-catalyst gives complex **II**. Oxidative cyclisation gives complex **III**. The reaction with an alcohol gives alkenyl-nickel **IV**. Cyclisation gives complex **V**, and subsequent β-alkoxide elimination releases the product. Transmetallation of the nickel alkoxide with triethylborane (**VII**) and subsequent β-hydride elimination gives nickel-hydride **VIII**. Reductive elimination closes the cycle and regenerates the active catalytic species.

4.5. Cyclisation Reactions Enabled by Reversible *E*/*Z* Isomerisation of the Alkenylnickel Species

The Lam group has recently developed nickel-catalysed arylative cyclisation reactions enabled by reversible *E*/*Z* isomerisation of the alkenylnickel species. Traditonally, addition across an alkyne is *syn*-selective, however, this methodology relies on the formal anti-carbometallaton of the arylnickel to enable cyclisation. This gives access to a wider range of products, which would be inaccessible using convential *syn*-addition-cyclisation methodologies, which have been widely reported.[45]

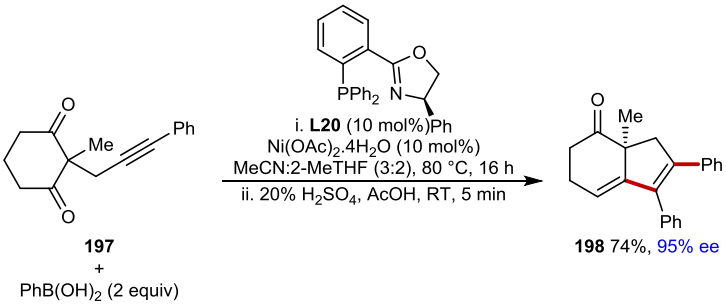
Previous studies have shown that organonickel complexes can add accross alkynes to give a mixture of *E*/*Z* isomers.[83] An example of the addition of an arylboronic acid across an alkyne using cobalt-catalysis has also been reported to give a 1:1 mixture of *E*/*Z* isomers.[84] This section discusses the recent reports of nickel-catalysed tandem cyclisation reactions enabled by reversible *E*/*Z* isomerisation of the alkenyl nickel species.

4.5.1. Synthesis of Bicyclic Systems



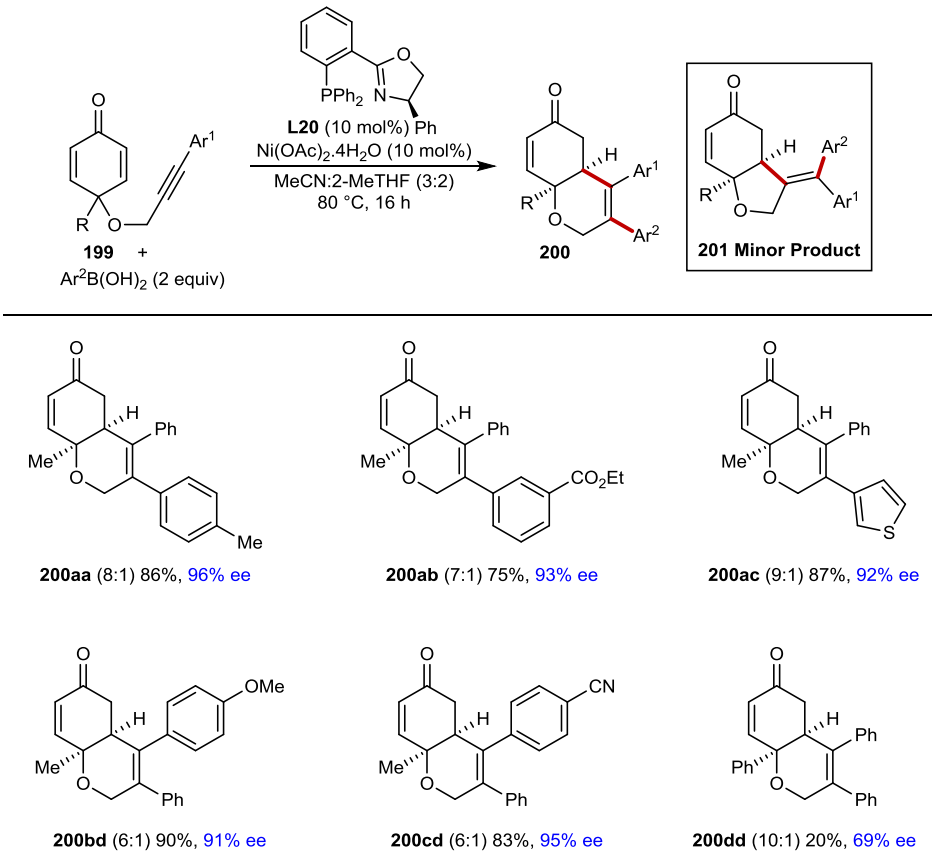
Scheme 134

In 2016, Lam and co-workers published a formal *anti*-carbometallative nickel-catalysed desymmetrisation of cyclic 1,3-diketones, affording chiral bicyclic 5,5-, 6,5-, and 6,6-ring systems with an internal alkene (Scheme 134).[45] Treatment of the 1,3-diketones **195** with phenylboronic acid in the presence of nickel acetate and (*R*)-PhPHOX (**L20**) afforded bicyclic compounds **196** in moderate to good yields with generally good to excellent enantioselectivities. This reaction was tolerant to substrates containing substituted aryl and heteroaromatic rings (**196af**-**196dg**), and a range of aryl- and heteroarylboronic acids (**196aa**-**196af**).



Scheme 135

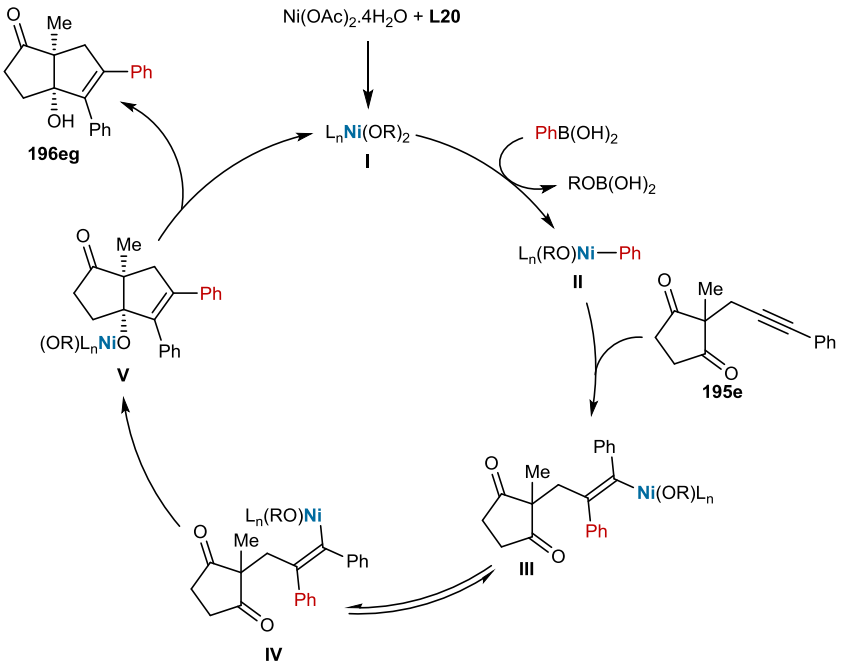
When this methodology was applied to a 6-membered 1,3-diketone **197**, a mixture of the cyclic alcohol and dehydrated product was obtained (Scheme 135). Treatment of the mixture with sulfuric acid in acetic acid afforded only the dehydrated product **198** in excellent yield and enantioselectivity.[45]



Scheme 136

The methodology was further applied to a desymmetrisation reaction of cyclic enones **199** (Scheme 136).[45] The desired 6,6-bicyclic products **200** were obtained in moderate to good yields, with excellent enantioselectivities. A range of arylboronic acids were well tolerated, with methyl- groups, carboethoxy- groups and heteroaryl boronic acids giving the corresponding

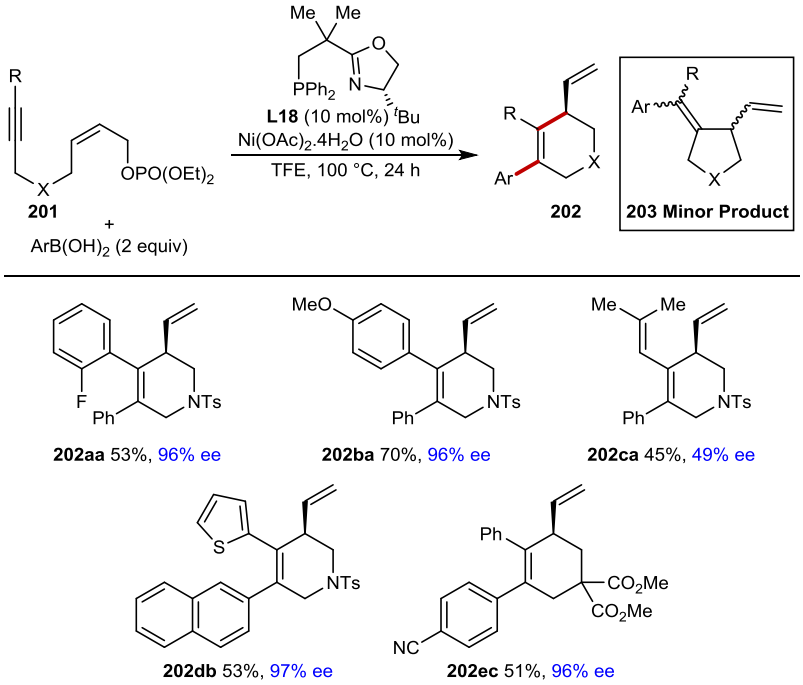
products in generally excellent yields and enantioselectivities (**200aa**-**200cd**). When the Me (**199d**) R group was replaced with a phenyl ring, the yield and enantioselectivity obtained was lower (**200dd**, 20%, 69% ee). The minor product **201** was also obtained in varying ratios, shown in parentheses, which is the product of addition of the arylnickel in the opposite regioselectivity. Products with this scaffold have been previously synthesised using rhodium catalysis, and is an example of a syn-addition-cyclisation reaction.[85]



Scheme 137

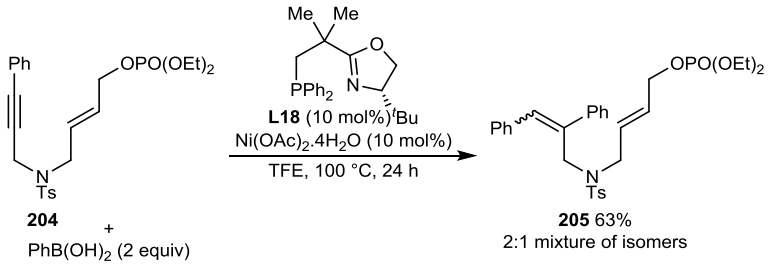
A catalytic cycle was proposed (Scheme 137). Coordination of **L20** to nickel acetate generates the chiral nickel complex **I**. Transmetallation of phenylboronic acid onto the active nickel species gives arylnickel complex **II**. Regioselective migratory insertion into **195e** in a *syn*-selective fashion gives alkenylnickel **III**. Reversible *E*/*Z* isomerisation of **III** to **IV** facilitates cyclisation, giving nickel alkoxide **V**. Protonolysis releases **196eg** and regenerates the nickel catalyst.

4.5.2. Allylic Alkenylation Reaction



Scheme 138

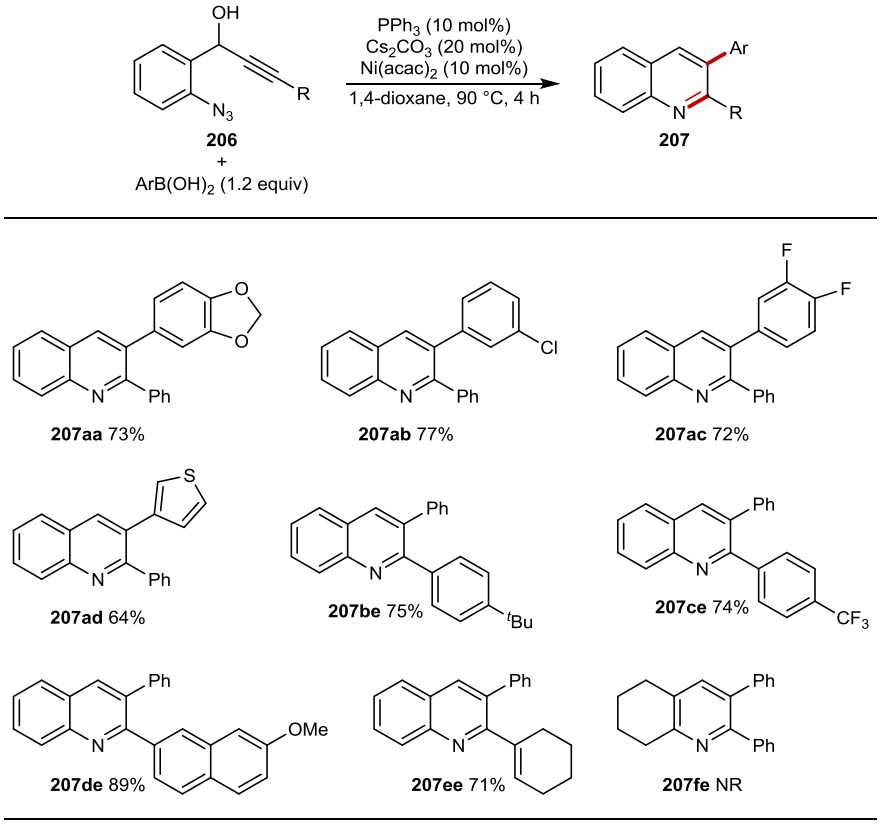
Following the initial discovery of the reversible *E*/*Z* isomerisation of the alkenylnickel species (Scheme 134-Scheme 136),[45] the methodology was applied to the synthesis of hetero- and carbocycles *via* an allylic alkenylation reaction.[46] Following modifications to the original reaction conditions, arylboronic acids reacted with an alkyne tethered to an allylic phosphonate ester (**201**) in the presence of a nickel catalyst and **L18** to give a range of substituted carbo- and heterocyclic products **202** (Scheme 138). Both electron-poor and electron-rich substituents on the aromatic ring on both the alkyne and the boronic acid were well-tolerated (**202aa** and **202ba**). Heterocyclic groups and bulky naphthyl groups also gave the corresponding products (**201d**) in moderate yields and enantioselectivities (**202db**). Pleasingly, the reaction was not limited to aryl groups at the alkyne, and **202ca** with an alkenyl group was obtained in modest yield and ee (Scheme 138). Small quantities of **203** were also observed by ^{1}H NMR spectroscopy of the crude mixture. Generally, the regioselectivity of the reaction was excellent and most products were obtained in a >19:1 ratio.



Scheme 139

For this reaction, it was necessary for the alkene to possess a (*Z*)-geometry. When the reaction was attempted on the corresponding (*E*)-alkene, only a mixture of hydroarylation products (**205**) were obtained (Scheme 139).[46]

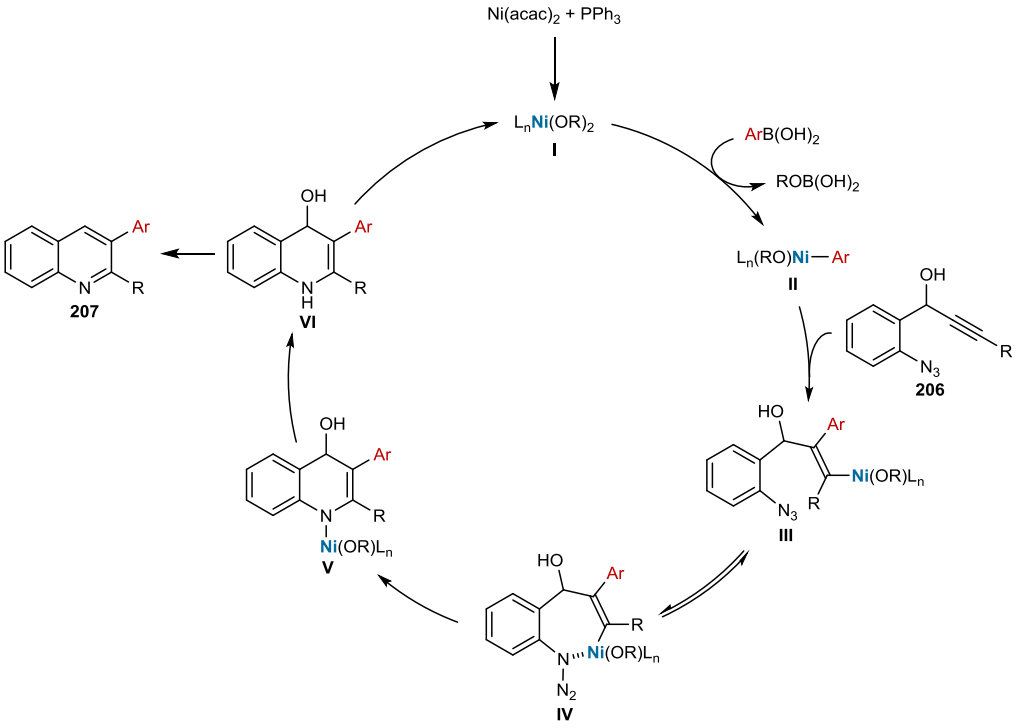
4.5.3. Synthesis of 2,3-Diarylquinolines



Scheme 140

In 2018, Reddy and co-workers reported the synthesis of 2,3-diarylquinolines from aryl azido alkynols **206** with arylboronic acids in the presence of a nickel catalyst.[86] A range of groups on the boronic acid were well-tolerated, representative examples are shown in Scheme 140. Electron-rich and electron-poor arylboronic acids reacted well, giving the corresponding quinolines (**207aa**-**207ac**) in moderate to excellent yields. 3-Thienylboronic acid also

gave quinoline **207ad** in a moderate 64% yield. A range of substituents on the aromatic ring of the alkyne were also tolerated. Substrates with electron-poor groups or bulky groups reacted successfully to give the corresponding quinolines **207be**-**207de** in moderate to excellent yields. An alkene in place of an aryl group at the alkyne also reacted successfully, and **207ee** was obtained in a 71% yield. This methodology required the presence of an aryl tether, as tetrahydroquinoline **207fe** was not obtained.



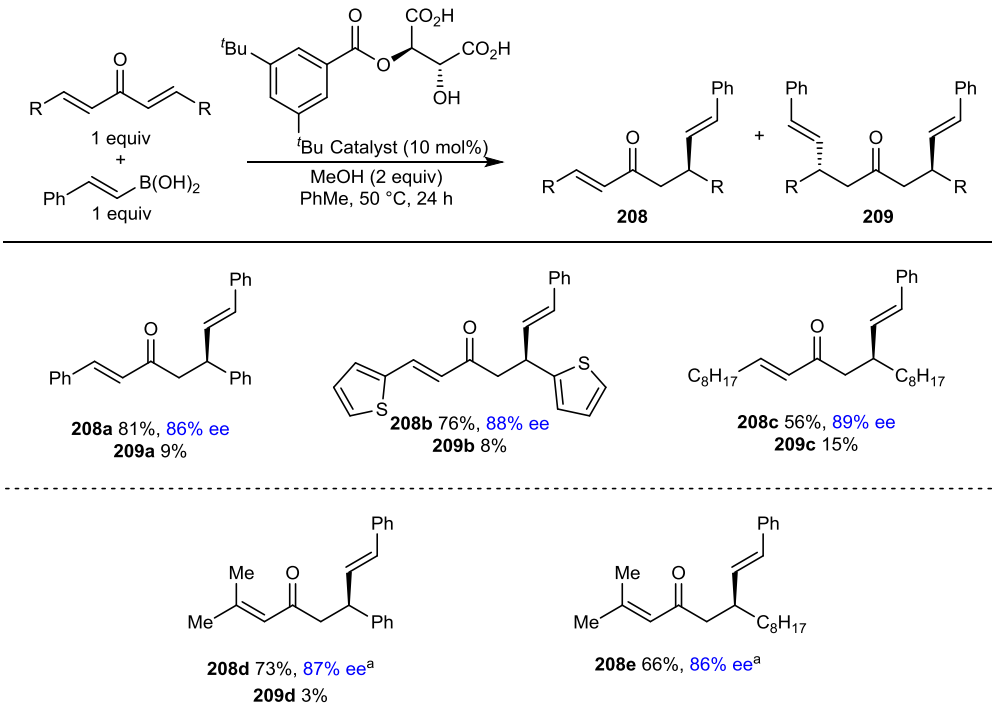
Scheme 141

A catalytic cycle was proposed (Scheme 141).[86] Transmetallation of the arylboronic acid onto the active nickel species gives complex **II**, which undergoes a regioselective migratory insertion across the alkyne to give alkenylnickel species **III**. Reversible *E*/*Z* isomerisation facilitates denitrogenative cyclisation forming intermediate **V**. Protonolysis followed by elimination of water gives the corresponding diarylquinoline **207**.

4.5.4. Synthesis of Chiral Cyclopent-2-enones

Cyclopentenones appear in a range of natural products, agrochemical and pharmaceutical compounds.[87] Desymmetrisation reactions to synthesise

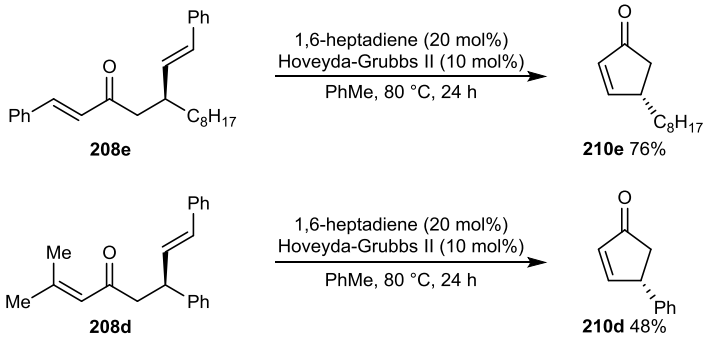
cyclopent-2-enones are underreported in the literature. This protocol provides a useful method to build complexity from symmetrical precursors.



[a] These reactios were carried out for 48 h

Scheme 142

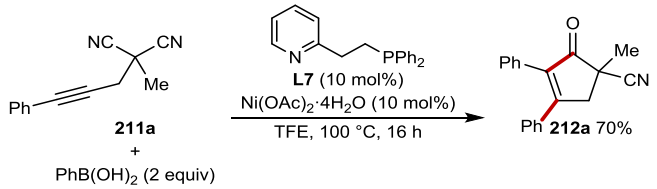
In 2014, Nakajima and co-workers reported an enantioselective conjugate addition of styrylboronic acid to dienones (Scheme 142).[88] Reactions with symmetrical dienones gave a mixture of the mono- and bis- alkenylated products, in varying ratios (**208**-**209**). Aryl-, alkyl-, and heteroaryl groups were all well-tolerated, and the corresponding products were obtained in generally good yields.



Scheme 143

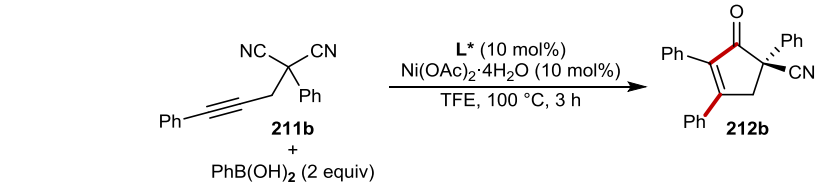
These products then underwent a ring-closing metathesis mediated by the Hoveyda-Grubbs II catalyst. The corresponding enantiomerically enriched cyclopent-2-enones were obtained modest to good yields (**210**, Scheme 143).[88]

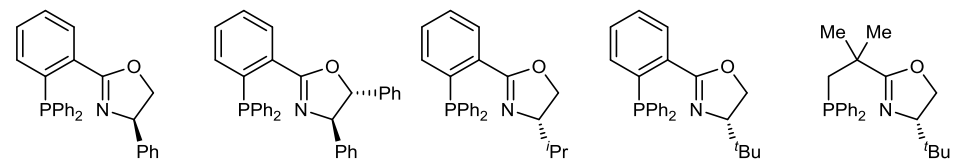
The Lam group has recently had success in developing cyclisation reactions enabled by *E*/*Z*-isomerisation of the alkenylnickel intermediate.[45,46] The aim was to apply this methodology to the synthesis of chiral cyclopent-2-enones *via* a nickel-catalysed desymmetrisation reaction of alkynyl malonate esters with arylboronic acids. This section describes the preliminary results of the project, and the optimisation undertaken.



Scheme 144: Reactions carried out by Dr. S. N. Karad and Dr. C. Clarke

This chemistry was first attempted *via* a desymmetrisation reaction of alkynyl malononitriles and phenylboronic acid. The conditions used were derived from previous work by the group on allylic alkenylation reactions (Scheme 138).[46] Pleasingly, the reaction afforded the desired cyclopent-2-enone in 70% ^{1}H NMR yield (Scheme 144). With this result in hand, chiral ligands were screened to access enantiomerically enriched cyclopent-2-enones.

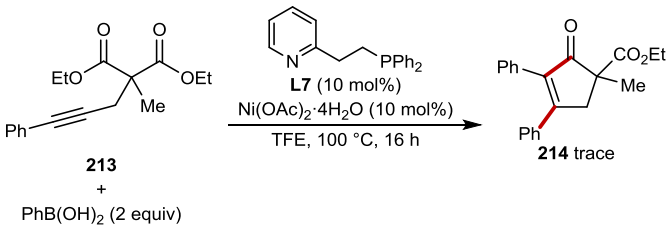




Scheme 145: Reactions carried out by Dr. S. N. Karad and Dr. C. Clarke

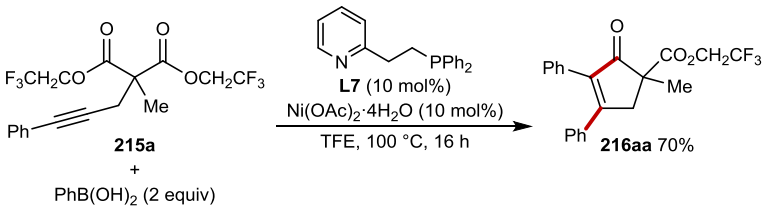
In the groups previous research, there had been success with chiral *P*,*N*-oxazoline based ligands, so these ligands were examined in this transformation (Scheme 145). Whilst yields ranged from moderate to good, the ee's obtained

were poor, ranging from 15-28%. Attention was then turned to modifying the substrate, to obtain the cyclopent-2-enones with improved enantioselectivities.



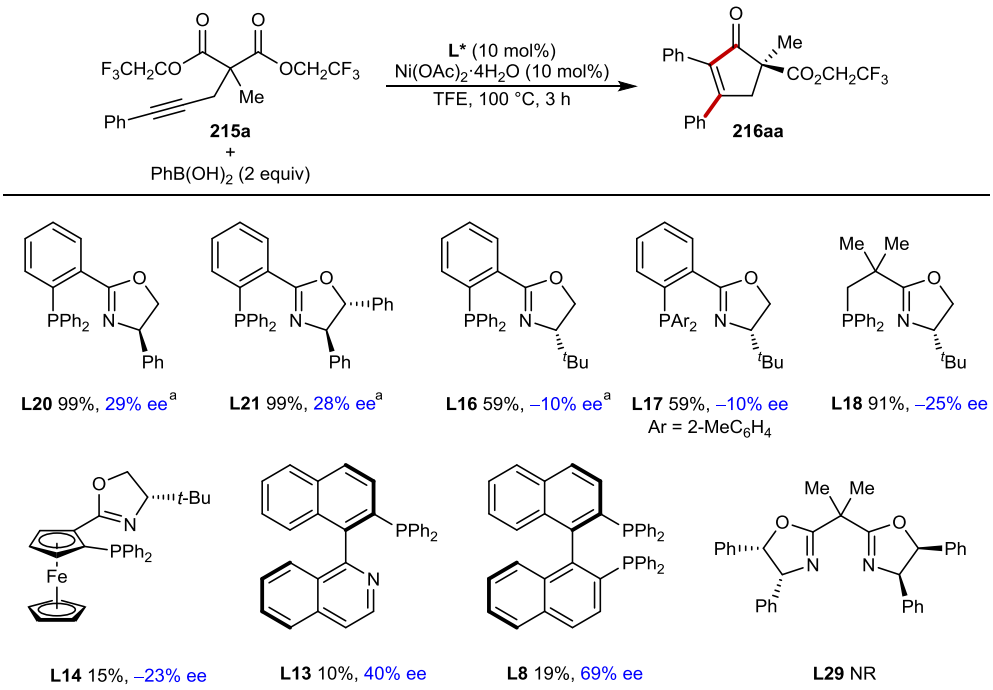
Scheme 146: Reactions carried out by Dr. S. N. Karad and Dr. C. Clarke

Cyclopent-2-enones could also be obtained from alkynyl malonate esters. The reaction was attempted on a substituted diethylmalonate ester, with phenylboronic acid, nickel acetate and achiral ligand pyphos (**L7**). Unfortunately, only a trace quantity of the desired cyclopent-2-enone **214** was observed by ^{1}H NMR spectroscopy (Scheme 146).



Scheme 147: Reactions carried out by Dr. S. N. Karad and Dr. C. Clarke

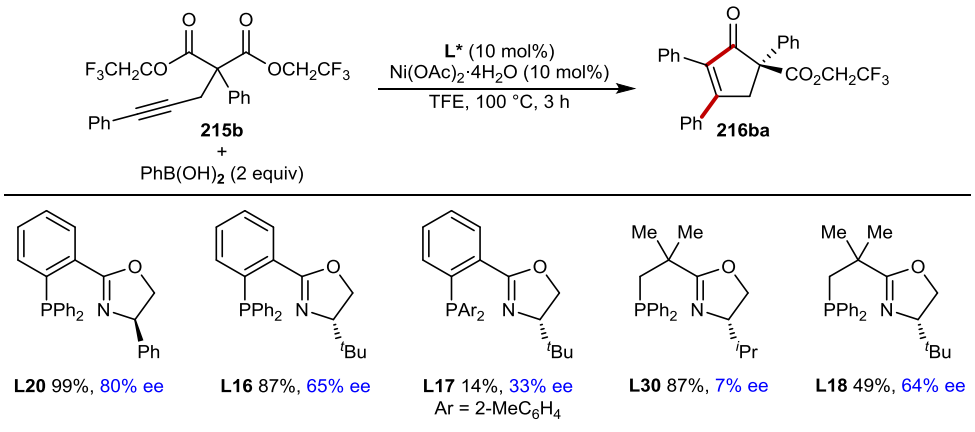
With the electrophilicity of the ester in mind, a substituted trifluoroethyl malonate ester was synthesised. Under the same reaction conditions, the corresponding cyclopent-2-enone **216** was obtained in 70% ^{1}H NMR yield (Scheme 147). This result was more promising, and so ligand screening for enantioselectivitiy was undertaken on the more activated malonate ester substrate.



[a] *These reactions were carried out for 15 h*

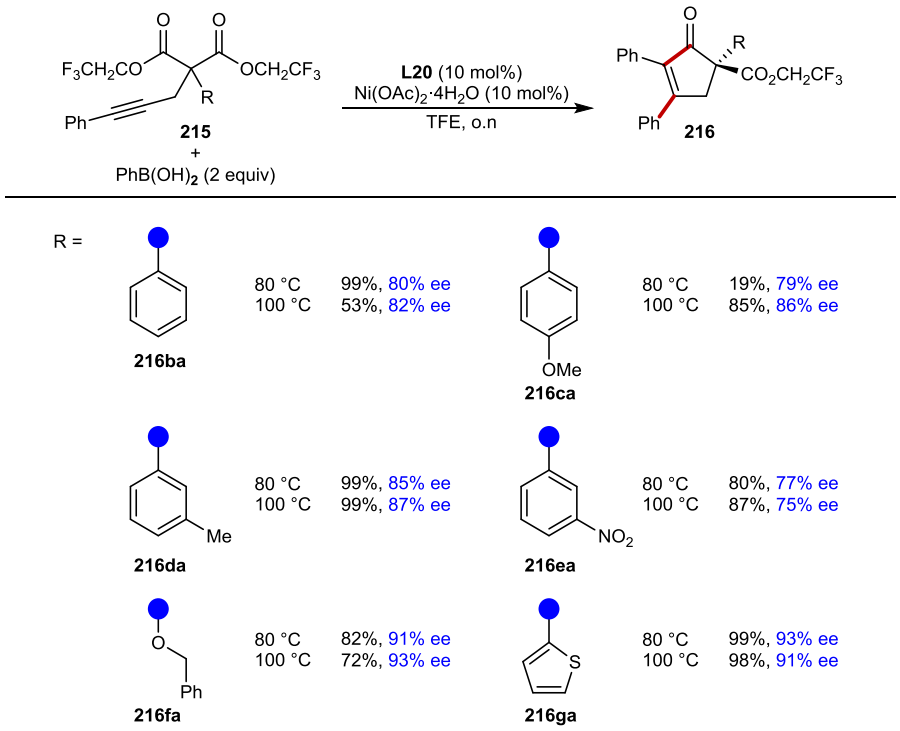
Scheme 148: Reactions carried out by Dr. S. N. Karad and Dr. C. Clarke

Ligand screening reactions were carried out on α-methyl malonate ester **215a**. Success with previous research in formal *anti*-carbometallative nickel catalysed cyclisations prompted an interest in testing *P*,*N* type oxazoline based ligands (Scheme 134-Scheme 138).[45,46] With ligands **L20**, **L21** and **L18**, a high yield of the corresponding cyclopent-2-enone **216aa** was obtained, but with low enantioselectivities. An improvement in the enantioselectivity was achieved with ligands **L13** and **L8**, but the reaction was less efficient than when (*R*)-PhPHOX (**L20**) was used and lower yields were obtained (Scheme 148).



Scheme 149: Reactions carried out by Dr. S. N. Karad and Dr. C. Clarke

Changing the group at the α-position to an aryl group led to an improvement in the NMR yields and enantioselectivity (Scheme 149). **L20** gave an excellent yield and enantioselectivity. (*R*)-PhPhox **L20** was therefore used in subsequent reactions.



Scheme 150: Reactions carried out by Dr. S. N. Karad and Dr. C. Clarke

Following the ligand screening, further variation of the substituent at the α-position and the temperature required was explored. The reactions were tested at both 100 °C and 80 °C, and in most cases, there was little difference in both yields and enantioselecitivies (Scheme 150). With a *para*-methoxyphenyl group at the α-position however, the elevated temperature of 100 °C gave an improved yield and higher ee than when the reaction was carried out at 80 °C.

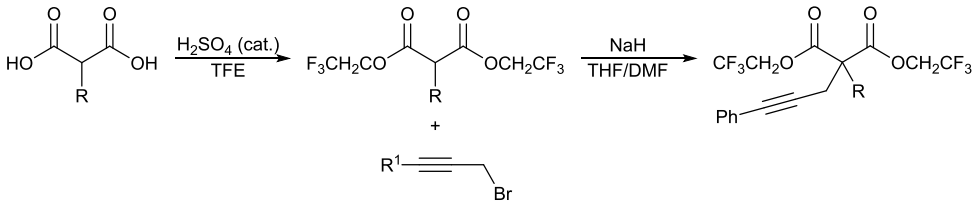
With suitable reaction conditions in hand, the scope and synthetic utility of the transformation was explored.

5. Synthesis of Chiral Cyclopent-2-enones: Results & Discussion

5.1. Aims & Objectives

Continuing the research into nickel-catalysed domino addition-cyclisation reactions, the aims of this project were to synthesise chiral cyclopent-2-enones *via* a desymmetrisation of alkynyl malonate esters.

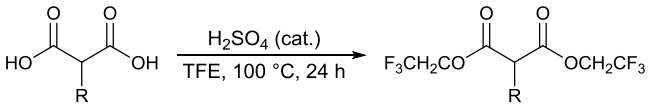
5.2. Synthesis of Substrates



Scheme 151

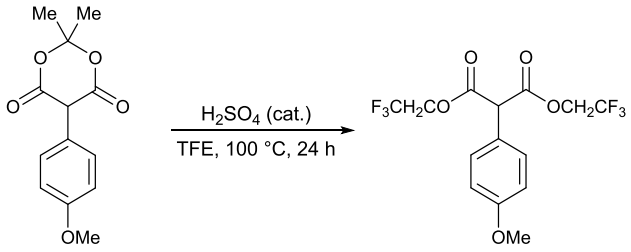
A range of alkynyl malonate esters were synthesised following the overall synthetic route shown in Scheme 151. Commerically available malonic acids were treated with trifluoroethanol under acid catalysis to give the esters. Subsequent alkylation with a range of propargyl bromides gave the corresponding substrates.

5.2.1. Synthesis of α-Substituted Malonates



Scheme 152

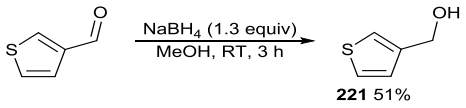
Synthesis of the alkynyl malonate esters was undertaken. α-Substituted malonate esters were synthesised from commercially available malonic acids. Malonic acid and phenylmalonic acid afforded the trifluoroethanol derived esters **217** and **218** in moderate yields (Scheme 152, 23% and 42% respectively).



219 **220** 79%

Scheme 153

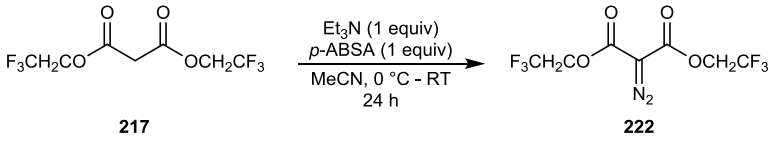
4-Methoxyphenyl substituted malonate ester **220** was obtained in 79% yield from **219** by treatment with trifluoroethanol in the presence of catalytic concentrated sulfuric acid (Scheme 153).



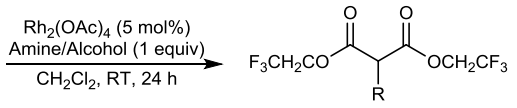
221 51%

Scheme 154

Thien-3-ylmethanol **221** was synthesised *via* a reduction reaction of thiophene-3-carbaldehyde and sodium borohydride (Scheme 154). The resulting alcohol **221** was obtained in 51% yield, and reacted with malonate ester **217**.



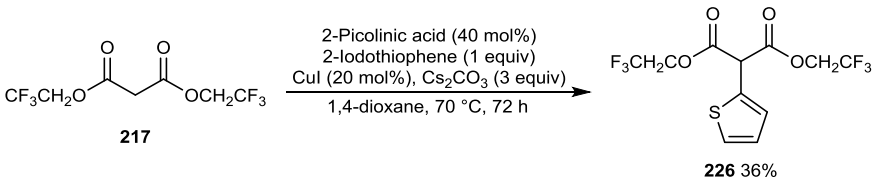
217 **222**



223 R = PhNMe 79%
224 R = *p*-TolNMe 71%
225 R = thien-3-ylmethoxy 82%

Scheme 155

α-Alkoxy and α-amino substituted malonates **223-225** were prepared from diazomalonate ester **221**. Treatment of ester **217** with 4-acetamidobenzenesulfonyl azide (*p*-ABSA) in the presence of triethylamine afforded diazo compound **222**. The reaction of **222** with the relevant alcohol or amine with catalytic rhodium acetate gave the desired alkoxy- or amine-substituted malonate esters **223-225**, *via* an oxygen- or nitrogen- insertion reaction, in good yields (Scheme 155).[89]

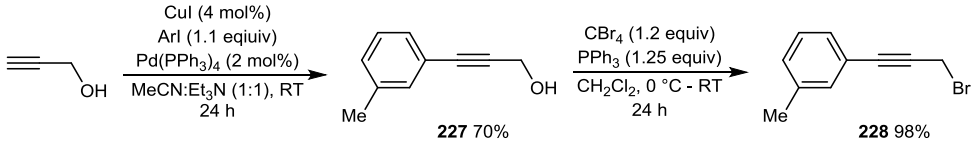


217 **226** 36%

Scheme 156

α-Thiophene substituted malonate ester **226** was obtained in 36% yield from a copper-catalysed arylation reaction with 2-iodothiophene from **217** (Scheme 156).

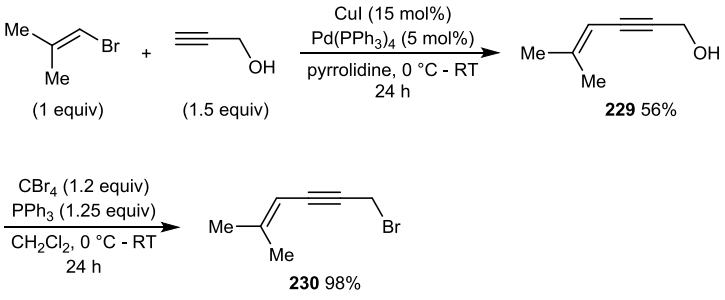
5.2.2. Synthesis of Substituted Propargyl Bromides



227 70% **228** 98%

Scheme 157

With a selection of α-substituted malonate esters in hand, the alkyne portion of the substrate was synthesised. Starting from commercially available propargyl alcohol, a Sonogashira reaction with a 3-methyliodobenzene afforded the aryl-substituted propargyl alcohol **227** in 70% yield (Scheme 157). An Appel reaction with carbon tetrabromide and triphenylphosphine gave the substituted propargyl bromide **228** in an excellent 98% yield (Scheme 157). Other aryl-substituted propargyl bromides were synthesised in an analogous fashion.



229 56%

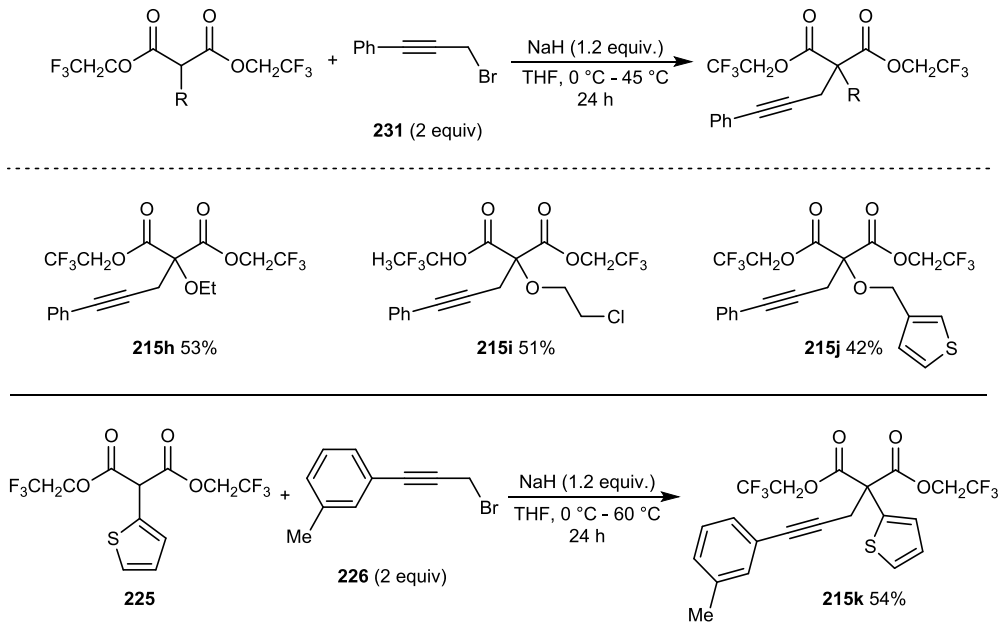
230 98%

Scheme 158

To synthesise an alkene-substituted propargyl bromide, propargyl alcohol was subjected to a Sonogashira cross-coupling with 1-bromo-2-methyl-1-propene. Enyne **229** was obtained in a modest 56% yield (Scheme 158). An Appel reaction afforded bromide **230** in an excellent 98% yield (Scheme 158).

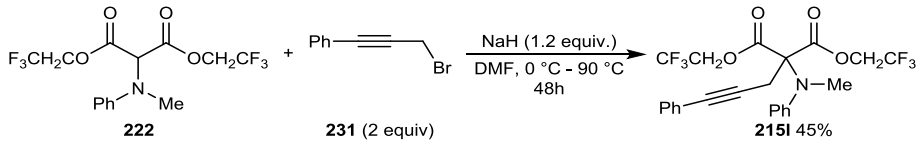
5.2.3. Synthesis of Alkynyl Malonate Esters

With a series of substituted malonate esters and substituted propargyl bromides in hand, alkylation reactions were carried out to give the final substrates.



Scheme 159

The malonate esters were reacted with the relevant propargyl bromides in the presence of sodium hydride. α-Alkoxy-substituted malonate esters underwent alkylation at 45 °C with propargyl bromide **231** to give the corresponding products in moderate yields (Scheme 159, **215h**: 53%, **215i**: 51%, **215j**: 42%). 2-Thiophene substituted malonate ester **225** underwent alkylation successfully at 60 °C with 3-methylphenylpropargyl bromide **226** to give **215k** in a moderate 54% yield (Scheme 159).



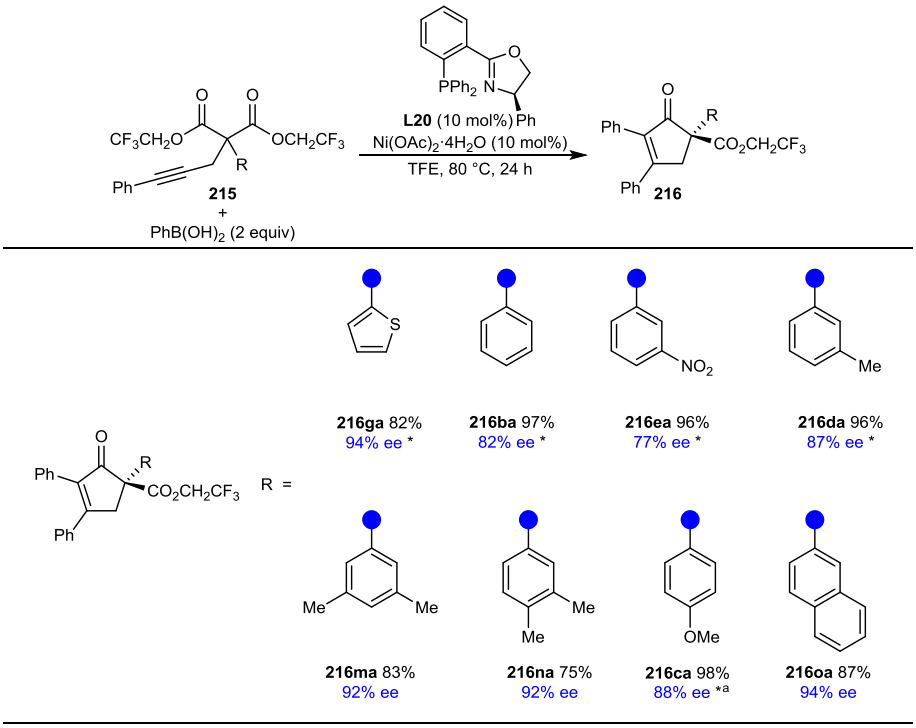
Scheme 160

The analogous reaction with *N*-methylaniline malonate ester **222** and propargyl bromide **231** was unsuccessful. Fortunately, switching the solvent to DMF and elevating the temperature afforded the corresponding malonate ester **215l** in a modest 45% yield (Scheme 160).

5.3. Enantioselective Synthesis of Chiral Cyclopent-2-enones

With a series of substrates in hand, the scope of the transformation was investigated with phenylboronic acid. Variation of the substituents at the α-position and alkyne were examined.

5.3.1. Malonate Scope

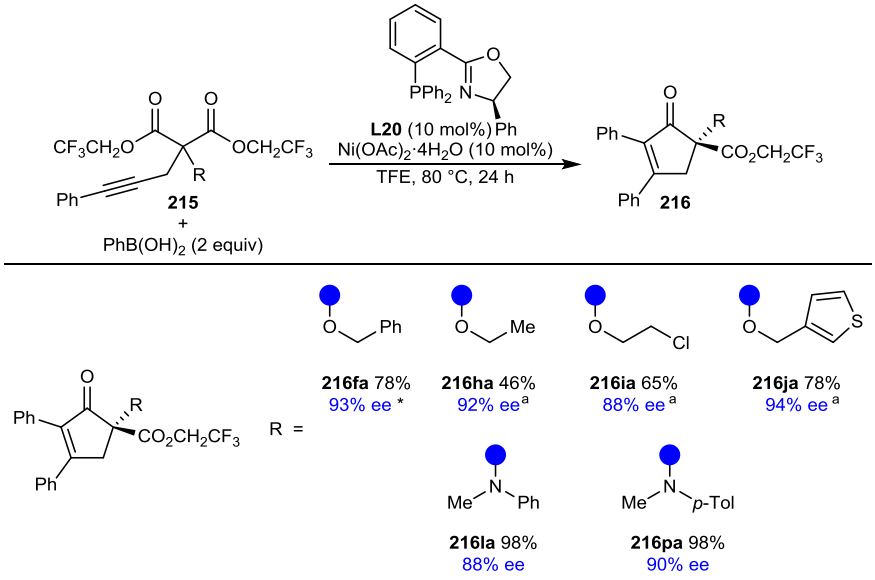


[a] *This reaction was carried out at 100 °C*

Scheme 161: * These reactions were carried out by either Dr. S. N. Karad and Dr. C. Clarke.

Pleasingly, aryl and heteroaryl groups at the α-position were well-tolerated (Scheme 161). α-2-Thienyl substituted malonate **215g** afforded the corresponding cyclopent-2-enone **216ga** in an excellent 82% yield and 94% ee. The absolute stereochemistry was confirmed by X-ray crystallography, by Dr. S. N. Karad. α-Phenyl substituted malonate **215b** also gave cyclopent-2-enone **216ba** in an excellent 97% yield and 82% ee. A variety of substituents on the aryl ring were also well-tolerated. Electron-poor groups (*m*-NO_2, **216ea**, 96% yield, 77% ee) and electron-rich groups (*p*-OMe, **216ca** 98% yield, 88% ee) were well-tolerated, with *para*-methoxyphenyl substituted malonate ester **215c** requiring an elevated temperature of 100 °C to improve the yield. 3-Methyl **215d**, 3,5-dimethyl, **215m** and 3,4-dimethyl **215n** substituents on the α-phenyl ring also gave the corresponding cyclopent-2-enones in excellent yields and

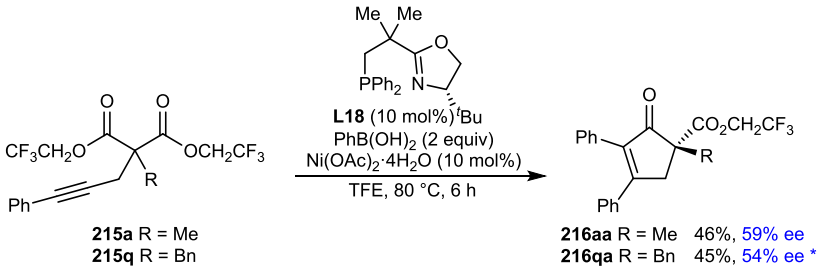
ee's (75-96% yield, 87-92% ee). α-2-Naphthyl substituted malonate ester **215o** was also successfully reacted, giving cyclopent-2-enone **216oa** in an 87% yield and 94% ee.



[a] *These reactions were carried out using 20 mol% $Ni(OAc)_2 \cdot 4H_2O$ & 20 mol%* ***LX***

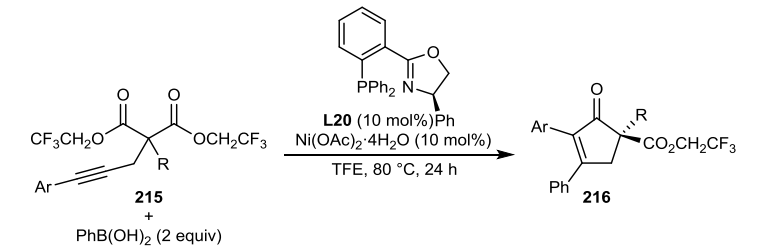
Scheme 162: * This reaction was carried out by either Dr. S. N. Karad or Dr. C. Clarke

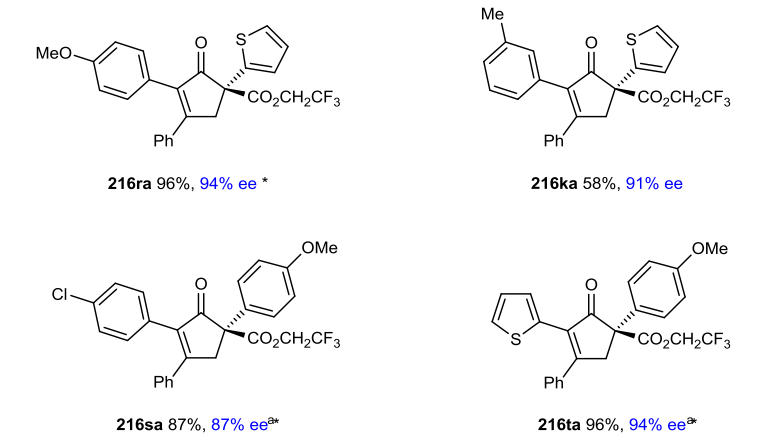
Interestingly, the transformation was not limited to aryl substituents at the α-position, and α-benzyloxy substituted malonate ester **215f** also afforded the corresponding cyclopent-2-enone **216fa** in 78% yield and 93% ee (Scheme 162). Other alkoxy substituted malonate esters were also investigated. Unfortunately, the reaction between α-ethoxy substituted malonate ester **215h** and phenylboronic acid was unsuccessful under the usual reaction conditions, and even at an elevated temperature (100 °C), only starting material was observed. Fortunately, increasing the catalyst loading to 20 mol% gave cyclopent-2-enone **216ha** in a moderate 46% yield and 92% ee. Similar issues were observed with α-thiophen-3-ylmethoxy substituted malonate ester **215i** and α-chloroethoxy substituted malonate ester **215j**. An increased catalyst loading of 20 mol% gave the corresponding cyclopent-2-enones in good yields, and excellent ee's (Scheme 162, **216ja**, 78%, 94% ee, and **216ia**, 65% yield, 88% ee). Pleasingly, *N*-methylaniline and *N*-methyl-*p*-toluidine substituted malonate esters **215l** and **215p** also underwent cyclisation successfully, affording the corresponding cyclopent-2-enones **216la** and **215pa** in an excellent yield and ee.



Scheme 163: * This reaction was carried out by Dr. S. N. Karad.

For α-alkyl substituted malonate esters **215a** and **215q**, it was evident from prior screening that (*R*)-PhPHOX (**L20**) was a less suitable ligand (Scheme 148). Changing the ligand to (*S*)-*tert*-butyl NeoPHOX (Scheme 163, **L18**) however afforded the desired α-methyl and α-benzyl cyclopentenones **216aa** and **216qa** in moderate yields (46% & 45% respectively), with modest ee's (59% and 54% respectively).



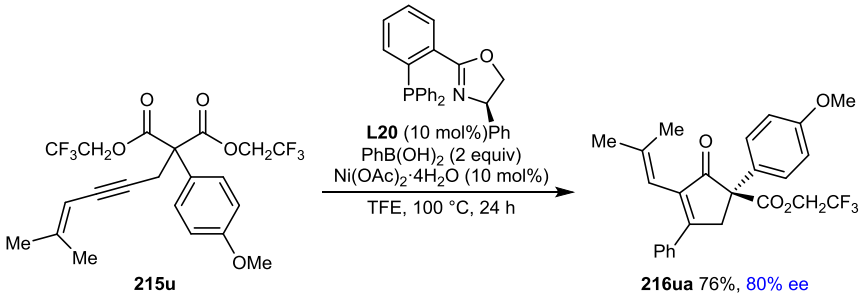


[a] *These reactions were carried out at 100 °C.*

Scheme 164: * These reactions carried out by either Dr. S. N. Karad or Dr. C. Clarke.

The scope with respect to substitution at the alkyne was also investigated (Scheme 164). Pleasingly, both substituted phenyl rings and heteroaryl systems were well-tolerated. Malonate ester **215r** with electron-rich *para*-methoxyphenyl group at the alkyne reacted successfully to give **216ra** in an excellent yield and enantioselectivity (96% and 94% ee). 3-Methylphenyl- and 4-chlorophenyl- groups at the alkyne were also tolerated, and gave cyclopent-

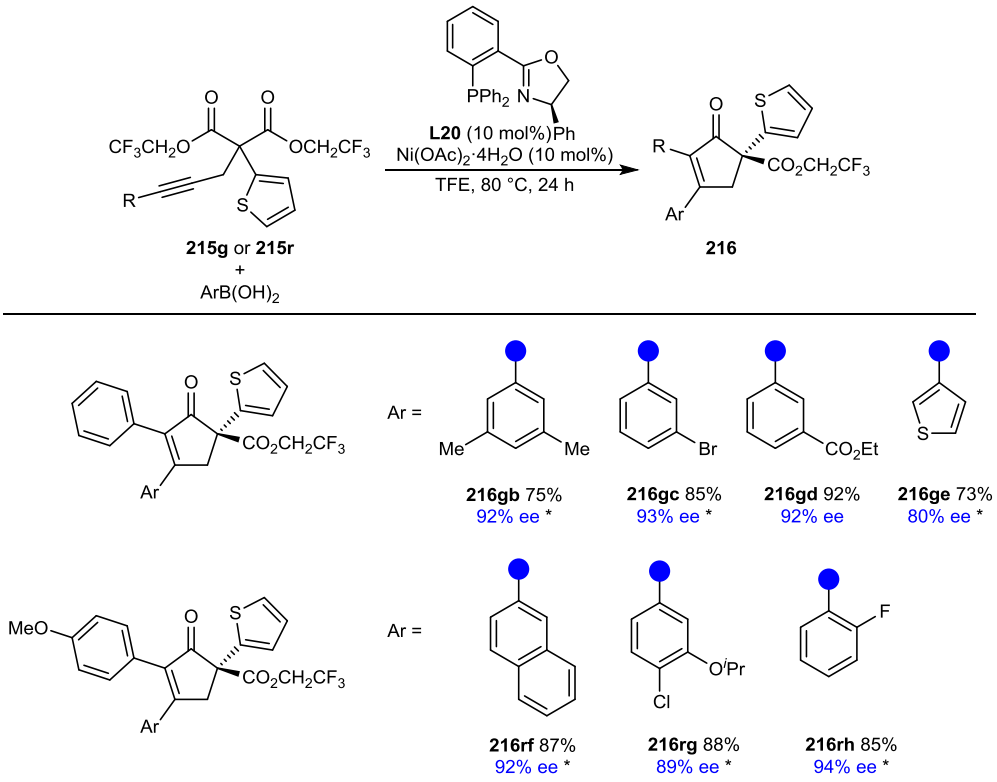
2-enones **216ka** and **216sa** in moderate to good yields, and good ee (58%, 91% ee and 87%, 87% ee respectively). A 2-Thiophene group at the alkyne was also tolerated, yielding the cyclopent-2-enone **216ta** in an excellent yield and ee (96%, 94% ee). Reactions with the *para*-methoxyphenyl group at the α-position required elevated temperatures to afford the desired products.



Scheme 165

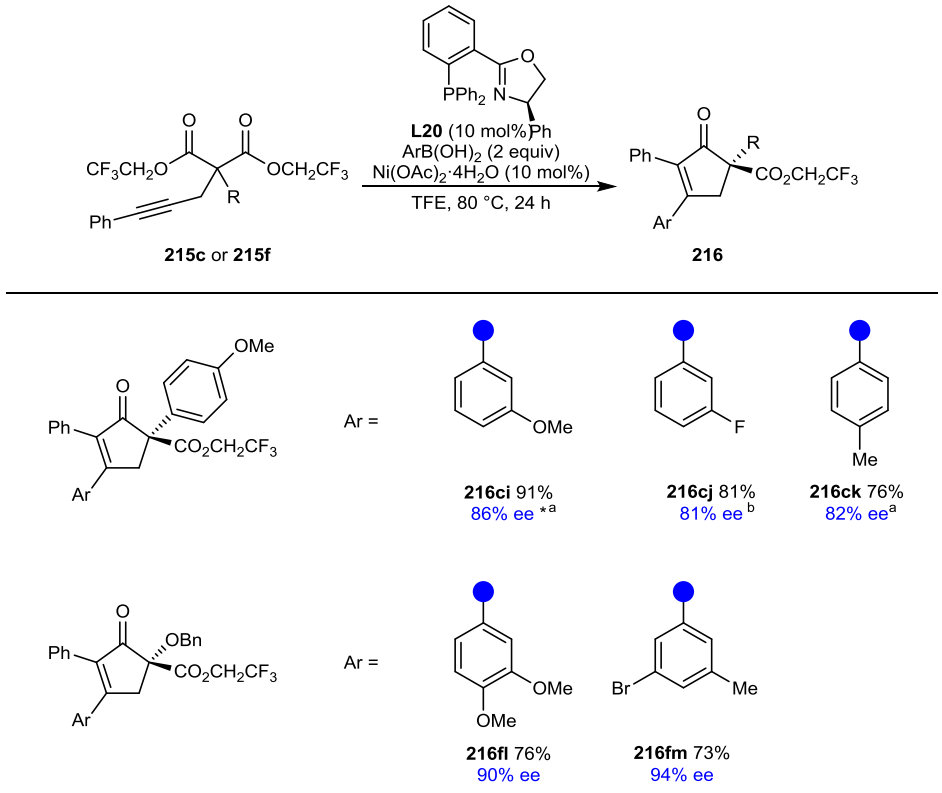
Fortuitously, the transformation was not limited to aryl substitution patterns at the alkyne. The reaction with enyne substituted malonate ester **215u** reacted successfully to give cyclopent-2-enone **216ua** in good yield and enantioselectivity (Scheme 165, 76%, 80% ee).

5.3.2. Boronic Acid Scope



Scheme 166: * These reactions carried out by either Dr. S. N. Karad or Dr. C. Clarke

Following the exploration of the substrate scope, various substituted arylboronic acids were also investigated. A range of boronic acids were reacted with two α-thiophene-substituted malonates **215g** and **215r**. Pleasingly, a range of substituted phenylboronic acids were well-tolerated. Mono-substituted boronic acids worked well, with 3-bromo-, 3-carboethoxy, and 2-fluorophenylboronic acids affording the corresponding chiral cyclopent-2-enones **216gc**, **216gd** and **216rh** in excellent yields and ee's (Scheme 166). 2-Naphthylboronic acid and 3-thienylboronic acid also afforded the corresponding cyclopentenones **216rf** and **216ge** in good yields and enantioselectivities. With these two substrates, two disubstituted phenylboronic acids were also tested. 3,5-Dimethylphenylboronic acid afforded cyclopent-2-enone **216gb** in good yield and excellent enantioselectivity (75% and 92% ee). 3-*iso*-Propoxy-4-chlorophenyl boronic acid was also well tolerated, affording the desired cyclopentenone **216rg** in 88% yield and 89% ee (Scheme 166).



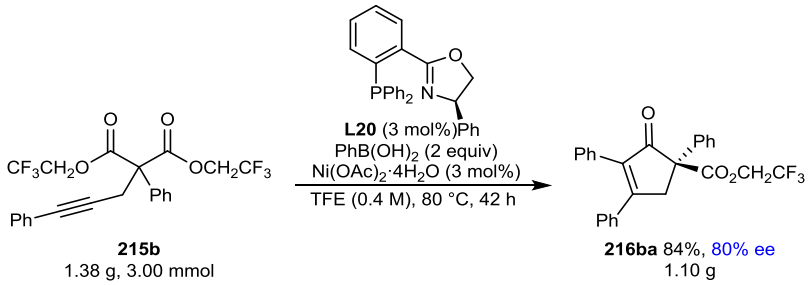
[a] *These reactions were carried out at 100 °C.* [b] *This reaction was carried out at 120 °C.*

Scheme 167: * This reaction was carried out by either Dr. S. N. Karad and Dr. C. Clarke

Further exploration of the scope with the substituted phenylboronic acids and α-*para*-methoxyphenyl and α-benzyloxy malonate esters **215c** and **215f** was

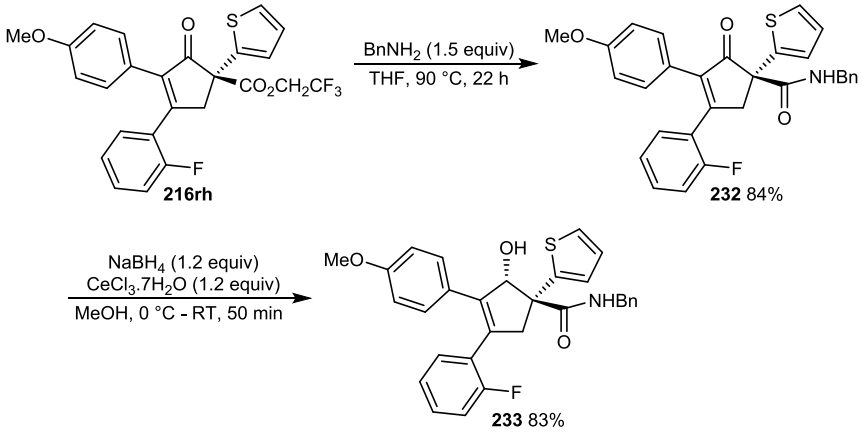
also undertaken. Both electron-rich, neutral and electron-poor substitution patterns on the boronic acids were well tolerated. All reactions with malonate ester **215c** required the higher temperature of 100 °C to obtain the good to excellent yields. Interestingly, the reaction with 3-fluorophenylboronic required a higher temperature still, with cyclopent-2-enone **216cj** obtained in 81% yield and 81% ee at 120 °C (Scheme 167).

5.4. Scalability and Further Transformations



Scheme 168: Reaction carried out by Dr. S. N. Karad.

The scalability of the reaction was also investigated. A gram-scale reaction was carried out on substrate **215b**, and cyclopent-2-enone **216ba** was obtained in an excellent 84% yield and 80% ee. Furthermore, this was achieved with a lower catalyst loading of 3 mol%, and increased reaction concentration of 0.4 M (Scheme 168). It is worth noting however, that this reaction required a longer reaction time of 42 hours.

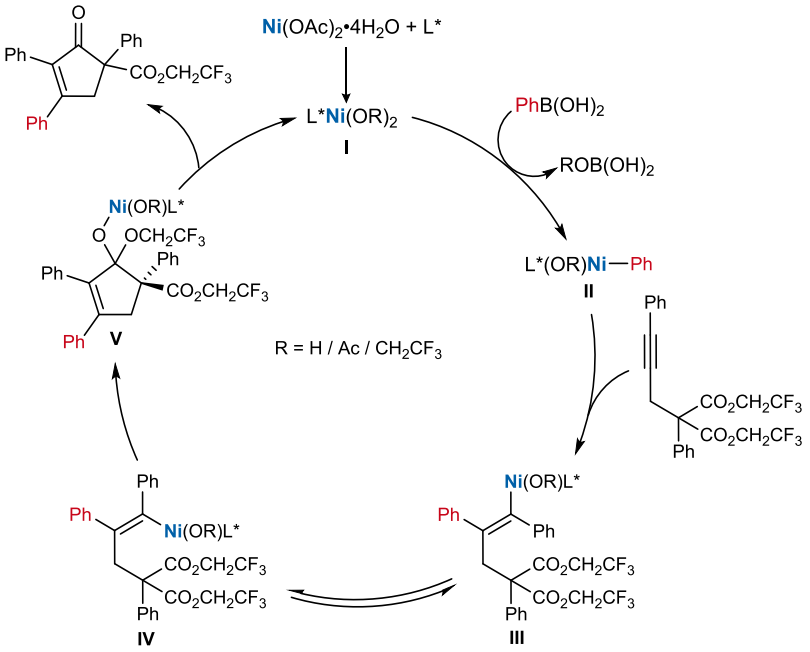


Scheme 169: Reactions carried out by Dr. S. N. Karad

To demonstrate the synthetic utility of the products, further transformations were undertaken, as trifluoroethyl esters are not common moieties in biologically active compounds or in natural products. Pleasingly, treatment of the cyclopent-2-enone **216rh** with benzylamine gave the corresponding amide

232 in 84% isolated yield (Scheme 169). Subsequent Luche reduction of the amide **232** gave alcohol **233** as a single observable diastereoisomer, in 83% isolated yield without purification.

5.5. Proposed Catalytic Cycle



Scheme 170

Based on previous literature and research in the group, a catalytic cycle is proposed (Scheme 170).[45,46] Coordination of the nickel-catalyst and the chiral ligand give the active catalytic species **I**. Transmetallation of the arylboronic acid gives the aryl-nickel complex **II**. Coordination to the alkyne followed by *syn*-selective migratory insertion of the arylnickel across the alkyne gives the alkenylnickel intermediate **III**. Reversible *E*/*Z* isomerisation of the alkenylnickel species gives intermediate **IV**, facilitating cyclisation. Cyclisation generates the nickel-alkoxide complex **V**, which then gives the corresponding cyclopent-2-enone after elimination of the ester group and regenerates the nickel catalyst.

6. Conclusions and Future Work

6.1. Conclusions

The enantioselective nickel-catalysed synthesis of chiral cyclopent-2-enones is described. The reaction is enabled by the reversible *E*/*Z*-isomerisation of the alkenylnickel species generated from migratory insertion of the arylnickel across the alkyne. Development of this methodology from its first report in 2016 has enabled access to a wider range of compound classes. The reaction between arylboronic acids and alkynyl malonate esters gives the corresponding cyclopent-2-enones in excellent yields and enantioselectivities.

With this research, the potential for scaling up is demonstrated. The reaction can tolerate a lower catalyst and ligand loading, as well as an increased concentration. The products can also be successfully manipulated to generate amides and alcohols.

6.2. Future Work

Whilst this methodology has been demonstrated on a range of substrate classes, the mechanism of addition and isomerisation is still unknown. Reaction monitoring and further research could aid in elucidating a more detailed explanation of the observed reactivity.

This work has demonstrated that arylboronic acids readily transmetallate and add across alkynes regioselectively. So far however, the methodology is limited to arylboronic acids. The scope of the transformation could be improved further if alkenyl- or alkylboronic acids also reacted successfully. Research into using other organometallic precursors such as organozincs or organoaluminium based compounds could also be beneficial.

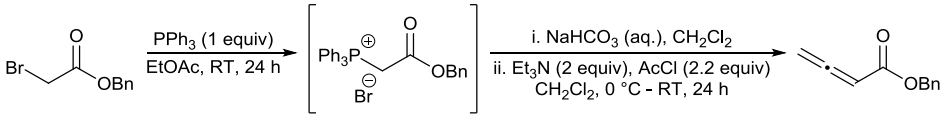
7. Experimental Section: General Information

All air-sensitive reactions were carried out under an inert atmosphere using oven-dried apparatus. All commercially available reagents were used as received unless otherwise stated. Petroleum ether refers to Sigma-Aldrich product 24587 (petroleum ether boiling point 40-60 °C). Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien 60F254 0.2 mm precoated plates. Compounds were visualised by exposure to UV light or by dipping the plates into solutions of potassium permanganate or vanillin followed by gentle heating. Flash column chromatography was carried out using silica gel (Fisher Scientific 60 Å particle size 35-70 micron or Fluorochem 60 Å particle size 40-63 micron). Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. The abbreviation (dec.) in parentheses refers to decomposition of the compound. The solvent of recrystallisation is reported in parentheses. Infrared (IR) spectra were recorded on Bruker platinum alpha FTIR spectrometer on the neat compound using the attenuated total reflection technique. NMR spectra were acquired on Bruker Ascend 400 or Ascend 500 spectrometers. ^{1}H and ^{13}C NMR spectra were referenced to external tetramethylsilane *via* the residual protonated solvent (^{1}H) or the solvent itself (^{13}C). Solvents were referenced as follows: $CDCl_3$: ^{1}H - 7.26; ^{13}C - 77.16; $(CD_3)_2CO$: ^{1}H - 2.05; ^{13}C - 206.26; $(CD_3)_2SO$: ^{1}H - 7.26; ^{13}C - 39.52; CD_3CN: ^{1}H - 2.50; ^{13}C - 118.26. All spectra were obtained at 298 K unless otherwise stated. All chemical shifts are reported in parts per million (ppm). Carbon spectra are proton decoupled unless otherwise stated. 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°. ^{19}F NMR spectra and ^{31}P NMR spectra were referenced through the solvent lock (^{2}H) signal according to IUPAC-recommended secondary referencing method according to Bruker protocols. ^{19}F, ^{11}B and ^{31}P spectra are not proton decoupled unless otherwise stated. NMR yields were measured against an internal standard (1,3,5-trimethoxybenzene). Abbreviations used in the description of resonances in ^{1}H NMR spectra are: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), hex (hextet), hept (heptet), app (apparent), br (broad) and m (multiplet). Characterisation abbreviations are as follows: Ar (aromatic); Al (aliphatic). High-resolution mass spectra were recorded using electrospray ionization (ESI) or

gas chromatography mass spectrometry (GC/MS) techniques. 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 1200 series instrument using 4.6 × 250 mm columns. Solvents were dried over alumina columns under Ar.

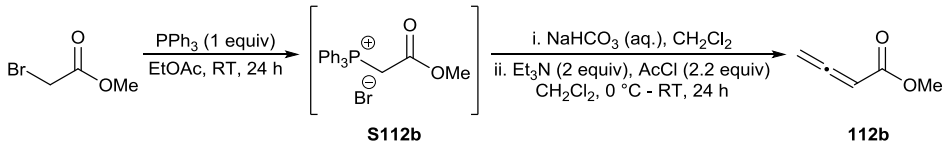
8. Experimental: Synthesis of 3-methyleneindan-1-ols

8.1. Synthesis of Allenes



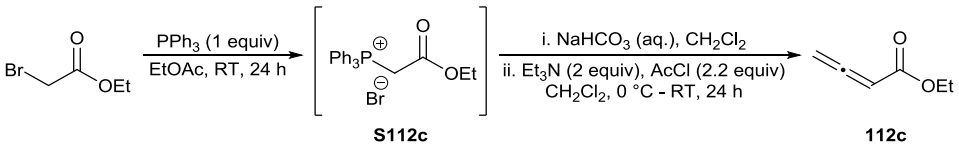
Benzyl buta-2,3-dienoate (112a). To a flask charged with PPh_3 (26.2 g, 100 mmol) in ethyl acetate (150 mL) was added benzyl bromoacetate (9.5 mL, 100 mmol). The resulting suspension was stirred at room temperature overnight. The phosphonium salt was isolated *via* vacuum filtration and used directly in the next step (assumed quantitative).

Phosphonium salt **S112a** was dissolved in CH_2Cl_2 (200 mL) and poured into a separating funnel and washed with saturated aqueous $NaHCO_3$ (3 × 150 mL), brine (150 mL), dried (Na_2SO_4), filtered and concentrated. The ylide was then dissolved in CH_2Cl_2 (100 mL) and cooled to 0 °C. Et_3N (14.0 mL, 100 mmol) was added followed by acetyl chloride (10.0 mL, 110 mmol) and the resulting solution was warmed to room temperature and stirred overnight. Then, the reaction mixture was cooled to 0 °C and a second equivalent of Et_3N (14.0 mL, 100 mmol) was added followed by a second equivalent of acetyl chloride (10.0 mL, 110 mmol). The resulting solution was warmed to room temperature and stirred for 1 h, then concentrated. The residue was suspended in petroleum ether/EtOAc (9:1, 250 mL) and silica was added. The suspension was stirred vigorously at room temperature for 40 min then filtered and concentrated. Purification by column chromatography (5% EtOAc/petroleum ether) gave the title compound as a colourless oil (3.91 g, 33%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.36 (4H, m, Ar**H**), 7.36-7.31 (1H, m, Ar**H**), 5.69 (1H, t, *J* = 6.6 Hz, C**H**), 5.24 (2H, d, *J* = 6.6 Hz, =C**H**$_2$), 5.20 (2H, s, C**H**$_2$Ph); ^{13}C NMR (126 MHz, $CDCl_3$) δ 216.1 (C), 165.7 (C), 136.0 (C), 128.7 (2 × CH), 128.4 (CH), 128.3 (2 × CH), 88.0 (CH), 79.6 (CH_2), 66.8 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{11}H_{10}O_2Na]^+$ $[M+Na]^+$: 197.0573, found: 197.0571. Spectroscopic data consistent with those previously reported.[90]



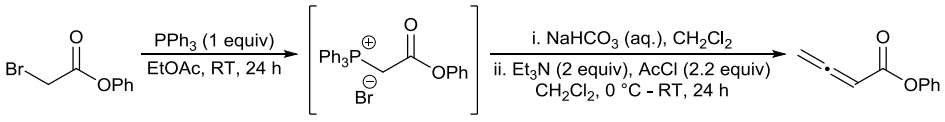
Methyl buta-2,3-dienoate (112b). To a flask charged with PPh_3 (26.2 g, 100 mmol) in ethyl acetate (150 mL) was added methyl bromoacetate (9.5 mL, 100 mmol). The resulting suspension was stirred at room temperature overnight. The phosphonium salt was isolated *via* vacuum filtration and used directly in the next step (assumed quantitative).

Phosphonium salt **S112b** was dissolved in CH_2Cl_2 (200 mL) and poured into a separating funnel and washed with saturated aqueous $NaHCO_3$ (3 × 150 mL), brine (150 mL), dried (Na_2SO_4), filtered and concentrated. The ylide was then dissolved in CH_2Cl_2 (100 mL) and cooled to 0 °C. Et_3N (14.0 mL, 100 mmol) was added followed by acetyl chloride (10.0 mL, 110 mmol) and the resulting solution was warmed to room temperature and stirred overnight. Then, the reaction mixture was cooled to 0 °C and a second equivalent of Et_3N (14.0 mL, 100 mmol) was added followed by a second equivalent of acetyl chloride (10.0 mL, 110 mmol). The resulting solution was warmed to room temperature and stirred for 1 h, then concentrated. The residue was suspended in petroleum ether/EtOAc (9:1, 250 mL) and silica was added. The suspension was stirred vigorously at room temperature for 40 min then filtered and concentrated. Purification by column chromatography (10% Et_2O/*n*-pentane) gave the title compound as a colourless oil (2.69 g, 27%). IR 2955, 1971, 1942, 1895, 1862, 1716 (C=O), 1438, 1344, 1302, 1261, 1238, 1195, 1165, 1080, 1009 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.64 (1H, t, *J* = 6.6 Hz, =C**H**), 5.22 (2H, d, *J* = 6.6 Hz, =C$\mathbf{H}_2$), 3.75 (3H, s, OC$\mathbf{H}_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 216.0 (C), 166.3 (C), 87.9 (CH), 79.4 (CH_2), 52.3 (CH_3). Spectroscopic data consistent with those previously reported.[91]



Ethyl buta-2,3-dienoate (112c). To a flask charged with PPh_3 (26.2 g, 100 mmol) in ethyl acetate (150 mL) was added ethyl bromoacetate (11.1 mL, 100 mL). The resulting suspension was stirred at room temperature overnight. The phosphonium salt was isolated *via* vacuum filtration and used directly in the next step (assumed quantitative).

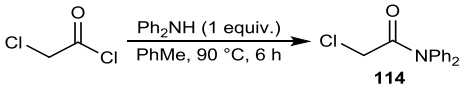
Phosphonium salt **S112c** was dissolved in CH_2Cl_2 (200 mL) and poured into a separating funnel and washed with saturated aqueous $NaHCO_3$ (3 × 150 mL), brine (150 mL), dried (Na_2SO_4), filtered and concentrated. The ylide was then dissolved in CH_2Cl_2 (100 mL) and cooled to 0 °C. Et_3N (14 mL, 100 mmol) was added followed by acetyl chloride (10.0 mL, 110 mmol) and the resulting solution was warmed to room temperature and stirred overnight. Then, the reaction mixture was cooled to 0 °C and a second equivalent of Et_3N (14 mL, 100 mmol) was added followed by a second equivalent of acetyl chloride (10.0 mL, 110 mmol). The resulting solution was warmed to room temperature and stirred for 1 h, then concentrated. The residue was suspended in petroleum ether/EtOAc (9:1, 250 mL) and silica was added. The suspension was stirred vigorously at room temperature for 40 min then filtered and concentrated. Purification by column chromatography (5% EtOAc/petroleum ether) gave the title compound as a colourless oil (11.2 g, 10%). IR 2985, 1970, 1941,1712 (C=O), 1640, 1466, 1425, 1391, 1369, 1333, 1299, 1254, 1161, 1095, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.63 (1H, t, *J* = 6.5 Hz, C**H**), 5.22 (2H, d, *J* = 6.5 Hz, =C**H**$_2$), 4.21 (2H, q, *J* = 7.1 Hz, OC**H**$_2$CH$_3$), 1.29 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.9 (C), 165.9 (C), 88.2 (CH), 79.4 (CH_2), 61.2 (CH_2), 14.4 (CH_3). Spectroscopic data consistent with those previously reported.[90]



Phenyl buta-2,3-dienoate (112f). To a flask charged with PPh_3 (6.11 g, 23.3 mmol) in ethyl acetate (24 mL) was added phenyl bromoacetate (5.00 g, 23.3 mmol). The resulting suspension was stirred at room temperature overnight.

The phosphonium salt was isolated *via* vacuum filtration and used directly in the next step (assumed quantitative).

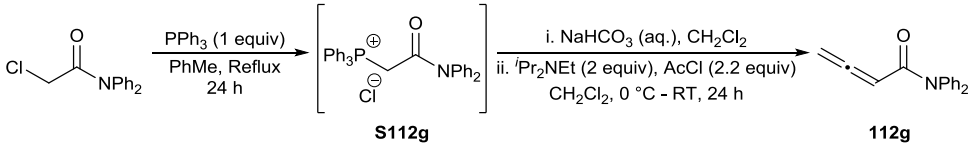
Phosphonium salt **S112f** was dissolved in CH_2Cl_2 (60 mL) and poured into a separating funnel and washed with saturated aqueous $NaHCO_3$ (3 × 50 mL), brine (50 mL), dried (Na_2SO_4), filtered and concentrated. The ylide was then dissolved in CH_2Cl_2 (25 mL) and cooled to 0 °C. Et_3N (3.24 mL, 23.3 mmol) was added followed by acetyl chloride (1.82 mL, 25.6 mmol) and the resulting solution was warmed to room temperature and stirred overnight. Then, the reaction mixture was cooled to 0 °C and a second equivalent of Et_3N (3.24 mL, 23.3 mmol) was added followed by a second equivalent of acetyl chloride (1.82 mL, 25.6 mmol). The resulting solution was warmed to room temperature and stirred for 1 h, then concentrated. The residue was suspended in petroleum ether/EtOAc (9:1, 200 mL) and silica was added. The suspension was stirred vigorously at room temperature for 40 min then filtered and concentrated. Purification by column chromatography (5% EtOAc/petroleum ether) gave the title compound as a colourless oil (878 mg, 24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.36 (2H, m, Ar**H**), 7.24 (1H, app ddt, *J* = 7.9, 6.9, 1.2 Hz, Ar**H**), 7.16-7.11 (2H, m, Ar**H**), 5.83 (1H, t, *J* = 6.5 Hz, C**H**), 5.34 (2H, d, *J* = 6.5 Hz, =C**H**$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 216.7 (C), 164.3 (C), 150.9 (C), 129.5 (2 × CH), 126.0 (CH), 121.7 (2 × CH), 87.8 (CH), 79.9 (CH-$_2$); HRMS (ESI) Exact mass calculated for $[C_{10}H_8O]^+$ $[M+H]^+$: 161.0597, found: 161.0604. Spectroscopic data consistent with those previously reported.[92]



114

2-Chloro-*N*,*N*-diphenylacetamide (**114)**. To a flask charged with diphenylamine (20.3 g, 120 mmol) in toluene (300 mL) was added chloroacetylchloride (9.55 mL, 120 mmol) drop-wise. The resulting solution was stirred at 90 °C for 6 h then cooled and concentrated. The solid was dissolved in CH_2Cl_2 and washed with sat. $NaHCO_3$ solution (3 × 100 mL), then filtered over silica (CH_2Cl_2) and concentrated to give the title compound (24.8 g, 84%) as a colourless solid. m.p 118-120 °C (Et_2O); ^{1}H NMR (500

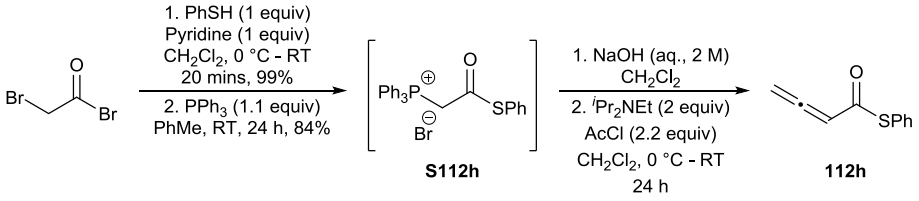
MHz, $(CD_3)_2SO$, 343 K) δ 7.50-7.37 (8H, m, Ar**H**), 7.36-7.29 (2H, m, Ar**H**), 4.15 (2H, s, C**H**$_2$); ^{13}C NMR (126 MHz, $(CD_3)_2SO$, 343 K) δ 165.1 (C), 141.8 (2 × C), 129.1 (4 × CH), 127.2 (br, 6 × CH), 42.5 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{14}H_{12}ClNNaO]^+$ $[M+Na]^+$: 268.0500, found: 268.0495. Spectroscopic data consistent with those previously reported.[93]



***N*,*N*-Diphenylbuta-2,3-dienamide (112g)**. To a flask charged with PPh_3 (22.3 g, 84.9 mmol) in toluene (85 mL) was added 2-chloro-*N*,*N*-diphenylacetamide (20.9 g, 84.9 mmol). The resulting suspension was stirred at reflux overnight then cooled to room temperature. The phosphonium salt was isolated *via* vacuum filtration (43.1 g, 92%).

Phosphonium salt **S112g** (1.00 g, 1.97 mmol) was dissolved in CH_2Cl_2 (50 mL) and poured into a separating funnel and washed with saturated aqueous $NaHCO_3$ (3 × 50 mL), brine (50 mL), dried (Na_2SO_4), filtered and concentrated. The ylide was then dissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C. $^{i}Pr_2NEt$ (0.34 mL, 1.97 mmol) was added followed by acetyl chloride (0.15 mL, 2.17 mmol) and the resulting solution was warmed to room temperature and stirred overnight. Then, the reaction mixture was cooled to 0 °C and a second equivalent of $^{i}Pr_2NEt$ (0.34 mL, 1.97 mmol) was added followed by a second equivalent of acetyl chloride (0.15 mL, 2.17 mmol). The resulting solution was warmed to room temperature and stirred for 1 h, then water was added and the suspension was stirred at room temperature for 15 min, then extracted with CH_2Cl_2 (3 × 20 mL). The combined organics were washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (10-30% EtOAc/petroleum ether) gave the title compound as a colourless solid (231 mg, 50% from **S112g**). IR 3050, 2975, 1965, 1656, 1590, 1490, 1453, 1427, 1358, 1275, 1254, 1176, 1158, 1074, 1030, 1002 cm^{-1}; m.p 105-107° ($Et_2O/CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.37 (5H, m, Ar**H**), 7.28-7.26 (5H, m, Ar**H**), 5.71 (1H, t, *J* = 6.5 Hz, =C**H**), 5.14 (2H, d, *J* = 6.5 Hz, =C**H**$_2$); ^{13}C NMR (126 MHz, $(CD_3)_2SO$, 323

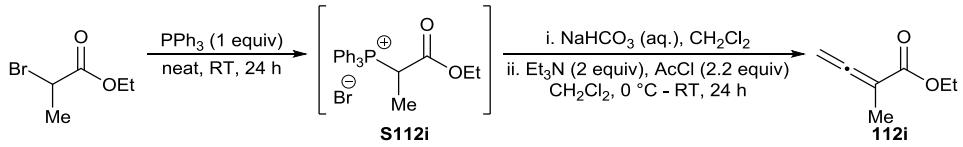
K) δ 214.0 (C), 163.2 (C), 142.5 (C), 129.1 (4 × CH), 127.5 (4 × CH), 126.8 (2 × CH), 88.6 (CH), 79.4 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{16}H_{14}NO]^+$ $[M+H]^+$: 236.1070, found: 236.1066. Spectroscopic data consistent with those previously reported.[94]



S-Phenyl buta-2,3-dienethioate (112h). To a flask charged with pyridine (2.80 mL, 34.0 mmol) in CH_2Cl_2 (60 mL) at 0 °C was added thiophenol (3.49 mL, 34.0 mmol) followed by the drop-wise addition of bromoacetyl bromide (3.00 mL, 34.0 mmol). The resulting suspension was stirred at 0 °C for 10 minutes then room temperature for 10 minutes, then diluted with CH_2Cl_2 (60 mL), washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered then concentrated to give *S*-phenyl 2-bromoethanethioate (**115**) as a yellow oil (7.82 g, 99%), which was used directly in the next step. To *S*-phenyl 2-bromoethanethioate **115** (7.82 g, 33.8 mmol) in toluene (15 mL) was added PPh_3 (9.76 g, 37.2 mmol). The resulting suspension was stirred at room temperature overnight. The phosphonium salt was isolated *via* vacuum filtration and used directly in the next step (13.98 g, 84% over 2 steps).

Phosphonium salt **S112h** (13.98 g, 28.3 mmol) was dissolved in CH_2Cl_2 (200 mL) and poured into a separating funnel, and washed with aqueous NaOH (2 M, 3 × 150 mL), brine (150 mL), dried (Na_2SO_4), filtered and concentrated. The ylide was then dissolved in CH_2Cl_2 (30 mL) and cooled to 0 °C. $^{i}Pr_2NEt$ (4.94 mL, 28.3 mmol) was added followed by acetyl chloride (2.22 mL, 31.2 mmol) and the resulting solution was warmed to room temperature and stirred for 2 h. Then, the reaction mixture was cooled to 0 °C and a second equivalent of $^{i}Pr_2NEt$ (4.94 mL, 28.3 mmol) was added followed by a second equivalent of acetyl chloride (2.22 mL, 31.2 mmol). The resulting solution was warmed to room temperature and stirred for 1 h, then water was added and the suspension was stirred at room temperature for 15 min, then extracted with CH_2Cl_2 (3 × 20 mL). The combined organics were washed with brine (50 mL), dried (Na_2SO_4),

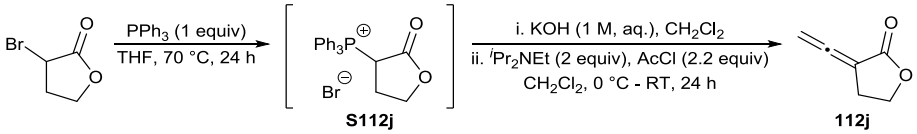
filtered and concentrated. The residue was suspended in *n*-pentane/Et_2O (1:1, 600 mL) and silica was added. The suspension was stirred vigorously at room temperature for 20 min then filtered and concentrated. Purification by column chromatography (0-5% EtOAc/petroleum ether) gave the title compound as a yellow oil (1.49 g, 30% from **S112h**). R_f = 0.46 (20% EtOAc/petroleum ether); IR 3061, 1967, 1670 (C=O), 1439, 1132, 1023, 850, 745, 687, 594 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.50-7.38 (5H, m, Ar**H**), 5.97 (1H, t, *J* = 6.5 Hz, C**H**), 5.43 (2H, d, *J* = 6.5 Hz, =C**H**$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.9 (C), 187.6 (C), 135.0 (2 × CH), 129.6 (CH), 129.3 (2 × CH), 127.6 (C), 95.6 (CH), 82.1 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{10}H_8NaOS]^+$ $[M+Na]^+$: 199.0188, found: 199.0211.



Ethyl 2-methylbuta-2,3-dienoate (112i). To a flask charged with ethyl 2-bromopropanoate (12.98 mL, 100 mmol) was added PPh_3 (26.2 g, 100 mmol). The resulting suspension was stirred at room temperature overnight. The phosphonium salt was isolated *via* vacuum filtration and washed with *n*-pentane (32.26 g, 73%).

Phosphonium salt **S112i** (10.0 g, 22.56 mmol) was dissolved in CH_2Cl_2 (100 mL) and poured into a separating funnel and washed with saturated aqueous $NaHCO_3$ (3 × 100 mL), brine (100 mL), dried (Na_2SO_4), filtered and concentrated. The ylide was then dissolved in CH_2Cl_2 (22 mL) and cooled to 0 °C. $^iPr_2NEt$ (3.93 mL, 22.56 mmol) was added followed by acetyl chloride (1.87 mL, 24.81 mmol) and the resulting solution was warmed to room temperature and stirred overnight. Then, the reaction mixture was cooled to to 0 °C and a second equivalent of $^iPr_2NEt$ (3.93 mL, 22.56 mmol) was added followed by a second equivalent of acetyl chloride (1.87 mL, 24.81 mmol). The resulting solution was warmed to room temperature and stirred for 1 h, then concentrated. The residue was suspended in petroleum ether/EtOAc (9:1, 250 mL) and silica was added. The suspension was stirred vigorously at room temperature for 20 min then filtered and concentrated. Purification by column

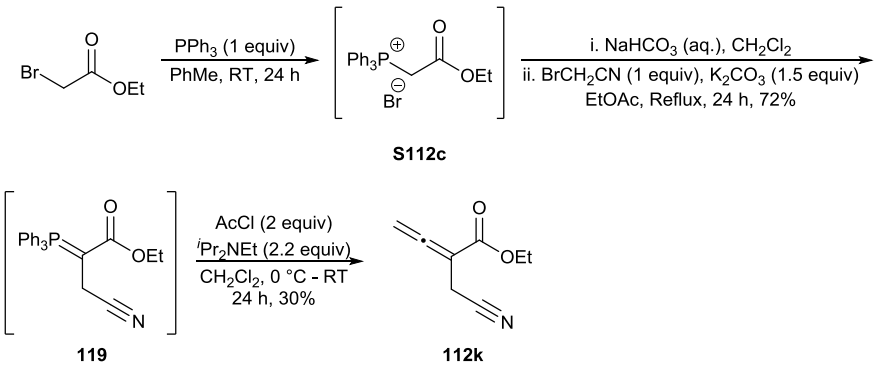
chromatography (0-5% EtOAc/*n*-pentane) gave the title compound as a colourless oil (80 mg, 3% from **S112i**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.06 (2H, q, *J* = 3.1 Hz, =C**H**$_2$), 4.20 (2H, q, *J* = 7.1 Hz, OC**H**$_2$), 1.87 (3H, t, *J* = 3.2 Hz, =CC**H**$_3$), 1.28 (3H, t, *J* = 7.1 Hz, OCH_2C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.1 (C), 167.7 (C), 95.6 (C), 77.9 (CH_2), 61.2 (CH_2), 14.9 (CH_3), 14.4 (CH_3); HRMS (ESI) Exact mass calculated for $[C_7H_{10}NaO_2]^+$ $[M+Na]^+$: 149.0573, found: 149.0575. Spectroscopic data consistent with those previously reported.[95]



3-Vinylidenedihydrofuran-2(3*H*)-one (112j). To a flask charged with PPh_3 (15.9 g, 60.6 mmol) in THF (25 mL) was added α-bromo-γ-butyrolactone (10.0 g, 60.6 mmol). The resulting suspension was stirred at reflux overnight then cooled to room temperature. The phosphonium salt was isolated *via* vacuum filtration (25.89 g, 88%).

Phosphonium salt **S112j** (5.00 g, 11.7 mmol) was dissolved in CH_2Cl_2 (30 mL) and poured into a separating funnel, and washed with saturated aqueous KOH (2 M, 3 × 20 mL), brine (20 mL), dried (Na_2SO_4), filtered and concentrated. The ylide was then dissolved in CH_2Cl_2 (12 mL) and cooled to 0 °C. $^{i}Pr_2NEt$ (2.00 mL, 11.7 mmol) was added followed by acetyl chloride (0.92 mL, 12.9 mmol) and the resulting solution was warmed to room temperature and stirred overnight. Then, the reaction mixture was cooled to 0 °C and a second equivalent of $^{i}Pr_2NEt$ (2.00 mL, 11.7 mmol) was added followed by a second equivalent of acetyl chloride (0.92 mL, 12.9 mmol). The resulting solution was warmed to room temperature and stirred for 1 h, then water was added and the suspension was stirred at room temperature for 15 min, then extracted with CH_2Cl_2 (3 × 20 mL). The combined organics were washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (5-15% EtOAc/petroleum ether) gave the title compound as a pale yellow oil (589 mg, 46% from **S112j**). R_f = 0.36 (20% EtOAc/petroleum ether); IR 2989, 2935, 1730 (C=O), 1653, 1378, 1280, 1193, 1157, 1091, 1066, 751, 699, 446 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.37 (2H, t, *J* = 5.1 Hz,

=C**H**$_2$), 4.39 (2H, t, *J* = 7.5 Hz, OC**H**$_2$), 3.07 (2H, tt, *J* = 7.5, 5.1 Hz, C**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.4 (=C=), 170.4 (C=O), 93.4 (C), 82.5 (CH_2), 66.2 (CH_2), 26.4 (CH_2); HRMS (ESI) Exact mass calculated for $[C_6H_7O]^+$ $[M+H]^+$: 111.0441, found: 111.0443.

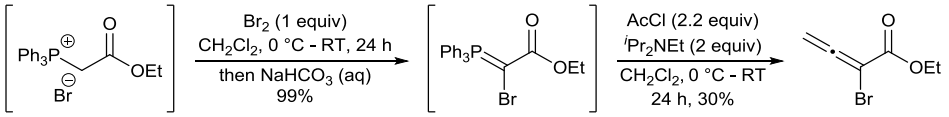


Ethyl 2-(cyanomethyl)buta-2,3-dienoate (112). To a flask charged with PPh_3 (26.2 g, 100 mmol) in ethyl acetate (150 mL) was added ethyl bromoacetate (11.1 mL, 100 mL). The resulting suspension was stirred at room temperature overnight. The phosphonium salt was isolated *via* vacuum filtration and used directly in the next step (41.0 g, 96%).

Phosphonium salt **S112c** (10.0 g, 23.29 mmol) was dissolved in CH_2Cl_2 (150 mL) and washed with $NaHCO_3$ (3 × 100 mL), brine (100 mL), dried (Na_2SO_4), filtered and concentrated. The ylide was suspended in EtOAc (60 mL) and K_2CO_3 (4.23 g, 34.94 mmol) and bromoacetonitrile (1.62 mL, 23.29 mmol) were added. The resulting suspension was stirred at reflux overnight then filtered and washed with EtOAc (50 mL). The combined organics were concentrated to give the substituted ylide **119** (6.51 g, 72%) as a brown oil, which was used directly in the next step.

Ylide **119** (6.51 g, 16.80 mmol) was then dissolved in CH_2Cl_2 (15 mL) and cooled to 0 °C. ^{i}Pr$_2$NEt (2.93 mL, 16.80 mmol) was added followed by acetyl chloride (1.31 mL, 18.48 mmol) and the resulting solution was warmed to room temperature and stirred overnight.Then, the reaction mixture was cooled to 0 °C and a second equivalent of ^{i}Pr$_2$NEt (2.93 mL, 16.80 mmol) was added followed by a second equivalent of acetyl chloride (1.31 mL, 18.48 mmol). The resulting solution was warmed to room temperature and stirred for 1 h then concentrated. The residue was suspended in petroleum ether/EtOAc (9:1, 300 mL) and silica was added. The suspension was stirred vigorously at room

temperature for 40 min then filtered and concentrated. Purification by column chromatography (2% EtOAc/petroleum ether) gave the title compound as a colourless oil (750 mg, 30% from **119**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.43 (2H, t, *J* = 3.1 Hz, =C**H**$_2$), 4.24 (2H, q, *J* = 7.1 Hz, OC**H**$_2$CH$_3$), 3.34 (2H, t, *J* = 3.1 Hz, C**H**$_2$CN), 1.30 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.3 (C), 165.0 (C), 116.7 (C), 92.7 (C), 82.6 (CH_2), 62.1 (CH_2), 18.4 (CH_2), 14.3 (CH_3); HRMS (ESI) Exact mass calculated for $[C_8H_9NNaO_2]^+$ $[M+Na]^+$: 174.0525, found: 174.0523. Spectroscopic data consistent with those previously reported.[96]

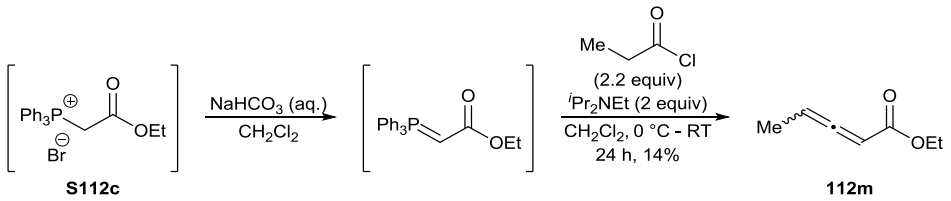


S112c **120** **112l**

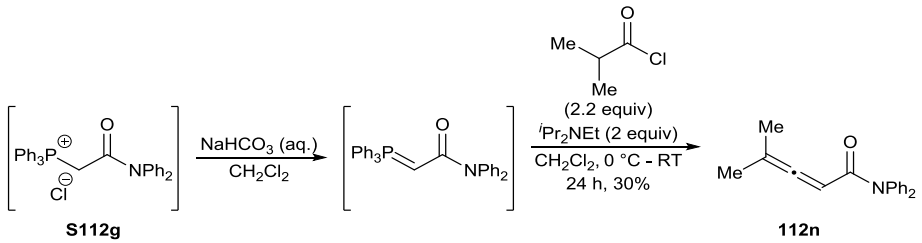
Ethyl 2-bromobuta-2,3-dienoate (112l). Phosphonium salt **S112c** (8.00 g, 18.64 mmol) was dissolved in CH_2Cl_2 (100 mL) and washed with $NaHCO_3$ (3 × 80 mL), brine (80 mL), dried (Na_2SO_4), filtered and concentrated. The ylide was suspended in CH_2Cl_2 (40 mL) and cooled to 0 °C. Bromine (0.95 mL, 18.64 mmol) in CH_2Cl_2 (2 mL) was added drop-wise, and the resulting solution was warmed to room temperature and stirred overnight, then quenched with water (40 mL) and extracted with CH_2Cl_2 (2 × 40 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ solution (3 × 40 mL), brine (40 mL), dried (Na_2SO_4), filtered and concentrated to give the substituted ylide **120** as a yellow solid (7.92 g, 99%).

Ylide **120** (7.92 g, 18.55 mmol) was then dissolved in CH_2Cl_2 (18 mL) and cooled to 0 °C. $^{i}Pr_2NEt$ (3.23 mL, 18.55 mmol) was added followed by acetyl chloride (1.45 mL, 20.40 mmol) and the resulting solution was warmed to room temperature and stirred overnight. Then, the reaction mixture was cooled to 0 °C and a second equivalent of $^{i}Pr_2NEt$ (3.23 mL, 18.55 mmol) was added followed by a second equivalent of acetyl chloride (1.45 mL, 20.40 mmol). The resulting solution was warmed to room temperature and stirred for 1 h then concentrated. The residue was suspended in petroleum ether/EtOAc (9:1, 250 mL) and silica was added. The suspension was stirred vigorously at room temperature for 40 min then filtered and concentrated. Purification by column

chromatography (0-5% EtOAc/petroleum ether) gave the title compound as a yellow oil (1.32 g, 37% from **120**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.28 (2H, s, =C**H**$_2$), 4.27 (2H, q, *J* = 7.1 Hz, OC**H**$_2$CH$_3$), 1.30 (3H, t, *J* = 7.1 Hz, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.0 (C), 162.0 (C), 118.2 (C), 84.3 (=CH_2), 63.1 (CH_2), 14.3 (CH_3); HRMS (ESI) Exact mass calculated for $[C_6H_7NaO_2Br]^+$ $[M+Na]^+$: 212.9522, found: 212.9513. Spectroscopic data consistent with those previously reported.[97]

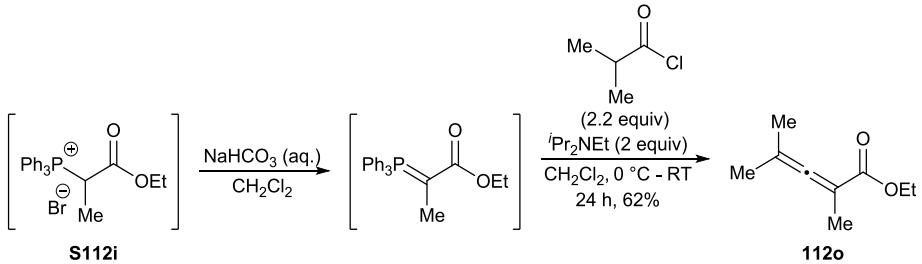


Ethyl penta-2,3-dienoate (112m). Phosphonium salt **S112c** (5.00 g, 11.65 mmol) was dissolved in CH_2Cl_2 (80 mL) and washed with $NaHCO_3$ (3 × 60 mL), brine (60 mL), dried (Na_2SO_4), filtered and concentrated. The ylide was suspended in CH_2Cl_2 (40 mL) and cooled to 0 °C. $^{i}Pr_2NEt$ (2.03 mL, 11.65 mmol) was added followed by propionyl chloride (1.12 mL, 12.81 mmol) and the resulting solution was warmed to room temperature and stirred overnight. Then, the reaction mixture was cooled to to 0 °C and a second equivalent of $^{i}Pr_2NEt$ (2.03 mL, 11.65 mmol) was added followed by a second equivalent of propionyl chloride (1.12 mL, 12.81 mmol). The resulting solution was warmed to room temperature and stirred for 1 h, then concentrated. The residue was suspended in petroleum ether/EtOAc (9:1, 400 mL) and silica was added. The suspension was stirred vigorously at room temperature for 20 min then filtered and concentrated. Purification by column chromatography (0-5% EtOAc/petroleum ether) gave the title compound as a colourless oil (206 mg, 14% from **S112c**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.65-5.50 (2H, m, 2 × =C**H**), 4.19 (2H, q, *J* = 7.1 Hz, OC**H**$_2$CH$_3$), 1.78 (3H, dd, *J* = 7.3, 3.3 Hz, =CC**H**$_3$), 1.28 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.1 (C), 166.4 (C), 90.4 (CH), 87.9 (CH), 61.0 (CH_2), 14.4 (CH_3), 13.0 (CH_3); HRMS (ESI) Exact mass calculated for $[C_7H_{10}NaO_2]^+$ $[M+Na]^+$: 149.0573, found: 149.0585. Spectroscopic data consistent with those previously reported.[90]



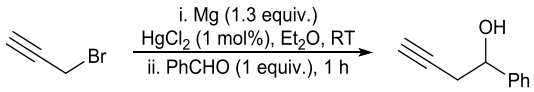
S112g **112n**

4-Methyl-*N*,*N*-diphenylpenta-2,3-dienamide (112n). Phosphonium salt **S112g** (5.00 g, 9.84 mmol) was dissolved in CH_2Cl_2 (50 mL) and washed with $NaHCO_3$ (3 × 50 mL), brine (50 mL), dried (Na_2SO_4), filtered and concentrated. The ylide was then dissolved in CH_2Cl_2 (12 mL) and cooled to 0 °C. $^{i}Pr_2NEt$ (1.46 mL, 8.36 mmol) was added followed by isobutyryl chloride (0.89 mL, 9.20 mmol) and the resulting solution was warmed to room temperature and stirred overnight. Then, the reaction mixture was cooled to 0 °C and a second equivalent of $^{i}Pr_2NEt$ (1.46 mL, 8.36 mmol) was added followed by a second equivalent of isobutyryl chloride (0.89 mL, 9.20 mmol). The resulting solution was warmed to room temperature and stirred for 1 h then concentrated. The residue was suspended in petroleum ether/EtOAc (9:1, 250 mL) and silica was added. The suspension was stirred vigorously at room temperature for 40 min then filtered and concentrated. Purification by column chromatography (10-30% EtOAc/petroleum ether) gave the title compound as an off-white solid (1.18 g, 54%). R_f = 0.45 (20% EtOAc/petroleum ether); m.p 110-112 °C ($Et_2O/CHCl_3$); IR 2978, 1755, 1654, 1592, 1399, 1290, 1221, 1176, 1072, 813, 752, 690 cm^{-1}; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 7.45-7.34 (4H, m, Ar**H**), 7.34-7.20 (6H, m, Ar**H**), 5.45 (1H, hept, J = 2.9 Hz, =C**H**), 1.61 (3H, s, C$\mathbf{H}_3$), 1.60 (3H, s, C$\mathbf{H}_3$); ^{13}C NMR (126 MHz, $(CD_3)_2SO$, 343 K) δ 207.8 (C), 163.9 (C), 142.8 (C), 128.8 (4 × CH), 127.3 (4 × CH), 126.3 (2 × CH), 98.9 (C), 87.6 (CH), 18.6 (2 × CH_3); HRMS (ESI) Exact mass calculated for $[C_{18}H_{17}NO]^+$ $[M+H]^+$: 264.1383, found: 264.1383.



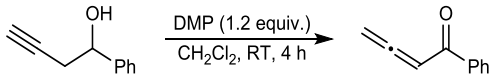
S112i **112o**

Ethyl 2,4-dimethylpenta-2,3-dienoate (112o). Phosphonium salt **S112i** (5.00 g, 11.28 mmol) was dissolved in CH_2Cl_2 (60 mL) and washed with $NaHCO_3$ (3 × 60 mL), brine (60 mL), dried (Na_2SO_4), filtered and concentrated. The ylide was then dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C. $^{i}Pr_2NEt$ (1.96 mL, 11.28 mmol) was added followed by isobutyryl chloride (1.19 mL, 12.41 mmol) and the resulting solution was warmed to room temperature and stirred overnight. Then, the reaction mixture was cooled to 0 °C and a second equivalent of $^{i}Pr_2NEt$ (1.96 mL, 11.28 mmol) was added followed by a second equivalent of isobutyryl chloride (1.19 mL, 12.41 mmol). The resulting solution was warmed to room temperature and stirred for 1 h then concentrated. The residue was suspended in petroleum ether/EtOAc (9:1, 250 mL) and silica was added. The suspension was stirred vigorously at room temperature for 40 min then filtered and concentrated. Purification by column chromatography (0-5% EtOAc/petroleum ether) gave the title compound as a colourless oil (1.08 g, 62%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.16 (2H, q, *J* = 7.1 Hz, OC**H**$_2$CH$_3$), 1.82 (3H, s, CH$_3$), 1.76 (6H, s, 2 × C**H**$_3$), 1.29-1.22 (3H, m, OCH$_2$C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.0 (C), 168.6 (C), 98.2 (C), 93.5 (C), 60.73 (CH_2), 19.8 (CH_3), 15.6 (CH_3), 14.5 (CH_3); HRMS (ESI) Exact mass calculated for $[C_9H_{15}O_2]^+$ $[M+H]^+$: 155.1067, found: 155.1051. Spectroscopic data consistent with those previously reported.[98]

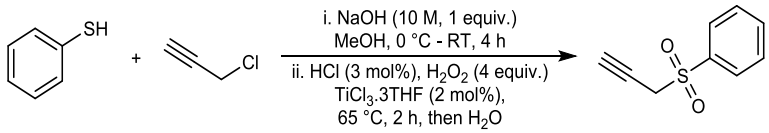


1-Phenylbut-3-yn-1-ol (121). To an oven dried flask charged with Mg turnings (321 mg, 13.2 mmol), $HgCl_2$ (2.7 mg, 0.1 mmol) in Et_2O (30 mL) under N_2 was added propargyl bromide (80% wt in toluene) (1.34 mL, 12.0 mmol) dropwise. When the solution became homogenous benzaldehyde (1.00 mL, 10.0 mmol) was added drop-wise and the resulting solution stirred at room temperature for 1 h then quenched with saturated NH_4Cl solution at 0 °C. The aqueous was extracted with Et_2O, and the combined organics were dried (Na_2SO_4), filtered, then concentrated. Purification by column chromatography (20% EtOAc/petroleum ether) gave the title compound as an orange oil (643 mg, 44%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.34 (4H, m, Ar**H**), 7.33-7.29

(1H, m, Ar**H**), 4.88 (1H, td, *J* = 6.4, 3.5 Hz, C**H**OH), 2.67-2.63 (2H, m, C**H**$_2$), 2.43 (1H, d, *J* = 3.5 Hz, O**H**), 2.08 (1H, t, *J* = 2.6 Hz, ≡C**H**); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.6 (C), 128.6 (2 × CH), 128.1 (CH), 125.9 (2 × CH), 80.8 (C), 72.5 (CH), 71.1 (CH), 29.6 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{10}H_{10}NaO]^+$ $[M+Na]^+$: 169.0624, found: 169.0628. Spectroscopic data consistent with those previously reported.[48]

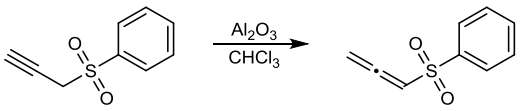


1-Phenylbuta-2,3-dien-1-one (112p). To a flask charged with DMP (644 mg, 1.51 mmol) in CH_2Cl_2 (10 mL) under N_2 was added 1-phenylbut-3-yn-1-ol **121** (185 mg, 1.26 mmol) in CH_2Cl_2 (3 mL). The reaction was stirred at room temperature for 4 h then diluted with Et_2O and washed with 1M NaOH solution (40 mL). The aqueous was extracted with Et_2O and the combined organics were washed with brine, dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (10% EtOAc/petroleum ether) gave the title compound as a brown oil (93 mg, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92-7.88 (2H, m, Ar**H**), 7.59-7.53 (1H, m, Ar**H**), 7.49-7.42 (2H, m, Ar**H**), 6.44 (1H. t, *J* = 6.5 Hz, =C**H**), 5.26 (2H, d, *J* = 6.5 Hz, =C**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.3 (C), 191.2 (C), 137.6 (C), 133.0 (CH), 128.8 (2 × CH), 128.5 (2 × CH), 93.4 (CH), 79.4 (CH_2). HRMS (ESI) Exact mass calculated for $[C_{10}H_8NaO]^+$ $[M+Na]^+$: 167.0467, found: 167.0483. Spectroscopic data consistent with those previously reported.[99]

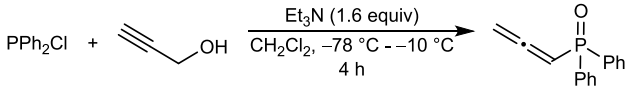


(Prop-2-yn-1-ylsulfonyl)benzene (125). To a 2-neck flask purged with N_2 was added thiophenol (3.00 mL, 28.4 mmol) and MeOH (30 mL). The solution was cooled to 0 °C and aq. NaOH (10 M, 2.84 mL, 28.4 mmol) was added followed by propargyl chloride (2.16 mL, 29.2 mmol). The resulting solution was warmed to room temperature and stirred for 4 h then HCl was added (~37%, 60.0 μL, 0.85 mmol) followed by $TiCl_3$.3THF (203 mg, 0.55 mmol). An excess of H_2O_2 (>30% w/v, 11.6 mL, 114 mmol) was added slowly

allowing the temperature to reach 65 °C, cooling with an ice bath as necessary. The resulting solution was stirred at 65 °C for 2 h then H_2O (30 mL) was added. The suspension was left to cool and stand overnight at room temperature then at 0 °C for 4 h. The crystals were isolated by vacuum filtration. Subsequent recrystallisation (H_2O) gave the title compound as colourless crystals (1.46 g, 28%). m.p 83-85 °C (H_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02-7.97 (2H, m, Ar**H**), 7.73-7.68 (1H, m, Ar**H**), 7.62-7.57 (2H, m, Ar**H**), 3.97 (2H, d, *J* = 2.7 Hz, C**H**$_2$), 2.37 (1H, t, *J* = 2.7 Hz, ≡C**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.7 (C), 134.5 (CH), 129.3 (2 × CH), 129.0 (2 × CH), 76.4 (CH), 71.7 (C), 48.5 (CH_2); HRMS (ESI) Exact mass calculated for $[C_9H_8SNaO_2]^+$ $[M+Na]^+$: 203.0137, found: 203.0140. Spectroscopic data consistent with those previously reported.[100]

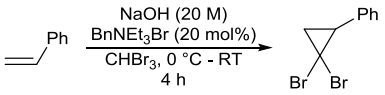


(Propa-1,2-dien-1-ylsulfonyl)benzene (112s). To a flask charged with (Prop-2-yn-1-ylsulfonyl)benzene **125** (200 mg, 1.11 mmol) in $CHCl_3$ (10 mL) was added alumina (neutral, Brockmann activity 1) (200 mg). The resulting suspension was stirred at room temperature for 3 h then filtered and concentrated to give the title compound as a yellow oil (159 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (2H, dd, *J* = 7.5, 1.2 Hz, Ar**H**), 7.67-7.62 (1H, m, Ar**H**), 7.59-7.52 (2H, m, Ar**H**), 6.25 (1H, t, *J* = 6.3 Hz, =C**H**), 5.45 (2H, d, *J* = 6.3 Hz, =C**H**$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.6 (C), 141.3 (C), 133.7 (CH), 129.4 (2 × CH), 127.8 (2 × CH), 101.1 (CH), 84.3 (CH_2); HRMS (ESI) Exact mass calculated for $[C_9H_8SNaO_2]^+$ $[M+Na]^+$: 203.0137, found: 203.0141. Spectroscopic data consistent with those previously reported.[95]

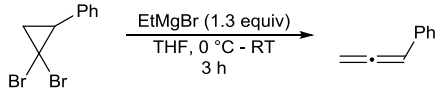


Diphenyl(propa-1,2-dien-1-yl)phosphine oxide (112t). A flask was charged with propargyl alcohol (1.16 mL, 20.0 mmol) and Et_3N (2.22 mL, 16.0 mmol) in CH_2Cl_2 (20 mL) and cooled to −78 °C. PPh_2Cl (1.79 mL, 10.0 mmol) in CH_2Cl_2 (15 mL) was added drop-wise and the resulting solution gradually

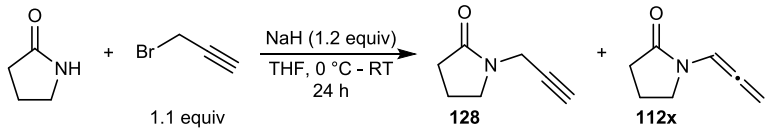
warmed to −10 °C and stirred for 4 h, then poured onto a mixture of concentrated HCl (0.5 mL) and water (20 mL) and extracted with CH_2Cl_2. The combined organics were washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude was recrystallised (CH_2Cl_2/*n*-hexane) to give the title compound as off-white crystals (860 mg, 36%). m.p 108-109 °C (CH_2Cl_2/*n*-hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78-7.71 (4H, m, Ar**H**), 7.55-7.52 (2H, m, Ar**H**), 7.49-7.43 (4H, m, Ar**H**), 5.85 (1H, td, *J* = 6.8, 3.9 Hz, C**H**), 4.89 (2H, dd, *J* = 11.2, 6.8 Hz, =C**H**$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.3 (C), 132.6 (d, $J_{C\text{-}P}$ = 108.1 Hz, 2 × C), 132.1 (d, $J_{C\text{-}P}$ = 3.0 Hz, 2 × CH), 131.5 (d, $J_{C\text{-}P}$ = 9.4 Hz, 4 × CH), 128.6 (d, $J_{C\text{-}P}$ = 12.6 Hz, 4 × CH), 84.8 (d, $J_{C\text{-}P}$ = 104.4 Hz, CH), 76.7 (d, $J_{C\text{-}P}$ = 12.7 Hz, CH_2); ^{31}P NMR (202 MHz, $CDCl_3$) δ 23.5 (app hex, *J* = 12.3 Hz); HRMS (ESI) Exact mass calculated for $[C_{15}H_{13}PNaO]^+$ $[M+Na]^+$: 263.0596, found: 263.0600. Spectroscopic data consistent with those previously reported.[101]



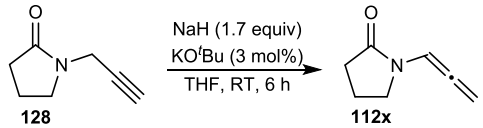
(2,2-Dibromocyclopropyl)benzene (127). To a flask charged with styrene (1.5 mL, 13.1 mmol) in bromoform (5 mL) at 0 °C was added benzyltriethylammonium bromide (71 mg, 0.26 mmol) and NaOH (20 M, 5 mL). The resulting suspension was stirred at 0 °C for 3 hours, then at room temperature for 1 h, then diluted with EtOAc and the layers separated. The organics were washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude was filtered over silica (petroleum ether) to give the title compound as a yellow oil (2.10 g, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.32 (3H, m, Ar**H**), 7.28-7.25 (2H, m, Ar**H**), 3.00-2.93 (1H, m, C**H**), 2.14 (1H, dd, *J* = 10.5, 7.7 Hz, C**H**$_a$H$_b$), 2.02 (1H, dd, *J* = 8.3, 7.7 Hz, , CH$_a$**H**$_b$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.1 (C), 129.0 (2 × CH), 128.4 (2 × CH), 127.8 (CH), 36.1 (CH), 28.6 (C), 27.4 (CH_2). Spectroscopic data consistent with those previously reported.[49]



Propa-1,2-dien-1-ylbenzene (112v). To a flask charged with (2,2-dibromocyclopropyl)benzene **127** (2.00 g, 7.25 mmol) in THF (15 mL) at 0 °C was added ethylmagnesium bromide (3M, 3.14 mL, 9.42 mmol). The resulting solution was warmed to room temperature and stirred for 3 h then quenched with water and extracted with EtOAc. The combined organics were washed with HCl (1 M), saturated aqueous $NaHCO_3$ solution then brine, dried (Na_2SO_4), filtered and concentrated. The crude was filtered over silica (petroleum ether) to give the title compound as a colourless oil (580 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.28 (4H, m, Ar**H**), 7.24-7.18 (1H, m, Ar**H**), 6.17 (1H, t, *J* = 6.8 Hz, C**H**), 5.15 (2H, d, *J* = 6.8 Hz, C**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.9 (C), 134.0 (C), 128.8 (CH), 127.0 (CH), 126.8 (CH), 94.1 (CH), 78.9 (CH_2). Spectroscopic data consistent with those previously reported.[49]



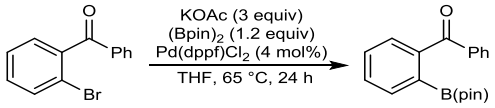
1-(Prop-2-yn-1-yl)pyrrolidin-2-one (128). An oven-dried flask was charged with NaH (480 mg, 12.0 mmol) in THF (15 mL) and cooled to 0 °C. A solution of pyrrolidinone (851 mg, 10.0 mmol) in THF (5 mL) was added drop-wise and the resulting suspension was stirred at 0 °C for 30 min. Propargyl bromide (80% wt in toluene, 1.23 mL, 11.0 mmol) was added and the suspension was warmed to room temperature and stirred overnight then quenched with water and extracted with EtOAc. The combined organics were washed with brine, dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (0-50% EtOAc/petroleum ether) gave the title compound as a yellow oil (634 mg, 52%) and allene **112x** as a yellow oil (179 mg, 15%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.08 (2H, t, *J* = 2.6 Hz, NC**H**$_2$CCH), 3.55 – 3.44 (2H, m, C**H**$_2$), 2.38 (2H, td, *J* = 8.2, 2.6 Hz, C**H**$_2$), 2.21 (1H, td, *J* = 2.6, 1.3 Hz, ≡C**H**), 2.10 – 1.98 (2H, m, C**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6 (C), 77.9 (C), 72.2 (CH), 46.4 (CH_2), 32.0 (CH_2), 30.8 (CH_2), 17.7 (CH). HRMS (ESI) Exact mass calculated for $[C_7H_{10}NO]^+$ $[M+H]^+$: 124.0757, found: 124.0762. Spectroscopic data consistent with those previously reported.[102]



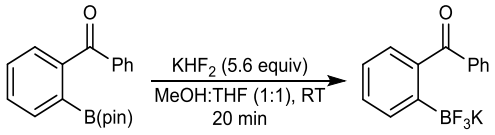
128 112x

1-(Propa-1,2-dien-1-yl)pyrrolidin-2-one (112x). A flask was charged with 1-(prop-2-yn-1-yl)pyrrolidin-2-one **128** (634 mg, 5.15 mmol) in THF (10 mL) and NaH (210 mg, 8.75 mmol) and KO^{t}Bu (173 mg, 1.54 mmol) were added at room temperature. The resulting suspension was stirred at room temperature for 6 h then quenched with water and extracted with EtOAc. The combined organics were dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (0-50% EtOAc/petroleum ether) gave the title compound as a yellow oil (430 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (1H, t, *J* = 6.4 Hz, =C**H**), 5.38 (2H, d, *J* = 6.4 Hz, =C**H**$_2$), 3.50 – 3.34 (2H, m, C**H**$_2$), 2.47 (2H, t, *J* = 8.1 Hz, C**H**$_2$), 2.07 (2H, app qd, *J* = 8.1, 6.8 Hz, C**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.9 (C), 173.1 (C), 96.0 (CH), 86.7 (CH_2), 45.9 (CH_2), 31.4 (CH_2), 17.6 (CH_2). HRMS (ESI) Exact mass calculated for $[C_7H_9NNaO]^+$ $[M+Na]^+$: 146.0576, found: 146.0591. Spectroscopic data consistent with those previously reported.[103]

8.2. Synthesis of Boronic Acids



Phenyl(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanone (129). To a flask charged with 2-bromobenzophenone (1.50 g, 5.74 mmol), KOAc (1.69 g, 17.22 mmol), and $(Bpin)_2$ (1.75 g, 6.89 mmol) in THF (36 mL) under N_2 was added $Pd(dppf)Cl_2$ (168 mg, 4 mol%). The resulting suspension was heated at 65 °C overnight then cooled and diluted with Et_2O. The organics were washed with H_2O then brine. Charcoal and Na_2SO_4 was added to the organics, which was then filtered and concentrated. Purification by column chromatography (2-5% EtOAc/petroleum ether) gave the title compound as a colourless solid (1.77 g, 79%). m.p 102-104 °C (Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80-7.73 (3H, m, Ar**H**), 7.58-7.41 (6H, m, Ar**H**), 1.18 (12H, s, 4 × C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.3 (C), 143.8 (C), 138.3 (C), 134.0 (CH), 132.5 (CH), 130.5 (CH), 130.2 (2 × CH), 129.8 (CH), 129.1 (CH), 128.3 (2 × CH), 84.2 (C), 25.2 (4 × CH_3); HRMS (ESI) Exact mass calculated for $[C_{19}H_{22}BO_3]^+$ $[M+H]^+$: 309.1657, found: 309.1657. Spectroscopic data consistent with those previously reported.[104]

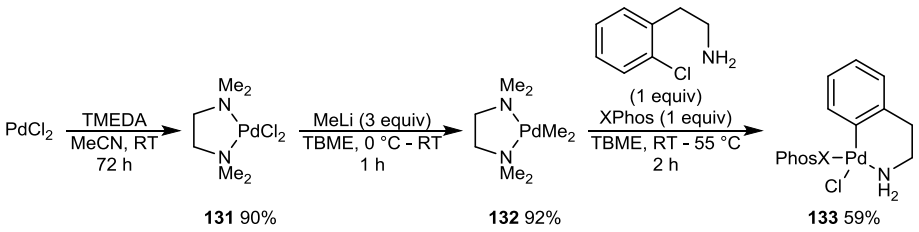


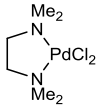
129 **130**

Potassium benzophenone-2-yltrifluoroborate (130). To a flask charged with phenyl(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanone **129** (900 mg, 2.92 mmol) in MeOH:THF (1:1, 20 mL) was added aqueous KHF_2 (4.5 M, 4.00 mL, 16.35 mmol). The resulting slurry was stirred at room temperature until TLC indicated complete consumption of the starting material (20 min) then concentrated. Hot acetone was added to the residue, which was then filtered and concentrated to afford the crude. Purification by recrystallisation (acetone/Et_2O) gave the title compound as colourless crystals (390 mg, 46%). m.p 173-174 °C (Acetone/Et_2O); ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 7.78-7.74 (2H, m, Ar**H**), 7.74-7.69 (1H, m, Ar**H**), 7.57-7.52 (1H,

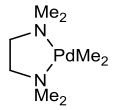
m, Ar**H**), 7.46-7.39 (2H, m, Ar**H**), 7.30 (1H, tdd, *J* = 7.4, 1.3, 0.7 Hz, Ar**H**), 7.17 (1H, td, *J* = 7.5, 1.4 Hz, Ar**H**), 7.04-6.99 (1H, m, Ar**H**); ^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 203.0 (C), 144.0 (C), 139.6 (C), 34.20 (q, *J* = 2.8 Hz, CH), 133.2 (CH), 131.2 (2 × CH), 128.8 (2 × CH), 128.7 (CH), 126.5 (CH), 125.5 (CH); ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ −138.6 (br, d, *J* = 60.3 Hz); ^{11}B NMR (128 MHz, $(CD_3)_2CO$) δ 3.18 (d, *J* = 53.5 Hz); HRMS (ESI) Exact mass calculated for $[C_{12}H_9OBF_3KNa]^+$ $[M+Na]^+$: 311.0228, found: 311.0225. Spectroscopic data consistent with those previously reported.[50]

8.2.1. Synthesis of Buchwald Pre-Catalyst

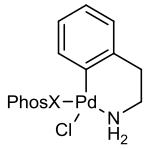




$Cl_2Pd(II)TMEDA$ (131). To a flask charged with palladium dichloride (2.5 g, 14.10 mmol) in MeCN (94 mL) was added TMEDA (14.8 mL, 98.69 mmol). The resulting suspension was stirred at room temperature for 72 h then filtered to give the title compound as a yellow solid (3.72 g, 90%). m.p. 227-231 °C (dec.) (CH_3CN); ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 2.72 (4H, br s, 2 × C**H**$_2$), 2.64 (12H, br s, 4 × C**H**$_3$); Anal. calculated for $C_6H_{16}Cl_2N_2Pd$: C, 24.55; H, 5.49; N, 9.54. Found: C, 24.59; H, 5.53; N, 9.42. Spectroscopic data consistent with those previously reported.[105,106]

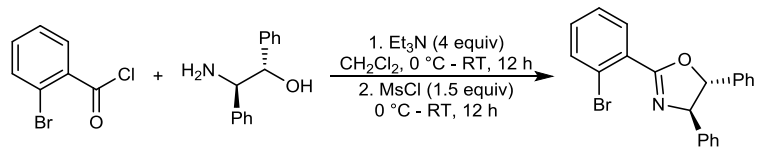


$Me_2Pd(II)TMEDA$ (132). A schlenk flask charged with $Cl_2Pd(II)TMEDA$ **131** (1.20 g, 4.09 mmol) was evacuated and back-filled with Ar (3 cycles). TBME (32 mL) was added and the solution was cooled to 0 °C. MeLi (1.6 M, 7.5 mL, 12.27 mmol) was added over 10 min. The resulting solution was stirred at room temperature for 1 h, then cooled to 0 °C and quenched *via* careful addition of H_2O (10 mL). The solution was extracted with TBME (4 × 50 mL), and the combined organics were dried (Na_2SO_4), filtered, then concentrated to give the title compound as an off-white solid (950 mg, 92%). IR 2967, 2832, 1455, 1283, 1182, 1158, 1143, 1095, 1060, 1046, 1024, 799, 769, 696, 520 cm^{-1}; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 2.58 (4H, s, 2 × C**H**$_2$), 2.42 (12H, s, 4 × NC**H**$_3$), -0.33 (6H, s, 2 × PdC**H**$_3$). Note: elemental analysis/m.p data not obtained due to the potentially explosive nature of the complex at high temperatures. Spectroscopic data consistent with those previously reported.[106]

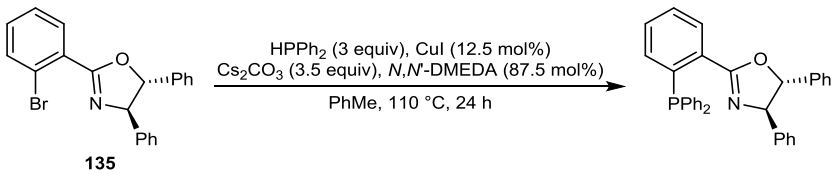


XPhos palladium (II) phenethylamine chloride (133). A schlenk flask charged with Me_2Pd(II)TMEDA **132** (390 mg, 1.47 mmol) was evacuated and back-filled with Ar (3 cycles). Under a flow of Ar, TBME (12 mL) and 2-chloro phenethylamine (0.22 mL, 1.47 mmol) were added, followed by XPhos (730 mg, 1.47 mmol). The schlenk flask was sealed with a septa and PTFE tape, and the resulting solution was stirred at 55 °C for 2 h, then cooled to room temperature. CH_2Cl_2 (5 mL) was added and the resulting solution was concentrated. TBME (4 mL) and *n*-hexane (40 mL) were added and the suspension was placed in a −20 °C freezer for 24 h then filtered to give the title compound as a 1:1 complex with TMBE. Subsequent reprecipitation of the solid from CH_2Cl_2/*n*-hexane gave the title compound as a colourless solid (639 mg, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (1H, br s, Ar**H**), 7.19 (1H, t, *J* = 7.6 Hz, Ar**H**), 7.05-6.94 (4H, m, Ar**H**), 6.91-6.74 (3H, m, Ar**H**), 6.43 (1H, t, *J* = 7.4 Hz, Ar**H**), 3.28 (2H, br s, Al**H**), 3.10 (2H, br s, Al**H**), 2.99-2.28 (4H, m, Al**H**), 2.01-1.04 (33H, br m, Al**H**), 1.01-0.79 (6H, br m, Al**H**), 0.64 (1H, br s, Al**H**), 0.26 (1H, br s, Al**H**); ^{31}P NMR (162 MHz, $CDCl_3$) δ 61.0; Anal. calculated for $C_{41}H_{59}ClNPPd$: C, 66.66; H, 8.05; N, 1.90. Found: C, 65.48; H, 8.07; N, 2.08. Spectroscopic data consistent with those previously reported.[52]

8.3. Synthesis of Chiral Ligands

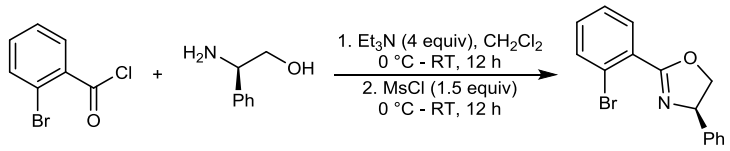


(4*R*,5*R*)-2-(2-Bromophenyl)-4,5-diphenyl-4,5-dihydrooxazole (135). A flask was charged with (1*S*,2*R*)-2-amino-1,2-diphenylethanol (1.66 g, 7.78 mmol) and Et_3N (4.34 mL, 31.12 mmol) in CH_2Cl_2 (40 mL) and was cooled to 0 °C. 2-bromobenzoyl chloride (1.12 mL, 8.56 mmol) was added drop-wise, and the resulting solution was warmed to room temperature and stirred overnight. The suspension was then cooled to 0 °C and MsCl (0.88 mL, 11.7 mmol) was added drop-wise. The solution was warmed to room temperature and stirred overnight, then quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2. The combined organics were washed with brine, dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (20% EtOAc/petroleum ether) afforded the title compound as a pale yellow oil (1.36 g, 47%). R_f = 0.27 (20% EtOAc/petroleum ether); IR 1647, 1493, 1321, 1259, 1025, 957, 913, 759, 733, 693, 542 cm^{-1}; $[\alpha]_D^{22}$ +16.0 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (1H, app dt, *J* = 7.6, 1.3 Hz, Ar**H**), 7.72 (1H, dd, *J* = 7.9, 1.3 Hz, Ar**H**), 7.45-7.32 (12H, m, Ar**H**), 5.43 (1H, dd, *J* = 8.0, 1.1 Hz, C**H**Ph), 5.31 (1H, dd, *J* = 8.0, 1.4 Hz, C**H**Ph); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7 (C), 141.8 (C), 140.2 (C), 134.2 (CH), 132.1 (CH), 131.8 (CH), 129.7 (CH), 129.1 (2 × CH), 129.0 (2 × CH), 128.7 (CH), 128.0 (CH), 127.4 (CH), 126.9 (2 × CH), 126.1 (2 × CH), 122.2 (C), 89.6 (CH), 79.3 (CH); HRMS (ESI) Exact mass calculated for $[C_{21}H_{17}NOBr]^+$ $[M+H]^+$: 378.0488, found: 378.0484.



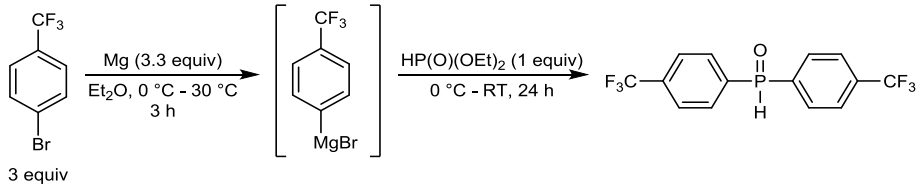
(4*R*,5*R*)-2-(2-(Diphenylphosphanyl)phenyl)-4,5-diphenyl-4,5-dihydrooxazole (L21). A schlenk flask was evacuated and back-filled with Ar (3 cycles). Under a flow of Ar, diphenylphosphine (0.69 mL, 3.97 mmol) and

CuI (31 mg, 12.5 mol%) were added, followed by degassed toluene (10 mL), *N*,*N*'-dimethylethylenediamine (0.12 mL, 1.16 mmol, 87.5 mol%) and **135** (500 mg, 1.32 mmol) in toluene (3 mL) were added followed by Cs_2CO_3 (1.62 g, 4.96 mmol). The flask was sealed with a septa and PTFE tape, and the resulting suspension was heated at 110 °C overnight, then filtered over celite and concentrated. The crude was loaded onto silica and purified by column chromatography (10% EtOAc/petroleum ether) to afford the title compound as a colourless solid. Recrystallisation (*n*-hexane) gave the title compound as colourless crystals (64 mg, 10%). R_f = 0.37 (20% EtOAc/petroleum ether); m.p. 103-105 °C (*n*-hexane); IR 1646, 1451, 1088, 1039, 999, 741, 693, 538, 500 cm^{-1}; $[\alpha]_D^{22}$ −44.0 (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (1H, ddd, *J* = 7.7, 3.7, 1.5 Hz, Ar**H**), 7.43 (1H, td, *J* = 7.6, 1.4 Hz, Ar**H**), 7.42-7.29 (14H, m, Ar**H**), 7.24-7.15 (5H, m, Ar**H**), 6.97 (1H, ddd, *J* = 7.8, 4.0, 1.4 Hz, Ar**H**), 6.92-6.88 (2H, m, Ar**H**), 5.13 (2H, m, 2 × C**H**); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.8 (d, $J_{C\text{-}P}$ = 3.6 Hz, C), 141.7 (C), 139.9 (C), 139.65 (d, $J_{C\text{-}P}$ = 27.1 Hz, C), 138.37 (d, $J_{C\text{-}P}$ = 26.6 Hz, C), 138.28 (d, $J_{C\text{-}P}$ = 24.6 Hz, C), 134.6 (d, $J_{C\text{-}P}$ = 21.0 Hz, 2 × CH), 134.2 (CH), 130.54 (d, $J_{C\text{-}P}$ = 2.8 Hz, 2 × CH), 131.4 (d, $J_{C\text{-}P}$ = 19.0 Hz, C), 130.9 (CH), 130.5 (d, $J_{C\text{-}P}$ = 2.8 Hz, CH), 128.9 (2 × CH), 128.8 (d, $J_{C\text{-}P}$ = 11.2 Hz, 2 × CH), 128.7 (2 × CH), 128.6 (4 × CH), 128.34 (d, $J_{C\text{-}P\ P}$ = 22.6 Hz, 2 × CH), 127.4 (CH), 126.8 (2 × CH), 126.3 (2 × CH) 89.0 (CH), 79.1 (CH); ^{31}P NMR (202 MHz, $CDCl_3$) δ −6.04; HRMS (ESI) Exact mass calculated for $[C_{33}H_{27}NOP]^+$ $[M+H]^+$: 484.1825, found: 484.1810.



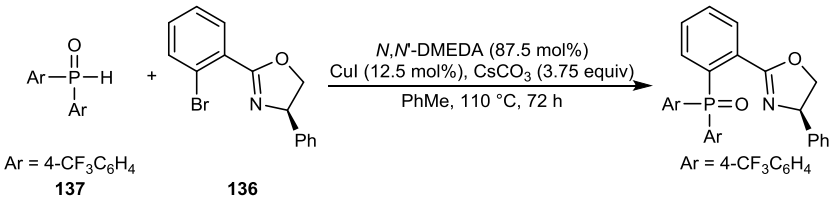
2-(2-Bromophenyl)-4-phenyl-4,5-dihydrooxazole (136). A flask was charged with (*R*)-phenylglycinol (5.00 g, 36.4 mmol) and Et_3N (20.3 mL, 146 mmol) in CH_2Cl_2 (150 mL) and was cooled to 0 °C. 2-bromobenzoyl chloride (5.22 mL, 40.1 mmol) was added drop-wise, and the resulting solution was then warmed to room temperature and stirred overnight. The suspension was then cooled to 0 °C and MsCl (4.23 mL, 54.7 mmol) was added drop-wise. The solution was

warmed to room temperature and stirred overnight, then quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2. The combined organics were washed with brine, dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (10% EtOAc/petroleum ether) afforded the title compound as a yellow oil (7.03 g, 64%). R_f = 0.22 (20% EtOAc/petroleum ether); $[\alpha]_D^{20}$ +40.0 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (1H, dd, *J* = 7.6, 1.9 Hz, Ar**H**), 7.68 (1H, dd, *J* = 7.9, 1.3 Hz, Ar**H**), 7.41-7.35 (5H, m, Ar**H**), 7.34-7.28 (2H, m, Ar**H**), 5.45 (1H, dd, *J* = 10.2, 8.4 Hz, C**H**Ph), 4.83 (1H, dd, *J* = 10.2, 8.4 Hz, C**H**$_a$H$_b$), 4.30 (1H, app t, *J* = 8.4 Hz, CH$_a$**H**$_b$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4 (C), 142.2 (C), 134.0 (CH), 131.9 (CH), 131.7 (CH), 129.8 (C), 128.9 (2 × CH), 127.8 (CH), 127.3 (CH), 126.9 (2 × CH), 122.1 (C), 75.2 (CH_2), 70.6 (CH); HRMS (ESI) Exact mass calculated for $[C_{15}H_{12}NOBrNa]^+$ $[M+Na]^+$: 323.9994, found: 323.9992. Spectroscopic data consistent with those reported previously.[107]



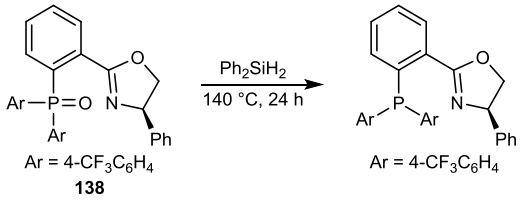
Bis(4-(trifluoromethyl)phenyl)phosphine oxide (137). An oven dried flask was charged with Mg metal (1.14 g, 47.7 mmol) in Et_2O (28 mL) and cooled to 0 °C. 4-Bromobenzotrifluoride (6.1 mL, 43.4 mmol) was added drop-wise and the colour changed to yellow then to black. The suspension was stirred at 0 °C for 20 min then warmed to 30 °C and stirred for a further 90 min, then transferred *via* cannula to an oven dried flask and cooled to 0 °C. Diethyl phosphite (1.9 mL, 14.4 mmol) was added drop-wise to the grignard solution and the resulting solution was warmed to room temperature and stirred overnight. The solution was cooled to 0 °C and quenched *via* the drop-wise addition of aqueous HCl (2 M) solution, then warmed to room temperature and extracted with EtOAc. The combined organics were washed with water then brine, dried (Na_2SO_4), filtered then concentrated onto silica. Purification by column chromatography (50-90% EtOAc/petroleum ether) afforded the title compound as an orange solid (3.01 g, 61%). R_f = 0.12 (50% EtOAc/petroleum ether); m.p. 64-66 °C ($CHCl_3$); IR 1504, 1396, 1318, 1162, 1121, 1098, 4058,

1014 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (1H, d, *J* = 491.4 Hz, P**H**), 7.98-7.74 (8H, m, Ar**H**); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.0 (d, $J_{C\text{-}P}$ = 99.3 Hz, C), 134.9 (app dd, $J_{C\text{-}F}$ = 33.1, $J_{C\text{-}P}$ = 3.1 Hz, C), 131.3 (d, $J_{C\text{-}P}$ = 11.8 Hz, 2 × CH), 126.2 (dq, $J_{C\text{-}P}$ = 12.1, $J_{C\text{-}F}$ = 3.6 Hz, 2 × CH), 123.4 (q, $J_{C\text{-}F}$ = 272.7 Hz, 2 × C); ^{31}P NMR (202 MHz, $CDCl_3$) δ 17.8 (dp, *J* = 491.9, 13.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.4 (s, 6 × F); HRMS (ESI) Exact mass calculated for $[C_{14}H_9OF_6PNa]^+$ $[M+Na]^+$: 361.0187, found: 361.0184;. Spectroscopic data consistent with those previously reported.[108]



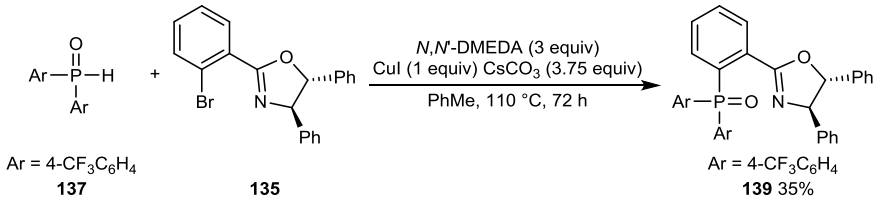
(*R*)-(2-(4-Phenyl-4,5-dihydrooxazol-2-yl)phenyl)bis(4-(trifluoromethyl)phenyl) phosphine oxide (138). A schlenk flask was evacuated and back-filled with Ar (3 cycles). Under a flow of Ar, CuI (39 mg, 0.21 mmol) and bis(4-(trifluoromethyl)phenyl)phosphine oxide (1.68 mg, 4.96 mmol) were added, followed by degassed toluene (12 mL). *N*,*N*′-dimethylethylenediamine (0.15 mL, 1.45 mmol) was added followed by (*R*)-2-(2-bromophenyl)-4-phenyl-4,5-dihydrooxazole (500 mg, 1.65 mmol) in toluene (4 mL) and Cs_2CO_3 (2.02 g, 6.21 mmol). The flask was sealed with a septa and PTFE tape, and the resulting suspension was stirred at 110 °C for 72 h then filtered over celite (EtOAc), concentrated and loaded onto silica. Purification by column chromatography (20% EtOAc/petroleum ether) afforded the title compound as a colourless solid (210 mg, 22%). R_f = 0.10 (50% EtOAc/petroleum ether); m.p 69-72 °C ($CHCl_3$); IR 1658, 1318, 1165, 1121, 1059, 948, 760, 697, 565 cm^{-1}; $[\alpha]_D^{23}$ −80.0 (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11-8.03 (1H, m, Ar**H**), 7.88-7.76 (4H, m, Ar**H**), 7.75-7.54 (7H, m, Ar**H**), 7.34-7.20 (3H, m, Ar**H**), 7.11-7.06 (2H, m, Ar**H**), 4.92 (1H, app t, *J* = 9.8 Hz, C**H**Ph), 4.35 (1H, dd, *J* = 10.1, 8.4 Hz, C$\mathbf{H}_a$CH_b), 3.86 (1H, dd, *J* = 9.5, 8.4 Hz, CH_aC$\mathbf{H}_b$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.5 (d, *J* = 2.7 Hz, C), 141.0 (C), 137.8 (d, *J* = 106.9 Hz, C), 137.3 (d, *J* = 106.5 Hz, C), 135.0 (d, *J* = 10.4 Hz, CH), 134.1-132.9 (m, 2 × C), 132.7 (d, *J* = 2.6 Hz, CH), 132.2 (d,

J = 10.4 Hz, 2 × CH), 131.9 (d, *J* = 6.3 Hz, C), 131.8 (d, *J* = 10.1 Hz, 2 × CH), 131.4 (d, *J* = 8.9 Hz, CH), 130.9 (d, *J* = 12.7 Hz, CH), 130.0 (C), 128.6 (2 × CH), 127.7 (CH), 126.7 (2 × CH), 125.3 (app dt, *J* = 12.6, 4.2 Hz, 4 × CH), 126.9-120.0 (m, 2 × C), 74.6 (CH_2), 70.1 (CH); ^{31}P NMR (202 MHz, $CDCl_3$) δ 28.3 (app q, *J*=13.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.10 (s, 6 × F), −63.13 (s, 3 × F) ; HRMS (ESI) Exact mass calculated for $[C_{29}H_{20}O_2F_6NPNa]^+$ $[M+Na]^+$: 582.1028, found: 582.1023.



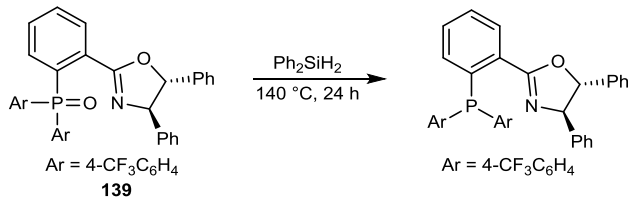
(*R*)-2-(2-(Bis(4-(trifluoromethyl)phenyl)phosphanyl)phenyl)-4-phenyl-4,5-dihydrooxazole (L22). A schlenk flask was evacuated and back-filled with Ar (3 cycles). Under a flow of Ar was added **138** (150 mg, 0.21 mmol) and Ph_2SiH_2 (2 mL). The resulting solution was stirred at 140 °C overnight then diluted with petroluem ether and loaded onto silica. Purification by column chromatography (0-10% EtOAc/petroleum ether) gave the title compound as a colourless solid (101 mg, 69%). R_f = 0.40 (20% EtOAc/petroleum ether); m.p 178-180 °C ($CHCl_3$); IR 2901, 1650, 321, 1121, 10259, 1015, 952, 831, 712, 697, 598 cm^{-1}; $[\alpha]_D^{23}$ −84.0 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (1H, ddd, *J* = 7.7, 3.8, 1.4 Hz, Ar**H**), 7.62-7.55 (3H, m, Ar**H**), 7.54-7.51 (2H, m, Ar**H**), 7.48 (1H, td, *J* = 7.6, 1.3 Hz, Ar**H**), 7.43-7.31 (5H, m, Ar**H**), 7.23-7.14 (3H, m, Ar**H**), 6.96-6.82 (3H, m, Ar**H**), 5.35 (1H, app t, *J* = 9.6 Hz, C**H**$_a$H$_b$), 4.68 (1H, dd, *J* = 10.2, 8.3 Hz, CH$_a$**H**$_b$), 4.06 (1H, t, *J* = 8.7 Hz, C**H**Ph); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.6 (d, $J_{C\text{-}P}$ = 3.4 Hz, C), 143.1 (d, $J_{C\text{-}P}$ = 10.2 Hz, C), 143.0 (d, $J_{C\text{-}P}$ = 4.4 Hz, C), 141.8 (C), 137.4 (d, $J_{C\text{-}P}$ = 25.4 Hz, C), 134.8 (d, $J_{C\text{-}P}$ = 21.1 Hz, 2 × CH), 134.2 (CH), 133.9 (d, $J_{C\text{-}P}$ = 20.1 Hz, 2 × CH), 131.5 (d, $J_{C\text{-}P}$ = 19.8 Hz, C), 131.3 (CH), 130.88 (C), 130.88 (d, $J_{C\text{-}P}$ = 63.5 Hz, C), 130.5 (d, $J_{C\text{-}P}$ = 3.2 Hz, CH), 129.1 (CH), 128.6 (2 × CH), 127.5 (CH) 126.4 (2 × CH), 125.7-125.2 (m, 4 × CH), 127.5-120.8 (m, 2 × CF_3), 74.4 (CH_2), 70.5 (CH); ^{31}P NMR (162 MHz, $CDCl_3$) δ −7.2 (s); ^{19}F NMR (376

MHz, $CDCl_3$) δ −62.6 (s, 3 × F), −62.8 (s, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{29}H_{20}OF_6NPNa]^+$ $[M+Na]^+$: 566.1079, found: 566.1077.

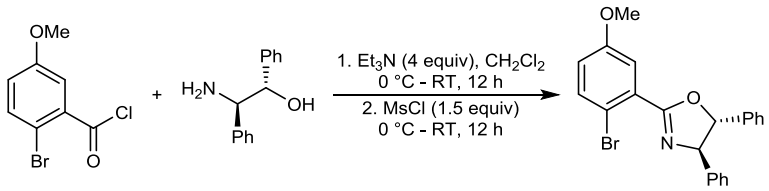


(2-((4*R*,5*R*)-4,5-Diphenyl-4,5-dihydrooxazol-2-yl)phenyl)bis(4-(trifluoromethyl)phenyl) phosphine oxide (139). A schlenk flask was evacuated and back-filled with Ar (3 cycles). Under a flow of Ar, CuI (389 mg, 2.04 mmol) and **137** (900 mg, 2.65 mmol) were added, followed by anhydrous, degassed toluene (7 mL). *N*,*N*′-dimethylethylenediamine (0.66 mL, 6.13 mmol) was added followed by **135** (773 mg, 2.04 mmol) as a solution in toluene (2 mL). Solid Cs_2CO_3 (2.46 g, 7.56 mmol) was added and the schlenk flask was sealed with a rubber septum and PTFE tape. The resulting suspension was stirred at 110 °C for 72 h then filtered over celite (EtOAc), concentrated and loaded onto silica. Purification by column chromatography (20-60% EtOAc/petroleum ether) afforded the title compound as a pale yellow solid (456 mg, 35%). R_f = 0.18 (50% EtOAc/petroleum ether); m.p. 78-80 °C ($CHCl_3$); IR 1658, 1398, 1319, 1166, 1124, 1105, 1060, 1016, 833, 710, 697, 565, 548 cm^{-1}; $[\alpha]_D^{23}$ −4.0 (*c* 1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.18 (1H, ddd, *J* = 7.8, 4.1, 1.3 Hz, Ar**H**), 7.86-7.70 (7H, m, Ar**H**), 7.67-7.60 (5H, m, Ar**H**), 7.31-7.27 (5H, m, Ar**H**), 7.08 (2H, dd, *J* = 7.4, 2.2 Hz, Ar**H**), 6.99-6.96 (2H, m, Ar**H**), 5.13 (1H, d, *J* = 10.0 Hz, C**H**Ph), 4.82 (1H, d, *J* = 10.0 Hz, C**H**Ph); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.5 (d, $J_{C\text{-}P}$ = 2.7 Hz, C), 140.5 (2 × C), 138.6 (d, $J_{C\text{-}P}$ = 108.6 Hz, C), 138.5 (2 × C), 137.2 (d, $J_{C\text{-}P}$ = 107.2 Hz, C), 135.3 (d, $J_{C\text{-}P}$ = 10.2 Hz, CH), 133.8 – 133.1 (m, C), 132.9 (d, $J_{C\text{-}P}$ = 2.7 Hz, CH), 132.6 (d, $J_{C\text{-}P}$ = 10.1 Hz, 2 × CH), 131.7 (d, $J_{C\text{-}P}$ = 10.7 Hz, 2 × CH), 131.6 (d, $J_{C\text{-}P}$ = 8.9 H, CH), 131.2 (d, $J_{C\text{-}P}$ = 12.3 Hz, CH), 131.0 (d, $J_{C\text{-}P}$ = 100.9 Hz, C), 128.8 (4 × CH), 128.7 (CH), 127.9 (CH), 127.0 (2 × CH), 126.2 (2 × CH), 125.3 (dq, *J* = 12.2, *J* = 3.8 Hz, 4 × CH), 127.0-119.6 (m, 2 × C), 89.6 (CH), 78.2 (CH); ^{31}P NMR (202 MHz, $CDCl_3$) δ 29.3 (d, *J* = 12.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.08 (s, 3 × F), −63.14 (s, 3 × F); HRMS (ESI)

Exact mass calculated for $[C_{35}H_{24}O_2F_6NPNa]^+$ $[M+Na]^+$: 658.1341, found: 658.1317.



(4*R*,5*R*)-2-(2-(Bis(4-(trifluoromethyl)phenyl)phosphanyl)phenyl)-4,5-diphenyl-4,5-dihydrooxazole (L23). A schlenk flask was evacuated and back-filled with Ar (3 cycles). Under a flow of Ar, **139** (450 mg, 0.71 mmol) was added followed by Ph_2SiH_2 (0.92 mL, 4.96 mmol). The flask was sealed with a rubber septa and PTFE tape. The resulting solution was stirred at 140 °C overnight then diluted with petroleum ether and loaded onto silica. Purification by column chromatography (0-10% EtOAc/petroleum ether) gave the title compound as a colourless solid (411 mg, 93%). R_f = 0.45 (20% EtOAc/petroleum ether); m.p 168-170 °C (*n*-hexane); IR 3069, 2130, 1428, 1323, 1167, 1115, 1059, 1016, 997, 816, 732, 696, 494 cm^{-1}; $[\alpha]_D^{22}$ −8.0 (*c* 1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.17 (1H, ddd, *J* = 7.8, 3.9, 1.4 Hz, Ar**H**), 7.59 (2H, d, *J* = 7.9 Hz, 2 × Ar**H**), 7.57-7.46 (3H, m, Ar**H**), 7.45-7.32 (9H, m, Ar**H**), 7.25-7.15 (4H, m, Ar**H**), 6.92 (1H, ddd, *J* = 7.8, 3.9, 1.2 Hz, Ar**H**), 6.84-6.80 (2H, m, Ar**H**), 5.18 (2H, s, 2 × C**H**Ph); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.8 (d, J_{C-P} = 3.7 Hz, C), 143.2 (d, J_{C-P} = 4.5 Hz, C), 143.1 (C), 141.4 (C), 139.8 (C), 137.8 (d, J_{C-P} = 25.9 Hz, C), 134.8 (d, J_{C-P} = 21.6 Hz, 2 × CH), 134.3 (CH), 133.9 (d, J_{C-P} = 20.1 Hz, 2 × CH), 131.4 (CH), 131.32-130.84 (m, 2 × C), 130.7 (d, J_{C-P} = 3.4 Hz, CH), 129.1 (CH), 129.0 (2 × CH), 128.7 (CH), 128.6 (2 × CH), 127.6 (CH), 126.5 (2 × CH), 126.3 (2 × CH), 125.5 (app ddd, *J* = 10.6, 7.1, 3.7 Hz, 4 × CH), 127.6-120.8 (m, 2 × C), 89.0 (CH), 79.1 (CH); ^{31}P NMR (162 MHz, $CDCl_3$) δ −7.3 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.6 (s), −62.8 (s); HRMS (ESI) Exact mass calculated for $[C_{35}H_{25}OF_6NP]^+$ $[M+H]^+$: 620.1572, found: 620.1579.

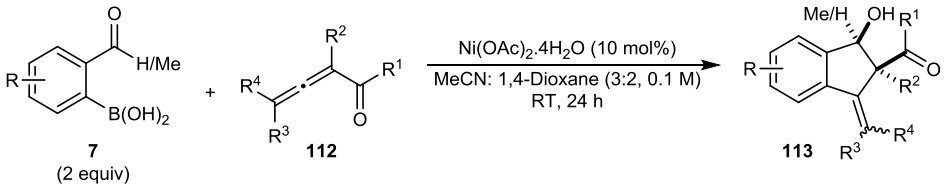


(4*R*,5*R*)-2-(2-Bromo-5-methoxyphenyl)-4,5-diphenyl-4,5-dihydrooxazole (140). A flask was charged with (1*S*,2*R*)-2-amino-1,2-diphenylethanol (500 mg, 2.34 mmol) and Et_3N (1.30 mL, 9.36 mmol) in CH_2Cl_2 (13 mL) and was cooled to 0 °C. 2-bromo-5-methoxybenzoyl chloride (643 mg, 2.58 mmol) in CH_2Cl_2 (2 mL) was added drop-wise, and the resulting solution was then warmed to room temperature and stirred overnight. The suspension was then cooled to 0 °C and MsCl (0.27 mL, 3.51 mmol) was added drop-wise. The solution was warmed to room temperature and stirred for 6 h, then quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2. The combined organics were washed with brine, dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (10% EtOAc/petroleum ether) afforded the title compound as a colourless oil (396 mg, 41%). R_f = 0.35 (20% EtOAc/petroleum ether); $[\alpha]_D^{22}$ +16.0 (*c* 1, $CHCl_3$); IR 1649, 1593, 1454, 1407, 1320, 1287, 1255, 1178, 1042, 1016, 962, 695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.58 (1H, d, *J* = 8.8 Hz, Ar**H**), 7.46-7.30 (11H, m, Ar**H**), 6.91 (1H, dd, *J* = 8.9, 3.1 Hz, Ar**H**), 5.43 (1H, d, *J* = 8.1 Hz, C**H**Ph), 5.29 (1H, d, *J* = 8.1 Hz, C**H**Ph), 3.84 (3H, s, OC**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.6 (C), 158.8 (C), 141.8 (C), 140.2 (C), 135.0 (C), 130.2 (C), 129.1 (2 × CH), 129.0 (2 × CH), 128.7 (CH), 128.0 (CH), 126.9 (2 × CH), 126.1 (2 × CH), 118.6 (CH), 116.7 (CH), 112.6 (C), 89.6 (CH), 79.3 (CH), 55.9 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{22}H_{18}NO_2NaBr]^+$ $[M+Na]^+$: 430.0413, found: 430.0411.

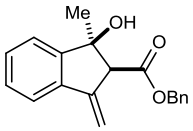
[Ni_2(*μ*-OH_2)(O_2CCMe_3)$_4$(HO_2CCMe_3)$_4$]. To a flask charged with $Ni(OH)_2$ (1.00 g, 10.79 mmol) in toluene (20 mL) was added pivalic acid (5.00 g, 50.7 mmol). The resulting solution was stirred at reflux for 3 h, then cooled and concentrated to approx. 10 mL solvent. Acetonitrile was added and the solid was isolated by filtration to give the title compound as a fine green powder (3.40 g, 33%). IR 2967, 1673, 1603, 1480, 1459, 1404, 1358, 1207, 875, 798, 601, 543 cm^{-1}; Anal. calculated for $C_{40}H_{78}O_{17}Ni_2$: C, 50.91; H, 8.35. Found: C, 50.69; H, 8.37. Spectroscopic data consistent with those previously reported.[54]

8.4. Synthesis of 3-methyleneindan-1-ols

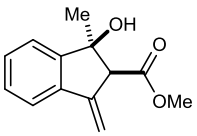
General Procedure A: Nickel-Catalysed Annulation of Allenes with 2-carbonylarylboronic acids.



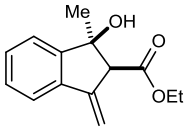
A flask was charged with $Ni(OAc)_2.4H_2O$ (7.5 mg, 10 mol%), 2-acetylphenylboronic acid (0.60 mmol, 2 equiv) and allene (0.30 mmol, 1 equiv). The flask was sealed with a rubber septa and purged with Ar. Degassed MeCN (1.8 mL) and degassed dioxane (1.2 mL) were added, and the resulting solution was stirred at room temperature overnight, then diluted with Et_2O (*ca.* 3 mL), filtered over silica with Et_2O as the eluent and concentrated to afford the crude. Purification gave the appropriate 3-methyleneindan-1-ol.



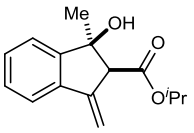
(±) Benzyl (1*S*,2*S*)-1-hydroxy-1-methyl-3-methylene-2,3-dihydro-1*H*-indene-2-carboxylate (113ba). The title compound was prepared according to **General Procedure A**, from benzyl buta-2,3-dienoate **112a** (52.3 mg, 0.30 mmol) and 2-acetylphenylboronic acid **7b** (98.4 mg, 0.60 mmol). Purification by column chromatography (10% EtOAc/petroleum ether) gave **113ba** as a pale yellow oil (74.2 mg, 84%). R_f = 0.27 (20% EtOAc/petroleum ether); IR 3485 (br, OH), 1717 (C=O), 1643, 1315, 1153, 1009, 845, 757, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.51-7.44 (2H, m, Ar**H**), 7.40-7.30 (7H, m, Ar**H**), 5.66 (1H, d, *J* = 1.8 Hz, =C**H**$_a$H$_b$), 5.27 (1H, d, *J* = 1.8 Hz, =CH$_a$**H**$_b$), 5.19 (2H, app d, *J* = 3.0 Hz, OC**H**$_2$), 3.86 (1H, t, *J* = 1.8 Hz, C**H**), 3.54 (1H, s, O**H**), 1.60 (3H, s, C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.0 (C), 149.6 (C), 144.4 (C), 137.9 (C), 135.7 (C), 129.8 (CH), 129.0 (CH), 128.8 (2 × CH), 128.5 (CH), 128.3 (2 × CH), 123.2 (CH), 120.9 (CH), 107.7 (CH_2), 79.9 (C), 67.0 (CH_2), 61.3 (CH), 28.9 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{19}H_{18}NaO_3]^+$ $[M+Na]^+$: 317.1148, found: 317.1140



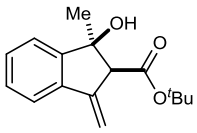
(±) Methyl (1*S*,2*S*)-1-hydroxy-1-methyl-3-methylene-2,3-dihydro-1*H*-indene-2-carboxylate (113bb). The title compound was prepared according to General Procedure **A**, from methyl buta-2,3-dienoate **112b** (29.4 mg, 0.30 mmol) and 2-acetylphenylboronic acid **7b** (98.4 mg, 0.60 mmol). Purification by column chromatography (0-10% EtOAc/*n*-pentane) gave **113bb** as an off-white solid (39.2 mg, 60%). R_f = 0.18 (20% EtOAc/petroleum ether); m.p 85-86 °C (Et_2O); IR 3426 (br, OH), 1724 (C=O), 1435, 1367, 1337, 1297, 1257, 1195, 1137, 951, 903, 761, 610, 563 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50-7.44 (2H, m, Ar**H**), 7.39-7.27 (2H, m, Ar**H**), 5.67 (1H, d, *J* = 1.8 Hz, =C**H**$_a$CH$_b$), 5.27 (1H, d, *J* = 1.8 Hz, =CH$_a$C**H**$_b$), 3.82 (1H, t, *J* = 1.8 Hz, C**H**), 3.75 (3H, s, OC**H**$_3$), 3.54 (1H, d, *J* = 0.9 Hz, O**H**), 1.60 (3H, d, *J* = 0.9 Hz, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6 (C), 149.6 (C), 144.5 (C), 137.9 (C), 129.8 (CH), 129.0 (CH), 123.3 (CH), 120.9 (CH), 107.5 (CH_2), 79.7 (C), 61.2 (CH), 52.4 (CH_3), 28.9 (CH_3); GCMS (EI) T_r: 10.86 $[M]^+$ $C_{13}H_{14}O_3$ found: 218.0.



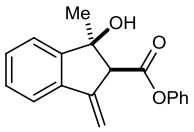
(±) Ethyl (1*S*,2*S*)-1-hydroxy-1-methyl-3-methylene-2,3-dihydro-1*H*-indene-2-carboxylate (113bc). The title compound was prepared according to General Procedure **A**, from ethyl buta-2,3-dienoate **112c** (33.6 mg, 0.30 mmol) and 2-acetylphenylboronic acid **7b** (98.4 mg, 0.60 mmol). Purification by column chromatography (10% EtOAc/petroleum ether) gave **113bc** as a yellow oil (60.0 mg, 86%). R_f = 0.23 (20% EtOAc/petroleum ether); IR 3441 (br, OH), 2978, 1718 (C=O), 1643, 1369, 1317, 1179, 1087, 1032, 927, 759 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.51-7.42 (2H, m, Ar**H**), 7.37-7.29 (2H, m, Ar**H**), 5.66 (1H, d, *J* = 1.8 Hz, =C**H**$_a$CH$_b$), 5.28 (1H, d, *J* = 1.8 Hz, =CH$_a$C**H**$_b$), 4.21 (2H, q, *J* = 7.1 Hz, OC**H**$_2$), 3.81-3.76 (1H, m, C**H**), 3.68 (1H, s, O**H**), 1.59 (3H, s, C**H**$_3$), 1.30 (3H, t, *J* = 7.1 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3 (C), 149.8 (C), 144.7 (C), 137.9 (C), 129.8 (CH), 129.0 (CH), 123.2 (CH), 120.9 (CH), 107.4 (CH_2), 79.7 (C), 61.3 (CH_2), 61.1 (CH), 28.9 (CH_3), 14.3 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{14}H_{16}NaO_3]^+$ $[M+Na]^+$: 255.0992, found: 255.0993.



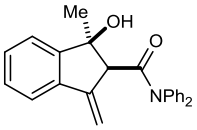
(±) Isopropyl (1*S*,2*S*)-1-hydroxy-1-methyl-3-methylene-2,3-dihydro-1*H*-indene-2-carboxylate (113bd). The title compound was prepared according to General Procedure **A**, from isopropyl buta-2,3-dienoate **112d** (37.8 mg, 0.30 mmol) and 2-acetylphenylboronic acid **7b** (98.4 mg, 0.60 mmol). Purification by column chromatography (0-5% EtOAc/*n*-pentane) gave **113bd** as an off-white solid (65.0 mg, 88%). R_f = 0.33 (20% EtOAc/petroleum ether); m.p. 58-60 °C (Et_2O/*n*-pentane); IR 3428 (br, OH), 1717 (C=O), 1369, 1339, 1325, 1254, 1207, 1104, 884, 772 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51-7.43 (2H, m, Ar**H**), 7.37-7.28 (2H, m, Ar**H**), 5.65 (1H, d, *J* = 1.9 Hz, =C**H**$_a$H$_b$), 5.28 (1H, d, *J* = 1.9 Hz, =CH$_a$**H**$_b$), 5.08 (1H, hept, *J* = 6.3 Hz, OC**H**(CH$_3$)$_2$), 3.81 (1H, d, *J* = 0.9 Hz, O**H**), 3.74 (1H, t, *J* = 1.9 Hz, C**H**), 1.58 (3H, d, *J* = 0.9 Hz, C**H**$_3$), 1.29 (3H, d, *J* = 6.2 Hz, OCH(C**H**$_3$)$_2$), 1.25 (3H, d, *J* = 6.2 Hz, OCH(C**H**$_3$)$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.9 (C), 149.9 (C), 144.8 (C), 137.8 (C), 129.8 (CH), 128.9 (CH), 123.2 (CH), 120.9 (CH), 107.2 (CH_2), 79.6 (C), 68.8 (CH), 61.0 (CH), 28.9 (CH_3), 22.0 (CH_3), 21.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{15}H_{18}NaO_3]^+$ [M+Na]$^+$: 269.1148, found: 269.1148.



(±) *tert*-Butyl (1*S*,2*S*)-1-hydroxy-1-methyl-3-methylene-2,3-dihydro-1*H*-indene-2-carboxylate (113be). The title compound was prepared according to General Procedure **A**, from *tert*-butyl buta-2,3-dienoate **112e** (42.1 mg, 0.30 mmol) and 2-acetylphenylboronic acid **7b** (98.4 mg, 0.60 mmol). Purification by preparative TLC (30% petroleum ether/CH_2Cl_2) gave **113be** as a colourless solid (53.1 mg, 68%). R_f = 0.33 (20% EtOAc/petroleum ether); m.p. 75-77 °C (Et_2O/*n*-pentane); IR 3432 (br, OH), 1718 (C=O), 1392, 1155, 1094, 1038, 937, 757, 563 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49-7.43 (2H, m, Ar**H**), 7.36-7.28 (2H, m, Ar**H**), 5.65 (1H, d, *J* = 1.8 Hz, =C**H**$_a$H$_b$), 5.27 (1H, d, *J* = 1.8 Hz, =CH$_a$**H**$_b$), 3.92 (1H, d, *J* = 1.0 Hz, O**H**), 3.68 (1H, t, *J* = 1.8 Hz, C**H**), 1.56 (3H, d, *J* = 1.0 Hz, C**H**$_3$), 1.47 (9H, s, 3 × C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8 (C), 150.1 (C), 145.1 (C), 137.9 (C), 129.7 (CH), 128.8 (CH), 123.2 (CH), 120.8 (CH), 106.9 (CH_2), 82.1 (C), 79.5 (C), 61.7 (CH), 29.0 (CH_3), 28.2 (3 × CH_3); HRMS (ESI) Exact mass calculated for $C_{16}H_{20}NaO_3$ [M+Na]$^+$: 283.1305, found: 283.1301.

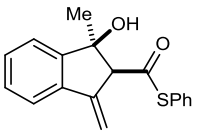


(±) Phenyl (1*S*,2*S*)-1-hydroxy-1-methyl-3-methylene-2,3-dihydro-1*H*-indene-2-carboxylate (113bf). The title compound was prepared according to General Procedure **A**, from phenyl buta-2,3-dienoate **112f** (48.1 mg, 0.30 mmol) and 2-acetylphenylboronic acid **7b** (98.4 mg, 0.60 mmol). Purification by column chromatography (10% EtOAc/petroleum ether) gave **113bf** as a pale yellow oil (69.8 mg, 83%). R_f = 0.27 (20% EtOAc/petroleum ether); IR 3501 (br, OH), 3070, 3042, 2971, 2928, 1740 (C=O), 1592, 1491, 1191, 1161, 1122, 1047, 950, 784, 728 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 (1H, dd, *J* = 6.7, 1.8 Hz, Ar**H**), 7.50-7.47 (1H, m, Ar**H**), 7.40-7.33 (4H, m, Ar**H**), 7.26-7.21 (1H, m, Ar**H**), 7.16-7.10 (2H, m, Ar**H**), 5.79 (1H, d, *J* = 1.8 Hz, =C**H**$_a$H$_b$), 5.45 (1H, d, *J* = 1.8 Hz, =CH$_a$**H**$_b$), 4.07 (1H, s, C**H**), 3.52-3.25 (1H, m, O**H**), 1.71 (3H, s, C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6 (C), 150.7 (C), 149.3 (C), 144.2 (C), 137.9 (C), 129.9 (CH), 129.6 (2 × CH), 129.2 (CH), 126.2 (CH), 123.3 (CH), 121.6 (2 × CH), 121.0 (CH), 108.2 (CH_2), 80.2 (C), 61.3 (CH), 29.0 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{18}H_{16}NaO_3]^+$ $[M+Na]^+$: 303.0992, found: 303.0990.

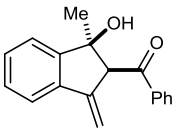


(±) (1*S*,2*S*)-1-Hydroxy-1-methyl-3-methylene-*N*,*N*-diphenyl-2,3-dihydro-1*H*-indene-2-carboxamide (113bg). The title compound was prepared according to General Procedure **A**, from *N*,*N*-diphenylbuta-2,3-dienamide **112g** (70.1 mg, 0.30 mmol) and 2-acetylphenylboronic acid **7b** (98.4 mg, 0.60 mmol). Purification by column chromatography (10-30% EtOAc/petroleum ether) gave **113bg** as a pale yellow solid (96.0 mg, 90%). R_f = 0.15 (20% EtOAc/petroleum ether); m.p. 120-122 °C (Et_2O/*n*-pentane); IR 3493 (br, OH), 1650 (C=O), 1633, 1585, 1488, 1370, 1291, 1119, 703, 694, 569, 506 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52-7.37 (7H, m, Ar**H**), 7.35-7.27 (4H, m, Ar**H**), 7.24 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.19 (1H, t, *J* = 7.4 Hz, Ar**H**), 5.60 (1H, d, *J* = 1.9 Hz, =C**H**$_a$H$_b$), 5.11 (1H, d, *J* = 1.9 Hz, =CH$_a$**H**$_b$), 4.28-4.24 (1H, m, C**H**), 4.06 (1H, d, *J* = 1.8 Hz, O**H**), 1.46 (3H, s, C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3 (C), 150.8 (C), 147.5 (C), 142.9 (C), 142.3 (C), 138.4 (C), 130.2 (CH), 129.7 (CH), 129.11 (2 × CH), 129.05 (CH), 128.7 (2 × CH), 128.3 (CH), 126.69 (CH),

126.65 (2 × CH), 123.1 (CH), 120.8 (2 × CH), 105.7 (CH_2), 80.2 (C), 59.0 (CH), 28.5 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{24}H_{21}NNaO_2]^+$ $[M+Na]^+$: 378.1464, found: 378.1460.

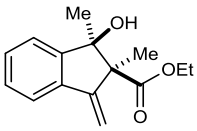


(±) *S*-phenyl (1*S*,2*S*)-1-hydroxy-1-methyl-3-methylene-2,3-dihydro-1*H*-indene-2-carbothioate (113bh). The title compound was prepared according to General Procedure **A**, from *S*-phenyl buta-2,3-dienethioate **112h** (52.9 mg, 0.30 mmol) and 2-acetylphenylboronic acid **7b** (98.4 mg, 0.60 mmol). Purification by column chromatography (5-20% EtOAc/petroleum ether) gave **113bh** as an orange oil (77.4 mg, 87%). R_f = 0.33 (20% EtOAc/petroleum ether); IR 3423 (br, OH), 1682 (C=O), 1477, 1440, 1250, 1013, 908, 839, 728, 688 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.51-7.46 (1H, m, Ar**H**), 7.46-7.37 (6H, m, Ar**H**), 7.32 (2H, m, Ar**H**), 5.75 (1H, d, *J* = 1.6 Hz, =C**H**$_a$H$_b$), 5.45 (1H, d, *J* = 1.6 Hz, =CH$_a$**H**$_b$), 4.11 (1H, t, *J* = 1.6 Hz, C**H**), 3.23 (1H, br s, O**H**), 1.62 (3H, s, C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.4 (C), 150.0 (C), 144.6 (C), 137.5 (C), 134.6 (2 × CH), 129.9 (CH), 129.7 (CH), 129.3 (2 × CH), 129.0 (CH), 127.4 (C), 123.0 (CH), 121.0 (CH), 108.3 (CH_2), 80.9 (C), 69.6 (CH), 29.5 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{18}H_{16}NaO_2S]^+$ $[M+Na]^+$: 319.0763, found: 319.0768.

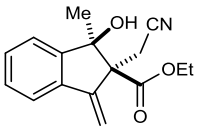


(±) ((1*S*,2*S*)-1-Hydroxy-1-methyl-3-methylene-2,3-dihydro-1*H*-inden-2-yl)(phenyl)methanone (113bp). The title compound was prepared according to General Procedure **A**, from 1-phenylbuta-2,3-dien-1-one **112p** (43.2 mg, 0.30 mmol) and 2-acetylphenylboronic acid **7b** (98.4 mg, 0.60 mmol). Purification by column chromatography (10% EtOAc/petroleum ether) gave **113bp** as a yellow solid (44.4 mg, 56%). R_f = 0.30 (20% EtOAc/petroleum ether); m.p. 102-103 °C (Et_2O/*n*-pentane); IR 3491 (br, OH), 1782 (C=O), 1660, 1461, 1373, 1258, 888, 759, 708, 678, 608, 583, 563, 519 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08-8.02 (2H, m, Ar**H**), 7.66-7.60 (1H, m, Ar**H**), 7.57-7.49 (3H, m, Ar**H**), 7.44 (1H, app dt, *J* = 7.6, 1.0 Hz, Ar**H**), 7.38 (1H, td, *J* = 7.4, 1.2 Hz, Ar**H**), 7.31 (1H, td, *J* = 7.4, 1.2 Hz, Ar**H**), 5.60 (1H, d, *J* = 1.6 Hz, =C**H**$_a$H$_b$), 4.98 (1H, d, *J* = 1.6 Hz, =CH$_a$**H**$_b$), 4.88 (1H, t, *J* = 1.6 Hz, C**H**), 4.17 (1H, d, *J* = 1.0

Hz, O**H**), 1.63 (3H, d, *J* = 1.0 Hz, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1 (C), 150.9 (C), 145.4 (C), 137.7 (C), 137.0 (C), 133.8 (CH), 129.9 (CH), 129.3 (2 × CH), 128.9 (2 × CH), 128.7 (CH), 122.9 (CH), 121.0 (CH), 108.0 (CH_2), 80.7 (C), 61.8 (CH), 29.4 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{18}H_{16}NaO_3]^+$ $[M+Na]^+$: 265.1223, found: 265.1213.

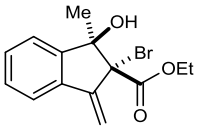


(±) Ethyl (1*R*,2*S*)-1-hydroxy-1,2-dimethyl-3-methylene-2,3-dihydro-1*H*-indene-2-carboxylate (113bi). The title compound was prepared according to General Procedure **A**, from ethyl 2ethyl 2-methylbuta-2,3-dienoate **112i** (37.8 mg, 0.30 mmol) and 2-acetylphenylboronic acid **7b** (98.4 mg, 0.60 mmol). Purification by column chromatography (0-10% EtOAc/petroleum ether) gave **113bi** as a colourless oil (37.9 mg, 51%). R_f = 0.33 (20% EtOAc/petroleum ether); IR 3423 (br, OH), 2981, 1702 (C=O), 1442, 1377, 1243, 1129, 1077, 882, 762 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.40 (2H, m, Ar**H**), 7.33 (1H, app td, *J* = 7.4, 1.3 Hz, Ar**H**), 7.32-7.23 (1H, m, Ar**H**), 5.63 (1H, app s, =C**H**$_a$H$_b$), 5.20 (1H, app s, =CH$_a$**H**$_b$), 4.16-4.02 (2H, m, OC**H**$_2$CH$_3$), 3.98 (1H, d, *J* = 0.9 Hz, O**H**), 1.54 (3H, s, C**H**$_3$), 1.36 (3H, d, *J* = 0.9 Hz, C**H**$_3$), 1.18 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8 (C), 150.0 (C), 137.3 (C), 129.6 (CH), 128.4 (CH), 122.6 (CH), 120.9 (CH), 106.4 (CH_2), 82.6 (C), 62.4 (C), 61.3 (CH_2), 25.7 (CH_3), 17.6 (CH_3), 14.0 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{15}H_{18}NaO_3]^+$ $[M+Na]^+$: 269.1148, found: 269.1151.

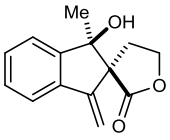


(±) Ethyl (1*R*,2*S*)-2-(cyanomethyl)-1-hydroxy-1-methyl-3-methylene-2,3-dihydro-1*H*-indene-2-carboxylate (113bk). The title compound was prepared according to **General** General Procedure **A**, from ethyl 2-(cyanomethyl)buta-2,3-dienoate **112k** (45.3 mg, 0.30 mmol) and 2-acetylphenylboronic acid **7b** (98.4 mg, 0.60 mmol). Purification by column chromatography (5-30% EtOAc/petroleum ether) gave **113bk** as a colourless solid (49.7 mg, 61%). R_f = 0.14 (20% EtOAc/petroleum ether); m.p. 121-123 °C (Et_2O/*n*-pentane); IR 3430 (br, OH), 2252 (CN), 1724 (C=O), 1370, 1288, 1021, 898, 791, 772 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51-7.45 (1H, m, Ar**H**), 7.47-7.41 (1H, m, Ar**H**), 7.41-7.30 (2H, m, Ar**H**), 5.81 (1H, d, *J* = 1.2 Hz, =C**H**$_a$H$_b$), 5.31 (1H, d, *J* = 1.2 Hz, =CH$_a$**H**$_b$), 4.30-4.15

(2H, m, OC**H**$_2$CH$_3$), 3.31 (1H, br s, O**H**), 2.97 (1H, d, *J* = 16.7 Hz, C**H**$_a$H$_b$CN), 2.93 (1H, d, *J* = 16.7 Hz, CH$_a$**H**$_b$CN), 1.57 (3H, s, C**H**$_3$), 1.24 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (126 MHz, CDCl$_3$) δ 170.6 (C), 148.0 (C), 146.2 (C), 136.6 (C), 130.3 (CH), 129.3 (CH), 122.8 (CH), 121.2 (CH), 117.5 (C), 108.8 (CH$_2$), 82.7 (C), 63.3 (C), 62.4 (CH$_2$), 24.6 (CH$_3$), 21.9 (CH$_2$), 14.0 (CH$_3$); HRMS (ESI) Exact mass calculated for [C$_{16}$H$_{17}$NNaO$_3$]$^+$ [M+Na]$^+$: 294.1101, found: 294.1102.

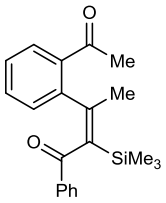


(±) Ethyl (1*R*,2*R*)-2-bromo-1-hydroxy-1-methyl-3-methylene-2,3-dihydro-1H-indene-2-carboxylate (113bl). The title compound was prepared according to General Procedure **A**, from ethyl 2-bromobuta-2,3-dienoate **112l** (57.3 mg, 0.30 mmol) and 2-acetylphenylboronic acid **7b** (98.4 mg, 0.60 mmol). Purification by column chromatography (10% EtOAc/petroleum ether) gave **113bl** as a yellow oil (22.1 mg, 24%). R_f = 0.20 (10% EtOAc/petroleum ether); IR 3449 (br, OH), 2924, 2854, 1737 (C=O), 1686, 1448, 1264, 1158, 1023, 909, 759 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.52-7.44 (2H, m, Ar**H**), 7.41-7.31 (2H, m, Ar**H**), 5.87 (1H, app s, =C**H**$_a$H$_b$), 5.83 (1H, app s, =CH$_a$**H**$_b$), 4.30-4.21 (2H, m, OC**H**$_2$CH$_3$), 4.06 (1H, s, O**H**), 1.77 (3H, s, C**H**$_3$), 1.29 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (126 MHz, CDCl$_3$) δ 169.9 (C), 146.3 (C), 146.2 (C), 136.2 (C), 130.1 (CH), 129.3 (CH), 123.0 (CH), 121.3 (CH), 111.7 (CH$_2$), 83.5 (C), 62.9 (CH$_2$), 27.1 (CH$_3$), 13.9 (CH$_3$); HRMS (ESI) Exact mass calculated for [C$_{14}$H$_{15}$NaO$_3$Br]$^+$ [M+Na]$^+$: 333.0097, found: 333.0092.

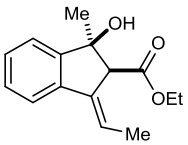


(±) (1'*R*,3*S*)-1'-Hydroxy-1'-methyl-3'-methylene-1',3',4,5-tetrahydro-2*H*-spiro[furan-3,2'-inden]-2-one (113bj). The title compound was prepared according to General Procedure **A**, from 3-vinylidenedihydrofuran-2(3*H*)-one **112j** (33.0 mg, 0.30 mmol) and 2-acetylphenylboronic acid **7b** (98.4 mg, 0.60 mmol). Purification by column chromatography (20-30% EtOAc/petroleum ether) gave **113bj** as a colourless solid (49.0 mg, 71%). R_f = 0.10 (20% EtOAc/petroleum ether); m.p. 110-111 °C (CHCl$_3$/Et$_2$O); IR 3410 (br, OH), 2969, 1738 (C=O), 1643, 1489, 1464, 1253, 1221, 1201, 1144, 1016, 931, 619, 503, 420 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.51-7.45 (2H, m, Ar**H**), 7.39 (1H, app. t, *J* = 7.4 Hz, Ar**H**), 7.35-

7.30 (1H, m, Ar**H**), 5.61 (1H, app s, =C**H**$_a$H$_b$), 5.21 (1H, app s, =CH$_a$**H**$_b$), 4.54-4.49 (2H, m, C**H**$_2$), 3.26 (1H, s, O**H**), 2.81 (1H, app dt, *J* = 13.3, 9.5 Hz, C**H**$_2$), 2.53 (1H, ddd, *J* = 13.3, 5.7, 3.8 Hz, C**H**$_2$), 1.37 (3H, s, C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.2 (C), 149.1 (C), 148.1 (C), 136.9 (C), 130.3 (CH), 129.0 (CH), 122.9 (CH), 121.1 (CH), 104.9 (CH_2), 81.4 (C), 66.5 (CH_2), 28.9 (CH_2), 26.2 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{14}H_{14}NaO_3]^+$ $[M+Na]^+$: 352.0835, found: 352.0832.

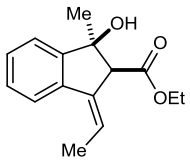


(*E*)-3-(2-Acetylphenyl)-1-phenyl-2-(trimethylsilyl)but-2-en-1-one (124). The title compound was prepared according to General Procedure **A**, from 1-phenyl-2-(trimethylsilyl)buta-2,3-dien-1-one **112q** (64.9 mg, 0.30 mmol) and 2-acetylphenylboronic acid **7b** (98.4 mg, 0.60 mmol). Purification by column chromatography (0-10%% EtOAc/*n*-pentane) gave **124** as a pale yellow oil (31 mg, 31%). R_f = 0.16 (10% EtOAc/petroleum ether); m.p. 85-87 °C (Et_2O); IR 3061, 1677 (C=O), 1651 (C=O), 1607, 1478, 1236, 1176, 1066, 1025, 884, 840, 772, 754, 690, 571 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36-8.28 (2H, m, Ar**H**), 7.88 (1H, dd, *J* = 7.8, 1.3 Hz, Ar**H**), 7.60-7.50 (4H, m, Ar**H**), 7.43 (1H, td, *J* = 7.6, 1.4 Hz), 7.35-7.27 (1H, m, Ar**H**), 2.67 (3H, s, C**H**$_3$), 1.86 (3H, s, C**H**$_3$), −0.29 (9H, s, Si(C**H**$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.8 (C), 199.1 (C), 151.5 (C), 144.4 (C), 140.7 (C), 138.0 (C), 135.5 (C), 133.2 (CH), 132.3 (CH), 131.1 (CH), 130.3 (CH), 129.9 (2 × CH), 128.8 (2 × CH), 127.8 (CH), 28.8 (CH_3), 25.2 (CH_3), −0.3 (3 × CH_3); HRMS (ESI) Exact mass calculated for $[C_{21}H_{24}NaO_2Si]^+$ $[M+Na]^+$: 359.1438, found: 359.1429.

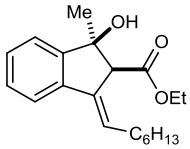


(±) Ethyl (1*S*,2*S*,*E*)-3-ethylidene-1-hydroxy-1-methyl-2,3-dihydro-1*H*-indene-2-carboxylate ((*E*)-113bm). The title compound was prepared according to General Procedure **A**, from ethyl penta-2,3-dienoate **112m** (37.8 mg, 0.30 mmol) and 2-acetylphenylboronic acid **7b** (98.4 mg, 0.60 mmol). Purification by column chromatography (0-5% EtOAc/*n*-pentane) gave **(*E*)-113bm** as a colourless oil (28.3 mg, 38%). R_f = 0.14 (10% EtOAc/petroleum ether); IR 3493 (br, OH), 2926, 1715 (C=O), 1445, 1311, 1153, 1034, 748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.33 (2H, m, Ar**H**), 7.28-7.22 (2H, m, Ar**H**), 6.18 (1H, qd, *J* =

7.1, 1.9 Hz, =C**H**), 4.24-4.12 (2H, m, OC**H**$_2$CH$_3$), 3.93-3.86 (1H, m, C**H**), 3.32 (1H, d, *J* = 1.2 Hz, O**H**), 1.87 (3H, dd, *J* = 7.1, 1.0 Hz, =CC**H**$_3$), 1.55 (3H, s, CH$_3$), 1.27 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); HRMS (ESI) Exact mass calculated for $[C_{15}H_{18}NaO_3]^+$ $[M+Na]^+$: 269.1148, found: 269.1150.

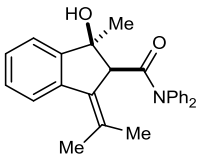


Ethyl (1*S*,2*S*,*Z*)-3-ethylidene-1-hydroxy-1-methyl-2,3-dihydro-1H-indene-2-carboxylate ((*Z*)-113bm). The title compound was prepared according to General Procedure **A**, from ethyl penta-2,3-dienoate **112m** (37.8 mg, 0.30 mmol) and 2-acetylphenylboronic acid **7b** (98.4 mg, 0.60 mmol). Purification by column chromatography (0-5% EtOAc/*n*-pentane) gave **(*Z*)-113bm** as a colourless oil (15.7 mg, 21%). R_f = 0.15 (10% EtOAc/petroleum ether); IR 3057 (br, OH), 2975, 1713 (C=O), 1367, 1321, 1177, 1085, 760 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59-7.54 (1H, m, Ar**H**), 7.49-7.45 (1H, m, Ar**H**), 7.33-7.29 (2H, m, Ar**H**), 5.88 (1H, qd, *J* = 7.3, 1.5 Hz, =C**H**), 4.17 (2H, qd, *J* = 7.2, 1.5 Hz, OC**H**$_2$CH$_3$), 3.77 (1H, d, *J* = 1.0 Hz, O**H**), 3.68 (1H, t, *J* = 1.4 Hz, C**H**), 2.04 (3H, dd, *J* = 7.3, 1.3 Hz, =CC**H**$_3$), 1.54 (3H, s, C**H**$_3$), 1.27 (3H, t, *J* = 7.2 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0 (C), 151.3 (C), 137.6 (C), 136.5 (C), 128.6 (CH), 128.5 (CH), 124.8 (CH), 123.0 (CH), 121.9 (CH), 79.1 (C), 63.0 (CH), 61.1 (CH_2), 28.8 (CH_3), 14.9 (CH_3), 14.3 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{15}H_{18}NaO_3]^+$ $[M+Na]^+$: 269.1148, found: 269.1145.

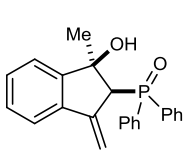


(±) Ethyl ((1*S*,2*S*,*E*)-3-heptylidene-1-hydroxy-1-methyl-2,3-dihydro-1*H*-indene-2-carboxylate (113br). The title compound was prepared according to General Procedure **A**, from ethyl deca-2,3-dienoate **112r** (59 mg, 0.3 mmol) and 2-acetylphenylboronic acid **7b** (98.4 mg, 0.60 mmol). Purification by column chromatography (5-10% EtOAc/petroleum ether) gave **112br** as a pale yellojw oil (14 mg, 15%). R_f = 0.21 (10% EtOAc/petroleum ether); IR 3436 (br, OH), 2928, 1715 (C=O), 1371, 1237, 1179, 1093, 1033, 759 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43-7.38 (2H, m, Ar**H**), 7.30-7.23 (2H, m, Ar**H**), 6.09 (1H, td, *J* = 7.6, 1.9 Hz, =C**H**), 4.16 (2H, q, *J* = 7.1 Hz, OC**H**$_2$CH$_3$), 3.88 (1H, d, *J* = 1.8 Hz, C**H**), 3.30 (1H, s, O**H**), 2.25 (2H, qd, *J* = 7.6, 1.6 Hz, C**H**$_2$), 1.54 (3H,

s, C**H**$_3$), 1.49-1.42 (2H, m, C**H**$_2$), 1.34 (4H, pd, J = 5.0, 4.4, 2.0 Hz, 2 × C**H**$_2$), 1.26 (3H, t, J = 7.1 Hz, OCH$_2$C**H**$_3$), 1.00-0.85 (3H, m, C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3 (C), 149.0 (C), 138.9 (C), 136.2 (C), 128.8 (CH), 128.6 (CH), 125.2 (CH), 123.1 (CH), 120.0 (CH), 80.4 (C), 61.1 (CH_2), 59.8 (CH), 31.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.2 (CH), 22.7 (CH_2), 14.3 (CH_3), 14.2 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{19}H_{26}NaO_3]^+$ $[M+Na]^+$: 325.1774, found: 325.1772.

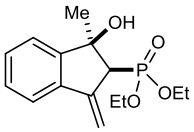


(±) (1*S*,2*S*)-1-Hydroxy-1-methyl-*N*,*N*-diphenyl-3-(propan-2-ylidene)-2,3-dihydro-1*H*-indene-2-carboxamide (113bn). The title compound was prepared according to General Procedure **A**, from 4-methyl-*N*,*N*-diphenylpenta-2,3-dienamide **112n** (79.0 mg, 0.30 mmol) and 2-acetylphenylboronic acid **7b** (98.4 mg, 0.60 mmol). Purification by column chromatography (0-20% EtOAc/petroleum ether) gave **113bn** as a colourless solid (35.8 mg, 31%). R_f = 0.18 (20% EtOAc/petroleum ether); m.p. 120-122 °C (Et_2O/*n*-pentane); IR 3433 (br, OH), 2921, 1676, 1658, 1490, 1348, 1295, 1236, 1091, 947, 753, 703, 691, 603 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62-7.52 (2H, m, Ar**H**), 7.52-7.45 (2H, m, Ar**H**), 7.44-7.35 (2H, m, Ar**H**), 7.35-7.23 (1H, m, Ar**H**), 7.23-7.13 (4H, m, Ar**H**), 4.04 (1H, s, C**H**), 3.01 (1H, s, O**H**), 2.11 (3H, s, C**H**$_3$), 1.88 (3H, s, C**H**$_3$), 1.43 (3H, s, C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3 (C), 151.3 (C), 143.0 (C), 142.8 (C), 140.2 (C), 133.8 (C), 129.7 (CH), 129.3 (CH), 128.9 (CH), 128.3 (2 × CH), 128.0 (CH), 127.2 (2 × CH), 126.9 (CH), 126.4 (CH), 124.4 (2 × CH), 122.6 (2 × CH), 80.5 (C), 61.2 (CH), 28.8 (CH_3), 24.6 (CH_3), 22.0 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{26}H_{25}NNaO_2]^+$ $[M+Na]^+$: 406.1777, found: 406.1782.



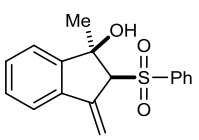
(±) ((1*R*,2*S*)-1-Hydroxy-1-methyl-3-methylene-2,3-dihydro-1*H*-inden-2-yl)diphenylphosphine oxide (113bt). The title compound was prepared according to General Procedure **A**, from diphenyl(propa-1,2-dien-1-yl)phosphine oxide **112t** (72.1 mg, 0.30 mmol) and 2-acetylphenylboronic acid **7b** (98.4 mg, 0.60 mmol). Purification by column chromatography (80% EtOAc/petroleum ether) gave **113bt** as a pale yellow solid (76 mg, 70%). R_f = 0.19 (80% EtOAc/petroleum

ether); m.p. 143-145 °C ($CHCl_3/Et_2O$); IR 3428 (br, OH), 2919, 1475, 1262, 1162, 1119, 782, 691, 500, 465 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.90 (2H, ddt, *J* = 11.5, 6.5, 1.7 Hz, Ar**H**), 7.72-7.64 (2H, m, Ar**H**), 7.58-7.50 (3H, m, Ar**H**), 7.48-7.43 (1H, m, Ar**H**), 7.42-7.38 (4H, m, Ar**H**), 7.32-7.24 (2H, m, Ar**H**), 5.38 (1H, dd, *J* = 5.5, 1.7 Hz, =C$\mathbf{H}_a$$H_b$), 4.64 (1H, s, O**H**), 4.15 (1H, dd, *J* = 4.7, 1.7 Hz, =$CH_a$$\mathbf{H}_b$), 3.97 (1H, dt, *J* = 10.3, 1.7 Hz, C**H**), 1.62 (3H, d, *J* = 1.7 Hz, C$\mathbf{H}_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.3 (C), 142.6 (d, J_{C-P} = 7.2 Hz, C), 138.3 (d, J_{C-P} = 3.6 Hz, C), 134.1 (d, J_{C-P} = 99.0 Hz, C), 132.0 (d, J_{C-P} = 8.9 Hz, 2 × CH), 131.8 (d, J_{C-P} = 3.3 Hz, 2 × CH), 131.2 (d, J_{C-P} = 8.4 Hz, 2 × CH), 131.0 (d, J_{C-P} = 101.1 Hz, C), 129.7 (CH), 128.9-128.6 (m, 3 × CH), 128.2 (d, J_{C-P} = 12.5 Hz, 2 × CH), 123.1 (CH), 120.2 (CH), 108.5 (d, J_{C-P} = 7.3 Hz, CH_2), 81.9 (d, J_{C-P} = 4.6 Hz, C), 56.6 (d, J_{C-P} = 67.1 Hz, CH), 31.7 (d, J_{C-P} = 4.8 Hz, CH_3); ^{31}P NMR (202 MHz, $CDCl_3$) δ 35.2; HRMS (ESI) Exact mass calculated for $[C_{23}H_{21}PNaO_2]^+$ $[M+Na]^+$: 383.1171, found: 383.1169.

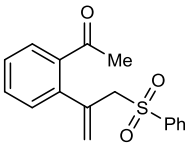


(±) Diethyl (1*R*,2*S*)-(1-hydroxy-1-methyl-3-methylene-2,3-dihydro-1H-inden-2-yl)phosphonate (113bu). The title compound was prepared according to General Procedure **A**, from diethyl propa-1,2-dien-1-ylphosphonate **112u** (52.8 mg, 0.30 mmol) and 2-acetylphenylboronic acid **7b** (98.4 mg, 0.60 mmol). Purification by column chromatography (80% EtOAc/petroleum ether) gave **113bu** as a yellow oil (57 mg, 64%). R_f = 0.11 (80% EtOAc/petroleum ether); IR 3336 (br, OH), 2976, 2927, 1229, 1162, 1021, 952, 757, 537 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.51-7.45 (1H, m, Ar**H**), 7.46-7.41 (1H, m, Ar**H**), 7.35-7.26 (2H, m, Ar**H**), 5.70 (1H, dd, *J* = 5.7, 2.1 Hz, =C$\mathbf{H}_a$$H_b$), 5.36 (1H, dd, *J* = 4.8, 2.1 Hz, =$CH_a$$\mathbf{H}_b$), 4.25-4.11 (2H, m, OC$\mathbf{H}_2$$CH_3$), 4.13-3.94 (2H, m, OC$\mathbf{H}_2$$CH_3$), 3.93 (1H, s, O**H**), 3.41 (1H, dt, *J* = 24.7, 2.1 Hz, C**H**P), 1.65 (3H, d, *J* = 1.8 Hz, CH_3), 1.34 (3H, t, *J* = 7.1 Hz, $OCH_2C\mathbf{H}_3$), 1.19 (3H, t, *J* = 7.0 Hz, $OCH_2C\mathbf{H}_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.4 (d, J_{C-P} = 2.8 Hz, C), 142.5 (d, J_{C-P} = 8.1 Hz, C), 138.3 (d, J_{C-P} = 6.9 Hz, C), 129.6 (CH), 128.9 (CH), 123.3 (CH), 120.5 (CH), 107.8 (d, J_{C-P} = 7.3 Hz, CH_2), 79.9 (d, J_{C-P} = 4.7 Hz, C), 62.8 (d, J_{C-P} = 7.0 Hz, CH_2), 62.3 (d, J_{C-P} = 7.1 Hz, CH_2), 54.7 (d, J_{C-P} = 138.0 Hz, CH), 30.7 (d, J_{C-P} = 5.5 Hz, CH_3), 16.5 (d, J_{C-P} = 6.3 Hz, CH_3), 16.4 (d, J_{C-P} = 5.8 Hz, CH_3). ^{31}P NMR (202 MHz, $CDCl_3$) δ 25.5 (dt, *J* = 23.9, 7.8 Hz). HRMS (ESI)

Exact mass calculated for $[C_{15}H_{24}PNaO_4]^+$ $[M+Na]^+$: 319.1070, found: 319.1067.

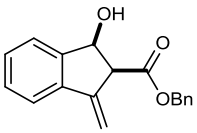


(±)-(1*R*,2*S*)-1-Methyl-3-methylene-2-(phenylsulfonyl)-2,3-dihydro-1H-inden-1-ol (113bs). The title compound was prepared according to General Procedure **A**, from (propa-1,2-dien-1-ylsulfonyl)benzene **112s** (54.1 mg, 0.30 mmol) and 2-acetylphenylboronic acid **7b** (98.4 mg, 0.60 mmol). Purification by column chromatography (0-30% EtOAc/*n*-pentane) gave **113bs** as a pale yellow oil (32.4 mg, 36%). R_f = 0.10 (20% EtOAc/petroleum ether); IR 3469 (br, OH), 1447, 1305, 1153, 1133, 1083, 757, 729, 687, 521 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ 7.90-7.85 (2H, m, Ar**H**), 7.67-7.61 (1H, m, Ar**H**), 7.56-7.47 (3H, m, Ar**H**), 7.37-7.26 (3H, m, Ar**H**), 5.83 (1H, d, *J* = 1.6 Hz, =C**H**$_a$H$_b$), 5.21 (1H, d, *J* = 1.6 Hz, =CH$_a$**H**$_b$), 4.57 (1H, t, *J* = 1.6 Hz, C**H**SO$_2$Ph), 3.83 (1H, s, O**H**), 1.42 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, CD_3CN) δ 149.8 (C), 140.9 (C), 140.6 (C), 138.2 (C), 134.4 (CH), 130.5 (CH), 130.1 (2 × CH), 129.8 (CH), 129.5 (2 × CH), 123.8 (CH), 121.2 (CH), 113.3 (CH_2), 80.7 (C), 78.0 (CH), 31.5 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{17}H_{26}SNaO_3]^+$ $[M+Na]^+$: 323.0712, found: 323.0713.

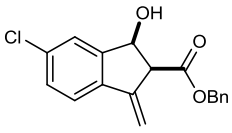


1-(2-(3-(Phenylsulfonyl)prop-1-en-2-yl)phenyl)ethan-1-one (126). The title compound was prepared according to General Procedure **A**, from (propa-1,2-dien-1-ylsulfonyl)benzene **112s** (54.1 mg, 0.30 mmol) and 2-acetylphenylboronic acid **7b** (98.4 mg, 0.60 mmol). Purification by column chromatography (0-30% EtOAc/*n*-pentane) gave **126** as a pale yellow oil (47 mg, 52%). R_f = 0.11 (30% EtOAc/petroleum ether); IR 1680, 1446, 1304, 1249, 1142, 1084, 754, 727, 713, 687, 599, 542, 527 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80-7.75 (2H, m, Ar**H**), 7.74-7.68 (1H, m, Ar**H**), 7.62-7.55 (1H, m, Ar**H**), 7.53-7.32 (4H, m, Ar**H**), 7.25-7.18 (1H, m, Ar**H**), 5.32 (1H, d, *J* = 0.9 Hz, =C**H**$_a$H$_b$), 5.25 (1H, d, *J* = 0.9 Hz, =CH$_a$**H**$_b$), 4.17 (2H, d, *J* = 0.9 Hz, C**H**$_2$SO$_2$Ph), 2.53 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.4 (C), 140.9 (C), 139.3 (C), 138.8, (C) 135.6 (C), 133.6 (CH), 133.6 (CH), 132.4 (CH), 132.0 (CH), 129.9 (2 × CH), 129.1 (CH), 128.4 (2 × CH), 128.2 (CH), 122.6 (CH_2), 63.5 (CH_2), 28.9 (CH_3); HRMS

(ESI) Exact mass calculated for $[C_{17}H_{16}SNaO_3]^+$ $[M+Na]^+$: 323.0712, found: 323.0714.



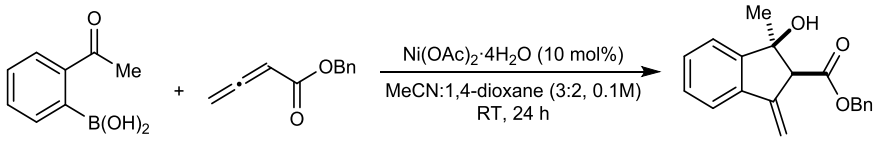
(±) Benzyl (1*S*,2*S*)-1-hydroxy-3-methylene-2,3-dihydro-1*H*-indene-2-carboxylate (113aa). The title compound was prepared according to **General Procedure A**, from benzyl buta-2,3-dienoate **112a** (52.3 mg, 0.30 mmol) and 2-formylphenylboronic acid **7a** (90 mg, 0.6 mmol). Purification by column chromatography (20% EtOAc/petroleum ether) gave **113aa** as a yellow oil (60.1 mg, 72%). R_f = 0.33 (20% EtOAc/petroleum ether); IR 3448 (br, OH), 3032, 2956, 1716 (C=O), 1643, 1319, 1242, 1153, 739, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56-7.47 (2H, m, Ar**H**), 7.42-7.30 (7H, m, Ar**H**), 5.67 (1H, d, *J* = 1.9 Hz, =C**H**$_a$H$_b$), 5.44 (1H, dd, *J* = 9.9, 7.1 Hz, C**H**OH), 5.30 (1H, d, *J* = 1.9 Hz, =CH$_a$**H**$_b$), 5.20 (2H, s, OC**H**$_2$Ph), 4.14 (1H, dt, *J* = 7.1, 1.9 Hz, C**H**), 3.31 (1H, d, *J* = 9.9 Hz, O**H**); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4 (C), 145.6 (C), 144.4 (C), 138.7 (C), 135.5 (C), 129.5 (CH), 129.0 (CH), 128.6 (2 × CH), 128.4 (CH), 128.2 (2 × CH), 125.0 (CH), 120.8 (CH), 107.3 (CH_2), 74.2 (CH), 66.9 (CH_2), 54.5 (CH); HRMS (ESI) Exact mass calculated for $[C_{18}H_{16}O_3Na]^+$ $[M+Na]^+$: 303.0992, found: 303.0992.



(±) Benzyl (2*S*,3*S*)-5-chloro-3-hydroxy-1-methylene-2,3-dihydro-1*H*-indene-2-carboxylate (113ha). The title compound was prepared according to **General Procedure A**, from benzyl buta-2,3-dienoate **112a** (52.3 mg, 0.30 mmol) and (4-chloro-2-formylphenyl)boronic acid **7h** (110.6 mg, 0.60 mmol). Purification by column chromatography (20% EtOAc/petroleum ether) gave **113ha** as a yellow oil (28 mg, 30%). R_f = 0.38 (20% EtOAc/petroleum ether); IR 3334 (br, OH), 1712 (C=O), 1386, 1312, 1238, 1130, 913, 732, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.49-7.47 (1H, m, Ar**H**), 7.41 (1H, d, *J* = 8.2 Hz, Ar**H**), 7.39-7.32 (5H, m, Ar**H**), 7.29 (1H, dd, *J* = 8.2, 2.0 Hz, Ar**H**), 5.63 (1H, d, *J* = 1.8 Hz, =C**H**$_a$H$_b$), 5.38 (1H, dd, *J* = 10.3, 7.1 Hz, C**H**OH), 5.30 (1H, d, *J* = 1.8 Hz, =CH$_a$**H**$_b$), 5.18 (2H, s, C**H**$_2$Ph), 4.13 (1H, dt, *J* = 7.1, 1.8 Hz, C**H**), 3.43 (1H, d, *J* = 10.3 Hz, O**H**); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3 (C), 147.5 (C), 143.5 (C), 137.3 (C), 135.41 (C), 135.44 (C), 129.6 (CH), 128.8 (2 × CH), 128.6

(CH), 128.4 (2 × CH), 125.3 (CH), 122.2 (CH), 108.1 (CH_2), 73.9 (CH), 67.2 (CH_2), 54.7 (CH); HRMS (ESI) Exact mass calculated for $[C_{18}H_{15}ClNaO_3]^+$ $[M+Na]^+$: 337.0602, found: 337.0600.

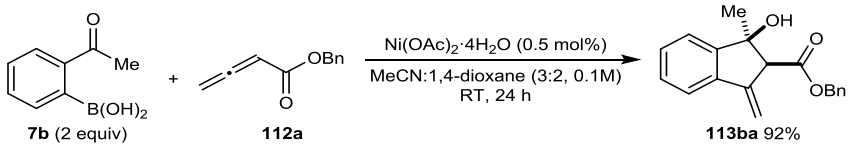
Air Atmosphere



To a flask charged with allene **112a** (52.3 mg, 0.30 mmol) and 2-acetylphenylboronic acid **7b** (98.4 mg, 0.60 mmol), $Ni(OAc)_2{\cdot}4H_2O$ (7.5 mg, 10 mol%) was added. The flask was sealed with a rubber septum and MeCN (1.8 mL) and 1,4-dioxane (1.2 mL) were added. The resulting solution was stirred at room temperature for 24 h then diluted with Et_2O, filtered over silica (Et_2O) and concentrated. Purification by column chromatography (10% EtOAc/petroleum ether) gave **113ba** as a pale yellow oil (68.0 mg, 77%)

See page **154** for full characterisation.

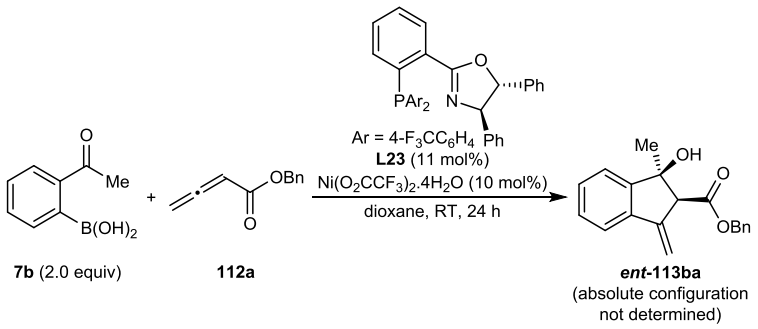
Scale Up



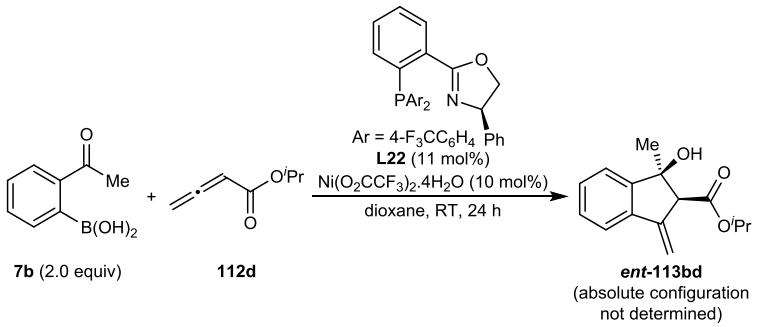
To a flask charged with allene **112a** (523 mg, 3.00 mmol) and 2-acetylphenylboronic acid **7b** (984 mg, 6.00 mmol), $Ni(OAc)_2{\cdot}4H_2O$ (3.8 mg, 0.5 mol%) was added. The flask was sealed with a rubber septum and purged with Ar. Degassed MeCN (18 mL) and degassed 1,4-dioxane (12 mL) were added and the resulting solution was stirred at room temperature for 24 h then diluted with Et_2O, filtered over silica (Et_2O) and concentrated. Purification by column chromatography (10% EtOAc/petroleum ether) gave **113ba** as a pale yellow oil (810 mg, 92%).

See page **154** for full characterisation.

8.4.1. Enantioselective Examples



Benzyl (1*S*,2*S*)-1-hydroxy-1-methyl-3-methylene-2,3-dihydro-1H-indene-2-carboxylate (*ent*-113ba). To a flask charged with $Ni(O_2CCF_3)_2 \cdot 4H_2O$ (10.7 mg, 10 mol%) and **L23** (20.4 mg, 11 mol%) under an Ar atmosphere was added degassed 1,4-dioxane (0.60 mL). The resulting suspension was stirred at 80 °C for 30 mins then cooled to room temperature. A solution of benzyl buta-2,3-dienoate **112ba** (52.3 mg, 0.30 mmol) and 2-acetylphenylboronic acid **7b** (98.4 mg, 0.60 mmol) in 1,4-dioxane (2.4 mL) was added and the resulting solution was stirred at room temperature for 24 h, then diluted with Et_2O, filtered over silica and concentrated. Purification by column chromatography (10% EtOAc/*n*-pentane) afforded the title compound as a pale yellow oil (67.5 mg, 76%). $[\alpha]_D^{21}$ −20.0 (*c* 1, $CHCl_3$); Enantiomeric excess was determined by HPLC with Chiralpak AD-H column (90:10 *iso*-hexane:EtOH, 1.0 mL/min, 254 nm, 25 °C); t_r (major) = 14.2 min, t_r (minor) = 18.9 min, 74% ee.
See compound **113ba** for full characterisation.



Isopropyl (1*S*,2*S*)-1-hydroxy-1-methyl-3-methylene-2,3-dihydro-1*H*-indene-2-carboxylate (*ent*-113bd). To a flask charged with $Ni(O_2CCF_3)_2.4H_2O$ (10.7 mg, 10 mol%) and **L22** (17.9 mg, 11 mol%) under an Ar atmosphere was added degassed 1,4-dioxane (0.60 mL). The resulting suspension was stirred at 80 °C for 30 mins then cooled to room temperature.

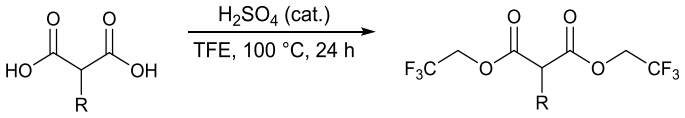
A solution of isopropyl buta-2,3-dienoate **112d** (37.8 mg, 0.30 mmol) and 2-acetylphenylboronic acid **7b** (98.4 mg, 0.60 mmol) in 1,4-dioxane (2.4 mL) was added and the resulting solution was stirred at room temperature for 24 h, then diluted with Et_2O, filtered over silica and concentrated. Purification by column chromatography (10% EtOAc/*n*-pentane) afforded the title compound as a pale yellow oil (70.1 mg, 95%). $[\alpha]_D^{24}$ +12.0 (*c* 1, $CHCl_3$); Enantiomeric excess was determined by HPLC with Chiralpak AS-H column (90:10 *iso*-hexane:EtOH, 1.0 mL/min, 254 nm, 25 °C); t_r (minor) = 7.5 min, t_r (major) = 10.6 min, 66% ee.

See compound **113bd** for full characterisation.

9. Experimental: Synthesis of Chiral Cyclopent-2-enones

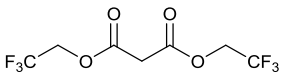
9.1. Synthesis of Malonate Esters:

General Procedure B: Esterification

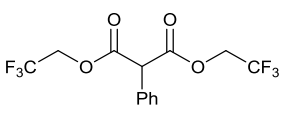


xx R = H
xx R = Ph

To a high-pressure flask charged with the relevant malonic acid (1 equiv) in TFE was added concentratd H_2SO_4 (10 mol%). The flask was sealed and stirred at 100 °C for 24 h then cooled and concentrated. Saturated aqueous $NaHCO_3$ (1 × organic volume) was added to the residue slowly and was extracted with Et_2O (3 × organic volume). The combined organics were washed with saturated aqueous $NaHCO_3$ (1 × organic volume) then brine (1 × organic volume), dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford the title compound.

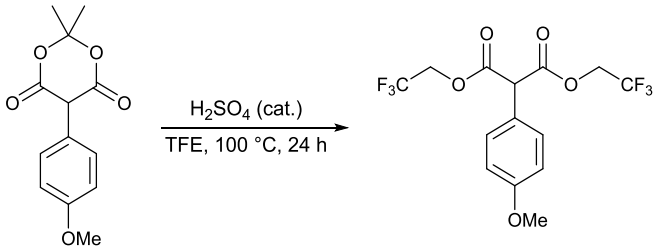


Bis(2,2,2-trifluoroethyl) malonate (217). The title compound was prepared according to General Procedure **B**, from malonic acid (10.0 g, 96.1 mmol), trifluoroethanol (TFE, 50 mL) and concentrated H_2SO_4 (0.51 mL, 9.61 mmol) as a colourless oil (6.01 g, 23%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.55 (4H, q, J = 8.2 Hz, 2 × C**H**$_2$CF$_3$), 3.61 (2H, s, C**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2 (2 × C), 122.64 (q, $J_{C\text{-}F}$ = 277.2 Hz, 2 × C), 61.34 (q, J = 37.3 Hz, 2 × CH_2), 40.3 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.9 (t, J = 8.2 Hz, 6 × F); HRMS (ESI) Exact mass calculated for $[C_7H_6O_4F_6Na]^+$ $[M+Na]^+$: 291.0062, found: 291.0059. Spectroscopic data consistent with those previously reported.[109]



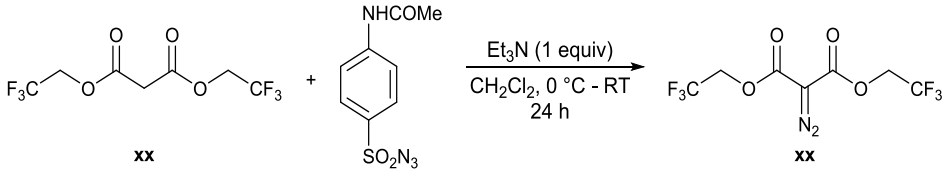
Bis(2,2,2-trifluoroethyl) 2-phenylmalonate (218). The title compound was prepared according to General Procedure **B**, from phenylmalonic acid (5.00 g, 27.8 mmol), trifluoroethanol (TFE, 25 mL) and concentrated H_2SO_4 (0.15 mL, 2.78

mmol) as a colourless oil (4.02 g, 42%). R_f = 0.20 (5% EtOAc/petroleum ether); IR 2980, 1755 (C=O), 1410, 1275, 1158, 1129, 1056, 979, 727, 547 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (5H, br s, Ar**H**), 4.83 (1H, s, C**H**Ph), 4.61-4.47 (4H, m, 2 × C**H**$_2$CF$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0 (2 × C), 130.8 (C), 129.3 (2 × CH), 129.2 (CH), 129.1 (2 × CH), 122.6 (q, J_{C-F} = 277.2 Hz, 2 × C), 61.5 (q, J_{C-F} = 37.3 Hz, 2 × CH_2), 56.8 (CH); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.8 (t, J = 8.2 Hz, 6 × F); HRMS (ESI) exact mass calculated for $[C_{13}H_{10}F_6NaO_4]^+$ $[M+Na]^+$: 367.0375, found: 367.0362.



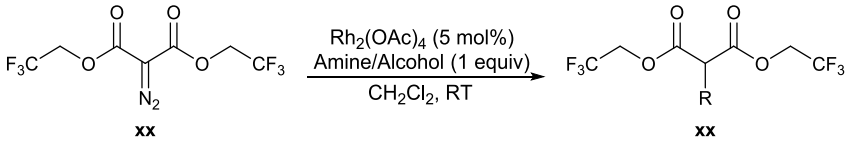
xx **xx**

Bis(2,2,2-trifluoroethyl) 2-(4-methoxyphenyl)malonate (220). To a high-pressure flask charged with 5-(4-methoxyphenyl)-2,2-dimethyl-1,3-dioxane-4,6-dione, **219** (2.18 g, 8.71 mmol) in TFE (50 mL) was added concentrated H_2SO_4 (0.05 mL, 0.94 mmol). The flask was sealed and stirred at 100 °C for 2 h then cooled to room temperature and diluted with a mixture of Et_2O/petroleum ether (3:7, 100 mL). This solution was washed with saturated aqueous Na_2CO_3 (3 × 100 mL) and brine (50 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford the title compound as a yellow-green oil (2.41 g, 79%). IR 2988, 1771 (C=O), 1756, 1518, 1409, 1257, 1125, 1050, 960, 759, 662, 534 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.28 (2H, m, Ar**H**), 6.94-6.90 (2H, m, Ar**H**), 4.77 (1H, s, ArC**H**), 4.61-4.47 (4H, m, 2 × C**H**$_2$CF$_3$), 3.81 (3H, s, OC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3 (2 × C), 160.2 (C), 130.5 (2 × CH), 122.8 (C), 122.7 (q, J_{C-F} = 277.3 Hz, 2 × C), 114.6 (2 × CH), 61.4 (q, J_{C-F} = 37.1 Hz, 2 × CH_2), 56.0 (CH), 55.5 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.8 (t, J = 8.2 Hz, 6 × F); HRMS (ESI) exact mass calculated for $[C_{14}H_{12}F_6NaO_5]^+$ $[M+Na]^+$: 397.0481, found: 397.0481.

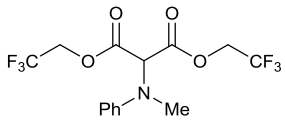


xx xx

Bis(2,2,2-trifluoroethyl) 2-diazomalonate (222). To a flask charged with bis(2,2,2-trifluoroethyl) malonate **217** (4.45 g, 16.60 mmol) in CH_2Cl_2 (90 mL) at 0 °C was added 4-acetamidobenzenesulfonyl azide (3.99 g. 16.60 mmol) and Et_3N (2.31 mL, 16.60 mmol). The resulting suspension was stirred at 0 °C for 15 min, then warmed to room temperature and stirred overnight, then diluted with Et_2O (100 mL), filtered, then concentrated. The residue was dissolved in CH_2Cl_2 (50 mL) and petroleum ether (50 mL) was added. The suspension was filtered and the filtrate was concentrated under reduced pressure to afford the title compound as a yellow oil (5.84 g, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.63 (4H, q, J = 8.2 Hz, 2 × C**H**$_2$CF$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7 (2 × C), 122.6 (q, $J_{C\text{-}F}$ = 277.4 Hz, 2 × C), 61.0 (q, J = 37.4 Hz, 2 × CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ −74.0 (t, J = 8.2 Hz, 6 × F). Spectroscopic data consistent with those previously reported.[109]

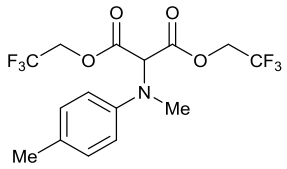


xx xx

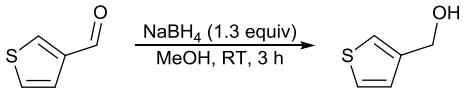


Bis(2,2,2-trifluoroethyl) 2-(methyl(phenyl)amino)malonate (223). To a flask charged with bis(2,2,2-trifluoroethyl) 2-diazomalonate **222** (1.50 g, 5.10 mmol) and *N*-methylaniline (0.55 mL, 5.10 mmol) in CH_2Cl_2 (15 mL) was added $Rh_2(OAc)_4$ (112.7 mg, 0.26 mmol). The resulting suspension was stirred at room temperature for 36 h then diluted with CH_2Cl_2 (15 mL) and filtered over silica (CH_2Cl_2, 75 mL). The filtrate was concentrated under reduced pressure to afford the title compound as an orange oil (1.50 g, 79%). R_f = 0.27 (10% EtOAc/petroleum ether); IR 1759 (C=O), 1275, 1160, 1114, 1052, 976, 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.26 (2H, m, Ar**H**), 6.88 (1H, tt, J = 7.4, 1.0 Hz Ar**H**), 6.85-6.81 (2H, m, Ar**H**), 5.35 (1H, s, C**H**), 4.66-4.53 (4H, m, 2 × C**H**$_2$CF$_3$), 3.07 (3H, s, NC**H**$_3$); ^{13}C NMR (101

MHz, $CDCl_3$) δ 165.6 (2 × C), 148.5 (C), 129.6 (2 × CH), 122.6 (q, $J_{C\text{-}F}$ = 277.4 Hz, 2 × C), 119.8 (CH), 114.1 (2 × CH), 65.8 (CH), 61.4 (q, $J_{C\text{-}F}$ = 37.3 Hz, 2 × CH_2), 35.9 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.7 (t, J = 8.1 Hz, 6 × F); HRMS (ESI) Exact mass calculated for $[C_{14}H_{13}NO_4F_6Na]^+$ $[M+Na]^+$: 396.0641, found: 396.0646.

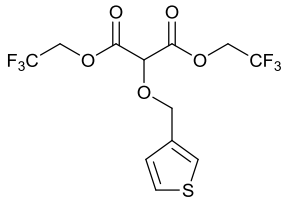


Bis(2,2,2-trifluoroethyl) 2-[methyl(4-methylphenyl)amino]malonate (224). To a flask charged with bis(2,2,2-trifluoroethyl) 2-diazomalonate **222** (1.00 g, 3.40 mmol) and *N*-methyl-*p*-toluidine (0.43 mL, 3.40 mmol) in CH_2Cl_2 (10 mL) was added $Rh_2(OAc)_4$ (150 mg, 0.34 mmol). The resulting suspension was stirred at room temperature for 48 h then diluted with CH_2Cl_2 (15 mL) and filtered over silica (CH_2Cl_2, 75 mL). The filtrate was concentrated under reduced pressure to afford the title compound as a yellow oil (940 mg, 71%). R_f = 0.38 (15% EtOAc/petroleum ether); IR 1759 (C=O), 1519, 1411, 1274, 1161, 1112, 1052, 972, 806, 649 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12-7.08 (2H, m, Ar**H**), 6.79-6.75 (3H, m, Ar**H**), 5.31 (1H, s, ArC**H**), 4.66-4.52 (4H, m, 2 × C**H**$_2$$CF_3$), 3.04 (3H, s, NC**H**$_3$), 2.28 (3H, s, ArC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7 (2 × C), 146.4 (C), 130.1 (2 × CH), 126.7 (C), 122.6 (q, $J_{C\text{-}F}$ = 277.3 Hz, 2 × C), 114.6 (2 × CH), 66.2 (CH), 61.3 (q, $J_{C\text{-}F}$ = 37.3 Hz, 2 × CH_2), 35.9 (CH_3), 20.4 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.7 (t, J = 8.2 Hz, 6 × F); HRMS (ESI) Exact mass calculated for $[C_{15}H_{15}F_6NO_4Na]^+$ $[M+Na]^+$: 410.0797, found: 410.0797.

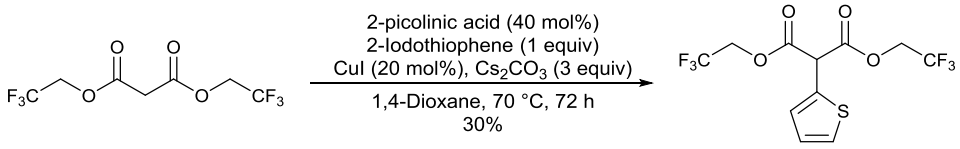


3-Hydroxymethylthiophene (221). To a flask charged with 3-thiophenecarboxaldehyde (1.00 mL, 11.41 mmol) in MeOH (10 mL) was added sodium borohydride (561 mg, 14.84 mmol) portion-wise. The resulting suspension was stirred at room temperature for 3 h then quenched with aqueous HCl solution (1 M, 12 mL) and extracted with CH_2Cl_2 (3 × 12 mL). The combined organics were washed with saturated aqueous brine solution (12 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure.

Purification by column chromatography (5-20% Et_2O/pentane) afforded the title compound as a pale yellow oil (659 mg, 51%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (1H, dd, *J* = 5.0, 2.9 Hz, Ar**H**), 7.25-7.20 (1H, m, Ar**H**), 7.10 (1H, dd, *J* = 5.0, 1.2 Hz, Ar**H**), 4.70 (2H, s, C**H**$_2$), 1.74 (1H, s, O**H**); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.4 (C), 126.9 (CH), 126.5 (CH), 122.1 (CH), 60.9 (CH_2); HRMS (ESI) Exact mass calculated for $[C_5H_6OSNa]^+$ $[M+Na]^+$: 137.0032, found: 137.0036. Spectroscopic data consistent with those previously reported.[110]

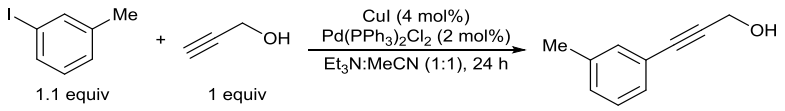


Bis(2,2,2-trifluoroethyl) 2-(thiophen-3-ylmethoxy)malonate (225). To a flask charged with bis(2,2,2-trifluoroethyl) 2-diazomalonate **222** (1.50 g, 5.10 mmol) and 3-thiophenylmethanol **221** (582 mg, 5.10 mmol) in CH_2Cl_2 (15 mL) was added $Rh_2(OAc)_4$ (112.7 mg, 0.26 mmol). The resulting suspension was stirred at room temperature for 24 h then diluted with CH_2Cl_2 (15 mL) and filtered over silica (CH_2Cl_2, 75 mL). The filtrate was concentrated under reduced pressure to afford the title compound as a yellow oil (1.60 g, 82%). R_f = 0.17 (10% EtOAc/petroleum ether); IR 1764 (C=O), 1412, 1280, 1156, 1054, 976, 858, 787, 693, 562 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (1H, dd, *J* = 5.0, 3.0 Hz, Ar**H**), 7.33-7.27 (1H, m, Ar**H**), 7.11 (1H, dd, *J* = 4.9, 1.3 Hz, Ar**H**), 4.77 (2H, d, *J* = 0.7 Hz, ArC**H**$_2$), 4.72 (1H, s, C**H**), 4.56 (4H, q, *J* = 8.2 Hz, 2 × C**H**$_2$CF$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6 (2 × C), 136.4 (C), 127.7 (CH), 127.0 (CH), 125.3 (CH), 122.5 (q, $J_{C\text{-}F}$ = 277.4 Hz, 2 × C), 76.3 (CH), 68.3 (CH_2), 61.5 (q, $J_{C\text{-}F}$ = 37.5 Hz, 2 × CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.7 (t, *J* = 8.1 Hz, 6 × F); HRMS (ESI) Exact mass calculated for $[C_{12}H_{10}O_5F_6SNa]^+$ $[M+Na]^+$: 403.0045, found: 403.0042.



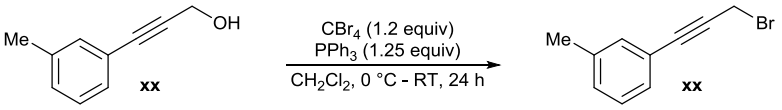
Bis(2,2,2-trifluoroethyl) 2-(thiophen-2-yl)malonate (226). A flask was charged CuI (355 mg, 1.86 mmol, 20 mol%), 2-picolinic acid (459 mg, 3.73 mmol, 40 mol%), Cs_2CO_3 (9.11 g, 28.0 mmol) and 2-iodothiophene (1.03 mL,

9.32 mmol) and was evacuated and backfilled with Ar. Anhydrous 1,4-dioxane (10 mL) was added followed by bis(2,2,2-trifluoroethyl) malonate **217** (5.00 g, 18.6 mmol). The resulting suspension was stirred at 70 °C for 72 h then diluted with saturated aqueous NH_4Cl solution (50 mL) and extracted with EtOAc (3 × 20 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford the crude. Purification by column chromatography (0-10% EtOAc/petroleum ether) afforded the title compound as a pale yellow oil (973 mg, 30%). R_f = 0.33 (10% EtOAc/petroleum ether); IR 1760 (C=O), 1411, 1281, 1228, 1166, 1051, 980, 859, 752, 707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (1H, dd, *J* = 5.2, 1.2 Hz, Ar**H**), 7.16 (1H, ddd, *J* = 3.6, 1.2, 0.6 Hz, Ar**H**), 7.03 (1H, dd, *J* = 5.2, 3.6 Hz, Ar**H**), 5.14 (1H, s, ArC**H**), 4.57 (4H, qd, *J* = 8.2, 3.1 Hz, 2 × C**H**$_2$CF$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2 (2 × C), 130.9 (C), 128.9 (CH), 127.5 (CH), 127.1 (CH), 122.5 (q, $J_{C\text{-}F}$ = 277.3 Hz, 2 × C), 61.7 (q, $J_{C\text{-}F}$ = 37.4 Hz, 2 × CH_2), 52.0 (CH); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.8 (t, *J* = 8.2 Hz, 6 × F); HRMS (ESI) Exact mass calculated for $[C_{11}H_8F_6NaO_4S]^+$ $[M+Na]^+$: 372.9940, found 372.9943.

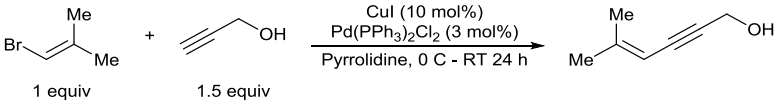


3-(*m*-Tolyl)prop-2-yn-1-ol (227). To a flask charged with $Pd(PPh_3)_2Cl_2$ (210 mg, 2 mol%), CuI (120 mg, 4 mol%), and 3-iodotoluene (2.12 mL, 16.5 mmol), in Et_3N:MeCN (1:1, 20 mL) was added propargyl alcohol (0.87 mL, 15.0 mmol). The resulting solution was stirred at room temperature overnight then diluted with saturated aqueous NH_4Cl solution and extracted with EtOAc (3 × 15 mL). The combined organics were washed with brine, dried (Na_2SO_4), filtered over charcoal and concentrated. Purification by column chromatography (20% EtOAc/petroleum ether) afforded the title compound as a brown oil (1.54 g, 70%). IR 3304, 2920, 2862, 2227, 1601, 1580, 1483, 1356, 1278, 1226, 1177, 1093, 1030, 999, 968, 907, 880, 847, 782, 690, 581, 519, 442 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.21 (3H, m, Ar**H**), 7.16-7.09 (1H, m, Ar**H**), 4.49 (2H, s, C**H**$_2$OH), 2.32 (3H, d, *J* = 1.0 Hz, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.1 (C), 132.4 (CH), 129.5 (CH), 128.9 (CH),

128.3 (CH), 122.5 (C), 87.0 (C), 86.0 (C), 51.8 (CH_2), 21.3 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{10}H_{10}ONa]^+$ $[M+Na]^+$: 169.0624, found: 169.0633. Spectroscopic data consistent with those previously reported.[111]

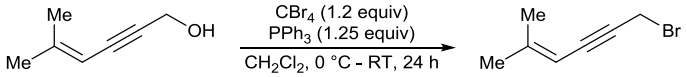


1-(3-Bromoprop-1-yn-1-yl)-3-methylbenzene (228). A flask was charged with 3-(*m*-tolyl)prop-2-yn-1-ol **227** (1.50 g, 10.2 mmol) and CBr_4 (4.08 g, 12.3 mmol) in CH_2Cl_2 (20 mL) and cooled to 0 °C. A solution of PPh_3 (3.36 g, 12.8 mmol) in CH_2Cl_2 (10 mL) was added drop-wise and the resulting solution was warmed to room temperature and stirred overnight. Ethanol (10 mL) was added and the solution was stirred for 20 min then concentrated. Purification by column chromatography afforded the title compound (100% petroleum ether) as a yellow oil (2.09 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.25 (1H, m, Ar**H**), 7.24-7.18 (1H, m, Ar**H**), 7.17-7.14 (1H, m, Ar**H**), 4.16 (2H, s, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2 (C), 132.6 (CH), 129.9 (CH), 129.1 (CH), 128.4 (CH), 122.1 (C), 87.1 (C), 84.0 (C), 21.3 (CH_3), 15.6 (CH_2). Spectroscopic data consistent with those previously reported.[111]



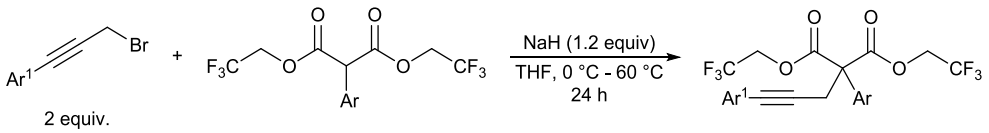
5-Methylhex-4-en-2-yn-1-ol (229). To a flask charged with $Pd(PPh_3)_4$ (856 mg, 0.741 mmol, 5 mol%) in pyrrolidine (15 mL) was added 1-bromo-2-methylprop-1-ene (1.52 mL, 14.8 mmol). The resulting solution was cooled to 0 °C and CuI (423 mg, 2.22 mmol, 15 mol%) was added followed by propargyl alcohol (1.29 mL, 22.2 mmol). The resulting solution was warmed to room temperature and stirred overnight then filtered over charcoal and silica and concentrated. Purification by column chromatography (20% EtOAc/petroleum ether) afforded the title compound as an orange oil (908 mg, 56%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.45-5.08 (1H, m, **H**C=C(CH_3)$_2$), 4.41 (2H, d, *J* = 1.8 Hz, C**H**$_2$OH), 1.89 (3H, s, C**H**$_3$), 1.80 (3H, s, C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.6 (C), 104.6 (CH), 89.3 (C), 83.9 (C), 51.9 (CH_2), 24.9 (CH_3), 21.1 (CH_3); HRMS (ESI) exact mass calculated for $[C_7H_{10}NaO]^+$

$[M+Na]^+$: 133.0624, found: 133.0619. Spectroscopic data consistent with those previously reported.[112]

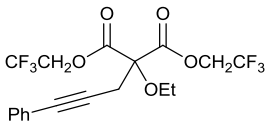


6-Bromo-2-methylhex-2-en-4-yne (230). A flask was charged with pent-4-en-2-yn-1-ol **229** (400 mg, 4.87 mmol) and CBr_4 (1.59 g, 5.85 mmol) in CH_2Cl_2 (5 mL) and cooled to 0 °C. A solution of PPh_3 (1.94 g, 6.09 mmol) in CH_2Cl_2 (5 mL) was added drop-wise and the resulting solution was warmed to room temperature and stirred overnight. Ethanol (5 mL) was added and the solution was stirred for 20 min then concentrated. Purification by column chromatography afforded the title compound (100% petroleum ether) as a yellow oil (2.09 g, 98%). R_f = 0.39 (100% petroleum ether); IR 2910, 2207, 1633, 1444, 1378, 1334, 1220, 816, 598, 531 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.29 (1H, app tt, *J* = 2.2, 1.2 Hz, **H**C=C(CH_3)$_2$), 4.12 (2H, d, *J* = 2.2 Hz, C**H**$_2$), 1.90 (3H, d, *J* = 1.1 Hz, =C(C**H**$_3$)$_2$), 1.81 (3H, d, *J* = 1.4 Hz, =C(C**H**$_3$)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.1 (C), 104.6 (CH), 86.2 (C), 85.5 (C), 25.0 (CH_3), 21.3 (CH_3), 16.3 (CH_2).

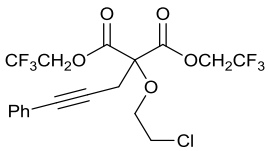
General Procedure C - Alkylation



A flask was charged with NaH (60%, 1.2 equiv) in anhydrous THF (0.35 M) and cooled to 0 °C. The appropriate α-substituted bis(2,2,2-trifluoroethyl) malonate ester (1 equiv) in THF (1.0 M) was added and the resulting solution was stirred at 0 °C for 30 min. The appropriate alkynyl bromide (2 equiv) was added, and the resulting suspension was stirred at the specified temperature overnight then cooled and quenched by the careful addition of water, diluted with Et_2O and the layers partitioned. The organics were washed with water, brine, dried (Na_2SO_4), filtered, and concentrated. The crude was loaded onto silica and purified by column chromatography to give the title compound.

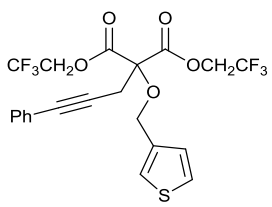


Bis(2,2,2-trifluoroethyl) 2-(3-(2-fluorophenyl)prop-2-yn-1-yl)-2-(thiophen-2-yl)malonate (215h). The title compound was prepared according to General Procedure **C**, from bis(2,2,2-trifluoroethyl) 2-ethoxymalonate (1.00 g, 3.20 mmol), NaH (154 mg, 3.84 mmol), and 1(3-bromoprop-1-yn-1-yl)benzene **231** (1.25 g, 6.41 mmol) in THF (9 mL) at 45 °C. Purification by column chromatography (0-5% EtOAc/petroleum ether) gave **215h** as a yellow oil (727 mg, 53%). R_f = 0.20 (10% EtOAc/petroleum ether); IR 1762 (C=O), 1411, 1282, 1220, 1160, 1116, 1082, 973, 757, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.25 (5H, m, Ar**H**), 4.68-4.54 (4H, m, 2 × C**H**$_2$CF$_3$), 3.72 (2H, q, J = 7.0 Hz, OC**H**$_2$), 3.26 (2H, s, C**H**$_2$C≡C), 1.31 (3H, t, J = 7.0 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0 (2 × C), 131.9 (2 × CH), 128.4 (CH), 128.3 (2 × CH), 122.9 (C), 122.6 (q, $J_{C\text{-}F}$ = 277.4 Hz, 2 × C), 84.5 (C), 83.8 (C), 81.5 (C), 63.1 (CH_2), 61.4 (q, $J_{C\text{-}F}$ = 37.4 Hz, 2 × CH_2), 26.2 (CH_2), 15.5 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.7 (t, J = 8.1 Hz, 6 × F); HRMS (ESI) Exact mass calculated for $[C_{18}H_{16}O_5F_6Na]^+$ $[M+Na]^+$: 449.0794, found: 449.0801.

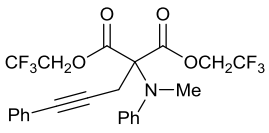


Bis(2,2,2-trifluoroethyl) 2-(2-chloroethoxy)-2-(3-phenylprop-2-yn-1-yl)malonate (215i). The title compound was prepared according to General Procedure **C**, from bis(2,2,2-trifluoroethyl) 2-(2-chloroethoxy)malonate (1.00 g, 2.89 mmol), NaH (138 mg, 3.46 mmol), and 1(3-bromoprop-1-yn-1-yl)benzene **231** (1.13 g, 5.77 mmol) in THF (9 mL) at 45 °C. Purification by column chromatography (0-5% EtOAc/petroleum ether) gave **215i** as a yellow oil (680 mg, 51%). R_f = 0.27 (10% EtOAc/petroleum ether); IR 1763 (C=O), 1283, 1162, 1097, 1067, 973, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.35 (2H, m, Ar**H**), 7.32-7.27 (3H, m, Ar**H**), 4.62 (4H, q, J = 8.1 Hz, 2 × C**H**$_2$CF$_3$), 4.02 (2H, t, J = 6.1 Hz, OC**H**$_2$), 3.71 (2H, t, J = 6.1 Hz, C**H**$_2$Cl), 3.28 (2H, s, C**H**$_2$C≡C); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5 (2 × C), 131.9 (2 × CH), 128.5 (CH), 128.4 (2 × CH), 122.7 (C), 122.5 (q, $J_{C\text{-}F}$ = 277.4 Hz, 2 × C), 84.8 (C), 83.8 (C), 81.2 (C), 67.6 (CH_2), 61.6 (q, $J_{C\text{-}F}$ = 37.5 Hz, 2 × CH_2), 42.2 (CH_2), 26.6 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.7 (t, J = 8.1 Hz, 6

× F); HRMS (ESI) Exact mass calculated for $[C_{18}H_{15}O_5F_6ClNa]^+$ $[M+Na]^+$: 483.0404, found: 483.0400.

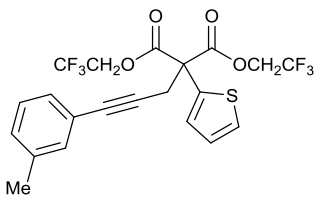


Bis(2,2,2-trifluoroethyl) 2-(3-phenylprop-2-yn-1-yl)-2-(thiophen-3-ylmethoxy)malonate (215j). The title compound was prepared according to General Procedure **C**, from bis(2,2,2-trifluoroethyl) 2-(thiophen-3-ylmethoxy)malonate **225** (1.00 g, 2.63 mmol), NaH (126 mg, 3.16 mmol), and 1(3-bromoprop-1-yn-1-yl)benzene **231** (1.02 g, 5.26 mmol) in THF (9 mL) at 45 °C. Purification by column chromatography (0-5% EtOAc/petroleum ether) gave **215j** as a yellow oil (546 mg, 42%). R_f = 0.19 (10% EtOAc/petroleum ether); IR 1762 (C=O), 1412, 1282, 1220, 1161, 1091, 1065, 973, 777, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.27 (7H, m, Ar**H**), 7.15-7.14 (1H, m, Ar**H**), 4.83 (2H, s, ArC$\mathbf{H}_2$O), 4.58 (4H, qd, J = 8.2, 1.3 Hz, 2 × C$\mathbf{H}_2CF_3$), 3.33 (2H, s, C$\mathbf{H}_2$C≡C); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8 (2 × C), 137.8 (C), 131.9 (2 × CH), 128.5 (CH), 128.4 (2 × CH), 127.5 (CH), 126.1 (CH), 123.6 (CH), 122.8 (C), 122.5 (q, $J_{C\text{-}F}$ = 277.4 Hz, 2 × C), 84.7 (C), 83.5 (C), 81.5 (C), 65.0 (CH_2), 61.5 (q, $J_{C\text{-}F}$ = 37.5 Hz, 2 × CH_2), 26.6 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.6 (t, J = 8.1 Hz, 6 × F); HRMS (ESI) Exact mass calculated for $[C_{21}H_{16}O_5F_6SNa]^+$ $[M+Na]^+$: 517.0515, found: 517.0509.



Bis(2,2,2-trifluoroethyl) 2-(methyl(phenyl)amino)-2-(3-phenylprop-2-yn-1-yl)malonate (215l). The title compound was prepared according to General Procedure **C**, from bis(2,2,2-trifluoroethyl) 2-(methyl(phenyl)amino)malonate **223** (1.00 g, 2.68 mmol), NaH (161 mg, 3.22 mmol), and 1(3-bromoprop-1-yn-1-yl)benzene **231** (1.05 g, 5.36 mmol) in DMF (9 mL) at 90 °C for 48 h. Purification by column chromatography (0-5% EtOAc/petroleum ether) gave **215l** as an orange oil (584 mg, 45%). R_f = 0.30 (10% EtOAc/petroleum ether); IR 1749 (C=O), 1493, 1280, 1158, 1072, 970, 756, 692, 650, 552 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.27 (7H, m, Ar**H**), 7.24-7.21 (2H, m, Ar**H**), 7.20-7.14 (1H, m, Ar**H**), 4.65 (2H, dq, J = 12.5, 8.2 Hz, 2 × C$\mathbf{H}_a$H$_b$CF$_3$), 4.55 (2H, dq, J = 12.5, 8.2 Hz, 2 × CH$_a$$\mathbf{H}_bCF_3$), 3.09 (2H, s, C$\mathbf{H}_2$C≡C), 3.06 (3H, s, NC$\mathbf{H}_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2 (2 × C), 147.7 (C), 131.8 (2 ×

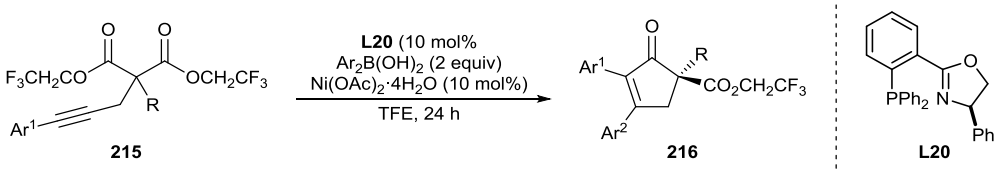
CH), 129.2 (2 × CH), 128.34 (2 × CH), 128.30 (CH), 126.8 (2 × CH), 125.84 (CH), 123.09 (C), 122.74 (q, $J_{C\text{-}F}$ = 277.2 Hz, 2 × C), 84.6 (C), 83.1 (C), 74.6 (C), 61.37 (q, $J_{C\text{-}F}$ = 37.3 Hz, 2 × CH_2), 40.9 (CH_3), 27.7 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.5 (t, J = 8.2 Hz); HRMS (ESI) Exact mass calculated for $[C_{23}H_{19}O_4NF_6Na]^+$ $[M+Na]^+$: 510.1110, found: 510.1105.



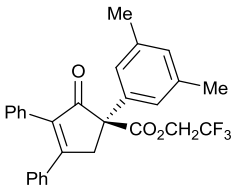
Bis(2,2,2-trifluoroethyl) 2-(thiophen-2-yl)-2-(3-(*m*-tolyl)prop-2-yn-1-yl)malonate (215k). The title compound was prepared according to General Procedure **C**, from bis(2,2,2-trifluoroethyl) 2-(thiophen-2-yl)malonate **226** (0.5 g, 1.43 mmol), NaH (68 mg, 1.71 mmol), and 1-(3-bromoprop-1-yn-1-yl)-3-methylbenzene **228** (72% wt in toluene, 829 mg, 2.86 mmol) in THF (7 mL). Purification by column chromatography (0-5% EtOAc/petroleum ether) gave **215k** as a yellow oil (366 mg, 54%). R_f = 0.29 (10% EtOAc/petroleum ether); IR 2976, 1757 (C=O), 1602, 1486, 1410, 1282, 1211, 1157, 1060, 973, 840, 784, 705, 691, 651, 553, 442 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (1H, dd, J = 5.2, 1.2 Hz, Ar**H**), 7.22 (1H, dd, J = 3.7, 1.2 Hz, Ar**H**), 7.18-7.07 (5H, m, Ar**H**), 7.04 (1H, dd, J = 5.2, 3.7 Hz, Ar**H**), 4.68-4.52 (4H, m, 2 × C**H**$_2$CF$_3$), 3.53 (2H, s, C**H**$_2$C≡C), 2.29 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8 (2 × C), 138.0 (C), 136.0 (C), 132.3 (CH), 129.4 (CH), 128.9 (CH), 128.2 (CH), 127.7 (CH), 127.2 (CH), 126.6 (CH), 122.6 (C), 122.6 (q, $J_{C\text{-}F}$ = 277.5 Hz, 2 × C), 85.4 (C), 82.3 (C), 61.8 (q, $J_{C\text{-}F}$ = 37.7 Hz, 2 × CH_2), 59.9 (C), 29.0 (CH_2), 21.3 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.7 (t, J = 8.1 Hz); HRMS (ESI) Exact mass calculated for $[C_{21}H_{16}O_4F_6SNa]^+$ $[M+Na]^+$: 501.0566, found: 501.0565.

9.2. Enantioselective Synthesis of Cyclopent-2-enones

General Procedure D - Enantioselective Entries

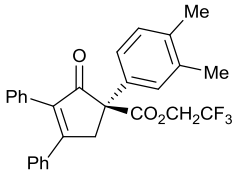


An oven-dried microwave vial fitted with a stirrer bar was charged with appropriate substrate **215** (0.30 mmol), the arylboronic acid (0.60 mmol), $Ni(OAc)_2 \cdot 4H_2O$ (7.5 mg, 0.03 mmol) and (*R*)-PhPhox (**L20** 12.2 mg, 0.03 mmol). The vial was capped with a crimp cap PTFE seal and evacuated and back filled with argon (5 cyles). 2,2,2-Trifluoroethanol (TFE) (3 mL) which had been freshly degassed (from 5 freeze-pump-thaw cycles) was then added under argon flow, the septum resealed with a layer of vacuum grease, and the contents stirred at room temperature for 10 min followed by stirring at the specified temperature for 24 h. The reaction was cooled to room temperature, diluted with EtOAc (5 mL) and washed with brine (10 mL). The aqueous layer was extracted with EtOAc (5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography to give the title compound.

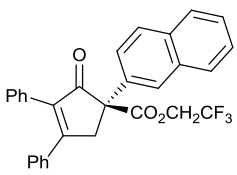


2,2,2-Trifluoroethyl (*R*)-1-(3,5-dimethylphenyl)-2-oxo-3,4-diphenylcyclopent-3-ene-1-carboxylate (216ma). The title compound was prepared according to General Procedure **D**, from malonate ester **215m** (145.9 mg mg, 0.30 mmol) and phenylboronic acid (73.1 mg, 0.60 mmol) at 80 °C. Purification by column chromatography (5% EtOAc/*n*-pentane) gave **216ma** as a yellow oil (115 mg, 83%). R_f = 0.11 (5% EtOAc/petroleum ether); IR 2920, 1763 (C=O), 1700 (C=O), 1599, 1351, 1282, 1154, 730, 693, 642 cm^{-1}; $[\alpha]_D^{23}$ –118.1 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.33 (6H, m, Ar**H**), 7.32-7.27 (3H, m, Ar**H**), 7.26-7.24 (1H, m, Ar**H**), 7.05-7.04 (2H, m, Ar**H**), 6.97-6.96 (1H, m, Ar**H**), 4.65-4.51 (2H, m, C**H**$_2CF_3$), 4.11 (1H, d, *J* = 18.2 Hz, =CC**H**$_a$H$_b$), 3.50 (1H, d, *J* = 18.2 Hz, =CCH$_a$**H**$_b$), 2.32 (6H, s, 2 × ArC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.0 (C), 169.5 (C), 166.0 (C), 138.5 (2 × C), 138.1 (C), 137.6 (C), 134.7 (C), 131.8 (C), 130.6 (CH), 129.8 (2 × CH), 129.7 (CH), 128.71 (2 × CH), 128.69 (2 × CH), 128.5 (3 × CH), 125.3 (2 × CH), 122.8 (q, $J_{C\text{-}F}$ = 278.0 Hz, C), 63.3 (C), 61.3 (q, $J_{C\text{-}F}$ = 36.8 Hz, CH_2), 44.1 (CH_2), 21.6 (2 × CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.5 (t, *J* = 8.3 Hz, 3 × F); HRMS (ESI) exact mass calculated for $[C_{28}H_{23}F_3NaO_3]^+$ $[M+Na]^+$: 487.1491, found: 487.1504. Enantiomeric excess was determined by HPLC

with Chiralpak AD-H column (98:2 *iso*-hexane:EtOH, 1.0 mL/min, 230 nm, 25 °C); t_r (minor) = 11.1 min, t_r (major) = 18.8 min, 92% ee.

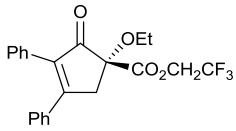


2,2,2-Trifluoroethyl (*R*)-1-(3,4-dimethylphenyl)-2-oxo-3,4-diphenylcyclopent-3-ene-1-carboxylate (216na). The title compound was prepared according to General Procedure **D**, from malonate ester **215n** (145.9 mg, 0.30 mmol) and phenylboronic acid (73.1 mg, 0.60 mmol) at 80 °C. Purification by column chromatography (5-10% EtOAc/pentane) gave **216na** as a yellow oil (104 mg, 75%). R_f = 0.17 (10% EtOAc/petroleum ether); IR 1762 (C=O), 1700 (C=O), 1444, 1351, 1281, 1156, 972, 730, 693, 476 cm^{-1}; $[\alpha]_D^{25}$ −92.0 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.26 (11H, m, Ar**H**), 7.23-7.15 (2H, m, Ar**H**), 4.59 (2H, q, *J* = 8.3 Hz, C**H**$_2$CF$_3$), 4.12 (1H, d, *J* = 18.2 Hz, =CC**H**$_a$CH$_b$), 3.54 (1H, d, *J* = 18.2 Hz, =CCH$_a$C**H**$_b$), 2.29 (3H, s, C**H**$_3$), 2.27 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1 (C), 169.6 (C), 165.9 (C), 137.5 (C), 137.2 (C), 136.6 (C), 135.5 (C), 134.7 (C), 131.7 (C), 130.6 (CH), 130.1 (CH), 129.7 (2 × CH), 128.8 (CH), 128.7 (4 × CH), 128.4 (2 × CH), 124.9 (CH), 122.8 (q, $J_{C\text{-}F}$ = 277.9 Hz, C), 62.9 (C), 61.3 (q, $J_{C\text{-}F}$ = 36.8 Hz, CH_2), 43.9 (CH_2), 20.1 (CH_3), 19.5 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.5 (t, *J* = 8.3 Hz, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{28}H_{23}F_3O_3Na]^+$ $[M+Na]^+$: 487.1491, found: 487.1493. Enantiomeric excess was determined by HPLC with Chiralpak AD-H column (95:5 *iso*-hexane:EtOH, 1.0 mL/min, 254 nm, 25 °C); t_r (major) = 28.2 min, t_r (minor) = 39.3 min, 92% ee.



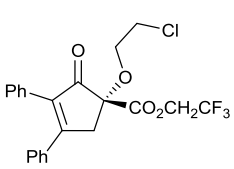
2,2,2-Trifluoroethyl (*R*)-1-(naphthalen-2-yl)-2-oxo-3,4-diphenylcyclopent-3-ene-1-carboxylate (216oa). The title compound was prepared according to General Procedure **D**, from malonate ester **215o** (152.5 mg, 0.30 mmol) and phenylboronic acid (73.1 mg, 0.60 mmol) at 80 °C. Purification by column chromatography (5-10% EtOAc/pentane) gave **216oa** as a yellow oil (127 mg, 87%). R_f = 0.17 (10% EtOAc/petroleum ether); IR 1761 (C=O), 1698 (C=O), 1407, 1351, 1280, 1154, 971, 816, 693, 475 cm^{-1}; $[\alpha]_D^{25}$ −76.0 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (1H, d, *J* = 2.0 Hz, Ar**H**), 7.91

(1H, d, J = 8.7 Hz, Ar**H**), 7.90-7.82 (2H, m, Ar**H**), 7.58 (1H, dd, J = 8.7, 2.0 Hz, Ar**H**), 7.53-7.49 (2H, m, Ar**H**), 7.43-7.36 (6H, m, Ar**H**), 7.34-7.30 (4H, m, Ar**H**), 4.62 (2H, qd, J = 8.3, 2.6 Hz, C**H**$_2$CF$_3$), 4.24 (1H, d, J = 18.2 Hz, =CC**H**$_a$H$_b$), 3.64 (1H, d, J = 18.2 Hz, =CCH$_a$**H**$_b$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 199.9 (C), 169.4 (C), 166.1 (C), 137.6 (C), 135.3 (C), 134.6 (C), 133.2 (C), 132.8 (C), 131.6 (C), 130.7 (CH), 129.7 (2 × CH), 128.8 (CH), 128.73 (2 × CH), 128.71 (2 × CH), 128.50 (CH), 128.47 (CH), 128.4 (2 × CH), 127.6 (CH), 126.64 (CH), 126.55 (CH), 126.3 (CH), 125.7 (CH), 122.8 (q, $J_{C\text{-}F}$ = 277.6 Hz, C), 63.4 (C), 61.4 (q, $J_{C\text{-}F}$ = 36.9 Hz, CH$_2$), 43.9 (CH$_2$); ^{19}F NMR (376 MHz, CDCl$_3$) δ −73.5 (t, J = 8.3 Hz, 3 × F); HRMS (ESI) Exact mass calculated for [C$_{30}$H$_{21}$O$_3$F$_3$Na]$^+$ [M+Na]$^+$: 509.1335, found: 509.1338. Enantiomeric excess was determined by HPLC with Chiralpak AD-H column (95:5 *iso*-hexane: *i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t$_r$ (major) = 47.1 min, t$_r$ (minor) = 50.8 min, 94% ee.

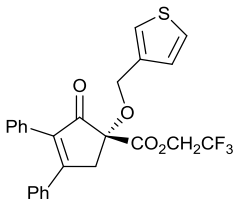


2,2,2-Trifluoroethyl (*R*)-1-ethoxy-2-oxo-3,4-diphenylcyclopent-3-ene-1-carboxylate (216ha). The title compound was prepared according to slightly modified General Procedure **D**, from malonate ester **215h** (127.9 mg, 0.30 mmol), phenylboronic acid (73.1 mg, 0.60 mmol), Ni(OAc)$_2$·4H$_2$O (15.0 mg, 0.06 mmol, 20 mol%) and (*R*)-PhPhox (**L20**, 24.4 mg, 0.06 mmol, 20 mol%) at 80 °C. Purification by column chromatography (5-10% EtOAc/*n*-pentane) gave **216ha** as an off-white solid (56 mg, 46%). R_f = 0.15 (10% EtOAc/petroleum ether); m.p. 128-130 °C (CHCl$_3$); IR 2854, 1747 (C=O), 1718 (C=O), 1437, 1358, 1281, 1232, 1171, 970, 669 cm^{-1}; $[\alpha]_D^{22}$ +72.0 (*c* 1, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.40-7.28 (8H, m, Ar**H**), 7.26-7.21 (2H, m, Ar**H**), 4.65 (1H, dq, J = 12.6, 8.3 Hz, OC**H**$_a$H$_b$CF$_3$), 4.55 (1H, dq, J = 12.6, 8.3 Hz, OCH$_a$**H**$_b$CF$_3$), 3.87 (2H, qd, J = 7.0, 3.4 Hz, OC**H**$_2$CH$_3$), 3.51 (1H, d, J = 17.8 Hz, =CC**H**$_a$CH$_b$), 3.29 (1H, d, J = 17.8 Hz, =CCH$_a$C**H**$_b$), 1.30 (3H, t, J = 7.0 Hz, C**H**$_3$); ^{13}C NMR (126 MHz, CDCl$_3$) δ 198.6 (C), 168.9 (C), 165.9 (C), 137.1 (C), 134.5 (C), 131.3 (C), 130.9 (CH), 129.5 (2 × CH), 128.7 (4 × CH), 128.5 (CH), 128.4 (2 × CH), 122.8 (q, $J_{C\text{-}F}$ = 277.5 Hz, C), 83.5 (C), 63.0 (CH$_2$), 61.0 (q, $J_{C\text{-}F}$ = 37.1 Hz, CH$_2$), 42.0 (CH$_2$), 15.8 (CH$_3$); ^{19}F NMR (376 MHz, CDCl$_3$) δ −73.7 (t, J = 8.3 Hz, 3 × F); HRMS (ESI) Exact mass

calculated for $[C_{22}H_{20}O_4F_3Na]^+$ $[M+H]^+$: 405.1308, found: 405.1308. Enantiomeric excess was determined by HPLC with Chiralpak OD-H column (95:5 *iso*-hexane: *i*-PrOH, 1.0 mL/min, 210 nm, 25 °C); t_r (major) = 10.6 min, t_r (minor) = 12.3 min, 92% ee.

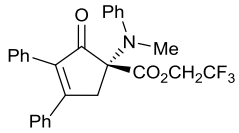


2,2,2-Trifluoroethyl (*R*)-1-(2-chloroethoxy)-2-oxo-3,4-diphenylcyclopent-3-ene-1-carboxylate (216ia). The title compound was prepared according to a slightly modified General Procedure **D**, from malonate ester **215i** (138.2 mg, 0.30 mmol), phenylboronic acid (73.1 mg, 0.60 mmol), $Ni(OAc)_2{\cdot}4H_2O$ (15.0 mg, 0.06 mmol, 20 mol%) and (*R*)-PhPhox (**L20**, 24.4 mg, 0.06 mmol, 20 mol%) at 80 °C. Purification by column chromatography (0-10% EtOAc/pentane) gave **216ia** as a colourless oil (85 mg, 65%). R_f = 0.16 (10% EtOAc/petroleum ether); IR 1756, 1715, 1629, 1444, 1358, 1280, 1161, 1095, 966, 778, 752, 693, 641 cm^{-1}; $[\alpha]_D^{24}$ +32.0 (*c* 1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.42-7.28 (8H, m, Ar**H**), 7.25-7.20 (2H, m, Ar**H**), 4.68 (1H, dq, *J* = 12.6, 8.2 Hz, C**H**$_a$H$_b$CF$_3$), 4.53 (1H, dq, *J* = 12.6, 8.2 Hz, CH$_a$**H**$_b$CF$_3$), 4.22 – 4.14 (2H, m, OC**H**$_2$), 3.70 (2H, td, *J* = 5.8, 2.8 Hz, C**H**$_2$Cl), 3.52 (1H, d, *J* = 17.9 Hz, =CC**H**$_a$H$_b$), 3.35 (1H, d, *J* = 17.9 Hz, =CCH$_a$**H**$_b$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.4 (C), 168.6 (C), 166.2 (C), 137.0 (C), 134.3 (C), 131.1 (C), 131.0 (CH), 129.5 (3 × CH), 128.8 (3 × CH), 128.6 (CH), 128.5 (2 × CH), 122.67 (q, $J_{C\text{-}F}$ = 277.4 Hz, C), 83.0 (C), 67.3 (CH_2), 61.1 (q, $J_{C\text{-}F}$ = 37.1 Hz, CH_2), 43.1 (CH_2), 42.6 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ -73.7 (t, *J* = 8.2 Hz, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{22}H_{18}O_4F_3ClNa]^+$ $[M+Na]^+$: 461.0738, found: 461.0746. Enantiomeric excess was determined by HPLC from a Chiralpak OD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 230 nm, 25 °C); t_r (major) = 9.6 min, t_r (minor) = 13.8 min, 88% ee.



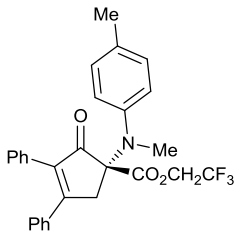
2,2,2-Trifluoroethyl (*R*)-2-oxo-3,4-diphenyl-1-(thiophen-3-ylmethoxy)cyclopent-3-ene-1-carboxylate (216ja). The title compound was prepared according to a slightly modified General Procedure **D**, from malonate ester **215j** (148.3 mg, 0.30 mmol), phenylboronic acid (73.1 mg, 0.60 mmol), $Ni(OAc)_2{\cdot}4H_2O$ (15.0 mg, 0.06 mmol, 20 mol%) and (*R*)-PhPhox (**L20**, 24.4

mg, 0.06 mmol, 20 mol%) at 80 °C. Purification by column chromatography (0-10% EtOAc/pentane) gave **216ja** as an orange oil (111 mg, 78%). R_f = 0.16 (10% EtOAc/petroleum ether); IR 1770, 102, 1354, 1156, 1077, 766, cm^{-1}; $[\alpha]_D^{23}$ +20.0 (*c* 1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.41-7.18 (13H, m, Ar**H**), 4.97 (2H, s, ArC**H**$_2$), 4.72 (1H, dq, *J* = 12.6, 8.3 Hz, OC**H**$_a$H$_b$CF$_3$), 4.56 (1H, dq, *J* = 12.6, 8.3 Hz, OCH$_a$**H**$_b$CF$_3$), 3.53 (1H, d, *J* = 18.0 Hz, =CC**H**$_a$H$_b$), 3.35 (1H, d, *J* = 18.0 Hz, =CCH$_a$**H**$_b$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.7 (C), 168.9 (C), 165.9 (C), 138.7 (C), 137.1 (C), 134.4 (C), 131.2 (C), 131.0 (CH), 129.6 (2 × CH), 128.8 (4 × CH), 128.6 (CH), 128.4 (2 × CH), 127.8 (CH), 126.1 (CH), 123.8 (CH), 122.8 (q, $J_{C\text{-}F}$ = 277.5 Hz, C), 82.9 (C), 64.7 (CH_2), 61.1 (q, $J_{C\text{-}F}$ = 37.1 Hz, CH_2), 42.9 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.6 (t, *J* = 8.3 Hz, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{25}H_{19}O_4F_3SNa]^+$ $[M+Na]^+$: 495.0848, found: 495.0845. Enantiomeric excess was determined by HPLC with Chiralpak OD-H column (95:5 *iso*-hexane: *i*-PrOH, 1.0 mL/min, 210 nm, 25 °C); t_r (minor) = 19.7 min, t_r (major) = 29.5 min, 93% ee.

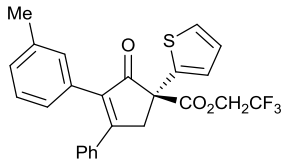


2,2,2-Trifluoroethyl (*R*)-1-(methyl(phenyl)amino)-2-oxo-3,4-diphenylcyclopent-3-ene-1-carboxylate (216la). The title compound was prepared according to General Procedure **D**, from malonate ester **215l** (146.2 mg, 0.30 mmol) and phenylboronic acid (73.1 mg, 0.60 mmol) at 80 °C. Purification by column chromatography (0% to 10% EtOAc/*n*-pentane) gave **216la** as an orange oil (137 mg, 98%). R_f = 0.13 (10% EtOAc/petroleum ether); IR 2973, 1743 (C=O), 1597, 1445, 1353, 1159, 1066, 909, 750, 731 cm^{-1}; $[\alpha]_D^{22}$ +220.0 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.23 (12H, m, Ar**H**), 6.95-6.89 (3H, m, Ar**H**), 4.54 (2H, qd, *J* = 8.3, 5.3 Hz, C**H**$_2$CF$_3$), 4.01 (1H, d, *J* = 18.0 Hz, =CC**H**$_a$CH$_b$), 3.35 (1H, d, *J* = 18.0 Hz, =CCH$_a$C**H**$_b$), 3.15 (3H, s, NC**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.4 (C), 169.4 (C), 167.7 (C), 149.5 (C), 136.7 (C), 134.5 (C), 131.4 (CH), 131.9 (CH), 129.6 (2 × CH), 129.1 (2 × CH), 128.8 (2 × CH), 128.7 (2 × CH), 128.6 (CH), 128.5 (2 × CH), 122.7 (q, $J_{C\text{-}F}$ = 277.5 Hz, C), 121.0 (CH), 119.1 (2 × CH), 74.6 (C), 61.4 (q, $J_{C\text{-}F}$ = 36.8 Hz, CH_2), 42.3 (CH_3), 38.8 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.5 (t, *J* = 8.3 Hz, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{27}H_{22}F_3NO_3Na]^+$

$[M+Na]^+$: 488.1444, found: 488.1448. Enantiomeric excess was determined by HPLC with Chiralpak AD-H column (95:5 *iso*-hexane: *i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (minor) = 11.0 min, t_r (major) = 20.4 min, 88% ee.

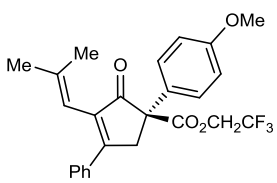


2,2,2-Trifluoroethyl (*R*)-1-[methyl(4-methylphenyl)amino]-2-oxo-3,4- diphenylcyclopent-3-ene-1-carboxylate (216pa). The title compound was prepared according to General Procedure **D**, from malonate ester **215p** (150.4 mg, 0.30 mmol) and phenylboronic acid (73.1 mg, 0.60 mmol) at 80 °C. Purification by column chromatography (5-10% EtOAc/pentane) gave **216pa** as an orange oil (141.0 mg, 98%). R_f = 0.30 (10% EtOAc/petroleum ether); IR 1769 (C=O), 1703 (C=O), 1514, 1445, 1353, 1290, 1156, 1072, 866, 665 cm^{-1}; $[\alpha]_D^{21}$ −156.0 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.21 (10H, m, Ar**H**), 7.06 (2H, d, *J* = 8.4 Hz, Ar**H**), 6.87-6.83 (2H, m, Ar**H**), 4.63-4.45 (2H, m, C**H**$_2CF_3$), 3.89 (1H, d, *J* = 18.0 Hz, =CC**H**$_a$CH$_b$), 3.33 (1H, d, *J* = 18.0 Hz, =CCH$_a$C**H**$_b$), 3.10 (3H, s, NC**H**$_3$), 2.28 (3H, s, ArC**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.7 (C), 169.5 (C), 167.4 (C), 147.2 (C), 136.8 (C), 134.6 (C), 131.5 (C), 131.1 (C), 130.8 (CH), 129.65 (2 × CH), 129.63 (2 × CH), 128.73 (2 × CH), 128.67 (2 × CH), 128.51 (CH), 128.45 (2 × CH), 122.8 (q, $J_{C\text{-}F}$ = 277.9 Hz, C), 120.3 (2 × CH), 74.1 (C), 61.3 (q, $J_{C\text{-}F}$ = 36.8 Hz, CH_2), 41.0 (CH_3), 39.2 (CH_2), 20.7 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.5 (t, *J* = 8.3 Hz, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{28}H_{24}F_3NO_3Na]^+$ $[M+Na]^+$: 502.1600, found: 502.1604. Enantiomeric excess was determined by HPLC with Chiralpak AD-H column (95:5 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (major) = 9.4 min, t_r (minor) = 15.7 min, 90% ee.



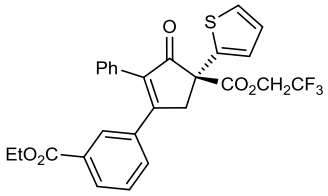
2,2,2-Trifluoroethyl (*R*)-2-oxo-4-phenyl-1-(2-thienyl)-3-(3-methylphenyl)cyclopent-3-ene-1-carboxylate (216ka). The title compound was prepared according to General Procedure **D**, from malonate ester **215k** (143.5 mg, 0.30 mmol) and phenylboronic acid (73.1 mg, 0.60 mmol) at 80 °C. Purification by column chromatography (5% EtOAc/*n*-pentane) gave **216ka** as a yellow oil (79 mg, 58%). R_f = 0.25 (10% EtOAc/petroleum ether); IR 2923,

1765 (C=O), 1704 (C=O), 1622, 1483, 1281, 1234, 1155, 841, 693 cm^{-1}; $[\alpha]_D^{24}$ –28.0 (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.41-7.37 (3H, m, Ar**H**), 7.34-7.30 (4H, m, Ar**H**), 7.22 (1H, t, *J* = 7.6 Hz, Ar**H**), 7.16-7.13 (1H, m, Ar**H**), 7.09-7.08 (1H, m, Ar**H**), 7.04 (1H, dd, *J* = 5.1, 3.7 Hz, Ar**H**), 6.99 (1H, dd, *J* = 7.6, 1.5 Hz, Ar**H**), 4.61 (1H, dq, *J* = 12.7, 8.3 Hz, C**H**$_a$H$_b$CF$_3$), 4.51 (1H, dq, *J* = 12.7, 8.3 Hz, CH$_a$**H**$_b$CF$_3$), 4.08 (1H, d, *J* = 18.0 Hz, =CC**H**$_a$H$_b$), 3.67 (1H, d, *J* = 18.0 Hz, =CCH$_a$**H**$_b$), 2.31 (3H, s, C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.9 (C), 168.6 (C), 165.9 (C), 139.1 (C), 138.4 (C), 136.8 (C), 134.5 (C), 131.4 (C), 130.8 (CH), 130.1 (CH), 129.3 (CH), 128.7 (2 × CH), 128.6 (CH), 128.4 (2 × CH), 126.9 (CH), 126.8 (CH), 126.7 (CH), 125.9 (CH), 122.7 (q, $J_{C\text{-}F}$ = 277.8 Hz, C), 61.6 (q, $J_{C\text{-}F}$ = 36.9 Hz, CH_2), 59.8 (C), 44.3 (CH_2), 21.5 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.6 (t, *J* = 8.2 Hz, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{25}H_{19}F_3NaO_3S]^+$ $[M+Na]^+$: 479.0899, found: 479.0902. Enantiomeric excess was determined by HPLC from a Chiralpak AD-H column (95:5 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 230 nm, 25 °C); t_r (minor) = 12.1 min, t_r (major) = 15.7 min, 91% ee.

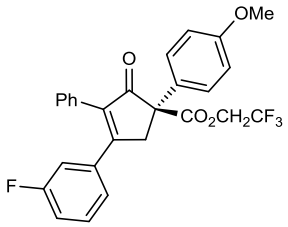


2,2,2-Trifluoroethyl (*R*)-1-(4-methoxyphenyl)-3-(2-methylprop-1-en-1-yl)-2-oxo-4-phenylcyclopent-3-ene-1-carboxylate (216ua). The title compound was prepared according to General Procedure **D**, from malonate ester **215u** (139.9 mg, 0.30 mmol) and phenylboronic acid (73.1 mg, 0.60 mmol) at 100 °C. Purification by column chromatography (0-10% EtOAc/*n*-pentane) gave **216ua** as a yellow oil (101.5 mg, 76%). R_f = 0.20 (10% EtOAc/petroleum ether); IR 2970, 1760 (C=O), 1698 (C=O), 1609, 1513, 1252, 1153, 972, 731, 648 cm^{-1}; $[\alpha]_D^{21}$ –190.0 (*c* 0.40, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.72-7.69 (2H, m, Ar**H**), 7.46-7.42 (3H, m, Ar**H**), 7.39-7.36 (2H, m, Ar**H**), 6.91-6.88 (2H, m, Ar**H**), 5.83-5.81 (1H, m, **H**C=C(Me)$_2$), 4.61-4.47 (2H, m, C**H**$_2$CF$_3$), 4.01 (1H, dd, *J* = 17.9, 2.1 Hz, =CC**H**$_a$H$_b$), 3.80 (3H, s, OC**H**$_3$), 3.45 (1H, dd, *J* = 17.9, 2.1 Hz, =CCH$_a$**H**$_b$), 1.90 (3H, d, *J* = 1.5 Hz, HC=C(C**H**$_3$)$_2$), 1.46 (3H, d, *J* = 1.2 Hz, HC=C(C**H**$_3$)$_2$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.6 (C), 169.9 (C), 164.0 (C), 159.2 (C), 141.8 (C), 135.4 (C), 130.6 (CH), 129.8 (C), 128.78 (2 × CH), 128.77 (2 × CH), 128.2 (2 ×

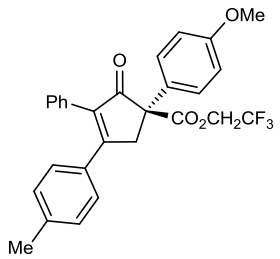
CH), 122.8 (q, $J_{C\text{-}F}$ = 277.3 Hz, C), 115.2 (CH), 114.2 (2 × CH), 62.0 (C), 61.2 (q, $J_{C\text{-}F}$ = 36.5 Hz, CH_2) 55.4 (CH_3), 43.0 (CH_2), 26.1 (CH_3), 20.7 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.6 (t, *J* = 8.3 Hz, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{25}H_{23}F_3NaO_4]^+$ $[M+Na]^+$: 467.1441, found: 467.1437. Enantiomeric excess was determined by HPLC from a Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 230 nm, 25 °C); t_r (major) = 16.0 min, t_r (minor) = 25.6 min, 80% ee.



Ethyl (*R*)-3-{3-oxo-2-phenyl-4-(2-thienyl)-4-[(2,2,2-trifluoroethoxy)carbonyl]cyclopent-1-en-1-yl}benzoate (216gd). The title compound was prepared according to General Procedure **D**, from malonate ester **215g** (139.3 mg, 0.30 mmol) and 3-(ethoxycarbonyl)phenylboronic acid (116.4 mg, 0.60 mmol) at 80 °C. Purification by column chromatography (0-10% EtOAc/*n*-pentane) gave **216gd** as a yellow oil (142 mg, 92%). R_f = 0.05 (10% EtOAc/petroleum ether); IR 2980, 1766 (C=O), 1709 (C=O), 1431, 1271, 1160, 909, 753, 733, 699 cm^{-1}; $[\alpha]_D^{23}$ −20.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (1H, td, *J* = 1.8, 0.6 Hz, Ar**H**), 8.06 (1H, dt, *J* = 7.7, 1.4 Hz, Ar**H**), 7.49 (1H, ddd, *J* = 7.9, 1.9, 1.3 Hz, Ar**H**), 7.38-7.30 (6H, m, Ar**H**), 7.24-7.20 (2H, m, Ar**H**), 7.05 (1H, dd, *J* = 5.2, 3.7 Hz, Ar**H**), 4.65-4.48 (2H, m, C**H**$_2$CF$_3$), 4.35 (2H, q, *J* = 7.1 Hz, OC**H**$_2$CH$_3$), 4.13 (1H, d, *J* = 18.1 Hz, =CC**H**$_a$H$_b$), 3.71 (1H, d, *J* = 18.1 Hz, =CCH$_a$**H**$_b$), 1.35 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.7 (C), 168.4 (C), 165.9 (C), 164.8 (C), 138.9 (C), 137.5 (C), 134.8 (C), 132.7 (CH), 131.6 (CH), 131.3 (C), 131.0 (C), 129.6 (2 × CH), 129.2 (CH), 128.85 (3 × CH), 128.77 (CH), 126.97 (CH), 126.93 (CH), 126.0 (CH), 122.7 (q, $J_{C\text{-}F}$ = 277.6 Hz, C), 61.6 (q, $J_{C\text{-}F}$ = 37.7 Hz, CH_2), 61.5 (CH_2) 59.9 (C), 44.3 (CH_2), 14.4 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.6 (t, *J* = 8.2 Hz, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{27}H_{21}F_3NaO_5S]^+$ $[M+Na]^+$: 537.0954, found: 537.0953. Enantiomeric excess was determined by HPLC from a Chiralpak ADH column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 230 nm, 25 °C); t_r (minor) = 14.9 min, t_r (major) = 17.6 min, 92% ee.

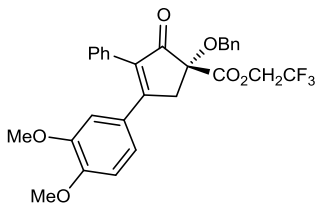


2,2,2-Trifluoroethyl (*R*)-4-(3-fluorophenyl)-1-(4-methoxyphenyl)-2-oxo-3-phenylcyclopent-3-ene-1-carboxylate (216cj). The title compound was prepared according to General Procedure **D**, from malonate ester **215c** (146.5 mg, 0.30 mmol) and 3-fluorophenylboronic acid (83.9 mg, 0.60 mmol) at 120 °C. Purification by column chromatography (0-10% EtOAc/*n*-pentane) gave **216cj** as a yellow oil (118 mg, 81%). R_f = 0.14 (10% EtOAc/petroleum ether); IR 2839, 1763 (C=O), 1705 (C=O), 1513, 1483, 1282, 1252, 1154, 1031, 732 cm^{-1}; $[\alpha]_D^{21}$ –80.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45-7.43 (2H, m, Ar**H**), 7.41-7.34 (3H, m, Ar**H**), 7.30-7.24 (3H, m, Ar**H**), 7.16 (1H, app dq, *J* = 8.0, 1.6 Hz, Ar**H**), 7.09-7.05 (2H, m, Ar**H**), 6.96-6.92 (2H, m, Ar**H**), 4.58 (2H, m, C**H**$_2$CF$_3$), 4.09 (1H, dd, *J* = 18.0, 2.2 Hz, =CC**H**$_a$H$_b$), 3.81 (3H, s, OC**H**$_3$), 3.51 (dd, *J* = 18.0, 2.2 Hz, =CCH$_a$**H**$_b$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.0 (C), 169.4 (C), 164.0 (C), 162.6 (d, $J_{C\text{-}F}$ = 247.7 Hz, CF), 159.3 (C), 138.3 (C), 136.7 (d, $J_{C\text{-}F}$ = 7.6 Hz, C), 131.2 (C), 130.3 (d, $J_{C\text{-}F}$ = 8.3 Hz, CH), 129.6 (2 × CH), 128.78 (2 × CH), 128.76 (2 × CH), 128.71 (CH), 128.66 (CH), 124.1 (d, $J_{C\text{-}F}$ = 8.3 Hz, CH), 122.8 (q, $J_{C\text{-}F}$ = 277.8 Hz, C), 117.5 (d, $J_{C\text{-}F}$ = 21.3 Hz, CH), 115.2 (d, $J_{C\text{-}F}$ = 22.7 Hz, CH), 114.3 (2 × CH), 62.4 (C), 61.3 (q, $J_{C\text{-}F}$ = 37.1 Hz, CH_2), 55.4 (CH_3), 43.7 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.6 (m, 3 × F), –111.7 (app q, *J* = 8.1 Hz, F); HRMS (ESI) exact mass calculated for $[C_{27}H_{20}F_4NaO_4]^+$ $[M+Na]^+$: 507.1190, found: 507.1187. Enantiomeric excess was determined by HPLC with Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 230 nm, 25 °C); t_r (minor) = 27.5 min, t_r (major) = 30.4 min, 81% ee.



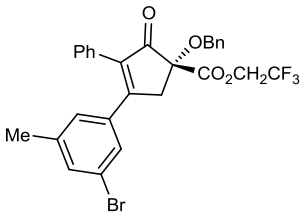
2,2,2-Trifluoroethyl (*R*)-1-(4-methoxyphenyl)-2-oxo-3-phenyl-4-(4-methylphenyl)cyclopent-3-ene-1-carboxylate (216ck). The title compound was prepared according to General Procedure **D**, from malonate ester **215c** (146.5 mg, 0.30 mmol) and 4-methylphenylboronic acid (81.6 mg, 0.60 mmol) at 100 °C. Purification by column chromatography (10% EtOAc/*n*-pentane) gave **216ck** as a yellow oil

(110 mg, 76%). R_f = 0.11 (10% EtOAc/petroleum ether); IR 2931, 1763 (C=O), 1698 (C=O), 1512, 1350, 1252, 1153, 1033, 818, 732 cm^{-1}; $[\alpha]_D^{21}$ –80.0 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.41 (2H, m, Ar**H**), 7.38-7.32 (3H, m, Ar**H**), 7.28-7.25 (4H, m, Ar**H**), 7.10 (2H, d, *J* = 7.9 Hz, Ar**H**), 6.93-6.90 (2H, m, Ar**H**), 4.56 (2H, m, C**H**$_2$$CF_3$), 4.08 (1H, d, *J* = 18.0 Hz, =CC**H**$_a$$H_b$), 3.81 (3H, s, OC**H**$_3$), 3.51 (1H, d, *J* = 18.0 Hz, =CCH_a**H**$_b$), 2.34 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1 (C), 169.7 (C), 165.8 (C), 159.2 (C), 141.3 (C), 136.8 (C), 132.0 (C), 131.7 (C), 129.9 (C), 129.7 (2 × CH), 129.4 (2 × CH), 128.8 (2 × CH), 128.7 (2 × CH), 128.4 (2 × CH), 128.3 (CH), 122.8 (q, $J_{C\text{-}F}$ = 277.9 Hz, C), 114.2 (2 × CH), 62.4 (C), 61.2 (q, $J_{C\text{-}F}$ = 36.7 Hz, CH_2), 55.4 (CH_3), 43.6 (CH_2), 21.5 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.5 (t, *J* = 8.2 Hz, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{28}H_{23}F_3NaO_4]^+$ $[M+Na]^+$: 503.1441, found: 503.1438. Enantiomeric excess was determined by HPLC with Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 230 nm, 25 °C); t_r (major) = 26.4 min, t_r (minor) = 29.8 min, 82% ee.

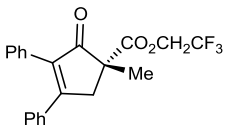


2,2,2-Trifluoroethyl (*R*)-1-(benzyloxy)-4-(3,4-dimethoxyphenyl)-2-oxo-3-phenylcyclopent-3-ene-1-carboxylate (216fl). The title compound was prepared according to General Procedure **D**, from malonate ester **215f** (146.5 mg, 0.30 mmol) and 3,4-dimethoxyphenylboronic acid (109.2 mg, 0.60 mmol) at 80 °C. Purification by column chromatography (0-10% EtOAc/*n*-pentane) gave **216fl** as a pale yellow oil (121 mg, 76%). R_f = 0.06 (10% EtOAc/petroleum ether); IR 3024, 1771 (C=O), 1699 (C=O), 1596, 1517, 1267, 1155, 1022, 749, 697 cm^{-1}; $[\alpha]_D^{22}$ +16.0 (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.45-7.39 (4H, m, Ar**H**), 7.37-7.34 (3H, m, Ar**H**), 7.32-7.28 (1H, m, Ar**H**), 7.26-7.24 (2H, m, Ar**H**), 7.07 (1H, dd, *J* = 8.5, 2.2 Hz, Ar**H**), 6.83 (1H, d, *J* = 8.5 Hz, Ar**H**), 6.78 (1H, d, *J* = 2.1 Hz, Ar**H**), 4.96 (1H, d, *J* = 11.0 Hz, OC**H**$_a$$H_b$Ph), 4.92 (1H, d, *J* = 11.0 Hz, OCH_a**H**$_b$Ph), 4.73 (1H, dq, *J* = 12.6, 8.3 Hz, C**H**$_a$$H_b$$CF_3$), 4.56 (1H, dq, *J* = 12.6, 8.3 Hz, CH_a**H**$_b$$CF_3$), 3.89 (3H, s, OC**H**$_3$), 3.54 (1H, d, *J* = 17.7 Hz, =CC**H**$_a$$H_b$), 3.43 (3H, s, OC**H**$_3$), 3.36 (1H, d, *J* = 17.7 Hz, =CCH_a**H**$_b$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.4

(C), 169.1 (C), 165.0 (C), 151.7 (C), 148.5 (C), 137.8 (C), 135.8 (C), 132.3 (C), 129.7 (2 × CH), 129.0 (2 × CH), 128.55 (2 × CH), 128.46 (CH), 128.3 (2 × CH), 128.0 (CH), 126.6 (C), 122.7 (q, $J_{C\text{-}F}$ = 277.2 Hz, C), 122.1 (CH), 112.0 (CH), 110.8 (CH), 82.9 (C), 69.4 (CH_2), 61.1 (q, $J_{C\text{-}F}$ = 37.1 Hz, CH_2), 56.1 (CH_3), 55.4 (CH_3), 42.4 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.6 (t, J = 8.3 Hz, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{29}H_{25}F_3NaO_6]^+$ $[M+Na]^+$: 549.1495, found 549.1479. Enantiomeric excess was determined by HPLC from a Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 210 nm, 25 °C); t_r (major) = 20.1 min, t_r (minor) = 36.7 min, 90% ee.



2,2,2-Trifluoroethyl (*R*)-1-(benzyloxy)-4-(3-bromo-5-methylphenyl)-2-oxo-3-phenylcyclopent-3-ene-1-carboxylate (216fm). The title compound was prepared according to General Procedure **D**, from malonate ester **215f** (146.5 mg, 0.30 mmol) and 3-bromo-5-methyl phenylboronic acid (128.9 mg, 0.60 mmol) at 80 °C. Purification by column chromatography (0-10% EtOAc/*n*-pentane) gave **216fm** as a pale yellow oil (122 mg, 73%). R_f = 0.10 (10% EtOAc/petroleum ether); IR 3033, 1772 (C=O), 1706 (C=O), 1347, 1283, 1160, 907, 854, 729, 700 cm^{-1}; $[\alpha]_D^{21}$ +24.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.41 (2H, m, Ar**H**), 7.38-7.28 (7H, m, Ar**H**), 7.24-7.23 (1H, m, Ar**H**), 7.22-7.16 (2H, m, Ar**H**), 7.01 (1H, td, J = 1.5, 0.8 Hz, Ar**H**), 4.96-4.89 (2H, m, OC**H**$_2$Ar), 4.72 (1H, dq, J = 12.6, 8.2 Hz, C**H**$_a$H$_b$CF$_3$), 4.57 (1H, dq, J = 12.6, 8.2 Hz, CH$_a$**H**$_b$CF$_3$), 3.48 (1H, d, J = 18.0 Hz, =CC**H**$_a$H$_b$), 3.30 (1H, d, J = 18.0 Hz, =CCH$_a$**H**$_b$), 2.22 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.4 (C), 168.7 (C), 164.2 (C), 140.5 (C), 137.8 (C), 137.6 (C), 136.2 (C), 134.3 (CH), 130.7 (C), 129.4 (2 × CH), 128.84 (CH), 128.77 (2 × CH), 128.6 (2 × CH), 128.3 (CH), 128.2 (2 × CH), 128.1 (CH), 127.7 (CH), 122.7 (q, $J_{C\text{-}F}$ = 277.8 Hz, C), 122.6 (C), 83.0 (C), 69.4 (CH_2), 61.1 (q, $J_{C\text{-}F}$ = 37.2 Hz, CH_2), 42.8 (CH_2), 21.2 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.6 (t, J = 8.2 Hz, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{28}H_{22}BrF_3NaO_4]^+$ $[M+Na]^+$: 581.0546, found 581.0547. Enantiomeric excess was determined by HPLC from a Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (major) = 8.6 min, t_r (minor) = 9.8 min, 94% ee.



2,2,2-Trifluoroethyl (*R*)-1-methyl-2-oxo-3,4-diphenylcyclopent-3-ene-1-carboxylate (216aa). A flask was charged with malonate ester **215a** (110.8 mg, 0.30 mmol), phenylboronic acid (73.1 mg, 0.60 mmol), $Ni(OAc)_2 \cdot 4H_2O$ (7.5 mg, 0.03 mmol) and (*S*)-^{t}Bu-NeoPHOX (**L5**, 11.0 mg, 0.03 mmol) and capped with a crimp cap PTFE seal and evacuated and back filled with argon (5 cycles). TFE (3 mL) which had been freshly degassed (from 5 freeze-pump-thaw cycles) was added under argon flow, the septum was resealed with a layer of vacuum grease, and the contents were stirred at room temperature for 10 min followed by stirring at 80 °C for 6 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 over anhydrous Na_2SO_4, filtered and concentrated. Purification by column chromatography (0-5% EtOAc/pentane) afforded the title compound as an off-white oil (52 mg, 46%). R_f = 0.17 (10% EtOAc/petroleum ether); IR 2934, 1760 (C=O), 1699 (C=O), 1623, 1352, 1154, 1097, 1073, 974, 694 cm^{-1}; $[\alpha]_D^{25}$ –24.3 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.28 (8H, m, Ar**H**), 7.25-7.21 (2H, m, Ar**H**), 4.60 (1H, dq, *J* = 12.7, 8.3 Hz, C**H**$_a$H$_b$CF$_3$), 4.47 (1H, dq, *J* = 12.7, 8.3 Hz, CH$_a$**H**$_b$CF$_3$), 3.62 (1H, d, *J* = 18.1 Hz, =CC**H**$_a$H$_b$), 2.96 (1H, d, *J* = 18.1 Hz, =CCH$_a$**H**$_b$), 1.63 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.9 (C), 170.5 (C), 166.3 (C), 137.1 (C), 134.9 (C), 131.7 (C), 130.6 (CH), 129.6 (2 × CH), 128.73 (2 × CH), 128.68 (2 × CH), 128.4 (CH), 128.3 (2 × CH), 122.9 (q, *J* = 277.5 Hz, CF_3), 61.1 (q, *J* = 36.7 Hz, CH_2), 54.3 (C), 43.2 (CH_2), 21.1 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ –73.8 (t, *J* = 8.3 Hz, 3 × F); HRMS (ESI) Exact mass calculated for $[C_{21}H_{17}NaO_3F_3]^+$ $[M+Na]^+$: 397.1022, found: 397.1028. Enantiomeric excess was determined by HPLC from a Chiralpak AD-H column (97:3 *iso*-hexane:*i*-PrOH, 0.8 mL/min, 254 nm, 25 °C); t_r (major) = 12.5 min, t_r (minor) = 13.5 min, 59% ee.

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