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Copper and Iridium Conjugate Addition –
Cyclisation Processes; Domino Reactions

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

By

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Supervised by
Prof. Hon Wai Lam

EaStCHEM School of Chemistry
College of Science and Engineering
December 2014
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.

Signed

Jorge Solana González
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First of all I would like to thank my supervisor Professor Hon Wai Lam for giving me the opportunity to work in his research group in Edinburgh and in Nottingham. For almost four years, Hon has been more than helpful with every single issue I have had in my PhD. But beyond the professional relationship I have with Hon, we also had many conversations about other things such as “pimientos del padrón”, where to go in Andalucia or “are you meeting the in-laws in Poland?” I would also like to thank the University of Edinburgh and the University of Nottingham and all the staff in both institutions for their help and support and the EPSRC for financial support.

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Barcelona, Madrid, Londres, etc… que me daban el aliento y la fuerza para poder continuar mi día a día sin ti en Edimburgo y Nottingham. Gracias por todo. Te quiero.
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
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</tr>
<tr>
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<td>Copper(I)</td>
</tr>
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<td>DEPT</td>
<td>Distortionless enhancement by polarisation transfer</td>
</tr>
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<td>Abbreviation</td>
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<td>-----------</td>
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</tr>
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<td>EWG</td>
<td>Electron-withdrawing group</td>
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<td>i-PrOH</td>
<td>iso-Propanol</td>
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<tr>
<td>kCal</td>
<td>Calories</td>
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<tr>
<td>KOt-Bu</td>
<td>Potassium tert-butoxide</td>
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<tr>
<td>m</td>
<td>Multiplet</td>
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<td>m.p.</td>
<td>Melting point</td>
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<td>n-Pentyl</td>
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<td>nbd</td>
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<td>N-Heterocyclic carbene</td>
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<td>NMR</td>
<td>Nuclear magnetic resonance</td>
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<tr>
<td>Nuc:</td>
<td>Nucleophile</td>
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<tr>
<td>OTf</td>
<td>Triflate</td>
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<tr>
<td>PCy$_3$</td>
<td>Tricyclohexylphosphine</td>
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<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>pin</td>
<td>Pinacol</td>
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</table>
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$_2$PPh 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$ t$ 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.\(^a\)

\[
\text{Enone Diones} + \text{B}_{2}(\text{pin})_2 \xrightarrow{\text{Cu(III), NaOEt, THF, r.t.}} \text{Bicyclic Alcohol}
\]

\[82\% \text{ yield} > 95.5 \text{ d.r.} > 98\% \text{ ee}\]

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.

\[
\text{Alkynones} + \text{PhB(OH)}_2 \xrightarrow{\text{Ir(III), KF, toluene, 85 °C}} \text{Tricyclic Compound}
\]

\[72\% > 95.5 \text{ d.r.}\]

\(^a\) 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. After oxidative addition and carboxylation 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.\textsuperscript{[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.\textsuperscript{[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](image)

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 \textit{et al.} in 2013. Applying copper catalysis, Ito’s group performed a borylative \textit{exo}-cyclization of alkenyl halides (24) with bis(pinacolato) diboron and Xantphos (L03) as ligand.\textsuperscript{[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).
Another example of borylative domino reaction using copper was published by Lin in 2013. In this case, an asymmetric borylative cyclization of cyclohexadiene-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. The catalytic system proposed is capable of differentiating between the unsaturated ketone and the alkyne. The conjugate borylation of the alkene is suppressed by the substituents on the cyclohexadiene 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).
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).\textsuperscript{[21]} In the presence of CO\textsubscript{2} and an amine, allyl chlorides \textbf{36} react to form allyl carbamates \textbf{37} under iridium catalysis using a phosphoramidite ligand.

\textbf{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,\textsuperscript{22} to acylation of symmetric diols\textsuperscript{23} or olefin metathesis\textsuperscript{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 established copper-catalysed conjugate addition of organozinc-reagents to α,β-unsaturated ketones to synthesize five-membered ring compounds containing all-carbon quaternary centres. 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](image)

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. Ph3SiH 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 pendant 1,3-dione to give bicycle 56 as a single diastereoisomer and with high levels of enantioselectivity (Scheme 10).

![Scheme 10: Copper domino reductive aldol cyclisation](image)
More recently, Mukherjee published the desymmetrisation of cyclopentene-1,3-diones 59 via an organocatalysed nucleophilic addition of deconjugated butenolides 58. The organocatalyst of choice for this transformation was an amino thiourea L08. A combination of (S)-tert-leucine and (1R,2R)-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,\textsuperscript{28} rhodium\textsuperscript{28b} and nickel\textsuperscript{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\textsuperscript{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 aminotroponenime lithium species 77 as a ligand exchange compound (aminotroponenime structures are known to act as chelating agents for copper),\textsuperscript{31} CuBr·Me₃S and \(n\)-BuLi the addition of two Grignard reagents occurred with low enantiocontrol (Scheme 12).\textsuperscript{32}

\[
\begin{align*}
\text{74} & \text{Br} & \text{CuBr·Me₃S} & \text{THF, −78 °C} & \text{75} \\
\text{74} & \text{Me₃S} & \text{THF, −78 °C} & \text{76}
\end{align*}
\]

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](image)

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 (L.07) 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 $\alpha$-$\beta$ 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).\[^{35}\]

Scheme 15 Copper catalysed conjugate addition of Grignard reagents

\(^{a}\) 0.5 mol\% CuBr $\cdot$ SMe$_2$

0.5 mol\% L09
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).[^16]

\[ \text{Scheme 16: Copper catalysed conjugate addition of organozinc reagents} \]

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).

\[ \text{Scheme 17: Copper catalysed conjugate addition of organozinc reagents} \]
Other groups have also used copper to catalyse the ECA of organozincs to electron-deficient alkene.\textsuperscript{[30]} For instance, Alexakis and co-workers reported the use of copper thiophenecarboxylate and a phosphoramidite ligand L\textsubscript{12} for the asymmetric addition of diethyl zinc to enones and nitro-olefins (Scheme 18).\textsuperscript{[38]}

![Scheme 18: Copper catalysed conjugate addition of organozinc reagents](image)

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\textsuperscript{[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).\textsuperscript{[40]}
More recently, using similar conditions but with \((R)\)-BINAP as a ligand, Alexakis has also reported the addition of organoaluminium reagents to \(\beta,\gamma\)-unsaturated \(\alpha\)-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]

![Method A: Grignard addition of boronic ester](image)

![Method B: Haloboration](image)

![Method C: Hydroboration](image)

Scheme 21: Synthesis of organoboron reagents

Recently, a new alternative to the well established 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]

A few years later, Miyaura et al. published a diboron addition to double-bonds using a platinum catalyst and B₂(pin). This procedure could be applied to a range of different unsaturated molecules in good yields (Scheme 23).[45]

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]

![Scheme 24: Platinum catalysed boration of alkenes](image)

### 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, B₂(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]

![Scheme 25: Copper catalysed conjugate boration of activated alkenes](image)

Mechanistically, Miyaura proposed the transmetalation of the copper(I) salt with the B₂(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).
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]

\[ \text{Scheme 26: Mechanism of the copper catalysed conjugate boration of activated alkenes} \]

\[ \begin{align*}
\text{B}_3\text{(pin)}_2 & \xrightarrow{\text{CuCl/KOAc}} \text{Cu-B(pin)} \\
129 & \xrightarrow{138} \xrightarrow{139} \xrightarrow{140} \xrightarrow{141}
\end{align*} \]

\[ 1. \text{0.1 mol\% CuCl, 0.1 mol\% Bu}_3\text{P} \]
\[ 1.1 \text{ equiv. B}_3\text{(pin)}_2, \text{DMF, r.t.} \]
\[ 2. \text{H}_3\text{O}^+ \]

\[ \text{Scheme 27: Copper catalysed conjugate boration of activated alkenes} \]

\[
\begin{align*}
\text{132} & \quad 72\% \text{ yield} \\
\text{142} & \quad 82\% \text{ yield} \\
\text{143} & \quad 82\% \text{ yield} \\
\text{144} & \quad 71\% \text{ yield}
\end{align*}
\]
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.\textsuperscript{[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, \textit{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\textsubscript{2}(pin)\textsubscript{2} to a broad scope of activated double bonds such as α,β-unsaturated esters, ketones, phosphonates or nitriles (Scheme 28).\textsuperscript{[49]}

![Scheme 28: Copper catalysed conjugate boration of activated alkenes](image)

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.
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 cinnaminitrile (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 29: Catalytic cycle of the copper catalysed conjugate boration of activated alkenes

Scheme 30: Copper catalysed asymmetric conjugate boration of activated alkenes
2.2.3.1. Asymmetric Conjugate Boration of $\alpha,\beta$-Unsaturated Esters

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

![Scheme 31: Copper catalysed asymmetric conjugate boration of activated alkenes](image)

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 phosphorus-nitrogen ligands for the conjugate addition of bis(pinacolato)diboron to \(\alpha,\beta\)-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](image)

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](image)
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).

Scheme 34: Copper catalyzed 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).
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).
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).

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 and Fernández 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 B₂(pin)₂ in high yields and enantioselectivity to a broad range of α,β-unsaturated esters (Scheme 39).
Nishiyama proposed a catalytic cycle through the formation of a rhodium enolate 199, which undergoes an exchange reaction with $\text{B}_2(\text{pin})_2$ to form the boron enolate 200 that is then hydrolysed to obtain the desired product.
Fernández explored the use of nickel and palladium to perform the asymmetric conjugate addition of $\text{B}_2(\text{pin})_2$ to $\alpha,\beta$-unsaturated esters.\textsuperscript{[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).

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)\textsuperscript{[58]}

![Scheme 44: Mechanistic studies on copper ECA processes](image)

Although phosphorus-nitrogen ligands did not provide excellent results for the boron conjugate addition to \(\alpha,\beta\)-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.\textsuperscript{[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 \(\text{CuPF}_6(\text{CH}_3\text{CN})_4\) 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).
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).

The copper-catalysed conjugate bortations 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 $\alpha$-$\beta$-unsaturated ketones, amides and carboxylates (Scheme 48).\[61\]

\[
\begin{array}{c}
\text{O} \\
\text{Ph} \\
\text{BPin}
\end{array}
\xrightarrow{5.0 \text{ mol}\% \text{ Cu(OH)}_2 \text{, 6.0 mol}\% \text{ AcOH}}
\begin{array}{c}
\text{O} \\
\text{Ph} \\
\text{B(pin)}
\end{array}
\xrightarrow{6.0 \text{ mol}\% \text{ ligand, 1.1 equiv. } \text{B}_2\text{(pin)}_2 \text{, H}_2\text{O, 5 }^\circ\text{C}}
\begin{array}{c}
\text{O} \\
\text{Ph} \\
\text{B(pin)}
\end{array}
\xrightarrow{\text{NaB} \text{O}_3}
\begin{array}{c}
\text{OH} \\
\text{Ph}
\end{array}
\]

\[
\begin{array}{c}
\text{Me}_2\text{N} \\
\text{O} \\
\text{OH} \\
\text{Ph}
\end{array}
\xrightarrow{88\% \text{ yield}}
\begin{array}{c}
\text{Me}_2\text{N} \\
\text{O} \\
\text{OH} \\
\text{Ph}
\end{array}
\xrightarrow{80\% \text{ yield, 86% ee}}
\begin{array}{c}
\text{Me}_2\text{N} \\
\text{O} \\
\text{OH} \\
\text{Ph}
\end{array}
\xrightarrow{76\% \text{ yield, 90% ee}}
\begin{array}{c}
\text{Me}_2\text{N} \\
\text{O} \\
\text{OH} \\
\text{Ph}
\end{array}
\xrightarrow{87\% \text{ yield, 97% ee}}
\begin{array}{c}
\text{Me}_2\text{N} \\
\text{O} \\
\text{OH} \\
\text{Ph}
\end{array}
\]

**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$_3$)$_2$2MeOH and SL-J001-1 Josiphos in the presence of $\text{i-PrOH}$ as a proton source gave the 1,6- rather than the 1,4-addition with high yields and enantioselectivity (Scheme 49).\[62\]

\[
\begin{array}{c}
\text{Me} \\
\text{Fe} \\
\text{PPH}_2\text{PCy}_2
\end{array}
\xrightarrow{0.2 \text{ mol}\% \text{ CuF(PPh}_3)_2 \text{, 2MeOH, 0.24 mol}\% \text{ (R,S)-Josiphos, 1.2 equiv. B}_2\text{(pin)}_2 \text{, 2 equiv } \text{i-PrOH, THF, r.t.}}
\begin{array}{c}
\text{Me} \\
\text{Fe} \\
\text{PPH}_2\text{PCy}_2
\end{array}
\xrightarrow{10 \text{ equiv. NaB} \text{O}_3 \text{, 4H}_2\text{O, 1:1 THF:H}_2\text{O, 0 }^\circ\text{C to r.t.}}
\begin{array}{c}
\text{Me} \\
\text{Fe} \\
\text{PPH}_2\text{PCy}_2
\end{array}
\]

\[
\begin{array}{c}
\text{Me} \\
\text{Fe} \\
\text{PPH}_2\text{PCy}_2
\end{array}
\xrightarrow{70\% \text{ yield, 95% ee}}
\begin{array}{c}
\text{Me} \\
\text{Fe} \\
\text{PPH}_2\text{PCy}_2
\end{array}
\xrightarrow{68\% \text{ yield, 95% ee}}
\begin{array}{c}
\text{Me} \\
\text{Fe} \\
\text{PPH}_2\text{PCy}_2
\end{array}
\xrightarrow{61\% \text{ yield, 95% ee}}
\begin{array}{c}
\text{Me} \\
\text{Fe} \\
\text{PPH}_2\text{PCy}_2
\end{array}
\]

**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 $\text{B}_2(\text{pin})_2$ 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](image)

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](image)
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 $\alpha,\beta$-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 mechanism 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).

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 55: Diastereoselective domino copper boration/aldol addition**

**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 B₂(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 enolates 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 established. 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). 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). 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).

![Scheme 59: Proposed domino borylation/aldol cyclisation process](image)

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,\textsuperscript{27} Suzuki-Miyaura coupling\textsuperscript{28} or amination.\textsuperscript{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).\textsuperscript{b}

\begin{center}
\begin{equation*}
\begin{array}{c}
\text{Me} \\
\text{O} \\
\text{O} \\
\text{Ph} \\
\end{array}
\begin{array}{c}
\text{O} \\
\text{Ph} \\
\text{O} \\
\text{Me} \\
\end{array}
\text{+} \\
\text{B}_{2}(\text{pin})_{2}
\end{equation*}
\begin{equation*}
\begin{array}{c}
\text{Me} \\
\text{O} \\
\text{O} \\
\text{Ph} \\
\end{array}
\begin{array}{c}
\text{O} \\
\text{Ph} \\
\text{O} \\
\text{Me} \\
\end{array}
\text{H}_{\text{pin}}
\end{equation*}
\begin{equation*}
\begin{array}{c}
\text{Me} \\
\text{O} \\
\text{O} \\
\text{Ph} \\
\end{array}
\begin{array}{c}
\text{O} \\
\text{Ph} \\
\text{O} \\
\text{Me} \\
\end{array}
\text{B}_{2}(\text{pin})
\end{equation*}
\begin{equation*}
\begin{array}{c}
\text{Me} \\
\text{O} \\
\text{O} \\
\text{Ph} \\
\end{array}
\begin{array}{c}
\text{O} \\
\text{Ph} \\
\text{O} \\
\text{Me} \\
\end{array}
\text{MeCN, 50 °C}
\end{equation*}
\end{equation*}
\end{center}

**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

\textsuperscript{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, B2(pin), NaOt-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).

Table 1: Ligand Screening

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Conversion</th>
<th>Cyclic-Acyclic</th>
<th>d.r.</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>P(OEt)3</td>
<td>95%</td>
<td>40:60</td>
<td>&gt;95:5</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>L02</td>
<td>62%</td>
<td>48:52</td>
<td>&gt;95:5</td>
<td>70%</td>
</tr>
<tr>
<td>3</td>
<td>L19</td>
<td>74%</td>
<td>32:68</td>
<td>&gt;95:5</td>
<td>10%</td>
</tr>
<tr>
<td>4</td>
<td>L07</td>
<td>35%</td>
<td>&lt;5:95</td>
<td>Not measured</td>
<td>Not measured</td>
</tr>
<tr>
<td>5</td>
<td>L09</td>
<td>&gt;95%</td>
<td>87:13</td>
<td>&gt;95:5</td>
<td>93%</td>
</tr>
<tr>
<td>6</td>
<td>L24</td>
<td>63%</td>
<td>&lt;5:95</td>
<td>Not measured</td>
<td>Not measured</td>
</tr>
</tbody>
</table>

I) Determined by 1H 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

a 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).

![Chemical structure](image)

**Table 2: Alcohol Screening**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alcohol</th>
<th>Conc (M)</th>
<th>Conversion</th>
<th>Cyclic-acyclic</th>
<th>d.r.</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH</td>
<td>0.1</td>
<td>&gt;95%</td>
<td>87:13</td>
<td>&gt;95:5</td>
<td>90%</td>
</tr>
<tr>
<td>2</td>
<td>None</td>
<td>0.1</td>
<td>&gt;62%</td>
<td>93:7</td>
<td>&gt;95:5</td>
<td>85%</td>
</tr>
<tr>
<td>3</td>
<td>MeOH</td>
<td>0.05</td>
<td>&gt;95%</td>
<td>72:28</td>
<td>&gt;95:5</td>
<td>95%</td>
</tr>
<tr>
<td>4</td>
<td>t-BuOH</td>
<td>0.05</td>
<td>&gt;95%</td>
<td>83:17</td>
<td>&gt;95:5</td>
<td>94%</td>
</tr>
<tr>
<td>5</td>
<td>i-PrOH</td>
<td>0.05</td>
<td>&gt;95%</td>
<td>84:16</td>
<td>&gt;95:5</td>
<td>94%</td>
</tr>
</tbody>
</table>

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. A copper salt transmetalates with B$_2$(pin)$_2$ to form copper-boron species 150. This species 150 then attacks the α-β unsaturated...
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 $\alpha,\beta$-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).\[70\]
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.\cite{71}

![Scheme 64: Ylide synthesis](image)

a) Bromine in a HBr/AcOH solution instead of CuBr$_2$ in CH$_2$Cl$_2$.
b) Synthesised by Darryl Low.

Figure 2

To synthesise this molecule, a Negishi coupling was first attempted.\cite{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. 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. 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).\textsuperscript{[74]}

![Scheme 68: Alkyl ylide synthesis](image)

### 3.3.2. Wittig Olefination Route

![Scheme 69: Substrate synthesis](image)

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 borat-ion-cyclisation process was performed.

To synthesise the aldehyde precursor, the corresponding cyclic diketone (2-methyl-1,3-cyclopentanediione 323 or 2-methyl-1,3-cyclohexanediione 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).\textsuperscript{[69b]}
Scheme 70: Aldehyde precursors synthesis

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 $\alpha,\beta$-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
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 an 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]
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]
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]

![Scheme 75: Precursor synthesis](image)

![Scheme 76: Substrate synthesis](image)

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 $\alpha,\beta$-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 $\alpha,\beta$-unsaturated ketone with high stereocontrol (Scheme 77).

![Scheme 77: Copper catalysed boration/aldol cyclisation](image-url)
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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>d.r.</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ar = 2-BrCC6H5</td>
<td>55:45</td>
<td>42% (48%)</td>
<td>68% (83%)</td>
</tr>
<tr>
<td>2</td>
<td>Ar = 3-F3CC6H5</td>
<td>23:77</td>
<td>60% (15%)</td>
<td>83% (89%)</td>
</tr>
<tr>
<td>3</td>
<td>Ar = 4-O2NC6H5</td>
<td>59:41</td>
<td>29% (49%)</td>
<td>86% (87%)</td>
</tr>
</tbody>
</table>

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).
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 diastereoccontrol 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 diastereomers 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](image)

**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](image)

Oxidation of the B-C bond using NaOH/H₂O₂ did not produce the expected alcohol. Therefore, Marsden’s conditions for the oxidation of organoboron compounds using NaBO₃ were applied and alcohol 398 was obtained in a 86% yield without damaging the enantiomeric excess (Scheme 84).[⁷⁹]

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 functionalise 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 BF₃K 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.

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

![Scheme 87: Proposed diastereomeric conformations](image)
were proposed. Following the same rationale 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).

Scheme 88: Proposed diastereomeric 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 bicyclic 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 as well 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.\textsuperscript{[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 metalla-cyle 415 and then reductive elimination. This mechanism functionalises a relative inert C-H bond creating a new carbon-metal bond which can undergo subsequent reactions (Scheme 89).\textsuperscript{[85]}

![Scheme 89: 1,4-Migration proposed mechanism](image)

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. In the presence of Pd(OAc)$_2$ the formation of benzofuran 418 from aryl iodide 417 was observed (Scheme 90).

![Scheme 90: Palladium catalysed 1,4-migration process](image)

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 421. 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](image)

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.

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](image)

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$_4$NCl respectively, Larock’s group synthesised fluorene structures such as 428 in moderate yields from diphenyl acetylene and substituted aryl iodides via a 1,4-palladium migration (Scheme 93).$^{[88]}

![Scheme 93: Palladium catalysed arylation/1,4-migration process](image)

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](image)

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](image)

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).
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).\[90\]

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 pallada cycle 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).
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).

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).
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.
More recently, Zhu’s group reported a nice example of a 1,4-palladium migration/cyclisation process towards the synthesis of fused oxindoles. Using PCy3·HBF4 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 sp³ 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.
Similarly, Buchwald and co-workers reported a catalytic intermolecular amination of 2,4,6-tri-tert-butylbromobenzene via 1,4-palladium shift (Scheme 108). 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.
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. 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](image)

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](image)
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](image)

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](image)
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 NaBPh₄ 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).\textsuperscript{[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-disubstituted 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).\textsuperscript{[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](image)

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 spirocycles of type 580 in good yields and enantiomeric excesses (Scheme 121).

![Scheme 117: Rhodium catalysed domino arylation/1,4-migration/cyclisation process](image)
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.\textsuperscript{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.\textsuperscript{[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](image1)

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).\textsuperscript{[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](image2)
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](image)

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).

![Scheme 123: Rhodium catalysed 1,4-migration/cyclisation process](image)

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

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).
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). 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.

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).
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.\textsuperscript{[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).\textsuperscript{[111]}
Scheme 131: Rhodium catalysed allylation of imines via 1,4-migration

It was proposed that first the allyltrifluoroborate 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.\[1^{12}\] 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 sp²-sp³ 1,4-migration to
form allyl-rhodium 663. Isomerisation to form electrophilic \( \pi \)-allylrhodium species 664 followed by nucleophilic attack of the enol gives the observed product 659 (Scheme 133).

\[
\begin{align*}
\text{Ph} & \quad \equiv \quad \text{Me} \\
0.1 \text{ equiv. AcOH} & \quad \text{dioxane, } 60 \degree \text{C, } 4 \text{ h} \quad \text{Ph} \\
1.5 \text{ mol\% } [\text{Cp}^*\text{RhCl}]_2 & \quad 2.1 \text{ equiv. Cu(OAc)}_2
\end{align*}
\]

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 alkenylcobalt species 667, 1,4-migration gives arylcobalt species 668, which upon aqueous work up gives alkene 666.\textsuperscript{113a}

![Scheme 134: Cobalt catalysed domino arylation/1,4-migration process](image)

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 disubstituted aryl compounds 669 (Scheme 135).

![Scheme 135: Cobalt catalysed domino arylation/1,4-migration process](image)
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.\(^\text{113b}\)

![Chemical Structure](image1)

**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).\(^\text{114}\)

![Chemical Structure](image2)

**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]

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]

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](image)

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,\textsuperscript{[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.

![Figure 3](image)

The mechanism proposed for the synthesis 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 \textit{via} a 1,4-migration process. (Scheme 141).

![Scheme 141](image)

\textbf{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 arylicative-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 arylicative-cyclisation

<table>
<thead>
<tr>
<th>Entry</th>
<th>n</th>
<th>Ar</th>
<th>Yield of 695</th>
<th>Yield of 698</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>4-MeOC6H4</td>
<td>38%</td>
<td>11%</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>phenyl</td>
<td>42%</td>
<td>12%</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>4-MeOC6H4</td>
<td>40%</td>
<td>9%</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>phenyl</td>
<td>39%</td>
<td>10%</td>
</tr>
</tbody>
</table>

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

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.\cite{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](image)

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**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ether</td>
<td>40</td>
<td>17%</td>
</tr>
<tr>
<td>2</td>
<td>CH$_2$Cl$_2$</td>
<td>40</td>
<td>24%</td>
</tr>
<tr>
<td>3</td>
<td>MeOH</td>
<td>60</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>i-PrOH</td>
<td>80</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>65</td>
<td>37%</td>
</tr>
<tr>
<td>6</td>
<td>THF</td>
<td>120</td>
<td>60%</td>
</tr>
<tr>
<td>7</td>
<td>Toluene</td>
<td>120</td>
<td>44%</td>
</tr>
</tbody>
</table>

1) Determined by $^1$H 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$_2$O 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv. of H$_2$O</th>
<th>Conversion$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.0</td>
<td>37%</td>
</tr>
<tr>
<td>2</td>
<td>1.2</td>
<td>56%</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>46%</td>
</tr>
</tbody>
</table>

$^1$ 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>Conversion$^1$ (65 °C)</th>
<th>Conversion$^1$ (120 °C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AgOTf</td>
<td>50%</td>
<td>97%</td>
</tr>
<tr>
<td>2</td>
<td>NaBF$_4$</td>
<td>50%</td>
<td>89%</td>
</tr>
<tr>
<td>3</td>
<td>YbOTf</td>
<td>48%</td>
<td>87%</td>
</tr>
</tbody>
</table>

$^1$ 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 Rf (The product was isolated but not fully characterised at that point) (Scheme 147).

Scheme 147: Optimised conditions for the Iridium 1,4-migration process using NaBPh₄

5.4. Replacing NaBPh₄ for PhB(OH)₂

NaBPh₄ 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 NaBPh₄ is only 55%, very low compared with to an almost 90% obtained for the same process using PhB(OH)₂.[121]

Early studies exchanging NaBPh₄ 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).⁸

---

⁸ Screening performed by Dr Benjamin M. Partridge
Table 8: Base screening

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Conversion</th>
<th>NMR yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>2</td>
<td>K₂CO₃</td>
<td>100%</td>
<td>62%</td>
</tr>
<tr>
<td>3</td>
<td>K₃PO₄</td>
<td>93%</td>
<td>62%</td>
</tr>
<tr>
<td>4</td>
<td>CsF</td>
<td>100%</td>
<td>64%</td>
</tr>
<tr>
<td>5</td>
<td>KF</td>
<td>89%</td>
<td>63%</td>
</tr>
</tbody>
</table>

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 H₂O 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). \(^b\)

---

\(^b\) Optimisation performed by Dr Benjamin M. Partridge
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).

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Concentration</th>
<th>Yield of 712</th>
<th>Yield of 714</th>
<th>Ratio 712:714</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.2 M</td>
<td>72%</td>
<td>27%</td>
<td>2.7</td>
</tr>
<tr>
<td>2</td>
<td>0.04 M</td>
<td>74%</td>
<td>15%</td>
<td>4.9</td>
</tr>
<tr>
<td>3</td>
<td>0.4 M</td>
<td>79%</td>
<td>17%</td>
<td>4.6</td>
</tr>
</tbody>
</table>

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 alkyrones 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 steric 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](image-url)
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).[^123]

[^123]: Substrates synthesised by Dr Benjamin M. Partdrige
Racemic $\beta$-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 $\beta$-keto ester 748 (Scheme 153).
Another acyclic substrate was synthesised following the same procedure as for the racemic \( \beta \)-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](image)

To study further the electrophilic part of the substrate, racemic \( \beta \)-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 \( \beta \)-ketoamide 763 in moderate yield (Scheme 155).

![Scheme 155: Substrate synthesis](image)

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 electrodeonating \( para \)-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 an 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).

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 an 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](image)

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](image)

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 steric 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](image)

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 NaBPh₄ instead of PhB(OH)₂ were tried but only gave either very complex mixtures or mainly starting materials. Similarly, malonate derivative 759 did not perform the arylative-cyclisation process, and only starting alkyne 759 was recovered (Scheme 162).
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 electron-withdrawing 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-substituted 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-naphthyl 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.\textsuperscript{120a}

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

![Scheme 165: Deuterium experiments for the 1,4-migration process](image)

### 5.7. Asymmetric Variant

Both rhodium and iridium were shown to perform the racemic arylation-cyclisation of alkyrones 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)\textsubscript{2}Cl\textsubscript{2}] and [Rh(C\textsubscript{2}H\textsubscript{4})\textsubscript{2}Cl\textsubscript{2}] using NaBPh\textsubscript{4} as arylative agent, showed complete inactivity towards the arylative-cyclisation process (Scheme 166).

\textsuperscript{1} Reactions performed by Dr Benjamin M. Partdrige
Scheme 166: Testing the background reaction using Ir and Rh catalysts

A range of catalysts were prepared \textit{(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 $[\text{Rh}(\text{C}_2\text{H}_4\text{Cl})_2]$ with $(S)$-Segphos \textbf{L32} and $(R)$-DTBM-Segphos \textbf{L37} showed similar levels of conversions to those achieved with $[\text{Rh}(\text{cod})\text{Cl}]_2$ 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 \textbf{L09}, $(R)$-BINAP \textbf{L02} or $(R)$-Difluorophos \textbf{L34} (Table 10).

**Table 10: Ligand screening with Rh**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Conversion$^I$</th>
<th>ee$^{II}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>\textbf{L32}</td>
<td>45%</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>\textbf{L37}</td>
<td>35%</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>\textbf{L09}</td>
<td>20%</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>\textbf{L02}</td>
<td>15%</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>\textbf{L34}</td>
<td>0%</td>
<td>Not measured</td>
</tr>
</tbody>
</table>

$^I$ 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 NaBPh₄ 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 L.02 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>X mol%</th>
<th>Ligand</th>
<th>Conversion</th>
<th>ee&lt;sup&gt;II&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>L02</td>
<td>20%</td>
<td>93%</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>L34</td>
<td>35%</td>
<td>95%</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>L32</td>
<td>10%</td>
<td>Not measured</td>
</tr>
</tbody>
</table>

I) Determined by <sup>1</sup>H NMR analysis of the crude reaction mixture (See Table 5)

II) Determined by Chiral HPLC

By increasing the temperature to 110 °C using Xylenes as the solvent and <i>t</i>-AmOH instead of <i>t</i>-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).<sup>a</sup>

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<sup>a</sup> Reactions performed by Dr Benjamin M. Partdrige
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 alkynones. Iridium catalysed asymmetric alylation is a well-known procedure therefore the allylation of alkynone 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 CH₂Cl₂, 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 ¹H NMR analysis. In this case, the boronic acid was stirred in a mixture of Et₂O and water for 30 minutes. The organic phase was separated, dried (Na₂SO₄), 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 60F₂₅₄ 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 CHCl₃. ¹H 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 (CHCl₃ 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 ¹³C 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 (CDCl₃ at 77.0 ppm, CD₃OD at 49.0 ppm). Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. Proton-decoupled ¹⁹F NMR spectra were recorded on a Bruker AVA400 (376 MHz) spectrometer. Chemical shifts (δ) are quoted in ppm downfield of CFCl₃ (δ = 0 ppm), using fluorobenzene (C₆H₅F at −113.5 ppm) or trifluoroacetic acid (CF₃CO₂H 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)

To a stirred solution of 2-methyl-1,3-cyclopentanedione (6.30 g, 50.0 mmol) in H₂O (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/CH₂Cl₂) to give the title compound 325 (7.01 g, 84%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 9.56 (1H, t, J = 1.0 Hz, CH₂O=CH), 2.71 (4H, s, O=CC(CH₃)₂C=O), 2.38 (2H, dt, J = 7.2, 0.9 Hz, CH₂(CH₃)₂O=CH), 1.81 (2H, t, J = 7.2 Hz, CH₂CH₂O=CH), 1.02 (3H, s, O=CCCH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 215.5 (C), 200.7 (2 x C), 55.0 (C), 38.3 (CH₂), 34.7 (2 x CH₂), 25.9 (CH₂), 19.3 (CH₃).

The data were in agreement with those reported in the literature.⁶⁹b
3-(1-Methyl-2,5-dioxocyclopentyl)propionaldehyde (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$_3$) $\delta$ 9.63 (1H, t, $J = 1.2$ Hz, CH$_2$O=CH), 2.56-2.61 (4H, m, O=CCCH$_2$CH$_2$CH$_2$C=O), 2.30 (2H, dt, $J = 7.1, 0.9$ Hz, CH$_2$CH$_2$O=CH), 2.05 (2H, dt, $J = 7.1, 0.9$ Hz, CH$_2$CH$_2$O=CH), 1.96-1.88 (2H, m, O=CCCH$_2$CH$_2$CH$_2$C=O), 1.23 (3H, s, O=CCCH$_3$); $^{13}$C NMR (125.8 MHz, CDCl$_3$) $\delta$ 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)

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 x 20 mL) and Et$_2$O (20 mL) and then dissolved in CH$_2$Cl$_2$ (50 mL). A solution of Na$_2$CO$_3$ (5.82 g, 55.0 mmol) in H$_2$O (50 mL) was added to the CH$_2$Cl$_2$ 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 CH₂Cl₂ (3 × 25 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo to give the title compound 304 as a yellow solid Rᵣ = 0.28 (90% EtOAc/hexane). \(^1\)H NMR (500 MHz, CDCl₃) δ 7.94 (2H, d, J = 9.0 Hz, ArH), 7.75-7.70 (6H, m, ArH), 7.56-7.54 (3H, m, ArH), 7.48-7.45 (6H, m, ArH), 6.87 (2H, d, J = 9.0 Hz, ArH), 4.36 (1H, s, Ph₃P=C), 3.83 (3H, s, OCH₃). ^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 (CH₃), 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 CH₂Cl₂ gave a bright yellow solid (18.2 g, 85%). Rᵣ = 0.53 (90% EtOAc/hexane). \(^1\)H NMR (500 MHz, CDCl₃) δ 8.20 (2H, d, J = 10.2 Hz, ArH), 8.09 (2H, d, J = 10.2 Hz, ArH) 7.75-7.68 (6H, m, ArH), 7.63-7.59 (3H, m, ArH), 7.54-7.47 (6H, m, ArH), 4.51 (1H, d, J = 23.0 Hz, Ph₃P=CH); ^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 CH₂Cl₂ gave a white solid (30.1 g, 80%). Rᵣ = 0.53 (90% EtOAc/hexane). \(^1\)H NMR (500 MHz, CDCl₃) δ 8.20 (2H, d, J = 10.2 Hz, ArH), 7.79 (2H, d, J = 10.2 Hz, ArH) 7.77-7.67 (6H, m, ArH), 7.63-7.59 (3H, m, ArH), 7.54-7.47 (8H, m, ArH), 4.45 (1H, d, J = 25.0 Hz, Ph₃P=CH).

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$_2$Cl$_2$ gave a bright yellow solid (4.10 g, 95%). $R_f$ = 0.25 (90% EtOAc/hexane). $\delta$ 7.88 (1H, dd, $J$ = 6.9, 2.0 Hz, ArH), 7.81-7.75 (6H, m, ArH), 7.51-7.46 (6H, m, ArH), 7.29 (1H, dt, $J$ = 8.1, 1.8 Hz, ArH), 6.99-6.92 (2H, m, ArH), 4.62 (1H, d, $J$ = 22.0 Hz, Ph$_3$P=CH), 3.91 (3H, s, OCH$_3$).

$^{13}$C NMR (125.8 MHz, CDCl$_3$) $\delta$ 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.\textsuperscript{[129]}

1-(3-Trifluoromethyl)-2-(triphenylphosphoranylidene)ethanone (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 dissolved in 50 mL of CH$_2$Cl$_2$. A solution of Na$_2$CO$_3$ (1.20 g, 11.0 mmol) in H$_2$O (25 mL) was added to the CH$_2$Cl$_2$ 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$_2$Cl$_2$ (3 x 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$_3$) $\delta$ 8.24 (1H, s, ArH), 8.15 (1H, d, $J$ = 7.8 Hz, ArH) 7.75-7.66 (6H,
m, ArH), 7.62-7.57 (3H, m, ArH), 7.55-7.45 (8H, m, ArH), 4.46 (1H, d, J = 23.0 Hz, Ph3P=CH); 13C NMR (125.8 MHz, CDCl3) δ 182.8 (C, d, J = 3.7 Hz), 141.9 (C, d, J = 14.4 Hz), 133.1 (6 × C, 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); 31P NMR (162 MHz, CDCl3) δ 29.1, 16.8; 19F NMR (376 MHz, CDCl3) δ: −75.5; HRMS (ESI) Exact mass calcd for C27H21OF3P [M+H]⁺: 449.1276, found: 449.1275.

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

To a refluxing suspension of CuBr₂ (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 CHCl₃ (10.0 mL) the resulting mixture was stirred for 18 hours under reflux conditions. The solution was filtered and then washed with Sat. NaHCO₃ (10 mL) and brine (10 mL). The organic layer was concentrated in vacuo and the residue was dissolved in toluene (100 mL) and PPh₃ (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 CH₂Cl₂. A solution of Na₂CO₃ (2.64 g, 20.0 mmol) in H₂O (100 mL) was added to the CH₂Cl₂ 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 CH₂Cl₂ (3 × 25 mL). The combined organic layers were dried (NaSO₄), filtered and concentrated in vacuo to give the title compound 306 as pale orange solid (4.53 g, 55%). Rᵣ = 0.26 (90% EtOAc/hexane); ¹H NMR (300 MHz, CDCl₃) δ 7.80-7.75 (5H, m, ArH), 7.71-7.66 (2H, m, ArH), 7.61-7.47 (12H, m, ArH), 4.41 (1H, d, J = 25.2 Hz, Ph₃P=CH).

The data were in agreement with those reported in the literature.¹³¹
1-(Pyridin-2-yl)-2-(triphenylphosphanylidene)ethan-1-one (310)

To a stirred solution of acetylpiperidine (6.05 g, 50.0 mmol) in 30% HBr/HOAc (60 mL) was added dropwise Br₂ (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 Et₂O (250 mL) and stirred for 30 min. The precipitate was filtered and washed with Et₂O (25 mL). The brown solid was then dissolved in Sat. NaHCO₃ (50 mL) and extracted with CH₂Cl₂ (3 x 25 mL). The combined organic layers were dried (NaSO₄), filtered and concentrated in vacuo. The residue was dissolved in toluene (100mL) and PPh₃ (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 CH₂Cl₂. A solution of Na₂CO₃ (2.64 g, 20.0 mmol) in H₂O (100 mL) was added to the CH₂Cl₂ 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 CH₂Cl₂ (3 x 25 mL). The combined organic layers were dried (NaSO₄), filtered and concentrated in vacuo to give the title compound 310 as an off-white gummy solid (13.9 g, 73%). Rf = 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, CDCl₃) δ 8.59 (1H, d, J = 4.0 Hz, ArH), 8.15 (1H, d, J = 7.9 Hz, ArH), 7.80-7.70 (6H, m, ArH), 7.60-7.53 (3H, m, ArH), 7.52-7.45 (6H, m, ArH), 7.31-7.25 (2H, m, ArH), 4.32 (1H, d, J = 21.4 Hz, Ph₃P=CH); ¹³C NMR (100.6 MHz, CDCl₃) 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); ³¹P NMR (162 MHz, CDCl₃) δ 17.4; HRMS (ESI) Exact mass calculated for C₂₅H₂₁NOP [M+H]+: 382.1365, found: 382.1369.

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

1H NMR (500 MHz, CDCl_3) δ 7.70-7.65 (5H, m, ArH), 7.58-7.54 (4H, m, ArH), 7.48-7.43 (6H, m, ArH), 7.40-7.27 (6H, m, ArH), 4.59 (2H, s, O=CC=H), 3.88 (2H, t, J = 7 Hz OCH_2CH_3), 2.69 (2H, t, J = 7 Hz OCH_2CH_3); 13C 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)

![Structure of 327 and 807](image)

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}; 1H
NMR (500 MHz, CDCl₃) δ 7.86 (2H, d, J = 8.6 Hz, ArH), 7.45 (2H, d, J = 8.6 Hz, ArH), 6.97 (1H, dt, J = 15.3, 6.8 Hz, CH₂CH=), 6.82 (1H, dt, J = 15.3, 1.3 Hz, =CHC≡O), 2.75-2.63 (4H, m, CH₂CH₂CH₂), 2.18-2.14 (2H, m, CH₂CH=), 2.03-1.91 (4H, m, CH₂CH₂CH₂, CH₂CH₂CH=), 1.32 (3H, s, CH₃); ¹³C NMR (125.8 MHz, CDCl₃) 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 × CH₂), 33.9 (CH₂), 28.2 (CH₂), 21.7 (CH₂), 17.5 (CH₃); HRMS (ESI) Exact mass calcd for C₁₈H₂₀O₂Cl [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/CH₂Cl₂) gave an orange solid (3.05 g, 88%). R₉ = 0.44 (1:1 hexane/EtOAc); m.p. 85-87 °C; IR 2967, 2922, 1721 (C=O), 1693 (C=O), 1670, 1618, 1599, 1574, 1327, 1256, 1030, 1015, 812 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.93 (2H, d, J = 9.3 Hz, ArH), 6.94 (2H, d, J = 9.3 Hz, ArH), 6.93-6.90 (1H, m, CH₂CH=), 6.86 (1H, d, J = 15.6 Hz, CH₂CH=CH), 3.87 (3H, s, OCH₃), 2.70-2.67 (4H, m, CH₂CH₂CH₂), 2.17-2.11 (2H, m, CH₂CH₂CH₂), 2.04-1.93 (4H, m, CH₂CH₂CH=), 1.31 (3H, s, CH₃); ¹³C NMR (125.8 MHz, CDCl₃) 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 (CH₃), 37.9 (2 × CH₂), 34.4 (CH₂), 28.0 (CH₂), 21.0 (CH₃), 17.5 (CH₂); HRMS (EI) Exact mass calcd for C₁₉H₂₂O₄ [M⁺]: 314.1513, found: 314.1515.

2-[(3E)-5-Oxo-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, 5.00 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%). R₉ = 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; ¹H NMR (500 MHz, CDCl₃) δ 7.92-7.90 (2H, m, ArH), 7.56 (1H, tt, J = 7.0, 1.3 Hz, ArH), 7.47 (2H, t, J = 7.9 Hz, ArH), 6.96-6.90 (1H,
2-[(3E)-7-(Benzyloxy)-5-oxohept-3-en-1-yl]-2-methylcyclohexane-1,3-dione (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$_2$Cl$_2$) to give the title compound 336 as pale yellow oil (950 mg, 65%). $R_f = 0.35$ (CH$_2$Cl$_2$); IR 2976, 2874, 1724 (C=O), 1694 (C=O), 1670, 1618, 1454, 1269, 1101, 912, 733 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.35-7.26 (5H, m, Ar H), 6.78-6.71 (1H, m, CH$_3$CH=CH), 6.08 (1H, dt, $J = 16.0$, 1.5 Hz, CH$_2$CH=CH), 4.52 (2H, s, CH$_3$Ph), 3.78 (2H, t, $J = 6.6$ Hz, OCH$_2$CH$_2$C=O), 2.84 (2H, t, $J = 6.6$ Hz, OCH$_2$CH$_2$C=O), 2.69-2.58 (4H, m, CH$_3$CH$_2$CH$_2$), 2.09-2.02 (2H, m, CH$_3$CH$_2$CH$_2$), 1.95-1.90 (4H, m, CH$_3$CH$_2$CH$_2$), 1.29 (3H, s, CH$_3$); $^{13}$C NMR (125.8 MHz, CDCl$_3$) $\delta$ 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$_3$), 64.8 (C), 40.0 (CH$_2$), 37.9 (CH$_3$), 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-
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 3105, 3067, 2953, 2918, 1722 (C=O), 1689 (C=O), 1657 (OH), 1531 (OH), 1494 (OH), 1217, 1026, 854, 696 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta 7.39-7.30 \) (5H, m, ArH), 6.91 (1H, dt, \( J = 15.7, 6.7 \) Hz, CH=), 5.85 (1H, dt, \( J = 15.7, 1.5 \) Hz, CH=), 5.17 (2H, s, CH\(_2\)Ph), 2.72-2.58 (4H, m, CH\(_2\)CH\(_2\)CH\(_2\)), 2.07-2.00 (2H, m, CH\(_2\)CH\(_2\)CH\(_2\)), 1.98-1.87 (4H, m, CH\(_2\)CH\(_2\)CH=), 1.28 (3H, s, CH\(_3\)); \(^{13}\)C NMR (125.8 MHz, CDCl\(_3\)) \( \delta 209.8 \) (2 \( \times \) C), 166.1 (C), 148.1 (CH), 136.0 (C), 128.5 (2 \( \times \) CH), 128.13 (CH), 128.12 (2 \( \times \) CH), 121.6 (CH), 66.0 (CH\(_2\)), 64.8 (C), 37.9 (2 \( \times \) CH\(_2\)), 33.9 (CH\(_2\)), 27.5 (CH\(_2\)), 21.3 (CH\(_3\)), 17.5 (CH\(_3\)); HRMS (ESI) Exact mass calcd for C\(_{19}\)H\(_{28}\)NO\(_4\) [M+H\(^+\)]: 332.1856, found 332.1859.

![2-[(E)-5-(4-Nitrophenyl)-5-oxopent-3-enyl]-2-methylcyclohexane-1,3-dione (331)](image)

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\(_2\)Cl\(_2\)/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\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta 8.32 \) (2H, d, \( J = 7.2 \) Hz, ArH), 8.04 (2H, d, \( J = 7.2 \) Hz, ArH), 7.05-6.98 (1H, m, CH=), 6.82 (1H, dt, \( J = 15.2, 1.0 \) Hz CH=), 2.78-2.72 (2H, m, CH=), 2.68-2.62 (2H, m, CH=), 2.21-2.14 (2H, m, CH=), 2.07-1.99 (3H, m, CH=), 1.98-1.89 (1H, m, CH=), 1.33 (3H, s, CH\(_3\)); \(^{13}\)C NMR (125.8 MHz, CDCl\(_3\)) \( \delta 209.9 \) (2 \( \times \) C), 189.1 (C), 150.5 (CH), 150.0 (C), 142.6 (C), 129.4 (2 \( \times \) CH), 125.9 (CH), 123.7 (2 \( \times \) CH), 64.8 (C), 38.0 (2 \( \times \) CH), 33.4 (CH), 28.4 (CH), 22.4 (CH), 17.5 (CH); HRMS (ESI) Exact mass calcd for C\(_{19}\)H\(_{28}\)NO\(_4\) [M+H\(^+\)]: 330.1336, found: 330.1337.

![2-[(E)-5-(3-Trifluoromethylphenyl)-5-oxopent-3-enyl]-2-methylcyclohexane-1,3-dione (332)](image)

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-trifluoromethylphenyl)-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\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 8.15 (1H, s, ArH), 8.08 (1H, d, \( J = 7.9 \) Hz, ArH), 7.82 (1H, d, \( J = 7.5 \) Hz, ArH), 7.62 (1H, t, \( J = 7.5 \) Hz, ArH), 7.05-6.89 (1H, m, CH\(_2\)CH=CH), 6.85 (1H, dt, \( J = 15.9, 1.5 \) Hz, CH\(_2\)CH=CH), 2.77-2.62 (4H, m, CH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\)), 2.19-2.16 (2H, m, CH\(_2\)CH\(_3\)), 2.04-1.93 (4H, m, CH\(_2\)CH\(_2\)CH\(_3\)) = 1.33 (3H, s, CH\(_3\)); \(^{13}\)C NMR (125.8 MHz, CDCl\(_3\)) \( \delta \) 194.9 (C), 149.4 (CH), 138.2 (C), 131.7 (CH), 131.1 (C, q, \(^2\)J\(_{CF} = 32.9 \) Hz), 129.2 (CH), 129.1 (CH, q, \(^3\)J\(_{CF} = 3.6 \) Hz), 125.7 (CH), 125.3 (CH, q, \(^3\)J\(_{CF} = 3.8 \) Hz), 123.7 (C, q, \(^1\)J\(_{CF} = 272.6 \) Hz), 64.8 (C), 37.9 (2 \( \times \) CH\(_2\)), 33.7 (CH\(_2\)), 28.2 (CH\(_2\)), 21.8 (CH\(_3\)), 17.5 (CH\(_3\)); \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \( \delta \) -63.8 (3F, s); HRMS (EI) Exact mass calcd for C\(_{19}\)H\(_{19}\)O\(_3\)Br \([M^+]\): 352.1286, found: 352.1277.

2-[(3R)-5-oxopent-3-yl]-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-(triphenylphosphanylidene)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\(_2\)Cl\(_2\)); IR 3056, 2963, 2936, 1724 (C=O), 1694 (C=O), 1657, 1618, 1427, 1300, 1024, 766 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.60 (1H, d, \( J = 8.4 \) Hz, ArH), 7.38 (1H, t, \( J = 8.4 \) Hz, ArH), 7.32-7.27 (2H, m, ArH), 6.60-6.54 (1H, m, CH\(_2\)CH=), 6.40 (1H, d, \( J = 16.2 \) Hz, CH\(_2\)CH=CH), 2.74-2.61 (4H, m, CH\(_2\)CH\(_2\)CH\(_3\)), 2.14-2.09 (2H, m, CH\(_2\)CH\(_2\)CH\(_3\)), 1.99-1.91 (4H, m, CH\(_2\)CH\(_2\)CH=), 1.29 (3H, s, CH\(_3\)); \(^{13}\)C NMR (125.8 MHz, CDCl\(_3\)) \( \delta \) 209.8 (2 \( \times \) 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 \( \times \) 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\(_{19}\)H\(_{19}\)O\(_3\)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, 1599, 1376, 1286, 1025 cm^{-1}; ^1H NMR (400 MHz, CDCl_3) δ 7.42-7.30 (2H, m, ArH), 6.94-6.85 (2H, m, ArH), 6.64 (1H, dt, J = 15.6, 6.3 Hz, CH_2CH=), 6.56 (1H, app d, J = 15.6 Hz, CH_3CH=CH), 3.76 (3H, s, OCH_3), 2.58 (4H, t, J = 6.9 Hz, CH_2CH_2CH_2 and CH_2CH_2CH=), 2.05-1.96 (2H, m, CH_2), 1.91-1.81 (4H, m, CH_2CH_2CH_2 and CH_2CH=), 1.19 (3H, s, CH_3); ^13C 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), 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, 996, 785, 744 cm^{-1}; ^1H NMR (400 MHz, CDCl_3) δ 8.70 (1H, ddd, J = 4.8, 1.7, 0.9 Hz, ArH), 8.11 (1H, dt, J = 7.9, 1.0 Hz, ArH), 7.85 (1H, td, J = 7.7, 1.7 Hz, ArH), 7.57 (1H, dt, J = 15.7, 1.5 Hz, CH_2CH=CH), 7.47 (1H, ddd, J = 7.6, 4.8, 1.2 Hz, ArH), 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); ^13C 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%). Rf = 0.25 (70:30 hexane/EtOAc); m.p. 76-78 °C; IR (film) 2924, 1723 (C=O), 1671 (C=O), 1642, 1454, 1421, 1265, 1093, 739, 704 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.87-7.83 (2H, dm, J = 8.5 Hz, ArH), 7.46-7.43 (2H, dm, J = 8.5 Hz, ArH), 6.90 (1H, dt, J = 15.4, 1.5 Hz, CH₂CH=), 6.79 (1H, d, J = 15.4 Hz, =C=O), 2.90-2.69 (4H, m, O=CC₂H₄C₂H₄C=O), 2.25-2.20 (2H, m, CH₂CH=), 1.89-1.86 (2H, m, CH₃CH₂CH=), 1.18 (3H, s, CH₃); ¹³C NMR (125.8 MHz, CDCl₃) 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×CH₂), 32.7 (CH₂), 27.8 (CH₂), 20.0 (CH₃); HRMS (ESI) Exact mass calcd for C₁₇H₁₈O₃Cl [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 CH₂Cl₂/hexane) gave an orange solid (2.75 g, 91%). Rf = 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, CDCl₃) δ 7.92 (2H, d, J = 8.8 Hz, ArH), 6.95 (2H, d, J = 8.8 Hz, ArH), 6.86-6.85 (2H, m, CH₂CH=CH), 3.88 (3H, s, OCH₃), 2.83-2.74 (4H, m, O=CC₂H₄C₂H₄C=O), 2.22-2.20 (2H, m, CH₃CH=), 1.90-1.87 (2H, m, CH₃CH₂CH=), 1.18 (3H, s, CH₃); ¹³C NMR (125.8 MHz, CDCl₃) 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 (CH₃), 35.0 (2×CH₂), 33.0 (CH₂), 27.8 (CH₂), 19.8 (CH₃); HRMS (EI) Exact mass calecd for C₁₉H₂₀O₄ [M⁺]: 305.1356, found: 300.1358.

4-Hydroxy-1,3-dimethyl-1,2-dihydroquinolin-2-one (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 H2O (50 mL) and CH2Cl2 (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, d, $J = 7.9$, 1.9 Hz, ArH), 7.64-7.60 (1H, m, ArH), 7.53 (1H, d, $J = 8.0$ Hz, ArH), 7.32-7.28 (1H, m, ArH), 3.73 (3H, s, NCH3), 2.15 (3H, s, CCH3).

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)

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 Et3N (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, CDCl3) δ 9.69 (1H, t, $J = 1.2$ Hz, CH=O), 8.01 (1H, dd, $J = 7.7$, 1.7 Hz, ArH), 7.66 (1H, td, $J = 7.3$, 1.8 Hz, ArH) 7.72-7.18 (2H, m, ArH), 3.48 (3H, s, NCH3), 2.42-2.29 (4H, m, CH2CH2), 1.49 (3H, s, CCH3); $^{13}$C NMR (125.8 MHz, CDCl3) 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 (CH2), 29.8 (CH3), 29.1 (CH3), 24.0 (CH3); HRMS (EI) Exact mass calcd for C14H15O3N [M]+: 245.1046, found: 245.1050.
3-[(3E)-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, CDCl₃) δ 8.03 (1H, dd, J = 7.9, 1.7 Hz, ArH), 7.75 (2H, dt, J = 8.7, 2.4 Hz, ArH), 7.62 (1H, ddd, J = 8.5, 7.4, 1.8 Hz ArH), 7.39 (2H, dt, J = 8.7, 2.4 Hz, ArH), 7.19 (1H, td, J = 7.7, 0.8 Hz, ArH), 7.13 (1H, d, J = 8.3 Hz, ArH), 6.92 (1H, dt, J = 15.4, 6.6 Hz, CH₂CH=), 6.67 (1H, dt, J = 15.4, 1.3 Hz, =CHC=O), 3.46 (3H, s, NCH₃), 2.30-2.21 (4H, m, CH₂CH₂), 1.49 (3H, s, CCH₃); ¹³C NMR (125.8 MHz, CDCl₃) 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 (CH₂), 29.8 (CH₃), 28.7 (CH₂), 25.0 (CH₃); HRMS (EI) Exact mass calcd for C₂₂H₂₀O₃ClN [M]+: 381.1126, found: 381.1130.

6.1.4. Copper-Catalysed Borylative Aldol Cyclisations

Representative Procedure for the Copper-Catalysed Conjugate Boration-Cyclisation

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

A solution of CuCl (1.5 mg, 0.015 mmol), ligand L09 (11 mg, 0.017 mmol), B₂(pin)₂ (84 mg, 0.33 mmol) and NaOt-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$_2$O (15 mL) and extracted with CH$_2$Cl$_2$ (3 × 15 mL). The combined organic phases were dried (Na$_2$SO$_4$), 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$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.06 (2H, $dd$, $J = 8.4$, 1.1 Hz, ArH), 7.59 (1H, $t$, $J = 7.4$ Hz, ArH), 7.47 (2H, $t$, $J = 7.8$ Hz, ArH), 4.83 (1H, s, O$H$), 3.59 (1H, $d$, $J = 12.0$ Hz, C$_2$HCO$_2$Ph), 2.66-2.56 (1H, $m$, O=CC$_2$H), 2.27 (1H, $dd$, $J = 15.4$, 5.3 Hz, O=CCH$_2$), 2.14 (1H, $dd$, $J = 14.4$, 14.3, 5.2 Hz, O=CCH$_2$CH$_2$CH$_3$), 2.06-1.99 (1H, m, C(CH$_3$)$_3$CH$_2$), 1.89-1.79 (1H, m, BCH), 1.71-1.47 (4H, m, O=CCH$_2$CH$_2$CH$_2$, C(CH$_3$)$_2$CH$_2$, O=CCH$_2$CH$_2$), 1.39-1.31 (1H, m, BCHCH$_2$), 1.23 (3H, s, C(CH$_3$)$_2$CH$_2$), 0.89 (6H, s, C(CH$_3$)$_2$), 0.86 (6H, s, C(CH$_3$)$_2$); $^1$C NMR (125.8 MHz, CDCl$_3$) $\delta$ 213.9 (C), 207.5 (C), 137.4 (C), 133.8 (CH), 132.6 (CH), 128.4 (CH), 75.3 (C), 54.6 (C), 47.2 (CH), 36.4 (CH$_2$), 29.6 (CH$_2$), 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$_5$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.

(4aS,5S,6R,8aS)-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$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.01 (2H, $d$, $J = 8.5$ Hz, ArH), 7.45 (2H, $d$, $J = 8.5$ Hz, ArH), 4.51 (1H, s, OH), 3.52 (1H, $d$, $J = 12.0$ Hz, CHCO$_2$Ar), 2.65-2.57 (1H, m, O=CCH$_2$), 2.27 (1H, $dd$, $J = 15.5$, 5.2 Hz, O=CCH$_2$), 2.15 (1H, dt, $J = 15.1$, 4.9 Hz, O=CCH$_2$CH$_2$CH$_3$), 2.05-2.01 (1H, m,
C(CH₃)CH₂), 1.85 (1H, ddd, J = 12.7, 12.6, 3.6 Hz, BCH), 1.69-1.55 (4H, m, C(CH₃)CH₂, 
O=C(CH₂)CH₂, BCHCH₂), 1.53-1.40 (1H, m, O=C(CH₂)CH₂), 1.33-1.25 (1H, m, 
O=C(CH₂)CH₂CH₂), 1.25 (3H, s, C(CH₃)CH₂), 0.95 (6H, s, C(CH₃)₂), 0.89 (6H, s, C(CH₃)₂);

¹³C NMR (125.8 MHz, CDCl₃) 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), 54.6 (C), 47.4 (CH), 36.4 (CH₂), 32.3 (CH₂), 29.6 (CH₂), 24.41 (2 × CH₂), 24.35 (2 × CH₂), 23.7 (CH₂), 22.9 (CH₃), 19.3 (CH₂), tertiary carbon (CH) next to boron not observed due to quadrupolar coupling effects of ¹¹B; HRMS (ESI) 
Exact mass calec for C₂₄H₃₃O₅BCl [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); tᵣ (major) = 9.5 min, tᵣ (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), B₂(pin)₂ (879 mg, 3.45 mmol) and NaOt-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. NaHCO₃ (aq.) (2 mL), diluted with 
H₂O (80 mL) and extracted with CH₂Cl₂ (3 × 100 mL). The combined organic phases were dried (Na₂SO₄), 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); tᵣ (major) = 
9.5 min, tᵣ (minor) = 11.2 min; 93% ee.

(4aS,5S,6R,8aS)-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 i-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; [α] D²₀ +16.4 (c 0.61, CHCl₃); IR 3429 (OH), 
2980, 2930, 1738 (C=O), 1694 (C=O), 1454, 1371, 1323, 1142, 847, 741 cm⁻¹; ¹H NMR 
(500 MHz, CDCl₃) δ 8.07-8.03 (2H, m, ArH), 6.96-6.91 (2H, m, ArH), 4.87 (1H, br s, OH),
3.89 (3H, s, OCH₃), 3.52 (1H, d, J = 12.0 Hz, CHCOAr), 2.67-2.56 (1H, m, O=CCH₂), 2.28 (1H, dd, J = 15.4, 5.2 Hz, O=CCH₂CH₂CH₂), 2.14 (1H, td, J = 14.4, 5.1 Hz, O=CCH₃), 2.05-1.99 (1H, m, C(CH₃)CH₃), 1.88-1.79 (1H, m, BCH), 1.71-1.49 (5H, m, C(CH₃)CH₂, O=CCH₂CH₂, BCHCH₂, O=CCH₂CH₂CH₂), 1.41-1.36 (1H, m, BCHCH₂), 1.24 (3H, s, C(CH₃)CH₂), 0.91 (6H, s, C(CH₃)₂), 0.88 (6H, s, C(CH₃)₂); ¹³C NMR (125.8 MHz, CDCl₃) 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 (CH₃), 54.6 (C), 46.7 (CH), 36.5 (CH₂), 32.3 (CH₂), 29.6 (CH₂), 24.4 (2 × CH₂), 24.3 (2 × CH₃), 23.8 (CH₃), 22.9 (CH₃), 19.4 (CH₂), tertiary carbon (CH) next to boron not observed due to quadrupolar coupling effects of ¹¹B; HRMS (ESI) Exact mass calcd for C₂₂H₂₈O₆¹⁰B [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); tᵣ (major) = 14.7 min, tᵣ (minor) = 16.4 min; >99% ee.

(4aS,5S,6R,8aR)-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. Rᵣ = 0.59 (3:2 hexane/EtOAc); m.p. 115-120 °C; [α]²⁰° +3.8 (c 0.53, CHCl₃); IR 3460 (OH), 2936, 1705 (C=O), 1657 (C=O), 1371, 1327, 1221, 1140, 920, 849, 716 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.07 (2H, dd, J = 8.3, 1.1 Hz, ArH), 7.56 (1H, t, J = 7.4 Hz, ArH), 7.46 (2H, t, J = 7.8 Hz, ArH), 5.52 (1H, ddt, J = 17.4, 10.0, 7.4 Hz, CH=CH₂), 5.09-4.99 (2H, m, =CH₂), 4.67 (1H, br s, OH), 3.61 (1H, d, J = 12.0 Hz, CHCOPh), 2.70 (1H, dd, J = 14.4, 7.6 Hz, O=CCH₂), 2.59-2.41 (2H, m, CH₃CH=), 2.31 (1H, dd, J = 15.0, 5.1 Hz, O=CCH₂), 2.23-2.12 (2H, m, O=CCH₂CH₂CH₂, CH₃CH₂CH₂), 1.84 (1H, td, J = 12.2, 3.8 Hz, BCH), 1.71-1.48 (4H, m, O=CCH₂CH₂CH₂, CH₂CH₂CH₂, O=CCH₂CH₂), 1.40-1.33 (1H, m, BCHCH₂), 1.32-1.20 (1H, m, BCHCH₂), 0.90 (6H, s, C(CH₃)₂), 0.86 (6H, s, C(CH₃)₂); ¹³C NMR (125.8 MHz, CDCl₃) 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 (CH₂), 83.3 (2 × C), 75.7 (C), 58.2 (C), 47.3 (CH), 39.3 (CH₂), 37.7 (CH₂), 32.1 (CH₂), 26.8 (CH₂), 24.35 (2 × CH₃), 24.32 (2 × CH₂), 23.6 (CH₂), 19.5 (CH₂), tertiary carbon (CH) next to boron not observed due to quadrupolar coupling effects of ¹¹B; HRMS (ESI) Exact mass calcd for C₂₂H₂₈O₆¹⁰B [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.

(4aS,5S,6R,8aS)-5-[3-(Benzyloxy)propanoyl]-4a-hydroxy-8a-methyl-6-(tetramethyl-1,3,2-dioxaborolan-2-yl)-decahydrophthalen-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); [\( \alpha \)]\textsubscript{D}\textsuperscript{20} +25.5 (c 0.47, CHCl\textsubscript{3}); IR 3442 (OH), 2974, 2930, 1701 (C=O), 1373, 1319, 1144, 1092, 849, 735 cm\(^{-1}\); \( \textsuperscript{1}H \) NMR (500 MHz, CDCl\textsubscript{3}) \( \delta \) 7.34-7.23 (5H, m, ArH), 4.47 (1H, d, \( J = 11.2 \) Hz, CH\textsubscript{2}Ph), 4.41 (1H, d, \( J = 11.2 \) Hz, CH\textsubscript{2}Ph), 3.99 (1H, ddd, \( J = 10.9, 8.8, 3.1 \) Hz, CH\textsubscript{2}OBn), 3.66 (1H, dt, \( J = 8.5, 4.1 \) Hz, CH\textsubscript{2}OBn), 3.32 (1H, ddd, \( J = 12.4, 8.8, 4.0 \) Hz, CH\textsubscript{2}CH\textsubscript{2}OBn), 3.28 (1H, d, \( J = 12.7 \) Hz, O=CC(CH\textsubscript{3})CH\textsubscript{2}B), 3.18 (1H, br s, O=CH), 2.49 (1H, td, \( J = 14.3, 6.9 \) Hz, O=CC(CH\textsubscript{2}CH\textsubscript{2})\textsubscript{2}), 2.39 (1H, dt, \( J = 7.4, 3.5 \) Hz, CH\textsubscript{2}CH\textsubscript{2}OBn), 2.21 (1H, td, \( J = 14.1, 4.6 \) Hz, O=CC(CH\textsubscript{2}CH\textsubscript{2})\textsubscript{2}), 2.15-2.08 (1H, m, O=CC(CH\textsubscript{2}CH\textsubscript{2})\textsubscript{2}), 1.91 (1H, td, \( J = 13.2, 4.3 \) Hz, C(CH\textsubscript{3})CH\textsubscript{2}), 1.71-1.65 (1H, m, BCHCH\textsubscript{2}), 1.64-1.56 (1H, m, BCH), 1.55-1.48 (1H, m, O=CC(CH\textsubscript{2}CH\textsubscript{2})\textsubscript{2}), 1.46-1.34 (2H, m, BCHCH\textsubscript{2}, O=CC(CH\textsubscript{2}CH\textsubscript{2})\textsubscript{2}), 1.34-1.26 (2H, m, C(CH\textsubscript{3})CH\textsubscript{2}, O=CC(CH\textsubscript{2}CH\textsubscript{2})\textsubscript{2}), 1.23 (3H, s, C(CH\textsubscript{3})CH\textsubscript{2}), 1.19 (6H, s, C(CH\textsubscript{3})\textsubscript{2}), 1.13 (6H, s, C(CH\textsubscript{3})\textsubscript{2}); \( \textsuperscript{13}C \) NMR (125.8 MHz, CDCl\textsubscript{3}) \( \delta \) 215.0 (C), 214.9 (C), 136.8 (C), 128.6 (CH), 128.3 (CH), 128.1 (CH), 83.3 (2 \( \times \) C), 78.3 (C), 73.9 (CH\textsubscript{2}), 67.5 (CH\textsubscript{2}), 58.7 (CH), 55.0 (C), 44.8 (CH\textsubscript{2}), 36.7 (CH\textsubscript{2}), 35.4 (CH\textsubscript{2}), 27.7 (CH\textsubscript{2}), 24.7 (2 \( \times \) CH\textsubscript{3}), 24.3 (2 \( \times \) CH\textsubscript{3}), 21.5 (CH\textsubscript{2}), 19.5 (CH\textsubscript{2}), 14.4 (CH\textsubscript{3}), tertiary carbon (CH) next to boron not observed due to quadrupolar coupling effects of \( \textsuperscript{11}B \); HRMS (ESI) Exact mass calcd for C\textsubscript{32}H\textsubscript{40}O\textsubscript{4}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); \( t_c \) (major) = 7.5 min, \( t_c \) (minor) = 10.0 min; 92% ee.

Benzyl-(1S,2R,4aS,8aS)-8a-hydroxy-4a-methyl-5-oxo-2-(tetramethyl-1,3,2-dioxaborolan-2-yl)-decahydrophthalene-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\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.39-7.30 (5H, m, ArH), 5.26 (1H, d, \( J = 12.4 \) Hz, CH\(_2\)Ph), 5.11 (1H, d, \( J = 12.4 \) Hz, CH\(_2\)Ph), 3.27 (1H, br s, OH), 2.99 (1H, d, \( J = 12.4 \) Hz, CHCO\(_2\)Bn), 2.57 (1H, td, \( J = 14.3, 6.7 \) Hz, O=CCH\(_2\)), 2.31-2.22 (1H, m, O=CCH\(_2\)), 2.04 (1H, qt, \( J = 13.7, 4.3 \) Hz, O=CCH\(_2\)CH\(_2\)), 1.94 (1H, ddd, \( J = 12.8, 12.6, 4.1 \) Hz, C(CH\(_3\))CH\(_2\)), 1.82-1.74 (1H, m, O=CCH\(_2\)CH\(_2\)), 1.73-1.67 (1H, m C(CH\(_3\))CH\(_2\)), 1.62-1.43 (3H, BCHCH\(_2\), BCH, O=CCH\(_2\)CH\(_2\)CH\(_2\)), 1.40-1.34 (1H, m, BCHCH\(_2\)), 1.23 (3H, s, C(CH\(_3\))CH\(_2\)), 1.21-1.16 (1H, m, O=CCH\(_2\)CH\(_2\)CH\(_2\)), 1.18 (6H, s, C(CH\(_3\))CH\(_2\)), 1.13 (6H, s, C(CH\(_3\))CH\(_2\)); \(^{13}\)C NMR (125.8 MHz, CDCl\(_3\)) \( \delta \) 214.4 (C), 174.3 (C), 135.2 (C), 128.6 (2 \( \times \) CH), 128.5 (CH), 128.2 (2 \( \times \) CH), 83.3 (2 \( \times \) 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 \( \times \) CH\(_3\)), 24.3 (2 \( \times \) 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\(_{23}\)H\(_{35}\)O\(_6\)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); \( t_f \) (major) = 8.3 min, \( t_f \) (minor) = 9.3 min; 93% ee.

\[ (4aR,5S,6R,8aR)-4a-Hydroxy-8a-methyl-5-[(4-nitrophenyl)carbonyl]-6-(tetramethyl-1,3,2-dioxaborolan-2-yl)-decahydronaphthalen-1-one \ (809a) \] and \[ (4aS,5S,6R,8aS)-4a-Hydroxy-8a-methyl-5-[(4-nitrophenyl)carbonyl]-6-(tetramethyl-1,3,2-dioxaborolan-2-yl)-decahydronaphthalen-1-one \ (809b) \]: The \textit{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), 3049, 1705 (C=O), 1655 (C=O), 1447, 1371, 1327, 1221, 1142, 920, 851 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 8.30-8.26 (2H, m, ArH), 8.14-8.10 (2H, m, ArH), 4.03 (1H, d, \( J = 12.5 \) Hz, CHCO\(_2\)Ar), 2.68 (1H, td, \( J = 14.4, 4.6 \) Hz, O=CCH\(_2\)CH\(_2\)CH\(_2\)), 2.30-2.23 (1H, m, O=CCH\(_2\)), 2.10 (1H, td, \( J = 13.2, 4.3 \) Hz, C(CH\(_3\))CH\(_2\)), 1.97-1.71 (4H, m, BCH, C(CH\(_3\))CH\(_2\), O=CCH\(_2\)CH\(_2\)), 1.62-1.42 (3H, m,
BCHCH₂, O=CCH₂CH₂), 1.37 (3H, s, C(CH₃)CH₂), 1.10 (6H, s, C(CH₃)₂), 1.00 (6H, s, C(CH₃)₂); δ C NMR (125.8 MHz, CDCl₃) 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 (CH₂), 35.6 (CH₂), 27.8 (CH₂), 24.7 (2 × CH₃), 24.2 (2 × CH₃), 21.6 (CH₂), 20.1 (CH₂), 14.4 (CH₃),

Enantiomeric excess was determined by HPLC with a CHIRALPAK IA-3 column (90:10 hexane:PrOH, 1.5 mL/min, 254 nm, 25 °C); tᵣ (major) = 7.2 min, tᵣ (minor) = 21.1 min; 86% ee.

Data for 809b: Rᵣ = 0.45 (3:2 hexane/EtOAc); m.p. 168-170 °C; [α]D²⁰ = −5.8 (c 0.52, CHCl₃);

IR 3418 (OH), 2974, 2929, 1734 (C=O), 1653 (C=O), 1449, 1371, 1325, 1225, 1142, 847 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.32 (2H, dd, J = 9.0, 2.0 Hz, ArH), 8.23 (2H, dd, J = 9.0, 2.0 Hz, ArH), 4.01 (1H, br s, OH), 3.58 (1H, d, J = 12.0 Hz, CHCOAr), 2.61 (1H, ddd, J = 15.2, 13.9, 7.9 Hz, O=CCH₂), 2.27 (1H, ddd, J = 15.4, 5.3 Hz, O=CCH₂), 2.17 (1H, dt, J = 14.5, 5.0 Hz, O=CCH₂CH₂), 2.09-2.01 (1H, m, C(CH₃)CH₂), 1.89 (1H, ddd, J = 12.6, 12.4, 3.2 Hz, BCH), 1.75-1.54 (4H, m, C(CH₃)CH₂, O=CCH₂CH₂, BCHCH₂), 1.46-1.31 (1H, m, O=CCH₂CH₂), 1.29-1.19 (1H, m, O=CCH₂CH₂CH₂), 1.24 (3H, s, C(CH₃)CH₂), 0.98 (6H, s, C(CH₃)₂), 0.89 (6H, s, C(CH₃)₂); ¹³C NMR (125.8 MHz, CDCl₃) 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 (CH₂), 32.4 (CH₂), 29.6 (CH₂), 24.6 (2 × CH₃), 24.3 (2 × CH₃), 23.6 (CH₂), 22.9 (CH₂), 19.2 (CH₃), tertiary carbon (CH) next to boron was not observed due to quadrupolar coupling effects of ¹¹B; HRMS (ESI) Exact mass calcd for C₂₄H₃₀O¹⁰BN [M+H]⁺: 457.2381, found: 457.2381; Enantiomeric excess was determined by HPLC with a CHIRALPAK IA-3 column (90:10 hexane:PrOH, 1.5 mL/min, 254 nm, 25 °C); tᵣ (major) = 6.8 min, tᵣ (minor) = 8.1 min; 87% ee.

(4aR,5S,6R,8aR)-4a-Hydroxy-8a-methyl-5-[(3-trifluoromethylphenyl)carbonyl]-6-(tetramethyl-1,3,2-dioxaborolan-2-yl)-decahydronaphthalen-1-one (810a) and (4aS,5S,6R,8aS)-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 \textbf{332} (106 mg, 0.30 mmol). Purification by column chromatography (9:1 hexane/EtOAc) gave \textbf{810a} as a colorless film (22 mg, 15%) and \textbf{810b} as a colorless film (86 mg, 60%).

Data for \textbf{810a}: $R_f = 0.29$ (3:2 hexane/EtOAc); $[\alpha]^{20}_{D} +2.0$ (c 1.0, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.23 (1H, s, ArH), 8.18 (1H, d, $J = 6.7$ Hz, ArH), 7.78 (1H, d, $J = 8.7$ Hz, ArH), 7.59 (1H, t, $J = 6.7$ Hz, ArH), 4.04 (1H, d, $J = 12.6$ Hz, CHCOAr), 2.67 (1H, dt, $J = 14.2$, 6.7 Hz, O=CCH$_2$), 2.49 (1H, dt, $J = 14.2$, 5.1 Hz, O=CCH$_2$CH$_2$CH$_3$), 2.27 (1H, td, $J = 14.7$, 2.2 Hz, O=CCH$_2$), 2.11 (1H, dt, $J = 13.6$, 4.6 Hz, C(CH$_3$)CH$_2$), 1.93-1.87 (1H, m, O=CCH$_2$CH$_2$), 1.85-1.77 (2H, m, O=CCH$_2$CH$_3$, BCHCH$_2$), 1.62-1.53 (2H, m, BCHCH$_2$, O=CCH$_2$CH$_2$CH$_3$), 1.48-1.44 (1H, m, O=CCH$_2$CH$_2$CH$_3$), 1.39 (3H, s, C(CH$_3$)CH$_2$), 1.09 (6H, s, C(CH$_3$)$_2$), 0.99 (6H, s, C(CH$_3$)$_2$); $^{13}$C NMR (125.8 MHz, CDCl$_3$) $\delta$ 214.2 (C), 203.6 (C), 140.6 (C), 132.0 (CH), 130.7 (C, $^2J_{CF} = 33.5$ Hz), 128.8 (CH), 128.7 (CH, q, $^3J_{CF} = 3.4$ Hz), 125.3 (CH, q, $^1J_{CF} = 3.5$ Hz), 123.9 (C, q, $^1J_{CF} = 275.5$ Hz), 83.6 (2 $\times$ 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 $\times$ CH$_3$), 24.1 (2 $\times$ CH$_3$), 21.7 (CH$_3$), 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$_3$) $\delta$ –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); $t_1$ (major) = 4.3 min, $t_1$ (minor) = 8.0 min; 82% ee.

Data for \textbf{810b}: $R_f = 0.49$ (3:2 hexane/EtOAc); $[\alpha]^{20}_{D} +5.9$ (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$_3$) $\delta$ 8.32 (1H, s, ArH), 8.23 (1H, d, $J = 7.9$ Hz, ArH), 7.85 (1H, d, $J = 7.8$ Hz, ArH), 7.62 (1H, t, $J = 7.8$ Hz, ArH), 4.31 (1H, br s, OH), 3.58 (1H, d, $J = 12.0$ Hz, CHCOAr), 2.61 (1H, ddd, $J = 15.2$, 13.9, 7.9 Hz, O=CCH$_3$), 2.29 (1H, ddd, $J = 15.4$, 5.3 Hz, O=CCH$_2$CH$_2$CH$_3$), 2.16 (1H, td, $J = 14.5$, 5.0 Hz, O=CCH$_3$), 2.08-2.01 (1H, m, O=CCH$_3$CH$_2$), 1.87 (1H, ddd, $J = 12.7$, 12.5, 2.7 Hz, C(CH$_3$)CH$_2$), 1.72-1.54 (4H, m, BCH, O=CCH$_2$CH$_2$, BCHCH$_2$, O=CCH$_2$CH$_2$CH$_3$), 1.50-1.37 (1H, m, BCHCH$_2$), 1.31-1.25 (1H, m, O=CCH$_2$CH$_2$), 1.24 (3H, s, C(CH$_3$)CH$_2$), 0.95 (6H, s, C(CH$_3$)$_2$), 0.86 (6H, s, C(CH$_3$)$_2$); $^{13}$C NMR (125.8 MHz, CDCl$_3$) $\delta$ 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, $^1J_{CF} = 3.6$ Hz), 129.0 (CH), 126.2 (CH, q, $^1J_{CF} = 3.7$ Hz), 123.6 (C, q, $^3J_{CF} = 276.2$ Hz), 83.4 (2 $\times$ 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 $\times$ CH$_3$), 24.2 (2 $\times$ CH$_3$), 23.6 (CH$_2$), 22.9 (CH$_3$), 19.2 (CH$_3$), tertiary carbon (CH) next to boron not observed due to quadrupolar coupling effects of $^{11}$B;
**19**F NMR (376 MHz, CDCl₃) δ -63.7 (3F, s); HRMS (EI) Exact mass calcd for C₁₂H₁₈O₅BF₃ [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); tᵣ (major) = 9.2 min, tᵣ (minor) = 13.2 min; 89% ee.

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(4aR,5S,6R,8aR)-4a-Hydroxy-8a-methyl-5-[(2-bromophenyl)carbonyl]-6-(tetramethyl-1,3,2-dioxaborolan-2-yl)-decahydronaphthalen-1-one (811a) and (4aS,5S,6R,8aS)-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, CHCl₃); 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, CDCl₃) δ 7.74 (1H, dd, \( J = 7.7, 1.6 \) Hz, ArH), 7.60 (1H, dd, \( J = 8.0, 1.0 \) Hz, ArH), 7.38 (1H, td, \( J = 7.6, 1.1 \) Hz, ArH), 7.26 (1H, td, \( J = 7.8, 1.7 \) Hz, ArH), 3.86 (1H, d, \( J = 12.3 \) Hz, CHCOAr), 2.67-2.57 (1H, m, O=CC₂H₂), 2.43 (1H, ddd, \( J = 18.0, 10.0, 4.5 \) Hz, O=CCH₂CH₂), 2.26 (1H, ddd, \( J = 6.0, 4.2, 2.3 \) Hz, O=CCH₂), 2.05 (1H, ddd, \( J = 13.3, 13.1, 4.1 \) Hz, C(CH₃)CH₂), 1.94-1.76 (5H, m, BCH, O=CCH₂CH₂, BCHCH₂, O=CCH₂CH₂CH₂, C(CH₃)CH₂), 1.53 (1H, ddd, \( J = 14.5, 14.1, 3.8 \) Hz, O=CCH₂CH₂), 1.41 (1H, ddd, \( J = 13.3, 3.9, 2.3 \) Hz, BCHCH₂), 1.25 (3H, s, C(CH₃)CH₂), 1.21 (6H, s, C(CH₃)₂), 1.13 (6H, s, C(CH₃)₂); \(^{13}\)C NMR (125.8 MHz, CDCl₃) 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 (CH₂), 35.6 (CH₂), 28.1 (CH₂), 24.7 (CH₃), 24.5 (CH₃), 21.7 (CH₂), 19.9 (CH₃), 14.4 (CH₃), tertiary carbon (CH) next to boron not observed due to quadrupolar coupling effects of \(^{11}\)B; HRMS (ESI) Exact mass calcd for C₂₅H₃₂O₅BF₃[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); tᵣ (major) = 8.9 min, tᵣ (minor) = 10.3 min; 68% ee

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Data for 811b: \( R_f = 0.39 \) (3:2 hexane/EtOAc); m.p. 117-120 °C; [\( \alpha \)]D

\(^{20}\) +2.0 (c 0.51, CHCl3); IR 3491 (OH), 2976, 2932, 1703 (C=O), 1661 (C=O), 1373, 1321, 1142, 1007, 851, 737 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl3) \( \delta \) 8.15 (1H, dd, \( J = 7.8, 1.6 \) Hz, ArH), 7.68 (1H, dd, \( J = 7.9, 1.1 \) Hz, ArH), 7.41 (1H, ddd, \( J = 7.7, 7.6, 1.2 \) Hz, ArH), 7.33 (1H, ddd, \( J = 7.7, 7.5, 1.7 \) Hz, ArH), 3.45 (1H, d, \( J = 12.2 \) Hz, CHCOAr), 3.27 (1H, br s, OH), 2.55 (1H, ddd, \( J = 15.2, 13.9, 7.9 \) Hz, O=CCH\(_3\)), 2.17 (2H, m, \( J = 14.5, 14.4, 4.6 \) Hz, O=CCH\(_2\)CH\(_2\), O=CCH\(_3\)), 2.04-1.98 (1H, m, C(CH\(_3\))CH\(_2\)), 1.92 (1H, ddd, \( J = 13.0, 12.8, 3.3 \) Hz, C(CH\(_3\))CH\(_2\)), 1.72-1.43 (6H, m, BCH, O=CCH\(_2\)CH\(_2\), BCH\(_2\), O=CCH\(_2\)CH\(_2\)CH\(_2\)), 1.22 (3H, s, C(CH\(_3\))CH\(_3\)), 1.11 (6H, s, C(CH\(_3\))\(_2\)), 1.03 (6H, s, C(CH\(_3\))\(_2\)); \(^{13}\)C NMR (125.8 MHz, CDCl3) \( \delta \) 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 calculated for C\(_2\)H\(_3\)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); \( t_i \) (major) = 6.7 min, \( t_i \) (minor) = 12.7 min; 83% ee.

(3aS,4S,5R,7aS)-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 \( \iota \)-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, CHCl3); IR 3416 (OH), 2974, 2928, 1734 (C=O), 1651 (C=O), 1369, 1325, 1225, 1140, 847 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl3) \( \delta \) 8.02-7.94 (2H, m, ArH), 7.61 (1H, t, \( J = 7.4 \) Hz, ArH), 7.48 (2H, t, \( J = 7.8 \) Hz, ArH), 4.67 (1H, br s, OH), 3.39 (1H, d, \( J = 12.0 \) Hz, CHCOPh), 2.48 (1H, ddd, 16.0, 8.8, 1.2 Hz, O=CCH\(_2\)), 2.31-2.21 (1H, m, O=CCH\(_2\)), 2.19-2.10 (2H, m, O=CCH\(_2\), CH\(_2\)CH\(_2\)CHB), 1.79 (1H, dq, \( J = 15.2, 7.7 \) Hz, CH\(_3\)CH\(_3\)), 1.75-1.69 (1H, m, BCH\(_2\)), 1.67-1.60 (2H, m, CH\(_2\)CH\(_3\), BCH), 1.60-1.55 (1H, m, O=CCH\(_2\)CH\(_3\)), 1.35-1.20 (2H, m, CH\(_2\)CH\(_2\)CHB, BCH\(_2\)), 0.90 (6H, s, C(CH\(_3\))\(_2\)), 0.84 (6H, s, C(CH\(_3\))\(_2\)), 0.75 (3H, t, \( J = 7.6 \) Hz, CH\(_2\)CH\(_3\)); \(^{13}\)C NMR (125.8 MHz, CDCl3) \( \delta \) 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 (CH₂), 30.8 (CH₂), 24.9 (CH₂), 24.4 (2 × CH₂), 24.34 (2 × CH₃), 24.27 (2 × CH₃), 7.3 (CH₃), tertiary carbon (CH) next to boron not observed due to quadrupolar coupling effects of $^{11}$B; HRMS (ESI) Exact mass calcd for C₂₄H₃₄O₅⁷⁸[B+M]+: 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); tᵣ (major) = 7.3 min, tᵣ (minor) = 12.7 min; 96% ee.

6.1.5. C-B Bond Transformations

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

To a stirred solution of 356 (127 mg, 0.30 mmol) in THF (1 mL) was added a suspension of NaBO₃·H₂O (149 mg, 1.50 mmol) in H₂O (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 H₂O (5 mL) and extracted with CH₂Cl₂ (3 × 5 mL). The combined organic phases were dried (Na₂SO₄), 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%). Rₒ = 0.40 (1:1 hexane/EtOAc); m.p. 180-185 °C; [α]_D⁰ −1.7 (c 0.58, CHCl₃); IR 3406 (OH), 2949, 2938, 1684 (C=O), 1651 (C=O), 1589, 1400, 1325, 1084, 1026, 833 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.96 (2H, d, J = 8.6 Hz, ArH), 7.47 (2H, d, J = 8.6 Hz, ArH), 4.83 (1H, s, O=CH), 4.37-4.32 (1H, m, CH₂OH), 3.43 (1H, d, J =10.3 Hz, CH₂OH), 2.63-2.55 (1H, m, O=CC₂H), 2.27 (1H, dd, J = 15.1, 5.3 Hz, O=CH₂), 2.18-2.05 (2H, m, CH₂CH₂CH₂, CH₂CH₂OH), 1.94-1.87 (1H, m, CH₂OH), 1.77-1.67 (3H, m, CH₂CH₂CH₂, CH₂CH₂OH), 1.43 (1H, d, J = 14.5 Hz, CH₂CH₂CH₂), 1.39-1.29 (1H, m, CH₂CH₂CH₂), 1.23 (3H, s, CH₃); ¹³C NMR (125.8 MHz, CDCl₃) 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 (CH₂), 32.5 (CH₂), 32.2 (CH₂), 27.7 (CH₂), 21.9 (CH₃), 19.4 (CH₂); HRMS (ESI) Exact mass calcd for C₁₉H₂₂ClO₄ [M+H]+: 337.1201, found: 337.1207.
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$_2$O (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$_2$SO$_4$), 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$_2$Cl$_2$); 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$^{-1}$; $^1$H NMR (500 MHz, CD$_3$OD) $\delta$ 8.01 (2H, d, $J = 9.3$ Hz, ArH), 7.45 (2H, d, $J = 9.3$ Hz, ArH), 3.39 (1H, d, $J = 12.0$ Hz, CHCOAr), 2.63-2.56 (1H, m, O=CCH$_2$), 2.16-2.06 (2H, m, O=CCH$_2$, O=CCH$_2$CH$_2$CH$_2$), 1.92 (1H, d, $J = 12.9$ Hz, CH$_2$CHB), 1.58-1.48 (3H, m, CH$_3$CH$_2$CHB, CH$_3$CH$_2$CH$_2$), 1.45-1.37 (2H, m, CH$_2$CH$_2$CHB, CH$_2$CH$_2$CH$_2$), 1.26 (1H, d, $J = 16.7$ Hz, O=CCH$_2$CH$_2$CH$_2$), 1.15 (s, 3H, CH$_3$); $^{13}$C NMR (125.8 MHz, CD$_3$OD) $\delta$ 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$_3$OD) $\delta$ 143.5; HRMS (ESI) Exact mass calcd for C$_{18}$H$_{20}$BClF$_3$O$_3$ [M-K$^-$]: 386.1188, found: 386.1190.

### 6.1.6 Stereochemical Determinations and X-ray Structures

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

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* X-Ray data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif149.
The absolute stereochemistry of all other products was assigned by analogy to 356.

The relative stereochemistry of product 311a (racemic material obtained using P(OEt)₃ as an achiral ligand) was determined by X-ray crystallography:

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 ¹H NMR spectra (see Figure 1).

The relative stereochemistry of product 389q (racemic material obtained using P(OEt)₃ as an achiral ligand) was determined by X-ray crystallography:

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¹) X-Ray data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif150.
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$_2$O (250 mL). After the frothing had finished,

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1) 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 CH₂Cl₂ (3 x 100 mL). The combined organic phases were dried (Na₂SO₄), 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%). Rᵣ = 0.15 (40% EtOAc/hexane); ¹H NMR (400 MHz, CDCl₃) δ 2.88-2.80 (4H, m, CH₂CH₂), 2.49 (2H, d, J = 2.8 Hz, CCH₂), 2.00 (1H, t, J = 2.8 Hz, C=CH), 1.15 (3H, s, CH₃).

The data were in agreement with those in the literature.¹²²⁻

2-Methyl-2-(prop-2-yn-1-yl)cyclohexane-1,3-dione (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 CH₂Cl₂ (2 x 200 mL). The combined organic phases were washed with brine (3 x 50 mL), dried (Na₂SO₄), 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%). Rᵣ = 0.17 (40% EtOAc/hexane); ¹H NMR (400 MHz, CDCl₃) δ 2.79-2.64 (6H, m, CH₂CH₂ and CCH₂), 2.08-1.92 (3H, m, CH₂CH₂CH₂ and C=CH), 1.33 (3H, s, CH₃).

The data were in agreement with those in the literature.¹³²⁻

Diethyl 2-methyl-2-(prop-2-yn-1-yl)malonate (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 cooled down to 0 °C and quenched with 10% aqueous HCl (10 mL). Brine (50 mL) was added and the mixture was extracted with Et₂O (2 × 25 mL). The combined organic phases were washed with brine (3 × 50 mL), dried (Na₂SO₄), 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, CDCl₃) \( \delta \) 4.22-4.16 (4H, m, O=CC₂H₃CH₃), 2.76 (2H, d, \( J = 2.7 \) Hz, CH₂C≡), 2.01 (1H, t, \( J = 2.7 \) Hz C≡CH), 1.53 (3H, s, CCH₃), 1.24 (6H, t, \( J = 7.06 \) Hz, O=CCH₂CH₃).

The data were in agreement with those in the literature.\(^{[133]}\)

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

![Chemical Structure](image)

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 cooled down to 0 °C and quenched with 10% aqueous HCl (10 mL). Brine (50 mL) was added and the mixture was extracted with Et₂O (2 × 25 mL). The combined organic phases were washed with brine (3 × 50 mL), dried (Na₂SO₄), 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, CDCl₃) \( \delta \) 4.26-4.19 (2H, m, O=CCH₂CH₃), 2.79-2.67 (2H, m, CH₂C≡), 2.01 (1H, t, \( J = 2.7 \) Hz C≡CH), 2.19 (3H, s, O=CCH₃), 2.02 (1H, t, \( J = 2.8 \) Hz), 1.49 (3H, s, CCH₃), 1.27 (3H, t, \( J = 7.13 \) Hz, O=CCH₂CH₃).

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(PPh₃)₂Cl₂ (140 mg, 0.199 mmol), CuI (106 mg, 0.557 mmol), and Et₃N (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 Et₂O (50 mL). The combined organic phases were washed with 10% aqueous HCl (3 × 20 mL), dried (Na₂SO₄), 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 (Et₂O/hexane); IR 2970, 1721 (C=O), 1412, 1065, 760 cm⁻¹; \(^1\)H NMR (400 MHz, CDCl₃) \( \delta \) 7.37-7.27 (5H, m, ArH), 2.90-2.80 (4H, m, CH₂C≡C), 2.70 (2H, s, CH₃C≡C), 1.19 (3H, s, CH₃); \(^1^{3}\)C NMR (126 MHz, CDCl₃) \( \delta \) 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 × CH₂), 25.9 (CH₂), 18.9 (CH₃); HRMS (ESI) Exact mass calcd for C₁₅H₁₈NO₂ [M+NH₄]^+: 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(PPh₃)₂Cl₂ (140 mg, 0.199 mmol), CuI (106 mg, 0.557 mmol), and Et₃N (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 Et₂O (50 mL). The organic layer was washed with 10% aqueous HCl (3 × 20 mL), dried (Na₂SO₄), 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. Rₚ = 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, CDCl₃) δ 7.26 (2H, d, J = 8.9 Hz, ArH), 6.80 (2H, d, J = 8.9 Hz, ArH), 3.80 (3H, s, OCH₃), 2.89-2.78 (4H, m, CH₂CH₂), 2.68 (2H, s, CH₂C≡C), 1.17 (3H, s, CH₃); ¹³C NMR (126 MHz, CDCl₃) 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 (CH₃), 36.0 (2 × CH₂), 26.2 (CH₂), 18.8 (CH₃); HRMS (ESI) Exact mass calcd for C₁₆H₁₇O₃ [M+H]⁺: 257.1178, found: 257.1173.

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

![Chemical Structure]

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), PPh₃ (262 mg, 1.00 mmol), CuI (106 mg, 0.56 mmol), and Et₃N (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 Et₂O (50 mL). The organic layer was washed with 10% aqueous HCl (3 × 20 mL), dried (Na₂SO₄), 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. Rₚ = 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, CDCl₃) δ 8.14 (2H, d, J = 8.9 Hz, ArH), 7.47 (2H, d, J = 8.9 Hz, ArH), 2.94-2.76 (4H, m, CH₂CH₂), 2.74 (2H, s, CH₂C≡C), 1.22 (3H, s, CH₃); ¹³C NMR (126 MHz, CDCl₃) 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 × CH₂), 25.0 (CH₂), 19.4 (CH₃); HRMS (EI) Exact mass calcd for C₁₅H₁₃O₄N [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), PPh₃ (189 mg, 0.721 mmol), CuI (68.6 mg, 0.360 mmol), and Et₃N (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 Et₂O (50 mL). The organic phase was washed with 10% aqueous HCl (3 × 20 mL), dried (Na₂SO₄), 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, CDCl₃) δ 7.35-7.33 (2H, m, ArH), 7.28-7.26 (3H, m, ArH), 2.87 (2H, s, C₆H₂C≡C), 2.73 (4H, td, J = 7.2, 2.1 Hz, C₆H₂CH₂CH₂), 2.01 (2H, qd, J = 7.2, 2.1 Hz, CH₂CH₂CH₂), 1.36 (3H, s, CH₃); ¹³C NMR (126 MHz, CDCl₃) 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 × CH₂), 26.4 (CH₂), 21.7 (CH₃), 17.3 (CH₂); HRMS (ESI) Exact mass calcd for C₁₆H₁₇O₂ [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), PPh₃ (262 mg, 1.00 mmol), CuI (106 mg, 0.557 mmol), and Et₃N (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
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 Et₂O (50 mL). The organic phase was washed with 10% aqueous HCl (3 × 20 mL), dried (Na₂SO₄), filtered, and concentrated \textit{in vacuo}. Purification of the residue by column chromatography (10% EtOAc/hexane) to give the \textit{title compound} 732 (2.21 g, 82%) as a pale yellow solid. 

\[ R_f = 0.28 \text{ (30\% EtOAc/hexane); m.p. 70-75 °C (hexane); IR 2695, 1721 (C=O), 1508, 1032, 841 cm}^{-1}; 7.30-7.24 (2H, m, ArH), 6.82-6.76 (2H, m, ArH), 3.79 (3H, s, OCH₃), 2.84 (2H, s, CH₂=C=C), 2.73 (4H, t, J = 3.8 Hz, CH₂CH₂CH₂₂), 2.08-1.92 (2H, m, CH₂CH₂CH₂₂), 1.34 (3H, s, CCH₃); ^{13}C NMR (126 MHz, CDCl₃) 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 (CH₃), 38.6 (2 × CH₂), 26.8 (CH₂), 21.5 (CH₃), 17.3 (CH₂); HRMS (ESI) Exact mass calcd for C₁₇H₁₉O₃ [M+H]$^+$: 271.1334, found: 271.1329.

\[
\text{1-Methyl-3-methyl-3-(2-propynyl)-1,3-dihydroquinoline-2,4-dione (762)}
\]

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 (Na₂SO₄), filtered and concentrated \textit{in vacuo}. Purification of the residue by column chromatography (20% EtOAc/hexane) gave the \textit{title compound} 762 (650 mg, 52%) as a yellow oil. 

\[ R_f = 0.33 \text{ (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, CDCl₃) δ 8.06-8.03 (1H, m, ArH), 7.68-7.63 (1H, m, ArH), 7.27-7.18 (2H, m, ArH), 3.51 (3H, s, NCH₃), 2.90 (2H, d, J = 2.6 Hz, CH₂), 1.84 (1H, t, J = 2.6 Hz, ≡CH), 1.47 (3H, s, CCH₃); ^{13}C NMR (126 MHz, CDCl₃) δ 195.8 (C), 172.4 (C), 143.2 (CH), 136.2 (CH), 128.3 (CH), 128.3 (CH), 120.0 (C), 114.8 (CH), 80.0 (C), 70.3 (CH), 56.8 (C), 29.9 (CH₃), 26.2 (CH₂), 24.4 (CH₃); HRMS (ESI) Exact mass calcd for C₁₄H₁₄NO₂ [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(PPh₃)₂Cl₂ (63.2 mg, 0.0900 mmol), CuI (34.3 mg, 0.180 mmol), and Et₃N (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 (Na₂SO₄), 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. Rᶠ = 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, CDCl₃) δ 8.08 (1H, dd, J = 7.7, 1.5 Hz, ArH), 7.67-7.62 (1H, m, ArH), 7.23-7.18 (2H, m, ArH), 7.16-7.12 (2H, m, ArH), 7.00-6.96 (2H, m, ArH), 3.50 (3H, s, NC₃H₃), 3.08 (1H, d, J = 16.2 Hz, CH₂), 3.02 (1H, d, J = 16.2 Hz, CH₂), 1.55 (3H, s, NCH₃), 3.08 (1H, d, J = 16.2 Hz, CH₂), 3.02 (1H, d, J = 16.2 Hz, CH₂), 1.55 (3H, s, NCH₃); ¹³C NMR (126 MHz, CDCl₃) 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 (CH₃), 29.0 (CH₃), 23.3 (CH₃); HRMS (ESI) Exact mass calcd for C₂₀H₁₇ClNO₂ [M+H]⁺: 338.0948, found: 338.0940.

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

Et₃N (40 mL) was added to a flask containing (MeCN)₂PdCl₂ (41.5 mg, 0.160 mmol), PPh₃ (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 NH₄Cl (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 (MgSO₄), 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; \(^1\)H NMR (500 MHz, CDCl₃) \( \delta 7.38-7.34 \) (2H, m, ArH), 7.31-7.27 (3H, m, ArH), 4.20 (2H, q, \( J = 7.1 \) Hz, O=CC₃H₂), 3.00-2.91 (2H, m, CH₂C≡C), 2.60-2.47 (2H, m, C₃H₂C=O and C₃H₂CH₂CH₂C=O), 2.43-2.28 (2H, m, CH₂C=O and CH₂CH₂CH₂C=O), 1.27 (3H, t, \( J = 7.1 \) Hz, CH₃); \(^13\)C NMR (126 MHz, CDCl₃) \( \delta 213.9 \) (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 (CH₂), 59.1 (C), 38.4 (CH₃), 32.8 (CH₂), 24.2 (CH₂), 19.9 (CH₂), 14.1 (CH₃); HRMS (ESI) Exact mass calcd for C₁₇H₁₉O₃ [M+H]^+: 271.1329, found: 271.1321.

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

\[
\begin{align*}
\text{Diethyl 2-methyl-2-(3-phenylprop-2-yn-1-yl)malonate (2.65 g, 10.0 mmol) was added to a solution of} & \text{ Pd(OAc)}_2 \text{ (44 mg, 0.20 mmol), PPh}_3 \text{ (209 mg, 0.80 mmol), CuI (76.2 mg, 0.40 mmol), and} \\
\text{Et}_3\text{N (1.53 mL, 11.1 mmol) in anhydrous DMSO (20 mL). Bromobenzene (1.57 mL, 15 mmol) was added and the mixture was stirred at 90 °C for 2 h. The reaction was cooled to} & \text{ room temperature, water (50 mL) was added, and the mixture was extracted with Et}_2\text{O (50 mL). The organic phase was washed with 10% aqueous HCl (3 × 20 mL), dried (Na}_2\text{SO}_4),} \\
\text{filtered, and concentrated in vacuo. Purification of the residue by column chromatography (10% EtOAc/hexane) gave the title compound 761 (2.33 g, 81%) as a colourless oil.} & \text{ R}_f = 0.7 \text{ (30% EtOAc/hexane); IR 3288, 2984, 1732 (C=O), 1599, 1450, 1294, 1022, 759 cm}^{-1;} \text{ 7.37-} \\
\text{7.34 (2H, m, ArH), 7.26-7.25 (3H, m, ArH), 4.25-4.17 (4H, m, O=CHCHCH₃), 3.00 (2H, s,} & \text{ CH₃C=)}, \text{ 1.60 (3H, s, CCH₃), 1.25 (3H, t, J = 4.5 Hz, O=CHCHCH₃);} \text{ ^13}\text{C NMR (126 MHz,} \\
\text{CDCl₃) } \delta 171.5 (2 \times C), 131.6 (2 \times CH), 128.2 (2 \times CH), 127.9 (CH), 123.3 (C), 84.7 (C), & \text{...}}
\end{align*}
\]
83.3 (C), 71.2 (C), 61.6 (2 × CH₂) 26.7 (CH₃), 19.9 (CH₃), 14.0 (2 × CH₃); HRMS (ESI) Exact mass calcd for C₁₇H₂₁O₄ [M+H]^+: 288.1362, found: 258.1324.

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

![Chemical structure](image)

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), PPh₃ (209 mg, 0.80 mmol), CuI (76.2 mg, 0.40 mmol), and Et₃N (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 Et₂O (50 mL). The organic phase was washed with 10% aqueous HCl (3 × 20 mL), dried (Na₂SO₄), 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, CDCl₃) δ 7.36-7.34 (2H, m, ArH), 7.28-7.25 (3H, m, ArH), 4.27-4.18 (2H, m, O=CC₃H₂CH₃), 3.00-2.89 (2H, m, CH₂C≡), 2.22 (3H, s, O=CC₃H₂), 1.54 (3H, s, CCH₃), 1.27 (3H, t, J = 7.0 Hz, O=CCH₂CH₃); ¹³C NMR (126 MHz, CDCl₃) 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 (CH₂), 59.3 (C), 26.1 (CH₃), 25.9 (CH₂), 19.3 (CH₃), 14.0 (CH₃); HRMS (ESI) Exact mass calcd for C₁₆H₁₉O₃ [M+H]^+: 258.1256, found: 258.1206.

### 6.2.3. Rhodium-Catalysed Arylative Cyclization of Alkynones

(±)-(3aR,9bR)-5-[(E)-Benzyldiene]-9b-hydroxy-3a-methyl-1,2,3a,4,5,9b-hexahydro-3H-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 NH₄Cl (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 (MgSO₄), 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.

$$\text{(±)-(3aR,9bR)-5-[(E)-Benzyldiene]-9b-hydroxy-3a-methyl-1,2,3a,4,5,9b-hexahydro-3H-cyclopenta[a]naphthalen-3-one (712).}$$

$$R_f = 0.42 \text{ (40% EtOAc/hexane); m.p. 144-145 °C (hexane); IR 3468 (OH), 2936, 1717 (C=O), 1207, 1076, 758, 694 cm}^{-1}; ^1\text{H NMR (500 MHz, CDCl}_3) \delta 7.72 (1H, dd, J = 7.7, 1.2 Hz, ArH), 7.68 (1H, dd, J = 7.9, 1.2 Hz, ArH), 7.43-7.32 (4H, m, ArH), 7.30-7.25 (3H, m, ArH), 7.24 (1H, d, J = 1.4 Hz, C=CH), 2.79 (1H, d, J = 14.1 Hz, CH₂C=O), 2.68-2.58 (2H, m, CH₂C= C and CH₂C=O), 2.53-2.29 (3H, m, CH₂C=O and CH₂COH), 1.83 (1H, d, J = 1.6 Hz, OH), 1.01 (3H, s, CH₃); ^13\text{C NMR (126 MHz, CDCl}_3) \delta 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 (CH₂), 35.2 (CH₂), 34.3 (CH₂), 13.9 (CH₃); HRMS (ESI) Exact mass calcd for C₂₁H₂₁O₂ [M+H]+: 305.1542, found: 305.1538.

$$2-[(E)-2,3-Diphenylprop-2-en-1-yl]-2-methylcyclopentane-1,3-dione (719).$$

$$R_f = 0.53 \text{ (40% EtOAc/hexane); m.p. 85-90 °C (CH}_2\text{Cl}_2/hexane) \text{ IR}$$
1742 (C=O), 1210, 929, 730, 702 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.54-7.52 (2H, m, ArH), 7.47-7.43 (2H, m, ArH), 7.37-7.33 (3H, m, ArH), 7.32-7.27 (3H, m, ArH), 6.67 (1H, s, C=C\(\text{H}\)), 3.26 (2H, s, C\(\text{H}\)\(_2\)C=C), 2.48-2.41 (2H, m, C\(\text{H}\)\(_2\)C\(\text{H}\)), 1.86-1.80 (2H, m, C\(\text{H}\)\(_2\)C\(\text{H}\)), 1.10 (3H, s, C\(\text{H}\)\(_3\)); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 216.7 (2\times C), 141.5 (C), 138.3 (C), 137.4 (C), 132.5 (CH), 128.9 (2 \times CH), 128.6 (2 \times CH), 128.3 (CH), 128.2 (2 \times CH), 128.0 (CH), 127.0 (CH), 55.5 (C), 36.7 (CH\(_2\)), 34.9 (2 \times CH\(_2\)), 22.1 (CH\(_3\)); HRMS (ESI) Exact mass calcld 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\(_2\)Cl\(_2\)/hexane); IR 1708 (C=O), 1215, 760, 702, 699 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.39-7.23 (6H, m, ArH), 7.20-7.17 (2H, m, ArH), 7.11-7.08 (2H, m, ArH), 2.85-2.64 (6H, m, CH\(_2\)CH\(_2\) and CH\(_2\)CH), 2.29-2.20 (1H, m, CH\(_3\)CH), 0.99 (3H, d, \(J = 6.4\) Hz, CH\(_3\)CH\(_3\)); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 211.5 (C), 207.5 (C), 144.6 (C), 140.8 (C), 139.2 (C), 138.3 (C), 128.9 (2 \times CH), 128.6 (2 \times CH), 128.5 (2 \times CH), 128.3 (2 \times CH), 127.8 (CH), 127.8 (CH), 45.2 (CH), 38.9 (CH\(_2\)), 37.6 (CH\(_2\)), 34.9 (2 \times CH\(_2\)), 15.6 (CH\(_3\)); HRMS (ESI) Exact mass calcld 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)-Benzyllidene]-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)

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 NH₄Cl (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 (MgSO₄), 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.

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

(±)-2-[(E)-3-{(3aS,9bS)-5-[(E)-Benzyldiene]-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). \( R_f = 0.13 \) (40% EtOAc/hexane); m.p. 206-208 °C (CH₂Cl₂/Et₂O); IR 3438 (OH), 2926, 1736 (C=O), 1721 (C=O), 1445, 1205, 1070 cm⁻¹; \(^1\)H NMR (400 MHz, CDCl₃) d 7.68 (1H, dd, \( J = 7.6, 1.3 \) Hz, ArH), 7.47 (1H, dd, \( J = 7.5, 1.4 \) Hz, ArH), 7.41 (1H, t, \( J = 7.6 \) Hz, ArH), 7.30-7.13 (7H, m, ArH), 6.94 (1H, s, C=CHPh), 6.78-6.84 (4H, m, ArH), 5.86 (1H, t, \( J = 7.5 \) Hz, CH₂CH=CPh), 2.72-2.42 (7H, m, O=CH₂CH₂C=O and CH₂CH=C and CH₂CH₂COH), 2.33-1.99 (5H, m, CH₂CH₂COH and CH₂COH and CH₃C=CH), 1.82 (1H, d, \( J = 1.4 \) Hz, OH), 1.14 (3H, s, CH₃C(O)=O₂), 0.83 (3H, s, CH₃C(OH); \(^{13}\)C NMR (101 MHz, CDCl₃) 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 (CH₂), 35.1 (CH₂), 34.9 (CH₂), 34.8 (CH₂), 34.73 (CH₂), 34.69 (CH₂), 16.7 (CH₃), 15.1 (CH₃); HRMS (ESI) Exact mass caled for C₃₆H₃₆NaO₄ [M+Na]⁺: 554.2349, found: 553.2325.
The title compound was prepared according to the Representative Procedure from alkyone 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 ({}-PrOH); IR 3468 (OH), 2953, 1717 (C=O), 1450, 1076, 959, 694 cm\(^{-1}\); \( ^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.74 (1H, d, \( J = 1.5 \) Hz, ArH), 7.69 (1H, dd, \( J = 7.9, 1.2 \) Hz, ArH), 7.41 (1H, ddd, \( J = 7.7, 1.3 \) Hz, ArH), 7.36 (1H, ddd, \( J = 7.9, 7.4, 1.5 \) Hz, ArH), 7.29-7.24 (1H, m, ArH), 7.22 (1H, d, \( J = 1.4 \) Hz, C=CH), 7.13-7.07 (3H, m, ArH), 2.81 (1H, d, \( J = 14.1 \) Hz, CH\(_2\)=C), 2.69-2.59 (2H, m, CH\(_3\)=C and CH\(_2\)=O), 2.51 (1H, ddd, \( J = 19.0, 9.0, 2.4 \) Hz, CH\(_2\)=O), 2.43 (1H, ddd, \( J = 13.6, 9.2, 2.4 \) Hz, CH\(_2\)COH), 2.40-2.26 (1H, m, CH\(_2\)COH), 2.37 (3H, s, ArCH\(_3\)), 1.86 (1H, s, OH), 1.03 (3H, s, CH\(_3\)); \( ^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 220.0 (C), 140.1 (C), 137.9 (C), 137.0 (C), 134.3 (C), 131.9 (C), 129.7 (CH), 128.7 (CH), 128.3 (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 calcld for C\(_{22}\)H\(_{33}\)NO\(_2\) [M+NH\(_4\)]\(^+\): 336.1964, found: 336.1958.

The title compound was prepared according to the Representative Procedure from alkyone 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\(^{-1}\); \( ^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.74 (1H, dd, \( J = 7.7, 1.5 \) Hz, ArH), 7.64 (1H, dd, \( J = 7.6, 1.5 \) Hz, ArH), 7.40-7.25 (6H, m, ArH), 7.24 (1H, d, \( J = 1.4 \) Hz, C=CH), 3.20 (1H, dd, \( J = 15.0, 2.0 \) Hz, CH\(_2\)=C), 2.81 (1H, dd, \( J = 15.0, 0.9 \) Hz, CH\(_2\)=C), 2.70 (1H, ddd, \( J = 14.9, 13.0, 6.6 \) Hz, CH\(_3\)=O), 2.46-2.37 (1H, m, CH\(_2\)=O), 2.34-2.13 (2H, m, CH\(_2\)COH), 2.02-1.94 (2H, m, CH\(_3\)CH\(_2\)COH and OH), 1.93-1.85 (1H, m, CH\(_3\)CH\(_2\)COH), 1.02 (3H, s, CH\(_3\)); \( ^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 213.7 (C), 142.1 (C), 137.2 (C), 133.9 (C), 132.0 (C), 129.2 (2 \( \times \) CH), 128.5 (CH), 128.4 (2 \( \times \) CH), 127.8 (CH), 127.08 (CH), 127.06 (CH), 125.3 (CH), 123.7 (CH), 78.4 (C), 53.3 (C), 36.9
(±)-(4aR,10aR)-4a-Hydroxy-9-[(E)-4-methoxybenzylidene]-10a-methyl-3,4,4a,9,10,10a-hexahydrophenanthren-1(2H)-one (795). The title compound was prepared according to the Representative Procedure from alkyne 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. Rf = 0.25 (30% EtOAc/hexane); m.p. 133-134 °C (Et2O/hexane); IR 3466 (OH), 2936, 1717 (C=O), 1452, 1238, 1034, 758, 694 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.73-7.70 (1H, m, ArH), 7.64-7.61 (1H, m, ArH), 7.36-7.29 (2H, m, ArH), 7.29-7.24 (2H, m, ArH), 7.17 (1H, d, J = 1.3 Hz, C=CH), 6.93-6.88 (2H, m, ArH), 3.84 (3H, s, OCH₃), 3.19 (1H, dd, J = 15.1, 1.2 Hz, C₂H₂C=C), 2.80 (1H, dd, J = 15.1, 1.2 Hz, CH₂C=C), 2.76-2.66 (1H, m, CH₂C=O), 2.46-2.40 (1H, m, CH₂C=O), 2.33-2.14 (2H, m, CH₂COH), 1.99-1.86 (3H, m, CH₂CH₂CH₂ and OH), 1.01 (3H, s, OCH₃); ¹³C NMR (126 MHz, CDCl₃) 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 (CH₃), 53.3 (C), 36.9 (CH₂), 36.8 (CH₂), 36.6 (CH₂), 20.9 (CH₂), 15.9 (CH₃); HRMS (ESI) Exact mass calcd for C₂₂H₂₃O₂ [M+H]+: m/z 366.2069, found: 366.2066.

(±)-(4aR,10aR)-4a-Hydroxy-9-[(E)-4-chlorobenzylidene]-10a-methyl-3,4,4a,9,10,10a-hexahydrophenanthren-1(2H)-one (796). The title compound was prepared according to the Representative Procedure from alkyne 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. Rf = 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, CDCl₃) δ 7.72 (1H, dd, J = 7.8, 1.3 Hz, ArH), 7.64 (1H, dd, J = 7.7, 1.4 Hz, ArH), 7.39-7.30 (4H, m, ArH), 7.26-7.20 (2H, m, ArH), 7.17 (1H, s, C=CH), 3.17 (1H, dd, J = 15.0, 2.0 Hz, CH₂C=C), 2.73 (1H, dd, J = 15.0, 0.8 Hz, CH₂C=C), 2.67 (1H, ddd, J = 15.0, 12.7, 6.6 Hz, CH₂C=O), 2.46-2.40 (1H, m, CH₂C=O), 2.32-2.14 (2H, m, CH₂COH), 2.02-1.96 (1H, m, CH₂CH₂CH₂), 1.94 (1H, d, J = 2.0 Hz, OH), 1.01 (3H, s, OCH₃); ¹³C NMR (126 MHz, CDCl₃) 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 (CH₃), 53.3 (C), 36.9 (CH₂), 36.8 (CH₂), 36.6 (CH₂), 20.9 (CH₂), 15.9 (CH₃); HRMS (ESI) Exact mass calcd for C₂₃H₂₅ClO₂ [M+H]+: m/z 382.1543, found: 382.1544.
1.92-1.84 (1H, m, CH₂CH₂CH₂), 1.02 (3H, s, CH₃); ¹³C NMR (126 MHz, CDCl₃) 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 (CH₂), 36.7 (CH₂), 36.6 (CH₂), 20.8 (CH₂), 16.1 (CH₃); HRMS (ESI) Exact mass calcd for C₂₂H₂₁⁵₂ClNaO₂ [M+Na]⁺: 375.1128, found: 375.1113.

(±)-(6aR,12bS)-8-[(E)-4-Chlorobenzylidene]-12b-hydroxy-5,6a-dimethyl-6a,7,12b-tetrahydro[κ]phenanthridin-6(5H)-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. Rᵣ = 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; ¹H NMR (400 MHz, D₆-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=CH), 7.08 (1H, dd, J = 8.1, 1.0 Hz, Ar'H), 7.00 (1H, br s, Ar'H), 5.71 (1H, s, OH), 3.22 (1H, br d, J = 16.1 Hz, CH₂), 3.09 (3H, s, NCH₃), 2.82 (1H, dd, J = 16.1, 2.4 Hz, CH₂), 1.00 (3H, s, CCH₃); ¹³C NMR (101 MHz, D₆-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 (CH₂), 28.9 (CH₃), 18.0 (CH₃); HRMS (ESI) Exact mass calcd for C₂₆H₂₃⁵₂ClNO₃ [M+H]⁺: 416.1417, found: 416.1413.

(±)-Ethyl (3aS,9bR)-5-[(E)-benzylidene]-9b-hydroxy-1,2,3,4,5,9b-hexahydro-3aH-cyclopenta[a]naphthalene-3a-carboxylate (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, ArH), 7.56 (1H, dd, J = 7.9, 1.3 Hz, ArH), 7.40-7.23 (6H, m, ArH), 7.07 (1H, d, J = 1.7 Hz, C=CH), 4.38 (1H, d, J = 2.2 Hz, OH), 3.93 (1H, dq, J = 10.7, 7.1 Hz, CH_2CH_3), 3.79 (1H, dq, J = 10.7, 7.1 Hz, CH_2CH_3), 3.50 (1H, d, J = 14.2 Hz, CH_2C=C), 2.71 (1H, dd, J = 14.2, 1.7 Hz, CH_2C=C), 2.44-2.36 (1H, m, CH_2COH), 2.20-2.01 (3H, m, CH_2CH_2CH_2COH), 1.93-1.81 (2H, m, CH_3CH_2CH_2OH and CH_2COH), 0.85 (3H, t, J = 7.1 Hz, CH_3); ^13C 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', 795' and 714' by comparison of the $^1$H NMR spectra.

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1, 3' X-Ray data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif168.
7.0 References


8. Appendix

8.1 Publications:
