Studies Towards Enantioselective Metal-Catalysed Nucleophilic Allylations Using Allenes

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

By

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“Chemical synthesis always has some element of planning in it. But, the planning should never be too rigid. Because, in fact, the specific objective which synthetic chemists use as the excuse for their activity is often not of special importance in the general sense; rather, the important things are those that one finds out in the course of attempting to reach the objective.”

R. B. Woodward

Declaration

I hereby declare that, except for where specific reference is made to other sources, the work contained within this thesis is the original work of my own research since the registration of the PhD degree in October 2015, 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.

Contents

Table of abbreviations

Ac	Acetyl
acac	Acetylacetonate
Ar	Aryl
BINAP	2,2’-bis(diphenylphosphino)-1,1’-binaphthalene
BINOL	1,1’-Binaphtol
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
cat	Catalyst
cod	Cyclooctadiene
Cy	Cyclohexyl
dba	Dibenzylidenacetone
DEMS	Diethoxymethylsilane
DFT	Density functional theory
DIPA	Diisopropylamine
DME	Dimethoxyethane
DMF	*N*,N-Dimethylformamide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dr	Diastereomeric ratio
DYKAT	Dynamic kinetic asymmetric transformation
ee	Enantiomeric excess
ent	Enantiomer
equiv	Equivalents
er	Enantiomeric ratio
ESI	Electronspray ionisation

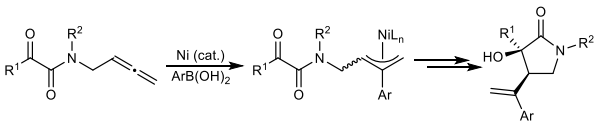
HOMO	Highest occupied molecular orbital
HPLC	High-performance liquid chromatography
HRMS	High resolution mass spectrometry
HWE	Horner Wadsworth Emmons
i.r.	Isomeric ratio
LA	Lewis Acid
LB	Lewis Base
L_n	Ligand
LUMO	Lowest unoccupied molecular orbital
MeCN	Acetonitrile
Mes	Mesityl
MS	Molecular sieves
MTBE	Methyl-*tert*-butyl ether
NHC	*N*-heterocyclic carbene
NMR	Nuclear magnetic resonance
NR	No reaction
Pc	Phthalocyanine
PHOX	Phosphinooxazoline
PIDA	Phenyliodine(III) diacetate
pin	Pinacolato
PMHS	Polymethylhydrosiloxane
PMP	*para*-Methoxyphenyl
R_f	Retention factor
R_L	Larger substituent
R_s	Smaller substituent
RT	Room temperature

TADDOL	α,α,α',α'-tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol
*t*Am	*tert*-Amiloyl
TBAF	Tetrabutylammonium fluoride
TBS	*Tert*-Butyldimethylsilyl
Tf	Triflyl
TFE	2,2,2-Trifluoroethanol
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMDS	Tetramethyldisiloxane
TMS	Trimethylsilyl
Ts	Tosyl

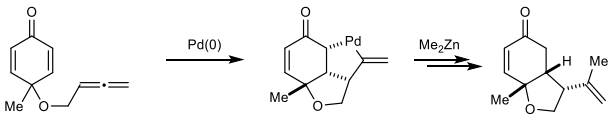
Abstract

The enantioselective intramolecular nickel-catalysed nucleophilic 1,2-allylation of ketones with (hetero)arylboronic acids or potassium vinyltrifluoroborate and progress towards the enantioselective intramolecular 1,4-allylation of enones with dialkylzinc nucleophiles are described. The first project is initiated by carbonickelation of allenes which gives the nucleophilic allylnickel species that cyclise by 1,2-allylation onto a tethered ketone to produce a range of chiral tertiary-alcohol containing aza- and carbocycles in excellent diastereo- and enantioselectivities. The second project is initiated by the oxidative cyclisation of Pd(0) with an allene tethered to an enone. The resulting palladacycle formed undergoes transmetalation with a dialkylzinc nucleophile, and subsequent reductive elimination affords 6,5-fused bicycles in high diastereoselectivity.

Enantioselective nickel-catalysed nucleophilic 1,2-allylation of ketones



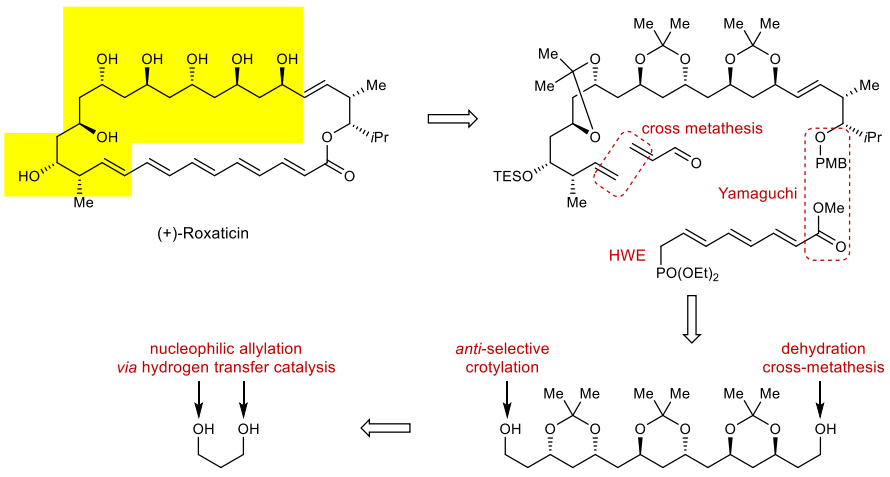
Progress towards the enantioselective 1,4-allylation of enones



1. Introduction

1.1. Metal-catalysed enantioselective nucleophilic allylations

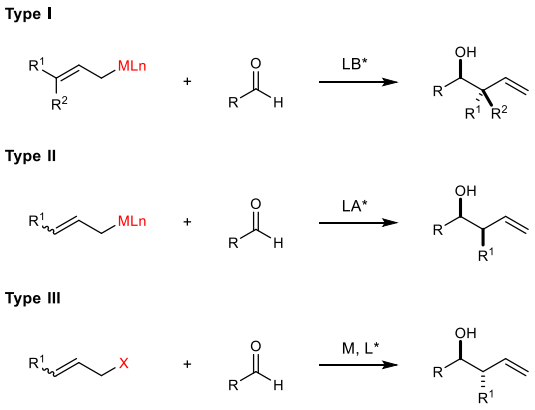
Catalytic enantioselective formation of C-C bonds is arguably one of the most important transformations in organic synthesis, since the skeleton of many biologically active compounds is made from carbon atoms bearing stereocentres. Catalysis can be utilised to achieve syntheses with lower waste production when compared to reactions employing stoichiometric quantities of reagents.[1] Furthermore, metal-catalysed enantioselective nucleophilic allylations are considered an important asset among this class of reactions.[2] Especially when the electrophile partner is an aldehyde/ketone or aldimine/ketimine, these reactions provide compounds with important functional groups, such as homoallylic alcohols and amines, in an enantioselective fashion, useful either for further manipulations or important for the final product. Krische's total synthesis of (+)-roxaticin (Scheme 1)[3] is a powerful example of the importance of metal-catalysed enantioselective nucleophilic allylations in organic synthesis. The Krische group used iteratively this type of reaction to install the polyketide backbone of this oxo-polyene macrolide (highlighted in yellow in Scheme 1). This strategy allowed the group to obtain (+)-roxaticin in 29 total steps, with the longest linear sequence being 20 steps. This result is impressive, considering that the Evans group synthesised the same compound in 52 steps with the longest linear sequence being 29 steps.[4]



Scheme 1. The nucleophilic allylation fully exploited by Krische in the synthesis of the polyketide (+)-Roxaticin

Organometallic catalysis in this context plays a pivotal role, since the metal centre brings the nucleophile, the electrophile and the chiral modifier into close proximity with each other, which allows the process to proceed with high levels of diastereo- and enantioselectivity (*vide infra*).

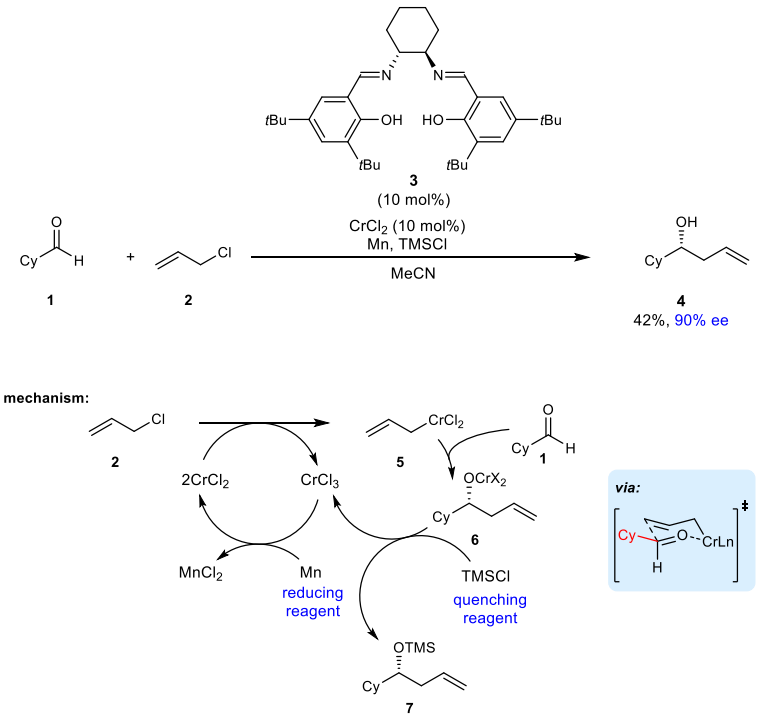
Historically, enantioselective metal-catalysed nucleophilic allylations can be classified into three classes (Scheme 2):[2d] a) Type I reactions, where the allylmetal species is pre-formed and the catalyst is a Lewis base, and give *syn* or *anti* diastereoselectivity based on the *Z/E* ratio of the allylmetal starting material; b) Type II reactions, where the allylmetal species is also pre-formed, but the catalyst is a Lewis acid and gives predominantly *syn* diastereoselectivity independently of the geometry of the allylmetal starting material; c) Type III reactions, where the allylmetal species is formed *in situ* with a metal catalyst, and provide predominantly *anti* diastereoselectivity independently of the geometry of the starting material.



Scheme 2. Classes of enantioselective nucleophilic allylations.

Since preparation, isolation and handling of toxic and air- and moisture-sensitive organometallic reagents can be dangerous, in the past decades, the majority of work has been focussed on the development of Type III allylations.[2]

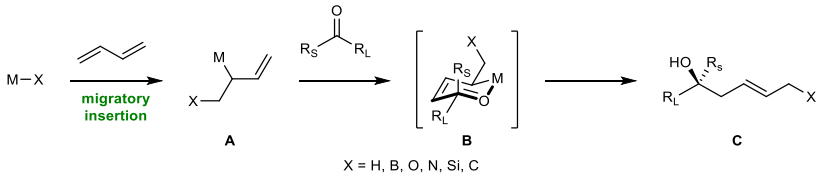
One of the first reports of catalytic enantioselective type III nucleophilic allylations was reported by Umani-Ronchi and Cozzi (Scheme 3).[5]



Scheme 3. One of the first reports of catalytic enantioselective nucleophilic allylations of type III.

It is proposed that two equivalents of $CrCl_2$ react with the allyl chloride to form $CrCl_3$ and an allyl chromium(III) (**5**). The allylchromium species reacts with the aldehyde through a Zimmerman-Traxler transition state[6] where the bulkier substituent on the aldehyde lies in the pseudo-equatorial position, affording the chromium alkoxide **6**. This chromium species reacts with trimethylsilyl chloride (TMSCl) to form chromium(III) chloride and the TMS-protected homoallylic alcohol **7** which will provide the product upon workup. Manganese powder reduces $CrCl_3$ to $CrCl_2$ closing the catalytic cycle.

Due to its importance in organic synthesis, a plethora of reports have been published on metal-catalysed enantioselective nucleophilic allylations, consequently covering this topic in a comprehensive fashion is a daunting task.[2] Therefore, this introduction will focus on the metal-catalysed enantioselective nucleophilic allylations initiated by a migratory insertion of a π-bond into a metal-(hetero)atom bond. A general scheme of the reactivity discussed in this introduction is depicted in Scheme 4.



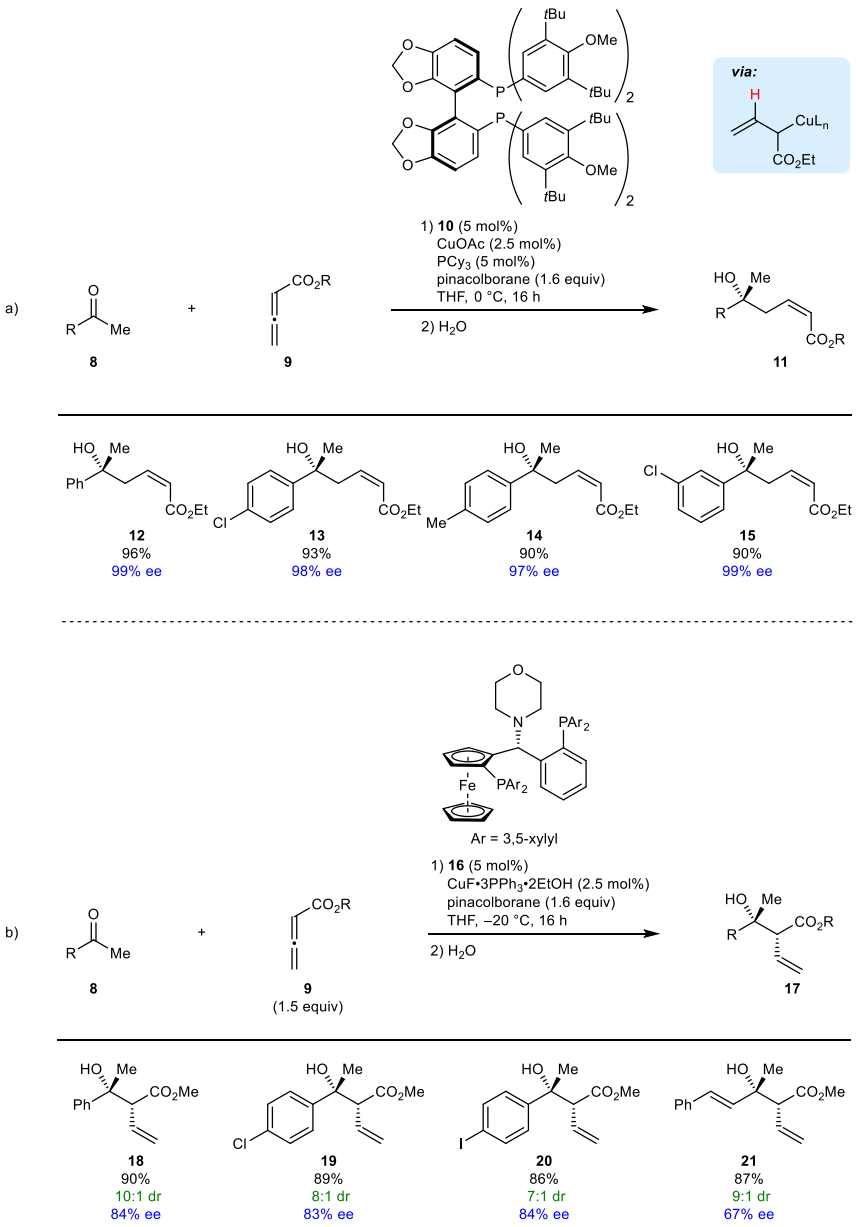
Scheme 4. General scheme of reactions presented in this introduction.

Whilst making the allylmetal species *in situ* from an allyl (pseudo)halide is an improvement with regard to the synthesis and handling of the allylmetal species, it requires the installation of a (pseudo)halide into the starting material. An alternative solution is to use π-bond in a starting material, which can form the nucleophile through migratory insertion of the π-bond into the M-X bond. Even though it is an appealing solution, the addition of another step in the reaction provides a further possibility to obtain side-products, thus a higher risk of an unsuccessful outcome. Therefore, these reactions require fine tuning of the conditions to provide the desired product in high yield, diastereo- and enantioselectivity.

1.2. Reductive migratory insertion of the π-bond starting material

1.2.1. Metalhydride catalysed processes

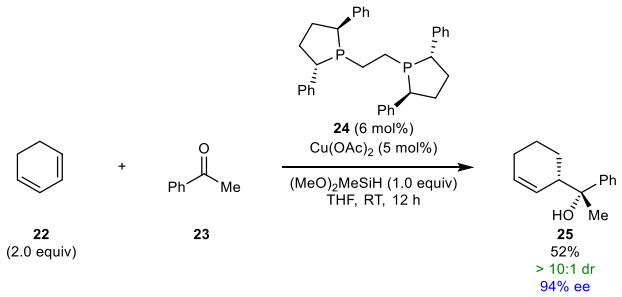
One of the most interesting solutions to produce an allylmetal species *in situ* is to start from a π-bond containing starting material, such as a 1,3-diene or an allene, and perform a hydrometallation reaction. Using this strategy, the group of Shibasaki and Kanai performed the first enantioselective metal-catalysed reductive allylation of ketones **8** using allenoates **9** (Scheme 5).[7] An interesting feature of this chemistry was the control over the regioselectivity using different chiral ligands for the copper catalyst. Using the SEGPHOS ligand **10**, the linear product **11** was obtained preferentially (Scheme 5a). Conversely, the use of the Taniaphos ligand **16** afforded mainly the branched product **17** (Scheme 5b).



Scheme 5. Shibasaki and Kanai reported the first enantioselective CuH-catalysed allylation of ketones.

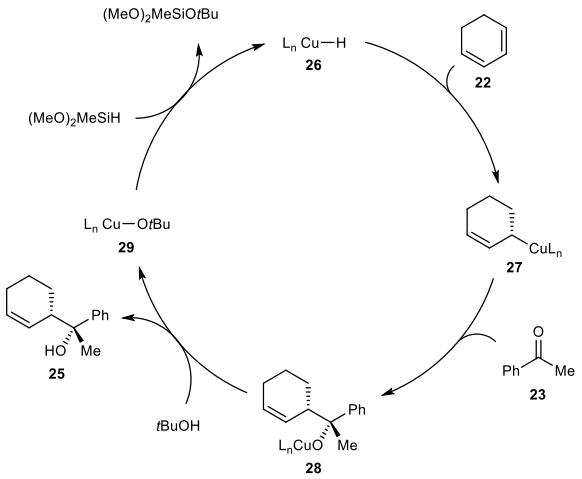
Similarly, in 2016 Buchwald reported a CuH-catalysed asymmetric 1,2-addition to ketones of allyl nucleophiles generated from the reductive coupling of alkenes.[8] A clever choice of the CuH catalyst system, rationalised *a priori* with DFT calculations, allowed the organocopper nucleophile to form from π-bond containing starting material. In this report, the group performed mainly the highly enantioselective propargylation of ketones using 1,3-enynes. However, they also reported a preliminary example of allylation using 1,3-cyclohexadiene **22**. This method

afforded the tertiary homoallylic alcohol **25** in high diastereo- and enantioselectivity (Scheme 6).



Scheme 6. Buchwald's preliminary example of highly enantioselective allylation of ketones using 1,3-cyclohexadiene.

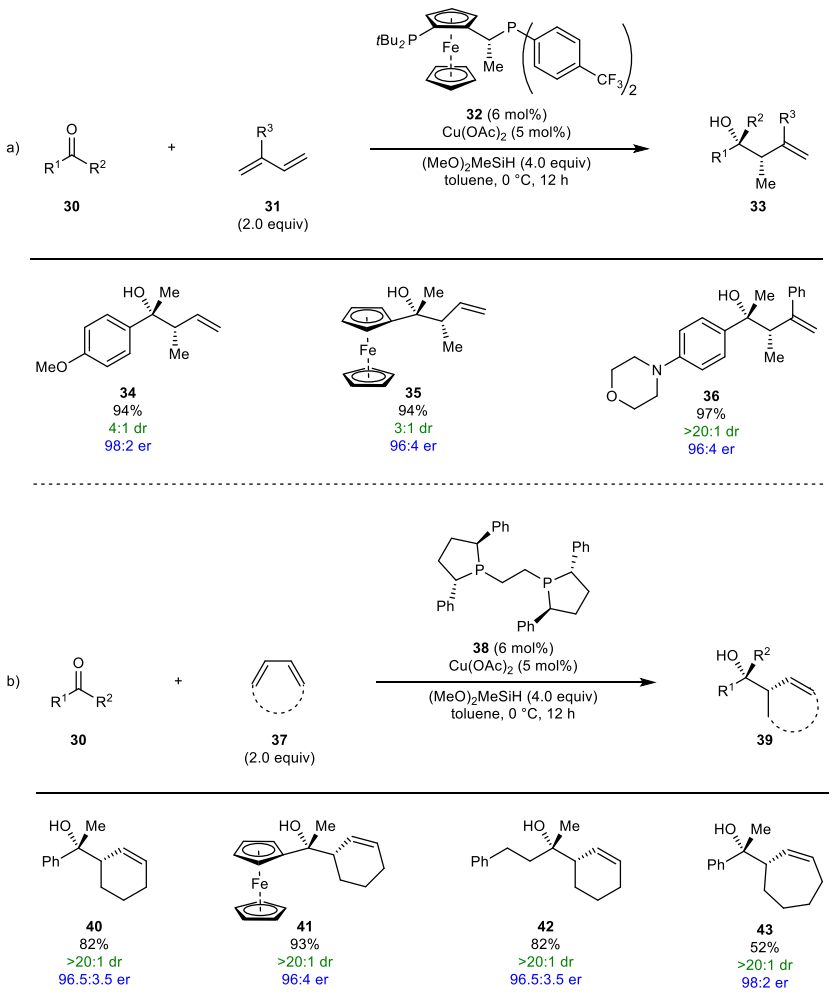
This transformation starts with the chiral CuH-catalyst **26** performing a hydrocupration of 1,3-cyclohexadiene **22**. This allylcopper nucleophile formed reacts with acetophenone to form copper-alkoxide **28** that is then protonated by *tert*-butanol to form the product **25** and copper *tert*-butoxide **29**. This latter species regenerates the copper hydride through σ-bond metathesis with the silane (Scheme 7).



Scheme 7. Proposed mechanism for the enantioselective allylation of ketones with 1,3-cyclohexadiene.

Building on this finding, in 2019 Buchwald[9] and Zhang[10] independently reported a CuH-catalysed enantioselective allylation of ketones starting from 1,3-dienes. However, Buchwald's report was wider in scope encompassing both cyclic and

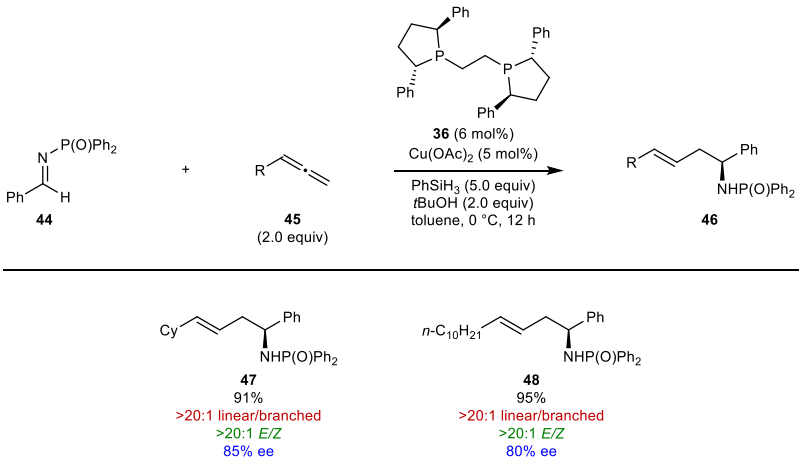
acyclic 1,3-dienes, whereas the report from Zhang was limited only to cyclic 1,3-dienes. It is worth noting that in Buchwald's report, different ligands were used for reactions with the acyclic (Scheme 8a) and cyclic 1,3-diene substrates (Scheme 8b). Furthermore, mechanistic insights were derived by means of DFT calculations. With these calculations in hand, they proposed the hydrocupration of the diene as the rate determining step of the catalytic cycle.



Scheme 8. Buchwald's work on enantioselective ketone allylation with 1,3-dienes: a)conditions with acyclic dienes; b) conditions with cyclic dienes.

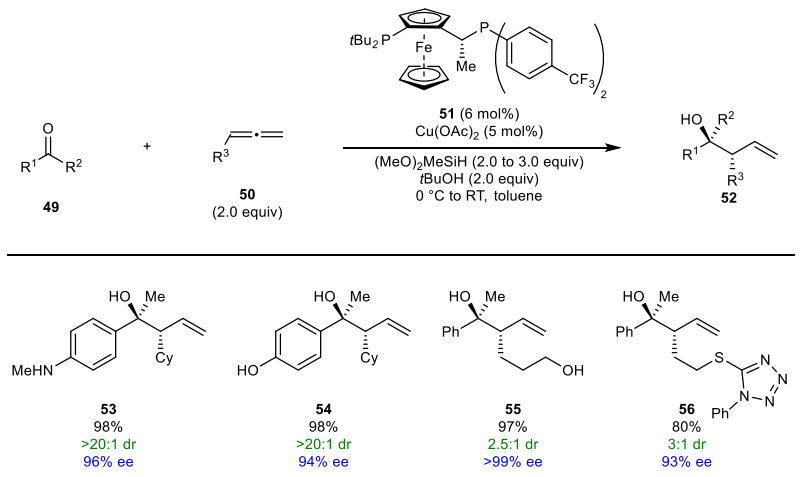
In 2016 Buchwald and co-workers reported the CuH-catalysed regiodivergent allylation of aldimines **44** using terminal allenes **45** (Scheme 9).[11] The study highlighted the importance of the protecting group on the aldimine **44** to obtain a linear or branched homoallylic amine. However, a highly enantioselective variant

using the (*S*,*S*)-Ph-BPE ligand **36** was reported only for the linear selective reaction. Whereas for the branched-selective variant a maximum *ee* of 11% was obtained.



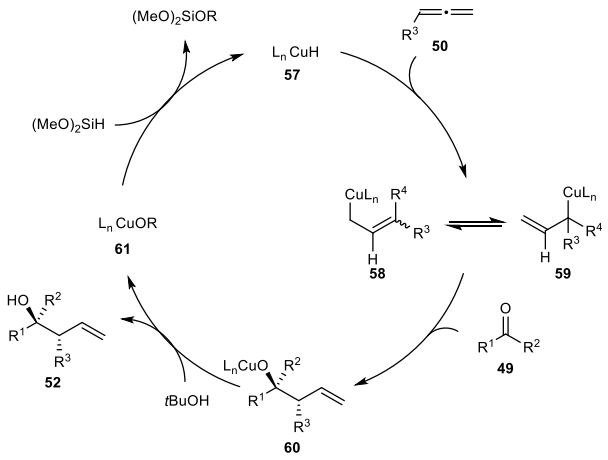
Scheme 9. Buchwald's preliminary report of enantioselective allylation of aldimines.

Following this discovery, the same group developed a highly enantioselective CuH-catalysed allylation of ketones **49** using terminal allenes **50** (Scheme 10).[12] This method provided high levels of branched selectivity to give the corresponding homoallylic tertiary alcohols **52**. Furthermore, with cyclohexyl allene and a variety of ketones, only one diastereoisomer was formed (see **53** and **54**). The relative configuration of the diastereoisomer obtained was consistent with reaction through a chair-like transition state.



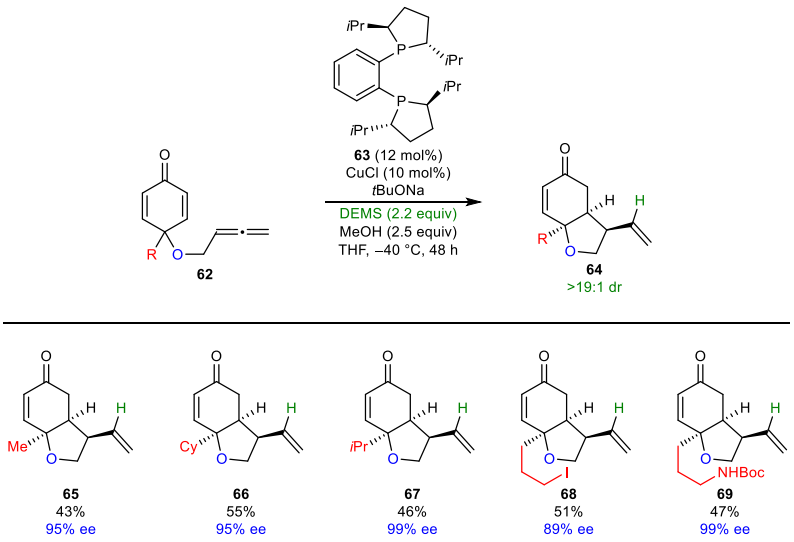
Scheme 10. Buchwald's work on CuH-catalysed allylation of ketones using terminal allenes.

The group managed to follow each step of the catalytic cycle with ^{1}H and ^{31}P NMR experiments, and using these studies, they proposed the allylation as the rate determining step. With this information, they presented the mechanism depicted in Scheme 11. The chiral CuH catalyst performs a hydrocupration on the allene **50** forming the two allylcopper species which are in equilibrium. Allylation of the ketone occurs as the rate determining step, affording the copper-alkoxide **60**. Protonation of this species and σ–bond metathesis with the silane close the catalytic cycle.



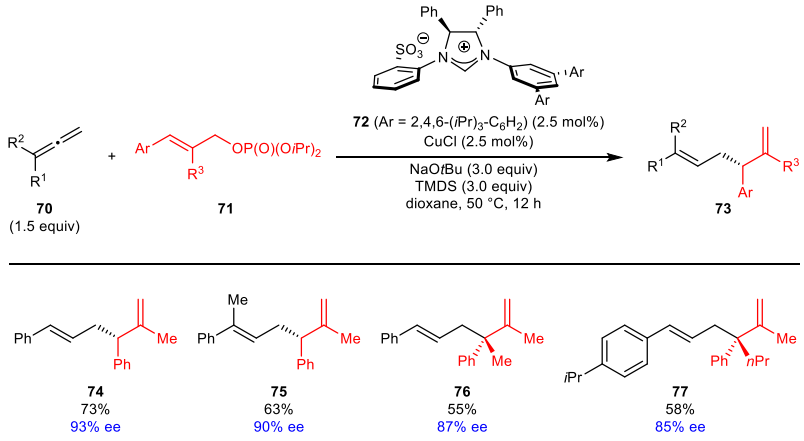
Scheme 11. NMR studies revealed this mechanism.

Chen, Tian, Lin and co-workers reported the first CuH-catalysed enantioselective intramolecular 1,4-allylation through reductive cyclisation of allenes tethered to enones **62** (Scheme 12).[13] This process afforded bicyclic *cis*-hydrobenzofurans **64** in modest yields but high levels of diastereo- and enantioselectivity. The authors noted that increasing the amount of diethoxymethylsilane (DEMS) was detrimental to the yield but extremely beneficial for the enantioselectivity. This trend was explained by a further reduction of one of the enantiomers of the enone product. Namely, a kinetic resolution that favoured the major enantiomer was taking place.



Scheme 12. Chen, Tian and Lin reported the first CuH-catalysed enantioselective intramolecular reductive coupling of allenes to enones.

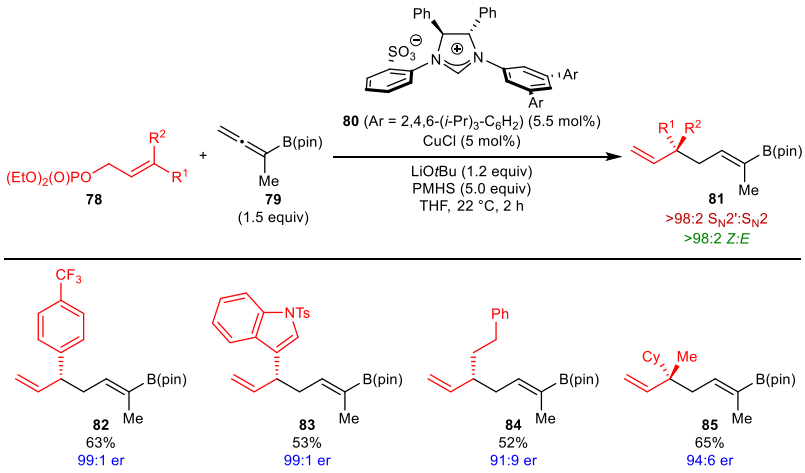
In 2019, the Xiong group performed the first copper-catalysed enantioselective reductive allyl-allyl cross-coupling using allenes **70** and allylic phosphates **71** as electrophiles (Scheme 13).[14] This method provided 1,5-dienes bearing tertiary or all-carbon quaternary stereocentres **73** in an enantioselective fashion. It showed great regiocontrol, functional group tolerance and a wide scope, and the only limitation of the study was the necessity to use aryl-substituted allyl phosphates.



Scheme 13. Xiong performed the first Cu-catalysed enantioselective reductive allyl-allyl cross-coupling.

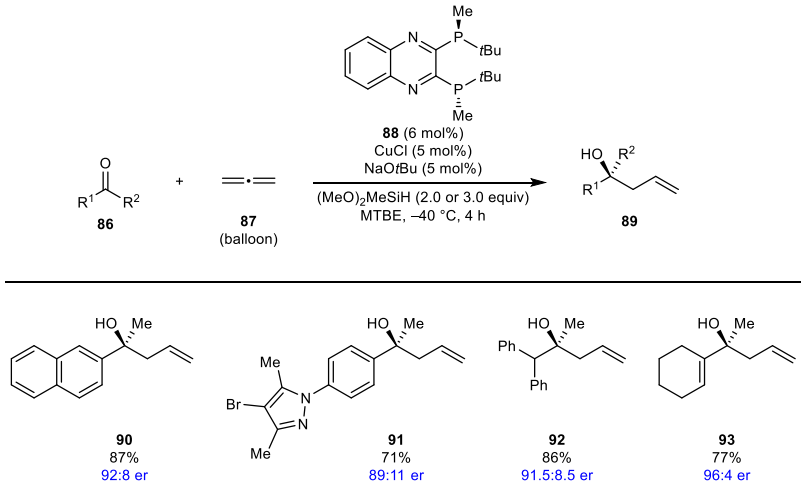
Further improvements on this chemistry were reported by Hoveyda soon after (Scheme 14).[15] The group found the optimal catalyst system which allowed the

chemistry to be performed without limiting it to aryl-substituted phosphates **78** and which was tolerant to allenylboronates. This protocol delivered highly valuable linear alkenylboronates **81**, starting from an allenylboronate **79** and an allylphosphate **78** using CuCl as the precatalyst and polymethylhydrosiloxane (PMHS), a by-product of the silicone polymer industry, as the hydride source. Notably, the use of the NHC ligand **80** was crucial to achieve the desired reactivity. This method showed good functional group compatibility and proceeded smoothly in the presence of other electrophiles such as esters or carbamates. However, with ketones, 1,2-reduction of the carbonyl group by CuH was an issue.



Scheme 14. Hoveyda improved the allyl-allyl cross-coupling further.

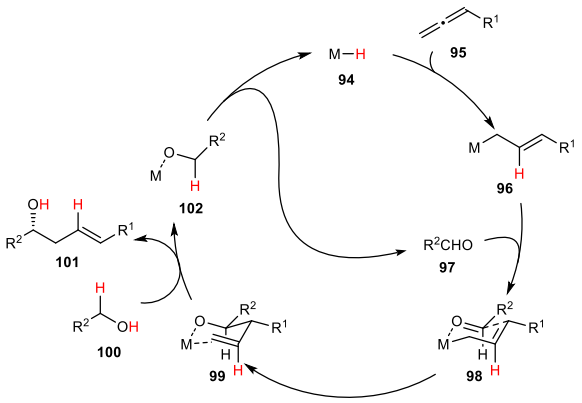
As seen in the reports already described, substituted allenes were widely utilised. However, the use of the parent allene, a compound considered a contaminant of propylene gas, was reported for the first time by Buchwald in 2019 for the allylation of ketones using CuH catalysis (Scheme 15).[16] To obtain high enantioselectivity, QuinoxP* **88**, a *P*-stereogenic ligand, was employed. Most notably, the chemistry gave good results even when an equimolar mixture of propylene, methylacetylene and allene was employed.



Scheme 15. Buchwald used the parent allene for the allylation of ketones under CuH-catalysis.

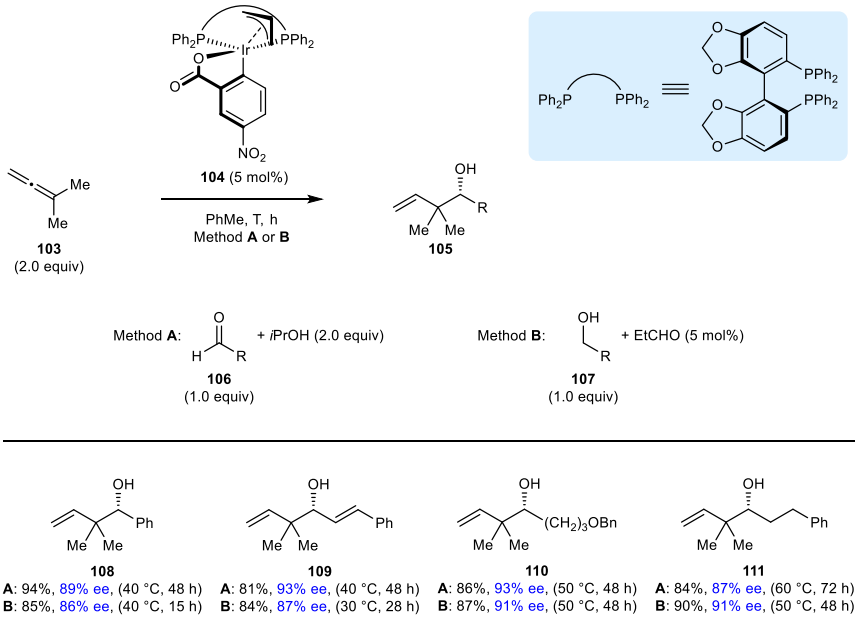
1.2.2. Hydrogen-borrowing catalysis

Using a metal hydride catalyst is a powerful tool to produce allylmetal nucleophiles *in situ*, allowing allylations of electrophiles to be performed. However, in all the examples presented so far, a stoichiometric reductant is required to form and regenerate the catalyst. A greener solution to avoid the necessity for stoichiometric reductants is to use hydrogen-borrowing catalysis.[17] In this branch of nucleophilic allylations, the homoallylic alcohol product can be generated from the alcohol *in lieu* of the higher oxidation state aldehyde. However, in many cases the authors report both the reaction starting from the alcohol and the reaction starting from the aldehyde substrate. In this latter case, a sacrificial secondary alcohol is used as the hydrogen source. A general scheme of this catalytic nucleophilic allylation is depicted in Scheme 16. A metal hydride reacts with an unsaturated substrate such as allene **95**. This allylmetal species **96** reacts with aldehyde **97** to form metal-alkoxide **99**. It is worth noting that the interaction between the metal and the alkene in this intermediate is fundamental, because it occupies the empty orbital on the metal catalyst that can perform β-hydride elimination on the homoallylic alcohol. Protonation of the metal-alkoxide provides the homoallylic alcohol and another metal-alkoxide **102**. This latter species has a dual function: a) to close the catalytic cycle by reforming the metalhydride catalyst *via* a β-hydride elimination; b) to form the aldehyde **97**.



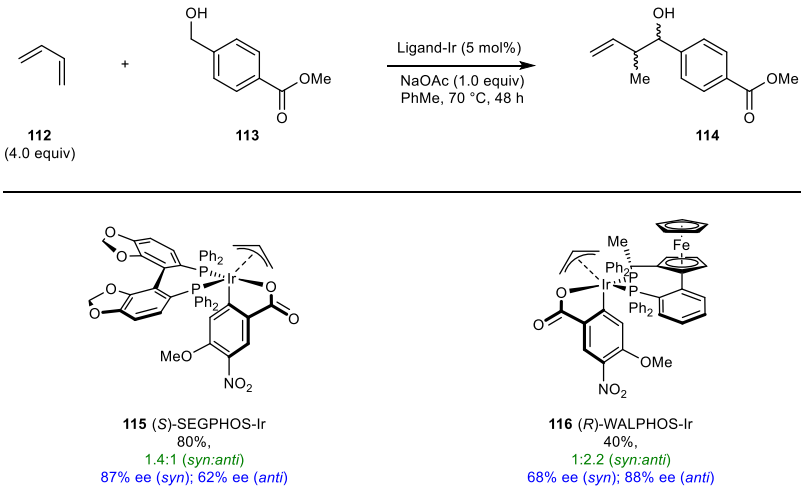
Scheme 16. General mode of reactivity for the nucleophilic allylation under hydrogen-borrowing catalysis.

The first use of allenes in enantioselective transfer hydrogenation was reported in 2009 by the Krische group, a pioneer in this field (Scheme 17).[18] Using 1,1-dimethylallene **103** as the prenyl donor, the group managed to form homoallylic alcohols (**105**) starting from the aldehyde or alcohol oxidation level. Notably, in the reaction starting from the aldehyde oxidation level, *i*PrOH was used as hydrogen donor (Method **A**). Even unactivated alcohols/aldehydes can perform this coupling efficiently. Mechanistic studies showed a rapid alcohol-aldehyde redox equilibration before carbonyl addition.



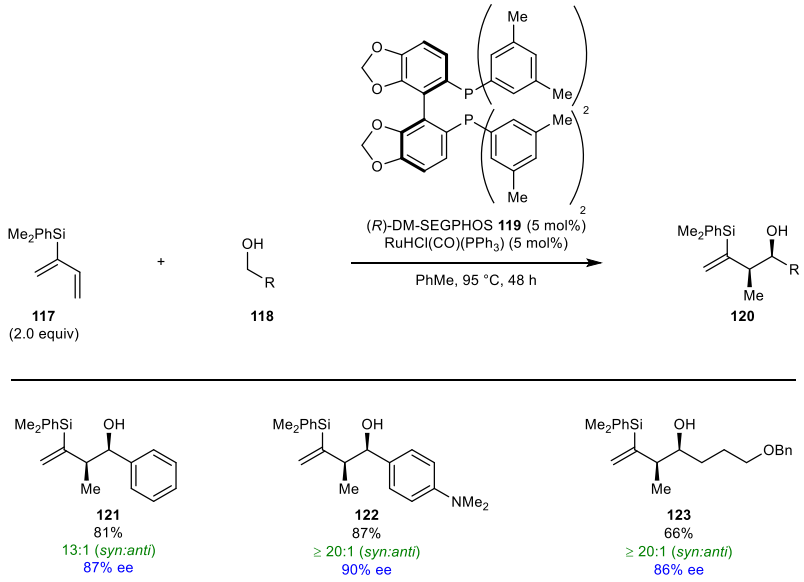
Scheme 17. Krische's seminal report of enantioselective prenylation using hydrogen-borrowing chemistry.

In 2010 the same group reported an iridium-catalysed hydrohydroxyalkylation of butadiene through hydrogen-borrowing chemistry (Scheme 18).[19] This work focussed on the diastereoselective reaction; however, a preliminary evaluation of the enantioselective version of this method was also performed. Interestingly, using (*S*)-SEGPHOS-Ir **115** or (*R*)-WALPHOS-Ir **116** as catalyst provided opposite diastereoisomers: (*S*)-SEGPHOS-Ir **115** gave predominantly the *syn*- and (*R*)-WALPHOS-Ir **116** the *anti*-diastereoisomer, albeit with modest selectivity. However, the major diastereoisomer was obtained with high enantioselectivity (Scheme 18).



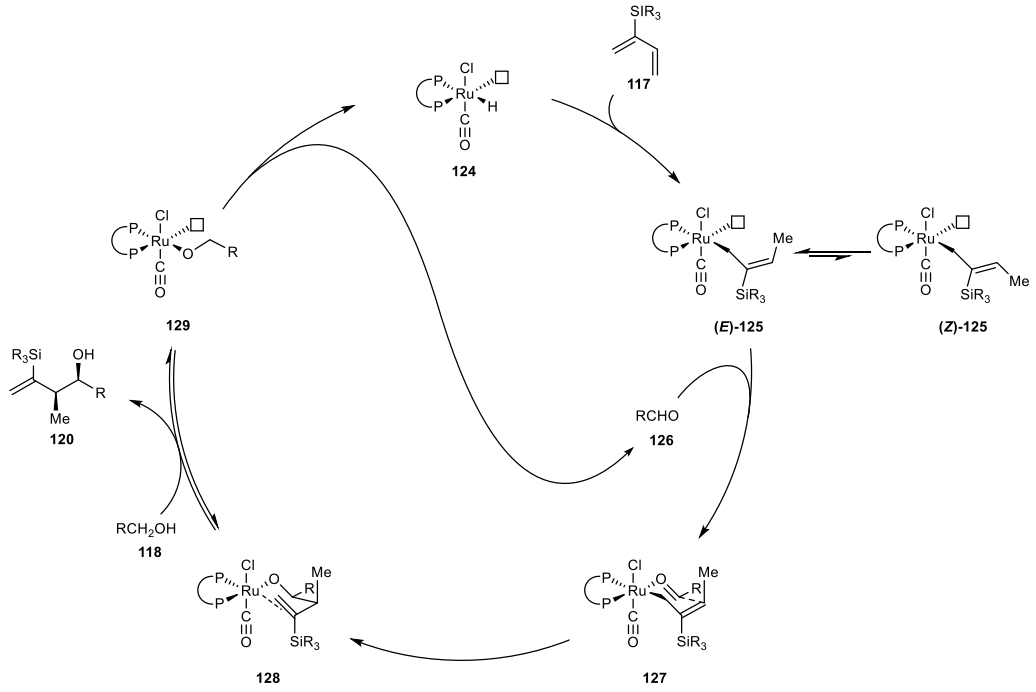
Scheme 18. Krische's preliminary result on catalyst controlled enantio- and diastereoinduction with crotylation of primary alcohols.

Krische attributed the low diastereoselectivity in butadiene hydrohydroxyalkylation to the fact that the (*E*)- and (*Z*)-σ-crotylmetal intermediates formed after butadiene hydrometallation are close in energy. This small energy difference between the two species led to an incomplete partitioning of the (*Z*) and (*E*)-σ-crotylmetal intermediate during the reaction that resulted in poor diastereoselectivity. Therefore, Krische and co-workers by-passed this problem by using a 2-silyl-substituted butadiene **117** to impart high diastereo- and enantioselectivities to this transformation (Scheme 19).[20] Adding TBAF in a two-step, one-pot reaction sequence gave the product of the conventional *syn*-crotylation through protodesilylation.



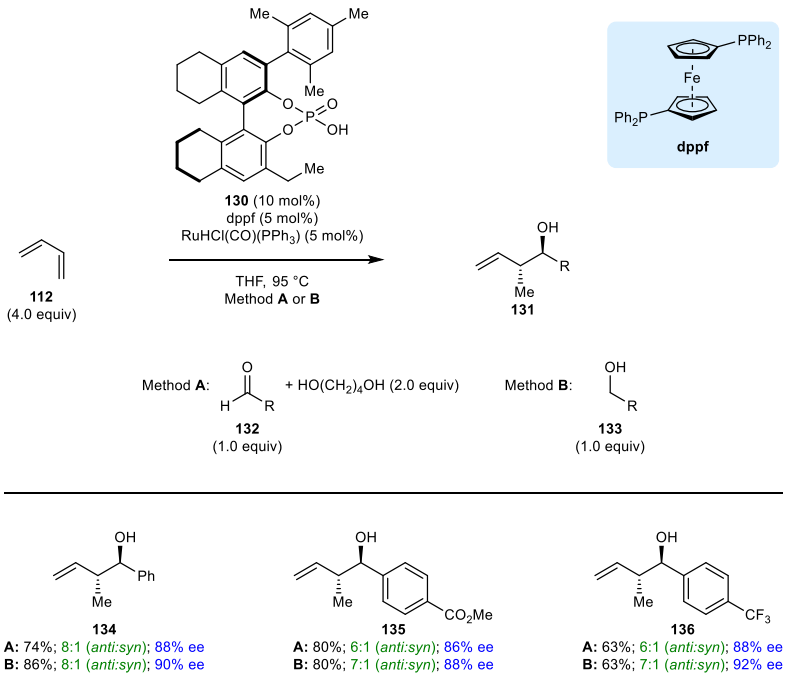
Scheme 19. Krische's solution to increase levels of diastereoselectivity in hydrohydroxyalkylation of 1,3-dienes.

The mechanism of this transformation is depicted in Scheme 20. The ruthenium catalyst performs hydrometallation of the silylated 1,3-diene **117** forming the allylruthenium species **125**. The bulky silyl group favours **(*E*)-125**, and having this intermediate "locked" in this configuration resulted in greater diastereoselectivity. Nucleophilic allylation of the aldehyde, protonation and *β*-hydride elimination regenerate the catalyst and produces the aldehyde **126**.



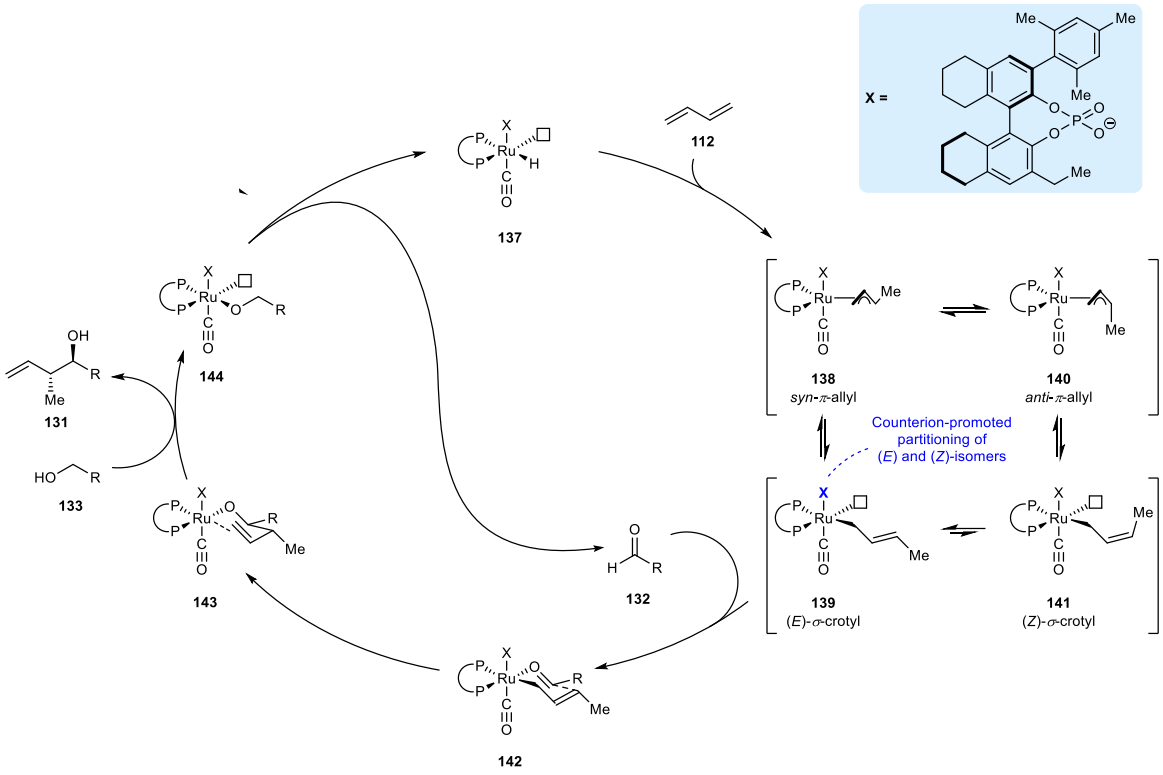
Scheme 20. Catalytic cycle proposed by Krische for the diastereoselective hydrohydroxyalkylation of 1,3-dienes.

In 2012 Krische advanced this methodology further. The group achieved good diastereoselectivity and yields along with excellent enantiocontrol without the need for pre-silylating the 1,3-butadiene (Scheme 21).[21] The success of this chemistry relied on the use of ruthenium-catalysis along with a BINOL-derived chiral non-racemic phosphoric acid **130** as counterion for the ruthenium catalyst and the chiral non-racemic dppf biphosphine ligand.



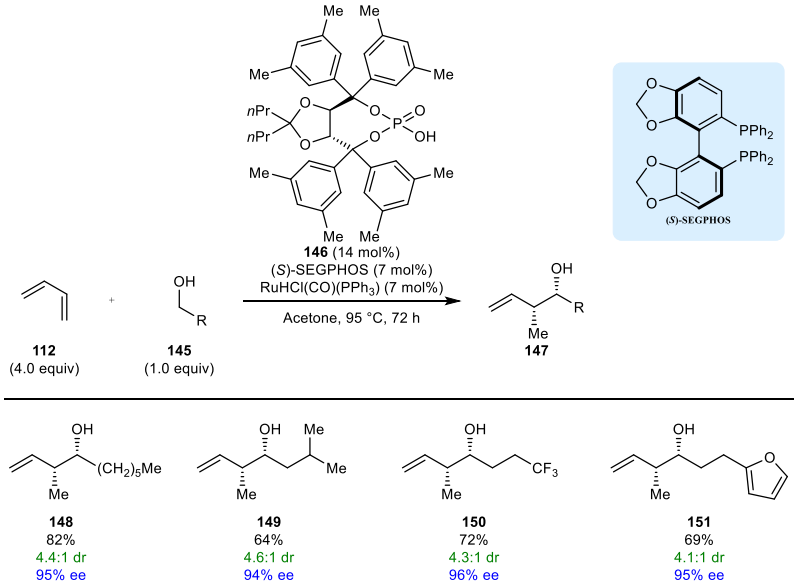
Scheme 21. Krische's method to bypass the need to premetallate the diene to impart high diastereoselectivity.

The rationale behind this idea was to increase the steric encumbrance at the ruthenium centre instead of adding a silyl group on the diene. As depicted in Scheme 22, after hydrometallation of the 1,3-diene, the chiral phosphate counterion pushes the equilibria towards the (*E*)-σ-crotyl diastereoisomer **139**, resulting in the high diastereoselectivity observed in the products.



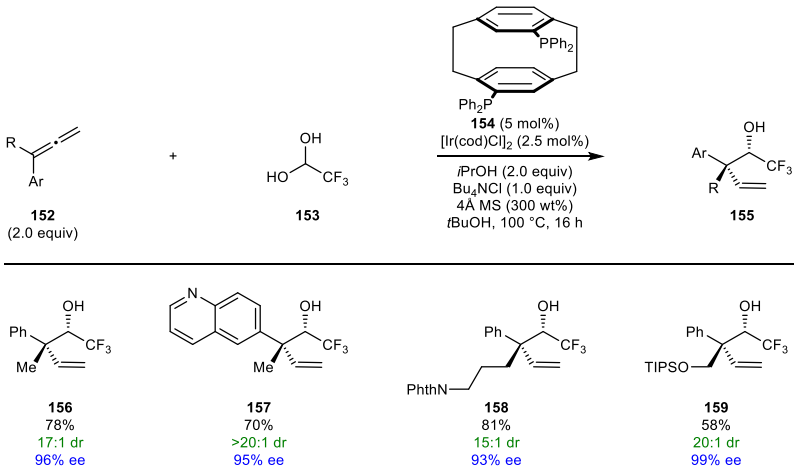
Scheme 22. Proposed mechanism for the counterion-promoted diastereo- and enantioselective crotylation using 1,3-diene.

To complement this method, later that year Krische also reported the use of a TADDOL-derived phosphoric acid **146** along with the chiral biphosphine ligand (*S*)-SEGPHOS, which reverted the diastereoselectivity of the product observed previously (Scheme 23).[22] This catalyst system delivered the *syn* product **147** by reverting the stereochemistry of the carbon bearing the alcohol functional group.



Scheme 23. Krische reporting the inversion of diastereo- and enantioselectivity in the butadiene hydrohydroxyalkylation.

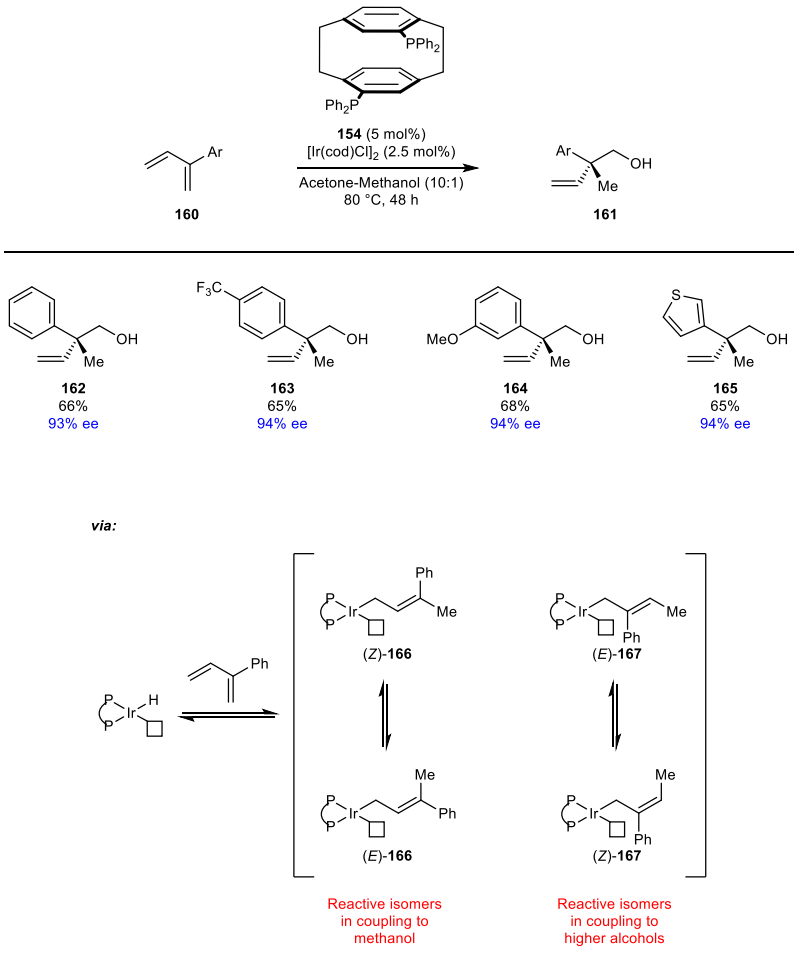
In 2019 Krische reported a highly regio-, diastereo- and enantioselective iridium-catalysed reductive coupling employing allenes **152** and fluoral **153** (Scheme 24).[23] This method afforded homoallylic alcohols containing a trifluoromethyl group **155**. The success of this chemistry relied on the use of a cyclometalated iridium complex formed *in situ* between $[Ir(cod)Cl]_2$ and PhanePhos **154**.



Scheme 24. Krische applying the hydrogen-borrowing chemistry to the enantioselective allylation of fluoral.

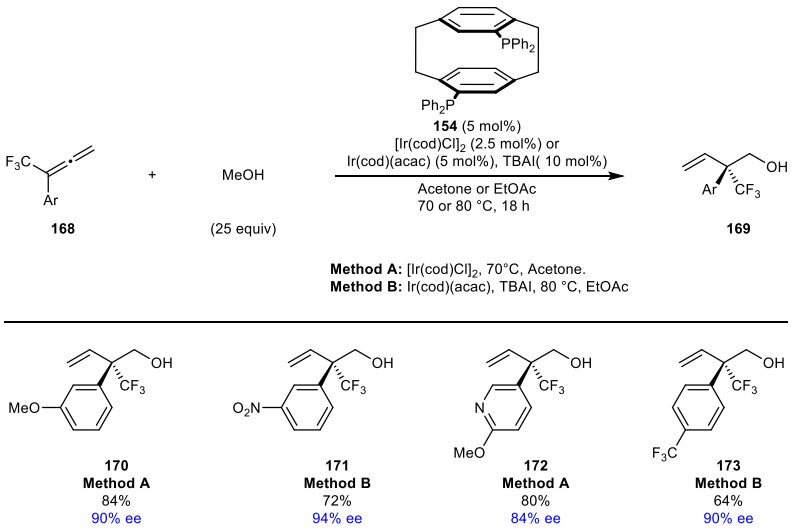
Most of the hydrogen-borrowing chemistry presented used primary alcohols as coupling partners, whereas the simple methanol has always been elusive. This can

be explained by the reversible and highly endothermic nature of methanol dehydrogenation ($\Delta H_{(MeOH)}$ = +20 kcal/mol *vs* $\Delta H_{(EtOH)}$ = +16 kcal/mol).[24] However, in 2016 Krische reported the first allylation of methanol through hydrogen-borrowing chemistry (Scheme 25).[25] With the iridium-PhanePhos catalyst system, methanol provided the coupling at C2 of the diene whereas higher alcohol homologues provided coupling at C3 of the diene. The authors proposed a Curtin-Hammett scenario dictating this C2-selectivity (Scheme 25). Namely, the 1,1-disubstituted allyliridium species (*E*)-**166** is both thermodynamically and kinetically preferred. However, with higher aldehyde homologues, rather than formaldehyde, the steric clash of the transition state with (*E*)-**166** is too high and favours the reaction with the less thermodynamically stable allyliridium species (*Z*)-**167**.



Scheme 25. Krische's report of the first allylation of methanol through hydrogen-borrowing chemistry.

In 2017, Krische used the same chemistry to form homoallylic alcohols with a CF_3-bearing all-carbon quaternary stereocentre in an enantioselective fashion, using 1,1-disubstituted allenes **168** and methanol (Scheme 26). [26] The PhanePhos ligand **154** was shown to be optimal, affording high regio- and enantioselectivities. However, yields and enantioselectivities were highly dependent on the allene substrate used, therefore, two sets of conditions were used. With allenes bearing electron-rich, neutral or slightly electron-deficient aryl moieties, $[Ir(cod)Cl]_2$ with acetone as the solvent at 70 °C were the best reaction conditions. With allenes bearing highly electron-deficient aryl moieties, Ir(cod)(acac) with ethyl acetate as the solvent at 80 °C showed the best results.



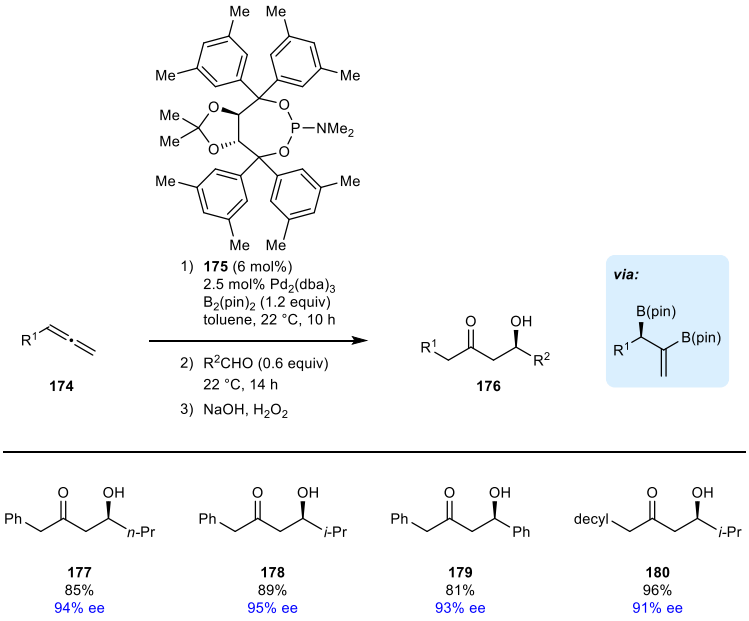
Scheme 26. Krische's method to form homoallylic primary alcohols with CF_3-bearing all-carbon quaternary stereocentres.

1.3. π-bond migratory insertion into metal-heteroatom bonds

The addition of a metal hydride into a starting material containing a π-bond is a powerful tool to perform nucleophilic allylation. However, a more complicated scenario is when more complex substituents, rather than hydrogen, are introduced into the newly formed allylmetal species. These substituents can include boron-, nitrogen-, oxygen- or silicon-containing groups.

1.3.1. Borylative migratory insertion

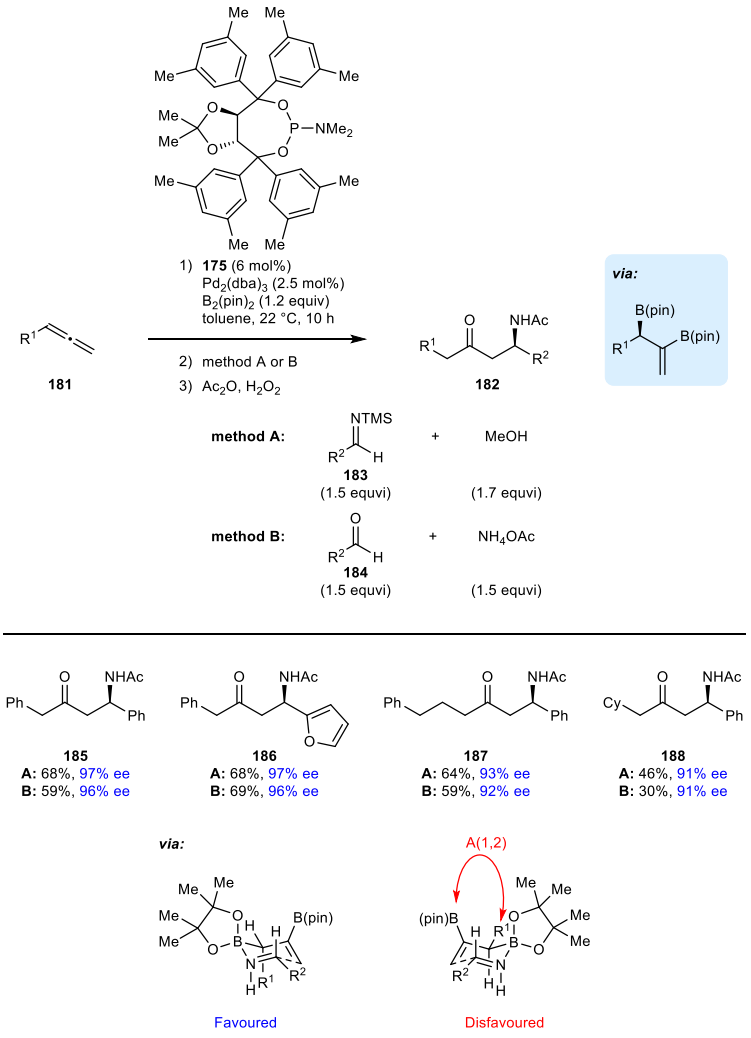
Morken reported in 2005 a two-step, one-pot diborylation-allylation using allenes **174**, bis(pinacolato)diboron [$B_2(pin)_2$] and aldehydes (R^2CHO) under palladium catalysis (Scheme 27).[27] The first step is a diborylation of the allene **174**, followed by the allylation of the aldehyde. This method allows the synthesis of enantioenriched homoallylic alcohols with a boronic ester functional group on the alkene. The boronic ester can be manipulated in multiple ways, such as oxidation (forming product **176**), iodination or Suzuki-Miyaura cross-coupling. The process can be performed in one-step by adding the aldehyde together with the allene and $B_2(pin)_2$, however the yield and enantioselectivity are slightly diminished when compared to the two-step method.



Scheme 27. Morken reports a cascade catalytic enantioselective diboration/allylation/functionalisation of allenes.

In 2006, Morken applied the asymmetric allene diborylation chemistry to the synthesis of amines using allenes **181**, $B_2(pin)_2$, aldehydes **184** and an ammonia source (Scheme 28).[28] The enantioselective step is the initial diborylation of the allene, which successively reacts with the imine, retaining high levels of the enantiomeric excess. The rationale behind which enantiomer is obtained can be

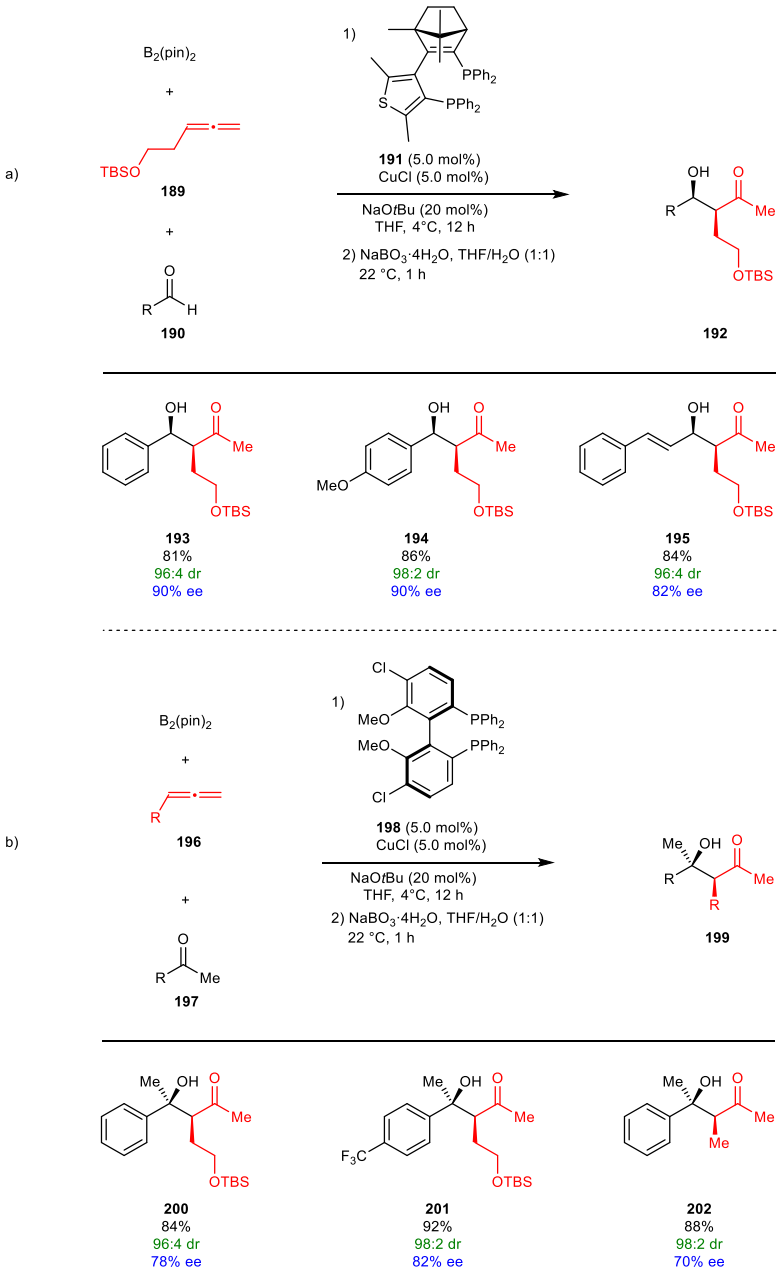
explained using the transition state for allylation of the imine, where the R^1 group sits in the axial position to avoid significant A(1,2) strain.



Scheme 28. Morken expanded the scope of the sequential diboration/allylation/functionalisation to imines.

In 2013 Hoveyda and co-workers developed the first enantioselective, one-pot, three-component cascade reaction between $B_2(pin)_2$, monosubstituted allenes **189** and aldehydes **190** (Scheme 29a) or ketones (Scheme 29b).[29] Fine tuning of the properties of the copper catalyst was essential as borylation can occur competitively at the carbonyl in a 1,2-addition, before the formation of the allylcopper species. Therefore, with more reactive aldehydes bearing electron-withdrawing groups, a superstoichiometric amount of allene was required. To ensure high enantioselectivity, a different chiral biphosphine is required for reactions with aldehydes than the biphosphine used for reaction with ketones. The 2-B(pin)-

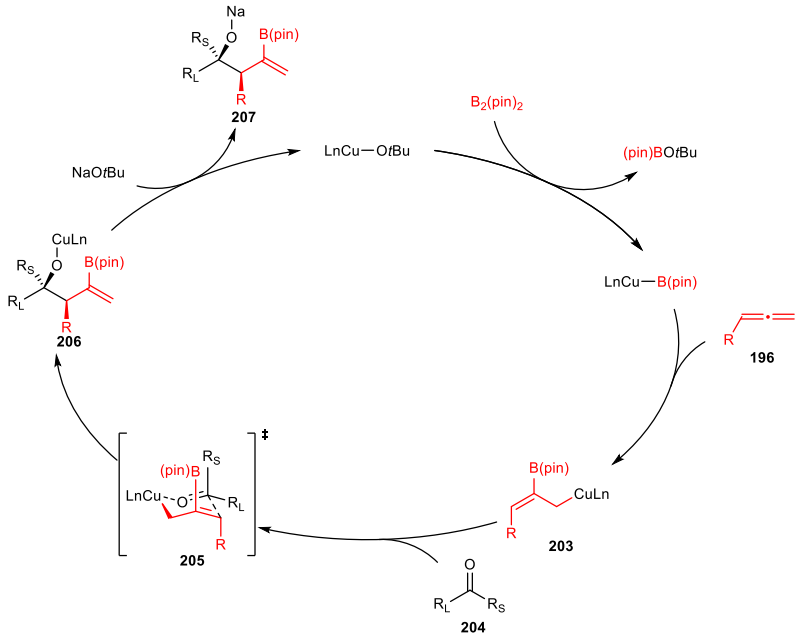
substituted homoallylic alkoxide was oxidised to give the corresponding ketone **192** upon workup. It is worth noting that the reactions with ketones gave lower enantioselectivities compared to aldehydes.



Scheme 29. Hoveyda reported the first enantioselective three-component allylation of carbonyls using allenes.

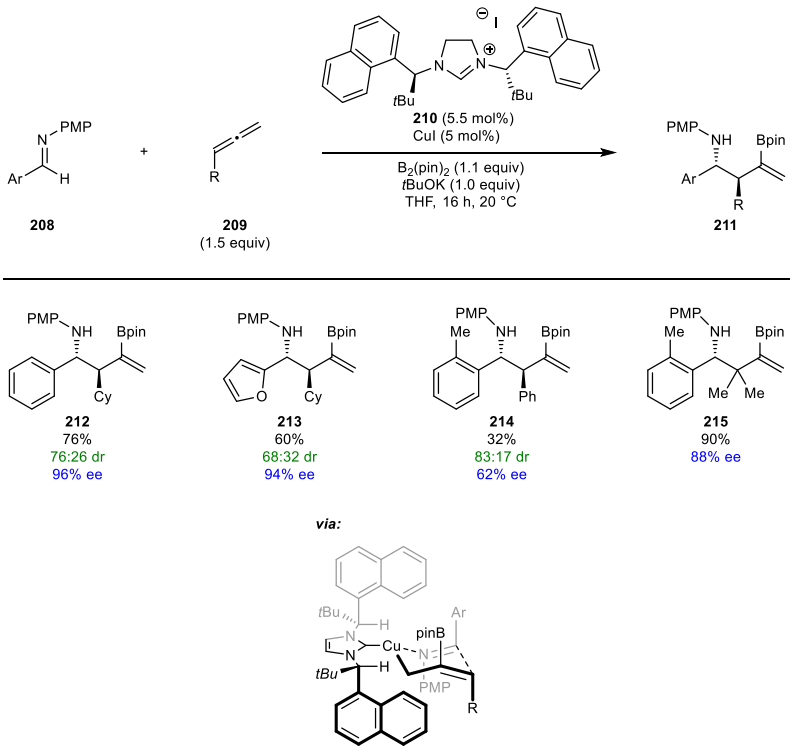
The mechanism underpinning this method (Scheme 30) starts with the chiral Cu-*tert*-butoxide that performs a transmetalation with the $B_2(pin)_2$. This Cu-B(pin) coordinates and performs a migratory insertion into allene **196** to form the Cu-allyl

species **203**. Nucleophilic allylation of the carbonyl **204** through a chairlike transition state forms the Cu-alkoxide **206** and NaO*t*Bu closes the catalytic cycle to reform the catalyst giving the desired product **207**.



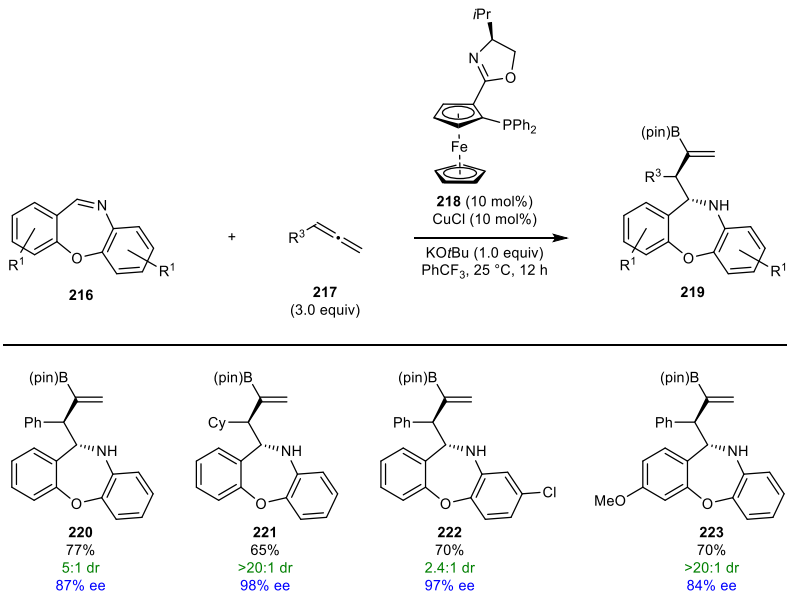
Scheme 30. Mechanism proposed by Hoveyda of the three-component reaction.

In a similar mechanistic vein, Procter and co-workers reported in 2016 the enantioselective Cu(I)-catalysed three-component allylation of imines. This was the first example of an enantioselective borocupration merged with allylcupration of imines (Scheme 31).[30] This method exploited an NHC-Cu(I) catalyst, affording highly valuable products that deliver an amino, alkenyl and boryl functional groups **211** that can be used for late stage functionalisation in drug discovery.



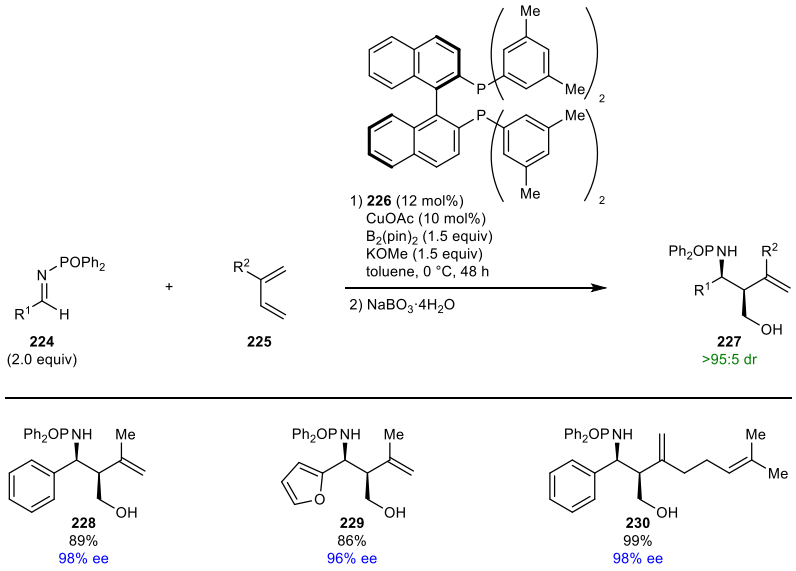
Scheme 31. Procter report of the first enantioselective borocupration merged with allylcupration of imines.

In 2019, Zhang and co-workers expanded the scope of the chemistry developed by Procter to arylallenes **217** and 7-membered-cyclic imines **216** (Scheme 32).[31] In contrast to Procter's imine allylation, the group used a *P*,*N*-ligand **218** along with CuCl as precatalyst to obtain good yields, modest to good diastereoselectivities and very good *ee* values.



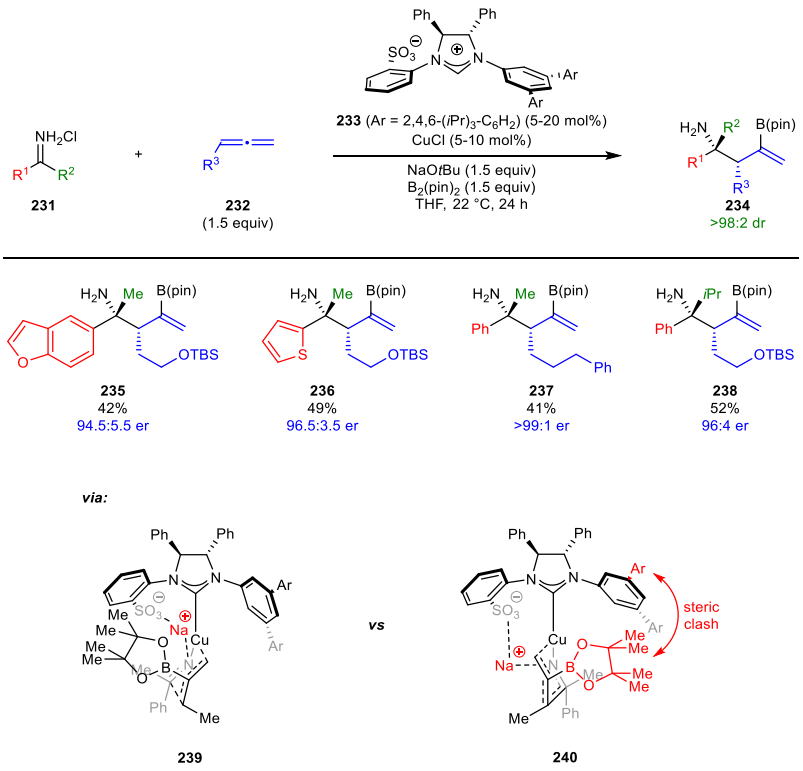
Scheme 32. The Zhang group expanded the scope of the borylative allylation to 7-membered-cyclic imines.

Enantioselective allylation of aldimines can be achieved also with 1,3-dienes as shown by Liao in 2016. [32] The group developed a highly diastereo- and enantioselective three-component borylative coupling of 1,3-dienes and *N*-protected aldimines using copper catalysis (Scheme 33). The use of the chiral non-racemic BINAP **226** in addition to low temperature, allowed coupling of a wide array of 1,3-dienes with aryl-aldimines and $B_2(pin)_2$, with electron-rich imines displaying the highest reactivity. Therefore, the authors suggested that this reactivity pattern could be due to a more facile coordination of the imine to the allylcopper intermediate. Furthermore, the products were isolated as alcohols after oxidation of the B(pin).



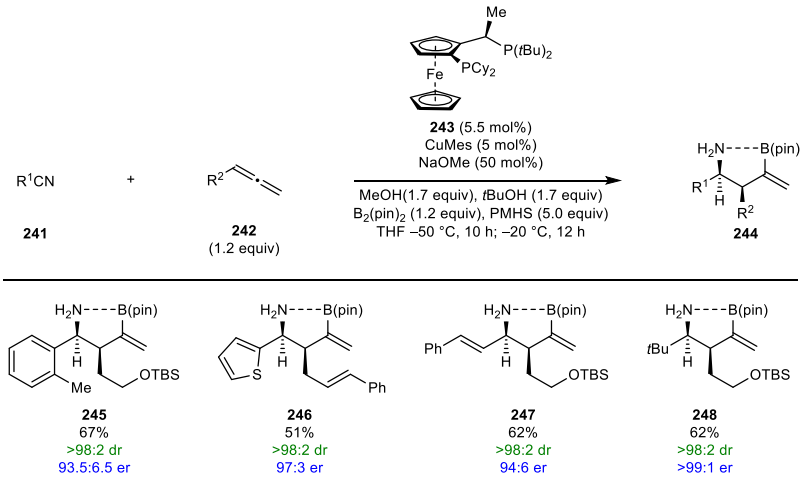
Scheme 33. Liao's enantioselective three-component borylative coupling of 1,3-dienes with aldimines.

Performing an enantioselective nucleophilic 1,2-addition on ketimines is more challenging than performing it on aldimines for two reasons. Firstly, ketimines are less reactive than aldimines and additionally, the size difference between the substituents flanking the ketone is reduced compared to the aldehyde. Nevertheless, the Hoveyda group in 2017 managed to perform the allylation of unprotected ketimines **231** obtaining tertiary homoallylic amines **234** using allenes **232** and $B_2(pin)_2$ under copper catalysis (Scheme 34).[33] The best ligand in terms of catalytic activity, diastereo- and enantioselectivity was the NHC ligand **233** bearing a sulfonate group. This finding was surprising since it was the first report where a sulfonate-containing NHC-Cu catalyst was optimal for a 1,2-addition reaction. The authors utilised DFT calculations to understand the origin of this selectivity. Based on the calculations, they proposed a N-Na interaction guided by the sulfonate anion to be the cause of the origin of the enantioselectivity (Scheme 34).



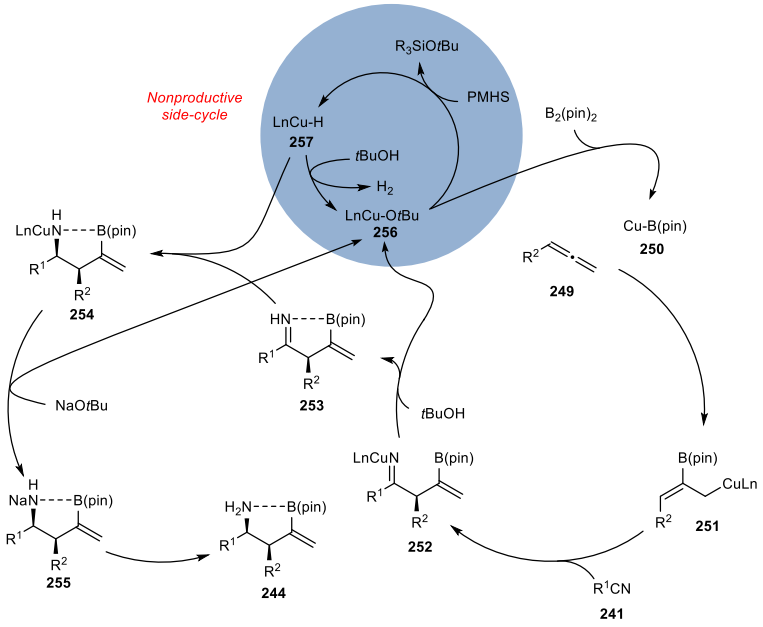
Scheme 34. Hoveyda reports the three component allylation of ketimines using NHC-Cu-catalysis.

Within the topic of making homoallylic amines through catalytic enantioselective allylations, the same group developed in 2019 a method to access the diastereo- and enantioselective allylation of nitriles with copper tandem catalysis (Scheme 35).[34]



Scheme 35. Delaying CuH formation allows to obtain homoallylic amines from nitriles.

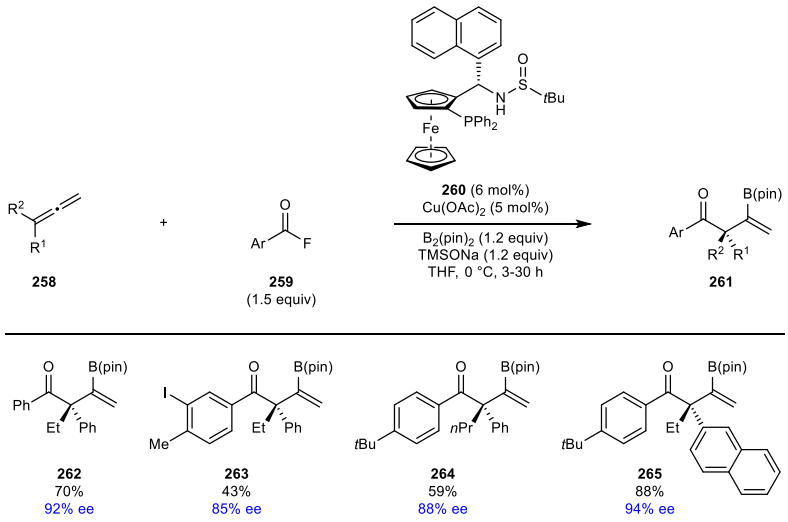
A few points worth noting about this method include the fact that nitriles are poorly reactive substrates, hence why they are often used as solvents. Also, a *tert*-butoxide source is necessary for the regeneration of the catalyst (Scheme 36) however it is also detrimental to the reaction since it transforms the homoallylic imine **253** into an allylic imine through isomerisation of the double bond. Finally, the copper catalyst, in the presence of both $B_2(pin)_2$ and the polymethylhydrosiloxane (PMHS), forms the CuH **257** species faster than the CuB(pin) **250**, with the CuH **257** adding more rapidly to the allene. However, it was noted that adding an excess of $B_2(pin)_2$ compared to PMHS does not favour the addition of CuB(pin) into the allene. Conversely, it favours the base-promoted alkene isomerisation slowing the homoallylic ketimine **253** reduction. The group overcame these problems by delaying the production of CuH **257** by adding a combination of methanol and *tert*-butanol. The alcohols delay the formation of the CuH by partially quenching it (blue circle in Scheme 36, only *t*BuOH is shown for simplicity). This delay lets the CuB(pin) react readily with the allene whilst allowing the concentration of the CuH **257** to be high enough to reduce the ketimine **253** with low alkene isomerisation.



Scheme 36. Catalytic cycle proposed by Hoveyda for the borylative allylation of nitriles.

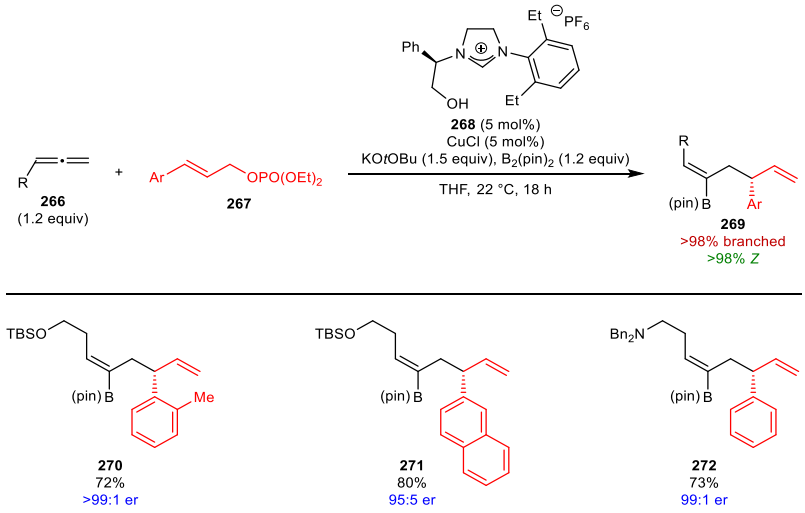
The last example of a borylative 1,2-allylation is represented in (Scheme 37). Zhang and co-workers reported for the first time a copper-catalysed enantioselective

allylation of acyl fluorides **259** using $B_2(pin)_2$ and 1,1-disubstituted allenes **258**.[35] The development of a new class of ferrocene-derived chiral sulphonamide phosphine ligands **260** was at the core of this method. This catalytic system provided *β*-boryl-*β,γ*-unsaturated ketones **261** bearing an all-carbon stereocentre in high yields and enantioselectivities. A limitation with this chemistry is the non-reactive nature of acyl fluorides bearing electron withdrawing groups.



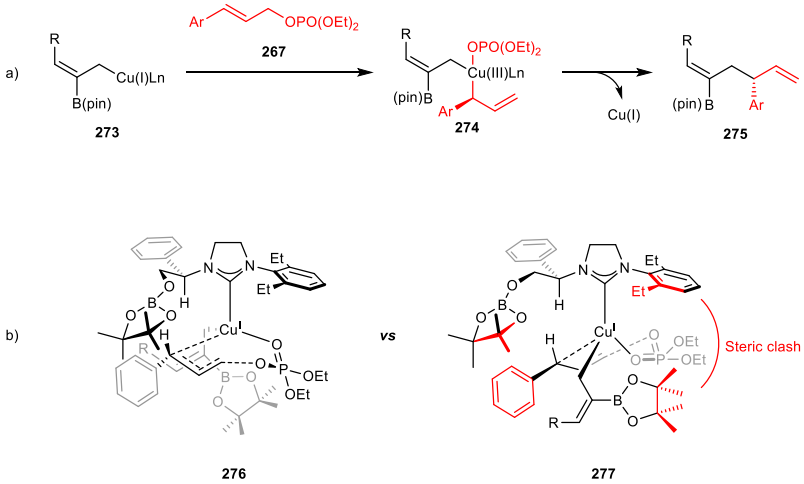
Scheme 37. Zhang reported the first Cu-catalysed enantioselective allylation of acyl fluorides.

In 2014, Hoveyda and co-workers developed a NHC-Cu catalysed multicomponent reaction that combines terminal allenes **266**, $B_2(pin)_2$ and an allylphosphate **267** to generate highly valuable alkenylboron fragments **269** (Scheme 38).[36] The products were obtained in a high chemo-, diastereo- and enantioselective fashion. The high efficiency of this methodology was attributed to the fine tuning of the sterics and electronics of the copper catalyst, plus, the alcohol moiety on the NHC ligand **268** was essential to impart high enantioselectivity (*vide infra*).



Scheme 38. Hoveyda reports an NHC-Cu-catalysed multicomponent allyl-allyl cross-coupling.

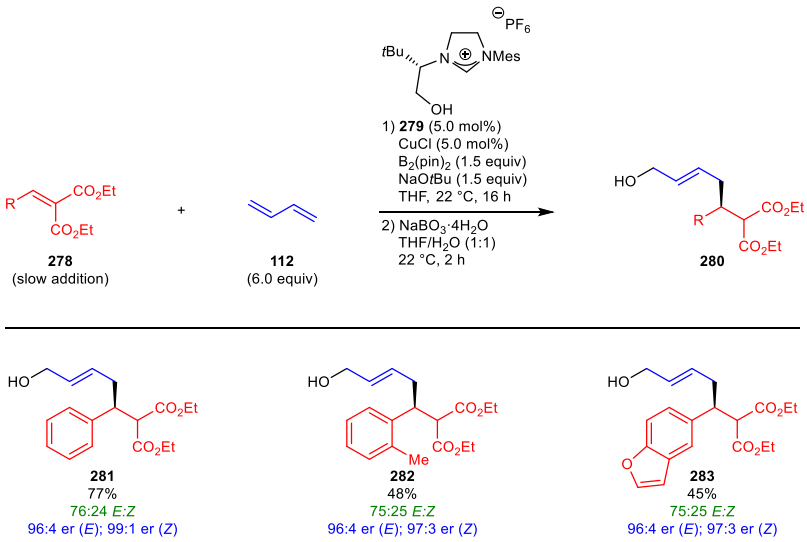
The key steps of this method are depicted in Scheme 39a and is a Cu(I)/Cu(III) process. After transmetalation and borylative migratory insertion to form the allylcopper species **273**, oxidative addition to form Cu(III) species **274** occurs. Rapid reductive elimination furnishes the product **275** and the Cu(I) catalyst. It is thought that the alcohol moiety of the NHC ligand **268** binds the B(pin) and amplifies the steric bulk around the copper catalyst in the enantio-determining step (Scheme 39b).



Scheme 39 a) cataltytic cycle proposed by Hoveyda; b) proposed transition state to explain the enantioselectivity.

In 2016, the same group reported a copper-catalysed enantioselective conjugate addition reaction of allylcopper intermediates generated *in situ* from 1,3-butadienes

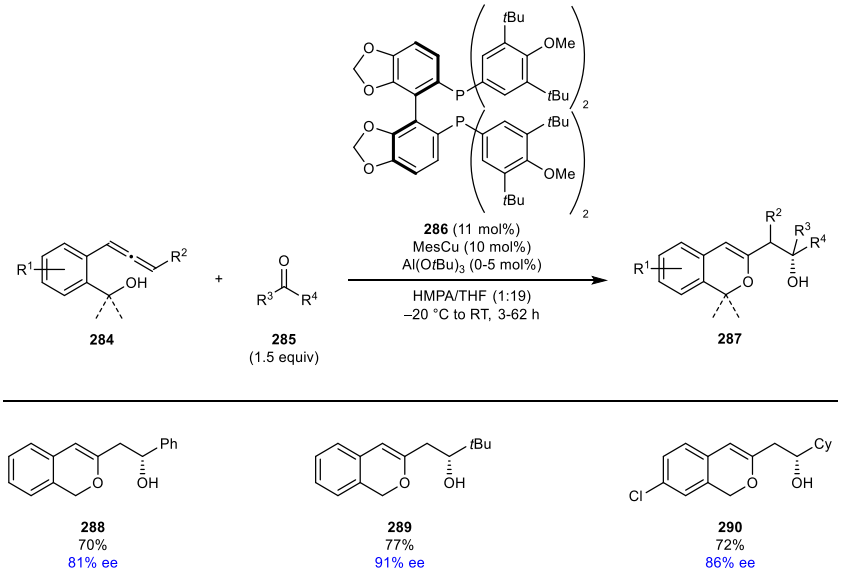
112 and $B_2(pin)_2$ (Scheme 40).[37] The NHC ligand **279** along with CuCl afforded a higher amount of the desired product and better enantioselectivity. However, the same ligand generated the largest amount of the 1,4-borylation among all the ligands screened. Hoveyda and co-workers bypassed this problem with a slow addition of the enoate. Keeping the concentration of the enoate low, larger amounts of the allylcopper species were present in the reaction mixture and were able to rapidly react with the enoate as it is added. The products were isolated as alcohols **280**, after oxidation of the B(pin) group.



Scheme 40. Hoveyda's report of the Cu-catalysed enantioselective three-component 1,4-allylation of enoates.

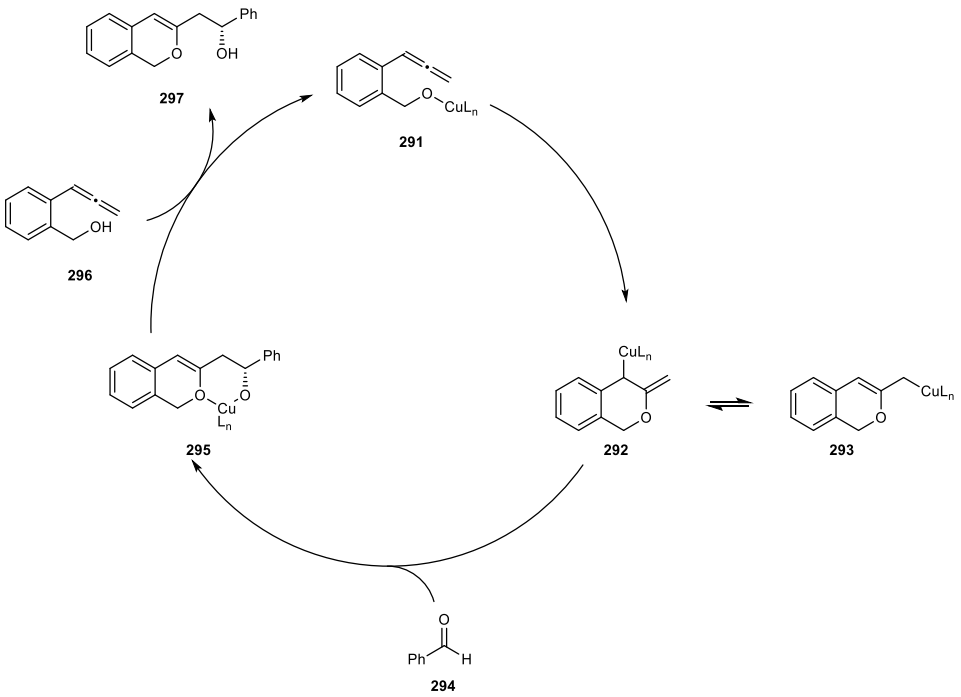
1.3.2. Migratory insertion of nitrogen, oxygen or silicon

Kanai and Shimizu reported an enantioselective allylation of carbonyl compounds using allenic alcohols **284**, a carbonyl compound **285** and a Cu(I) source as the catalyst to form isochromene skeletons **287** (Scheme 41).[38] Excellent yields and enantioselectivities were obtained with mesitylcopper as the catalyst and aluminium *tert*-butoxide as the cocatalyst. The carbonyl scope mainly constituted of aldehydes, and the only ketone allylated was acetophenone, with slightly lower yield and moderate enantioselectivity (77% *ee*).



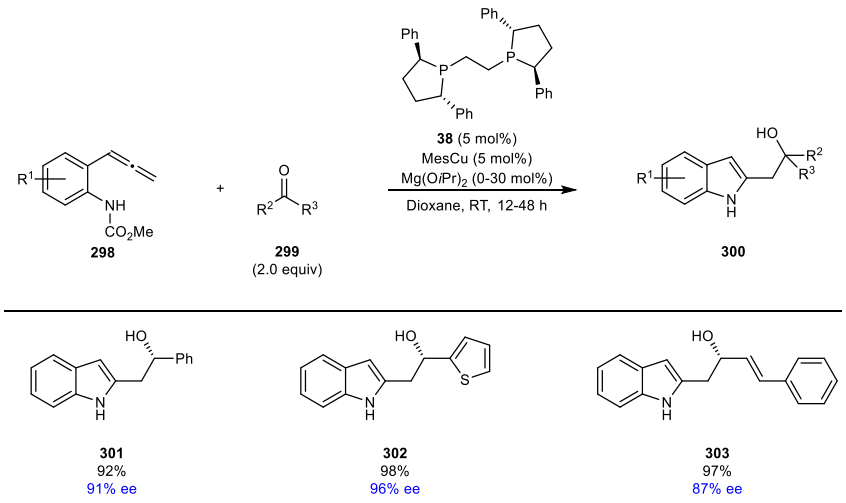
Scheme 41. Kanai and Shimizu's method to synthesise isochromene skeletons.

This method provides isochromene skeletons **287** through oxycupration of the allene **284** and nucleophilic allylation of the carbonyl compound **285** (Scheme 42). Considering that the aluminium co-catalyst increases the yield but not the enantioselectivity, the group proposed that the co-catalyst is involved in the liberation of the product closing the catalytic cycle.



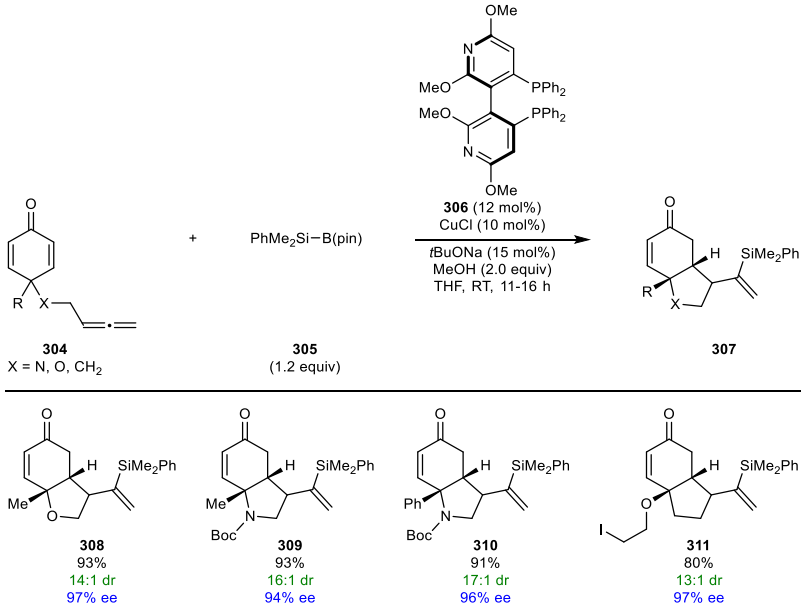
Scheme 42. Mechanism proposed by Kanai and Shimizu for the synthesis of the isochromene skeleton.

The Kanai group in 2014 extended this chemistry to encompass the synthesis of indoles **300** through an amidocupration of allenes **298** and successive enantioselective nucleophilic attack on carbonyls **299** (Scheme 43).[39] In this instance, Mg(*i*OPr)$_2$ was used as a Lewis acid, facilitating the coupling of less reactive aliphatic carbonyls.



Scheme 43. Kanai extended this chemistry to the synthesis of indoles.

In 2015 Tian and co-workers reported the first enantioselective 1,4-addition of β-silylated allylcopper intermediates (Scheme 44).[40] The key to perform this copper-catalysed Michael addition was to tether an α,β-unsaturated carbonyl compound and the allene, as shown in substrate **304**. This tether favoured the 1,4-allylation hampering the copper-catalysed 1,4-silylation due to the amount of steric hindrance.



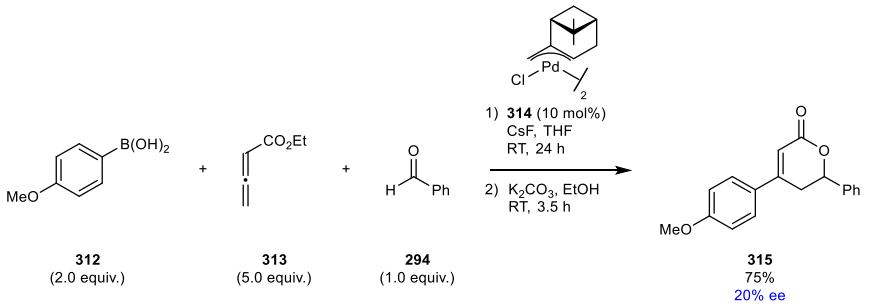
Scheme 44. Tian reported the first enantioselective 1,4-addition of β-silylated allylcopper intermediates.

1.4. Arylative, alkynylative and alkylative migratory insertions of π-bond containing compounds

Construction of new C-C bonds is at the heart of organic synthesis. Therefore, making multiple C-C bonds in an enantioselective fashion through a cascade reaction dramatically improves the efficiency of a synthetic pathway. Discussed here are enantioselective metal-catalysed nucleophilic allylations where two C-C bonds are constructed.

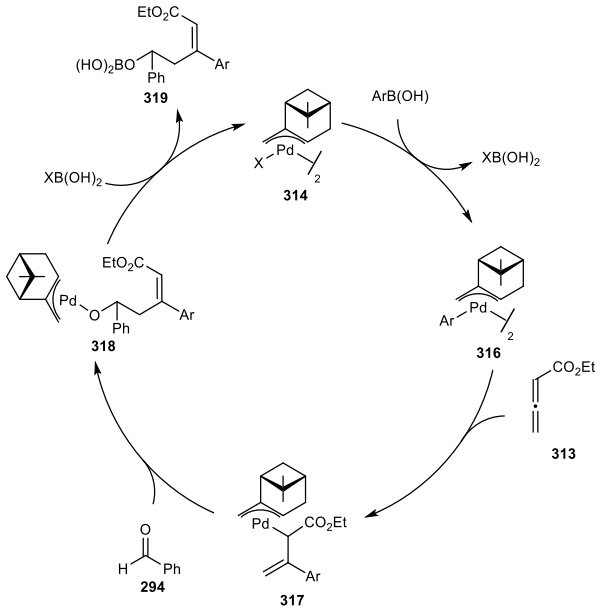
The first report of this type was from Malinakova (Scheme 45).[41] This group used palladium catalyst **314** derived from β-pinene to obtain di-functionalisation of allenes **313** using arylboronic acids and aldehydes **294**. The *ee* value was calculated only for the example shown in Scheme 45, however it presented poor enantioselectivity. The use of potassium carbonate in the second step allowed the

lactonisation to happen at a faster rate, therefore increasing the yield of the desired product **315**.



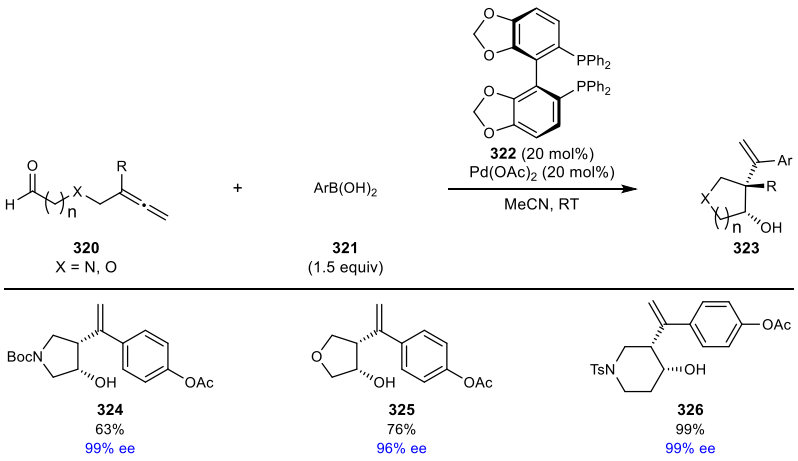
Scheme 45. Malinakova's report of a Pd-catalysed multicomponent coupling of allenyl esters with arylboronic acids and aldehydes.

During the catalytic cycle (Scheme 46), transmetalation affords the arylpalladium species **316**. Migratory insertion of the allene **313** gives an unsymmetrical bis-π-allylpalladium complex **317**. The η^1-bonded allyl ligand performs the nucleophilic attack onto the carbonyl forming the palladium-alkoxide species **318** which then is liberated by the boron species to close the catalytic cycle and gives the desired product **319**.



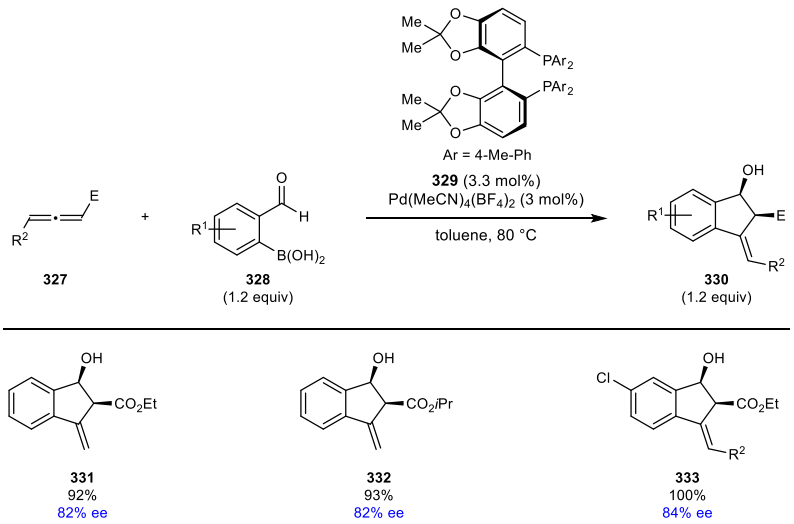
Scheme 46. Catalytic cycle proposed by Malinakova.

In 2008. Tsukamoto and co-workers developed the first enantioselective cyclisation of allenals **320** using palladium catalysis and diphosphine **322** as the ligand (Scheme 47).[42] The reaction proceeded at room temperature with high yields and enantioselectivities (up to 99% yield and 99% *ee*). However, the use of ketones as the electrophilic partner required harsher reaction conditions which led to a drop in yield and enantioselectivity (79%, 51% *ee*).



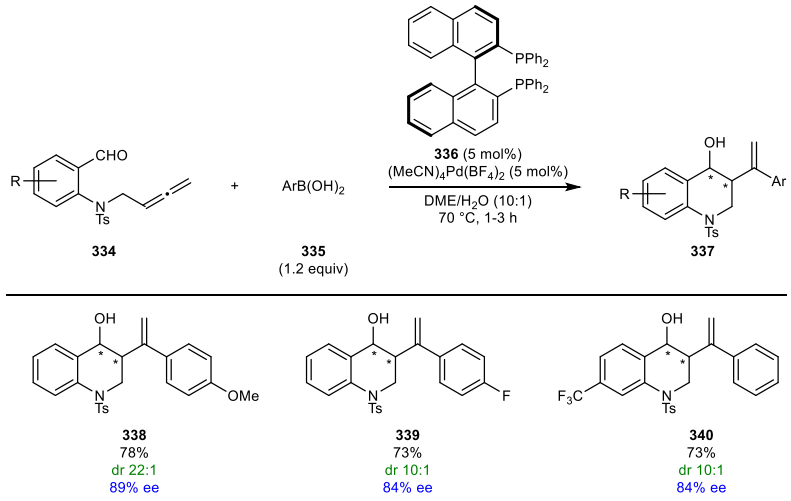
Scheme 47. Tsukamoto's Pd-catalysed enantioselective coupling of arylboronic acids with allenes tethered to aldehydes.

Lu and co-workers developed an enantioselective cyclisation of arylboronic acids bearing an aldehyde moiety **328** and allenes **327** using a cationic palladium catalyst (Scheme 48).[43] Remarkably, a cationic palladium species was nucleophilic enough to catalyse the nucleophilic allylation into a carbonyl. The reaction was superior when electron-deficient allenes were utilised, however there was no enantioselective variant reported with a ketone electrophile.



Scheme 48. Lu's cationic Pd-catalysed enantioselective cyclisation of boronic acids and allenes.

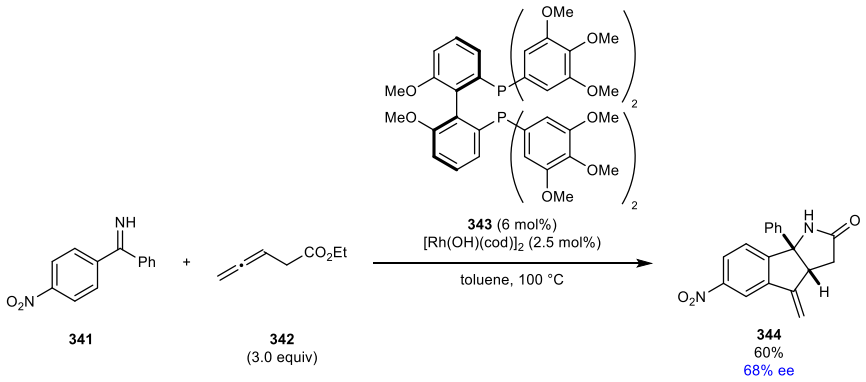
The same group extended this methodology to the diastereo- and enantioselective synthesis of tetrahydroquinoline derivatives **337** tethering the allene to the aldehyde **334** and using a boronic acid (Scheme 49).[44]



Scheme 49. Han and Lu synthesis of tetrahydroquinolines through arylative allylation of aldehydes.

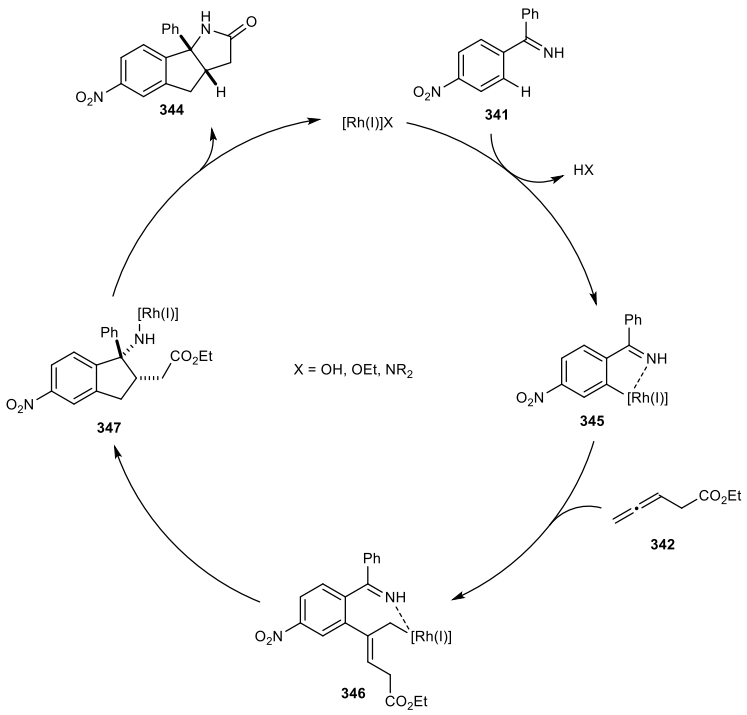
Arylboronic acids are useful reagents to form new C-C bonds. However, a more sustainable method to form these bonds is using a C-H activation strategy. Using this strategy, Cramer and co-workers developed in 2010 a *syn*-selective Rh(I)-catalysed allylation of ketimines **341**.[45] This work was focussed on the diastereoselective

process, however a preliminary report of the enantioselective variant was reported (Scheme 50).



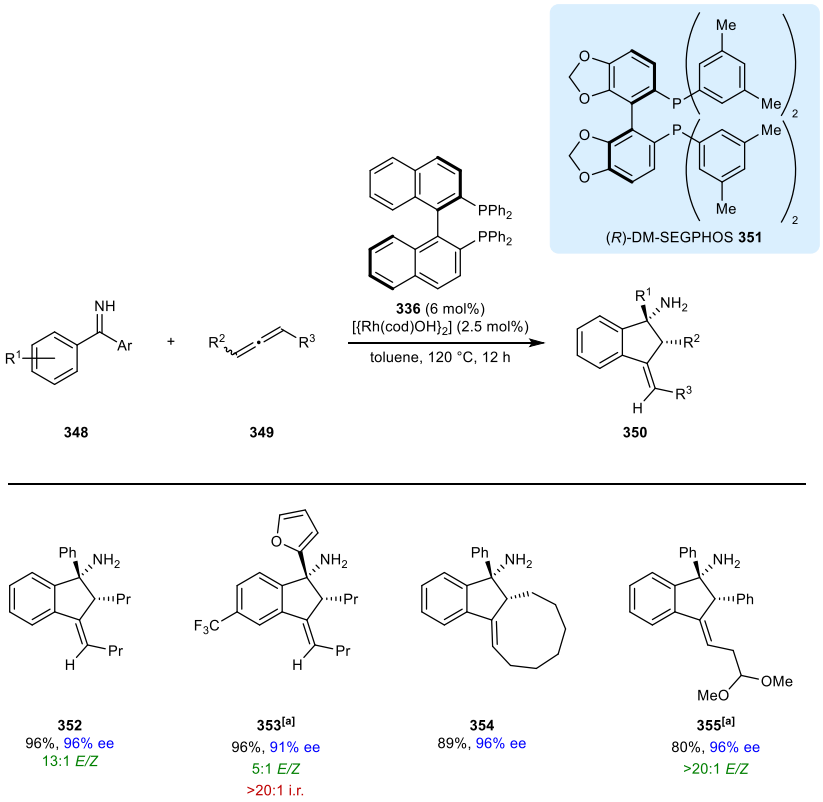
Scheme 50. Cramer's preliminary report of an enantioselective C-H activation/cyclisation of ketimines and allenes.

Interestingly, the imine directing group could potentially be involved in the process *via* a reductive elimination step from intermediate **345** in Scheme 51, leading to the formation of a C-N bond. Instead, the nucleophilic allylation was obtained exclusively leading to intermediate **346** that cyclises to form product **344**.



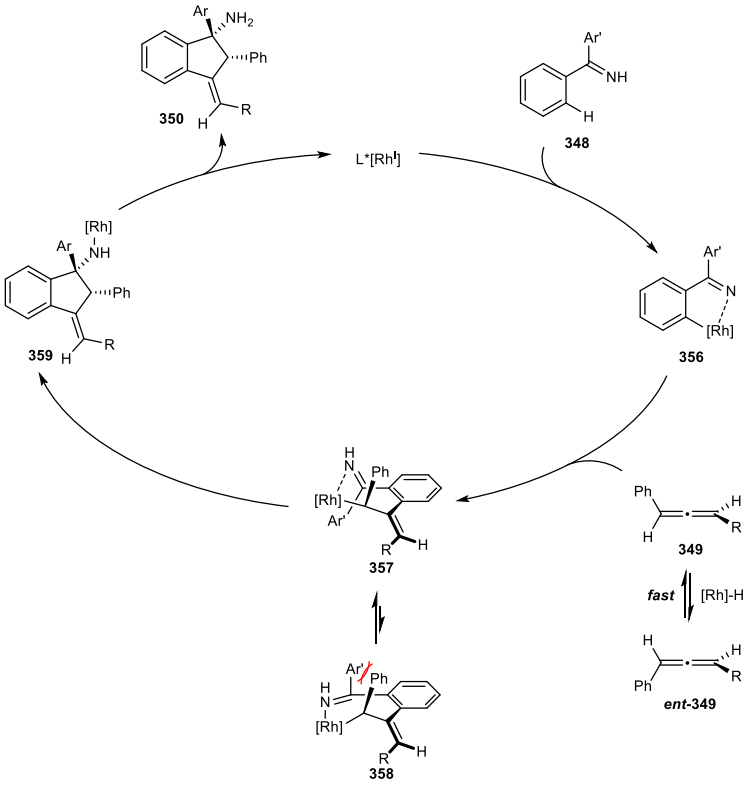
Scheme 51. Proposed catalytic cycle for Cramer's C-H activation/allylation process.

Three years later, the same group reported another use of the C-H activation strategy for the arylation of internal allenes **349** (Scheme 52).[46] They managed to achieve high enantioselectivities by means of a Dynamic Kinetic Asymmetric Transformation (DYKAT) using Rh(I) catalysis. The ligand that showed the best activity was BINAP **336**, providing excellent yields, good chemoselectivity with asymmetric ketimine substrates, very good diastereoselectivity with regard to the *E/Z* isomer obtained and excellent enantioselectivity. However, in some instances, the use of DM SEGPHOS **351** as the ligand, instead of BINAP, was necessary to achieve the best results.



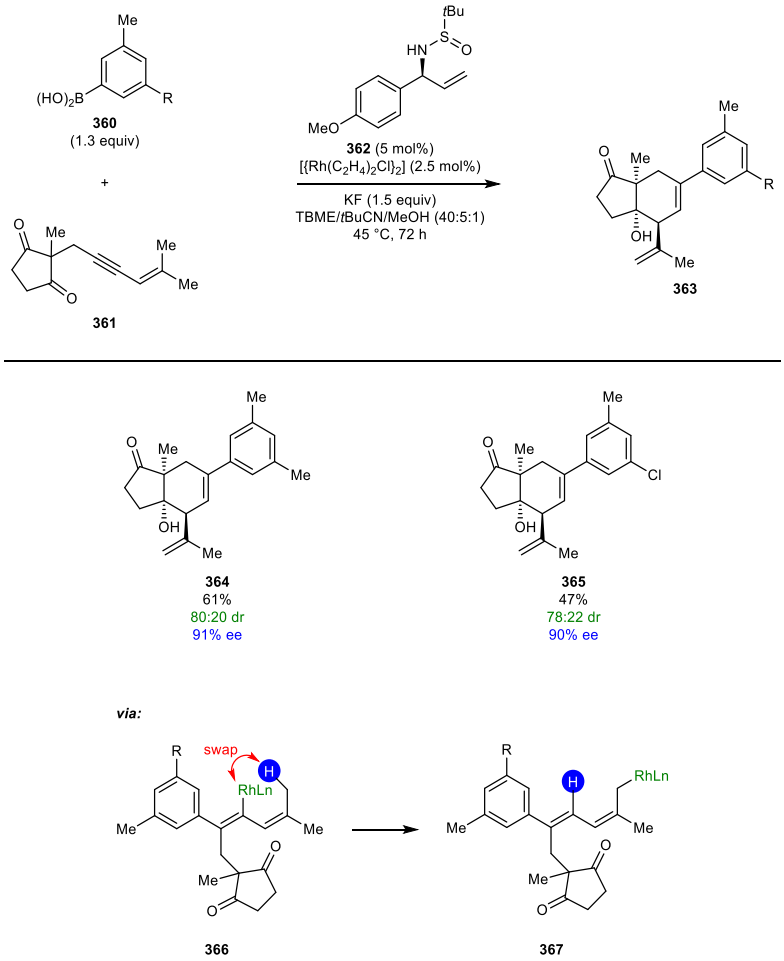
Scheme 52. Cramer's Dynamic Kinetic Asymmetric Transformation of allenes. [a] with (R)-DM-SEGPHOS as ligand.

Mechanistically, the strategy relies upon fast racemisation of the allenes **349** and ***ent*-349** catalysed by the Rh catalyst (Scheme 53). The arylrhodium intermediate **356** reacts with the matching enantiomer of the racemic allene and a diastereoselective allylation of the imine occurs with a transition state **357** that places the two aryl substituents away from each other, affording the *syn* product **350**.



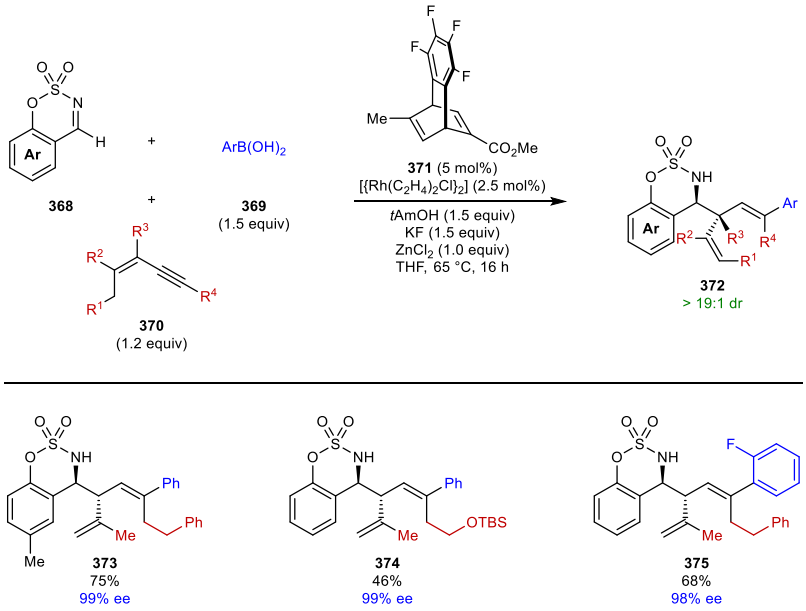
Scheme 53. The mechanism proposed by Cramer for the DYKAT method.

As already stated, C-H activation is a powerful tool in organic synthesis and Lam and co-workers used the activation of an (sp^3)C-H bond by means of Rh(I)-1,4 migration to achieve diastereoselective allylation of ketones.[47] The group also reported the preliminary efforts to make this reaction enantioselective. Using a chiral sulphinamide allowed the desired product to be obtained in up to 91% *ee* (Scheme 54). The method used an arylboronic acid **360** and an 1,3-enyne tethered to a ketone **361**. The key step of this reaction is the alkenyl-to-allyl 1,4-rhodium(I) migration which had never been reported before. The allylrhodium(I) **367** is nucleophilic enough to perform a 1,2-allylation into the tethered ketone affording the cyclised product **363**.



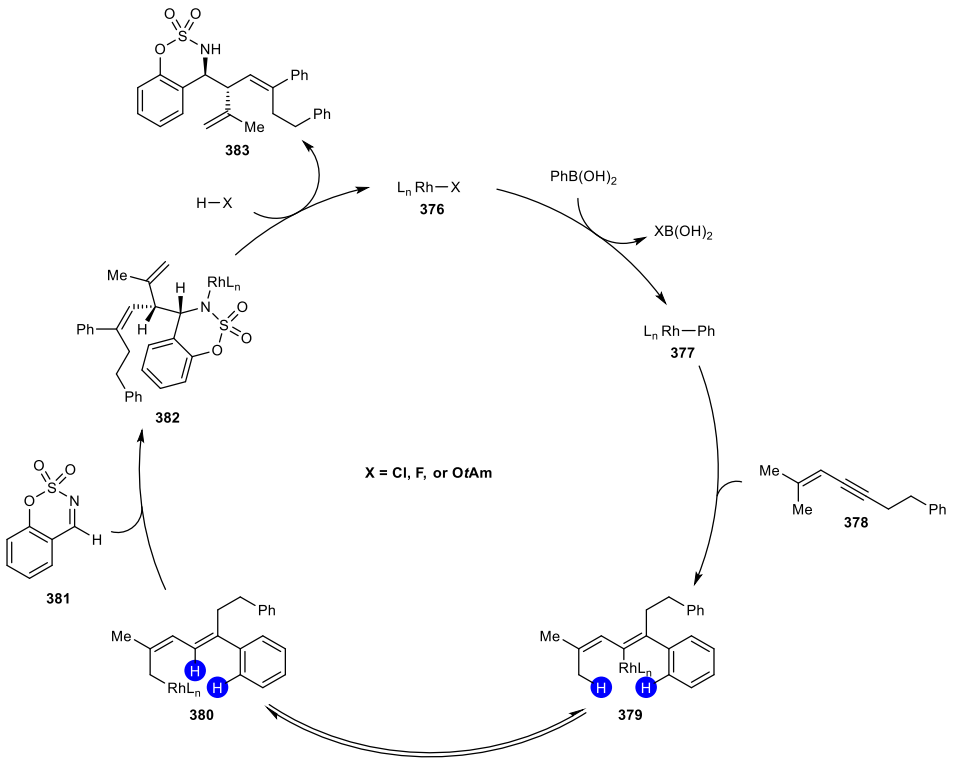
Scheme 54. Lam reports the preliminary enantioselective allylation of ketones through 1,4-migration.

The same group reported in 2017 the extension of this work to the intermolecular variant (Scheme 55).[48] This three-component reaction used a cyclic imine **368**, 1,3-enyne **370** and an arylboronic acid. The difficulty associated with this process was greatly increased for a number of reasons. Firstly, Rh(I) can catalyse the 1,2-addition of arylboronic acids directly into the imine. The alkenylrhodium intermediate, formed after carborhodation of the alkyne, can also add into the imine directly. Additionally, 1,4-migration can occur onto the *ortho*-position of the aryl ring and promote the 1,2-arylation of the imine and finally, the allylrhodium species can perform 1,2-allylation to form a branched or a linear product. Notably, this method allows the allylation of a ketimine too, by changing the solvent system to THF/MeCN (19:1) instead of THF alone.



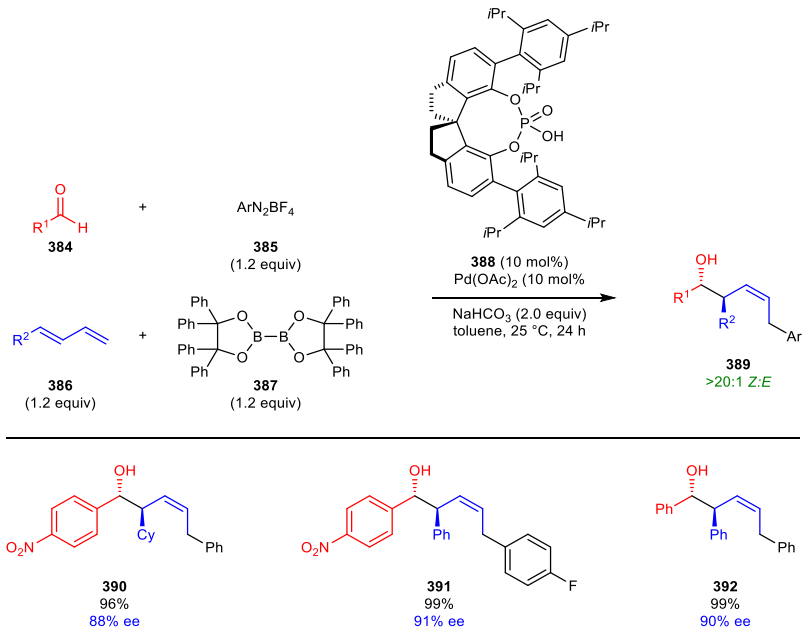
Scheme 55. Lam reports a three-component allylation of imines through Rh(I)-1,4-migration.

The mechanism proposed by Lam is represented in Scheme 56. Transmetalation affords phenylrhodium **377** and subsequent carborhodation provides the alkenylrhodium **379** that performs alkenyl-to-allyl 1,4-Rh(I) migration. Enantioselective allylation of the imine and subsequent protonation provide the product **383**.



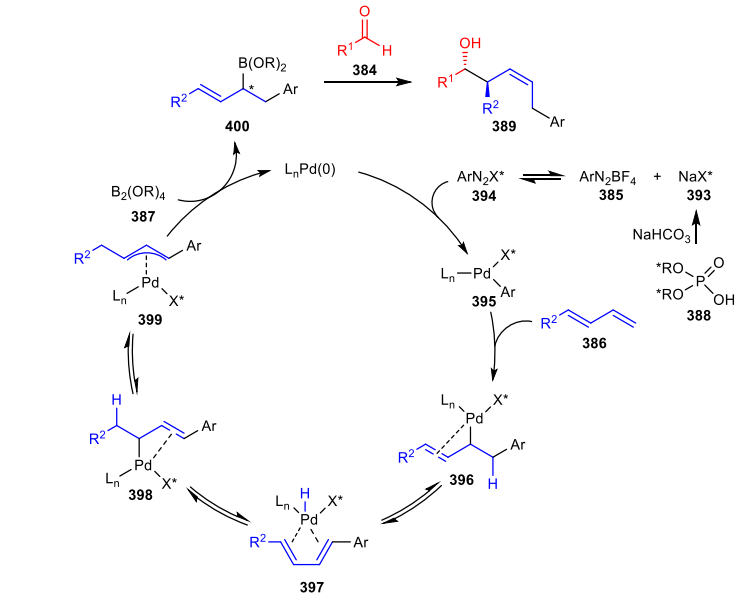
Scheme 56. Proposed mechanism for the allylation through Rh(I)-1,4-migration.

An interesting cascade four-component transformation was reported by Gong in 2016 (Scheme 57).[49] This method coupled 1,3-dienes **386**, aryldiazonium salts **385** and aldehydes **384** through the mediation of the diborate compound **387** under chiral anion phase transfer palladium-catalysis using a chiral phosphoric acid **388**. The regio-, enantio- and *E*/*Z* diastereoselectivity were all controlled in this transformation to obtain products **389** selectively. However, this chemistry was limited to only aryldiazonium salts. Other organodiazonium salts were too unstable under these conditions.



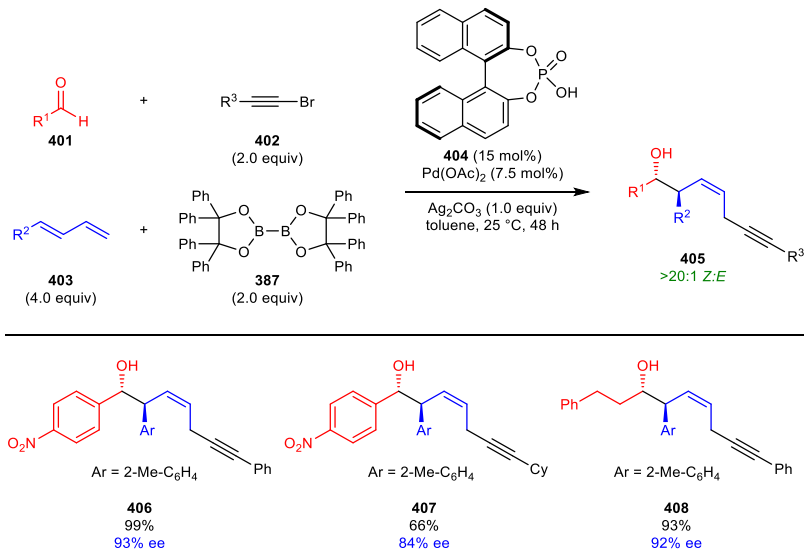
Scheme 57. Gong's report of the Pd-catalysed enantioselective allylation of aldehydes with diazonium salts and 1,3-dienes.

With regard to the mechanism (Scheme 58), anion metathesis of the diazonium salt with the chiral phosphoric acid **388** affords the chiral diazonium salt **393**. Oxidative addition of Pd(0) with the chiral diazonium salt gives the chiral arylpalladium(II) **395**. Migratory insertion and subsequent isomerisation lead to the enantioenriched borylated product **400**. Allylation of the aldehyde through a chair-like transition state affords product **389**.



Scheme 58. Postulated mechanism by Gong and co-workers.

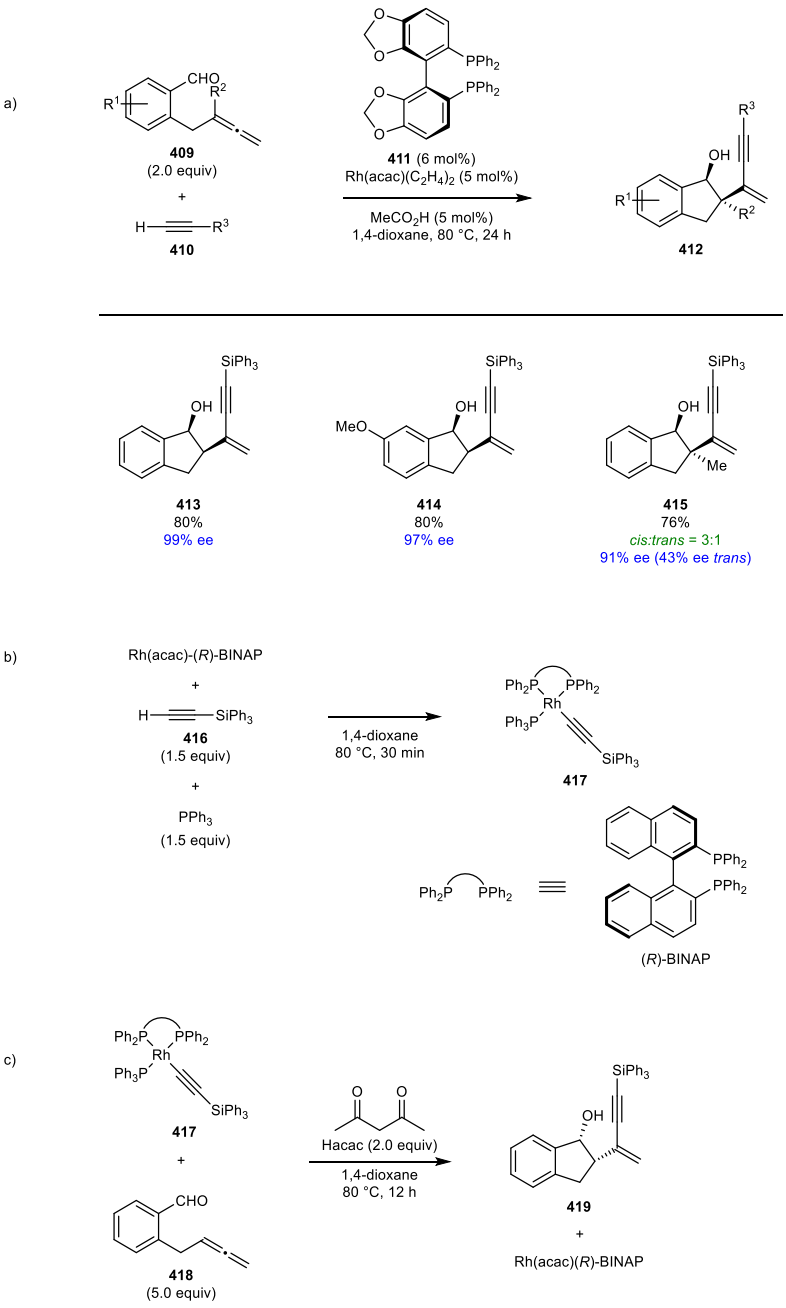
The same group expanded this chemistry to the alkynyl bromides **402** (Scheme 59).[50] The reactivity is similar to that observed in the previous paper. However, silver carbonate is used to aid the process by performing anion metathesis between silver and palladium making the latter a more cationic species.



Scheme 59. The Gong group expanded the scope to alkynyl bromides as coupling partners.

In terms of alkynylative migratory insertion, only one other process is reported in the literature. In 2010 Hayashi and Nishimura reported a Rh(I) catalysed

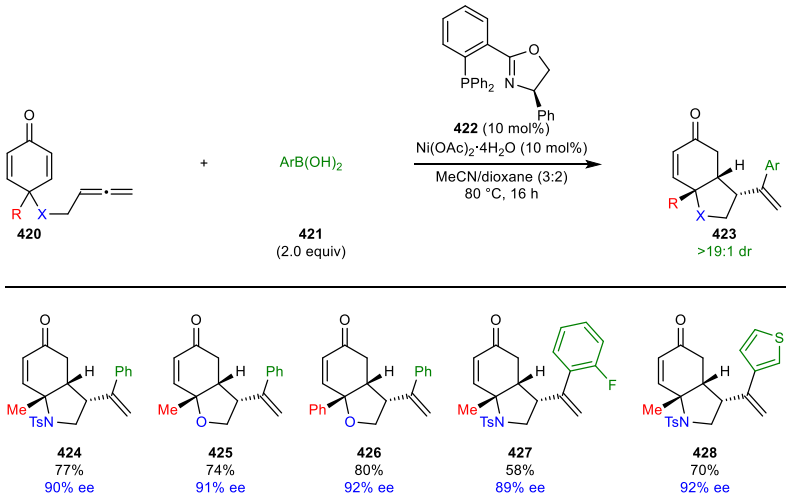
enantioselective alkynylative cyclisation of allenyl aldehydes **409** with terminal alkynes **410** (Scheme 60a).[51] The highest yields and enantioselectivities were obtained with Rh(acac)(C_2H_4) with SEGPHOS **411** as the ligand. Mechanistically, they showed that Rh(I) formed an alkynylrhodium(I) **417** starting from Rh(acac)-(*R*)-BINAP, terminal alkyne **416**, triphenylphosphine and acetic acid (Scheme 60b). This latter reagent was essential for the formation of the alkynylrhodium(I) species. Subjecting this compound to the reaction conditions, afforded the desired product **419** (Scheme 60c). This result provided evidence that the alkynylrhodium(I) species is involved in the catalytic cycle.



Scheme 60. a) Hayashi and Nishimura Rh(I)-catalysed process; b) synthesis of the alkynylrhodium(I) species; c) using alkynylrhodium(I) species with reaction conditions affords the desired product.

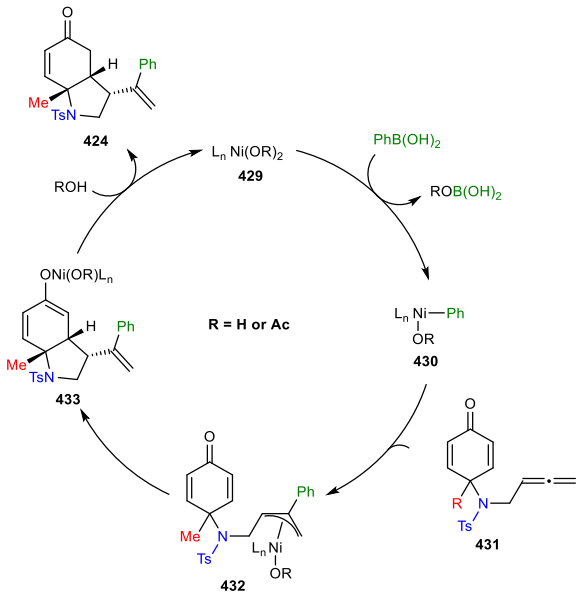
Most of the allylation reactions discussed in this chapter are 1,2-allylations. The only enantioselective metal-catalysed 1,4-allylation reported to date initiated by a carbometallation of a π-bond containing reagent, was reported by Lam in 2018 (Scheme 61).[52] The group reported the desymmetrisation of allenyl cyclohexa-2,5-diones **420** with arylboronic acids **421** under nickel catalysis using the PHOX ligand **422**. This method provided bicyclic products **423** that bear three contiguous

stereocentres, one of which is quaternary, in high levels of diastereo- and enantioselectivity.



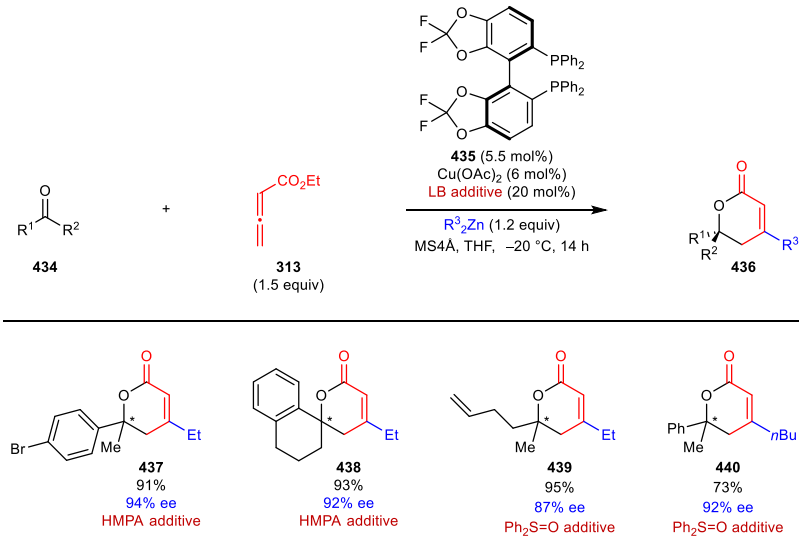
Scheme 61. Lam described the desymmetrisation of allenyl-cyclohexa-2,5-dienones.

Mechanistically (Scheme 62), transmetalation of Ni(II) catalyst provides arylnickel species **430**. After coordination of the allene and subsequent migratory insertion of the aryl group, the allylnickel species **432** performs a 1,4-allylation/desymmetrisation. Protonation of the nickel enolate **433** closes the catalytic cycle affording product **424**.



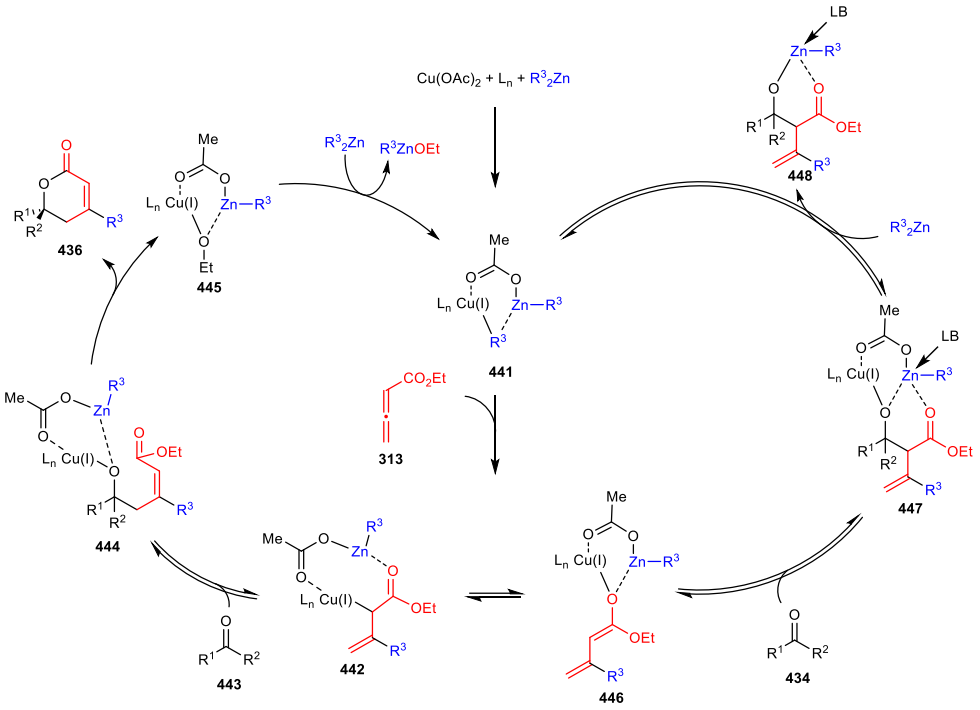
Scheme 62. Mechanism proposed by Lam.

Alkylative processes are less common than the arylative ones. One example was reported by the Shibasaki and Kanai's group where they managed to couple ketones **434**, allenoates **313** and dialkylzinc reagents to form lactones **436** in high yields and enantioselectivity (Scheme 63).[53]



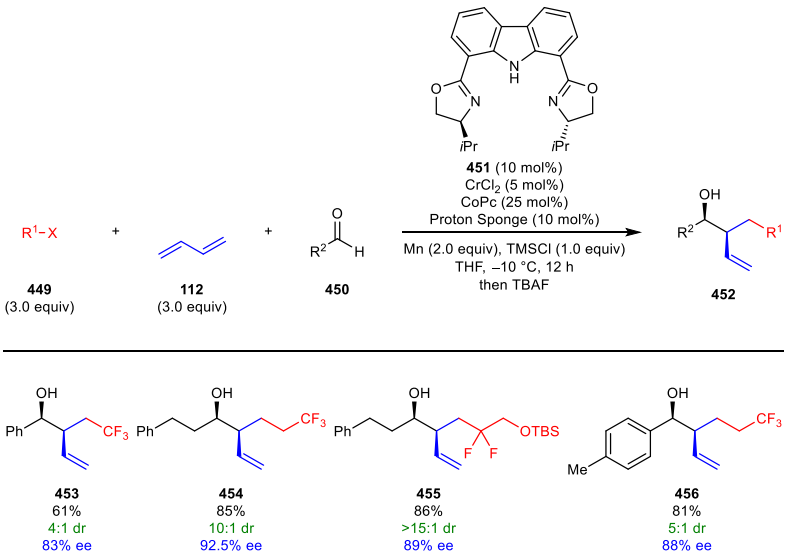
Scheme 63. Shibasaki and Kanai's copper-catalysed alkylative allylation of ketones.

The use of a Lewis base (LB) additive was necessary to obtain high selectivity for the linear product **436**. This additive has the function to reverse the equilibrium that leads to the aldol product **448** by binding the Zn (Scheme 64). The desired pathway encompasses formation of the Cu(I) catalytic active species **441**. Migratory insertion with allenoate **313** forms the enolate in the two forms **442** and **446** which are in equilibrium. This latter form reacts with the ketone **443** to form the copper-alkoxide **444** that irreversibly cyclises to form the product **436**. Transmetalation with another molecule of dialkylzinc closes the catalytic cycle.



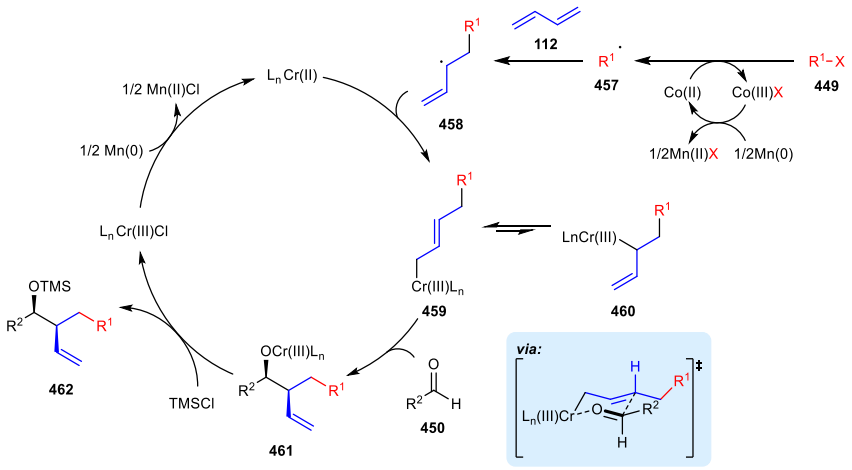
Scheme 64. The desired product can be obtained by controlling the reversible α-aldolisation process.

Lastly, it is worth noting the work by the Zhang group which reported the first enantioselective alkylation and hydroxyalkylation of 1,3-butadiene **112** through a radical pathway (Scheme 65).[54] This method used alkyl halides **449** and aldehydes **450** along with 1,3-butadiene **112** and even though the mechanism does not encompass a migratory insertion step, it provides the allylmetal species by a formal migratory insertion (*vide infra*). To obtain the best results, the group used a combination of Co(III)phtalocyanine (CoPc) and $CrCl_2$ catalysts. The products obtained showed high enantioselectivity and good to excellent diastereoselectivities and yields.



Scheme 65. Zhang reported the first enantioselective allylation of aldehydes with 1,3-butadiene through a radical pathway.

The mechanism proposed by Zhang is shown in Scheme 66. The cobalt catalyst forms the alkyl radical **457** which adds into the 1,3-diene **112** forming the more stable allyl radical **458**. Cr(II) catalyst traps the allyl radical **458** forming an allylCr(III) species that reacts with the aldehyde through a chairlike transition state. Stoichiometric TMSCl and Mn powder allow the turnover of the Cr(III) and Co(III) catalysts.



Scheme 66. Mechanism proposed by Zhang and co-workers.

In conclusion, enantioselective metal-catalysed nucleophilic allylation is a powerful tool in organic synthesis that provides products with highly valuable products. Increasing the complexity of the process by forming the allylmetal nucleophile *in situ* through migratory insertion gives increased value in terms of efficiency and sustainability. However, there are limited reports of these methods that form multiple C-C bonds in a cascade fashion and with high efficiency and enantioselectivity using cheap and earth-abundant metal catalysts. Furthermore, enantioselective nucleophilic allylation of ketones is even less available. Therefore, the development of further catalytic methods that deliver on these features, would be beneficial to the synthetic chemists.

2. Results and discussion

2.1. Enantioselective nucleophilic 1,2-allylation of ketones

2.1.1. Aims

Pyrrolidin-2-ones with a tertiary alcohol at C3 is a current motif in natural products such as pramanicin,[55] norsecurinamine A,[56] and cytochalasin Z_{10},[57] and also appears in herbicides[58] (Figure 1). Even though catalytic enantioselective methods providing benzannulated derivatives of this motif are widely described,[59] it is surprising that there is only limited precedence for the pyrrolidin-2-one with a tertiary alcohol at C3.[60] Therefore, new and more sustainable methods to provide this important scaffold in an enantioselective fashion will be beneficial to organic chemists.

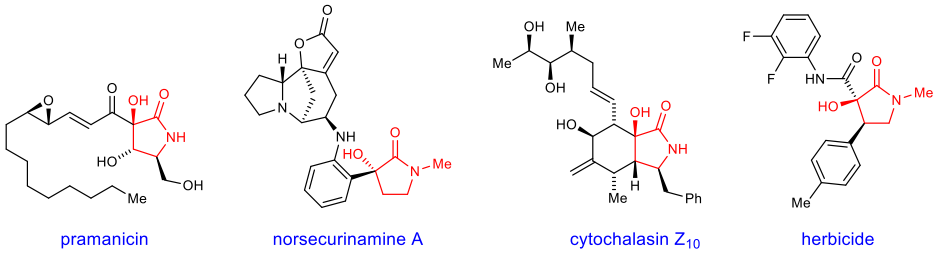
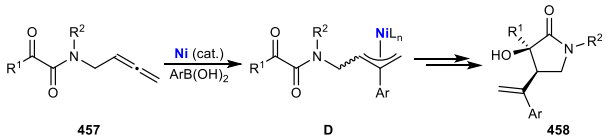


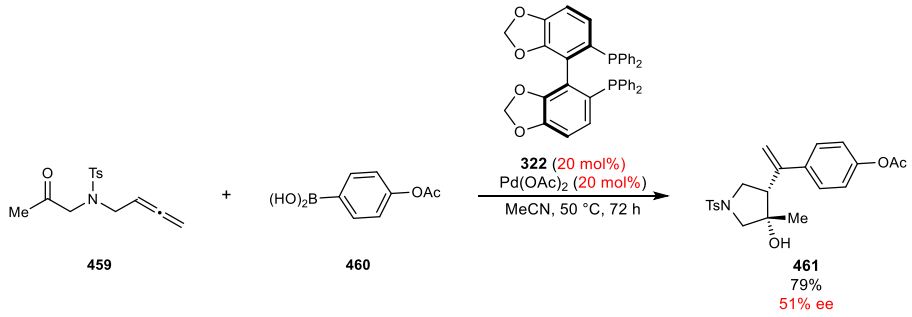
Figure 1. The occurrence of pyrrolidin-2-ones with a tertiary alcohol at the 3-position in natural products and herbicidal compounds.

On the basis of the ongoing work in the Lam group in enantioselective nucleophilic allylation,[61] we hypothesised that these chiral pyrrolidin-2-ones with a C3 tertiary alcohol might be prepared *via* a nucleophilic allylation of a ketone tethered to an allene under nickel catalysis (Scheme 67). Nickel-catalysed arylnickelation of the allene would give the allylnickel intermediate **D** that could perform a nucleophilic 1,2-allylation on the ketone to give the corresponding product **458**.



Scheme 67. Proposed synthesis of pyrrolidin-2-ones with a C3 tertiary alcohol.

A similar approach was used by the Tsukamoto[62a] and Lu[62b] groups, however, their methods used palladium catalysis and reactive allenals. Ketones are more challenging substrates to perform enantioselective allylation because they are significantly less reactive than aldehydes and the size difference between the substituents on either side of ketones is smaller compared to aldehydes. Unsurprisingly, the single example reported of the enantioselective allylation-cyclisation of the allenyl ketone **459** (Scheme 68) required harsher reaction conditions and provided modest enantioselectivity.[62a] Furthermore, in the broader picture of enantioselective nucleophilic allylations with allylmetal species formed through carbometallation, only a handful of examples can perform the reaction achieving high enantioselectivities.[63]



Scheme 68. Single example of enantioselective allylation-cyclisation of allenyl ketones.

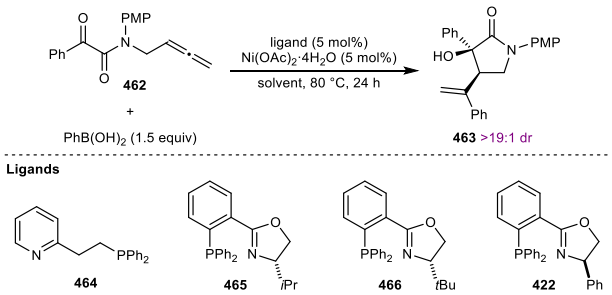
Considering the limited precedence and the difficulties associated with performing enantioselective nucleophilic additions of ketones, our aim was to develop a new way of making the pyrrolidin-2-one scaffold with a C3 tertiary alcohol with high enantioselectivity, using the cheap and earthabundant nickel as the catalyst.

2.1.2. Reaction optimisation

We started our study with the reaction of allenyl ketone **462**, $PhB(OH)_2$ (1.5 equiv) and $Ni(OAc)_2{\cdot}4H_2O$ (5 mol%) in MeCN/1,4-dioxane (3:2) at 80 °C for 24 h, which gave racemic **463** in 37% NMR yield as a single observable diastereoisomer (Table 1, entry 1). A better yield was obtained with the addition of 5 mol% of the *P*,*N*-ligand **464** (entry 2), whereas no reaction occurred without the nickel catalyst (entry 3). Pleasingly, we observed that the chiral (*S*)-*i*Pr-PHOX ligand **465** gave **463** in 55%

yield and 90% *ee* (entry 4). Improvements were made using (*S*)-*t*Bu-PHOX ligand **466** (78% yield and 98% *ee*, entry 5), and (*R*)-Ph-PHOX ligand **422** which gave similar results to ligand **465** (entry 6, compare with entry 4). We were pleased to find that using 2,2,2-trifluoroethanol (TFE) increased the yield significantly and a small reduction of enantioselectivity. Furthermore, the product **463** was obtained pure after filtration over a plug of silica gel from the reaction mixture with a reaction time of 7 h (entry 9).

Table 1. Evaluation of reaction conditions.[a]

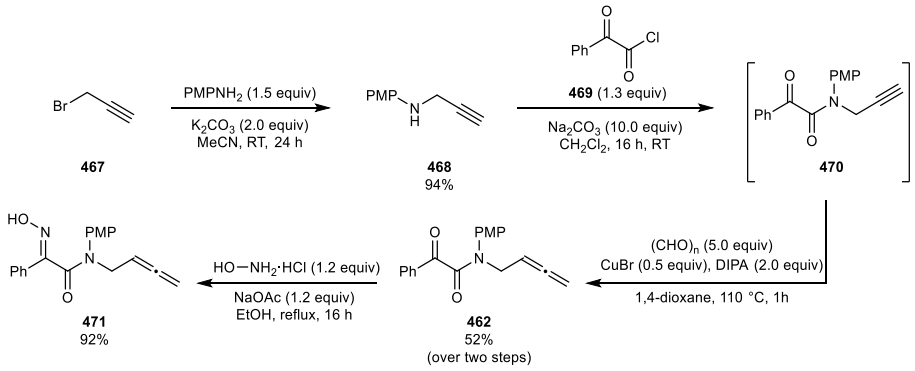


Entry	Ligand	Solvent(s)	Yield (%)	ee (%)
1	-	MeCN/1,4-dioxane (3:2)	37	-
2[d]	**464**	MeCN/1,4-dioxane (3:2)	77	-
3[e]	**464**	MeCN/1,4-dioxane (3:2)	-	-
4[d]	**465**	MeCN/1,4-dioxane (3:2)	55	90
5[d]	**466**	MeCN/1,4-dioxane (3:2)	78	98
6[d]	**422**	MeCN/1,4-dioxane (3:2)	61	–91[f]
7[d]	**466**	MeCN	78	98
8[d]	**466**	1,4-dioxane	59	98
9[g]	**466**	TFE	>99	96

[a] Reactions were conducted using 0.10 mmol of **462**. [b] Determined by ^{1}H NMR analysis of the crude reactions using 1,3,5-dimethoxybenzene as an internal standard. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Performed by Thi Le Nhon Nguyen. [e] Reaction conducted without $Ni(OAc)_2 \cdot 4H_2O$. [f] The major product was the enantiomer of **463**. PMP = *p*-methoxyphenyl. [g] Pure product after filtration over a plug of silica gel of the reaction mixture with a reaction time of 7 h.

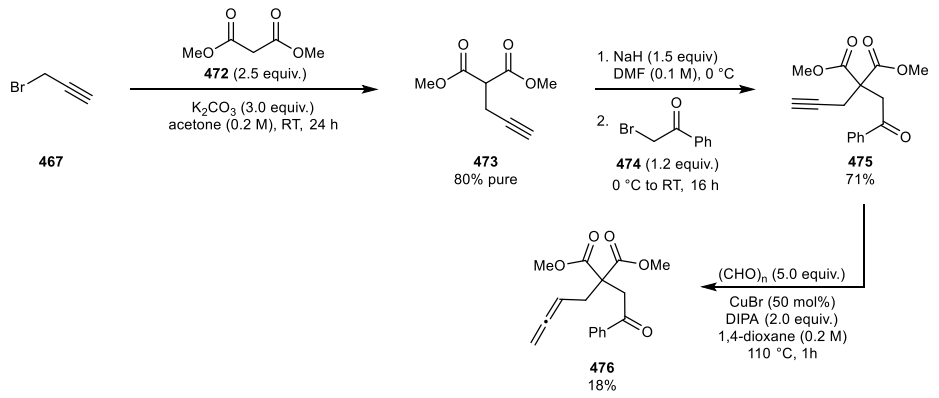
2.1.3. Synthesis of allenyl ketones starting materials

The synthesis of substrate **462** started with the propargylation of anisidine ($PMPNH_2$) using propargyl bromide and potassium carbonate to quench the hydrobromic acid formed, affording aniline **468** (Scheme 69). Amide bond formation with acyl chloride **469** formed *in situ*, provided amide **470** which, without purification by column chromatography, was subjected to the homologation reaction developed by Crabbé[64] providing allene **462** in 52% yield over two steps. Oxime **471** was synthesised from allenyl ketone **462** using hydroxylamine hydrochloride, with sodium acetate as the base in refluxing ethanol for 16 h.



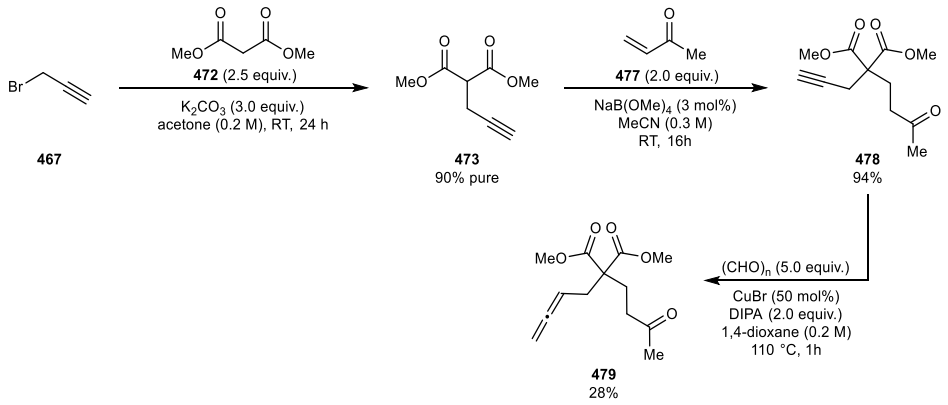
*Scheme 69. Synthetic route for compounds **462** and **471**.*

The malonate substrate **476** was synthesised in three steps starting with propargylation of dimethyl malonate using potassium carbonate as the base (Scheme 70). This reaction afforded a non-separable mixture of the mono-propargylated malonate **473** and the di-propargylated adduct (not shown). This mixture was subjected to alkylation conditions to provide alkyne **475** in 71% yield; subsequent homologation gave allene **476** in 18% yield.



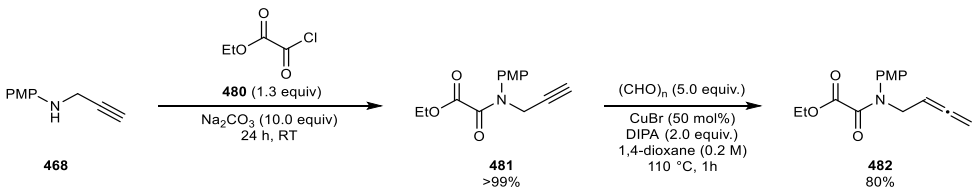
*Scheme 70. Synthetic route for compound **476**.*

The synthesis of malonate **479** started with propargylation of dimethylmalonate **472** (Scheme 71), and alkylation of this intermediate was achieved using the conditions developed by Echavarren and Cuerva,[65] providing alkyne **478**. Homologation of alkyne **478** provided allene **479**.



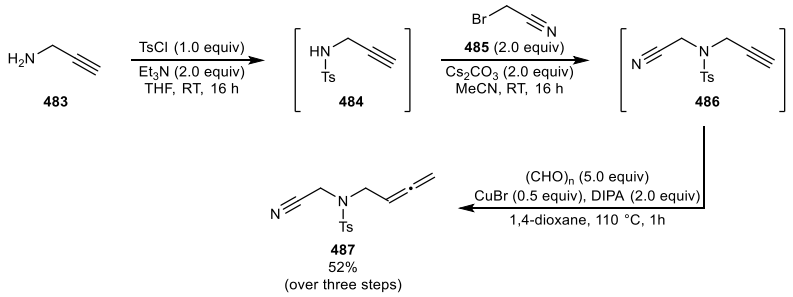
*Scheme 71. Synthetic route for compound **479**.*

Substrate **482** bearing an ester functional group was synthesised starting from amine **468** and commercial acyl chloride **480** providing alkyne **481**, which was subjected to the Crabbé homologation to afford allene **482** (Scheme 72).



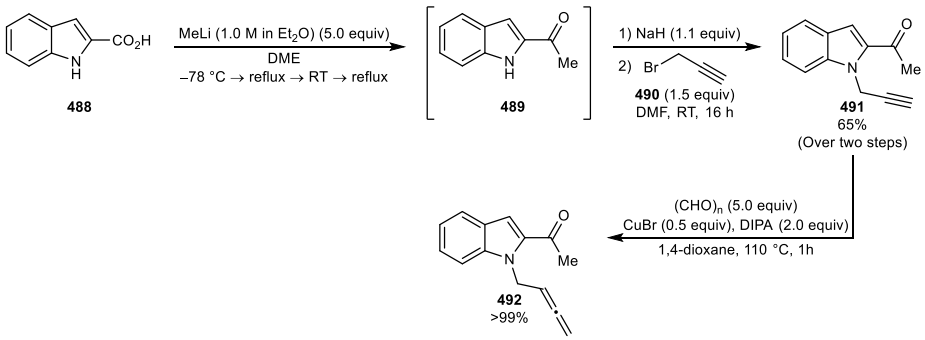
*Scheme 72. Synthetic route for compound **482**.*

The allene bearing the nitrile functional group **487** was obtained in three steps starting from propargyl amine **483** and tosyl chloride (Scheme 73). The sulfonamide **484** was alkylated with bromide **485** affording alkyne **486** which was subjected to homologation to afford allene **487** in 52% yield over three steps.



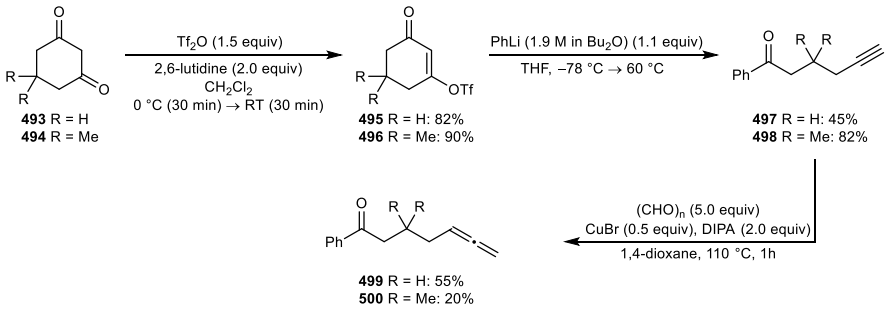
*Scheme 73. Synthetic route for compound **487**.*

Allene **492** bearing an indole moiety was prepared converting carboxylic acid **488** into ketone **489** using MeLi (Scheme 74). *N*-Propargylation of the indole moiety afforded alkyne **491** in 65% yield over two steps, which then was subjected to the homologation reaction to give allene **492** in quantitative yield.



*Scheme 74. Synthetic route for compound **492**.*

Allenes **499** and **500** with all-carbon backbones, required a different approach to be synthesised (Scheme 75). Starting from 1,3-cyclohexadienones **493** or **494** and using triflic anhydride, vinyl triflates **495** and **496** were obtained. These triflates were subjected to the fragmentation developed by Dudley[66] which afforded alkynes **497** and **498**. Finally, allenes **499** and **500** were made *via* Crabbé homologation.



*Scheme 75. Synthetic route for compounds **499** and **500**.*

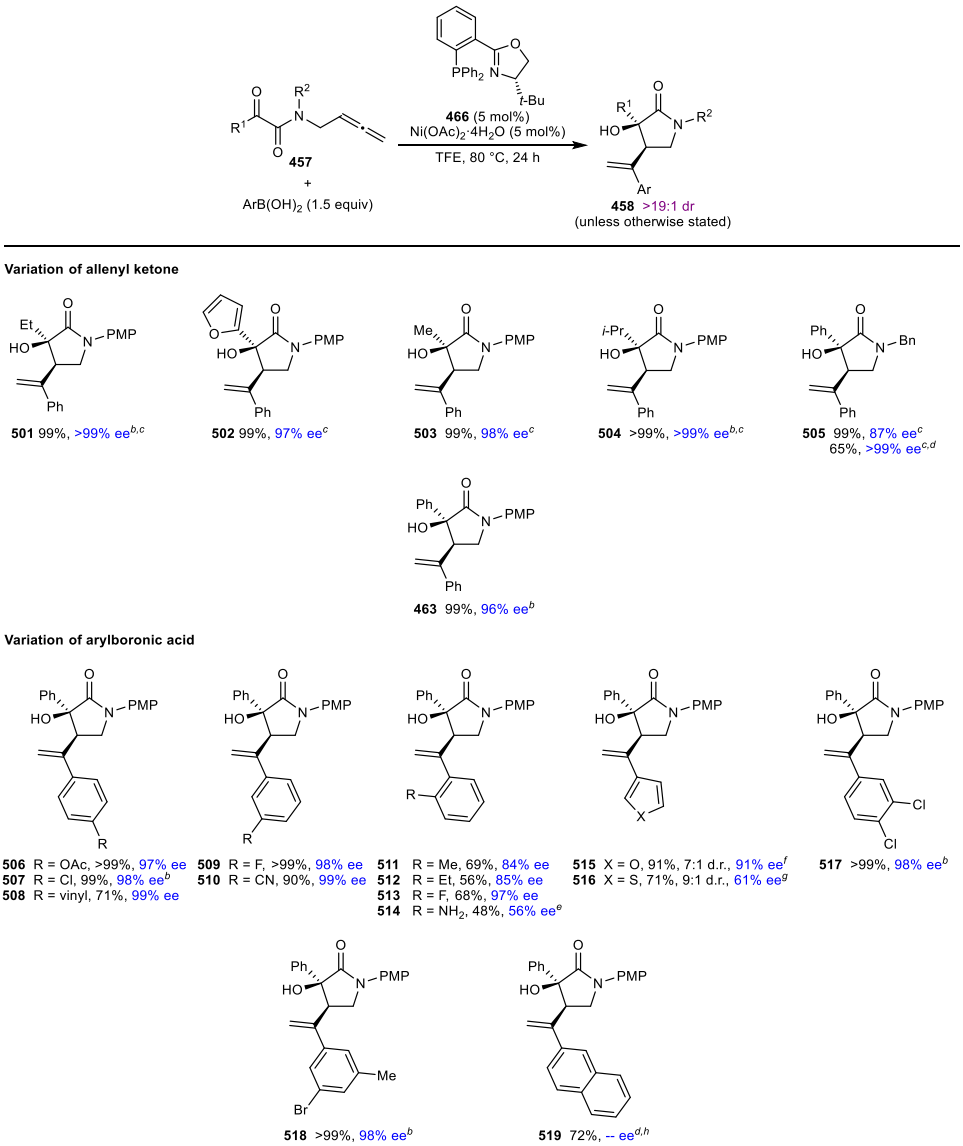
2.1.4. Scope and limitations

Having finalised the reaction conditions[67] and synthesised the starting materials, the scope of this method was explored towards the synthesis of different chiral pyrrolidin-2-ones (Table 2). Pleasingly, several allenyl ketones reacted successfully with $PhB(OH)_2$ to give pyrrolidin-2-ones **501**-**519** in quantitative or almost quantitative yields, as a single diastereomer and in excellent enantioselectivities (97 to >99% *ee*). With regard to the ketone substituent, phenyl (**463**), 2-furyl (**502**), alkyl (**501** and **503**), and branched alkyl (**404**) were well tolerated. Benzyl protecting groups on the nitrogen can be used with this chemistry, albeit product **505** was obtained in 87% *ee*. However, changing the solvent to MeCN afforded **505** in >99% *ee* albeit in 65% yield.

The reaction was also tolerant of additional arylboronic acids reacting with ketone **462** (Table 2). Several *para*- (**506**-**508**), *meta*- (**509**, **510** and **518**), *ortho*- (**511**-**514**), disubstituted (**517** and **518**) and naphthyl (**519**) arylboronic acids were successful reactants. Different functional groups on the phenylboronic acid are supported with this method, such as esters (**506**), halides (**507**, **509**, **513**, **517** and **518**), alkenes (**508**) and nitriles (**510**). Notably, heteroarylboronic acids also reacted to give **515** and **516**, albeit product **516** with thienylboronic acid gave lower enantioselectivity (61% *ee*).

These two examples were the only two instances where the minor diastereomer was detected (7:1 dr and 9:1 dr as determined by ^{1}H NMR analysis of the crude reaction mixture).

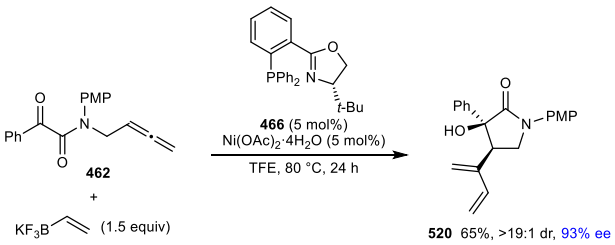
Table 2. Enantioselective synthesis of chiral pyrrolidin-2-ones. [a]



[a] Reactions were conducted using 0.30 mmol of **457.** Yields are of isolated products. Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reaction mixtures. Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase. [b] Pure product after filtration of the crude reaction mixture through plug of silica gel. [c] Performed by Thi Le Nhon Nguyen. [d] Conducted in MeCN instead of TFE. [e] Conducted using the pinacol boronate instead of the boronic acid. [f] The diastereomeric ratio of the crude reaction mixture was 7:1. Isolated as a 7:1 mixture of inseparable diastereomers. [g] The diastereomeric ratio of the crude reaction mixture was 9:1. Isolated as a 9:1 mixture of inseparable diastereomers. [h] The conditions to determine the enantiomeric excess were not found.

Noteworthy from a medicinal chemistry standpoint, this method sustains *N*-containing arylboronic esters in the *ortho*-position (**514**, 48% yield and 56% *ee*), since finding methods that tolerate nitrogen heteroatoms in biologically active molecules is a challenge in synthetic chemistry.[68]

Pleasingly, this process is not restricted to the use of (hetero)arylboronic acids and esters, as shown in Scheme 76, potassium vinyltrifluoroborate is a valuable coupling partner to provide 1,3-diene-containing pyrrolidin-2-one **520** in 65% yield and 93% *ee*.



Scheme 76. Notably, potassium vinyltrifluoroborate is tolerated with these reaction conditions.

Furthermore, compound **513** and **516** were characterised by X-ray crystallography, which allowed us to determine the absolute and relative stereochemistry. In particular, compound **516**, which bears a heavy atom such as sulfur, presents a Flack parameter value of 0.00(2) (Figure 2). If the value of the Flack parameter is close to 0 and with a small standard uncertainty value, such as the one shown by compound **516**, then the likelihood that the compound has the proposed absolute stereochemistry is high. It must be noted that the Flack parameter of compound **513** (see Crystal data on page 142) has a negative value of -0.09(9). This unrealistic value (Flack parameters are usually found to be between 0 and 1) must be taken with caution because the anomalous dispersion effect used to determine the Flack parameter is most effective when the crystal contains both lighter and heavier atoms. Therefore, the Flack parameter associated to compound **516** that bears also a heavy atom such as sulfur is more reliable than compound **513** bearing only lighter atoms.

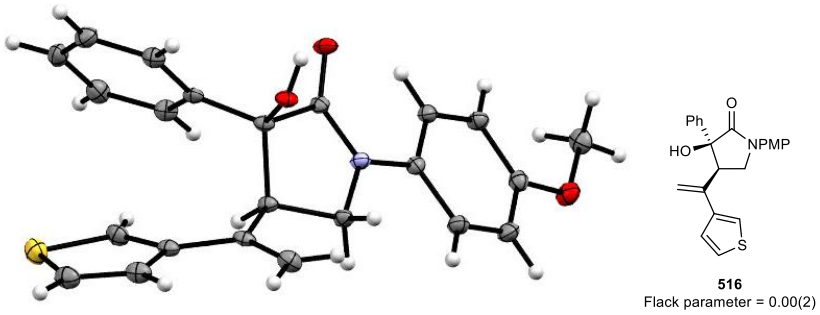
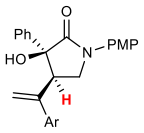
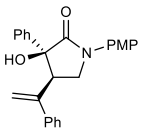
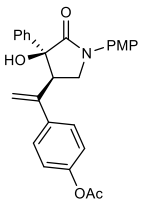


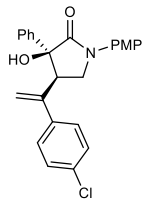
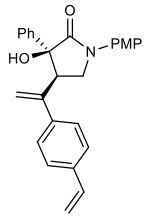
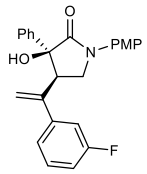
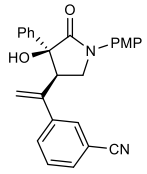
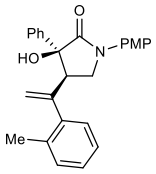
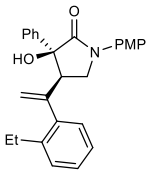
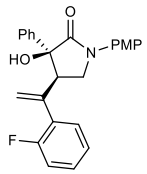
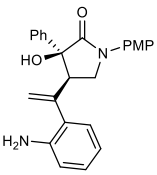
*Figure 2 compound **516** X-ray crystallography reveals absolute and relative stereochemistry of this compound.*

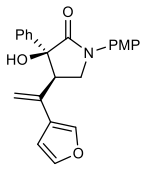
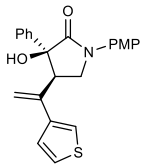
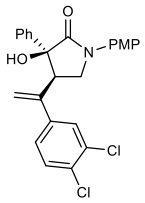
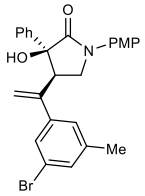
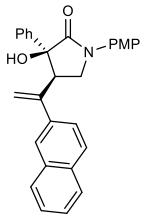
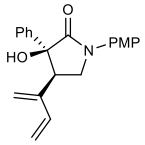
The absolute and relative stereochemistry of the other compounds were assigned by analogy. To understand whether the same diastereoisomer was obtained for all the compounds that were not analysed by X-ray crystallography, the significant ^{1}H NMR signals were tabulated and compared (Table 3). The signal of the proton highlighted in red in Table 3 was chosen since it's the closest to both stereocentres.

Table 3 ^{1}H NMR of the significant signals of each compound was analysed to justify the diastereomer obtained



Entry	Compound	Shift, multiplicity and *J* coupling constant (Major diastereomer)
1		3.79–3.73 (m)
2		3.70 (dd, *J* = 6.5, 4.9 Hz)

3		3.67 (t, *J* = 5.7 Hz)
4		3.79–3.72 (m)
5		3.73–3.67 (m)
6		3.65 (t, *J* = 5.9 Hz)
7		3.63–3.52 (m)
8		3.54 (t, *J* = 5.9 Hz)
9[a]		3.77 (dd, *J* = 6.6, 5.5 Hz)
10		3.70–3.63 (m)

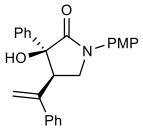
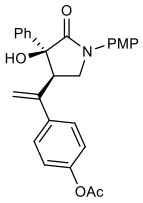
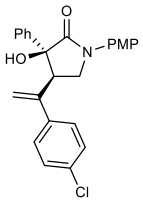
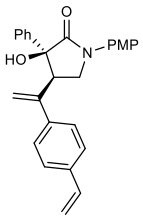
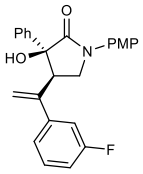
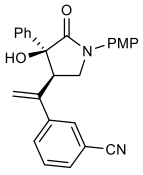
11[b]		3.57–3.49 (m)
12[a,b]		3.76–3.67 (m)
13		3.66–3.58 (m)
14		3.64 (t, *J* = 6.2 Hz)
15		3.88 (t, *J* = 5.9)
16		3.53 (dd, *J* = 6.8, 4.0)

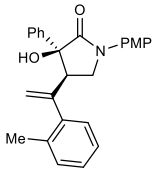
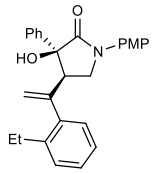
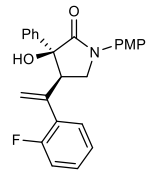
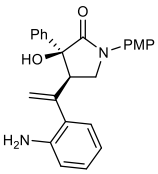
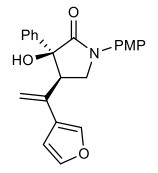
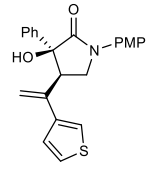
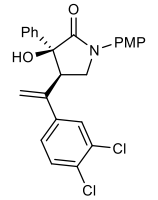
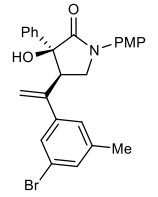
[a]X-ray structure available for these compounds; [b] Despite the fact that the other diastereoisomer of these compounds could be seen by ^{1}H-NMR, the characteristic signal was not possible to report since was overlapping with other signals in the spectrum.

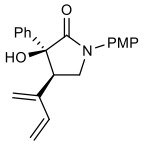
The data displayed in Table 3 shows that all the chemical shifts, multiplicity and *J* coupling constants of the characteristic signal are consistent. Therefore, it is likely that the diastereoisomer obtained in all these compounds is the one shown.

To have a more critical overview of the results obtained and to more easily observe anomalous results in the data, the stereochemical data relative to each of the products derived from varying the boronic acid were presented in Table 2:

Table 4: Results of the products derived from varying the boronic acid

Entry	Compound	$[\alpha]_D$	column	major enantiomer (elution)	*ee*	Stereochemical assignment
1		+ 16.0	IC	2nd	96%	3*S*,4*R*
2		+16.0	OD-H	2nd	97%	3*R*,4*S*
3		+12.0	IC	2nd	98%	3*S*,4*R*
4		+8.0	IC	2nd	99%	3*S*,4*R*
5		+28.0	IC	2nd	98%	3*S*,4*R*
6		+16.0	OD-H	2nd	99%	3*R*,4*S*

7		–10.0	IC	2nd	84%	3*S*,4*R*
8		+4.0	IC	2nd	85%	3*S*,4*R*
9		–12.0	IC	2nd	94%	3*S*,4*R*
10		–6.0	OD-H	1st	56%	3*S*,4*R*
11		+48.0	OD-H	2nd	91%	3*S*,4*R*
12		+36.0	OD-H	2nd	61%	3*S*,4*R*
13		+8.0	IC	2nd	98%	3*S*,4*R*
14		+20.0	IC	2nd	98%	3*S*,4*R*

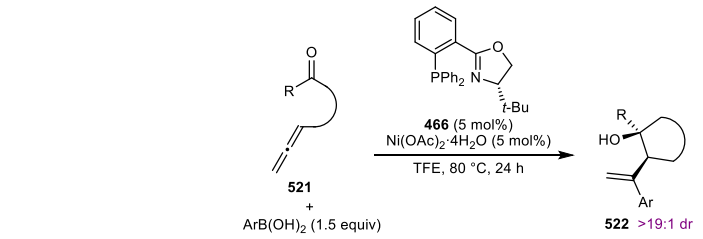
15		+92.0	OD-H	2nd	93%	3*S*,4*R*

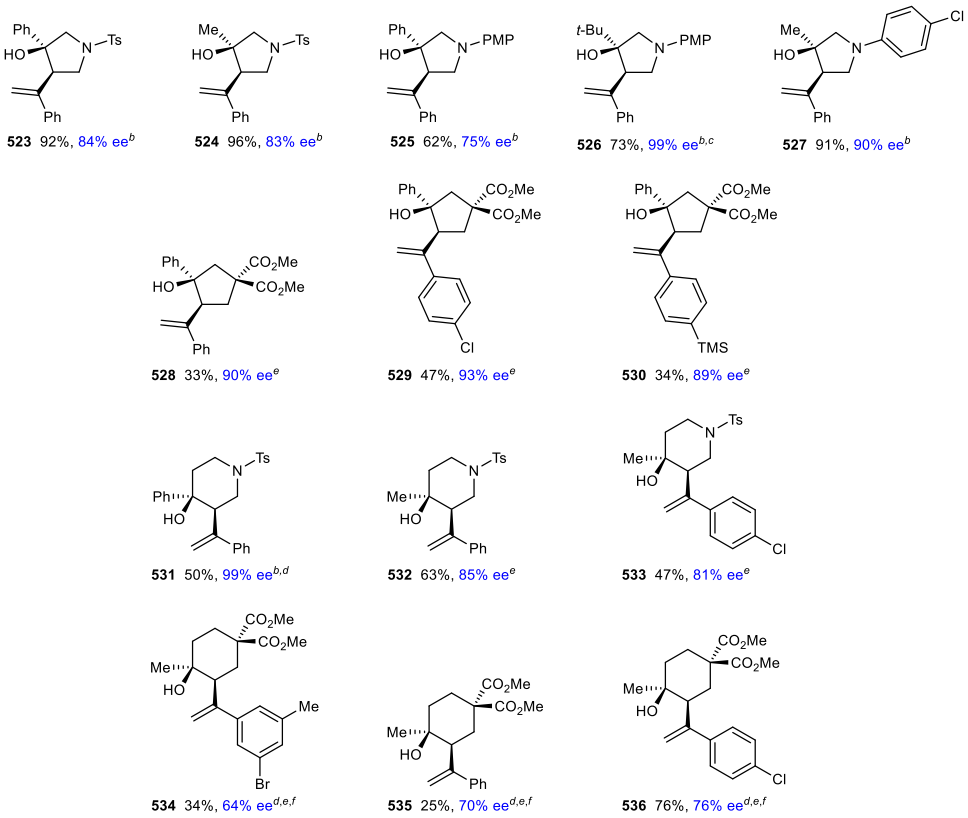
In most cases the $[\alpha]_D$ value is positive (Table 4), however three entries (Entry 7, 9 and 10) show a negative value. These three entries all possess an *ortho*- substituent on the aryl, which may affect the rotation of the plane-polarised light (with the exception of the ethyl group in Entry 8). However, in the case of the *ortho*-aminophenyl group (Entry 10), not only is the value of the optical rotation negative, but the order of elution of the minor and major enantiomers are reversed when compared to the other entries. These observations might suggest that, in the case of compound **514**, the absolute stereochemistry (3*S*,4*R*) of this compound must be taken with caution. Therefore the acquisition of an X-ray structure can be helpful in determining the absolute stereochemistry of compound **514**.

Another interesting feature shown in this table is that the lowest enantiomeric excesses were obtained with *ortho*-aminophenyl (Entry 10) and the 3-thienyl (Entry 12) substituents. One possible explanation for this behaviour is that the nitrogen of the amino group and the sulfur of the thiophene can coordinate to the nickel catalyst and hamper the enantioinduction in the enantiodetermining step.

Once the robustness of the process was established with regard to the boronic acid coupling partners and the substituent flanking the ketone, we tested the applicability of this chemistry towards the synthesis of other scaffolds. We were pleased to discover that different types of aza- and carbocycles were synthesised, which were obtained from 25-96% yield and in 75-99% *ee* (Table 5). In some cases, MeCN proved to be a better solvent than TFE (**528**-**530** and **532**-**536**). Pyrrolidines (**523**-**527**), cyclopentanes (**528**-**530**), piperidines (**531**-**533**) and cyclohexanes (**534**-**536**) were synthesised. Different nitrogen-protecting groups, such as tosyl (**523**, **524**, **531**-**533**), *para*-methoxyphenyl (**525** and **526**), *para*-chlorophenyl (**527**), were tolerated. With regard to the substituent on the ketone, methyl (**524**, **527**, **532**-**536**), *tert*-butyl (**526**) and phenyl (**523**, **525**, **528**-**531**) were compatible.

Table 5. Further exploration of substrate scope.[a]

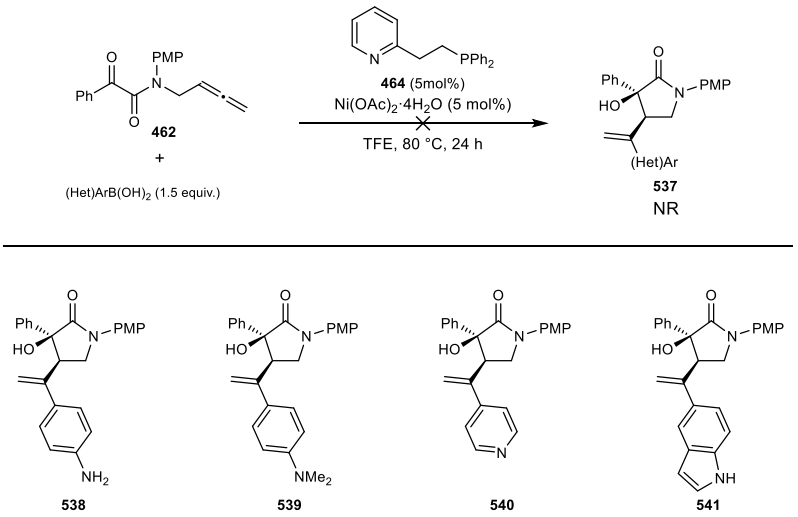




[a] Reactions were conducted using 0.30 mmol of **521.** Yields are of isolated products. Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reaction mixture. Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase. [b] reaction conducted by Thi Le Nhon Nguyen. [c] A 7.7:1 inseparable mixture of **526** and the starting allene was obtained (the yield of **526** has been adjusted accordingly). [d] The reaction time was 48 h. [e] Using MeCN as the solvent in place of TFE. [f] Conducted using 10 mol% each of $Ni(OAc)_2·4H_2O$ and **466**.

With reagrd to the limitations of this chemistry, *N*-containing (hetero)arylboronic acids presented in Table 6 are not compatible with this method.

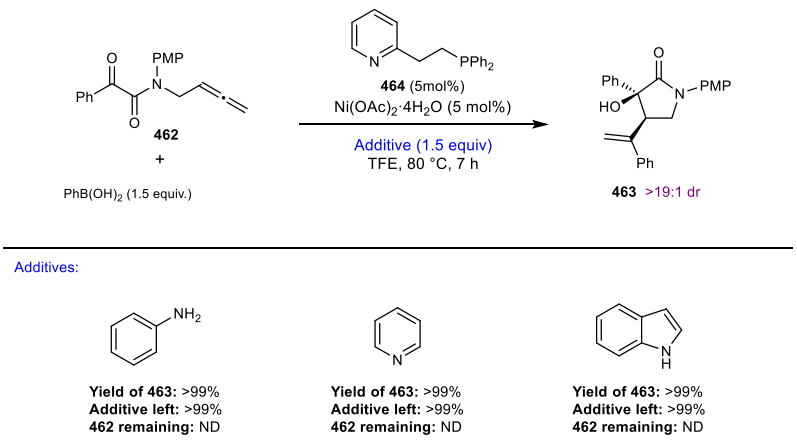
Table 6. Heteroarylboronic acids not tolerated.[a]



[a] Reactions were conducted using 0.05 mmol of **462**.

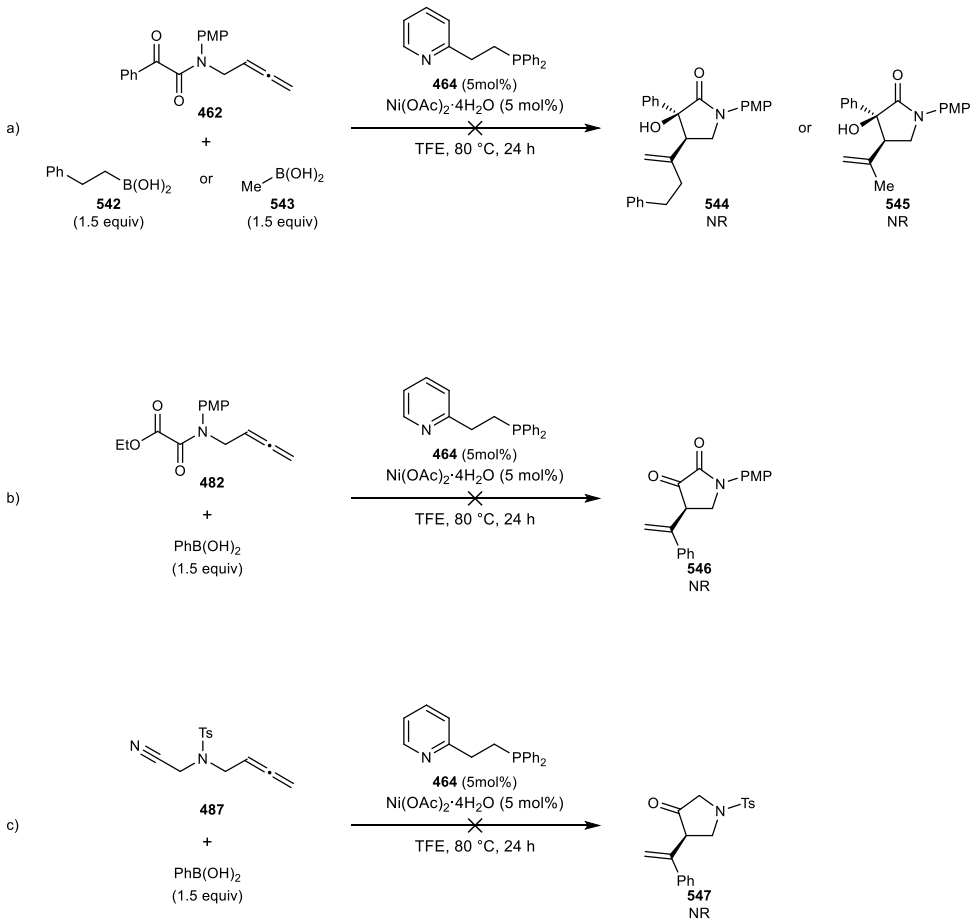
Two possible justifications for the negative outcome of the reactions shown in Table 6 can be either the instability of the boronic acids or the low tolerance of the catalytic system to the Lewis acidic nitrogen. Therefore, to get further understanding on the versatility of this chemistry, the robustness screening developed by Glorius[69] was tested (Table 7). Pleasingly, the reactions with **462** and phenylboronic acid in the presence of each additive, gave the same results as the reaction without the additive (compare with Scheme 67, entry 9) with full recovery of this latter compound. With these results in hand, it is probable that the limitation presented in Table 1 can be attributed to the poor stability of the boronic acids exposed to the reaction conditions and not to the intolerance to the nitrogen present in the reaction mixture.

Table 7. Robustness screening for the compatibility of N-containing arylboronic acids.



Reactions were conducted using 0.10 mmol of **462**. Yields and additive recovered determined by ^{1}H NMR analysis of the crude reactions using 1,3,5-dimethoxybenzene as an internal standard. Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reaction mixture.

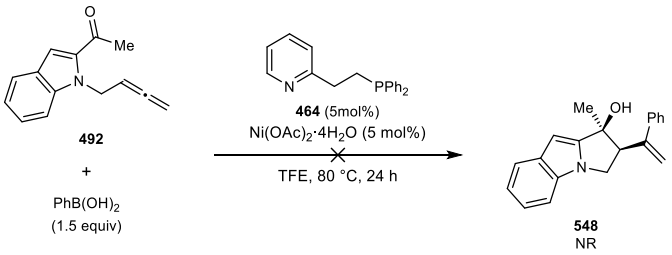
Further limitations are depicted in Scheme 77. C(sp^3)-boronic acids such as **542** and **543** are not suitable coupling partners (Scheme 77a); furthermore the 1,2-allylation failed on esters **482** (Scheme 77b) and nitriles **487** (Scheme 77c), presumably because of their less reactive nature.



Scheme 77. The method is not compatible with a) C(sp^3)-boronic acids; b) allylation of esters; c) allylation of nitriles.

We tried to obtain tricyclic compound **548** using our enantioselective nucleophilic allylation strategy, however only starting material was recovered (Table 8). It was considered that the electron-rich indole can lower the electrophilicity of the ketone, therefore Lewis acids such as $ZnCl_2$, $Sc(OTf)_3$, as well as the Brønsted acid AcOH were tried without any success.

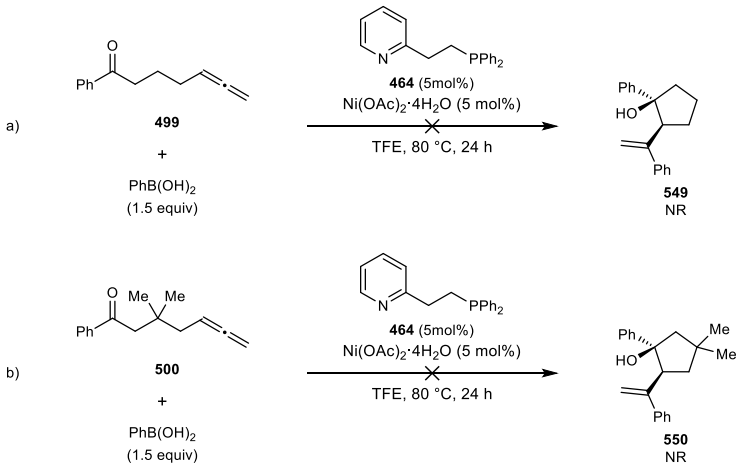
Table 8. Synthesis of complex tricyclic molecule was tried.[a]



Entry	Deviation from standard conditions	Yield (%)
1	$ZnCl_2$ (1.0 equiv) additive	-
2	$Sc(OTf)_3$ (10 mol%) additive	-
3	AcOH (1.0 equiv) additive	-

[a] Reactions were conducted using 0.05 mmol of **492.**

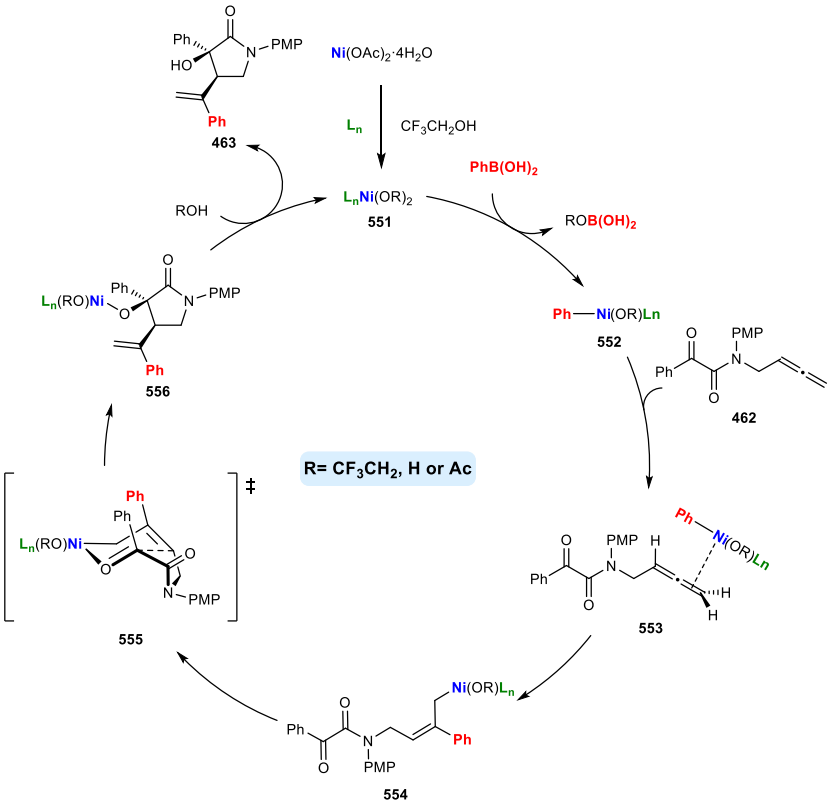
A negative yet interesting result was obtained with the all-carbon allenyl ketones **499** and **500** in Scheme 78. None of these compounds provided the desired product and the starting material was fully recovered, suggesting that a heteroatom is required in the skeleton of the allenyl ketone. Furthermore, since compound **500** (Scheme 78b) was also unreactive, it is thought that the Thorpe-Ingold effect does not play a pivotal role in the reactivity of these scaffolds. A similar trend was observed already in palladium catalysis where the authors proposed that the heteroatom coordinates the catalyst stabilising the intermediate formed.[70]



Scheme 78. A heteroatom is required to obtain the cyclisation.

2.1.5. Possible mechanism

A possible mechanism is shown in Scheme 79. Precatalytic $Ni(OAc)_2 \cdot 4H_2O$ forms the active catalyst **551** which performs a transmetallation with phenylboronic acid to form phenyl-nickel compound **552**. This latter coordinates to the allenyl ketone **562** and the π-bond inserts into the Ni-Ph bond. This step is performed with the nickel approaching from the less hindered face of the allene (**553**) to provide (*Z*)-allylnickel species **554**. Nucleophilic allylation through a closed-shell chair-like transition state **555** provides the nickel-alkoxylate **556** that upon protonation affords the product **563** and regenerates the catalyst.

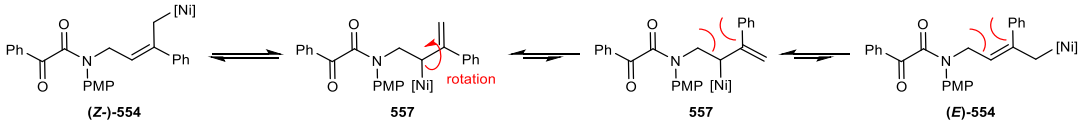


Scheme 79. Possible catalytic cycle.

The diastereo- and enantiodetermining nucleophilic allylation step is thought to go through a Zimmerman-Traxler transition state,[71] consistently with the Type III allylations discussed in the introduction (Paragraph 1.1) A stereochemical model to justify the diastereo- and enantioselectivity of the process must take into account three factors: firstly the geometry of the double bond of the allylnickel species **554**,

secondly the relative position of the two phenyl groups in the chair-like transition state **555** and finally which enantiotopic face of both the allyl and the ketone reacts.

With regard to the geometry of the double bond, once the migratory insertion step occurs from the less hindered face of the allene, the (*Z*)-allylnickel compound **(*Z*)-554** is formed. This compound can isomerise to the (*E*)-allyl-nickel diastereoisomer **(*E*)-554** through a σ–π–σ-isomerisation, however this latter isomer is less favoured due to the steric hindrance (Scheme 80). Therefore, the reactive geometry of the double bond in the stereodetermining step is the (*Z*)-allylnickel diastereoisomer **(*Z*)-554**.



Scheme 80. Isomerisation that favours the (Z)-allylnickel species.

Concerning the relative position of the two phenyl groups, the nucleophilic addition is thought to go through an intramolecular chair-like transition state **555** which forms a 5,6-bicyclic structure. It is well known that the *cis*-5,6-fused bicyclic compound are more stable than the *trans* ones due to the higher strain. Based on this feature, it is reasonable to infer that the *cis*-5,6-bicyclicliike transition state **555** (Scheme 79) is lower in energy than the *trans*. Therefore, the two phenyl groups are likely to be *cis* in the diastereo- and enantiodetermining step.

Lastly, which enantiotopic face of both the allyl and ketone groups react is dependent on the *trans*-influence of the phosphorous and nitrogen atoms binding the nickel. The *trans*-influence has been defined as "the extent to which a ligand weakens the bond *trans* to itself".[72]

R_3P has a higher trans influence than R_3N,[73] which means that the bond between the allyl and nickel is the one *trans* to the phosphorous and it is believed that the enantiotopic faces reacting are those where the steric clash with the *tert*-butyl group and the phenyl are minimised (Figure 3).

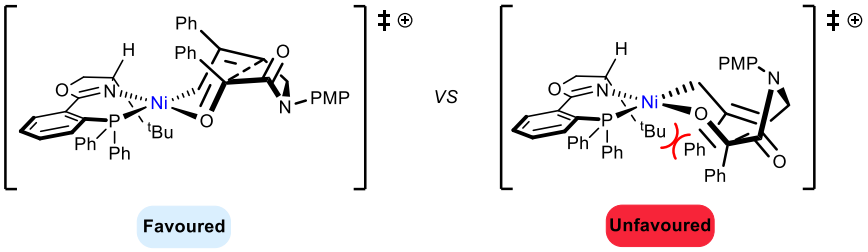


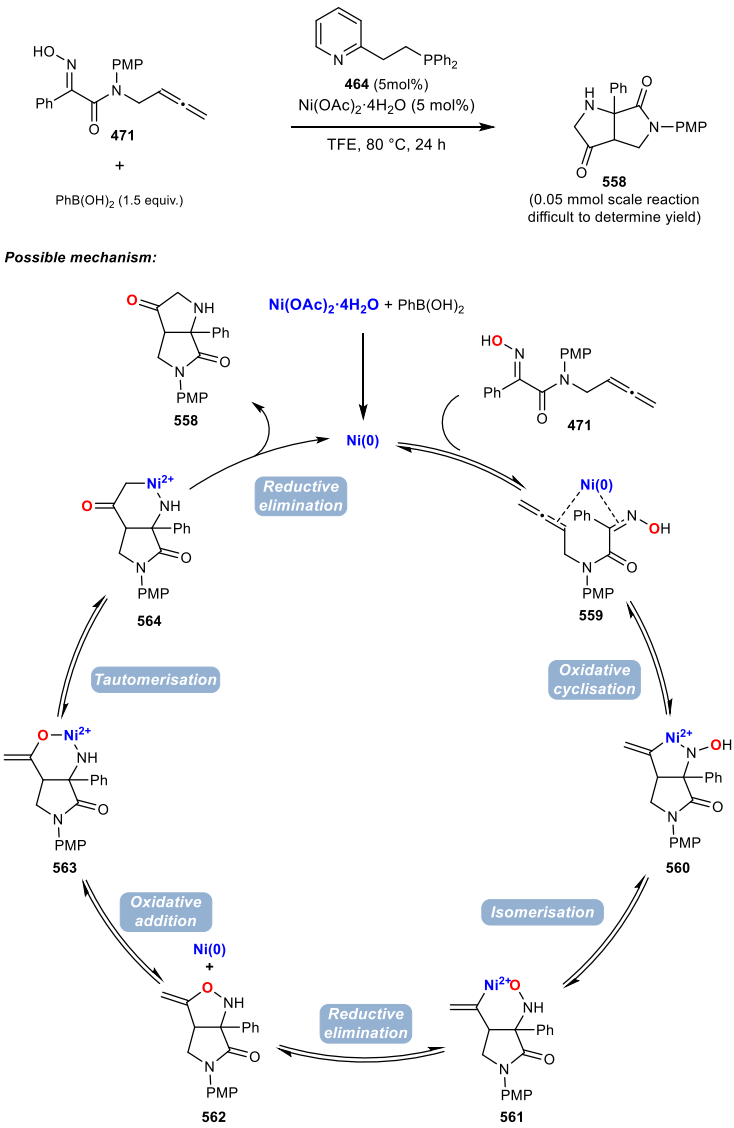
Figure 3. Possible stereochemical model to account for the observed enantiomer formed.

It should be also noted that the two transition states envisaged are cationic species. It is known that more polar solvents such as TFE [E^N_T = 0.898, where E^N_T (Me_4Si) = 0 and E^N_T (water) = 1][74] facilitate the dissociation of the acetate anion from metal centres making the metal more cationic.[75]

Nevertheless, different hypotheses about the rationale for the observed enantioselectivity cannot be ruled out at this stage and DFT calculations should be undertaken to prove this hypothesis.

2.1.6. Unexpected result with oxime starting material

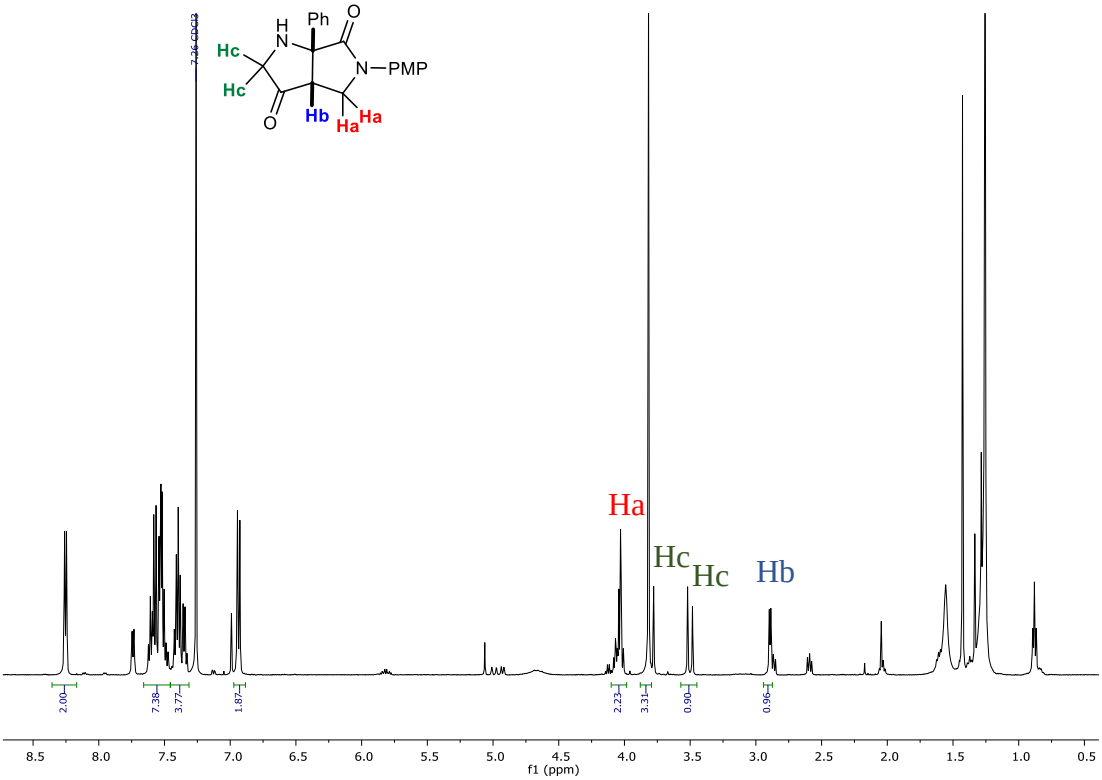
To expand the substrate scope of this method, oxime **471** (Scheme 81) was synthesised and subjected to the reaction conditions with achiral ligand **464**. Notably, the bicyclic product **558** was obtained instead of the γ-lactam obtained with the other substrates. A possible mechanism for this interesting rearrangement is depicted in Scheme 81, where the nickel(II) precatalyst is reduced to nickel(0) by the phenylboronic acid. Coordination of the allenyloxime **571** to the nickel(0) and subsequent oxidative cyclisation forms the 5-membered nickelacycle **560**. Isomerisation of the cycle to form the 6-membered nickelacycle **561** and reductive elimination form nickel(0) and the bicyclic structure **562**. The N-O bond oxidises nickel(0) to form intermediate **563**, subsequent tautomerisation and reductive elimination closees the catalytic cycle to form product **558**.



Scheme 81. Unexpected product obtained starting from the oxime tethered to the allene and possible mechanism.

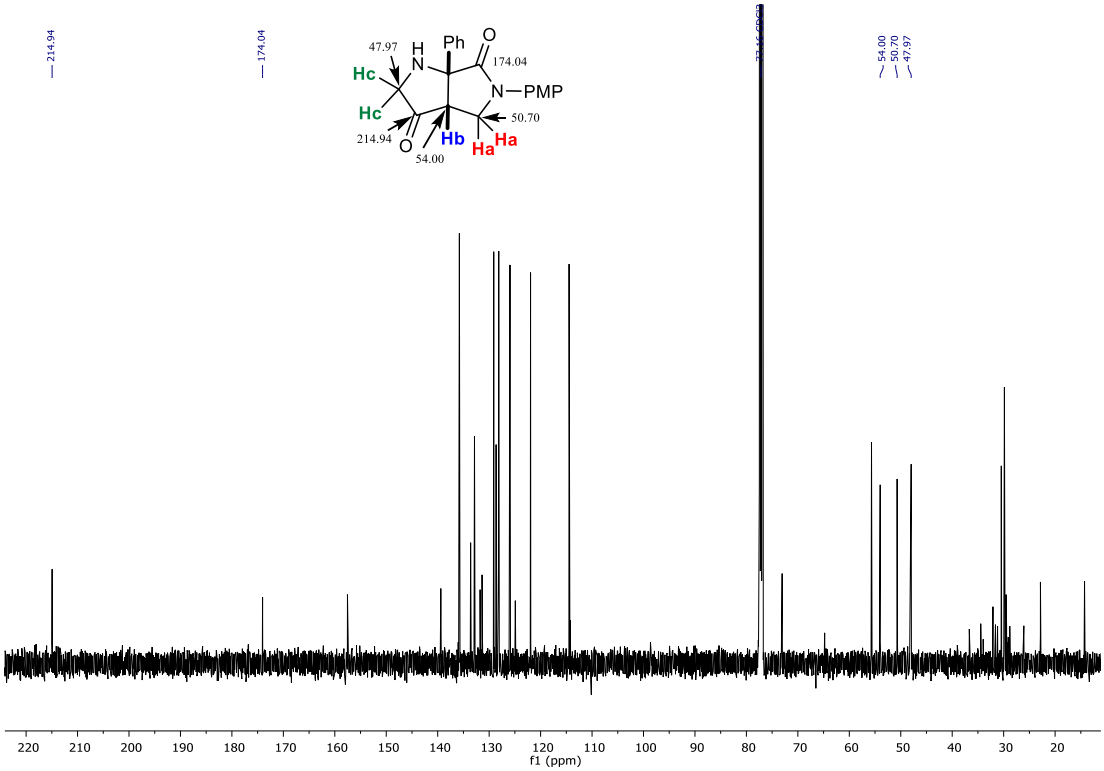
This test reaction was carried out at 0.05 mmol scale and, due to time constraints, could not be repeated. Therefore, further work will be pursued to optimise the reaction conditions and to make the bicyclic compound enantioselectively. Nevertheless, the 0.05 mmol scale was good enough to determine the structure of the bicyclic product **558** *via* 2D NMR analysis.

^{1}H-NMR



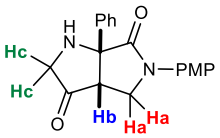
Chemical shifts of the distinctive protons are consistent with the structure. Both diastereotopic protons Ha next to an electronegative amidic nitrogen (around 4 ppm); Hc next to an electronegative nitrogen and a carbonyl (around 3.5 ppm) and Hb next to a carbonyl (between 2 and 3 ppm).

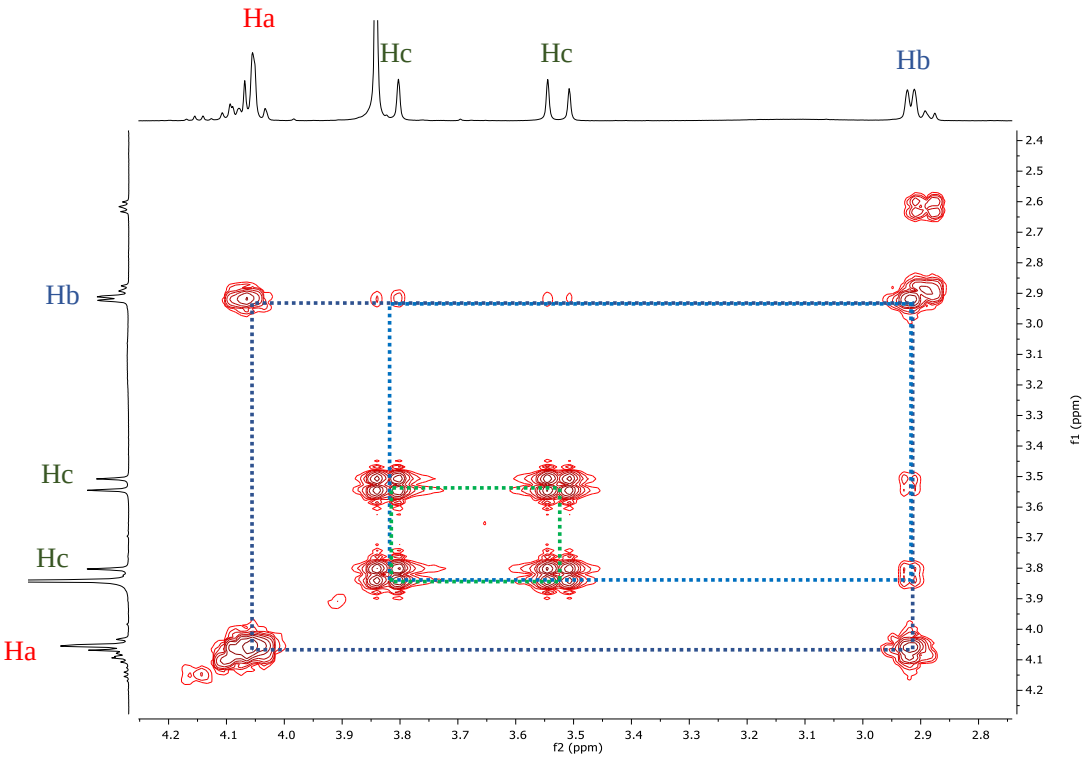
^{13}C-NMR



Highlighted are the distinctive peaks of the structure: 214.9 (C=O in a five-membered ring); 174.0 (C=O of a γ-lactam); Ha, Hb and Hc between 40 and 60 ppm, consistent with the shifts of aliphatic ^{13}C next to electronegative functional groups. Analysis of HSQC spectrum helped in assign the peaks.

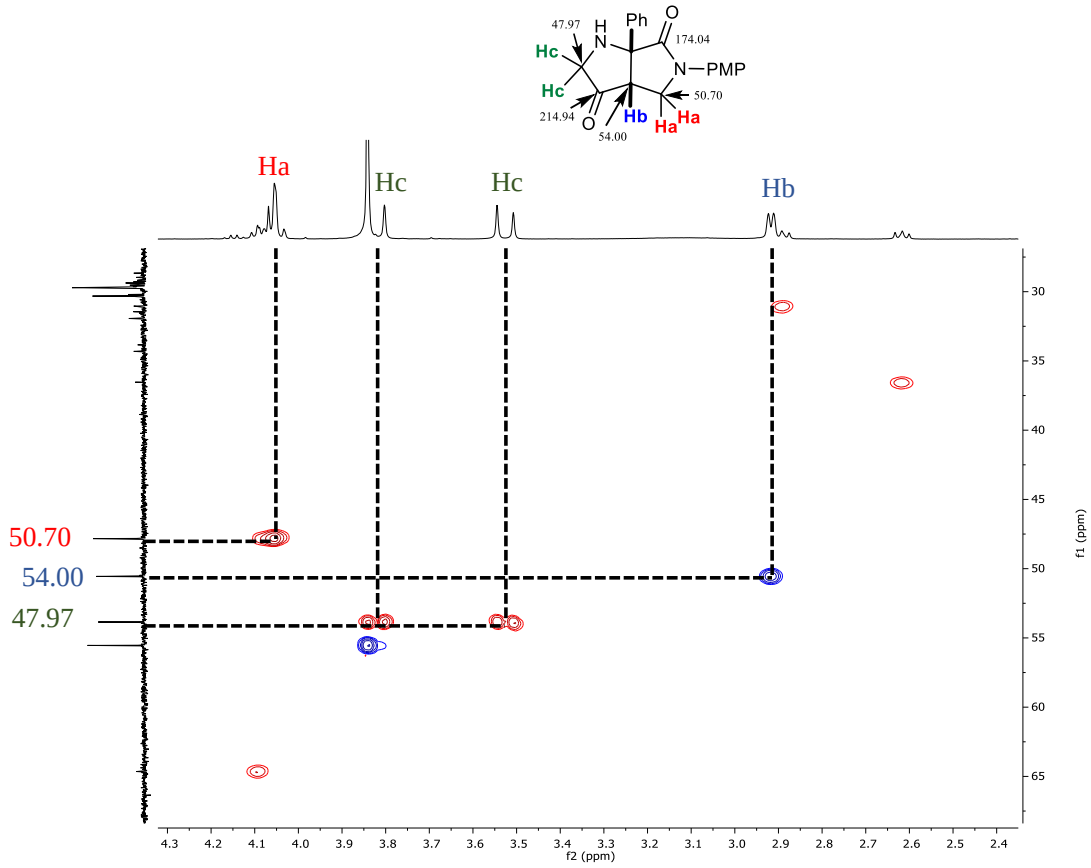
COSY





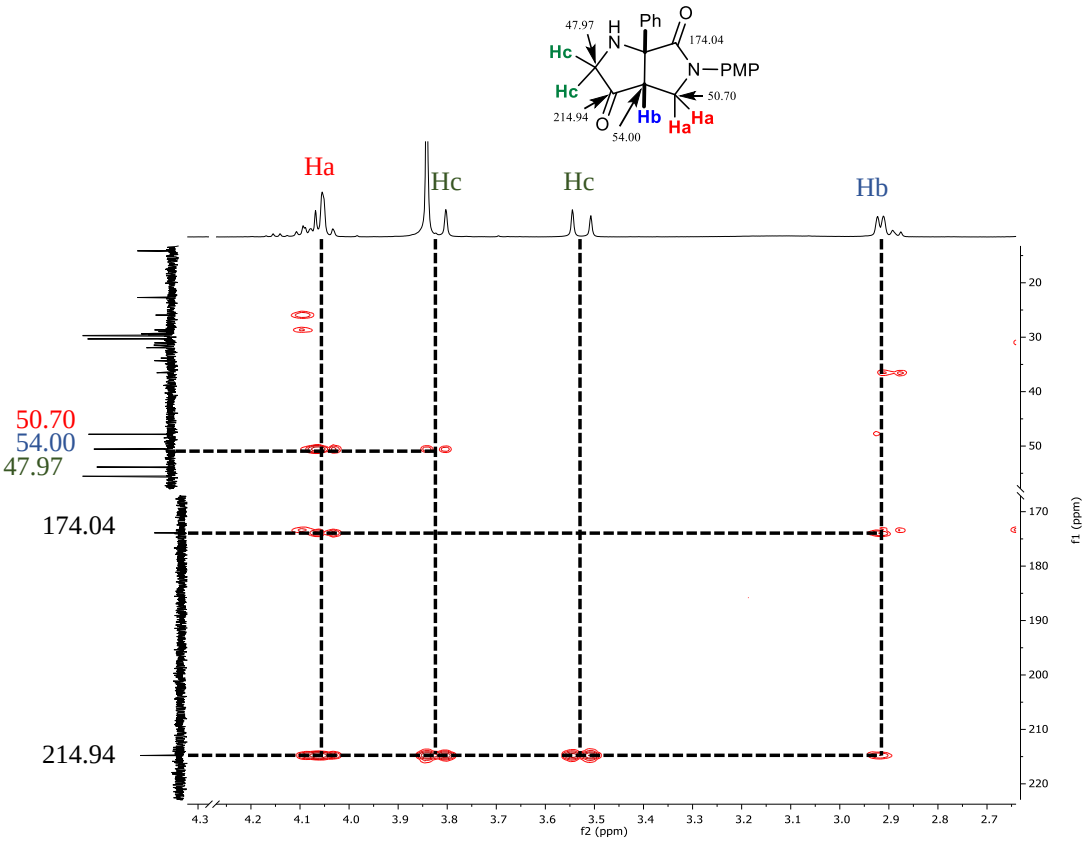
With the COSY spectrum it is possible to note that: Ha has a strong interaction with Hb; the two doublets of each proton Hc interact strongly between themselves and have also a weak interaction with Hb; whereas, there is no interaction between Ha and Hc.

HSQC



With the HSQC spectrum it is possible to assign the signals of the carbons bearing the distinctive protons.

HMBC



Analysing the HMBC spectrum it can be noted that Ha has a J_3 interaction with both the ^{13}C of the amidic carbonyl and of the ketone, plus, it has a J_2 interaction with the ^{13}C bearing Hb; Hc has a J_2 interaction with the ^{13}C of the ketone and a small J_3 interaction with the ^{13}C bearing Hb; Hb has a J_4 interaction with the ^{13}C of the amidic carbonyl and a J_2 interaction with the ^{13}C of the ketone.

2.2. Progress towards the nucleophilic 1,4-allylation-desymmetrisation of ketones

2.2.1. Aims

Cis-fused hexahydroindol-5-ones and hexahydrobenzofuran-5-ones are important core structures that appear in several natural products such as runanine,[76] acutumine,[77] millingtonine[78] and cryptocaryone[79] (Figure 4).

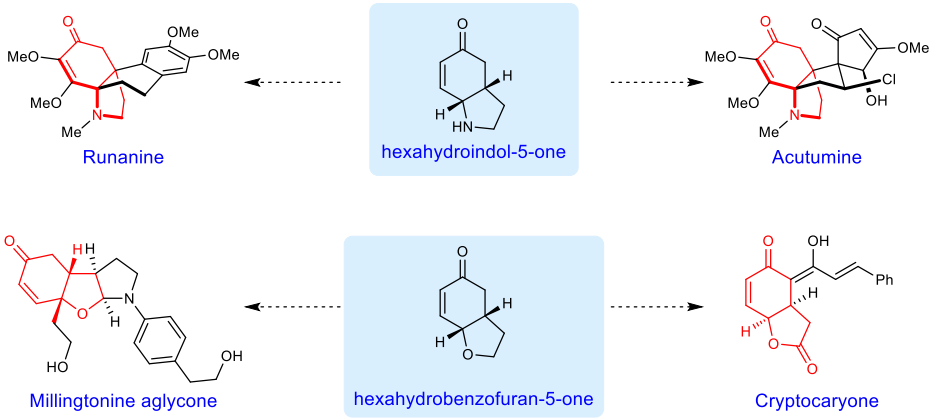


Figure 4. Cis-fused hexahydroindol-5-one and hexahydrobenzofuran-5-one structures found in natural products.

Compared to the metal-catalysed nucleophilic 1,2-allylation, the enantioselective 1,4-addition of allylmetal nucleophiles is considerably underdeveloped.[80] Therefore, the discovery of new catalytic enantioselective 1,4-allylations will provide highly valuable alternatives for the synthesis of organic molecules.

Our group has reported the only enantioselective, metal-catalysed 1,4-allylation initiated by a carbonickelation of allenes (Figure 5).[80i] A chiral phopshinooxazoline-nickel complex was highly effective in promoting this desymmetrisation, coupling allenyl ketones such as **431** with arylboronic acids.

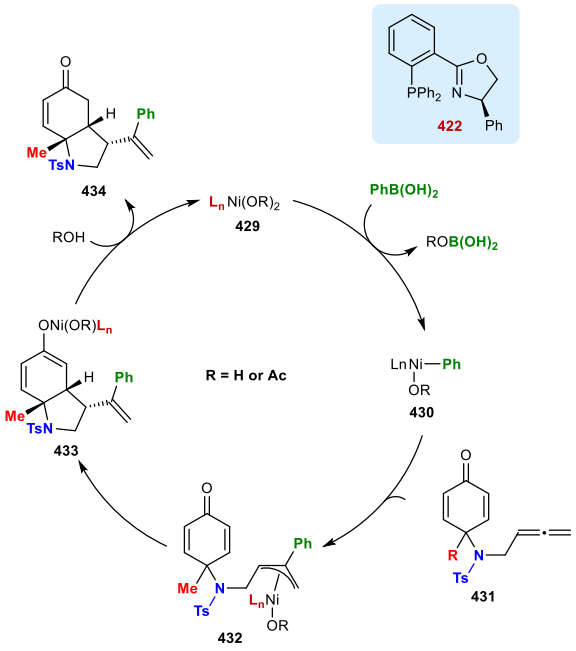


Figure 5. Our group reported the desymmetrisation of allenyl-cyclohexa-2,5-dienones through nucleophilic 1,4-allylation.[80i]

We questioned whether we could expand the utility of this chemistry to C(sp^3) organometallic nucleophiles, such as dialkylzinc reagents, as coupling partners, preserving the high diastereo- and enantioselectivity. The key step will be the formation of the allylmetal species formed through migratory insertion of the allene into the catalyst-C(sp^3) bond forming intermediate **E**. Cyclisation *via* nucleophilic 1,4-allylation will give the desired *cis*-fused 6,5-bicycle **566** (Figure 6).

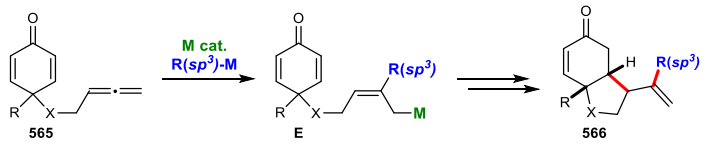


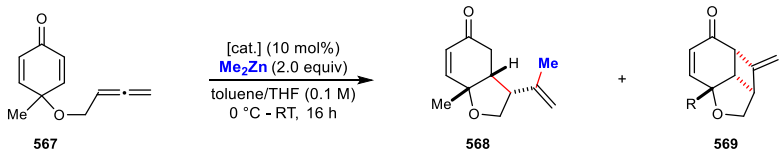
Figure 6. Proposed synthesis of cis-fused hexahydroindol-5-one and hexahydrobenzofuran-5-one.

2.2.2. Reaction optimisation

Our investigation began with the reaction of allenyl cyclohexadienone **567**, with dimethylzinc (2.0 M in toluene) (2.0 equiv) in the presence of $Ni(acac)_2$ (10 mol%) in THF at 0 °C for 16 h (Table 9).[81] Pleasingly, we noticed that the reaction proceeded in full conversion and the 6,5-bicycle **568** was obtained, albeit in 1:10 ratio favouring

the cyclobutene byproduct **569** (Table 9, entry 1). Changing the nickel catalyst to $NiBr_2$(DME) improved the ratio to 1:2 still in favour of **569** (entry 2). However, changing the ligand to PPh_3 changed the ratio in favour of the desired product **568** (entries 3,4) and increasing the concentration of the reaction to 0.5 M gave only the desired product (entry 5). Furthermore, we were pleased to notice that changing precatalyst from Ni(II) sources to $Pd(OAc)_2$ afforded only the desired product **568** with no other diastereoisomer observed, in quantitative yield after filtration through plug of silica gel leading to our optimised conditions (entry 6).

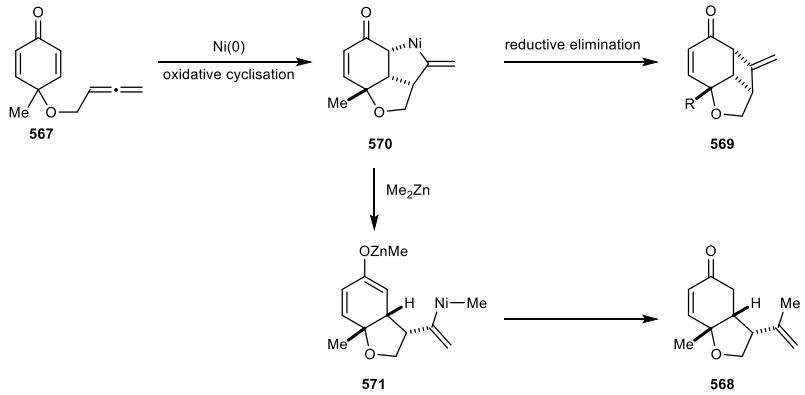
Table 9. Evaluation of reaction conditions.[a]



Entry	[Cat]	Conversion[b]	568:569
1	$Ni(acac)_2$	>99%	1:10
2	$NiBr_2$(DME)	>99%	1:2
3	$NiBr(PPh)_3$	>99%	2:1
4	$NiCl_2(PPh_3)_2$	81%	2.6:1
5[c]	$NiBr_2(PPh_3)_2$	>99%	>19:1
6[d]	$Pd(OAc)_2$	>99%	>19:1

[a] Reactions were conducted using 0.10 mmol of **567**. [b] Determined by ^{1}H NMR analysis of the crude reactions using 1,3,5-dimethoxybenzene as an internal standard. [c] Reaction conditions: 0°C, 1h, 0.5 M. [d] reaction conditions: 0°C, 1h, 0.1 M. **568** was obtained pure and as single observable diastereoisomer after filtration of the crude reaction mixture through plug of silica gel.

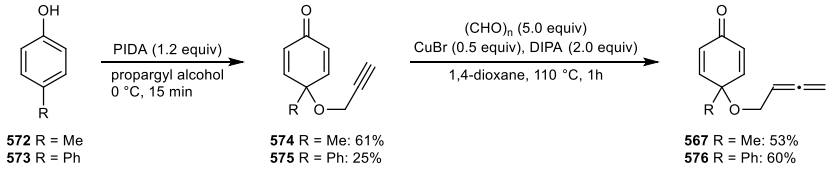
The data obtained from this optimisation study deserves more details. The tricyclic product **569** can derive from the reductive cyclisation of Ni(0) with the allenyl ketone **567** (Scheme 82) similar to the protocol developed by Montgomery for the synthesis of (-)-α-kainic acid.[82] Hence, more concentrated conditions (Table 9, entry 5) favour the trapping of nickellacycle **570** by dimethylzinc, and affords intermediate **571** which leads to the desired product **568**.



Scheme 82. Possible mechanism involving an oxidative cyclisation pathway.

2.2.3. Synthesis of allenyl ketones starting materials

Allenes with an oxygen tether to the cyclohexadienone moiety **567** and **576** were synthesised in two steps starting from the corresponding *p*-cresol derivative **572** or **573**. Oxidation with phenyliodine(III) diacetate (PIDA) using propargyl alcohol as the solvent afforded alkyne **574** or **575** that upon Crabbé homologation provided allenes **567** or **576**.



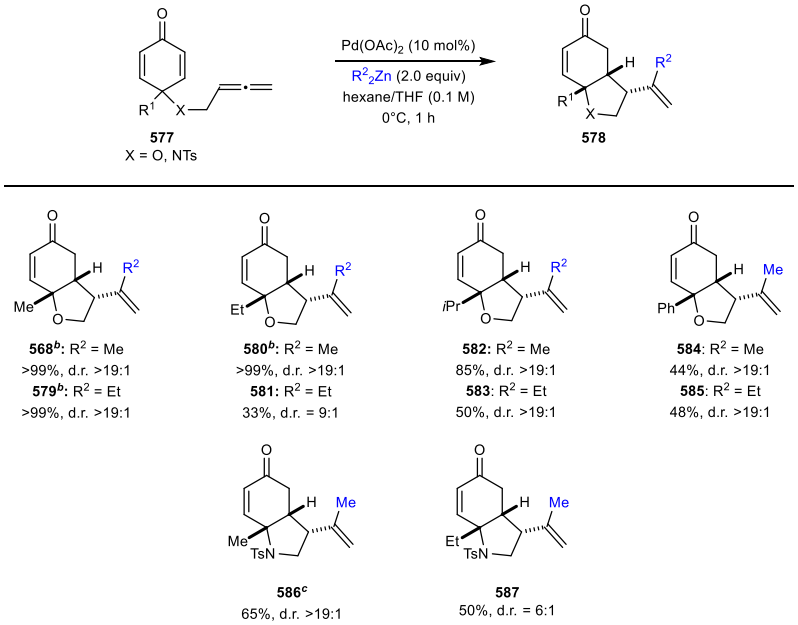
*Scheme 83. Synthesis of compound **567** and **576**.*

2.2.4. Preliminary scope and limitations

To test whether these conditions could be applied to other allenyl ketones and dialkylzinc nucleophiles and not limited to the substrates tested in Table 9, a preliminary screening of the viability of the reaction was investigated before proceeding with the chiral catalyst screening. Both *N*-sulfonyl-tethered and *O*-tethered substrates reacted successfully to give the bicycles **568**-**587** (Table 10) in good yields and diastereoselectivities. Compounds **568**, **579** and **580** were obtained pure after filtration over a plug of silica gel of the reaction mixture. Changing substituent R^1 on the allene starting material from methyl (**568**, **579** and **586**) to ethyl

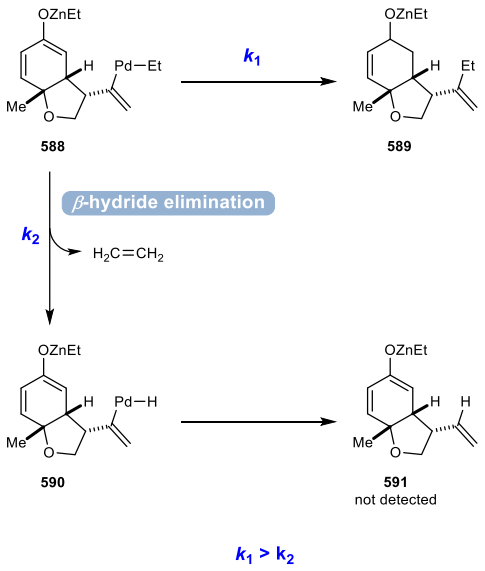
(**580**, **581** and **587**) isopropyl (**582** and **583**) and phenyl (**584** and **585**) afforded good to excellent yields.

Table 10. Diastereoselective cyclisation of enones tethered to allenes.[a]



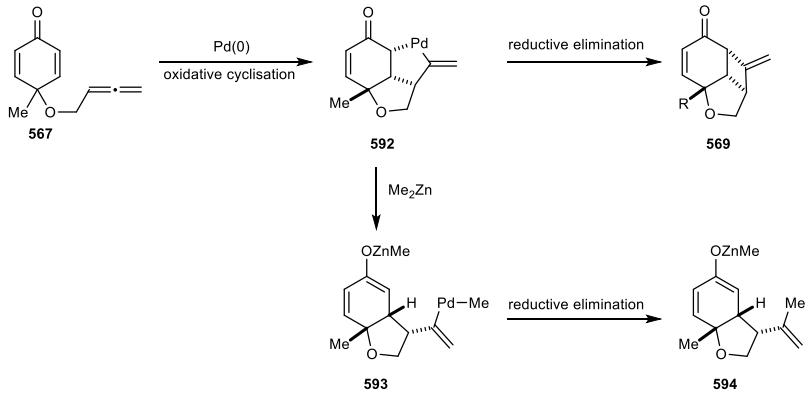
[a] Reactions were conducted using 0.30 mmol of **577**. Yields are of isolated products. Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reactions. [b] Pure product after filtration of the crude reaction mixture through plug of silica gel. [c] Reaction carried out with $NiBr_2(PPh_3)$.

More importantly, changing the nucleophile from dimethyl- to diethylzinc afforded the products **579**, **581**, **583** and **585** suggesting that the reductive elimination step is faster than the β-hydride elimination (Scheme 84).



Scheme 84. Reductive elimination is faster than β-hydride elimination on this process.

With these data in hand, a series of different enantiomerically pure ligands were screened to obtain the desired product in an enantioselective fashion. However, the products were always obtained with no or poor enantiomeric excess (these reactions were performed by Thi Le Nhon Nguyen, another PhD student in the Lam group and the list of ligands screened with the enantioselectivities obtained can be found in her thesis). A possible explanation for this lack of enantioselectivity could be due to the high reactivity of the Pd(0) species formed. As depicted in Scheme 85, Pd(0) performs the oxidative cyclisation to form palladacycle **592** containing a new chiral centre. The involvement of a highly reactive Pd(0) species in this enantiodetermining step can make the desymmetrisation such a fast process that the reactivity-selectivity principle applies, leading to poor enantioselectivities when using the most reactive catalysts.[83] To try and increase the enantioselectivity, further studies to optimise the catalyst by lowering the reactivity will be performed, so that the reaction will be slower and therefore greater enantioselectivity could be obtained.

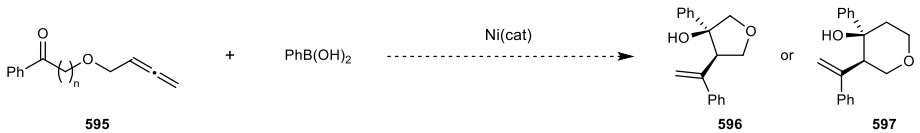


Scheme 85. Possible mechanism with Pd(0).

2.3. Conclusions and future work

Metal-catalysed nucleophilic allylations initiated by the carbometallation of π-bonds are of key importance in organic synthesis when achieved in high diastereo- and enantioselectivity. Literature precedence and the research discussed in this thesis attest to the high utility of this class of reactions. Especially the 1,2-allylation project established the benefits of allylnickel species generated *in situ* when allenes perform migratory insertion into the Ni-Ar bond. Compared with related palladium-catalysed reactions reported, this method showed that suitable allylnickel species can be effective nucleophilic partners of the less reactive ketones to enable the synthesis of tertiary alcohol containing aza- and carbocycles.

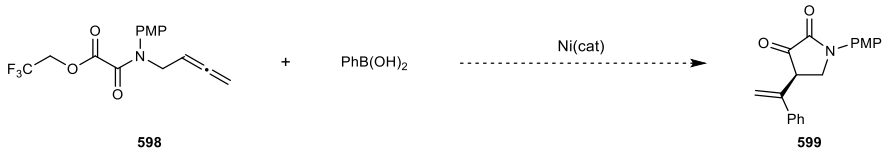
Future work on the 1,2-allylation can be envisaged regarding the expansion of the substrate scope (Scheme 86). Using an oxygen tether can provide valuable oxygenated heterocycles such as tetrahydrofurans **596** and tetrahydropyrans **597**.



Scheme 86. Future work ongoing with regard to the expansion of the substrate scope.

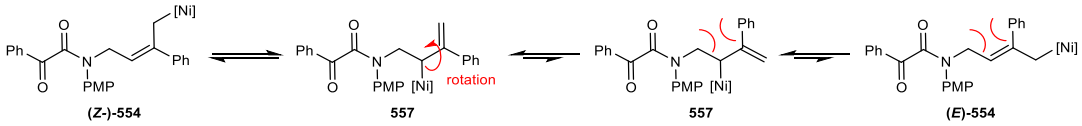
Further work can be done to overcome the limitations of the chemistry described, such as the use of esters as suitable coupling partners. In this case, increasing the reactivity of esters with the use of trifluoroethyl carboxylate **598** can provide the

desired product **599**. Other possible solutions are the use of Lewis acids to decrease the LUMO of the ester functional group or using a more nucleophilic nickel catalyst (e.g. with the use of NHC ligands) to increase the HOMO of the allylnickel nucleophile.



Scheme 87. Increasing the reactivity of the ester can lead to the desired product.

Further mechanistic studies can be envisaged to elucidate the mechanism shown in Scheme 79. DFT calculations can help to justify both the favoured (*Z*)-**554** isomer shown in Scheme 80 and also to justify the stereochemical model proposed in Figure 3 (pag. 78) by comparing the relative energies of the two transition states.



Scheme 88. Isomerisation that favours the (Z)-allylnickel species.

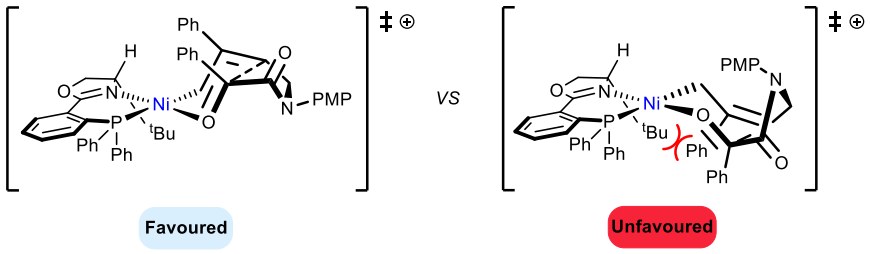
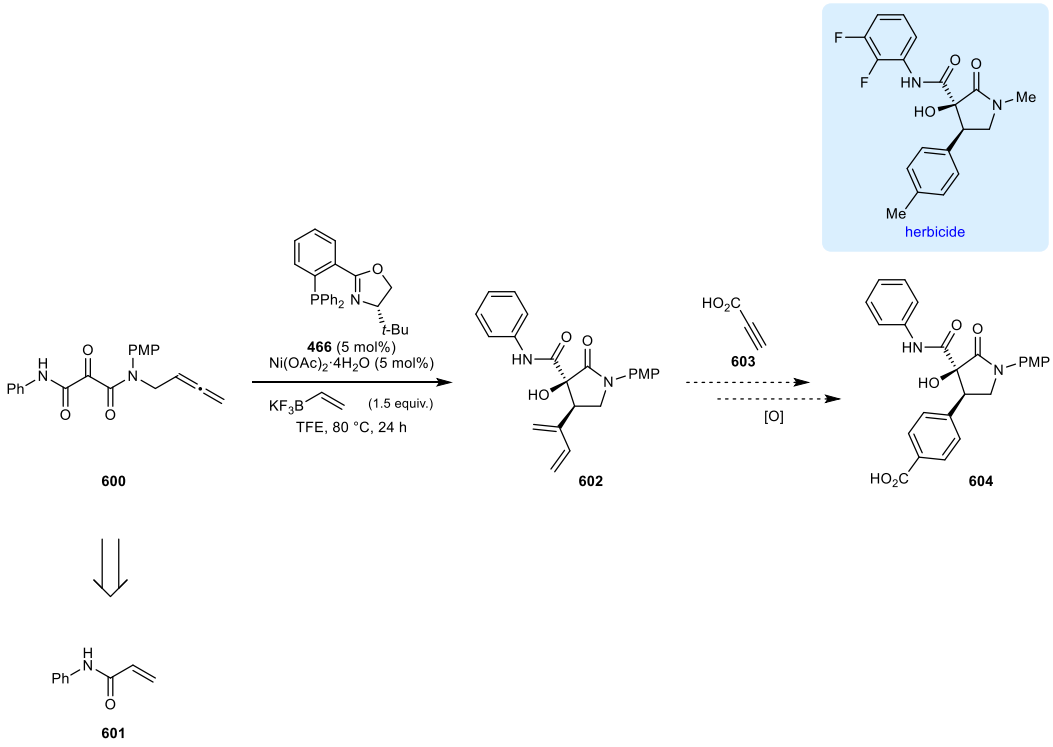


Figure 7. Possible stereochemical model to account for the observed enantiomer formed.

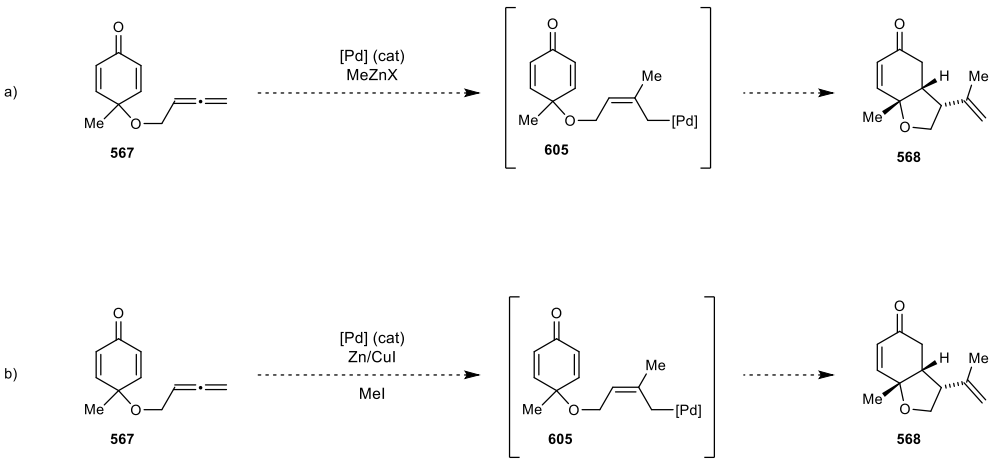
Finally, manipulations of the products can increase the utility of the protocol. Above all, the synthesis of an analogue of an herbicide[58] can be envisaged with the synthetic plan shown in Scheme 89. Starting from the allene **600**, which can be synthesised starting from acrylamide **601**,[84] the nickel-catalysed enantioselective nucleophilic cyclisation using vinyltrifluoroborate leads to compound **602**. Diels-Alder reaction

with propiolic acid **603**[85] and further oxidation of the adduct to the aryl derivative would deliver the herbicide analogue **604**.



Scheme 89. Strategic plan to synthesise an analogue of the herbicide bearing the γ-lactam framework.

With regard to the palladium-catalysed nucleophilic 1,4-allylation reaction, future work can be done to achieve high enantioselectivity. Firstly, an extensive screening of chiral ligands will have to be envisaged. Secondly, as discussed in Scheme 82 and Scheme 85, highly reactive Ni(0) and Pd(0) can be the culprit for the low enantioselectivity observed. Therefore, keeping the metal catalyst to a higher oxidation state, such as Ni(II) and Pd(II), will avoid the formation of the nickellacycle **570** (Scheme 82) or palladacycle **592** (Scheme 85) and be a possible solution to the low enantioselectivity obtained. To achieve this goal alkylzinc halides can be used (Scheme 90a) or a slow release of the alkylzinc nucleophile in the reaction mixture using Li's conditions[86] could also be envisaged (Scheme 90b)



Scheme 90. Possible future work on 1,4-allylation of allenyl ketones.

3. Experimental

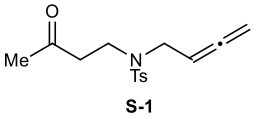
3.1. General information

All air-sensitive reactions were carried out under an inert atmosphere using oven-dried apparatus. 2,2,2-trifluoroethanol (TFE) was purchased from Alfa Aesar and used as received. MeCN was dried and purified by passage through activated alumina columns using a solvent purification system. All commercially available reagents were used as received unless otherwise stated. Dimethylzinc was used as 1.2 M solution in toluene purchased from Sigma-Aldrich. Diethylzinc was used as 0.9 M solution in hexane purchased from Sigma-Aldrich. Petroleum ether refers to Sigma-Aldrich product 24587 (petroleum ether boiling point 40–60 °C). Thin layer chromatography (TLC) was performed on Merck DF Alufoilien 60F254 0.2 mm precoated plates. Compounds were visualized by exposure to UV light or by dipping the plates into solutions of potassium permanganate or vanillin followed by gentle heating. Column chromatography was carried out using silica gel (Fisher Scientific 60 Å particle size 35-70 micron or Fluorochem 60 Å particle size 40-63 micron). Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. The solvent of recrystallization is reported in parentheses. Infrared (IR) spectra were recorded on a Bruker platinum ALPHA FTIR spectrometer on the neat compound using the attenuated total refraction technique. NMR spectra were acquired on Bruker Ascend 400 or Ascend 500 spectrometers. ^{1}H and ^{13}C NMR spectra were referenced to external tetramethylsilane via the residual protonated solvent (^{1}H) or the solvent itself (^{13}C). All chemical shifts are reported in parts per million (ppm). For $CDCl_3$, the shifts are referenced to 7.26 ppm for ^{1}H NMR spectroscopy and 77.16 ppm for ^{13}C NMR spectroscopy. Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sept (septet), br (broad) and m (multiplet) Coupling constants (*J*) are quoted to the nearest 0.1 Hz. ^{13}C NMR assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. High-resolution mass spectra were recorded using electrospray ionization (ESI) on a Bruker microTOF II instrument. Chiral HPLC analysis was performed on an Agilent 1290 series instrument with diode array detector using 4.6 × 250 mm columns as indicated for specific

compounds. 2-[2-(Diphenylphosphino)ethyl]pyridine was used as an achiral ligand to obtain authentic racemic compounds.

3.2. Nickel-catalysed enantioselective nucleophilic 1,2-allylation of ketones

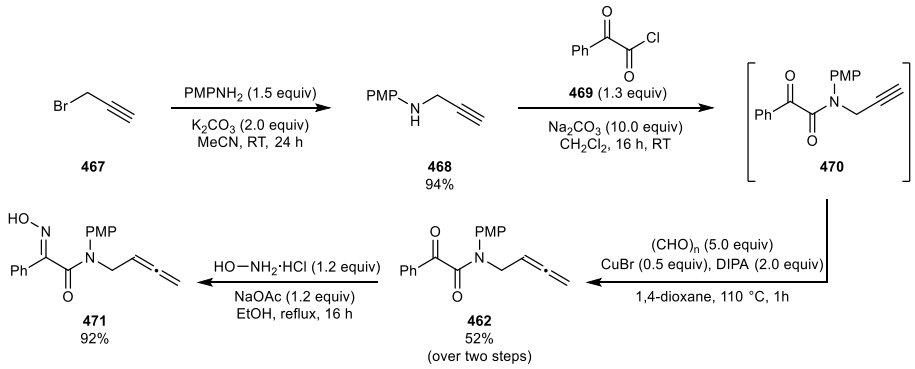
3.2.1. Synthesis of substrates

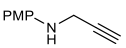


S-1

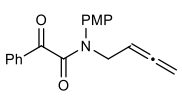
Substrate **S-1** was synthesised by Naeem Iqbal.[87]

*Preparation of Allenyl Ketone **462** and allenyl oxime **471***





4-Methoxy-*N*-(prop-2-yn-1-yl)aniline (468) was prepared according to a previously reported procedure,[88] using anisidine (18.4 g, 150 mmol), K_2CO_3 (27.6 g, 200 mmol), MeCN (100 mL) and propargyl bromide (80% in toluene) (15.0 mL, 100 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.86 – 6.78 (2H, m, Ar**H**), 6.72 – 6.63 (2H, m, Ar**H**), 3.90 (2H, d, *J* = 2.4 Hz, C**H**$_2$), 3.76 (3H, s, OC**H**$_3$), 3.61 (1H, br s, N**H**), 2.20 (1H, t, *J* = 2.4 Hz, C**H**); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 153.1 (C), 141.0 (C), 115.3 (2 × CH), 115.0 (2 × CH), 81.5 (C), 71.4 (CH), 55.9 (CH_3), 34.7 (CH_2).



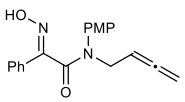
***N*-(Buta-2,3-dien-1-yl)-*N*-(4-methoxyphenyl)-2-oxo-2-phenylacetamide (462)**. Benzoylformic acid (3.60 g, 23.8 mmol)

was dissolved in CH_2Cl_2 (20 mL) under Ar. Dichloromethyl methyl ether (2.32 mL, 25.7 mmol) was added dropwise at room temperature and the reaction mixture was stirred for 2 h. Anhydrous Na_2CO_3 (20.1 g, 190 mmol) was added followed by a solution of amine **468** (3.10 g, 19.0 mmol) in CH_2Cl_2 (70 mL). The reaction was stirred at room temperature for 16 h, diluted EtOAc (100 mL) and filtered through a plug of silica (6 cm in height and 7 cm wide). The silica plug was washed with EtOAc (300 mL), the solvent was evaporated under reduced pressure to leave the propargyl amide **470** that was pure enough to proceed with the following step. The crude mixture of alkyne **470** (5.60 g, 19.0 mmol), CuBr (1.40 g, 9.50 mmol) and $(CHO)_n$ (2.90 g, 95.0 mmol) were dissolved in 1,4-dioxane (95 mL). Diisopropylamine (5.3 mL, 38.0 mmol) was added and the reaction mixture was immersed in a pre-heated oil-bath at 110 °C. The reaction was stirred at the same temperature for 1 h, cooled to room temperature, diluted with EtOAc (100 mL) and filtered through a plug of silica (6 cm in height and 7 cm wide). The silica plug was washed with EtOAc (300 mL) and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (10% to 30% EtOAc/petroleum ether) to give the title compound **462** (3.02 g, 52% over two steps) as a yellow solid as a 11:1 mixture of rotamers. R_f = 0.27 (30% EtOAc/petroleum ether); m.p. 50-53 °C (EtOAc); IR 2957, 1959 (C=C=C), 1653 (C=O), 1591 (C=O), 1508, 1449, 1399, 1240, 1168, 944 cm^{-1}; HRMS (ESI) Exact mass calculated for $[C_{19}H_{18}NO_3]^+$ $[M+H]^+$: 308.1281, found: 308.1283.

NMR data for major rotamer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87–7.81 (2H, m, Ar**H**), 7.60–7.51 (1H, m, Ar**H**), 7.45–7.38 (2H, m, Ar**H**), 7.09–7.02 (2H, m, Ar**H**), 6.74–6.67 (2H, m, Ar**H**), 5.31 (1H, quint, *J* = 6.6 Hz, CH_2C**H**), 4.80 (2H, dt, *J* = 6.6, 2.7 Hz, NC**H$_2$**), 4.44 (2H, dt, *J* = 6.7, 2.7 Hz, =C**H$_2$**), 3.71 (3H, s, OC**H$_3$**); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 209.8 (C), 190.9 (C), 167.0 (C), 159.4 (C), 134.3 (CH), 133.6 (C), 132.0 (C), 129.8 (2 × CH), 129.4 (2 × CH), 128.8 (2 × CH), 114.5 (2 × CH), 85.9 (CH), 77.0 (CH_2), 55.4 (CH_3), 47.8 (CH_2);

Characteristic NMR data for minor rotamer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08–8.03 (2H, m, Ar**H**), 7.69–7.61 (2H, m, Ar**H**), 7.34–7.28 (2H, m, Ar**H**), 7.00–6.95

(2H, m, Ar**H**), 5.13 (1H, quint, *J* = 6.5 Hz, CH_2C**H**), 4.58 (2H, dt, *J* = 6.5, 2.7 Hz, NC**H₂**), 4.19 (2H, dt, *J* = 6.6, 2.7 Hz, =C**H₂**), 3.83 (3H, s, OC**H₃**); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 130.1 (CH), 129.0 (CH), 128.3 (CH), 114.7 (CH), 110.1 (CH);

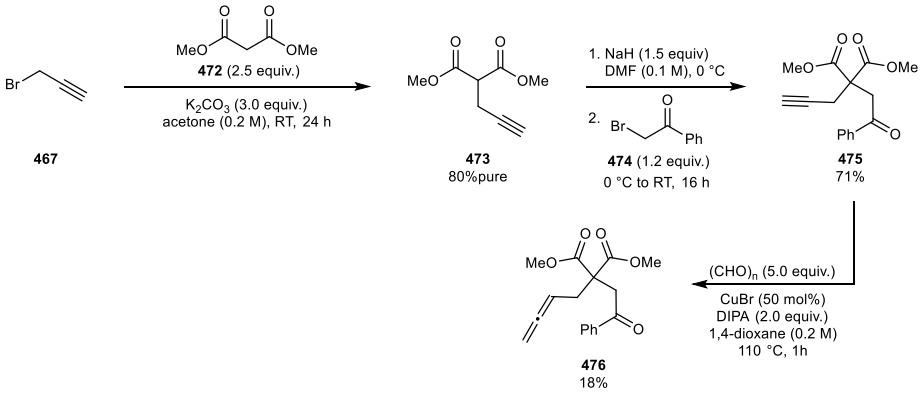


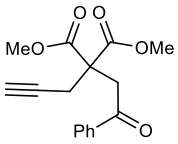
(*E*)-*N*-(buta-2,3-dien-1-yl)-2-(hydroxyimino)-*N*-(4-methoxyphenyl)-2-phenylacetamide (471). A suspension of allene **462** (307 mg, 1.00 mmol), hydroxylamine hydrochloride (83.4 mg, 1.20 mmol) and sodium acetate (98.4 mg, 1.20 mmol) in ethanol (10 mL) was heated to reflux and stirred for 16 h. The reaction mixture was then filtered while still hot and the solvent of the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography (5% EtOAc/petroleum ether to 50%) to give the title compound **471** (296 mg, 92%) as an off-white oil as a 12:1 mixture of rotamers. R_f = 0.14 (30% EtOAc/petroleum ether); IR 3270 (OH), 2837, 1954, 1631, 1509, 1440, 1297, 1247, 1211, 1068, 729 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) HRMS (ESI) Exact mass calculated for $[C_{19}H_{19}N_2O_3]^+$ $[M+H]^+$: 323.1390, found: 323.1393.

NMR data for major rotamer: δ 9.12 (1H, br, O**H**), 7.44 – 7.37 (2H, m, Ar**H**), 7.34 – 7.29 (1H, m, Ar**H**), 7.30 – 7.22 (2H, m, Ar**H**), 7.02 – 6.95 (2H, m, Ar**H**), 6.67 – 6.56 (2H, m, Ar**H**), 5.29 (1H, quin, *J* = 6.7 Hz, C**H**), 4.71 (2H, dt, *J* = 6.6, 2.5 Hz, CC**H₂**), 4.40 (2H, dt, *J* = 6.8, 2.6 Hz, NC**H₂**), 3.70 (3H, s, OC**H₃**); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 209.8 (C), 164.3 (C), 159.6 (C), 155.1 (C), 132.5 (C), 131.6 (C), 130.1 (CH), 129.1 (2 × CH), 128.6 (2 × CH), 126.3 (2 × CH), 113.9 (2 × CH), 86.2 (CH), 76.7 (CH_2), 55.5 (CH_3), 47.8 (CH_2);

Characteristic NMR data for minor rotamer: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.48 (1H, br, O**H**), 7.70 (2H, m, Ar**H**), 6.95–6.91 (2H, m, Ar**H**), 4.98 (1H, p, *J* = 6.7 Hz, C**H**), 4.45 (2H, dt, *J* = 6.6, 2.5 Hz, CC**H₂**), 4.13 (2H, dt, *J* = 6.9, 2.5 Hz, NC**H₂**), 3.79 (3H, s, OC**H₃**); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 114.7 (CH), 77.4 (CH_2).

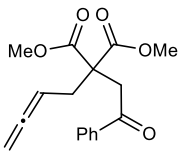
*Preparation of allenyl malonate **476***





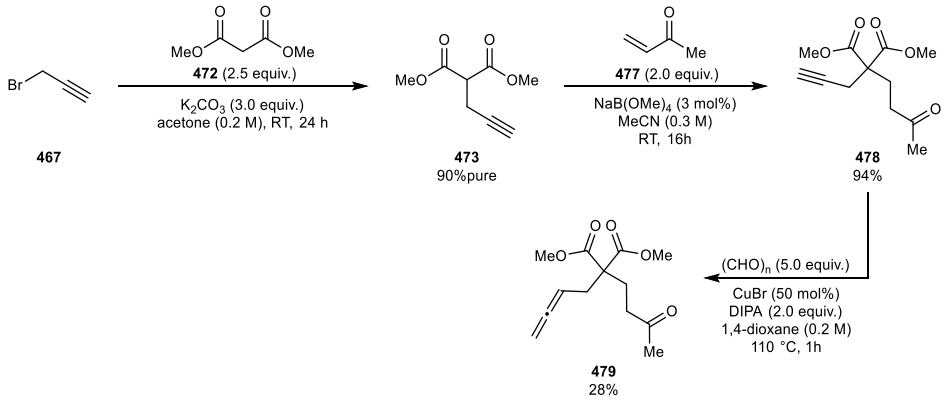
Dimethyl 2-(2-oxo-2-phenylethyl)-2-(prop-2-yn-1-yl)malonate (475) was prepared according to a previously reported procedure[89] with minor changes. A solution of dimethyl malonate (20.0 mL, 175 mmol) in dry acetone (350 mL) was added to anhydrous K_2CO_3 (29.0 g, 210 mmol) and stirred for 10 min, then propargyl bromide (80% in toluene) (7.8 mL, 70.0 mmol) was added dropwise and let stir at room temperature for 24 h. The reaction was quenched with a saturated aqueous solution of ammonium chloride (150 mL) and let stir for 20 min. The mixture was extracted four times with dichloromethane and the organic phases collected were dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the excess malonate was distilled off, affording an inseparable mixture of mono- and dipropargylated malonate (80:20 respectively). The mixture was used for the next step without further purification. Alkyne **473** (80% pure) (1.10 g, 5.00 mmol) was dissolved in DMF (50 mL) under argon, cooled to 0 °C. NaH (60% in mineral oil) (300 mg, 7.50 mmol) was added and the mixture was stirred for 5 min (until no more gas evolution occurred). Bromoacetophenone (1.20 g, 6.00 mmol) was dissolved in DMF (20 mL) and added *via* cannula technique to the first mixture at 0 °C. The reaction was warmed to RT and stirred overnight. The reaction was quenched with water (10 mL) and extracted with Et_2O four times. The organic phases were joined and washed with brine four times and dried over magnesium sulfate. The solvent was evaporated under reduced pressure. Purification by column chromatography (0% EtOAc/petroleum ether to 20%) afforded the title compound **475** (1.0 g, 71%) as a yellow oil. The data matched the one found in the literature.[89]

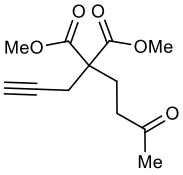
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04–7.97 (2H, m, Ar**H**), 7.64–7.55 (1H, m, Ar**H**), 7.52–7.42 (2H, m, Ar**H**), 3.93 (2H, s, C**H**$_2$C=O), 3.77 (6H, s, OC**H**$_3$), 3.13 (2H, d, *J* = 2.7 Hz, (≡CC**H**$_2$), 2.00 (1H, t, *J* = 2.7 Hz, (≡C–**H**); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 196.8 (C), 169.9 (2 × C), 136.4 (C), 133.7 (CH), 128.8 (2 × CH), 128.3 (2 × CH), 79.4 (C), 72.0 (CH), 54.7 (C), 53.3 (2 × CH_3), 41.2 (CH_2), 23.5 (CH_2).



Dimethyl 2-(buta-2,3-dien-1-yl)-2-(2-oxo-2-phenylethyl)malonate (476). Alkyne **475** (1.00 g, 3.50 mmol), CuBr (0.251 g, 1.75 mmol) and $(CHO)_n$ (0.530 g, 7.00 mmol) were dissolved in 1,4-dioxane (20 mL). Diisopropylamine (0.98 mL, 12.0 mmol) was added and the reaction mixture was immersed in a pre-heated oil-bath at 110 °C. The reaction was stirred at the same temperature for 1 h, cooled to room temperature, diluted with EtOAc (50 mL) and filtered through a plug of silica (6 cm in height and 7 cm wide). The silica plug was washed with EtOAc (200 mL) and the solvent was evaporated under reduced pressure. Purification by column chromatography (5% EtOAc/pentane to 10%) afforded the allene **476** (0.200 g, 18%) as a colourless oil. R_f = 0.41 (30% EtOAc/petroleum ether); IR 2952, 1954 (C=C=C), 1732 (C=O), 1685 (C=O), 1596, 1580, 1404, 1198, 1179, 1067 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.00–7.94 (2H, m, Ar**H**), 7.61–7.54 (1H, m, Ar**H**), 7.5–7.43 (2H, m, Ar**H**), 4.97 (1H, tt, *J* = 8.1, 6.7 Hz, =C**H**), 4.51 (2H, dt, *J* = 6.7, 2.4 Hz, =C**H**$_2$), 376 (6H, s, OC**H**$_3$), 3.75 (2H, s, C**H**$_2$C=O), 2.83 (2H, dt, *J* = 8.1, 2.4 Hz, =CHC**H**$_2$); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 210.2 (C), 196.8 (C), 170.9 (C), 136.6 (C), 133.5 (CH), 128.8 (2 × CH), 128.2 (2 × CH), 84.8 (CH), 74.9 (CH_2), 55.7 (C), 53.0 (2 × CH_3), 41.4(CH_2), 32.9 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{17}H_{19}NO_5]^+$ $[M+H]^+$: 303.1227, found: 303.1223.

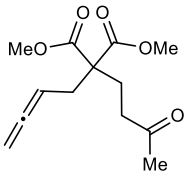
*Preparation of allenyl malonate **479***





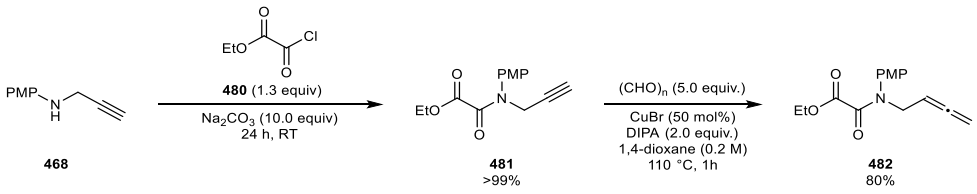
Dimethyl 2-(3-oxobutyl)-2-(prop-2-yn-1-yl)malonate (478) was prepared according to a previously reported procedure[90] with minor changes. A solution of dimethyl malonate (20.0 mL, 175 mmol) in dry acetone (350 mL) was added to anhydrous K_2CO_3 (29.0 g, 210 mmol) and stirred for 10 min, then propargyl bromide (80% in toluene) (7.8 mL, 70.0 mmol) was added dropwise and let stir at room temperature for 24 h. The reaction was quenched with a saturated aqueous solution of ammonium chloride (150 mL) and let stir for 20 min. The mixture was extracted four times with dichloromethane and the organic phases collected were dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the excess malonate was distilled off, affording an inseparable mixture of mono- and dipropargylated malonate (85:15 respectively). The mixture was used for the next step without further purification. Sodium tetramethoxyborate (93.0 mg, 600 μmol) was suspended in acetonitrile (60 mL). Malonate **473** (85% pure) (4.00 g, 20.0 mmol) and vinyl methyl ketone (90% pure) (3.6 mL, 40.0 mmol) were added and the reaction mixture was stirred overnight at room temperature. The solvent was evaporated under reduced pressure and purification by column chromatography (5% EtOAc/petroleum ether to 40%) afforded the title compound (4.47 g, 94%) as a colourless oil. The data matched the one previously reported.[90] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.74 (6H, s, OC**H**$_3$), 2.82 (2H, d, J = 2.7 Hz, ≡CC**H**$_2$), 2.50 (2H, dd, J = 8.7, 6.6 Hz, C**H**$_2$C=O), 2.38–2.29 (2H, m, C**H**$_2$CH$_2$), 2.15 (3H, s, CC**H**$_3$), 2.03 (1H, t, J = 2.7 Hz, ≡C**H**); ^{13}C NMR ($CDCl_3$,

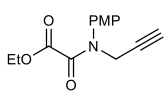
100.6 MHz) δ 207.1 (C), 170.5 (2 × C), 78.6 (C), 71.9 (CH), 56.2 (C), 53.0 (2 × CH_3), 38.7 (CH_2), 30.0 (CH_3), 26.6 (CH_2), 24.0 (CH_2).



Dimethyl 2-(buta-2,3-dien-1-yl)-2-(3-oxobutyl)malonate (479). Alkyne **478** (1.40 g, 6.00 mmol), CuBr (0.430 g, 3.00 mmol) and $(CHO)_n$ (0.900 g, 30.0 mmol) were dissolved in 1,4-dioxane (30 mL). Diisopropylamine (1.7 mL, 12.0 mmol) was added and the reaction mixture was immersed in a pre-heated oil-bath at 110 °C. The reaction was stirred at the same temperature for 1 h, cooled to room temperature, diluted with EtOAc (50 mL) and filtered through a plug of silica (6 cm in height and 7 cm wide). The silica plug was washed with EtOAc (200 mL) and the solvent was evaporated under reduced pressure. Purification by column chromatography (5% EtOAc/pentane to 20%) afforded the allene **479** (0.423 g, 28%) as a colourless oil. R_f = 0.25 (30% EtOAc/petroleum ether); IR 2954, 1955 (C=C=C), 1729 (C=O), 1435, 1372, 1198, 1093, 1044, 915, 848 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.95 (1H, tt, *J* = 8.0, 6.7 Hz, =C**H**), 4.67 (2H, dt, *J* = 6.7, 2.4 Hz, =C**H₂**), 3.72 (6H, s, OC**H₃**), 2.60 (2H, dt, *J* = 8.0, 2.5 Hz, =CHC**H₂**), 2.46 (2H, dd, *J* = 8.8, 6.8 Hz, C**H₂**C=O), 2.23–2.15 (2H, m, C**H₂**CH_2C=O), 2.13 (3H, s, O=CC**H₃**); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 210.2 (C), 207.3 (C), 171.4 (2 × C), 84.2 (CH), 74.9 (CH_2), 57.1 (C), 52.7 (2 × CH_3), 38.7 (CH_2), 33.2 (CH_2), 30.1 (CH_3), 26.6 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{13}H_{19}NO_5]^+$ [M+H]$^+$: 255.1227, found: 255.1227.

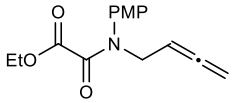
*Preparation of allenyl ester **482***





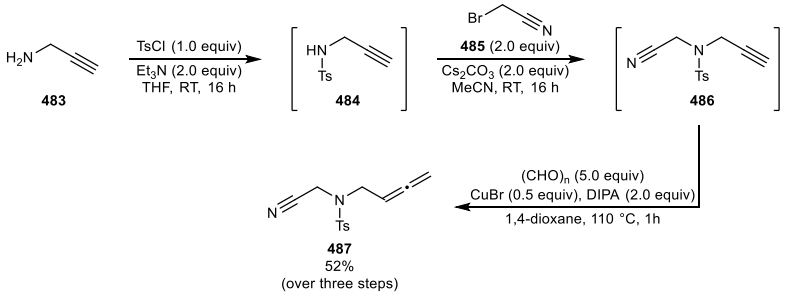
Ethyl 2-((4-methoxyphenyl)(prop-2-yn-1-yl)amino)-2-oxoacetate (481). Amine **468** (1.00 g, 6.00 mmol) was dissolved in CH_2Cl_2 (30 mL) and ethyl 2-chloroacetoacetate (0.87 mL, 7.80 mmol) was added dropwise to the mixture, then anhydrous sodium carbonate (6.40 g, 60.0 mmol) was added. The

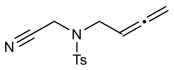
reaction mixture was left stirring for 24 h at room temperature. The reaction was diluted in EtOAc (30 mL) and filtered through a plug of silica (6 cm in height and 7 cm wide). The silica plug was washed with EtOAc (100 mL), the solvent was evaporated under reduced pressure affording the title compound **481** (1.57 g, quant.) as an orange oil. R_f = 0.23 (30% EtOAc/petroleum ether); IR 3279 (≡C–H), 2980, 1738 (C=O), 1665 (C=O), 1607, 1585, 1509, 1195, 1022, 862 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.30–7.21 (2H, m, Ar**H**), 6.93–6.86 (2H, m, Ar**H**), 4.49 (2H, d, *J* = 2.5 Hz, NC**H₂**), 4.02 (2H, q, *J* = 7.1 Hz, CH_3C**H₂**), 3.82 (3H, s, O**Me**), 2.24 (1H, t, *J* = 2.5 Hz, C**H**), 1.03 (3H, t, *J* = 7.1 Hz, CH_2C**H₃**); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 162.3 (C), 161.7 (C), 160.1 (C), 131.6 (C), 129.6 (2 × CH), 114.6 (2 × CH), 77.7 (C), 73.3 (CH), 61.8 (CH_2), 55.6 (CH_3), 37.9 (CH_2), 13.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{14}H_{16}NO_4]^+$ $[M+H]^+$: 262.1074, found: 262.1072.



Ethyl 2-(buta-2,3-dien-1-yl(4-methoxyphenyl)amino)-2-oxoacetate (482). Alkyne **481** (1.57 g, 6.00 mmol), CuBr (0.430 g, 3.0 mmol) and $(CHO)_n$ (0.91 g, 30.0 mmol) were dissolved in 1,4-dioxane (30 mL). Diisopropylamine (1.7 mL, 12.0 mmol) was added and the reaction mixture was immersed in a pre-heated oil-bath at 110 °C. The reaction was stirred at the same temperature for 1 h, cooled to room temperature, diluted with EtOAc (50 mL) and filtered through a plug of silica (6 cm in height and 7 cm wide). The silica plug was washed with EtOAc (200 mL) and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (30% EtOAc/petroleum ether) to give allene **482** (1.32 g, 80% yield) as a yellow oil. R_f = 0.30 (30% EtOAc/petroleum ether); IR 2980, 1956 (C=C=C), 1738 (C=O), 1662 (C=O), 1509, 1441, 1297, 1224, 1191, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.20–7.13 (2H, m, Ar**H**), 6.90–6.84 (2H, m, Ar**H**), 5.21 (1H, quint, *J* = 6.7 Hz, =C**H**), 4.74 (2H, dt, *J* = 6.6, 2.5 Hz, =C**H₂**), 4.31 (2H, dt, *J* = 6.8, 2.6 Hz, NC**H₂**), 4.01 (2H, q, *J* = 7.1 Hz, CH_3C**H₂**), 3.81 (3H, s, OC**H₃**), 1.02 (3H, t, *J* = 7.1 Hz, C**H₃**CH_2); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 209.8 (C), 162.7 (C), 161.9 (C), 159.7 (C), 132.4 (C), 129.4 (2 × CH), 114.5 (2 × CH), 85.5 (CH), 76.8 (CH_2), 61.7 (CH_2), 55.6 (CH_3), 47.7 (CH_2), 13.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{15}H_{18}NO_4]^+$ $[M+H]^+$: 276.1230, found: 276.1228.

*Preparation allenyl nitrile **487***

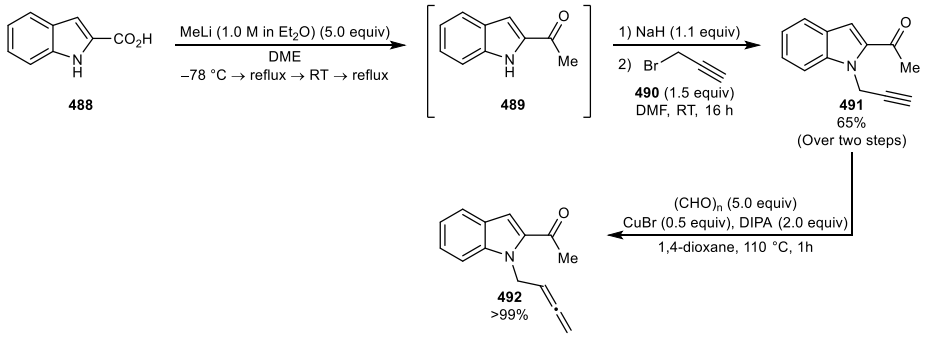


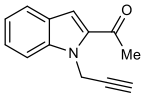


_N_-(buta-2,3-dien-1-yl)-_N_-(cyanomethyl)-4-methylbenzenesulfonamide (487). Tosyl chloride (3.80 g, 20 mmol) was added to a stirring solution of propargylamine (1.4 mL, 20 mmol) and triethylamine (5.6 mL, 40 mmol) in THF (30 mL) at room temperature and the reaction mixture was left stirring for 16 h. The reaction was quenched with an aqueous solution of hydrochloric acid (2 M) (20 mL) and the mixture was extracted three times with CH_2Cl_2. The organic phases were joined and dried over magnesium sulfate, the solvent was evaporated under reduced pressure affording the crude mixture enough pure for the next step. The crude mixture and Cs_2CO_3 (13.0 g, 40 mmol), were suspended in MeCN (200 mL) and left stir for 5 min at room temperature. Bromide **485** (2.8 mL, 40 mmol) was added and the reaction mixture was left stirring for 16 h at room temperature. The mixture was diluted in CH_2Cl_2 (100 mL), added water (100 mL) and the organic phase was separated from the aqueous. The aqueous phase was extracted three times with CH_2Cl_2 and the organic phases were joined and dried over magnesium sulfate. The solvent was evaporated under reduced pressure affording the crude mixture enough pure for the next step. The crude mixture, CuBr (1.40 g, 10.0 mmol) and $(CHO)_n$ (3.00 g, 100 mmol) were dissolved in 1,4-dioxane (100 mL). Diisopropylamine (5.6 mL, 40.0 mmol) was added and the reaction mixture was immersed in a pre-heated oil-bath at 110 °C. The reaction was stirred at the same temperature for 1 h, cooled to room temperature, diluted with EtOAc (200 mL) and filtered through a plug of silica (6 cm in height and 7 cm wide). The silica plug was washed with EtOAc (500 mL) and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (10% EtOAc/petroleum ether to 30%) to give allene **487** (2.71 g, 52% yield) as a pale

yellow solid. R_f = 0.32 (30% EtOAc/petroleum ether); IR 2997, 1952 (C=C=C), 1596, 1424, 1159, 1091, 1009, 903, 859, 659 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.78–7.71 (2H, m, Ar**H**), 7.37 (2H, d, *J* = 8.1 Hz, Ar**H**), 5.04 (1H, quint, *J* = 7.0 Hz, C**H**), 4.86 (2H, dt, *J* = 6.6, 2.4 Hz C**H₂**CH), 4.28 (2H, s, C**H₂**NTs), 3.85 (2H, dt, *J* = 7.2, 2.4 Hz, C=C**H₂**), 2.45 (3H, s, C**H₃**); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 210.3 (C), 144.9 (C), 134.6 (C), 130.3 (2 × CH_2), 127.7 (2 × CH_2), 113.6 (C), 84.7 (CH), 77.4 (CH_2), 47.1 (CH_2), 34.6 (CH_2), 21.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{13}H_{15}N_2O_2S]^+$ $[M+H]^+$: 263.0849, found: 263.0847.

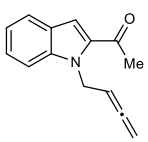
*Preparation of indolyl allene **492***





1-(1-(Prop-2-yn-1-yl)-1H-indol-2-yl)ethan-1-one (491) was prepared according to a previously reported procedure[91] with minor changes. A solution of 1H-indole-2-carboxylic acid (1.60 g, 10.0 mol) in DME (100 mL) was cooled to –78 °C, then a solution of MeLi (1.0 M in Et_2O) (30.0 mL, 30.0 mmol) was added dropwise and the reaction mixture was heated gradually to reflux and stirred. After 1 h, the reaction mixture was cooled to room temperature and a further portion of MeLi solution (1.0 M in Et_2O) (20.0 mL, 20.0 mmol) was added and the reaction was heated to reflux and stirred for 7 h. The reaction was quenched with a saturated aqueous solution of ammonium chloride (50 mL). The mixture was extracted three times with Et_2O and the organic phases collected were dried over Na_2SO_4. The solvent was evaporated under reduced pressure to leave the indole **489** that was pure enough to proceed with the following step. The crude mixture was dissolved in DMF (20 mL) and NaH (60% dispersion in mineral oil) (440 mg, 11.0 mmol) was added. The mixture was stirred at room temperature for 30 min, then

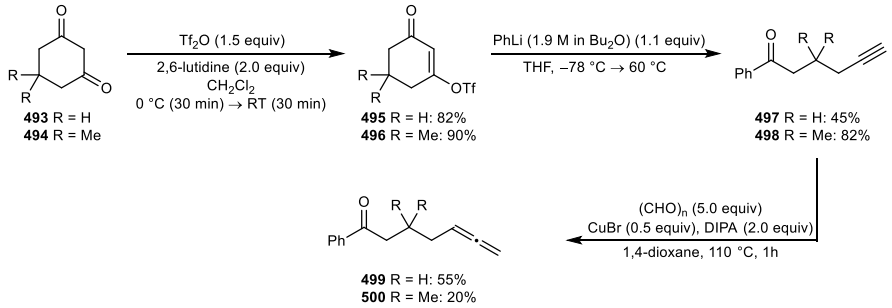
propargyl bromide (80% in toluene) (1.67 mL, 15.0 mmol) was added dropwise and the reaction mixture was stirred for 24 h at room temperature. The reaction was quenched with water (20 mL) then extracted four times with Et_2O and the organic phases collected washed four times with water. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (100% CH_2Cl_2) to afford the title compound **491** (1.28 g, 65% over two steps) as a yellow solid. The data matched the one found in the literature.[91] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.7 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.5–7.5 (1H, m, Ar**H**), 7.4 (1H, ddd, *J* = 8.4, 6.9, 1.2 Hz, Ar**H**), 7.3 (1H, d, *J* = 0.9 Hz, Ar**H**), 7.2 (1H, ddd, *J* = 8.0, 6.9, 1.1 Hz, Ar**H**), 5.5 (2H, d, *J* = 2.5 Hz, C**H$_2$**), 2.6 (3H, s, C**H$_3$**), 2.2 (1H, t, *J* = 2.5 Hz, C**H**); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 191.7 (C), 139.6 (C), 133.8 (C), 126.6 (CH), 126.2 (C), 123.2 (CH), 121.5 (CH), 113.6 (CH), 110.8 (CH), 79.0 (C), 72.0 (CH), 34.3 (CH_2), 28.0 (CH_3).



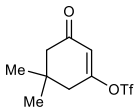
1-(1-(Buta-2,3-dien-1-yl)-1H-indol-2-yl)ethan-1-one (492). Alkyne **491** (789 mg, 4.00 mmol), CuBr (287 mg, 2.00 mmol) and $(CHO)_n$ (606 mg, 5.00 mmol) were dissolved in 1,4-dioxane (20 mL). Diisopropylamine (1.1 mL, 8.00 mmol) was added and the reaction mixture was immersed in a pre-heated oil-bath at 110 °C. The reaction was stirred at the same temperature for 1 h, cooled to room temperature, diluted with EtOAc (50 mL) and filtered through a plug of silica (6 cm in height and 7 cm wide). The silica plug was washed with EtOAc (200 mL) and the solvent was evaporated under reduced pressure. Purification by column chromatography (5% EtOAc/pentane) afforded the allene **492** (842 mg, >99%) as a yellow oil. R_f = 0.50 (20% EtOAc/petroleum ether); IR 3059, 1954 (C=C=C), 1655 (C=O), 1612, 1512, 1454, 1348, 1116, 1016, 963 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.7 (1H, dt, *J* = 8.0, 1.0 Hz Ar**H**), 7.5–7.3 (2H, m, Ar**H**), 7.3 (1H, d, *J* = 0.9 Hz, Ar**H**), 7.2 (1H, ddd, *J* = 8.0, 6.8, 1.1 Hz, Ar**H**), 5.4 (1H, quin, *J* = 6.5 Hz, CH_2C**H**), 5.2 (2H, dt, *J* = 6.5, 2.7 Hz, C**H$_2$**=CH), 4.7 (2H, dt, *J* = 6.6, 2.7 Hz, C=C**H$_2$**), 2.6 (3H, s, C**H$_3$**); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 209.0 (C), 191.5 (C), 139.7 (C), 134.3 (C), 126.2 (CH), 123.1 (CH), 121.0 (CH), 112.7 (CH), 111.1 (CH), 110.1 (CH), 88.1 (CH), 77.4 (CH_2), 43.8 (CH_2), 28.1 (CH_3);

HRMS (ESI) Exact mass calculated for $[C_{14}H_{14}NO]^+$ $[M+H]^+$: 212.1070, found: 212.1073.

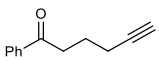
*Preparation of allenyl ketone **499** and **500***



3-Oxocyclohex-1-en-1-yl trifluoromethanesulfonate (495) was prepared according to a previously reported procedure.[92] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.06 (1H, d, *J* = 1.4 Hz, C**H**), 2.69 (2H, td, *J* = 6.2, 1.4 Hz, C**H₂**), 2.45 (2H, dd, *J* = 7.5, 6.0 Hz, C**H₂**), 2.13 (2H, quint, *J* = 6.4 Hz, CH_2C**H₂**CH_2); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 197.3 (C), 167.3 (C), 119.3 (CH), 118.5 (q, *J* = 320.7 Hz, CF_3), 36.3 (CH_2), 28.5 (CH_2), 20.8 (CH_2).

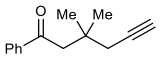


5,5-Dimethyl-3-oxocyclohex-1-en-1-yl trifluoromethanesulfonate (496)was prepared according to a previously reported procedure. [93] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.07 (1H, s, C**H**), 2.55 (2H, d, *J* = 1.4 Hz, C**H₂**), 2.31 (2H, s, C**H₂**), 1.14 (6H, s, C**H₃**); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 197.5 (C), 166.1 (C), 118.5 (q, *J* = 320.7 Hz, CF_3), 118.4 (CH), 50.7 (CH_2), 42.5 (CH_2), 33.5 (C), 28.1 (2 × CH_3).

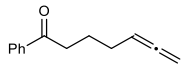


1-Phenylhex-5-yn-1-one (497) was prepared according to a previously reported procedure.[92] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04–7.95 (2H, m, Ar**H**), 7.61–7.53 (1H, m, Ar**H**), 7.47 (2H, dd, *J* = 8.4, 7.0 Hz, Ar**H**), 3.14 (2H, t, *J* = 7.2 Hz, O=CC**H₂**), 2.34 (2H, td, *J* = 6.8, 2.6 Hz, C**H₂**C), 2.04–1.92 (3H, m, C**H** + C**H₂**CH_2C); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 199.7 (C), 137.1 (C),

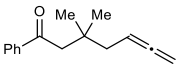
133.2 (CH), 128.7 (2 × CH), 128.2 (2 × CH), 83.9 (C), 69.3 (CH), 37.2 (CH_2), 22.9 (CH_2), 18.1 (CH_2).



3,3-Dimethyl-1-phenylhex-5-yn-1-one (498) was prepared according to a previously reported procedure.[92] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.99–7.92 (2H, m, Ar**H**), 7.59–7.51 (1H, m, Ar**H**), 7.45 (2H, dd, *J* = 8.4, 6.9 Hz, Ar**H**), 3.02 (2H, s, O=CC**H₂**), 2.36 (2H, d, *J* = 2.6 Hz CC**H₂**C), 2.01 (1H, t, *J* = 2.7 Hz, C**H**), 1.15 (6H, s, C**H₃**); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 199.8 (C), 138.4 (C), 133.0 (CH), 128.7 (2 × CH), 128.2 (2 × CH), 82.4 (C), 70.6 (CH), 47.0 (CH_2), 33.9 (C), 31.9 (CH_2), 27.48 (2 × CH_3).



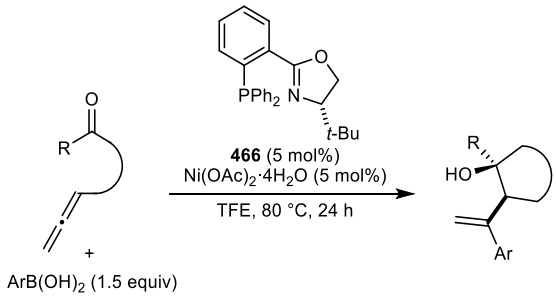
1-Phenylhepta-5,6-dien-1-one (499). Alkyne **497** (517 mg, 3.00 mmol), CuBr (215 mg, 1.50 mmol) and $(CHO)_n$ (455 mg, 15.0 mmol) were dissolved in 1,4-dioxane (15 mL). Diisopropylamine (0.8 mL, 6.00 mmol) was added and the reaction mixture was immersed in a pre-heated oil-bath at 110 °C. The reaction was stirred at the same temperature for 1 h, cooled to room temperature, diluted with EtOAc (20 mL) and filtered through a plug of silica (6 cm in height and 7 cm wide). The silica plug was washed with EtOAc (200 mL) and the solvent was evaporated under reduced pressure. Purification by column chromatography (10% EtOAc/pentane) afforded the allene **499** (309 mg, 55%) as a yellow oil. R_f = 0.14 (10% Et_2O/petroleum ether); IR 2936, 1954 (C=C=C), 1681 (C=O), 1597, 1580, 1447, 1226, 1365, 1000, 841 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.00–7.92 (2H, m, Ar**H**), 7.59–7.52 (1H, m, Ar**H**), 7.50–7.42 (2H, m, Ar**H**), 5.12 (1H, quin, *J* = 6.7 Hz, C**H**), 4.67 (2H, dt, *J* = 6.5, 3.2 Hz C=C**H₂**), 3.02 (2H, t, *J* = 7.3 Hz, O=CC**H₂**), 2.12 (2H, m, C**H₂**CH), 1.89 (2H, quin, *J* = 7.3 Hz, CH_2C**H₂**CH_2); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 208.8 (C), 200.3 (C), 137.2 (C), 133.1 (CH), 128.7 (2 × CH), 128.2 (2 × CH), 89.5 (CH), 75.2 (CH_2), 37.9 (CH_2), 27.9 (CH_2), 23.7 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{13}H_{15}O]^+$ $[M+H]^+$: 187.1117, found: 187.1121.



3,3-Dimethyl-1-phenylhepta-5,6-dien-1-one (500). Alkyne **498** (801 mg, 4.00 mmol), CuBr (287 mg, 2.00 mmol) and $(CHO)_n$ (606 mg, 20.0 mmol) were dissolved in 1,4-dioxane (20 mL). Diisopropylamine (1.1 mL, 8.00 mmol) was added and the reaction mixture was immersed in a pre-heated oil-bath at 110 °C. The reaction was stirred at the same temperature for 1 h, cooled to room temperature, diluted with EtOAc (20 mL) and filtered through a plug of silica (6 cm in height and 7 cm wide). The silica plug was washed with EtOAc (200 mL) and the solvent was evaporated under reduced pressure. Purification by column chromatography (5% EtOAc/pentane to 20%) afforded the allene **500** (174 mg, 20%) as a yellow oil. R_f = 0.41 (10% EtOAc/petroleum ether); IR 2957, 1953 (C=C=C) 1672 (C=O), 1596, 1579, 1466, 1357, 1222, 1006, 747 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.96–7.89 (2H, m, Ar**H**), 7.62–7.50 (1H, m, Ar**H**), 7.45 (2H, dd, *J* = 8.4, 7.0 Hz, Ar**H**), 5.09 (1H, tt, *J* = 8.1, 6.6 Hz, C**H**), 4.59 (2H, dt, *J* = 6.7, 2.4 Hz, C=C**H₂**), 2.89 (2H, s, O=CC**H₂**), 2.14 (2H, dt, *J* = 8.1, 2.4 Hz, C**H₂**CH), 1.07 (6H, s, C**H₃**); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 210.1 (C), 200.3 (C), 138.7 (C), 132.9 (CH), 128.6 (2 × CH), 128.2 (2 × CH), 86.2 (CH), 73.7 (CH_2), 47.6 (CH_2), 41.8 (CH_2), 34.9 (C), 27.5 (2 × CH_3); HRMS (ESI) Exact mass calculated for $[C_{15}H_{19}O]^+$ $[M+H]^+$: 215.1430, found: 215.1431.

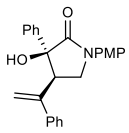
3.2.2. Nucleophilic 1,2-allylation of ketones

General procedure

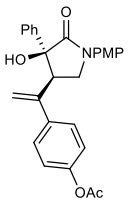


To an oven-dried microwave vial charged with a magnetic stirrer, $Ni(OAc)_2{\cdot}4H_2O$ (3.7 mg, 15 μmol), (*S*)-^{t}BuPHOX (**466**, 5.8 mg, 15 μmol), and boronic acid (0.450 mmol) were added. The vial was sealed and flushed with nitrogen or argon for 10 min. TFE (1.5 mL) was added, the solution was immerged in an oil bath pre-heated

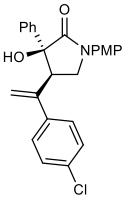
to 80 °C and stirred for 10 min. The allene (0.300 mmol) was added to a separate vial that was sealed and flushed with argon for 10 min. TFE (0.75 mL) was added to the allene and the resulting solution was added dropwise to the one containing the first vial containing the chiral nickel complex. The vial originally containing the substrate was rinsed with additional TFE (0.75 mL) and the rinsing solution was transferred to the first microwave vial *via* syringe. The reaction mixture was stirred at 80 °C for 24 h, cooled to room temperature, diluted with EtOAc (5 mL), filtered through a short pad of silica (3 cm height × 2 cm wide) using EtOAc (20 mL) as eluent, and concentrated *in vacuo*. If necessary, the crude mixture was purified by column chromatography gave the title compound.



(3*S*,4*R*)-3-Hydroxy-1-(4-methoxyphenyl)-3-phenyl-4-(1-phenylvinyl)pyrrolidin-2-one (463). The general procedure was followed using allene **462** (92.2 mg, 0.300 mmol) and phenylboronic acid (54.9 mg, 0.450 mmol). Filtration through silica pad without purification through column chromatography gave 115 mg (99%) of the title compound as a white solid. R_f = 0.26 (30% EtOAc/petroleum ether); m.p. 125-127 °C (Et_2O); IR 3417 (OH), 2954, 1682 (C=O), 1584, 1508, 1397, 1245, 1179, 1057, 828 cm^{-1}; $[\alpha]_D^{20}$ +16.0 (*c* 1.00, $CHCl_3$) ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61–7.55 (2H, m, Ar**H**), 7.41–7.37 (2H, m, Ar**H**), 7.36–7.20 (8H, m, Ar**H**), 6.98–6.92 (2H, m, Ar**H**), 5.51 (1H, s, =C**H**$_2$), 5.35 (1H, s, =C**H**$_2$), 4.03–3.92 (2H, m, C**H**$_2$N), 3.83 (3H, s, OC**H**$_3$), 3.79–3.73 (1H, m, C**H**CH_2), 3.26 (1H, s, O**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.1 (C), 157.3 (C), 146.1 (C), 142.1 (C), 141.9 (C), 131.9 (C), 128.6 (2 × CH), 128.3 (2 × CH), 128.1 (CH), 127.6 (CH), 126.9 (2 × CH), 125.6 (2 × CH), 121.9 (2 × CH), 115.9 (CH_2), 114.4 (2 × CH), 81.2 (C), 55.6 (CH_3), 51.1 (CH_2), 49.9 (CH); HRMS (ESI) Exact mass calculated for $[C_{25}H_{24}NO_3]^+$ $[M+H]^+$: 386.1751, found: 386.1756; Enantiomeric excess was determined by HPLC with a Chiralpak IC column (80:20 *i*hexane:*i*PrOH), 1.0 mL/min, 254 nm, 25 °C; t_r (minor) = 25.7 min; t_r (major) = 33.2 min, 96% *ee*.

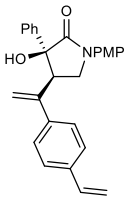


4-{1-[(3*R*,4*S*)-4-Hydroxy-1-(4-methoxyphenyl)-5-oxo-4-phenylpyrrolidin-3-yl]vinyl}phenyl acetate (506). The general procedure was followed using allene **462** (92.2 mg, 0.300 mmol) and 4-acetoxyphenylboronic acid (81.0 mg, 0.450 mmol). Purification by flash column chromatography (5% EtOAc/pentane to 30%) gave 133.0 mg (>99%) of the title compound as a white solid. R_f = 0.26 (30% EtOAc/petroleum ether); m.p. 57-59 °C (Et_2O); IR 3365 (OH), 2935, 1752 (C=O), 1686 (C=O), 1510, 1247, 1194, 908, 829, 697 cm^{-1}; $[\alpha]_D^{28}$ +16.0 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.63–7.52 (2H, m, Ar**H**), 7.40–7.34 (2H, m, Ar**H**), 7.34–7.21 (5H, m, Ar**H**), 6.98–6.88 (4H, m, Ar**H**), 5.48 (1H, s, =C**H**$_2$), 5.34 (1H, s, =C**H**$_2$), 4.04–3.89 (2H, m, C**H**$_2$N), 3.82 (3H, s, OC**H**$_3$), 3.70 (1H, dd, *J* = 6.5, 4.9 Hz, C**H**CH_2), 3.31 (1H, s, O**H**), 2.28 (3H, s, CC**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.0 (C), 169.5 (C), 157.2 (C), 150.1 (C), 145.1 (C), 142.0 (C), 139.6 (C), 131.9 (C), 128.6 (2 × CH), 128.1 (CH), 128.0 (2 × CH), 125.6 (2 × CH), 121.9 (2 × CH), 121.3 (2 × CH), 116.2 (CH_2), 114.4 (2 × CH), 81.1 (C), 55.6 (CH_3), 51.1 (CH_2), 50.0 (CH), 21.2 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{27}H_{25}NNaO_5]^+$ $[M+Na]^+$: 466.1625, found: 466.1619; Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (90:10 *i*hexane:EtOH), 1.0 mL/min, 210 nm, 25 °C; t_r (minor) = 29.0 min; t_r (major) = 37.0 min, 97% *ee*.

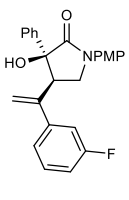


(3*S*,4*R*)-4-[1-(4-Chlorophenyl)vinyl]-3-hydroxy-1-(4-methoxyphenyl)-3-phenylpyrrolidin-2-one (507). The general procedure was followed using allene **462** (92.2 mg, 0.300 mmol) and 4-chlorophenylboronic acid (70.4 mg, 0.450 mmol). Filtration through silica pad without purification through column chromatography gave 125.5 mg (>99%) of the title compound as a white solid. R_f = 0.21 (30% EtOAc/petroleum ether); m.p. 54-56 °C (Et_2O); IR 3401 (OH), 2905, 1672 (C=O), 1511, 1489, 1395, 1247, 1102, 830, 516 cm^{-1}; $[\alpha]_D^{20}$ +12.0 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (2H, d, *J* = 9.1 Hz, Ar**H**), 7.34–7.26 (5H, m, Ar**H**); 7.22–7.11 (4H, m, Ar**H**), 7.00–6.89 (2H, m, Ar**H**), 5.46 (1H, s, =C**H**$_2$), 5.33 (1H, s, =C**H**$_2$), 3.95 (2H, d, *J* = 5.9 Hz, C**H**$_2$N), 3.82 (3H, s, OC**H**$_3$), 3.67 (1H, t, *J* = 5.7 Hz, C**H**CH_2), 3.39 (1H, s, O**H**); ^{13}C (100.6 MHz, $CDCl_3$) δ 173.1 (C), 157.2 (C), 144.6 (C), 141.9 (C), 140.4

(C), 133.3 (C), 131.8 (C), 128.5 (2 × CH), 128.3 (2 × CH), 128.2 (2 × CH), 128.0 (CH), 125.5 (2 × CH), 121.9 (2 × CH), 116.4 (CH_2), 114.3 (2 × CH), 81.1 (C), 55.6 (CH_3), 50.8 (CH_2), 50.0 (CH); HRMS (ESI) Exact mass calculated for $[C_{25}H_{23}Cl^{35}NO_3]^+$ $[M+H]^+$: 420.1361, found: 420.1362. Enantiomeric excess was determined by HPLC with a Chiralpak IC column (80:20 *i*hexane:*i*PrOH), 1.0 mL/min, 210 nm, 25 °C; t_r (minor) = 22.1 min; t_r (major) = 29.3 min, 98% *ee*.

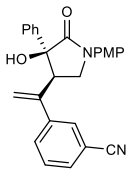


(3*S*,4*R*)-3-Hydroxy-1-(4-methoxyphenyl)-3-phenyl-4-[1-(4-vinyl-phenyl)-vinyl]pyrrolidin-2-one (508). The general procedure was followed using allene **462** (92.2 mg, 0.300 mmol) and 4-vinylphenylboronic acid (66.6 mg, 0.450 mmol). Purification by flash column chromatography (5% EtOAc/pentane to 30%) gave 87.6 mg (71%) of the title compound as a white solid. R_f = 0.26 (30% EtOAc/petroleum ether); m.p. 117-119 °C (Et_2O); IR 3404 (OH), 2921, 1684 (C=O), 1508, 1397, 1244, 1179, 1027, 828, 752, 710 cm^{-1}; $[\alpha]_D^{21}$ +8.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.56 (2H, m, Ar**H**), 7.42–7.37 (2H, m, Ar**H**), 7.37–7.20 (7H, m, Ar**H**), 7.00–6.90 (2H, m, Ar**H**), 6.68 (1H, dd, *J* = 17.6, 10.9 Hz, C**H**=CH_2), 5.72 (1H, dd, *J* = 17.6, 0.9 Hz, CH=C**H₂**), 5.53 (1H, s, C=C**H₂**), 5.33 (1H, s, C=C**H₂**), 5.24 (1H, dd, *J* = 10.9, 0.9 Hz, CH=C**H₂**), 4.05–3.91 (2H, m, C**H₂**N), 3.83 (3H, s, OC**H₃**), 3.79–3.72 (1H, m, C**H**CH_2), 3.10 (1H, s, O**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.1 (C), 157.3 (C), 145.7 (C), 142.1 (C), 141.4 (C), 136.9 (C), 136.4 (CH), 131.9 (C), 128.7 (2 × CH), 128.1 (CH), 127.0 (2 × CH), 126.2 (2 × CH), 125.6 (2 × CH), 121.9 (2 × CH), 115.5 (CH_2), 114.4 (2 × CH), 114.0 (CH_2), 81.2 (C), 55.7 (CH_3), 51.1 (CH_2), 49.6 (CH); HRMS (ESI) Exact mass calculated for $[C_{27}H_{26}NO_3]^+$ $[M+H]^+$: 412.1907, found: 412.1908; Enantiomeric excess was determined by HPLC with a Chiralpak IC column (80:20 *i*hexane:*i*PrOH), 1.0 mL/min, 254 nm, 25 °C; t_r (minor) = 26.5 min; t_r (major) = 33.3 min, 99% *ee*.



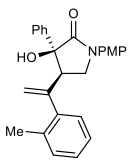
(3*S*,4*R*)-4-[1-(4-Fluorophenyl)vinyl]-3-hydroxy-1-(4-methoxy-phenyl)-3-phenylpyrrolidin-2-one (509). The general procedure was followed using allene **462** (92.2 mg, 0.300 mmol) and 3-fluorophenylboronic acid (63.0 mg, 0.450 mmol). Filtration through

silica pad without purification through column chromatography gave 136.5 mg (>99%) of the title compound as a white solid. R_f = 0.17 (30% EtOAc/petroleum ether); m.p. 120-121 °C (Et_2O); IR 3378 (OH), 2925, 1672 (C=O), 1580, 1512, 1247, 1064, 829, 695, 528 cm^{-1}; $[\alpha]_D^{22}$ +28.0 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.64–7.54 (2H, m, Ar**H**), 7.40–7.34 (2H, m, Ar**H**), 7.34–7.25 (3H, m, Ar**H**), 7.19 (1H, td, *J* = 8.0, 6.0 Hz, Ar**H**), 7.04 (1H, ddd, *J* = 7.8, 1.7, 1.0 Hz, Ar**H**), 7.00–6.88 (4H, m, Ar**H**), 5.51 (1H, s, =C**H₂**), 5.36 (1H, s, =C**H₂**), 4.03–3.92 (2H, m, C**H₂**N), 3.83 (3H, s, OC**H₃**), 3.73–3.67 (1H, m, C**H**CH_2), 3.21 (1H, s, O**H**); ^{13}C (100.6 MHz, $CDCl_3$) δ 173.0 (C), 162.7 (d, $J_{C\text{-}F}$ = 245.6 Hz, C), 157.3 (C), 145.0 (d, $J_{C\text{-}F}$ = 2.1 Hz, C), 144.3 (d, $J_{C\text{-}F}$ = 7.6 Hz, C), 141.9 (C), 131.9 (C), 129.7 (d, $J_{C\text{-}F}$ = 8.3 Hz, CH), 128.7 (2 × CH), 128.2 (CH), 125.5 (2 × CH), 122.6 (d, $J_{C\text{-}F}$ = 2.8 Hz, CH), 121.8 (2 × CH), 116.6 (CH_2), 114.41 (2 × CH), 114.38 (d, $J_{C\text{-}F}$ = 21.1 Hz, CH), 114.0 (d, $J_{C\text{-}F}$ = 22.0 Hz, CH), 81.2 (C), 55.7 (CH_3), 51.0 (CH_2), 49.8 (CH); HRMS (ESI) Exact mass calculated for $[C_{25}H_{22}FNNaO_3]^+$ $[M+Na]^+$: 426.1476, found: 426.1479. Enantiomeric excess was determined by HPLC with a Chiralpak IC column (80:20 *i*hexane:*i*PrOH), 1.0 mL/min, 254 nm, 25 °C; t_r (minor) = 19.7 min; t_r (major) = 25.1 min, 98% *ee*.

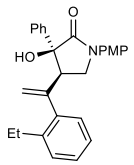


3-{1-[(3*R*,4*S*)-4-Hydroxy-1-(4-methoxyphenyl)-5-oxo-4-phenyl-pyrrolidin-3-yl]vinyl}benzonitrile (510). The general procedure was followed using allene **462** (92.2 mg, 0.300 mmol) and 3-cyanophenylboronic acid (66.1 mg, 0.450 mmol). Purification by flash column chromatography (5% EtOAc/pentane to 50%) gave 110.6 mg (90%) of the title compound as a white solid. R_f = 0.18 (30% EtOAc/petroleum ether); m.p. 76-78 °C (Et_2O); IR 3349 (OH), 2931, 2228 (CN), 1679 (C=O), 1510, 1398, 1246, 1180, 829, 697 cm^{-1}; $[\alpha]_D^{20}$ +16.0 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.59–7.53 (2H, m, Ar**H**), 7.47–7.43 (2H, m, Ar**H**), 7.43–7.40 (1H, m, Ar**H**), 7.32–7.25 (6H, m, Ar**H**), 6.97–6.91 (2H, m, Ar**H**), 5.47 (1H, s, =C**H₂**), 5.38 (1H, s, =C**H₂**), 3.97 (2H, d, *J* = 5.9 Hz, C**H₂**N), 3.81 (3H, s, OC**H₂**), 3.65 (1H, t, *J* = 5.9 Hz, C**H**CH_2), 3.24 (1H, s, O**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.9 (C), 157.3 (C), 143.9 (C), 143.1 (C), 141.6 (C), 131.7 (C), 131.5 (CH), 130.9 (CH), 130.7 (CH) ,129.0 (CH), 128.6 (2 × CH), 128.3 (CH), 125.5 (2 × CH), 121.9 (2 × CH), 118.8 (CN), 117.9

(CH_2), 114.4 (2 × CH), 112.3 (C), 81.1 (C), 55.6 (CH_3), 50.6 (CH_2), 50.1 (CH); HRMS (ESI) Exact mass calculated for $[C_{26}H_{23}N_2O_3]^+$ $[M+H]^+$: 411.1703, found: 411.1707; Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (80:20 *i*hexane:EtOH), 1.0 mL/min, 254 nm, 25 °C; t_r (minor) = 35.2 min; t_r (major) = 50.2 min, 99% *ee*.

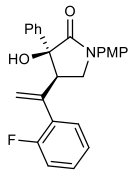


(3*S*,4*R*)-3-Hydroxy-1-(4-methoxyphenyl)-3-phenyl-4-(1-(o-tolyl)vinyl)pyr-rolidin-2-one (511). The general procedure was followed using allene **462** (92.2 mg, 0.300 mmol) and 2-methylphenylboronic acid (61.2 mg, 0.450 mmol). Purification by flash column chromatography (5% EtOAc/pentane to 30%) gave 83.2 mg (69%) of the title compound as a white solid. R_f = 0.43 (30% EtOAc/petroleum ether); m.p. 147-149 °C ($CHCl_3$); IR 3373 (OH), 2914, 1673 (C=O), 1511, 1444, 1245, 1032, 962, 828, 616 cm^{-1}; $[\alpha]_D^{25}$ -10.0 (*c* 1.00, $CHCl_3$) ; ($CDCl_3$, 400 MHz) δ 7.60–7.48 (2H, m, Ar**H**), 7.35–7.18 (5H, m, Ar**H**), 7.15–7.01 (4H, m, Ar**H**), 7.00–6.88 (2H, m, Ar**H**), 5.49 (1H, d, *J* = 1.1 Hz, =C**H₂**), 5.21 (1H, d, *J* = 1.0 Hz, =C**H₂**), 3.98–3.85 (2H, m, C**H₂**N), 3.82 (3H, s, OC**H₃**), 3.63–3.52 (1H, m, C**H**CH_2), 3.25 (1H, s, O**H**), 2.25 (3H, s, ArC**H₃**); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.3 (C), 157.2 (C), 145.3 (C), 142.0 (C), 141.7 (C), 134.8 (C), 132.0 (C), 130.2 (CH), 128.9 (CH), 128.4 (2 × CH), 127.9 (CH), 127.2 (CH), 125.7 (2 × CH), 125.5 (CH), 122.0 (2 × CH), 117.8 (CH_2), 114.3 (2 × CH), 81.3 (C), 55.6 (CH_3), 51.1 (CH), 50.6 (CH_2), 20.2 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{26}H_{26}NO_3]^+$ $[M+H]^+$: 400.1907, found: 400.1905; Enantiomeric excess was determined by HPLC with a Chiralpak IC column (90:10 *i*hexane:*i*PrOH), 1.0 mL/min, 254 nm, 25 °C; t_r (minor) = 39.3 min; t_r (major) = 47.3 min, 84% *ee*.



(3*S*,4*R*)-4-(1-(2-Ethylphenyl)vinyl)-3-hydroxy-1-(4-methoxy-phenyl)-3-phenylpyrrolidin-2-one (512). The general procedure was followed using allene **462** (92.2 mg, 0.300 mmol) and 2-ethylphenylboronic acid (67.5 mg, 0.450 mmol). Purification by flash column chromatography (5% EtOAc/pentane to 15%) gave 70.4 mg (56%) of the title compound as a yellow oil. R_f = 0.28 (30% EtOAc/petroleum ether); IR 3366

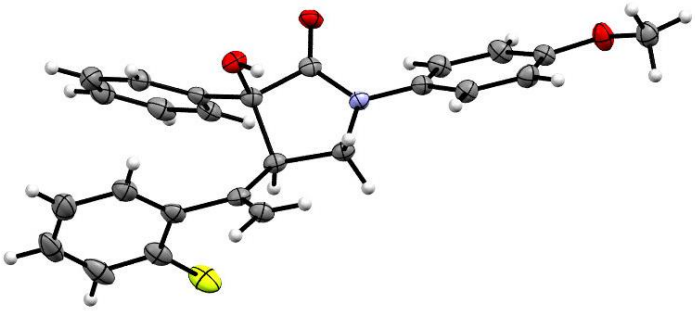
(OH), 2962, 1678 (C=O), 1509, 1441, 1244, 1179, 1030, 827, 748, 696 cm^{-1}; $[\alpha]_D^{25}$ +4.00 (*c* 1.00, $CHCl_3$); ($CDCl_3$, 400 MHz) δ 7.55–7.46 (2H, m, Ar**H**), 7.36–7.30 (2H, m, Ar**H**), 7.32–7.20 (3H, m, Ar**H**), 7.20–7.09 (3H, m, Ar**H**), 7.06 (1H, m, Ar**H**), 6.96–6.89 (2H, m, Ar**H**), 5.50 (1H, s, =C**H₂**), 5.21 (1H, s, =C**H₂**), 3.95–3.84 (2H, m, C**H₂**N), 3.82 (3H, s, OC**H₃**), 3.54 (1H, t, *J* = 5.9 Hz, C**H**CH_2), 3.28 (1H, br m, O**H**), 2.58 (2H, qd, *J* = 7.4, 3.1 Hz, ArC**H₂**CH_3), 1.16 (3H, t, *J* = 7.5 Hz, $ArCH_2$C**H₃**); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.2 (C), 157.2 (C), 145.2 (C), 141.8 (C), 141.5 (C), 141.0 (C), 132.0 (C), 129.1 (CH), 128.4 (2 × CH), 128.3 (CH), 128.0 (CH), 127.5 (CH), 125.8 (2 × CH), 125.4 (CH), 122.1 (2 × CH), 117.9 (CH_2), 114.3 (2 × CH), 81.3 (C), 55.6 (CH_3), 51.5 (CH), 50.7 (CH_2), 26.0 (CH_2), 15.9 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{27}H_{28}NO_3]^+$ $[M+H]^+$: 414.2064, found: 414.2060; Enantiomeric excess was determined by HPLC with a Chiralpak IC column (90:10 *i*hexane:*i*PrOH), 1.0 mL/min, 254 nm, 25 °C; t_r (minor) = 35.0 min; t_r (major) = 40.6 min, 85% *ee*.

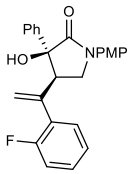


(3*S*,4*R*)-4-[1-(2-Fluorophenyl)vinyl]-3-hydroxy-1-(4-methoxyphenyl)-3-phenylpyrrolidin-2-one (513). The general procedure was followed using allene **462** (92.2 mg, 0.300 mmol) and 2-fluorophenylboronic acid (63.0 mg, 0.450 mmol). Purification by flash column chromatography (5% EtOAc/pentane to 30%) gave 82.3 mg (68%) of the title compound as a white solid. R_f = 0.22 (30% EtOAc/petroleum ether); m.p. 167-170 °C (Et_2O); IR 3398 (OH), 2844, 1672 (C=O), 1513, 1486, 1303, 1245, 1230, 831, 758 cm^{-1}; $[\alpha]_D^{20}$ –12.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.50 (2H, m, Ar**H**), 7.31–7.18 (6H, m Ar**H**), 7.16 (1H, dddd, *J* = 8.2, 7.2, 5.2, 1.9 Hz, Ar**H**), 7.03 (1H, td, *J* = 7.5, 1.2 Hz, Ar**H**), 6.96–6.90 (2H, m, Ar**H**), 6.84 (1H, ddd, *J* = 10.8, 8.2, 1.2 Hz, Ar**H**), 5.46 (1H, s, =C**H₂**), 5.38 (1H, s, =C**H₂**), 4.03 (1H, dd, *J* = 9.8, 5.5 Hz, C**H₂**N), 3.97 (1H, dd, 9.8, 6.6 Hz, C**H₂**N), 3.82 (3H, s, OC**H₃**), 3.77 (1H, dd, *J* = 6.6, 5.5 Hz, C**H**CH_2), 3.09 (1H, s, O**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.1 (C), 159.5 (d, $J_{C\text{-}F}$ = 245.1 Hz, C), 157.2 (C), 141.3 (d, $J_{C\text{-}F}$ = 55.8 Hz, C), 132.0 (C), 131.0 (d, $J_{C\text{-}F}$ = 3.7 Hz, CH), 129.7 (d, $J_{C\text{-}F}$ = 14.0 Hz, C), 129.2 (d, $J_{C\text{-}F}$ = 8.6 Hz, CH), 128.4 (2 × CH), 127.9 (CH), 125.7 (2 × CH), 124.1 (d, *J* = 3.6 Hz, CH), 122.0 (2 × CH), 119.2 (CH_2), 115.4 (d, $J_{C\text{-}F}$ = 22.7 Hz, CH), 114.3 (2 ×

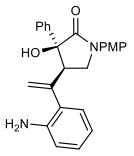
CH), 110.1 (C), 81.2 (C), 55.7 (CH_3), 50.4 (d, $J_{C\text{-}F}$ = 2.8 Hz, CH), 50.3 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{25}H_{23}FNO_3]^+$ $[M+H]^+$: 404.1656, found: 404.1652; Enantiomeric excess was determined by HPLC with a Chiralpak IC column (85:15 *i*hexane:*i*PrOH), 1.0 mL/min, 254 nm, 25 °C; t_r (minor) = 27.5 min; t_r (major) = 32.9 min, 94% *ee*.

Slow diffusion of petroleum ether into a solution of **513** in EtOAc gave crystals that were suitable for X-ray crystallography.



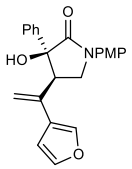


Flack parameter = -0.09(9)



(3S,4R)-4-(1-(2-Aminophenyl)vinyl)-3-hydroxy-1-(4-methoxyphenyl)-3-phenylpyrrolidin-2-one (514). The general procedure was followed using allene **462** (92.2 mg, 0.300 mmol) and 2-aminophenylboronic acid pinacol ester (98.6 mg, 0.450 mmol). Purification by flash column chromatography (20% EtOAc/pentane to 50%) gave 57.2 mg (48%) of the title compound as a white solid. R_f = 0.13 (30% EtOAc/petroleum ether); m.p. 68-70 °C ($CHCl_3$); IR 3364 (OH), 2927, 1657 (C=O), 1615, 1510, 1325, 1121, 1071, 928, 695 cm^{-1}; $[\alpha]_D^{24}$ -6.00 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47 (2H, dd, *J* = 9.2, 2.7 Hz, Ar**H**), 7.40 – 7.34 (2H, m, Ar**H**), 7.32 – 7.21 (3H, m, Ar**H**), 7.01 (1H, td, *J* = 7.7, 1.5 Hz, Ar**H**), 6.94 – 6.86 (3H, m, Ar**H**), 6.67 – 6.59 (2H, m, Ar**H**), 5.45 (1H, d, *J* = 1.5 Hz, =C**H**$_2$), 5.30 (1H, d, *J* = 1.2 Hz, =C**H**$_2$), 4.03 (3H, br s, N**H**$_2$ + O**H**), 3.97 – 3.84 (2H, m, C**H**$_2$N), 3.81 (3H, s, OC**H**$_3$), 3.70 – 3.63 (1H, m, C**H**CH$_2$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.1 (C), 157.2 (C), 143.9 (C), 143.1 (C), 141.9

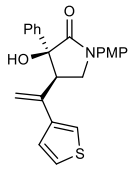
(C), 132.0 (C), 129.1 (CH), 128.54 (C) 128.51 (2 × CH), 128.46 (CH), 128.0 (CH), 125.7 (2 × CH), 122.1 (2 × CH), 118.8 (CH_2), 118.7 (CH), 116.4 (CH), 114.3 (2 × CH), 81.4 (C), 55.6 (CH_3), 51.5 (CH), 50.4 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{25}H_{25}N_2O_3]^+$ $[M+H]^+$: 401.1860, found: 401.1862; Enantiomeric excess was determined by HPLC with a Chiralpak ODH column (70:30 *i*hexane:*i*PrOH), 1.5 mL/min, 254 nm, 25 °C; t_r (major) = 12.6 min; t_r (minor) = 18.3 min, 56% *ee*.



(3*S*,4*R*)-4-[1-(Furan-3-yl)vinyl]-3-hydroxy-1-(4-methoxyphenyl)-3-phenylpyrrolidin-2-one (515). The general procedure was followed using allene **462** (92.2 mg, 0.300 mmol) and 3-furylboronic acid (50.4 mg, 0.450 mmol). Purification through column chromatography (5% EtOAc/pentane to 30%) gave 102.5 mg (91%) of the title compound as a white solid in an inseparable mixture of diastereomers (7:1). R_f = 0.22 (30% EtOAc/petroleum ether); m.p. 160-162 °C (Et_2O); IR 3309 (OH), 2949, 1687 (C=O), 1510, 1396, 1291, 1273, 1214, 906, 698 cm^{-1}; $[\alpha]_D^{25}$ +48.0 (*c* 1.00, $CHCl_3$); HRMS (ESI) Exact mass calculated for $[C_{23}H_{22}NO_4]^+$ $[M+H]^+$: 376.1543, found: 376.1542; Enantiomeric excess was determined by HPLC with a Chiralpak ODH column (85:15 *i*hexane:*i*PrOH), 1.0 mL/min, 254 nm, 25 °C; t_r (minor) = 18.1 min; t_r (major) = 20.9 min, 91% *ee*.

NMR data for major diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.59 (2H, m, Ar**H**), 7.49–7.42 (2H, m, Ar**H**), 7.42–7.31 (4H, m, Ar**H**), 7.15 (1H, t, *J* = 1.2 Hz, Ar**H**), 7.05–6.94 (2H, m, Ar**H**), 6.48 (1H, dd, *J* = 1.9, 0.9 Hz, Ar**H**), 5.54 (1H, s, =C**H**$_2$), 5.23 (1H, s, =C**H**$_2$), 4.05–3.93 (2H, m, C**H**$_2$N), 3.85 (3H, s, OC**H**$_3$), 3.57–3.49 (1H, m, C**H**CH_2), 3.23 (1H, s, O**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.9 (C), 157.3 (C), 143.3 (CH), 142.4 (C), 139.5 (CH), 136.5 (C), 131.9 (C), 128.8 (2 × CH), 128.3 (CH), 127.2 (C), 125.5 (2 × CH), 121.8 (2 × CH), 114.4 (2 × CH), 113.6 (CH_2), 108.8 (CH), 80.8 (C), 55.6 (CH_3), 50.7 (CH_2), 49.9 (CH);

Characteristic NMR data for minor diastereoisomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.14 (1H, t, *J* = 1.2 Hz, Ar**H**), 5.54 (1H, s, =C**H**$_2$), 5.22 (1H, s, =C**H**$_2$), 3.35 (1H, s, O**H**); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 128.8 (CH), 125.5 (CH).

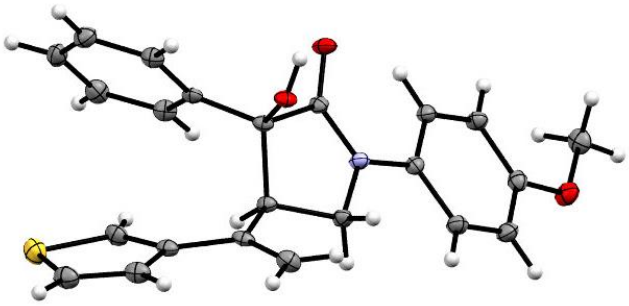


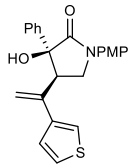
(3*S*,4*R*)-3-Hydroxy-1-(4-methoxyphenyl)-3-phenyl-4-(1-(thio-phen-3-yl)vinyl)pyrrolidin-2-one (516). The general procedure was followed using allene **462** (92.2 mg, 0.300 mmol) and 3-thienylboronic acid (57.6 mg, 0.450 mmol). Purification through column chromatography (5% EtOAc/pentane to 30%) gave 83.4 mg (71%) of the title compound as a white solid in an inseparable mixture of diastereomers (9:1). R_f = 0.24 (30% EtOAc/petroleum ether); m.p. 147-150 °C (Et_2O); IR 3414 (OH), 3148, 1682 (C=O), 1608, 1508, 1398, 1284, 1246, 806, 746 cm^{-1}; $[\alpha]_D^{25}$ +36.0 (*c* 1.00, $CHCl_3$); HRMS (ESI) Exact mass calculated for $[C_{23}H_{22}NO_3S]^+$ $[M+H]^+$: 392.1315, found: 392.1312; Enantiomeric excess was determined by HPLC with a Chiralpak ODH column (85:15 *i*hexane:*i*PrOH), 1.0 mL/min, 254 nm, 25 °C; t_r (minor) = 21.4 min; t_r (major) = 24.7 min, 61% *ee*.

NMR data for major diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.58 (2H, m, Ar**H**), 7.46–7.40 (2H, m, Ar**H**), 7.39–7.27 (3H, m, Ar**H**), 7.20 (1H, dt, *J* = 4.4, 2.2 Hz, Ar**H**), 7.11 (1H, dt, *J* = 5.1, 1.9 Hz, Ar**H**), 7.01–6.92 (3H, m, Ar**H**), 5.62 (1H, s, =C**H**$_2$), 5.29 (1H, s, =C**H**$_2$), 4.03–3.91 (2H, m, C**H**$_2$N), 3.83 (3H, s, OC**H**$_3$), 3.76–3.67 (1H, m, C**H**CH_2), 3.13 (1H, s, O**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.0 (C), 157.3 (C), 142.8 (C), 142.4 (C), 140.3 (C), 131.9 (C), 128.8 (2 × CH), 128.3 (CH), 126.5 (CH), 125.6 (CH), 125.5 (2 × CH), 121.9 (2 × CH), 121.5 (CH), 114.5 (CH_2), 114.4 (2 × CH), 81.0 (C), 55.7 (CH_3), 50.9 (CH_2), 49.9 (CH);

Characteristic NMR data for minor diastereoisomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.2 (1H, s, O**H**);

Slow diffusion of petroleum ether into a solution of **516** in EtOAc gave crystals that were suitable for X-ray crystallography.





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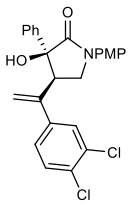
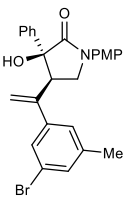
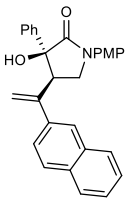


(3*S*,4*R*)-4-[1-(3,4-Dichlorophenyl)vinyl]-3-hydroxy-1-(4-methoxyphenyl)-3-phenylpyrrolidin-2-one (517). The general procedure was followed using allene **462** (92.2 mg, 0.300 mmol) and 3,4-dichlorophenylboronic acid (85.9 mg, 0.450 mmol). Filtration through silica pad without purification through column chromatography gave 136.3 mg (>99%) of the title compound as a white solid. R_f = 0.27 (30% EtOAc/petroleum ether); m.p. 61-64 °C (Et_2O); 3348 (OH), 2954, 1677 (C=O), 1509, 1469, 1396, 1244, 1027, 825, 696 cm^{-1}; $[\alpha]_D^{25}$ +8.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.53 (2H, m, Ar**H**), 7.32–7.23 (7H, m, Ar**H**), 7.05 (1H, dd, *J* = 8.3, 2.2 Hz, Ar**H**), 6.97–6.91 (2H, m, Ar**H**), 5.47 (1H, s, =C**H**$_2$), 5.35 (1H, d, *J* = 0.9 Hz, =C**H**$_2$), 3.96 (2H, d, *J* = 5.9 Hz, C**H**$_2$N), 3.83 (3H, s, OC**H**$_3$), 3.66–3.58 (1H, m, C**H**CH_2), 3.42 (1H, s, O**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.0 (C), 157.3 (C), 143.7 (C), 142.0 (C), 141.7 (C), 132.2 (C), 131.8 (C), 131.4 (C), 130.0 (CH), 129.0 (CH), 128.6 (2 × CH), 128.2 (CH), 126.3 (CH), 125.5 (2 × CH), 121.9 (2 × CH), 117.2 (CH_2), 114.4 (2 × CH), 81.1 (C), 55.6 (CH_3), 50.7 (CH_2), 50.0 (CH); HRMS (ESI) Exact mass calculated for $[C_{25}H_{22}Cl^{35}{}_2NO_3]^+$ $[M+H]^+$: 454.0971, found: 454.0972; Enantiomeric excess was determined by HPLC with a Chiralpak IC column (80:20 *i*hexane:*i*PrOH), 1.0 mL/min, 254 nm, 25 °C; t_r (minor) = 19.2 min; t_r (major) = 25.3 min, 98% *ee*.

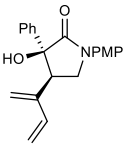


(3*S*,4*R*)-4-[1-(3-Bromo-5-methylphenyl)vinyl]-3-hydroxy-1-(4-methoxy-phenyl)-3-phenylpyrrolidin-2-one (518). The general procedure was followed using allene **462** (92.2 mg, 0.300 mmol) and 3-methyl-5-bromophenylboronic acid (96.7 mg, 0.450 mmol). Filtration through silica pad without purification through column chromatography gave 145.0 mg (>99%) of the title compound as a white solid. R_f = 0.31 (30% EtOAc/petroleum ether); m.p. 59-62 °C (Et_2O); IR 3359 (OH), 2916, 1678 (C=O), 1510, 1442, 1246, 1180, 1140, 1030, 827 cm^{-1}; $[\alpha]_D^{25}$ +20.0 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.61–7.55 (2H, m, Ar**H**), 7.36–7.21 (5H, m, Ar**H**), 7.15 (2H, dd, *J* = 1.6, 0.8 Hz, Ar**H**), 6.96–6.91 (2H, m, Ar**H**), 6.84 (1H, td, *J* = 1.5, 0.8 Hz, Ar**H**), 5.48 (1H, s, =C**H₂**), 5.36 (1H, d, *J* = 0.9 Hz, =C**H₂**), 4.02–3.90 (2H, m, C**H₂**N), 3.82 (3H, s, OC**H₃**), 3.64 (1H, t, *J* = 6.2 Hz C**H**CH_2), 3.45 (1H, s, O**H**), 2.19 (3H, d, *J* = 0.8 Hz, ArC**H₃**); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.0 (C), 157.2 (C), 144.3 (C), 143.7 (C), 141.8 (C), 139.8 (C), 131.9 (C), 131.0 (CH), 128.5 (2 × CH), 128.1 (CH), 127.1 (CH), 126.4 (CH), 125.6 (2 × CH), 122.1 (C), 121.9 (2 × CH), 116.8 (CH_2), 114.4 (2 × CH), 81.1 (C), 55.6 (CH_3), 50.9 (CH_2), 50.0 (CH), 21.2 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{26}H_{25}Br^{79}NO_3]^+$ $[M+H]^+$: 478.1012, found: 478.1023; Enantiomeric excess was determined by HPLC with a Chiralpak IC column 90:10 (*i*hexane:*i*PrOH), 1.0 mL/min, 254 nm, 25 °C; t_r (minor) = 41.2 min; t_r (major) = 54.2 min, 98% *ee*.

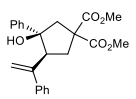


(3*S*,4*R*)-3-Hydroxy-1-(4-methoxyphenyl)-4-(1-(naphthalen-2-yl)vinyl)-3-phenylpyrrolidin-2-one (519). The general procedure was followed using $Ni(OAc)_2 \cdot 4H_2O$ (3.7 mg, 15 μmol), (*S*)-^{t}BuPHOX (11.6 mg, 15 μmol), allene **462** (90.7 mg, 0.300 mmol), 2-naphtylboronic acid (77.4 mg, 0.450 mmol) and MeCN as the solvent. The reaction mixture was left stirring at 80 °C for 24 h. Purification by column chromatography (5% EtOAc/pentane to 30%) gave 94.4 mg (72%) of the title compound as a white solid. R_f = 0.14 (20% EtOAc/petroleum ether); m.p. 101-103 °C (Et_2O); IR 3319 (OH), 1685 (C=O), 1510, 1471, 1403, 1244, 1032, 971, 769, 702 cm^{-1}; $[\alpha]_D^{25}$ +20.0 (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.83–7.77 (1H, m, Ar**H**), 7.77–7.66 (2H, m, Ar**H**), 7.65–7.55 (3H, m, Ar**H**), 7.50–7.38 (5H, m, Ar**H**), 7.35–7.22 (3H, m, Ar**H**),

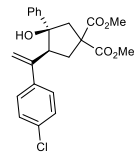
6.94 (2H, d, *J* = 9.0 Hz, Ar**H**), 5.67 (1H, s, =C**H**$_2$), 5.47 (1H, s, =C**H**$_2$), 4.02 (2H, dd, *J* = 5.9, 1.2 Hz, C**H**$_2$N), 3.88 (1H, t, *J* = 5.9 Hz, C**H**CH$_2$), 3.82 (3H, s, OC**H**$_3$), 3.41 (1H, s, O**H**); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 173.1 (C), 157.2 (C), 145.5 (C), 142.1 (C), 139.2 (C), 133.2 (C), 132.7 (C), 132.0 (C), 128.6 (3 × CH), 128.3 (CH), 128.1 (CH), 127.8 (CH), 127.5 (CH), 126.2 (CH), 126.0 (CH), 125.7 (2 × CH), 125.1 (CH), 121.8 (2 × CH), 116.4 (CH_2), 114.3 (2 × CH), 81.2 (C), 55.6 (CH_3), 51.2 (CH_2), 49.9 (CH); HRMS (ESI) Exact mass calculated for $[C_{29}H_{26}NO_3]^+$ $[M+H]^+$: 436.1907, found: 436.1908; Determining the enantiomeric excess was challenging for this compound.



(3*S*,4*R*)-4-(Buta-1,3-dien-2-yl)-3-hydroxy-1-(4-methoxyphenyl)-3-phenylpyrrolidin-2-one (520). The general procedure was followed using allene **462** (92.2 mg, 0.300 mmol) and potassium vinyltrifluoroborate (60.3 mg, 0.450 mmol). Purification through column chromatography (5% EtOAc/pentane to 30%) gave 83.4 mg (65%) of the title compound as a white oil. R_f = 0.26 (30% EtOAc/petroleum ether); IR 3369 (OH), 2931, 1681 (C=O), 1593, 1510, 1441, 1399, 1245, 1180, 828 cm^{-1}; $[\alpha]_D^{25}$ +92.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.61 (2H, m, Ar**H**), 7.47–7.40 (2H, m, Ar**H**), 7.40–7.28 (3H, m, Ar**H**), 7.00–6.93 (2H, m, Ar**H**), 6.41 (1H, ddd, *J* = 17.5, 10.9, 0.8 Hz, CH$_2$=C**H**), 5.36 (1H, s, C**H**$_2$=C), 5.20 (1H, d, *J* = 1.0 Hz, C**H**$_2$=C), 5.12 (1H, d, *J* = 17.5 Hz, C**H**$_2$=CH), 5.04 (1H, dd, *J* = 11.0, 0.9 Hz, CHC**H**$_2$), 3.93 (1H, dd, *J* = 10.0, 6.8 Hz, C**H**$_2$N), 3.88–3.84 (1H, m, C**H**$_2$N), 3.83 (3H, s, OC**H**$_3$), 3.53 (1H, dd, *J* = 6.8, 4.0 Hz, C**H**CH$_2$N), 3.18 (1H, s, O**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.1 (C), 157.2 (C), 143.3 (C), 142.3 (C), 138.8 (CH), 131.9 (C), 128.8 (2 × CH), 128.2 (CH), 125.5 (2 × CH), 121.7 (2 × CH), 117.2 (CH_2), 114.6 (CH_2), 114.4 (2 × CH), 80.8 (C), 55.6 (CH_3), 50.7 (CH_2), 46.3 (CH); HRMS (ESI) Exact mass calculated for $[C_{21}H_{22}NO_3]^+$ $[M+H]^+$: 336.1594, found: 336.1589; Enantiomeric excess was determined by HPLC with a Chiralpak ODH column (90:10 *i*hexane:*i*PrOH), 1.0 mL/min, 230 nm, 25 °C; t_r (minor) = 16.7 min; t_r (major) = 20.6 min, 93% *ee*.

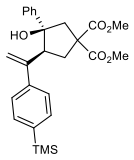


Dimethyl (3*S*,4*S*)-3-hydroxy-3-phenyl-4-(1-phenylvinyl)cyclopentane-1,1-dicarboxylate (528). The general procedure was followed using $Ni(OAc)_2 \cdot 4H_2O$ (3.7 mg, 15 μmol), (*S*)-^{t}BuPHOX (11.6 mg, 15 μmol), allene **476** (90.7 mg, 0.300 mmol), phenylboronic acid (54.9 mg, 0.450 mmol) and MeCN as the solvent. The reaction mixture was left stirring at 80 °C for 24 h. Purification by column chromatography (5% EtOAc/pentane to 20%) gave 37.1 mg (33%) of the title compound as a yellow oil. R_f = 0.41 (30% EtOAc/petroleum ether); IR 3520 (OH), 2952, 1726, 1624, 1494, 1434, 1251, 1198, 1168, 697 cm^{-1}; $[\alpha]_D^{20}$ +0.3 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30 – 7.24 (2H, m, Ar**H**), 7.09 (2H, t, *J* = 7.6 Hz, Ar**H**), 7.07 – 6.99 (4H, m, Ar**H**), 6.94 – 6.87 (2H, m, Ar**H**), 5.34 (2H, apparent s, =C**H₂**), 3.81 (3H, s, OC**H₃**), 3.80 (3H, s, OC**H₃**), 3.73 (1H, dd, *J* = 12.5, 7.3 Hz, C**H**CH_2), 2.89 (1H, dd, *J* = 13.6, 12.5 Hz, CHC**H₂**), 2.84 (2H, d, *J* = 1.9 Hz, HOCC**H₂**), 2.69 (1H, dd, *J* = 13.6, 7.3 Hz, CHC**H₂**), 2.47 (1H, br s, O**H**); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 173.5 (C), 172.9 (C), 146.7 (C), 143.4 (C), 142.5 (C), 127.91 (2 × CH), 127.90 (2 × CH), 127.1 (CH), 126.8 (2 × CH), 126.7 (CH), 125.2 (2 × CH), 116.5 (CH_2), 82.2 (C), 57.2 (C), 54.8 (CH), 53.2 (CH_3), 53.1 (CH_3), 50.5 (CH_2), 38.4 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{23}H_{25}O_5]^+$ $[M+H]^+$: 381.1697, found: 381.1698; Enantiomeric excess was determined by HPLC with a Chiralpak ODH column (90:10 *i*hexane:*i*PrOH), 1.0 mL/min, 210 nm, 25 °C; t_r (major) = 9.06 min; t_r (major) = 10.5 min, 90% *ee*.

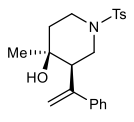


Dimethyl (3*S*,4*S*)-4-(1-(4-chlorophenyl)vinyl)-3-hydroxy-3-phenylcyclopentane-1,1-dicarboxylate (529). The general procedure was followed using allene **476** (90.7 mg, 0.300 mmol), 4-chlorophenylboronic acid (70.4 mg, 0.450 mmol) and MeCN as the solvent. Purification by flash column chromatography (5% EtOAc/pentane to 40%) gave 57.9 mg (47%) of the title compound as a colourless oil. R_f = 0.42 (30% EtOAc/petroleum ether); IR 3523 (OH), 2953, 1726 (C=O), 1622, 1491, 1434, 1250, 1099, 964, 731 cm^{-1}; $[\alpha]_D^{25}$ 40.00 (*c* 1.00, $CHCl_3$) ; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20 – 7.15 (2H, m, Ar**H**), 7.06 – 6.94 (3H, m, Ar**H**), 6.93 – 6.86 (2H, m, Ar**H**), 6.77 – 6.70 (2H, m, Ar**H**), 5.27 (1H, s, =C**H₂**), 5.25 (1H, s, =C**H₂**), 3.73 (3H, s, C**H₃**), 3.72 (3H, s, C**H₃**), 3.62–3.50 (1H, m, C**H**CH_2), 2.78 (1H, dd, *J* = 13.6, 12.4 Hz, CHC**H₂**), 2.76 (2H, s,

HOCC**H**$_2$), 2.60 (1H, dd, *J* = 13.6, 7.3 Hz, CHC**H**$_2$), 2.36 (1H, s, O**H**); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 173.4 (C), 172.9 (C), 145.5 (C), 143.2 (C), 140.9 (C), 132.9 (C), 128.1 (2 × CH), 128.00 (2 × CH), 127.95 (2 × CH), 126.8 (CH), 125.1 (2 × CH), 117.0 (CH_2), 82.3 (C), 57.1 (C), 55.0 (CH), 53.25 (CH_3), 53.19 (CH_3), 50.5 (CH_2), 38.3 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{23}H_{24}Cl^{35}O_5]^+$ $[M+H]^+$: 415.1307, found: 415.1305; Enantiomeric excess was determined by HPLC with a Chiralpak ADH column (90:10 *i*hexane:*i*PrOH), 1.0 mL/min, 254 nm, 25 °C; t_r (minor) = 12.3 min; t_r (major) = 21.2 min, 93% *ee*.

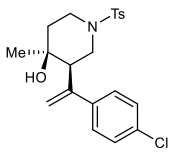


Dimethyl (3*S*,4*S*)-3-hydroxy-3-phenyl-4-(1-(4-(trimethyl-silyl)phenyl)-vinyl)cyclopentane-1,1-dicarboxylate (530). The general procedure was followed using allene **476** (90.7 mg, 0.300 mmol), 4-(trimethylsilyl)phenylboronic acid (87.3 mg, 0.450 mmol) and MeCN as the solvent. Purification by flash column chromatography (5% EtOAc/pentane to 20%) gave 46.0 mg (34%) of the title compound as a colourless oil. R_f = 0.56 (30% EtOAc/petroleum ether); IR 3523 (OH), 2953, 1729 (C=O), 1597, 1495, 1247, 1168, 1092, 908, 826 cm^{-1}; $[\alpha]_D^{25}$ +32.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26 (2H, d, *J* = 7.2 Hz, Ar**H**), 7.20 – 7.13 (2H, m, Ar**H**), 7.11 – 7.03 (2H, m, Ar**H**), 7.03 – 6.97 (1H, m, Ar**H**), 6.89 – 6.83 (2H, m, Ar**H**), 5.36 (1H, s, =C**H**$_2$), 5.34 (1H, s, =C**H**$_2$), 3.81 (3H, s, OC**H**$_3$), 3.79 (3H, s, OC**H**$_3$), 3.70 (1H, dd, *J* = 12.4, 7.2 Hz, C**H**CH_2), 2.89 (1H, dd, *J* = 13.6, 12.5 Hz, CHC**H**$_2$), 2.84 (2H, s, HOCC**H**$_2$), 2.68 (1H, dd, *J* = 13.6, 7.3 Hz, CHC**H**$_2$), 2.44 (1H, br s ,O**H**), 0.20 (9H, s, SiC**H**$_3$); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 173.3 (C), 172.8 (C), 146.6 (C), 143.3 (C), 142.6 (C), 138.9 (C), 132.8 (2 × CH), 127.8 (2 × CH), 126.6 (CH), 126.0 (2 × CH), 125.1 (2 × CH), 116.4 (CH_2), 82.2 (C), 57.0 (C), 54.8 (CH), 53.1 (CH_3), 53.0 (CH_3), 50.4 (CH_2), 38.2 (CH_2), -1.2 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{26}H_{33}O_5Si]^+$ $[M+H]^+$: 453.2092, found: 453.2083; Enantiomeric excess was determined by HPLC with a Chiralpak ASH column (97:3 *i*hexane:*i*PrOH), 1.0 mL/min, 254 nm, 25 °C; t_r (major) = 11.3 min; t_r (minor) = 13.2 min, 89% *ee*.



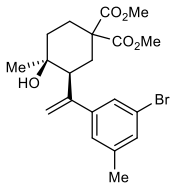
(2*S*,3*S*)-3-Methyl-2-(1-phenylvinyl)-1-tosylpiperidin-3-ol (532). The general procedure was followed using allene **S-1** (88.0 mg, 0.300 mmol), phenylboronic acid (54.9 mg, 0.450 mmol) and MeCN as the solvent.

Purification by column chromatography (5% EtOAc/pentane to 30%) gave 70.6 mg (63%) of the title compound as an off-white solid. R_f = 0.35 (30% EtOAc/petroleum ether); m.p. decomposed at 275 °C; IR 3373 (OH), 2914, 1673, 1511, 1301, 1245, 1094, 1005, 770, 652 cm^{-1}; $[\alpha]_D^{24}$ +36.0 (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.69–7.67 (2H, m, Ar**H**), 7.37–7.26 (7H, m), 5.41 (1H, s, =C**H**$_2$), 5.04 (1H, s, =C**H**$_2$), 3.73 (1H, ddd, *J* = 11.3, 3.9, 2.0 Hz, C**H**$_2$N), 3.67 (1H, ddt, *J* = 11.5, 4.8, 2.3 Hz, C**H**$_2$N), 2.98 (1H, dd, *J* = 12.1, 3.9 Hz, C**H**$_2$N), 2.75–2.67 (2H, m, C**H**$_2$N and C**H**CH$_2$), 2.45 (3H, s, ArC**H**$_3$), 1.81–1.67 (2H, m, C**H**$_2$CH$_2$N), 1.52 (1H, s, O**H**), 0.94 (3H, s, C**H**$_3$COH); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 148.3 (C), 143.7 (C), 143.6 (C), 133.7 (C), 129.9 (2 × CH), 128.8 (2 × CH), 127.9 (CH), 127.8 (2 × CH), 126.4 (2 × CH), 115.6 (CH$_2$), 68.7 (C), 49.0 (CH), 47.1 (CH$_2$), 42.3 (CH$_2$), 38.3 (CH$_2$), 29.8 (CH$_3$), 21.7 (CH$_3$); HRMS (ESI) Exact mass calculated for $[C_{21}H_{26}NO_3S]^+$ $[M+H]^+$: 372.1628, found: 372.1617; Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (90:10 *i*hexane:*i*-PrOH, 1.5 mL/min, 210 nm, 25 °C) t_r (major) = 29.3 min, t_r (minor) = 35.2 min, 85% *ee*.

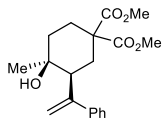


(2*S*,3*S*)-2-(1-(4-Chlorophenyl)vinyl)-3-methyl-1-tosylpiperi-din-3-ol (533). The general procedure was followed using allene **S-1** (88.0 mg, 0.300 mmol), 4-chlorophenylboronic acid (70.3 mg, 0.450 mmol) and MeCN as the solvent. Purification by column chromatography (5% EtOAc/pentane to 30%) gave 58.7 mg (47%) of the title compound as a white solid. R_f = 0.28 (30% EtOAc/petroleum ether); m.p.: 146-148 °C (Et_2O); IR 3523 (OH), 2926, 1597, 1492, 1175, 1089, 1010, 930, 835, 783 cm^{-1}; $[\alpha]_D^{23}$ +140 (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.67 (2H, dd, *J* = 8.7, 2.3 Hz, Ar**H**), 7.37–7.27 (6H, m, Ar**H**), 5.40 (1H, s, =C**H**$_2$), 5.06 (1H, s, =C**H**$_2$), 3.81–3.51 (2H, m, C**H**$_2$N), 2.90 (1H, dd, *J* = 12.1, 3.9 Hz, C**H**$_2$N), 2.78–2.63 (2H, m, C**H**$_2$N and C**H**CH$_2$N), 2.44 (3H, s, ArC**H**$_3$), 1.84–1.65 (2H, m, CC**H**$_2$), 1.49 (1H, s, O**H**), 0.93 (3H, s, C**H**$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.0 (C), 143.7(C), 142.1 (C), 133.8 (C), 133.7 (C), 129.9 (2 × CH), 128.9 (2 × CH), 127.8 (2 × CH), 127.7 (2 × CH), 116.2 (CH$_3$), 68.7 (C), 49.0 (CH), 47.1 (CH$_2$), 42.3 (CH$_2$), 38.4 (CH$_2$), 29.7 (CH$_3$), 21.7 (CH$_3$); HRMS (ESI) Exact mass calculated for $[C_{21}H_{25}Cl^{35}NO_3S]^+$ $[M+H]^+$: 406.1165, found: 406.0671; Enantiomeric excess was determined by HPLC with a Chiralpak AS-H

column (90:10 *i*hexane:*i*PrOH), 1.5 mL/min, 210 nm, 25 °C; t_r (major) = 31.3 min; t_r (minor) = 41.2 min, 81% *ee*.

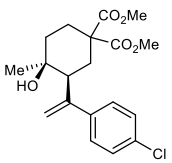


Dimethyl (3*S*,4*S*)-3-(1-(3-bromo-5-methylphenyl)vinyl)-4-hydroxy-4-methylcyclohexane-1,1-dicarboxylate (534). The general procedure was followed using $Ni(OAc)_2 \cdot 4H_2O$ (7.5 mg, 30 μmol), (*S*)-^{t}BuPHOX (11.6 mg, 30 μmol), allene **479** (76.3 mg, 0.300 mmol), phenylboronic acid (96.7 mg, 0.450 mmol) and MeCN as the solvent. The reaction mixture was left stirring at 80 °C for 48 h. Purification by column chromatography (5% EtOAc/pentane to 20%) gave 43.7 mg (34%) of the title compound as ayellow oil. R_f = 0.42 (30% EtOAc/petroleum ether); IR 3547 (OH), 2952, 1726 (C=O), 1594, 1561, 1433, 1375, 1244, 1150, 1034 cm^{-1}; $[\alpha]_D^{25}$ +48.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28 (1H, s, Ar**H**), 7.23 (1H, s, Ar**H**), 7.08 (1H, s, Ar**H**), 5.39 (1H, s, =C**H**$_2$), 5.28 (1H, s, =C**H**$_2$), 3.84 (3H, s, OC**H**$_3$), 3.73 (3H, s, OC**H**$_3$), 2.72 (1H, dd, *J* = 12.8, 3.7 Hz, C**H**CH_2), 2.33 (3H, s, ArC**H**$_3$), 2.38–2.24 (2H, m, C**H**$_2$$CCH_2$), 2.25–2.17 (2H, m, CHC**H**$_2$), 1.74 (1H, dt, *J* = 14.3, 3.5 Hz, HOCC**H**$_2$), 1.62 (1H, br s, O**H**), 1.55–1.46 (1H, m, HOCC**H**$_2$), 0.93 (3H, s, C**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.4 (C), 171.7 (C), 149.7 (C), 146.8 (C), 140.3 (C), 131.1(CH), 126.5 (CH), 125.8 (CH), 122.5 (C), 116.1 (CH_2), 69.8 (C), 55.6 (C), 52.9 (CH_3), 52.8 (CH_3), 47.0 (CH), 36.7 (CH_2), 33.6 (CH_2), 30.0 (CH_3), 26.6 (CH_2), 21.4 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{20}H_{25}Br^{79}NaO_5]^+$ $[M+Na]^+$: 447.0778, found: 447.0775; Enantiomeric excess was determined by HPLC with a Chiralpak IC column (95:5 *i*hexane:*i*PrOH), 1.0 mL/min, 254 nm, 25 °C; t_r (minor) = 15.2 min; t_r (major) = 30.6 min, 64% *ee*.



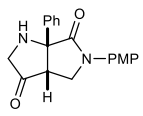
Dimethyl (3*S*,4*S*)-4-hydroxy-4-methyl-3-(1-phenylvinyl)cyclo-hexane-1,1-dicarboxylate (535). The general procedure was followed using $Ni(OAc)_2 \cdot 4H_2O$ (7.5 mg, 30 μmol), (*S*)-^{t}BuPHOX (11.6 mg, 30 μmol), allene **479** (76.3 mg, 0.300 mmol), phenylboronic acid (54.9 mg, 0.450 mmol) and MeCN as the solvent. The reaction mixture was left stirring at 80 °C for 48 h. Purification by column chromatography (gradient 5% to 20% EtOAc/pentane) gave 25.1 mg (25%) of the title compound as a yellow oil. R_f = 0.38

(30% EtOAc/petroleum ether); IR 3543 (OH), 2952, 1726 (C=O), 1432, 1305, 1227, 1097, 1021, 918, 893 cm^{-1}; $[\alpha]_D^{25}$ +72.0 (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.41–7.29 (4H, m, Ar**H**), 7.30–7.22 (1H, m, Ar**H**), 5.42 (1H, s, =C**H₂**), 5.24 (1H, s, =C**H₂**), 3.82 (3H, s, OC**H₃**), 3.73 (3H, s, OC**H₃**), 2.88 (1H, dd, *J* = 13.0, 3.7 Hz, C**H**CH_2), 2.43–2.26 (2H, m, C**H₂**CCH_2), 2.26–2.12 (2H, m, CHC**H₂**), 1.75 (1H, dt, *J* = 14.2, 3.5 Hz, HOCC**H₂**), 1.65 (1H, br s, O**H**), 1.54–1.41 (1H, m, HOCC**H₂**), 0.90 (3H, s, C**H₃**); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.5 (C), 171.9 (C), 150.9 (C), 144.8 (C), 128.6 (2 × CH), 127.5 (CH), 126.3 (2 × CH), 115.2 (CH_2), 69.7 (C), 55.6 (C), 52.9 (CH_3), 52.7 (CH_3), 46.9 (CH), 36.6 (CH_2), 33.5 (CH_2), 30.1 (CH_3), 26.6 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{19}H_{25}O_5]^+$ $[M+H]^+$: 333.1697, found: 333.1690; Enantiomeric excess was determined by HPLC with a Chiralpak IC column (95:5 *i*hexane:*i*PrOH), 1.0 mL/min, 254 nm, 25 °C; t_r (minor) = 15.2 min; t_r (major) = 32.7 min, 70% *ee*.



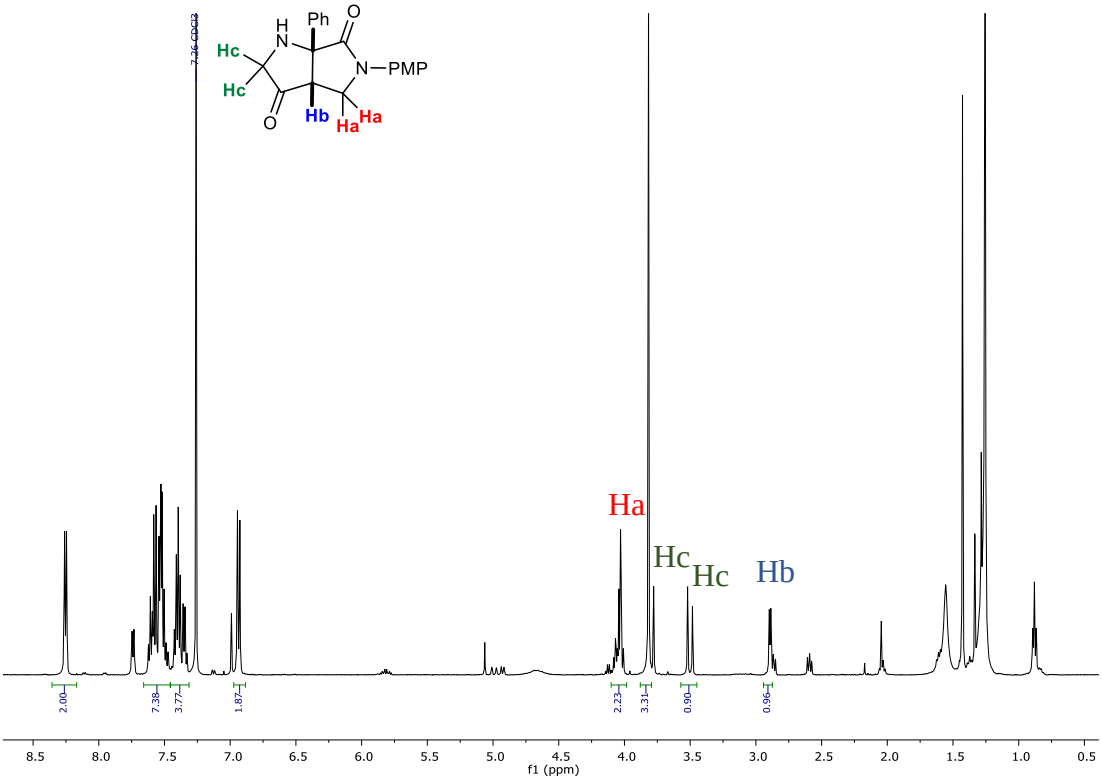
Dimethyl (3*S*,4*S*)-3-(1-(4-chlorophenyl)vinyl)-4-hydroxy-4-methyl-cyclohexane-1,1-dicarboxylate (536). The general procedure was followed using $Ni(OAc)_2 \cdot 4H_2O$ (7.5 mg, 30 μmol), (*S*)-^{t}BuPHOX (11.6 mg, 30 μmol), allene **479** (76.3 mg, 0.300 mmol), 4-chlorophenylboronic acid (70.4 mg, 0.450 mmol) and MeCN as the solvent. The reaction mixture was left stirring at 80 °C for 48 h. Purification by column chromatography (5% EtOAc/pentane to 20%) gave 83.2 mg (76%) of the title compound as a yellow oil. R_f = 0.29 (30% EtOAc/petroleum ether); IR 3538 (OH), 2952, 1721 (C=O), 1489, 1431, 1302, 1226, 1155, 1119, 893 cm^{-1}; $[\alpha]_D^{25}$ +88.0 (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.31–7.27 (4H, m, Ar**H**), 5.40 (1H, s, =C**H₂**), 5.27 (1H, s, =C**H₂**), 3.81 (3H, s, OC**H₃**), 3.73 (3H, s, OC**H₃**), 2.82 (1H, dd, *J* = 13.2, 3.4 Hz, C**H**CH_2), 2.33 (1H, ddd, *J* = 13.3, 3.5, 2.2 Hz, CHC**H₂**), 2.28–2.13 (3H, m, CHC**H**$_2$ and C**H₂**), 1.74 (1H, ddd, *J* = 14.3, 3.9, 2.9 Hz, HOCC**H₂**), 1.61 (1H, br s, O**H**), 1.45 (1H, ddd, *J* = 14.4, 13.4, 4.8 Hz, HOCC**H₂**), 0.90 (3H, s, C**H₃**); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.4 (C), 171.9 (C), 149.7 (C), 143.2 (C), 133.4 (C), 128.8 (2 × CH), 127.6 (2 × CH), 115.7 (CH_2), 69.7 (C), 55.5 (C), 52.9 (CH_3), 52.7 (CH_3), 46.8 (CH), 36.7 (CH_2), 33.6 (CH_2), 30.0 (CH_3), 26.5 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{19}H_{24}Cl^{35}O_5]^+$ $[M+H]^+$: 367.1307, found: 367.1307;

Enantiomeric excess was determined by HPLC with a Chiralpak IC column (95:5 *i*hexane:*i*PrOH), 1.0 mL/min, 210 nm, 25 °C; t_r (minor) = 14.5 min; t_r (major) = 28.9 min, 76% *ee*.



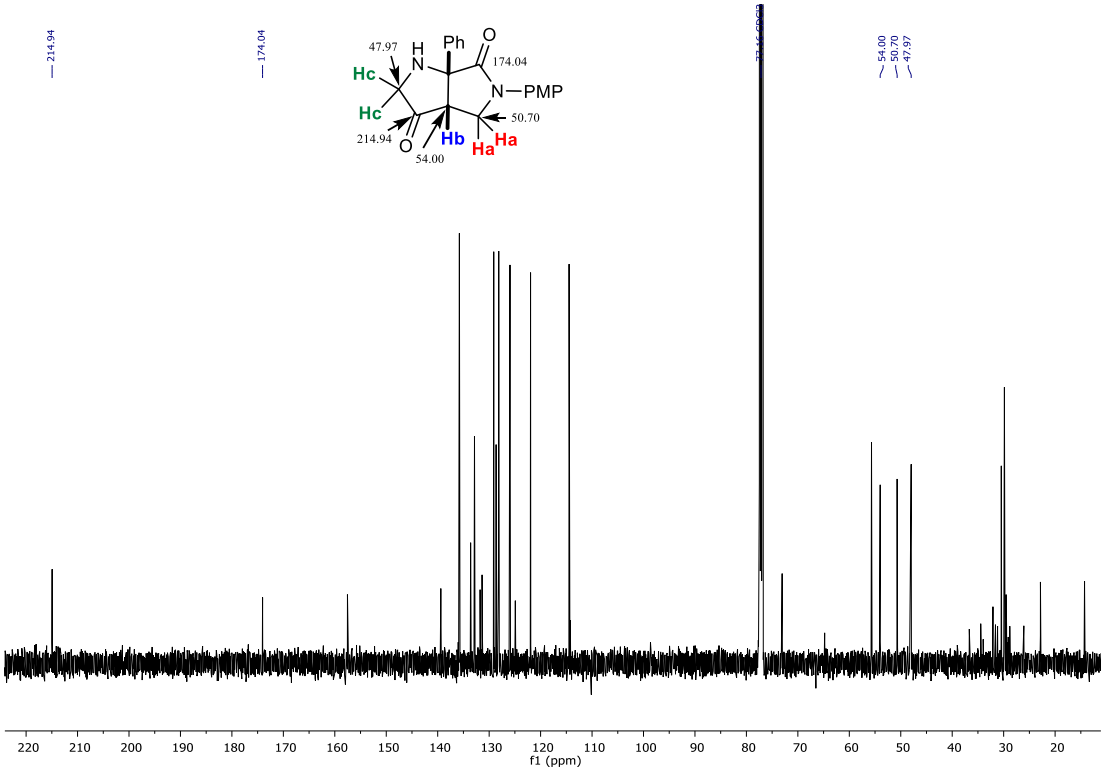
5-(4-Methoxyphenyl)-6a-phenylhexahydropyrrolo[3,4-b]pyr-role-3,6-dione (558). The general procedure was followed using $Ni(OAc)_2 \cdot 4H_2O$ (0.6 mg, 2.5 μmol), 2-[2-(diphenylphosphino)-ethyl]pyridine (0.9 mg, 2.5 μmol), allene **471** (16.1 mg, 0.050 mmol), phenylboronic acid (9.1 mg, 0.0750 mmol) and TFE (0.5 mL) as the solvent. Purification by preparative thin layer chromatography of compound **558** proved to be challenging and the product was obtained mixed with the allene **471** The yield could not be obtained accurately. R_f = 0.17 (40% EtOAc/petroleum ether); The NMR of the isolated compound shows that the sample is around 75% pure, however it is possible to determine the major compound present. Distinctive signals: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.05–4.00 (2H, m, C**H**$_2$NPMP), 3.80 (1H, d, *J* = 18.6 Hz, C**H**$_2$NH), 3.50 (1H, d, *J* = 18.6 Hz, C**H**$_2$NH), 2.89 (1H, d, *J* = 6.2 Hz, C**H**CH_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 214.9 (C), 174.0 (C), 54.0 (CH_2), 50.7 (CH_2), 48.0 (CH); HRMS (ESI) Exact mass calculated for $[C_{19}H_{18}N_2O_3Na]^+$ $[M+Na]^+$: 345.1210, found: 345.1201.

^{1}H-NMR



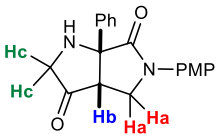
Chemical shifts of the distinctive protons are consistent with the structure. Both diastereotopic protons Ha next to an electronegative amidic nitrogen (around 4 ppm); Hc next to an electronegative nitrogen and a carbonyl (around 3.5 ppm) and Hb next to a carbonyl (between 2 and 3 ppm).

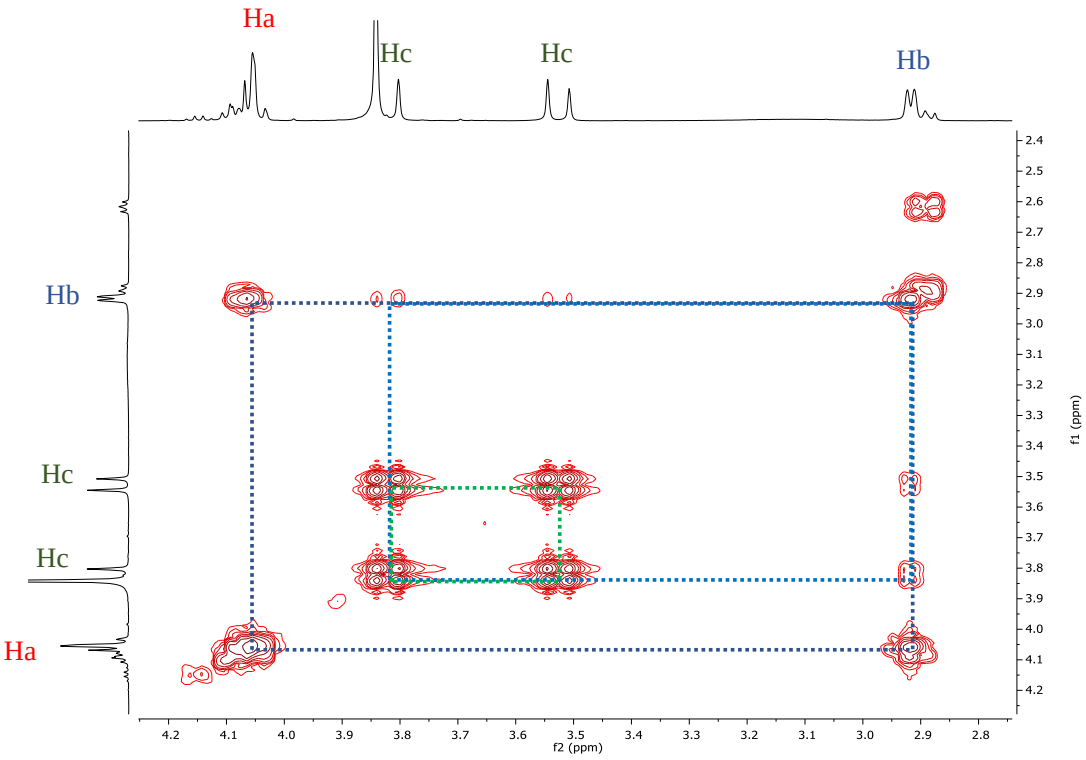
^{13}C-NMR



Highlighted are the distinctive peaks of the structure: 214.9 (C=O in a five-membered ring); 174.0 (C=O of a γ-lactam); Ha, Hb and Hc between 40 and 60 ppm, consistent with the shifts of aliphatic ^{13}C next to electronegative functional groups. Analysis of HSQC spectrum helped in assign the peaks.

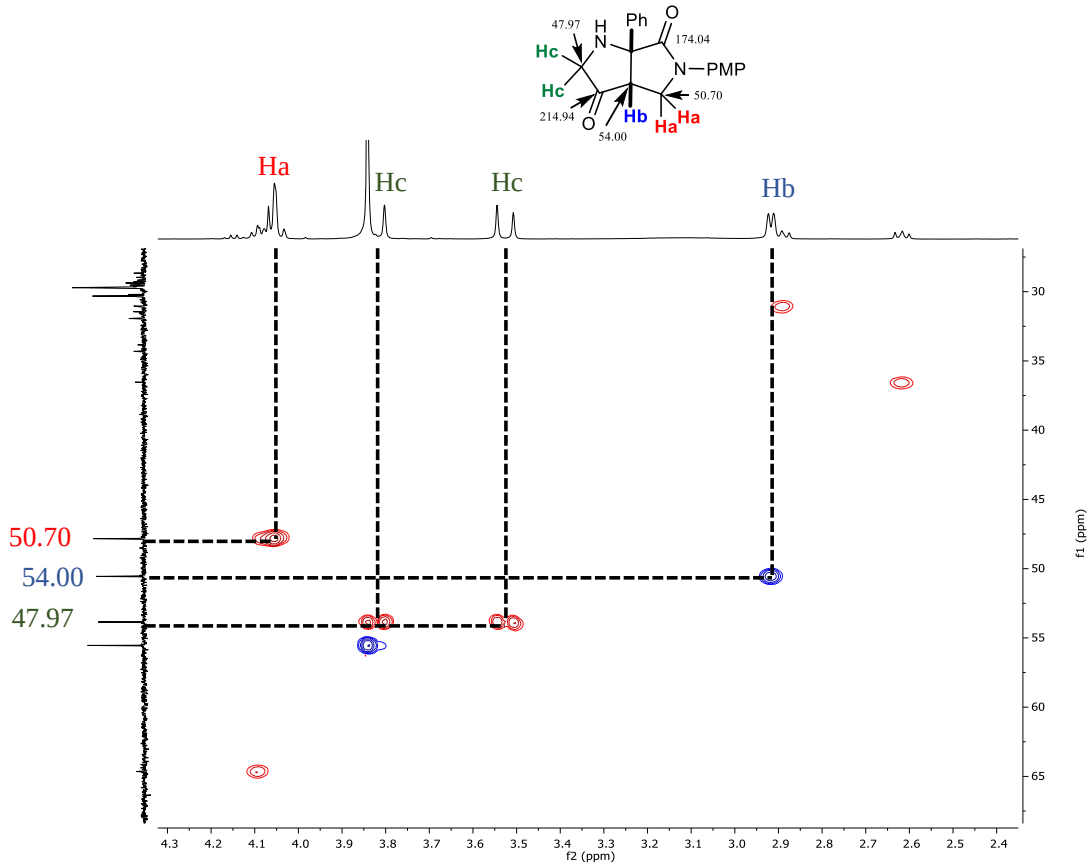
COSY





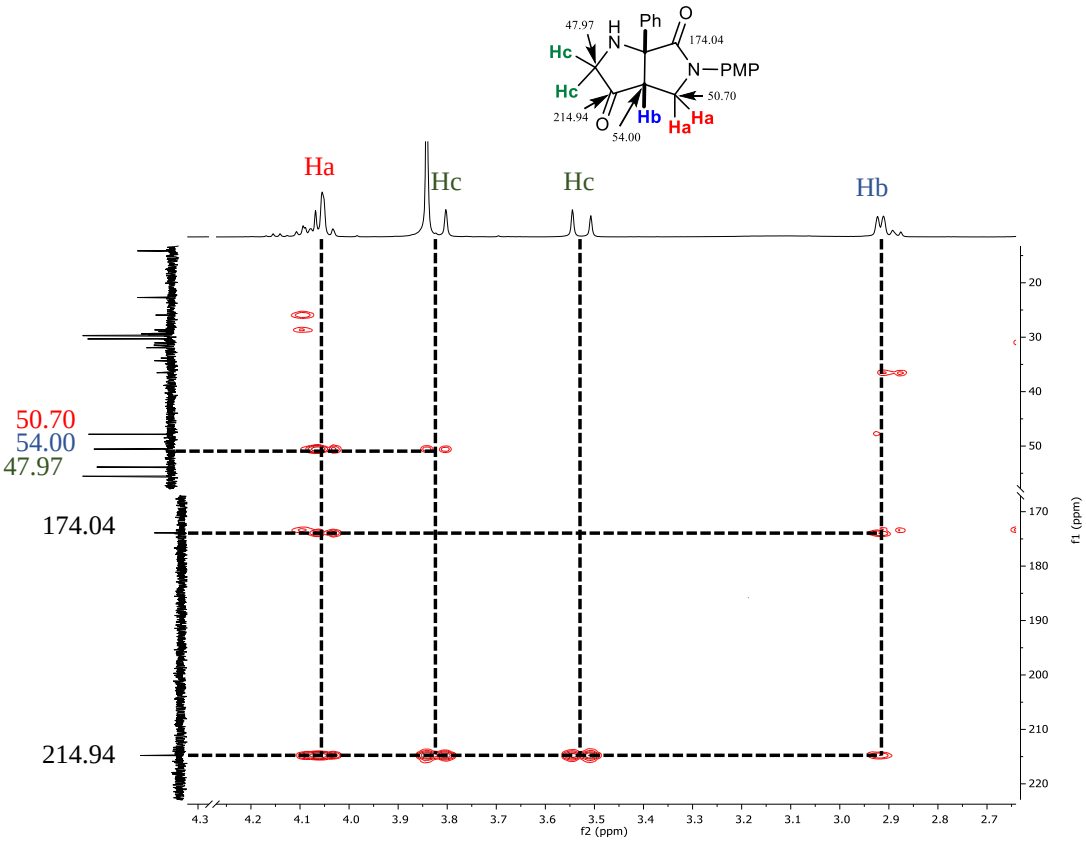
With the COSY spectrum it is possible to note that: Ha has a strong interaction with Hb; the two doublets of each proton Hc interact strongly between themselves and have also a weak interaction with Hb; whereas, there is no interaction between Ha and Hc.

HSQC



With the HSQC spectrum it is possible to assign the signals of the carbons bearing the distinctive protons.

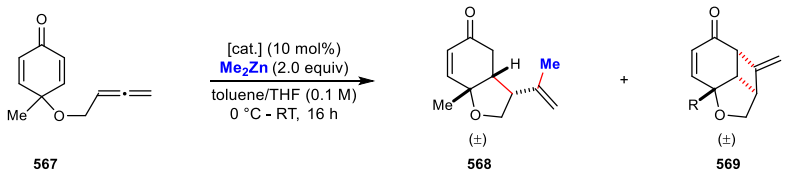
HMBC



Analysing the HMBC spectrum it can be noted that Ha has a J_3 interaction with both the ^{13}C of the amidic carbonyl and of the ketone, plus, it has a J_2 interaction with the ^{13}C bearing Hb; Hc has a J_2 interaction with the ^{13}C of the ketone and a small J_3 interaction with the ^{13}C bearing Hb; Hb has a J_4 interaction with the ^{13}C of the amidic carbonyl and a J_2 interaction with the ^{13}C of the ketone.

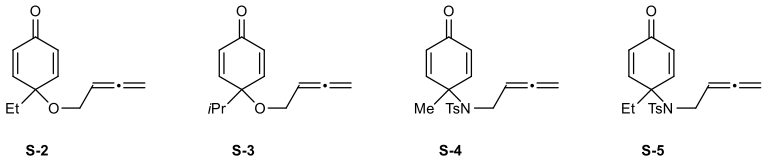
3.3. Progress towards the nucleophilic 1,4-allylation-desymmetrisation of ketones

3.3.1. Reaction development complete screening



Entry	[cat.]	R(sp^3)-M	temp.	time	Conc.	Conv.	568:569
1	-	Me_2Zn	0 °C to RT	16 h	0.1 M	<1%	-
2	$NiBr_2(DME)$	Me_2Zn	0 °C to RT	16 h	0.1 M	>99%	1:2
3	$NiBr_2(PPh_3)_2$	Me_2Zn	0 °C to RT	16 h	0.1 M	>99%	2:1
4	$Ni(acac)_2$	Me_2Zn	0 °C to RT	16 h	0.1 M	>99%	1:10
5	NiI_2	Me_2Zn	0 °C to RT	16 h	0.1 M	91%	1:1.6
6	$Ni(TFA)_2$	Me_2Zn	0 °C to RT	16 h	0.1 M	71%	1:6.7
7	$Ni(OH)_2$	Me_2Zn	0 °C to RT	16 h	0.1 M	<1%	-
8	$NiCl_2(DME)$	Me_2Zn	0 °C to RT	16 h	0.1 M	94%	1:2.8
9	$NiCl_2(PPh_3)_2$	Me_2Zn	0 °C to RT	16 h	0.1 M	81%	2.6:1
10	$NiCl_2(DME)$	Me_2Zn	0 °C	30 min	0.1 M	85%	>1:19
11	NiI_2	Me_2Zn	0 °C	30 min	0.1 M	92%	>1:19
12	$NiBr_2(PPh_3)_2$	Me_2Zn	0 °C	1 h	0.5 M	>99%	>19:1
13	$Pd(OAc)_2$	Me_2Zn	0 °C	1 h	0.1 M	>99%	>19:1
14	$Pd(OAc)_2$	Me_3Al	0 °C	1 h	0.1 M	>99%	messy

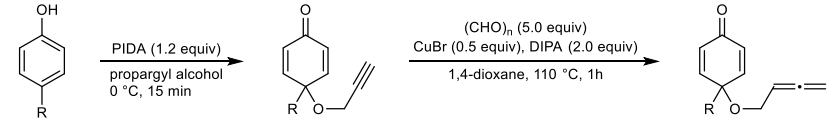
3.3.2. Substrate synthesis



S-2 **S-3** **S-4** **S-5**

Substrates **S-2**,[40] **S-3**, [40] **S-4**[52] and **S-5**[52] were prepared by Thi Le Nhon Nguyen following known procedures.

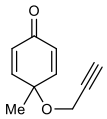
*Preparation of oxygen-tethered allenes **567** and **576***



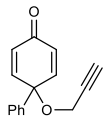
572 R = Me
573 R = Ph

574 R = Me: 61%
575 R = Ph: 25%

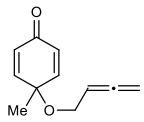
567 R = Me: 53%
576 R = Ph: 60%



4-Methyl-4-(prop-2-yn-1-yloxy)cyclohexa-2,5-dien-1-one (574) was synthesised following a known procedure.[40] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.79-6.85 (m, 2H, MeCC**H**), 6.28-6.32 (m, 2H, O=CC**H**), 3.98 (d, *J* = 2.4 Hz, 2H, OC**H₂**), 2.46 (t, *J* = 2.4 Hz, 1H, CH_2CC**H**), 1.47 (s, 3H, C**H₃**); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 184.9, 150.5, 130.5, 80.2, 74.9, 73.3, 53.7, 26.3.

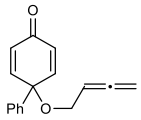


1-(Prop-2-yn-1-yloxy)-[1,1'-biphenyl]-4(1*H*)-one (575) was synthesised following a known procedure. [40] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.53–7.44 (2H, m, Ar**H**), 7.42–7.30 (3H, m, Ar**H**), 6.93–6.83 (2H, m, PhCC**H**), 6.47–6.35 (2H, m, O=CC**H**), 4.24 (2H, d, *J* = 2.4 Hz, OC**H₂**), 2.50 (1H, t, *J* = 2.4 Hz, CH_2CC**H**); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 185.4, 149.5, 137.6, 130.2, 128.9, 128.6, 125.8, 80.4, 77.1, 75.2, 53.5.



4-(Buta-2,3-dien-1-yloxy)-4-methylcyclohexa-2,5-dien-1-one (567) was synthesised following a known procedure. [40] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.82 (2H, d, *J* = 10.2 Hz, MeCC**H**), 6.29 (2H, d, *J* = 10.2 Hz,

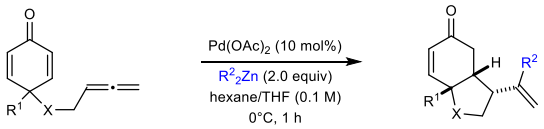
O=CC**H**), 5.21 (1H, quin, *J* = 6.8 Hz, CH_2C**H**), 4.77 (2H, dt, *J* = 6.6, 2.4 Hz, OC**H**$_2$), 3.87 (2H, dt, *J* = 7.1, 2.4 Hz, CC**H**$_2$), 1.45 (3H, s, C**H**$_3$); ^{13}C ($CDCl_3$, 100.6 MHz,) δ 209.5, 185.3, 151.9, 130.2, 88.6, 76.2, 72.9, 64.2, 26.6.



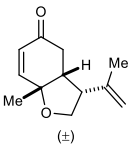
1-(Buta-2,3-dien-1-yloxy)-[1,1'-biphenyl]-4(1*H*)-one (576) was synthesised following a known procedure.[40] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.56–7.43 (2H, m, Ar**H**), 7.43–7.28 (3H, m, Ar**H**), 6.92–6.76 (2H, m, MeCC**H**), 6.46–6.25 (2H, m, O=CC**H**), 5.33 (1H, quin, *J* = 6.7 Hz, CH_2C**H**), 4.82 (2H, dt, *J* = 6.6, 2.6 Hz, OC**H**$_2$), 4.12 (2H, dt, *J* = 6.8, 2.6 Hz, CC**H**$_2$); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 209.4, 185.8, 150.7, 138.2, 129.8, 129.0, 128.5, 125.9, 88.7, 76.7, 76.5, 63.6.

3.3.3. Nucleophilic 1,4-allylation of ketones

General procedure

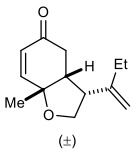


To an oven-dried microwave vial charged with a magnetic stirrer, the allene (0.300 mmol), $Pd(OAc)_2$ (6.7 mg, 30.0 μmol) or $NiBr_2(PPh)_3$ (22.4 mg, 30.0 μmol) were added, sealed and flushed with Ar for 5 min. THF was added to the vial and the mixture was cooled to to 0 °C. Dialkylzinc (0.60 mmol) was added. The reaction was left at 0 °C for 1 h. The reaction was quenched with Et_2O (2 mL), warmed to room temperature, filtered through a short pad of silica using Et_2O (15 mL) as eluent and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography to give the title compound.

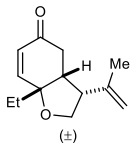


(±) 7a-methyl-3-(prop-1-en-2-yl)-2,3,3a,7a-tetrahydrobenzofuran-5(4*H*)-one (568). The general procedure was followed using allene **567** (52.9 mg, 0.300 mmol), $Pd(OAc)_2$ (6.7 mg, 30.0 μmol), THF (3 mL), dimethylzinc (1.2 M solution in toluene, 0.5 mL, 0.600 mmol). Filtration through

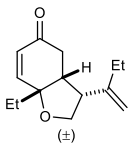
silica pad (Et_2O) without purification through column chromatography gave 57.4 mg (>99%) of the title compound as a yellow oil. R_f = 0.17 (20% EtOAc/petroleum ether); IR 2972, 1681 (C=O), 1650, 1447, 1372, 1295, 1117, 1062, 950, 870 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.59 (1H, d, *J* = 10.2 Hz, C**H**=CHC=O), 5.96 (1H, d, *J* = 10.2 Hz, CH=C**H**C=O), 4.93 (1H, s, C=C**H₂**), 4.63 (1H, s, C=C**H₂**), 4.03 (1H, dd, *J* = 8.8, 7.4 Hz, Hz, OC**H₂**), 3.94 (1H, dd, *J* = 10.2, 8.9 Hz, OC**H₂**), 3.18 (1H, q, *J* = 8.0 Hz, OCH_2C**H**), 2.65 (1H, dd, *J* = 15.6, 7.9 Hz, $O=CCH_2C$**H**), 2.34 (1H, dd, *J* = 16.7, 9.0 Hz, O=CC**H₂**), 2.24 (1H, dd, *J* = 16.7, 6.7 Hz, O=CC**H₂**), 1.75 (3H, s, C**H₃**$C=CH_2$), 1.44 (3H, s, C**H₃**CO); ^{13}C (125.7 MHz, $CDCl_3$) δ 199.1 (C), 150.2 (CH), 140.5 (C), 128.6 (CH), 113.2 (CH_2), 78.6 (C), 69.2 (CH_2), 48.5 (CH), 44.0 (CH), 35.5 (CH_2), 27.7 (CH_3), 24.0 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{12}H_{16}NaO_2]^+$ $[M+Na]^+$: 215.1046, found: 215.1043.



(±) 3-(But-1-en-2-yl)-7a-methyl-2,3,3a,7a-tetrahydrobenzofuran-5(4*H*)-one (579). The general procedure was followed using allene **567** (52.9 mg, 0.300 mmol), $Pd(OAc)_2$ (6.7 mg, 30.0 μmol), THF (2.3 mL), diethylzinc (0.9 M solution in toluene, 0.7 mL, 0.600 mmol). Filtration through silica pad (Et_2O) without purification through column chromatography gave 62.0 mg (>99%) of the title compound as a yellow oil. R_f = 0.17 (20% EtOAc/petroleum ether); IR 2966, 1682 (C=O), 1644, 1457, 1411, 1295, 1203, 1117, 1032, 894 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.58 (1H, d, *J* = 10.2 Hz, C**H**=CHC=O), 6.04–5.88 (1H, m, CH=C**H**C=O), 4.94 (1H, s, C=C**H₂**), 4.66 (1H, s, C=C**H₂**), 4.03 (1H, dd, *J* = 8.8, 7.4 Hz, OC**H₂**), 3.94 (1H, dd, *J* = 10.4, 8.8 Hz, OC**H₂**), 3.29–3.15 (1H, m, OCH_2C**H**), 2.70–2.56 (1H, m, $O=CCH_2C$**H**), 2.31 (1H, dd, *J* = 16.7, 8.8 Hz, O=CC**H₂**), 2.23–2.15 (1H, m, O=CC**H₂**), 2.11–1.89 (2H, m, C**H₂**CH_3), 1.44 (3H, s, C**H₃**C), 1.05 (3H, t, *J* = 7.4 Hz, CH_2C**H₃**); ^{13}C (100.6 MHz, $CDCl_3$) δ 199.1 (C), 150.2 (CH), 146.0 (C), 128.6 (CH), 110.9 (CH_2), 78.6 (C), 69.5 (CH_2), 47.3 (CH), 44.1 (CH), 35.7 (CH_2), 30.1 (CH_2), 27.7 (CH_3), 12.2 (CH); HRMS (ESI) Exact mass calculated for $[C_{13}H_{18}NaO_2]^+$ $[M+Na]^+$: 229.1199, found: 229.1198.

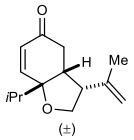


(±) 7a-ethyl-3-(prop-1-en-2-yl)-2,3,3a,7a-tetrahydrobenzofuran-5(4*H*)-one (580). The general procedure was followed using allene **S-2** (57.1 mg, 0.300 mmol), $Pd(OAc)_2$ (6.7 mg, 30.0 μmol), THF (2.5 mL), dimethylzinc (1.2 M solution in toluene, 0.5 mL, 0.600 mmol). Filtration through silica pad (Et_2O) without purification through column chromatography gave 61.8 mg (>99%) of the title compound as a red oil. R_f = 0.26 (20% EtOAc/petroleum ether); IR 2967, 1682 (C=O), 1649, 1459, 1412, 1380, 1252, 1198, 1119, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.57 (1H, d, *J* = 10.3 Hz, C**H**=CHC=O), 6.05 (1H, d, *J* = 10.3 Hz, CH=C**H**C=O), 4.94 (1H, q, *J* = 1.3 Hz, CH_3C=C**H₂**), 4.63 (1H, q, *J* = 1.1 Hz, CH_3C=C**H₂**), 3.99 (1H, dd, *J* = 8.8, 7.2 Hz, OC**H₂**), 3.89 (1H, dd, *J* = 10.1, 8.8 Hz, OC**H₂**), 3.14–3.03 (1H, m, OCH_2C**H**), 2.70 (1H, td, *J* = 8.1, 7.1 Hz, O=CCH_2C**H**), 2.35 (1H, dd, *J* = 16.8, 8.2 Hz, O=CC**H₂**), 2.25 (1H, dd, *J* = 16.8, 7.1 Hz, O=CC**H₂**), 1.83–1.67 (5H, m, C**H₃**C=CH_2 and CC**H₂**), 0.93 (3H, t, *J* = 7.6 Hz, C**H₃**CH_2); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 199.2 (C), 149.4, (CH) 140.7 (C), 129.7 (CH), 113.3 (CH_2), 81.6 (C), 68.8 (CH_2), 48.8 (CH), 41.1 (CH), 35.8 (CH_2), 33.2 (CH_2), 24.0 (CH_3), 8.9 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{13}H_{22}NO_2]^+$ $[M+H_4N]^+$: 224.1645, found: 224.1647.

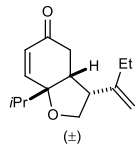


(±) 3-(But-1-en-2-yl)-7a-ethyl-2,3,3a,7a-tetrahydrobenzofuran-5(4*H*)-one (581). The general procedure was followed using allene **S-2** (57.1 mg, 0.300 mmol), $Pd(OAc)_2$ (6.7 mg, 30.0 μmol), THF (2.3 mL) diethylzinc (0.9 M solution in hexane, 0.7 mL, 0.600 mmol). Purification by flash column chromatography (10% EtOAc/pentane) gave 22.1 mg (33%) of the title compound as a yellow oil. R_f = 0.26 (20% EtOAc/petroleum ether) ; IR 2965, 2879, 1682 (C=O), 1644, 1460, 1412, 1297, 1198, 1147, 928 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.56 (1H, d, *J* = 10.3 Hz, C**H**=CHC=O), 6.04 (1H, d, *J* = 10.3 Hz, CH=C**H**C=O), 4.94 (1H, s, CH_3C=C**H₂**), 4.65 (1H, s, CH_3C=C**H₂**), 3.99 (1H, dd, *J* = 8.8, 7.2 Hz, OC**H₂**), 3.89 (1H, dd, *J* = 10.3, 8.8 Hz, OC**H₂**), 3.17 – 3.08 (1H, m, OCH_2C**H**), 2.69 (1H, td, *J* = 8.1, 7.0 Hz, O=CCH_2C**H**), 2.32 (1H, dd, *J* = 16.8, 8.1 Hz, O=CC**H₂**), 2.21 (1H, dd, *J* = 16.8, 7.1 Hz, O=CC**H₂**), 2.12–1.87 (2H, m,

C=CC**H₂**), 1.75 (2H, qd, *J* = 7.6, 4.0 Hz, OCC**H₂**), 1.05 (3H, t, *J* = 7.4 Hz, C=CCH₂C**H₃**), 0.93 (3H, t, *J* = 7.6 Hz, OCCH₂C**H₃**); ^{13}C (100.6 MHz, $CDCl_3$) δ 199.2 (C), 149.4 (CH), 146.2(C), 129.8 (CH), 111.0 (CH_2), 81.6 (C), 69.1 (CH_2), 47.7 (CH), 41.2 (CH), 36.1 (CH_2), 33.2 (CH_2), 30.1 (CH_2), 12.2 (CH_3), 8.9 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{14}H_{20}NaO_2]^+$ $[M+Na]^+$: 243.1356, found: 243.1359.

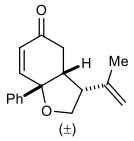


(±) 7a-Isopropyl-3-(prop-1-en-2-yl)-2,3,3a,7a-tetrahydrobenzofuran-5(4*H*)-one (582). The general procedure was followed using allene **S-3** (62.2 mg, 0.300 mmol), $Pd(OAc)_2$ (6.7 mg, 30.0 μmol), THF (2.5 mL), dimethylzinc (1.2 M solution in toluene, 0.5 mL, 0.600 mmol). Filtration through silica pad (Et_2O) without purification through column chromatography gave 56.4 mg (85%) of the title compound as a red oil. R_f = 0.26 (20% EtOAc/petroleum ether); IR 2962, 2877, 1682 (C=O), 1649, 1468, 1384, 1258, 1116, 1052, 938 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.55 (1H, d, *J* = 10.4 Hz, C**H**=CHC=O), 6.11 (1H, d, *J* = 10.4 Hz, CH=C**H**C=O), 4.94 (1H, s, C=C**H₂**), 4.61 (1H, s, C=C**H₂**), 3.93 (1H, dd, *J* = 8.9, 6.9 Hz, OC**H₂**), 3.76 (1H, dd, *J* = 10.2, 8.9 Hz, OC**H₂**), 2.97 (1H, dd, *J* = 17.2, 8.7 Hz, OCH₂C**H**), 2.75 (1H, dd, *J* = 14.5, 8.2 Hz, O=CCH₂C**H**), 2.37 (1H, dd, *J* = 17.1, 6.4 Hz, O=CC**H₂**), 2.27 (1H, dd, *J* = 17.0, 7.6 Hz, O=CC**H₂**), 1.97 (1H, sept, *J* = 6.9 Hz, CH₃C**H**CH₃), 1.72 (3H, s, C**H₃**C=CH₂), 1.01 (3H, d, *J* = 6.9 Hz, C**H₃**CHCH₃), 0.94 (3H, d, *J* = 6.9 Hz, CH₃CHC**H₃**); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 198.9 (C), 148.0 (CH), 140.8 (C), 130.4 (CH), 113.5 (CH_2), 83.6 (C), 68.3 (CH_2), 49.6 (CH), 39.2 (CH), 36.6 (CH), 36.4 (CH_2), 23.9 (CH_3), 17.5 (CH_3), 17.2 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{14}H_{20}NaO_2]^+$ $[M+Na]^+$: 243.1356, found: 243.1357.

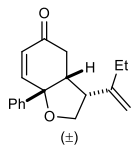


(±) (3*R*,3aR,7a*R*)-3-(But-1-en-2-yl)-7a-isopropyl-2,3,3a,7a-tetrahydrobenzofuran-5(4*H*)-one (583). The general procedure was followed using allene **S-3** (61.3 mg, 0.300 mmol), $Pd(OAc)_2$ (6.7 mg, 30.0 μmol), THF (2.3 mL), diethylzinc (0.9 M solution in hexane, 0.7 mL, 0.600 mmol). Purification by flash column chromatography (10% EtOAc/pentane) gave 35.4 mg (50%) of the title compound as a yellow oil. R_f = 0.26 (20% EtOAc/petroleum ether); IR 2962, 2876, 1683 (C=O), 1644, 1463, 1384, 1258, 1116,

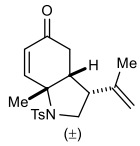
1011, 935 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.55 (1H, d, *J* = 10.4 Hz, C**H**=CHC=O), 6.11 (1H, d, *J* = 10.4 Hz, C**H**C=O), 4.95 (1H, s, C=C**H₂**), 4.64 (1H, s, C=C**H₂**), 3.94 (1H, dd, *J* = 8.9, 6.9 Hz, OC**H₂**), 3.76 (1H, dd, *J*=10.4, 8.9 Hz, OC**H₂**), 3.08–2.92 (1H, m, OCH_2C**H**), 2.74 (1H, ddd, *J*=8.8, 7.6, 6.3 Hz, $O=CCH_2C$**H**), 2.34 (1H, dd, *J*=17.0, 6.3 Hz, O=CC**H₂**), 2.24 (1H, dd, *J*=17.1, 7.6 Hz, O=CC**H₂**), 2.12–1.87 (3H, m, CH_3C**H** and CH_3C**H₂**), 1.04 (3H, t, *J* = 7.4 Hz, C**H₃**CH_2), 1.01 (3H, d, *J*=7.0 Hz, C**H₃**CH), 0.95 (3H, d, *J* = 6.9 Hz, C**H₃**CH); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 199.1 (C), 148.2 (CH), 146.4 (C), 130.6 (CH), 111.2 (CH_2), 83.8 (C), 68.7 (CH_2), 48.6 (CH), 39.4 (CH), 36.8 (CH_2), 36.7 (CH), 30.2 (CH_2), 17.6 (CH_3), 17.4 (CH_3), 12.2 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{15}H_{22}NaO_2]^+$ $[M+Na]^+$: 257.1512, found: 257.1509.



(±) 7a-phenyl-3-(prop-1-en-2-yl)-2,3,3a,7a-tetrahydrobenzofuran-5(4*H*)-one (584). The general procedure was followed using allene **576** (71.5 mg, 0.300 mmol), $Pd(OAc)_2$ (6.7 mg, 30.0 μmol), THF (2.5 mL), dimethylzinc (1.2 M solution in toluene, 0.5 mL, 0.600 mmol). Purification by flash column chromatography (10% EtOAc/pentane) gave 33.9 mg (44%) of the title compound as a colourless oil. R_f = 0.26 (20% EtOAc/petroleum ether); IR 2978, 2878, 1684 (C=O), 1646, 1488, 1408, 1295, 1258, 1163, 1075 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 (4H, d, *J* = 4.3 Hz, Ar**H**), 7.34–7.28 (1H, m, Ar**H**), 6.57 (1H, d, *J* = 10.1 Hz, C**H**=CHC=O), 6.11 (1H, dd, *J* = 10.1, 0.7 Hz, CH=C**H**C=O), 4.94 (1H, d, *J* = 1.3 Hz, C=C**H₂**), 4.67 (1H, d, *J* = 1.1 Hz, CH_3C=C**H₂**), 4.34–4.23 (2H, m, OC**H₂**), 3.06–2.90 (2H, m, OCH_2C**H** and $O=CCH_2C$**H**), 2.52–2.38 (1H, m, O=CC**H₂**), 2.31 (1H, ddd, *J* = 16.2, 5.7 Hz, O=CC**H₂**), 1.66 (3H, s, C**H₃**); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 199.5 (C), 148.0 (CH), 144.8 (C), 140.1 (C), 128.7 (2 × CH), 128.6 (CH), 127.8 (CH), 125.3 (2 × CH), 112.9 (CH_2), 83.0 (C), 69.7 (CH_2), 47.3 (CH), 46.7 (CH), 37.6 (CH_2), 23.6 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{17}H_{18}NaO_2]^+$ $[M+Na]^+$: 277.1199, found: 277.1196.

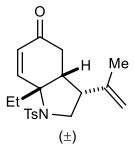


(±) (3*R*,3a*R*,7a*R*)-3-(but-1-en-2-yl)-7a-phenyl-2,3,3a,7a-tetrahydro-benzofuran-5(4*H*)-one (585). The general procedure was followed using allene **576** (71.5 mg, 0.300 mmol), $Pd(OAc)_2$ (6.7 mg, 30.0 μmol), THF (2.3 mL), diethylzinc (0.9 M solution in hexane, 0.7 mL, 0.600 mmol). Purification by flash column chromatography (10% EtOAc/pentane) gave 38.6 mg (48%) as a colourless oil. R_f = 0.30 (20% EtOAc/petroleum ether); IR 2967, 2884, 1685 (C=O), 1642, 1407, 1378, 1236, 1129, 1078, 927 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.42–7.35 (4H, m, Ar**H**), 7.35–7.28 (1H, m, Ar**H**), 6.57 (1H, d, *J* = 10.1 Hz, C**H**=CHC=O), 6.11 (1H, d, *J* = 10.0 Hz, C**H**C=O), 4.95 (1H, s C=C**H₂**), 4.72 (1H, s, C=C**H₂**), 4.35–4.21 (2H, m, OC**H₂**), 3.11–2.89 (2H, m, OCH_2C**H** and $O{=}CCH_2C$**H**), 2.43 (1H, dd, *J*=16.3, 10.8 Hz, O=CC**H₂**), 2.28 (1H, dd, *J*=16.3, 6.0 Hz,), 2.06–1.92 (1H, m, CH_3C**H₂**), 1.91–1.78 (1H, m, CH_3C**H₂**), 0.96 (3H, t, *J* = 7.4 Hz, C**H₃**CH_2); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 199.4 (C), 147.9 (CH), 145.5 (C), 144.6 (C), 128.6 (2 × CH), 128.5 (CH), 127.6 (CH), 125.2 (2 × CH), 110.4 (CH_2), 82.9 (C), 69.8 (CH_2), 46.7 (CH), 46.2 (CH), 35.7 (CH_2), 29.5 (CH_2), 12.0 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{18}H_{21}O_2]^+$ $[M+H]^+$: 269.1536, found: 269.1542.



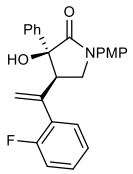
(±) 7a-Methyl-3-(prop-1-en-2-yl)-1-tosyl-1,2,3,3a,4,7a-hexahydro-5*H*-indol-5-one (586). The general procedure was followed using allene **S-4** (98.2 mg, 0.300 mmol), $NiBr_2(PPh)_3$ (22.4 mg, 30.0 μmol), THF (3 mL) dimethylzinc (1.2 M solution in toluene, 0.5 mL, 0.600 mmol). Purification by column chromatography (20% EtOAc/pentane to 30%) gave 67.7 mg (65%) of the title compound as a yellow oil. R_f = 0.45 (40% EtOAc/petroleum ether); IR 2929, 1684 (C=O), 1650, 1598, 1336, 1131, 1110, 984, 897, 708 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68 (2H, d, *J* = 8.3 Hz, Ar**H**), 7.26 (2H, d, *J* = 7.6 Hz, Ar**H**), 7.20 (1H, d, *J* = 10.3 Hz, C**H**=CHC=O), 5.93 (1H, d, *J* = 10.2 Hz, CH=C**H**C=O), 4.91 (1H, d, *J* = 1.2 Hz, C=C**H₂**), 4.57 (1H, s, C=C**H₂**), 3.66 (1H, dd, *J* = 9.4, 7.5 Hz, NC**H₂**), 3.42 (1H, dd, *J* = 10.9, 9.4 Hz, NC**H₂**), 3.20–3.10 (1H, m, NCH_2C**H**), 2.57 (1H, dt, *J* = 13.0, 5.4 Hz, $O{=}CCH_2C$**H**), 2.39 (3H, s, ArC**H₃**), 2.00 (1H, dd, *J* = 16.4, 5.4 Hz, O=CC**H₂**), 1.81 (1H, dd, *J* = 16.4, 12.9 Hz, O=CC**H₂**), 1.70 (3H, s, C**H₃**$C{=}CH_2$), 1.68 (3H, s, C**H₃**CN); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 198.5 (C),

149.3 (CH), 143.6 (C), 139.7 (C), 136.9 (C), 129.7 (2 × CH), 128.2 (CH), 127.2 (2 × CH), 112.8 (CH_2), 64.0 (C), 49.2 (CH_2), 47.7 (CH), 44.1 (CH), 34.5 (CH_2), 28.7 (CH_3), 22.8 (CH_3), 21.6 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{19}H_{23}NNaO_3S]^+$ $[M+Na]^+$: 368.1291, found: 368.1291.



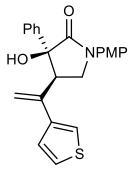
(±) 7a-Ethyl-3-(prop-1-en-2-yl)-1-tosyl-1,2,3,3a,4,7a-hexahydro-5*H*-indol-5-one (587). The general procedure was followed using allene **S-5** (103.0 mg, 0.300 mmol), $Pd(OAc)_2$ (3.4 mg, 15.0 μmol), THF (2.5 mL) dimethylzinc (1.2 M solution in toluene, 0.5 mL, 0.600 mmol). Purification by flash column chromatography (30% EtOAc/pentane) gave 102 mg (91%) of the title compound as a colourless oil. R_f = 0.45 (40% EtOAc/petroleum ether); IR 2922, 1681 (C=O), 1650, 1597, 1461, 1385, 1259, 1160, 1090, 894 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (2H, d, *J* = 8.3 Hz, Ar**H**), 7.19 (2H, d, *J* = 8.0 Hz, Ar**H**), 7.10 (1H, d, *J* = 10.4 Hz, C**H**=CHC=O), 5.97 (1H, dd, *J* = 10.3, 0.9 Hz, CH=C**H**C=O), 4.84 (1H, d, *J* = 1.3 Hz, C=C**H₂**), 4.50 (1H, s, C=C**H₂**), 3.57 (1H, dd, *J* = 9.4, 7.5 Hz, NC**H₂**), 3.33 (1H, dd, *J* = 11.0, 9.4 Hz, NC**H₂**), 3.02 (1H, dt, *J* = 11.2, 7.0 Hz, NCH_2C**H**), 2.67 (1H, dt, *J* = 13.0, 5.4 Hz, $O{=}CCH_2C$**H**), 2.33 (3H, s, Ar**CH₃**), 2.30–2.18 (1H, m, O=CC**H₂**), 1.97–1.82 (2H, m, O=CC**H₂** and CH_3C**H₂**), 1.68–1.58 (4H, m, CH_3C**H₂** and C**H₃**$C{=}CH_2$), 0.80 (3H, t, *J* = 7.5 Hz, C**H₃**CH_2); ^{13}C (100.6 MHz, $CDCl_3$) δ 198.5 (C), 148.5 (CH), 143.6 (C), 139.8 (C), 136.7 (C), 130.2 (CH), 129.6 (2×CH), 127.2 (2×CH) 112.7 (CH_2), 68.2 (C), 48.9 (CH_2), 44.0 (CH), 42.4 (CH), 34.5 (CH_2), 33.0 (CH_2), 22.8 (CH_3), 21.6 (CH_3), 10.0 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{20}H_{25}NNaO_3S]^+$ $[M+Na]^+$: 382.1447, found: 382.1437.

4. Crystal data



Crystal data and structure refinement for 513

Identification code	RSHLOB_2
Empirical formula	$C_{25}H_{22}FNO_3$
Formula weight	403.43
Temperature/K	120(2)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	8.3268(4)
b/Å	13.2914(6)
c/Å	17.8977(6)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1980.82(14)
Z	4
ρ_{calc}g/cm^3	1.353
μ/mm^{-1}	0.776
F(000)	848.0
Crystal size/mm^3	0.262 × 0.058 × 0.052
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.286 to 149.066
Index ranges	$-10 \leq h \leq 8$, $-16 \leq k \leq 16$, $-22 \leq l \leq 22$
Reflections collected	20191
Independent reflections	3993 [R_{int} = 0.0568, R_{sigma} = 0.0377]
Data/restraints/parameters	3993/0/281
Goodness-of-fit on F^2	1.060
Final R indexes [I>=2σ (I)]	R_1 = 0.0369, wR_2 = 0.0833
Final R indexes [all data]	R_1 = 0.0428, wR_2 = 0.0869
Largest diff. peak/hole / e Å^{-3}	0.16/-0.18
Flack parameter	-0.09(9)



Crystal data and structure refinement for 516.

Identification code	RSHLOD
Empirical formula	$C_{23}H_{21}NO_3S$
Formula weight	391.47
Temperature/K	120(2)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	12.7365(2)
b/Å	5.79722(10)
c/Å	12.7552(3)
α/°	90
β/°	102.537(2)
γ/°	90
Volume/Å^3	919.34(3)
Z	2
ρ_{calc}g/cm^3	1.414
μ/mm^{-1}	1.770
F(000)	412.0
Crystal size/mm^3	0.512 × 0.086 × 0.07
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	7.1 to 149.566
Index ranges	$-10 \leq h \leq 15$, $-7 \leq k \leq 7$, $-15 \leq l \leq 14$
Reflections collected	6374
Independent reflections	3631 [R_{int} = 0.0236, R_{sigma} = 0.0316]
Data/restraints/parameters	3631/1/255
Goodness-of-fit on F^2	1.029
Final R indexes [I>=2σ (I)]	R_1 = 0.0420, wR_2 = 0.1103
Final R indexes [all data]	R_1 = 0.0424, wR_2 = 0.1109
Largest diff. peak/hole / e Å^{-3}	0.25/-0.29
Flack parameter	0.00(2)

5. Acknowledgments

The best way to finish this PhD thesis is by thanking the people that have been important during these 4 years (and even longer than that).

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Along with my parents, there is another person that has meant everything to me in these past **four** years, my partner Carla. I don't even know whether I could have finished my doctoral studies if it wasn't for you to support me every day. If I'll obtain the PhD title, it will be yours as much as mine.

My family as a whole has always been important to me and for my accomplishments, above all my granny Chiara, aunts and uncles Anna, Piero, Nicola, Titta, Silvana and my cousins Chiara, Andrea, Federico, Marco, Giordano and Paolo, plus others that are not anymore on this earth, above all nonno Giordano, my source of inspiration. Furthermore, Eugenio and Valentina, whom I consider as family members.

I would like to take the opportunity to thank my mentor, Hon. Choosing you as supervisor has been one of the smartest choices I've ever made. There are many qualities that I learned to appreciate about you, one of which is your humility. As a matter of fact, I think you are so humble that you don't even realise how many things you have taught me (not forcefully related to chemistry).

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Another thing to be grateful about is to be surrounded by very talented and smart people. Therefore, I would like to thank the past and present members of the Lam, Ball, Woodward and Denton groups, I have learned very valuable lessons from each one of you, and these lessons will not be forgotten. Above all, Stamatis, Heena, Somnath, Emma and Lorenzo have been of paramount importance in these four years. Furthermore, I would like also to thank Thi Le Nhon Nguyen, Naeem Iqbal and Lawrence Taylor for all the help provided for the projects described in this thesis.

Emmanouil, honestly, I am happy I found a friend like you. By the way, it was a real pleasure to bring you back to reality giving you some lessons at pool in the past year.

I am sure that the education I received was the linchpin for pursuing my doctoral studies. Therefore, I want to thank my first organic chemistry professor, Prof. Antonella Fontana, and two very special chemists that taught me the basics of lab practice, Prof. Janos Sapi and Dr. Marie Cochard.

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And so, with these last words my journey started in London in 2014 comes to an end. It has been a fantastic odyssey full of ups and downs. Every single experience though was fundamental to teach me those "important things" that Robert Burns Woodward was referring to. Probably, the best way to summarise this journey is by using this quote: "*So if I were to wrap this up tight with a bow or whatever, I guess I'd say my armor, it was never a distraction or a hobby, it was a cocoon. And now I'm a changed man. You can take away my house, all my tricks and toys. One thing you can't take away: I AM IRON MAN.*"

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81 For a complete list of conditions screened, see the supporting information

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