THE UNIVERSITY *of* EDINBURGH

Copper and Iridium Conjugate Addition – Cyclisation Processes; Domino Reactions

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By

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Declaration

I hereby declare that, except where specific reference is made to other sources, the work contained within this thesis is the original work of my own research since the registration of the PhD degree in January 2011, and any collaboration is clearly indicated. This thesis has been composed by myself and has not been submitted, in whole or part, for any other degree, diploma or other qualification.

Jorge Solana González

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Barcelona, Madrid, Londres, etc… que me daban el aliento y la fuerza para poder continuar mi dia a dia sin ti en Edimburgo y Nottingham. Gracias por todo. Te quiero.

List of abbreviations

1,2-DCE	1,2-Dichloroethane
Ac	Acetyl
acac	Acetylacetonate
ACN	Acetonitrile
AcOH	Acetic acid
Anh	Anhydrous
Aq	Aqueous
atm	Atmosphere
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bu	Butyl
d.r.	Diastereomeric ratio
dba	Dibenzylideneacetone
cat	Catechol
calcd	Calculated
coe	Cyclooctene
cod	Cyclooctadiene
CsOPiv	Caesium pivalate
CuTC	Copper(I)
d	Doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane
DEPT	Distortionless enhancement by polarisation transfer

DFT	Density functional theory
DMA	Dimethylacetamide
DME	Dimethoxyethane
DMF	Dimetheylformamide
DMSO	Dimethylsulfoxide
dppb	1,4-Bis(diphenylphosphino)butane
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1′-Bis(diphenylphosphino)ferrocene
dppm	1,1-Bis(diphenylphosphino)methane
dppp	1,3-Bis(diphenylphosphino)propane
ECA	Enantioselective conjugate addition
EDG	Electron-donating group
ee	Enantiomeric excess
EI	Electron ionization
Et	Ethyl
et al.	*et alli*
equiv	Equivalent
ESI	Electrospray ionization
EWG	Electron-withdrawing group
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
i.e.	*id est*
i-PrOH	*iso*-Propanol

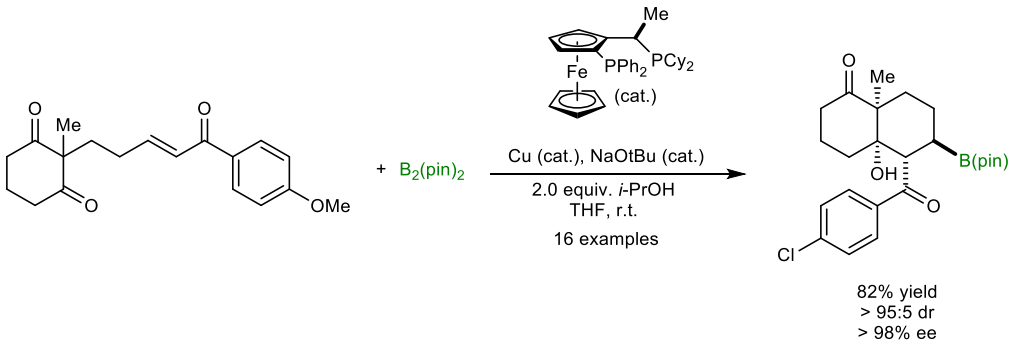
IR	Infra-red
kCal	Calories
KO*t*-Bu	Potassium *tert*-butoxide
m	Multiplet
m.p.	Melting point
Me	Methyl
mg	Miligram
mL	Millilitre
mmol	Millimol
n-Bu	*n*-Butyl
n-Pent	*n*-Pentyl
nbd	Norbornadiene
NHC	N-Heterocyclic carbene
NMR	Nuclear magnetic resonance
Nuc:	Nucleophile
o-Tol	*o*-Tolyl
OAc	Acetate
OPiv	Pivalate
O*t*-Bu	*tert*-Butoxide
OTf	Triflate
PCy_3	Tricyclohexylphosphine
Ph	Phenyl
pin	Pinacol

ppm	Parts per million
q	Quartet
r.t.	Room temperature
rac	Racemic
R_f	Retardation factor
s	Singlet
sat	Saturated
t	Triplet
t-Am	*tert*-Amyl
t-Bu	*tert*-Butyl
t-Bu_2PPh	Di-tert-butylphenylphosphine
t-BuOH	*tert*-Butanol
TC	thiophene-2-carboxylate
TFP	Tri(2-furyl)phosphine
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
t_r	Retention time
UV	Ultraviolet

Abstract

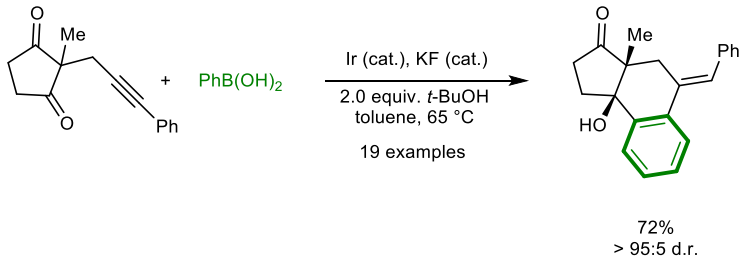
I . Enantioselective Copper(I)-Catalysed Borylative Aldol Cyclisations of Enone Diones

Asymmetric conjugate addition of bis(pinacolato)diboron followed by aldol cyclisation of enone diones under the action of a chiral copper catalyst has been developed.[1] This enantioselective process, using a chiral bisphosphine as ligand, allows the formation of bicyclic alcohols with four contiguous stereocentres in high diastero- and enantioselectivity. This catalytic system has been applied to the parallel kinetic resolution of a racemic β-ketoamide. Further functionalization of the bicyclic alcohols synthesised was also possible.[a]



II. Iridium-Catalysed Arylative Cyclization of Alkynones by 1,4-Iridium Migration

A domino addition of arylboronic acids and cyclisation of alkynones *via* an undescribed iridium 1-4-migration process has been developed.[2] A range of tricyclic compounds using a variety of arylboronic acids have been synthesised in good yields and high diasteroselectivity. The use of chiral bisphosphine ligand together with an iridium salt allows the formation of enantioenriched compounds in moderate yield.



[a] Stereocentres are drawn following McMillan and Evan's group style. Triangular wedges are used for

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1. Introduction

1.1. Domino Reactions

One of the main challenges in modern organic chemistry is the use of more environmentally friendly reactions. Traditional organic chemistry does not usually follow the principles of Green chemistry,[3] which can be used as guidelines for the development of more sustainable processes. A common way to synthesise complex organic compounds is to form one molecular bond at a time. This multistep approach often requires work-up and purification at each stage and can produce a large amount of waste. It also increases the length of the synthesis and, therefore, increases the energy required for the process.

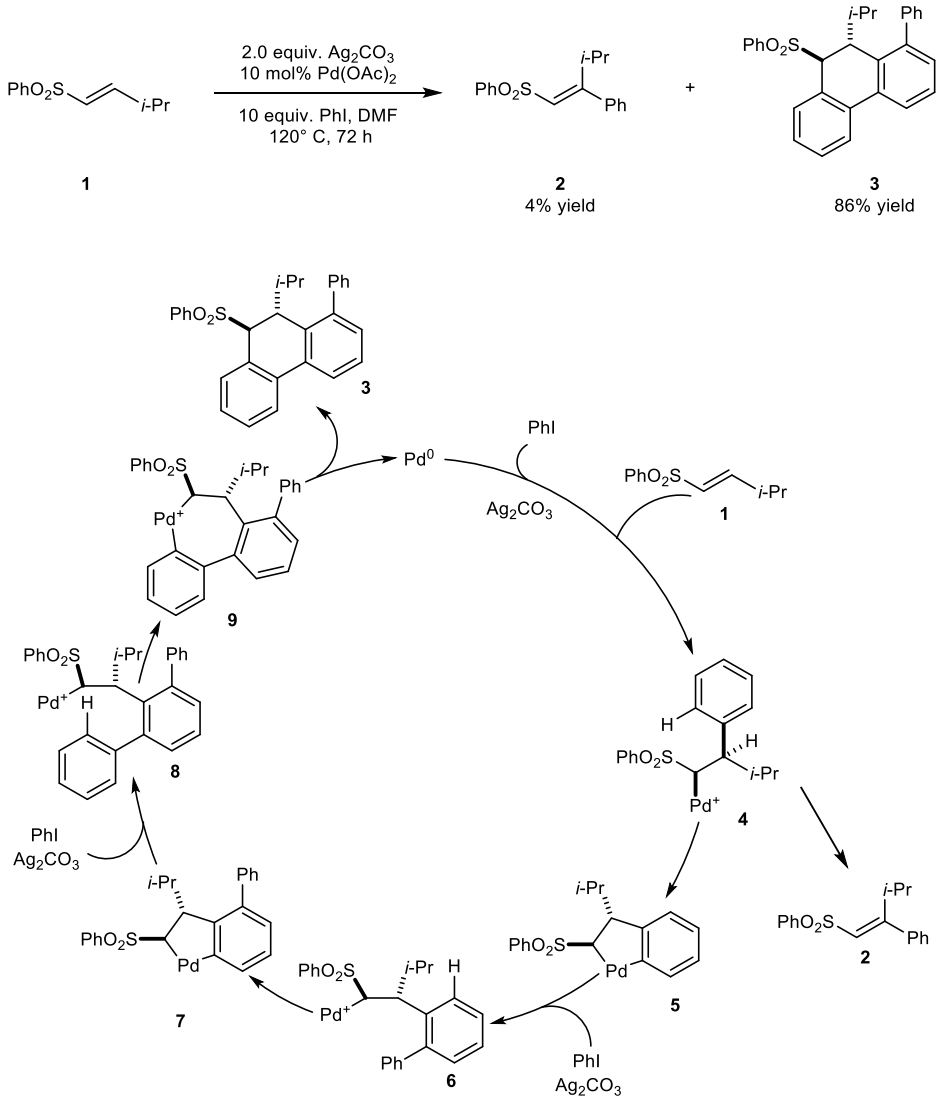
Domino reactions can be viewed as a green approach to complex molecule synthesis. A domino reaction, defined by Professor Lutz F. Tietze as a "*Transformation of two or more bond-forming reactions under identical reaction conditions, in which the latter transformations take place at the functionalities obtained in the former-bond forming reactions*" would reduce the amount of waste by decreasing the number of steps in a synthesis, and, therefore the number of individual work-ups and purifications.[4] In this manner, the transformation would be closer to the definition of a green or sustainable process making it more environmentally friendly.

Domino reactions have been intensively studied in the last few decades.[5] This type of process has been utilised to form numerous complex natural products using multiple strategies;[6] from cationic catalysts[7] to enzymatic transformations.[8] However, recently, special interest has been shown towards the use of transition metals in order to perform domino reactions.[9]

Several transition metals have been shown to facilitate domino processes but rhodium[10], palladium[11] and ruthenium[12] stand out among the rest. More recently, copper has also been utilised to perform these transformations.[13] Other non-precious metals such as cobalt, nickel and iron have also been utilised in domino reactions, but their use is less common.[14]

A good example of a palladium-catalysed domino reaction was reported by Carretero in 2001 where the process is initiated by a Mizoroki-Heck reaction.[15] After aryl palladation of the α-β-unsaturated sulfone **1**, palladium can undergo β-hydride elimination to form the *syn*-

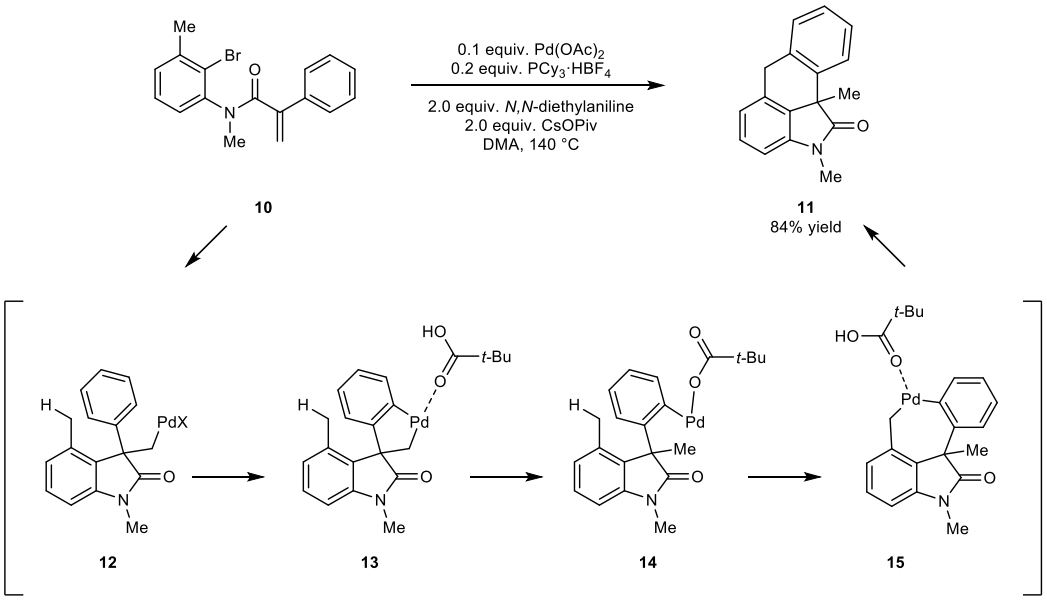
alkene **2**. However, palladium is also capable of forming a five-membered palladacycle **5** through a C-H activation process. This palladacycle **5** can react with a second equivalent of phenyl iodide in a Suzuki-Miyaura-type reaction forming a new C-C bond. At this point palladium could, again undergo β-hydride elimination, but instead undergoes a second C-H activation as before to give **7**. Finally, a seven-membered palladacycle **9** is formed, which, after reductive elimination give almost exclusively the tricyclic compound **3** (Scheme 1).



Scheme 1: Palladium domino arylation/cyclisation process

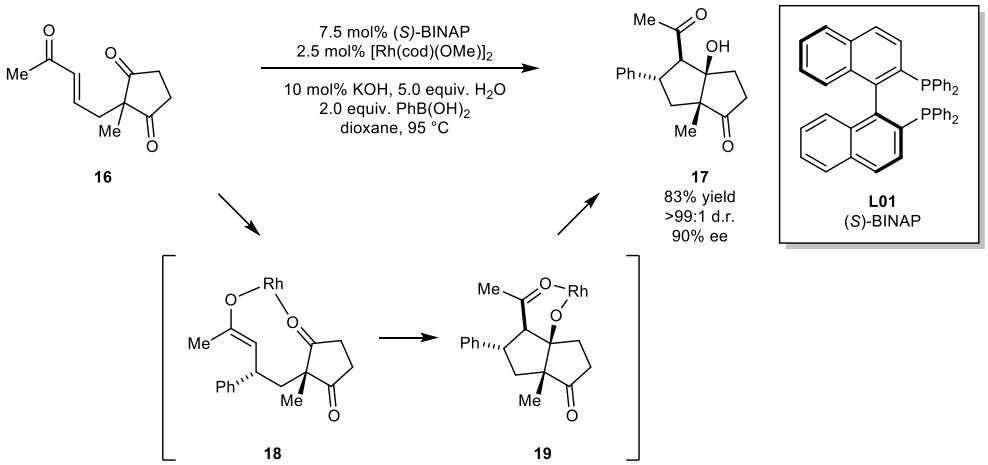
More recently, Zhu published the synthesis of fused oxindoles by a domino process from anilides of type **10** using palladium catalysis.[16] After oxidative addition and carbopalladation of **10** to give **12**, a five-membered ring palladacycle **13** is formed *via* C-H activation. This palladium species **13** then activates the aromatic methyl group to form a

seven-membered ring palladacycle **15**, which, after reductive elimination, gave tricyclic compound **11** (Scheme 2).



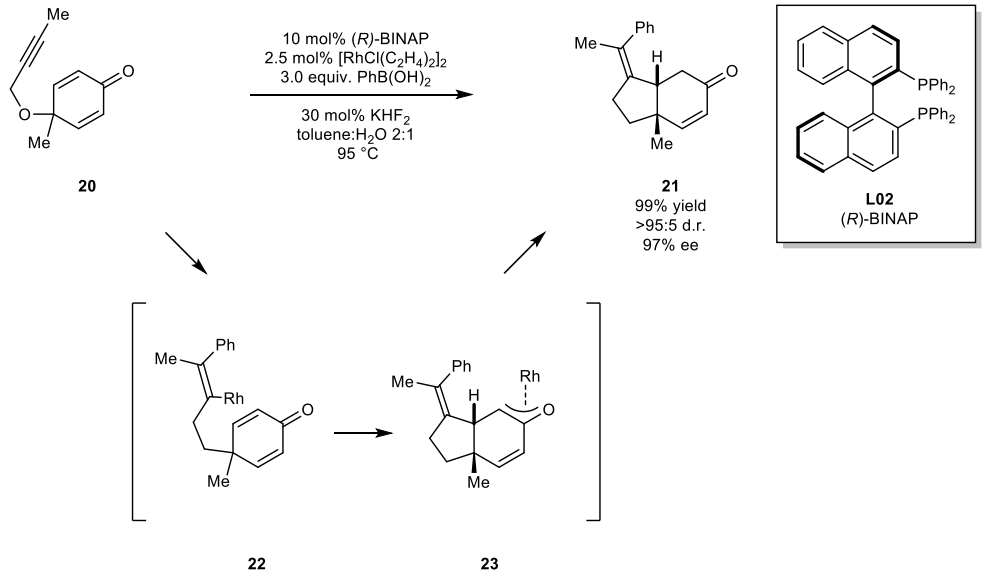
Scheme 2: Palladium domino intramolecular arylation/cyclisation process

The rhodium-catalysed asymmetric hydroarylation of alkenes has been well established in the last few years by several groups. Krische and co-workers used this methodology to perform an asymmetric domino arylation-cyclisation process.[17] Applying standard rhodium-catalysed hydroarylation conditions with (*S*)-BINAP (**L01**) as ligand, Krische's group achieved very high levels of both diastereo- and enantiocontrol in the desymmetrisation of enone-diones **16** (Scheme 3).



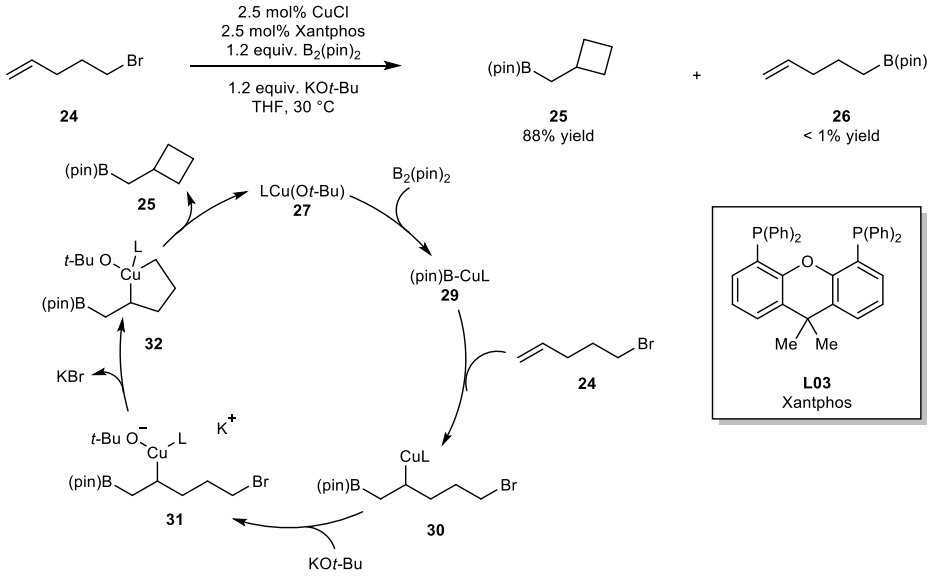
Scheme 3: Rhodium domino arylation/aldol cyclisation process

A more recent example of a domino reaction involving an arylative process catalysed by rhodium was published in 2013 by the Lin group. They applied rhodium-catalysed hydroarylation conditions to symmetric cyclohexadienone-containing 1,6-dienynes **20**.[18] Using (*R*)-BINAP (**L02**) as ligand, the initial arylation occurs exclusively on the alkyne (no hydroarylation of the alkenes was observed). The alkenylrhodium species formed **22** then adds on to the α-β-unsaturated ketone to form *cis*-hydrobenzofurans **21** in a highly diastereo- and enantioselective manner (Scheme 4).



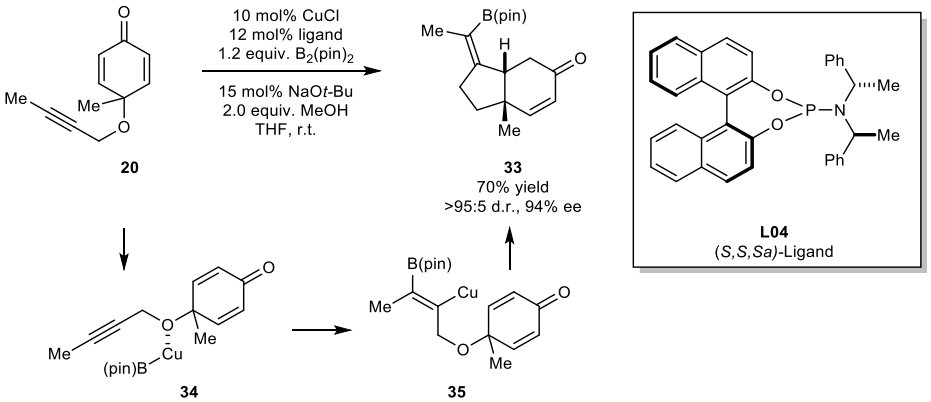
Scheme 4: Rhodium domino arylation/Michael addition process

As mentioned previously, copper-catalysed domino processes have been developed recently as an alternative to more expensive precious transition-metal catalysed transformations. An example of such a transformation was reported by Ito *et al.* in 2013. Applying copper catalysis, Ito's group performed a borylative *exo*-cyclization of alkenyl halides (**24)** with bis(pinacolato) diboron and Xantphos (**L03)** as ligand.[19] One of the main challenges of this process was the control of the chemoselectivity. With alkenyl bromides or chlorides in the presence of Xantphos (**L03)**, the borylation occurred exclusively on the alkene without any traces of the simple boryl substitution product **26**. Mechanistically, the copper-Xantphos catalyst performs the borylation on the unactivated alkene forming alkyl-copper species **30**. This species **30** forms an ate complex **31** by coordination with the base present to then, after sequential oxidative addition and reductive elimination, give the desired cyclic compound **25** (Scheme 5).



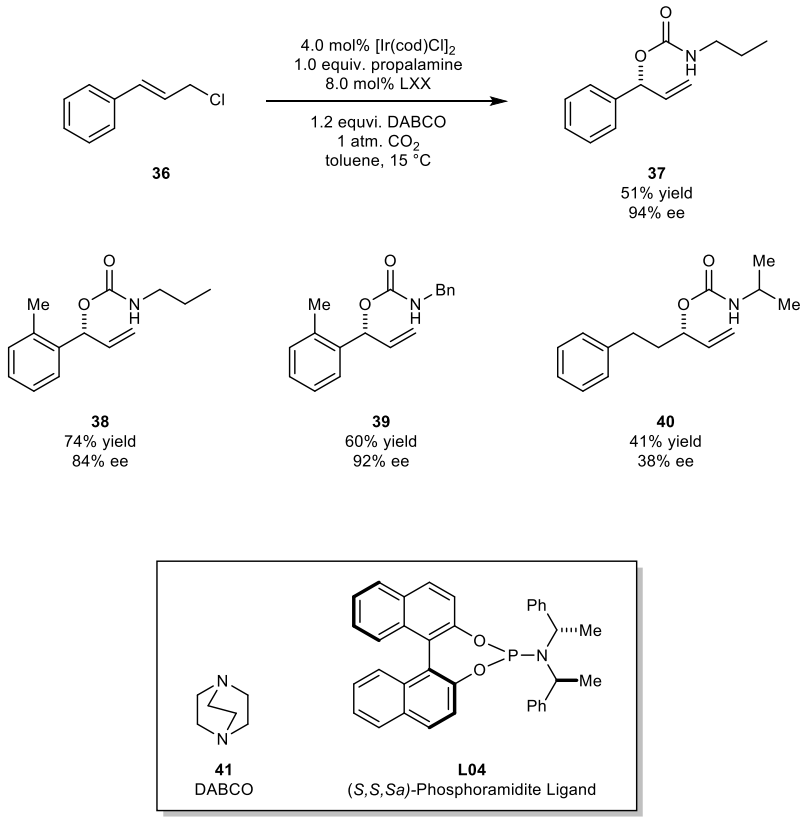
Scheme 5: Copper domino borylation/cyclisation process

Another example of borylative domino reaction using copper was published by Lin in 2013. In this case, an asymmetric borylative cyclization of cyclohexadione-containing 1,6-enynes was reported. Similarly as Ito (Scheme 6), Lin's group applied borylation conditions with a chiral phosphoramidite ligand (**L04**) to achieve the formation of oxygen-containing bicycles.[20] The catalytic system proposed is capable of differentiating between the unsaturated ketone and the alkyne. The conjugate borylation of the alkene is supressed by the substituents on the cyclohexadione and the borylation of the alkyne is facilitated through coordination of the copper-boron species to the oxygen of the propargyl ether unit (**34**). After the borylation, asymmetric conjugate addition to the α,β-unsaturated ketone takes place to give the desired bicycle **33** (Scheme 6).



Scheme 6

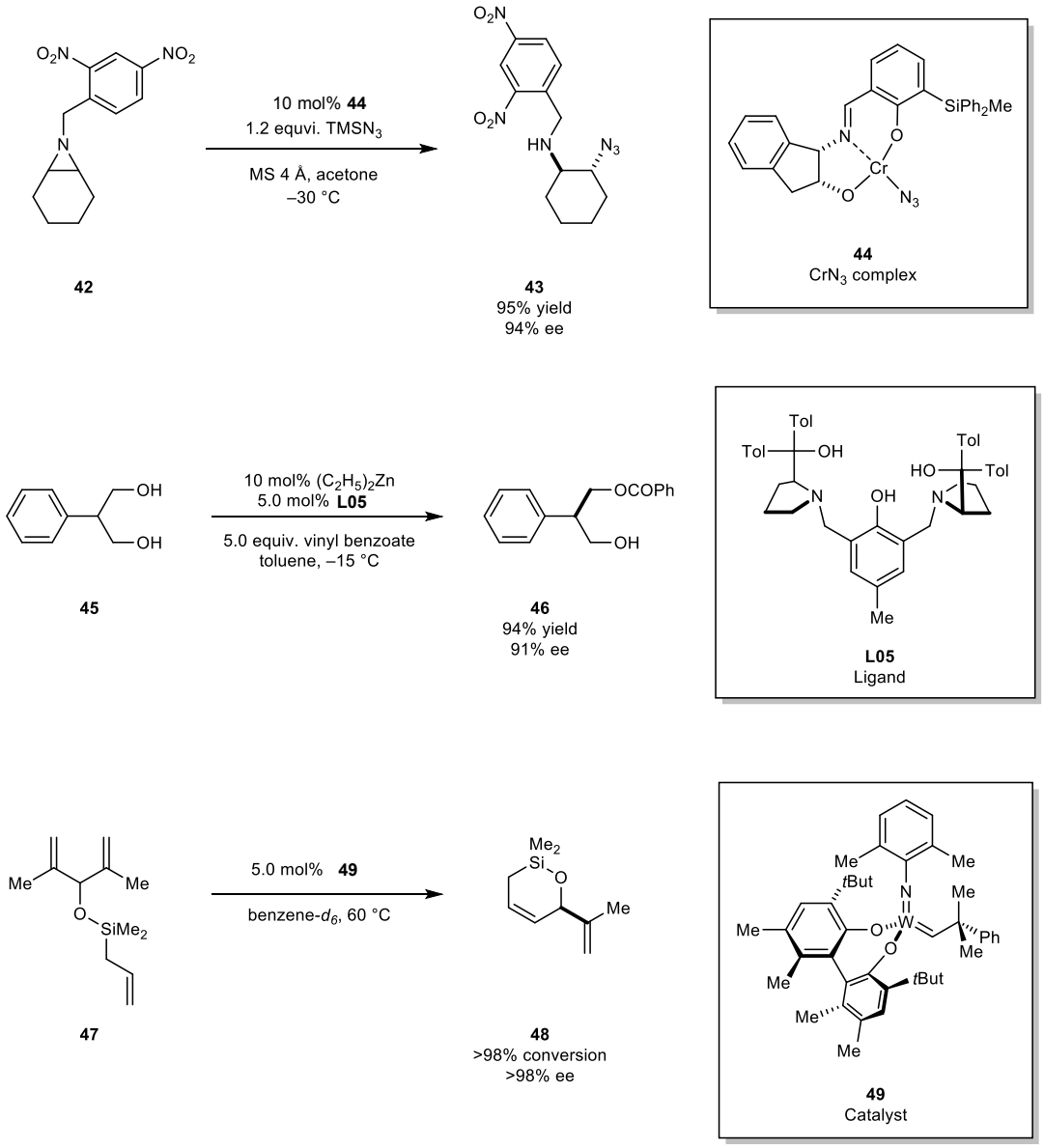
As mentioned previously, other metals have been shown to carry out domino processes. Although there is very little in the literature on domino reactions using iridium as a catalyst, it is worth mentioning the work done by Zhao's group in 2014 towards the synthesis of allyl carbamates *via* a multicomponent domino process catalysed by iridium (Scheme 7).[21] In the presence of CO_2 and an amine, allyl chlorides **36** react to form allyl carbamates **37** under iridium catalysis using a phosphoramidite ligand.



Scheme 7: Iridium catalysed allyl carbamate synthesis

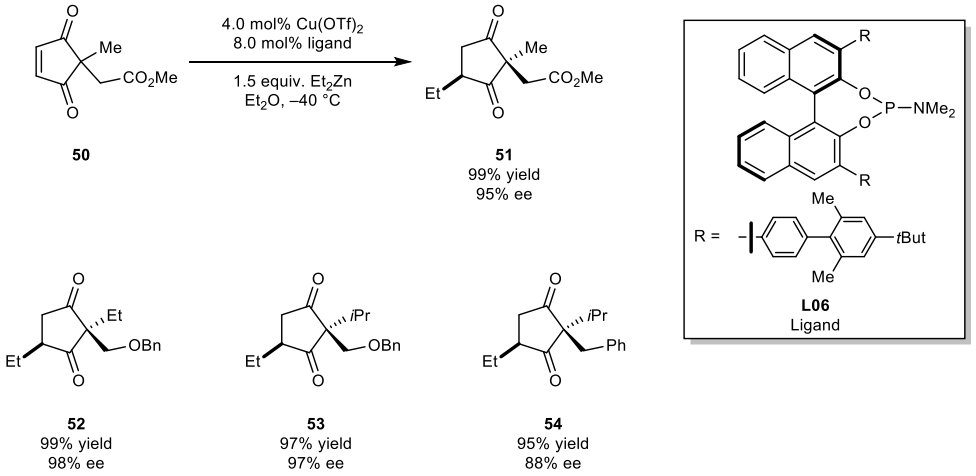
1.2. Desymmetrisation Reactions of 1,3-Diones

Enantioselective desymmetrisation is a very powerful tool to generate chiral compounds with more than one stereocentre in a single step. Examples of this type of chemistry have been extensively reported in the last few decades. Many different strategies have been applied to a wide range of symmetric compounds; from ring-opening of aziridines,[22] to acylation of symmetric diols[23] or olefin metathesis[24] (Scheme 8).



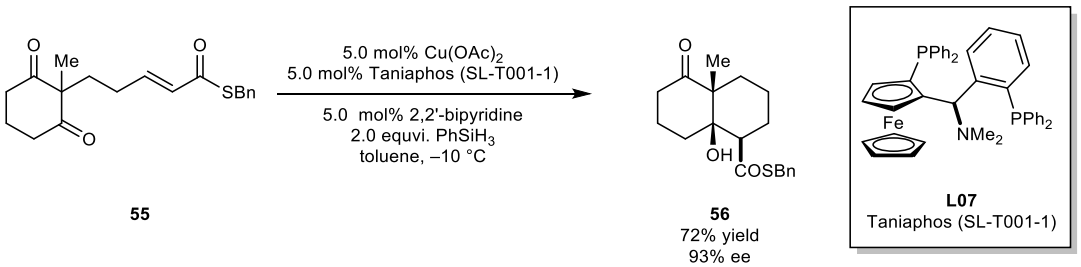
Scheme 8: Desymmetrisation examples

A very useful type of substrate for desymmetrisation processes are 1,3-dione containing compounds. The diketone moiety can promote a number of different types of reaction. For instance, Mikami *et al.* applied the well stablished copper-catalysed conjugate addition of organozinc-reagents to α,β-unsaturated ketones to synthesise five-membered ring compounds containing all-carbon quaternary centres.[25] The alkylation of cyclic pentadiones **50** using a phosphoramidite ligand (**L06**) gave the desired product with high levels of enantiocontrol and, in most cases, a single diastereoisomer (Scheme 9).



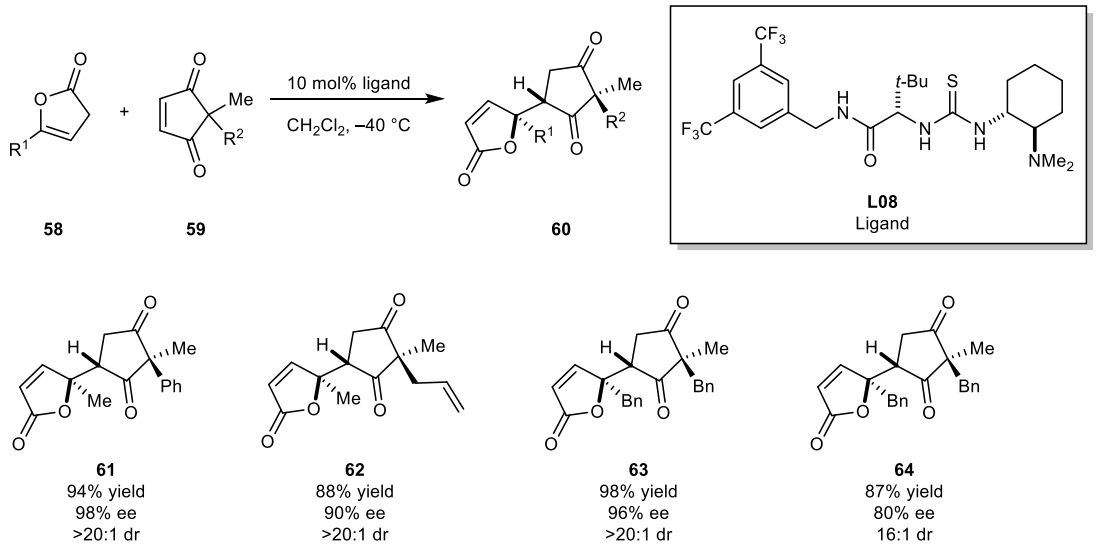
Scheme 9: Copper catalysed conjugate addition for the desymmetrisation of 1,3-diones

Another example of the desymmetrisation of 1,3-diones was reported by Chiu in 2012 where a reductive aldol cyclisation of enethioate derivatives **55** using copper-bisphosphine complex was reported.[26] Ph_3SiH and copper acetate in the presence of a Taniaphos ligand perform a conjugate reduction of the electron deficient alkene of substrates of type **55**. Then the enolate formed during the reduction is intramolecularly trapped by the pendent 1,3-dione to give bicycle **56** as a single diasteroisomer and with high levels of enantioselectivity (Scheme 10).



Scheme 10: Copper domino reductive aldol cyclisation

More recently, Mukherjee published the desymmetrisation of cyclopentene-1,3-diones **59** *via* an organocatalysed nucleophilic addition of deconjugated butenolides **58**.[27] The organocatalyst of choice for this transformation was an amino thiourea **L08**. A combination of (*S*)-*tert*-leucine and (1*R*, 2*R*)-diaminocyclohexane with a 3,5-bis(trifluoromethyl)benzyl group on the amide nitrogen **L08** proved to be superior. The addition of different deconjugated butenolides to a range of cyclopentene-1,3-diones **59** gave the desired products with high d.r. and enantiomeric excess (Scheme 11).



Scheme 11: Organocatalyzed desymmetrisation of 1,3-diones

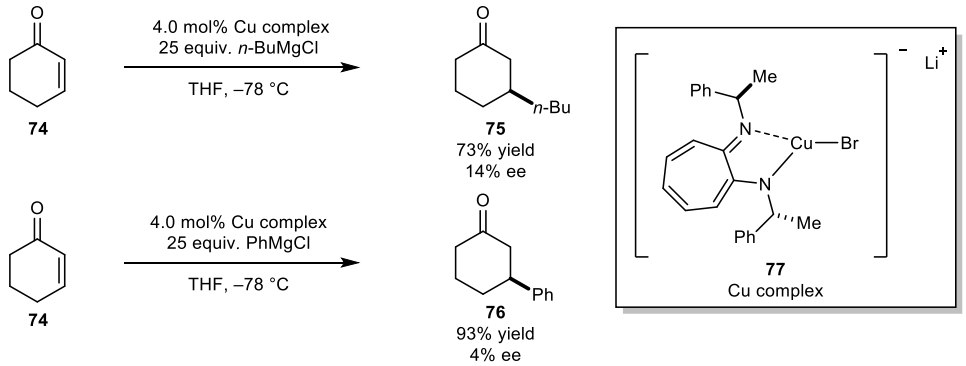
2. Introduction to Enantioselective Copper(I)-Catalysed Borylative Aldol Cyclisations of Enone Diones

2.1. Copper-Catalysed Asymmetric Conjugate Addition

In the past few decades conjugate addition reactions, in particular, those catalysed by transition metals have been one of the most useful tools in organic chemistry to create molecular complexity.

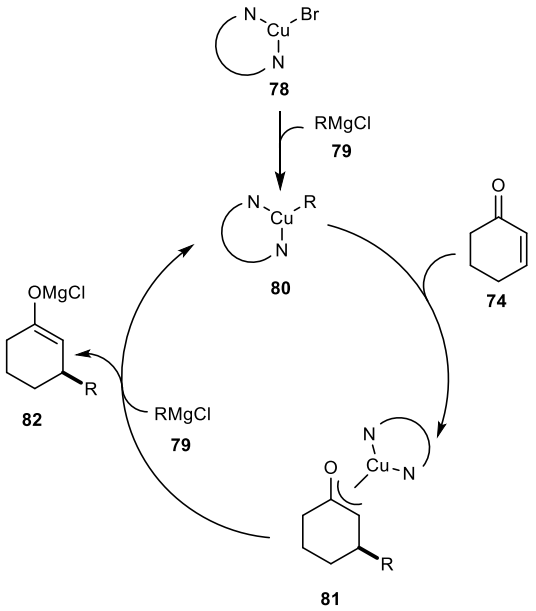
Palladium,[28] rhodium[28b] and nickel[29] have been applied in enantioselective conjugate additions (ECA) but lately, due to its low cost and toxicity and its capability to perform addition of alkyl nucleophiles[30], copper has been the metal of focus of many groups for developing ECAs. Chiral-copper complexes can be easily transmetalated with various organometallic reagents and then add in 1,4- or 1,6-fashion to various electron-deficient alkenes.

The first report on copper-catalysed ECA was published by Lippard in 1988. Using a *N,N'*-disubstituted aminotroponeimine lithium species **77** as a ligand exchange compound (aminotropenimine structures are known to act as chelating agents for copper),[31] CuBr·Me_2S and *n*-BuLi the addition of two Grignard reagents occurred with low enantiocontrol (Scheme 12).[32]



Scheme 12: First copper catalysed conjugated addition of enones

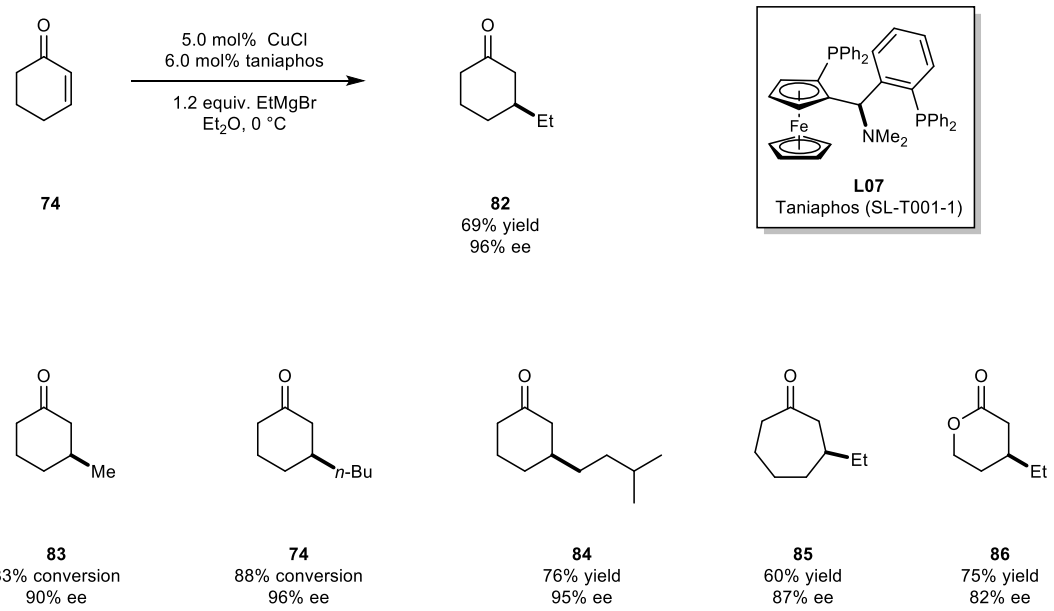
A catalytic cycle was proposed where, after coordination of the copper salt with the chiral ligand the transmetalation step occurs to form a chiral copper alkyl complex **80**. This complex then adds to cyclohexenone giving exclusively the 1,4-adduct plus some homocoupling product (Scheme 13).[32]



Scheme 13: Copper catalysed conjugate addition catalytic cycle

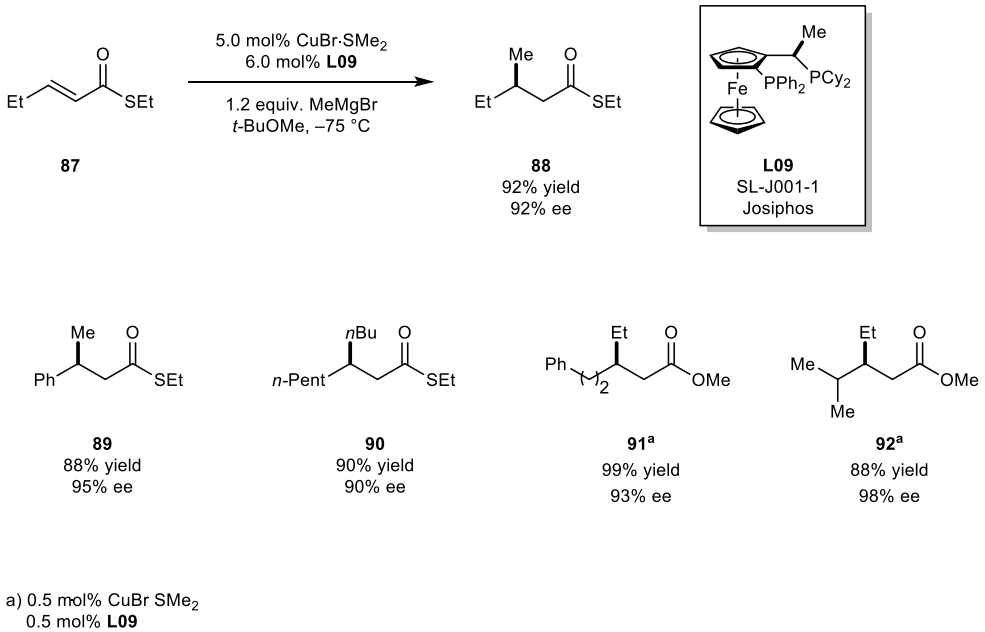
After Lippard's success, several groups investigated this chemistry applying different ligands and achieving better enantiocontrol for the 1,4-addition of Grignard reagents to enones.[33] However, it was not until Feringa using bisphosphine ligands for the process that the catalyst loading could be decreased to levels below 10% while still maintaining high enantioselectivity.[34]

Although classic bisphosphine ligands such as BINAP, Trost ligands or DuPhos proved to be inferior to the nitrogen or sulphur-based ligands used previously; Feringa and co-workers found that ferrocenyl-based bisphosphine ligands delivered high levels of enantiocontrol in copper-catalysed ECA of Grignard reagents.[34] From all the ferrocenyl-based ligands screened by Feringa's group, Taniaphos (**L07)** appeared to be the most adequate for the conjugate addition of a range of alkyl Grignard reagents to cyclohexanone, cycloheptanone and dihydropyranones (Scheme **14**).



Scheme 14: Copper catalysed conjugate addition of Grignard reagents

Further studies by Feringa showed that acyclic α-β unsaturated esters and thioesters also undergo conjugate addition using similar conditions. However, SL-J001-1 Josiphos (**L09**) proved to be superior for these substrates (Scheme 15).[35]

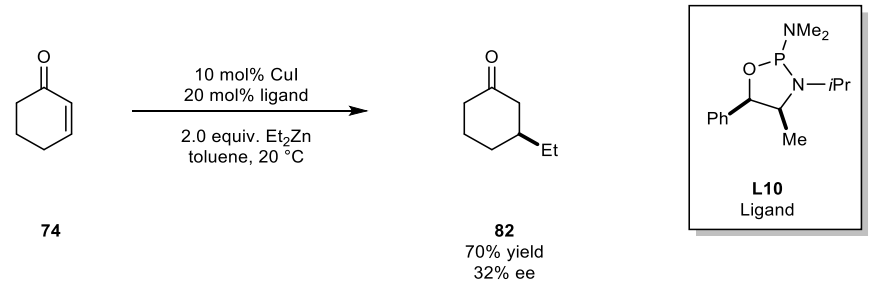


a) 0.5 mol% $CuBr\,SMe_2$
0.5 mol% **L09**

Scheme 15 Copper catalysed conjugate addition of Grignard reagents

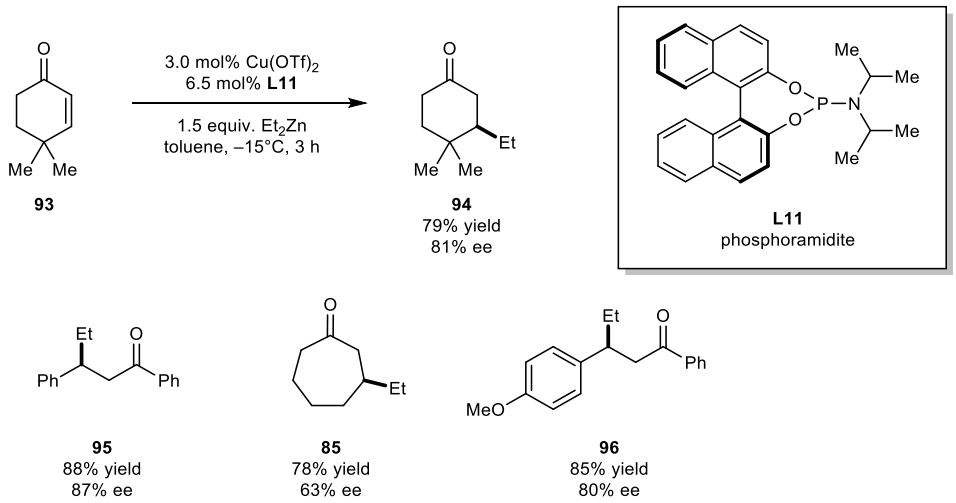
Although excellent results were obtained by several groups using Grignard reagents for the conjugate addition, in some cases the chemoselectivity was still low and significant amounts of 1,2-adduct were observed.

The other main organometallic reagent used in copper-catalysed ECA is organozinc compounds. Alexakis's group in 1993, while investigating the use of organolithium reagents for the conjugate addition of cyclohexanone using a new family of trivalent phosphorus ligands **L10**, observed that diethyl zinc also produced the desired product with an encouraging 32% enantiomeric excess and 70% yield (Scheme 16).[36]



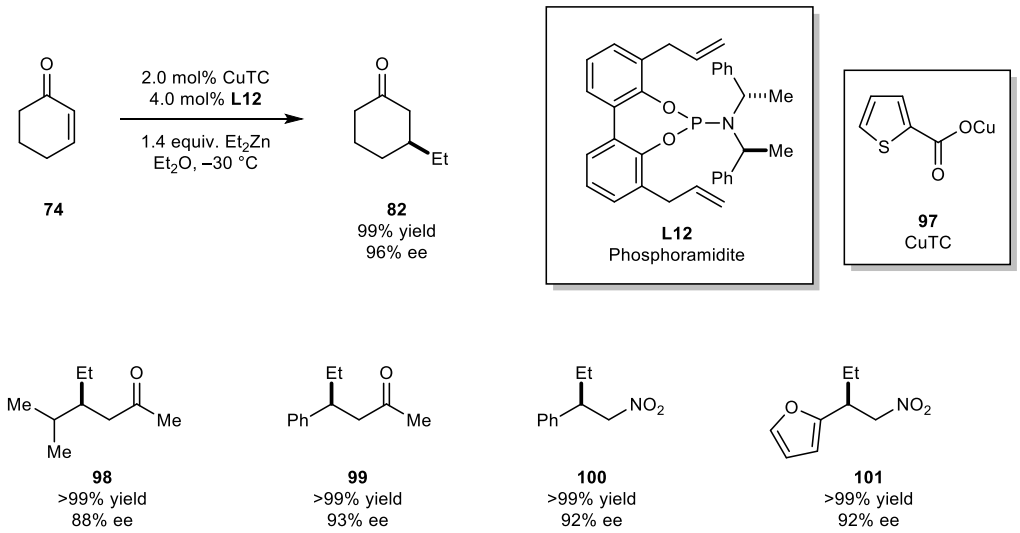
Scheme 16 : Copper catalysed conjugate addition of organozinc reagents

In 1996, Feringa *et al.* developed further this chemistry applying a phosphoramidite ligand **L11**.[37] The 1,4-addition of diethyl zinc to a range of enones was reported by Feringa with high enantioselectivity, not observing any traces of the 1,2-addition product and achieving levels of enantioselectivity similar or higher to those with Grignard reagents (Scheme 17).



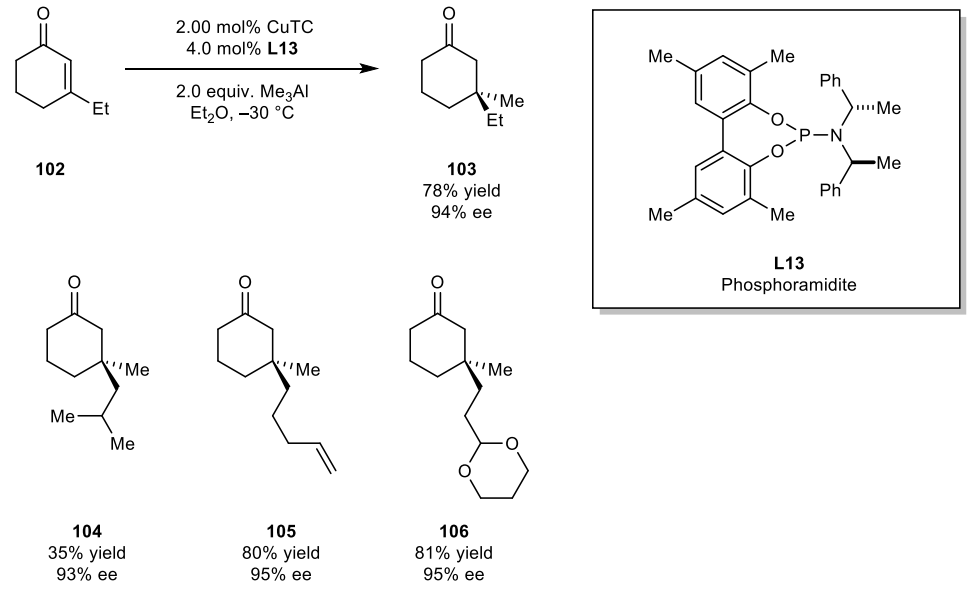
Scheme 17: Copper catalysed conjugate addition of organozinc reagents

Other groups have also used copper to catalyse the ECA of organozincs to electrondeficient alkene.[30] For instance, Alexakis and co-workers reported the use of copper thiophenecarboxylate and a phosphoramidite ligand **L12** for the asymmetric addition of diethyl zinc to enones and nitro-olefins (Scheme 18).[38]



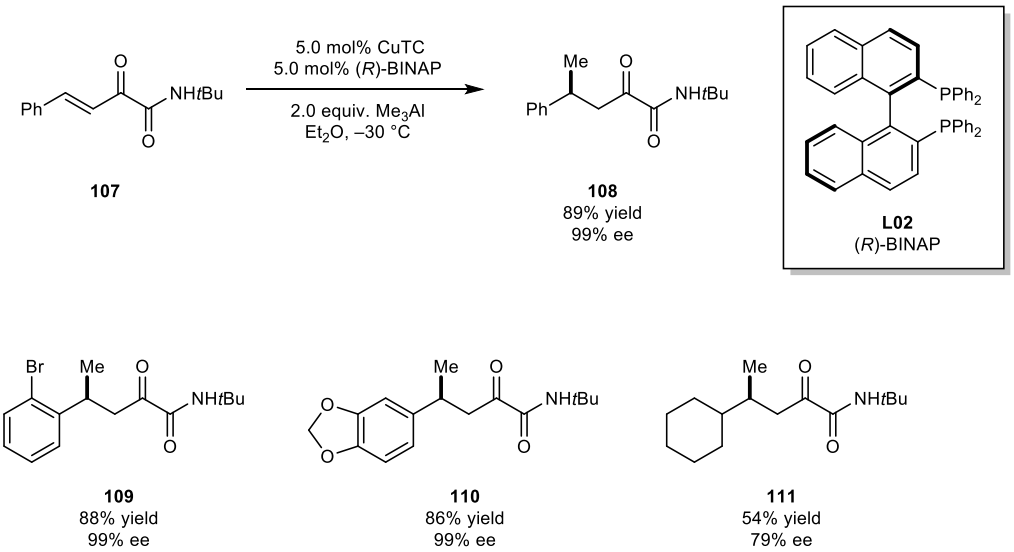
Scheme 18: Copper catalysed conjugate addition of organozinc reagents

Besides organozinc reagents and Grignard reagents, copper also catalyses conjugate additions of organoaluminium reagents to olefins. ECA of β-disubstituted-alkenes with the organometallic reagents described before was unsuccessful, probably due to steric effects. In 2003 the Alexakis group addressed this challenge using alkylaluminium reagents. The conjugate addition of these compounds to enones was reported by several groups[39] with moderate enantioselectivity using a variety of ligands. However, it was only the conditions developed by Alexakis, using copper thiophenecarboxylate and a phosphoramidite ligand, that were capable of performing the addition of trimethyl aluminium to β-disubstituted cyclohexanones (Scheme 19).[40]



Scheme 19: Copper catalysed conjugate addition of organoaluminium reagents

More recently, using similar conditions but with (*R*)-BINAP as a ligand, Alexakis has also reported the addition of organoaluminium reagents to β,γ-unsaturated α-ketoamides with high yields (Scheme 20).[41]



Scheme 20: Copper catalysed conjugate addition of organoaluminium reagents

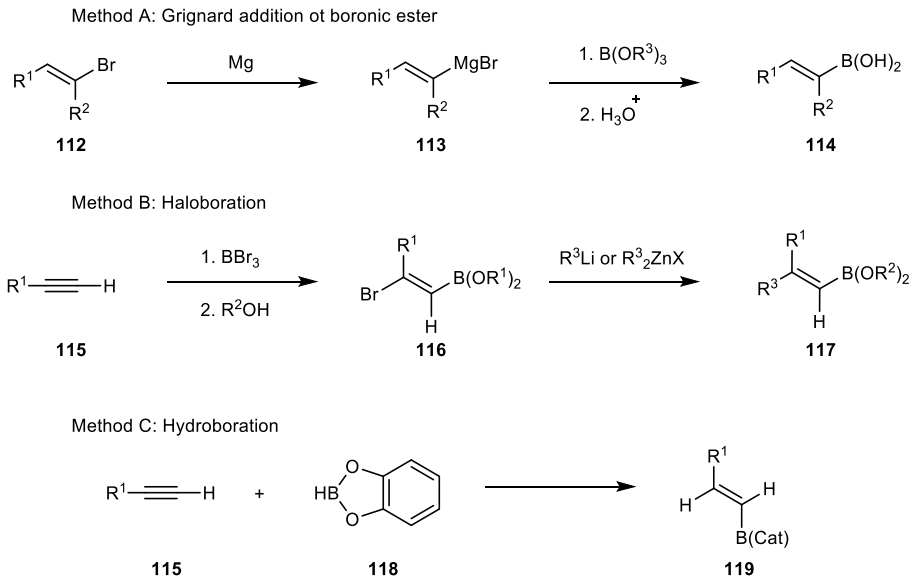
Nowadays the use of copper to catalyse conjugate addition reactions of organometallic reagents is a common tool to create complex molecules. Moreover several groups have

developed a variety of chiral ligands which, in combination with copper salts, led to high levels of enantiocontrol in asymmetric conjugate addition reactions. In the last decade the use of copper catalyst has been applied in the conjugate addition of boron reagents to alkenes as a cheaper alternative to the well-developed rhodium-catalysed hydroboration.

2.2 Copper-Catalysed Asymmetric Conjugate Borylation

As described on the previous chapter, copper performs conjugate addition processes through transmetalation with organometallic reagents. The conjugate borylation of olefinic system has been a field of significant study in the last decade, *via* the transmetalation with boron reagents.

Organoboron compounds play an important role in modern-day organic chemistry. Hydroboration-oxidation of olefins to obtain alcohols, nucleophilic allylation of aldehydes or palladium-catalysed cross-coupling chemistry using arylboronic acids to form C-C bonds are just some of the various reactions which involve organoboron compounds. Organoboron compounds can be synthesised *via* a range of methods. For example, though the reaction of a boron ester and the corresponding Grignard reagent (Scheme 21, Method A); haloboration of terminal alkynes with boron tribromide (Scheme 21, Method B) and; hydroboration of alkynes or alkenes (Scheme 21, Method C).[42]

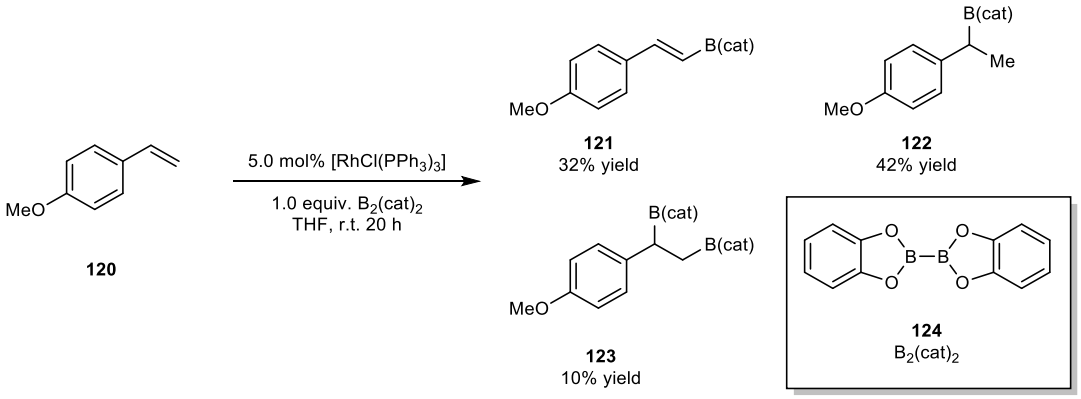


Scheme 21: Synthesis of organoboron reagents

Recently, a new alternative to the well stablished rhodium-catalysed hydroboration of alkenes for the synthesis of alkyl boron compounds has been developed; namely, the metal-catalysed boron conjugate addition to activated double bonds.[43]

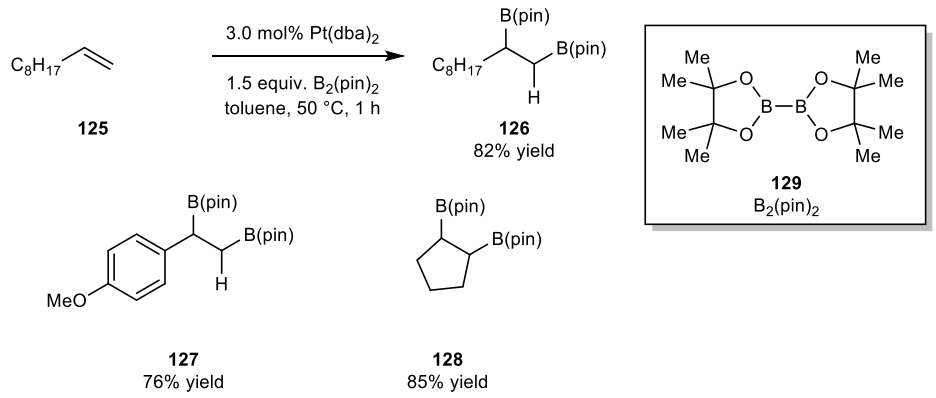
2.2.1. Metal-Catalysed Boron Addition to Double Bonds

The boron addition to double bonds has been performed racemically using different transition metals as catalysts. In 1995, Baker and Marder reported the first mono- and diboronation of alkenes using a rhodium complex and bis(catecholato)diboron. Three borylated products were observed **121**, **122** and **123**, being the hydroboration structure **122** the main product (Scheme 22).[44]



Scheme 22: Rhodium catalysed boron addition of alkenes

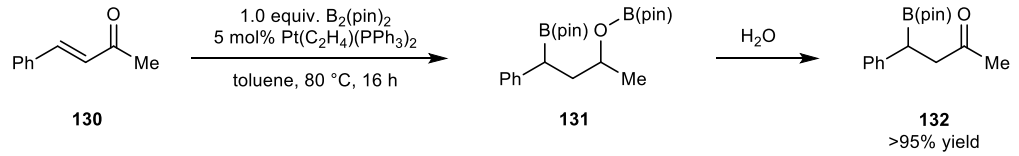
A few years later, Miyaura *et al.* published a diboron addition to double-bonds using a platinum catalyst and $B_2(pin)_2$. This procedure could be applied to a range of different unsaturated molecules in good yields (Scheme 23).[45]



Scheme 23: Platinum catalysed diboration of alkenes

Shortly after this report by Miyaura, Rice *et al.* were able to perform the first *mono*-boronate addition to alkenes using a platinum catalyst. Rice observed a complete conversion of the

vinyl ketone to the boron enol ester which, after aqueous work up, afforded the mono-boronate species in quantitative yield (Scheme 24).[46]

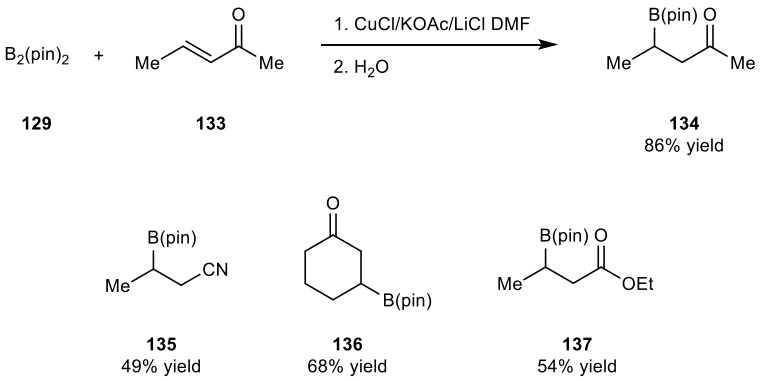


130 **131** **132**
>95% yield

Scheme 24: Platinum catalysed boration of alkenes

2.2.2. Copper-Catalysed Racemic Conjugate Boron Addition to Activated Olefins

The copper-catalysed conjugate addition of boron species to activated double bonds has been studied extensively over the last decade. In 2000, Miyaura *et al.* reported the first copper-mediated mono-boration of a variety of activated alkenes using a stoichiometric quantity of copper(I) chloride, $B_2(pin)_2$ and potassium acetate in DMF with moderate yields. Acyclic and cyclic enones, α,β-unsaturated nitriles and esters were all effective substrates (Scheme 25).[47]



129 **133** **134**
86% yield

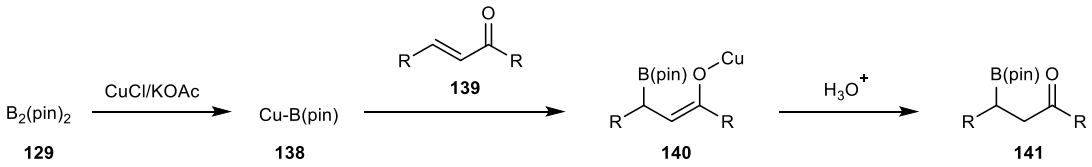
135
49% yield

136
68% yield

137
54% yield

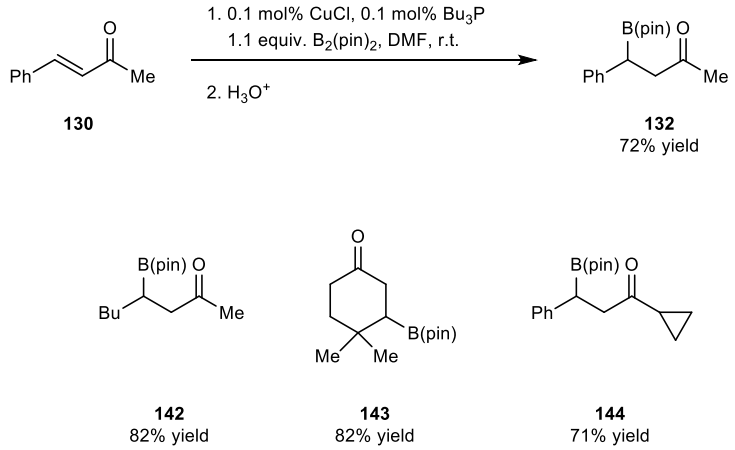
Scheme 25: Copper catalysed conjugate boration of activated alkenes

Mechanistically, Miyaura proposed the transmetalation of the copper (I) salt with the $B_2(pin)_2$ to give boron-copper species **138**. This newly created boron species **138** would then attack the double bond to form copper enolate **140** which after aqueous work up would give the observed product **141** (Scheme 26).



Scheme 26: Mechanism of the copper catalysed conjugate boration of activated alkenes

A few months after this report by Miyaura, Hosomi and co-workers reported the first catalytic copper boration of activated alkenes. The use of a phosphine ligand was essential for the process, not observing the desired product in absence of ligand. The catalytic system was successfully applied to cyclic and non-cyclic enones (Scheme 27).[48]

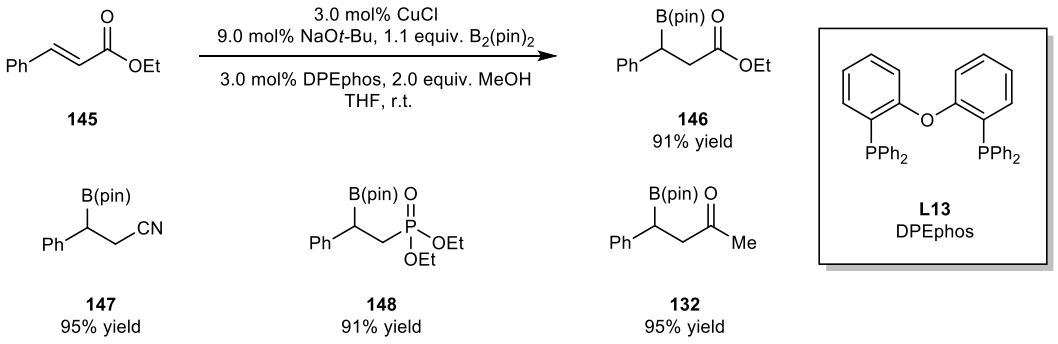


Scheme 27: Copper catalysed conjugate boration of activated alkenes

2.2.3. Copper-Catalysed Asymmetric Conjugate Boron Addition to Activated Double Bonds

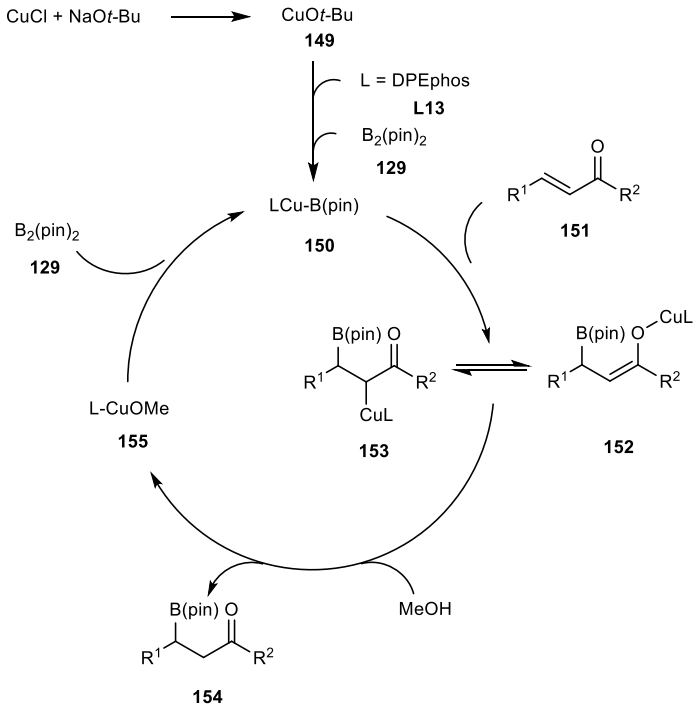
The major challenge for transition-metal-catalysed conjugate boration was to compete with the high enantio- and regioselectivity of the complementary rhodium-catalysed hydroboration.[43c] Even though rhodium and platinum can be used to perform conjugate boration reactions, most of the effort in this area has been invested in the use of copper(I) salts in combination with phosphorus or nitrogen-based chiral ligands. Although there have been reports recently of boron addition to unactivated double-bonds (See Chapter 2.1.2.4.), most additions are to activated olefins, *i.e.* those conjugated to electron-withdrawing groups such as esters, ketones and nitriles.

Most of the studies on asymmetric conjugate boration in the past ten years have been carried out with α,β-unsaturated esters or ketones, but the first report of this type of reaction was on an α,β-unsaturated nitrile. In 2006 Yun and co-workers reported a catalytic non-asymmetric system for the conjugate addition of $B_2(pin)_2$ to a broad scope of activated double bonds such as α,β-unsaturated esters, ketones, phosphonates or nitriles (Scheme 28).[49]



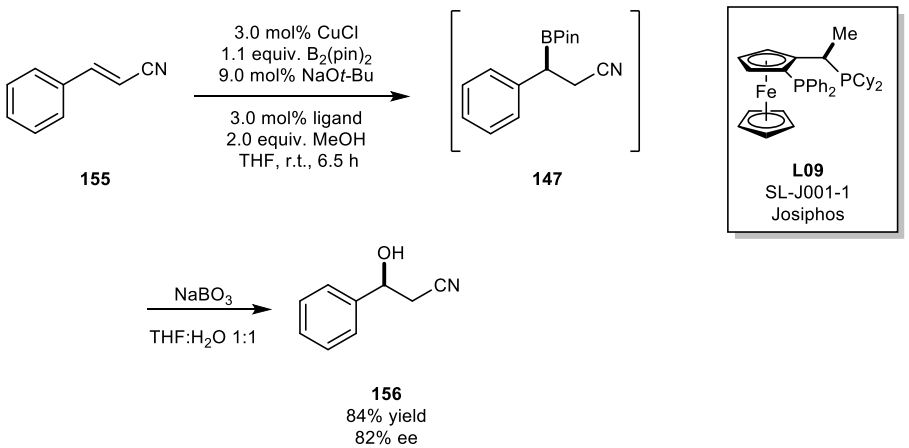
Scheme 28: Copper catalysed conjugate boration of activated alkenes

The proposed catalytic cycle (Scheme 29) indicates the formation of the phosphine-ligated copper species **150** and its conjugate addition to the double bond to form a copper enolate **152**. The copper enolate **152** is hydrolysed with methanol to give the boron compound **154** and a copper alkoxide **155**, the active copper-species, which then re-enters the catalytic cycle.



Scheme 29: Catalytic cycle of the copper catalysed conjugate boration of activated alkenes

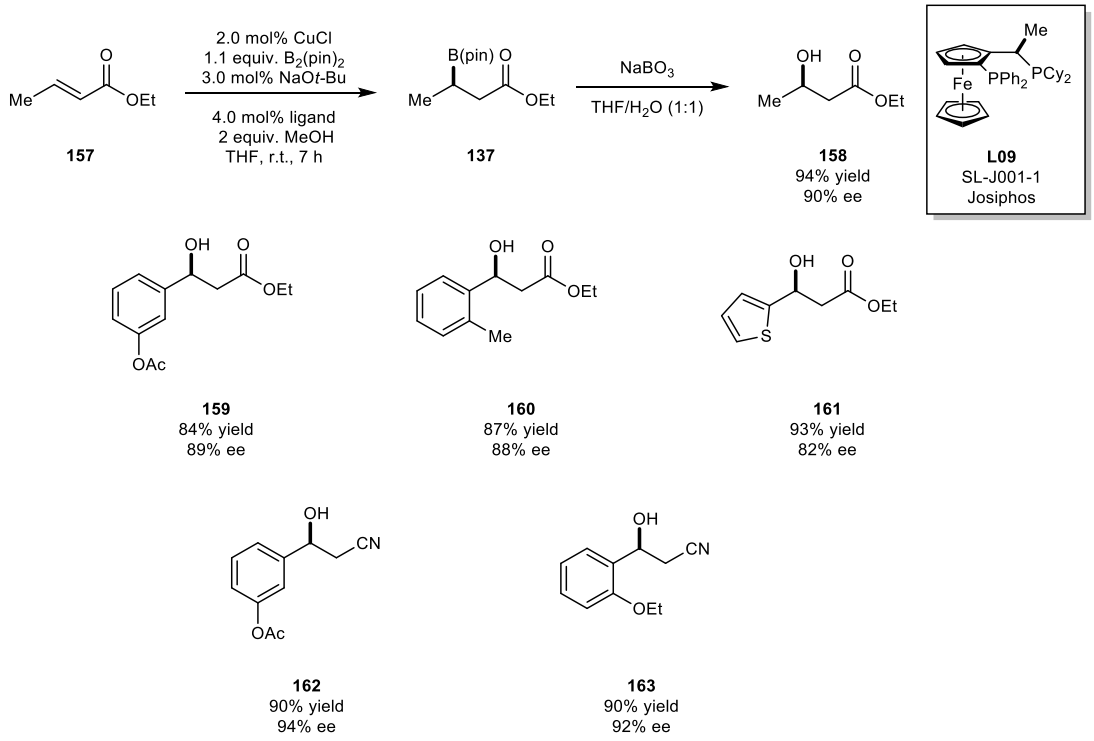
Since the transition state of the proposed mechanism involved the conjugation of the copper complex with the double bond, it was proposed that the use of a chiral phosphine might lead to an enantioselective process. Accordingly, using SL-J001-1 Josiphos, Yun achieved the asymmetric addition of bis(pinacolato)diboron to cinnamonitrile (**155**).[49] The product was isolated in 84% yield and with 82% enantiomeric excess after the oxidation of the borylated intermediate **156** to the alcohol **157** (Scheme 30).



Scheme 30: Copper catalysed asymmetric conjugate boration of activated alkenes

2.2.3.1. Asymmetric Conjugate Boration of α,β-Unsaturated Esters

The copper-phosphine ligand system developed by Yun for asymmetric boration of α,β-unsaturated nitriles was applied two years later to a range of different α,β-unsaturated carboxylic esters and nitriles (Scheme 31).[50]

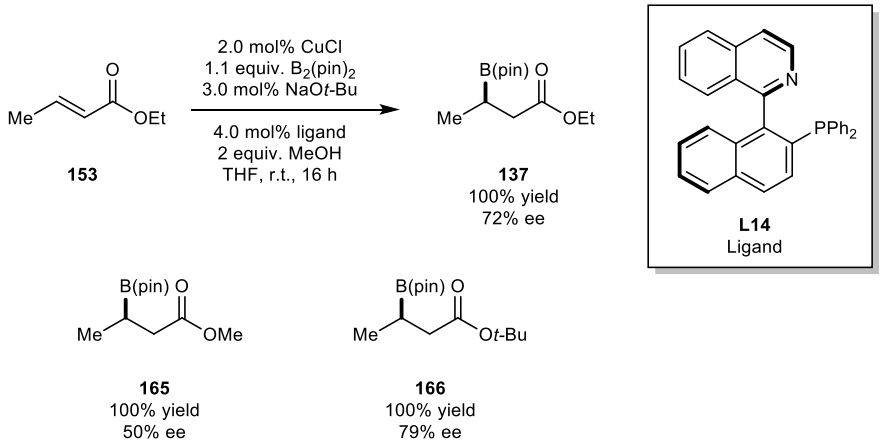


Scheme 31: Copper catalysed asymmetric conjugate boration of activated alkenes

As shown, the reactivity and stereoselectivity of the addition to ester substrates decreased slightly with respect to that observed for the nitrile substrates, which might imply that the strength of the electron-withdrawing group effect is a key factor for such reactions. Although the electron-withdrawing effect of the nitrile *vs* ester substrates was important in terms of yields and stereoselectivity, no real effect was observed when different esters were used. After screening a range of chiral phosphine ligands SL-J001-1 Josiphos provided the highest reactivity and stereoselectivity, with yields over 90% and enatioselectivities of 80 to 95% (Scheme 31).

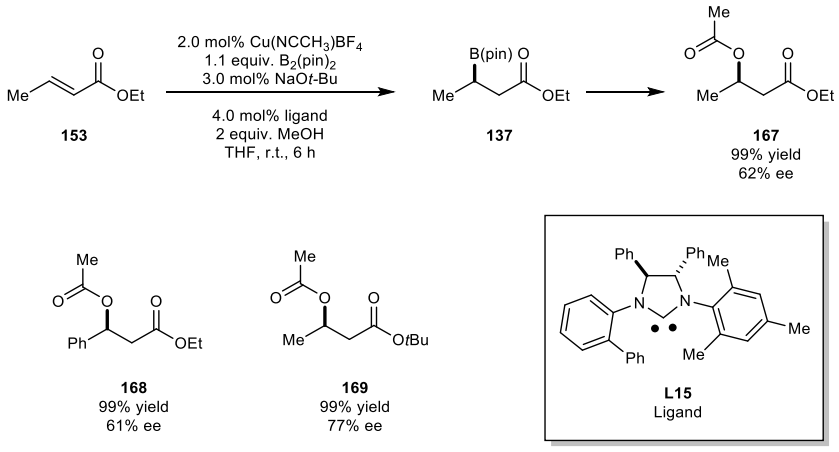
Chiral phosphine ligands are not the only class of ligand to have been used for the boron conjugate addition to activated double bonds. In 2009, Fernandez and co-workers reported

the use of phosphorous-nitrogen ligands for the conjugate addition of bis(pinacolato)diboron to α,β-unsaturated esters.[51] The yield of the process was improved but the stereocontrol that the phosphorus-nitrogen ligands provided was decreased compared with Yun's conditions using SL-J001-1 Josiphos (Scheme 32).



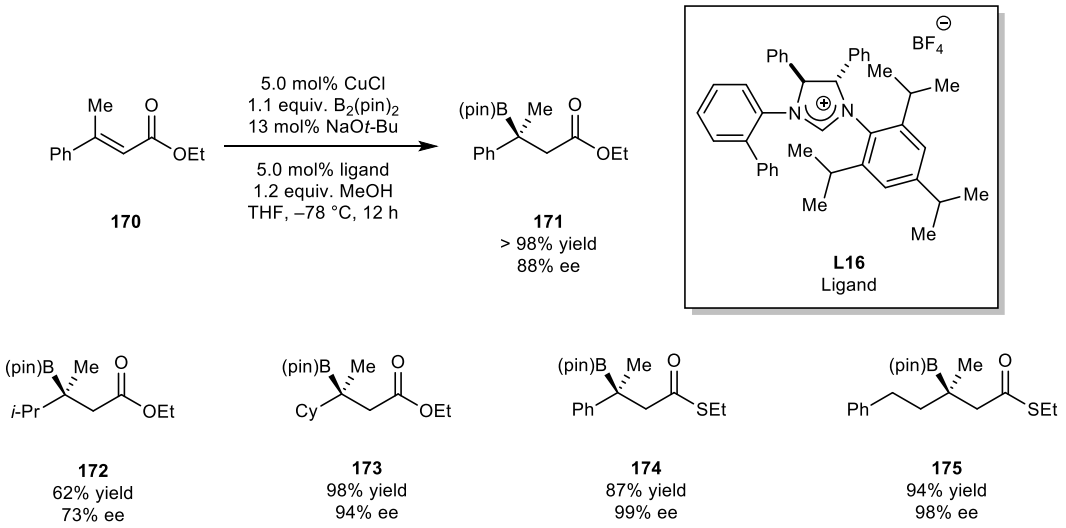
Scheme 32: Copper catalysed asymmetric conjugate boration of activated alkenes

For the past two decades, *N*-heterocyclic carbene (NHC) ligands have been successfully utilised in transition-metal-catalysed asymmetric transformations.[52] The first attempt to use these type of ligands in the conjugate boration of activated olefins was reported by Fernandez *et al.* in 2009.[53] Although the yield and stereocontrol achieved was lower than using phosphine ligands, good conversions and moderate enantiomeric excesses were still achieved using different NHC ligands. The boronates obtained were transformed into esters **167**, **168**, or **169** , *via* oxidation and acylation, to aid analysis (Scheme 33).



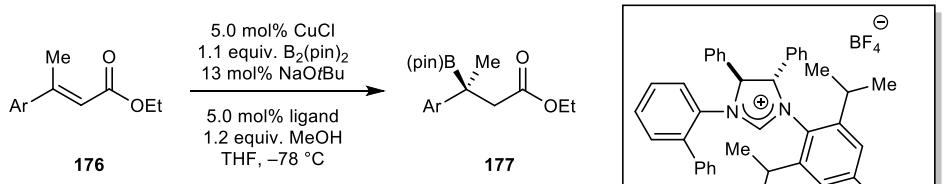
Scheme 33: Copper catalysed asymmetric conjugate boration of activated alkenes

In 2010, Hoveyda and co-workers confirmed the capacity of NHC ligands to induce high stereocontrol in copper-catalysed conjugate boration reactions. Substituted α,β-unsaturated esters and thioesters underwent boration with moderate to high yields and very high enantioselectivity (Scheme 34).[54]



Scheme 34: Copper catalysed asymmetric conjugate boration of activated alkenes

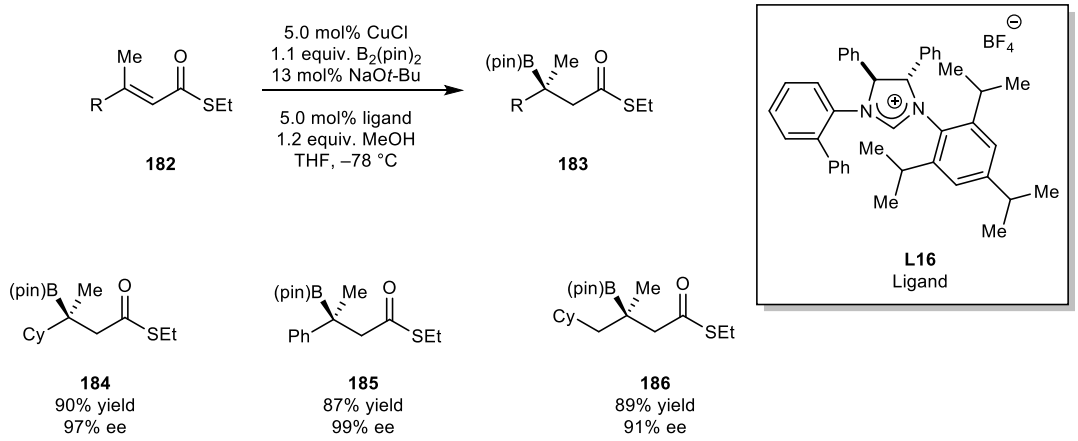
To increase the enantiocontrol of the catalytic system, the temperature was decreased to −78 °C. Additionally, to ensure the hydrolysis of the boron enolate at −78 °C, an acidic methanol solution needed to be added. Control experiments, without acidic methanol, indicated that if the reactions were not properly quenched at −78 °C, adventitious conjugate addition of the remaining bis(pinacolato)diboron could occur as the mixture is allowed to warm to r.t., leading to lower enantiomeric purity of the product. The robustness of the catalytic system was demonstrated by the application of the optimum conditions to a range of substrates. Transformations with substrates bearing an *ortho*-bromo group on the aromatic ring (**178**), proceeded to afford the desired boronate with very good conversions and enantioselectivity. However, *ortho*-methyl (**181**) and *para*-methoxy (**179**) substituted aromatic alkenes were less reactive and gave lower enantioselectivity (Scheme 35).



Ar	Conversion (%)	*ee* (%)	
o-BrC_6H_4	> 98	95	**178**
p-$OMeC_6H_4$	38	53	**179**
p-$CF_3C_6H_4$	> 98	99	**180**
o-MeC_6H_4	38	53	**181**

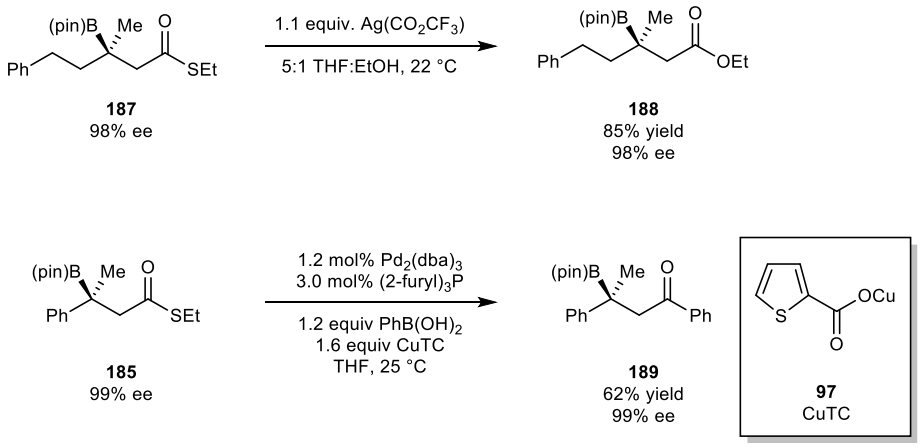
Scheme 35: Copper catalysed asymmetric conjugate boration of activated alkenes

Stereocontrol could be further improved by using thioester substrates rather than carboxylic esters (Scheme 36).



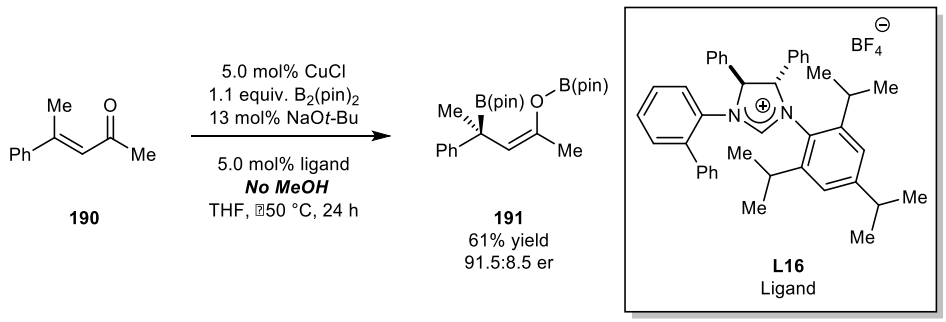
Scheme 36: Copper catalysed asymmetric conjugate boration of activated alkenes

Hoveyda demonstrated the utility of these organoboron compounds by generating esters and ketones through silver-mediated and palladium-catalysed procedures respectively from the thioester products. No loss of enantiomeric purity was observed in any of these reactions (Scheme 37).



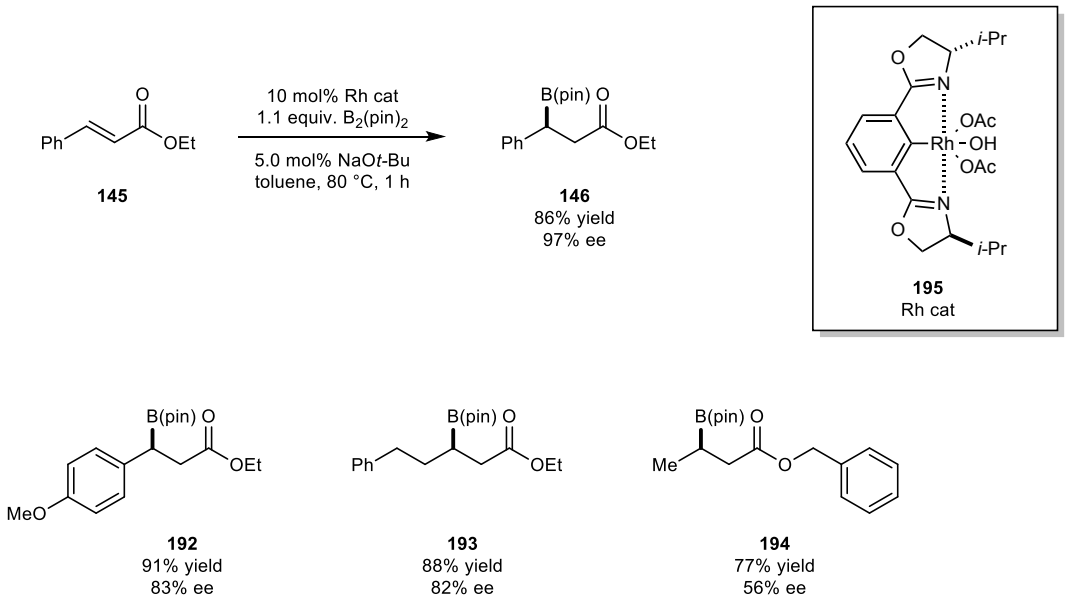
Scheme 37: Copper catalysed asymmetric conjugate boration of activated alkenes

The use of methanol had been assumed to be necessary for good conversions and faster reaction rates in the copper-catalysed conjugate boration of olefins. However Hoveyda demonstrated that for the copper-NHC system, the alcohol additive was not necessary to perform the reaction successfully isolating boron enolate **191** in good yields (Scheme 38).[54]



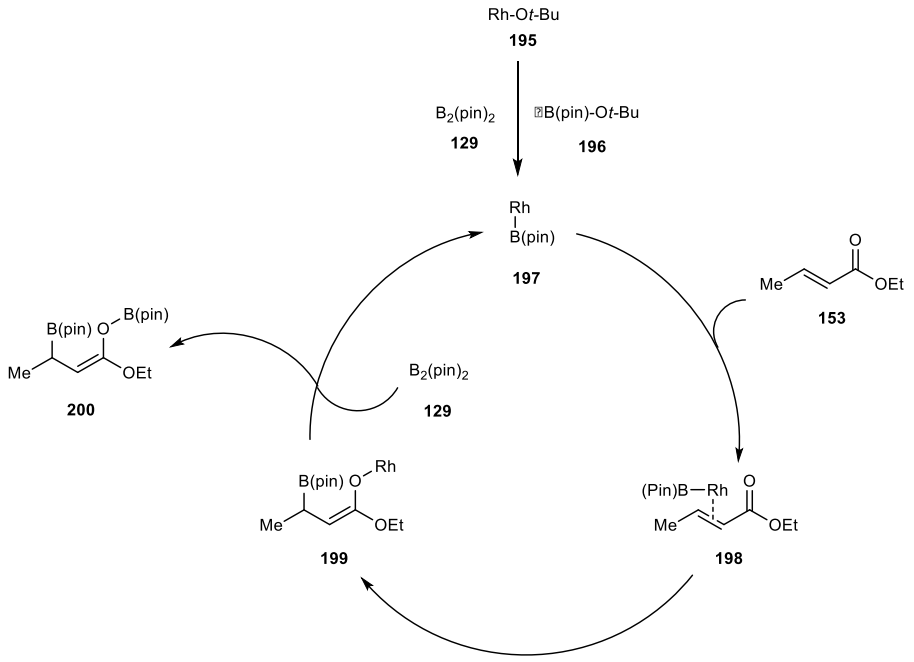
Scheme 38: Copper catalysed asymmetric conjugate boration of activated alkenes

Even though copper catalysis is very efficient for the conjugate boration of alkenes, other metals have been utilised to perform this type of reaction. In 2009 the groups of Nishiyama[55] and Fernández[56] reported the conjugate addition of boron to α,β-unsaturated carboxylic esters using rhodium and nickel catalysts, respectively. Thus, new type of rhodium complexes designed by Nishiyama *et al.* could perform the conjugate addition of $B_2(pin)_2$ in high yields and enantioselectivity to a broad range of α,β-unsaturated esters (Scheme 39).[55]



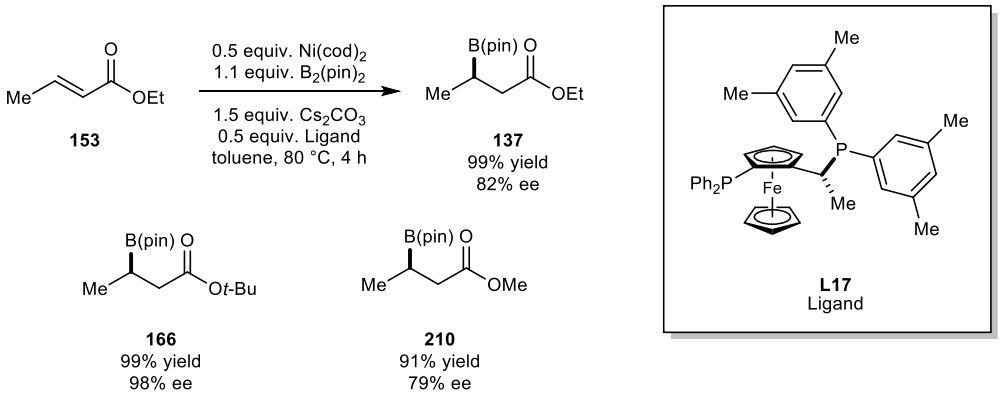
Scheme 39: Rhodium catalysed asymmetric conjugate boration of activated alkenes

Nishiyama proposed a catalytic cycle through the formation of a rhodium enolate **199**, which undergoes an exchange reaction with $B_2(pin)_2$ to form the boron enolate **200** that is then hydrolysed to obtain the desired product.

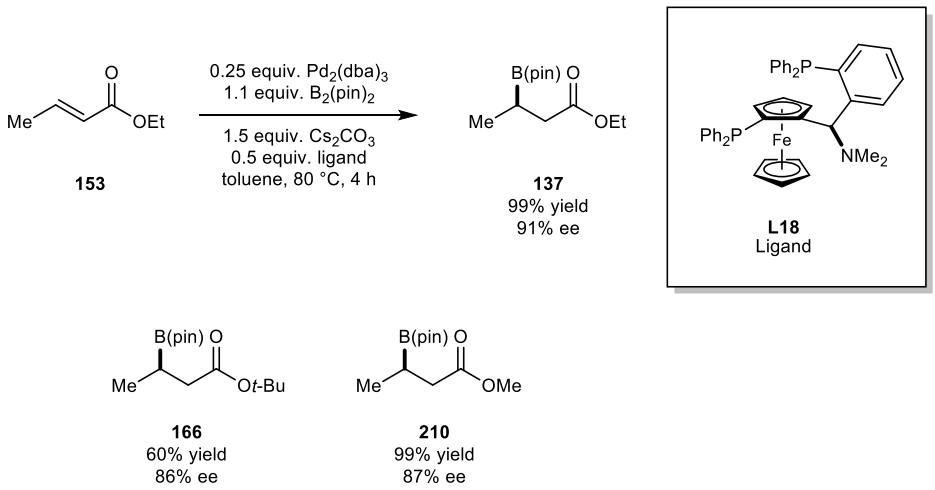


Scheme 40: Catalytic cycle of the Rhodium catalysed conjugate boration of activated alkenes

Fernández explored the use nickel and palladium to perform the asymmetric conjugate addition of $B_2(pin)_2$ to α,β-unsaturated esters.[56] Both palladium and nickel seemed to be efficient transition-metals for catalysing the conjugate boration of activated olefins. However, the scope of the reaction was relatively narrow and only variations of the ester part were tested (Scheme 41 and Scheme 42).



Scheme 41: Nickel catalysed asymmetric conjugate boration of activated alkenes

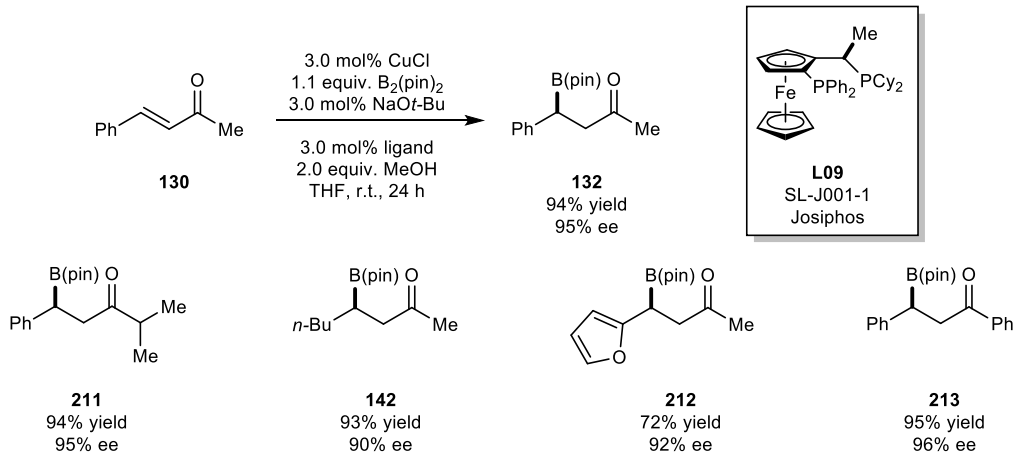


Scheme 42: Palladium catalysed asymmetric conjugate boration of activated alkenes

2.2.3.2. Asymmetric Conjugate Boration of α,β-Unsaturated Ketones

In parallel to the studies with α,β-unsaturated esters, detailed in the previous sections, several groups have been working on the analogous conjugate addition to α,β-unsaturated ketones.

Yun *et al.* reported the first boron conjugate addition to acyclic enones in 2009.[57] The same catalytic system used for α,β-unsaturated esters (Scheme 31) was successfully applied to a range of enones. As occurred in the boration of α,β-unsaturated ester, the addition to α,β-unsaturated ketone requires the presence of an alcohol additive for the reaction to proceed at a satisfactory rate (Scheme 43).

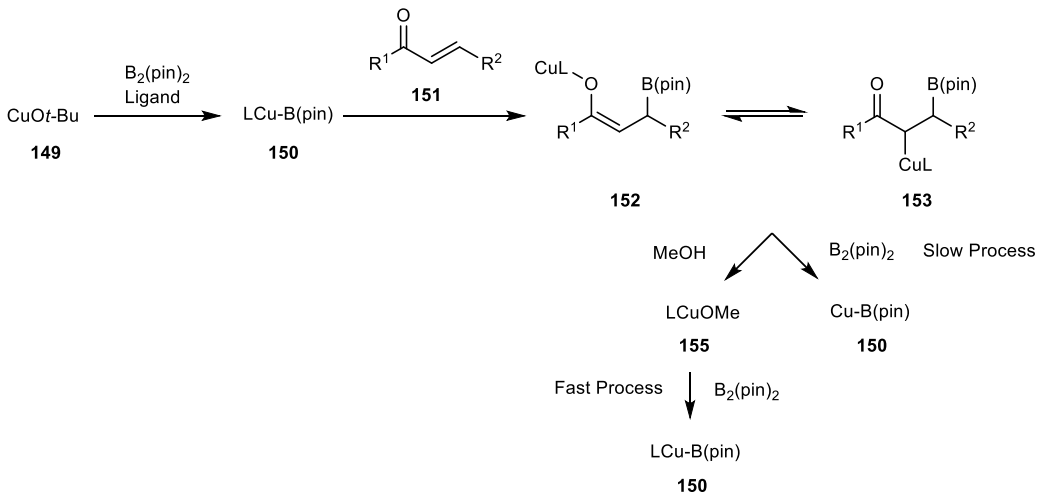


Scheme 43: Copper catalysed asymmetric conjugate boration of activated alkenes

Yun explained this addition with a similar catalytic cycle to that reported for α,β-unsaturated esters where at the end of the cycle the copper enolate is protonated with methanol to form a copper-alkoxide species. When the reaction was conducted using deuterated methanol, the reaction proceeds with deuterium incorporated at the α-position in accordance with the proposed mechanism (See Chapter 2.1.2.3 Scheme 29).

The acceleration caused by the addition of methanol can be explained by the facile formation of the copper methoxide species followed by the fast boration of the copper methoxide with bis(pinacolato)diboron to regenerate the active species. This proposition was supported by DFT calculations reported by Marder, Lin and co-workers in their mechanistic studies of the diboration of aldehydes. It was proposed that the energy barrier in the σ-bond metathesis

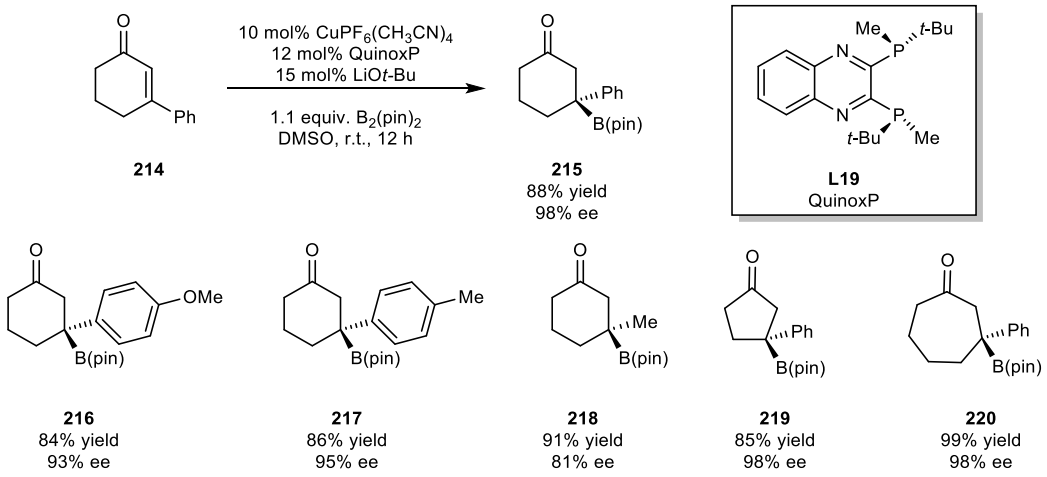
between a Cu-O bond and a B-B bond (1.4 kcal/mol) is much lower than the same process between a Cu-C bond and a B-B bond (15.6 kcal/mol). Therefore a process without alcohol, which implies the direct transmetalation of the copper enolate with the boron species, is in some cases slower (Scheme 45).[58]



Scheme 44: Mechanistic studies on copper ECA processes

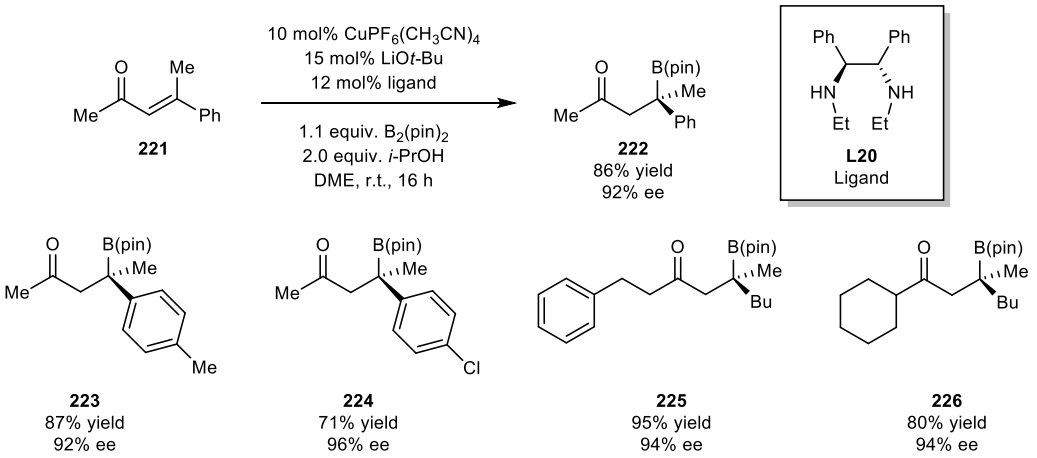
Although phosphorus-nitrogen ligands did not provide excellent results for the boron conjugate addition to α,β-unsaturated esters (See Chapter 2.1.2.3.1. Scheme 32), in 2009 Shibasaki and co-workers reported a phosphorus-nitrogen ligand copper catalytic system that performed the conjugate boration of substituted cyclic enones in high yields and stereocontrol.[59]

Attempts to perform the conjugate boration of enone **214** showed that Yun's conditions were not appropriate. After screening a variety of conditions the optimum system was found to be a combination of $CuPF_6(CH_3CN)_4$ and lithium *tert*-butoxide in DMSO; the addition of methanol was not required and also not recommended owing to a 10% decrease in yield for most of the substrates when methanol was added (Scheme 46).



Scheme 45: Copper catalysed asymmetric conjugate boration of activated alkenes

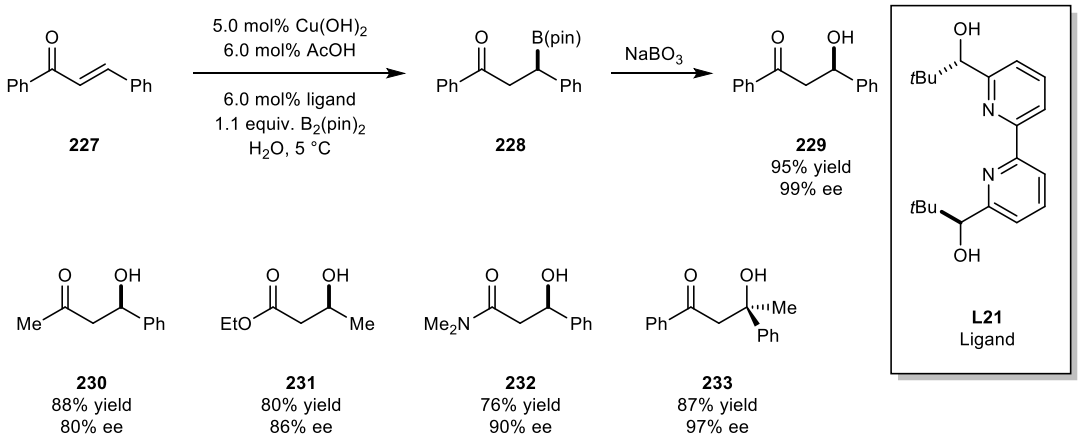
However, despite this success, chiral phosphorous-nitrogen ligands did not provide good yields or stereocontrol when acyclic α,β-unsaturated ketones were employed as substrates. Shibasaki *et al.* overcame this issue by changing the ligand to a secondary diamine. Different chiral secondary diamine ligands were screened with the best results obtained with the diphenyl-substituted diamine **L20**. This Cu-diamine system was applied to a wide range of substituted acyclic enone with high yields and enantioselectivity (Scheme 47).[60]



Scheme 46: Copper catalysed asymmetric conjugate boration of activated alkenes

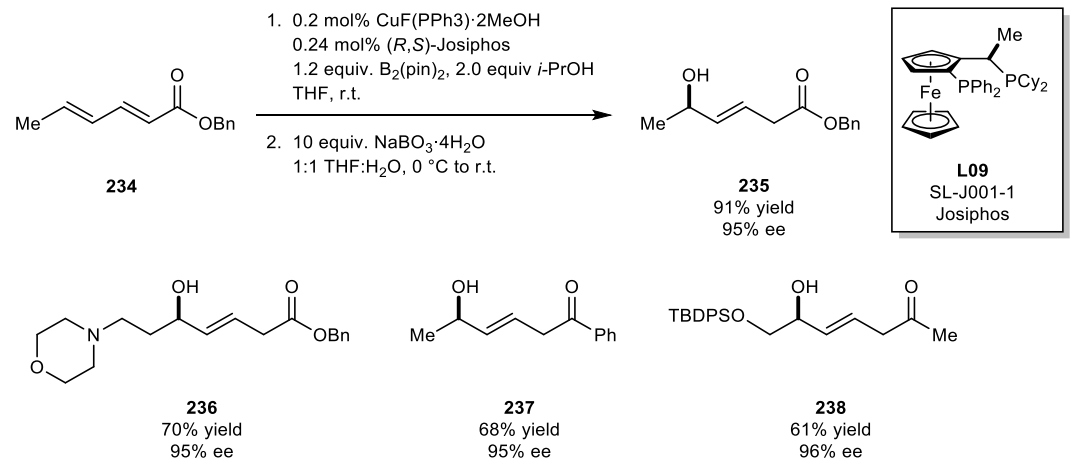
The copper-catalysed conjugate borations described so far were assumed to be-water sensitive as anhydrous conditions are usually employed, but in 2012 Kobayashi reported the addition of $B_2(pin)_2$ to α,β-unsaturated carbonyl compounds in water (Scheme 48). Copper(II) hydroxide in the presence of 2,2'-bipyridine ligand **L21** and AcOH as additive in

water gave excellent yield and enantiomeric excess in the boration of α-β-unsaturated ketones, amides and carboxylates (Scheme 48).[61]



Scheme 47: Copper catalysed asymmetric conjugate boration of activated alkenes

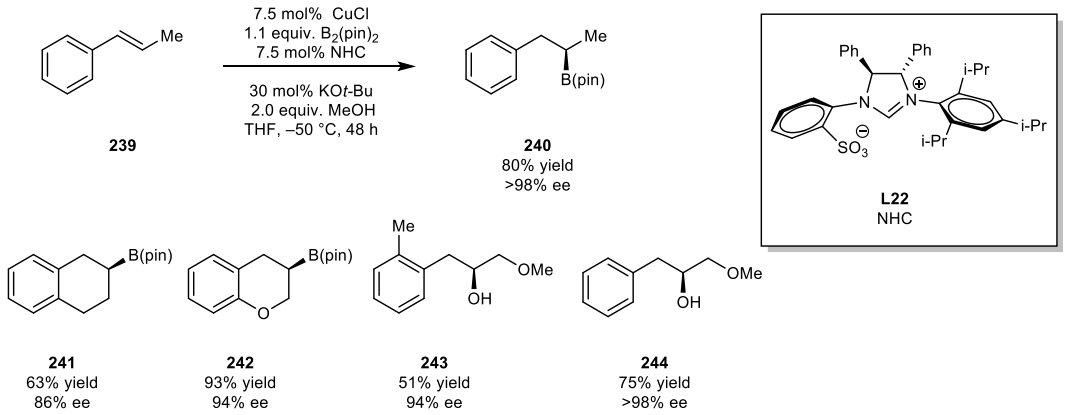
The conjugate borylation of activated olefinic systems was recently extended by Lam and co-workers towards the asymmetric synthesis of allylboronates *via* a 1,6-boration of dienes catalysed by copper. A combination of $CuF(PPh_3)\cdot 2MeOH$ and SL-J001-1 Josiphos in the presence of *i*-PrOH as a proton source gave the 1,6- rather than the 1,4-addition with high yields and enantioselectivity (Scheme 49).[62]



Scheme 48: Copper catalysed asymmetric conjugate 1,6-boration of activated dienes

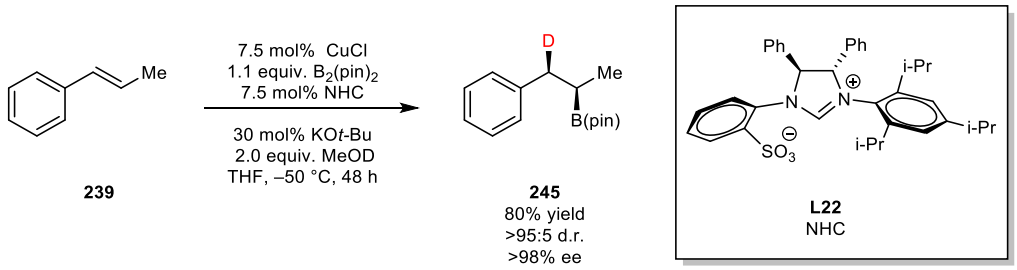
2.2.4. Boron Addition to Weakly-Activated Double Bonds

Hydroboration is still the most effective strategy for forming a C-B bond from a simple non activated double bond. To date, Hoveyda's group is the only one to report the addition of $B_2(pin)_2$ to a non-activated double bond using a copper(I) salt and an NHC ligand (Scheme 50).[63]



Scheme 49: Copper catalysed asymmetric conjugate boration of weakly activated alkenes

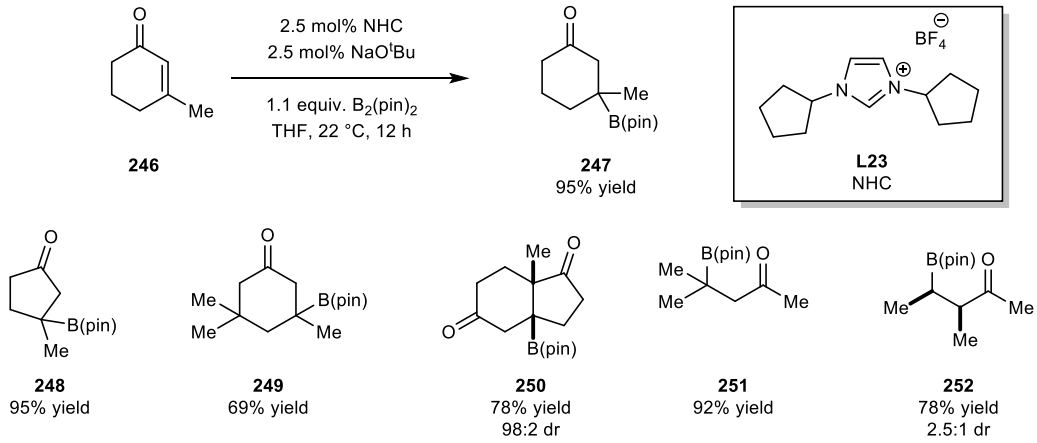
Phosphine ligands were also evaluated but resulted in much lower conversions. As observed in many conjugate borations, the addition of methanol seemed to be crucial. Even if a stoichiometric quantity of NHC-Cu complex was added after 10 minutes, the conversion was less than 20%. However, if methanol was added after 10 minutes, complete conversion was obtained. When deuterated methanol was added to the system the addition of deuterium alpha to the C-B bond was observed. This fact could imply that the mechanism will go through the protonation of a C-Cu bond, as described previously in the conjugate boration of activated double bonds (Scheme 50).



Scheme 50: Deuterated experiments on copper borylation

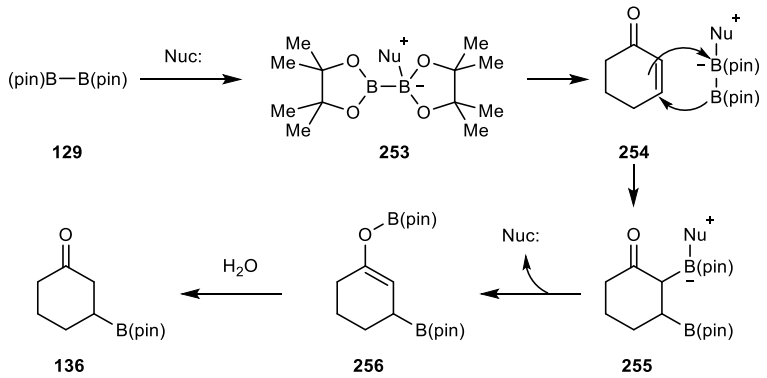
2.2.5. Organocatalytic Conjugate Boron Addition to Double Bonds

The latest studies in the conjugate boration of activated olefins showed that this reaction can also be performed in the absence of a transition-metal catalyst. In 2010, Hoveyda reported the first metal-free (non-asymmetric) conjugate boration of enones promoted by NHCs.[64] As shown in Scheme 51, organocatalyst **L23** promoted the addition of $B_2(pin)_2$ to a variety of enone substrates with high yield and in the absence of an alcohol additive.



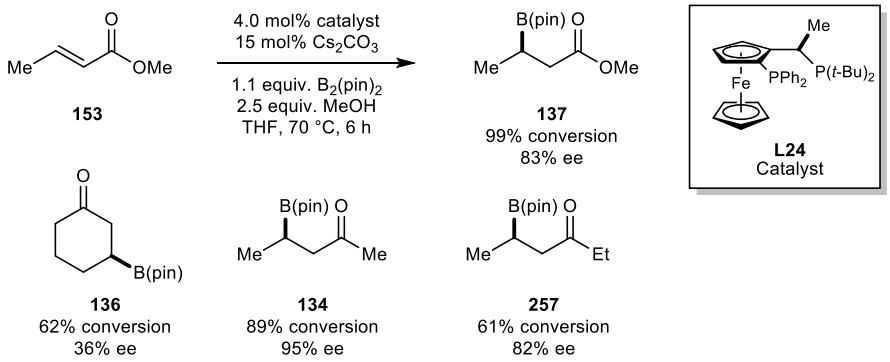
Scheme 51: NHC catalysed conjugate boration of enones

Hoveyda proposed a mechanism where the $B_2(pin)_2$ undergoes a nucleophilic attack from the NHC to polarise the B-B bond. This polarised B-B species **253** would then be able to attack the enone to form a boron enolate **256**, which, after an aqueous work-up, would be hydrolysed to the desired boron species **136** (Scheme **52**).



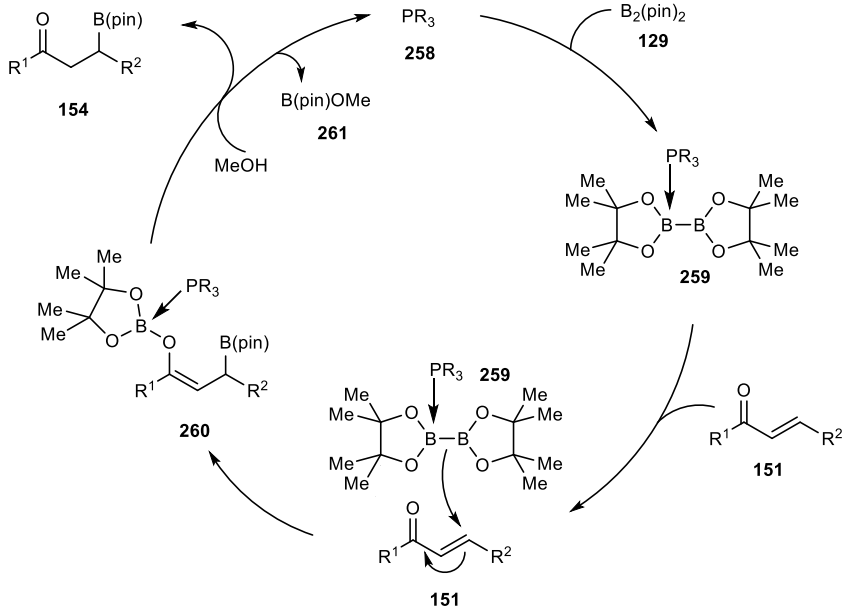
Scheme 52: Proposed mechanism for NHC borylation of enones

Shortly after Hoveyda developed the organocatalytic NHC-catalysed system, Fernández reported a similar catalytic system using chiral phosphine ligands. This approach was applied to cyclic and acyclic enones and α,β-unsaturated esters with moderate to high conversions and enantiomeric excess's. A combination of caesium carbonate and Josiphos-type ligand **L23** in the presence of methanol were the optimal conditions for performing this transition metal-free conjugate boration (Scheme 53).[65]



Scheme 53: Phosphine catalysed conjugate boration of activated alkenes

Fernández *et al.* proposed where the nucleophilic attack of a phosphine ligand **258** to the $B_2(pin)_2$ promotes the conjugate addition to the alkene **151** and the formation of the boron enolate **260** which after protonation forms the desired compound **154** (Scheme 54).

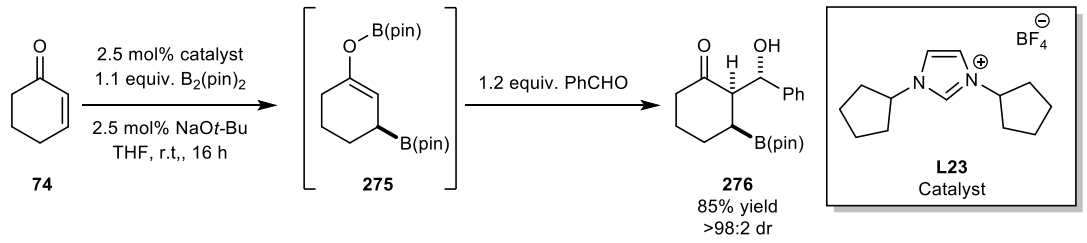


Scheme 54: Proposed mechanim for the phosphine catalysed borylation of activated alkenes

2.3. Domino Conjugate Boration/Electrophilic Trapping

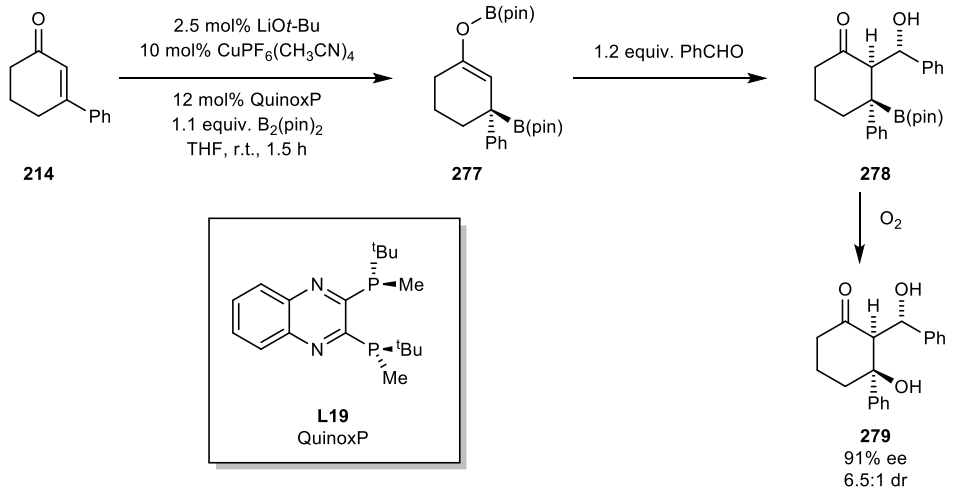
As described previously, the accepted mechanism for the conjugate boration of olefins involves the formation of a copper- or boron-enolate, which is then protonated using methanol or another proton source to generate the product (See Chapter 2.1.2.3. Scheme 29).

In 2009, Shibasaki and Hoveyda both reported the electrophilic trapping of the enolate, formed after the boration of an activated alkene, with benzaldehyde.[59, 64] Hoveyda *et al.* were able to perform this type of reaction in a transition metal-free fashion using a achiral NHC ligand. The aldol product **276**, was obtained as a single diastereoisomer (Scheme 55).



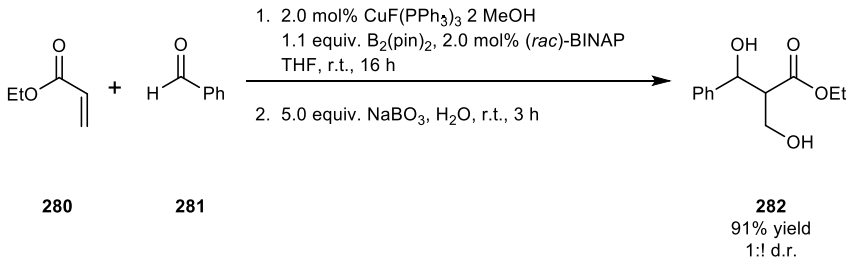
Scheme 55: Diastereoselective domino copper boration/aldol addition

Before our work, Shibasaki *et al.* reported the first and only example of an asymmetric boration and enolate trapping of activated alkenes. Using a phosphorous-nitrogen ligand (**L19**) in the presence of lithium *tert*-butoxide, the boration of 2-phenyl-2-cyclohexen-1-one (**214**) and the trapping of the resultant enolate using benzaldehyde was achieved with 91% enantiomeric excess and a 6.5:1 diastereomeric ratio (Scheme 56).



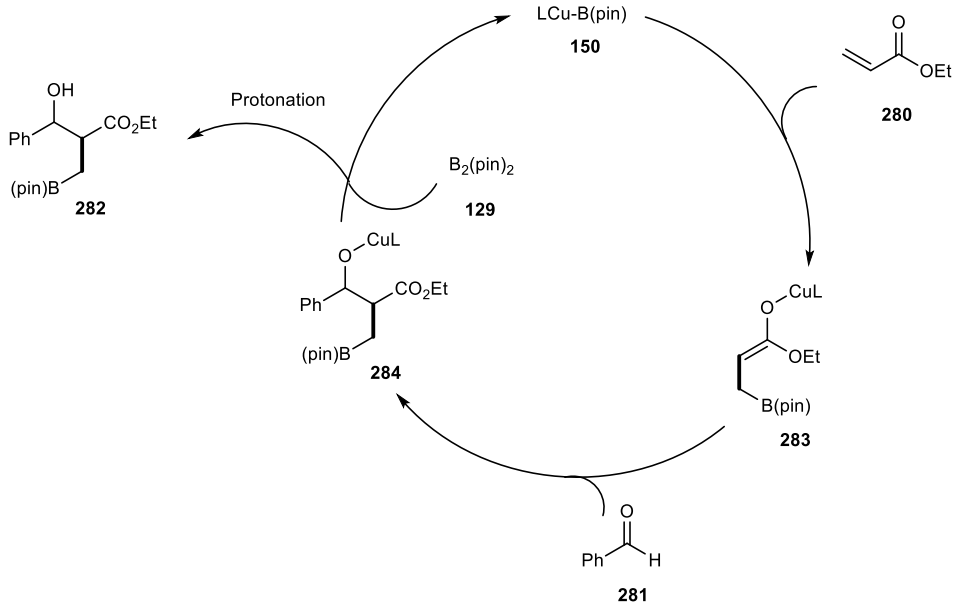
Scheme 56: Enantioselective domino copper boration/aldol addition

A more extensive study on this type of chemistry was reported by Riant's group in 2012. Conjugate borylation of α-β-unsaturated esters and amides followed by enolate trapping with a range of aldehydes was performed using a combination of copper(I) chloride and racemic BINAP. Although it is a high yielding process, there was no control of the enantioselectivity and poor diastereomeric ratios were obtained (Scheme 57).[66]



Scheme 57: Racemic intermolecular conjugate domino boration/aldol addition

The mechanism proposed by Riant follows the accepted mechanism reported by Yun (Chapter 2.1.2.3, Scheme 29). After boration of the acrylate the enolate formed **283** is trapped by the aldehyde to form a copper alkoxide **284**. The intermediate undergoes σ-bond metathesis with the $B_2(pin)_2$ to regenerate the active catalyst and formed, after hydrolysis, the desired alcohol (Scheme 58).



Scheme 58: Proposed mechanism for the conjugate domino boration/aldol addition

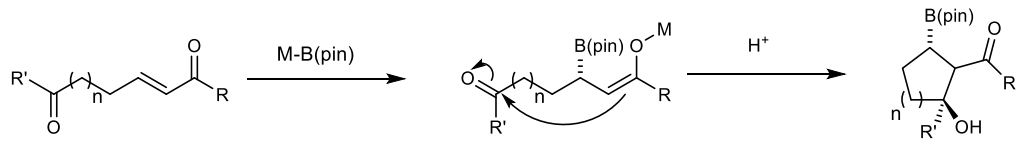
The conjugate boration of activated alkenes catalysed by copper has been well explored by several groups. Moreover the application of this reaction in domino process has been applied to the synthesis of complex molecules. It has been proposed the formation of a copper enolate during the borylation process. These copper enolate is usually protonated but it can also be trapped with a nucleophile in a domino process to formed more complex structures. Although the borylation of activated alkenes have been developed the trapping of the enolate formed during the process has not been well stablished. In the literature only poor diastereo and /or enantioselective process have been published. Other areas that could be investigated is the used of functional groups to activate the alkene other than carbonyl or nitrile groups.

3. Copper Catalysed Conjugate Boration–Aldol Cyclisation Domino Process

3.1. Aims and Objectives

As described in Chapter 2.1.2.3 (Scheme 29), the formation of an enolate intermediate in the conjugate boration of activated olefins has been reported by several research groups during the past decade. This enolate is usually protonated with a proton source, methanol in most cases, to obtain the desired boronate. As demonstrated in Chapter 2.1.3., prior to the beginning of this research project, there had only been two reports of the trapping of an enolate formed in a conjugated boration reaction (Schemes 55 and 56).[59, 64] Additionally, during the course of the project, Riant's group published a racemic intermolecular conjugate boration/enolate trapping process (Chapter 2.1.3., Scheme 57).[67] Therefore an opportunity existed to develop a range of asymmetric intramolecular domino conjugate boration-electrophilic trapping reactions to generate complex products with multiple stereocentres, hopefully, with good control over both the relative and absolute stereochemistry.

This project aimed to apply the well-established conjugate boration of activated olefins to substrates which allowed for an intramolecular electrophilic enolate trapping to form a carbon-carbon bond and generate complex cyclic structures with multiple stereocentres (Scheme 59).



285 286 287

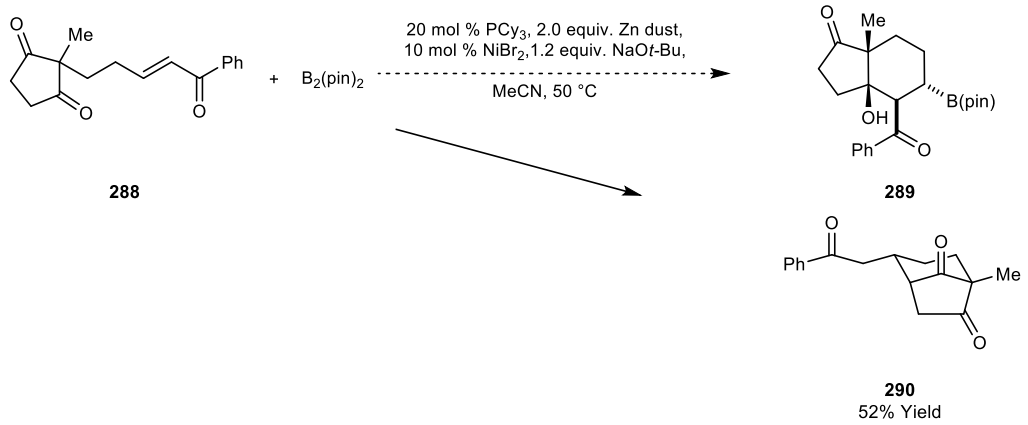
Scheme 59: Proposed domino borylation/aldol cyclisation process

It was hoped that, with the judicious choice of conditions and the appropriate use of a chiral ligand, the conjugate boration–cyclisation would be achieved in good yield and with high levels of both diastereo- and enantiocontrol. Once optimum reaction conditions were developed, this methodology was applied to a range of different substrates to illustrate the

scope and discover the limitations of this type of chemistry. Finally, to demonstrate the utility of the conjugate boration–cyclisation process, a range of different transformations would be carried out with the B-C bond, *i.e.* oxidation to alcohol,[27] Suzuki-Miyaura coupling[28] or amination.[29]

3.2. Conjugate Boration–Domino Trapping Process Screening

The first attempt to perform this type of chemistry was carried out recently within the Lam group. Asymmetric boration and enolate cyclisation of enone **288** would afford the aldol-type product **289** *via* the mechanism proposed in Scheme 61. However, the chemistry did not proceed to give the boration-cyclisation product. In fact, when diketo-enone **288** was treated with $NiBr_2/PCy_3$, a Michael addition took place to form bicyclo[3.2.1]octane **290** in 52% yield (Scheme 60).[b]



288 **289**

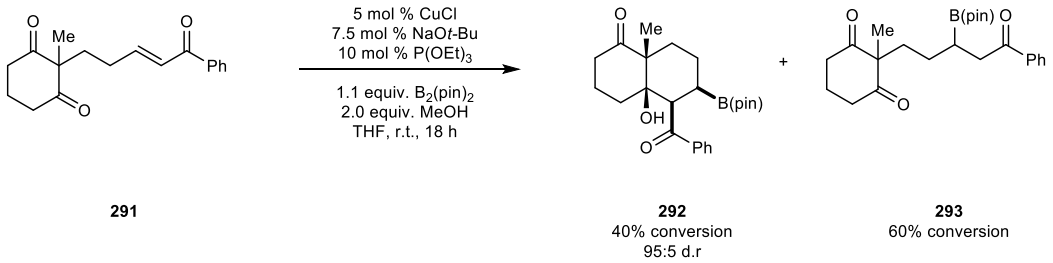
290
52% Yield

Scheme 60: First attempts on the boration/aldol cyclisation process

It was not until a $CuCl/P(OEt)_3$ catalytic system was applied, that success was achieved (Scheme 61). The use of the phosphite ligand was crucial to obtain the cyclised product. Full conversion of the enone **291** was observed after 18 h at r.t. However, not only the desired

[b] Reaction performed by Darryl Low

cyclised product **292** was formed, 60% conversion of the non-cyclised product **293** was also observed (Scheme 61).[c]



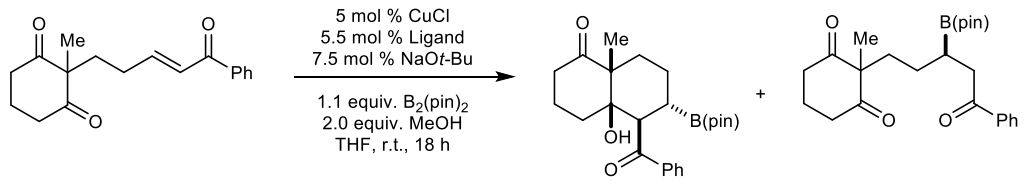
Scheme 61: Copper catalysed racemic boration/aldol cyclisation process

The screening studies commenced with commercially available phosphine ligands in an attempt to make the conjugate boration–cyclisation process both diastereo- and enantioselective.

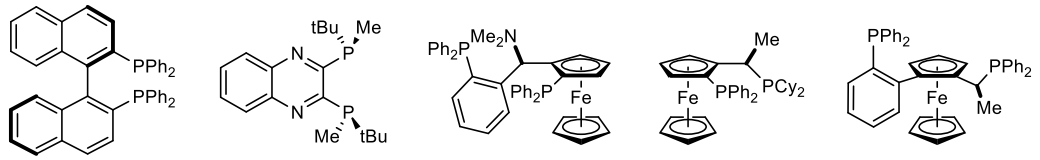
[c] Reaction performed by Dr Alan R. Burns

Fortunately SL-J00-1 Josiphos ligand (**L09**) gave excellent results in combination with CuCl, $B_2(pin)_2$, NaO*t*-Bu as base and MeOH as additive in THF, delivering product **292** in high conversion an acceptable ratio of cyclised product and very good diastereo- and enantiocontrol (Table 1, Entry 2). Other bisphosphine ligands proved to be inferior in every aspect (Table 1, Entries 3-6).[d]

Table 1: Ligand Screening



291 **292** **293**



L02 (*R*)-Binap

L19 (*R,R*)-Quinox-P

L07 SL-T001-1 Taniaphos

L09 SL-J001-1 Josiphos

L25 SL-W002-1 Walphos

Entry	Ligand	Conversion[I]	Cyclic-Acyclic[I]	d.r.[I]	ee[II]
1	$P(OEt)_3$	95%	40:60	>95:5	-
2	L02	62%	48:52	>95:5	70%
3	L19	74%	32:68	>95:5	10%
4	L07	35%	<5:95	Not measured	Not measured
5	L09	>95%	87:13	>95:5	93%
6	L24	63%	<5:95	Not measured	Not measured

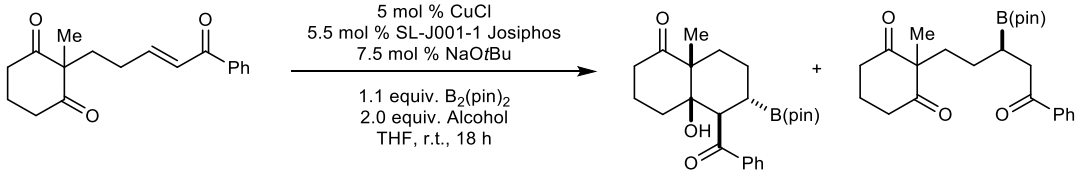
I) Determined by ^{1}H NMR analysis of the crude reaction mixture (disappearance of a signal of 1H, m at 6.85-6.89 Hz and appearance of a signal of 1H, d at 3.59 Hz)

II) Determined by chiral HPLC

[d] Screening performed by Dr Alan R. Burns

As it could have been expected the absence of a proton source in the reaction mixture increased the proportion of cyclised product. However, surprisingly, the enantioselectivity of the process was diminished (Table 2, Entry 2). Different strategies to promote the formation of the cyclic product were applied. The first attempt was the dilution of the reaction which increased the stereocontrol as well as the amount of uncyclised product (Table 2, Entry 3). The second strategy was to use a different proton source: when a bulkier alcohol as *t*-BuOH was added the ratio of cyclisation increased while the stereocontrol was preserved (Table 2, Entry 4). *i*-PrOH was marginally more efficient (Table 2, Entry 5). Therefore, it was these conditions that were used to study the scope of the process (Table 2).[e]

Table 2: Alcohol Screening



291 **292** **293**

Entry	Alcohol	Conc (M)	Conversion[I]	Cyclic-acyclic[I]	d.r.[I]	ee[II]
1	MeOH	0.1	>95%	87:13	>95:5	90%
2	None	0.1	>62%	93:7	>95:5	85%
3	MeOH	0.05	>95%	72:28	>95:5	95%
4	*t*-BuOH	0.05	>95%	83:17	>95:5	94%
5	*i*-PrOH	0.05	>95%	84:16	>95:5	94%

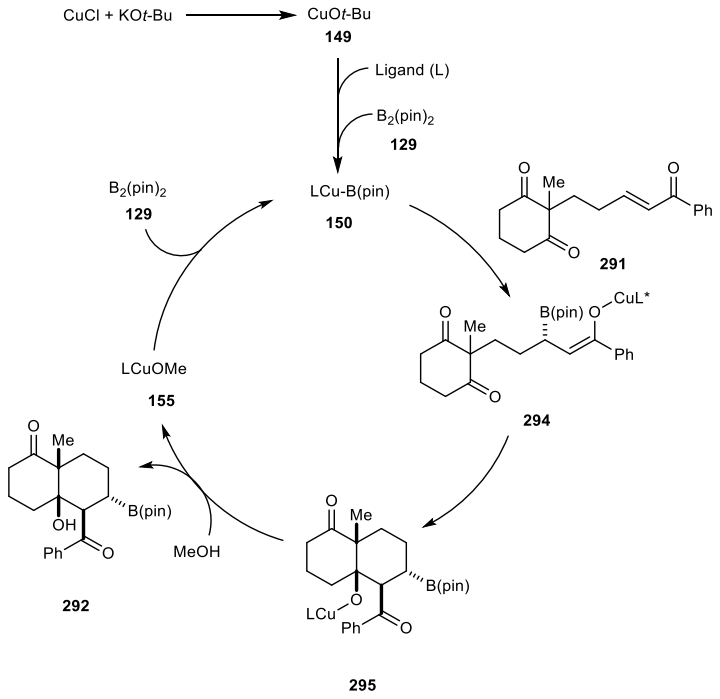
I) Determined by ^{1}H NMR analysis of the crude reaction mixture (Table 1)

II) Determined by Chiral HPLC

The catalytic cycle proposed for this process is in accordance with the mechanism described by Yun's group in their conjugate boration studies.[49] A copper salt transmetalates with $B_2(pin)_2$ to form copper-boron species **150**. This species **150** then attacks the α-β unsaturated

[e] Screening performed by Dr Alan R. Burns

ketone to form copper enolate **294**. In this particular case, enolate **294** it is trapped by the tether ketone instead of protonation by the alcohol additive forming copper alkoxide intermediate **295**. Finally the alcohol regenerates the active copper species and protonates the intermediate to form the observed alcohol **292** (Scheme 62).



Scheme 62: Catalytic cycle for the boration/aldol cyclisation process

With these optimised conditions in hand, the chemistry was applied to a range of enone diones. To synthesise the required substrates, two different routes were developed.

3.3. Substrate Synthesis

To enable the generation of a broad range of substrates to study the scope of the domino process, it was proposed to modify three parts of the enone starting material. The three parts to be modified were: i) the size and nature of the ring of the 1,3-diketone compound; ii) the length of the chain between the diketone ring and the alkene and; iii) the substituents in the aromatic ring adjacent to the α,β-unsaturated ketone (Figure 1).[68]

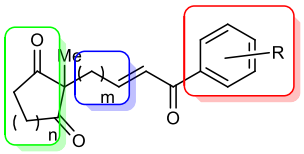
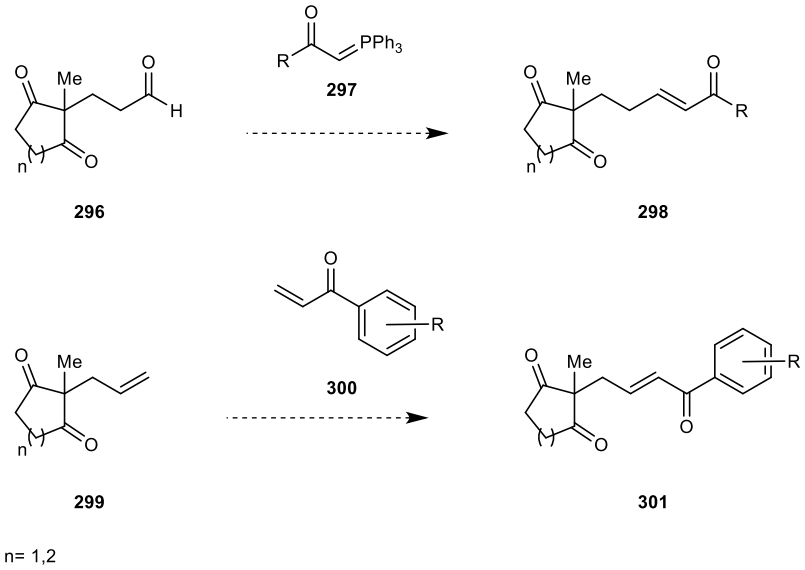


Figure 1: Proposed modification on dione substrate

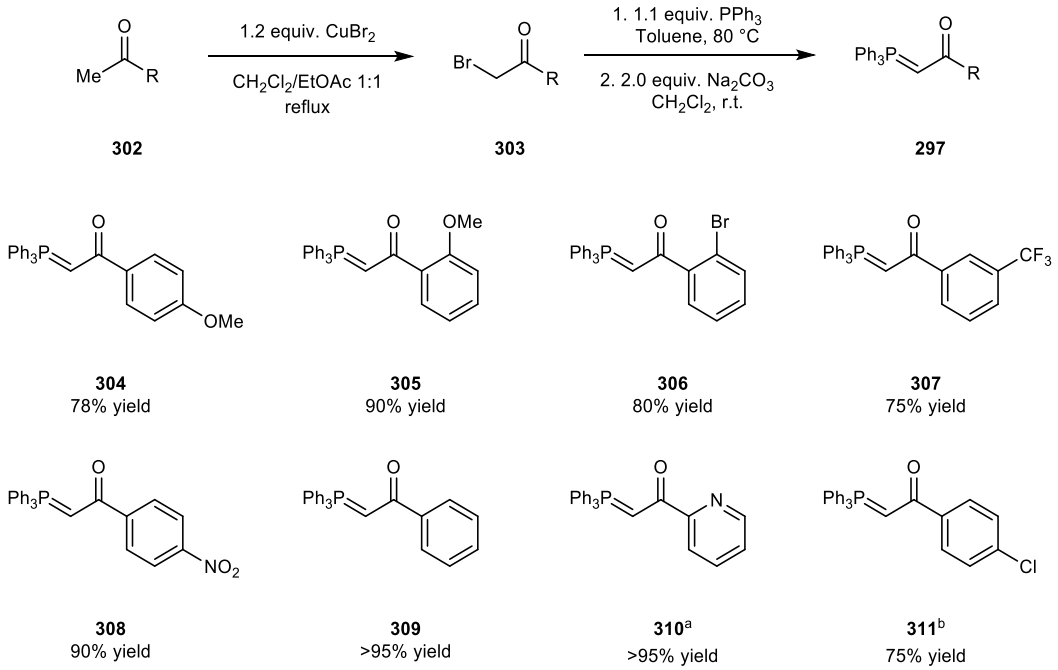
Two routes were applied to achieve the modifications proposed. The first route involved a Wittig olefination of aldehydes **296** with ylides **297**, and the second was a cross-metathesis of alkenes **299** with α,β-unsaturated ketones **300**, which were synthesised from the corresponding ylide and formaldehyde.[69]



Scheme 63: Substrate synthesis

3.3.1. Ylide Synthesis

The ylides required for both routes were, on the whole, prepared from the corresponding α-bromoketone. These α-bromoketones were either commercially available or prepared from the ketone by bromination using copper(II) bromide. Thus, ylides **297** were prepared in overall yields of 78-90% for the two steps (Scheme 66).[70]

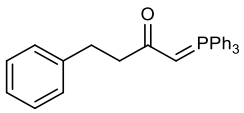


Scheme 64: Ylide synthesis

a) Bromine in a HBr/AcOH solution instead of $CuBr_2$ in CH_2Cl_2.

b) Synthesised by Darryl Low.

One particular ylide was synthesised in a different fashion. An ylide containing an alkyl ketone was required to test the effect of having an alkyl chain next to the α,β-unsaturated ketone rather than an aromatic group. An ylide containing a methyl or an ethyl ketone could have been used for that purpose but the lack of a chromophore in the final cyclised product would make enantiomeric excess analysis through chiral HPLC more difficult. After surveying the literature, ylide **312** was targeted for synthesis as it has an alkyl chain next to the α-β-unsaturated ketone and a chromophore at the end of the chain.[71]

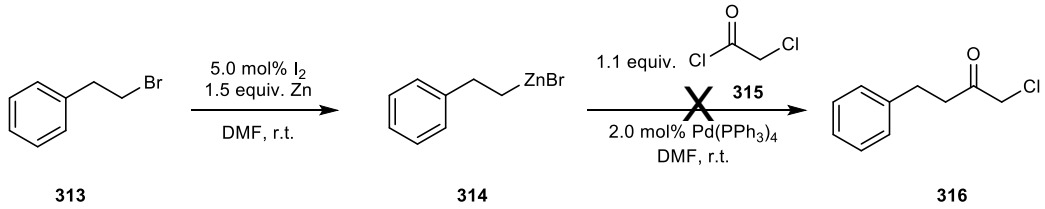


312

Figure 2

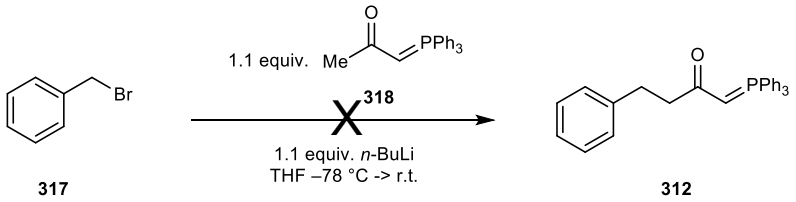
To synthesise this molecule, a Negishi coupling was first attempted.[72] Thus, organozinc **314** was prepared and reacted with chloroacetyl chloride under Pd(0)-catalysis (Scheme 65).

Unfortunately, the corresponding chloroketone **316** was not detected observing a unseparable complex mixtures.



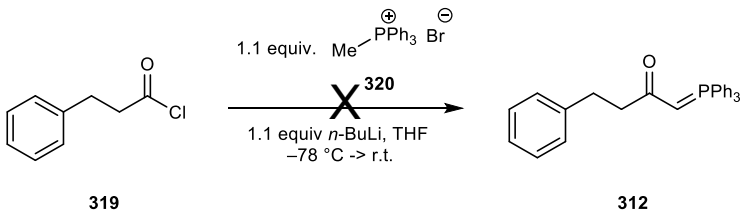
Scheme 65: Attempted ylide synthesis

Therefore, a second strategy to synthesise ylide **312** was sought. Accordingly, using a method from Stevens and Ellis, ylide **318** was deprotonated with *n*-BuLi and reacted with benzyl bromide **317**.[71a] However, again the desired ylide was not detected observing mainly starting benzyl bromide (Scheme 66).



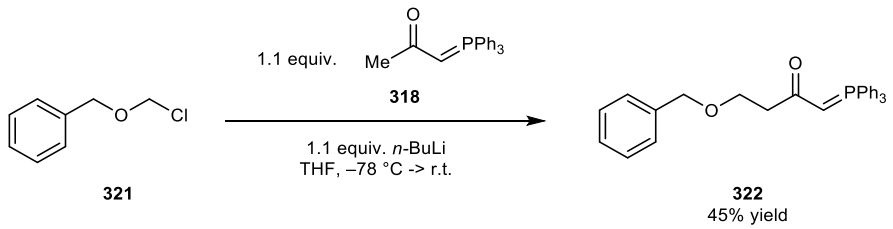
Scheme 66: Attempted ylide synthesis

The last strategy attempted to synthesise ylide **312** was to react hydrocinnamoyl chloride **319** with methyltriphenylphosphonium bromide **320** in presence of *n*-BuLi.[73] As in the previous attempt, the base should deprotonate the methyl group of the phosphonium salt and then attack the acyl chloride. Nevertheless, the ylide was, unfortunately, not obtained (Scheme 67).



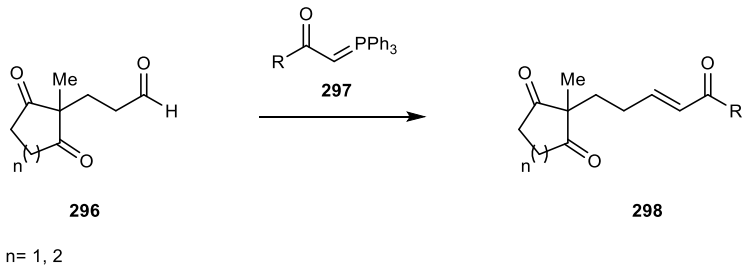
Scheme 67: Attempted ylide synthesis

Given these setbacks, it was proposed to synthesise a different ylide. Ylide **322** was a structure already described in the literature and also had the properties required; *i.e.* alkyl chain plus chromophore. To synthesise ylide **322**, methyl ylide **318** was deprotonated using *n*-BuLi to then attack the halide **321** to form the desired ylide **322**. Pleasingly, this reaction was successful and delivered ylide **322** in a moderate 45% yield (Scheme 68).[74]



Scheme 68: Alkyl ylide synthesis

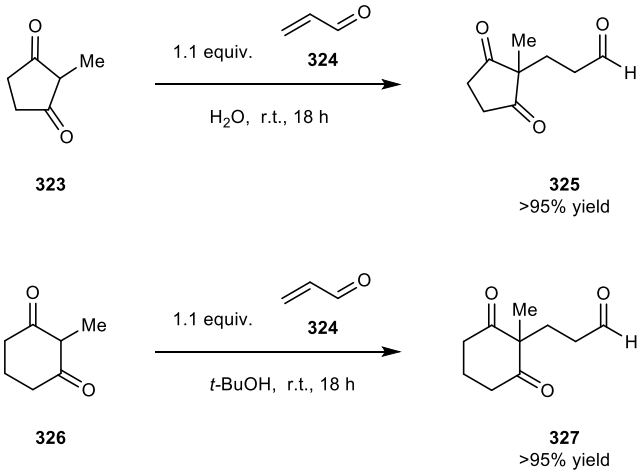
3.3.2. Wittig Olefination Route



Scheme 69: Substrate synthesis

The double bond position was thought to be the ideal disconnection to synthesise substrates of type **298** through a Wittig reaction of aldehydes of type **296** with the corresponding ylides **297**. This type of substrate would result in products which would give a six-membered ring after the boration-cyclisation process was performed.

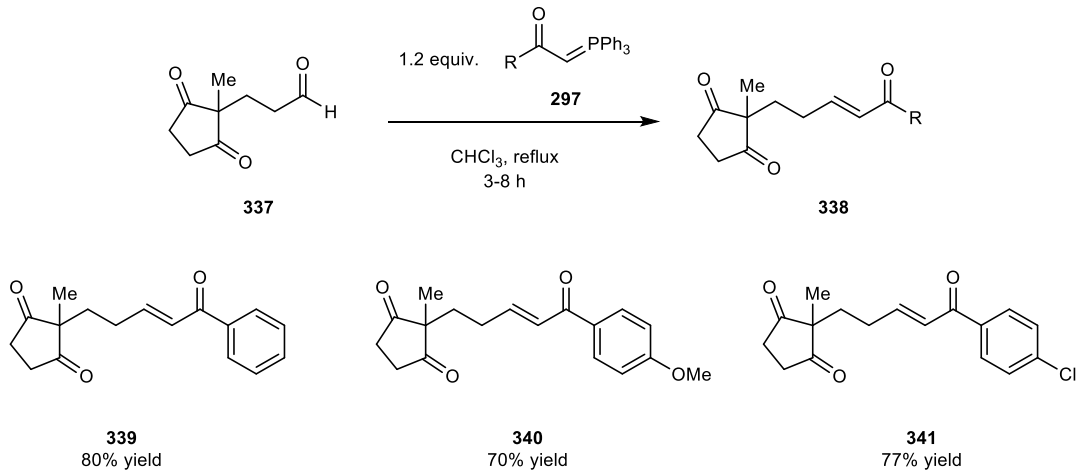
To synthesise the aldehyde precursor, the corresponding cyclic diketone (2-methyl-1,3-cyclopentanedione **323** or 2-methyl-1,3-cyclohexanedione **326**) was treated with acrolein in water to perform a Michael addition. Diketone **326** was completely insoluble in water and very low yields were achieved when the Michael addition was performed in water, therefore the solvent was changed to *t*-BuOH (Scheme 70).[69b]



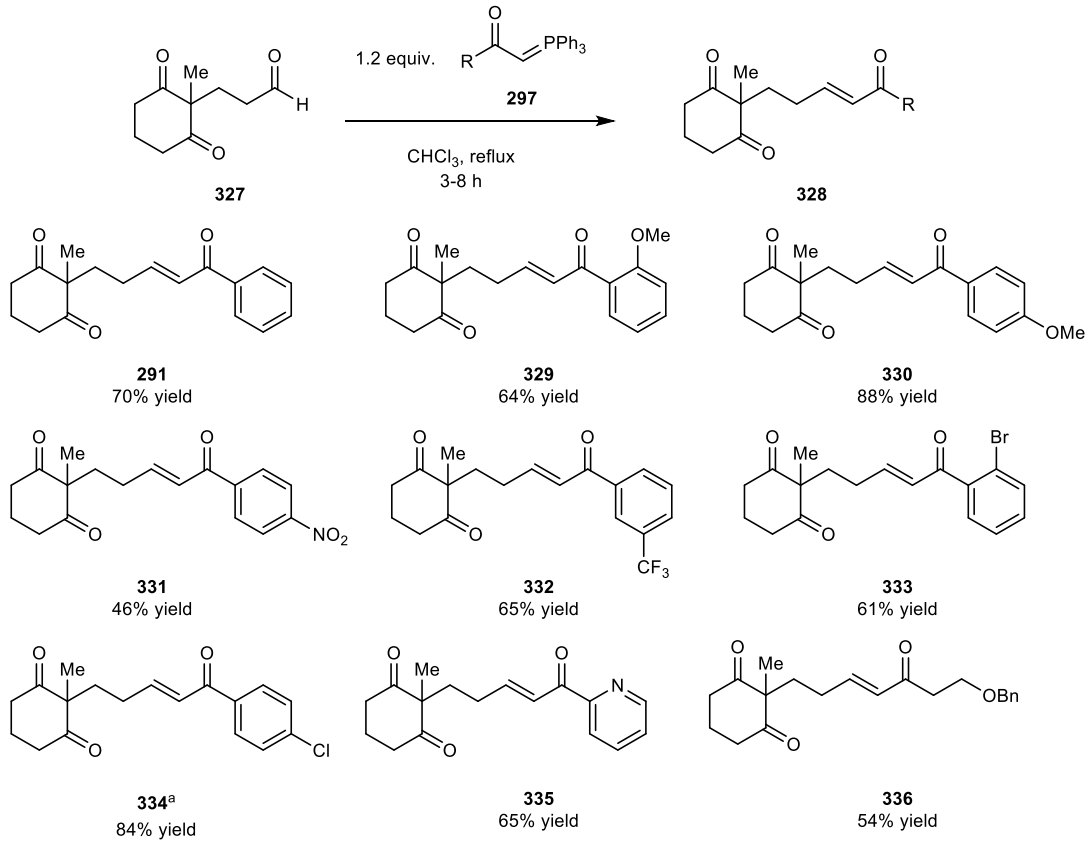
Scheme 70: Aldehyde precursors sysnthesis

For cyclohexadione **326**, simple evaporation of the reaction solvent provided a quantitative yield of aldehyde **327**. For cyclopentadione **323**, a filtration through a pad of silica was required to deliver pure aldehyde **327**, also in quantitative yield.

The next step of the route was to form the α,β-unsaturated ketone through a Wittig olefination with ylides **297**, which gave the final products with yields between 46 and 88% after purification *via* flash column chromatography on silica gel (Scheme 71 and Scheme 72).



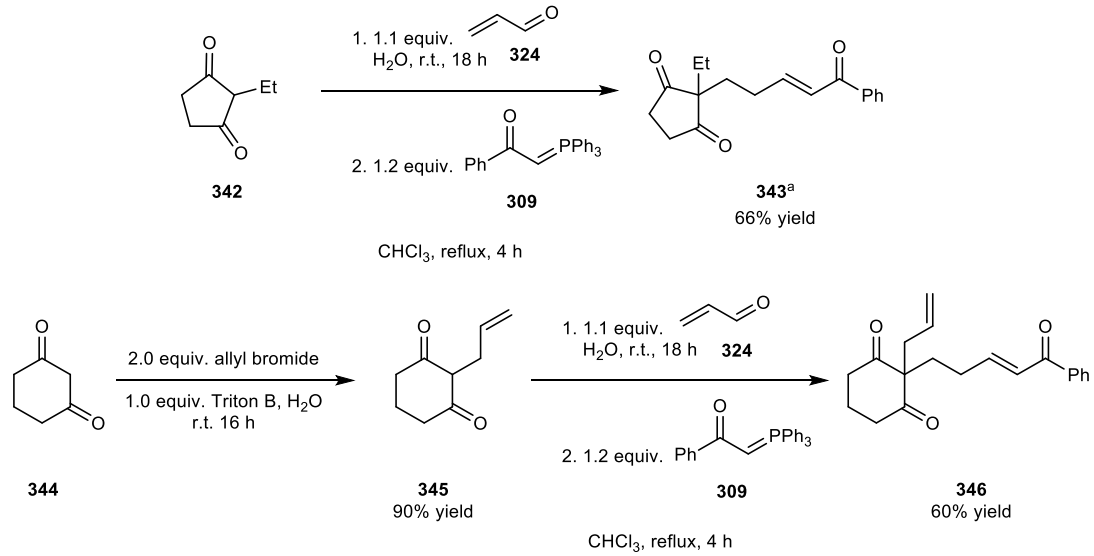
Scheme 71: Substrate synthesis



Scheme 72: Substrate synthesis

a) Substrate synthesised by Dr Alan R. Burns

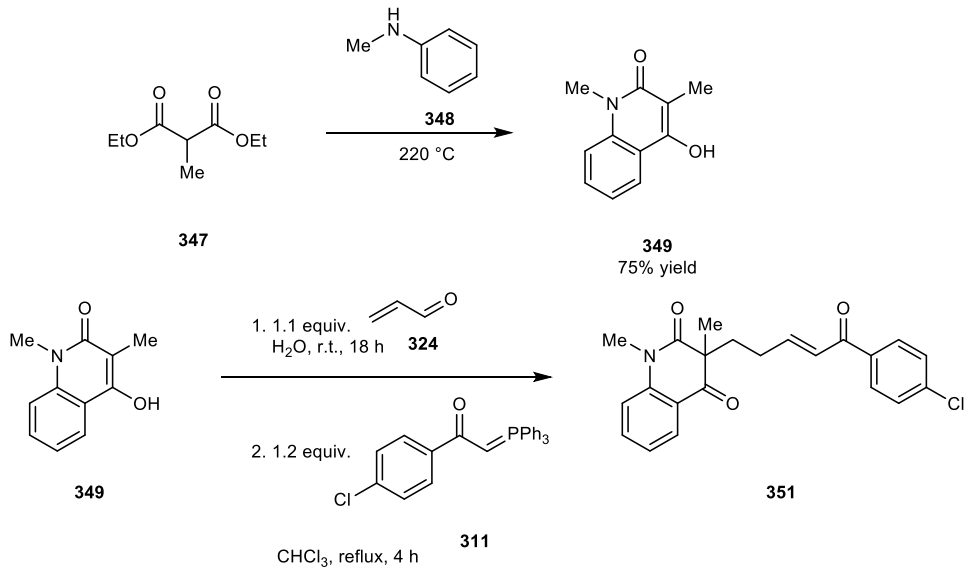
Using the previously described route, two more substrates were synthesised modifying the substitution between the diketone and also the nature of the electrophilic part. The methyl substituent was modified for an ethyl and a allyl group. To achieve the corresponding aldehyde, 2-ethyl-1.3-cyclopentadione was reacted with acrolein in water. After concentrating under vacuum, the aldehyde was isolated and reacted with ylide **309** to obtain the corresponding α-β-unsaturated ketone **343**. To synthesise the allyl-substituted substrate **346**, 1,3-cyclohexadione **344** was first reacted with allyl bromide in the presence of Triton B in water. Once allyl diketone **345** was obtained, the previously described route yielded product **346** (Scheme 73).[75]



Scheme 73: Substrate synthesis

a) Product synthesised by Darryl Low.

Additionally, racemic cyclic β-ketoamide **351** was prepared to study if our system would be capable of performing a parallel kinetic resolution. The condensation of N-methylaniline **348** and diethyl methyl malonate **347** at 220 °C gave β-ketoamide **349**, which was then subjected to the Michael addition with acrolein and Wittig reaction with ylide **311** to result in dione **351** (Scheme 74).[76]

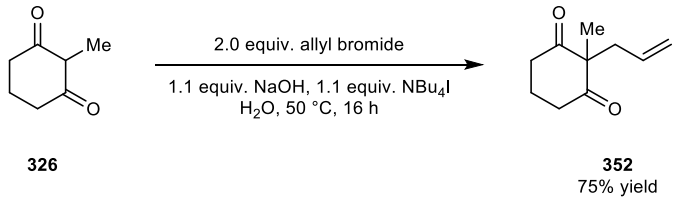


Scheme 74: Substrate synthesis

3.3.3. Cross-Metathesis Route

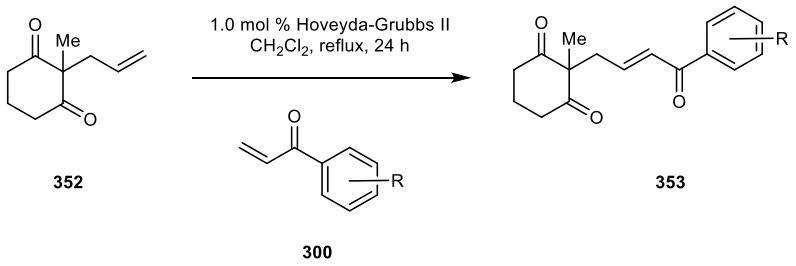
The second strategy to modify the enone substrate was to apply a cross-metathesis reaction to reduce the length of the linker between the olefin and the ketone.

Therefore, using the Hoveyda-Grubbs 2nd generation catalyst, the reaction between alkene **352** and α-β-unsaturated ketones **300** gave the desired enones **353** in moderate yields. The α,β-unsaturated ketones were obtained after a Wittig reaction of the corresponding ylide and formaldehyde (Scheme 75 and 76).[77]



326 **352**
75% yield

Scheme 75: Precursor synthesis



352 **300** **353**

354[a] **355**[a]
50% yield 57% yield

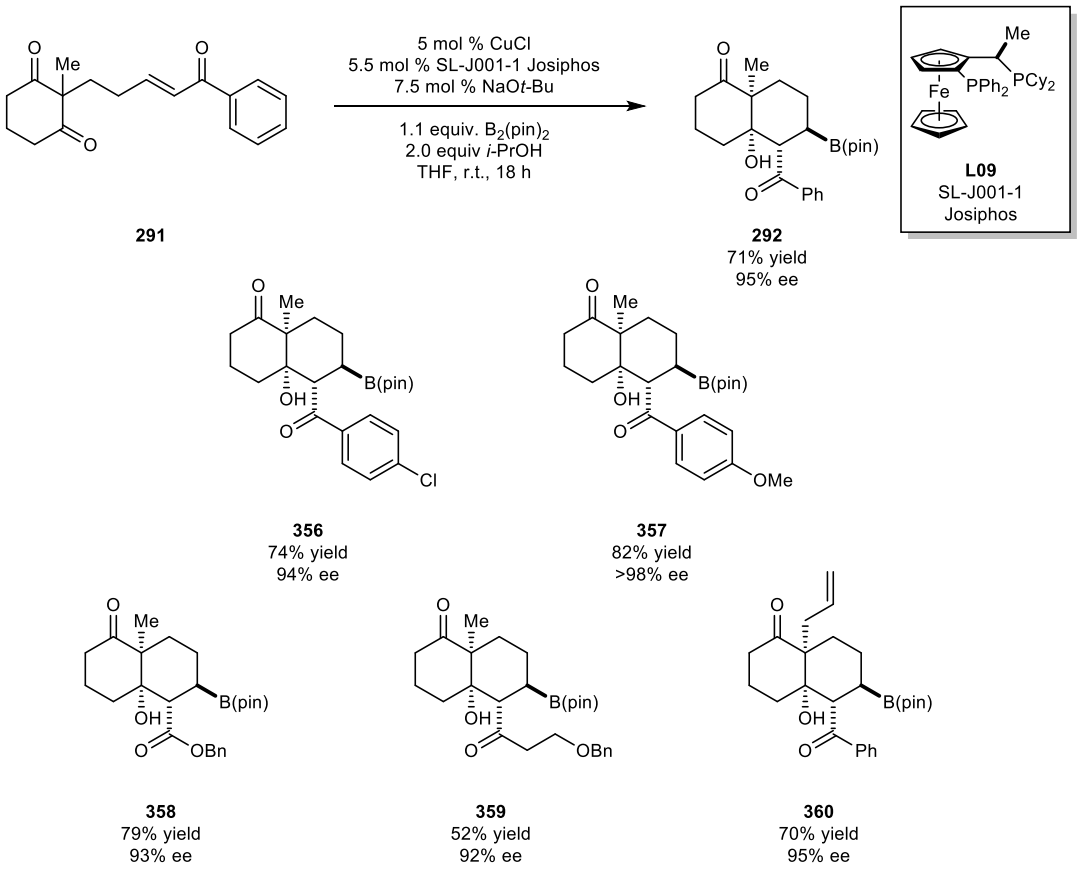
Scheme 76: Substrate synthesis

a) Product synthesised by Dr Alan R. Burns.

3.4. Scope of the process

The substrates synthesised through the routes shown on chapter 2.2.3. were used to investigate the scope of the borylation aldol cyclisation process.

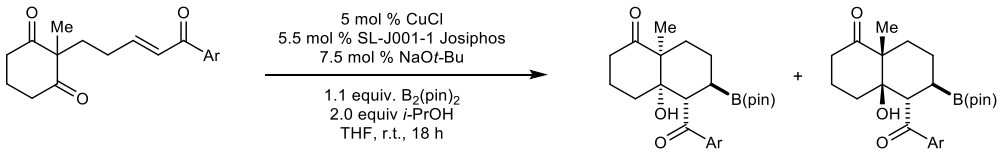
Following the previously optimised conditions for the reaction of enone **291**, substitutions on the benzene ring were well tolerated. Substrates with both electron-donating and electron-withdrawing substituents performed well under the optimised conditions to give the desired cyclised products in high yields and high enantioselectivities as a single diastereoisomer. We also observed that the reaction is not limited to aromatic α,β-unsaturated ketones. The copper-catalysed process achieved the synthesis of product **358**, which contains an ester group as the activating group for the double-bond, and also product **359**, where an alkyl chain was placed next to the α,β-unsaturated ketone with high stereocontrol (Scheme 77).



Scheme 77: Copper catalysed boration/aldol cyclisation

Ortho substitution in the aromatic ketone proved to be more challenging. Substrate containing a *ortho*-bromophenyl ketone gave poor diastereoselectivity (almost 1:1) and mediocre enantioselectivity especially in the case of the newly observed diastereoisomer (68% enantiomeric excess) (Table 3, Entry 1). In the case of *meta*-substitution, the diastereoselectivity was improved to almost 4:1 in favour of the new diastereoisomer observed in the previous experiments and the enantioselectivity was still high for both isomers (Table 3, Entry 2). Surprisingly, when a strong electronwithdrawing group was introduced in the aromatic ketone the diastereomeric ratio was inverted to the new diastereoisomer observed (3:2) although the enantiocontrol was still high (Table 3, Entry 3).

Table 3: Electron-Poor Aromatic Ketones



381 382 383

Entry	Substrate	d.r.[I]	Yield	ee[II]
1	Ar = 2-$BrCC_6H_5$	55:45	42% (48%)[III]	68% (83%)[IV]
2	Ar = 3-$F_3CC_6H_5$	23:77	60% (15%)[III]	83% (89%)[IV]
3	Ar = 4-$O_2NC_6H_5$	59:41	29% (49%)[III]	86% (87%)[IV]

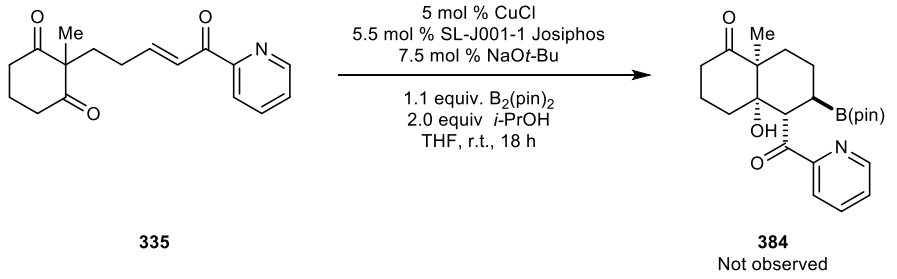
I) Determined by ^{1}H NMR analysis of the crude reaction mixture (Signal of the CHCOAr in each diastereoisomer)

II) Determined by Chiral HPLC

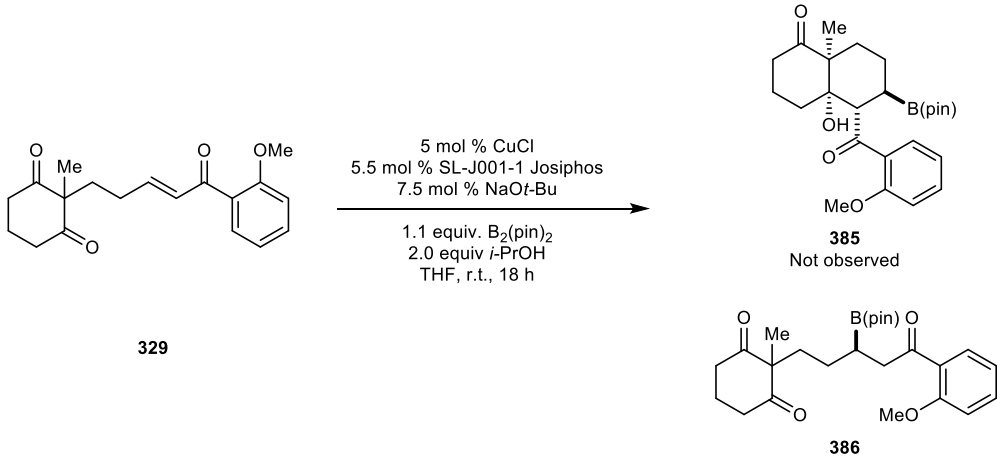
III) Yield of new diastereoisomer

IV) ee of new diastereoisomer

Pyridyl and *ortho*-methoxide substituted substrates **335** and **329** did not produce the desired cyclic products **384** and **385**. A complex mixture was recovered upon work-up in the case of pyridyl substituted dione **385** and mainly the non-cyclic product **386** was observed in the crude of the reaction of the *ortho*-methoxy substituted substrate **329** (Scheme 78 and 79).



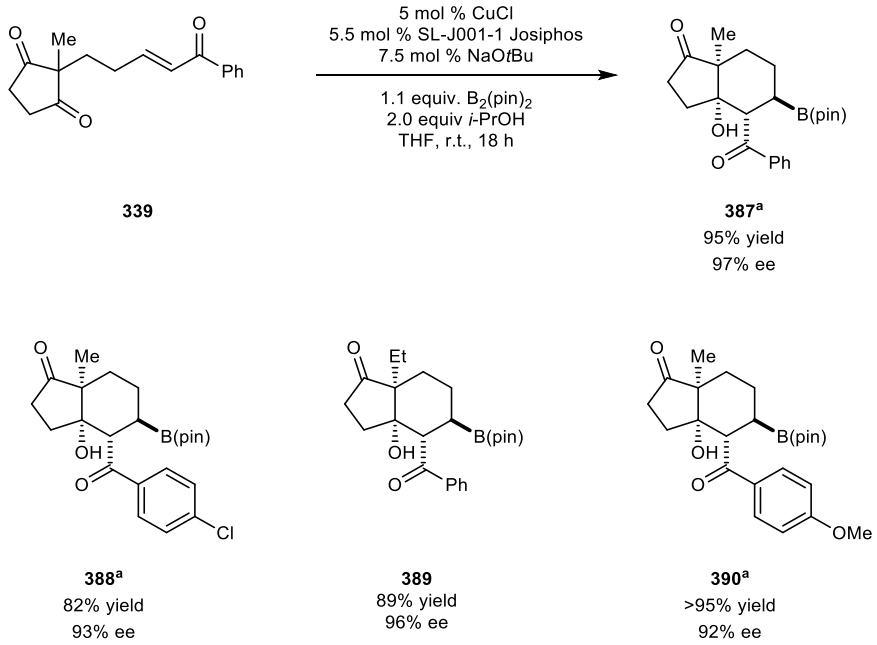
Scheme 78: Attempted substrate



Scheme 79: Attempted substrate

The length between the diketone and the alkene as well, as the ring size of the cyclic 1,3-diketone was also studied. In these cases the use of *t*-BuOH as additive instead of *i*-PrOH gave a marginal increase in the overall yields.

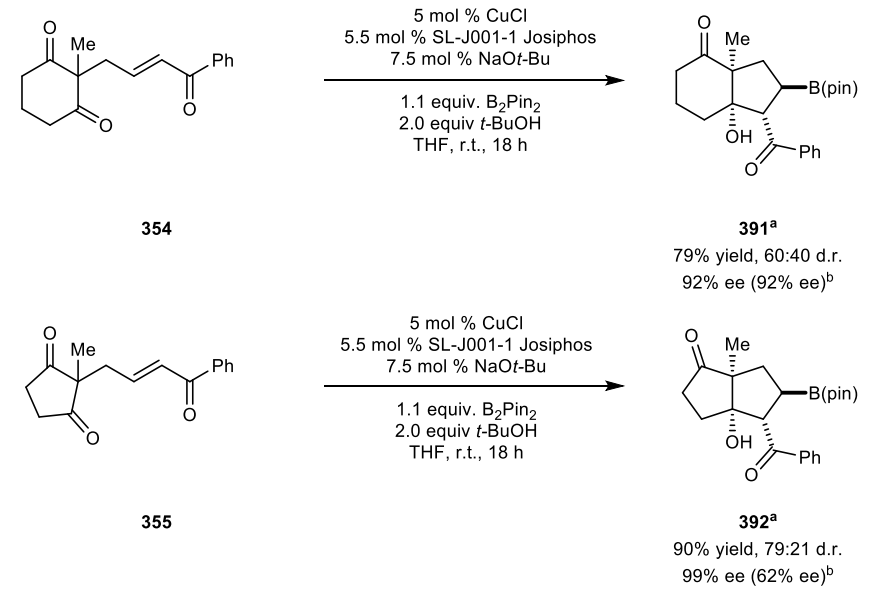
When the size of the cyclic dione was reduced from cyclohexadione to cyclopentadione, an increase on the overall yield of the process was achieved. In the case of simple phenyl ketone product **387** a significant 20% increase of yield was obtained as well as a slight increase in the enantiocontrol. Both electron-rich and electron-poor aromatic ketones **390** and **388** gave a better yield maintaining the enantiomeric excess. We also observed that this process tolerates substitutions other than a methyl group at the 2-position for cyclopentadione substrates. Ethyl-substituted alcohol **389** was obtained in both good yields and enantiomeric excess. As well as for most of the cyclohexadione products, only one diastereoisomer was observed with the same relative stereochemistry (Scheme 80).



Scheme 80: Copper catalysed boration/aldol cyclisation

a) Product synthesised by Dr Alan R. Burns.

The diastereocontrol was clearly diminished when a cyclopentane was formed during the aldol cyclisation, but high levels of enantioselectivity were still achieved (Scheme 81).



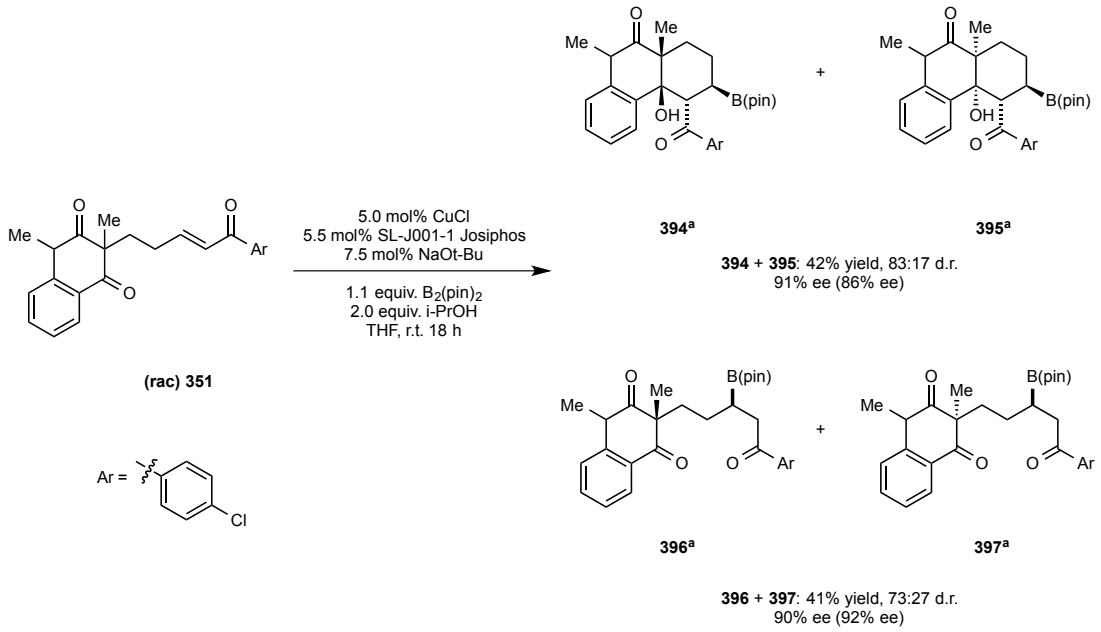
Scheme 81: Copper catalysed boration/aldol cyclisation

a) Product synthesised by Dr Alan R. Burns.

b) ee of minor diastereoisomer.

3.5. Parallel Kinetic Resolution

Parallel kinetic resolution is a well-established tool to separate a mixture of enantiomers thanks to the different reaction rates in a chemical or enzymatic reaction of each enantiomer.[78] In order to test the capacity of this methodology to separate a mixture of enantiomers, a parallel kinetic resolution study was performed. A racemic substrate containing a cyclic β-ketoamide **351** was subjected to the optimised conditions using *i*-PrOH as additive. As a result, a mixture of diastereomer of tricycles **393** and **394** and uncyclised products **395** and **396** was obtained with high enantioselectivity. This indicates that the parallel kinetic resolution of racemic cyclic β-ketoamide **351** was not achieved effectively. A reaction performed with triethyl phosphite gave similar diastereomeric ratios, which might indicate that the diastereoselectivity of the process is controlled by the substrate rather than by the chiral copper complex. (Scheme 82)



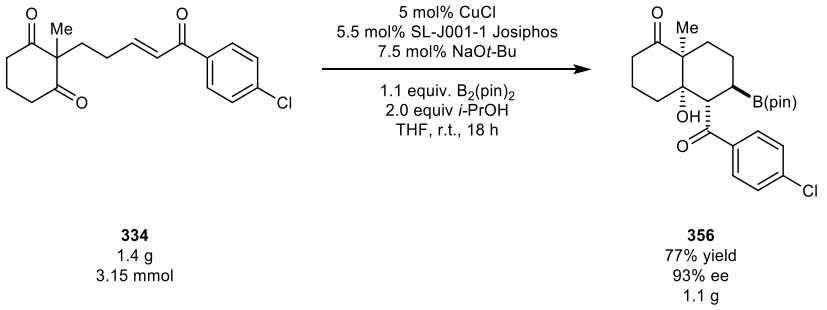
Scheme 82

a) Product synthesised by Dr Alan R. Burns.

b) ee of minor diastereoisomer.

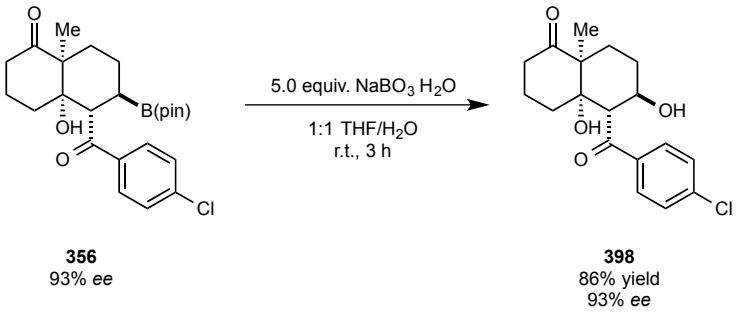
3.6. C-B Bond Transformations

A series of well-known procedures to modify boron-carbon bonds were applied to *para*-chloro substituted aromatic ketone **356**. To be able to try the transformations proposed and to prove that the developed methodology was scalable, 1.4 g of **334** was subjected to the borylation-cyclisation process obtaining similar yield and stereocontrol as in the small-scale reaction (Scheme 83).



Scheme 83: Gram scale copper catalysed boration/aldol cyclisation process

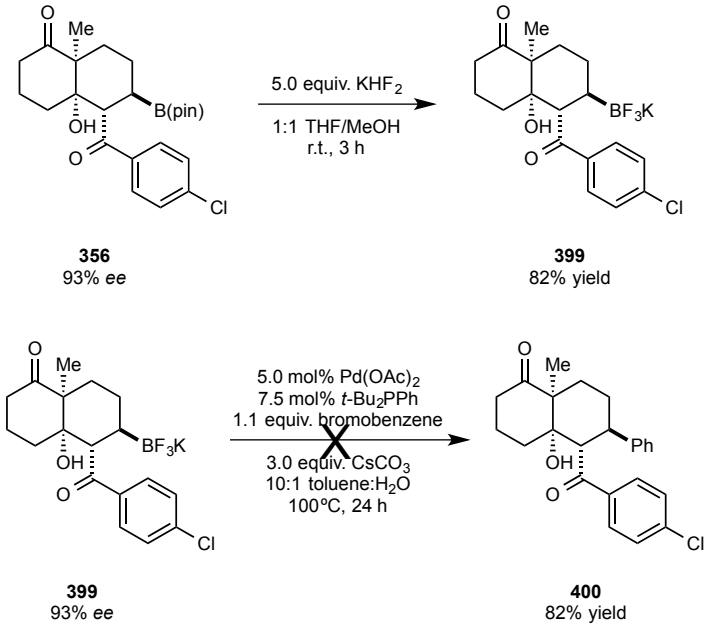
Oxidation of the B-C bond using $NaOH/H_2O_2$ did not produce the expected alcohol. Therefore, Marsden's conditions for the oxidation of organoboron compounds using $NaBO_3$ were applied and alcohol **398** was obtained in a 86% yield without damaging the enantiomeric excess (Scheme 84).[79]



Scheme 84: Further transformations, oxidation

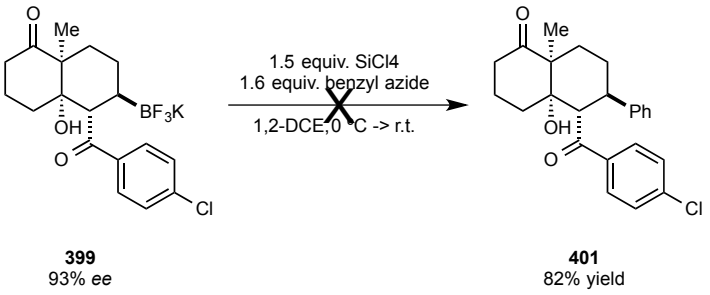
In order to perform further transformations, the corresponding trifluoroborate salt **399** was synthesised using Aggarwal's conditions.[80] It was proposed to use Suzuki-Miyaura coupling conditions in order to further fuctionalise the products synthesised. Unfortunately coupling

with bromobenzene using various conditions was not achieved. Either only starting salt **399** or a complex mixture of products was observed (Scheme 85).[81]



Scheme 85: Further transformations, palladium catalysed Suzuki coupling

Another transformation studied was the amination of the C-B bond. However, when salt **399** was subjected to Matesson's conditions[82] for the amination of BF_3K salts, a complex mixture of products was observed and the expected amine **401** was not isolated (Scheme 86).

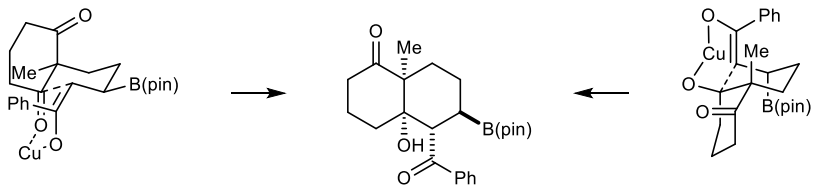


Scheme 86: Further transformations, amination

3.7. Proposed Conformations to Explain the Diasterochemical Outcomes

The methodology developed for the conjugate boration-cyclisation of enone gives only two diastereoisomers (in the case of cyclohexadione substrates). In order to propose the most plausible transition state different diastereomeric conformations were studied. *Cis*-decalin **292**, isolated in most of the cases, comes from an aldol cyclisation process. Assuming the formation of a copper-enolate after the borylation of the double bond, one could expect the formation of either a *Z*-enolate or an *E*-enolate. To achieve the desired diasteroselectivity in the case of a *Z*-enolate, a chair-like transition state **402** would be required. In the case of an *E*-enolate, it would go through a twist-boat transition state **403**. It was proposed that the observed product **292** comes from the chair-like transition state **402** due to a series of factors (Scheme 87):

a) The formation of a *Z*-enolate is generally more favourable, in the case of a copper-enolate intermediate, than an *E*-enolate.[83]
b) Generally, chair-like transition states have lower energy barriers than twist-boat transition states.
c) In the case of transition state **402**, the B(pin) and phenyl enolate substituents are in pseudo-equatorial positions. For twist-boat transition state **403**, both of these substituents are pseudo-axial incurring energy penalties due to 1,3-diaxial interactions making this transition state less favourable.



402
Chair-like TS

292

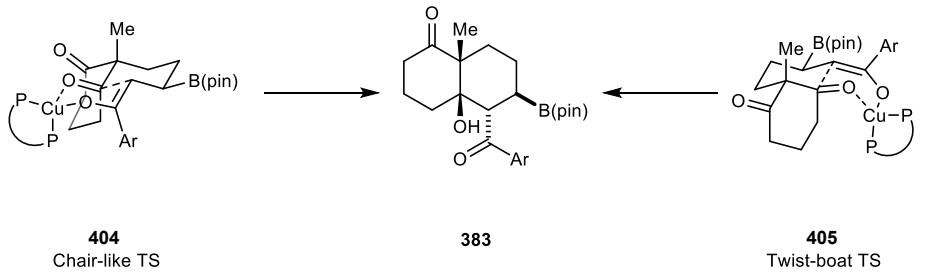
403
Twist-boat TS

Scheme 87: Proposed diasteromeric conformations

A different diastereoisomer **383** was observed when electron-poor aromatic ketone substrates were subjected to the domino process. Assuming the same premises as before, a chair-like transition state **404** from an *E*-enolate and a twist-boat transition state **405** from a *Z*-enolate

were proposed. Following the same rational as previously, it is not straightforward to state which of the transition states is more favourable (Scheme 88):

a) On the one hand, the chair-like transition state **404** has a low energy conformation but it comes from an *E*-enolate, which, as mentioned before, is less favourable for copper enolates.
b) On the other hand the twist-boat transition state **405** is a high energy conformation; however, it comes from a *Z*-enolate which is preferable in the formation of copper enolates (Scheme 90).



404
Chair-like TS

383

405
Twist-boat TS

Scheme 88: Proposed diasteromeric conformations

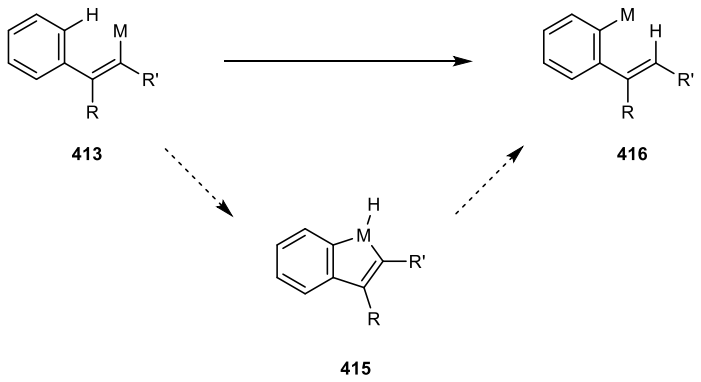
Further studies would be required to have a clearer picture of the process and to be able to confirm which of the transition states proposed for both diastereoisomers is the more probable.

3.8. Conclusions

A new copper-catalysed system for the domino conjugate boration-cyclisation of enones has been developed achieving yields between 55 and >95%. 16 new byciclic structures were obtained with four contiguous stereocentres with both high diastereo- and enantioselectivity (up to 95:5 dr and >98 % ee). This new system has proven to be robust enough to be applied to a broad range of enone-dione substrates with different electronic properties on the aromatic part. The catalytic system was demonstrated to be moderately effective for the parallel kinetic resolution of a racemic β-ketoamide. Further transformations were performed to demonstrate the utility of the cyclised products. Although the system was applied to a wide range of substrates this methodology can still be applied to other structures. Modifications on the electrophilic part used to trap the enolate part aswell as modification on the functional group to activate the alkene can be investigated. This methodology works well for this intramolecular process, another challenge still present is the borylation and enolate trapping with an external electrophile. Examples of such a process have been shown in the literature but achieving lower diastereo and enantiocontrol than in our research.

4. Introduction to the Iridium-Catalysed Arylative Cyclisation of Alkynones by 1,4-Iridium Migration

As described in chapter 1.1., transition metal-catalysed domino reactions are a powerful tool for the synthesis of complex molecules. One mode of reactivity for metals used to carry out domino reactions is a 1,4-metal migration.[84] One the most common 1,4-metal shifts occurs between an alkenyl-metal **413** an aryl-metal species **416**. This transformation is usually described as an oxidative insertion to form a metallacyle **415** and then reductive elimination. This mechanism fuctionalises a relative inert C-H bond creating a new carbon-metal bond which can undergo subsequent reactions (Scheme 89).[85]

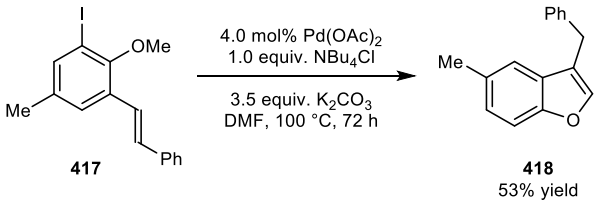


Scheme 89: 1,4-Migration proprosed mechanism

The metals of choice for this type of transformation have been mainly palladium and rhodium but cobalt, nickel, platinum and very recently iridium have also shown the to perform a 1,4-migration.

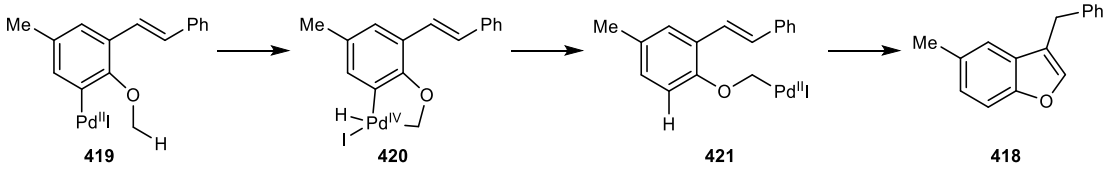
4.1. 1,4-Palladium Migration

The first 1,4-palladium migration process was described by Dyker *et al.* in while investigating a palladium catalysed C-H activation.[86] In the presence of $Pd(OAc)_2$ the formation of benzofuran **418** from aryl iodide **417** was observed (Scheme 90).[87]



Scheme 90: Palladium catalysed 1,4-migration process

The mechanism proposed for the formation of benzofuran **418** starts with oxidative insertion of palladium into the aryl iodide to give arylpalladium(II) species **419**. C-H activation of the methoxy group by oxidative insertion forms palladacycle **420**. This palladacycle **420**, upon reductive elimination, could perform a 1-4-migration to give alkylpalladium species **42**1. Finally Pd intermediate **421** would cyclise on to the reactive double bond to give benzofuran **418**. (Scheme 91).



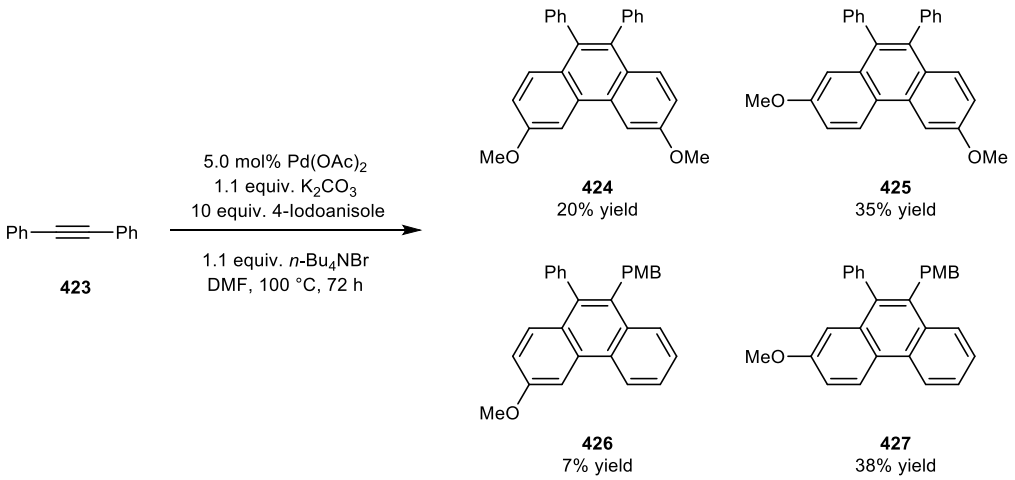
Scheme 91: Mechanism proposed for the Palladium catalysed 1,4-migration process

Since this early report by Dyker, many groups have used palladium-catalysed 1,4-migration as a step in a domino process toward the synthesis of complex structures.[84a]

4.1.1. Palladium-Catalysed Arylation of Alkynes/1,4-Migration Domino Processes

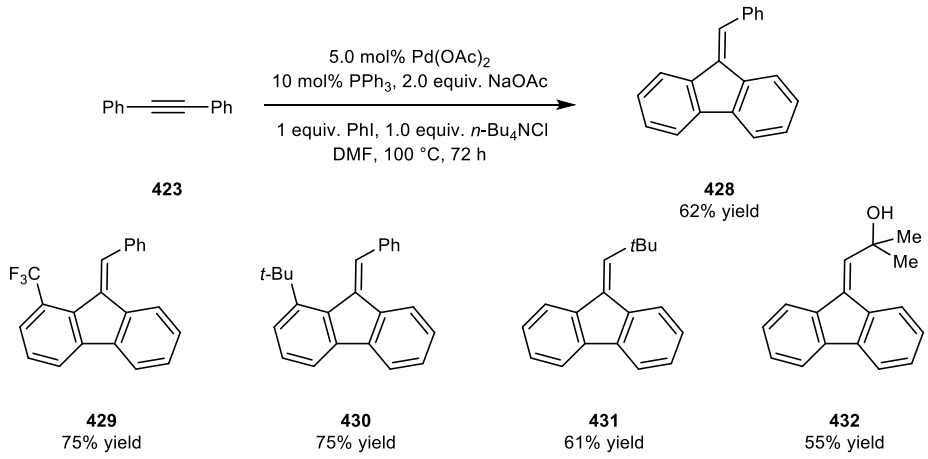
One of the methodologies where 1,4-palladium migration has been applied is the arylation of alkynes. Dyker's group reported a palladium-catalysed cascade alkyne arylation/C-H

activation reaction to form polycyclic structures (Scheme 92). It was observed that, in the presence of $Pd(OAc)_2$, 4-iodoanisole reacted with diphenyl acetylene **423** to give 9,10-diphenylphananthrene structures **424**, **425**, **426** and **427** with poor regioselectivity.[86c, 86e]



Scheme 92: Palladium catalysed arylation/C-H activation process

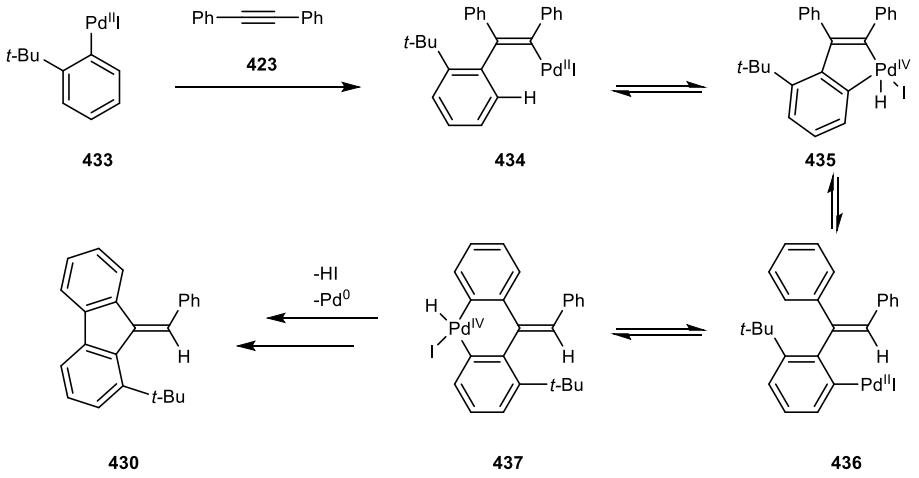
By changing the reaction conditions, the outcome of the process was altered. By adding PPh_3, and changing the base and the ammonium salt to NaOAc and *n*-Bu_4NCl respectively, Larock's group synthesised fluorene structures such as **428** in moderate yields from diphenyl acetylene and substituted aryliodides *via* a 1,4-palladium migration (Scheme 93).[88]



Scheme 93: Palladium catalysed arylation/1,4-migration process

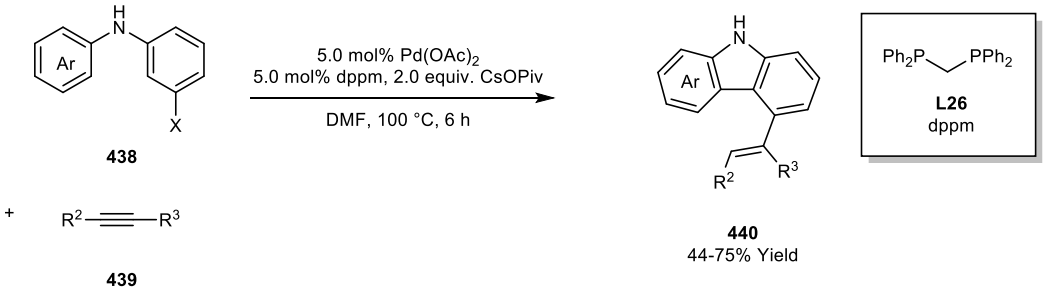
Larock proposed that the mechanism begins with the arylation of the triple bond to form alkenyl-palladium intermediate **434** which undergoes C-H insertion to give metallacycle **435**.

Reductive elimination would form arylpalladium species **436** which undergoes C-H activation to give palladacycle **437**. Finally two consecutive reductive eliminations yield the observed fluorene **430** and regenerate the palladium catalyst (Scheme 95).



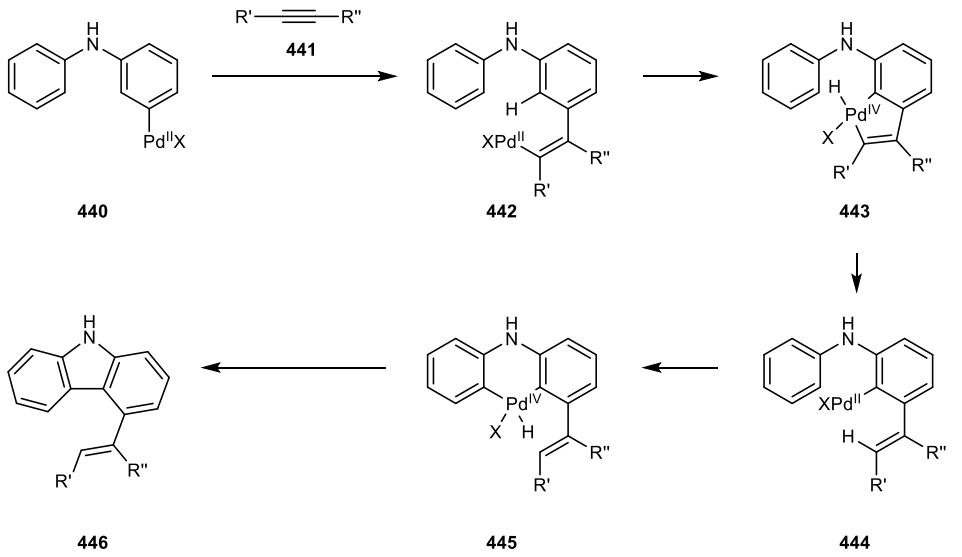
Scheme 94: Mechanism for the palladium catalysed arylation/1,4-migration process

Since this first article, Larock became a key player in this field, publishing several papers on alkyne arylation/1,4-migration domino processes. One example is the synthesis of complex carbazoles **440** through reacting diaryl amines **438** and disubstituted alkynes **439** in the presence of a palladium catalyst (Scheme 96).[89]



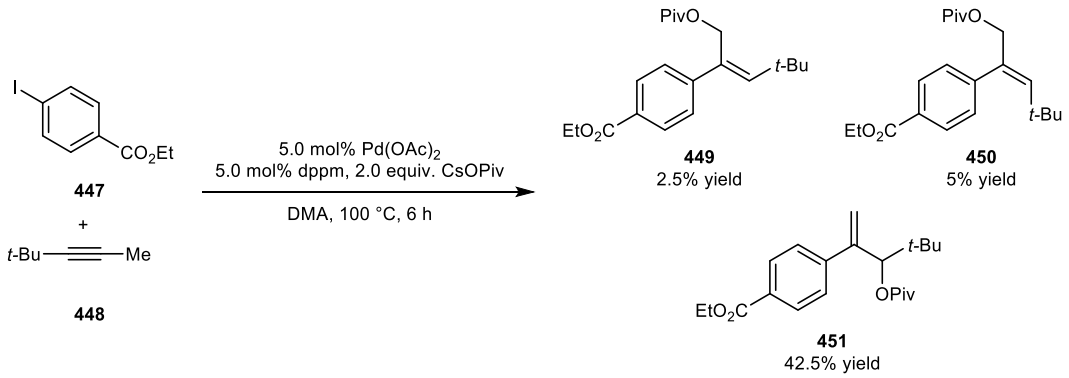
Scheme 95: Palladium catalysed arylation/1,4-migration process

It was suggested that after oxidative insertion to form Pd(II) species **440** carbopalladation with an alkyne would give alkenyl Pd(II) intermediate **442**. C-H insertion gives palladacycle **443** which, after reductive elimination, gives species **444**. The 6-membered ring intermediate **445** is formed through a second C-H insertion. Finally, reductive elimination gives the observed carbazole **446** (Scheme 97).



Scheme 96: Mechanism for the palladium catalysed arylation/1,4-migration process

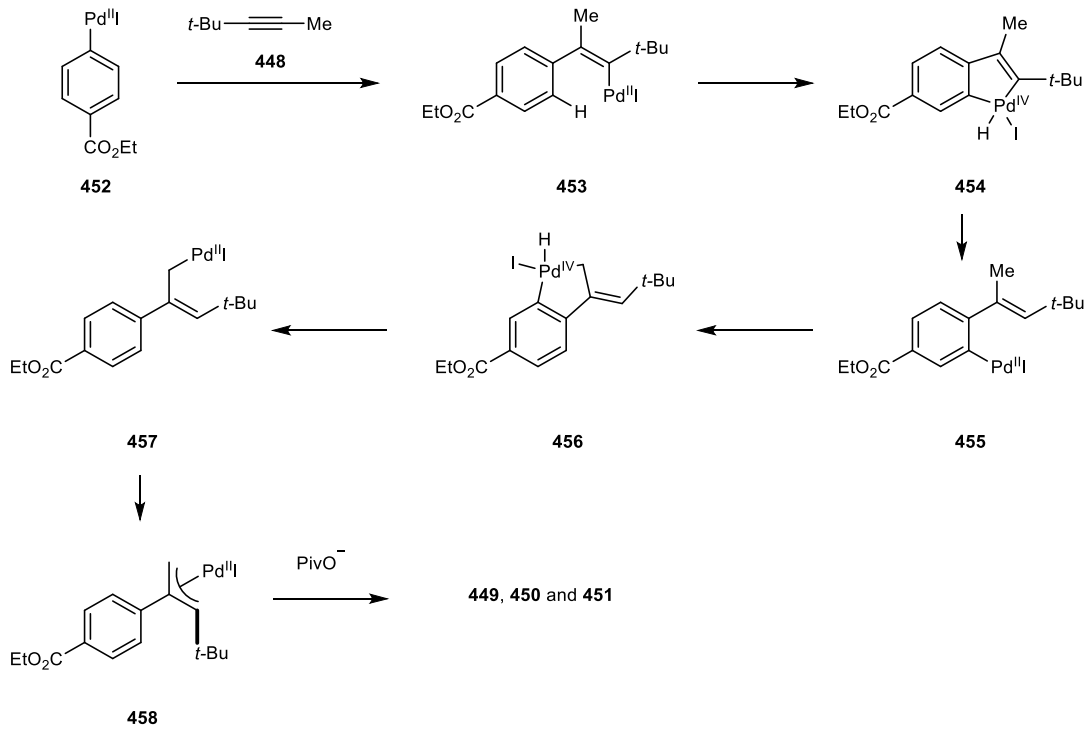
The ability of palladium to perform consecutive migration was also described by Larock *et al.* When a *tert*-butylmethylacetylene **448** reacts with an electron-poor aryl halide **447** in the presence of a Pd(0) catalyst three different alkene esters **449**, **450** and **451** are formed (Scheme 98).[90]



Scheme 97: Palladium catalysed arylation/1,4-migration process

Larock suggested that the three products **449**, **450** and **451** came from the reaction of a pivalate anion with a π-allyl palladium species **458**. The mechanism proposed starts with the arylation of alkyne **448** which then leads to a first palladium 1,4-migration to form arylpalladium species **455**. A second 1,4-migration *via* the C-H activation of the methyl group gives alkylpalladium **457** through palladacycle **456**. This intermediate **457** rapidly

isomerizes to π-allylpalladium species **458** which reacts with the pivalate anion to give each of the isolated products **449**, **450** and **451** (Scheme 99).

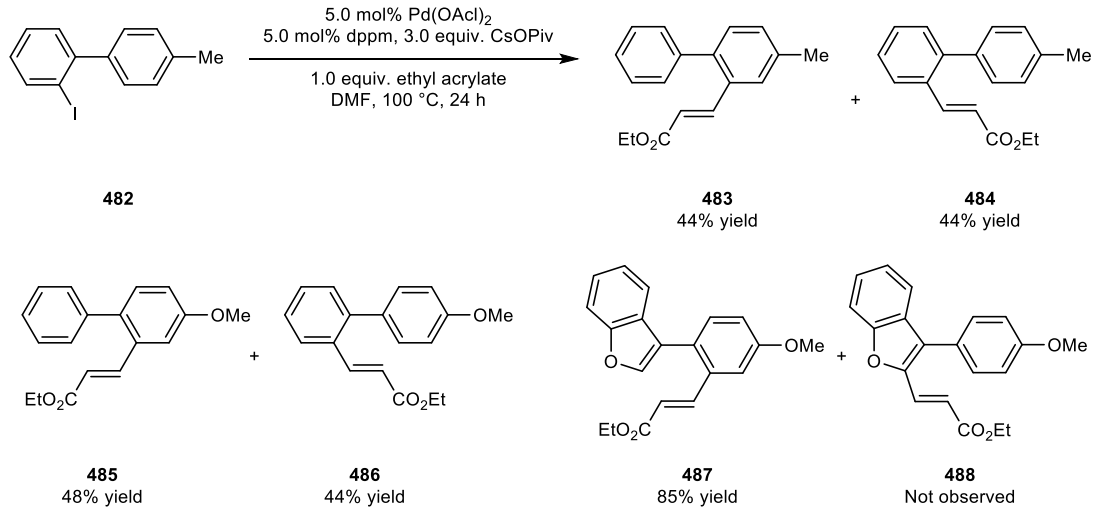


Scheme 98: Mechanism for the palladium catalysed arylation/1,4-migration process

4.1.2. Palladium 1,4-Migration/Alkene Arylation Domino Processes

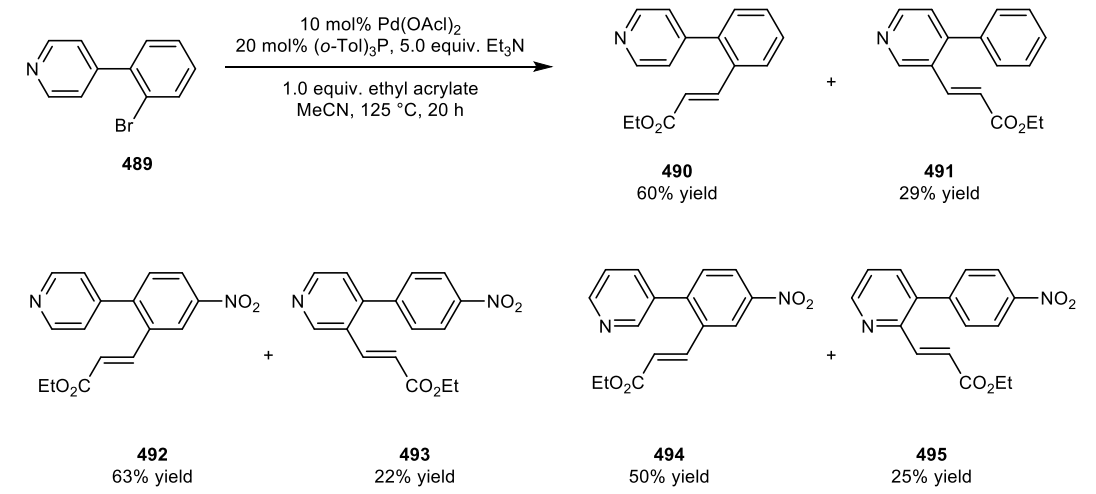
As described previously, the 1,4-migration of palladium can take place after the arylation of an alkyne. However, this palladium shift can also occur after the oxidative insertion of palladium with an aryl halide. Both Larock and Gallagher independently reported this process with the oxidative insertion/1,4-palladium migration of *ortho*-iodobiaryls **482** followed by addition to ethyl acrylate (Scheme 99 and 100 respectively).[91]

Larock's conditions, using dppm (**L85)** as ligand, gave diaryl substituted alkenes in good yields. The regioselectivity was poorly controlled in the case of the methyl and methoxide substituted diaryls, with the formation of both 1,4-migration (**483** and **485**) and Heck products (**484** and **486**) in an almost 1:1 ratio. In the case of a benzofuran derivative, the 1,4-migration product **487** was isolated exclusively (Scheme 99).



Scheme 99: : Palladium catalysed 1,4-migration/arylation process

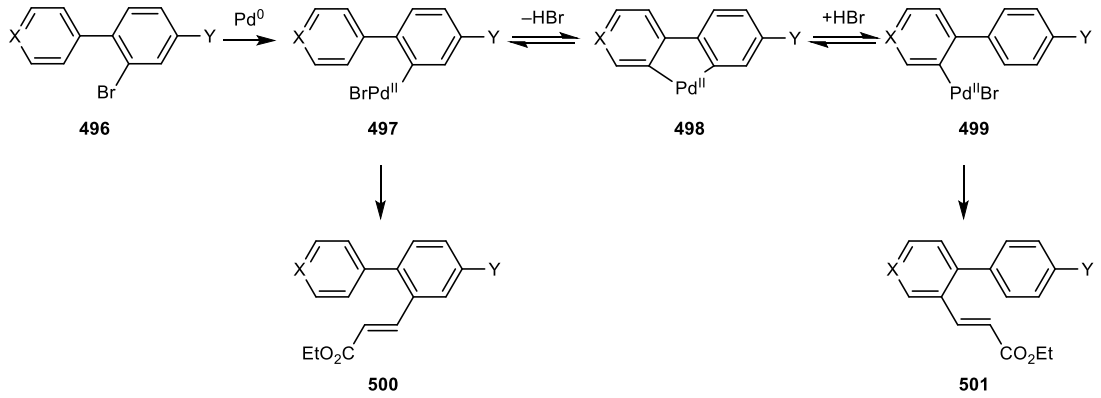
In the case of Gallagher's conditions, inferior regioselectivity towards the 1,4-migration product was achieved. The palladium catalyst system applied to aryl-pyridyl substituted structures and ethyl acrylate gave complete consumption of the starting materials. However, the main product isolated was always the expected Heck product **490**, **492** and **494** (Scheme 100).



Scheme 100: Palladium catalysed 1,4-migration/arylation process

Both authors proposed a similar mechanism (Scheme 101). Oxidative insertion of Pd(0) to the biaryl substrate gives intermediate **497**. This aryl Pd(II) species **497** is in equilibrium with aryl Pd(II) species **499** via a 1,4-migration process. It was proposed that the

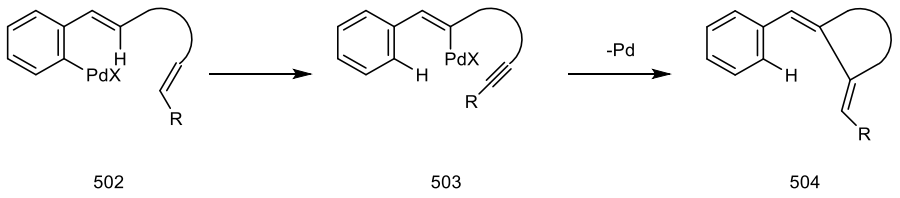
equilibrium between the two aryl-palladium species **497** and **499** determines the ratio between the Heck and the 1,4-product **500** and **501** respectively.



Scheme 101: Mechanism proposed for the palladium catalysed 1,4-migration/arylation

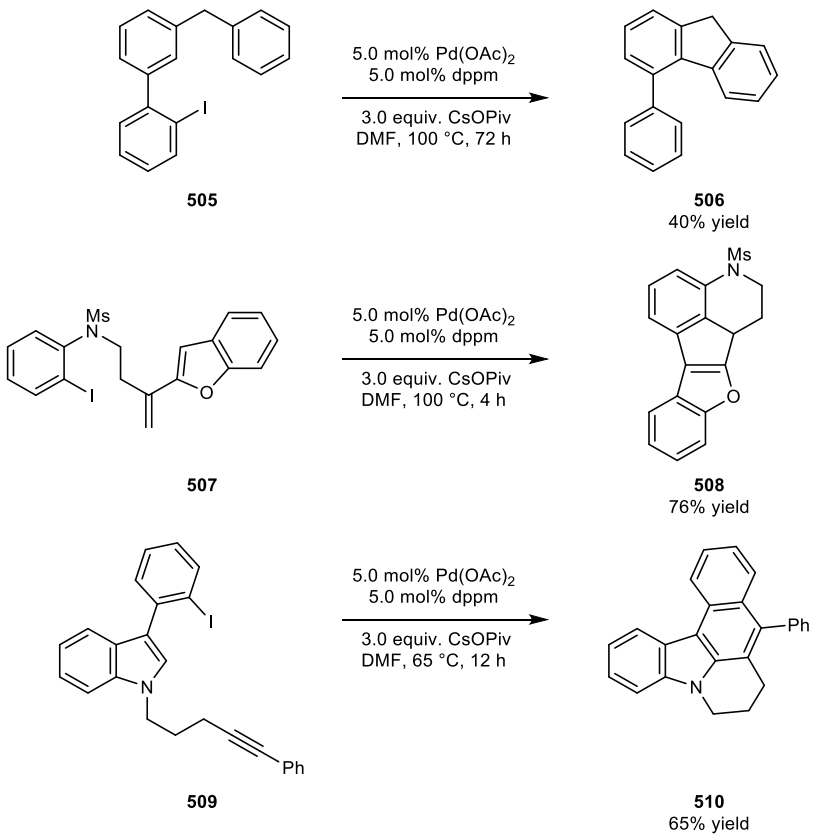
4.1.3. Palladium 1,4-Migration/Cyclisation

As described in the previous section, palladium can undergo 1,4-migration after the oxidative insertion with an aryl halide. After the 1,4-migration the palladium species created **503** could undergo intramolecular insertion with an appropriate tether, which would open an opportunity to synthesise complex cyclic structures **504** in one single step (Scheme 102).



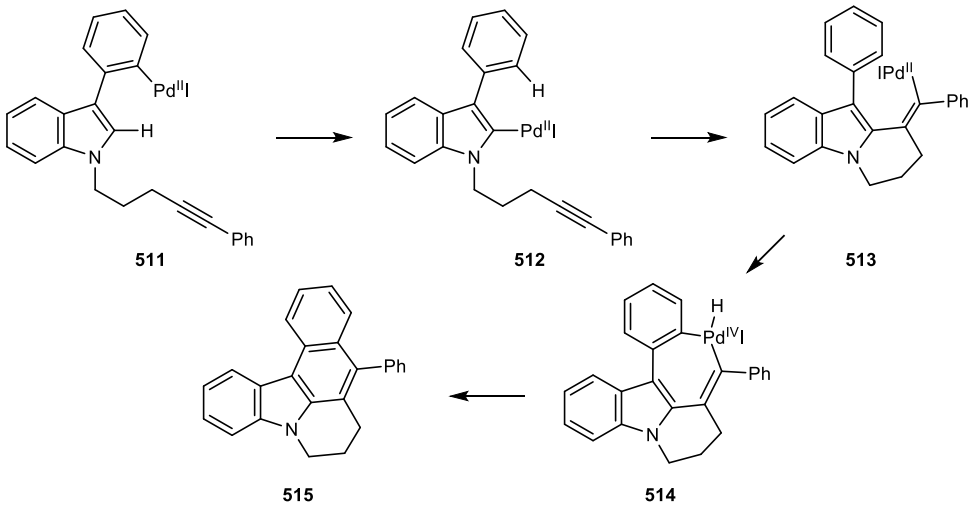
Scheme 102: Proposed mechanism for the 1,4-migration/cyclisation process

Larock's group investigated such a palladium catalysed cyclisation process. They reported the synthesis of multiple polycyclic structures using a 1,4-palladium migration *via* C-H activation of aryl groups (Scheme 103). Applying the conditions already described in chapter 3.1.1.2. (Scheme 99), various polycycles were synthesised in good yields (Scheme 103).[92]



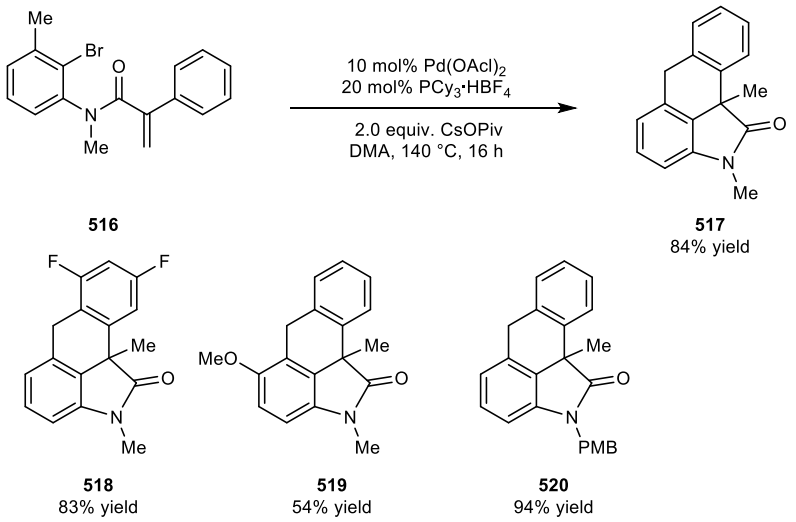
Scheme 103: Palladium catalysed 1,4-migration/cyclisation process

Larock suggested the reaction proceeded by initial oxidative addition of Pd(0) with aryliodide to give species **511** (Scheme 104). 1,4-Palladium migration occurs giving indole-palladium species **512**. Arylation to the pendant alkyne gives alkene palladium intermediate **513**. Finally a C-H activation would form palladacycle **514**, which after reductive elimination gives the observed product **515**.



Scheme 104: Mechanism proposed for the Palladium catalysed 1,4-migration/cyclisation

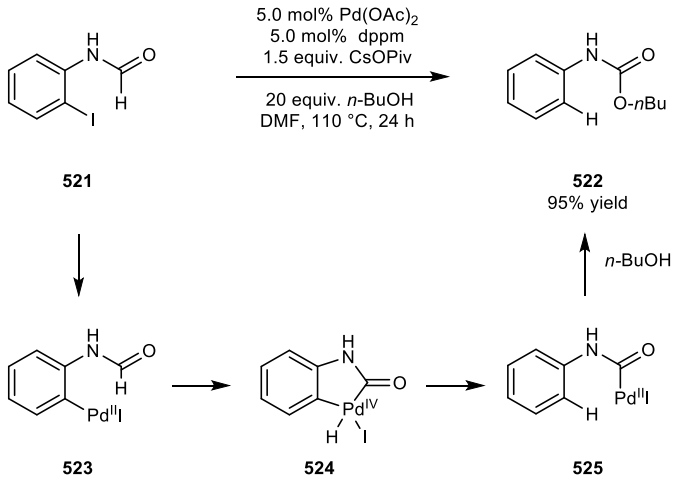
More recently, Zhu's group reported a nice example of a 1,4-palladium migration/cyclisation process towards the synthesis of fused oxindoles. Using $PCy_3 \cdot HBF_4$ as ligand and through a series of 1,4-palladium migrations and cyclometallations, complex oxindoles were isolated in very good yields (Scheme 105 and Chapter 1.1 Scheme 2).[16]



Scheme 105: Palladium catalysed 1,4-migration/cyclisation process

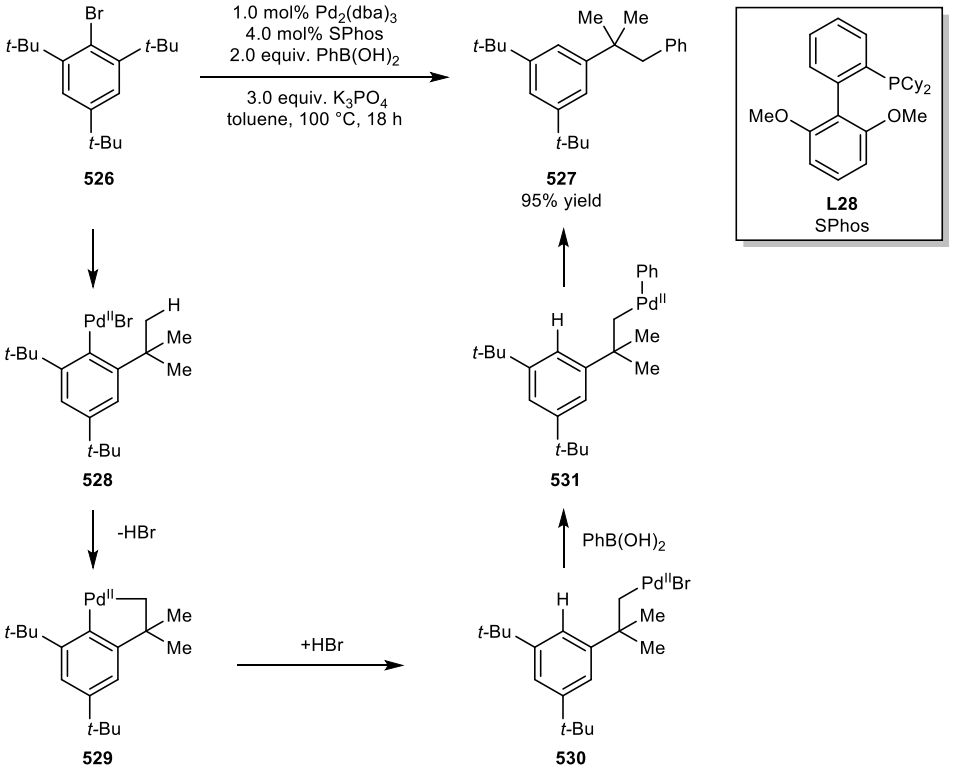
4.1.4. Other Domino Processes Involving Palladium 1,4-Migration

Many other reactions can be triggered by 1,4-palladium migration. For instance, Larock reported an acyl C-H activation *via* 1,4-migration of palladium to form carbamates and esters.[93] It was observed that in the presence of a palladium catalyst, formamide **521** reacts with *n*-BuOH to form carbamate **522**.[93] Larock proposed that, after palladium oxidative addition to formamide **521** to give aryl-palladium species **523**, acyl C-H insertion would form palladacycle **524** Finally, reductive elimination would give Pd(II) intermediate **525** which will be trapped by the alcohol to give carbamate **522** (Scheme 106).



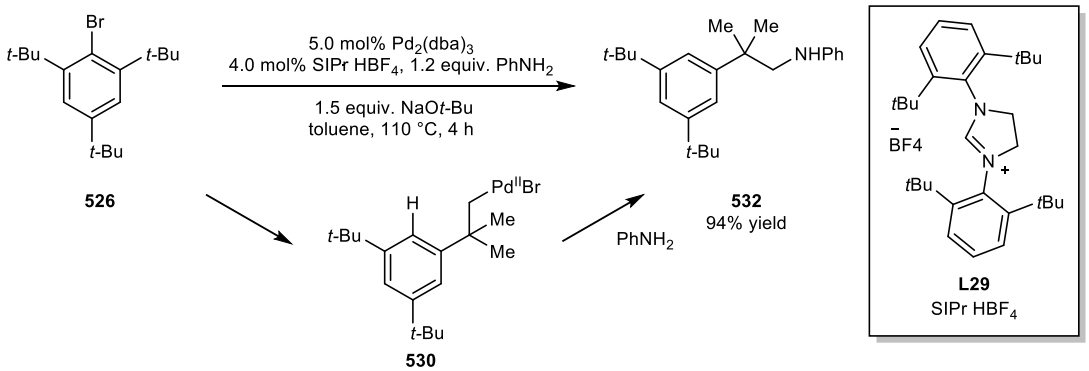
Scheme 106: Palladium catalysed C-H activation *via* 1,4-migration

In 2005, Buchwald reported a domino 1,4-migration/Suzuki-Miyaura coupling of 2,4,6-tri-*tert*-butylbromobenzene **526** with boronic acids (Scheme 107).[94] The mechanism proposed is as follows: after oxidative insertion of the Pd(0) to form aryl-palladium species **528**, C-H oxidative insertion followed by reductive elimination gives palladacycle **529**. Then, selective protonation of the less hindered sp^3 C-Pd bond in palladacycle **529** forms alkyl-palladium species **530**. Transmetalation with the boronic acid give intermediate **531** which, upon reductive elimination, forms the isolated structure **527**.



Scheme 107: Palladium catalysed 1,4-migration/Suzuki coupling process

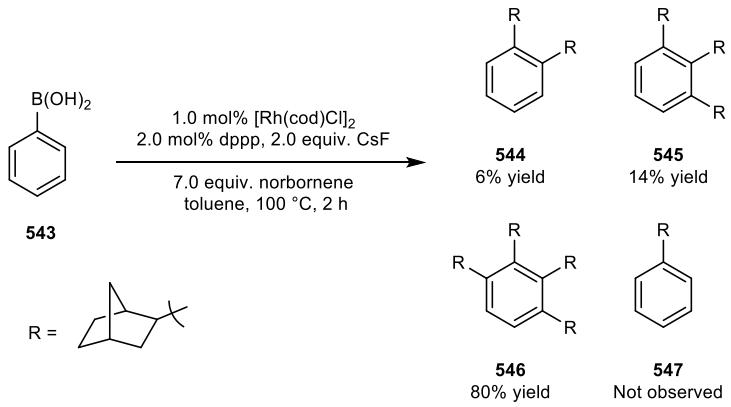
Similarly, Buchwald and co-workers reported a catalytic intermolecular amination of 2,4,6-tri-*tert*-butylbromobenzene *via* 1,4-palladium shift (Scheme 108).[95] They observed the formation of amine **532** when aryl bromide **526** was subjected to palladium catalysis in the presence of aniline. As described in Scheme 107, *tert*-butyl substituted phenyl rings under palladium catalysis form alkyl-palladium species **530** *via* oxidative insertion/1,4-migration. This species can then react with aniline to form the desired amine **532**.



Scheme 108: Palladium catalysed 1,4-migration/amination process

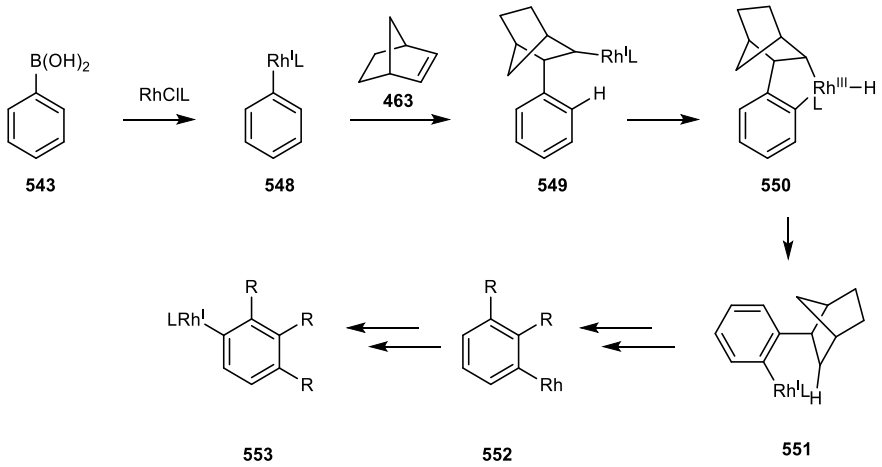
4.2. 1,4-Rhodium Migration

The first report of a 1,4-rhodium migration was by Miura and co-workers in 2000. The reaction between arylboronic acids and norbornene was reported.[96] However, instead of observing the expected arylative product **547**, they isolated a range of multi-alkylated phenyl rings **544**, **545** and **546**. (Scheme 109).



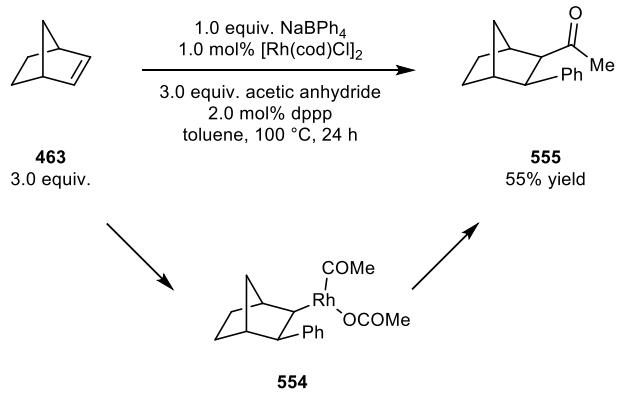
Scheme 109: Rhodium catalysed 1,4-migration/arylation process

Miura suggested that the formation of these multialkylated products came from a sequence of 1,4-rhodium migrations. It was proposed that norbornene **463** was first arylated to give alkylrhodium species **549**, then a first C-H activation event takes place to form rhodium metallacycle **550**. Reductive elimination then gives a new arylrhodium species **551**, ready to perform a second arylation to a second norbornene molecule. This process occurred up to three times to give tetrasubstituted structure **546** (Scheme 110).



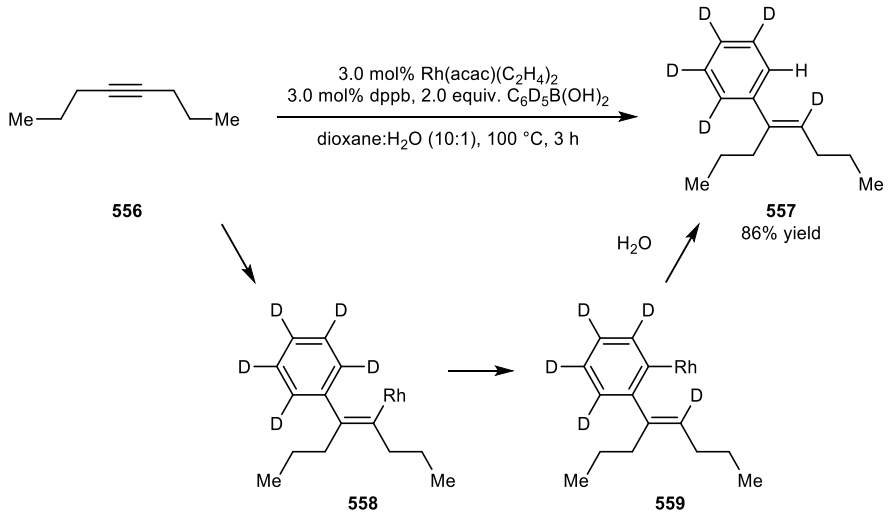
Scheme 110: Mechanism proposed for the Rhodium catalysed 1,4-migration/arylation

Miura's group found that if acetic anhydride was present in the reaction, the 1,4-migration was prevented, and gave disubstituted norbornane **555**. It was suggested that oxidative addition of rhodium species **549** (Scheme 110) to acetic anhydride would form Rh(III) intermediate **554** which was unable to undergo 1,4-migration (Scheme 111).[97]



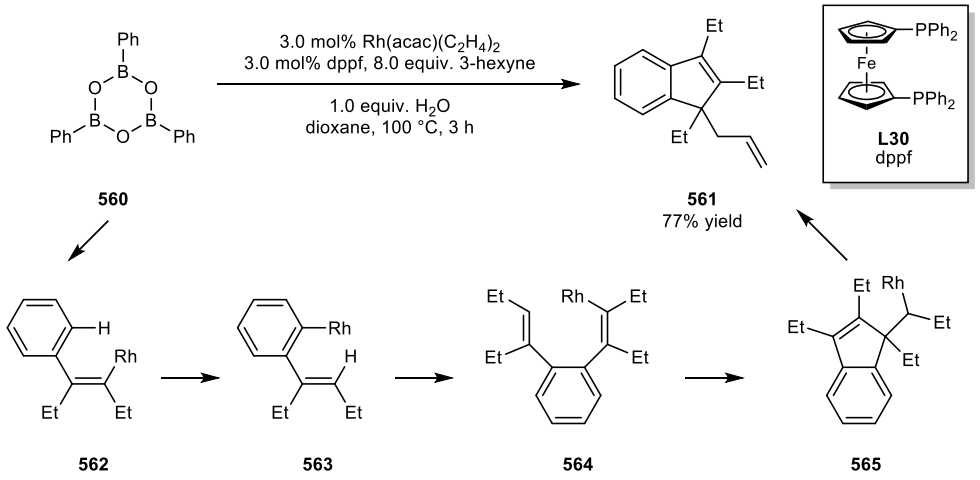
Scheme 111: Rhodium 1,4-migration process

Independently, Hayashi's group also reported a rhodium 1,4-migration process during the investigation into the addition of aryl boron species to alkynes. It was observed that if a deuterated phenyl boronic acid was added to alkyne **556**, alkene **557** was isolated with >93% of deuterium exchange. Hayashi proposed that after arylation to form alkenylrhodium species **558**, a 1,4-migration takes place. The new arylrhodium intermediate **559** formed would then be hydrolysed to form the observed product **557** (Scheme 112).[98]



Scheme 112: Deuterium experiments on Rh 1,4-migration process

The formation of substituted indene **561** from 3-hexyne and triphenylboroxine **560** under rhodium catalysis, also supported the 1,4-migration event proposed. Hayashi suggested the arylation of 3-hexyne to give alkenylrhodium species **562**. Then 1,4-migration gives arylrhodium intermediate **563**. This intermediate **563** would then attack another alkyne to form structure **564**. Then intramolecular carborhodation followed by reductive elimination gives intermediate **565**. Finally, β-hydride elimination followed by isomerisation of the double-bond forms the observed indene **561** (Scheme 113).



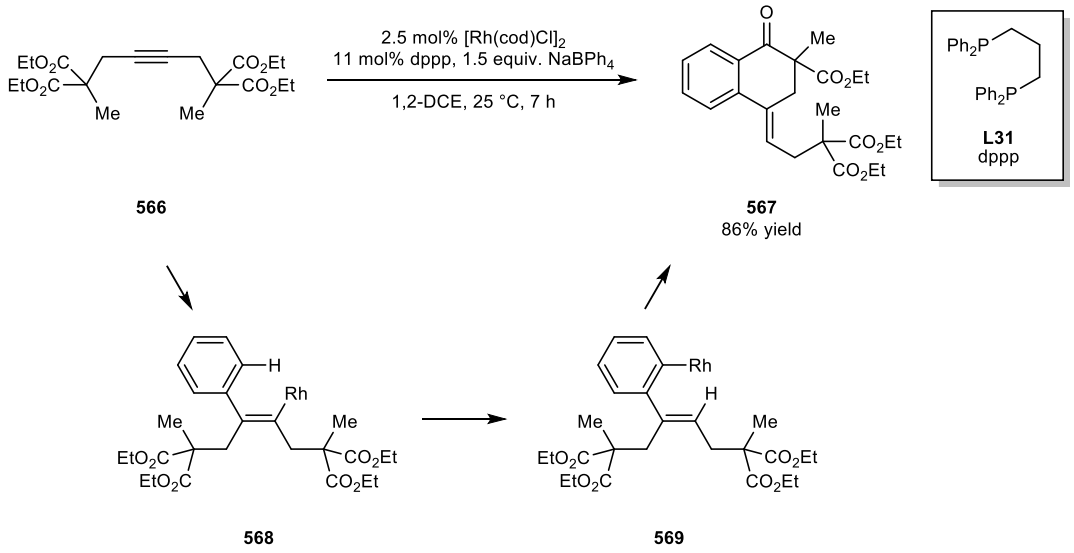
Scheme 113: Rhodium catalysed domino arylation/1,4-migration/cyclisation process

These seminal papers by Miura and Hayashi opened an alternative to palladium 1,4-migration. Since these reports, many other groups have used 1,4-rhodium migration in their methodology leading to a field which is now as developed as that of palladium 1,4-migration.

4.2.1. Rhodium Catalysed Arylation of Alkynes/1,4-Migration Domino Processes

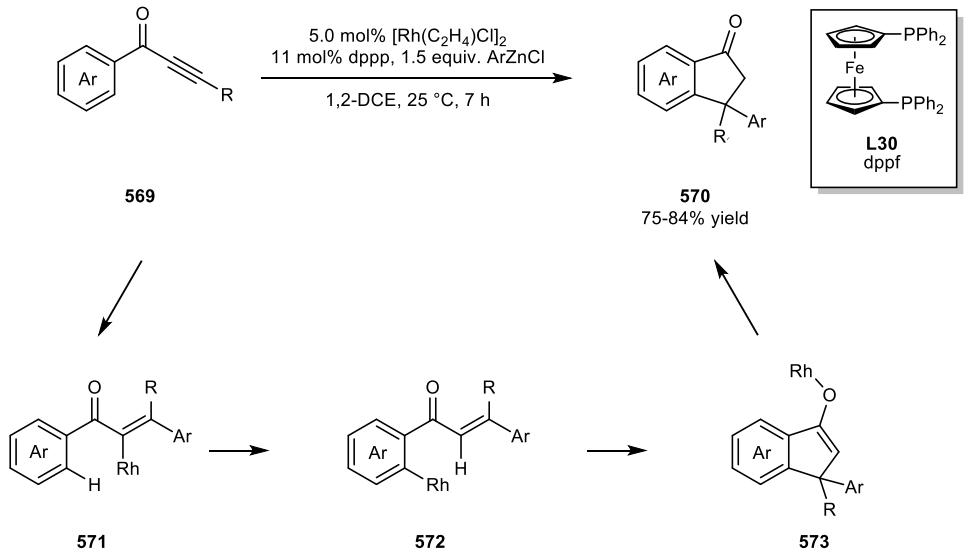
As described for palladium in the previous chapter, rhodium-catalysed arylation of alkynes generates alkenylrhodium species capable of performing 1,4-migration. Murakami's group described this process when $NaBPh_4$ was added to symmetrical alkynes **566**. Murakami suggested that after arylation to give alkenylrhodium species **568**, a 1,4-migration took place

forming arylrhodium intermediate **589**. Addition of the organorhodium to the pendant ester gave the observed tetralone **567** (Scheme 114).[85]



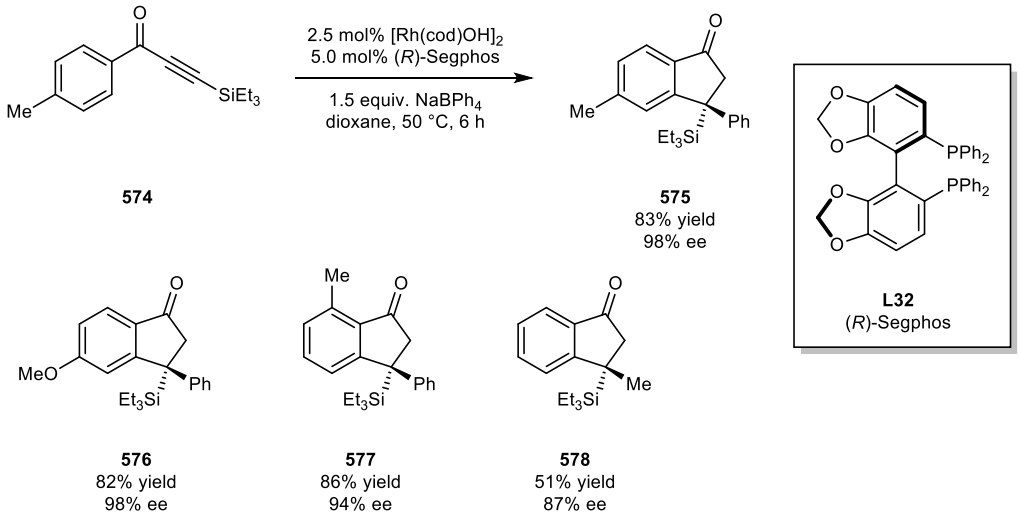
Scheme 114: Rhodium catalysed domino arylation/1,4-migration/cyclisation process

Similarly, Hayashi's group described the addition of arylzinc reagent to alkynyl-ketones **569** to give racemic β,β-disubstitued indanones **570**. Hayashi proposed that arylation of alkynone **569** would give alkenylrhodium species **571**. 1,4-Rhodium migration forms arylrhodium species **572** which undergoes intramolecular 1,4-addition to the α-β-unsaturated ketone to give the observed indanones **570** in moderate yields (Scheme 115).[99]



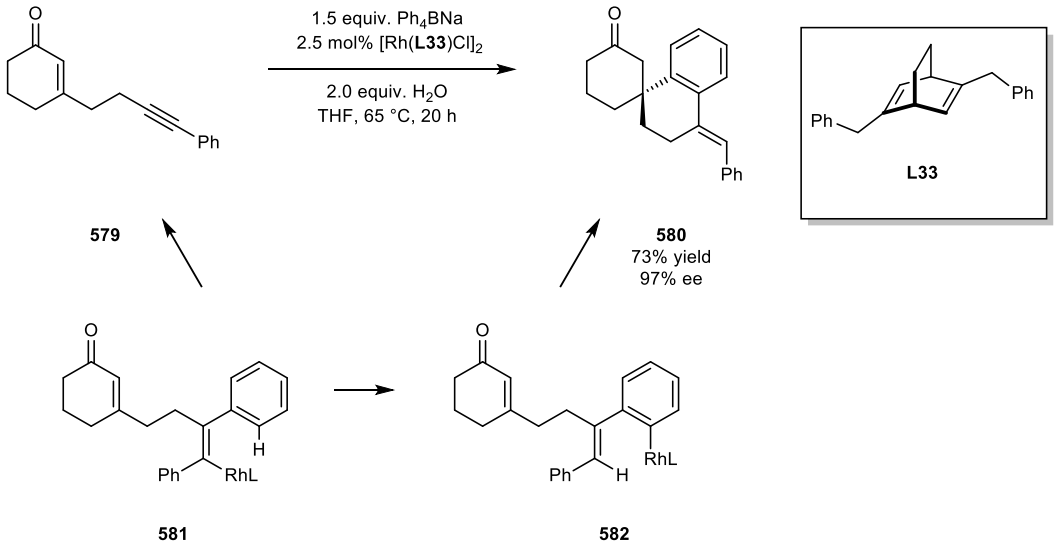
Scheme 115: Rhodium catalysed domino arylation/1,4-migration/cyclisation process

Following this investigation towards the synthesis of disubstituted indanones *via* rhodium catalysed arylative cyclisation, Hayashi and co-workers reported an asymmetric version of the reaction using rhodium ligated with (*R*)-Segphos (**L32**). The reaction of arylboronates, gave indanones of type **575** in high yields and enantiomeric excesses (Scheme 116).[100]



Scheme 116: Rhodium catalysed domino arylation/1,4-migration/cyclisation process

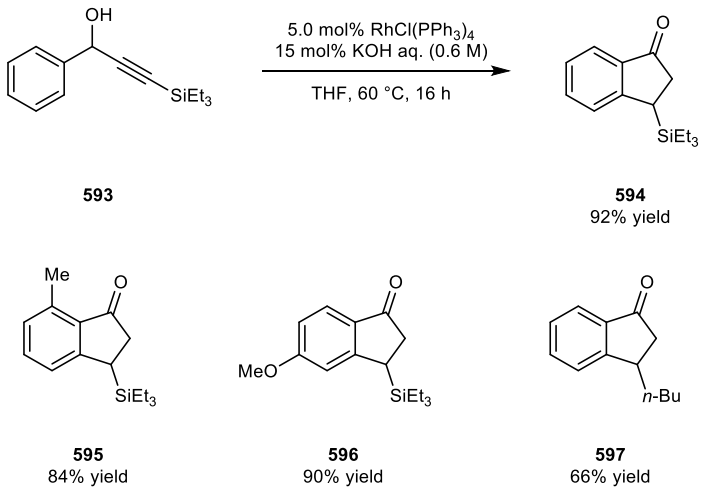
Applying similar conditions, Hayashi also reported the asymmetric synthesis of spirocarbocycles.[101] Using a rhodium catalyst ligated with chiral diene **L33**, a range of sodium tetraarylborates were reacted with alkyne **579** to give spyrocycles of type **580** in good yields and enantiomeric excesses (Scheme 121).



Scheme 117: Rhodium catalysed domino arylation/1,4-migration/cyclisation process

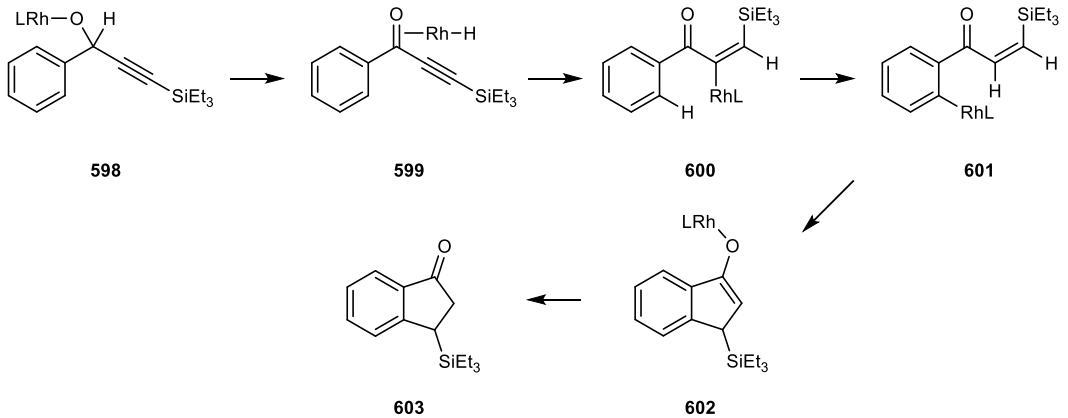
4.2.2. Rhodium 1,4-Migration/Cyclisation Processes

The 1,4-rhodium migration has also been applied to the formation of polycycles *via* intramolecular addition. Hayashi applied this to the synthesis of indanones.[102] It was observed that α-arylpropargyl alcohol **593** reacted in the presence of a rhodium catalyst to give indanone **594** in good yield (Scheme 118).



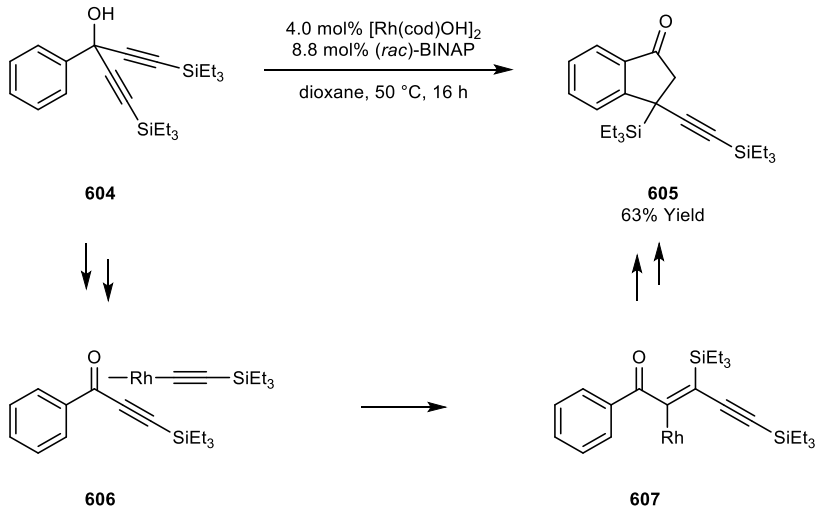
Scheme 118: Rhodium catalysed 1,4-migration/cyclisation process

Hayashi suggested that after rhodium insertion to the O-H bond of the alcohol, β-hydride elimination gives ketone **599**. Hydrorhodation forms alkenylrhodium species **600**, which could undergo 1,4-rhodium migration to give arylrhodium intermediate **601**. Intramolecular 1,4-addition of arylrhodium **601** to the α,β-unsaturated ketone and hydrolysis of the rhodium enolate **602** then gives the observed indanone **603** (Scheme 119).



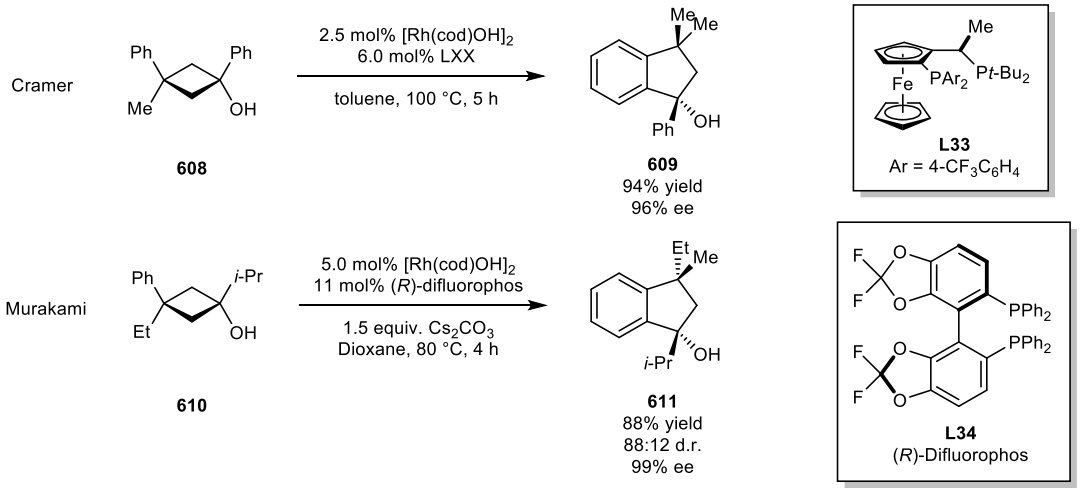
Scheme 119: Mechanism proposed for the Rhodium catalysed 1,4-migration/cyclisation

An analogous reaction of symmetrical bis(alkynyl) carbinols **604** was also reported by Hayashi.[103] In this case the key step of the process is a β-carbon elimination to give intermediate **606**. This intermediate would undergo alkynylrhodation to form alkenylrhodium species **607**. This species would then follow the mechanism proposed previously by Hayashi (Scheme 119) to form the observed indanones (Scheme 120).



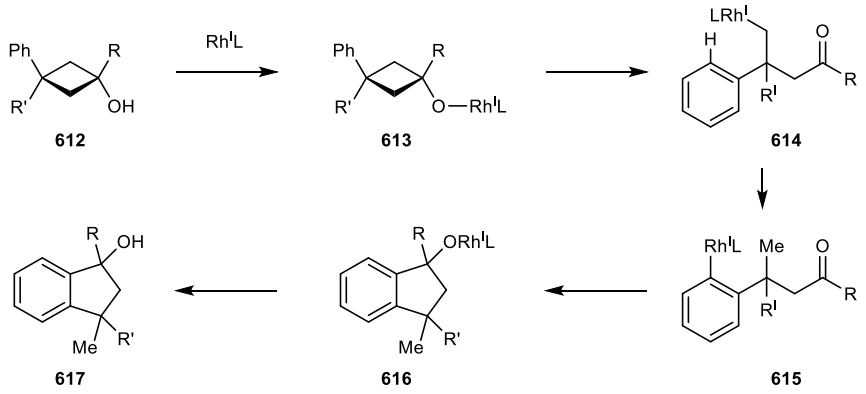
Scheme 120: Rhodium catalysed 1,4-migration/cyclisation process

Similarly, Cramer and Murakami reacted aryl-substituted cyclobutanol **608** and **610** with a rhodium catalyst and observed the formation of indanols **609** and **610** (Scheme 121).[104] A wide range of ligands were applied by both groups achieving the best results when a Josiphos type **L33** and (*R*)-difluorophos **L34** were applied respectively.



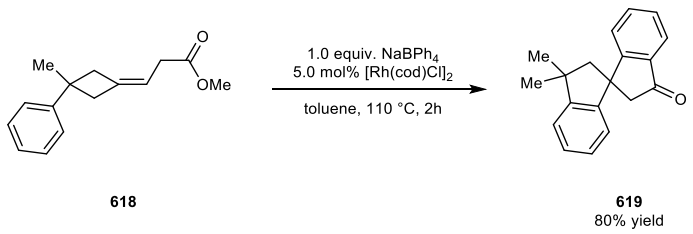
Scheme 121: Rhodium catalysed 1,4-migration/cyclisation process

Both Cramer and Murakami suggested similar mechanisms. The reaction mechanism is initiated by the formation of rhodium-alkoxide **613** from alcohol **612**. Ring opening of the cyclobutane through β-carbon-elimination of the alkoxide **613** gives alkylrhodium species **614**. 1,4-Rhodium migration gives arylrhodium species **615** which undergoes intramolecular addition to the carbonyl group to give the observed indanol **617** (Scheme 122).



Scheme 122: Mechanism proposed for the Rhodium catalysed 1,4-migration/cyclisation

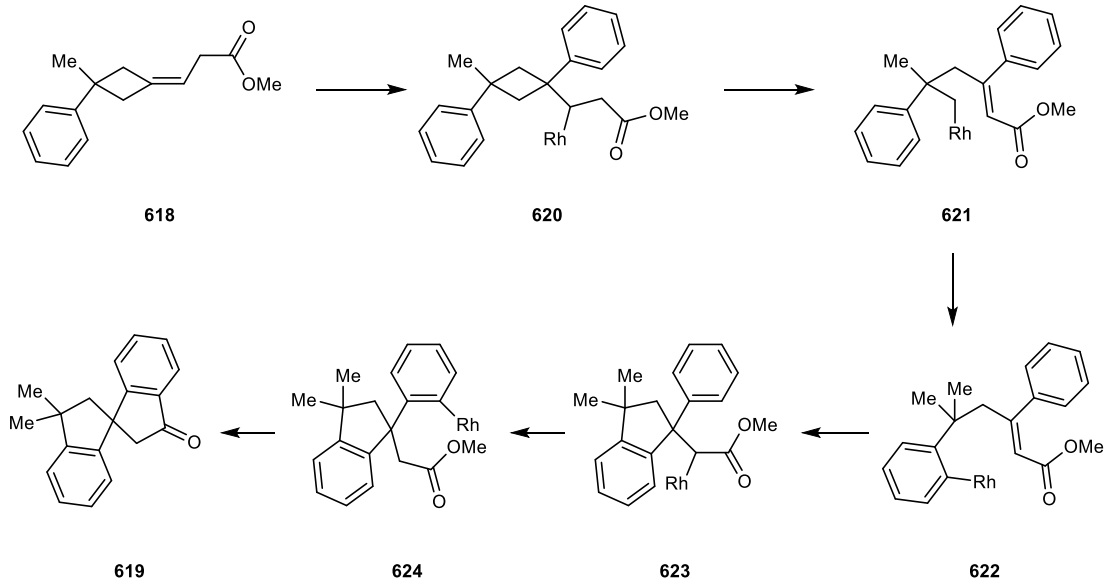
More recently Takahashi reported the arylation/1,4-migration/cyclisation of (3-arylcyclobutylidene)acetates **618** by rhodium-catalysis to form spiro-ketone **619** (Scheme 123).[105]



Scheme 123: Rhodium catalysed 1,4-migration/cyclisation process

Interesting, in this process two 1,4-migration processes are needed to form the observed tetracyclic structure **619**. Takahashi proposed that, after arylation of the double bond to form alkylrhodium species **620**, ring opening of the cyclobutane through a β-carbon elimination gives β-phenethylrhodium intermediate **621**. 1,4-Migration then occurs to give arylrhodium species **622**, which undergoes intramolecular conjugate addition to form alkylrhodium intermediate **623**. A second 1,4-rhodium migration from the alkyl to the aryl ring gives

arylrhodium species **624**. This then undergoes 1,2-addition to the ester to give spiro-ketone **619** (Scheme 124).

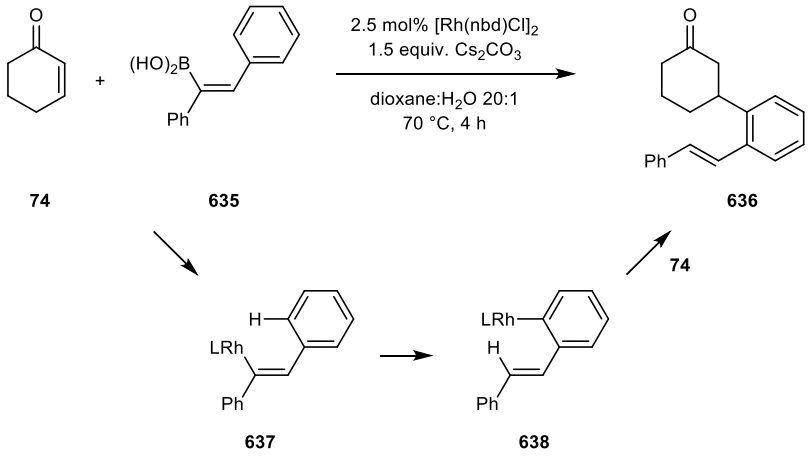


Scheme 124: Mechanism proposed for the Rhodium catalysed 1,4-migration/cyclisation

4.2.3. Recent Developments in Domino Processes Involving Rhodium 1,4-Migrations

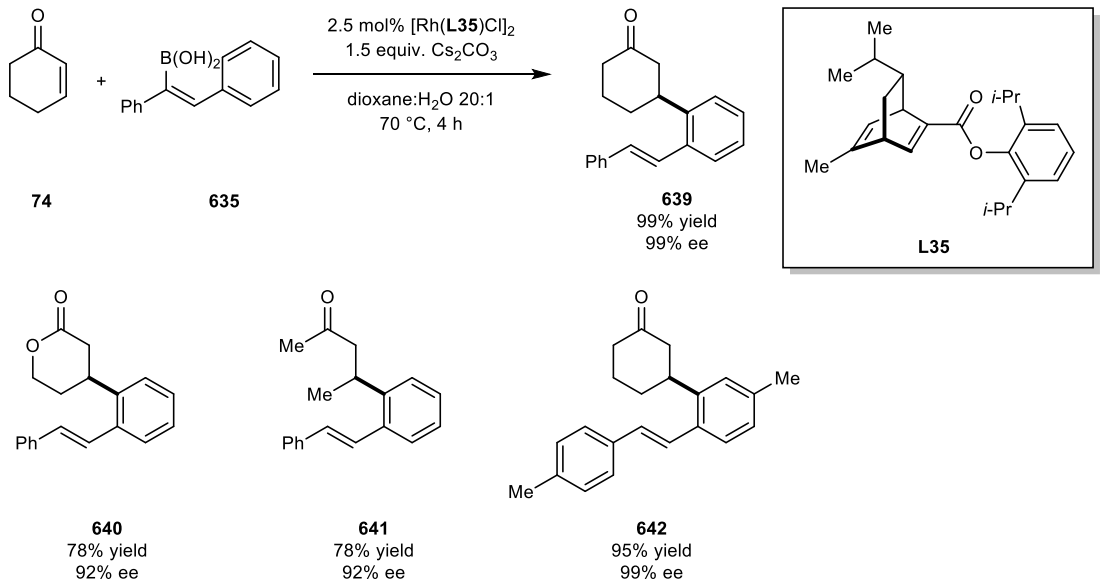
The use of rhodium to carry out 1,4-migration transformations is still a topic of great interest. Recently many groups have reported new reactions where rhodium performs domino processes, including 1,4-migrations, to synthesise complex structures.

In 2012 Hayashi and Kantchev reported a domino 1,4-migration/1,4-addition of diphenylethenylboronic acid to enones.[106] It was proposed that, after transmetallation of rhodium with boronic acid **635**, a 1,4-rhodium migration occurred to give arylrhodium species **638**. Finally, 1,4-addition of this arylrhodium species to enone **74** gave product **636** (Scheme 125).



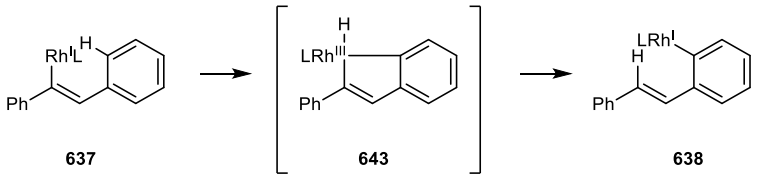
Scheme 125: Rhodium catalysed 1,4-migration/arylation process

By replacing the norbornadiene ligand with a chiral diene **L35** the asymmetric tandem 1,4-migration/1,4-addition of *cis*-2-arylethenylboronic acids **635** to both cyclic and acyclic enones in good yield and high enantiomeric excesses was achieved (Scheme 126).[107]



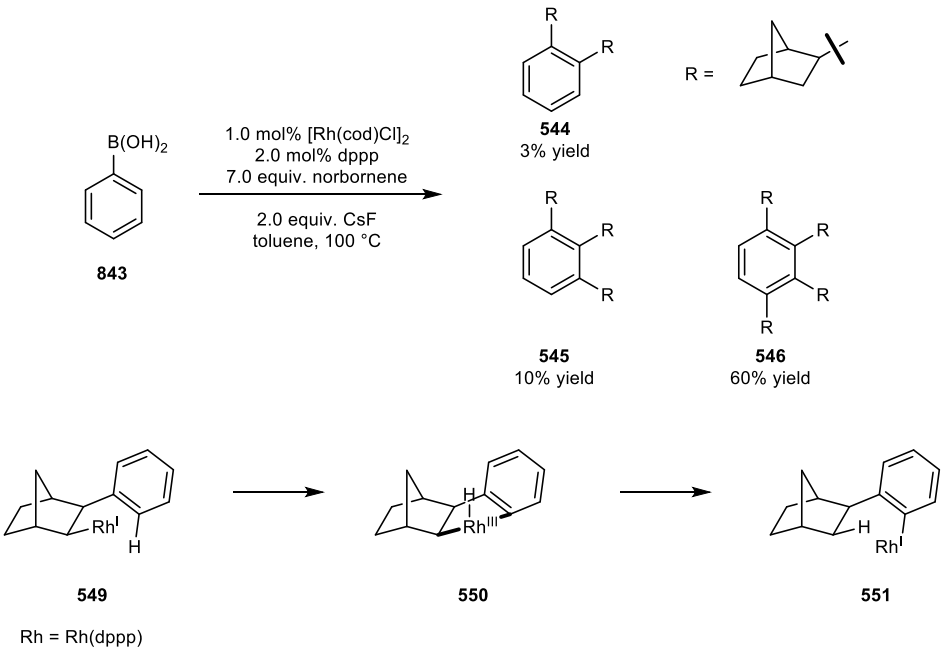
Scheme 126: Asymmetric Rhodium catalysed 1,4-migration/arylation process

Kantchev performed DFT calculations for the above process and proposed an oxidative insertion/reductive elimination mechanism was in operation. The formation of an unstable Rh(III) **643** species as an intermediate between the alkenylrhodium **637** and the arylrhodium species **638** was suggested (Scheme 127).



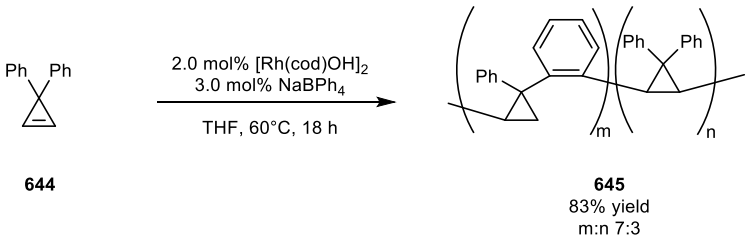
Scheme 127: Rh^{III} intermediate proposed for the the 1,4-migration process

Recent investigations by Kantchev and Su reported the formation of a similar intermediate in the C-H activation by domino 1,2-addition/1,4-rhodium migration of phenyl boronic acid to norbornene (Scheme 128).[108] The DFT calculations supported that the transition between alkylrhodium **549** and arylrhodium **551** occurred via a Rh(III) species **550**. It was also suggested that the higher barrier energy of the protonolysis of alkylrhodium **549** (20.9 kCal mol^{-1}) compared to the protonolysis of arylrhodium **551** (16.7 kCal mol^{-1}) drives the equilibrium toward the formation of arylrhodium species **551**.



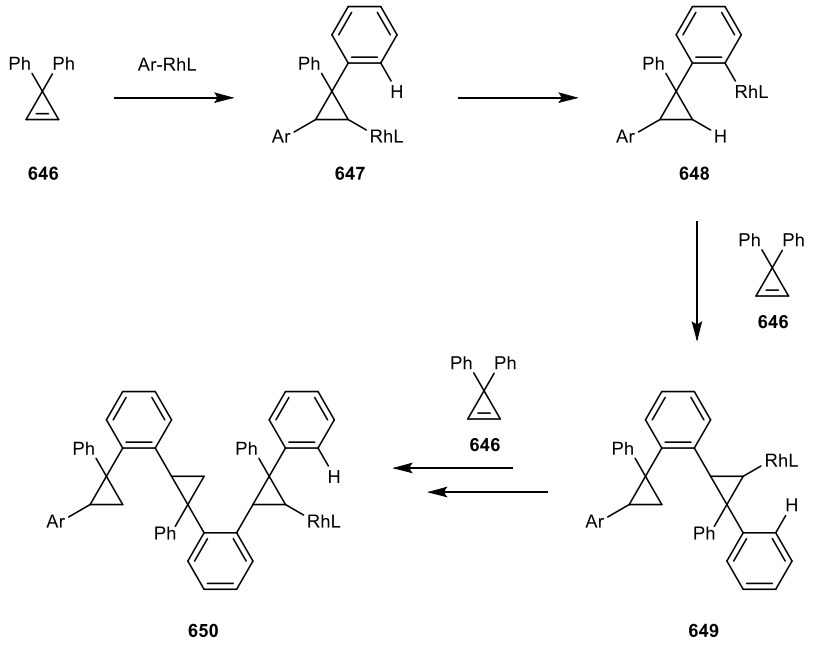
Scheme 128: Mechanism proposed for the Rh catalysed 1,4-migration process

Another recent example of 1,4-rhodium migration was described by Nozaki's group in 2014. They reported the polymerization of 3,3-diarylcyclopropenes **644** through a rhodium catalysed continuous arylation-1,4-migration process. The use of different boronic acids as initiators and a variety of ligands such as cod, (*rac*)-BINAP or nbd allowed the synthesis of polymers from 900 to 7900 g/mol (Scheme 129).[109]



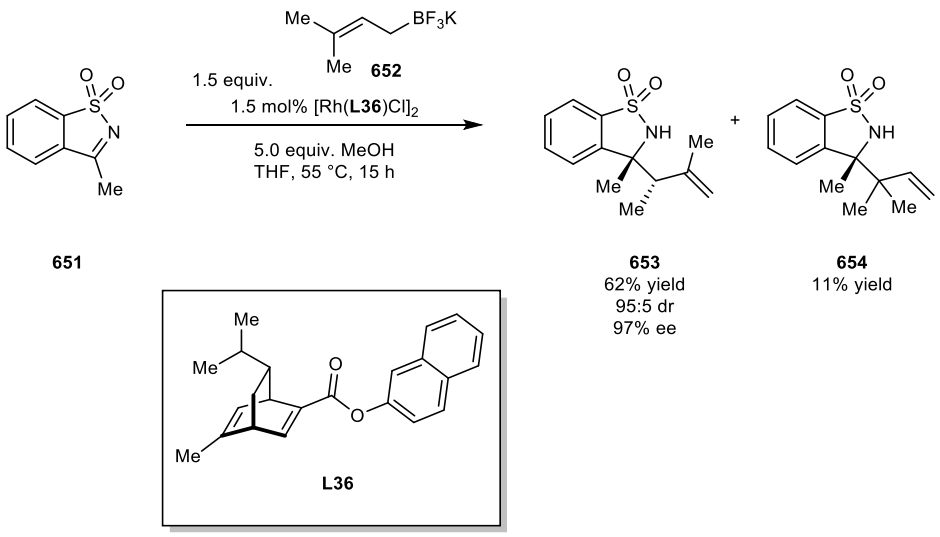
Scheme 129: Polimer synthesis *via* Rhodium 1,4-migration

The proposed mechanism starts with the arylation of cyclopropene **646** to give alkylrhodium intermediate **647**. 1,4-Rhodium migration from the alkyl to the aryl position gives arylrhodium **648**, which undergoes arylation to another cyclopropene substrate **646**. Sequential 1,4-rhodium migration and arylation then gives different polymers depending on the ligand and the initiator used (Scheme 130).



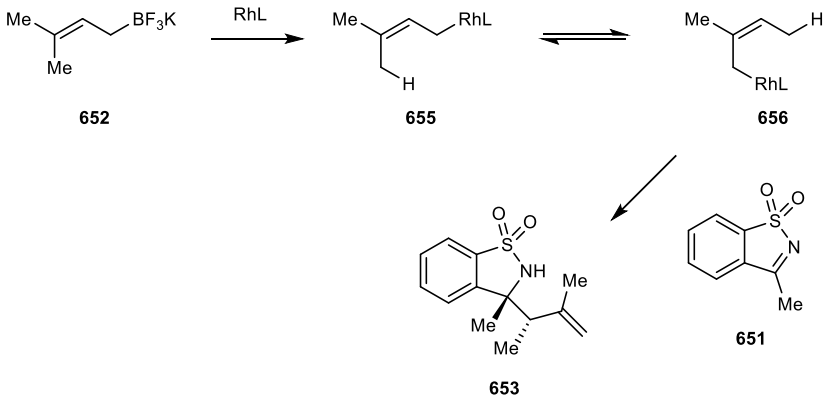
Scheme 130: Mechanism proposed for the Rh catalysed synthesis of polimers

Very recently, the Lam group demonstrated two new process involving a rhodium 1,4-migration. In 2012, the enantioselective rhodium-catalysed allylation of imines was reported.[110] During these investigations, when allyltrifluoroborate salt **652** was used in the reaction, the formation of sulfonamide **653** as well as the expected allylation product **654** was observed. Using a diene ligand **L36** the synthesis of various cyclic sulfonamides in good yields and high enantiomeric excesses was achieved (Scheme 131).[111]



Scheme 131: Rhodium catalysed allylation of imines *via* 1,4-migration

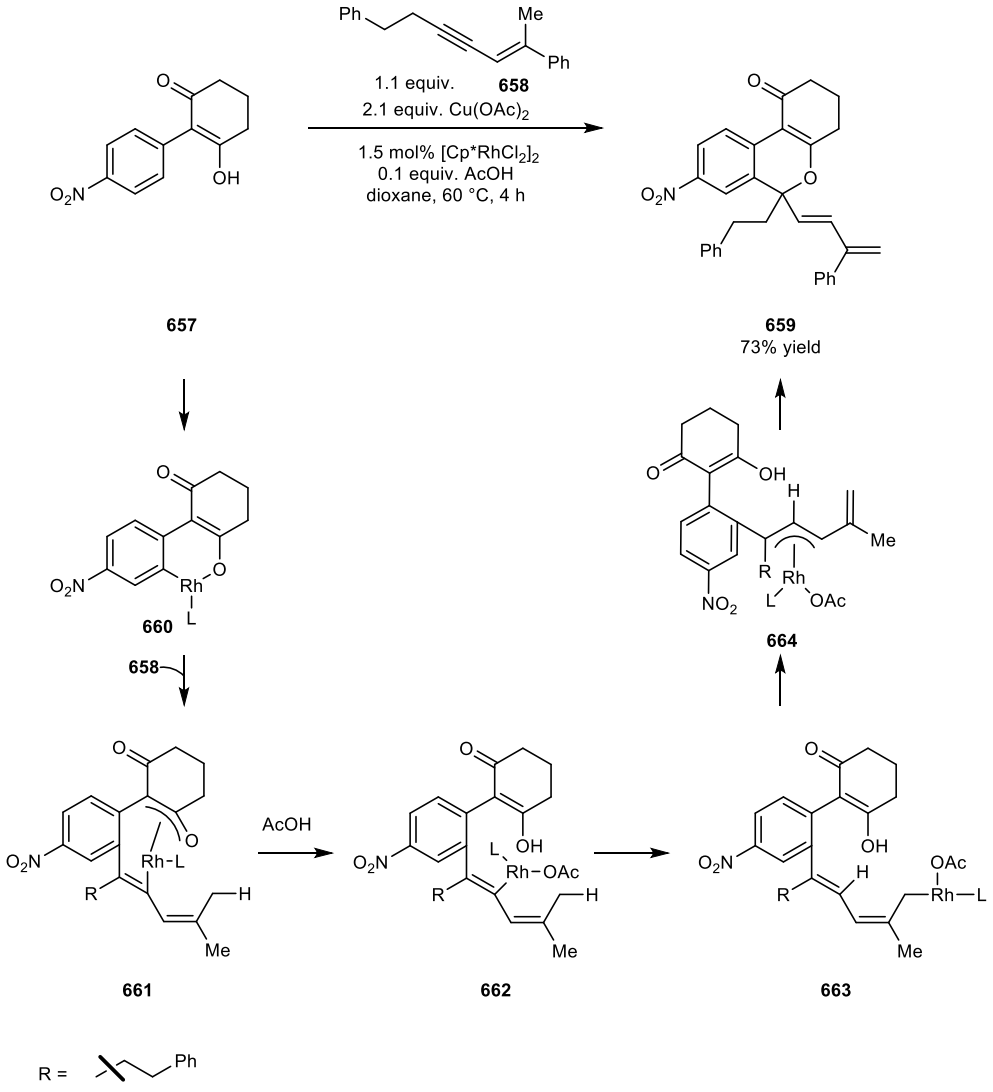
It was proposed that first the allyltrifluroborate **652** transmetalates with rhodium to give allylrhodium species **653**. Then a reversible 1,4-migration process takes places to give allylrhodium species **654**. Finally, reaction of this allylrhodium species **654** with imine **651** would give sulfonamide **653** (Scheme 132).



Scheme 132: Mechanism proposed for the Rh catalysed allylation of iminies

In 2014, Lam reported in a second paper on the topic of rhodium 1,4-migration processes. Through the investigation of the C-H activation/oxidative annulation of 2-aryl cyclic 1,3-dicarbonyl compounds **657** with enyne **658**, the formation of tricyclic compound **659** was observed.[112] It was suggested that nucleophilic arylrhodium(III) species **660**, formed *via* C-H activation, gives intermediate **661** *via* migratory insertion into enyne **658**. Then, protonolysis gives alkenylrhodium species **662** that undergoes a sp^2-sp^3 1,4-migration to

form allyl-rhodium **663**. Isomerisation to form electrophilic π-allylrhodium species **664** followed by nucleophilic attack of the enol gives the observed product **659** (Scheme 133).



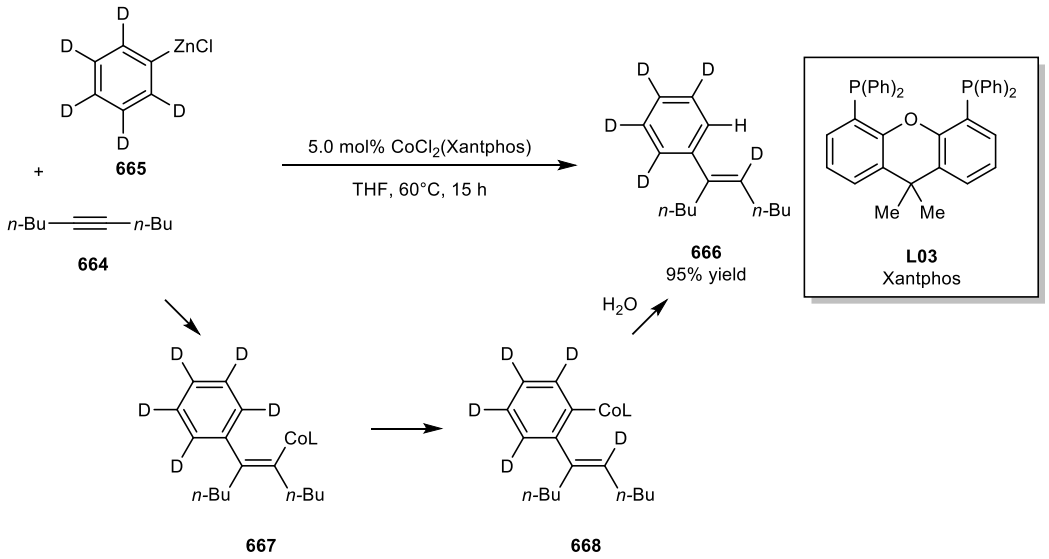
Scheme 133: Rhodium catalysed C-H activation/1,4-migration process

4.3. 1,4-Migration Catalysed by Other Transition Metals

As shown previously in chapter 3.1. and 3.2, rhodium and palladium are very effective catalysts for 1,4-migration processes. Other metals such as cobalt, nickel, platinum or iridium have also been shown to undergo 1,4-migration.

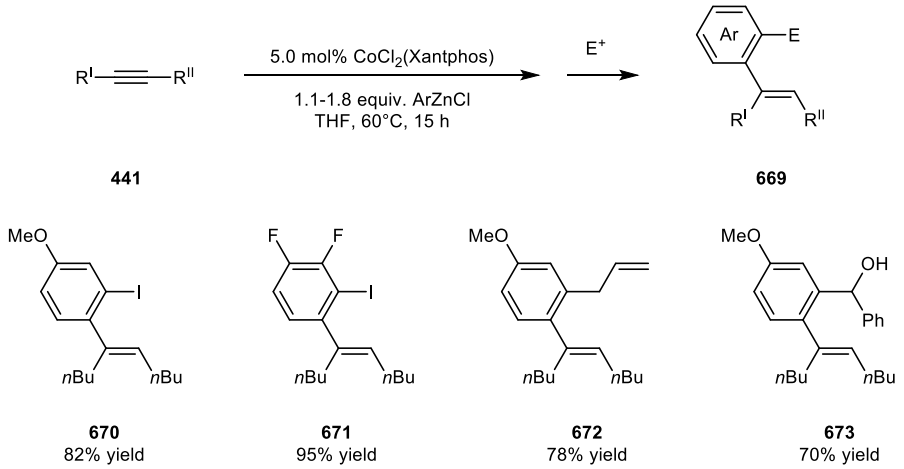
Cobalt has been used by Yoshikai to perform the addition of arylzinc reagents to alkynes (Scheme 134).[113] Similar to Hayashi's rhodium arylation/1,4-migration (Chapter 3.2.,

Scheme 117), Yoshikai reported that, when reacting a deuterated phenylzinc reagent **665** with alkyne **664** under cobalt catalysis, alkene **666** was isolated with exclusive deuterium incorporation at the olefinic position. This suggested that, after arylation to form alkenyl-cobalt species **667**, 1,4-migration gives arylcobalt species **668**, which upon aqueous work up gives alkene **666**.[113a]



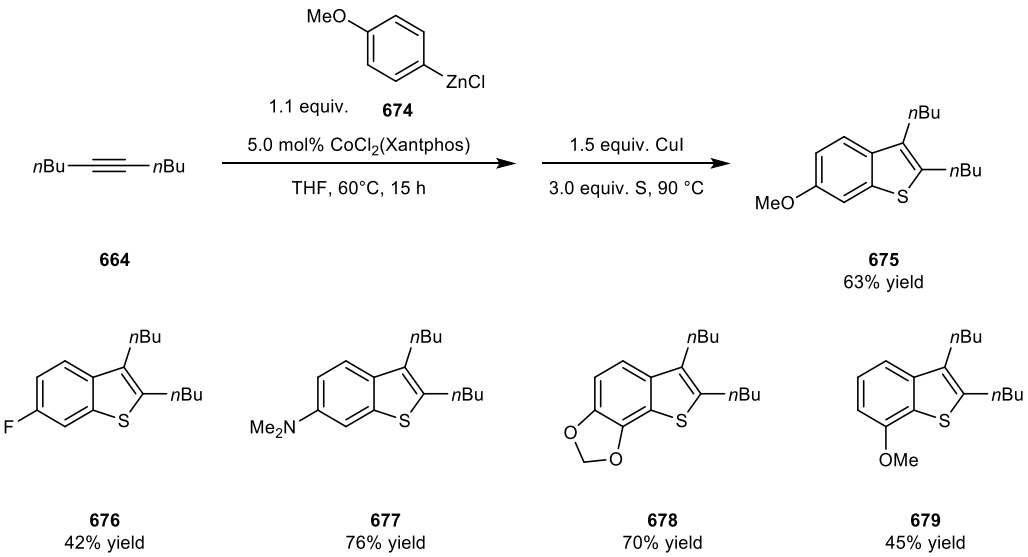
Scheme 134: Cobalt catalysed domino arylation/1,4-migration process

Yoshikai used these conditions, introducing an electrophile to trap the nucleophilic arylcobalt species **668** (created after the 1,4-migration process Scheme 134) to give a range of disubstitued aryl compounds **669** (Scheme 135).



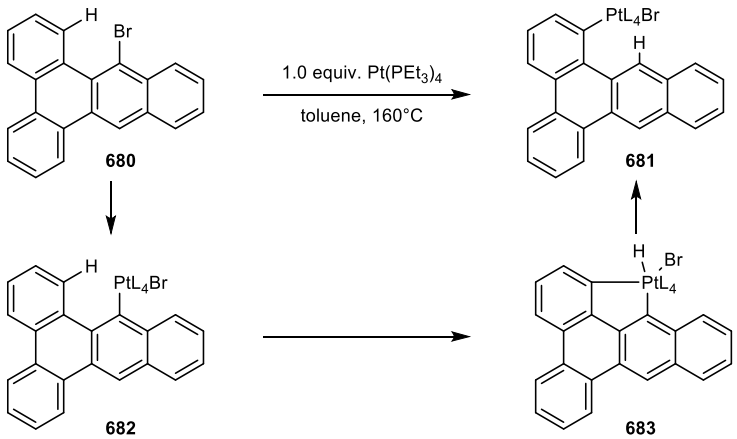
Scheme 135: Cobalt catalysed domino arylation/1,4-migration process

Yoshikai and co-workers observed that if the electrophile used to trap the arylcobalt species **668** (Scheme 134) was sulphur in the presence of CuI, benzothiophenes **675-679** were isolated (Scheme 136). Using this one-pot method, a wide range of substituted benzothiophenes were synthesised in moderate yields.[113b]



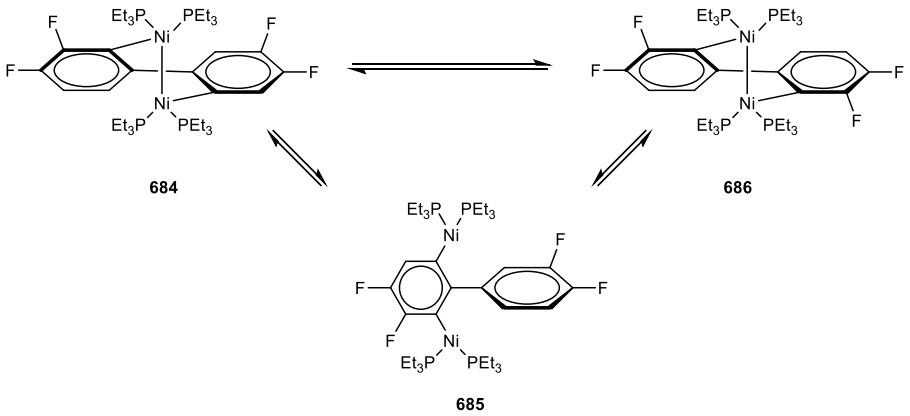
Scheme 136: Cobalt catalysed domino arylation/1,4-migration process

Other metals have been described to undergo a 1,4-shift, but no synthetic applications have been developed using those metals. Sharp's group reported the 1,4-migration of a platinum complex through the reaction of $Pt(PEt_3)_4$ with 9-bromodibenz[a,c]anthracene **680**. After initial oxidative addition to form Pt(II) species **682** 1,4-migration occurred to give **681** which was isolated and characterised (Scheme 137).[114]



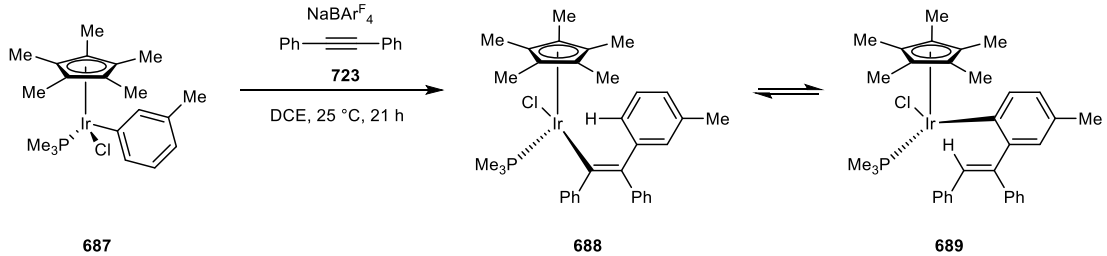
Scheme 137: Platinum catalysed 1,4-migration process

In 2007, Johnson reported the 1,4-migration of nickel through heating biarylyl complex **684**. It was suggested that the isomerisation between complex **684** and complex **686** occurred through the formation of intermediate **685**, which involves the 1,4-migration of nickel between aryl positions (Scheme 138).[115]



Scheme 138: Nickel catalysed 1,4-migration process

More recently, in 2014, iridium 1,4-migration was reported but not applied in any synthetic methodology. Ishii *et al.* observed that in the presence of diphenyl acetylene **723**, Ir(III) complex **687** reacted to give a mixture of two different species (Observed by ^{31}P NMR); alkenyliridium complex **688** and an aryliridium complex **689** (Scheme 139). After arylation of the alkyne to give alkenyliridium species **688**, it was suggested that aryliridium species **689** would presumably be formed by a 1,4-iridium migration process.[116]



Scheme 139: Iridium catalysed 1,4-migration process

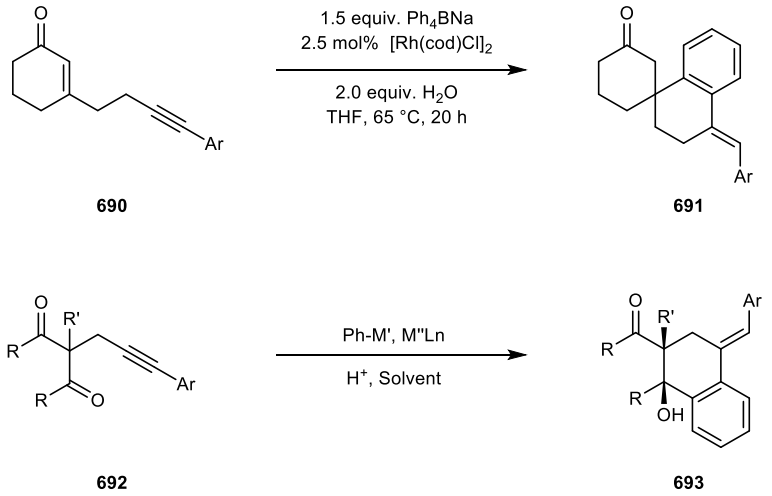
Transition metal-catalysed 1,4-migrations has been widely applied into domino processes to synthesised complex structures. Rh and Pd are usually the metals of choice to catalyse this process. Other metals have been reported to undergo 1,4-migration but only cobalt has shown synthetic applications.

5. Arylative Cyclisation Via a 1,4-Iridium Migration

5.1. Aims and Objectives

In chapter 3.1 the versatility of transition metals to catalysed domino arylation-cyclisation processes involving a 1,4-shift of the catalyst was reviewed.

With our previous experience in the desymmetrisation of diones,[1] it was suggested that a process similar to Hayashi's Rhodium-catalysed asymmetric synthesis of spirocarbocycles (Chapter 3.1.2., Scheme 117) could be investigated. In this case the electrophile would be a symmetrical diketone **692** instead of a prochiral α-β unsaturated ketone **690** (Scheme 140).

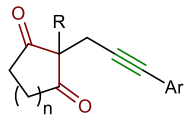


Scheme 140: Proposed arylation/1,4-migration/aldol cyclisation process

The aim was to design a substrate where we could carry out the process, identify a metal to perform the reaction and a ligand to control both absolute and relative stereochemistry.

5.2. Arylation-Cyclisation of Alkynyl-Diones

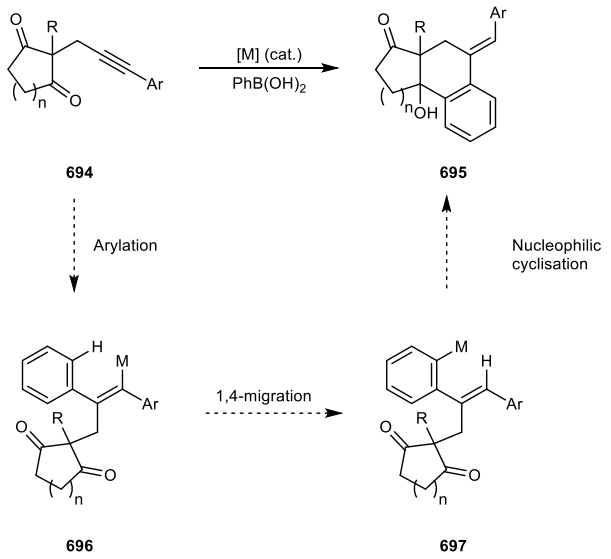
Due to our success in the desymmetrisation of 1,3-cyclopentadiones and 1,3-cyclohexadiones in previous projects,[1] symmetric alkyndiones **694** were proposed as possible substrate for our investigations. These particular substrates would have the two motifs needed for our proposed arylation-cyclisation process; an alkyne that can be arylated, and a ketone that would be able to accept a nucleophilic addition.



694

Figure 3

The mechanism proposed for the synthesise of polycyclic alcohol **695** was to first perform an aryl metallation of alkyne **694** to give intermediate **696**. 1,4-metal migration from the alkenyl position to and aryl position would give species **697**. Finally, intramolecular addition by the aryl-metal to the ketone, followed by protonation, would afford polycyclic alcohol **695**. In this manner, with the adequate metal complex, we would be able to functionalise a remote C-H bond *via* a 1,4-migration process. (Scheme 141).



Scheme 141: Mechanism for the proposed arylation/1,4-migration/aldol cyclisation process

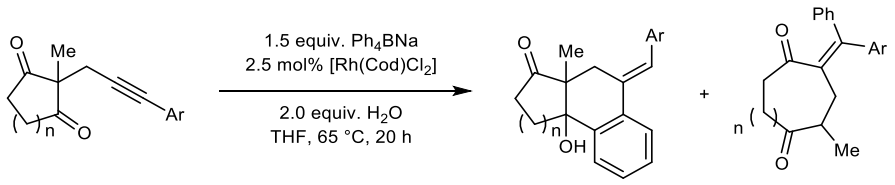
This C-H activation would lead to the formation of complex polycyclic alcohols **695**, hopefully, with high levels of diastero and enantioselectivity.

5.3. Identifying a Metal Catalyst

As described in Chapter 3.1.2, Rh(I) complexes are capable of perform arylation of alkynes as well as 1,4-migration processes. Taking Hayashi's synthesis of chiral spirocarbocycles through arylative-cyclisation as inspiration (Chapter 3.1.2., Scheme 117).[101] It was proposed to use Rh(I) catalysts as a starting point for our investigations.

Four different alkynes **694** were subjected to react with sodium tetraphenyl borate in the presence of $[Rh(cod)Cl]_2$ and water in THF. After 16 hours at 65 °C the alkyne was completely consumed and two new products were detected **695** and **698**. For each of the alkynes the desired cyclised product **695** was isolated in moderate yield and as a single diastereoisomer, as determined by ^1H NMR spectroscopy of the crude reaction mixture. A second product **698** was also isolated with a lower yield. The remainder of the mass balance was a complex mixture (Table 4).

Table 4: Rhodium arylative-cyclisation



694
n = 1,2

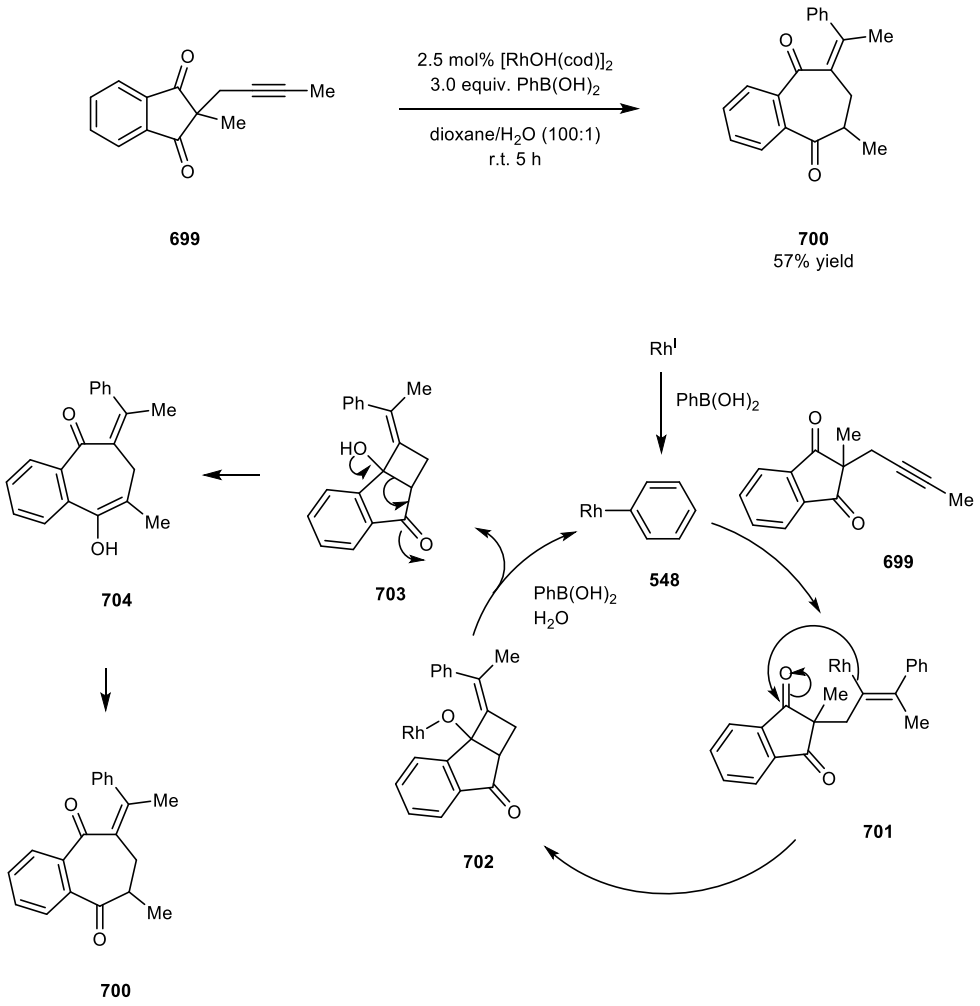
695

698

Entry	n	Ar	Yield of 695	Yield of 698
1	1	4-$MeOC_6H_4$	38%	11%
2	1	phenyl	42%	12%
3	2	4-$MeOC_6H_4$	40%	9%
4	2	phenyl	39%	10%

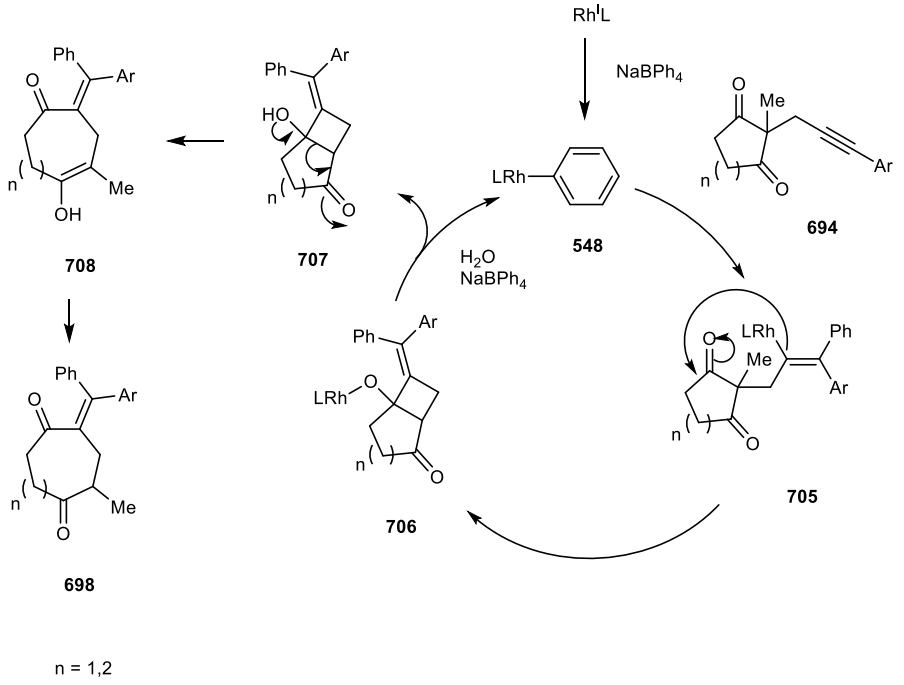
The second product isolated **698** was presumably formed by a process already described by Murakami *et al.* in 2005. They reported a rhodium-catalysed reaction of alkyndione with aryl boronic acids to give a ring expansion product **700** (Scheme 142). Murakami suggested that

cis-arylation of alkyne **699** gives alkenylrhodium **701**. Then intramolecular nucleophilic addition to the ketone would give cyclobutane **702**. Hydrolysis of **702** gives alcohol **703** which forms the observed product **700** after retro-aldol reaction.[117]



Scheme 142: Rhodium catalysed 1,4-migration process

In the case of the alkynes studied the 8- and 9-membered ring cycles isolated **698** were formed by initial arylation of the alkyne **694** with the opposite regioselectivity compared to tricycle **695**, to give intermediate **705**. After the arylation, nucleophilic attack by the alkenylrhodium species **705** on to the pendant ketone forms cyclobutane **706**. Then after hydrolysis to give alcohol **707** a retro-aldol reaction gives the isolated product **698** (Scheme 143).



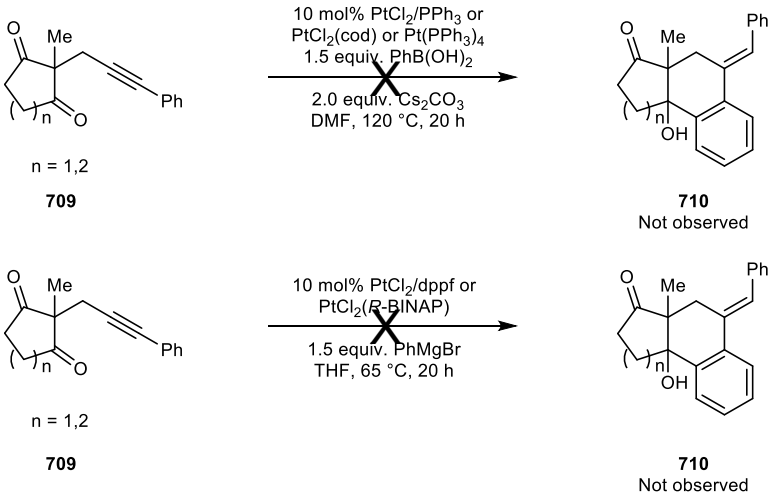
Scheme 143: Mechanism proposed for the ring opening product observed

In search of a metal that would perform the arylation more selectively and with higher yields other metals known to undergo transmetalation with organometallic reagents were also studied.

As described in Chapter 3.1., palladium was the first metal reported to undergo 1,4-migratory insertion processes. Therefore a variety of Pd^{II} and Pd^{0} pre-catalysts were trialled using either aryl-boronic acids or aryl-halides as the aryl source. However, no productive reaction was observed, with either starting material alkynone **694** returned or a complex mixture recovered.[f]

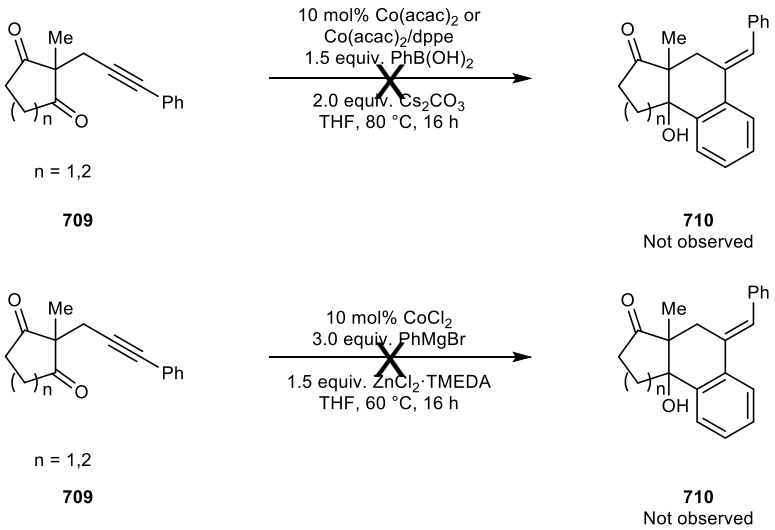
Platinum hydroarylation of alkynes has not been reported in the literature, however platinum does undergo transmetalation with Grignard reagents and arylboronic acids,[118] in addition platinum has been reported to undergo 1,4-migration (Chapter 3.1.3, Scheme 137).[114] It was proposed then that the arylplatinum species formed could be capable of perform the arylation-1,4-migration process expected in our investigation. Therefore different platinum catalyst system with both Grignard reagents and arylboronic acids were tried. Unfortunately either the starting alkyne **709** or very complexes mixtures were observed (Scheme 144).

[f] Screening performed by Dr Benjamin M. Partridge



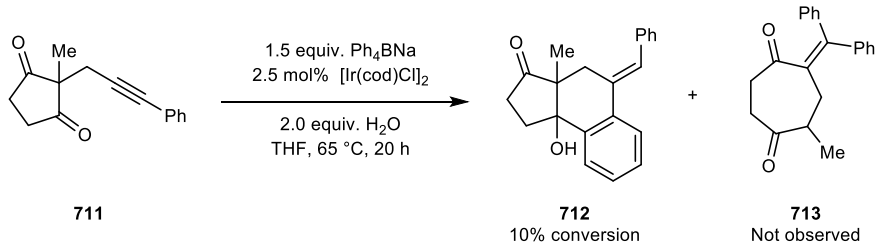
Scheme 144: Metal screening for the proposed 1,4-migration process

As described in Chapter 3.1.3 (Scheme 134) cobalt has also been reported to perform domino arylation-1,4-migration processes. Both Yoshikai's conditions for the addition of arylzinc reagents to alkynes and Chien Hong's hydroarylation of alkynes with organoboronic acids were tested on alkynone **709**. In both cases neither the desired product **710** nor the ring expansion side product **698** were isolated. Only the starting alkyne **709** or complex mixtures were observed (Scheme 145).[113a, 119]



Scheme 145: Metal screening for the proposed 1,4-migration process

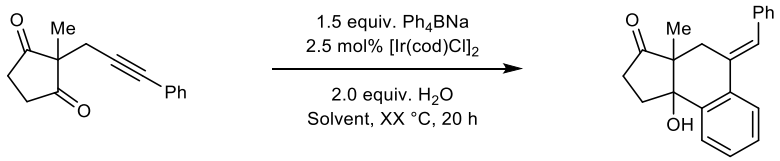
Other metals that had not been reported to undergo 1,4-migration were tried without success until iridium complex $[Ir(cod)Cl]_2$ was applied. The transmetalation of iridium complexes with arylboronic for the arylation of alkenes has been reported.[120] However, to the best of our knowledge, the 1,4-Iridium migration was not reported before our investigations. Despite this, to our delight, the arylative process using $[Ir(cod)Cl]_2$ and $NaBPh_4$ gave a 10% conversion to tricycle **712** with no ring expansion product **713** observed (Scheme 146).



Scheme 146: Metal screening for the proposed 1,4-migration process

Different solvents and temperature were screened to try to increase the yield of tricycle **712**. THF at 120 °C in a sealed vial gave the highest conversion of alcohol **712** (Table 5, Entry 6). It was also found that the use of polar protic solvents such as MeOH and *i*-PrOH seemed to inhibit the reaction (Table 5, entries 3 and 4).

Table 5: Solvent and temperature screening

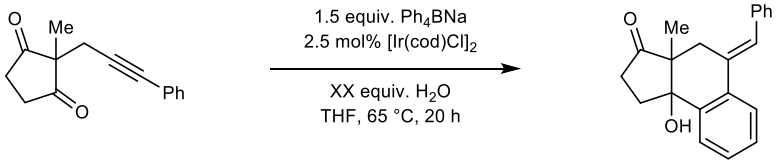


Entry	Solvent	T (°C)	Conversion[I]
1	Ether	40	17%
2	CH_2Cl_2	40	24%
3	MeOH	60	0%
4	*i*-PrOH	80	0%
5	THF	65	37%
6	THF	120	60%
7	Toluene	120	44%

I) Determined by ^1H NMR analysis of the crude reaction mixture, (disappearance of a signal of 3H, s at 1.19 Hz and appearance of a signal of 3H, s at 1.01 Hz)

Next, the effect of the amount of water in the reaction was studied. It was observed that 1.2 equivalents of water was the optimum amount for the arylative process (Table 6, Entry 2). 2.0 equivalent of H_2O led to a reduced conversion of 37%, and a water free reaction also gave a lower conversion 46% (Table 6).

Table 6: Water amount screening



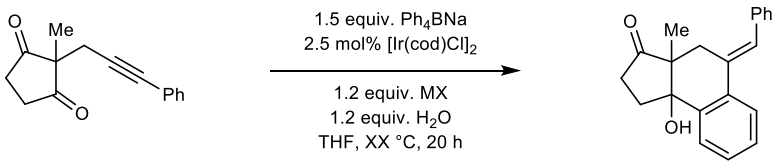
711 712

Entry	Equiv. of H_2O	Conversion[I]
1	2.0	37%
2	1.2	56%
3	0	46%

I) Determined by ^{1}H NMR analysis of the crude reaction mixture (See Table 5)

The use of additives to try to make the ketone more prone to nucleophilic attack was also studied. Different Lewis acids gave similar conversions as without additive but more reproducible results (The reaction sometimes gave lower conversions in absence of metal additive) (Table 7).

Table 7: Lewis acid additive screening

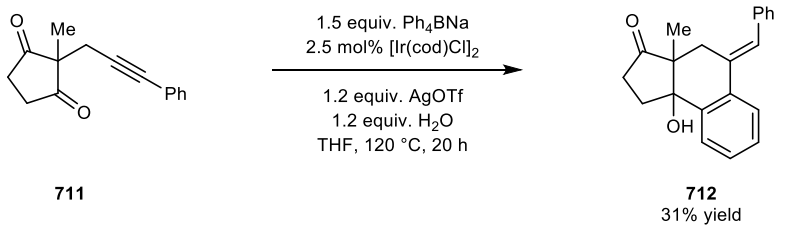


711 712

Entry	Lewis acid	Conversion[I] (65 °C)	Conversion[I] (120 °C)
1	AgOTf	50%	97%
2	$NaBF_4$	50%	89%
3	YbOTf	48%	87%

I) Determined by ^{1}H NMR analysis of the crude reaction mixture (See Table 5)

Complete conversion of the starting alkyne **711** was achieved using AgOTf as an additive and at higher temperature (Table 7, Entry 1). However, upon scale up the desire product **712** was isolated in only 31% yield. A second side product was also observed with a very low R_f (The product was isolated but not fully characterised at that point) (Scheme 147).



711

712
31% yield

Scheme 147: Optimised conditions for the Iridium 1,4-migration process using $NaBPh_4$

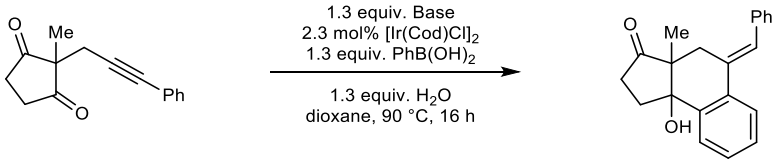
5.4. Replacing $NaBPh_4$ for $PhB(OH)_2$

$NaBPh_4$ is commercially available, however other sodium tetraaryl borate reagents are difficult to find and if they are found they are usually much more expensive. Beside that it was proposed to use arylboronic acids from a sustainable point of view. The atom economy of the domino process using $NaBPh_4$ is only 55%, very low compared with to an almost 90% obtained for the same process using $PhB(OH)_2$.[121]

Early studies exchanging $NaBPh_4$ for $PhB(OH)_2$ were not too promising only detecting traces of the desired product detected. However, when a base was added to the reaction mixture both the conversion and the NMR yield were improved. From all the bases studied KF seemed to be more appropriate for the desired process giving a 63% yield despite incomplete conversion of starting alkynone **711** (Table 8).[g]

[g] Screening performed by Dr Benjamin M. Partridge

Table 8: Base screening



711 712

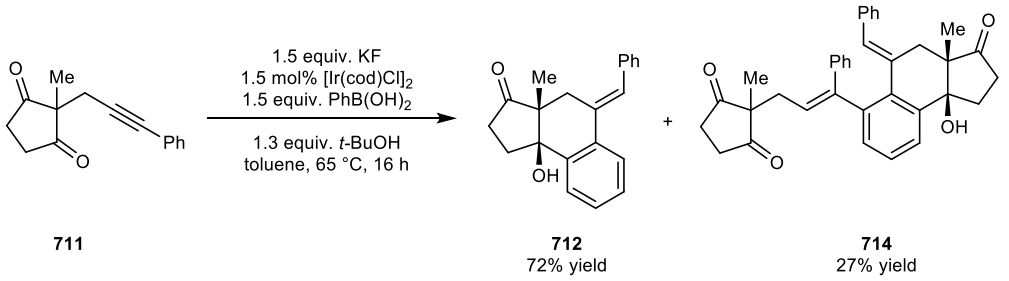
Entry	Base	Conversion[I]	NMR yield[II]
1	-	5%	5%
2	K_2CO_3	100%	62%
3	K_3PO_4	93%	62%
4	CsF	100%	64%
5	KF	89%	63%

I) Determined by ^{1}H NMR analysis of the crude reaction mixture (See Table 5)

II) Determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard (Comparing 3H peak at 1.01 from desired product and 3H peak at 6.10 Hz from 1,3,5-trimethoxybenzene).

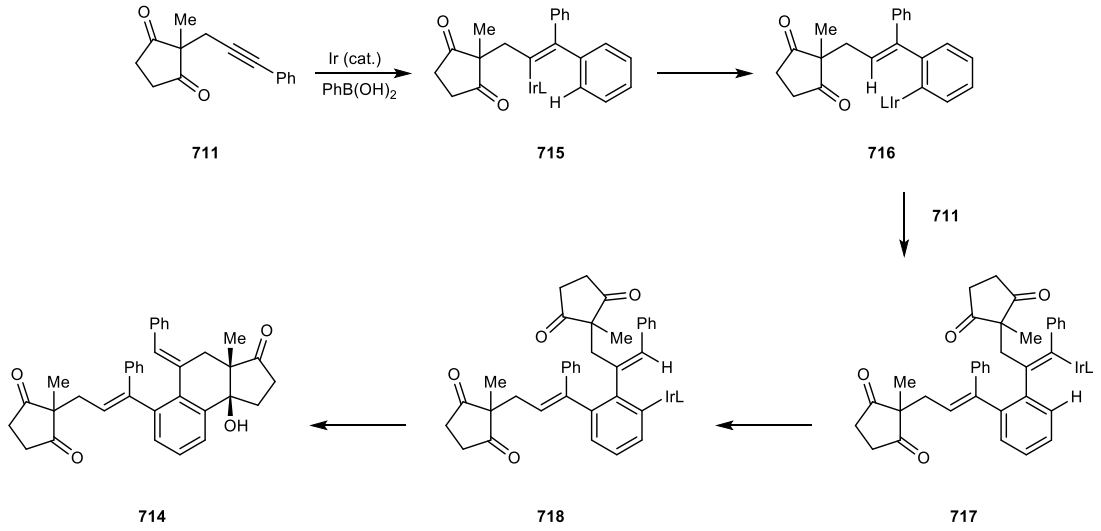
Further screening investigated the reaction solvent, additive, and temperature. It was found that the reaction of alkyne **711** with phenylboronic acid in the presence of *t*-BuOH instead of H_2O in toluene at 65 °C gave a 79% NMR yield. It needs to be mentioned that the loading of iridium dimer was decreased to 1.5 mol% without diminishing the yield obtained from when 2.3 mol% of the catalyst was applied. Once the reaction was scaled up to 0.3 mmol, the desired cyclised product **712** was isolated in 72% yield together with an unknown side product **714**. The structure of this new product was elucidated *via* NMR spectroscopy and X-ray crystallography (Scheme 148).[h]

[h] Optimisation performed by Dr Benjamin M. Partridge



Scheme 148: Optimised conditions for the Iridium 1,4-migration process using $PhB(OH)_2$

The mechanism for the formation of the side product was proposed to start with the arylation of the alkyne **711** to give intermediate **715**. 1,4-iridium migration to the aryl position gave **716**. This intermediate **716** does not react intramolecularly, instead attacks a second molecule of starting alkyne **711** to form structure **717**. Finally a second 1,4-migration followed by cyclisation of the aryl iridium onto the ketone would give structure **713** (Scheme 149).

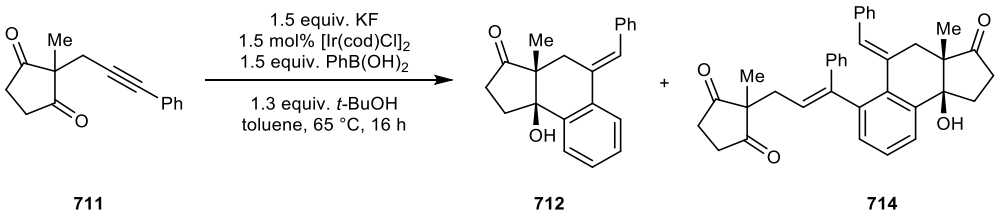


Scheme 149: Mechanism proposed for the formation of the observed side product

The formation of side product **714** rise from two factors; the arylation with opposite regioselectivity compare to desired product **712** and the intermolecular addition of intermediate **716** to a second starting alkyne **711** (Scheme 153). It was proposed that the intermolecular step could be supressed by the dilution of the reaction mixture. In this manner less starting alkyne would be "wasted" in the formation of side product **714** and therefore a higher yielding process would be achieved. As predicted, when the concentration was

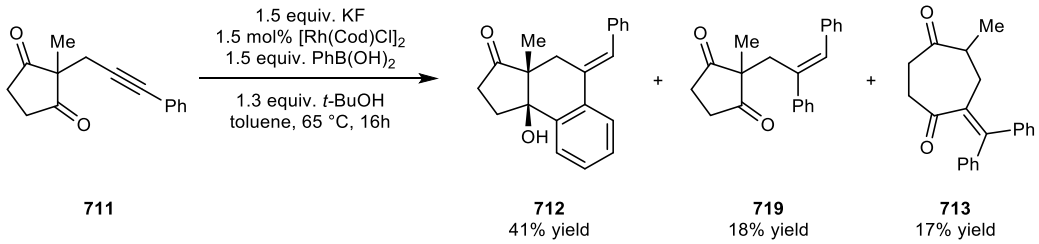
decreased from 0.2 to 0.04 the ratio **711**:**714** was increased. However, the increase in the yield of **711** was negligible (Table 9, Entry 2). Surprisingly, in an experiment at a higher concentration the ratio **711**:**714** was also increased compare to the experiment a 0.2 M. Even though a slightly higher yield was achieved when the concentration was increased, the optimum condition were established at 0.2 M due to a solubility problems with some of the others substrates (Table 9).

Table 9: Concentration screening



Entry	Concentration	Yield of 712	Yield of 714	Ratio 712:714
1	0.2 M	72%	27%	2.7
2	0.04 M	74%	15%	4.9
3	0.4 M	79%	17%	4.6

The optimised conditions using phenyl boronic acids were applied using $[Rh(cod)Cl]_2$ instead of $[Ir(cod)Cl]_2$ in order to find out if Ir was still a better catalyst than rhodium under this conditions. The desired alcohol **712** was isolated in a lower 41% yield, along with 17% of dione **713**. Although adduct was not observed with Rh; 18% yield of hydroarylation product **719** was reported (Scheme 150).



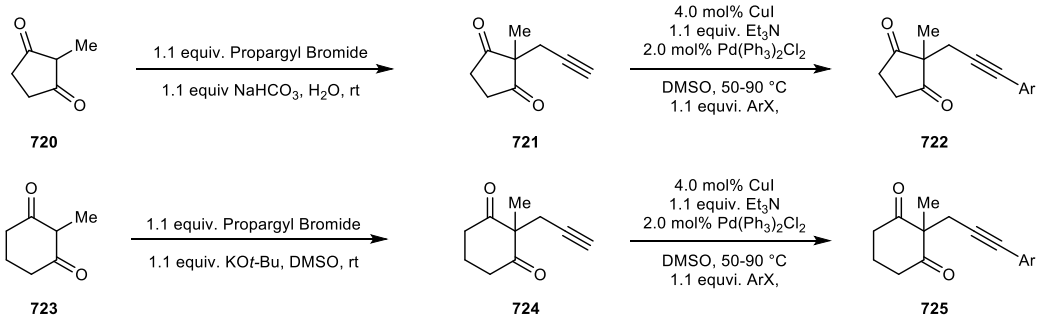
Scheme 150: Rh catalysed arylation/1,4-migration/aldol cyclisation process

5.5. Substrate Synthesis

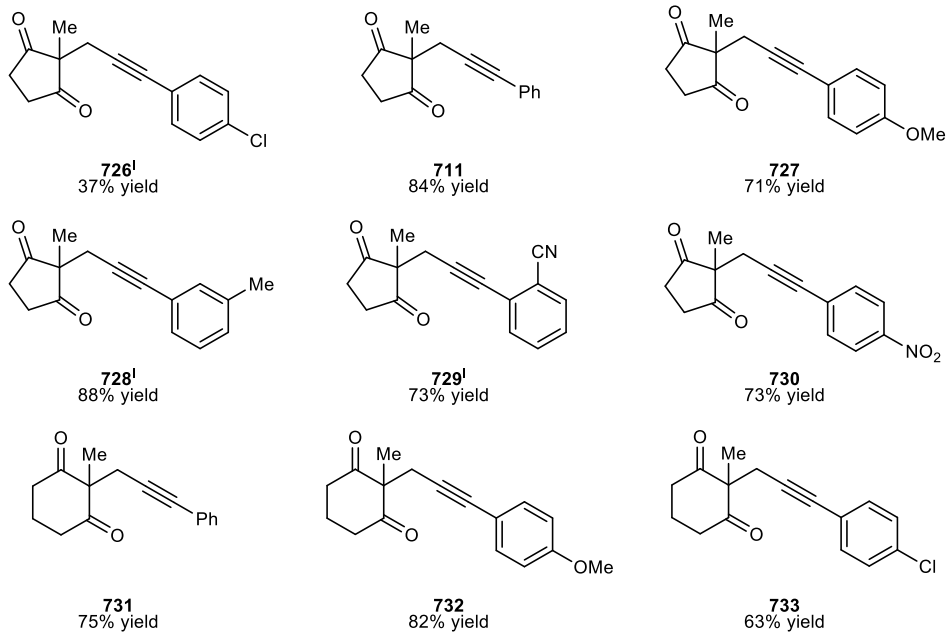
With conditions for the arylative cyclisation process developed, investigation of the scope of the reaction to find the limitations of this particular process began. For this purpose, a broad range of substrates were synthesised.

A simple route to access symmetric and asymmetric, cyclic and acyclic alkynones was developed. Propargylation of commercially available 2-methyl-1,3-cyclopentadione **720** or 2-methyl-1,3-cyclohexadione **723** gave terminal alkynes **721** and **724**. Subsequent Sonogashira coupling with an aryl halide led to the formation of different cyclic 1,3 diketones **722** and **725**. This was designed so we could study the effect of the electronics and the sterics of the aromatic substituent. Both electronwithdrawing and electrondonating groups were introduced on *para* as well as modifications on *meta* and *ortho* position (Scheme 151 and Figure 4). [122]

Changes in the conditions of the Sonogashira reaction were applied in some cases in order to increase the yield of the process (See Chapter 4.2 for more details).



Scheme 151: Substrate synthesis



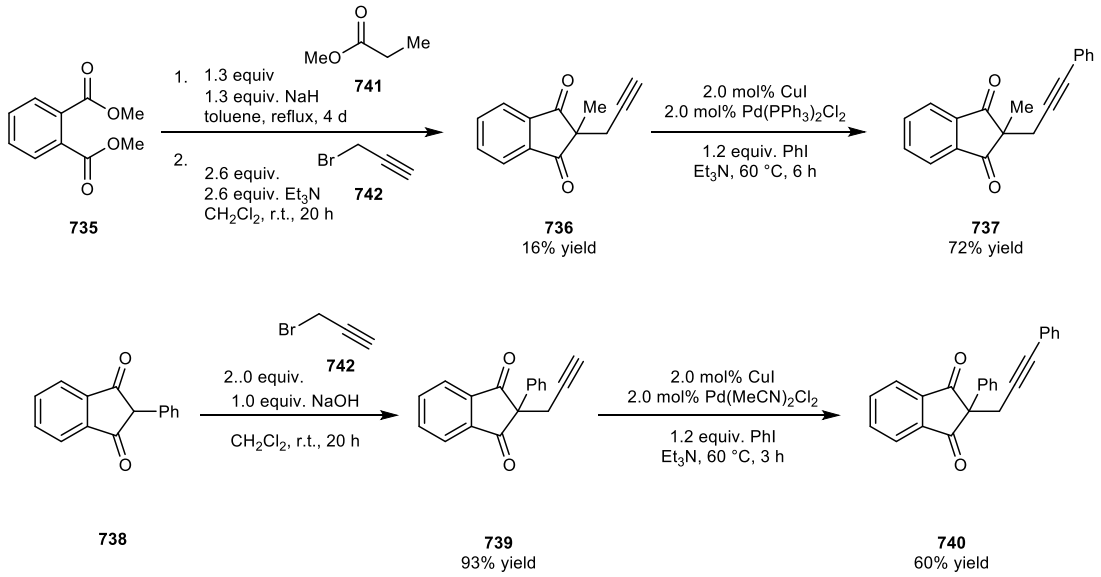
726[I] 37% yield
711 84% yield
727 71% yield
728[I] 88% yield
729[I] 73% yield
730 73% yield
731 75% yield
732 82% yield
733 63% yield

Figure 4

I) Substrates synthesised by Dr Benjamin M. Partridge

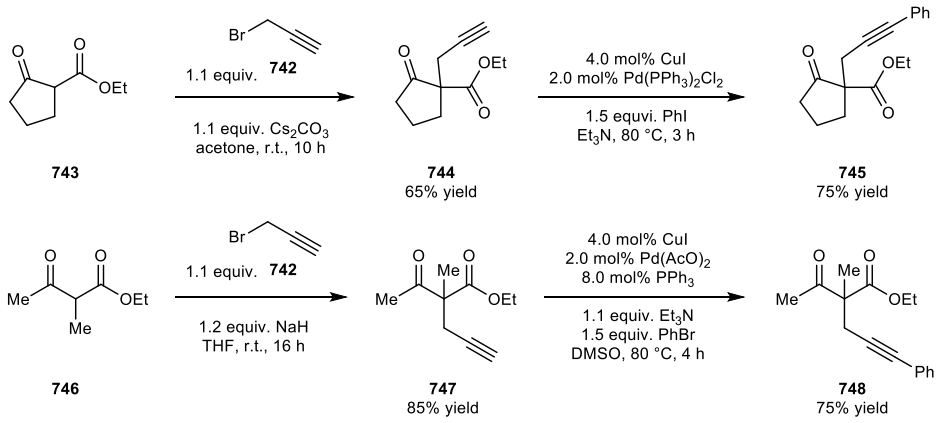
The electrophilic diketone was also modified. Terminal alkyne **736** was synthesised in two steps from dimethyl phthalate, through reaction with methyl propionate **741** and propargyl bromide **742**. Commercially available 2-phenyl-1,3-indandione **738** was reacted with propargyl bromide **742** affording alkyne **739**. The corresponding terminal alkynes **736** and **739** were subjected to Sonogashira coupling with phenyl iodide to give **737** and **740** in good yields (Scheme 152).[i][123]

[i] Substrates synthesised by Dr Benjamin M. Partdrige



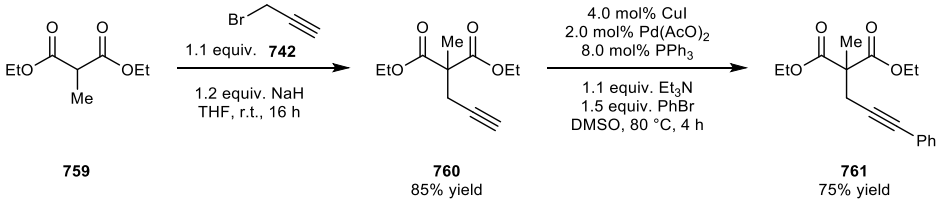
Scheme 152: Substrate synthesis

Racemic *β*-keto esters **745** and **748** were also synthesised to explore the scope of the dielectrophilic part. Propargylation of 2-cyclopentanonecarboxylic acid ethyl ester **743** gave terminal alkyne **744** which under Sonogashira coupling conditions with PhI gave **745**. Similarly methyl acetoacetate **746** was reacted with propargyl bromide **742** to give alkyne **747** and then Sonogashira coupling with bromobenzene gave acyclic *β*-keto ester **748** (Scheme 153). [124]



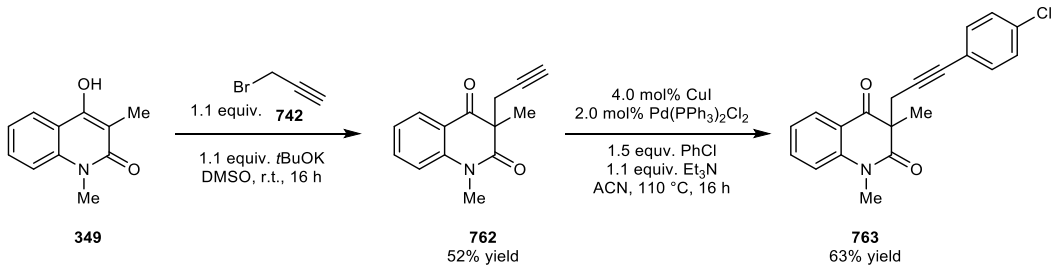
Scheme 153: Substrate synthesis

Another acyclic substrate was synthesised following the same procedure as for the racemic *β*-ketoester **748**. Diethyl malonate **759** was treated with propargyl bromide in the presence of NaH affording alkyne **760**, Sonogashira coupling of alkyne **761** with bromobenzene gave in good yield (Scheme 154).



Scheme 154: Substrate synthesis

To study further the electrophilic part of the substrate, racemic *β*-ketoamide **763** was synthesised. Amide **349** (Chapter 2.2.3, Scheme 64) was reacted with propargyl bromide to give alkyne **762**. Finally coupling of alkyne **762** with chlorobenzene gave *β*-ketoamide **763** in moderate yield (Scheme 155).



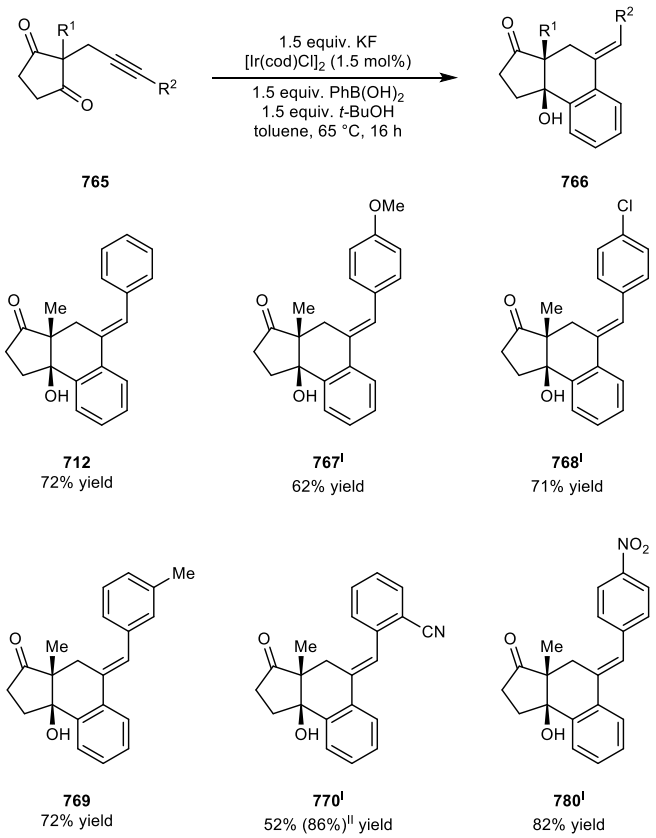
Scheme 155: Substrate synthesis

5.6. Scope of the Reaction

The conditions obtained from the screening on alkynone **711** were applied to the different substrates synthesised.

Cyclopentadiones containing different substitutions on the aromatic ring where first studied (Scheme 160). When a strong electron withdrawing groups such as NO_2 was introduced at the *para*-position, the yield of tricycle **780** increased compare to product **766** with no substitution in the aromatic ring. Following this pattern, an electrodonating *para*-OMe

substituent gave a lower yield of tricycle **767**. Substitution at the 3-position of the aromatic ring was also tolerated; *meta*-methyl substituted product **769** was obtained in good yield. When a *ortho*-nitrile group was introduced on the phenyl ring, a higher iridium catalyst loading was used to obtain an acceptable yield of tricycle **770** (Scheme 156).

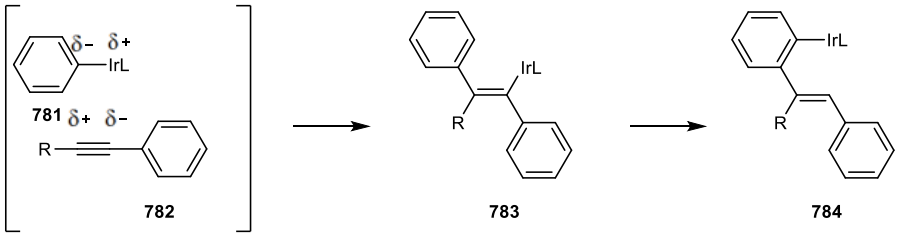


Scheme 156: Scope of the Ir catalysed 1,4-migration process

I) Product synthesised by Dr Benjamin M. Partridge
II) Yield using 2.5 mol% of $[Ir(cod)Cl]_2$

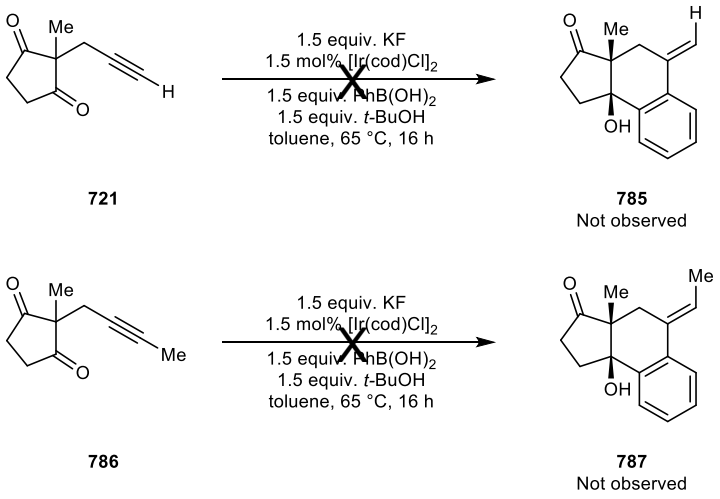
According to these results, the arylation towards the formation of the desired cyclic product is favoured with electron-poor aromatic alkynes. The phenyl ring is a moderate EWG which polarises the alkyne leaving a partial negative charge on the carbon next to the aromatic group and a partial positive charge on the other carbon **782**. Therefore, the arylation takes place preferably with the regioselectivity to give alcohol **695** (See Chapter 3.2.2 Scheme 141). When a EWG is placed on the aromatic ring, this effect is increased making more favourable the arylation towards the desired alcohol **695**. In the case of electron-rich aromatic alkynes, the aryl ring still pulls electrons from the alkyne but, due to the EDG, less effectively. Therefore, the arylation towards the formation of alcohol **767** (62% yield) is less

favoured than with more electron-poor aryl-alkynes **712** (72% yield) or **780** (82% yield) (Scheme 156 and 157).



Scheme 157: Polarisation of the triple bond by the aromatic ring

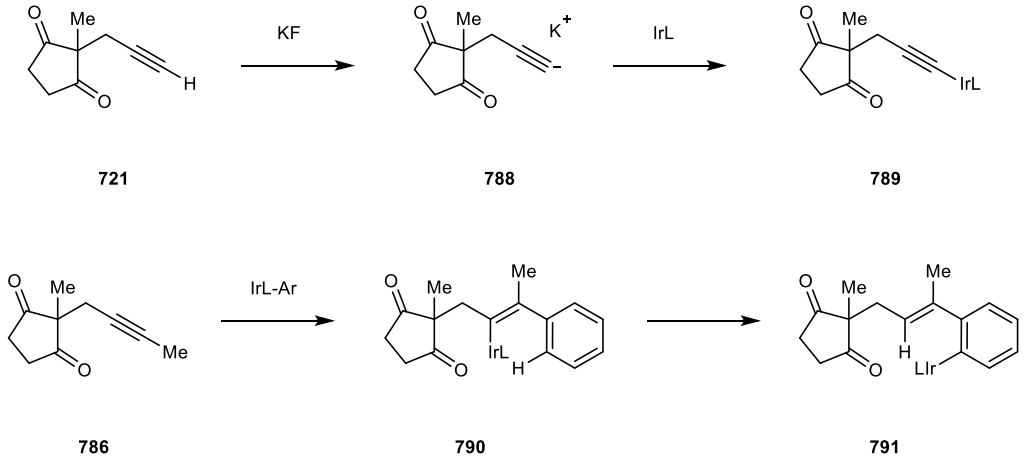
Further experiments demonstrated that the aryl substituent is needed for the process to take place. Neither a terminal alkyne **721** nor methyl substituted **786** reacted with $PhB(OH)_2$ with only starting alkynes recovered from the reactions (Scheme 158).



Scheme 158: Scope of the 1,4-migration process

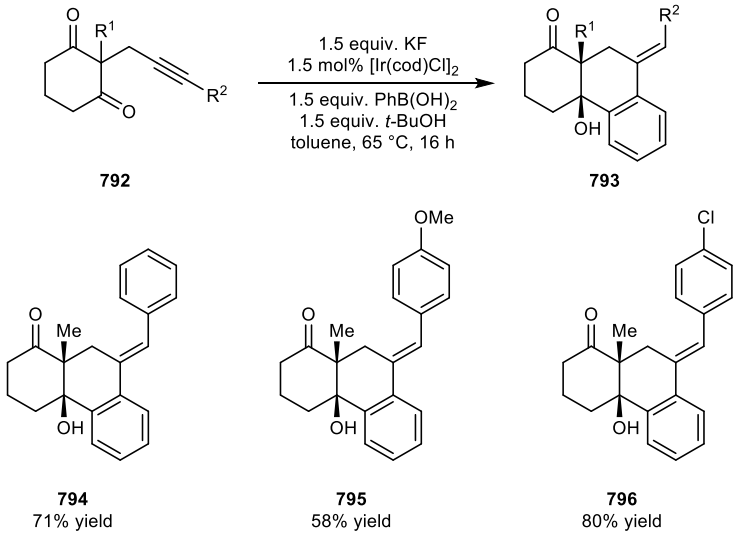
Tricycle **785** is presumably not formed due to deprotonation of the terminal alkyne by KF and complexation with iridium to form an unreactive alkynyl-iridium species **789**. In the case of the less electrophilic methyl-substituted substrate **786**, due to sterics the arylation presumably occurs on the less hindered carbon to give intermediate **790**. This alkyliridium species **790** could undergo 1,4-migration but the corresponding aryliridium **791** is set up to perform the cyclisation process to the formation of a less favourable 7-membered ring. Since no other products were detected, it could be argued that both the aryliridium **790** and the

alkyliridium intermediates **791**, are not reactive enough to perform any other reaction consuming the iridium catalyst (Scheme 159).



Scheme 159: Proposed rationale for the unreactivity of certain substrates

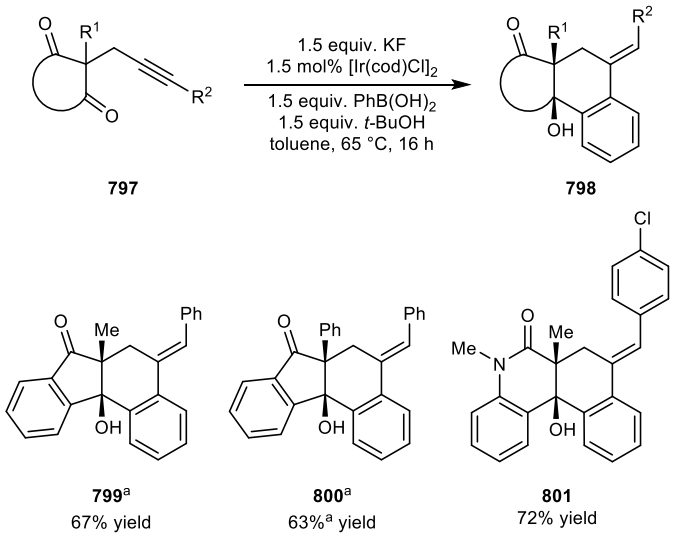
Similarly to the cyclopentadione substrates, cyclohexadiones **792** performed well in the arylative cyclisation reaction. The same electronic pattern was observed in this case achieving the highest yield in the case of electron poor 4-chloro substituted polycyclic alcohol **796** and the lowest yield for *para*-methoxide substituted tricycle **795** (Scheme 160).



Scheme 160: Scope of the 1,4-migration process

Modifications on the electrophilic part of the starting alkyne were also tolerated. An indane-1,3-dione derivative with a methyl substituent between the ketones **799** performed

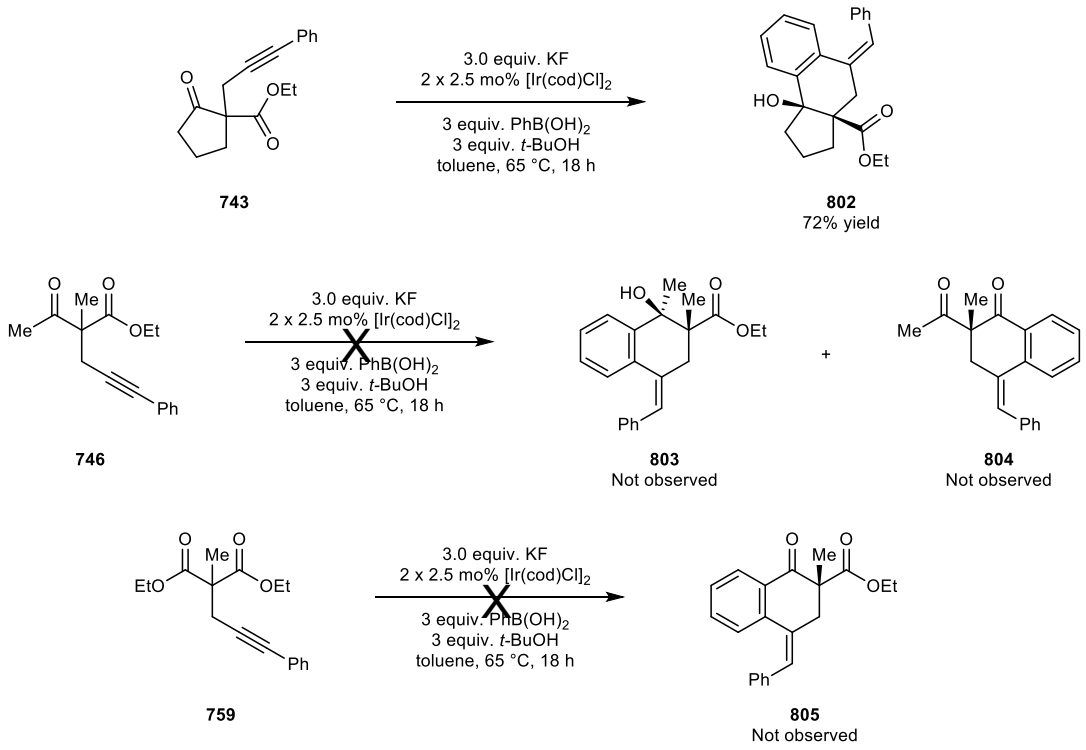
well with a 67% yield. When a bulkier substituent was introduced between the ketones of the indane-1,3-dione a higher catalyst loading was again needed to afford the desired product with modest yield (**800)**. The β-ketoamide proved to be a valid substrate for the reaction performing the arylative cyclisation on to the more reactive carbonyl in high yield (**801)** (Scheme 161).



Scheme 161: Scope of the 1,4-migration process

a) Product synthesised by Dr Benjamin M. Partridge

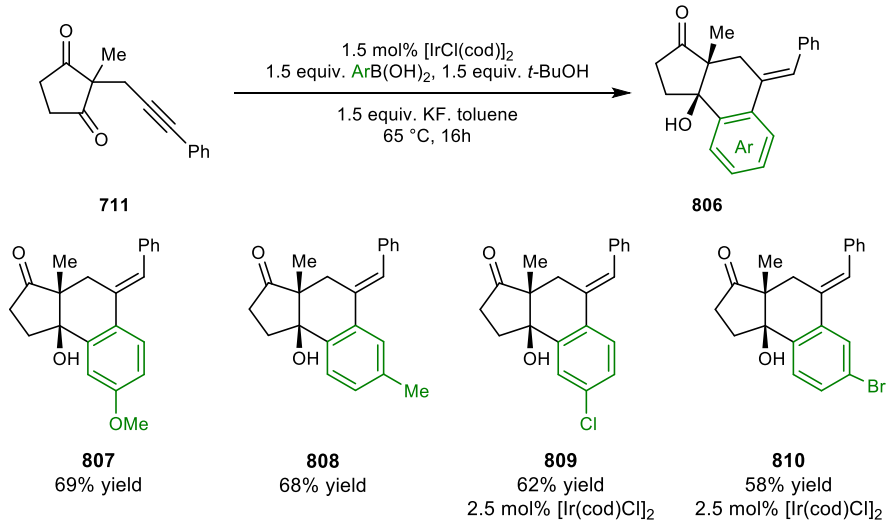
The two β-keto ester substrates synthesised **743** and **746** showed to be more challenging. Ketone **743** needed sequential additions of a solution of iridium catalyst to afford the desired tricycle **802** with acceptable yields. Acetoacetate derivative **746** proved to be even more challenging. Higher catalyst loadings and temperatures, different solvents and the use of $NaBPh_4$ instead of $PhB(OH)_2$ were tried but only gave either very complex mixtures or mainly starting materials. Similarly, malonate derivate **759** did not perform the arylative-cyclisation process, and only starting alkyne **759** was recovered (Scheme 162).



Scheme 162: Scope of the 1,4-migration process

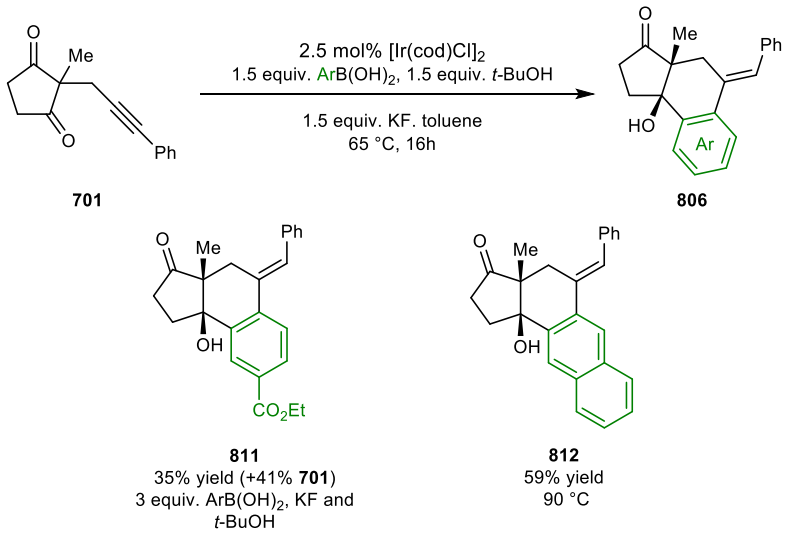
The scope of the boronic acid was also studied. The use of both electron-rich and electron-poor arylboronic acids was tolerated. Both *para*-methoxy and *meta*-methyl substituted aryl boronic acids gave good yields and in the case of the *meta*-substituted boronic acid only one regioisomer **808** was observed (presumably due to sterics in the 1,4-iridium migration process). *Para* and *meta* electronwithdrawing substituents in the arylboronic acid proved to be more challenging needing a higher catalyst loading to perform the reaction (Scheme 163).[j]

[j] Reactions performed by Dr Benjamin M. Partdrige



Scheme 163: Scope of the 1,4-migration process using different boronic acids

Even increasing the catalyst loading in the case of the 4-substitued carboxylate boronic acid the reaction does not go to completion and a 41% yield of the starting alkyne was recovered with a 39% of product **811**. In the case of 2-napthyl boronic acid an increase of the catalyst loading together with a higher temperature was needed. With tetracycle **822** formed in good yield with complete conversion of the starting alkyne **701** (Scheme 164).[k]

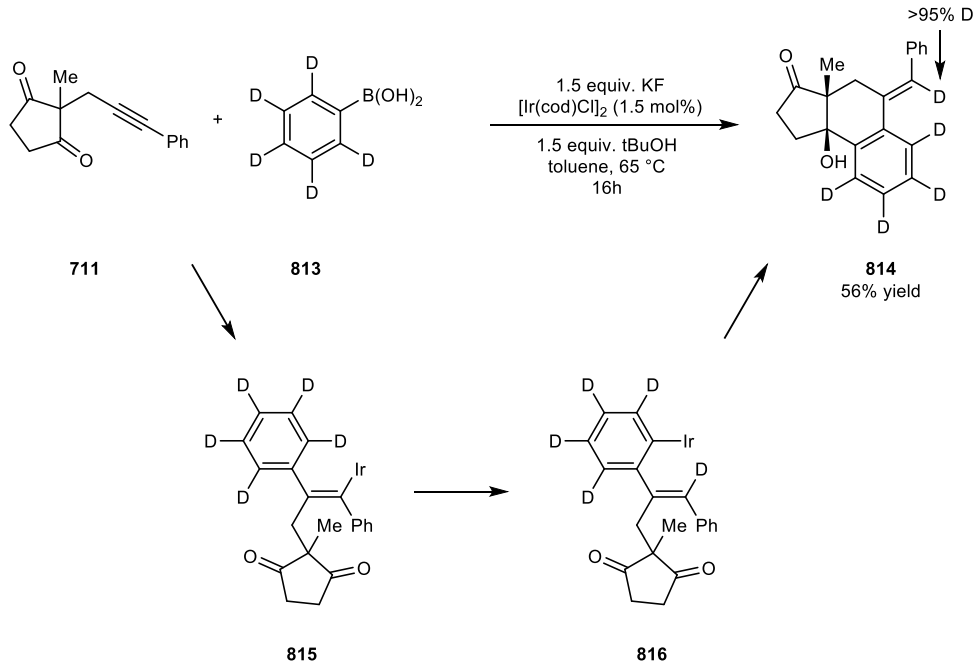


Scheme 164: Scope of the 1,4-migration process using different boronic acids

[k] Reactions performed by Dr Benjamin M. Partdrige

The fact that electron-poor arylboronic acids are less reactive towards arylation-cyclisation is presumably due to the less favourable transmetalation of the boronic acid with the iridium complex.[120a]

The reaction of pentadeuteriophenylboronic acid **813** gave tricyclic alcohol **814** in a 56% yield. Exclusive deuterium incorporation was observed on the alkene position by ^{1}H NMR spectroscopy. This provides strong evidence that a 1,4-migration shift occurs during this process (Scheme 165).[l]



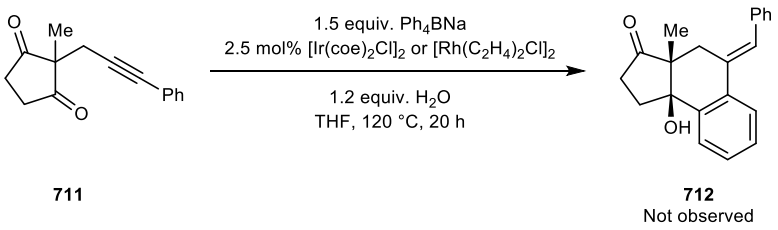
Scheme 165: Deuterium experiments for the 1,4-migration process

5.7. Asymmetric Variant

Both rhodium and iridium were shown to perform the racemic arylation-cyclisation of alkynones using cod as ligand. Commercially available and synthesised chiral ligands were tried in order to achieve a high enantioenriched process.

The reaction in the presence of both $[Ir(coe)_2Cl]_2$ and $[Rh(C_2H_4)_2Cl]_2$, using $NaBPh_4$ as arylative agent, showed complete inactivity towards the arylative-cyclisation process (Scheme 166).

[i] Reactions performed by Dr Benjamin M. Partdrige



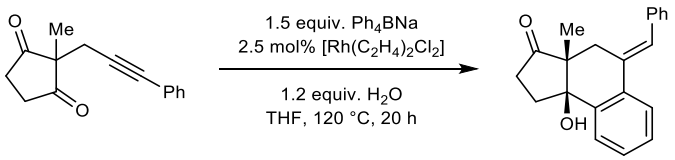
711 712
Not observed

Scheme 166: Testing the background reaction using Ir and Rh catalysts

A range of catalysts were prepared (*in situ*) from these two complexes and a wide variety of chiral ligands. Various commercially available phosphine ligands were the first evaluated to see if they generated a suitable chiral catalyst for the arylative-cyclisation process.

In the case of rhodium, the combination of $[Rh(C_2H_4)_2Cl]_2$ with (*S*)-Segphos **L32** and (*R*)-DTBM-Segphos **L37** showed similar levels of conversions to those achieved with $[Rh(cod)Cl]_2$ but no enantioselectivity was induced in the reaction (Table 10 Entry 1). Lower conversion and still no enantiocontrol was observed with other commercially available phosphine ligands such as (*R*,*S*)-Josiphos **L09** , (*R*)-BINAP **L02** or (*R*)-Difluorophos **L34** (Table 10).

Table 10: Ligand screening with Rh

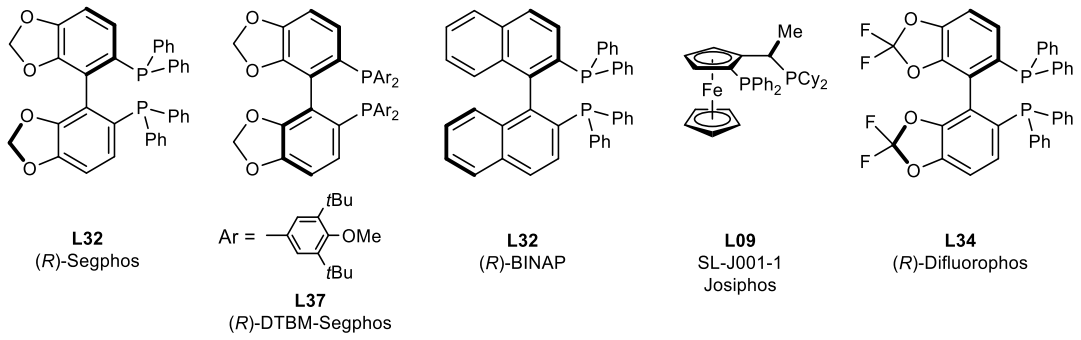


711 712

Entry	Ligand	Conversion[I]	ee[II]
1	**L32**	45%	0%
2	**L37**	35%	0%
3	**L09**	20%	0%
4	**L02**	15%	0%
5	**L34**	0%	Not measured

I) Determined by ^{1}HNMR analysis of the crude reaction mixture (See Table 5)

II) Determined by Chiral HPLC

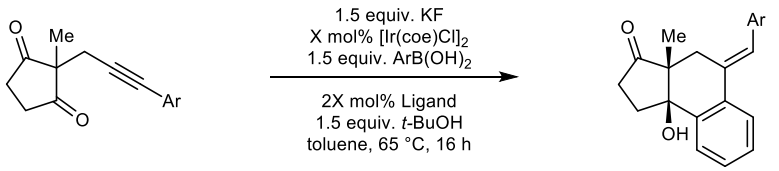


At low loading, iridium catalyst showed no activity unless cycloctadiene was present in the complex. A wide range of phosphine, phosphoramidite and diene ligands were applied but only starting material was observed. Applying the optimised conditions using phenylboronic acid gave similar results to those observed with $NaBPh_4$ when using either iridium or rhodium catalyst.

It was proposed to run a few selected ligands with a higher catalyst loadings to examine if catalyst turnover was a problem. Reaction of alkynone **726** with phenylboronic acid in the presence of 20 mol% of iridium dimer and 40 mol% of (*R*)-BINAP **L02** led to formation of tricyclic alcohol **768** in good enantioselectivity albeit with low conversion. The conversion increased when using (*R*)-Difluorophos as ligand maintaining the levels enantiocontrol. Surprisingly (*R*)-Segphos as ligand, that showed good conversion with rhodium, led to only low conversion of alkynone **726** under iridium catalysis. Other classes of ligands were also screened but the enantioselectivities achieved were much inferior to those showed with phosphine ligands (Table 11).[m]

[m] Screening performed by Dr Benjamin M. Partdrige

Table 11: Ligand screening with Ir



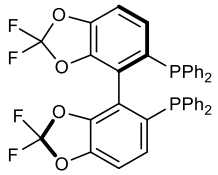
726
Ar = 4-ClC$_6$H$_5$

768

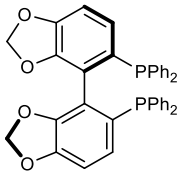
Entry	X mol%	Ligand	Conversion[I]	ee[II]
1	20	**L02**	20%	93%
2	15	**L34**	35%	95%
3	15	**L32**	10%	Not measured

I) Determined by ^{1}HNMR analysis of the crude reaction mixture (See Table 5)

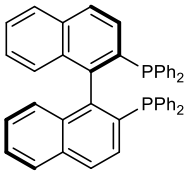
II) Determined by Chiral HPLC



L34
(*R*)-Difluorophos



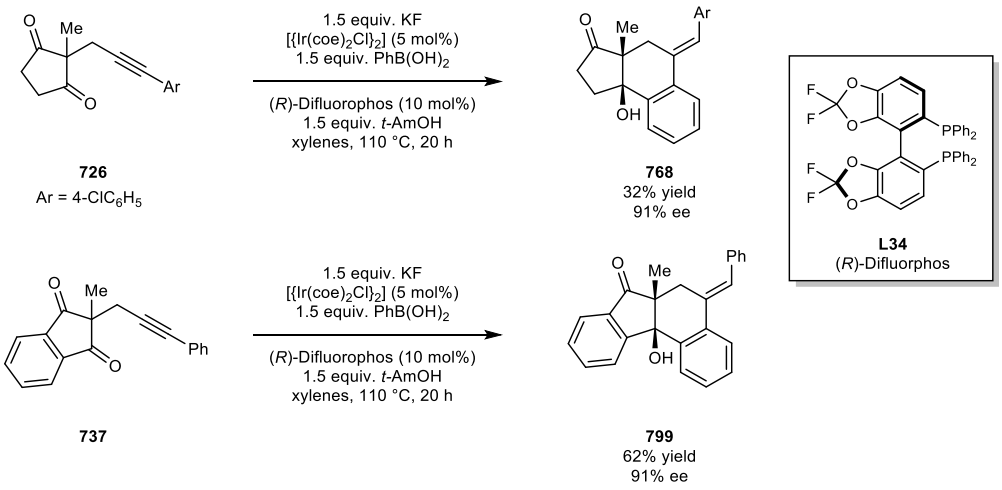
L32
(*R*)-Segphos



L02
(*R*)-BINAP

By increasing the temperature to 110 °C using Xylenes as the solvent and *t*-AmOH instead of *t*-BuOH, led to the formation of alcohol **768** in moderate yield and excellent enantiomeric excess, using only a 5 mol% of iridium dimer. While alcohol **768** is formed selectively (no other side products were isolated), catalyst decomposition presumably was the cause of the low yield as 56% of unreacted starting alkyne **726** was also recovered. This same conditions were applied to substrate **737** obtaining a 62% yield of tetracycle **799** with a 91% enantiomeric excess and recovering 35% of the starting alkyne (Scheme 167).[n]

[n] Reactions performed by Dr Benjamin M. Partdrige



Scheme 167: Ir catalysed asymmetric 1,4-migration process

5.8. Conclusions

Rhodium has been used for the arylation of alkynes followed by 1,4-migration and intramolecular 1,4-conjugate addition of α-β-unsaturated ketone. When rhodium was applied to a arylation/1,4-migration/aldol cyclisation process showed to be unsuccessful. Instead a iridium-catalysed system achieve successfully the arylation/1,4-migration/aldol cyclisation domino process. Yields between 58 and 82% were obtained observing a single diastereomer in each case racemically. This first 1,4-iridium migration has been applied to a wide range of alkynones synthesising up to 20 complex polycyclic structures in a single step. An asymmetric variant has been developed and applied obtaining high levels of enantiocontrol and moderate yields. Further investigations would be needed to improve the enantioselective process to achieve better yields with a lower catalyst loading and applying it to a wider range of alkyndiones. Iridium catalysed asymmetric alyllation is a well-known procedure therefore the allylation of alkyndione substrate can also be explored. As described in previous chapters palladium and rhodium 1,4-migration process are well explored. Knowing that iridium also undergoes 1,4-migration, iridium catalyst can be investigated as an alternative for process when rhodium and/or palladium do not produced the desired products.

6. Experimental Procedure

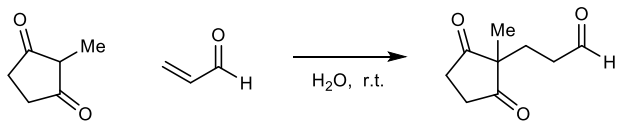
All non-aqueous reactions were carried out under a nitrogen atmosphere in oven-dried apparatus. Anhydrous CH_2Cl_2, THF, Toluene and MeCN were dried and purified by passage through activated alumina columns using a solvent purification system from www.glasscontour.com. Arylboronic acids were used as received unless the sample contained >10% boroxine as determined by ^{1}H NMR analysis. In this case, the boronic acid was stirred in a mixture of Et_2O and water for 30 minutes. The organic phase was separated, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give the corresponding boronic acid which was used without further purification. 'Petrol' refers to that fraction of light petroleum ether boiling in the range 40-60 °C. All other commercially available reagents were used as received. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien $60F_{254}$ 0.2 mm precoated plates. Product spots were visualized by UV light at 254 nm, and subsequently developed using potassium permanganate or vanillin solution as appropriate. Flash column chromatography was carried out using silica gel (Fisher Scientific 60 Å particle size 35-70 micron) employing the method of Still and co-workers.[125] Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Jasco FT/IR-460 Plus, a Shimadzu IRAffinity-1 or a Nicolet Avatar 360 FT instrument as a thin film on sodium chloride plates or as a dilute solution in $CHCl_3$. ^{1}H NMR spectra were recorded on Bruker AVA500 (500 MHz) spectrometer or a Bruker AVA400 (400 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard ($CHCl_3$ at 7.27 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q, (quartet), app (apparent), br (broad), m (multiplet). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker AVA500 (125.8 MHz) spectrometer or a Bruker AVA400 (100.6 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard ($CDCl_3$ at 77.0 ppm, CD_3OD at 49.0 ppm). Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. Proton-decoupled ^{19}F NMR spectra were recorded on a Bruker AVA400 (376 MHz) spectrometer. Chemical shifts (δ) are quoted in ppm downfield of $CFCl_3$ (δ = 0 ppm), using fluorobenzene (C_6H_5F at –113.5 ppm) or trifluoroacetic acid (CF_3CO_2H at −76.55 ppm), as internal standard. High resolution mass spectra were recorded using electrospray ionization (ESI) or electron impact (EI) techniques at the EPSRC National Mass

Spectrometry Service Centre, Swansea University, at the School of Chemistry, University of Edinburgh or at the School of Chemistry, University of Nottingham. Optical rotations were performed on an Optical Activity POLAAR 20 polarimeter or on a Bellingham and Stanley ADP 400 polarimeter. X-Ray diffraction data were collected at 120 K on either an Agilent SuperNova diffractometer using Mo Kα radiation at 0.71 Å or on an Agilent GV1000 using CuKα radiation, and refined in SHELXTL by the cristalography teams at the University of Edinburgh and the University of Nottingham . Chiral HPLC analysis was performed on an Agilent Technologies 1260 Infinity instrument using CHIRALPAK® 4.6 × 250 mm columns.

6.1. Enantioselective Copper(I)-Catalysed Borylative Aldol Cyclisations of Enone Diones

6.1.1. Diketone Precursors Synthesis

3-(1-Methyl-2,5-dioxocyclopentyl)propionaldehyde (325)

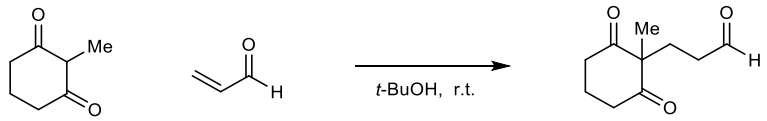


323 **324** **325**

To a stirred solution of 2-methyl-1,3-cyclopentanedione (6.30 g, 50.0 mmol) in H_2O (250 mL) was added acrolein (5.01 mL, 75.0 mmol) in one portion and the resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was then concentrated *in vacuo* and the residue was purified by column chromatography (50% EtOAc/CH_2Cl_2) to give the *title compound* **325** (7.01 g, 84%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.56 (1H, t, *J* = 1.0 Hz, CH_2O=C**H**), 2.71 (4H, s, O=CC**H**$_2$C**H**$_2$C=O), 2.38 (2H, dt, *J* = 7.2, 0.9 Hz, CH_2C**H**$_2$O=CH), 1.81 (2H, t, *J* = 7.2 Hz, C**H**$_2$$CH_2$O=CH), 1.02 (3H, s, O=CCC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 215.5 (C), 200.7 (2 x C), 55.0 (C), 38.3 (CH_2), 34.7 (2 x CH_2), 25.9 (CH_2), 19.3 (CH_3).

The data were in agreement with those reported in the literature.[69b]

3-(1-Methyl-2,5-dioxocyclopentyl)propionaldehyde (327)



326 324 327

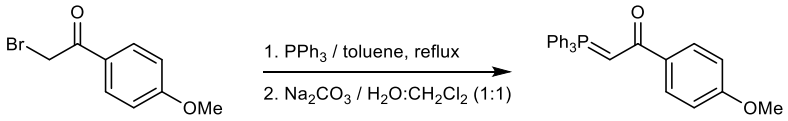
To a stirred solution of 2-methyl-1,3-cyclohexanedione (12.6 g, 100 mmol) in *t*-BuOH (500 mL) was added acrolein (10.0 mL, 150 mmol) in one portion and the resulting mixture stirred at room temperature for 18 hours. The reaction mixture was then concentrated *in vacuo* to give the *title compound* **327** (17.05 g, 95%) as a yellow-brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.63 (1H, t, *J* = 1.2 Hz, CH_2O=C**H**), 2.56-2.61 (4H, m, O=CC**H**$_2$CH$_2$C**H**$_2$C=O), 2.30 (2H, dt, *J* = 7.1, 0.9 Hz, CH_2C**H**$_2$O=CH), 2.05 (2H, dt, *J* = 7.1, 0.9 Hz, C**H**$_2$CH$_2$O=CH), 1.96-1.88 (2H, m, O=CCH$_2$C**H**$_2$CH$_2$C=O), 1.23 (3H, s, O=CCC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 209.8 (2 x C), 201.0 (C), 64.3 (C), 39.3 (CH_2), 37.8 (2 x CH_2), 27.1 (CH_2), 21.6 (CH_2), 17.5 (CH_3).

The data were in agreement with those reported in the literature.[69b]

6.1.2. Ylide Synthesis

Representative procedure A: Synthesis of ylides

1-(4-Methoxyphenyl)-2-(triphenylphosphoranylidene)ethanone (304)

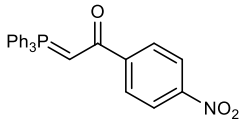


800 304

To a stirred solution of triphenylphosphine (15.7 g, 60.0 mmol) in toluene (100 mL) was added a solution of 2-bromo-4-methoxycetophenone (9.20 g, 50.0 mmol) in toluene (100 mL) and the resulting mixture was stirred for 5 h at 80 °C. After cooling to room temperature, the solid formed was filtered, washed with toluene (3 × 20 mL) and Et_2O (20 mL) and then dissolved in CH_2Cl_2 (50 mL). A solution of Na_2CO_3 (5.82 g, 55.0 mmol) in H_2O (50 mL) was added to the CH_2Cl_2 solution and the resulting mixture was stirred for 18 h at room temperature. The organic layer was separated and the aqueous layer was extracted

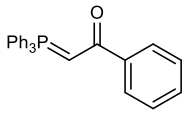
with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the *title compound* **304** as a yellow solid R_f = 0.28 (90% EtOAc/hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (2H, d, *J* = 9.0 Hz, Ar**H**), 7.75-7.70 (6H, m, Ar**H**), 7.56-7.54 (3H, m, Ar**H**), 7.48-7.45 (6H, m, Ar**H**), 6.87 (2H, d, *J* = 9.0 Hz, Ar**H**), 4.36 (1H, s, Ph_3P=C**H**), 3.83 (3H, s, OC**H**$_3$) ; ^{13}C NMR 184.4 (C, d, *J* = 3.5 Hz), 134.0 (CH, d, *J* = 14.0 Hz), 133.1 (5 x CH, d, *J* = 9.4 Hz), 132.1 (C), 131.9 (3 x CH, d, *J* = 2.9 Hz, ArC), 128.8 (5 x CH, d, *J* = 12.6 Hz), 128.5 (2 x CH), 128.4 (2 x CH), 127.3 (3 x C, d, *J* = 90.8 Hz), 55.2 (CH_3), 49.4 (CH, d, *J* = 117.5 Hz).

The data were in agreement with those reported in the literature.[126]



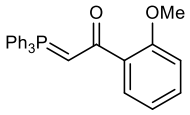
1-(4-Nitrophenyl)-2-(triphenylphosphoranylidene)ethanone (308) The *title compound* was prepared according to the Representative Procedure from 2-bromo-4-nitroacetophenone (12.1 g, 50.0 mmol) and triphenylphosphine (15.7 g, 60.0 mmol). Extraction with CH_2Cl_2 gave a bright yellow solid (18.2 g, 85%). R_f = 0.53 (90% EtOAc/hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (2H, d, *J* = 10.2 Hz, Ar**H**), 8.09 (2H, d, *J* = 10.2 Hz, Ar**H**) 7.75-7.68 (6H, m, Ar**H**), 7.63-7.59 (3H, m, Ar**H**), 7.54-7.47 (6H, m, Ar**H**), 4.51 (1H, d, *J* = 23.0 Hz, Ph_3P=C**H**); ^{13}C NMR 183.4 (C, d, *J* = 2.9 Hz), 133.1 (5 x CH, d, *J* = 10.1 Hz), 132.4 (3 x CH, d, *J* = 10.7 Hz), 132.0 (C d, *J* = 3.2 Hz), 129.0 (5 x CH, d, *J* = 12.8 Hz), 127.7 (2 x CH), 126.1 (3 x C, d, *J* = 92.8 Hz), 123.1 (2 x CH), 49.4 (CH, d, *J* = 117.5 Hz).

The data were in agreement with those reported in the literature.[127]



1-Phenyl-2-(triphenylphosphoranylidene)ethanone (309) The *title compound* was prepared according to the Representative Procedure from 2-bromoacetophenone (19.7 g, 100 mmol) and triphenylphosphine (31.4 g, 120 mmol). Extraction with CH_2Cl_2 gave a white solid (30.1 g, 80%). R_f = 0.53 (90% EtOAc/hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (2H, d, *J* = 10.2 Hz, Ar**H**), 7.79 (2H, d, *J* = 10.2 Hz, Ar**H**) 7.77-7.67 (6H, m, Ar**H**), 7.63-7.59 (3H, m, Ar**H**), 7.54-7.47 (8H, m, Ar**H**), 4.45 (1H, d, *J* = 25.0 Hz, Ph_3P=C**H**).

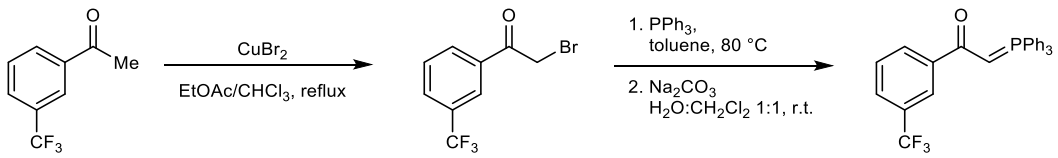
The data were in agreement with those reported in the literature.[128]



1-(2-Methoxyphenyl)-2-(triphenylphosphoranylidene)ethanone (305) The *title compound* was prepared according to the Representative Procedure from 2-bromo-2-methoxycetophenone (1.93 g, 10.5 mmol) and triphenylphosphine (3.14 g, 12.0 mmol). Extraction with CH_2Cl_2 gave a bright yellow solid (4.10 g, 95%). R_f = 0.25 (90% EtOAc/hexane). δ 7.88 (1H, dd, *J* = 6.9, 2.0 Hz, Ar**H**), 7.81-7.75 (6H, m, Ar**H**), 7.59-7.54 (3H, m, Ar**H**), 7.51-7.46 (6H, m, Ar**H**), 7.29 (1H, dt, *J* = 8.1, 1.8 Hz, Ar**H**), 6.99-6.92 (2H, m, Ar**H**), 4.62 (1H, d, *J* = 22.0 Hz, Ph_3P=C**H**), 3.91 (3H, s, OC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 183.9 (C, d, *J* = 2.8 Hz), 157.4 (CH), 133.2 (5 x CH, d, *J* = 8.5 Hz), 132.05 (CH, d, *J* = 10.1) , 131.9 (3 x CH, d, *J* = 2.8 Hz, ArC), 129.7 (C, d, *J* = 8.5 Hz), 128.8 (5 x CH, d, *J* = 12.3 Hz), 128.5 (2 x CH, d, *J* = 12.0 Hz), 127.3 (3 x C, d, *J* = 90.3 Hz, ArC), 120.3 (CH), 111.5 (CH), 55.9 (CH_3), 55.2 (CH, d, *J* = 106.4 Hz).

The data were in agreement with those reported in the literature. [129]

1-(3-Trifluromethyl)-2-(triphenylphosphoranylidene)ethanone (307)

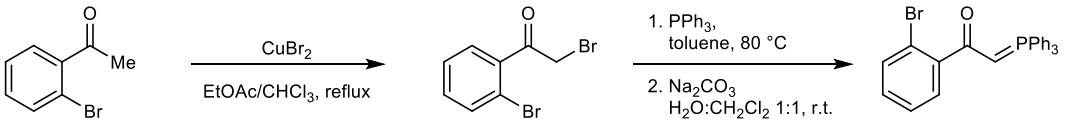


801 **802** **307**

To a refluxing suspension of $CuBr_2$ (3.30 g, 11.1 mmol) in EtOAc (7.50 mL) was added a solution of 3'-(trifluoromethyl)-acetophenone (1.12 g, 6.00 mmol) in $CHCl_3$ (7.50 mL) the resulting mixture was stirred for 18 hours under reflux conditions. The solution was filtered and then washed with sat. $NaHCO_3$ (aq.) (5 mL) and brine (5 mL).). The organic layer was concentrated *in vacuo* and the residue was dissolved in toluene (50mL) and PPh_3 (1.88 g, 7.20 mmol) was added. The solution was heated at 80 °C for 14h. The solid formed during the reaction was filtered and washed with diethyl ether (3 x 10 ml) and disolved in 50 mL of CH_2Cl_2. A solution of Na_2CO_3 (1.20 g, 11.0 mmol) in H_2O (25 mL) was added to the CH_2Cl_2 solution and the resulting mixture was stirred for 18 h at room temperature. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($NaSO_4$), filtered and concentrated *in vacuo* to give the *title compound* **307** as a pale-orange solid (2.40 g, 85%). R_f = 0.48 (1:9 hexane/EtOAc); m.p. 120-122 °C; IR 3071, 1620 (C=O), 1527, 1479, 1435, 1387, 1323, 1126, 718, 692 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (1H, s, Ar**H**), 8.15 (1H, d, *J* = 7.8 Hz, Ar**H**) 7.75-7.66 (6H,

m, Ar**H**), 7.62-7.57 (3H, m, Ar**H**), 7.55-7.45 (8H, m, Ar**H**), 4.46 (1H, d, *J* = 23.0 Hz, Ph_3P=C**H**); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 182.8 (C, d, *J* = 3.7 Hz), 141.9 (C, d, *J* = 14.4 Hz), 133.1 (6 × CH, d, *J* =10.1 Hz), 132.2 (CH, d, *J* = 2.6 Hz), 132.0 (CH, d, *J* = 10.2 Hz), 131.9 (CH, d, *J* = 2.6 Hz), 130.2 (CH), 128.9 (6 × CH, d, *J* = 12.0 Hz), 128.4 (CH, d, *J* = 12.2 Hz), 128.1 (CH), 126.5 (3 × C, d, *J* = 91.9 Hz,), 124.8 (CH, dm, *J* = 91.9 Hz), 51.6 (CH, d, *J* = 106.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.1, 16.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −75.5; HRMS (ESI) Exact mass calcd for $C_{27}H_{21}OF_3P$ $[M+H]^+$: 449.1276, found: 449.1275.

1-(2-Bromophenyl)-2-(triphenylphosphoranylidene)ethanone (306)

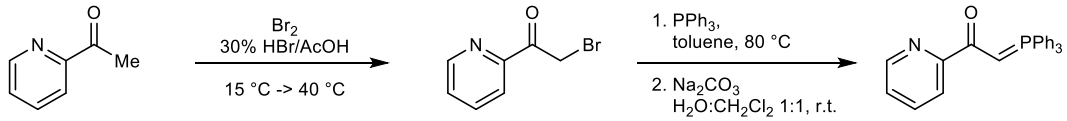


803 **804** **306**

To a refluxing suspension of $CuBr_2$ (9.91 g, 33.3 mmol) in EtOAc (10.0 mL) was added a solution of 2'-bromoacetophenone (3.58 g, 18.0 mmol) in $CHCl_3$ (10.0 mL) the resulting mixture was stirred for 18 hours under reflux conditions. The solution was filtered and then washed with Sat. $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was concentrated *in vacuo* and the residue was dissolved in toluene (100mL) and PPh_3 (5.21 g, 20.0 mmol) was added. The solution was heated at 80 °C for 14h. The solid formed during the reaction was filtered and washed with diethyl ether (3 x 30 ml) and dissolved in 100 mL of CH_2Cl_2. A solution of Na_2CO_3 (2.64 g, 20.0 mmol) in H_2O (100 mL) was added to the CH_2Cl_2 solution and the resulting mixture was stirred for 18 h at room temperature. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried ($NaSO_4$), filtered and concentrated *in vacuo* to give the *title compound* **306** as pale orange solid (4.53 g, 55%). R_f = 0.26 (90% EtOAc/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.80-7.75 (5H, m, Ar**H**), 7.71-7.66 (2H, m, Ar**H**) 7.61-7.47 (12H, m, Ar**H**), 4.41 (1H, d, *J* = 25.2 Hz, Ph_3P=C**H**).

The data were in agreement with those reported in the literature.[130]

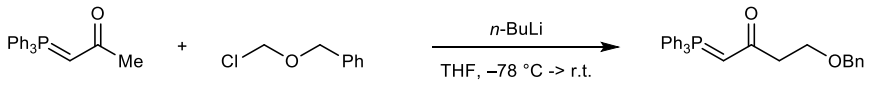
1-(Pyridin-2-yl)-2-(triphenylphosphanylidene)ethan-1-one (310)



805 **806** **310**

To a stirred solution of actetylpyridine (6.05 g, 50.0 mmol) in 30% HBr/HOAc (60 mL) was added dropwise Br_2 (2.57 mL, 50 mmol) at 15 °C then the mixture was stirred at 40 °C for 2 h. The mixture was cooled to r.t., diluted with Et_2O (250 mL) and stirred for 30 min. The precipitate was filtered and washed Et_2O (25 mL). The brown solid was then dissolved in Sat. $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried (NaSO4), filtered and concentrated *in vacuo*. The residue was dissolved in toluene (100mL) and PPh_3 (14.3 g, 55.0 mmol) was added. The solution was heated at 80 °C for 14 h. The solid formed during the reaction was filtered and washed with diethyl ether (3 x 30 ml) and dissolved in 100 mL of CH_2Cl_2. A solution of Na_2CO_3 (2.64 g, 20.0 mmol) in H_2O (100 mL) was added to the CH_2Cl_2 solution and the resulting mixture was stirred for 18 h at room temperature. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried ($NaSO_4$), filtered and concentrated *in vacuo* to give the *title compound* **310** as an off-white gummy solid (13.9 g, 73%). R_f = 0.18 (9/18/73 MeOH/EtOAc/petroleum ether); IR 2959, 2928, 1724 (C=O), 1572, 1522, 1483, 1438, 1397, 1239, 1107 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.59 (1H, d, *J* = 4.0 Hz, Ar**H**), 8.15 (1H, d, *J* = 7.9 Hz, Ar**H**), 7.80-7.70 (6H, m, Ar**H**), 7.60-7.53 (3H, m, Ar**H**), 7.52-7.45 (6H, m, Ar**H**), 7.31-7.25 (2H, m, Ar**H**), 4.32 (1H, d, *J* = 21.4 Hz, Ph_3P=C**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 196.5 (C, d, *J* = 5.7 Hz), 148.0 (CH), 141.1 (C) 136.6 (CH), 133.3 (6 x CH, d, *J* = 10.2 Hz), 132.1 (3 x CH, d, *J* = 2.7 Hz), 128.9 (6 x CH, d, *J* = 12.3 Hz), 126.1 (3 x C, d, *J* = 91.5 Hz), 124.1 (CH), 120.6 (CH), 51.9 (CH, d, *J* = 110.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 17.4; HRMS (ESI) Exact mass calculated for $C_{25}H_{21}NOP$ $[M+H]^+$: 382.1365, found: 382.1369.

1-(Benzyloxy)-3-triphenylphosphoranylidene-2-propanone (201)



318 **321** **322**

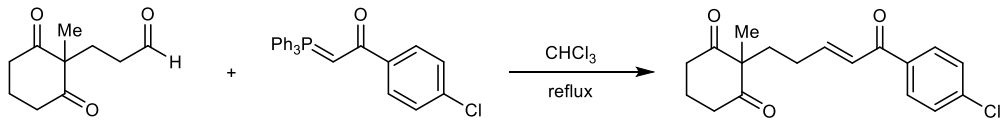
To a −78 °C suspension of 1-(triphenylphosphoranylidene)acetone (3.66 g. 11.50 mmol) in THF (100 mL) was added dropwise *n*-BuLi [1.6 M solution in hexane (7.90 mL, 12.65 mmol)], the resulting mixture was stirred at −78 °C for 3 hours then benzyl chloromethyl ether (1.97 g, 12.6 mmol) was added. The reaction mixture was warmed to room temperature and stirred for 16 hours. The brown reaction mixture was then concentrated *in vacuo* and the residue was purified by column chromatography (95% EtOAc/MeOH) to afford the *title compound* **322** as a pearl white solid (2.19 g, 45% yield). R_f = 0.11 (90% EtOAc/hexane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70-7.65 (5H, m, Ar**H**), 7.58-7.54 (4H, m, Ar**H**), 7.48-7.43 (6H, m, Ar**H**), 7.40-7.27 (6H, m, Ar**H**), 4.59 (2H, s, O=CC**H**$_2$O), 3.88 (2H, t, *J* = 7 Hz OC**H**$_2$CH$_2$), 2.69 (2H, t, *J* = 7 Hz OCH$_2$C**H**$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 190.5 (C, d, *J* = 2.9 Hz), 138.9 (CH), 133.0 (5 x CH, d, *J* =10.0 Hz, ArC), 132.0 (CH, d, *J* = 9.9 Hz), 131.9 (3 x CH, d, *J* = 2.8 Hz), 128.7 (5 x CH, d, *J* = 12.0 Hz), 128.4 (CH, d, *J* = 11.6 Hz), 128.1 (2 x CH), 127.5 (2 x CH) 127.2 (C), 127.0 (3 x C, d, *J* = 91.0 Hz), 72.8 (CH$_2$), 68.4 (CH$_2$), 52.2 (CH, d, *J* = 112.3 Hz), 41.7 (CH$_2$, d, *J* = 15.6 Hz).

The data were in agreement with those reported in the literature.[77a]

6.1.3. Enone-Dione Synthesis

Representative Procedure for the Synthesis of Cyclization Precursors *via* Wittig Reaction

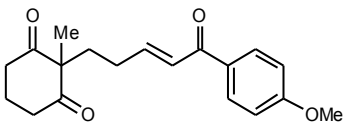
2-[(*E*)-5-(4-Chlorophenyl)-5-oxopent-3-enyl]-2-methylcyclohexane-1,3-dione (334)



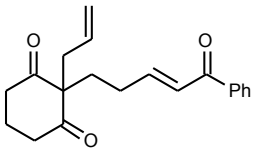
327 **807** **334**

To a stirred solution of 3-(1-methyl-2,6-dioxocyclohexyl)propanal (2.22 g, 12.1 mmol) in $CHCl_3$ (120 mL) was added 1-(4-chlorophenyl)-2-(triphenylphosphoranylidene)ethanone (5.59 g, 13.5 mmol) in one portion at room temperature and the resulting mixture was stirred under reflux for 4 h. The reaction mixture was then concentrated *in vacuo* to afford the crude residue. Purification of the residue by column chromatography (4:1 hexane/EtOAc) gave the *title compound* **334** (2.52 g, 65%) as a white solid. R_f = 0.33 (3:2 hexane/EtOAc); m.p. 96-98 °C; IR 2955, 1724 (C=O), 1693 (C=O), 1667, 1615, 1588, 1402, 1305, 1092, 666 cm^{-1}; ^{1}H

NMR (500 MHz, $CDCl_3$) δ 7.86 (2H, d, *J* = 8.6 Hz, Ar**H**), 7.45 (2H, d, *J* = 8.6 Hz, Ar**H**), 6.97 (1H, dt, *J* = 15.3, 6.8 Hz, $CH_2C\mathbf{H}$=), 6.82 (1H, dt, *J* = 15.3, 1.3 Hz, =C**H**C=O), 2.75-2.63 (4H, m, $C\mathbf{H}_2CH_2C\mathbf{H}_2$), 2.18-2.14 (2H, m, $C\mathbf{H}_2CH$=), 2.03-1.91 (4H, m, $CH_2C\mathbf{H}_2CH_2$, $C\mathbf{H}_2CH_2CH$=), 1.32 (3H, s, $C\mathbf{H}_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 209.9 (2 × C), 189.2 (C), 148.5 (CH), 139.2 (C), 136.0 (C), 129.9 (2 × CH), 128.9 (2 × CH), 125.9 (CH), 64.9 (C), 38.0 (2 × CH_2), 33.9 (CH_2), 28.2 (CH_2), 21.7 (CH_2), 17.5 (CH_3); HRMS (ESI) Exact mass calcd for $C_{18}H_{20}O_3Cl$ $[M+H]^+$: 319.1095, found: 319.1098.



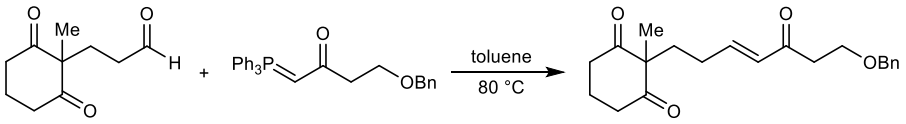
2-[(*E*)-5-(4-Methoxyphenyl)-5-oxopent-3-enyl]-2-methylcyclohexane-1,3-dione (330). The *title compound* was prepared according to the Representative Procedure from 3-(1-methyl-2,6-dioxocyclohexyl)propanal (2.00 g, 10.9 mmol) and 1-(4-methoxyphenyl)-2-(triphenylphosphoranylidene)ethanone (4.96 g, 12.1 mmol). Purification by column chromatography (80:20 hexane/CH_2Cl_2) gave an orange solid (3.05 g, 88%). R_f = 0.44 (1:1 hexane/EtOAc); m.p. 85-87 °C; IR 2967, 2922, 1721 (C=O), 1693 (C=O), 1663, 1614, 1599, 1574, 1327, 1256, 1030, 1015, 812 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (2H, d, *J* = 9.3 Hz, Ar**H**), 6.94 (2H, d, *J* = 9.3 Hz, Ar**H**), 6.93-6.90 (1H, m, $CH_2C\mathbf{H}$=), 6.86 (1H, d, *J* =15.6 Hz, CH_2CH=C**H**), 3.87 (3H, s, $OC\mathbf{H}_3$), 2.70-2.67 (4H, m, $C\mathbf{H}_2CH_2C\mathbf{H}_2$), 2.17-2.11 (2H, m, $CH_2C\mathbf{H}_2CH_2$), 2.04-1.93 (4H, m, $C\mathbf{H}_2C\mathbf{H}_2CH$=), 1.31 (3H, s, $C\mathbf{H}_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 209.9 (2 × C), 188.7 (C), 163.3 (C), 146.6 (CH), 130.8 (2 × CH), 130.5 (C), 126.1 (CH), 113.7 (2 × CH), 64.9 (C), 55.4 (CH_3), 37.9 (2 × CH_2), 34.4 (CH_2), 28.0 (CH_2), 21.0 (CH_3), 17.5 (CH_2); HRMS (EI) Exact mass calcd for $C_{19}H_{22}O_4$ $[M]^+$: 314.1513, found: 314.1515.



2-[(3*E*)-5-Oxo-5-phenylpent-3-en-1-yl]-2-(prop-2-en-1-yl)cyclohexane-1,3-dione (346). The *title compound* was prepared according to the Representative Procedure from 3-[2,6-dioxo-1-(prop-2-en-1-yl)cyclohexyl]propanal (1.01 g, 5.50 mmol) and 1-phenyl-2-(triphenylphosphoranylidene)ethanone (2.97 g, 7.80 mmol). Purification by column chromatography (4:1 hexane/EtOAc) gave a white solid (1.00 g. 60%). R_f = 0.35 (3:2 hexane/EtOAc), m.p. 59-60 °C; IR (film) 2957, 2926, 1714 (C=O), 1688 (C=O), 1670, 1618, 1444, 1290, 1221, 1022, 924, 772, 691 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92-7.90 (2H, m, Ar**H**), 7.56 (1H, tt, *J* = 7.0, 1.3 Hz, Ar**H**), 7.47 (2H, t, *J* = 7.9 Hz, Ar**H**), 6.96-6.90 (1H,

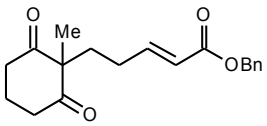
m, $CH_2CH_2C\mathbf{H}$=), 6.83 (1H, dt, *J* = 15.8, 0.9 Hz, CH_2CH=C**H**), 5.62-5.53 (1H, m, C**H**=CH_2), 5.11-5.06 (2H, m, =C**H**$_2$), 2.67-2.60 (4H, m, C**H**$_2CH_2C\mathbf{H}_2$), 2.52 (2H, d, *J* = 7.5 Hz, $CH_2C\mathbf{H}_2CH_2$), 2.14-2.10 (2H, m, C**H**$_2$CH=CH_2), 2.07-1.99 (3H, m, C**H**$_2C\mathbf{H}_2$CH=), 1.94-1.85 (1H, m, C**H**$_2CH_2$CH=); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 209.9 (2 × C), 190.7 (C), 147.9 (CH), 137.7 (C), 132.7 (CH), 131.8 (CH), 128.5 (4 × CH), 126.4 (CH), 119.7 (CH_2), 68.3 (C), 41.7 (CH_2), 39.4 (2 × CH_2), 32.9 (CH_2), 28.2 (CH_2), 16.9 (CH_2); HRMS (ESI) Exact mass calcd for $C_{20}H_{23}O_4$ $[M+H]^+$: 311.1642, found: 311.1647.

2-[(3*E*)-7-(Benzyloxy)-5-oxohept-3-en-1-yl]-2-methylcyclohexane-1,3-dione (336)



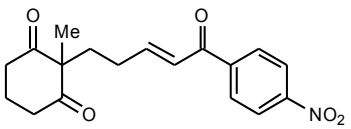
327 **322** **336**

To a stirred solution of 3-(1-methyl-2,6-dioxocyclohexyl)propanal (728 mg, 4.00 mmol) in toluene (20 mL) was added [4-(benzyloxy)-2-oxobutylidene]triphenylphosphorane (2.19 g, 5.00 mmol) in one portion and the resulting mixture was stirred at 80 °C for 16 h. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography (CH_2Cl_2) to give the *title compound* **336** as pale yellow oil (950 mg, 65%). R_f = 0.35 (CH_2Cl_2); IR 2976, 2874, 1724 (C=O), 1694 (C=O), 1670, 1618, 1454, 1269, 1101, 912, 733 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.26 (5H, m, Ar**H**), 6.78-6.71 (1H, m, $CH_2C\mathbf{H}$=CH), 6.08 (1H, dt, *J* = 16.0, 1.5 Hz, CH_2CH=C**H**), 4.52 (2H, s, C**H**$_2$Ph), 3.78 (2H, t, *J* = 6.6 Hz, OC**H**$_2CH_2$C=O), 2.84 (2H, t, *J* = 6.6 Hz, $OCH_2C\mathbf{H}_2$C=O), 2.69-2.58 (4H, m, C**H**$_2CH_2C\mathbf{H}_2$), 2.09-2.02 (2H, m, $CH_2C\mathbf{H}_2CH_2$), 1.95-1.90 (4H, m, C**H**$_2C\mathbf{H}_2$CH=), 1.29 (3H, s, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 209.9 (2 × C), 198.3 (C), 146.4 (CH), 138.1 (C) 130.8 (CH), 128.3 (2 × CH), 127.7 (2 × CH), 127.6 (CH), 73.2 (CH_2), 65.4 (CH_2), 64.8 (C), 40.0 (CH_2), 37.9 (CH_2), 33.8 (2 × CH_2), 27.9 (CH_2), 21.7 (CH_3), 17.5 (CH_2); HRMS (ESI) Exact mass calcd for $C_{21}H_{27}O_4$ $[M+H]^+$: 343.1904, found: 343.1908.

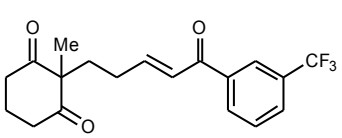


2-[(*E*)-5-(2-Methoxyphenyl)-5-oxopent-3-enyl]-2-methylcyclohexane-1,3-dione (361). The *title compound* was prepared according to the Representative Procedure from 3-(1-methyl-2,6-dioxocyclohexyl)propanal (1.82 g, 10.0 mmol) and 1-benzyl-2-

(triphenylphosphoranylidene)ethanone (5.13 g, 12.5 mmol). Purification by column chromatography (4:1 hexane/EtOAc) gave a colorless oil (1.100 g, 75%). R_f = 0.45 (1:1 hexane/EtOAc); IR 2953, 2941, 1719 (C=O), 1694 (C=O), 1653, 1265, 1169, 1026, 739, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39-7.30 (5H, m, Ar**H**), 6.91 (1H, dt, *J* = 15.7, 6.7 Hz, CH_2CH=), 5.85 (1H, dt, *J* = 15.7, 1.5 Hz, CH_2CH=C**H**), 5.17 (2H, s, CH_2Ph), 2.72-2.58 (4H, m, C$H_2CH_2CH_2$), 2.07-2.00 (2H, m, $CH_2CH_2CH_2$), 1.98-1.87 (4H, m, CH_2CH_2CH=), 1.28 (3H, s, CH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 209.8 (2 × C), 166.1 (C), 148.1 (CH), 136.0 (C), 128.5 (2 × CH), 128.13 (CH), 128.12 (2 × CH), 121.6 (CH), 66.0 (CH_2), 64.8 (C), 37.9 (2 × CH_2), 33.9 (CH_2), 27.5 (CH_2), 21.3 (CH_3), 17.5 (CH_2); HRMS (ESI) Exact mass calcd for $C_{19}H_{26}NO_4$ $[M+NH_4]^+$: 332.1856, found 332.1859.

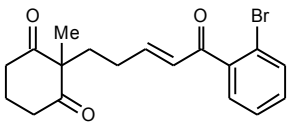


2-[(*E*)-5-(4-Nitrophenyl)-5-oxopent-3-enyl]-2-methylcyclohexane-1,3-dione (331). The *title compound* was prepared according to the Representative Procedure from 3-(1-methyl-2,6-dioxocyclohexyl)propanal (2.00 g, 10.9 mmol) and 1-(4-nitrophenyl)-2-(triphenylphosphoranylidene)ethanone (5.14 g, 12.1 mmol). Purification by column chromatography (95:5 CH_2Cl_2/EtOAc) gave an orange solid (1.64 g, 46%). R_f = 0.34 (1:1 hexane/EtOAc); m.p. 119-121 °C; IR 3105, 3067, 2953, 2918, 1722 (C=O), 1689 (C=O), 1672, 1622, 1520 (NO_2), 1344 (NO_2), 1217, 1026, 854, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.32 (2H, d, *J* = 7.2 Hz, Ar**H**), 8.04 (2H, d, *J* = 7.2 Hz, Ar**H**), 7.05-6.98 (1H, m, CH_2CH=), 6.82 (1H, dt, *J* = 15.2, 1.0 Hz CH_2CH=C**H**), 2.78-2.72 (2H, m, C$H_2CH_2CH_2$), 2.68-2.62 (2H, m, C$H_2CH_2CH_2$), 2.21-2.14 (2H, m, $CH_2CH_2CH_2$), 2.07-1.99 (3H, m, CH_2CH_2CH=), 1.98-1.89 (1H, m, CH_2CH_2CH=), 1.33 (3H, s, CH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 209.9 (2 × C), 189.1 (C), 150.5 (CH), 150.0 (C), 142.6 (C), 129.4 (2 × CH), 125.9 (CH), 123.7 (2 × CH), 64.8 (C), 38.0 (2 × CH_2), 33.4 (CH_2), 28.4 (CH_2), 22.4 (CH_3), 17.5 (CH_2); HRMS (ESI) Exact mass calcd for $C_{18}H_{19}NO_5$ $[M+H]^+$: 330.1336, found: 330.1337.

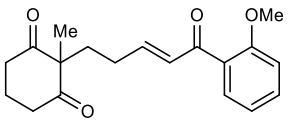


2-[(*E*)-5-(3-Trifluoromethylphenyl)-5-oxopent-3-enyl]-2-methylcyclohexane-1,3-dione (332). The *title compound* was prepared according to the Representative Procedure from 3-(1-methyl-2,6-dioxocyclohexyl)propanal (546 mg, 3.00 mmol) and 1-(3-trifluormethylphenyl)-2-(triphenylphosphoranylidene)ethanone (**S2**) (1.79 g, 4.00 mmol). Purification by column chromatography (80:20 hexane/EtOAc) gave an orange solid (720

mg, 70%). R_f = 0.35 (3:2 hexane/EtOAc); m.p. 60-62 °C; IR 2963, 2940, 1726 (C=O), 1694 (C=O), 1668, 1618, 1331, 1163, 1124, 1072, 804, 690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.15 (1H, s, Ar**H**), 8.08 (1H, d, *J* = 7.9 Hz, Ar**H**), 7.82 (1H, d, *J* = 7.5 Hz, Ar**H**), 7.62 (1H, t, *J* = 7.5 Hz, Ar**H**), 7.05-6.89 (1H, m, $CH_2C\mathbf{H}$=CH), 6.85 (1H, dt, *J* = 15.9, 1.5 Hz, CH_2CH=C**H**), 2.77-2.62 (4H, m, C**H**$_2CH_2C\mathbf{H}_2$), 2.19-2.16 (2H, m, $CH_2C\mathbf{H}_2CH_2$), 2.04-1.93 (4H, m, C**H**$_2C\mathbf{H}_2$CH=), 1.33 (3H, s, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 209.8 (2 × C), 189.1 (C), 149.4 (CH), 138.2 (C), 131.7 (CH), 131.1 (C, q, $^2J_{CF}$ = 32.9 Hz), 129.2 (CH), 129.1 (CH, q, $^3J_{CF}$ = 3.6 Hz), 125.7 (CH), 125.3 (CH, q, $^3J_{CF}$ = 3.8 Hz), 123.7 (C, q, $^1J_{CF}$ = 272.6 Hz), 64.8 (C), 37.9 (2 × CH_2), 33.7 (CH_2), 28.2 (CH_2), 21.8 (CH_3), 17.5 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$) δ −63.8 (3F, s); HRMS (EI) Exact mass calcd for $C_{19}H_{19}O_3F_3$ $[M]^+$: 352.1286, found: 352.1277.

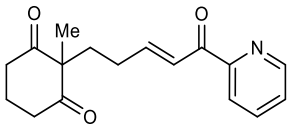


2-[(*E*)-5-(2-Bromophenyl)-5-oxopent-3-enyl]-2-methylcyclohexane-1,3-dione (333). The *title compound* was prepared according to the Representative Procedure from 3-(1-methyl-2,6-dioxocyclohexyl)propanal (335 mg, 1.80 mmol) and 1-(2-bromophenyl)-2-(triphenylphosphoranylidene)ethanone (1.05 g, 2.30 mmol). Purification by column chromatography (80:20 hexane/EtOAc) gave a colorless oil (450 mg, 70%). R_f = 0.40 (CH_2Cl_2); IR 3056, 2963, 2936, 1724 (C=O), 1694 (C=O), 1657, 1618, 1427, 1300, 1024, 766 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.60 (1H, d, *J* = 8.4 Hz, Ar**H**), 7.38 (1H, t, *J* = 8.4 Hz, Ar**H**), 7.32-7.27 (2H, m, Ar**H**), 6.60-6.54 (1H, m, $CH_2C\mathbf{H}$=), 6.40 (1H, d, *J* = 16.2 Hz, CH_2CH=C**H**), 2.74-2.61 (4H, m, C**H**$_2CH_2C\mathbf{H}_2$), 2.14-2.09 (2H, m, $CH_2C\mathbf{H}_2CH_2$), 1.99-1.91 (4H, m, C**H**$_2C\mathbf{H}_2$CH=), 1.29 (3H, s, C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 209.8 (2 × C), 194.9 (C), 151.1 (CH), 140.7 (C), 133.2 (CH), 131.1 (CH), 130.5 (CH), 128.8 (CH), 127.1 (CH), 119.2 (C), 64.7 (C), 37.9 (2 × CH_2), 33.4 (CH_2), 28.1 (CH_2), 21.8 (CH_3), 17.4 (CH_2); HRMS (EI) Exact mass calcd for $C_{18}H_{19}O_3{}^{79}Br$ $[M]^+$: 362.0512, found: 362.0508.

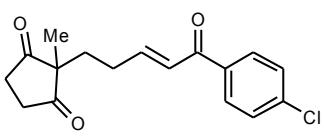


2-[(*E*)-5-(2-methoxyphenyl)-5-oxopent-3-en-1-yl]-2-methylcyclohexane-1,3-dione (329). The *title compound* was prepared according to a modification of the Representative Procedure from 3-(1-methyl-2,6-dioxocyclohexyl)propanal (455 mg, 2.50 mmol) and 1-(2-methoxyphenyl)-2-(triphenylphosphanylidene)ethan-1-one (1.23 g, 3.00 mmol), using toluene (30 mL) as solvent and by heating to 90 °C for 16 h.

Purification by column chromatography (30 to 40% EtOAc/petroleum ether) gave a yellow oil (504 mg, 66%). R_f = 0.25 (40% EtOAc/petroleum ether); IR 2943, 2841, 1726 (C=O), 1696 (C=O), 1662, 1617, 1599, 1376, 1286, 1025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.30 (2H, m, Ar**H**), 6.94-6.85 (2H, m, Ar**H**), 6.64 (1H, dt, *J* = 15.6, 6.3 Hz, CH_2CH=), 6.56 (1H, app d, *J* = 15.6 Hz, CH_2CH=C**H**), 3.76 (3H, s, OCH_3), 2.58 (4H, t, *J* = 6.9 Hz, $CH_2CH_2CH_2$), 2.05-1.96 (2H, m, CH_2CH=), 1.91-1.81 (4H, m, $CH_2CH_2CH_2$ and CH_2CH_2CH=), 1.19 (3H, s, CCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 209.7 (2 x C), 192.9 (C), 157.5 (C), 146.5 (CH), 132.4 (CH), 130.8 (CH), 129.7 (CH), 128.6 (C), 120.2 (CH), 111.3 (CH), 64.6 (C), 55.3 (CH_3), 37.6 (2 x CH_2), 34.0 (CH_2), 27.6 (CH_2), 20.7 (CH_3), 17.2 (CH_2); HRMS (ESI) Exact mass calculated for $C_{19}H_{23}O_4$ $[M+H]^+$: 315.1588, found: 315.1591.

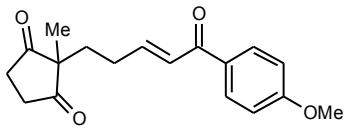


2-Methyl-2-[(*E*)-5-oxo-5-(pyridin-2-yl)pent-3-en-1-yl]cyclohexane-1,3-dione (335). The *title compound* was prepared according to the Representative Procedure from 3-(1-methyl-2,6-dioxocyclohexyl)propanal (547 mg, 3.00 mmol) and 1-(pyridin-2-yl)-2-(triphenylphosphanylidene)ethan-1-one (1.30 g, 3.41 mmol). Purification by column chromatography (20 to 40 to 50% EtOAc/petroleum ether) gave a grey solid (608 mg, 71%). R_f = 0.22 (40% EtOAc/petroleum ether); m.p. 73-74 °C (cyclohexane/EtOAc); IR 2931, 1722, 1688 (C=O), 1675 (C=O), 1627, 1582, 1329, 1220, 1136, 1036, 996, 785, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.70 (1H, ddd, *J* = 4.8, 1.7, 0.9 Hz, Ar**H**), 8.11 (1H, dt, *J* = 7.9, 1.0 Hz, Ar**H**), 7.85 (1H, td, *J* = 7.7, 1.7 Hz, Ar**H**), 7.57 (1H, dt, *J* = 15.7, 1.5 Hz, CH_2CH=C**H**), 7.47 (1H, ddd, *J* = 7.6, 4.8, 1.2 Hz, Ar**H**), 7.13 (1H, dt, *J* = 15.7, 6.7 Hz, CH_2CH=), 2.69 (4H, app t, *J* = 6.6 Hz, $CH_2CH_2CH_2$), 2.25-2.16 (2H, m, CH_2CH=), 2.09-2.02 (2H, m, CH_2CH_2CH=), 2.01-1.89 (2H, m, $CH_2CH_2CH_2$), 1.31 (3H, s, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 209.9 (2 x C), 189.3 (C), 154.0 (C), 148.8 (CH), 148.0 (CH), 137.0 (CH), 126.8 (CH), 125.0 (CH), 122.9 (CH), 65.0 (C), 38.0 (2 x CH_2), 34.5 (CH_2), 28.1 (CH_2), 20.5 (CH_3), 17.6 (CH_2); HRMS (ESI) Exact mass calculated for $C_{17}H_{19}NNaO_3$ $[M+Na]^+$: 308.1257, found: 308.1245.



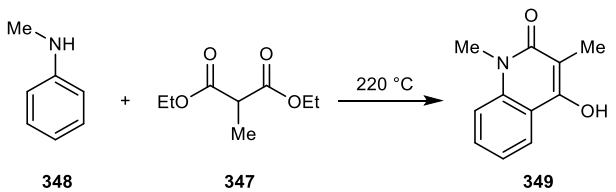
2-[(*E*)-5-(4-Chlorophenyl)-5-oxopent-3-enyl]-2-methylcyclopentane-1,3-dione (341). The *title compound* was prepared according to the Representative Procedure from 3-(1-

methyl-2,5-dioxocyclopentyl)propanal (673 mg, 4.00 mmol) and 1-(4-chlorophenyl)-2-(triphenylphosphoranylidene)ethanone (1.99 g, 4.80 mmol). Purification by column chromatography (7:3 Petroleum ether/EtOAc) gave a white solid (943 mg, 77%). R_f = 0.25 (70:30 hexane/EtOAc); m.p. 76-78 °C; IR (film) 2924, 1723 (C=O), 1671 (C=O), 1621, 1454, 1421, 1265, 1093, 739, 704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.87-7.83 (2H, dm, *J* = 8.5 Hz, Ar**H**), 7.46-7.43 (2H, dm, *J* = 8.5 Hz, Ar**H**), 6.90 (1H, dt, *J* = 15.4, 1.5 Hz, CH_2C**H**=), 6.79 (1H, d, *J* = 15.4 Hz, =C**H**C=O), 2.90-2.69 (4H, m, O=CC$\mathbf{H_2}$C$\mathbf{H_2}$C=O), 2.25-2.20 (2H, m, C$\mathbf{H_2}$CH=), 1.89-1.86 (2H, m, C$\mathbf{H_2}$$CH_2$C=), 1.18 (3H, s, C$\mathbf{H_3}$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 215.8 (2 × C), 189.0 (C), 147.8 (CH), 139.3 (C), 135.9 (C), 129.9 (2 × CH), 128.9 (2 × CH), 126.1 (CH), 56.1 (C), 35.0 (2 × CH_2), 32.7 (CH_2), 27.8 (CH_2), 20.0 (CH_3); HRMS (ESI) Exact mass calcd for $C_{17}H_{18}O_3Cl$ $[M+H]^+$: 305.0939, found: 305.0942.



2-[(*E*)-5-(4-Methoxyphenyl)-5-oxopent-3-enyl]-2-methylcyclopentane-1,3-dione (340). The *title compound* was prepared according to the Representative Procedure from 3-(1-methyl-2,5-dioxocyclopentyl)propanal (1.68 g, 10.0 mmol) and 1-(4-methoxyphenyl)-2-(triphenylphosphoranylidene)ethanone (4.92 g, 12.0 mmol). Purification by column chromatography (4:1 CH_2Cl_2/hexane) gave an orange solid (2.75 g, 91%). R_f = 0.75 (1:1 hexane/EtOAc); m.p. 88-90 °C; IR (film) 2931, 1719 (C=O), 1660 (C=O), 1587, 1417, 1338, 1257, 1224, 1026, 974 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 (2H, d, *J* = 8.8 Hz, Ar**H**), 6.95 (2H, d, *J* = 8.8 Hz, Ar**H**), 6.86-6.85 (2H, m, CH_2C**H**=C**H**), 3.88 (3H, s, OC$\mathbf{H_3}$), 2.83-2.74 (4H, m, O=CC$\mathbf{H_2}$C$\mathbf{H_2}$C=O), 2.22-2.20 (2H, m, C$\mathbf{H_2}$CH=), 1.90-1.87 (2H, m, C$\mathbf{H_2}$$CH_2$CH=), 1.18 (3H, s, CC$\mathbf{H_3}$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 215.9 (2 × C), 188.5 (C), 163.4 (C) 146.1 (CH), 130.8 (2 × CH), 130.4 (C), 126.3 (CH), 113.8 (2 × CH), 56.1 (C), 55.4 (CH_3), 35.0 (2 × CH_2), 33.0 (CH_2), 27.8 (CH_2), 19.8 (CH_3); HRMS (EI) Exact mass calcd for $C_{18}H_{20}O_4$ $[M]^+$: 300.1356, found: 300.1358.

4-Hydroxy-1,3-dimethyl-1,2-dihydroquinolin-2-one (349)

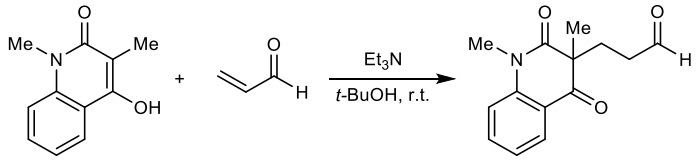


348 **347** **349**

A mixture of diethyl methylmalonate (4.70 mL, 27.6 mmol) and *N*-methylaniline (2.98 mL, 27.6 mmol) was heated to 220 °C in a 50 mL round bottomed flask topped with a short path distillation head until EtOH stopped distilling over. The mixture solidified upon cooling to room temperature. The crude product was washed with H_2O (50 mL) and CH_2Cl_2 (50 mL) and dried *in vacuo* to leave the title compound **349** as a yellow solid (3.12 g, 60%). R_f = 0.85 (1:1 MeOH/EtOAc); ^{1}H NMR (500 MHz, MeOD) δ 8.06 (1H, dd, *J* = 7.9, 1.9 Hz, Ar**H**), 7.64-7.60 (1H, m, Ar**H**), 7.53 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.32-7.28 (1H, m, Ar**H**), 3.73 (3H, s, NC**H**$_3$), 2.15 (3H, s, CC**H**$_3$).

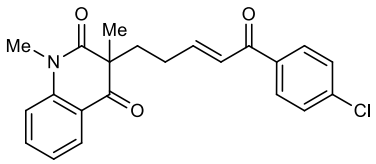
The data were in agreement with those reported in the literature.[131]

3-(1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl)propanal (808)



349 **324** **808**

To a solution of **349** (2.50 g, 13.3 mmol) in *t*-BuOH (30 mL) at room temperature was added acrolein (1.34 mL, 19.9 mmol) and Et_3N (2.21 mL, 15.9 mmol) in one portion and the resulting mixture was stirred for 18 h. The mixture was concentrated *in vacuo* to leave the *title compound* **808** as a colorless oil (3.02 g, 92%), which was used in the next step without further purification. R_f = 0.11 (7:3 hexane/EtOAc); IR 2976, 2941, 1721 (C=O), 1694 (C=O), 1655 (C=O), 1603, 1471, 1375, 1348, 1098, 758 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.69 (1H, t, *J* = 1.2 Hz, C**H**=O), 8.01 (1H, dd, *J* = 7.7, 1.7 Hz, Ar**H**), 7.66 (1H, td, *J* = 7.3, 1.8 Hz, Ar**H**) 7.72-7.18 (2H, m, Ar**H**), 3.48 (3H, s, NC**H**$_3$), 2.42-2.29 (4H, m, C**H**$_2$C**H**$_2$), 1.49 (3H, s, CC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 200.9 (CH), 196.7 (C), 173.0 (C), 143.0 (C), 136.2 (CH), 128.2 (CH), 123.3 (CH), 120.0 (C), 114.8 (CH), 56.4 (C), 39.6 (CH_2), 29.8 (CH_3), 29.1 (CH_2), 24.0 (CH_3); HRMS (EI) Exact mass calcd for $C_{14}H_{15}O_3N$ $[M]^+$: 245.1046, found: 245.1050.

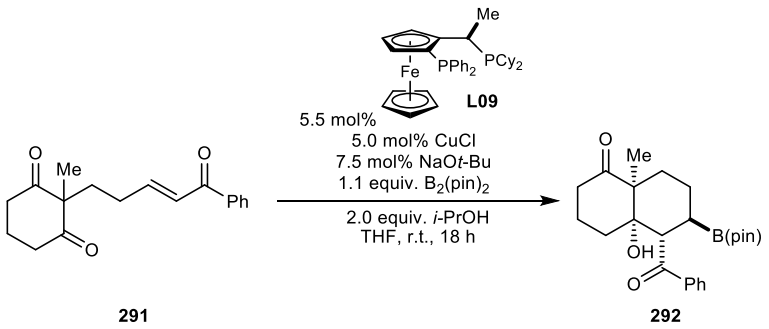


3-[(3*E*)-5-(4-Chlorophenyl)-5-oxopent-3-en-1-yl]-1,3-dimethyl-1,2,3,4-tetrahydroquinoline-2,4-dione (351). The *title compound* was prepared according to the Representative Procedure from the aldehyde **808** (1.61 g, 6.55 mmol) and 1-(4-chlorophenyl)-2-(triphenylphosphoranylidene)ethanone (3.26 g, 7.86 mmol). Purification by column chromatography (4:1 hexane/EtOAc) gave a pale yellow oil (1.35 g, 54%). R_f = 0.26 (4:1 hexane/EtOAc); IR 2923, 1694 (C=O), 1659 (C=O), 1618, 1601, 1587, 1472, 1348, 1092, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (1H, dd, *J* = 7.9, 1.7 Hz, Ar**H**), 7.75 (2H, dt, *J* = 8.7, 2.4 Hz, Ar**H**), 7.62 (1H, ddd, *J* = 8.5, 7.4, 1.8 Hz Ar**H**), 7.39 (2H, dt, *J* = 8.7, 2.4 Hz, Ar**H**), 7.19 (1H, td, *J* = 7.7, 0.8 Hz, Ar**H**), 7.13 (1H, d, *J* = 8.3 Hz, Ar**H**), 6.92 (1H, dt, *J* = 15.4, 6.6 Hz, CH_2C**H**=), 6.67 (1H, dt, *J* = 15.4, 1.3 Hz, =C**H**C=O), 3.46 (3H, s, NC$\mathbf{H}_3$), 2.30-2.21 (4H, m, C$\mathbf{H}_2$C$\mathbf{H}_2$), 1.49 (3H, s, CC$\mathbf{H}_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 196.9 (C), 189.0 (C), 173.2 (C), 148.6 (CH), 143.1 (C), 139.0 (C), 136.2 (CH), 136.0 (C), 129.8 (2 × CH), 128.8 (2 × CH), 128.1 (CH), 125.8 (CH), 123.2 (CH), 120.0 (C), 114.8 (CH), 56.7 (C), 35.9 (CH_2), 29.8 (CH_3), 28.7 (CH_2), 25.0 (CH_3); HRMS (EI) Exact mass calcd for $C_{22}H_{20}O_3ClN$ $[M]^+$: 381.1126, found: 381.1130.

6.1.4. Copper-Catalysed Borylative Aldol Cyclisations

Representative Procedure for the Copper-Catalysed Conjugate Boration-Cyclisation

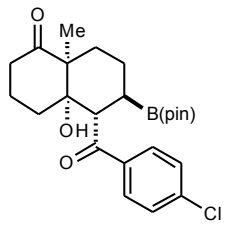
(4a*S*,5*S*,6*R*,8a*S*)-5-Benzoyl-4a-hydroxy-8a-methyl-6-(tetramethyl-1,3,2-dioxaborolan-2-yl)-decahydronaphthalen-1-one (292)



291 **292**

A solution of CuCl (1.5 mg, 0.015 mmol), ligand **L09** (11 mg, 0.017 mmol), $B_2(pin)_2$ (84 mg, 0.33 mmol) and NaO*t*-Bu (2.2 mg, 0.023 mmol) in THF (4 mL) was stirred at room temperature for 30 min. A solution of enone **291** (85 mg, 0.30 mmol) in THF (2 mL) was added *via* cannula, followed by *i*-PrOH (46 μL, 0.60 mmol) and the resulting mixture was

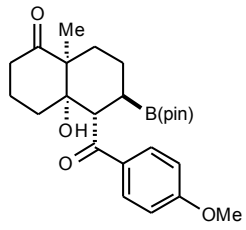
stirred at room temperature for 18 h. The reaction mixture was quenched with 50:50 10% HCl (aq.)/MeOH (0.2 mL) then neutralized with sat. $NaHCO_3$ (aq.) (0.2 mL), diluted with H_2O (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resultant crude product was purified by column chromatography (9:1 hexane/EtOAc) to give the *title compound* **292** as a colorless glassy film (88 mg, 71%) as a >95:5 ratio of diastereomers. R_f = 0.25 (4:1 hexane/EtOAc); $[\alpha]_D^{20}$ +7.1 (*c* 0.70, $CHCl_3$); IR 3456 (OH), 2930, 1705 (C=O), 1653 (C=O), 1449, 1371, 1325, 1219, 1142, 1009, 851, 708 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 (2H, dd, *J* = 8.4, 1.1 Hz, Ar**H**), 7.59 (1H, t, *J* = 7.4 Hz, Ar**H**), 7.47 (2H, t, *J* = 7.8 Hz, Ar**H**), 4.83 (1H, s, O**H**), 3.59 (1H, d, *J* = 12.0 Hz, C**H**COPh), 2.66-2.56 (1H, m, O=CC**H**$_2$), 2.27 (1H, dd, *J* = 15.4, 5.3 Hz, O=CC**H**$_2$), 2.14 (1H, ddd, *J* = 14.4, 14.3, 5.2 Hz, O=CCH_2CH_2C**H**$_2$), 2.06-1.99 (1H, m, C(CH_3)C**H**$_2$), 1.89-1.79 (1H, m, BC**H**), 1.71-1.47 (4H, m, O=CCH_2CH_2C**H**$_2$, C(CH_3)C**H**$_2$, O=CCH_2C**H**$_2$), 1.39-1.31 (1H, m, BCHC**H**$_2$), 1.30-1.19 (1H, m, BCHC**H**$_2$), 1.23 (3H, s, C(C**H**$_3$)CH_2), 0.89 (6H, s, C(C**H**$_3$)$_2$), 0.86 (6H, s, C(C**H**$_3$)$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 213.9 (C), 207.5 (C), 137.4 (C), 133.8 (CH), 129.4 (CH), 128.4 (CH), 83.2 (2 × C), 75.3 (C), 54.6 (C), 47.2 (CH), 36.4 (CH_2), 32.3 (CH_2), 29.6 (CH_2), 24.4 (CH_3), 24.3 (CH_2), 23.8 (CH_3), 22.9 (CH_3), 19.2 (CH_2), tertiary carbon (CH) next to boron not observed due to quadrupolar coupling effects of ^{11}B; HRMS (ESI) Exact mass calcd for $C_{24}H_{34}O_5{}^{10}B$ $[M+H]^+$: 412.2530, found: 412.2538; Enantiomeric excess was determined by HPLC with a CHIRALPAK IA-3 column (95:5 hexane:*i*-PrOH, 2.0 mL/min, 254 nm, 25 °C); t_r (major) = 5.8 min, t_r (minor) = 6.8 min; 95% ee.



(4a*S*,5*S*,6*R*,8a*S*)-5-[(4-Chlorophenyl)carbonyl]-4a-hydroxy-8a-methyl-6-(tetramethyl-1,3,2-dioxaborolan-2-yl)-decahydronaphthalen-1-one (356). The *title compound* was prepared according to the Representative Procedure from enone **334** (96 mg, 0.30 mmol). Purification by column chromatography (9:1 hexane/EtOAc) gave a white solid (97 mg, 74%) as a >95:5 ratio of diastereomers. R_f 0.25 (4:1 hexane/EtOAc); m.p. 163-165 °C; $[\alpha]_D^{20}$ +17.3 (*c* 0.52, $CHCl_3$); IR 3460 (OH), 2945, 1703 (C=O), 1661 (C=O), 1585, 1371, 1219, 1143, 1091, 851 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.01 (2H, d, *J* = 8.5 Hz, Ar**H**), 7.45 (2H, d, *J* = 8.5 Hz, Ar**H**), 4.51 (1H, s, O**H**), 3.52 (1H, d, *J* = 12.0 Hz, C**H**COAr), 2.65-2.57 (1H, m, O=CC**H**$_2$), 2.27 (1H, dd, *J* = 15.5, 5.2 Hz, O=CC**H**$_2$), 2.15 (1H, dt, *J* = 15.1, 4.9 Hz, O=CCH_2CH_2C**H**$_2$), 2.05-2.01 (1H, m,

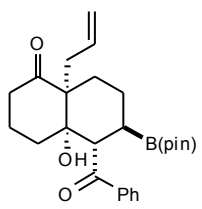
$C(CH_3)CH_2$), 1.85 (1H, ddd, J = 12.7, 12.6, 3.6 Hz, BC**H**), 1.69-1.55 (4H, m, $C(CH_3)CH_2$, $O{=}CCH_2CH_2$, $BCHCH_2$), 1.53-1.40 (1H, m, $O{=}CCH_2CH_2$), 1.33-1.25 (1H, m, $O{=}CCH_2CH_2CH_2$), 1.25 (3H, s, $C(CH_3)CH_2$), 0.95 (6H, s, $C(CH_3)_2$), 0.89 (6H, s, $C(CH_3)_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 213.8 (C), 206.4 (C), 140.3 (C) 136.0 (C), 130.8 (2 × CH), 128.6 (2 × CH), 83.4 (2 × C), 75.3 (C), 54.6 (C), 47.4 (CH), 36.4 (CH_2), 32.3 (CH_2), 29.6 (CH_2), 24.41 (2 × CH_3), 24.35 (2 × CH_3), 23.7 (CH_2), 22.9 (CH_3), 19.3 (CH_2), tertiary carbon (CH) next to boron not observed due to quadrupolar coupling effects of ^{11}B; HRMS (ESI) Exact mass calcd for $C_{24}H_{33}O_5{}^{10}BCl$ $[M+H]^+$: 446.2140, found: 446.2142; Enantiomeric excess was determined by HPLC with a CHIRALPAK IA-3 column (98:2 hexane:EtOH, 1.0 mL/min, 254 nm, 25 °C); t_r (major) = 9.5 min, t_r (minor) = 11.2 min; 94% ee.

Gram-scale experiment: A solution of CuCl (15.6 mg, 0.16 mmol), ligand **L09** (111 mg, 0.17 mmol), $B_2(pin)_2$ (879 mg, 3.45 mmol) and NaO*t*-Bu (22.7 mg, 0.24 mmol) in THF (40 mL) was stirred at room temperature for 30 min. A solution of enone **334** (1.00 g, 3.15 mmol) in THF (20 mL) was added *via* cannula, followed by *i*-PrOH (484 μL, 6.30 mmol) and the resulting mixture was stirred at room temperature for 18 h. The reaction mixture was quenched with 50:50 10% HCl (aq.)/MeOH (22 mL) then neutralized with sat. $NaHCO_3$ (aq.) (2 mL), diluted with H_2O (80 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by column chromatography on (9:1 hexane/EtOAc) gave a white solid (1.06 g, 77%) as a >95:5 ratio of diastereomers. Enantiomeric excess was determined by HPLC with a CHIRALPAK IA-3 column (98:2 hexane:EtOH, 1.0 mL/min, 254 nm, 25 °C); t_r (major) = 9.5 min, t_r (minor) = 11.2 min; 93% ee.



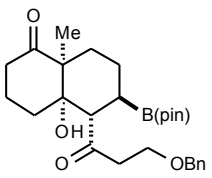
(4a*S*,5*S*,6*R*,8a*S*)-4a-Hydroxy-8a-methyl-5-[(4-methoxyphenyl)carbonyl]-6-(tetramethyl-1,3,2-dioxaborolan-2-yl)-decahydronaphthalen-1-one (357). The *title compound* was prepared according to a slight modification of the Representative Procedure from enone **330** (94 mg, 0.30 mmol) and *t*-BuOH (10 M in THF, 60 μL, 0.60 mmol) in place of *i*-PrOH. Purification by column chromatography (9:1 hexane/EtOAc) gave a white solid (109 mg, 82%) as a >95:5 ratio of diastereomers. R_f = 0.44 (3:2 hexane/EtOAc); m.p. 188-190 °C; $[\alpha]_D^{20}$ +16.4 (*c* 0.61, $CHCl_3$); IR 3429 (OH), 2980, 2930, 1738 (C=O), 1694 (C=O), 1454, 1371, 1323, 1142, 847, 741 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07-8.03 (2H, m, Ar**H**), 6.96-6.91 (2H, m, Ar**H**), 4.87 (1H, br s, O**H**),

3.89 (3H, s, OC**H**$_3$), 3.52 (1H, d, *J* = 12.0 Hz, C**H**COAr), 2.67-2.56 (1H, m, O=CC**H**$_2$), 2.28 (1H, dd, *J* = 15.4, 5.2 Hz, O=CCH$_2$CH$_2$C**H**$_2$), 2.14 (1H, td, *J* = 14.4, 5.1 Hz, O=CC**H**$_2$), 2.05-1.99 (1H, m, C(CH$_3$)C**H**$_2$), 1.88-1.79 (1H, m, BC**H**), 1.71-1.49 (5H, m, C(CH$_3$)C**H**$_2$, O=CCH$_2$C**H**$_2$, BCHC**H**$_2$, O=CCH$_2$CH$_2$C**H**$_2$), 1.41-1.36 (1H, m, BCHC**H**$_2$), 1.24 (3H, s, C(C**H**$_3$)CH$_2$), 0.91 (6H, s, C(C**H**$_3$)$_2$), 0.88 (6H, s, C(C**H**$_3$)$_2$); ^{13}C NMR (125.8 MHz, CDCl$_3$) δ 214.1 (C), 205.6 (C), 164.3 (C), 131.9 (CH), 130.4 (C), 113.5 (C), 83.2 (2 × C), 75.3 (C), 55.6 (CH$_3$), 54.6 (C), 46.7 (CH), 36.5 (CH$_2$), 32.3 (CH$_2$), 29.6 (CH$_2$), 24.4 (2 × CH$_3$), 24.3 (2 × CH$_3$), 23.8 (CH$_2$), 22.9 (CH$_3$), 19.4 (CH$_2$), tertiary carbon (CH) next to boron not observed due to quadrupolar coupling effects of ^{11}B; HRMS (ESI) Exact mass calcd for $C_{25}H_{36}O_6{}^{10}B$ [M+H]$^+$: 442.2636, found: 442.2638; Enantiomeric excess was determined by HPLC with a CHIRALPAK IA-3 column (98:2 hexane:EtOH, 1.0 mL/min, 254 nm, 25 °C); t_r (major) = 14.7 min, t_r (minor) = 16.4 min; >99% ee.

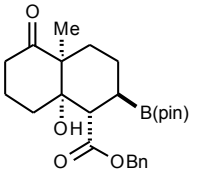


(4a*S*,5*S*,6*R*,8a*R*)-5-Benzoyl-4a-hydroxy-8a-(prop-2-en-1-yl)-6-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)-decahydronaphthalen-1-one (360). The *title compound* was prepared according to the Representative Procedure from enone **346** (93 mg, 0.30 mmol). Purification by column chromatography (9:1 hexane/EtOAc) gave a pale yellow solid (92 mg, 70%) as a >95:5 ratio of diastereomers. R_f = 0.59 (3:2 hexane/EtOAc); m.p. 115-120 °C; $[\alpha]_D^{20}$ +3.8 (*c* 0.53, CHCl$_3$); IR 3460 (OH), 2936, 1705 (C=O), 1657 (C=O), 1371, 1327, 1221, 1140, 920, 849, 716 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.07 (2H, dd, *J* = 8.3, 1.1 Hz, Ar**H**), 7.56 (1H, t, *J* = 7.4 Hz, Ar**H**), 7.46 (2H, t, *J* = 7.8 Hz, Ar**H**), 5.52 (1H, ddt, *J* = 17.4, 10.0, 7.4 Hz, C**H**=CH$_2$), 5.09-4.99 (2H, m, =C**H**$_2$), 4.67 (1H, br s, O**H**), 3.61 (1H, d, *J* = 12.0 Hz, C**H**COPh), 2.70 (1H, dd, *J* = 14.4, 7.6 Hz, O=CC**H**$_2$), 2.59-2.41 (2H, m, C**H**$_2$CH=), 2.31 (1H, dd, *J* = 15.0, 5.1 Hz, O=CC**H**$_2$), 2.23-2.12 (2H, m, O=CCH$_2$CH$_2$C**H**$_2$, C**H**$_2$CH$_2$CHB), 1.84 (1H, td, *J* = 12.2, 3.8 Hz, BC**H**), 1.71-1.48 (4H, m, O=CCH$_2$CH$_2$C**H**$_2$, C**H**$_2$CH$_2$CHB, O=CCH$_2$C**H**$_2$), 1.40-1.33 (1H, m, BCHC**H**$_2$), 1.32-1.20 (1H, m, BCHC**H**$_2$), 0.90 (6H, s, C(C**H**$_3$)$_2$), 0.86 (6H, s, C(C**H**$_3$)$_2$); ^{13}C NMR (125.8 MHz, CDCl$_3$) δ 212.2 (C). 207.4 (C), 137.4 (C), 133.9 (CH), 132.7 (CH), 129.4 (2 × CH), 128.4 (2 × CH), 118.1 (CH$_2$), 83.3 (2 × C), 75.7 (C), 58.2 (C), 47.3 (CH), 39.3 (CH$_2$), 37.7 (CH$_2$), 32.1 (CH$_2$), 26.8 (CH$_2$), 24.35 (2 × CH$_3$), 24.32 (2 × CH$_3$), 23.6 (CH$_2$), 19.5 (CH$_2$), tertiary carbon (CH) next to boron not observed due to quadrupolar coupling effects of ^{11}B; HRMS (ESI) Exact mass calcd for $C_{26}H_{36}O_5{}^{10}B$ [M+H]$^+$: 438.2687, found: 438.2690; Enantiomeric excess was determined by

HPLC with a CHIRALPAK IA-3 column (90:10 hexane:*i*-PrOH, 1.5 mL/min, 254 nm, 25 °C); t_r (major) = 5.2 min, t_r (minor) = 7.1 min; 95% ee.

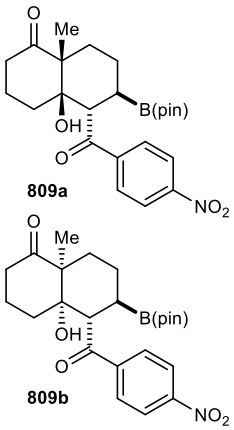


(4a*S*,5*S*,6*R*,8a*S*)-5-[3-(Benzyloxy)propanoyl]-4a-hydroxy-8a-methyl-6-(tetramethyl-1,3,2-dioxaborolan-2-yl)-decahydronaphthalen-1-one (359). The *title compound* was prepared according to the Representative Procedure from enone **336** (103 mg, 0.30 mmol). Purification by column chromatography (9:1 hexane/EtOAc) gave a colorless film (73 mg, 52%) as a >95:5 ratio of diastereomers. R_f = 0.38 (3:2 hexane/EtOAc); $[\alpha]_D^{20}$ +25.5 (*c* 0.47, $CHCl_3$); IR 3442 (OH), 2974, 2930, 1701 (C=O), 1373, 1319, 1144, 1092, 849, 735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.23 (5H, m, Ar**H**), 4.47 (1H, d, *J* = 11.2 Hz, C**H**$_2$Ph), 4.41 (1H, d, *J* = 11.2 Hz, C**H**$_2$Ph), 3.99 (1H, ddd, *J* = 10.9, 8.8, 3.1 Hz, C**H**$_2$OBn), 3.66 (1H, dt, *J* = 8.5, 4.1 Hz, C**H**$_2$OBn), 3.32 (1H, ddd, *J* = 12.4, 8.8, 4.0 Hz, C**H**$_2$CH$_2$OBn), 3.28 (1H, d, *J* = 12.7 Hz, O=CC**H**CHB), 3.18 (1H, br s, O**H**), 2.49 (1H, td, *J* = 14.3, 6.9 Hz, O=CC**H**$_2$CH$_2$CH$_2$), 2.39 (1H, dt, *J* = 7.4, 3.5 Hz, C**H**$_2$CH$_2$OBn), 2.21 (1H, td, *J* = 14.1, 4.6 Hz, O=CCH$_2$CH$_2$C**H**$_2$), 2.15-2.08 (1H, m, O=CC**H**$_2$CH$_2$CH$_2$), 1.91 (1H, td, *J* = 13.2, 4.3 Hz, C(CH$_3$)C**H**$_2$), 1.71-1.65 (1H, m, BCHC**H**$_2$), 1.64-1.56 (1H, m, BC**H**), 1.55-1.48 (1H, m, O=CCH$_2$C**H**$_2$CH$_2$), 1.46-1.34 (2H, m, BCHC**H**$_2$, O=CCH$_2$C**H**$_2$CH$_2$), 1.34-1.26 (2H, m, C(CH$_3$)C**H**$_2$, O=CCH$_2$CH$_2$C**H**$_2$), 1.23 (3H, s, C(C**H**$_3$)CH$_2$), 1.19 (6H, s, C(C**H**$_3$)$_2$), 1.13 (6H, s, C(C**H**$_3$)$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 215.0 (C), 214.9 (C), 136.8 (C), 128.6 (CH), 128.3 (CH), 128.1 (CH), 83.3 (2 × C), 78.3 (C), 73.9 (CH_2), 67.5 (CH_2), 58.7 (CH), 55.0 (C), 44.8 (CH_2), 36.7 (CH_2), 35.4 (CH_2), 27.7 (CH_2), 24.7 (2 × CH_3), 24.3 (2 × CH_3), 21.5 (CH_2), 19.5 (CH_2), 14.4 (CH_3), tertiary carbon (CH) next to boron not observed due to quadrupolar coupling effects of ^{11}B; HRMS (ESI) Exact mass calcd for $C_{27}H_{40}O_6{}^{10}B$ $[M+H]^+$: 470.2949, found: 470.2940; Enantiomeric excess was determined by HPLC with a CHIRALPAK IA-3 column (90:10 hexane:*i*-PrOH, 1.5 mL/min, 254 nm, 25 °C); t_r (major) = 7.5 min, t_r (minor) = 10.0 min; 92% ee.



Benzyl-(1*S*,2*R*,4a*S*,8a*S*)-8a-hydroxy-4a-methyl-5-oxo-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)-decahydronaphthalene-1-carboxylate (358). The *title compound* was prepared according to the Representative Procedure from enone **361** (94 mg, 0.30 mmol). Purification by column chromatography (9:1 hexane/EtOAc) gave a colorless film (104 mg, 79%) as a >95:5 ratio of

diastereomers. R_f = 0.86 (3:2 hexane/EtOAc); $[\alpha]_D^{20}$ −25.5 (*c* 0.51, $CHCl_3$); IR 3478 (OH), 1730 (C=O), 1703 (C=O), 1454, 1379, 1321, 1142, 968, 847, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39-7.30 (5H, m, Ar**H**), 5.26 (1H, d, *J* = 12.4 Hz, C**H**$_2$Ph), 5.11 (1H, d, *J* = 12.4 Hz, C**H**$_2$Ph), 3.27 (1H, br s, O**H**), 2.99 (1H, d, *J* = 12.4 Hz, C**H**CO_2Bn), 2.57 (1H, td, *J* = 14.3, 6.7 Hz, O=CC**H**$_2$), 2.31-2.22 (1H, m, O=CC**H**$_2$), 2.04 (1H, qt, *J* = 13.7, 4.3 Hz, O=CCH_2C**H**$_2$), 1.94 (1H, ddd, *J* = 12.8, 12.6. 4.1 Hz, C(CH_3)C**H**$_2$), 1.82-1.74 (1H, m, O=CCH_2C**H**$_2$), 1.73-1.67 (1H, m C(CH_3)C**H**$_2$), 1.62-1.43 (3H, BCHC**H**$_2$, BC**H**, O=CCH_2CH_2C**H**$_2$), 1.40-1.34 (1H, m, BCHC**H**$_2$), 1.23 (3H, s, C(C**H**$_3$)CH_2), 1.21-1.16 (1H, m, O=CCH_2CH_2C**H**$_2$), 1.18 (6H, s, C(C**H**$_3$)$_2$), 1.13 (6H, s, C(C**H**$_3$)$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 214.4 (C), 174.3 (C), 135.2 (C), 128.6 (2 × CH), 128.5 (CH), 128.2 (2 × CH), 83.3 (2 × C), 76.9 (C), 66.9 (CH_2), 54.4 (C), 50.4 (CH), 36.8 (CH_2), 35.1 (CH_2), 28.6 (CH_2), 24.7 (2 × CH_3), 24.3 (2 × CH_3), 21.6 (CH_2), 19.9 (CH_2), 14.9 (CH_3), tertiary carbon (CH) next to boron not observed due to quadrupolar coupling effects of ^{11}B; HRMS (ESI) Exact mass calcd for $C_{25}H_{36}O_6{}^{10}B$ $[M+H]^+$: 442.2636, found: 442.2637; Enantiomeric excess was determined by HPLC with a CHIRALPAK IA-3 column (90:10 hexane:*i*-PrOH, 1.2 mL/min, 254 nm, 25 °C); t_r (major) = 8.3 min, t_r (minor) = 9.3 min; 93% ee.

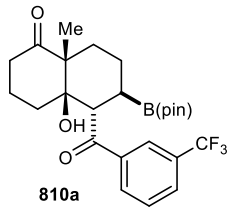


(4a*R*,5*S*,6*R*,8a*R*)-4a-Hydroxy-8a-methyl-5-[(4-nitrophenyl)carbonyl]-6-(tetramethyl-1,3,2-dioxaborolan-2-yl)-decahydronaphthalen-1-one (809a) and **(4a*S*,5*S*,6*R*,8a*S*)-4a-Hydroxy-8a-methyl-5-[(4-nitrophenyl)carbonyl]-6-(tetramethyl-1,3,2-dioxaborolan-2-yl)-decahydronaphthalen-1-one (809b)**. The *title compounds* **809a** and **809b** were prepared according to the Representative Procedure from enone **351** (99 mg, 0.30 mmol). Purification by column chromatography (9:1 hexane/EtOAc) gave **809a** as a yellow solid (67 mg, 49%) and **809b** as an off-white solid (40 mg, 29%).

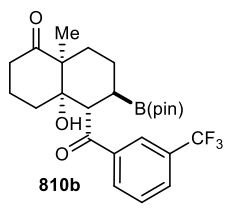
Data for **809a**: R_f = 0.32 (3:2 hexane/EtOAc); m.p. 198-200 °C; $[\alpha]_D^{20}$ +12.2 (*c* 0.49, $CHCl_3$); IR 3460 (OH), 2949, 1705 (C=O), 1655 (C=O), 1447, 1371, 1327, 1221, 1142, 920, 851 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.30-8.26 (2H, m, Ar**H**), 8.14-8.10 (2H, m, Ar**H**), 4.03 (1H, d, *J* = 12.5 Hz, C**H**COAr), 2.68 (1H, td, *J* = 14.4, 6.7 Hz, O=CC**H**$_2$), 2.48 (1H, td, *J* = 14.4, 4.6 Hz, O=CCH_2CH_2C**H**$_2$), 2.30-2.23 (1H, m, O=CC**H**$_2$), 2.10 (1H, td, *J* = 13.2, 4.3 Hz, C(CH_3)C**H**$_2$), 1.97-1.71 (4H, m, BC**H**, C(CH_3)C**H**$_2$, O=CCH_2C**H**$_2$), 1.62-1.42 (3H, m,

BCHC**H**$_2$, O=CCH$_2$CH$_2$C**H**$_2$), 1.37 (3H, s, C(C**H**$_3$)CH$_2$), 1.10 (6H, s, C(C**H**$_3$)$_2$), 1.00 (6H, s, C(C**H**$_3$)$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 214.0 (C), 203.7 (C), 149.7 (C), 144.7 (C), 129.5 (2 × CH), 123.4 (2 × CH), 83.6 (2 × C), 78.8 (C), 55.6 (C), 52.4 (CH), 36.6 (CH_2), 35.6 (CH_2), 27.8 (CH_2), 24.7 (2 × CH_3), 24.2 (2 × CH_3), 21.6 (CH_2), 20.1 (CH_2), 14.4 (CH_3), tertiary carbon (CH) next to boron not observed due to quadrupolar coupling effects of ^{11}B; HRMS (ESI) Exact mass calcd for $C_{24}H_{33}O_7{}^{10}BN$ $[M+H]^+$: 457.2381, found: 457.2381; Enantiomeric excess was determined by HPLC with a CHIRALPAK IA-3 column (90:10 hexane:*i*-PrOH, 1.5 mL/min, 254 nm, 25 °C); t_r (major) = 7.2 min, t_r (minor) = 21.1 min; 86% ee.

Data for **809b**: R_f = 0.45 (3:2 hexane/EtOAc); m.p. 168-170 °C; $[\alpha]_D^{20}$ −5.8 (*c* 0.52, $CHCl_3$); IR 3418 (OH), 2974, 2929, 1734 (C=O), 1653 (C=O), 1449, 1371, 1325, 1225, 1142, 847 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (2H, dd, *J* = 9.0, 2.0 Hz, Ar**H**), 8.23 (2H, dd, *J* = 9.0, 2.0 Hz, Ar**H**), 4.01 (1H, br s, O**H**), 3.58 (1H, d, *J* = 12.0 Hz, C**H**COAr), 2.61 (1H, ddd, *J* = 15.2, 13.9, 7.9 Hz, O=CC**H**$_2$), 2.27 (1H, dd, *J* = 15.4, 5.3 Hz, O=CC**H**$_2$), 2.17 (1H, dt, *J* = 14.5, 5.0 Hz, O=CCH$_2$CH$_2$C**H**$_2$), 2.09-2.01 (1H, m, C(CH$_3$)C**H**$_2$), 1.89 (1H, ddd, *J* = 12.6, 12.4, 3.2 Hz, BC**H**), 1.75-1.54 (4H, m, C(CH$_3$)C**H**$_2$, O=CCH$_2$C**H**$_2$, BCHC**H**$_2$), 1.46-1.31 (1H, m, O=CCH$_2$C**H**$_2$), 1.29-1.19 (1H, m, O=CCH$_2$CH$_2$C**H**$_2$), 1.24 (3H, s, C(C**H**$_3$)CH$_2$), 0.98 (6H, s, C(C**H**$_3$)$_2$), 0.89 (6H, s, C(C**H**$_3$)$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 213.4 (C), 206.5 (C), 150.5 (C), 142.4 (C), 130.2 (2 × CH), 123.5 (2 × CH), 83.6 (2 × C), 75.5 (C), 54.7 (C), 48.4 (CH), 36.3 (CH_2), 32.4 (CH_2), 29.6 (CH_2), 24.6 (2 × CH_3), 24.3 (2 × CH_3), 23.6 (CH_2), 22.9 (CH_3), 19.2 (CH_2), tertiary carbon (CH) next to boron not observed due to quadrupolar coupling effects of ^{11}B; HRMS (ESI) Exact mass calcd for $C_{24}H_{33}O_7{}^{10}BN$ $[M+H]^+$: 457.2381, found: 457.2380; Enantiomeric excess was determined by HPLC with a CHIRALPAK IA-3 column (90:10 hexane:*i*-PrOH, 1.5 mL/min, 254 nm, 25 °C); t_r (major) = 6.8 min, t_r (minor) = 8.1 min; 87% ee.



810a



810b

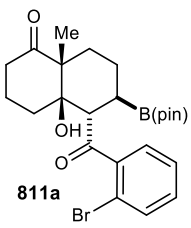
(4a*R*,5*S*,6*R*,8a*R*)-4a-Hydroxy-8a-methyl-5-[(3-trifluoromethylphenyl)carbonyl]-6-(tetramethyl-1,3,2-dioxaborolan-2-yl)-decahydronaphthalen-1-one (810a) and **(4a*S*,5*S*,6*R*,8a*S*)-4a-Hydroxy-8a-methyl-5-[(3-trifluoromethylphenyl)carbonyl]-6-(tetramethyl-1,3,2-dioxaborolan-2-yl)-decahydronaphthalen-1-one (810b)**. The *title compounds* **810a** and **810b** were prepared according to the

Representative Procedure from enone **332** (106 mg, 0.30 mmol). Purification by column chromatography (9:1 hexane/EtOAc) gave **810a** as a colorless film (22 mg, 15%) and **810b** as a colorless film (86 mg, 60%).

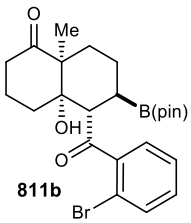
Data for **810a**: R_f = 0.29 (3:2 hexane/EtOAc); $[\alpha]_D^{20}$ +2.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (1H, s, Ar**H**), 8.18 (1H, d, *J* = 6.7 Hz, Ar**H**), 7.78 (1H, d, *J* = 8.7 Hz, Ar**H**), 7.59 (1H, t, *J* = 6.7 Hz, Ar**H**), 4.04 (1H, d, *J* = 12.6 Hz, C**H**COAr), 2.67 (1H, dt, *J* = 14.2, 6.7 Hz, O=CC**H**$_2$), 2.49 (1H, dt, *J* = 14.2, 5.1 Hz, O=CCH$_2$CH$_2$C**H**$_2$), 2.27 (1H, td, *J* = 14.7, 2.2 Hz, O=CC**H**$_2$), 2.11 (1H, dt, *J* = 13.6, 4.6 Hz, C(CH$_3$)C**H**$_2$), 1.93-1.87 (1H, m, O=CCH$_2$C**H**$_2$), 1.85-1.77 (2H, m, O=CCH$_2$C**H**$_2$, BCHC**H**$_2$), 1.62-1.53 (2H, m, BCHC**H**$_2$, O=CCH$_2$CH$_2$C**H**$_2$), 1.48-1.44 (1H, m, O=CCH$_2$CH$_2$C**H**$_2$), 1.39 (3H, s, C(C**H**$_3$)CH$_2$), 1.09 (6H, s, C(C**H**$_3$)$_2$), 0.99 (6H, s, C(C**H**$_3$)$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 214.2 (C), 203.6 (C), 140.6 (C), 132.0 (CH), 130.7 (C, q, $^2J_{CF}$ = 33.5 Hz), 128.8 (CH), 128.7 (CH, q, $^3J_{CF}$ = 3.4 Hz), 125.3 (CH, q, $^3J_{CF}$ = 3.5 Hz), 123.9 (C, q, $^1J_{CF}$ = 275.5 Hz), 83.6 (2 × C), 78.7 (C), 55.5 (C), 51.9 (CH), 36.7 (CH$_2$), 35.6 (CH$_2$), 27.9 (CH$_2$), 24.6 (2 × CH$_3$), 24.1 (2 × CH$_2$), 21.7 (CH$_2$), 20.1 (CH$_3$), 14.4 (CH$_2$), tertiary carbon (CH) next to boron not observed due to quadrupolar coupling effects of ^{11}B; ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.5 (3F, s); *m/z* (ESI) 503 ([M+Na]$^+$, 50), 481 ([M+H]$^+$, 45); Enantiomeric excess was determined by HPLC with a CHIRALPAK IA-3 column (90:10 hexane:*i*-PrOH, 1.5 mL/min, 254 nm, 25 °C); t_r (major) = 4.3 min, t_r (minor) = 8.0 min; 82% ee.

Data for **810b**: R_f = 0.49 (3:2 hexane/EtOAc); $[\alpha]_D^{20}$ +5.9 (*c* 0.51, $CHCl_3$); IR 3443 (OH), 2976, 2936, 1705 (C=O), 1659 (C=O), 1371, 1323, 1211, 1167, 1142, 1072, 999, 851 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (1H, s, Ar**H**), 8.23 (1H, d, *J* = 7.9 Hz, Ar**H**), 7.85 (1H, d, *J* = 7.8 Hz, Ar**H**), 7.62 (1H, t, *J* = 7.8 Hz, Ar**H**), 4.31 (1H, br s, O**H**), 3.58 (1H, d, *J* = 12.0 Hz, C**H**COAr), 2.61 (1H, ddd, *J* = 15.2, 13.9, 7.9 Hz, O=CC**H**$_2$), 2.29 (1H, dd, *J* = 15.4, 5.3 Hz, O=CCH$_2$CH$_2$C**H**$_2$), 2.16 (1H, td, *J* = 14.5, 5.0 Hz, O=CC**H**$_2$), 2.08-2.01 (1H, m, C(CH$_3$)C**H**$_2$), 1.87 (1H, ddd, *J* = 12.7, 12.5, 2.7 Hz, C(CH$_3$)C**H**$_2$), 1.72-1.54 (4H, m, BC**H**, O=CCH$_2$C**H**$_2$, BCHC**H**$_2$, O=CCH$_2$CH$_2$C**H**$_2$), 1.50-1.37 (1H, m, BCHC**H**$_2$), 1.31-1.25 (1H, m, O=CCH$_2$C**H**$_2$), 1.24 (3H, s, C(C**H**$_3$)CH$_2$), 0.95 (6H, s, C(C**H**$_3$)$_2$), 0.86 (6H, s, C(C**H**$_3$)$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 213.7 (C), 206.6 (C), 138.4 (C), 132.3 (CH), 131.1 (C, q, $^2J_{CF}$ = 33.0 Hz), 129.9 (CH, q, $^3J_{CF}$ = 3.6 Hz), 129.0 (CH), 126.2 (CH, q, $^3J_{CF}$ = 3.7 Hz), 123.6 (C, q, $^1J_{CF}$ 272.6 Hz), 83.4 (2 × C), 75.4 (C), 54.6 (C), 47.7 (CH), 36.3 (CH$_2$), 32.4 (CH$_2$), 29.6 (CH$_2$), 24.4 (2 × CH$_3$), 24.2 (2 × CH$_2$), 23.6 (CH$_2$), 22.9 (CH$_3$), 19.2 (CH$_2$), tertiary carbon (CH) next to boron not observed due to quadrupolar coupling effects of ^{11}B;

^{19}F NMR (376 MHz, $CDCl_3$) δ −63.7 (3F, s); HRMS (EI) Exact mass calcd for $C_{25}H_{32}O_5{}^{10}BF_3$ $[M]^+$: 480.2404, found: 480.2404; Enantiomeric excess was determined by HPLC with a CHIRALPAK IA-3 column (98:2 hexane:EtOH, 1.0 mL/min, 254 nm, 25 °C); t_r (major) = 9.2 min, t_r (minor) = 13.2 min; 89% ee.



811a

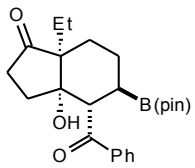


811b

(4a*R*,5*S*,6*R*,8a*R*)-4a-Hydroxy-8a-methyl-5-[(2-bromophenyl)carbonyl]-6-(tetramethyl-1,3,2-dioxaborolan-2-yl)-decahydronaphthalen-1-one (811a) and **(4a*S*,5*S*,6*R*,8a*S*)-4a-Hydroxy-8a-methyl-5-[(2-bromophenyl)carbonyl]-6-(tetramethyl-1,3,2-dioxaborolan-2-yl)-decahydronaphthalen-1-one (811b)**. The *title compounds* **811a** and **811b** were prepared according to the Representative Procedure from enone **333** (109 mg, 0.30 mmol). Purification by column chromatography (9:1 hexane/EtOAc) gave **811a** as an off-white solid (70 mg, 48%) and **811b** as an off-white solid (62 mg, 42%).

Data for **811a**: R_f = 0.32 (3:2 hexane/EtOAc); m.p. 138-140 °C; $[\alpha]_D^{20}$ +12.0 (*c* 0.50, $CHCl_3$); IR 3493 (OH), 2978, 2934, 1699 (C=O), 1678 (C=O), 1377, 1325, 1219, 1142, 1018, 849, 741 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (1H, dd, *J* = 7.7, 1.6 Hz, Ar**H**), 7.60 (1H, dd, *J* = 8.0, 1.0 Hz, Ar**H**), 7.38 (1H, td, *J* = 7.6, 1.1 Hz, Ar**H**), 7.26 (1H, td, *J* = 7.8, 1.7 Hz, Ar**H**), 3.86 (1H, d, *J* = 12.3 Hz, C**H**COAr), 2.67-2.57 (1H, m, O=CC**H**$_2$), 2.43 (1H, ddd, *J* = 18.0, 10.0, 4.5 Hz, O=CCH$_2$CH$_2$C**H**$_2$), 2.26 (1H, ddd, *J* = 6.0, 4.2, 2.3 Hz, O=CC**H**$_2$), 2.05 (1H, ddd, *J* = 13.3, 13.1, 4.1 Hz, C(CH$_3$)C**H**$_2$), 1.94-1.76 (5H, m, BC**H**, O=CCH$_2$C**H**$_2$, BCHC**H**$_2$, O=CCH$_2$CH$_2$C**H**$_2$, C(CH$_3$)C**H**$_2$), 1.53 (1H, ddd, *J* = 14.5, 14.1, 3.8 Hz, O=CCH$_2$C**H**$_2$), 1.41 (1H, ddd, *J* = 13.3, 3.9, 2.3 Hz, BCHC**H**$_2$), 1.25 (3H, s, C(C**H**$_3$)CH$_2$), 1.21 (6H, s, C(C**H**$_3$)$_2$), 1.13 (6H, s, C(C**H**$_3$)$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 214.2 (C), 206.6 (C), 143.3 (C), 134.2 (CH), 131.3 (CH), 129.3 (CH), 127.1 (CH), 118.6 (C), 83.5 (2 × C), 78.9 (C), 56.5 (CH), 55.5 (C), 36.7 (CH_2), 35.6 (CH_2), 28.1 (CH_2), 24.7 (CH_3), 24.5 (CH_3), 21.7 (CH_2), 19.9 (CH_2), 14.4 (CH_3), tertiary carbon (CH) next to boron not observed due to quadrupolar coupling effects of ^{11}B; HRMS (ESI) Exact mass calcd for $C_{24}H_{33}O_5{}^{10}B^{79}Br$ $[M+H]^+$: 490.1635, found: 490.1634; Enantiomeric excess was determined by HPLC with a CHIRALPAK IA-3 column (90:10 hexane:*i*-PrOH, 1.5 mL/min, 254 nm, 25 °C); t_r (major) = 8.9 min, t_r (minor) = 10.3 min; 68% ee

Data for **811b**: R_f = 0.39 (3:2 hexane/EtOAc); m.p. 117-120 °C; $[\alpha]_D^{20}$ +2.0 (*c* 0.51, $CHCl_3$); IR 3491 (OH), 2976, 2932, 1703 (C=O), 1661 (C=O), 1373, 1321, 1142, 1007, 851, 737 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.15 (1H, dd, *J* = 7.8, 1.6 Hz, Ar**H**), 7.68 (1H, dd, *J* = 7.9, 1.1 Hz, Ar**H**), 7.41 (1H, ddd, *J* = 7.7, 7.6, 1.2 Hz, Ar**H**), 7.33 (1H, ddd, *J* = 7.7, 7.5, 1.7 Hz, Ar**H**), 3.45 (1H, d, *J* = 12.2 Hz, C**H**COAr), 3.27 (1H, br s, O**H**), 2.55 (1H, ddd, *J* = 15.2, 13.9, 7.9 Hz, O=CC**H**$_2$), 2.17 (2H, m, *J* = 14.5, 14.4, 4.6 Hz, O=CCH$_2$CH$_2$C**H**$_2$, O=CC**H**$_2$), 2.04-1.98 (1H, m, C(CH$_3$)C**H**$_2$), 1.92 (1H, ddd, *J* = 13.0, 12.8, 3.3 Hz, C(CH$_3$)C**H**$_2$), 1.72-1.43 (6H, m, BC**H**, O=CCH$_2$C**H**$_2$, BCHC**H**$_2$, O=CCH$_2$CH$_2$C**H**$_2$), 1.22 (3H, s, C(C**H**$_3$)CH$_2$), 1.11 (6H, s, C(C**H**$_3$)$_2$), 1.03 (6H, s, C(C**H**$_3$)$_2$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 213.8 (C), 207.1 (C), 139.5 (C), 135.0 (CH), 132.6 (CH), 131.9 (CH), 126.7 (CH), 120.6 (C), 83.5 (2 × C), 75.8 (C), 55.1 (C), 51.7 (CH), 36.3 (CH_2), 31.9 (CH_2), 29.8 (CH_2), 24.7 (2 × CH_3), 24.5 (2 × CH_3), 23.3 (CH_2), 22.9 (CH_3), 18.7 (CH_2), tertiary carbon (CH) next to boron not observed due to quadrupolar coupling effects of ^{11}B; HRMS (ESI) Exact mass calcd for $C_{24}H_{33}O_5{}^{10}B{}^{79}Br$ $[M+H]^+$: 490.1635, found: 490.1631; Enantiomeric excess was determined by HPLC with a CHIRALPAK IA-3 column (50:50 hexane:EtOH, 1.2 mL/min, 254 nm, 25 °C); t_r (major) = 6.7 min, t_r (minor) = 12.7 min; 83% ee.

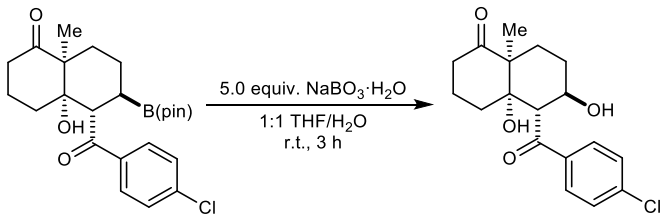


(3a*S*,4*S*,5*R*,7a*S*)-4-Benzoyl-3a-hydroxy-7a-ethyl-5-(tetramethyl-1,3,2-dioxaborolan-2-yl)-octahydro-1H-inden-1-one (389). The *title compound* was prepared according to a slight modification of the Representative Procedure from enone **343** (85 mg, 0.30 mmol) and *t*-BuOH (10 M in THF, 60 μL, 0.60 mmol) in place of *i*-PrOH. Purification by column chromatography (9:1 → 4:1 hexane/EtOAc) gave a white solid (110 mg, 89%) as a >95:5 ratio of diastereomers. R_f = 0.24 (4:1 hexane/EtOAc); m.p. 98-100 °C; $[\alpha]_D^{20}$ +33.0 (*c* 2.30, $CHCl_3$); IR 3416 (OH), 2974, 2928, 1734 (C=O), 1651 (C=O), 1369, 1325, 1225, 1140, 847 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.02-7.94 (2H, m, Ar**H**), 7.61 (1H, t, *J* = 7.4 Hz, Ar**H**), 7.48 (2H, t, *J* = 7.8 Hz, Ar**H**), 4.67 (1H, br s, O**H**), 3.39 (1H, d, *J* = 12.0 Hz, C**H**COPh), 2.48 (1H, ddd, 16.0, 8.8, 1.2 Hz, O=CC**H**$_2$), 2.31-2.21 (1H, m, O=CC**H**$_2$), 2.19-2.10 (2H, m, O=CCH$_2$C**H**$_2$, C**H**$_2$CH$_2$CHB), 1.79 (1H, dq, *J* = 15.2, 7.7 Hz, C**H**$_2$CH$_3$), 1.75-1.69 (1H, m, BCHC**H**$_2$), 1.67-1.60 (2H, m, C**H**$_2$CH$_3$, BC**H**), 1.60-1.55 (1H, m, O=CCH$_2$C**H**$_2$), 1.35-1.20 (2H, m, C**H**$_2$CH$_2$CHB, BCHC**H**$_2$), 0.90 (6H, s, C(C**H**$_3$)$_2$), 0.84 (6H, s, C(C**H**$_3$)$_2$), 0.75 (3H, t, *J* = 7.6 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 216.9 (C), 207.2 (C), 138.1 (C), 133.9 (CH), 128.8 (2 × CH), 128.6 (2 × CH), 83.3 (2 × C), 77.6 (C), 56.8 (C), 48.5 (CH),

34.8 (CH_2), 30.8 (CH_2), 24.9 (CH_2), 24.4 (2 × CH_2), 24.34 (2 × CH_3), 24.27 (2 × CH_3), 7.3 (CH_3), tertiary carbon (CH) next to boron not observed due to quadrupolar coupling effects of ^{11}B; HRMS (ESI) Exact mass calcd for $C_{24}H_{34}O_5{}^{10}B$ $[M+H]^+$: 412.2530, found: 412.2520; Enantiomeric excess was determined by HPLC with a CHIRALPAK IA-3 column (90:10 hexane:*i*-PrOH, 1.5 mL/min, 254 nm, 25 °C); t_r (major) = 7.3 min, t_r (minor) = 12.7 min; 96% ee.

6.1.5. C-B Bond Transformations

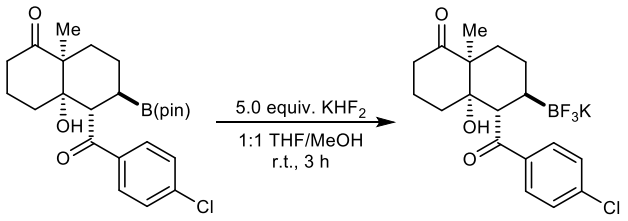
(4a*S*,5*S*,6*R*,8a*S*)-5-[(4-Chlorophenyl)carbonyl]-4a,6-dihydroxy-8a-methyldecahydronaphthalen-1-one (395)



356 **395**

To a stirred solution of **356** (127 mg, 0.30 mmol) in THF (1 mL) was added a suspension of $NaBO_3 \cdot H_2O$ (149 mg, 1.50 mmol) in H_2O (1 mL) in one portion and the resulting was mixture stirred vigorously at room temperature for 3 h open to air. The reaction mixture was then diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (1:1 hexane/EtOAc) gave the *title compound* **395** as a white solid (87 mg, 86%). R_f = 0.40 (1:1 hexane/EtOAc); m.p. 180-185 °C; $[\alpha]_D^{20}$ −1.7 (*c* 0.58, $CHCl_3$); IR 3406 (OH), 2949, 2938, 1684 (C=O), 1651 (C=O), 1589, 1400, 1325, 1084, 1026, 833 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (2H, d, *J* = 8.6 Hz, Ar**H**), 7.47 (2H, d, *J* = 8.6 Hz, Ar**H**), 4.83 (1H, s, O**H**), 4.37-4.32 (1H, m, C**H**OH), 3.43 (1H, d, *J* =10.3 Hz, C**H**CHOH), 2.63-2.55 (1H, m, O=CC$\mathbf{H}_2$), 2.27 (1H, dd, *J* = 15.1, 5.3 Hz, O=CC$\mathbf{H}_2$), 2.18-2.05 (2H, m, $CH_2CH_2C\mathbf{H}_2$, $C\mathbf{H}_2CH_2CHOH$), 1.94-1.87 (1H, m, $C\mathbf{H}_2CHOH$), 1.77-1.67 (3H, m, $CH_2C\mathbf{H}_2CH_2$, $C\mathbf{H}_2C\mathbf{H}_2CHOH$), 1.43 (1H, d, *J* = 14.5 Hz, $CH_2CH_2C\mathbf{H}_2$), 1.39-1.29 (1H, m, $CH_2C\mathbf{H}_2CH_2$), 1.23 (3H, s, CH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 213.1 (C), 206.8 (C), 140.7 (C), 137.0 (C), 130.1 (2 × CH), 129.2 (2 × CH), 78.1 (C), 71.5 (CH), 54.1 (C), 53.8 (CH), 36.3 (CH_2), 32.5 (CH_2), 32.2 (CH_2), 27.7 (CH_2), 21.9 (CH_3), 19.4 (CH_2); HRMS (ESI) Exact mass calcd for $C_{18}H_{22}ClO_4$ $[M+H]^+$: 337.1201, found: 337.1207.

(4a*S*,5*S*,6*R*,8a*S*)-5-[(4-Chlorophenyl)carbonyl]-4a-hydroxy-8a-methyl-6-trifluoroborate potassium (396)



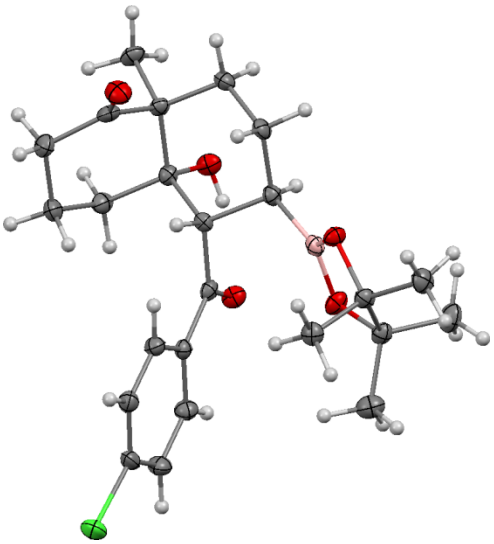
356 **396**

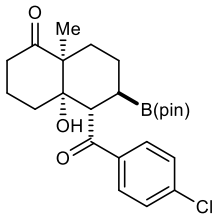
To a stirred suspension of **356** (133 mg, 0.30 mmol) in MeOH (1 mL) was added a solution of KHF_2 (149 g, 1.50 mmol) in H_2O (1 mL) in one portion and the resulting mixture was stirred vigorously at room temperature for 3 h. The solvent was evaporated *in vacuo* and the white solid obtained was washed with acetone (5 × 15 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the *title compound* **396** as a white solid (104 mg, 82%). R_f = 0.60 (2:1 MeOH/CH_2Cl_2); m.p. 210-220 °C; $[\alpha]_D^{20}$ +16.3 (*c* 0.49, MeOH); IR 3443, 2936, 1703 (C=O), 1665 (C=O), 1587, 1400, 1092, 1031, 959 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 8.01 (2H, d, *J* = 9.3 Hz, Ar**H**), 7.45 (2H, d, *J* = 9.3 Hz, Ar**H**), 3.39 (1H, d, *J* = 12.0 Hz, C**H**COAr), 2.63-2.56 (1H, m, O=CC**H**$_2$), 2.16-2.06 (2H, m, O=CC**H**$_2$, O=CCH$_2$CH$_2$C**H**$_2$), 1.92 (1H, d, *J* = 12.9 Hz, C**H**$_2$CHB), 1.58-1.48 (3H, m, C**H**$_2$C**H**$_2$CHB, CH$_2$C**H**$_2$CH$_2$), 1.45-1.37 (2H, m, C**H**$_2$CH$_2$CHB, CH$_2$C**H**$_2$CH$_2$), 1.26 (1H, d, *J* = 16.7 Hz, O=CCH$_2$CH$_2$C**H**$_2$), 1.15 (s, 3H, C**H**$_3$); ^{13}C NMR (125.8 MHz, CD_3OD) δ 216.5 (C), 211.0 (C), 140.1 (C), 139.3 (C), 131.5 (2 × CH), 129.6 (2 × CH), 77.0 (C), 56.1 (C), 50.3 (CH), 37.2 (CH_2), 33.3 (CH_2), 31.4 (CH_2), 24.9 (CH_2), 23.8 (CH_3), 20.1 (CH_2), tertiary carbon (CH) next to boron not observed due to quadrupolar coupling effects of ^{11}B; ^{19}F NMR (376 MHz, CD_3OD) δ 143.5; HRMS (ESI) Exact mass calcd for $C_{18}H_{20}{}^{10}BClF_3O_3$ $[M\text{-}K^+]^-$: 386.1188, found: 386.1190.

6.1.6 Stereochemical Determinations and X-ray Structures

The relative and absolute stereochemistry of product **356**[o] (enantiomerically pure material) was determined by X-ray crystallography:

[o] X-Ray data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif149.

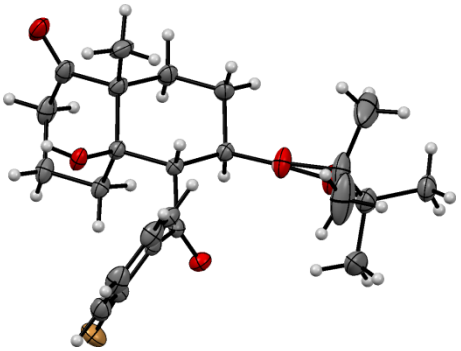


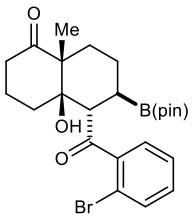


356

The absolute stereochemistry of all other products was assigned by analogy to **356**.

The relative stereochemistry of product **311a**[p] (racemic material obtained using $P(OEt)_3$ as an achiral ligand) was determined by X-ray crystallography:





811a

The relative stereochemistries of products **292**, **357**, **358**, **359**, **360**, **311b**, **810a**, **810b**, **809a** and **809b** were assigned by analogy to the X-ray structures of **356** and **811a** and by comparison of the ^{1}H NMR spectra (see Figure 1).

The relative stereochemistry of product **389**[q] (racemic material obtained using $P(OEt)_3$ as an achiral ligand) was determined by X-ray crystallography:

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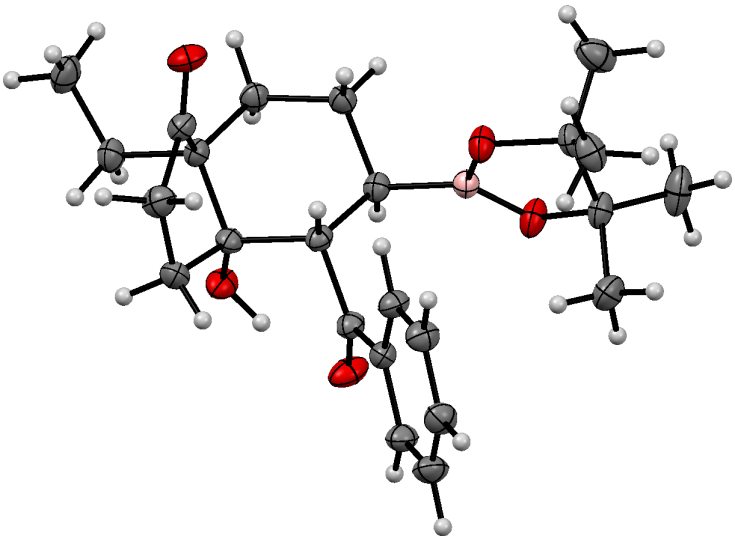
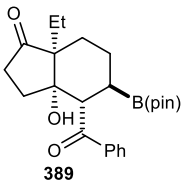
[p] I) X-Ray data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif150.





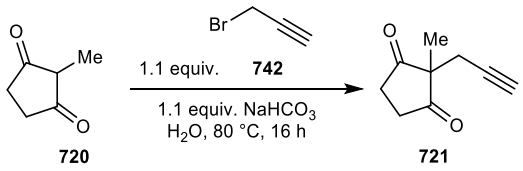
389

The relative stereochemistry of the major diastereomers of products **387**, **388**, **390**, **391** and **392** was assigned by analogy to the X-ray crystal structures of **389** and on the similarity of their respective ^{1}H NMR spectra.

6.2. Iridium-Catalysed Arylative Cyclization of Alkynones by 1,4-Iridium Migration

6.2.1. Substrate Precursor Synthesis

2-Methyl-2-(prop-2-yn-1-yl)cyclopentane-1,3-dione (721)



$NaHCO_3$ (5.89 g, 56.1 mmol) was gradually added to a stirred suspension of 2-methyl-1,3-cyclopentadione (5.72 g, 51.0 mmol) in H_2O (250 mL). After the frothing had finished,

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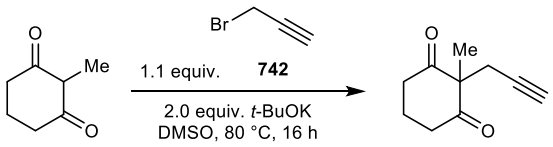
[q] I) X-Ray data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif150.

propargyl bromide (6.25 mL, 56.1 mmol) was added and the resulting mixture was heated at 80 °C for 16 h. The reaction was cooled to room temperature and the mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (1:1 hexane:EtOAc) gave the *title compound* **721** as a white solid (7.1 g, 84%). R_f = 0.15 (40% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.88-2.80 (4H, m, C**H**$_2$C**H**$_2$), 2.49 (2H, d, J = 2.8 Hz, CC**H**$_2$C), 2.00 (1H, t, J = 2.8 Hz, C≡C**H**), 1.15 (3H, s, C**H**$_3$).

The data were in agreement with those in the literature.[122a]

2-Methyl-2-(prop-2-yn-1-yl)cyclohexane-1,3-dione (724)

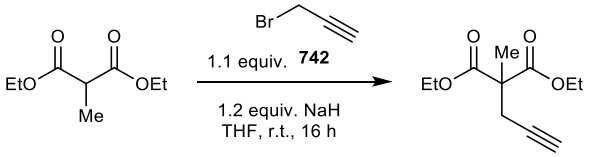


723 **724**

Propargyl bromide (12.3 mL, 110 mmol) was slowly added to a solution of 2-methyl-1,3-cyclohexadione (12.6 g, 100 mmol), *t*-BuOK (12.3 g, 220 mmol) in DMSO (250 mL). The resulting mixture at 80 °C for 16 h. The reaction was cooled to room temperature, water (250 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 × 200 mL). The combined organic phases were washed with brine (3 × 50 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (1:1 hexane:EtOAc) gave the *title compound* **724** as a white solid (17.1 g, 95%). R_f = 0.17 (40% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.79-2.64 (6H, m, C**H**$_2$CH$_2$C**H**$_2$ and CC**H**$_2$C), 2.08-1.92 (3H, m, CH$_2$C**H**$_2$CH$_2$ and C≡C**H**), 1.33 (3H, s, C**H**$_3$).

The data were in agreement with those in the literature.[132]

Diethyl 2-methyl-2-(prop-2-yn-1-yl)malonate (760)

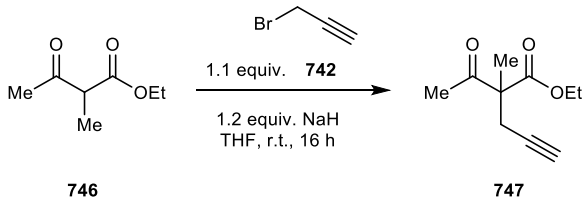


759 **760**

To a suspension of NaH (0.92 g, 24 mmol) in THF (50 mL) was added dropwise diethyl methyl malonate (3.40 mL, 20.0 mmol) at 0 °C. The reaction was warmed to room temperature and stirred for 1 h. Propargyl bromide (2.45 mL, 22.0 mmol) was added dropwise and left stirring at room temperature for 16 h. The reaction mixture was cold down to 0 °C and quenched with 10% aqueous HCl (10 mL). Brine (50 mL) was added and the mixture was extracted with Et_2O (2 × 25 mL). The combined organic phases were washed with brine (3 × 50 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (7:3 hexane:EtOAc) gave the *title compound* **XX** as a white solid (4.1 g, 78%). R_f = 0.45 (30% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22-4.16 (4H, m, O=CC**H**$_2$CH$_3$), 2.76 (2H, d, *J* = 2.7 Hz, C**H**$_2$C≡), 2.01 (1H, t, *J* = 2.7 Hz C≡C**H**), 1.53 (3H, s, CC**H**$_3$), 1.24 (6H, t, *J* = 7.06 Hz, O=CCH$_2$C**H**$_3$).

The data were in agreement with those in the literature.[133]

Ethyl 2-acetyl-2-methylpent-4-ynoate (747)



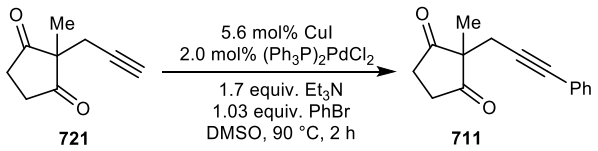
746 **747**

To a suspension of NaH (0.92 g, 24 mmol) in THF (50 mL) was added dropwise ethyl 2-methylacetoacetate (3.76 mL, 20.0 mmol) at 0 °C. The reaction was warmed to room temperature and stirred for 1 h. Propargyl bromide (2.45 mL, 22.0 mmol) was added dropwise and left stirring at room temperature for 16 h. The reaction mixture was cold down to 0 °C and quenched with 10% aqueous HCl (10 mL). Brine (50 mL) was added and the mixture was extracted with Et_2O (2 × 25 mL). The combined organic phases were washed with brine (3 × 50 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (6:4 hexane:EtOAc) gave the *title compound* **XX** as a white solid (3.7 g, 86%). R_f = 0.33 (30% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26-4.19 (2H, m, O=CC**H**$_2$CH$_3$), 2.79-2.67 (2H, m, C**H**$_2$C≡), 2.01 (1H, t, *J* = 2.7 Hz C≡C**H**), 2.19 (3H, s, O=CC**H**$_3$), 2.02 (1H, t, *J* = 2.8 Hz), 1.49 (3H, s, CC**H**$_3$), 1.27 (3H, t, *J* = 7.13 Hz, O=CCH$_2$C**H**$_3$).

The data were in agreement with those in the literature.[134]

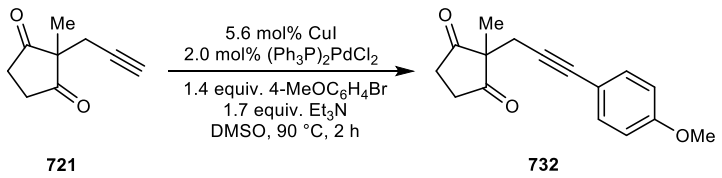
6.2.2. Substrate Synthesis

2-Methyl-2-(3-phenylprop-2-yn-1-yl)cyclopentane-1,3-dione (711)



2-Methyl-2-propargyl-1,3-cyclopentanedione (**721**) (1.50 g, 10.0 mmol) was added to a solution of $Pd(PPh_3)_2Cl_2$ (140 mg, 0.199 mmol), CuI (106 mg, 0.557 mmol), and Et_3N (2.4 mL, 17.2 mmol) in anhydrous DMSO (20 mL). Bromobenzene (1.08 mL, 10.3 mmol) was added and the mixture was stirred at 90 °C for 2 h. The reaction was cooled to room temperature, water (50 mL) was added, and the mixture was extracted with Et_2O (50 mL). The combined organic phases were washed with 10% aqueous HCl (3 × 20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/hexane) gave the *title compound* **711** (1.90 g, 84%) as a pale yellow solid. R_f = 0.35 (30% EtOAc/hexane); m.p. 64-65 °C (Et_2O/hexane); IR 2970, 1721 (C=O), 1412, 1065, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.27 (5H, m, Ar**H**), 2.90-2.80 (4H, m, C**H**$_2$C**H**$_2$), 2.70 (2H, s, C**H**$_2$C≡C), 1.19 (3H, s, C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.6 (2 × C), 131.6 (2 × CH), 128.3 (CH), 128.3 (2 × CH), 122.5 (C), 83.9 (C), 82.9 (C), 55.5 (C), 36.0 (2 × CH_2), 25.9 (CH_2), 18.9 (CH_3); HRMS (ESI) Exact mass calcd for $C_{15}H_{18}NO_2$ $[M+NH_4]^+$: 244.1338, found: 244.1332.

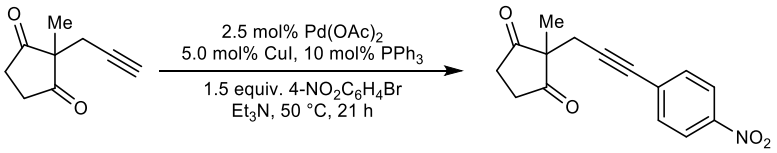
2-[3-(4-Methoxyphenyl)prop-2-yn-1-yl]-2-methylcyclopentane-1,3-dione (732)



2-Methyl-2-propargyl-1,3-cyclopentanedione (**721**) (1.50 g, 10.0 mmol) was added to a solution of $Pd(PPh_3)_2Cl_2$ (140 mg, 0.199 mmol), CuI (106 mg, 0.557 mmol), and Et_3N (2.4 mL, 17.2 mmol) in anhydrous DMSO (20 mL). 4-Bromoanisole (1.72 mL, 13.7 mmol) was added and the mixture was stirred at 90 °C for 2 h. The reaction was cooled to room

temperature, water (50 mL) was added, and the mixture was extracted with Et_2O (50 mL). The organic layer was washed with 10% aqueous HCl (3 × 20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/hexane) gave the *title compound* **732** (1.82 g, 71%) as a brown solid. R_f = 0.33 (30% EtOAc/hexane); m.p. 80-85 °C (hexane); IR 2965, 1722 (C=O), 1508, 1242, 1032, 833 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.80 (2H, d, *J* = 8.9 Hz, Ar**H**), 3.80 (3H, s, OC**H**$_3$), 2.89-2.78 (4H, m, C**H**$_2$C**H**$_2$), 2.68 (2H, s, C**H**$_2$C≡C), 1.17 (3H, s, CC**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.8 (2 × C), 159.6 (C), 133.0 (2 × CH), 114.6 (C), 113.9 (2 × CH), 82.7 (C), 82.4 (C), 55.5 (C), 55.3 (CH_3), 36.0 (2 × CH_2), 26.2 (CH_2), 18.8 (CH_3); HRMS (ESI) Exact mass calcd for $C_{16}H_{17}O_3$ $[M+H]^+$: 257.1178, found: 257.1173.

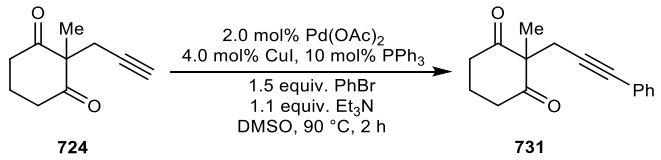
2-Methyl-2-[3-(4-nitrophenyl)prop-2-yn-1-yl]cyclopentane-1,3-dione (730)



721 **730**

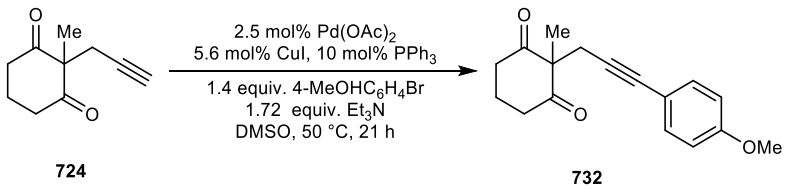
2-Methyl-2-propargyl-1,3-cyclopentanedione (**721**) (1.50 g, 10.0 mmol) was added to a solution of $Pd(OAc)_2$ (56 mg, 0.25 mmol), PPh_3 (262 mg, 1.00 mmol), CuI (106 mg, 0.56 mmol), and Et_3N (2.4 mL, 17.2 mmol) in anh. DMSO (20 mL). A solution of 1-Bromo-4-nitrobenzene (2.70 g, 11.0 mmol) in anh. DMSO (5 mL) was added and the mixture was stirred at 90 °C for 2 h. The reaction was cooled to room temperature, water (50 mL) was added, and the mixture was extracted with Et_2O (50 mL). The organic layer was washed with 10% aqueous HCl (3 × 20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/hexane) gave the *title compound* **730** (1.82 g, 71%) as a pale orange solid. R_f = 0.29 (30% EtOAc/hexane); m.p. 124-126 °C (EtOAc/hexane); IR 1720 (C=O), 1338, 1076, 853, 745, 687 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.14 (2H, d, *J* = 8.9 Hz, Ar**H**), 7.47 (2H, d, *J* = 8.9 Hz, Ar**H**), 2.94-2.76 (4H, m, C**H**$_2$C**H**$_2$), 2.74 (2H, s, C**H**$_2$C≡C), 1.22 (3H, s, CC**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.6 (2 × C), 147.1 (C), 132.4 (2 × CH), 129.5 (C), 123.5 (2 × CH), 89.9 (C), 81.1 (C), 55.3 (C), 35.6 (2 × CH_2), 25.0 (CH_2), 19.4 (CH_3); HRMS (EI) Exact mass calcd for $C_{15}H_{13}O_4N$ $[M]^+$: 271.0839, found: 271.0840.

2-Methyl-2-(3-phenylprop-2-yn-1-yl)cyclohexane-1,3-dione (731)



2-Methyl-2-(1-propyn-3-yl)cyclohexane-1,3-dione (**724**) (1.48 g, 9.01 mmol) was added to a solution of $Pd(OAc)_2$ (40.4 mg, 0.180 mmol), PPh_3 (189 mg, 0.721 mmol), CuI (68.6 mg, 0.360 mmol), and Et_3N (1.38 mL, 9.90 mmol) in anhydrous DMSO (20 mL). A solution of 3-bromobenzene (1.41 mL, 13.5 mmol) in anhydrous DMSO (10 mL) was added and the mixture was stirred at 90 °C for 2 h. The reaction was cooled to room temperature, water (50 mL) was added, and the mixture was extracted with Et_2O (50 mL). The organic phase was washed with 10% aqueous HCl (3 × 20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/hexane) gave the *title compound* **731** (1.63 g, 75%) as a pale yellow solid. R_f = 0.33 (30% EtOAc/hexane); m.p. 60-65 °C (hexane); IR 2967, 1694 (C=O), 1410, 1315, 1022, 766 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.33 (2H, m, Ar**H**), 7.28-7.26 (3H, m, Ar**H**), 2.87 (2H, s, C**H**$_2$C≡C), 2.73 (4H, td, *J* = 7.2, 2.1 Hz, C**H**$_2$CH$_2$C**H**$_2$), 2.01 (2H, qd, *J* = 7.2, 2.1 Hz, CH$_2$C**H**$_2$CH$_2$), 1.36 (3H, s, C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.3 (2 × C), 131.6 (2 × CH), 128.2 (2 × CH), 128.0 (CH), 123.1 (C), 85.6 (C), 83.0 (C), 64.0 (C), 38.5 (2 × CH_2), 26.4 (CH_2), 21.7 (CH_3), 17.3 (CH_2); HRMS (ESI) Exact mass calcd for $C_{16}H_{17}O_2$ $[M+H]^+$: 241.1223, found: 241.1211.

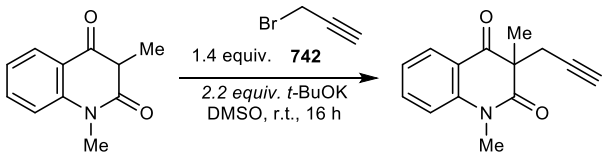
2-[3-(4-Methoxyphenyl)prop-2-yn-1-yl]-2-methylcyclopentane-1,3-dione (732)



2-Methyl-2-(1-propyn-3-yl)cyclohexane-1,3-dione (**724**) (1.64 g, 10.0 mmol) was added to a solution of $Pd(OAc)_2$ (56 mg, 0.25 mmol), PPh_3 (262 mg, 1.00 mmol), CuI (106 mg, 0.557 mmol), and Et_3N (2.4 mL, 17.2 mmol) in anhydrous DMSO (20 mL). A solution of 4-bromoanisole (1.72 mL, 13.7 mmol) in anhydrous DMSO (10 mL) was added and the

mixture was stirred at 90 °C for 2 h. The reaction was cooled to room temperature, water (50 mL) was added, and the mixture was extracted with Et_2O (50 mL). The organic phase was washed with 10% aqueous HCl (3 × 20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/hexane) to give the *tittle compound* **732** (2.21 g, 82%) as a pale yellow solid. R_f = 0.28 (30% EtOAc/hexane); m.p. 70-75 °C (hexane); IR 2695, 1721 (C=O), 1508, 1244, 1032, 841 cm^{-1}; 7.30-7.24 (2H, m, Ar**H**), 6.82-6.76 (2H, m, Ar**H**), 3.79 (3H, s, OC**H**$_3$), 2.84 (2H, s, C**H**$_2$C≡C), 2.73 (4H, t, *J* = 3.8 Hz, C**H**$_2$CH$_2$C**H**$_2$), 2.08-1.92 (2H, m, CH$_2$C**H**$_2$CH$_2$), 1.34 (3H, s, CC**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.4 (2 × C), 159.4 (C), 133.0 (2 × CH), 115.2 (C), 113.8 (2 × CH), 83.9 (C), 82.9 (C), 64.0 (C), 55.3 (CH_3), 38.6 (2 × CH_2), 26.8 (CH_2), 21.5 (CH_3), 17.3 (CH_2); HRMS (ESI) Exact mass calcd for $C_{17}H_{19}O_3$ $[M+H]^+$: 271.1334, found: 271.1329.

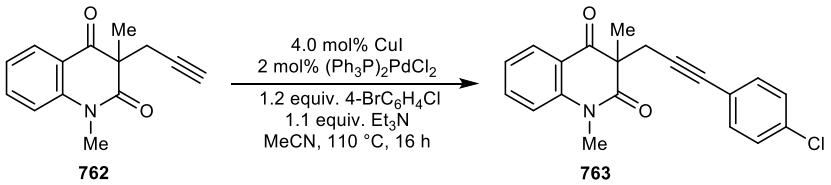
1-Methyl-3-methyl-3-(2-propynyl)-1,3-dihydroquinoline-2,4-dione (762)



349 **762**

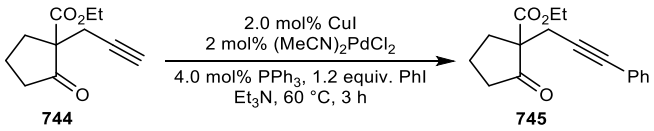
Propargyl bromide (80% solution in toluene, 858 µL, 7.70 mmol) was added to a solution of 1,3-dimethyl-1,2,3,4-tetrahydroquinoline-2,4-dione (**349**) (1.04 g, 5.50 mmol) and *t*-BuOK (678 mg, 6.04 mmol) in DMSO (50 mL). The mixture was stirred at room temperature for 16 h, diluted with water (50 mL), and extracted with EtOAc (3 × 25 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/hexane) gave the *title compound* **762** (650 mg, 52%) as a yellow oil. R_f = 0.33 (25% EtOAc/petroleum ether); IR 3272 (C≡**C**-**H**), 1698 (C=O), 1656 (C=O), 1375, 1102, 758 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06-8.03 (1H, m, Ar**H**), 7.68-7.63 (1H, m, Ar**H**), 7.27-7.18 (2H, m, Ar**H**), 3.51 (3H, s, NC**H**$_3$), 2.90 (2H, d, *J* = 2.6 Hz, C**H**$_2$), 1.84 (1H, t, *J* = 2.6 Hz, ≡C**H**), 1.47 (3H, s, CC**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.8 (C), 172.4 (C), 143.2 (CH), 136.2 (CH), 128.3 (CH), 123.2 (CH), 120.0 (C), 114.8 (CH), 80.0 (C), 70.3 (CH), 56.8 (C), 29.9 (CH_3), 26.2 (CH_2), 24.4 (CH_3); HRMS (ESI) Exact mass calcd for $C_{14}H_{14}NO_2$ $[M+H]^+$: 228.1025, found: 228.1026.

3-[3-(*4*-Chlorophenyl)-2-propynyl]-1-methyl-3-methyl-1,3-dihydroquinoline-2,4-dione (763)



Alkyne **762** (1.02 g, 4.49 mmol) was added to a solution of $Pd(PPh_3)_2Cl_2$ (63.2 mg, 0.0900 mmol), CuI (34.3 mg, 0.180 mmol), and Et_3N (691 µL, 4.96 mmol) in anhydrous MeCN (15 mL) in a sealed tube. A solution of 4-chlorobromobenzene (1.29 g, 5.41 mmol) in anhydrous MeCN (5 mL) was added, the tube was sealed, and the mixture was stirred at 110 °C for 16 h. The reaction was cooled to room temperature, water (50 mL) was added, and the mixture was extracted with EtOAc (50 mL). The organic phase was washed with aqueous 10% HCl (3 × 20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/hexane) gave the *title compound* **763** (0.95 g, 63%) as a yellow solid. R_f = 0.46 (25% EtOAc/petroleum ether); m.p. 96-98 °C (MeOH/hexane); IR 2943, 1687 (C=O), 1651 (C=O), 1472, 1375, 1088, 758 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.08 (1H, dd, *J* = 7.7, 1.5 Hz, Ar**H**), 7.67-7.62 (1H, m, Ar**H**), 7.23-7.18 (2H, m, Ar**H**), 7.16-7.12 (2H, m, Ar**H**), 7.00-6.96 (2H, m, Ar**H**), 3.50 (3H, s, NC**H**$_3$), 3.08 (1H, d, *J* = 16.2 Hz, C**H**$_2$), 3.02 (1H, d, *J* = 16.2 Hz, C**H**$_2$), 1.55 (3H, s, CC**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.1 (C), 172.6 (C), 143.4 (C), 136.2 (CH), 133.8 (C), 132.7 (2 × CH), 128.3 (2 × CH), 128.2 (CH), 123.2 (CH), 121.5 (C), 120.4 (C), 114.8 (CH), 86.1 (C), 81.8 (C), 56.6 (C), 29.9 (CH_3), 29.0 (CH_2), 23.3 (CH_3); HRMS (ESI) Exact mass calcd for $C_{20}H_{17}{}^{35}ClNO_2$ $[M+H]^+$: 338.0948, found: 338.0940.

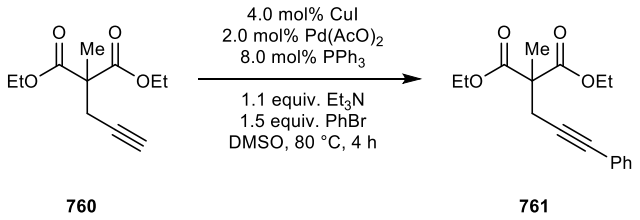
Ethyl 2-oxo-1-(3-phenyl-2-propynyl)cyclopentanecarboxylate (745)



Et_3N (40 mL) was added to a flask containing $(MeCN)_2PdCl_2$ (41.5 mg, 0.160 mmol), PPh_3 (83.9 mg, 0.320 mmol), and CuI (30.5 mg, 0.160 mmol). The mixture was stirred at room temperature for 5 min, ethyl 2-oxo-1-(2-propynyl)cyclopentanecarboxylate (**744**) (1.56 g, 8.03 mmol) and iodobenzene (1.1 mL, 9.8 mmol) were added, and the mixture was stirred at

60 °C for 8 h. The reaction was cooled to room temperature, water (50 mL) and saturated aqueous NH_4Cl (25 ml) were added, and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine (75 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/hexane) gave the *title compound* **745** (1.74 g, 80%) as a yellow oil. R_f = 0.23 (10% EtOAc/petroleum ether); IR 2978, 1751 (C=O), 1726 (C=O), 1227, 1148, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.34 (2H, m, Ar**H**), 7.31-7.27 (3H, m, Ar**H**), 4.20 (2H, q, *J* = 7.1 Hz, OC$\mathbf{H}_2$), 3.00-2.91 (2H, m, C$\mathbf{H}_2$C≡C), 2.60-2.47 (2H, m, C$\mathbf{H}_2$C=O and C$\mathbf{H}_2$CH$_2$CH$_2$C=O), 2.43-2.28 (2H, m, C$\mathbf{H}_2$C=O and C$\mathbf{H}_2$CH$_2$CH$_2$C=O), 2.18-2.04 (2H, m, C$\mathbf{H}_2$CH$_2$C=O), 1.27 (3H, t, *J* = 7.1 Hz, C$\mathbf{H}_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.9 (C), 170.5 (C), 131.6 (2 × CH), 128.2 (2 × CH), 128.0 (CH), 123.2 (C), 85.3 (C), 82.8 (C), 61.7 (CH_2), 59.1 (C), 38.4 (CH_2), 32.8 (CH_2), 24.2 (CH_2), 19.9 (CH_2), 14.1 (CH_3); HRMS (ESI) Exact mass calcd for $C_{17}H_{19}O_3$ $[M+H]^+$: 271.1329, found: 271.1321.

Diethyl 2-methyl-2-(3-phenylprop-2-yn-1-yl)malonate (761)

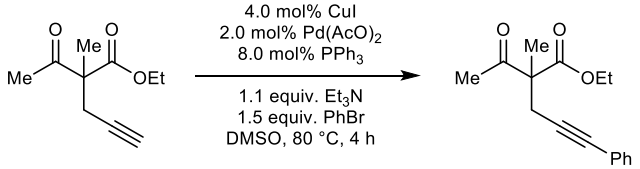


760 **761**

Diethyl 2-methyl-2-(prop-2-yn-1-yl)malonate (2.65 g, 10.0 mmol) was added to a solution of $Pd(OAc)_2$ (44 mg, 0.20 mmol), PPh_3 (209 mg, 0.80 mmol), CuI (76.2 mg, 0.40 mmol), and Et_3N (1.53 mL, 11.1 mmol) in anhydrous DMSO (20 mL). Bromobenzene (1.57 mL, 15 mmol) was added and the mixture was stirred at 90 °C for 2 h. The reaction was cooled to room temperature, water (50 mL) was added, and the mixture was extracted with Et_2O (50 mL). The organic phase was washed with 10% aqueous HCl (3 × 20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/hexane) gave the *title compound* **761** (2.33 g, 81%) as a colourless oil. R_f = 0.7 (30% EtOAc/hexane); IR 3288, 2984, 1732 (C=O), 1599, 1450, 1294, 1022, 759 cm^{-1}; 7.37-7.34 (2H, m, Ar**H**), 7.26-7.25 (3H, m, Ar**H**), 4.25-4.17 (4H, m, O=CC$\mathbf{H}_2$CH$_3$), 3.00 (2H, s, C$\mathbf{H}_2$C≡), 1.60 (3H, s, CC$\mathbf{H}_3$), 1.25 (3H, t, *J* = 4.5 Hz, O=CCH$_2$C$\mathbf{H}_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5 (2 × C), 131.6 (2 × CH), 128.2 (2 × CH), 127.9 (CH), 123.3 (C), 84.7 (C),

83.3 (C), 71.2 (C), 61.6 (2 × CH_2) 26.7 (CH_2), 19.9 (CH_3), 14.0 (2 × CH_3); HRMS (ESI) Exact mass calcd for $C_{17}H_{21}O_4$ $[M+H]^+$: 288.1362, found: 258.1324.

Ethyl 2-acetyl-2-methyl-5-phenylpent-4-ynoate (747)

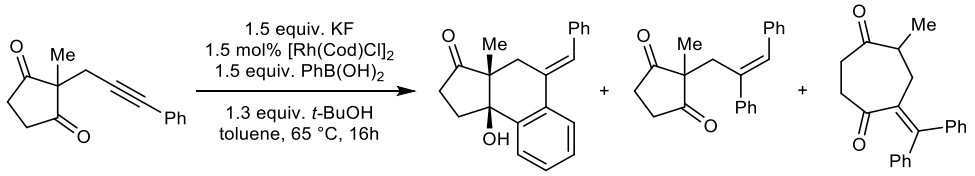


746 **747**

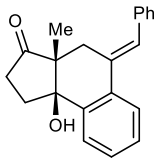
Ethyl 2-acetyl-2-methylpent-4-ynoate (1.82 g, 10.0 mmol) was added to a solution of $Pd(OAc)_2$ (44 mg, 0.20 mmol), PPh_3 (209 mg, 0.80 mmol), CuI (76.2 mg, 0.40 mmol), and Et_3N (1.53 mL, 11.1 mmol) in anhydrous DMSO (20 mL). Bromobenzene (1.57 mL, 15 mmol) was added and the mixture was stirred at 90 °C for 2 h. The reaction was cooled to room temperature, water (50 mL) was added, and the mixture was extracted with Et_2O (50 mL). The organic phase was washed with 10% aqueous HCl (3 × 20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/hexane) gave the *title compound* **747** (1.94 g, 75%) as a colourless oil. R_f = 0.6 (30% EtOAc/hexane); IR 2984, 1720 (C=O), 1716 (C=O), 1598, 1491, 1105, 858 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.34 (2H, m, Ar**H**), 7.28-7.25 (3H, m, Ar**H**), 4.27-4.18 (2H, m, O=CC**H**$_2$$CH_3$), 3.00-2.89 (2H, m, C**H**$_2$C≡), 2.22 (3H, s, O=CC**H**$_3$), 1.54 (3H, s, CC**H**$_3$), 1.27 (3H, t, J = 7.0 Hz, O=CH_2C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.9 (C), 171.5 (C), 131.5 (2 × CH), 128.1 (2 × CH), 127.9 (CH), 123.1 (C), 84.8 (C), 83.4 (C), 61.7 (CH_2), 59.3 (C), 26.1 (CH_3), 25.9 (CH_2), 19.3 (CH_3), 14.0 (CH_3); HRMS (ESI) Exact mass calcd for $C_{16}H_{19}O_3$ $[M+H]^+$: 258.1256, found: 258.1206.

6.2.3. Rhodium-Catalysed Arylative Cyclization of Alkynones

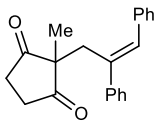
(±)-(3a*R*,9b*R*)-5-[(*E*)-Benzylidene)-9b-hydroxy-3a-methyl-1,2,3a,4,5,9b-hexahydro-3*H*-cyclopenta[*a*]naphthalen-3-one (2a), 2-[(*E*)-2,3-diphenylprop-2-en-1-yl]-2-methylcyclopentane-1,3-dione (5), and (±)-5-(diphenylmethylidene)-7-methylcycloheptane-1,4-dione (6)



Alkynone **711** (90.5 mg, 0.400 mmol), phenylboronic acid (73.2 mg, 0.600 mmol), $[Rh(cod)Cl]_2$ (3.0 mg, 0.006 mmol), and KF (34.8 mg, 0.600 mmol) were added to an oven-dried microwave vial. The vial was sealed with a septum-lined cap and purged with nitrogen for 1 h. Anhydrous toluene (4.0 mL) and *t*-BuOH (57 μL, 0.60 mmol) were added, and the mixture was stirred at 65 °C for 16 h. The reaction was cooled to room temperature, water (5 mL) and saturated aqueous NH_4Cl (5 mL) were added, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The mixture was subjected to column chromatography (10% EtOAc/petroleum ether) leading to isolation of *compound* **712** (49.5 mg, 41%) as a white solid, *compound* **719** (22.0 mg, 18%) as a pale yellow solid and *compound* **713** (20.5 mg, 17%) as a white solid.

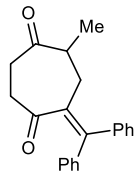


(±)-(3a*R*,9b*R*)-5-[(*E*)-Benzylidene)-9b-hydroxy-3a-methyl-1,2,3a,4,5,9b-hexahydro-3*H*-cyclopenta[*a*]naphthalen-3-one (712). R_f = 0.42 (40% EtOAc/hexane); m.p. 144-145 °C (hexane); IR 3468 (OH), 2936, 1717 (C=O), 1207, 1076, 758, 694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (1H, dd, *J* = 7.7, 1.2 Hz, Ar**H**), 7.68 (1H, dd, *J* = 7.9, 1.2 Hz, Ar**H**), 7.43-7.32 (4H, m, Ar**H**), 7.30-7.25 (3H, m, Ar**H**), 7.24 (1H, d, *J* = 1.4 Hz, C=C**H**), 2.79 (1H, d, *J* = 14.1 Hz, C$\mathbf{H}_2$C=C), 2.68-2.58 (2H, m, C$\mathbf{H}_2$C=C and C$\mathbf{H}_2$C=O), 2.53-2.29 (3H, m, C$\mathbf{H}_2$C=O and C$\mathbf{H}_2$COH), 1.83 (1H, d, *J* = 1.6 Hz, O**H**), 1.01 (3H, s, C$\mathbf{H}_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 219.9 (C), 140.1 (C), 137.1 (C), 134.3 (C), 132.1 (C), 129.1 (2 × CH), 128.8 (CH), 128.4 (2 × CH), 128.2 (CH), 127.9 (CH), 127.1 (CH), 126.5 (CH), 124.2 (CH), 80.1 (C), 54.1 (C), 35.9 (CH_2), 35.2 (CH_2), 34.3 (CH_2), 13.9 (CH_3); HRMS (ESI) Exact mass calcd for $C_{21}H_{21}O_2$ $[M+H]^+$: 305.1542, found: 305.1538.



2-[(*E*)-2,3-Diphenylprop-2-en-1-yl]-2-methylcyclopentane-1,3-dione (719). R_f = 0.53 (40% EtOAc/hexane); m.p. 85-90 °C (CH_2Cl_2/hexane) IR

1742 (C=O), 1210, 929, 730, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.54-7.52 (2H, m, Ar**H**), 7.47-7.43 (2H, m, Ar**H**), 7.37-7.33 (3H, m, Ar**H**), 7.32-7.27 (3H, m, Ar**H**), 6.67 (1H, s, C=C**H**), 3.26 (2H, s, C**H**$_2$C=C), 2.48-2.41 (2H, m, C**H**$_2$C**H**$_2$), 1.86-1.80 (2H, m, C**H**$_2$C**H**$_2$), 1.10 (3H, s, C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 216.7 (2 × C), 141.5 (C), 138.3 (C), 137.4 (C), 132.5 (CH), 128.9 (2 × CH), 128.6 (2 × CH), 128.3 (CH), 128.2 (2 × CH), 128.0 (CH), 127.0 (CH), 55.5 (C), 36.7 (CH_2), 34.9 (2 × CH_2), 22.1 (CH_3); HRMS (ESI) Exact mass calcd for $C_{21}H_{20}NaO_2$ $[M+Na]^+$: 327.1356, found: 327.1354.

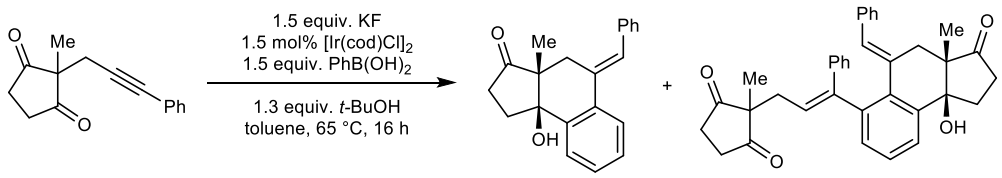


(±)-5-(Diphenylmethylidene)-7-methylcycloheptane-1,4-dione (713). R_f = 0.62 (40% EtOAc/hexane); m.p. 110-120 °C (CH_2Cl_2/hexane); IR 1708 (C=O), 1215, 760, 702, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39-7.23 (6H, m, Ar**H**), 7.20-7.17 (2H, m, Ar**H**), 7.11-7.08 (2H, m, Ar**H**), 2.85-2.64 (6H, m, C**H**$_2$C**H**$_2$ and C**H**$_2$CH), 2.29-2.20 (1H, m, C**H**CH$_3$), 0.99 (3H, d, J = 6.4 Hz, CHC**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.5 (C), 207.5 (C), 144.6 (C), 140.8 (C), 139.2 (C), 138.3 (C), 128.9 (2 × CH), 128.6 (2 × CH), 128.5 (2 × CH), 128.3 (2 × CH), 127.8 (CH), 127.8 (CH), 45.2 (CH), 38.9 (CH_2), 37.6 (CH_2), 34.4 (CH_2), 15.6 (CH_3); HRMS (ESI) Exact mass calcd for $C_{21}H_{21}O_2$ $[M+H]^+$: 305.1536, found: 305.1527

6.2.4. Racemic Iridium Catalysed Arylative Cyclizations

Representative procedure for the iridium-catalysed arylative cyclisation of alkynones

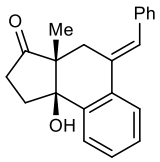
(±)-(3aR,9bR)-5-[(E)-Benzylidene)-9b-hydroxy-3a-methyl-1,2,3a,4,5,9b-hexahydro-3H-cyclopenta[a]naphthalen-3-one (712) and **(±)-2-[(E)-3-{(3aS,9bS)-5-[(E)-benzylidene]-9b-hydroxy-3a-methyl-3-oxo-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[a]naphthalen-6-yl}-3-phenylallyl]-2-methylcyclopentane-1,3-dione (714)**



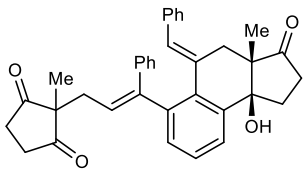
711 **712** **714**

Alkynone **711** (90.5 mg, 0.400 mmol), phenylboronic acid (73.2 mg, 0.600 mmol), $[Ir(cod)Cl]_2$ (4.0 mg, 0.0060 mmol), and KF (34.8 mg, 0.600 mmol) were added to an oven-

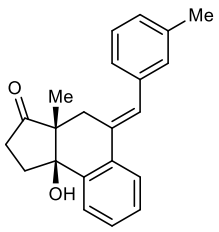
dried microwave vial. The vial was sealed with a septum-lined cap and purged with nitrogen for 1 h. Anhydrous toluene (4.0 mL) and *t*-BuOH (57 μL, 0.60 mmol) were added, and the mixture was stirred at 65 °C for 16 h. The reaction was cooled to room temperature, water (5 mL) and saturated aqueous NH_4Cl (5 mL) were added, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The mixture was subjected to column chromatography (40% EtOAc/petroleum ether) leading to the isolation of *compound* **712** (88.0 mg, 72%) as a white solid and *compound* **714** (28.4 mg, 27%) as a white solid.



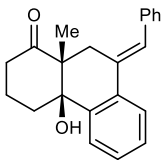
(±)-(3a*R*,9b*R*)-5-[(*E*)-Benzylidene)-9b-hydroxy-3a-methyl-1,2,3a,4,5,9b-hexahydro-3*H*-cyclopenta[*a*]naphthalen-3-one (712). Data as described above.



(±)-2-[(*E*)-3-{(3a*S*,9b*S*)-5-[(*E*)-Benzylidene]-9b-hydroxy-3a-methyl-3-oxo-2,3,3a,4,5,9b-hexahydro-1*H*-cyclopenta[*a*]naphthalen-6-yl}-3-phenylallyl]-2-methylcyclopentane-1,3-dione (714). R_f = 0.13 (40% EtOAc/hexane); m.p. 206-208 °C (CH_2Cl_2/Et_2O); IR 3438 (OH), 2926, 1736 (C=O), 1721 (C=O), 1445, 1205, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.68 (1H, dd, *J* = 7.6, 1.3 Hz, Ar**H**), 7.47 (1H, dd, *J* = 7.5, 1.4 Hz, Ar**H**), 7.41 (1H, t, *J* = 7.6 Hz, Ar**H**), 7.30-7.13 (7H, m, Ar**H**), 6.94 (1H, s, C=C**H**Ph), 6.78-6.84 (4H, m, Ar**H**), 5.86 (1H, t, *J* = 7.5 Hz, CH_2C**H**=CPh), 2.72-2.42 (7H, m, O=CC**H**$_2$C**H**$_2$C=O and C**H**$_2$CH=C and C**H**$_2$CH$_2$COH), 2.33-1.99 (5H, m, C**H**$_2$CH$_2$COH and C**H**$_2$COH and C**H**$_2$C=CH), 1.82 (1H, d, *J* = 1.4 Hz, O**H**), 1.14 (3H, s, C**H**$_3$C(C=O)$_2$), 0.83 (3H, s, C**H**$_3$CCOH); ^{13}C NMR (101 MHz, $CDCl_3$) d 219.7 (C), 215.1 (2 × C), 147.8 (C), 142.4 (C), 142.1 (C), 139.4 (C), 136.9 (C), 134.8 (C), 133.9 (CH), 132.3 (CH), 132.1 (C), 129.7 (2 × CH), 129.1 (2 × CH), 128.1 (2 × CH), 127.8 (CH), 127.6 (2 × CH), 127.0 (CH), 126.9 (CH), 125.2 (CH), 123.1 (CH), 80.7 (C), 57.1 (C), 54.6 (C), 35.8 (CH_2), 35.1 (CH_2), 34.9 (CH_2), 34.8 (CH_2), 34.73 (CH_2), 34.69 (CH_2), 16.7 (CH_3), 15.1 (CH_3); HRMS (ESI) Exact mass calcd for $C_{36}H_{34}NaO_4$ $[M+Na]^+$: 554.2349, found: 553.2325.

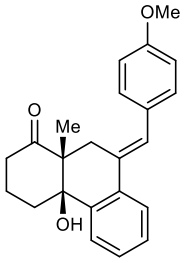


(±)-(3a*R*,9b*R*)-9b-Hydroxy-5-[(*E*)-3-methylbenzylidene]-3a-methyl-1,2,3a,4,5,9b-hexahydro-3*H*-cyclopenta[*a*]naphthalen-3-one (769). The *title compound* was prepared according to the Representative Procedure from alkynone **728** (96.0 mg, 0.400 mmol) and phenylboronic acid (73.2 mg, 0.600 mmol). Purification by column chromatography (10% EtOAc/hexane) gave **769** (91.1 mg, 72%) as a white solid. R_f = 0.29 (30% EtOAc/hexane); m.p. 110-120 °C (*i*-PrOH); IR 3468 (OH), 2953, 1717 (C=O), 1450, 1076, 959, 694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (1H, d, *J* = 1.5 Hz, Ar**H**), 7.69 (1H, dd, *J* = 7.9, 1.2 Hz, Ar**H**), 7.41 (1H, ddd, *J* = 7.7, 7.4, 1.3 Hz, Ar**H**), 7.36 (1H, ddd, *J* = 7.9, 7.4, 1.5 Hz, Ar**H**), 7.29-7.24 (1H, m, Ar**H**), 7.22 (1H, d, *J* = 1.4 Hz, C=C**H**), 7.13-7.07 (3H, m, Ar**H**), 2.81 (1H, d, *J* = 14.1 Hz, C$\mathbf{H}_2$C=C), 2.69-2.59 (2H, m, C$\mathbf{H}_2$C=C and C$\mathbf{H}_2$C=O), 2.51 (1H, ddd, *J* = 19.0, 9.0, 2.4 Hz, C$\mathbf{H}_2$C=O), 2.43 (1H, ddd, *J* = 13.6, 9.2, 2.4 Hz, C$\mathbf{H}_2$COH), 2.40-2.26 (1H, m, C$\mathbf{H}_2$COH), 2.37 (3H, s, ArC$\mathbf{H}_3$), 1.86 (1H, s, O**H**), 1.03 (3H, s, CC$\mathbf{H}_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 220.0 (C), 140.1 (C), 137.9 (C), 137.0 (C), 134.3 (C), 131.9 (C), 129.8 (CH), 128.7 (CH), 128.3 (CH), 128.1 (CH), 128.1 (CH), 127.9 (CH), 126.5 (CH), 126.2 (CH), 124.1 (CH), 80.1 (C), 54.2 (C), 35.9 (CH_2), 35.2 (CH_2), 34.4 (CH_2), 21.5 (CH_3), 13.8 (CH_3); HRMS (ESI) Exact mass calcd for $C_{22}H_{26}NO_2$ $[M+NH_4]^+$: 336.1964, found: 336.1958.

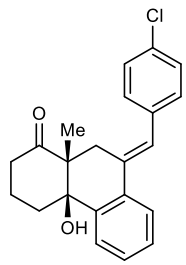


(±)-(4a*R*,10a*R*)-9-[(*E*)-Benzylidene]-4a-hydroxy-10a-methyl-3,4,4a,9,10,10a-hexahydrophenanthren-1(2*H*)-one (794). The *title compound* was prepared according to the Representative Procedure from alkynone **731** (96.0 mg, 0.400 mmol) and phenylboronic acid (73.2 mg, 0.600 mmol). Purification by column chromatography (10% EtOAc/hexane) gave **794** (90.4 mg, 71%) as a white solid. R_f = 0.29 (30% EtOAc/hexane); m.p. 170-171 °C (MeOH); IR 3503 (OH), 2934, 1686 (C=O), 1167, 982, 754, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (1H, dd, *J* = 7.7, 1.5 Hz, Ar**H**), 7.64 (1H, dd, *J* = 7.6, 1.5 Hz, Ar**H**), 7.40-7.25 (6H, m, Ar**H**), 7.24 (1H, d, *J* = 1.4 Hz, C=C**H**), 3.20 (1H, dd, *J* = 15.0, 2.0 Hz, C$\mathbf{H}_2$C=C), 2.81 (1H, dd, *J* = 15.0, 0.9 Hz, C$\mathbf{H}_2$C=C), 2.70 (1H, ddd, *J* = 14.9, 13.0, 6.6 Hz, C$\mathbf{H}_2$C=O), 2.46-2.37 (1H, m, C$\mathbf{H}_2$C=O), 2.34-2.13 (2H, m, C$\mathbf{H}_2$COH), 2.02-1.94 (2H, m, C$\mathbf{H}_2$CH_2COH and O**H**), 1.93-1.85 (1H, m, C$\mathbf{H}_2$CH_2COH), 1.02 (3H, s, C$\mathbf{H}_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.7 (C), 142.1 (C), 137.2 (C), 133.9 (C), 132.0 (C), 129.2 (2 × CH), 128.5 (CH), 128.4 (2 × CH), 127.8 (CH), 127.08 (CH), 127.06 (CH), 125.3 (CH), 123.7 (CH), 78.4 (C), 53.3 (C), 36.9

(CH_2), 36.8 (CH_2), 36.7 (CH_2), 20.9 (CH_2), 15.9 (CH_3); HRMS (ESI) Exact mass calcd for $C_{22}H_{23}O_2$ $[M+H]^+$: 319.1698, found: 319.1696.

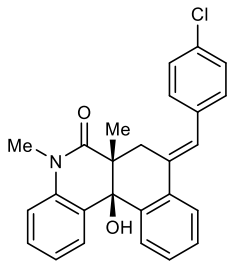


(±)-(4a*R*,10a*R*)-4a-Hydroxy-9-[(*E*)-4-methoxybenzylidene]-10a-methyl-3,4,4a,9,10,10a-hexahydrophenanthren-1(2*H*)-one (795). The *title compound* was prepared according to the Representative Procedure from alkynone **732** (108 mg, 0.400 mmol) and phenylboronic acid (73.2 mg, 0.600 mmol). Purification by column chromatography (10% EtOAc/hexane) gave **795** (80.7 mg, 58%) as a white solid. R_f = 0.25 (30% EtOAc/hexane); m.p. 133-134 °C (Et_2O/hexane); IR 3466 (OH), 2936, 1717 (C=O), 1452, 1238, 1034, 758, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) d 7.73-7.70 (1H, m, Ar**H**), 7.64-7.61 (1H, m, Ar**H**), 7.36-7.29 (2H, m, Ar**H**), 7.29-7.24 (2H, m, Ar**H**), 7.17 (1H, d, *J* = 1.3 Hz, C=C**H**), 6.93-6.88 (2H, m, Ar**H**), 3.84 (3H, s, OC**H**$_3$), 3.19 (1H, dd, *J* = 15.1, 1.9 Hz, C**H**$_2$C=C), 2.80 (1H, dd, *J* = 15.1, 1.2 Hz, C**H**$_2$C=C), 2.76-2.66 (1H, m, C**H**$_2$C=O), 2.46-2.40 (1H, m, C**H**$_2$C=O), 2.33-2.14 (2H, m, C**H**$_2$COH), 1.99-1.86 (3H, m, CH_2C**H**$_2$$CH_2$ and O**H**), 1.01 (3H, s, CC**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.8 (C), 158.6 (C), 141.9 (C), 134.3 (C), 130.6 (2 × CH), 130.5 (C), 129.8 (C), 128.2 (CH), 127.7 (CH), 126.8 (CH), 125.1 (CH), 123.6 (CH), 113.9 (2 × CH), 78.4 (C), 55.3 (CH_3), 53.3 (C), 36.9 (CH_2), 36.8 (CH_2), 36.6 (CH_2), 20.9 (CH_2), 15.9 (CH_3); HRMS (ESI) Exact mass calcd for $C_{23}H_{25}O_3$ $[M+H]^+$: 366.2069, found: 366.2066.



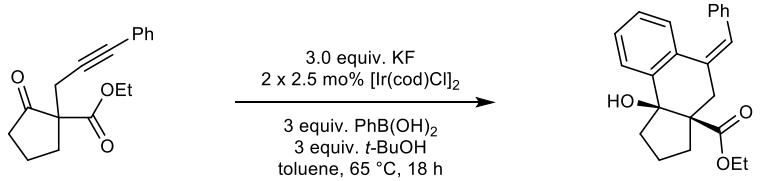
(±)-(4a*R*,10a*R*)-4a-Hydroxy-9-[(*E*)-4-chlorobenzylidene]-10a-methyl-3,4,4a,9,10,10a-hexahydrophenanthren-1(2*H*)-one (796). The *title compound* was prepared according to the Representative Procedure from alkynone **733** (110 mg, 0.400 mmol) and phenylboronic acid (73.2 mg, 0.600 mmol). Purification by column chromatography (10% EtOAc/cyclohexane) gave **796** (112.6 mg, 80%) as a white solid. R_f = 0.36 (30% EtOAc/hexane); m.p. 166-167 °C (MeOH); IR 3497 (OH), 2953, 1682 (C=O), 1489, 1190, 870, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (1H, dd, *J* = 7.8, 1.3 Hz, Ar**H**), 7.64 (1H, dd, *J* = 7.7, 1.4 Hz, Ar**H**), 7.39-7.30 (4H, m, Ar**H**), 7.26-7.20 (2H, m, Ar**H**), 7.17 (1H, s, C=C**H**), 3.17 (1H, dd, *J* = 15.0, 2.0 Hz, C**H**$_2$C=C), 2.73 (1H, dd, *J* = 15.0, 0.8 Hz, C**H**$_2$C=C), 2.67 (1H, ddd, *J* = 15.0, 12.7, 6.6 Hz, C**H**$_2$C=O), 2.46-2.40 (1H, m, C**H**$_2$C=O), 2.32-2.14 (2H, m, C**H**$_2$COH), 2.02-1.96 (1H, m, CH_2C**H**$_2$$CH_2$), 1.94 (1H, d, *J* = 2.0 Hz, O**H**),

1.92-1.84 (1H, m, $CH_2CH_2CH_2$), 1.02 (3H, s, CH_3);^{13}C NMR (126 MHz, $CDCl_3$) δ 213.4 (C), 142.1 (C), 142.1 (C), 135.7 (C), 133.7 (C), 132.9 (C), 130.5 (2 × CH), 128.7 (CH), 128.6 (2 × CH), 127.9 (CH), 125.7 (CH), 125.4 (CH), 123.8 (CH), 78.3 (C), 53.4 (C), 36.9 (CH_2), 36.7 (CH_2), 36.6 (CH_2), 20.8 (CH_2), 16.1 (CH_3); HRMS (ES) Exact mass calcd for $C_{22}H_{21}{}^{35}ClNaO_2$ $[M+Na]^+$: 375.1128, found: 375.1113.



(±)-(6a*R*,12b*S*)-8-[(*E*)-4-Chlorobenzylidene)-12b-hydroxy-5,6a-dimethyl-6a,7,8,12b-tetrahydrobenzo[*k*]phenanthridin-6(5*H*)-one (801). The *title compound* was prepared according to the Representative Procedure from alkynone **763** (135 mg, 0.400 mmol) and phenylboronic acid (73.2 mg, 0.600 mmol). Purification by column chromatography (10% EtOAc/hexane) gave **801** (120 mg, 72%) as a white solid. R_f = 0.38 (30% EtOAc/petroleum ether); m.p. 174-176 °C (MeOH/hexane); IR 3293 (OH), 2936, 1638 (C=O), 1377, 1018, 752 cm^{-1}; ^{1}H NMR (400 MHz, D_6-DMSO, 85 °C) δ 7.88-7.84 (1H, m, Ar**H**), 7.57-7.47 (3H, br m, Ar**H**), 7.46-7.42 (2H, m, Ar**H**), 7.36 (1H, ddd, *J* = 8.1, 7.5, 1.6 Hz, Ar**H**), 7.32-7.26 (1H, m, Ar**H**), 7.20-7.13 (3H, m, Ar**H** and C=C**H**), 7.08 (1H, dd, *J* = 8.1, 1.0 Hz, Ar**H**), 7.00 (1H, br s, Ar**H**), 5.71 (1H, s, O**H**), 3.22 (1H, br d, *J* = 16.1 Hz, C$\mathbf{H}_2$), 3.09 (3H, s, NC$\mathbf{H}_3$), 2.82 (1H, dd, *J* = 16.1, 2.4 Hz, C$\mathbf{H}_2$), 1.00 (3H, s, CC$\mathbf{H}_3$); ^{13}C NMR (101 MHz, D_6-DMSO, 85 °C) δ 171.7 (C), 138.3 (C), 137.5 (C), 136.2 (C), 134.5 (C), 133.6 (C), 130.8 (C), 130.5 (2 × CH), 130.4 (C), 128.0 (CH), 127.8 (2 × CH), 127.5 (CH), 126.9 (CH), 126.8 (CH), 126.5 (CH), 123.3 (CH), 123.1 (CH), 121.9 (CH), 113.9 (CH), 72.2 (C), 45.8 (C), 32.3 (CH_2), 28.9 (CH_3), 18.0 (CH_3); HRMS (ESI) Exact mass calcd for $C_{26}H_{23}{}^{35}ClNO_3$ $[M+H]^+$: 416.1417, found: 416.1413.

(±)-Ethyl (3a*S*,9b*R*)-5-[(*E*)-benzylidene]-9b-hydroxy-1,2,3,4,5,9b-hexahydro-3a*H*-cyclopenta[*a*]naphthalene-3a-carboxylate (802)

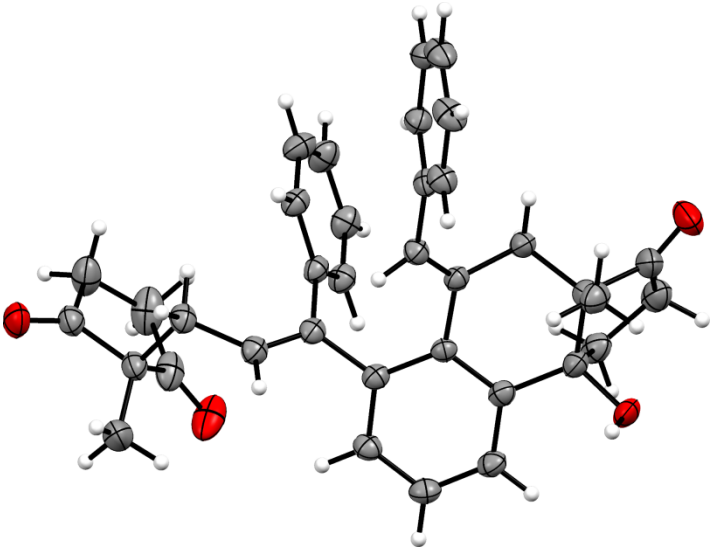


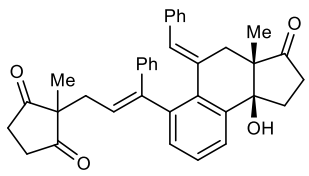
743 **802**

Alkynone **743** (108 mg, 0.400 mmol), phenylboronic acid (146 mg, 1.21 mmol), $[Ir(cod)Cl]_2$ (6.7 mg, 0.010 mmol), and KF (69.7 mg, 1.20 mmol) were added to an oven-dried microwave vial. The vial was sealed with a septum-lined cap and purged with nitrogen for 1 h. Anhydrous toluene (4.0 mL) and *t*-BuOH (126 µL, 1.32 mmol) were added and the mixture was stirred at 65 °C for 4 h. A solution of $[Ir(cod)Cl]_2$ (6.7 mg, 0.010 mmol) in anhydrous toluene (1.0 mL) was added, and the mixture was stirred at 65 °C for 14 h. The reaction was cooled to room temperature, water (5 mL) and saturated aqueous NH_4Cl (5 mL) were added, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (10% hexane/toluene) to give *compound* **802** (100 mg, 72%) as a white solid. R_f = 0.30 (10% EtOAc/hexane); m.p. 100-105 °C (CH_2Cl_2/hexane); IR 3482 (OH), 2969, 1693 (C=O), 1313, 1201, 1020 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (1H, dd, *J* = 7.7, 1.2 Hz, Ar**H**), 7.56 (1H, dd, *J* = 7.9, 1.3 Hz, Ar**H**), 7.40-7.23 (6H, m, Ar**H**), 7.07 (1H, d, *J* = 1.7 Hz, C=C**H**), 4.38 (1H, d, *J* = 2.2 Hz, O**H**), 3.93 (1H, dq, *J* = 10.7, 7.1 Hz, C**H**$_2$CH$_3$), 3.79 (1H, dq, *J* = 10.7, 7.1 Hz, C**H**$_2$CH$_3$), 3.50 (1H, d, *J* = 14.2 Hz, C**H**$_2$C=C), 2.71 (1H, dd, *J* = 14.2, 1.7 Hz, C**H**$_2$C=C), 2.44-2.36 (1H, m, C**H**$_2$COH), 2.20-2.01 (3H, m, C**H**$_2$C**H**$_2$CH$_2$COH), 1.93-1.81 (2H, m, C**H**$_2$CH$_2$CH$_2$COH and C**H**$_2$COH), 0.85 (3H, t, *J* = 7.1 Hz, C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.2 (C), 141.8 (C), 137.5 (C), 134.3 (C), 134.1 (C), 129.1 (2 × CH), 128.4 (CH), 128.3 (2 × CH), 127.2 (CH), 127.0 (CH), 126.8 (CH), 126.2 (CH), 123.7 (CH), 81.9 (C), 60.7 (CH_2), 57.7 (C), 41.2 (CH_2), 36.1 (CH_2), 34.5 (CH_2), 20.7 (CH_2), 13.5 (CH_3); HRMS (ESI) Exact mass calcd for $C_{23}H_{24}NaO_3$ $[M+Na]^+$: 371.1618, found: 371.1622.

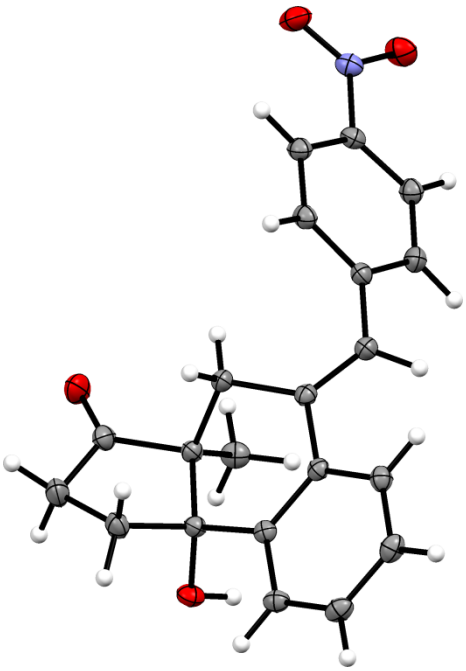
6.2.5 X-Ray Structures

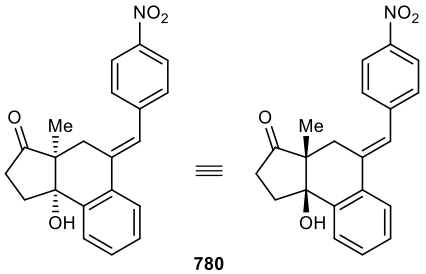
The relative stereochemistries of all products were assigned by analogy to the X-ray structures of **780**[r], **795**[r] and **714**[s] by comparison of the ^{1}H NMR spectra.





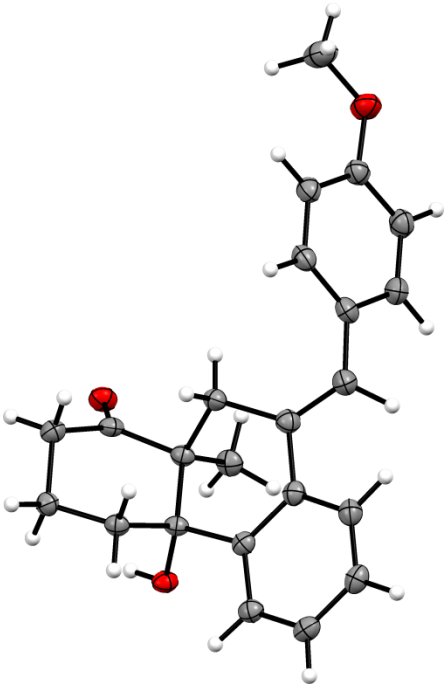
714

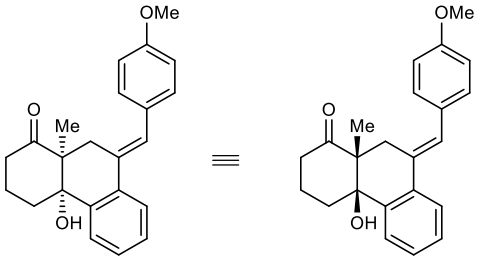




780

[r,r] and [s] I) X-Ray data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif168.





795

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8. Appendix

8.1 Publications:

1. **Enantioselective Copper(I)-Catalyzed Borylative Aldol Cyclizations of Enone–Diones,** A. R. Burns, **J. Solana González**, H. W. Lam, *Angewandte Chemie International Edition* **2012**, *51*, 10827-10831.
2. **Iridium-Catalyzed Arylative Cyclization of Alkynones by 1,4-Iridium Migration,** B. M. Partridge, **J. Solana González**, H. W. Lam, *Angewandte Chemie International Edition* **2014**, *53*, 6523-6527.