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Enantioselective Nickel-Catalyzed Arylative Intramolecular Allylations of Allenyl Electrophiles

A thesis submitted to The University of Nottingham for the degree of Doctor of Philosophy

By

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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 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. I confirm that the work submitted is my own, except work which has formed part of jointly-authored publications. The contributions of myself and other authors to this work have been specifically indicated where relevant. I confirm that appropriate credit has been given with the thesis where references has been made to the work of others.

The following thesis contains results reported in the following publications:

"Enantioselective nickel-catalyzed arylative intramolecular 1,4-allylations", T.L.N. Nguyen, C. A. Incerti-Pradillos, W. Lewis, H.W. Lam, *Chem. Commun.*, **2018**, 54, 5622-5625.

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Contents

Abstract

Catalytic enantioselective conjugate additions of organometallic reagents to electron-deficient alkenes and asymmetric allylation of carbonyl compounds are important reactions for the construction of new carbon-carbon bonds. However, a method using an allylnickel species to perform catalytic nucleophilic allylation enantioselectively remains considerably underdeveloped and only a handful of examples have been described. In this thesis, enantioselective nickel-catalyzed arylative and alkenylative intramolecular allylations of allenyl electrophiles with boronic acids are described.

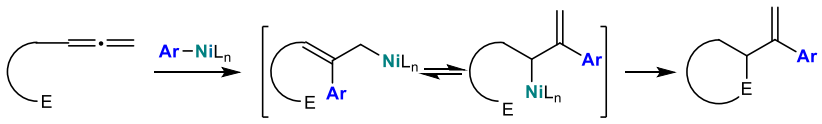


Figure 1. Nickel-catalyzed arylative cyclization of an electrophile tethered allene

Enantioselective nickel-catalyzed arylative intramolecular 1,4-allylations

An asymmetric nickel-catalyzed desymmetrization of allenyl cyclohexa-2,5-dienones by reaction with arylboronic acids is reported. In this study, nucleophilic allylnickel species, formed by nickel-catalyzed arylation of the allene, undergo 1,4-allylation-cyclization reaction to furnish hexahydroindol-5-ones and hexahydrobenzofuran-5-ones with three contiguous stereocenters in high diastereo- and enantioselectivities (87−99% ee).

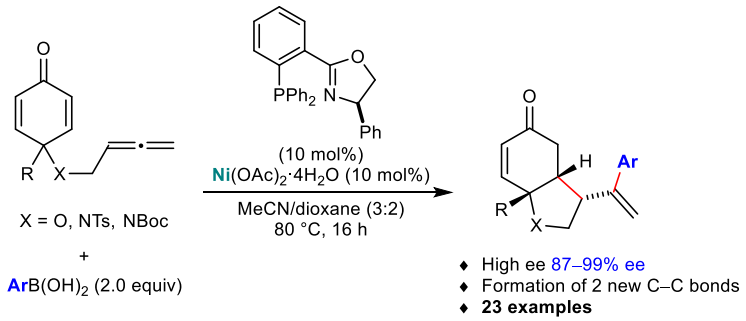


Figure 2. Enantioselective nickel-catalyzed arylative cyclization of allenyl cyclohexa-2,5-dienones

Enantioselective nickel-catalyzed arylative and alkenylative intramolecular 1,2-allylations

An asymmetric nickel-catalyzed cascade reaction of allenyl ketones with boronic acids is described. In this project, a nickel-catalyzed arylation and alkenylation of the allene gives allylnickel species, which undergo a 1,2-allylation-cyclization with tethered ketones to furnish 3-hydroxypyrrolidin-2-ones, 3-hydroxypyrrolidines and 4-hydroxypiperidines in high diastereo- and enantioselectivities.

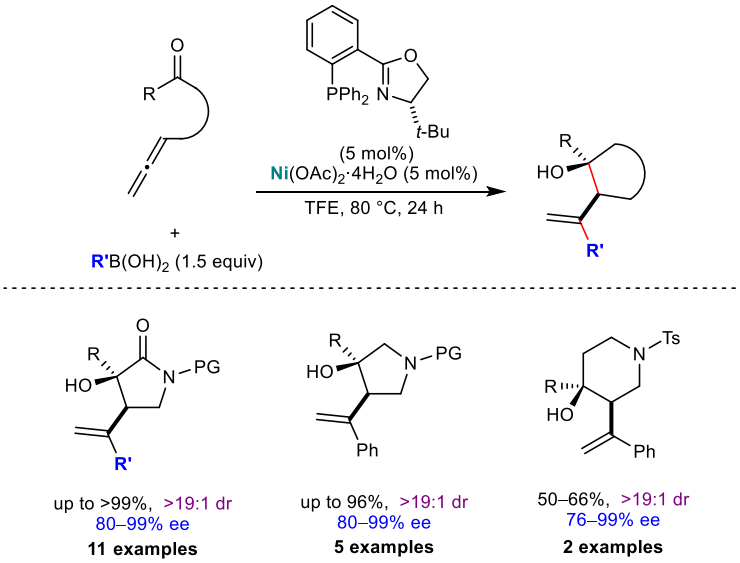


Figure 3. Enantioselective synthesis of chiral pyrrolidine-2-ones, pyrrolidines and piperidines

List of Abbreviations

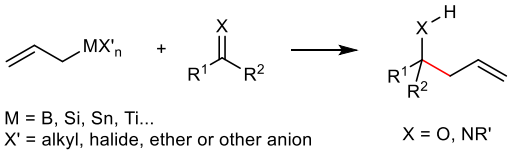
Ac	acetyl
acac	acetylacetonate
Aq.	aqueous
Ar	aryl
Atm	atmosphere
Bn	Benzyl
Boc	*t*-butyloxycarbonyl
Br	broad
Bu	Butyl
cat.	catalytic or catalyst
Cbz	Carboxybenzyl
cod	1,5-cyclooctadiene
Cy	cyclohexyl
d	Doublet
DBA	dibenzylideneacetone
dtt	doublet of triplet of triplets
DMA	Dimethylacetamide
DME	Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
EDG	electron-donating group
ee	enantiomeric excess
equiv	equivalent
Et	ethyl
EWG	electron-withdrawing group
g	gram
h	hour(s)
hex	hexyl

HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
i	iso
IR	infrared
IPA	iso-propanol
LG	leaving group
m	multiplet
Me	methyl
mg	milligram
MHz	megahertz
min	minute(s)
mL	millilitre(s)
mmol	millimole
m.p.	melting point
Ms	mesylate
M.S.	molecular sieves
m/z	mass to charge ratio
NHC	*N*-heterocyclic carbene
Nu	nucleophile
Ph	phenyl
PIDA	(Diacetoxyiodo)benzene
PMP	*para*-methoxyphenyl
rt	room temperature
rr	regioisomeric ratio
t	triplet
TBAF	tetrabutylammonium fluoride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
t	tert(iary)
Ts	*para*-toluenesulfonyl

Throughout this work, “wedges” have been used to indicate stereochemistry at quaternary centres and “blocks” have been used to indicate stereochemistry at tertiary centres. Compounds used as ligands on metal centres are prefaced with the letter L.

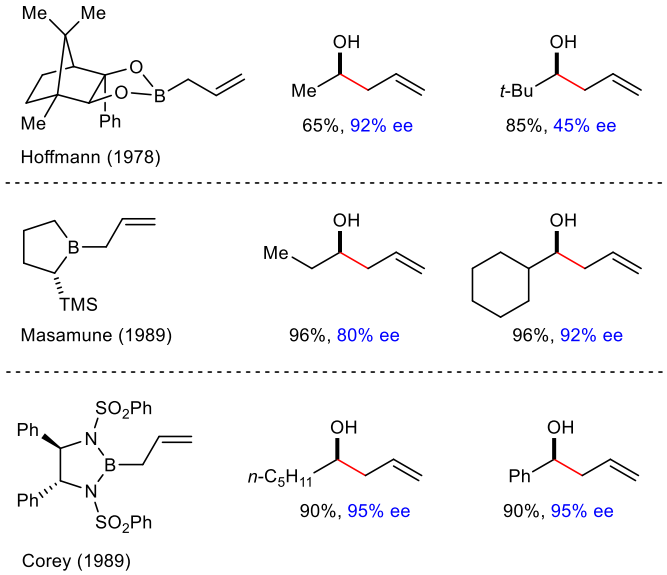
1. Introduction

The catalytic enantioselective carbonyl nucleophilic allylation reaction is one of the most significant reactions in organic synthesis for the asymmetric formation of carbon–carbon and heteroatom-carbon bonds, whilst simultaneously forming a valuable alkene as a versatile motif for further transformations (Scheme 1).[1-10]



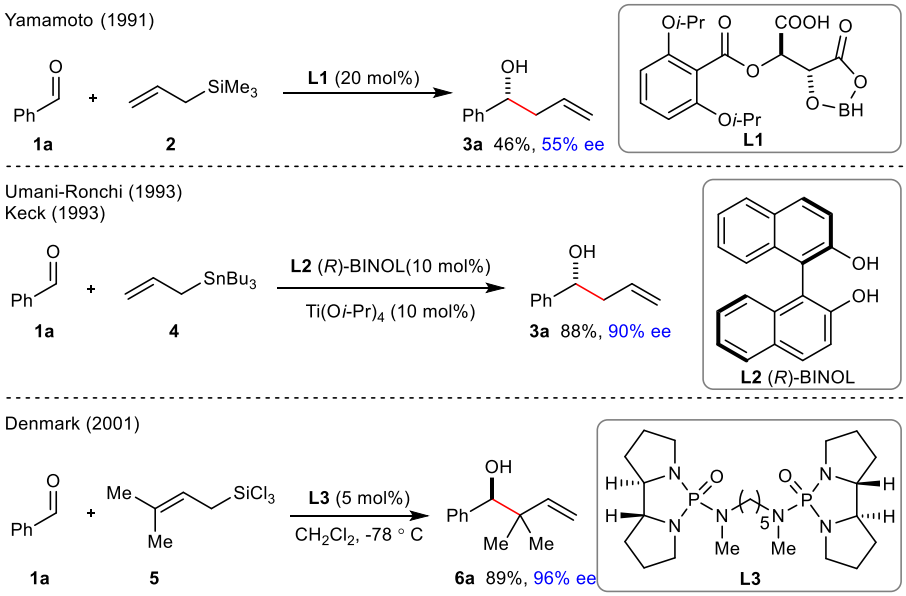
Scheme 1. Allylation reaction

The first carbonyl allylations were reported by Mikhailo and Bubno with the use of isolable allyl boron reagents[11] and Homosi and Sakurai with the use of allyl silanes.[12] Subsequently, Hoffmann et al. established an enantioselective synthesis of allyl alcohols *via* chiral allylborane, considered as the first discovery of using a chiral allyl metal reagent and aldehyde in carbonyl allylation.[13] Since then, a vast majority of protocols for asymmetric carbonyl allylation have been developed based on the use of chirally changed allyl metal compounds (Scheme 2).[14-24]



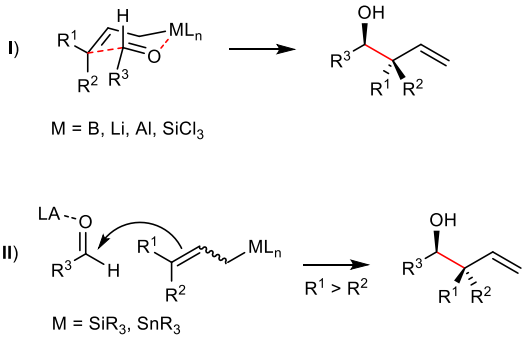
Scheme 2. Selected pioneering examples for enantioselective carbonyl allylation by chiral modified allylmetal compounds

The Yamamoto group reported the first example of chiral Lewis acid-catalyzed asymmetric allylation of aldehydes **1a** with allylsilanes **2** and chiral acyloxy borane **L1**.[25] Following Umani-Ronchi's [26] and Keck's [27] development, highly enantioselective homoallylic alcohols **3a** were obtained with allyltributyltin **4** and chiral complex of **L2** (*R*)-BINOL and Ti(O*i*-Pr)$_4$ in 1993. In the following year, Denmark et al. revealed the first study using chiral Lewis bases for the asymmetric allylation of aldehydes with allyltrichlorosilanes and chiral phosphoramides.[28] In 2001, the same group introduced an elegant study for enantioselective construction of quaternary carbon centers using **5** and **L3** in the same fashion.[29]



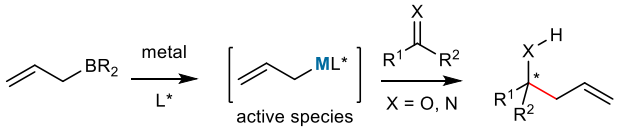
Scheme 3. Early examples of enantioselective carbonyl allylations

For these methods, Denmark and co-workers classified two types of addition pathways for various allylation reagents.[3] In the first approach, allylic organometallic reagents can cooperate with the carbonyl to form a closed six-membered chair-like intermediate furnishing a γ-allylation (Scheme 4i). On the other hand, the carbonyl compound can be activated by an external Lewis acid and attacked by an allyl trialkylsilane or allyl trialkylstannane through an open transition state (Scheme 4ii). Greater degree of regio- and diastereoselectivity is usually achieved in reactions proceeding *via* the closed chair-like transition state.



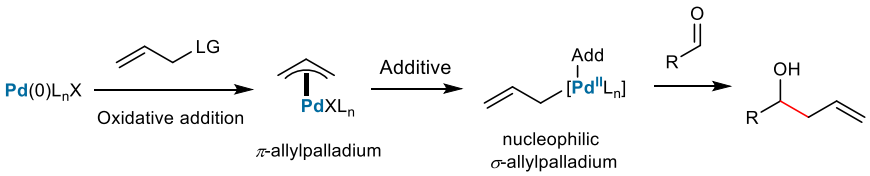
Scheme 4. Two approaches of enantioselective allylation reactions.

In metal-catalyzed enantioselective allylation reactions, which are considered as third type of carbonyl allylation, allylorganometallics react in the presence of metal salts and chiral ligands. The reaction undergoes a transmetallation step consisting of allylorgano-reagents and metal-ligand complex. The stereoselectivity is controlled by chiral ligands associated with the metal (Scheme 5). The asymmetric allylation of substrates including C=O and C=N bonds has been well-documented to furnish homoallylic alcohols or amines.[30-41]



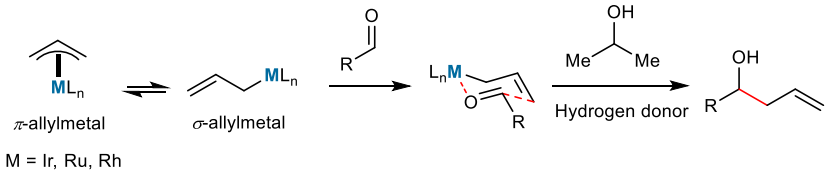
Scheme 5. Metal-catalyzed enantioselective allylation.

One major approach for enantioselective carbonyl allylations involves the reduction of π-allylmetal complexes formed from allylic alcohols, allylic halides or allylic carboxylates (Scheme 6). These reactions required stoichiometric quantities of metallic reductants such as Et_2Zn, SmI_2 and $SnCl_2$, which considered as 'umpolung' process, to generate the corresponding nucleophilic allyl-metal species. These species were trapped by electrophiles such as aldehydes or ketones to give homoallylic alcohols.[42]



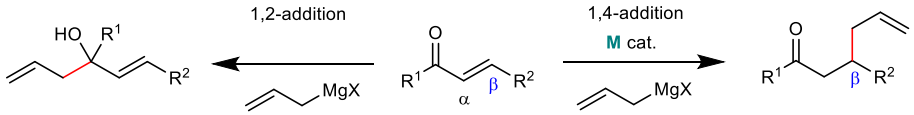
Scheme 6. 'Umpolung' nucleophilic allylation

In addition, asymmetric carbonyl additions may develop in the absence of preformed organometallic reagents or metallic reductants. One alternative approach is based on C−C bond-forming transfer hydrogenation (Scheme 7). [7,10,43]



Scheme 7. Carbonyl addition through transfer hydrogenation

Apart from carbonyl or imine compounds, α,β-unsaturated ketones also play a role as attractive electrophiles because they can either undergo a 1,2-addition when nucleophiles attack at the carbonyl group or a 1,4-addition when nucleophiles attack the β-carbon (Scheme 8).[44-47] Both additions are valuable, however, the products of 1,4-addition still have carbonyl groups that serve as the amenable group for further manipulations.



Scheme 8. Addition reactions of α,β-unsaturated ketones

In the literature review of this thesis, each section will describe a general discussion of the mechanistic aspects of transition-metal-catalyzed asymmetric carbonyl allylations with representative examples. Methods *via* nucleophilic allylmetal complexes will illustrate both 1,2-addition and 1,4-addition to carbonyl compounds for transition-metal-catalyzed enantioselective allylation reactions. Then an approach to allylations using domino reactions with allenes as allyl donors will be discussed.

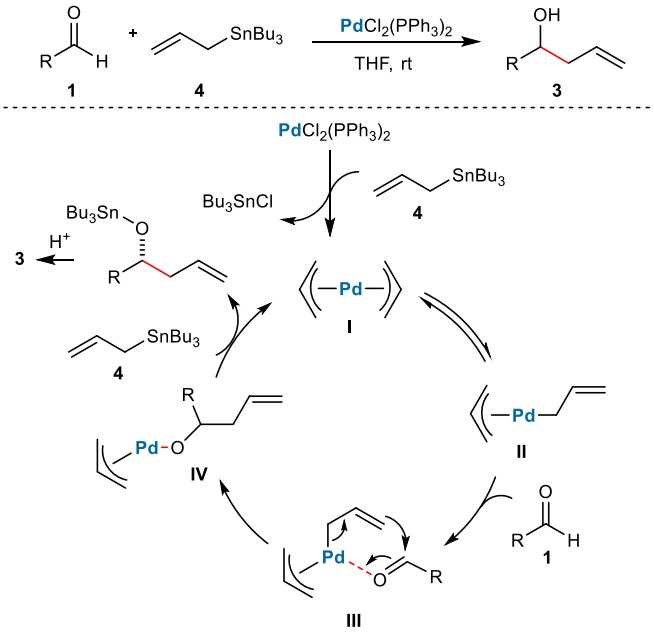
1.1. Transition-metal-catalyzed enantioselective nucleophilic allylation

1.1.1. Pd-catalyzed enantioselective nucleophilic allylation

There have been several major approaches to palladium-catalyzed enantioselective allylation of carbonyl or imines *via* formation of nucleophilic complexes. First, the substrates may allylate with allylorganometallics through bis(allyl)palladium.[48] The second method is *via* ‘umpolung’ reactivity of π-allylpalladium. Another approach is using metal pincer complex catalysis.

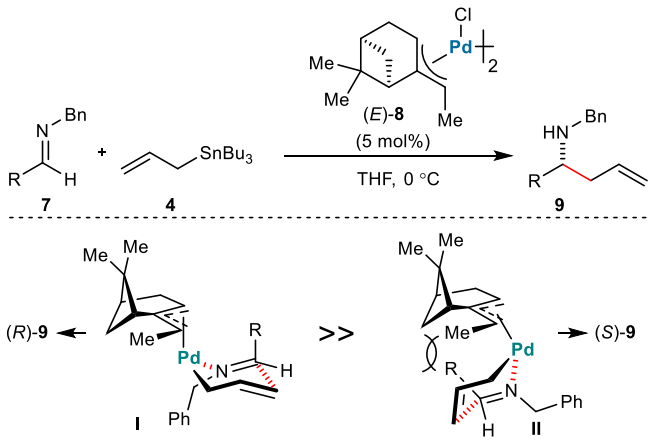
1.1.1.1. Chiral bis-π-allylpalladium complexes

Yamamoto et. al introduced the first example using the nucleophilic bis-π-allylpalladium complexes to react with aldehydes, ketones and imines (Scheme 9).[49] The authors suggested that bis-π-allylpalladium complexes **I** form *in situ* from transmetallation of allyl stannanes **4** with a Pd(II) or a mono-allyl palladium complex. These species convert into a η^1- or η^3- allylpalladium **II**, which are nucleophilic enough to react with the electrophile, followed by transmetallation with allyl stannane to regenerate the catalyst species **I**.



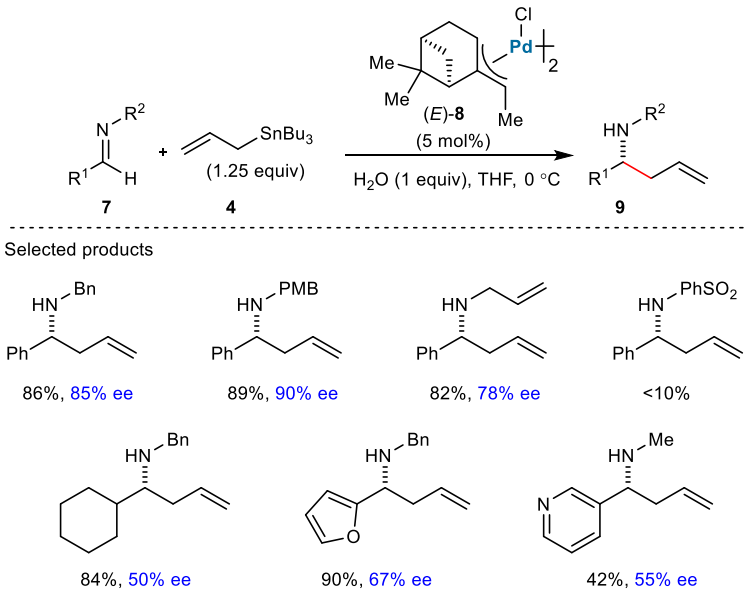
Scheme 9. Bis-π-allylpalladium complexes from allyl-stannanes

Inspired by this work, the group developed the first Pd-catalyzed asymmetric allylation of imines **7** using of allyltributylstannane **4** and bis-π-allylpalladium catalyst **8**.[50] It is suggested that the bis-π-allylpalladium coordinates with the nitrogen atom of the imine to facilitate an intramolecular nucleophilic attack of the chiral η^1-allyl ligand, and then would proceed *via* a six-membered chair-like transition state. The reaction preferentially proceeds through a transition state **I**, where the imine is added from the less-hindered backside, to give (*R*)-**9** products (Scheme 10).



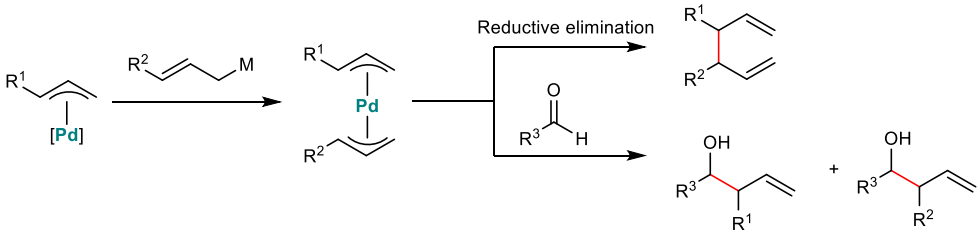
Scheme 10. Asymmetric allylation of imines using bis-π-allylpalladium complexes

Later, the group discovered that the addition of water to this catalytic reaction can give a broad substrate scope, while retaining the enantioselectivities and chemical yields for a variety of imines (Scheme 11).[51]



Scheme 11. Allylation of imines with allyltributylstannane

However, using bis-π-allylpalladium complexes can lead to undesired by-products from allyl-allyl cross-coupling reactions and selectivity problems can occur when palladium complexes containing two different substituted allylic moieties (Scheme 12). It also showed the limitations in the term of the scope of the reaction. [50-52]

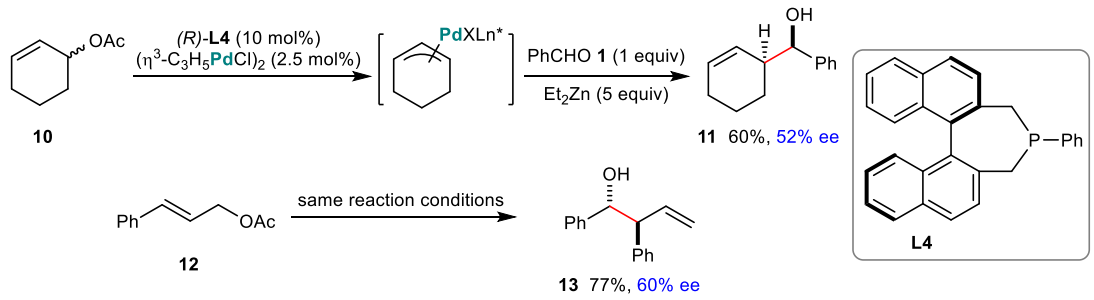


Scheme 12. Some drawbacks when using bis-*π*-allylpalladium complexes

1.1.1.2. 'Umpolung' process

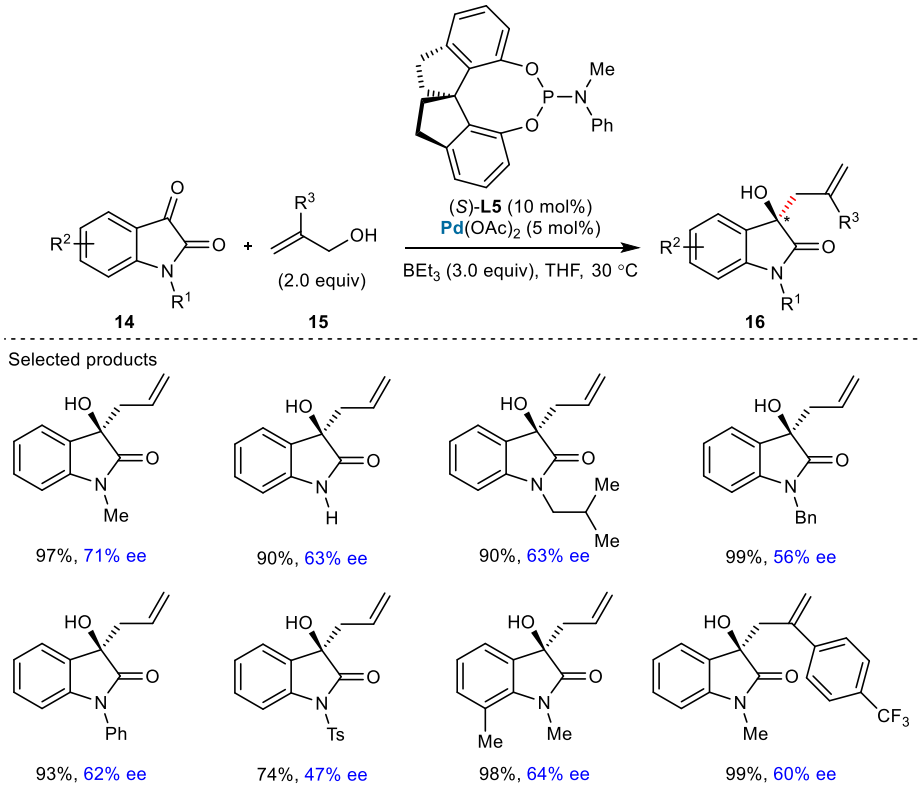
In general, an 'umpolung' process involves *π*-allylpalladium intermediates of palladium(0) catalysts relying on treatment with a low-valent metal compound or reducing agents such as indium or zinc compounds to generate the corresponding nucleophilic allyl-palladium species (Scheme 6).[42]

In 2004, Zanoni and co-workers pioneered the first enantioselective allylation of carbonyl compounds by the umpolung π-allyl palladium complexes using a chiral monodentate phosphorous ligand **L4** (Scheme 13).[53] The chiral alcohol **11** with moderate enantioselectivity was observed by the umpolung Tsuji-Trost reaction of **10** with aldehydes in the presence of Et_2Zn. One example of chiral homoallylic alcohol **13** was obtained from acyclic cinnamyl acetate **12** as a π-allyl precursor in the reaction conditions.



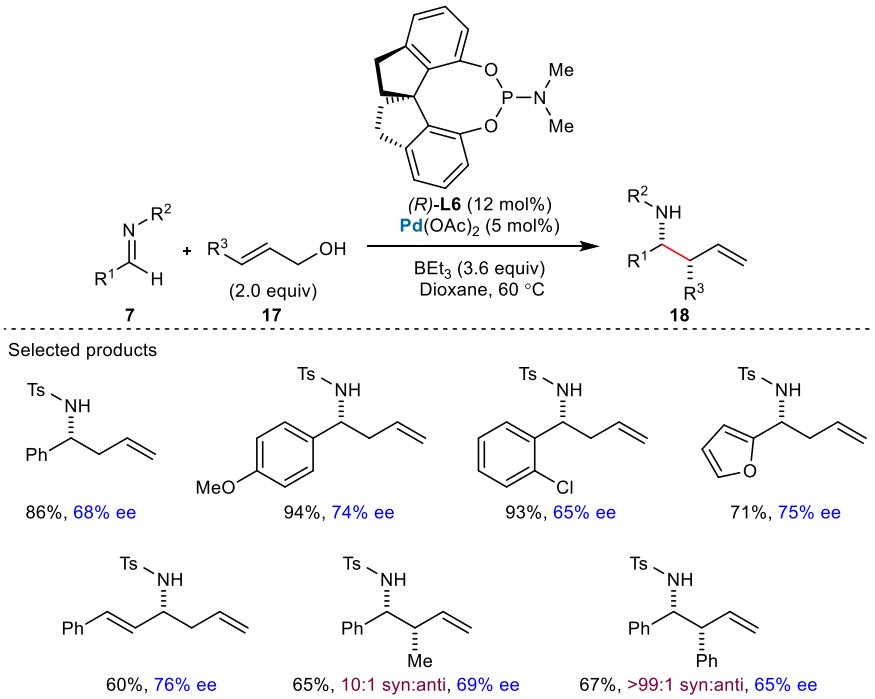
Scheme 13. Enantioselective Pd-catalyzed allylation of a carbonyl compound *via* 'umpolung'

The first palladium-catalyzed asymmetric allylation ketones **14** with allylic alcohol **15** as the allylating reagent was found by Zhou et al. in 2009 (Scheme 14).[54] The study gave a variety of chiral benzannulated pyrrolidin-2-ones **16** in good yields but moderate to good enantioselectivities (47−71% ee).



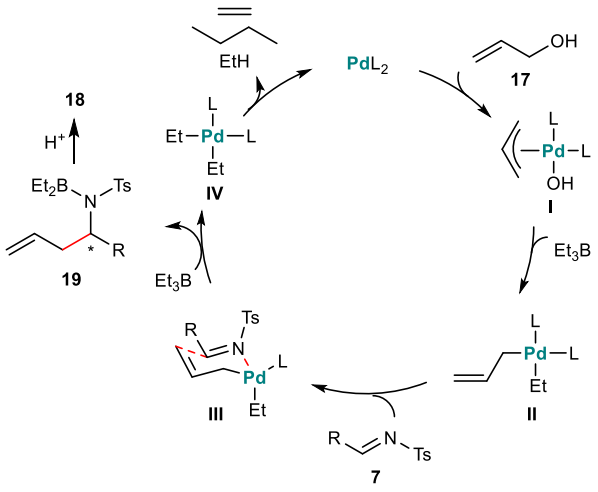
Scheme 14. Asymmetric allylation of ketones with allylic alcohols

Inspired by the work as mentioned above, the group continued palladium-catalyzed asymmetric allylation of imines **7** with allylic alcohols **17**.[39] Using chiral phosphoramidite **L6** gave various homoallylic amines **18** in high yields with moderate to good enantioselectivities (Scheme 15).



Scheme 15. Palladium-catalyzed asymmetric allylation of imines with allylic alcohols

The authors proposed a mechanism of the umpolung reactivity using the nucleophilic π-allyl palladium (Scheme 16). First, the formation of η^3-allylpalladium complex **I** is triggered by oxidative addition of the allylic alcohol **17**, followed by the transfer of the electron-rich ethyl group from boron to palladium, which forms nucleophilic η^1-allylpalladium **II**. The intermediate would undergo a chair-like cyclic transition state **III** to give **19** and finally protonolysis furnishes the corresponding amine **18**.

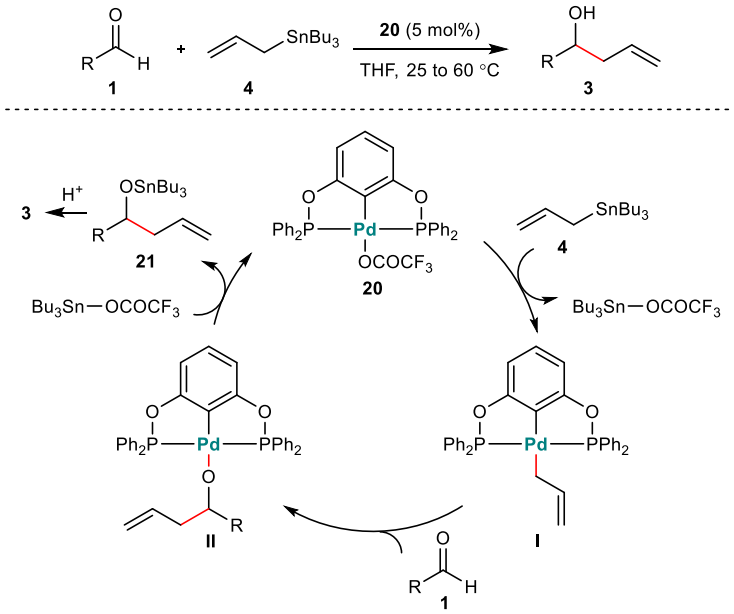


Scheme 16. Proposed mechanism of the umpolung process

1.1.1.3. Metal pincer complex catalysts

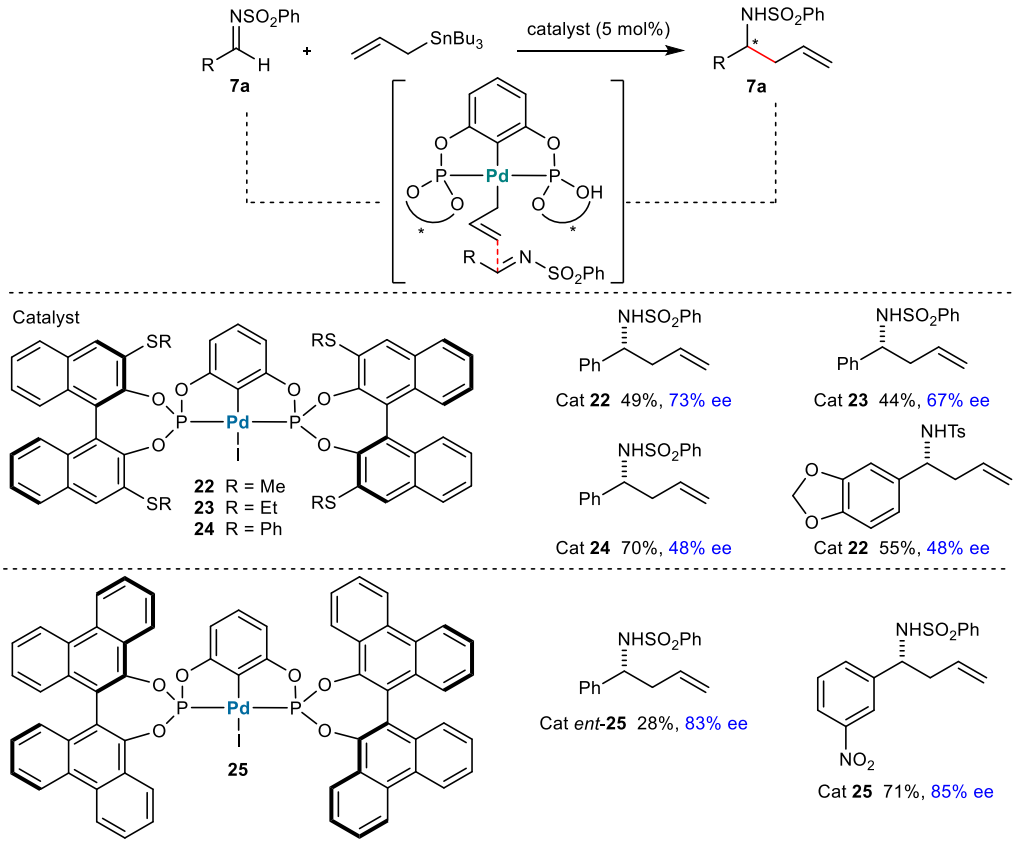
Another approach for palladium-catalyzed asymmetric allylation of carbonyl groups or imines is based on the utility of chiral pincer complexes and allylorganometallics reagents. Using the metal pincer complex catalysis, allylation reactions could be performed without the formation of bis(allyl)palladium species. Generally, the complexes are known to readily undergo transmetallation with organometallic reagents. In the complex, the ligand binding to the palladium is bulky, thus only one coordination site in a complex is available for the allyl moiety. Therefore, a η^1-allyl complex is formed and has a nucleophilic character that reacts with electrophiles to furnish corresponding alcohol or amine.[55]

Szabó et al. reported a new nucleophilic mono-allylpalladium complex for allylation to obtain homoallylic alcohols **3** (Scheme 17).[56] The metal pincer complex **20** reacts with allylstannane **4** to give a nucleophilic η^1-allylpalladium species **I**, which undergoes chair-like transition state to form alkoxide **II**. The intermediate **II** reacts with $Bu_3SnOC(O)CF_3$ to give **21** and regenerate the pincer catalyst **20**.



Scheme 17. Using mono-allyl palladium complex for allylations of aldehydes

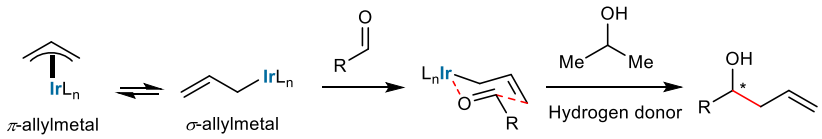
Later, the group introduced new chiral pincer palladium catalyst for highly enantioselective allylation of sulfonimines (Scheme 18).[57] Using a series of ligand BINOL as chiral ligands for palladium pincer complexes gave the corresponding homoallylic sulfoamines with high enantioselectivities (80−85% ee).



Scheme 18. Chiral pincer palladium-catalyzed for asymmetric allylation of sulfoimines

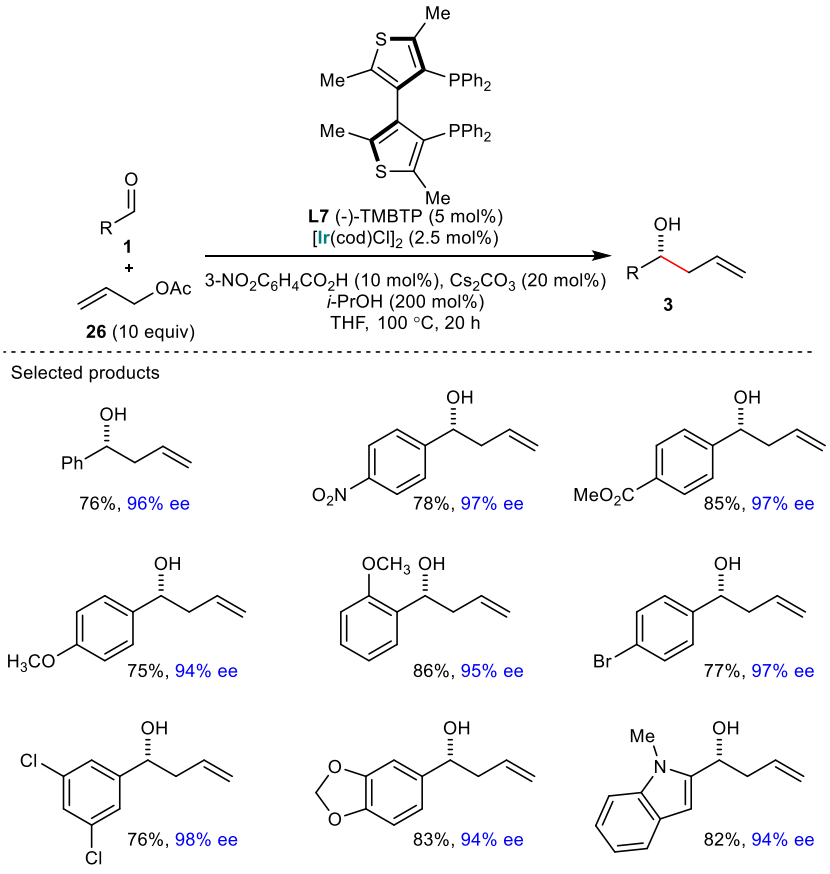
1.1.2. Ir-catalyzed enantioselective nucleophilic allylation

In 2008, Krische and colleagues reported the first examples using iridium-catalyzed allylation of carbonyl compounds under catalytic hydrogenation conditions.[58,59] They used allyl acetate as an alternative for allylmetal reagent and proposed the reaction occurred *via* an intermediate allyl iridium as a nucleophile, which is remarkable (Scheme 19).



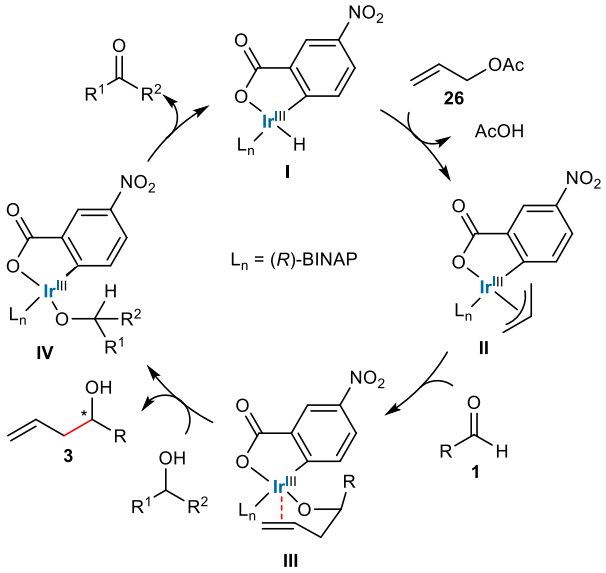
Scheme 19. Carbonyl allylation *via* nucleophile allyl iridium

The allylation of aldehydes **1** and allylic acetate **26** was illustrated in the report with the use of isopropanol as the terminal reductant and **L7** (-)-TMBTP as the ligand. The products **3** were obtained with high enantioselectivity and in good to excellent isolated yields (Scheme 20).



Scheme 20. Carbonyl allylation of allyl acetate and aldehydes by iridium-catalyzed reaction

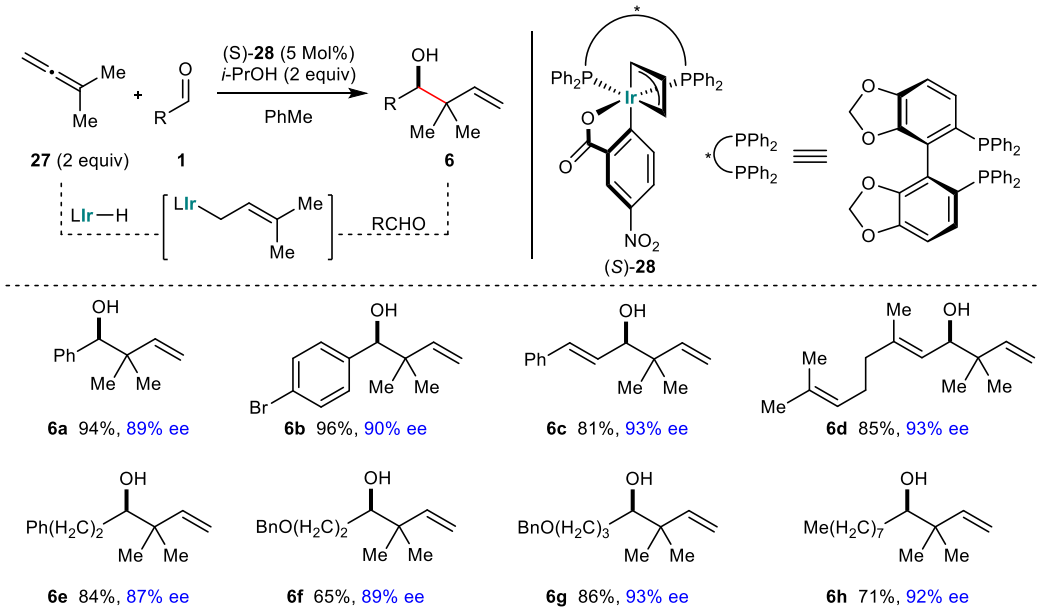
An iridium(III)-π-allyl complex, which could serve as active catalyst of this carbonyl allylation, was synthezized and analyzed by single-crystal X-ray diffraction. The proposed mechanism (Scheme 21) began with the formation of intermediates **I**, the *ortho*-cyclometalated iridium complexes, followed by the hydrogen transfer process to give intermediates **II**, the iridium(III) active catalysts. The allyl group transferred and added to aldehydes **1** through a chair-like transition state to afford intermediates **III**. These species exchanged with the isopropanol or a reactant alcohol to give the homoallylic alcohols **3** and the intermediates **IV**. Through β-hydride elimination process, the intermediate **I** was regenerated and completed the catalytic cycle.



Scheme 21. Proposed mechanism of iridium-catalyzed carbonyl allylation

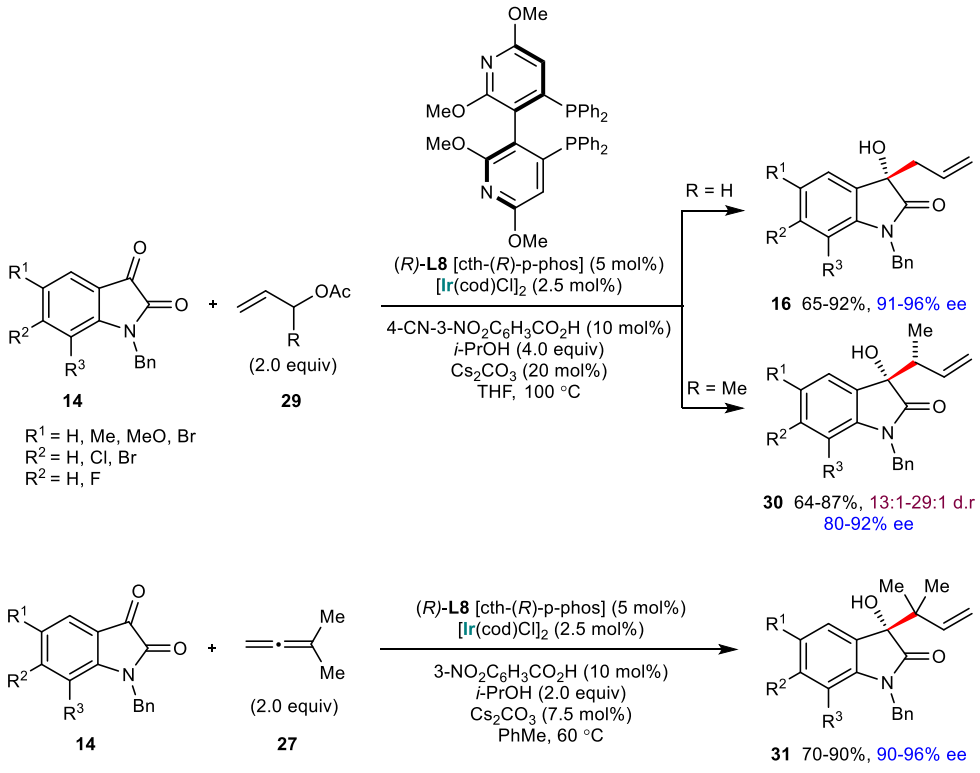
Then the group developed the asymmetric transfer-hydrogenative allylation of the carbonyl group with 1,1-dimethylallene,[60] allyl acetate, α-methyl allyl acetate,[61] or α-(trimethylsilyl)allyl acetate [62] by using nucleophilic iridium complexes and propan-2-ol as hyride donor.

The first use of 1,1-dimethylallene **27** as a prenyl donor for allylation to give enantiomerically enriched adducts **6** was reported in 2009 (Scheme 22). [60] The reactions were tolerated with aromatic aldehydes (**1a**, **1b**), α,β-unsaturated aldehydes (**1c**, **1d**), and aliphatic aldehydes (**1e-1h**) to give adducts **6a-6h** in good to excellent isolated yields (65−96%) and enantioselectivities (87−93% ee).



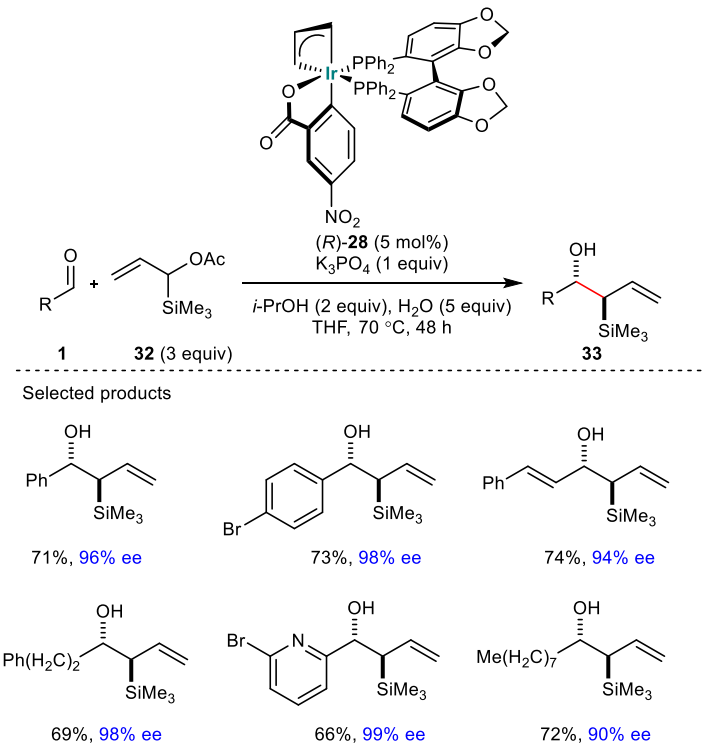
Scheme 22. Asymmetric Ir-catalyzed carbonyl allylation from aldehydes

The first use of activated ketones **14** for asymmetric iridium-catalyzed allylation in the presence of allyl acetate **26**, α-methyl allyl acetate **29**, or 1,1-dimethylallene **27** was investigated.[61] The products **16**, **30** and **31** were furnished in high yield and excellent enantioselectivities (Scheme 23).



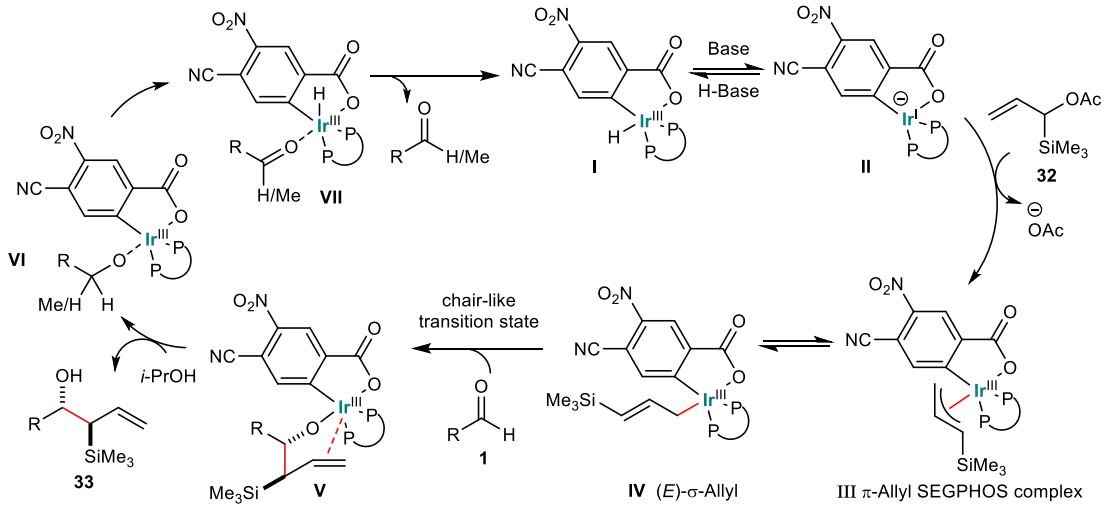
Scheme 23. Asymmetric iridium-catalyzed allylation of activated ketone

In 2010, Krische group demonstrated the enantioselective iridium-catalyzed transfer-hydrogenative allylation of (trimethylsilyl)allyl acetate **32** in the presence of aldehydes **1**.[62] The reaction was also mediated by 2-propanol and afforded the products **33** with exceptional levels of *anti*-diastereoselectivities and excellent enantioselectivities (Scheme 24).

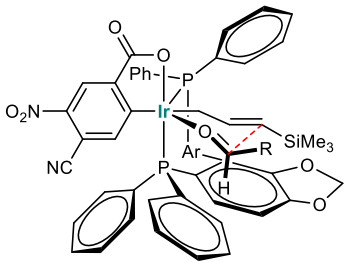


Scheme 24. Enantioselective Ir-catalyzed allylation of (trimethylsilyl)allyl acetate

In general, the mechanism proceeds in a similar approach to iridium transfer-hydrogenative allylation (Scheme 21) and is shown in Scheme 25. The reaction also began with the formation of the *ortho*-cyclometalated iridium complexes **I**, followed by the hydrogen transfer process to give the iridium(III) active catalysts **III**. The reaction was suggested to proceed *via* an (*E*)-σ-allyl intermediate (**IV**). The *anti*-diastereoselectivity is observed in most of the cases demonstrating that carbonyl addition happens through a chair-like transition state of an intermediate **V** (Scheme 26). These species exchanged with the isopropanol or a reactant alcohol to give the homoallylic alcohols **33** and the intermediates **VI**. Through β-hydride elimination process, the intermediate **I** was regenerated and completed the catalytic cycle.

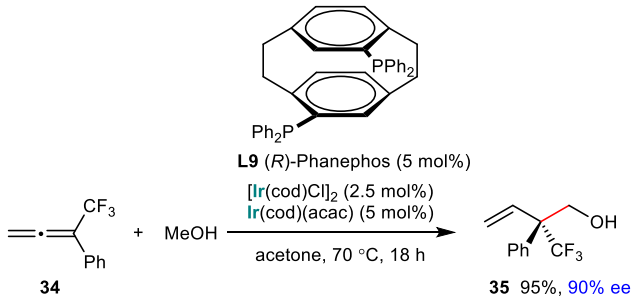


Scheme 25. Proposed mechanism for carbonyl (trimethylsilyl)allylation



Scheme 26. Stereochemical intermediate

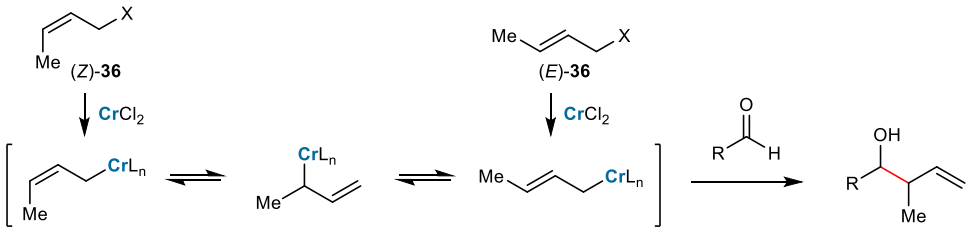
In 2017, Krische and co-workers reported a highly enantioselective iridium (I)-PhanePhos-catalyzed coupling of methanol with a 1,1-disubstituted CF_3-allenes **34** to afford **35** of hydrohydroxymethylation as single regioisomers with high enantioselectivity (Scheme 27).[63] The carbonyl addition also occurs through iridium transfer-hydrogenative process with a nucleophilic allyliridium intermediate.



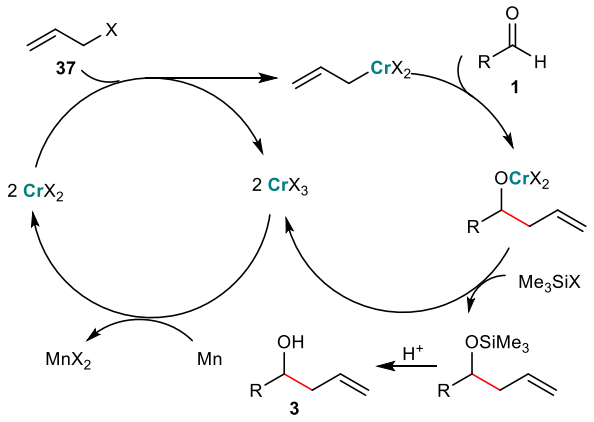
Scheme 27. Ir-catalyzed asymmetric allylation of trifluoromethyl substituted allene and methanol

1.1.3. Cr-catalyzed enantioselective nucleophilic allylation

The first example of chromium-mediated addition of allylic halides **36** to aldehydes was reported by Nozaki, Hiyama and colleagues. Their study showed a highly chemoselective reaction towards aldehyde (Scheme 28).[64] Later Fürstner and Shi reported allylation of aldehydes with allylhalide in the presence of $CrCl_2$ and excess Mn and TMSCl (Scheme 29).[65]

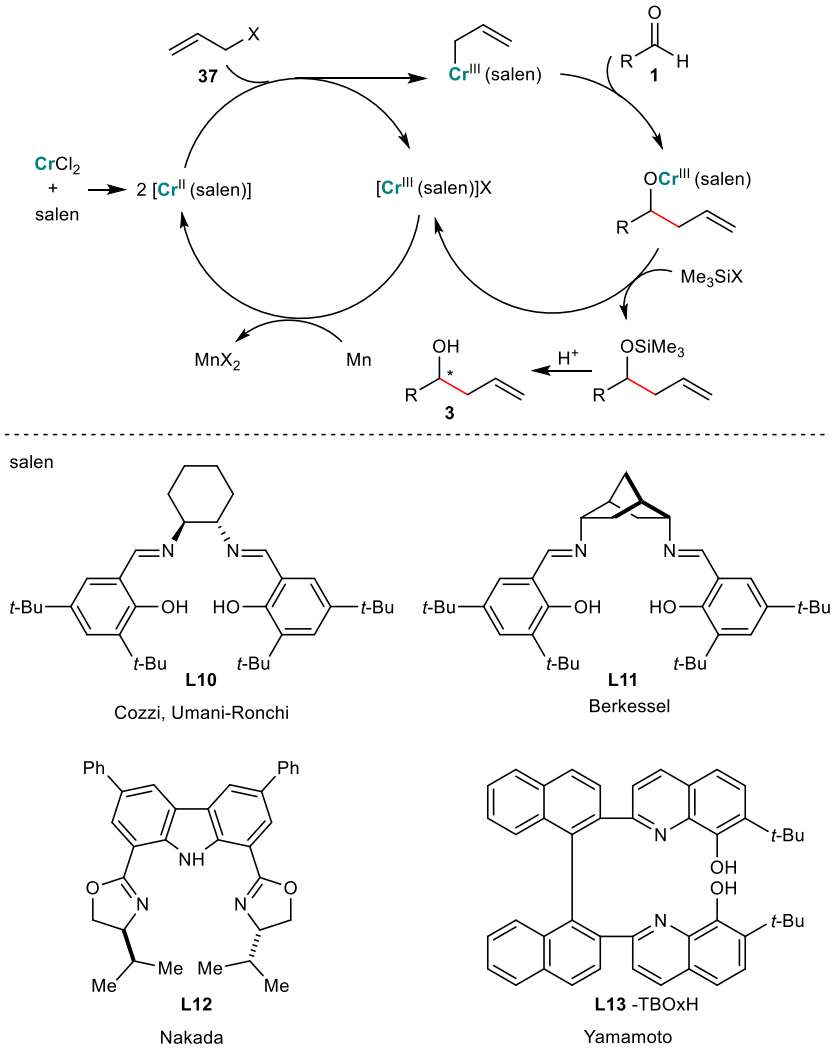


Scheme 28. The addition of 2-butenyl halides to aldehydes- Nozaki-Kiyama-Kishi reactions



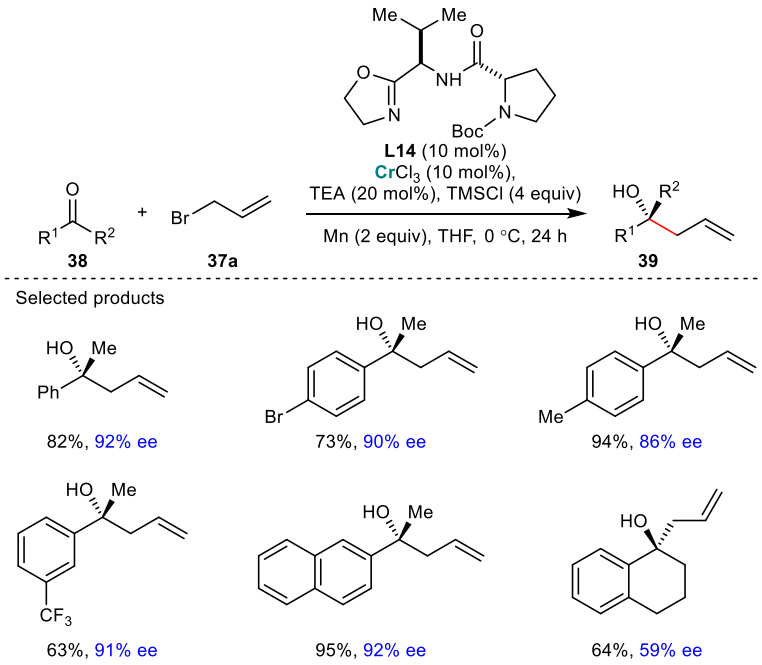
Scheme 29. Fürstner and Shi catalytic system

Following these groundbreaking findings, Cozzi, Umani-Ronchi et al. reported the first enantioselective chronium-catalyzed allylation of aldehydes **1** using chromium(II) salen complex with ligand **L10**.[66] The proposed mechanism is shown in Scheme 30. Later Berkessel et al. used an analogous catalyst derived from **L11** [67] and Nakada and co-workers used a bis(oxazolinyl)arbazole ligands **L12** to get modest to high enantioselectivities (86−97% ee) for allylation of aldehydes.[68] Yamamoto group developed a new class of chiral ligand, tethered bis(8-quinolinol) **L13** (TBOxH) for chromium-catalyzed Nozaki-Hiyama allylations of aldehydes to obtain homoallylic alcohol **3** high yields (up to 95%) and high enantioselectivities (up to 99%).[69]



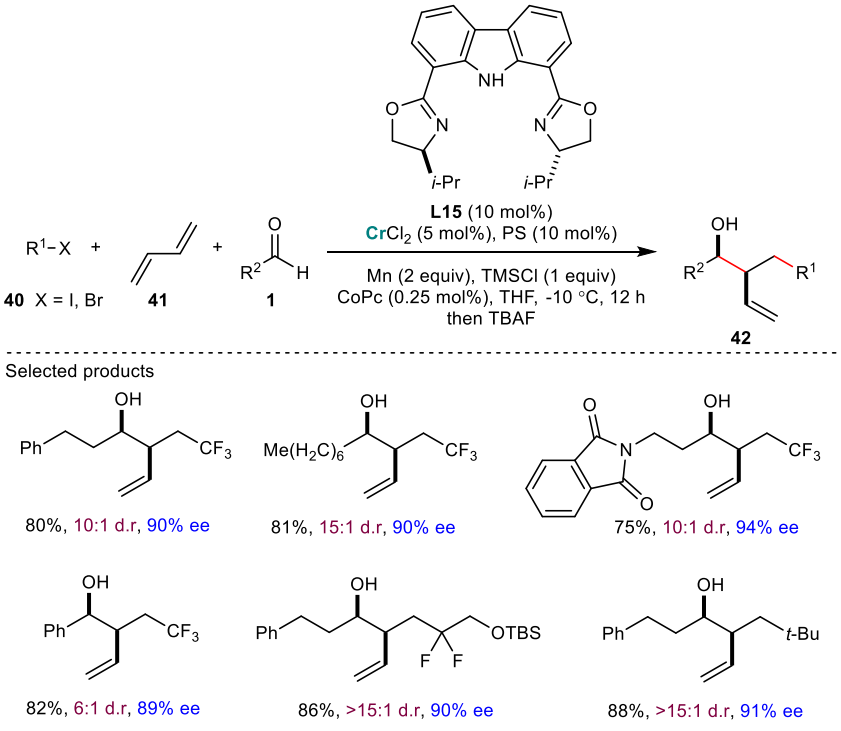
Scheme 30. Enantioselective chronium-mediated allylations for Nozaki-Hiyama reactions

Miller and Sigman reported the first example of chromium-catalyzed enantioselective allylation of ketones **38** using allylic bromides **37a**. With the simple ligand **L14**, allylation of acetophenones led to corresponding tertiary homoallylic alcohols **39** with high enantioselectivities (up to 92% ee) (Scheme 31).[70]



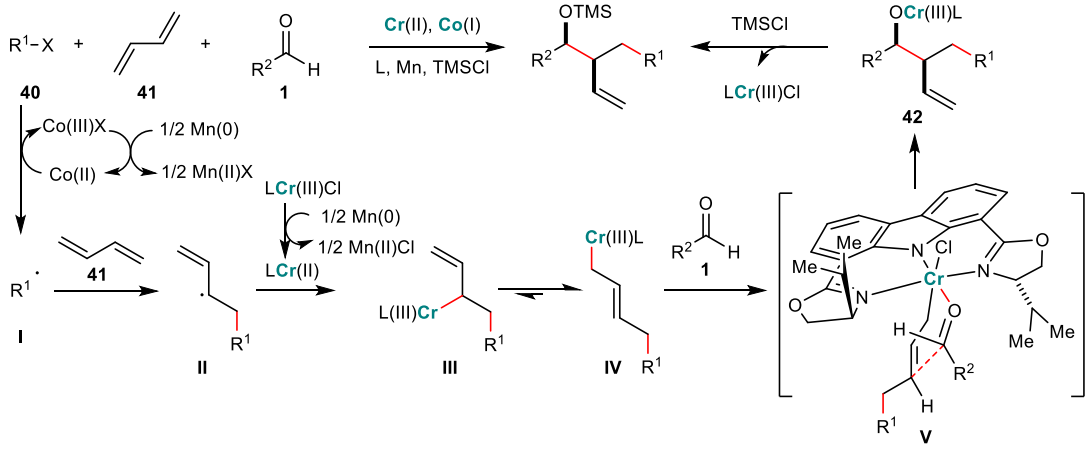
Scheme 31. Chromium-catalyzed an entioselective allylation of ketones using allylic bromides

In 2018, Zhang group demonstrated a carbonyl allylation with a variety of fluorinated and nonfluorinated alkyl halides **40**, alkene **41** and aldehydes **1** based on a Cr/Co bimetallic catalytic system.[71] Using ligand **L15** gave products **42** in good yields with excellent diastereomeric and enantiomeric selectivities (Scheme 32).



Scheme 32. Cr/Co bimetallic catalysis system for carbonyl allylation

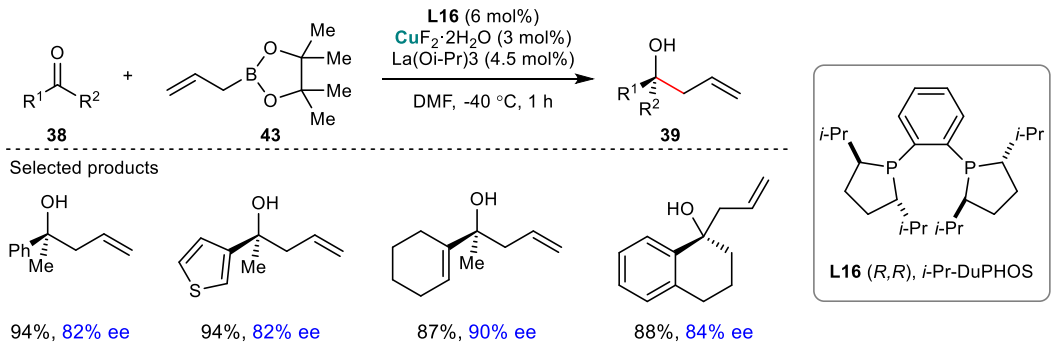
The proposed mechanism is shown in Scheme 33. First, CoPc initiates the formation of the alkyl radicals **I**, followed by addition to 1,3-butadiene **41**. The π-allyl radical species **II** then reacts with Cr(II) complex, followed by subsequent isomerization and carbonyl allylation to furnish the final product **42**. Manganese acts as a reducing agent for both Co and Cr catalytic systems.



Scheme 33. Proposed mechanism of Cr/Co bimetallic system for carbonyl allylation

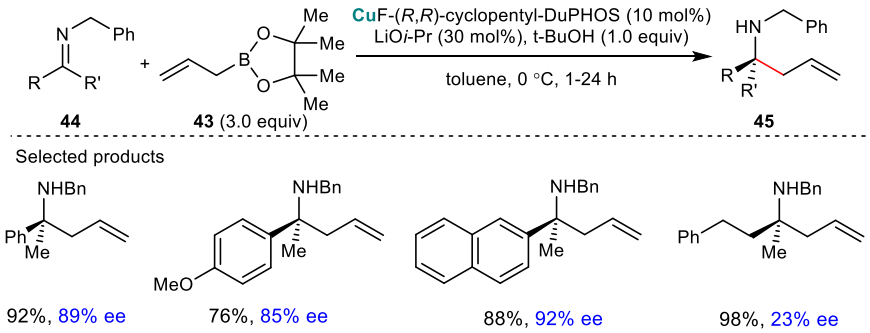
1.1.4. Cu-catalyzed enantioselective nucleophilic allylation

In 2004, Kanai and Shibasaki et al. studied the first enantioselective carbonyl allylation using allylborane **43** *via* an active nucleophile allylcopper in the presence of chiral catalyst CuF-*i*-Pr-DuPHOS and La(O*i*-Pr)$_3$ as a cocatalyst.[72] The Cu-catalyzed reaction afforded high enantioselective products **39** (up to 93% ee) from aromatic, heteroaromatic, cyclic, aliphatic ketones (Scheme 34). Use of cocatalyst La(O*i*-Pr)$_3$ significantly increased reactivity, but the precise mechanism of rate enhancement is still unclear.

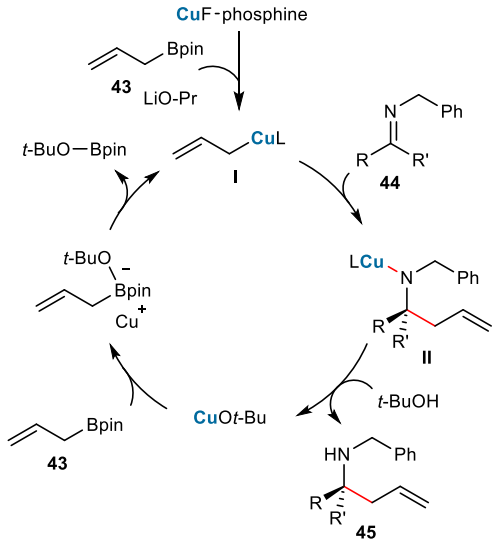


Scheme 34. Cu-catalyzed enantioselective carbonyl alylation using allylborane

The group continued developing a general Cu-mediated allylation of simple ketoimines using CuF·3PPh$_3$ as a catalyst and La(O*i*-Pr)$_3$ as the cocatalyst and they discovered the first enantioselective example when using the CuF−cyclopentyl−DuPHOS as a chiral catalyst and LiO*i*-Pr as cocatalyst.[73] Homoallylamines **45** were obtained with high enantioselectivity from aromatic ketoimines **44** (Scheme 35). Scheme 36 illustrates the proposed mechanism where the nucleophilic allylcopper **I** generated by transmetallation of CuF−cyclopentyl −DuPHOS complex with allylboronate **43**. The use of LiO*i*-Pr remarkably enhanced both reactivity and enantioselectivity, as compared to La(O*i*-Pr)$_3$.



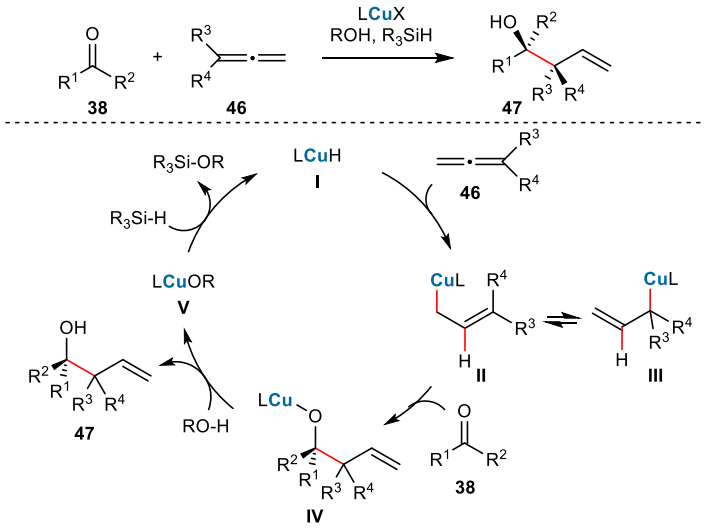
Scheme 35. Cu-catalyzed allylation of ketoimines



Scheme 36. Proposed mechanism of Cu-catalyzed of allylation of ketoimines

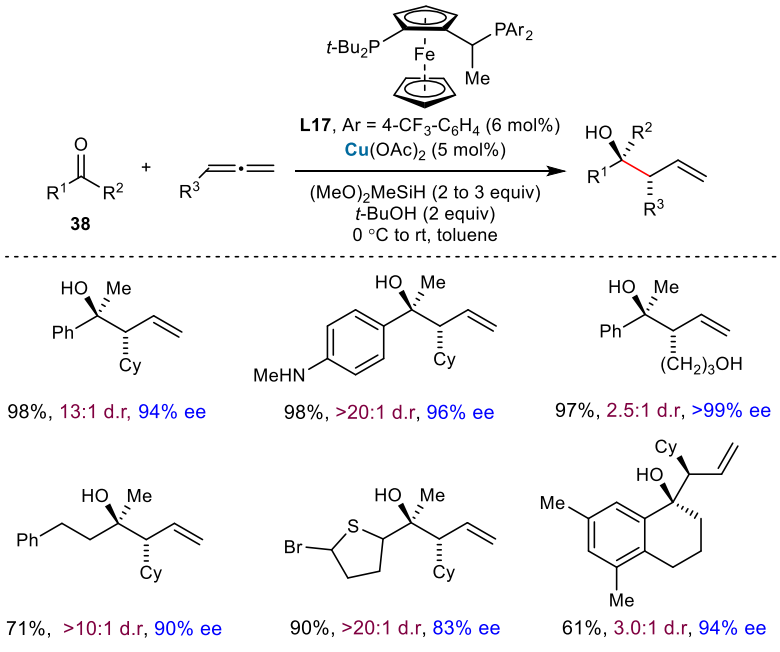
In 2018, Buchwald et al. developed a highly enantioselective CuH-catalyzed allylation of ketones **38** using terminal allenes **46** as an allyl donor.[74] Allene was a substitution compounds to the allylmetal reagent for the formation of nucleophilic allylcopper species. The proposed mechanism was suggested as in Scheme 37.

Copper hydride complexes **I** insert into allene **46** to generate a mixture of allylcopper species **II** and **III**. Then the copper-mediate species undergo regioselective stereoselective addition to a carbonyl group. To complete the cycle, copper intermediate **IV** can undergo ligand exchange with an auxiliary alcohol to form corresponding alcohol **47** or L*CuOR **V** undergo metathesis with a hydrosilane to regenerate initial hydride **I**.



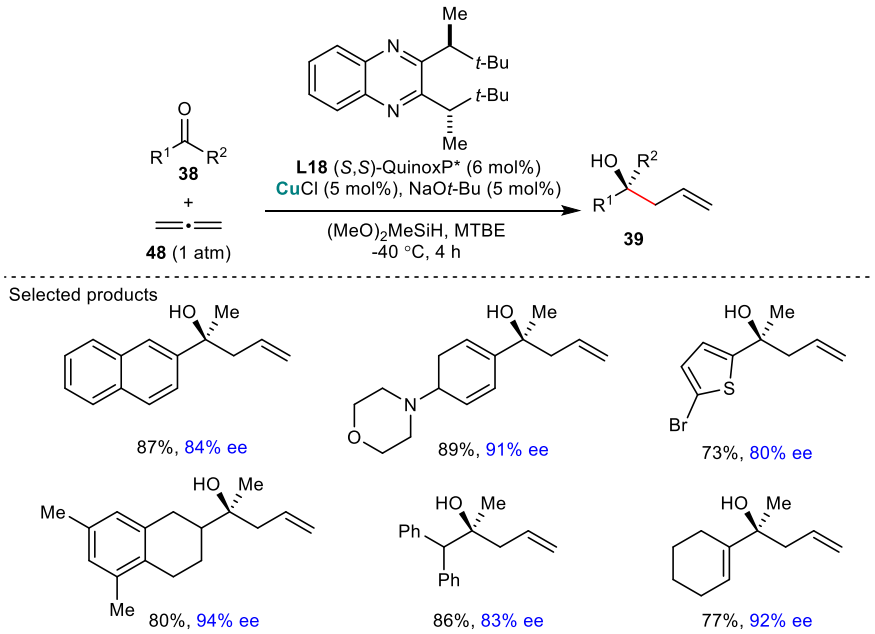
Scheme 37. CuH-catalyzed allylations of ketones

The reaction tolerated various substrates **38** bearing electron-donating, or electron-withdrawing substituents as well as heterocycles and those with a functional group. Using ligand **L17** gave chiral alcohols with high enantioselectivities (Scheme 38).



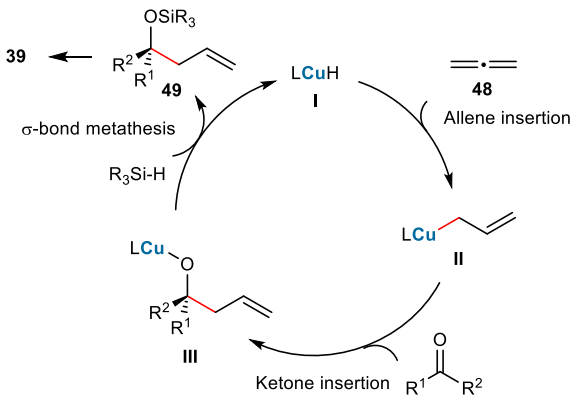
Scheme 38. Selected examples of CuH-catalyzed allylations

In 2019, the Buchward group continued developing an enantioselective copper-catalyzed allylation using allenes **49**, copper salts and **L18** to give chiral tertiary alcohols **39** with high enantioselectivites.[75] The reactions were tolerated with a variety of substrates **38** with many functional groups (Scheme 39).



Scheme 39. Selected exmamples of enantioselective Cu-catalyzed allylation using allene gas

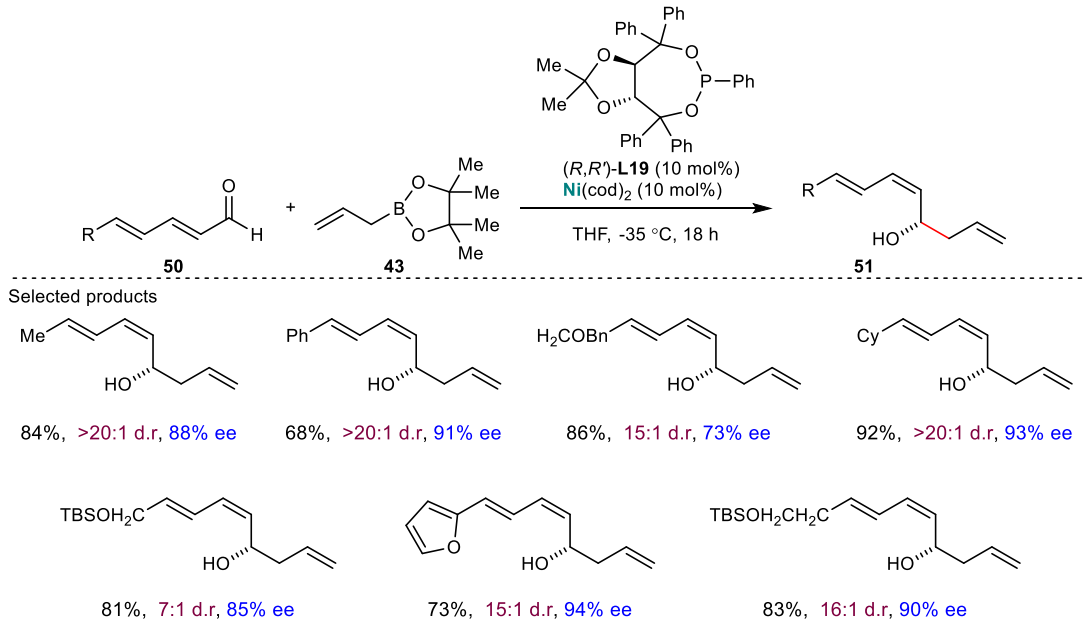
The proposed mechanism was suggested to be similar to that described in Scheme 37. Initially, a hydride complex **I** is generated from a copper salt, phosphine ligand and silane reductant, then insertion of allene **48** into the complex affords nucleophilic allylcopper(I) species **II**. Those species can then react with a ketone **38** through a six-membered transition state to give an alkoxide **III**. Followed by metathesis with the hydrosilane, the silane-protected product **49** is formed leading to regeneration of the Cu-complex **I**. The desired product **39** is furnished after working up (Scheme 40).



Scheme 40. Proposed mechanism of enantioselective Cu-catalyzed allylation using allene gas

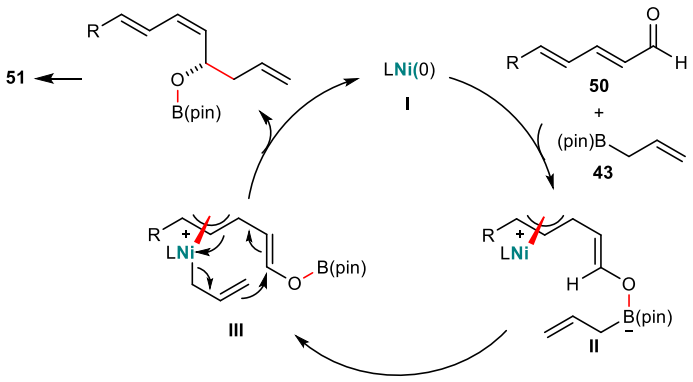
1.1.5. Ni-catalyzed enantioselective nucleophilic allylation

Morken and co-workers developed enantioselective nickel-catalyzed allylation of δ-substituted dienal **50** with allylboronic acid pinacol ester **43** in the presence of Ni(II) and the chiral phosphonite **L19**.[76] Aromatic and aliphatic substituents were tolerated and predominant (*E*,*Z*)-stereoisomer products were formed in high yields and enantioselectivities (Scheme 41).



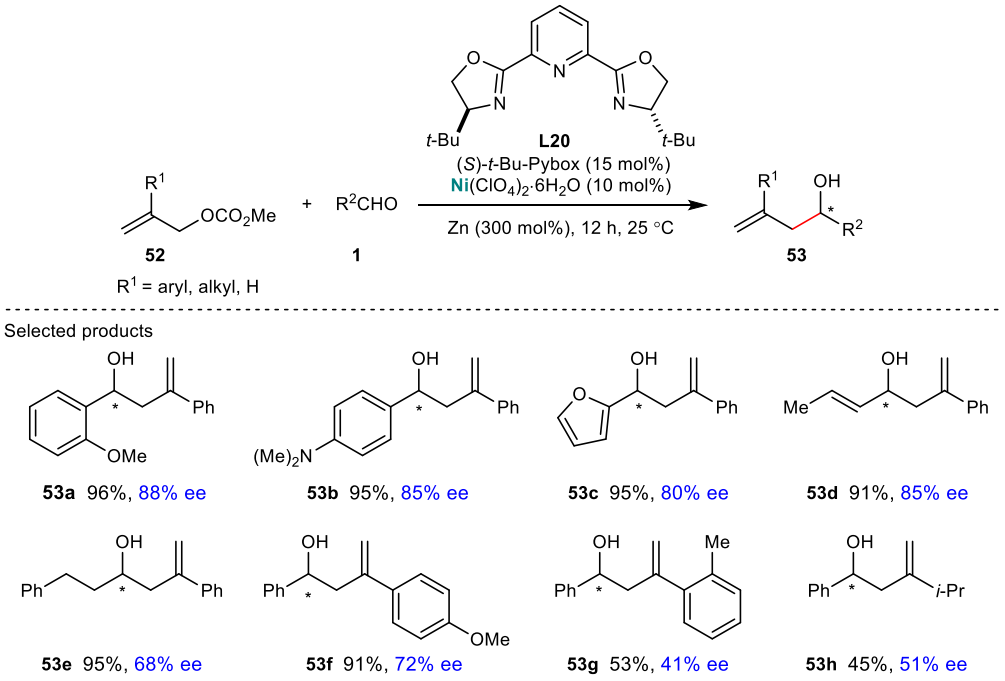
Scheme 41. Enantioselective nickel-catalyzed allylation of δ-substituted dienal

Scheme 42 illustrated the proposed mechanism. The boron pinacol ester **43** has been invoked to account for the ability of electron transfer from Ni(0) to the enal to form nickel complexes. The intermediate **I** undergoes a transmetallation of the allyl group from B to Ni to form a bis(allyl)metal species **III**. Then these intermediates underwent a 3,3'-reductive elimination and work up to furnish allylation products **51**.



Scheme 42. Proposed mechanism of enantioselective nickel-catalyzed 1,2-allylation

Qian and Gong et. al demonstrated the first asymmetric Ni-catalyzed reductive allylation of aldehydes **1** with allylic carbonates **52** (Scheme 43).[77] They suggested an electronic nature of the allylic partners is important in the control of enantioselectivites and a possible equilibrium between η^1-(*E*)-allyl-Ni and (*Z*)-allyl-Ni complexes with the presence of substituents at the C1 or C3 position of allylic carbonates. The addition of the weak nucleophilic allylnickel species to aldehydes and the formation of nickel-π-allyl complexes is one of the significant steps in the catalytic process. The coupling of 2-aryl allylic acetates with a variety of aldehydes **1a**-**1c** were demonstrated. The aldehyde substrates without electron-withdrawing groups generally gave high enantioselectivites. (*E*)-but-2-enal (**1d**), aliphatic 3-phenylpropanal (**1e**) also gave homoallylic alcohols in high enantioselectivites. The reation of benzaldehyde (**1f**) and methoxy phenyl allylic carbonate (**52f**) also furnish product **53f** in good enantioselectivity. The process worked with the sterically more hindered 2-(2-methyl)phenyl- (**52g**) and 2-isopropyl- (**52h**) allylic carbonates but diminished enantioselectivities.

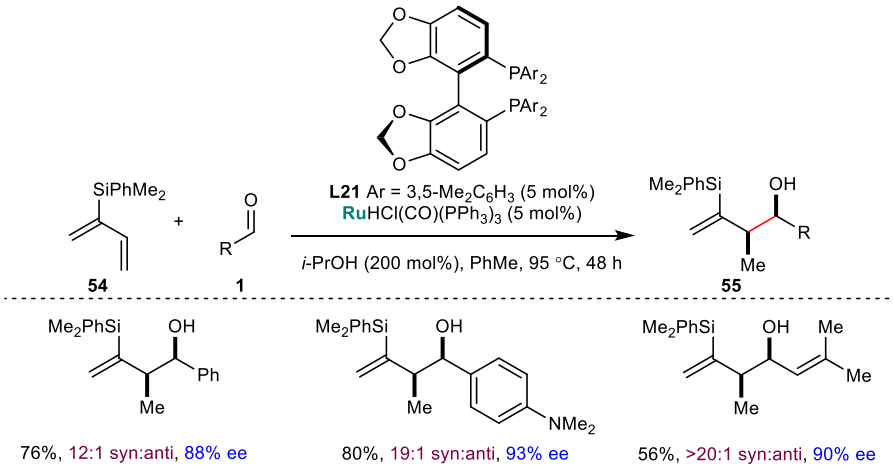


Scheme 43. Selected examples of asymmetric Ni-catalyzed reductive allylations

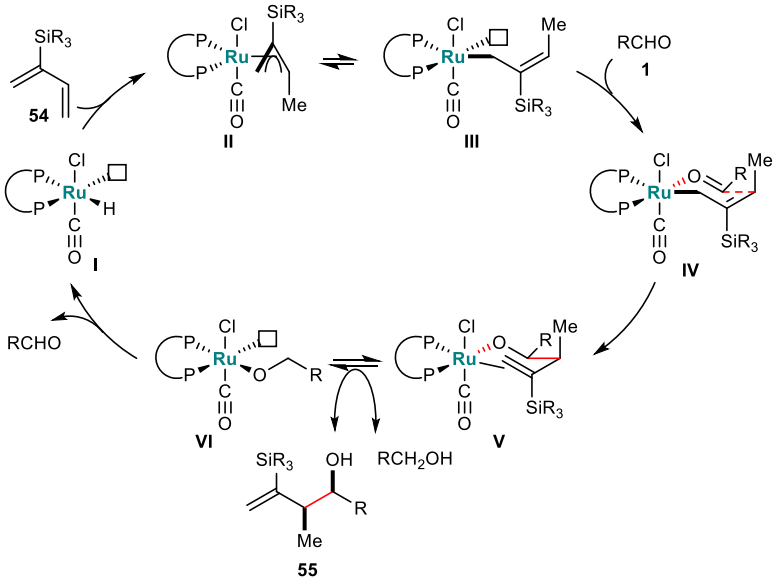
1.1.6. Ru-catalyzed enantioselective nucleophilic allylation

In 2011, Krische et al. developed an enantioselective ruthenium-catalyzed redox-neutral intermolecular coupling of aldehydes and 1,3-dienes **54**.[78] The homoallylic

alcohols was generated with perfect regioselectivity and good to excellent levels of diastereo- and enantioselectivites (Scheme 44). The process involves transfer hydrogenation and carbonyl addition in a ruthenium complex and chiral ligand **L21** (Scheme 45). The hydrogen transfer between ruthenium complex **I** and 1,3-dienes **54** generates allylruthenium intermediates **II**, followed by an addition to aldehyde. Allylruthenium-aldehyde transition state **IV** undergoes a coupling reaction to give **V**. Using propan-2-ol as an external reducing agent releases alcohol **55** and regenerates the ruthenium catalyst to finish the catalytic cycle.



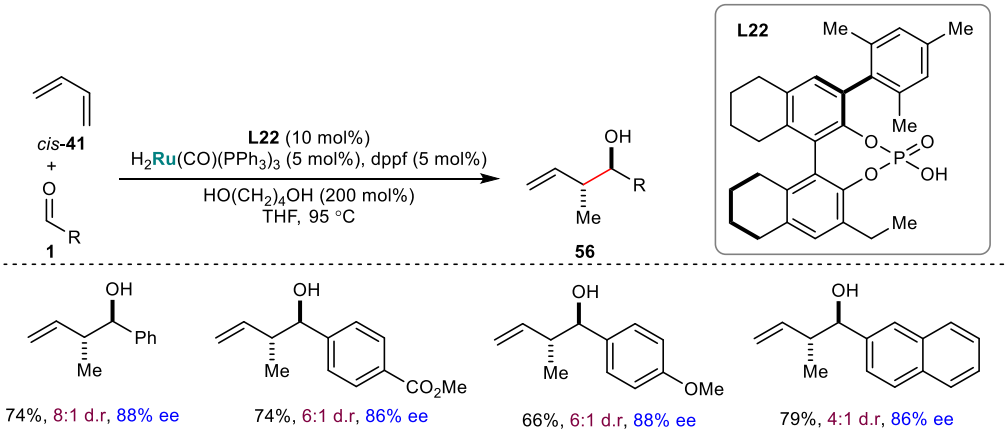
Scheme 44. Enantioselective ruthenium-catalyzed hydrohydroxyalkylation of 2-silyl-butadienes



Scheme 45. Proposed catalytic mechanism for ruthenium-catalyzed hydrohydroxymethylation

Inspired by the work, Krische and co-workers developed an enantioselective ruthenium-catalyzed asymmetric direct redox-triggered carbon-carbon coupling of

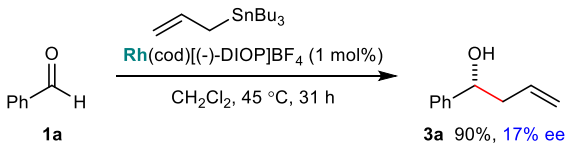
aldehyde and butadiene (Scheme 46). The chiral phosphoric acid **L22** was employed in the catalysis system.[79] The products of carbonyl crotylation with high diastereoselectivity and enantioselectivity without a formation of stoichiometric by-products. The products of carbonyl crotylation were afforded through the same fashion showed previously (Scheme 45). A hydrometallation of butadiene furnished a π-allylruthenium complex, followed by a closed transtition structure to give σ-crotylruthenium complex. The given homoallylic ruthenium alkoxide had all occupied coordination sites at the metal center and then exchange with a reactant alcohol to release product **56** and ruthenium complex.



Scheme 46. Enantioselective ruthenium-catalyzed asymmetric coupling of aldehyde and alkene

1.1.7. Rh-catalyzed enantioselective nucleophilic allylation

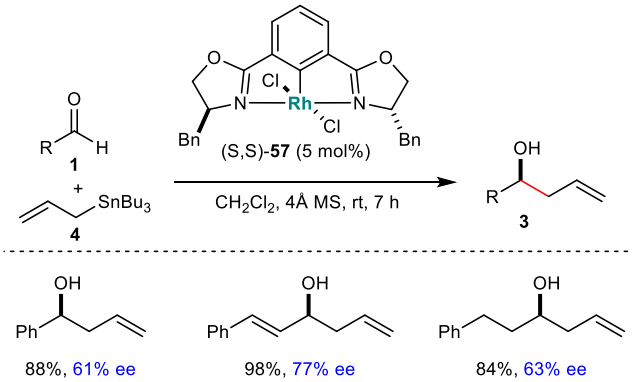
A rhodium-catalyzed enantioselective allylation was initially discovered by Nuss group.[80] The addition of allylic stannane to benzaldehyde **1a** gave chiral alcohol **3a** in high yield but a small degree of asymmetric induction (17% ee) (Scheme 47).



Scheme 47. Initial rhodium-catalyzed enantioselective allylation

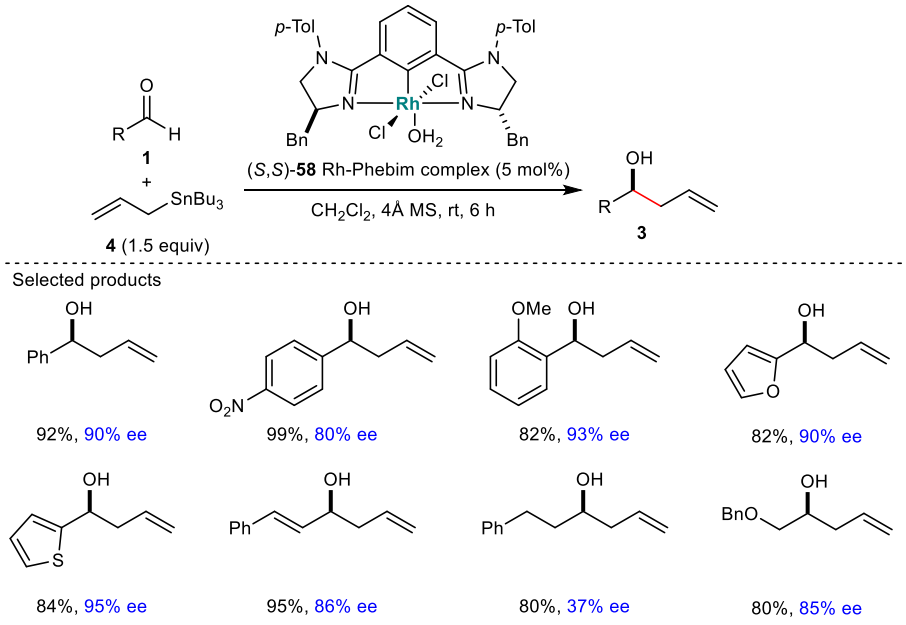
Nishiyama group observed an improvement in enantioselective allylation of allylic stannanes **4** to aldehyde **1** using chiral bis(oxazolinyl)phenylrhodium(III) complexe **57** as the catalyst (Scheme 48).[81] They proposed the nucleophilic transition structure,

approached from the *Si*-face of the complexed aldehyde due to the shielding of the *Re*-face by the oxazoline substituent, formed the asymmetric product.



Scheme 48. Rhodium-catalyzed enantioselective allylation of stannanes to aldehydes

In 2013, Gong and Song et. al reported a chiral pincer rhodium(III) complexe **58** was effectively applied for the allylation of aldehydes **1** and allyltributyltin **4**.[82] Using ligand bis(imidazolinyl)phenyl in the system gave chiral homoallylic alcohols **3** in high yields with enantioselectivitites of up to 95% ee (Scheme 49).



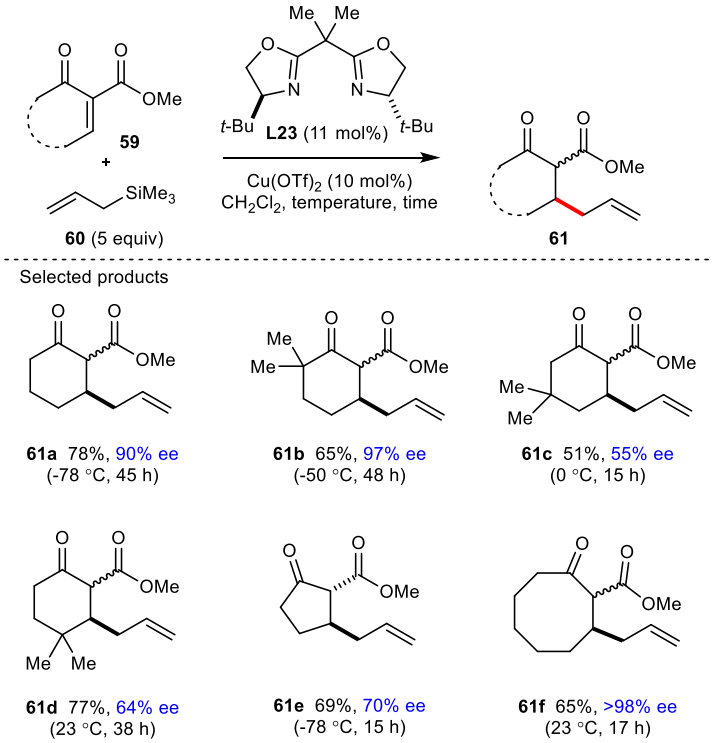
Scheme 49. Chiral NCN pincer rhodium(III) complexes for allylation

1.2. Transition-metal-catalyzed enantioselective 1,4-addition of allylorganometallic reagents to electron-deficient alkenes

Whilst 1,2-allylations are well-documented, asymmetric 1,4-allylation reactions are in their infancy.[83,84] As outlined in the abstract, we desired to develop new types of catalytic enantioselective 1,4-allylations to contribute to this under-investigated chemistry. The following literature review will describe an overview of asymmetric transition-metal-catalyzed 1,4-additions of allylorganometallic reagents into activated alkenes.

1.2.1. Copper-catalyzed enantioselective 1,4-allylation

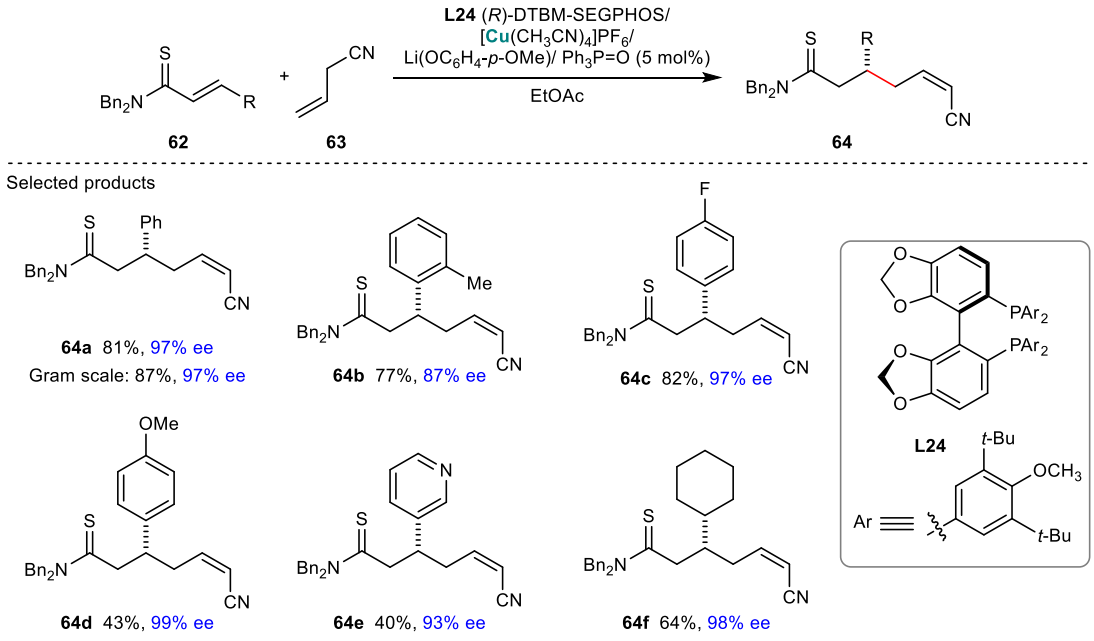
In 2008, Snapper et al. reported the first effective method for catalyzing the asymmetric 1,4-addition of allyltrimethylsilane **60** to activate cyclic unsaturated ketoesters **59**.[85] The process used copper (II) triflate and di(*tert*-butyl)bis(oxazoline) (box) ligand **L23** which is commercially available as well as a stable allyltrimethylsilane nucleophile addition to cyclic enones to furnish enantio-enriched products **61** up to 98% ee.



Scheme 50. Copper-catalyzed enantioselective Homosi-Sakurai conjugate allylation of unsaturated ketoesters.

Catalytic enantioselective Hosomi-Sakurai allylations were studied with a variety of substrates and nucleophilic methallyltrimethylsilane to form allylated five-, six-, and eight- membered ring products (Scheme 50). Six-membered ring enone **61b**, with *gem*-dimethyl substitution at the 6-position, was synthesized with high enantioselectivity (97% ee, 65% yield). When examining steric hindrance at 4- and 5-position of the cycle to observe product **61c** and **61d**, higher reaction temperatures were applied in order to get high conversion, however; the selectivity was decreased to 55% ee and 64% ee respectively. Enone **61e** was obtained in moderate selectivity (70% ee, 69% yield), whereas the eight-membered ring product **61f** was furnished in excellent enantioselectivity (>98% ee and 65% yield).

In 2011, Kumagai and Shibasaki et al reported a copper-catalyzed asymmetric conjugate addition of allyl cyanide to α,β-unsaturated thioamides, affording substrates through a copper-catalyzed cascade C−C and S−N bond formation.[86] Some selective examples with the *Z* selectivity are shown in Scheme 51.

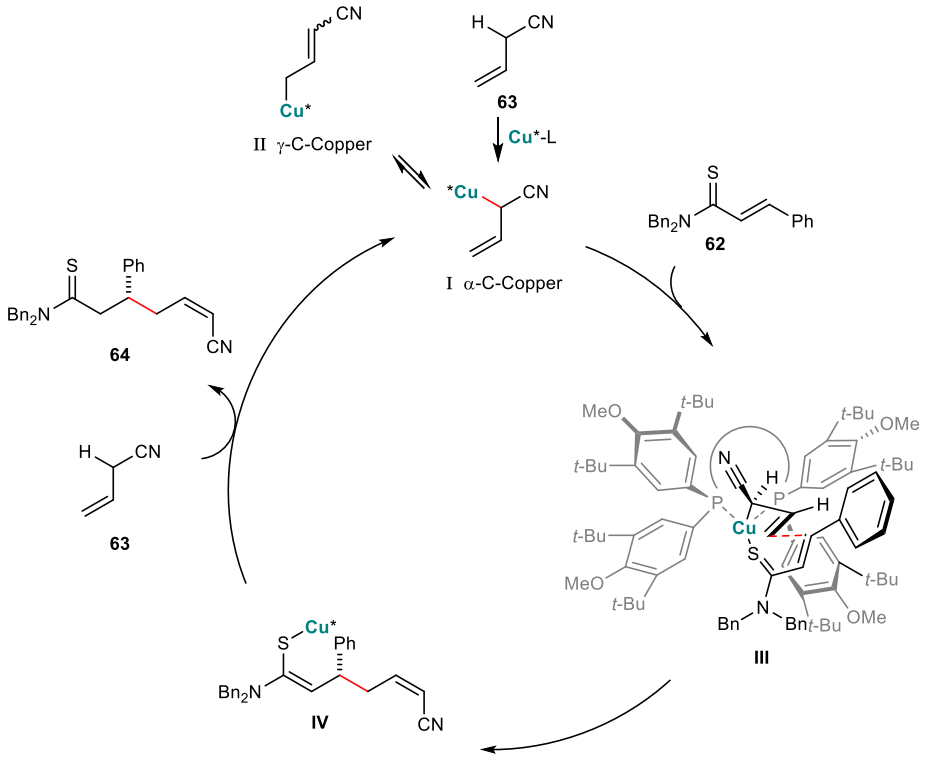


Scheme 51. Copper-catalyzed asymmetric conjugate addition of allyl cyanide to α,β-unsaturated thioamides

The reaction of **64a** was carried out on gram-scale without a change in enantioselectivity (97% ee). However, the enantioselectivity decreased to 87% ee with *ortho* substituents (**64b**). In addition, the reactivity of the thioamide depended

on its electronic nature. Halogen substituents (**64c**) were well-tolerant in 82% and 97% ee, whereas the methoxy-substituted thioamide gave product **64d** with only 43% ee. *β*-3-Pyridyl thioamide give **64e** in high enantioselectivity but moderate yield.

The exclusive *Z*-olefin formation can be proposed as shown in Scheme 52. At first, allylcyanide **63** reacted with copper complex to form the deprotonated *α*-C-copper nucleophile **I**. This copper species coordinates with the *α*,*β*-unsaturated thioamide **62** as the eight-membered transition state **III** to form the copper thioamide enolate **IV**. This intermediate **IV** served as a Brønsted base to deprotonate the allylcyanide to generate the active nucleophile, releasing the product **64**.



Scheme 52. Proposed catalytic cycle and plausible transition state

In 2013, the Nakada group reported a copper-catalyzed asymmetric Hosomi-Sakurai reaction of *α*-alkylidene *β*-keto imides **65** and allyltrimethylsilane **66**.[87] The acidic imide hydrogen can form an internal hydrogen bond to restrict the free rotation of imide as shown in Figure 4. In addition, the bisoxazoline substituent shields one side of the alkene, therefore reactions are expected to obtain high enantioselective products. Selected examples of **67** were described in Scheme 53 with high yields

(80−95%) and excellent enantioselectivies (90-97% ee) by using $Cu(OTf)_2$ and ligand **L25**.

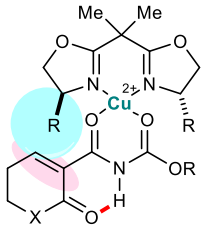
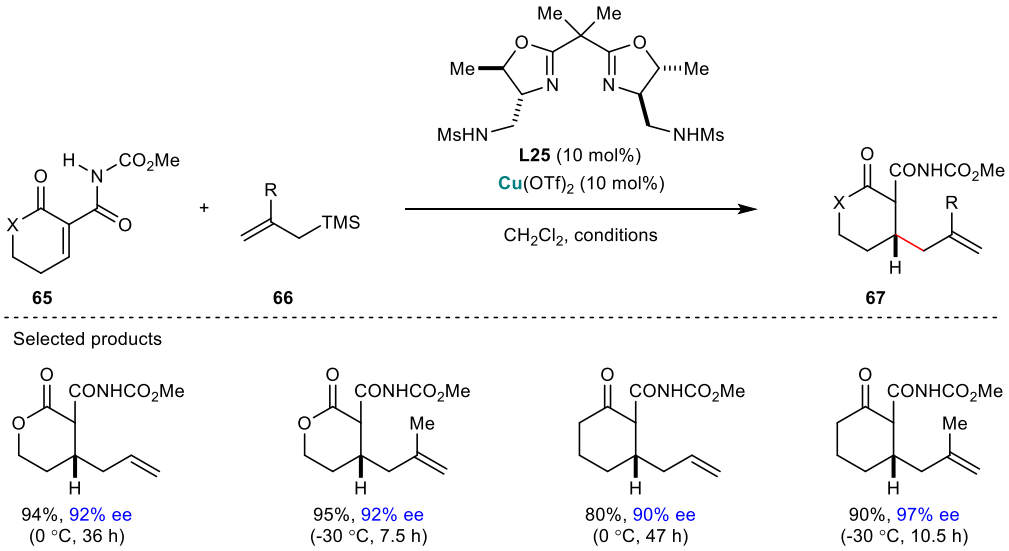
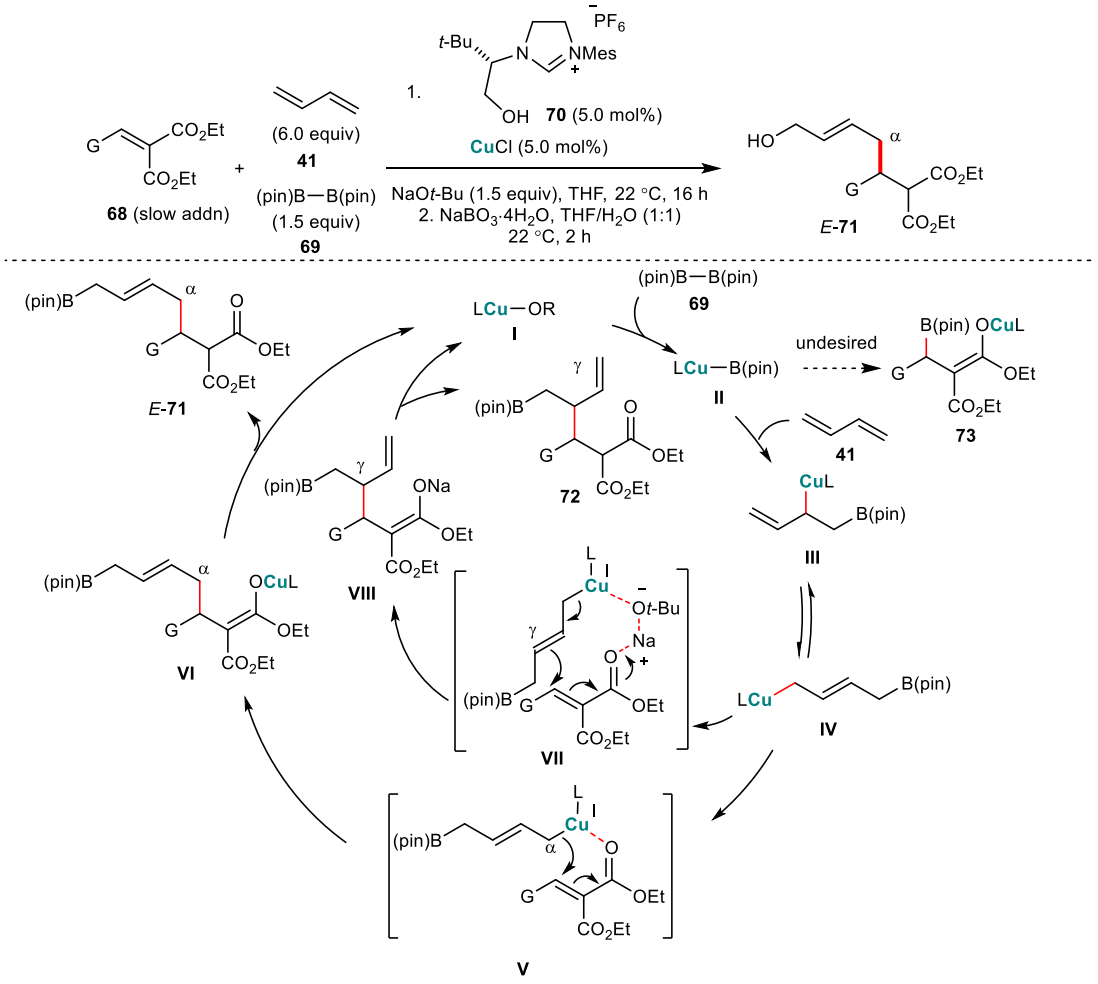


Figure 4. Proposed structure of copper complex of *α*-alkylidene *β*-keto imide



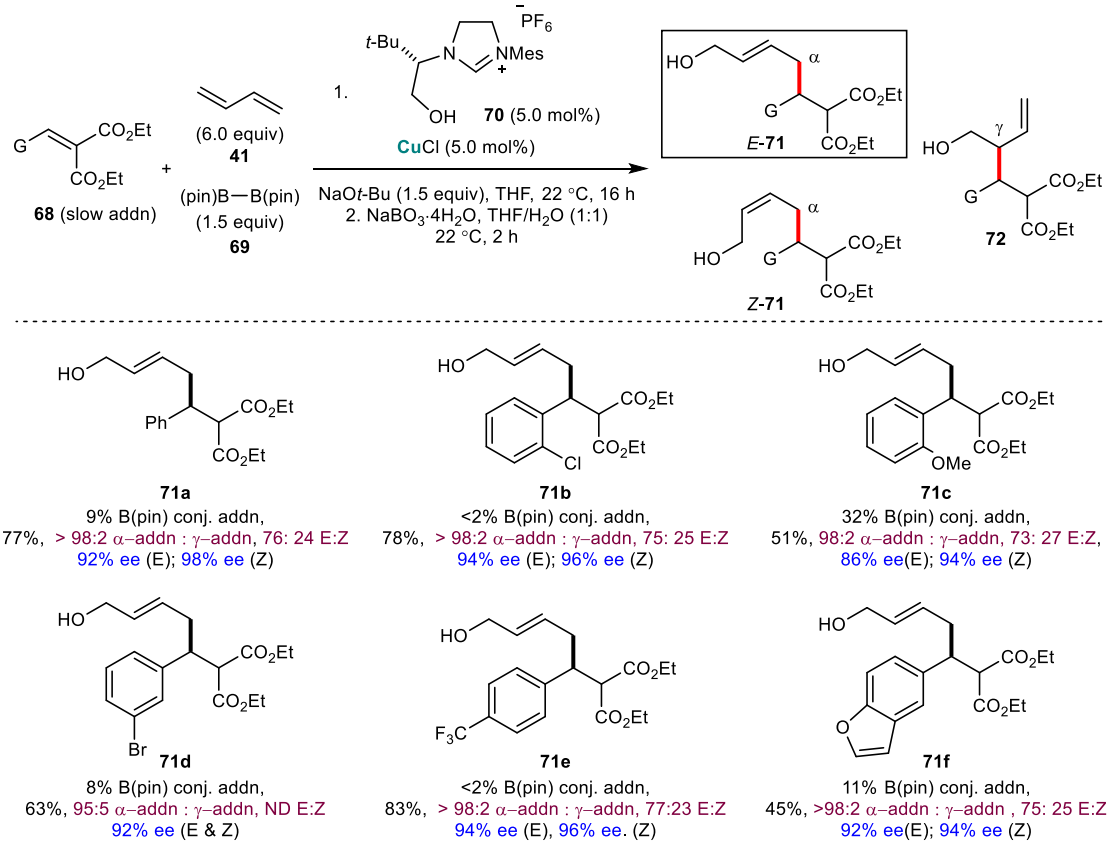
Scheme 53. Copper-catalyzed asymmetric Hosomi-Sakurai reaction

In 2016, Hoveyda reported a catalytic enantioselective conjugate addition reaction with butadiene **41**, an enoate **68** and $B_2(pin)_2$ **69**.[88] The catalytic cycle (Scheme 54) would begin with the transmetallation of copper complex **I** with $B_2(pin)_2$ **69** to form copper species **II**, which is followed by the addition to 1,3-diene forming allylcopper species **III** and **IV**. These allylcopper species would undergo 1,4-addition to the enoate forming *α*- vs. *ɤ*-addition products. However, there might be an option that boryl conjugate addition would competitively react with the enoate to form **73**.



Scheme 54. Proposed catalytic cycle for the copper-catalyzed conjugate addition

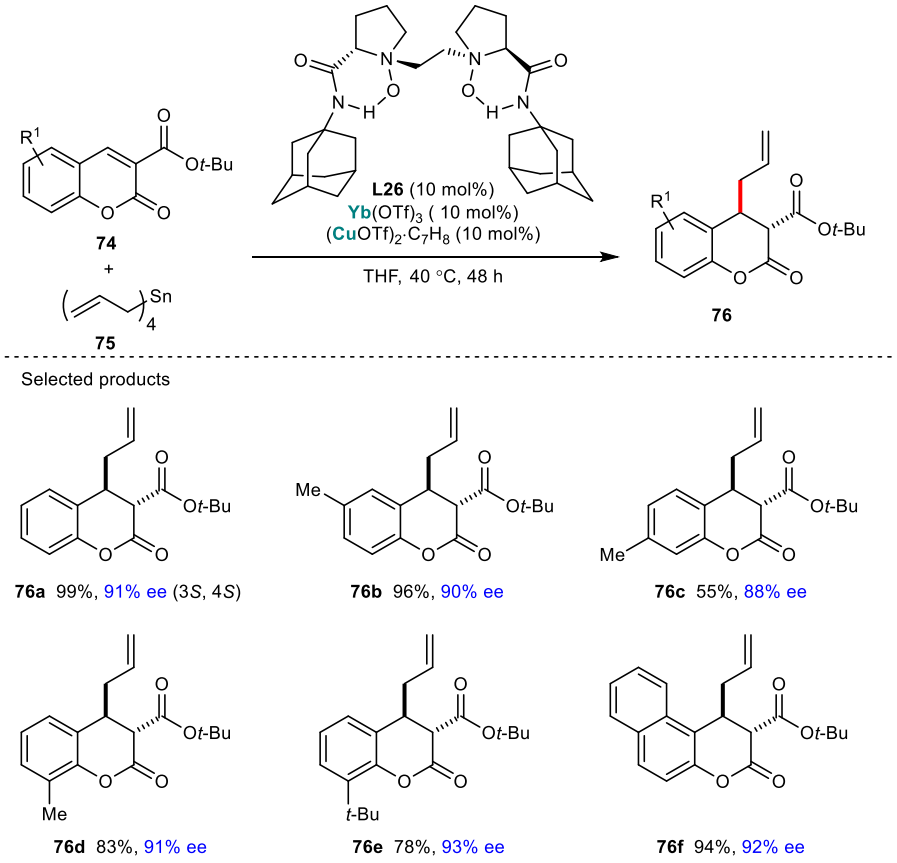
The α-addition products **71** were exclusively afforded when the enoate **68** was slowly added with the imidazolinium salt **70**. The selected results were showed in Scheme 55 demonstrating the desired products in up to 83% yield and 98:2 enantiomeric ratio. A variety of enoates **68** with different substituents on aryl groups were tolerated in this process. Electron withdrawing on *ortho*-, *meta*-, and *para*-substituted substrates were suitable and gave good yields and excellent enantioselectivities. With electron-donating substituents, the boryl carbonyl by-product through 1,4 addition of $B_2(pin)_2$ to the enoate **71c** was formed in 32% yield. This result showed that the reaction of allylcopper intermediate was influenced by the enoates electrophilicity.



Scheme 55. Scope of the copper-catalyzed 1,4-addition of an allyl moiety

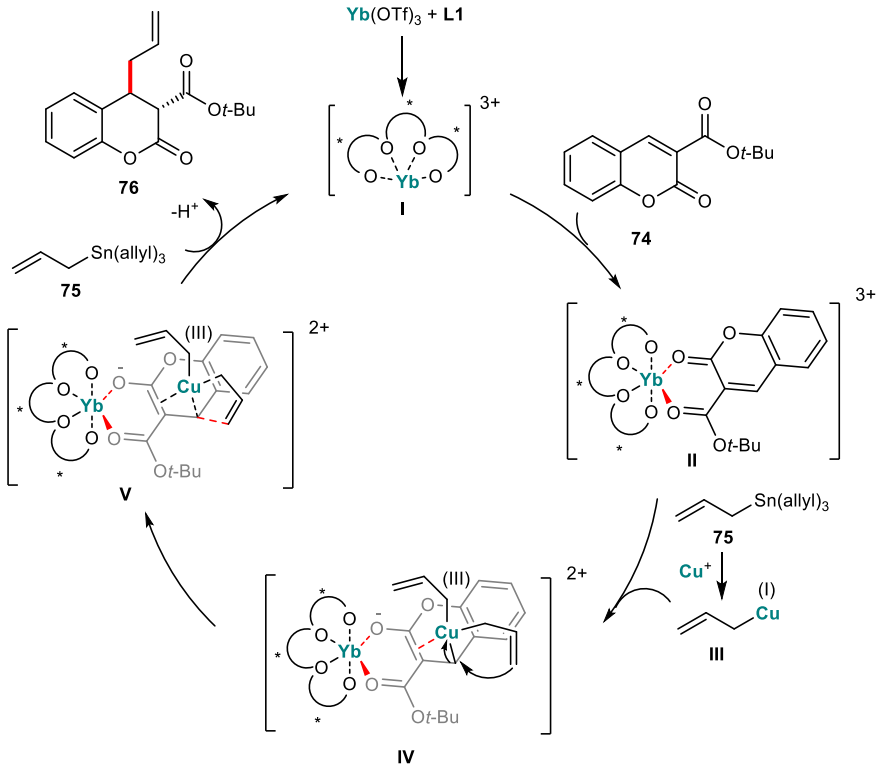
1.2.2. Yb-catalyzed enantioselective 1,4-allylations

In 2011, the Feng group [89] reported a Yb(III)-catalysed asymmetric conjugate allylation of coumarins **74** with tetraallyltin **75** and a dual activation strategy by using a cocatalyst $(CuOTf)_2 \cdot C_7H_8$. Their investigation showed that substrates containing a bulky ester group could afford higher stereoselectivities. The substituted coumarin derivatives afforded enriched enantioselective products up to a 93% ee and 99% yield (Scheme 56). Coumarins with 7- and 8-substitution patterns (**76c** and **76d**) gave lower yields compared with 6-substituted coumarins (**76b**) in a 55-83% yield and 96% yield, respectively. In addition, fused ring coumarin derivatives afforded product **76f** in high yield (94%) and enantioselectivity (92% ee).



Scheme 56. Catalytic asymmetric conjugate allylation of coumarin derivatives

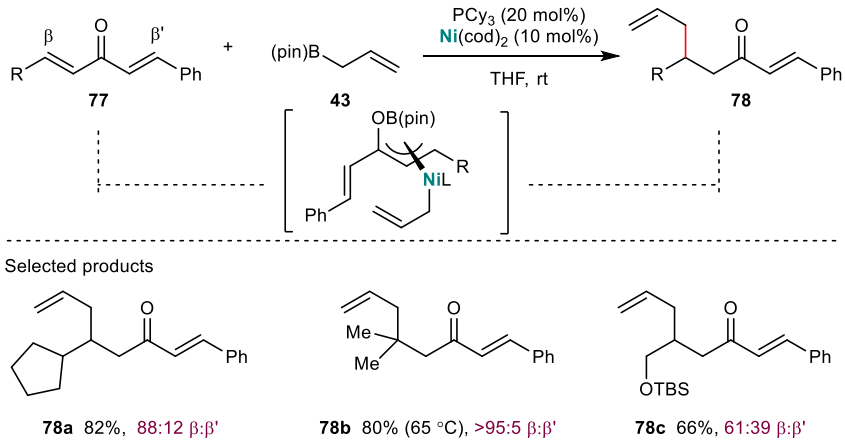
From their control experiments, the proposed catalytic cycle was demonstrated in Scheme 57. Firstly, ligand **L26** and $Yb(OTf)_3$ form **L**-$Yb(OTf)_3$ complex **I**, followed by coordination with coumarin **74**, generating to furnish intermediate **II**. The allyl copper(I) complex **III** generated from transmetallation of $(CuOTf)_2{\cdot}C_7H_8$ and tetraallyltin **75** would undergo charge transfer to the substrate and form the intermediate **IV**, followed by the cleavage of the allyl-Cu^{III} bond. Then, tetraallyltin interacts with intermediate **V** to form tin complex, which gives the product **76** by protonation in the work-up procedure, regenerating the active allyl copper(I) species.



Scheme 57. Proposed catalytic cycle of catalytic asymmetric conjugate allylation of coumarin

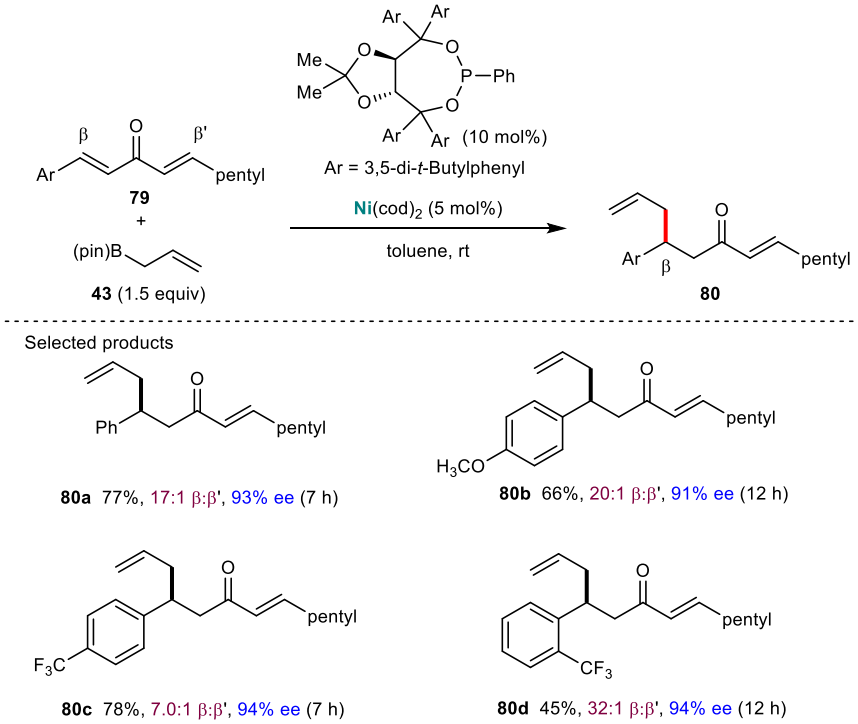
1.2.3. Ni-catalyzed enantioselective 1,4-allylation

In 2007, the Morken group reported the first catalytic example of nickel-catalyzed 1,4-allylation of allylboron compounds to activated unsymmetrical alkene ketones.[90] Catalyst $Ni(cod)_2$ and ligand PCy_3 were used in the reaction of allylB(pin) **43** and styryl ketones **77** to achieve excellent regioselectivities. 1,4-Addition allylation occurs at the more hindered site in good yield with an exception of the allylic ether (Scheme 58). The allyl ether also gives the conjugate addition product **78c** in good yield (66%).



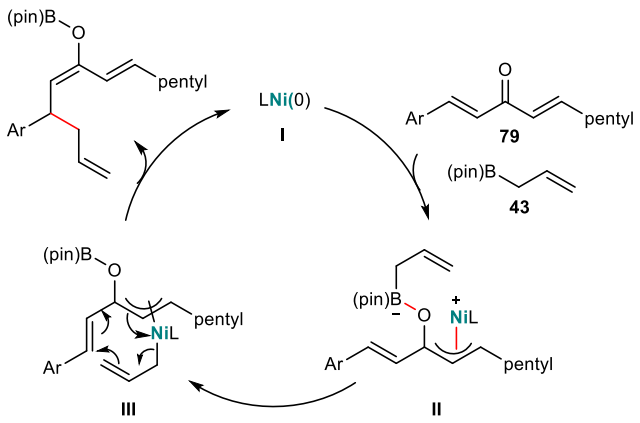
Scheme 58. Nickel-catalyzed 1,4-allylation of styryl ketones

In the following year, the same group found the first nickel-catalyzed enantioselective 1,4-allylation of unsymmetrical dialkylidene ketones **79** with a TADDOL-derived monophosphoramidite ligand, **L27** (Scheme 59).[91] The products were generated in good yields, high regio- and enantioselectivities with favoured conjugate allylation at the arylidene site. Substrates bearing electron-deficient arenes at the *para*-position gave **80c** with excellent enantioselectivities (94% ee) but lower chemoselectivities, whereas electron-rich arenes gave **80b** with high regio- and enantioselectivities (91% ee). Substrates with a substituent at the *ortho*-position on the arene gave dramatically increased chemoselectivities (**80d**). However, the reactions were limited to aryl-substituted dialkylidene ketone substrates.



Scheme 59. Nickel-catalyzed enantioselective 1,4-allylation of nonsymmetric ketones

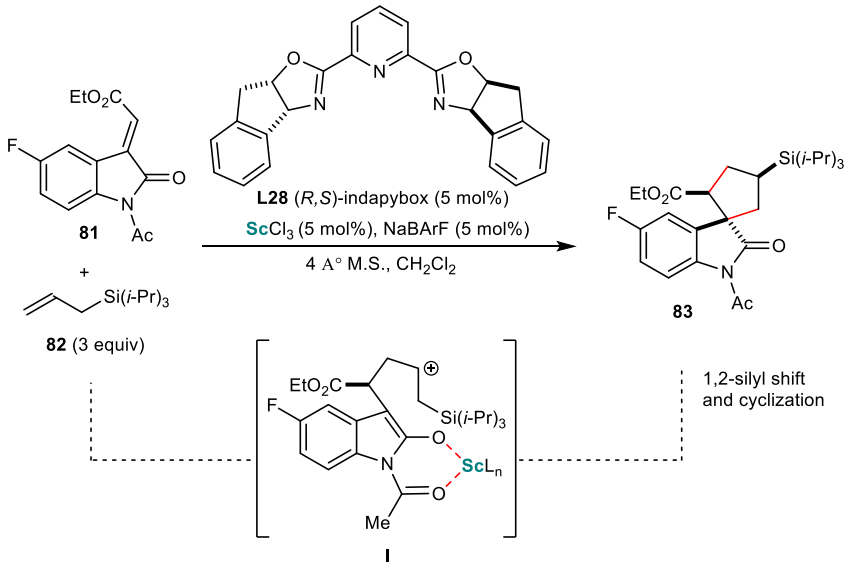
The mechanism of the reaction was investigated and supported by DFT calculations. The reaction proceeded *via* a Lewis acid-induced oxidative addition of nickel to the less-hindered alkylidene enone to give intermediate **II**, followed by an S_E'-type transmetallation and a 3,3′- reductive elimination process (Scheme 60).



Scheme 60. Proposed catalytic mechanism of asymmetric Ni-catalyzed 1,4-allylation of enones

1.2.4. Sc-catalyzed enantioselective 1,4-additions

In 2014, Franz *et al.* reported the first catalytic asymmetric carboannulation of **81** with allylsilanes **82** by using a scandium(III)-catalyzed system with a chiral indapybox ligand **L28** and tetrakis-[3,5-bis(trifluoromethyl)phenyl]-borane (BArF).[92] The substrates underwent 1,4-allylation, followed by cyclization, trapping of the *β*-silyl carbocation to furnish the functionalized cyclopentanes **83** with high stereoselectivities (Scheme 61).

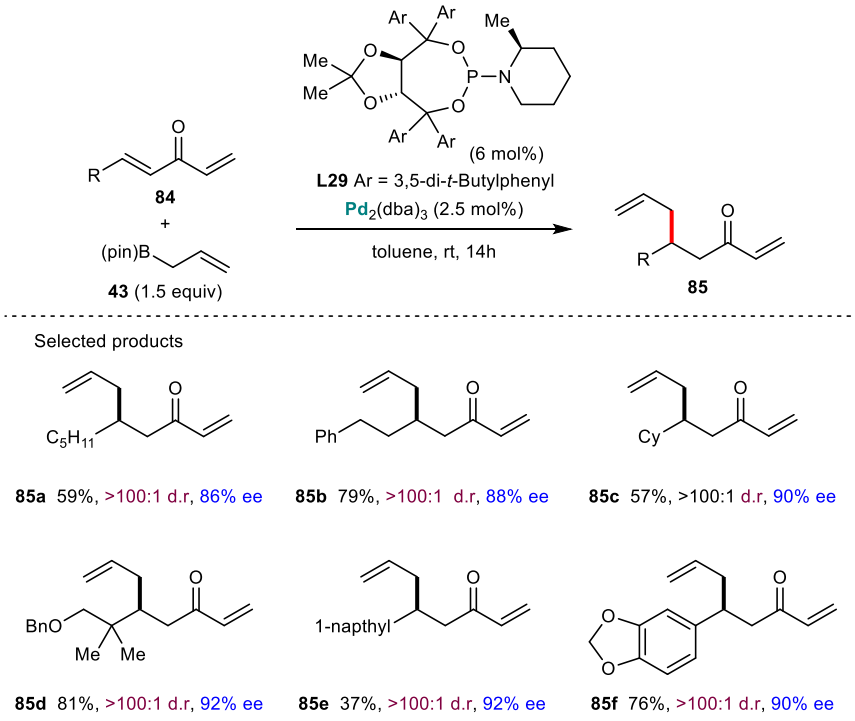


Scheme 61. Catalytic asymmetric addition of allylsilanes to α,β-unsaturated carbonyl reagents

1.2.5. Pd-catalyzed enantioselective 1,4-allylations

In 2011, the Morken group reported the Pd-catalyzed enantioselective 1,4-allylation of unsaturated methylidene ketones.[93] The process exhibits similar reactivity with

previous work using a nickel catalyst demonstrated in Section 1.2.3. However, the chemistry overcame the limitation of using aryl substituted alkylidene substrates. In this report, 1,4-allylation of unsymmetrical dialkylidene ketone was suitable for both aryl- and alkyl-substituted substrates. The reaction was carried out with the less sterically hindered methylidene ketones and a chiral monophosphoramidite ligand **L29** affording products in excellent regio- and enantioselectivites (Scheme 62). The first example of catalytic enantioselective 1,4-allylation of simple acyclic aliphatic enone (**85a**) was reported in good yield and high enantioselectivities (59% yield and 86% ee). Substrates containing aliphatic enones and aromatic rings were also tolerated in 79% yield and 88% ee (**85b**). The study showed that the methylidene ketones bearing branched substituents or oxygenation in the side chain afforded products **85c**, **85d** in good yields (57% and 81% respectively), high regio- and enantioselectivities. In addition, aromatic enones were well-tolerated under the reaction conditions (**85e**, **85f**).

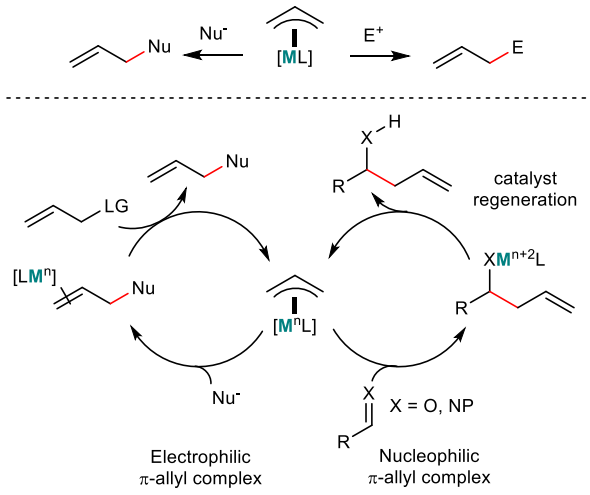


Scheme 62. Palladium-catalysed enantioselective 1,4-allylation

1.3. Transition-metal-catalyzed domino allylation using allenes

As indicated above, most of the previous reports in the field use allylmetal precursors and the reactions generally afford stoichiometric amount of metal waste, with the exception of the Krische group.[7] In addition, the required reagents are often expensive or unstable. Furthermore, the catalytic systems are often made of non-commercial ligands. On the other hand, transition-metal-catalyzed domino allylation is attractive because transition-metal catalyst *via* a cascade reaction enables an efficient construction of highly regio-, diastereo- and enatio- selective structures in a single step. There are studies that have shown that the nucleophilic allylmetal species can form *in situ* from the unsaturated hydrocarbon and further react with electrophiles.[10,42]

Addition to electrophiles as a trapping step for the cascade reaction is challenging because it is well-known that π-allylmetal complex is electrophilic and will react with nucleophiles. The reactivity of π-allylmetal reagents with electrophiles faces two main challenges shown in Scheme 63. Firstly, the metal properties need to be changed or controlled by utilizing additives and/or ligands. Secondly, catalyst regeneration needs to be ensured to furnish the enolate and allow for good catalytic turnover.



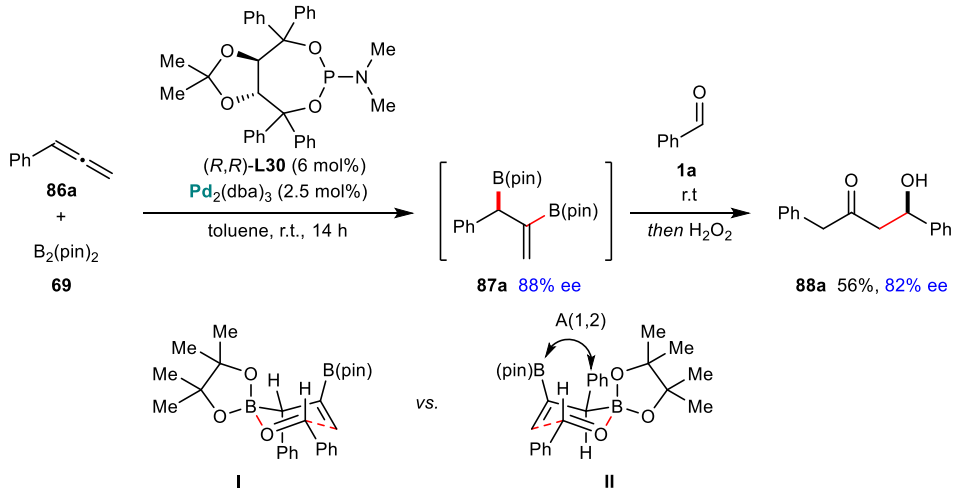
Scheme 63. Electrophilic *vs.* nucleophilic π-allyl reagents

There are several ways to change the electrophilicity of electrophilic π-allylmetal species: through addition of reducing reagents, through transmetallation from preformed allyl-metal reagents, through transfer hydrogenation strategies or through

metal coordination with ligands in the reactions.[42] The π-allylmetal species can be formed from unsaturated carbon compounds such as alkenes, alkynes, dienes or allenes. Allenes own two orthogonal π-bonds with specific electronic nature so it can be used as an attractive functional group. The following section will illustrate cascade reactions using different catalytic systems where the nucleophilic allylmetal species are formed *in situ* by insertion into allene and followed by addition into a carbonyl group.

1.3.1. Pd-catalyzed domino allylation

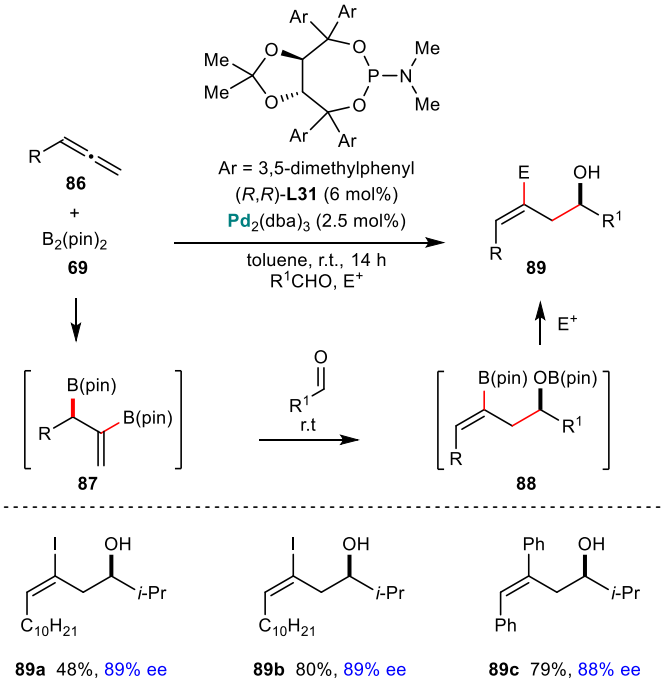
Morken group introduced a palladium-catalyzed asymmetric diboration of allene, where the obtained product was a stable compound and could react with an appropriate electrophile.[94] Scheme 64 illustrates a reaction of allene **86a** and $B_2(pin)_2$ **69** to afford a diboron intermediate **87a**, followed by addition of benzaldehyde **1a** and basic hydrogen peroxide, resulting in formation of the *β*-hydroxyketone **88a** in 82% ee. The authors suggested the allylation pathway proceeded preferentially through transition state **I**, which might be a result of an unfavourable A(1,2) interaction of transition state **II**. They also proposed that the reaction pathway through intermediate **II** was energetically less favourable compared to pathway through intermediate **I**.



Scheme 64. Tandem reaction using palladium-catalyzed diboration and carbonyl addition

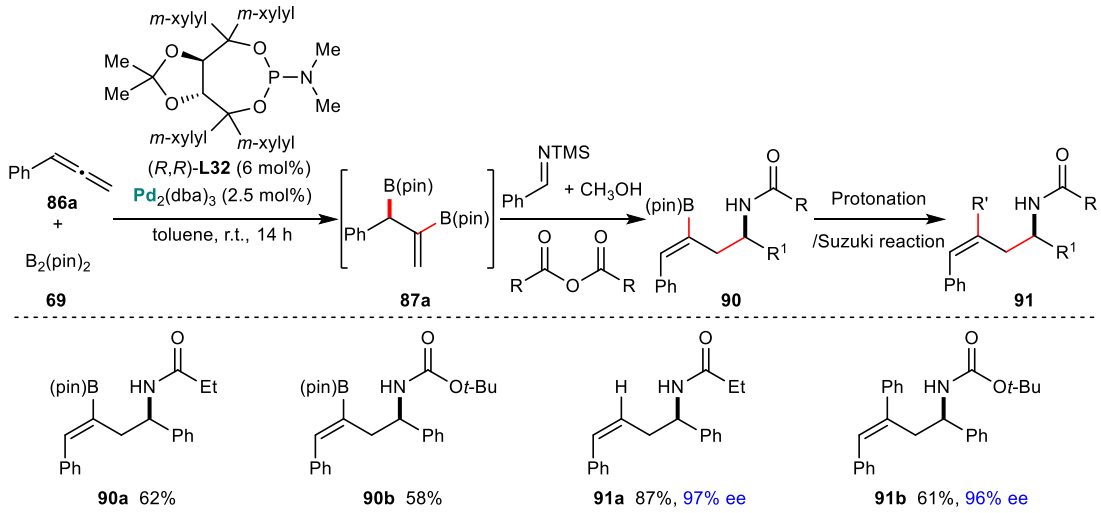
The group developed the above idea and reported a palladium-catalyzed enantioselective diboration-allylation-cascade reaction (Scheme 65).[95] Allene **86** reacted with $B_2(pin)_2$ **69** to give diboron intermediate **87**, followed by addition to

aldehyde to furnish vinylboronic ester **88**. This allylboration reation mixture was then filtered through a pad of silica and treated with aqueous NaOH and I_2 to give **89a** in 49% and 89% ee. **89b** was observed when heating reaction mixture with acetic acid. In addition, addition of idobenzene and KOH to mixture gave **89c** in good yield and high enantioselectivity.



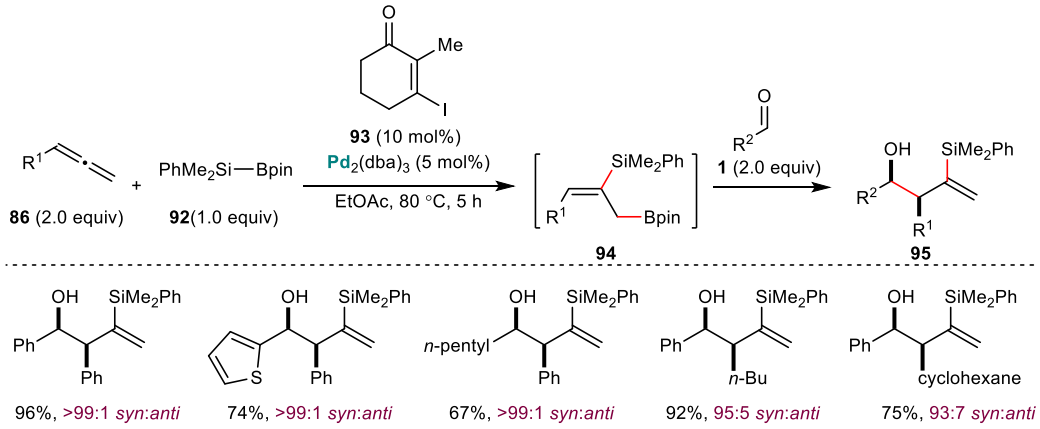
Scheme 65. Palladium-catalyzed enantioselective diboration-allylation-cascade reaction

This group later reported the first palladium-catalyzed enantioselective diboration-α-aminoallylation to give chiral homoallylic amine.[96] Chiral addition products were obtained through a multicomponent α-aminoallylation involving an allene **86a**, a diboron ester **69**, and *N*-(trimethylsilyl)benzaldimine. A protonation product (**91a**) and a Suzuki cross-coupling product (**91b**) of the vinyl boronate were obtained in enriched enantioselectivities (Scheme 66).



Scheme 66. Pd-catalyzed asymmetric allene diboration/α -aminoallylation

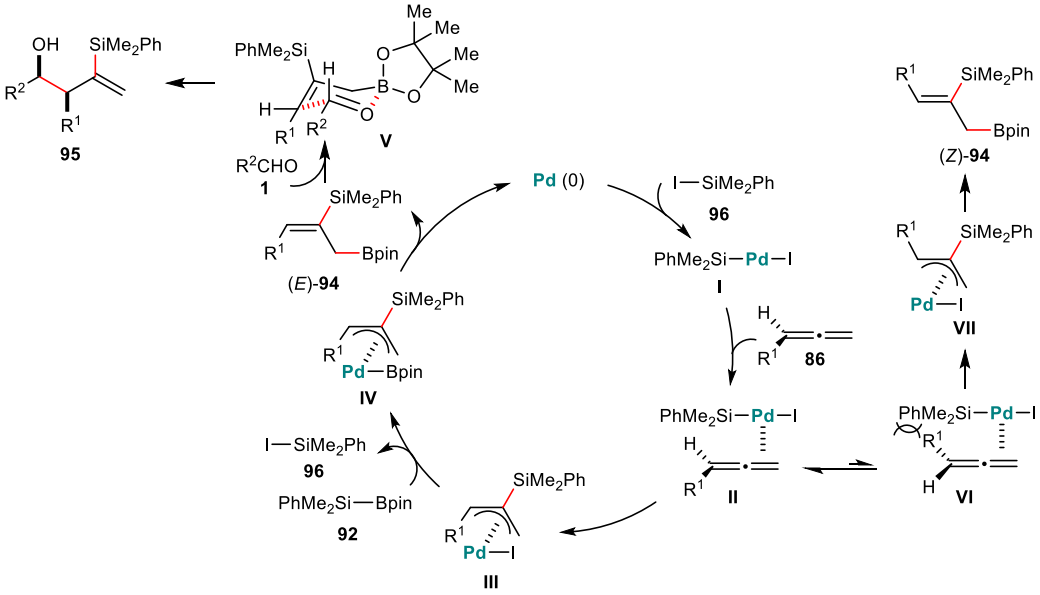
The Cheng group reported palladium-catalyzed silylative-carbonyl addition of allenes **86**, borylsilane **92** and aldehydes **1** to give homoallylic alcohols **95**. [97] The products **95** were obtained in good to excellent yields, with high *syn* selectivities with various aromatic and aliphatic aldehydes or allenes (Scheme 67).



Scheme 67. Palladium-catalyzed stereoselective allylation of aldehydes

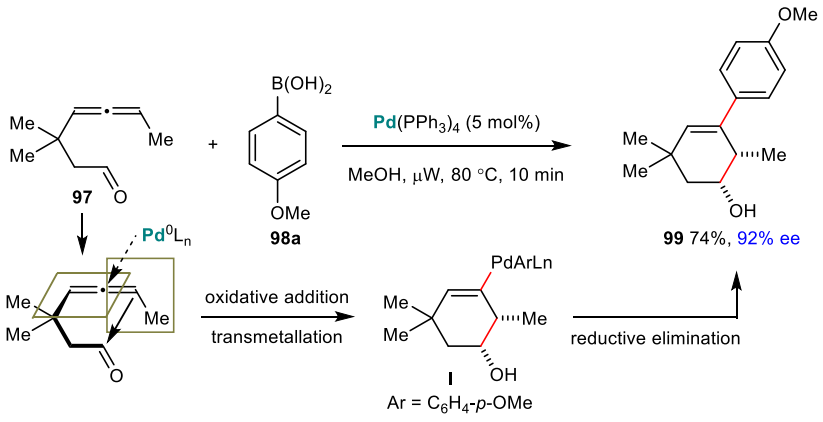
The mechanism of reaction was shown in Scheme 68. The organic halide **93** has been invoked to account for the initiated silaboration of allenes **86** by acting as an initiator undergoing oxidative addition with Pd(0) to give the palladium(II) intermediate. This intermediate reacts with allene **86** and subsequent borylsilane **92** to give silyl iodide **96**. This silyl iodide reacts with Pd(0) to begin the catalytic cycle. Oxidative addition of **96** to Pd(0) species gives Pd(II) intermediate **I**, followed by coordination and insertion of allene **86** to furnish Pd-allyl species **III**. These species undergo

transmetalation with borylsilane **92** to regenerate silyl iodide **96** and afford Pd-allyl species **IV**. Reductive elimination of **IV** yields the silaboration product **94** and regenerates the Pd(0) catalyst. The silylallylboronate **94** undergoes allylation with aldehydes **1** *via* a six-membered chair cyclic transition state to give the final homoallylic alcohols **95**.



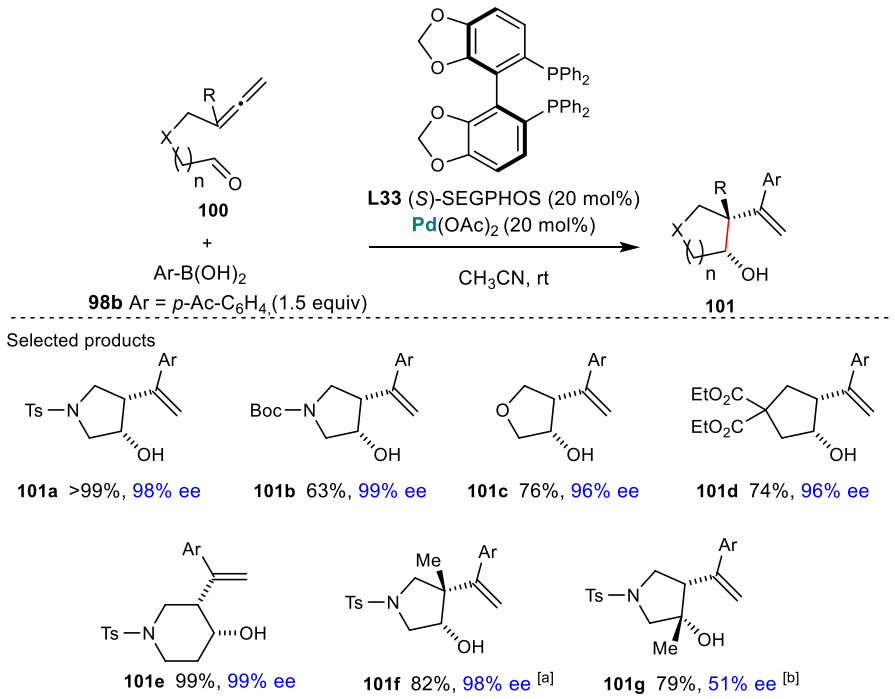
Scheme 68. Proposed mechanism of palladium-catalyzed stereoselective allylation of aldehydes

The Tsukamoto group reported a palladium-catalyzed intramolecular cyclization of 1,3-disubstituted allene aldehyde **97** under microwave irradiation (Scheme 69).[98] They proposed an intramolecular electrophilic addition of the carbonyl and concerted transmetallation with boronic acid **98a** to form intermediate **I**, followed by reductive eliminiation to give the cyclization product **99**. One enantioselective example was shown in high yield (74%) and excellent enantioselectivity (92% ee).



Scheme 69. Palladium(0)-catalyzed arylative cyclization of allenyl aldehydes

The group introduced the first palladium(II)-catalyzed enantioselective arylative cyclization of 3,4- and 4,5-dienals **100** with arylboronic acids **98b** to give *cis*-fused five- and six-membered cyclic alcohols.[99] The homoallylic alcohols **101** were obtained in good yields and high enantioselectivities with allenyl aldehydes containing tosyl-protected nitrogen, Boc-protected nitrogen, ether oxygen and tertiary carbon (Scheme 70). However, using methyl ketone required higher reaction time and the cyclization product **101g** was observed in moderate optical yield (51% ee).

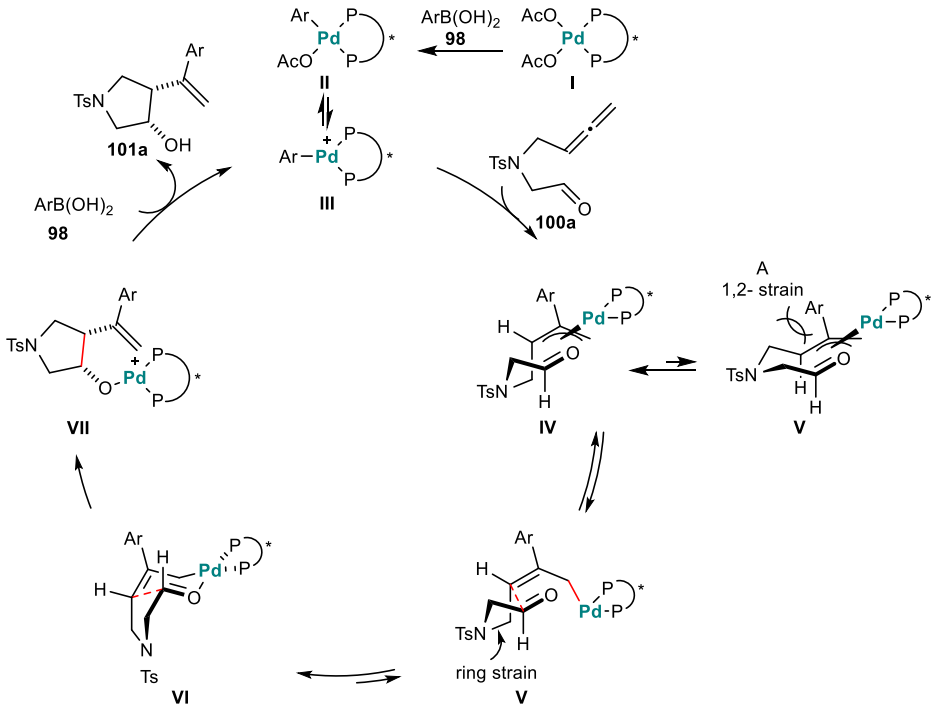


Scheme 70. Palladium-catalyzed enantioselective arylative cyclization of allenyl aldehydes

[a] Reaction with 10 mol % of catalysts. [b] Reaction at 50 °C.

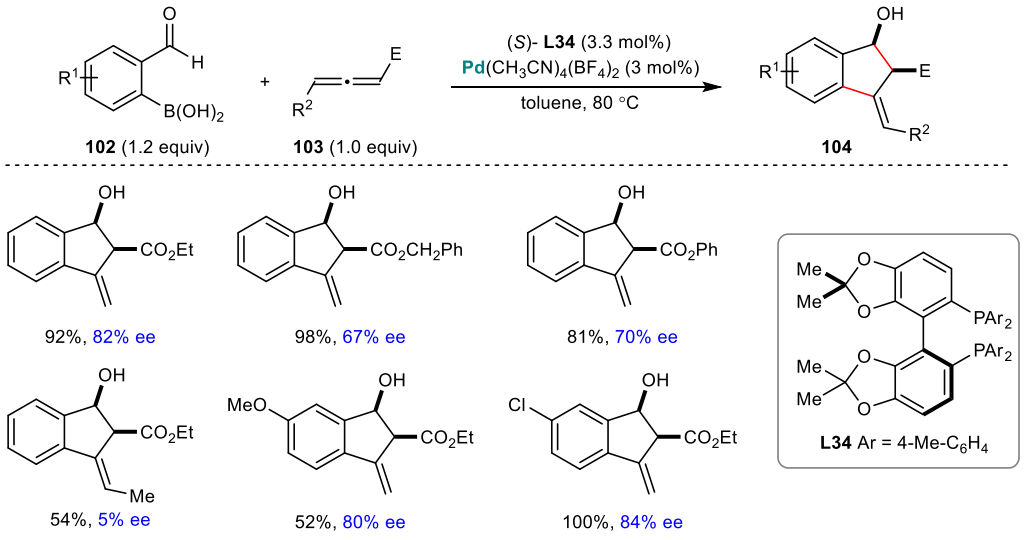
The mechanism for this arylative cyclization was proposed as shown in Scheme 71. Reaction is initiated with the formation of arylpalladium(II) intermediate **II** by transmetallation of palladium(II)-diphosphine complex **I** with aryl boronic acid **98**. The authors suggested that polar solvents would promote dissociation of the acetate anion from **II** to give cationic arylpalladium(II) **III**. This intermediate would undergo carbopalladation with allene **100a** from the less hindered side of distal allene π-system to furnish *anti*-η^3-allylpalladium(II) (**IV**), followed by isomerization to give η^1-allylpalladium(II) (**VI**, **VII**). The intramolecular allylation of the carbonyl could occur through six-membered cyclic transition states **VII**. Transmetallation of **VIII** or

protonation of **VIII** with arylboronic acids regenerates arylpalladium(II) (**III**) and releases the addition product **101**.



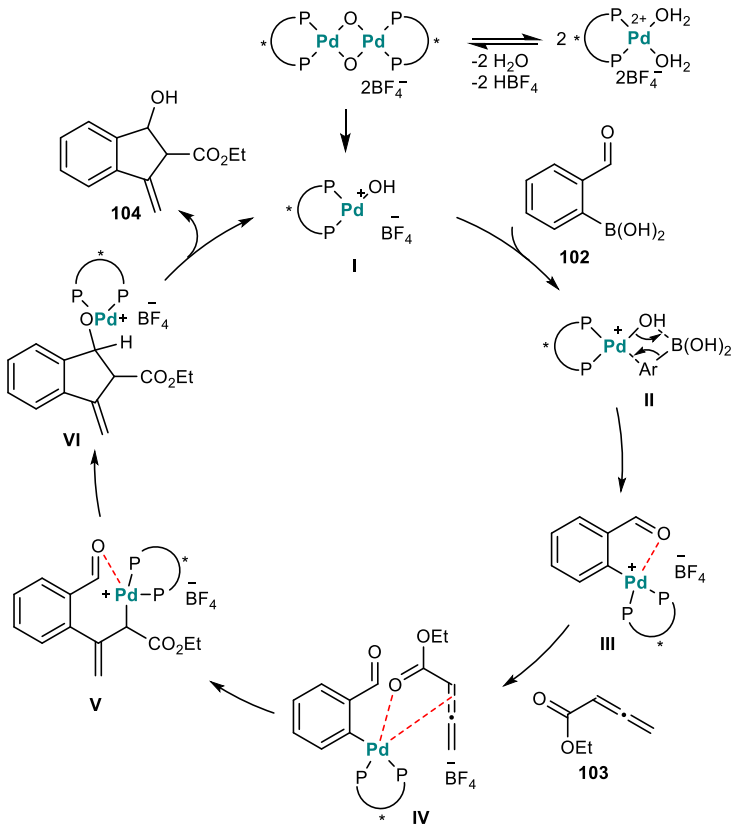
Scheme 71. Proposed mechanism of asymmetric palladium(II)-catalyzed arylative cyclization

Lu and co-workers developed a cationic palladium complex catalyzed [3+2] cascade reactions of 2-formylarylboronic acids **102** and allenoates **103**.[100] Various indenol derivatives **104** containing two stereocenters were obtained with different boronic acids and allenes in moderate to good yield and enantioselectivities up to 84% ee using chiral ligand **L34** (Scheme 72).



Scheme 72. Cationic palladium complex catalyzed enantioselective tandem annulation

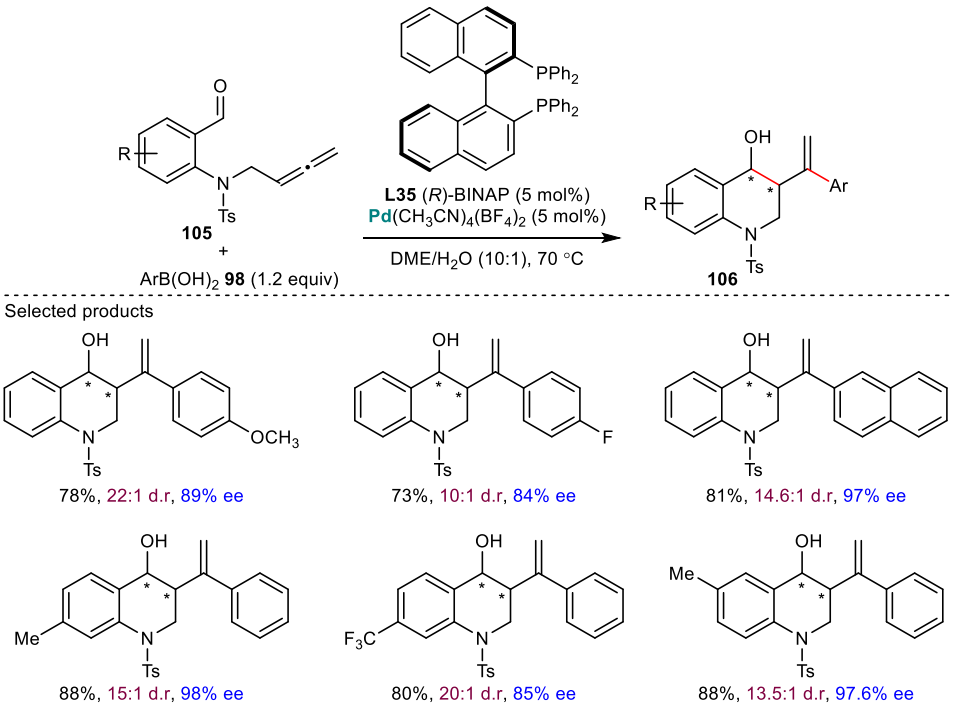
The group suggested the possible mechanism as shown in Scheme 73. The palladium hydroxo complex **I** is formed and undergoes a transmetallation with arylboronic acid to give intermediate **II** and **III**. Allene then coordinates with palladium center of cationic palladium complex to give intermediate **IV**, followed by allenoate insertion to form allylpalladium **V**. These species undergo intramolecular 1,2-addition to furnish intermediate **VI** and subsequent hydrolysis to give the product **104**, regenerate palladium catalyst and complete the catalytic cycle.



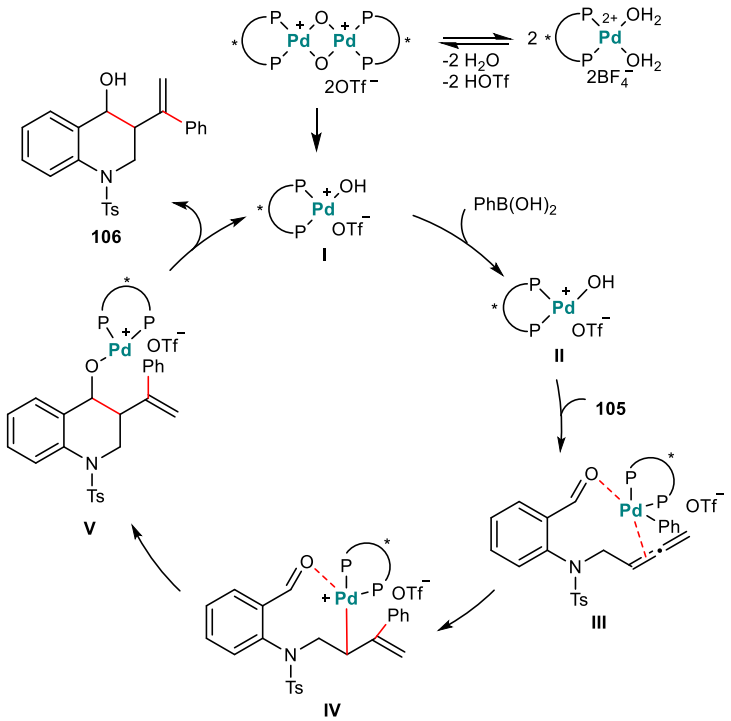
Scheme 73. Proposed mechanism of cationic-palladium-catalyzed tandem annulation

Inspired by the work, the group developed enantioselective cationic palladium-catalyzed annulation of allenyl aldehydes **105** with arylboronic acids **98** in 2015.[101] A variety of chiral hydroquiolines **106** were synthesized in high yields and diastereo- and enantioselectivites (Scheme 74). They suggested the reaction proceeds through mechanism as shown in Scheme 75. In a similar fashion to the previous report, the reaction is initiated with formation of palladium-phosphine complex **I**, followed by transmetallation with arylboronic acid to give the intermediate **II**. Allenyl aldehydes **98** will coordinate to the Pd center of **II** to give **III**. Insertion of the allene to the arylpalladium species affords the nucleophilic η^1-allylpalladium complex **IV**. The

palladium center in **IV** is highly Lewis acidic and thus can coordinate with carbonyl group to undergo the 1,2-addition to furnish intermediate **V**. The protonation of **V** gives the cyclization product **106** and regenerates the palladium complex.



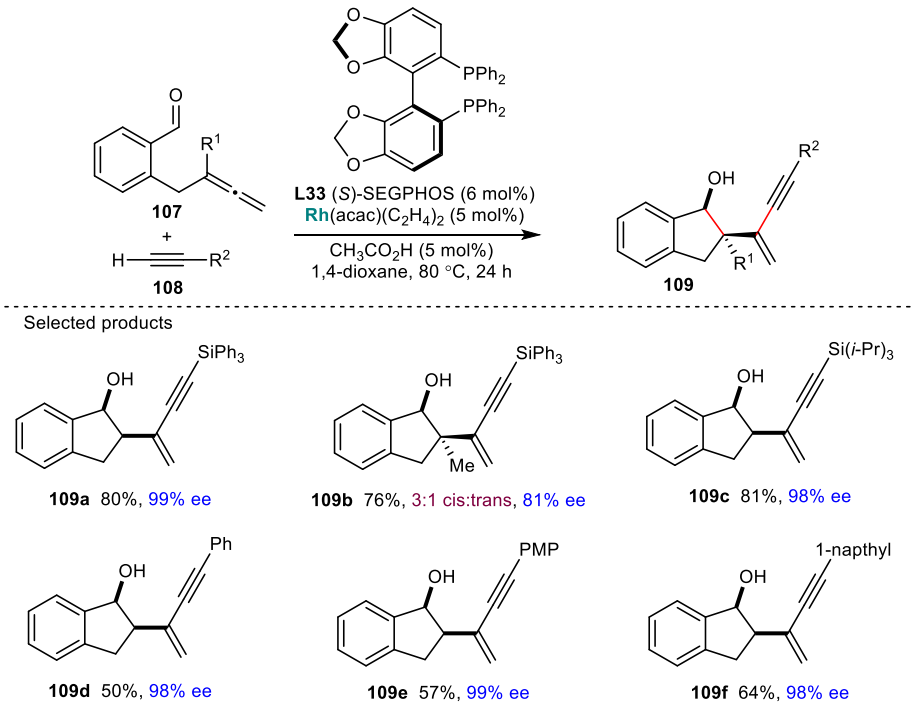
Scheme 74. Cationic palladium-catalyzed enantioselective annulation of allenyl aldehydes



Scheme 75. Plausible mechanism for the palladium-catalyzed annulations

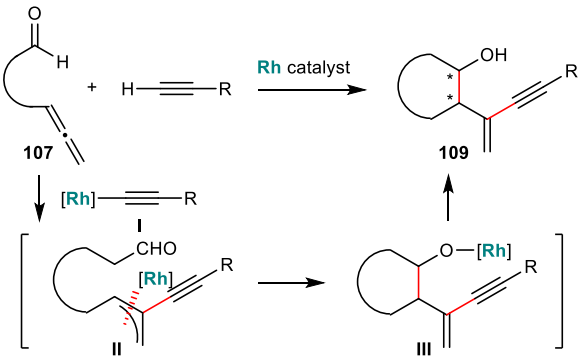
1.3.2. Rh-catalyzed domino allylations

In 2010, Nishimura and Hayashi et al. reported asymmetric rhodium-catalyzed alkynylative cyclization of allenyl aldehydes **107**.[102] The corresponding chiral indanols **109** were obtained in good yields with high enantioselectivities (Scheme 76). Allene containing 1,1-disubstitutions gave indanol **109b** with a quaternary stereocenter in 76% yield with 81% ee although the diastereoselectivity was moderate (*cis*:*trans* = 3:1).



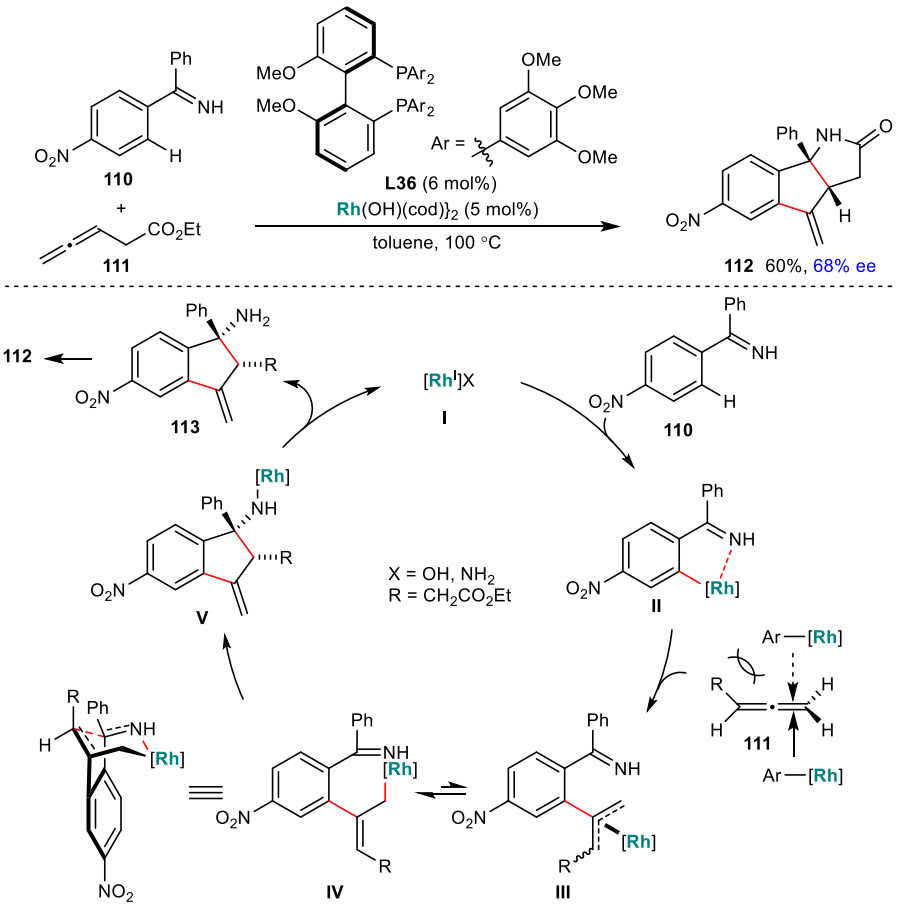
Scheme 76. Rh-catalyzed asymmetric addition of terminal alkynes to allenyl aldehydes

The alkynylrhodium(I) intermediate **I** was suggested to react with allene **107** to give the nucleophilic π-allylrhodium(I) intermediate **II**, followed by intramolecular 1,2-addition to the aldehyde moiety to give a rhodium alkoxide **III**. These species would undergo protonolysis to give chiral cycloalkanol **109** (Scheme 77).



Scheme 77. Proposed mechanism for Rh-catalyzed alkynylative cyclization of allenyl aldehydes

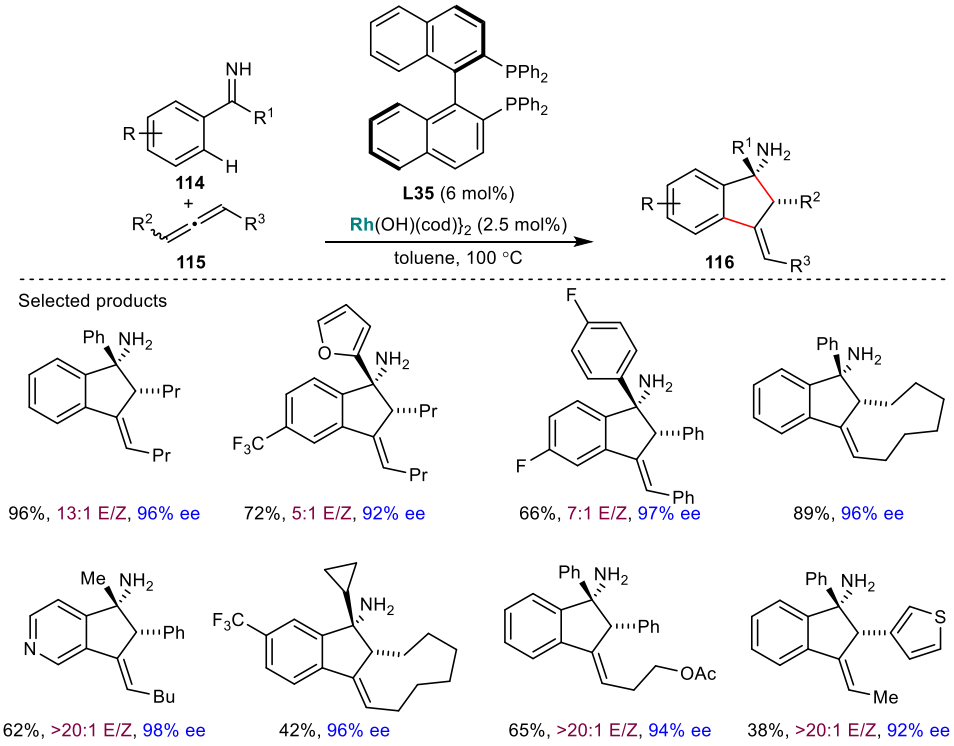
The Cramer group developed a rhodium(I)-catalyzed cyclization of ketimines **110** and allenes **111** to form amines through a directed C−H activation and allene addition.[103] They demonstrated an enantioselective rhodium-catalyzed domino C−H activation-cyclization reaction using **L36** in 60% yield and 68% ee Scheme 78. The reaction was suggested to begin with C-H activation of a rhodium (I) complex **I** and **110** to give intermediate **II**, followed by carborhodation of terminal double bond of allene **111** to give allyl rhodium(I) species (**III** and **IV**). The nucleophilic intermediate **IV** undergoes allylation of the imine moiety to afford rhodium amido complex **V**. Subsequently, protonation would occur to release the amine **113** and regenerate the catalyst. The intramolecular condensation of amine and carboxylate groups would form the amide compound **112** (Scheme 78).



Scheme 78. Enantioselective rhodium-catalyzed C-H activation/cyclization

The group continued with the idea to provide highly selective approach to indanylamines by rhodium(I)-catalyzed cascade C−H activation-carborhodation-cyclization of ketimines **114** and allenes **115** in 2013.[104] They reported different

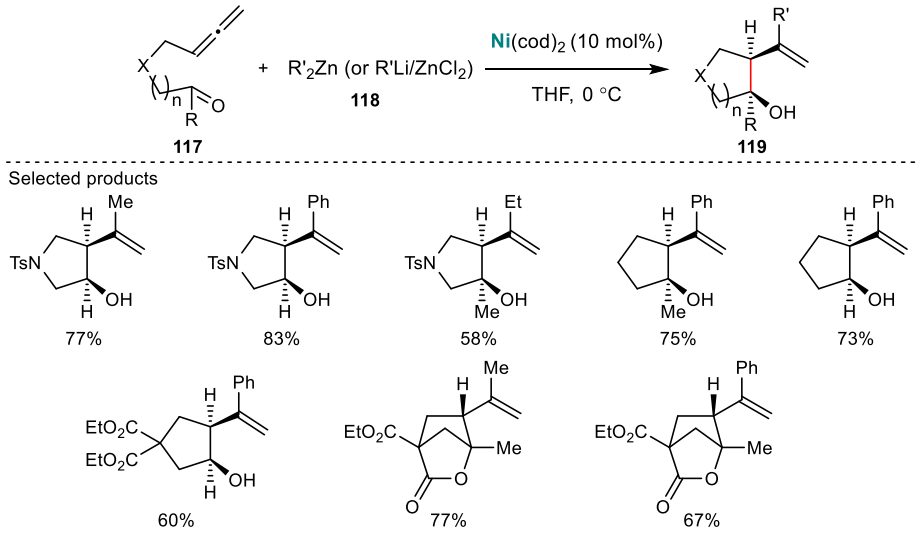
substitution patterns on the arylimines and allenes to give cyclization products **116** in high diastereo- and enantioselectivities using chiral ligand **L35** (Scheme 79).



Scheme 79. Rhodium(I)-catalyzed cascade C−H activation-carborhodation-cyclization

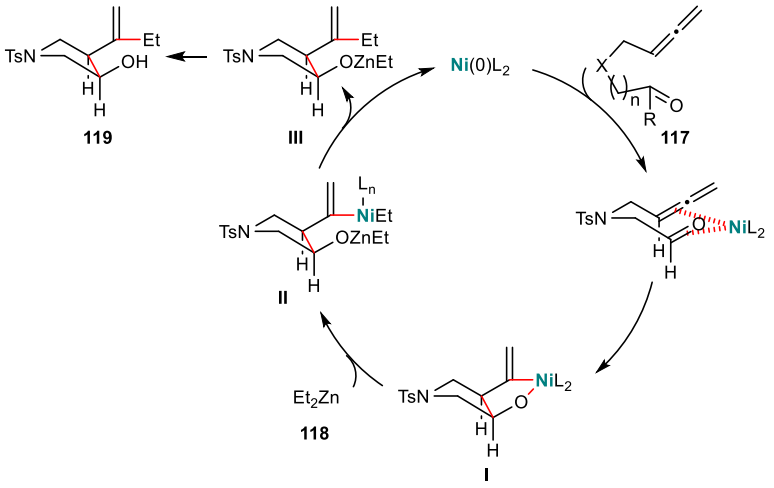
1.3.3. Nickel-catalyzed domino allylations

The Kang group reported nickel(0)-catalyzed alkylative/arylative cyclization of allenyl ketones **117** with organozinc reagents **118** to give *cis*-stereoselective alkenylcyclopentanol **119** (Scheme 80).[105]



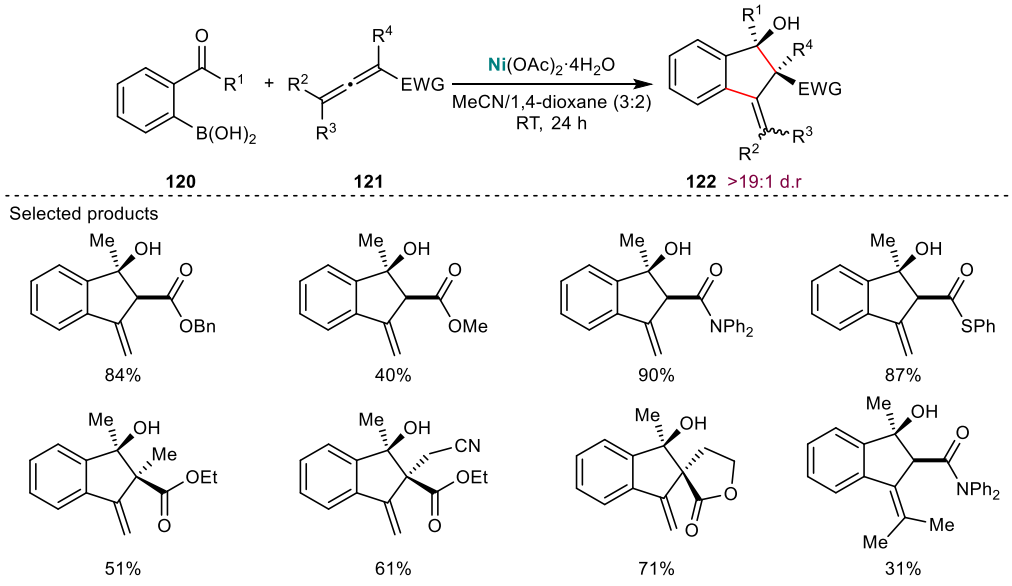
Scheme 80. Nickel(0)-catalyzed alkylative/arylative cyclization

The reaction mechanism was proposed as shown in Scheme 81. The reaction is initated with oxidative cyclization of Ni(0)-allenyl-aldehyde complex to form oxametallacycle **I**. This intermediate **I** is then transmetalated with an organozinc reagent to afford intermediate **II**, followed by reductive elimination to furnish zinc alkoxide **III** and regenerate Ni(0) complex. The alkoxide **III** undergoes protonolysis to form product **119**.



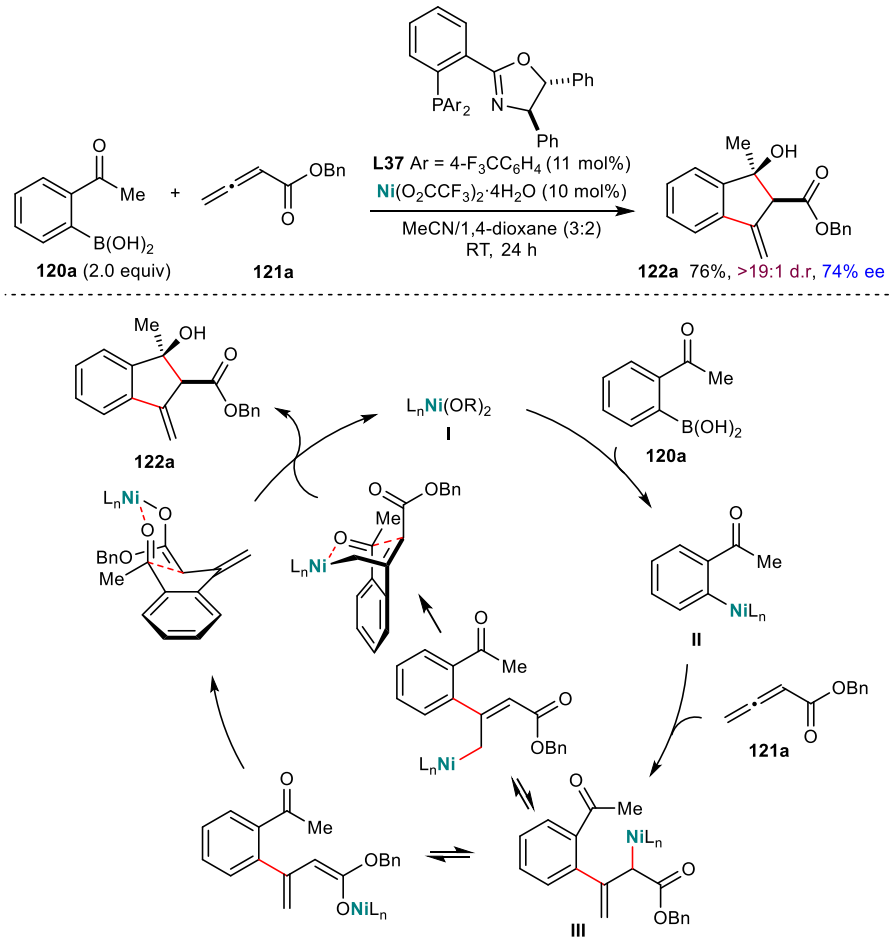
Scheme 81. Proposed mechanism of nickel(0)-catalyzed alkylative/arylative cyclization

The Lam group developed nickel-catalyzed domino addition-cyclization reactions of 2-acetylphenylboronic acids **120** with allenoates **121** to give 3-methyleneindan-1-ols **122** in moderate to excellent yields (Scheme 82).[106]



Scheme 82. Nickel-catalyzed domino addition-cyclization reactions

The group demonstrated an enantioselective variant of this nickel-catalyzed domino addition-cyclization using $Ni(O_2CCF_3)_2 \cdot 4H_2O$ and phosphinooxazoline **L37** as ligand to furnish 3-methyleneidan-1-ol **122a** in good yield with 74% ee (Scheme 83). The proposed mechanism is shown in Scheme 83. First, nickel complex **I** is transmetallated with arylboronic acid **120a** to give arylnickel species **II**, followed by arylnickelation to allene **121a** to afford allylnickel species **III**. This is followed by an intramolecular allylation of ketone to furnish 3-methyleneidan-1-ol **122a** through a cyclic six-membered transition state.

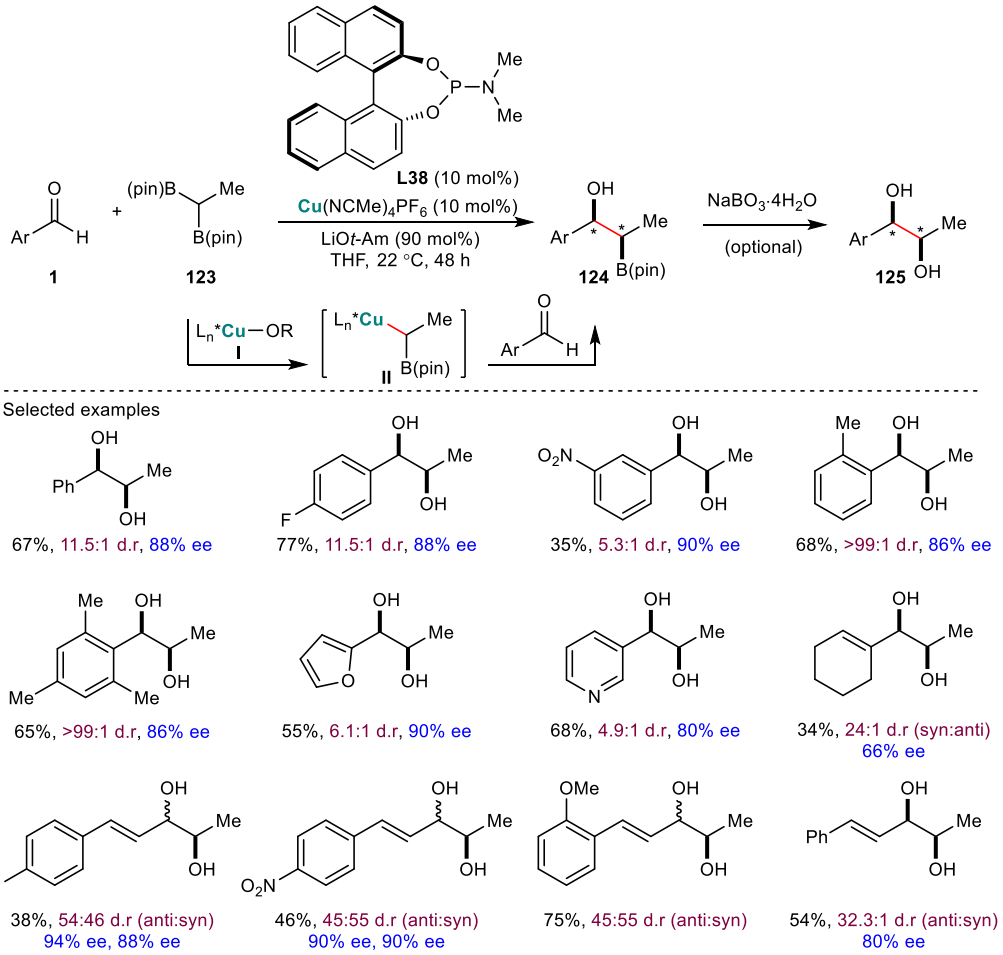


Scheme 83. Enantioselective nickel-catalyzed domino addition-cyclization

1.3.4. Cu-catalyzed domino allylations

Meek and co-workers introduced the first copper-catalyzed diastereo- and enantioselective additions of alkylboronates **123** to aldehydes **1** using chiral monodentate phosphoramidite **L38**.[107] The products 1,2-hydroxyboronates **124** were formed and oxidized to the corresponding diols **125** in good enantioselectivities and

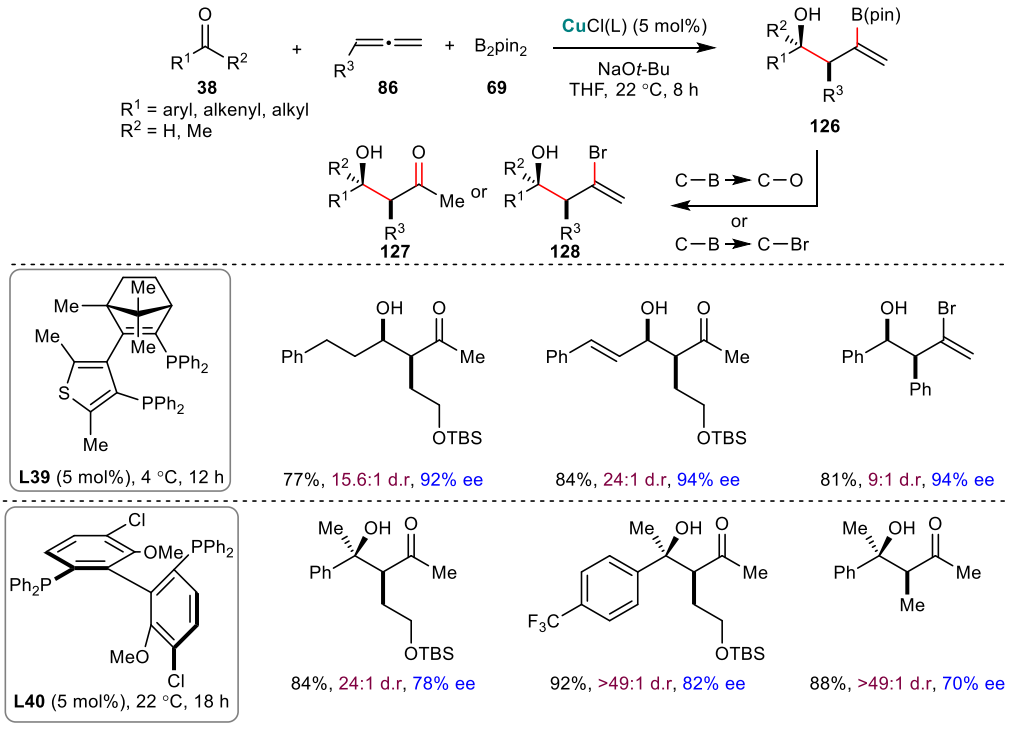
the reaction was tolerant to aryl and vinyl aldehydes (Scheme 84). The aryl groups bearing electron-withdrawing and electron-donating substituents were compatible, heteroaryl aldehydes and cyclohexene derived vinyl aldehydes also underwent smooth diastereoselective 1,2-addition. Reaction is initiated with Cu salts and monodentate phosphine **L38** to form the copper complex **I**, followed by transmetallation with an alkyl 1,1-diboron reagents to form intermediate **II**. These species undergo 1,2-addition to aldehyde to form 1,2- hydroxyboronate products **124**.



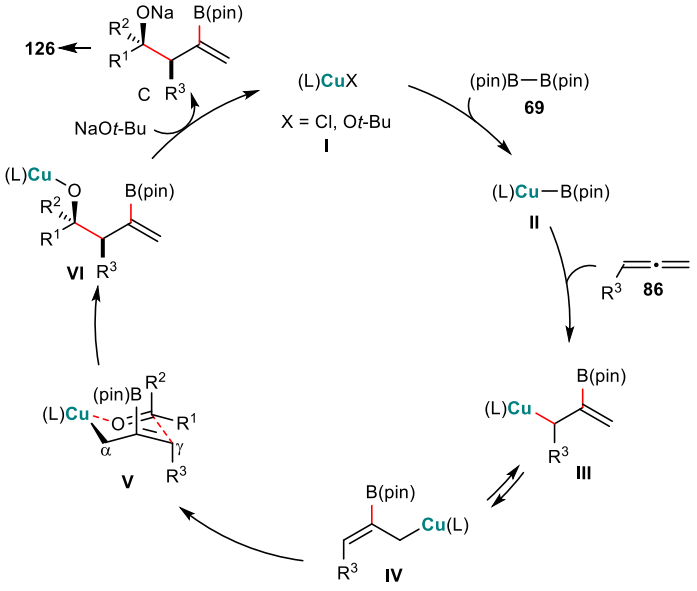
Scheme 84. Cu-catalyzed 1,2-addition of borane and aldehydes

In 2013, Hoveyda et al. developed the first copper-catalyzed enantioselective nucleophilic additions of 2-boryl-allyl units to ketones.[108] Reactions with aryl-, alkenyl-, alkyl-substituted ketones gave products in high enantioselectivities by using chiral biphosphine ligands **L39**, **L40** and Cu complexes (Scheme 85). The proposed reaction mechanism is shown in Scheme 86. Transmetallation of copper source **I** and boronane **69** forms Cu−B(pin) **II**, followed by addition to allene to furnish (pin)B-substituted allylcopper complex **III** and **IV**, which might be in equilibrium. The

reaction could proceed through the less congested Cu center of intermediate **IV** which could react with aldehyde to yield product **VI** through chair-like transition state **V**. Protonolysis of metal enolate forms the 2-B(pin)-substituted homoallylic alcohol **126**. Then oxidation of the C-B bond would form **127** or bromide derivatives **128**.



Scheme 85. Cu-catalyzed enantioselective coupling of allene with carbonyls



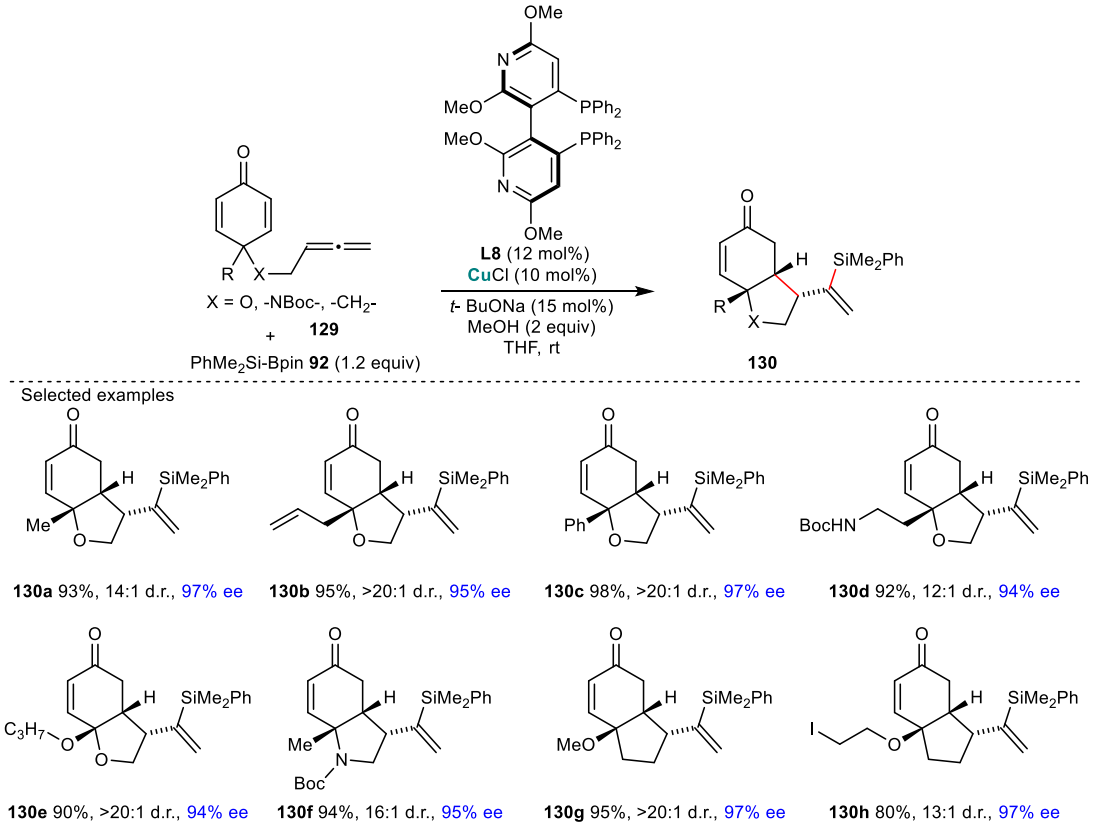
Scheme 86. Proposed mechanism of enantioselective additions of aldehydes and ketones

1.4. Transition-metal-catalyzed enantioselective domino 1,4-addition-cyclization reactions using allenes

From the previous section, we have seen that the domino reaction has offered the efficient construction of highly regio-, diastereo- and enatio- selective products in a single step. There are few reports of transition-metal-catalyzed reactions between electrophiles and allenes,[100-104] however; there are just a handful of examples of cascade reactions where nucleophilic allyl transition-metal species attacked electrophiles tethered through a 1,4-addition along with cyclization. The following literature will describe the transition-metal-catalyzed enantioselective cascade 1,4-addition reactions including allenes and organometallic reagents. Transition-metal complexes undergo transmetallation with organometallic species, followed by addition to allenes to form allyl transition-metal nucleophilic species. The nucleophilic species then attacks electrophiles tethered through 1,4-addition and cyclization to form desired products.

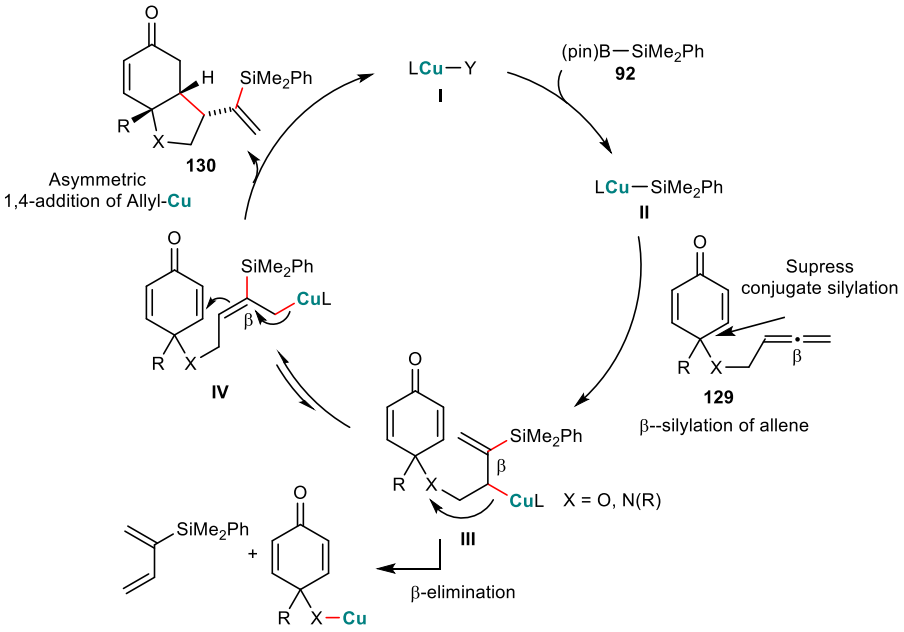
1.4.1. Cu-catalyzed domino 1,4-addition-cyclization reactions

In 2015, Tian and Lin et al. reported the first copper-catalyzed enantioselective silylative cyclization of cyclohexadienone tethered allenes **129** *via* 1,4-addition of *β*-functionalized allylcopper to *α*,*β*-unsaturated carbonyls.[109] Allenes and *α*,*β*-unsaturated carbonyls were used to favour 1,4-addition and avoid 1,2-addition into a carbonyl group due to the nature of site restrictions. The results showed that these cascade reactions gave *cis*-hydrobenzofuran (**130a**-**e**), *cis*-hydroindole (**130f**) and *cis*-hydroindene (**130g**-**h**) derivatives in excellent yields and enantioselectivities (Scheme 87). The reaction tolerated different substituents such as alkyl (**130a**), allyl (**130b**), phenyl (**130c**) groups in 93−98% yield and 95−97% ee. Moreover, different enone core structures were obtained in excellent yields (80−94%) and enantioselectivites (95−97% ee) and could undergo further transformations to furnish bicyclic- or tricyclic- products.



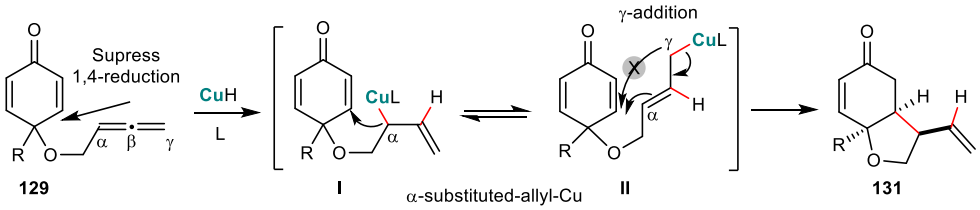
Scheme 87. Selected examples of copper-catalyzed asymmetry silylative cyclization

The mechanism for this transformation is proposed in Scheme 88. At first, the copper complex **I** transmetallates with $PhMe_2Si$-Bpin to form copper species **II** which undergoes *β*-silylation of the allene **129**. It is suggested that 1,4-addition silylation to cyclohexadienone could be suppressed by a steric hindrance of adjacent atoms to get regioselective products. Moreover, *β*-silylated allylcopper intermediate **IV** is likely favoured versus **III** because of the preferentially addition position of Cu located at the less-hindered site of the allene. The *β*-elimination pathway was not applicable for heteroatom-linked substrates due to the high reactivity of the cyclohexadienone. From intermediate **IV**, products **130** with chiral *cis*-bicyclic cores where afforded through intramolecular 1,4-addition.



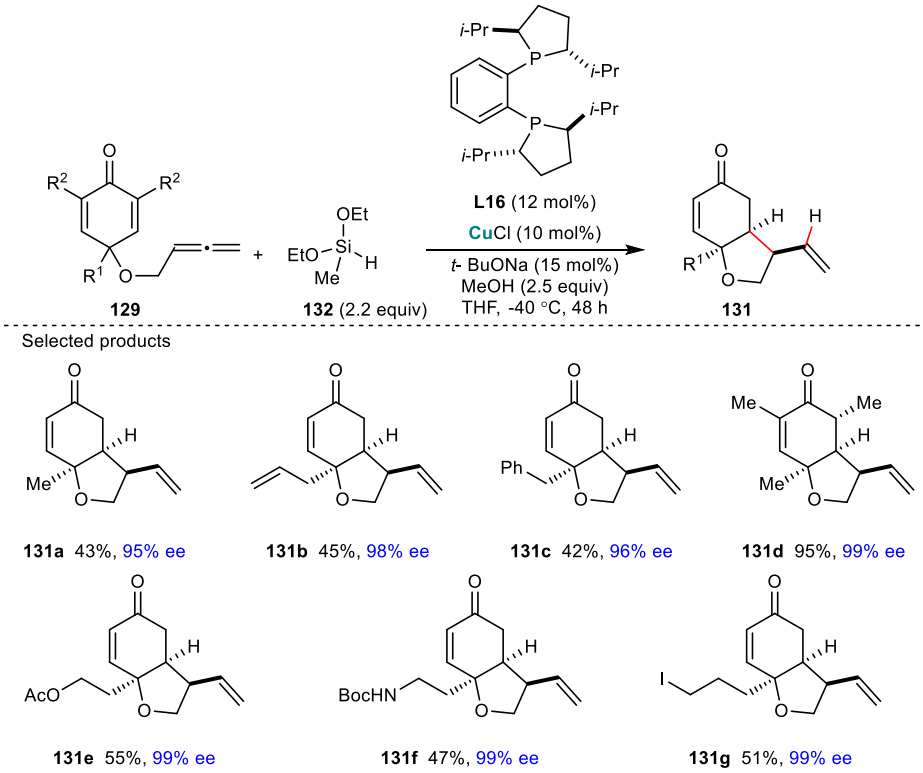
Scheme 88. Proposed catalytic cycle of copper-catalyzed asymmetry silylative cyclization

In 2018, the same group reported CuH-catalysed 1,4-reductive coupling of allenes to enones with cyclohexadieneone substrates **129**.[110] The reaction pathway occurs *via* a α-substituted allylcopper intermediates **I** or **II** which origins from the insertion of CuH into the terminal allene. Regioselective insertion occurs as the Cu prefers the less hindered site, followed by 1,4-addition to the carbonyl group to afford bicycle-products **131** (Scheme 89). The 1,8-asymmetric induction product by the ɤ-addition pathway was not obtained in this report.



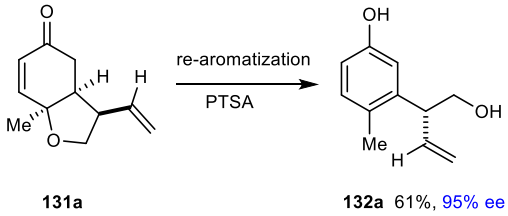
Scheme 89. Proposed CuH-catalyzed reductive coupling of allenes to enones

Excellent enatioselective *cis*-hydrobenzofuran products were obtained by using chiral ligand (*R*,*R*)-*i*-Pr-DuPhos **L16**, copper salt and diethoxymethylsilane **132** (Scheme 90). Substrates with R^1 substituents as alkyl (**131a**), allyl (**131b**), and benzyl (**131c**) groups or R^1 substituents including heteroatoms were tolerated without the observation of nucleophilic substitution product (**131e-g**). Allene **129d** give **131d** in a remarkable yield (95%) and excellent enantioselectivity (99% ee).



Scheme 90. CuH-catalyzed asymmetric allylation of enone-tethered allenes

In addition, the re-aromatization of *cis*-hydrobenzofuran **131a** occurred under acidic conditions and afforded the *meta*-substituted phenol **132a** with high enantioselectivity (Scheme 91).

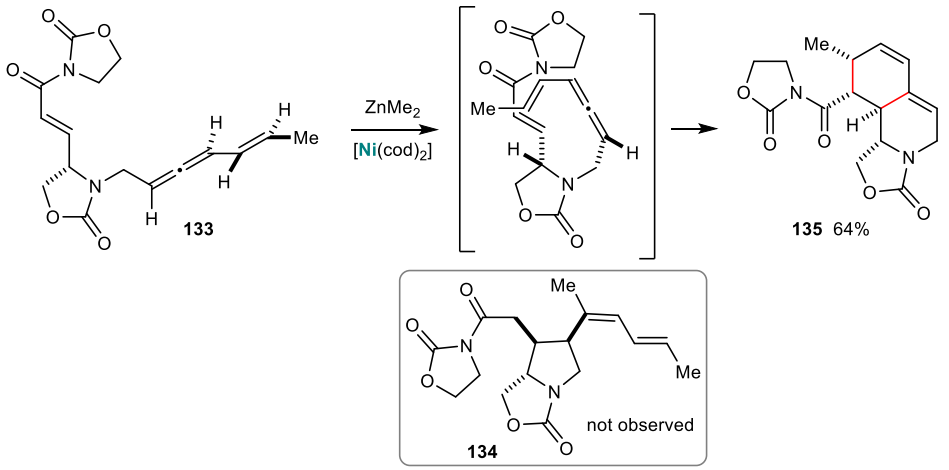


Scheme 91. Further re-aromatization transformation

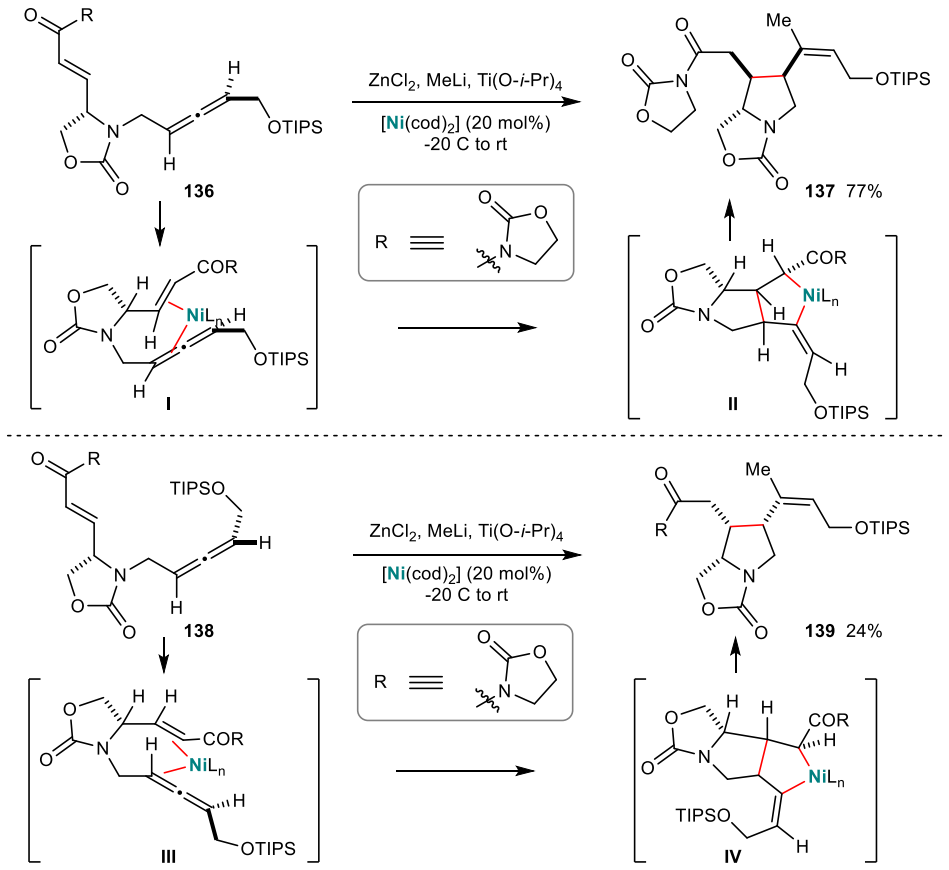
1.4.2. Ni-catalyzed 1,4-addition reactions

For nickel-catalyzed 1,4-allylations, there is only limited precedent within the literature, with examples demonstrated by Sieber and Morken [91] (section 1.2.3) and by Montgometry et al.[111] In 2011, the Montgometry group illustrated the first example of intramolecular nickel(0)-catalyzed cyclizations utilizing enolates and chiral allenes to afford functionalized pyrrolidine derivatives. First, substrate **133** was synthesized and subjected to the reaction conditions involving a Ni(0) catalyst and $ZnMe_2$, unfortunately, a Diels-Alder cycloaddition product **135** was formed

instead of the 1,4-allylation product **134** (Scheme 92). Then substrates **136** and **138** were prepared and successfully gave the products **137**, **139** through the proposed mechanism shown in Scheme 93. The hypothesis involves a Ni(0)-π complex (**I**, **III**) and metallacycle (**II**, **IV**) to furnish five-membered 1,4-addition cyclization products **137**, **139**. It is possible to infer the importance of allene chirality in stereochemical arrangement from the results.



Scheme 92. First attempt of using nickel(0) catalyst



Scheme 93. Nickel (0)-catalyzed alkylative cyclization of an enoate/chiral allene

In summary, the transition-metal-catalyzed enantioselective 1,4-addition of allyl nucleophiles remains considerably under-exploited, therefore, developing new methods for the catalytic enantioselective 1,4-allylation would give a variety of desirable products. In addition, there is only limited precedent utilizing abundant and inexpensive first-row transition metals which would be more beneficial and increase the sustainability in the synthetic process.

Moreover, there are limited examples of 1,4-addition of allyl nucleophiles being incorporated into addition-cyclization cascade process and no highly enantioselective methods have been described. As a result, the development of an enantioselective intramolecular 1,4-allylation process, forming three contiguous chiral carbons with high levels of regio- and stereocontrol as well as having broad functionality group tolerance would significantly enhance the utility of this chemistry.

2. Enantioselective nickel-catalyzed arylative intramolecular 1,4-allylations

2.1. Introduction

Asymmetric transition-metal-catalyzed nucleophilic allylations are important reactions in organic synthesis. While enantioselective 1,2-allylations have been the focus of many investigations (Sections 1.1 and 1.3), enantioselective 1,4-allylations have been rather under-investigated (Sections 1.2 and 1.4). Therefore, developing new methodologies for catalytic enantioselective 1,4-allylations is highly desired.

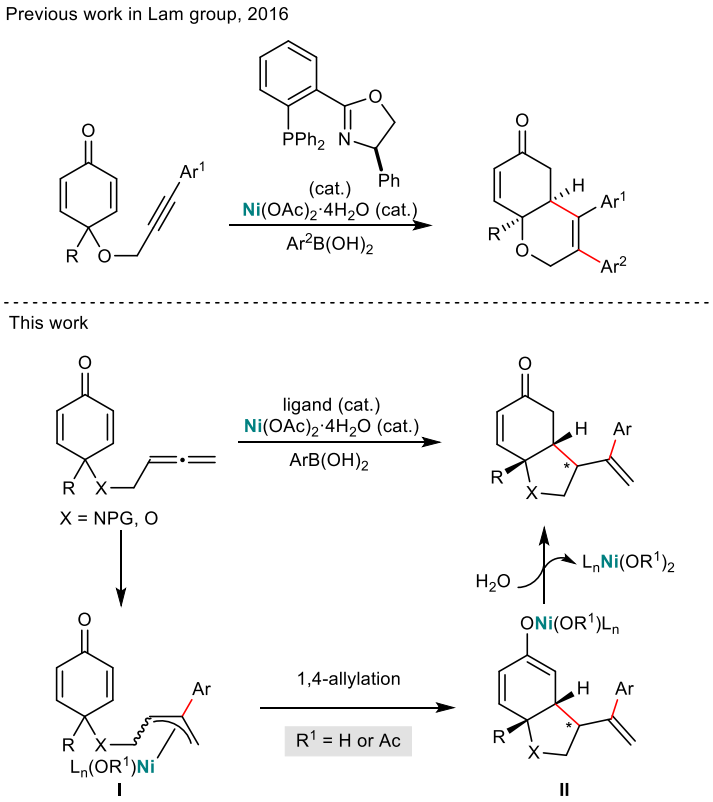
In addition, domino reactions offer an efficient method for the construction of molecules in high regio-, diastereo- and enatio- selectivity in a single step (Sections 1.3 and 1.4). There are several examples, reported by Tian and Lin, demonstrating asymmetric silylative cyclizations or reductive cyclizations using a copper catalytic system to give 1,4-allylation products (Section 1.4.1). In their studies, cyclohexa-2,5-dienones were used to favour 1,4-addition rather than 1,2-addition onto a carbonyl group.

As described in the previous chapter, there are only two studies of nickel-catalyzed 1,4-allylations by Sieber and Morken (Section 1.2.3, Scheme 59) and Montgometry (Section 1.4.2). Sieber and Morken reported the first enantioselective 1,4-allylation using nickel(0) catalysis with a TADDOL-derived monophosphoramidite ligand.[91] However, the reactions were limited in term of substrates to unsymmetrical dialkylidene ketones. Montgomery reported the diastereoselective nickel-catalyzed alkylative cyclizations of allenes to furnish a formal 1,4-allylation product but no enantioselective process was reported.[111]

2.2. Aims and objectives

The Lam group previously reported the enantioselective nickel-catalyzed *anti*-carbometallative cyclizations of alkynyl cyclohexa-2,5-dienones with arylboronic acids (Scheme 94).[112] In this process, carbometallation occurs by insertion of an arylboronic acid to the alkyne, followed by 1,4-addition to a tethered enone to obtain a bicyclic product. Inspired by this work, we designed an allenyl cyclohexa-2,5-

dienone to explore 1,4-allylations. Our aim was to investigate the first example of nickel-catalyzed enantioselective intramolecular 1,4-allylation, using a nucleophilic allylnickel species **I** to cyclize onto an enone as an electrophilic trap (Scheme 94).

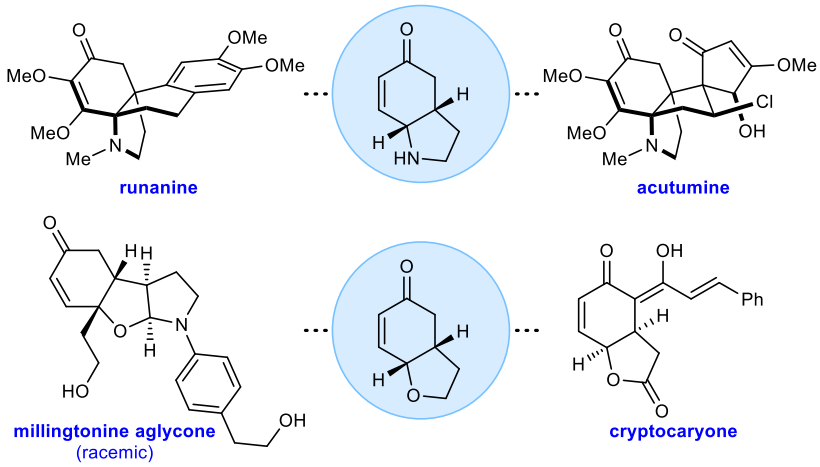


Scheme 94. Proposed nickel-catalyzed arylative cyclization of an allenyl cyclohexa-2,5-dienones

We questioned whether the use of a nickel(II) salt and a chiral ligand could promote an asymmetric cascade reaction of cyclohexa-2,5-dienone-tethered allenes with arylboronic acids to give products of 1,4-allylations with three consecutive chiral centers in one step. The nickel(II)-catalyzed addition of arylboronic acids to allenes would give nucleophilic allylnickel species, which could undergo subsequent enantioselective intramolecular 1,4-allylation to an enone.

The successful realization of this work would be of significance as it would be an example of an enantioselective 1,4-allylation. Furthermore, the framework of the products obtained from this process, *cis*-fused hexahydroindol-5-ones or hexahydrobenzofuran-5-ones, are important structures that appear in several natural products such as runanine,[113] acutumine,[114] millingtonine,[115] and cryptocaryone [116] (Scheme 95). In addition, the enone in these structures could undergo further

transformations to give octahydroindole and octahydrobenzofuran derivatives, which are also the core structures in many other natural products.



Scheme 95. *Cis*-fused hexahydroindol-5-one and hexahydrobenzofuran-5-one natural products

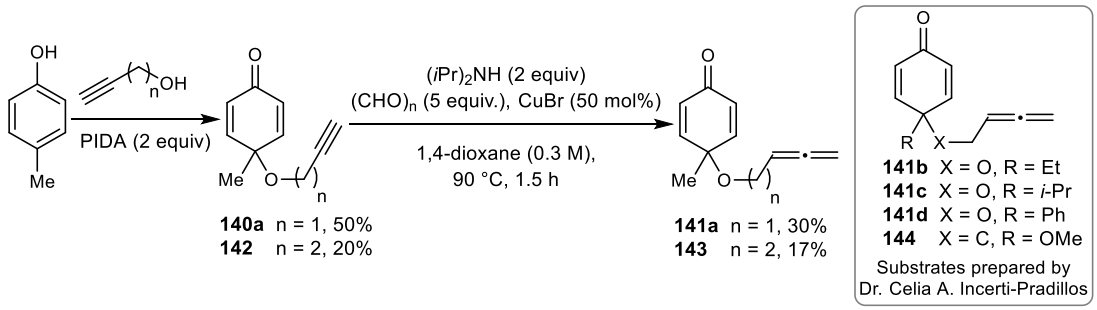
2.3. Reaction development

To execute this project, various catalytic systems were studied to determine the optimal conditions which show the best balance between yield and selectivity. At the same time, a range of substrates was synthesized to explore the reaction scope. Furthermore, various boronic acids were also investigated.

2.3.1. Synthesis of substrates

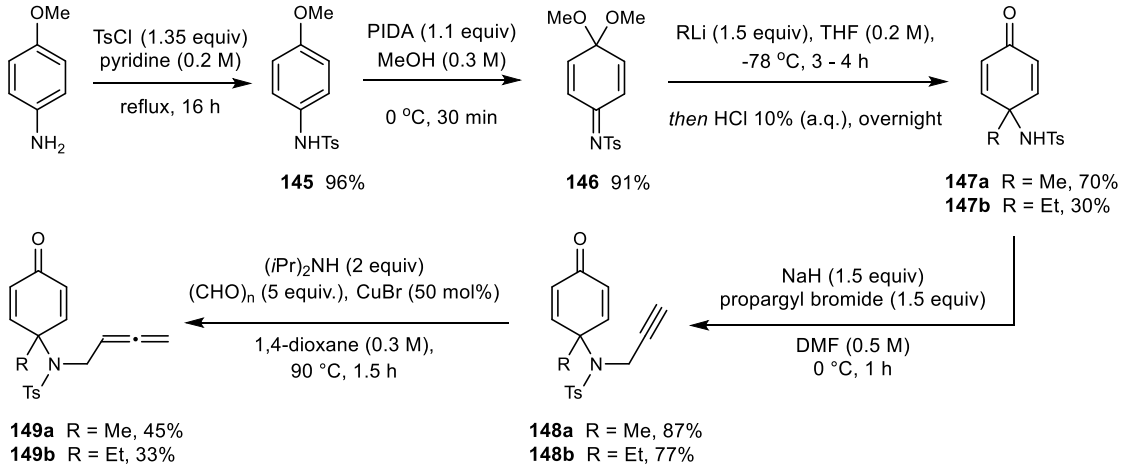
This study began with the synthesis of allenyl cyclohexa-2,5-dienones with *O*-, *N*-sulfonyl, *N*-Boc and *C*- tethers (Scheme 96−Scheme 98).

The oxygen-tethered substrates were prepared as shown in Scheme 96. The alkynyl oxygen-tethered substrates **140a** and **142** were synthesized through iodine(III)-mediated oxidative dearomatization of the appropriate phenols using propargyl alcohol as a solvent. Allenes **141a** and **143** were prepared through Crabbé homologation of terminal alkynes using formaldehyde, $(i\text{-Pr})_2NH$ and CuBr in dioxane. The substituent at the quarternary center with Et, *i*-Pr, Ph of O-tethered and a carbon-tethered substrate were synthesized using similar chemistry by Dr. Celia A. Incerti-Pradillos.



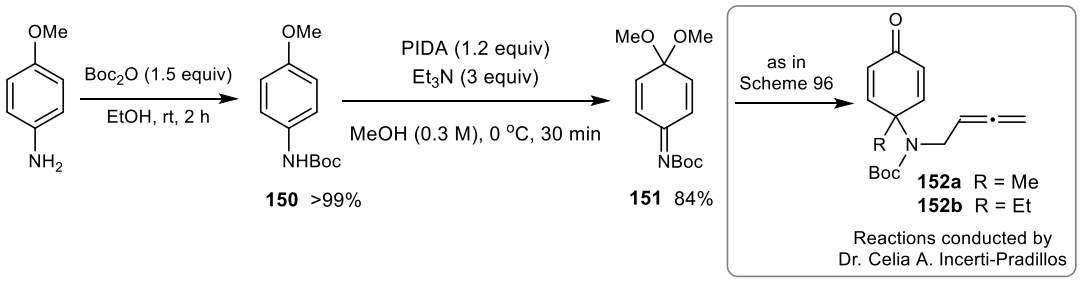
Scheme 96. Preparation of allenyl cyclohexa-2,5-dienones with *O*- tethers

The *N*-sulfonyl-tethered substrates were prepared as shown in Scheme 97. Tosylation of *p*-anisidine furnished **145**, which was subjected to a PIDA oxidation reaction, affording benzenesulfonamide **146** (Scheme 97). Imine **146** was transformed to tertiary sulfoamides **147a-b** through alkylations, followed by a propargylation, forming alkynes **148a-b**. Installation of the requisite allenes **149a-b** were accomplished through a Crabbé homologation reaction of terminal alkynes using formaldehyde, (*i*-Pr)$_2$NH and CuBr in dioxane.



Scheme 97. Preparation of allenyl cyclohexa-2,5-dienones with *N*-sulfonyl tethers

The same strategy was used to synthesize the *N*-Boc tethered substrates (Scheme 98). *N*-*tert*-Butyloxycarbonylation of *p*-anisidine afforded **150**, which underwent PIDA oxidation to give carbamate **151** (Scheme 98). The allenes were prepared by Dr. Celia A. Incerti-Pradillos.

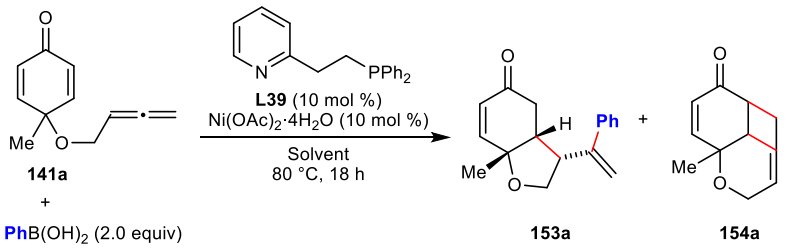


Scheme 98. Preparation of allenyl cyclohexa-2,5-dienones with *N*-Boc tethers

2.3.2. Investigation of solvent

In a previous report, the Lam group showed that chiral phosphinooxazoline ligands could effectively promote enantioselective nickel-catalyzed carbometallative cyclizations of alkylnyl electrophiles with aryboronic acids (section 2.2, Scheme 94).[112] Therefore, we began our investigations with similar conditions to test the reactivity. Reactions with allenyl cyclohexa-2,5-dienone **141a** and $PhB(OH)_2$ (2.0 equiv) in the presence of $Ni(OAc)_2{\cdot}4H_2O$ (10 mol%) and *P*,*N*-ligand **L39** (10 mol%), showed excellent reactivity in previous nickel-catalyzed carbometallative cyclizations (section 2.2, Scheme 94).[112] Therefore, various solvents were investigated using these conditions (Table 1).

Table 1. Solvent investigation

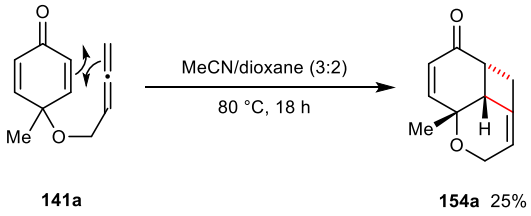


Entry [a]	Solvent	Yield of **153a**[b] (%)	Yield of **154a** [b] (%)
1	MeCN/2-MeTHF (3:2)	61	15
2	MeCN	34	9
3	2-MeTHF	23	8
4	MeCN/1,4-Dioxane (3:2)	71	9
5	1,4-Dioxane	28	9

[a] Reactions were conducted with 0.1 mmol of **141a** at 0.1 M concentration. [b] Determined by ^1H NMR analysis of the crude reactions using 1,3,5-trimethoxybenzene as an internal standard.

Pleasingly, these reactions gave the desired cyclization product **154a**, which could possibly be formed by our proposed outline (section 2.2). Overall, the yields increased when mixtures of MeCN and an ethereal solvent were used (Table 1, entries 1 and 4). Initially, a mixture of MeCN and 2-MeTHF was used, as described previously,[112] and 6,5-bicycle **153a** was obtained in 61% ^{1}H NMR yield as a single diastereomer (Table 1, entry 1). The yield of **153a** was improved to 71% when using a mixture of MeCN and 1,4-dioxane (Table 1, entry 4). In MeCN, 2-MeTHF or 1,4-dioxane individually, the yields are much lower (23% to 34%) (Table 1, entries 2, 3, 5).

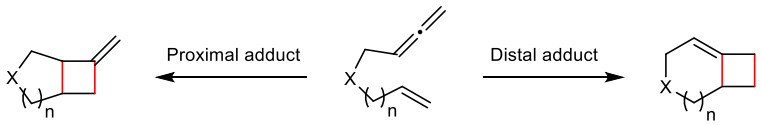
In addition, along with the 6,5-bicycles, we also obtained by-product **154a** resulting from a [2+2] cycloaddition of **141a** (Scheme 99).



141a **154a** 25%

Scheme 99. Intramolecular [2+2] cycloaddition of allenyl 2,5-hexadienone *O*-tethered substrate

Two possible regioisomers can be formed from intramolecular [2+2] cycloaddition of allenes **156** (Scheme 100).[117] The proximal cyclic product **155** is furnished by reaction with the internal 2π component of the allene moiety and the distal cyclic product **157** is obtained by reaction with the external 2π component of the allene moiety.

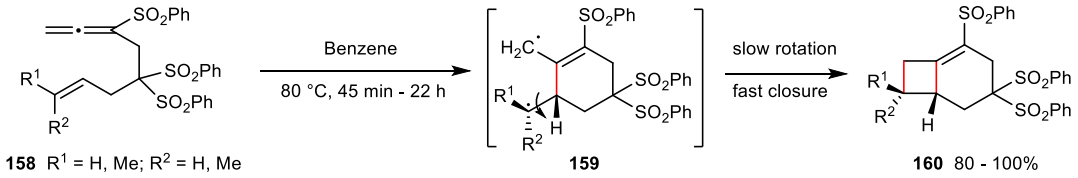


155 **156** **157**

Scheme 100. Intramolecular [2+2] cycloaddition of allenenes

Padwa and co-workers have reported the [2+2]-cycloaddition reaction of α-tethered allenyl sulfone **158**, which formed distal cycloadduct **160** *via* diradical **159**.[118] Then a variety of substituents on the allene moiety such as various groups on α- or ɤ-tethered allenyl sulfones were investigated in the thermal intramolecular [2+2]

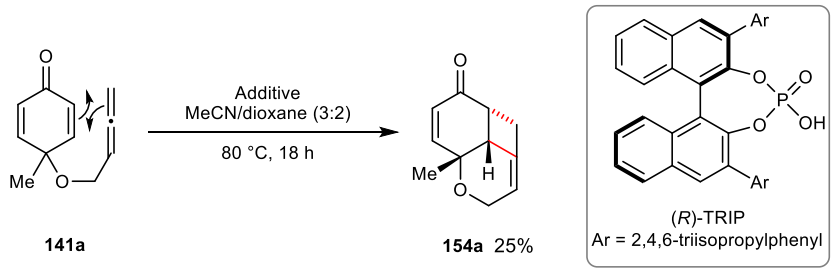
cycloaddition.[119] The corresponding distal cycloadducts **160** were afforded in excellent yields (Scheme 101).



Scheme 101. Intramolecular [2+2] cycloaddition of α-tethered allenyl sulfones

The [2+2]-cycloaddition reaction is known to occur under thermal conditions or photochemical conditions. [117] Therefore, control experiments were performed to establish the origin of reactivity (Table 2).

Table 2. Intramolecular [2+2] cycloaddition of 141a



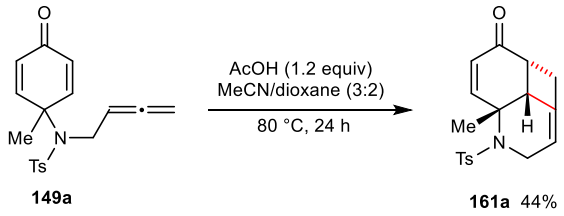
Entry	Additive	Yield of **154a**[c] (%)	Yield of **141a**[c] (%)
1	n.a.	25	65
2[a]	n.a.	27	72
3[a]	AcOH (10 mol%)	25	68
4	AcOH (10 mol%)	29	75
5[b]	(*R*)-TRIP (10 mol%)	24	62

[a] The reaction was carried out in absence of light by covering reaction with aluminium foil. [b] Product **154a** was obtained as racemic mixture. [c] Determined by ^{1}H NMR analysis of the crude reactions using 1,3,5-trimethoxybenzene as an internal standard.

Heating **141a** in MeCN/1,4-dioxane (3:2) at 80 °C for 18 h, in the absence of $PhB(OH)_2$ and $Ni(OAc)_2{\cdot}4H_2O$ gave **154a** in 25% yield, which demonstrates this [2+2] cycloaddition is a thermally promoted process rather than a nickel-catalyzed reaction. Then absence of light or addition of acid was applied; however, product

154a was obtained in nearly the same yields (25-29%) (Table 2), demonstrating that formation of **154a** is not affected by light or acidic conditions. A chiral phosphonic acid *(R)*-TRIP was used in the system; however, a racemic of the product was obtained in 24% yield (Table 2, entry 5). Therefore, in this study, intramolecular [2+2] cycloaddition of **141a** is performed through a thermally-promoted background reaction.

The *N*-sulfonyl-tethered allene **149a** also underwent thermal [2+2] cycloaddition under the same conditions to give **161a** (Scheme 102).



Scheme 102. Intramolecular [2+2] cycloaddition of *N*-sulfonyl tethered allenyl 2,5-hexadienone

Slow diffusion of petroleum ether into a solution of **161a** in EtOAc gave crystals that were suitable for X-ray crystallography. The structure of **161a** was verified in Figure 5.

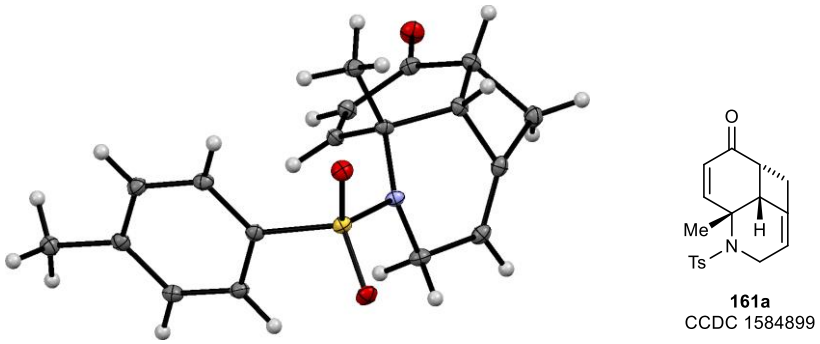


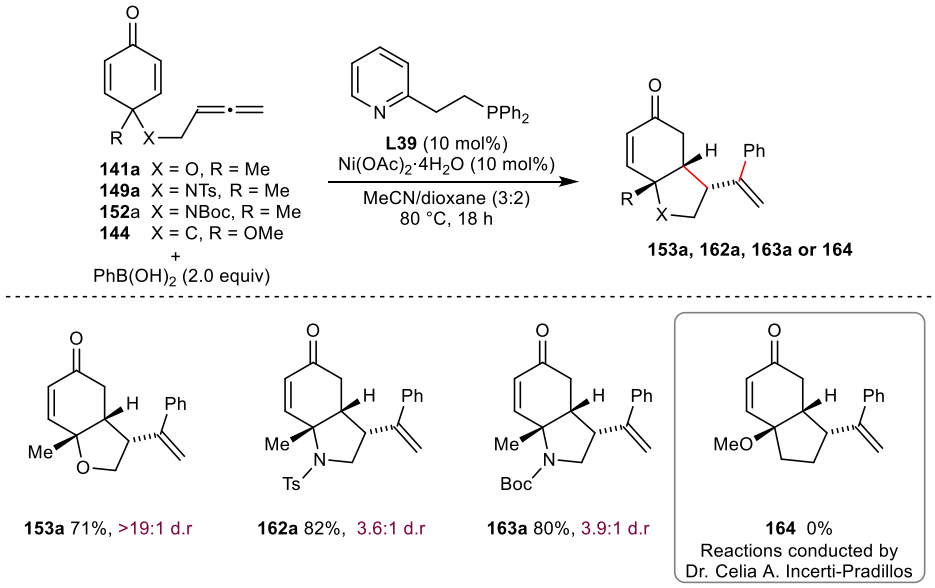
Figure 5. X-ray crystal structure of 161a. X-ray crystallography carried out by Dr. W. Lewis.

2.3.3. Initial investigation of substrates

Different types of allenyl cyclohexa-2,5-dienones were then subjected to the conditions with $PhB(OH)_2$ (2.0 equiv), $Ni(OAc)_2 \cdot 4H_2O$ (10 mol%) and achiral ligand **L39** (10 mol%) in MeCN/1,4-dioxane (3:2) at 80 °C for 18 h to test their activity (Table 3).

Pleasingly, use of allenyl 2,5-hexadienone *O*-tethered **141a** gave **153a** in good yield (71%) as a single diastereomer. An *N*-sulfonyl tethered subtrate **149a** furnished 6,5-bicycle product **162a** in the highest yield (82%) as a 3.6:1 ratio of diastereomers. Substrate **152a** with the different protecting group on the *N*-tether also afforded product **163a** in 80% yield as a 3.9:1 ratio of diastereomers. However, the desired product **164** was not obtained when using *C*-tethered **144**; the reaction was conducted by Dr. Celia A. Incerti-Pradillos.

Table 3. Initial substrate evaluation[a]



[a] Reactions were conducted with 0.1 mmol of **141a, 149a, 152a, 144** at 0.1 M concentration. Yields were determined by ^{1}H NMR analysis of the crude reactions using 1,3,5-trimethoxybenzene as an internal standard.

O-tethered substrate **141a**, which gave single diastereomer product **153a**, and *N*-sulfonyl tethered substrate **149a**, which gave product **162a** in the best yield were used for the screening of chiral ligands.

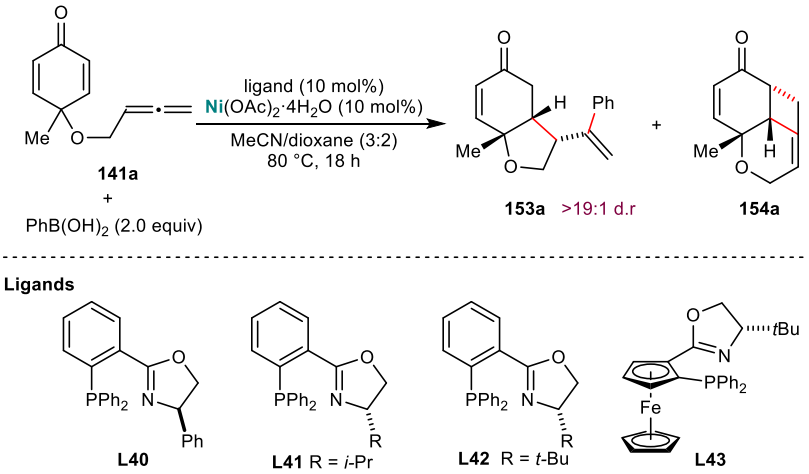
2.3.4. Investigation of ligands to make asymmetric variant

Next, we evaluated the diastereo- and enantioselectivity of our reaction under our standard conditions by replacing the achiral *P*,*N*-ligand with chiral ligands using *O*-tethered substrate **141a** and *N*-sulfonyl tethered substrate **149a**.

Interestingly, the 6,5-bicycle product **153a** can be obtained as a single diastereomer with the use of only $Ni(OAc)_2 \cdot 4H_2O$ without a ligand, though in only 31% yield

(Table 4, entry 1). Using chiral *P*,*N*-containing phosphinooxazoline (PHOX) ligand **L40** gave the most promising result in 76% yield with 91% ee (entry 2). Reactions using bulkier ligands **L41** to **L42** were unfavorable to the reaction with the yield decreasing to 58% and 39%; however, the enantioselectivity increased up to 99% ee (entries 3-4). Using ferrocene-containing ligand **L43** resulted in product **153a** in low yield (12%) and enantioselectivity (27% ee). As a result, (*R*)-Ph-PHOX (**L40**) showed the best balance between yield and enantioselectivity (entry 2).

Table 4. Selected examples of screening ligands of *O*-tethered allenyl cyclohexa-2,5-dienone [a]



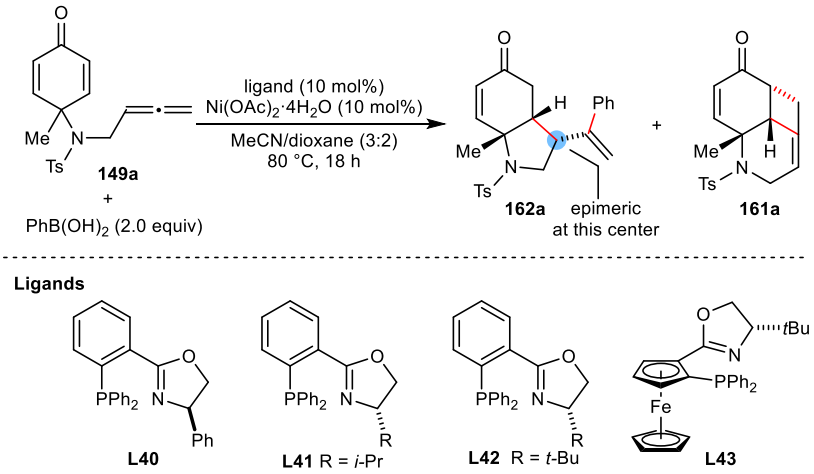
entry	ligand	yield of **153a** (%)[b]	yield of **154a** (%)[b]	ee of **153a** (%)[c]
1	–	31	11	–
2	**L40**	76	8	91
3	**L41**	58	13	–95[d]
4	**L42**	39	21	–99[d]
5	**L43**	12	24	–27[d]

[a] Reactions were conducted with 0.1 mmol of **141a** at 0.1 M concentration. [b] Determined by ^{1}H NMR analysis of the crude reactions using 1,3,5-trimethoxybenzene as an internal standard. [c] Determined by chiral HPLC analysis. The absolute configuration was assigned by analogy of **162a**.

On the other hand, the reaction of allenyl cyclohexa-2,5-dienone *N*-sulfonyl tethered **149a** was investigated with different ligands, the results showed in Table 5. Overall, it could be seen that **149a** underwent cyclization *via* a similar fashion as with the *O*-tethered substrate. In the absence of ligand, we were pleased to observe that 6,5-bicycle product **162a** was formed in 35% yield as a 2.0:1 ratio of diastereomers (entry 1). This reaction also gave cyclobutanone **161a** in 11% yield which resulted

from a thermal intramolecular [2+2] cycloaddition. Chiral phosphinooxazoline (PHOX) ligands **L40**–**L43** successfully gave enantioenriched products with varying levels of efficiency (entries 2–5). Ligand (*R*)-Ph-PHOX **L40** afforded **162a** in excellent yield (89%) as a single diastereomer (entry 2). Increasing the steric bulk on the ligand to *iso*-propyl (**L41**) and *tert*-butyl (**L42**) was detrimental to the reaction, decreasing the yield and lowering regiocontrol and enantioselectivity (entries 3 and 4). Ligand **L43** gave product **162a** in low yield (16%) and low enantioselectivity (68% ee).

Table 5. Selected examples of screening ligands of *N*-sulfonyl-tethered allenyl cyclohexa-2,5-dienone [a]



entry	ligand	yield of **162a** (%)[b]	yield of **161a** (%)[b]	dr of **162a**	ee of **162a** (%)[c]
1	–	35	11	2.0:1	–
2	**L40**	89	10	>19:1	90
3	**L41**	62	14	14:1	–91[d]
4	**L42**	33	22	5.3:1	–87[d]
5	**L43**	16	26	0.6:1[e]	–68, [d] 69 [e]

[a] Reactions were conducted with 0.1 mmol of **149a** at 0.1 M concentration. [b] Determined by ^{1}H NMR analysis of the crude reactions using 1,3,5-trimethoxybenzene as an internal standard. [c] Determined by chiral HPLC analysis. [d] The major product was the enantiomer of **162a**. [e] The major product was the diastereomer of **162a**, obtained in 69% ee.

The absolute stereochemistry of **162a** was determined by X-ray crystallography (Figure 6). The single crystals were prepared by slow diffusion of petroleum ether into a solution of **162a** in EtOAc.

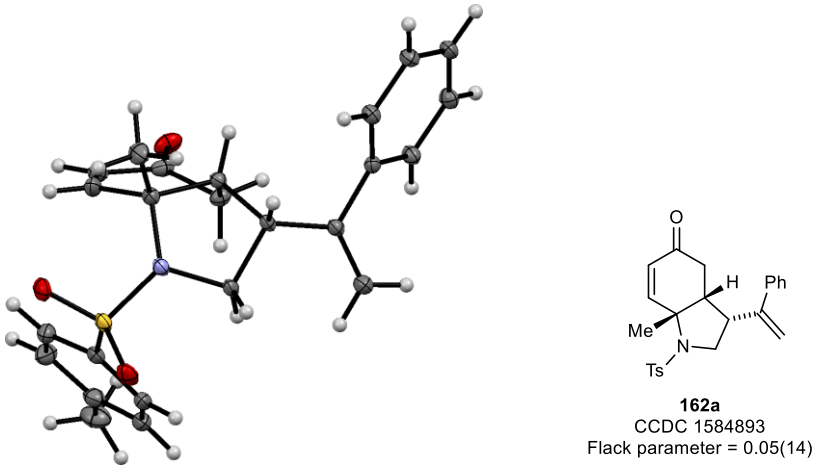
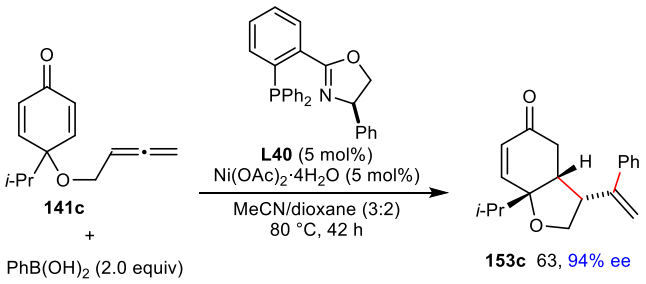


Figure 6. X-ray structure of 162a. X-ray crystallography carried out by Dr. W. Lewis

We were pleased that we established efficient conditions for these cascade reactions, but we also desired to improve the sustainability of the process. Nickel is able to catalyze this reaction and it is an earth-abundant metal, which is favourable in terms of cost. To improve the practicality of this reaction, lower quantity of catalyst was tested. However, decreasing the catalyst loading was detrimental (Scheme 103), with results inferior to that of 10 mol% of the chiral nickel complex although the reaction was carried out for longer time (Scheme 103).

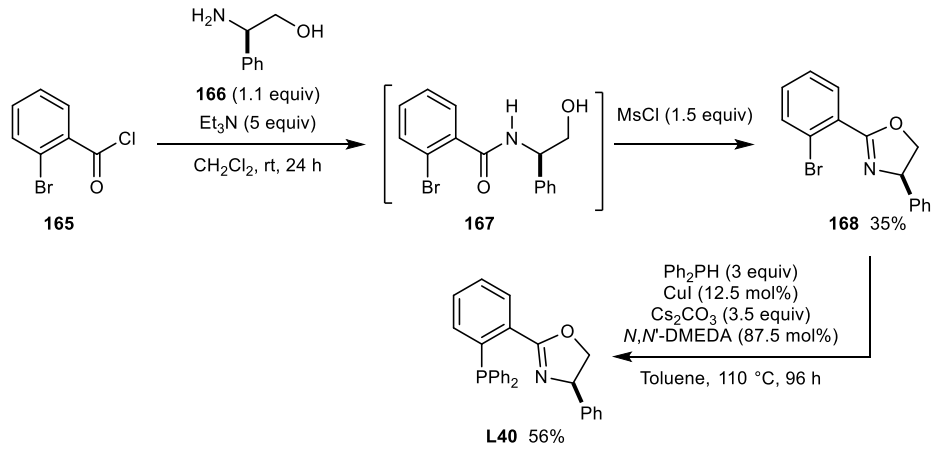


Scheme 103. Investigation of catalyst loading [a]

[a] Reactions were conducted with 2.0 mmol of **141c**. Enantioselectivity was determined by chiral HPLC analysis.

Ligand **L40** (*R*)-Ph-PHOX is no longer commercially available. However, the Williams group reported a synthetic route to **L40** from *o*-flourobenzonitrile.[120] Then Stoltz and co-workers reported a facile synthesis of phosphinooxazolines using a copper(I)-catalyzed coupling of phosphines and aryl halides.[121] Here, we employed the latter approach using slightly modified conditions which gave ligand **L40** in gram-scale quantities (Scheme 104).[122] The synthesis began with a reaction between

acyl chloride **165** and amine **166** to form the amide *in situ*, followed by mesylation to give aryl bromide **167** and dehydrative cyclization to furnish oxazoline **168**. Then, Ullmann-type coupling of diphenylphosphine with aryl bromide afforded ligand **L40** (*R*)-Ph-PHOX.



Scheme 104. Synthesis of L40 (*R*)-Ph-PHOX

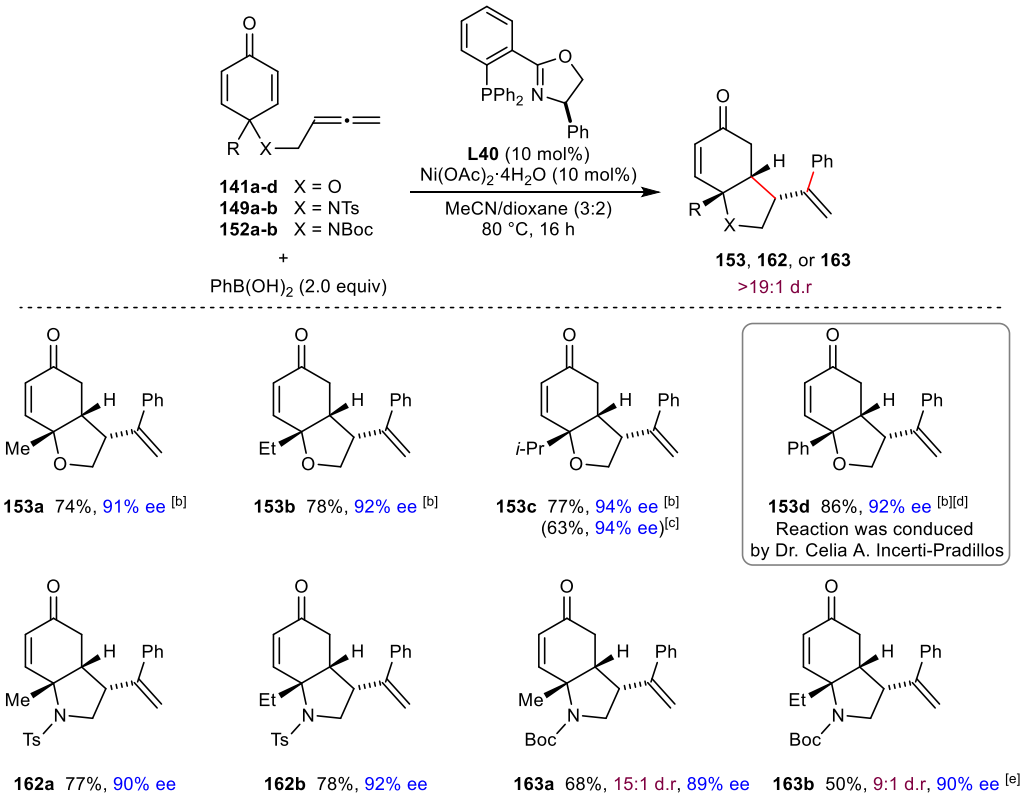
2.4. Exploration of allenyl cyclohexa-2,5-dienone substrate scope

With the optimized conditions and a variety of substrates in hand, we investigated the generality of our procedure regarding the allenyl substrates.

The reaction with a variety of allenyl substrates was examined with our optimized conditions with $PhB(OH)_2$ (Table 6). The 6,5-bicycles products **153a-d**, **162a-b**, **163a-b** were successfully synthesized, in most cases in good yields (50-87%) and high enantioselectivities (89-95% ee). Substitution at the quaternary center of *O*-tethered and *N*-sulfonyl-tethered substrates was well tolerated, and they could be changed from methyl (**153a** and **162a**), ethyl (**153b** and **162b**), isopropyl (**153c**) or phenyl (**153d**) with no significant change in terms of selectivity, with a single diastereomer and excellent enantioselectivities. In the case of *N*-Boc-tethered substrates, reactions occurred in moderate yields with no considerable difference in selectivity when using a methyl (**163a**) substituent at the quaternary carbon center but lowering regiocontrol when using an ethyl (**163b**) substituent.

In all reactions, small quantities of [2+2] cycloaddition by-products (either **154a** or analogous to **154a**) were also formed. Most of these compounds were separable by column chromatography except for the reactions forming **153a**, **153c**, **153d**.

Table 6. Scope of allenyl substrates [a]



[a] Reactions were conducted with 0.30 mmol of **141**, **149**, **152** at 0.1 M concentration. Yields are isolated products. Enantiomeric excesses were determined by chiral HPLC analysis. [b] Products **153c**, **153d** were isolated together with cyclobutene side products as inseparable mixtures in ratios of between 11:1 and 20:1. Yields have been adjusted accordingly. [c] Value in parentheses are of a reaction conducted with 2.0 mmol of **141c** at 0.4 M concentration for 42 h, using 5 mol% each of $Ni(OAc)_2 \cdot 4H_2O$ and **L4**. [d] Conducted with 0.15 mmol of **141d**. [e] Product **163b** was isolated together with diastereomer products as inseparable mixtures in ratios of between 9:1. Yields have been adjusted accordingly.

The absolute stereochemistry of **162a** and **162b** was determined by X-ray crystallography (Firgures 6 and 7). The single crystals were prepared by slow diffusion of petroleum ether into a solution of **162a** or **162b** in EtOAc.

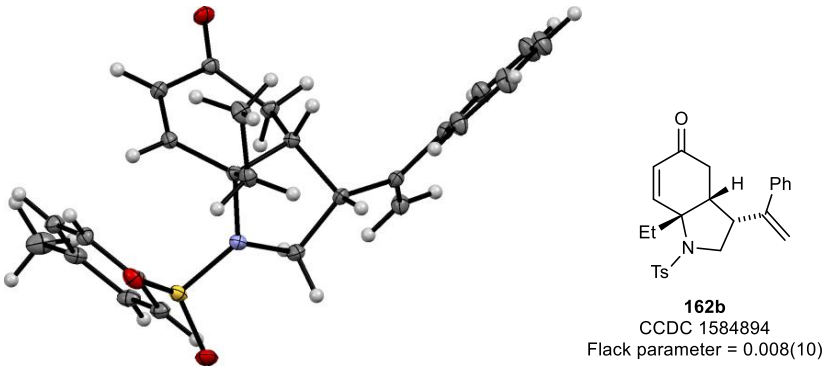
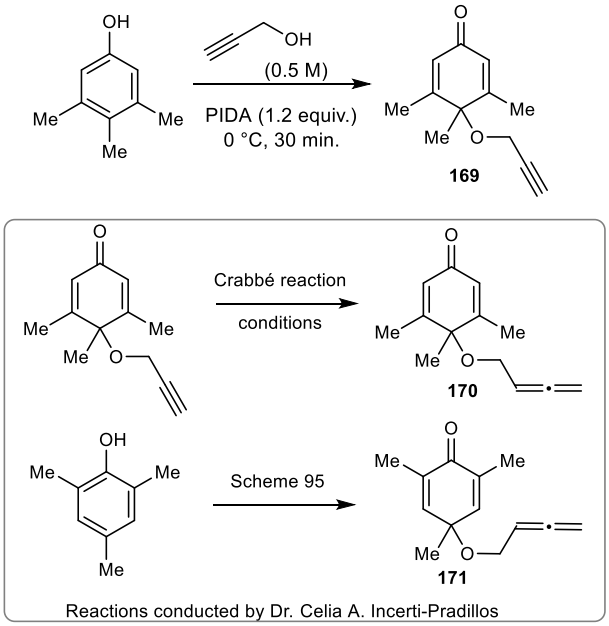


Figure 7. X-ray structure of 162b. X-ray crystallography carried out by Dr. W. Lewis

2.5. Further exploration of other allenyl electrophiles

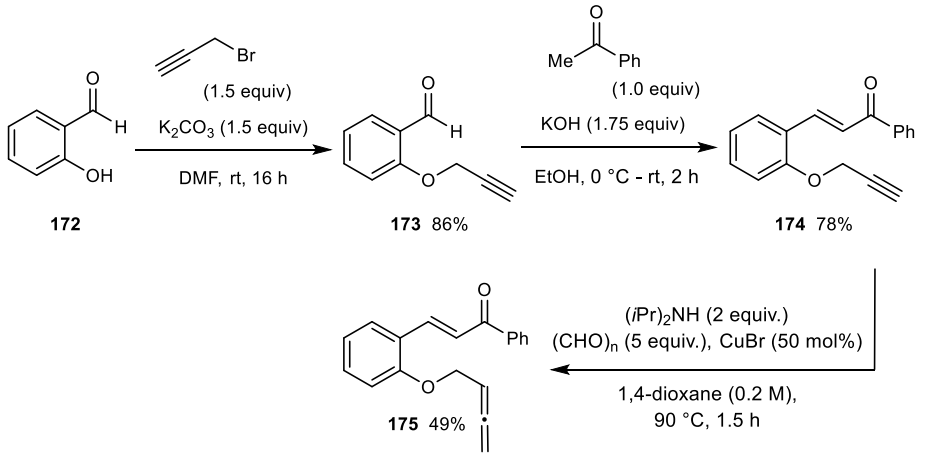
We have illustrated a successful process with different heteroatom-tethered substrates and various substituents at the quarternary center in good yields and high enantioselectivities. To expand the scope of our reaction beyond the formation of 6,5-bicycles, we synthesized a variety of other substrates.

In the same fashion as described in section 2.3.1, synthesizing substrates with more substituents on the cyclohexa-2,5-dienone was carried out (Scheme 105). Alkynyl oxygen-tethered substrates **169** were synthesized through iodine(III)-mediated oxidative dearomatization of phenols in the present of propargyl alcohol as solvents (Scheme 105). The requisite allenyl cyclohexa-2,5-dienone oxygen-tethered substrates **170** and **171** were synthesized by Dr. Celia A. Incerti Pradillos.



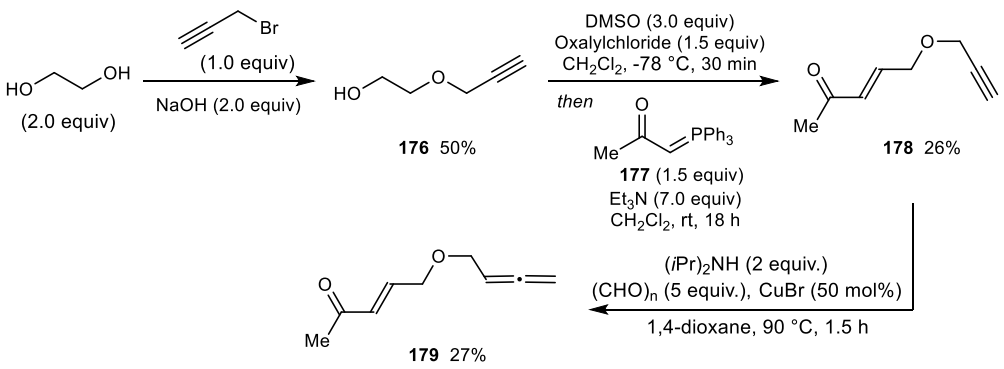
Scheme 105. Preparation of other allenyl cyclohexa-2,5-dienone

An allenyl *O*-linked substrate containing a benzene tether **175** was synthesized through a propargylation of 2-hydroxybenzaldehyde **172**, followed by a Claisen-Schmidt condensation and Crabbé homologation reactions (Scheme 106). The 2-(prop-2-yn-1-yloxy)benzaldehyde **173** was obtained from the reaction of **172** with propargyl bromide in DMF and potassium carbonate as a base. The alkyne **173** was then subjected to Claisen-Schmidt condensation reaction to afford chalcone **174**. The aldol condensation reaction was carried out under basic conditions using KOH in ethanol as the solvent.[123] The allene **175** was then prepared by Crabbé homologation of **174** using formaldehyde, (*i*-Pr)$_2$NH and CuBr in 1,4-dioxane.[124]



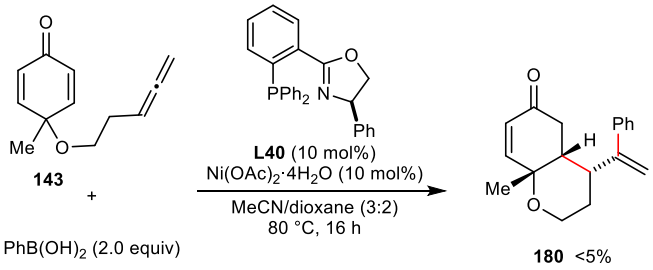
Scheme 106. Preparation of allenyl *O*-linked substrate containing a benzene tether 175

Reaction of propargyl bromide with ethylene glycol afforded **176**, which was oxidized using Swern conditions to give the aldehyde, which was reacted with 1-(triphenylphosphoranylidene)-2-propanone **177** to give **178** (Scheme 107). The allene **179** was formed by Crabbé homologation reaction in the presence of formaldehyde, (*i*-Pr)$_2$NH and CuBr in 1,4-dioxane.



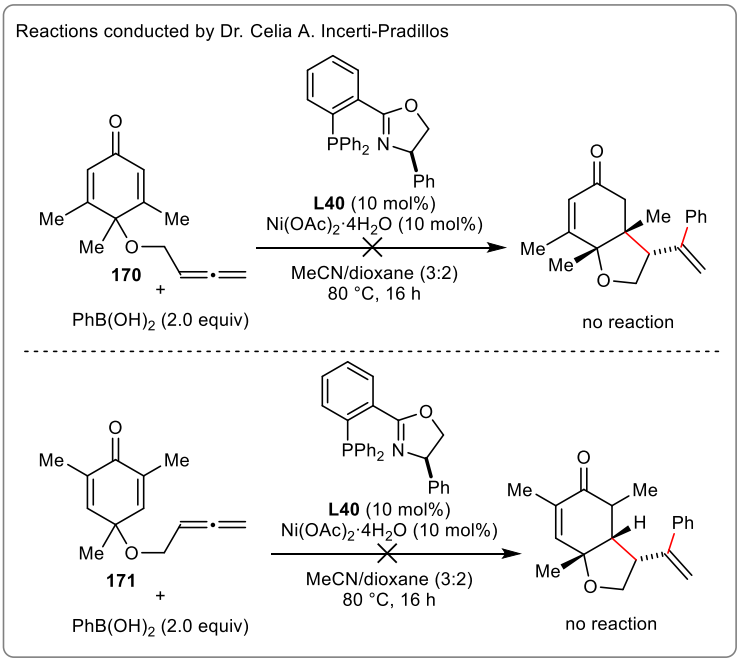
Scheme 107. Preparation of allenyl electrophile 179

With new substrates **169-171**, **175** and **179** prepared, we subjected them to our nickel-catalyzed arylative cyclization conditions. First, a substrate with a longer tether between the allene and cyclohexa-2,5-dienone **143** was investigated (Scheme 108). The reaction was unsuccessful and only a trace (< 5%) of 6,6-bicycle **180** was obtained, recovering most of the starting material.



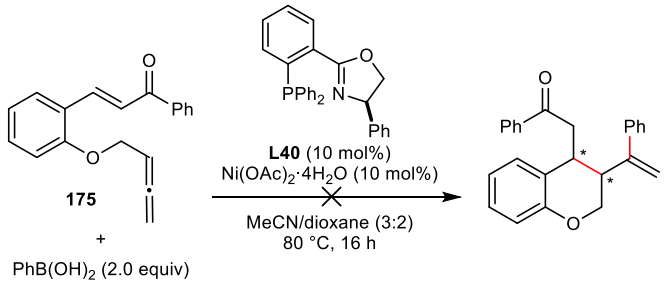
Scheme 108. Reaction of allenyl cyclohexa-2,5-dieneone 180

Cyclohexa-2,5-dienone-tethered allene with methyl substituents at the 3- and 5-positions (**170**) or 2- and 6-positions (**171**) were subjected to the optimized reaction conditions with $Ni(OAc)_2 \cdot 4H_2O$, **L40** and $PhB(OH)_2$, by Dr. Celia A. Incerti-Pradillos. This would allow us to see the steric and electronic effect of substituents on the cyclohexadienone. Unfortunately, no product formation was observed in either case (Scheme 109). This is likely because of the increased steric hindrance imports by the methyl groups.



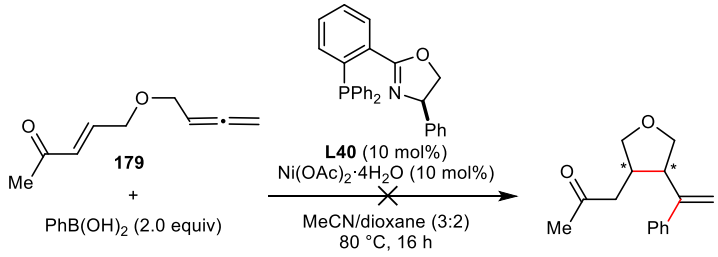
Scheme 109. Examined reaction with cyclohexa-2,5-dienone-tethered allene 170 and 171

We also questioned whether our catalytic process would be capable of reacting with other electrophiles. Thus, the allenyl acyclic enone substrate containing a benzene tether **175** was subjected to the reaction conditions (Scheme 110). Unfortunately, we did not obtain the desired product and a messy crude reaction resulting from a mixture of unidentified products was observed.



Scheme 110. Examined reaction with allene substrate containing benzene tether 175

An acyclic substrate was also considered, and this would give us a monocyclic product, increasing the diversity of accessible compounds. Allene **179** was subjected to the standard reaction conditions (Scheme 111). However, we were disappointed with no product formation and a messy crude NMR spectrum was obtained.

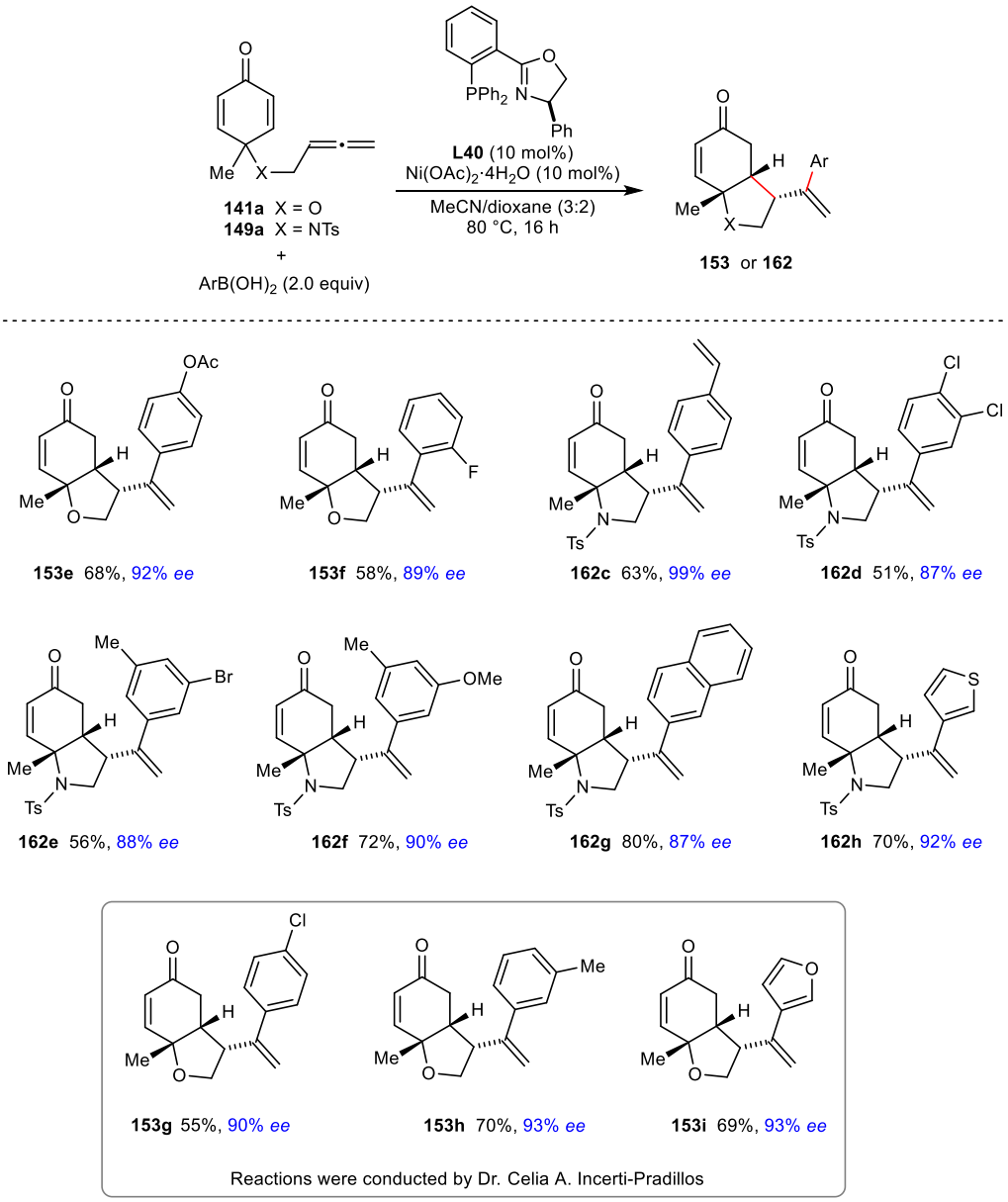


Scheme 111. Examined reaction for a fully acyclic substrate 179

2.6. Exploration of boronic acid scope

After exploration of the allenyl electrophile scope, we were interested in the reactions of various arylboronic acids. Use of two substrates **141a** and **149a** for the reactions with diverse arylboronic acids gave products **153e-153i** and **162c-162h** in 51−80% yield with high enantioselectivities (Table 7).

Table 7. Boronic acid evaluation[a]



[a] Reactions were conducted with 0.30 mmol of **141a**, **149a** at 0.1 M concentration. Yields are isolated products. Enantiomeric excesses were determined by chiral HPLC analysis.

With *O*-tethered substrate **141a**, the reactions are tolerant of *para*- (**153e** and **153g**), *meta*- (**153h**), and *ortho*- (**153f**) substituted boronic acids and are also compatible with both electron-withdrawing (**153f** and **153g**) and electron-donating (**153e**) substituents. Table 7 has illustrated examples with acetoxy (**153e**), halide (**153f** and **153g**), methyl (**153h**) and 3-furanylboronic acid (**153i**). The products are obtained in 55−70% yield with high enantioselectivities (89−93% ee).

The absolute stereochemistry of product **153e** obtained from *O*-tethered substrate **141e** was determined by X-ray crystallography (Figure 8). The single crystals were prepared by slow diffusion of petroleum ether into a solution of **153e** in EtOAc.

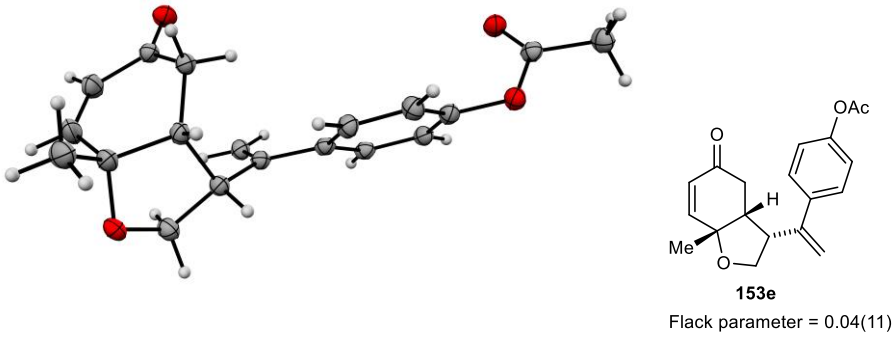


Figure 8. Xray structure of 153e. X-ray crystallography carried out by Dr. W. Lewis

With the *N*-sulfonyl-tethered substrate **149**, the use of *para*-vinyl benzeneboronic acid gave product **162c** in good yield and outstanding enantioselectivity. The reaction was compatible with a variety of disubstitued arylboronic acids, with mixed electronics and different substitution arranged positions. The products **162c-h** were obtained in moderate to good yields (51-72%) and high enantioselectivities (from 87-90% ee). In addition, the use of 2-napthylboronic acid, as an example of a sterically more demanding boronic acid, afforded product **162g** in high yield (80%) and enantioselectivity (87% ee). Pleasingly, 3-thienylboronic acid also reacted well to give **162h** in good yield (69%) and excellent enantioselectivity (92% ee).

We also obtained absolute configurations of products **162c**, **162d**, and **162g** determined by X-ray crystallography in Figure 9.

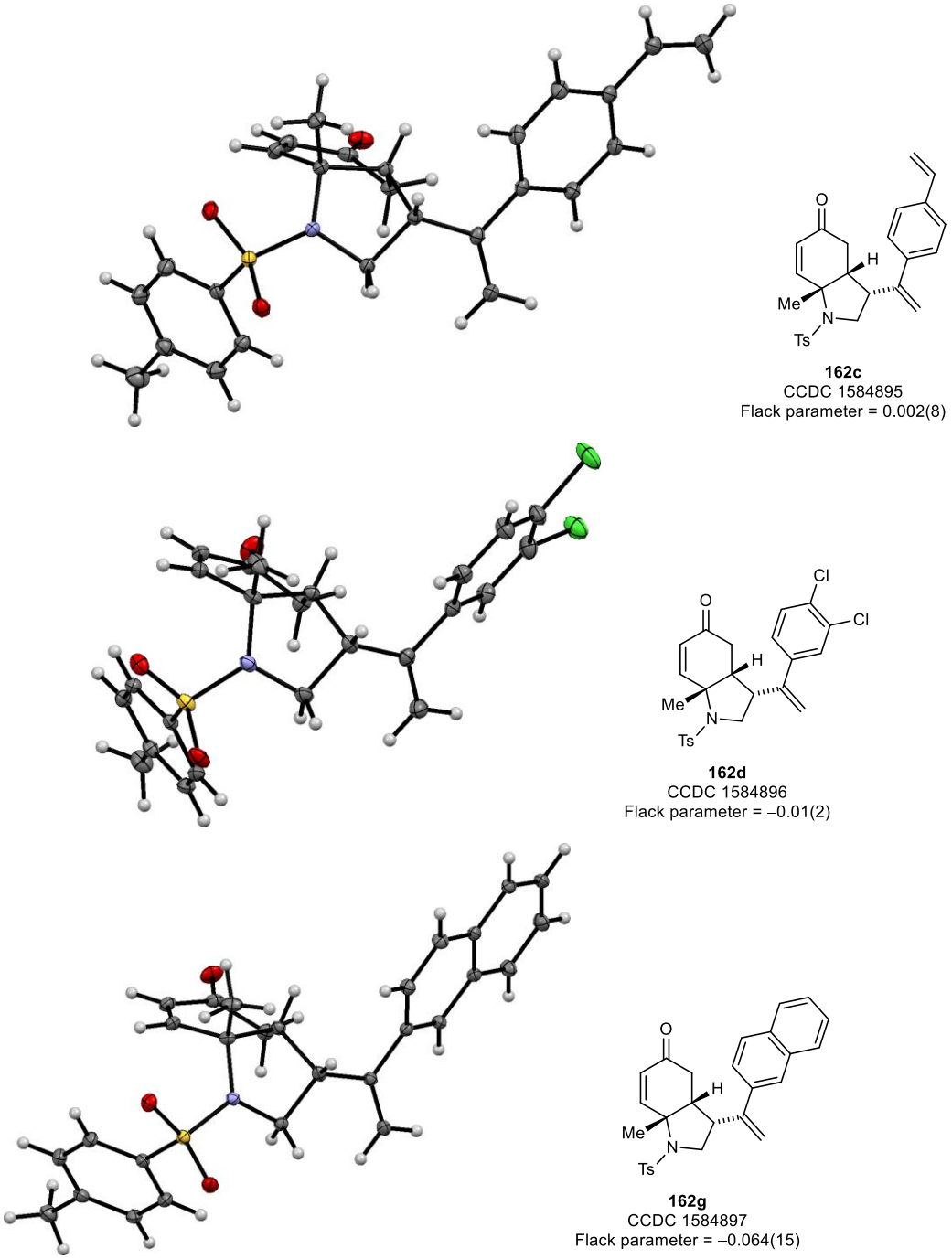
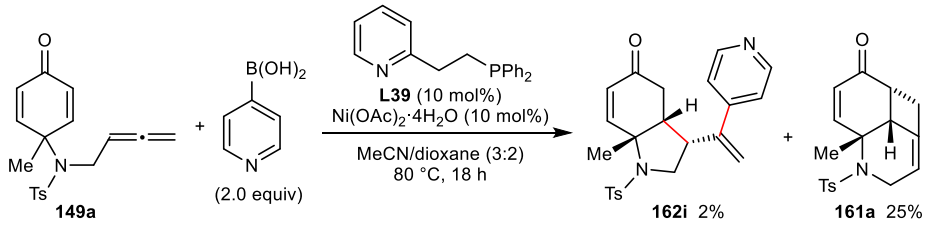


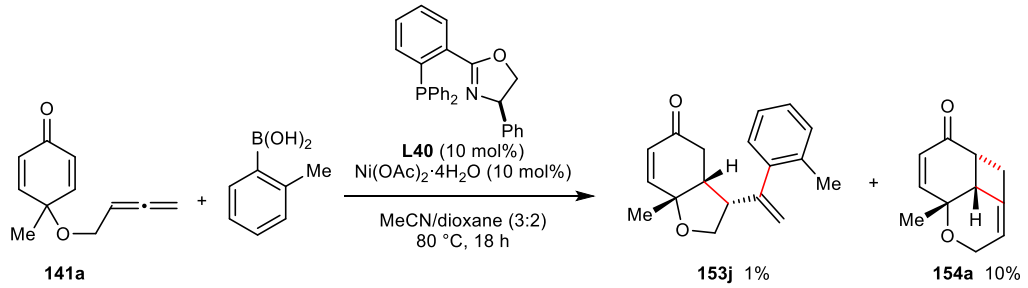
Figure 9. Xray structure of 162c, 162d, 162g. X-ray crystallography carried out by Dr. W. Lewis

Unfortunately, 4-pyridinylboronic acid gave only a trace of the product (2% yield, determined by ^{1}H NMR analysis of the crude reactions using 1,3,5-dimethoxybenzene) and 25% yield of by-product **161a** and returned 71% of the starting material **149a** (Scheme 112).



Scheme 112. Exploration with 4-pyridinylboronic acid

Subjecting *o*-tolylboronic acid to determine the effect of the bulky group on the *ortho*- position was performed. Unfortunately, product **153j** was formed in only a trace amount (1%) together with cyclobutane side product **154a** (10%) and retuned 38% of the starting material **141a** (Scheme 113).



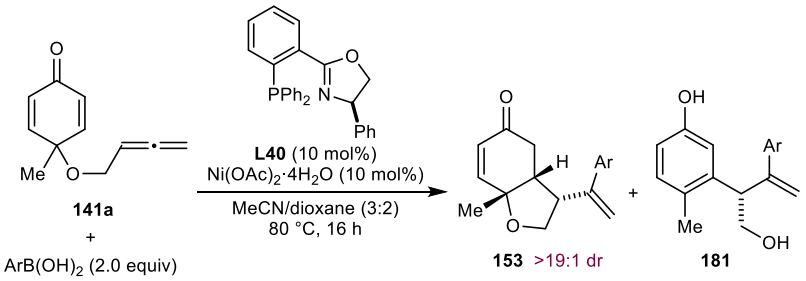
Scheme 113. Exploration with *o*-tolylboronic acid

2.7. Formation of phenol side products

During the exploration of certain arylboronic acids in this process, we observed the formation of interesting by-products, in addition to the expected 6,5-bicycles, which were 3,4-disubstituted phenols **181** (Table 8).

In each case, both products were formed with high enantioselectivities (89–93% ee). In most cases, the results showed that the use of strongly electron-withdrawing group at the *para*- or *meta*- position on arylboronic acids such as 4-acetyl, 3-cyano, or 3-carboethoxy groups gave the formation of phenols **181k**, **181m** and **181n** in varying yields (16–59%) but high enantioselectivities (91–92% ee). Furthermore, use of 4-trimethylsilylphenylboronic acid also furnished 14% of phenol **181l**.

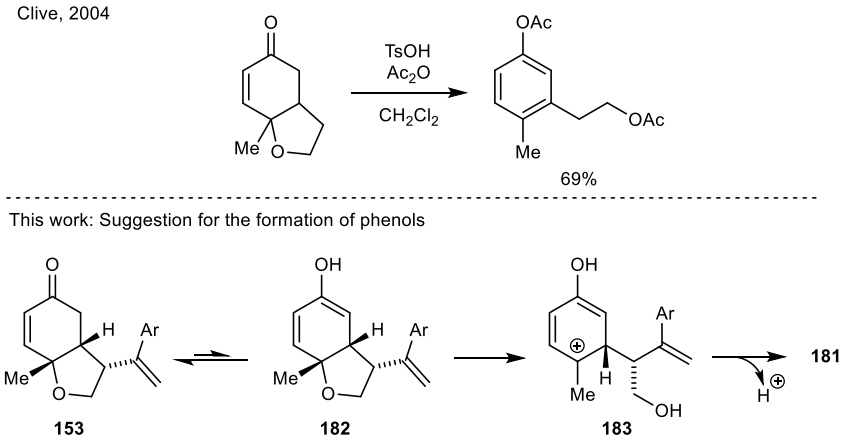
Table 8. Reactions producing phenols [a]



entry	Ar	6,5-bicycle		phenol	
1[b]	4-AcC_6H_4	**153k**	51%, 89% ee	**181k**	16%, 92% ee
2	4-$Me_3SiC_6H_4$	**153l**	35%, 93% ee	**181l**	14%, 94% ee
3	3-NCC_6H_4	**153m**	28%, 89% ee	**181m**	59%, 91% ee
4	3-$EtO_2CC_6H_4$	**153n**	64%, 91% ee	**181n**	22%, 91% ee

[a] Reactions were conducted with 0.30 mmol of **141a**. Yields are of isolated products. Enantiomeric excesses were determined by chiral HPLC analysis. [b] Reaction was carried out by Dr. Celia A. Incerti-Pradillos.

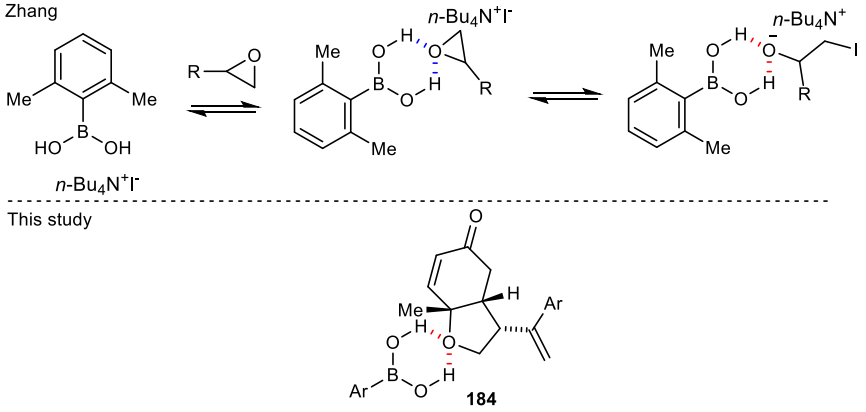
The formation of phenol **181** is possible by enolization of the ketone **153** to furnish **182**, ring-opening of furan **182** affords **183**. It is presumably promoted by a Brønsted acid or hydrogen-bond-donor (Scheme 114). The process is followed by proton loss from **183** to give **181**. Clive and co-workers reported a similar process which is shown in Scheme 114.[125]



Scheme 114. Suggestion for the formation of phenols

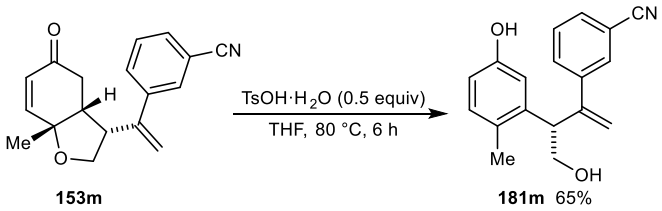
Possibly, the boronic acid might serve as a hydrogen-bond-donor to promote the ring-opening. Zhang suggested that boronic acids can be regarded as hydrogen-bond

donors for the activation of organic molecules and ring-opening of epoxides (Scheme 115).[126] First, the epoxide ring is activated by the hydroxyl group of the boronic acid *via* hydrogen bond interaction. Then, the ring opens through a nucleophilic attack by iodine. A similar procedure might be occurring in our process through intermediate **184** because only certain arylboronic acids gave the phenols in appreciable quantities.



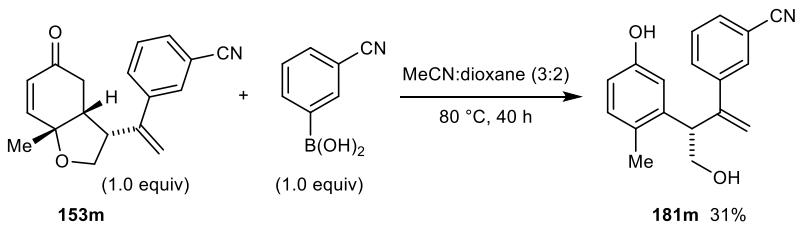
Scheme 115. Boronic acid as a hydrogen-bond-donor to promote ring-opening epoxide

To confirm the ability of acid to promote the formation of phenols, the 6,5-bicycle **153m** was heated with TsOH·H_2O (0.5 equiv) in THF at 80 °C. The phenol **181m** was observed in 65% yield (Scheme 116).



Scheme 116. Acid-catalyzed of hexahydrobenzofuran-5-one 153m into phenol 181m

In addition, the hexahydrobenzofuran-5-one **153m** also transformed to phenol **181m** in 31% yield in the presence of arylboronic acid under heating (Scheme 117).

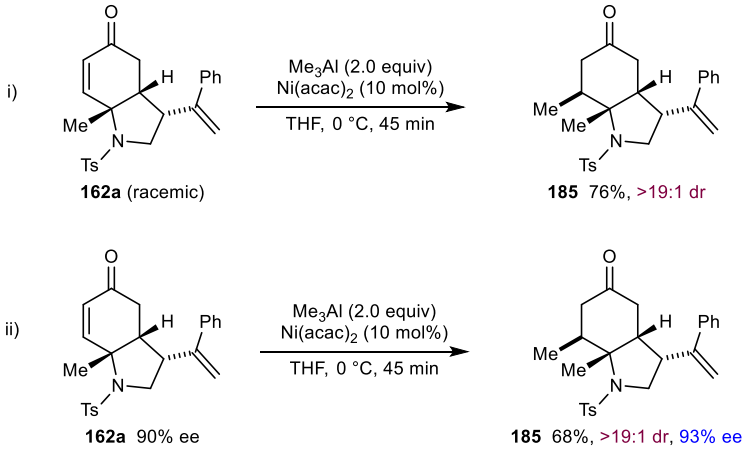


Scheme 117. Use of boronic acid for the formation of phenols [a]

[a] Reaction was conducted with 0.012 mmol of **6l** at 0.1 M concentration and yield was determined by ^{1}H NMR analysis of the crude reactions using 1,3,5-trimethoxybenzene as an internal standard.

2.8. Further transformation

To investigate the potential synthetic utility of the obtained products, various product manipulations were conducted. Compound **162a** was treated with Me_3Al in the presence of catalytic $Ni(acac)_2$. Pleasingly, 1,4-addition product **185** was obtained as a single diastereomer in 76% yield (Scheme 118). A methyl group was added to the less hindered convex face of **162a**, and the relative configuration was confirmed by NOE spectroscopy (Figure 10). The yield was slightly decreased when using enriched enantio-product **162a**, however, the resulting compound was also obtained as a single diastereomer and high enantioselectivity (Scheme 118).



Scheme 118. Further transformation of 185 by 1,4-addition

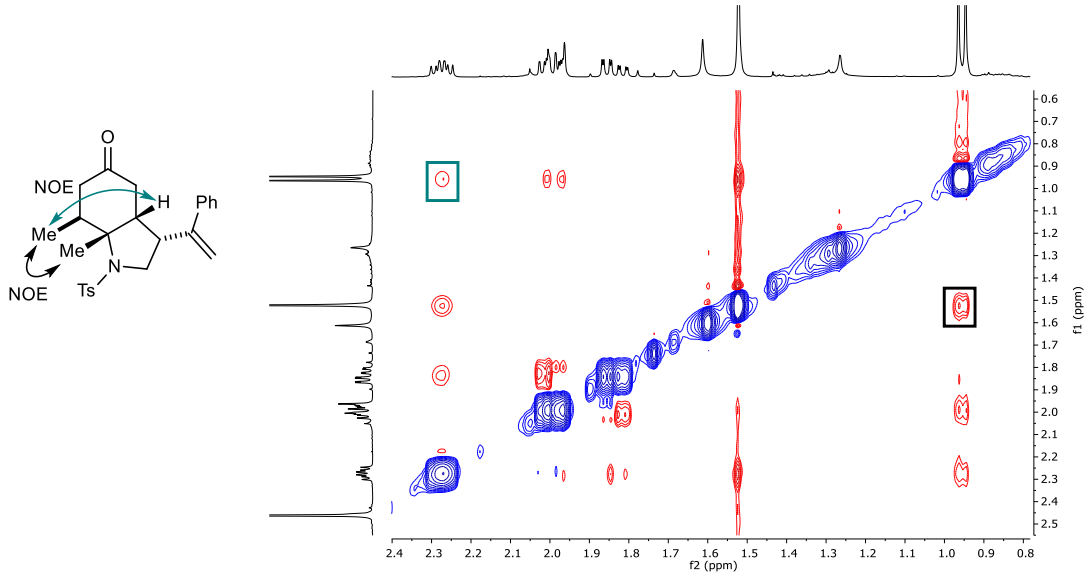


Figure 10. NOE spectrum of 185

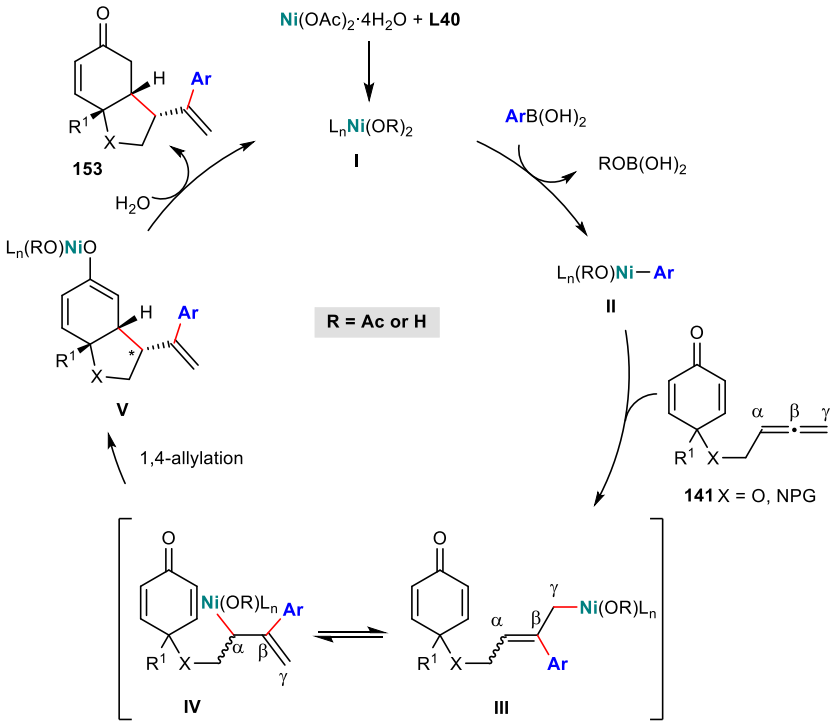
In addition, we tried to find another application for the product by transforming the carbonyl group to a secondary alcohol. A Luche reduction of selected 6,5-bicycle

162e was conducted and furnished allylic alcohol **186** in 99% yield and as a single diastereomer (Scheme 119).

Scheme 119. Luche reduction of 162e

2.9. Proposed mechanism

We propose a catalytic cycle for the nickel-catalyzed cascade reaction of an arylboronic acid to an allenyl cyclohexa-2,5-dienone in Scheme 120.



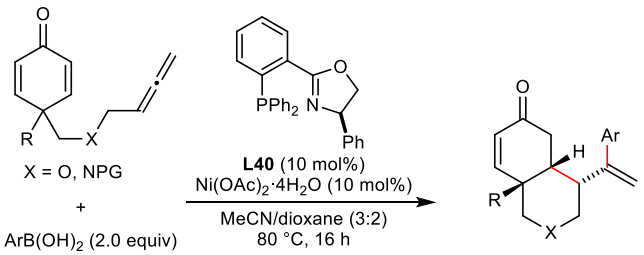
Scheme 120. Proposed arylative intramolecular 1,4-allylations of allenyl cyclohexa-2,5-dienones

Once ligated nickel **I** is formed, transmetallation of $PhB(OH)_2$ gives arylnickel species **II**. Coordination followed by migratory insertion of **141** gives the nucleophilic allylnickel species. These species could be a primary allylnickel intermediate **III**, which might exist in equilibrium with secondary allylnickel species **IV**. Either **III** or **IV** could attack the tethered electrophile to give nickel enolate **V** *via*

intramolecular 1,4-allylation. Protonolysis of this intermediate **V** would release 6,5-bicycle **153** and regenerate the active nickel(II) complex **I** to complete the catalytic cycle.

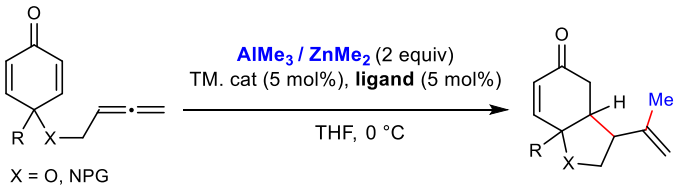
2.10. Future work

Our method is currently limited to the formation of 6,5-bicycles with arylboronic acids. Successful arylative cyclization of different structures (**187**) to form 6,6-bicycles would broaden the diversity of this methodology (Scheme 121).



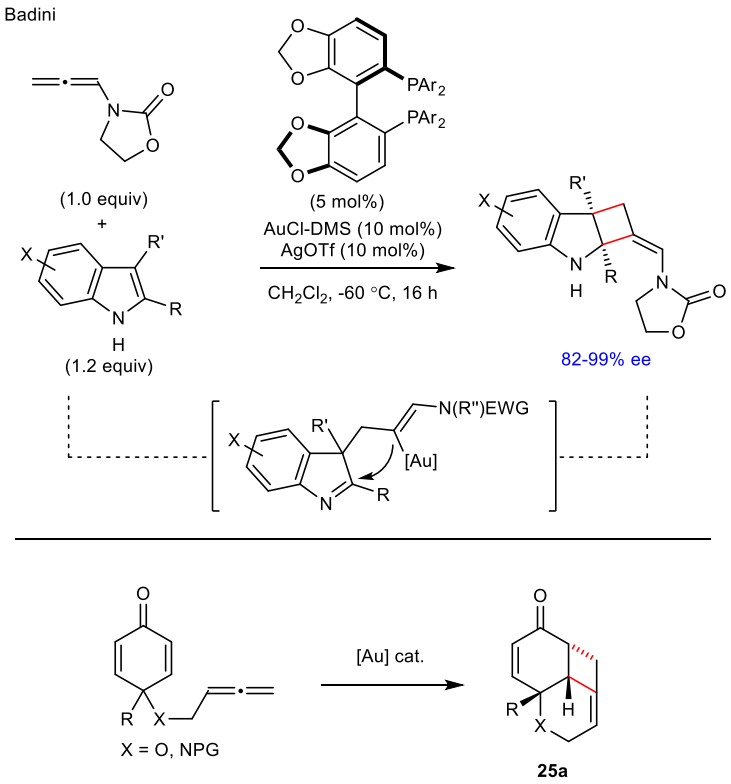
Scheme 121. Arylative cyclization of different structures

In addition, other classes of pronucleophiles could be explored, for example organometallic reagents such as $AlMe_3$, $ZnMe_2$ or alkenyl and alkyl boronic acids. The extension of this methodology beyond arylative cyclizations would be beneficial (Scheme 122).



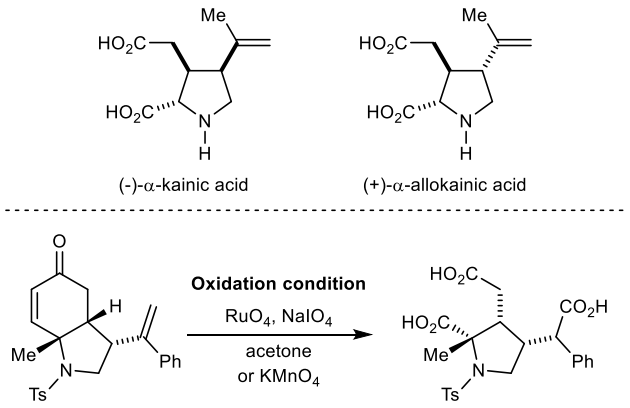
Scheme 122. Transition-metal-catalyzed alkylative cyclizations

Moreover, [2+2] cyclization products have been isolated as interesting by-products. Therefore, to develop enantioselective methodologies for the formation of these products would be of benefit. In 2015, the Badini group reported an enantioselective gold-catalyzed [2+2]-cycloaddition of indoles and allenamides.[127] They obtained highly enantioenriched 2,3-indole cyclobutanes with two consecutive quaternary stereogenic centers (>20:1 d.r, ee up to 99%). We also questioned whether the enantioselective [2+2] cyclization could form with gold catalysis (Scheme 123).



Scheme 123. Au-catalyzed enantioselective [2+2] cyclization

On the other hand, *cis*-fused hexahydroindol-5-one and hexahydrobenzofuran-5-one products could form an analog of kainic acid. Kainic acid is an analog of the excitatory aminoacid transmitter glutamate and is the most common neurotoxin.[128] We also expect that using oxidative conditions could afford an analogue of kainic acid (Scheme 124).



Scheme 124. Proposed reaction for a formation of an analogue of kainic acid

2.11. Conclusion

In summary, a new nickel-catalyzed arylative 1,4-allylation has been investigated *via in situ* formation of nucleophilic σ-allylnickel species. This method makes active contributions in nickel-catalyzed desymmetrization of allenyl cyclohexa-2,5-dienones by reaction with arylboronic acids. In addition, the combination of nickel(II)-catalyzed addition of an arylboronic acid to allenes and subsequently enantioselective intramolecular 1,4-allylation contributes to rare examples of catalytic enantioselective domino-1,4-addition-cyclizations. This methodology provides a broad range of hexahydroindol-5-ones and hexahydrobenzofuran-5-ones with three contiguous stereocenters in high diastereo- and enantioselectivities. The products could undergo further diastereoselective transformations to give a range of products.

3. Enantioselective Nickel-Catalyzed Arylative Intramolecular 1,2-Allylations of Allenyl Ketones

3.1. Introduction

Alkaloids with pyrrolidine-2-ones including a tertiary alcohol are key structural motifs existing in many natural products and biologically active compounds such as Norsecuramine A,[129] Cytochalasin Z_{10},[130] Rigidiusculamide A,[131] Herbicide[132] (Figure 11). The stereocenters in these densely functionalized molecules can be essential for promising biological and pharmaceutical activities. For instance, Norsecuramine A has potential biological activity on central nervous system cytoxicity, [129] Cytochalasin Z_{10} has been shown to be an anticancer compound [130] and Rigidiusculamide A has modest cytoxicities against human tumor cell lines Hela and MCF-7.[131] Therefore, new methods for the rapid synthesis of these chiral structures in high enantioselectivites have been of interest to synthetic chemists.

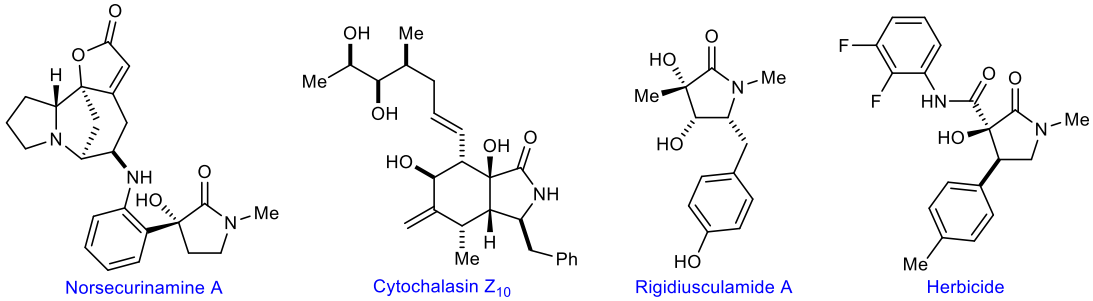
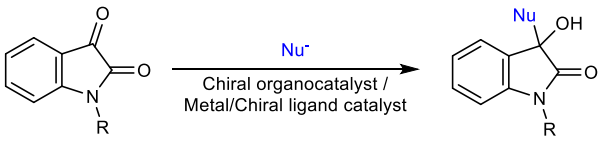


Figure 11. Alkaloids with pyrrolidine-2-ones

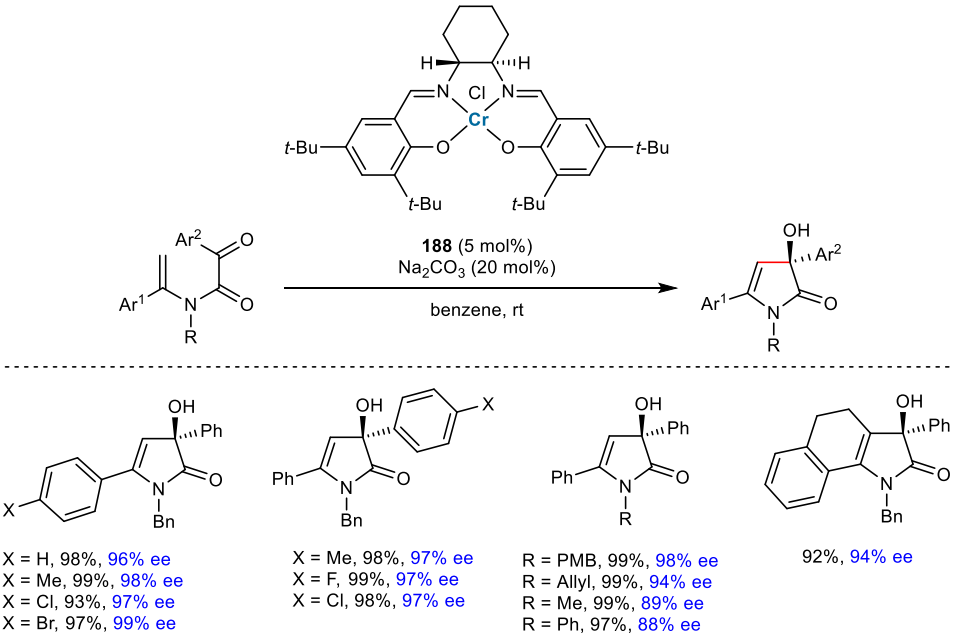
There have been many reports of asymmetric catalytic methodologies to give chiral oxindole scaffolds with a teriary alcohol at C3 (Scheme 125).[133]



Scheme 125. Formation of chiral benzannulated derivatives

However, to our knowledge, there are few examples of the methodology to forming enantioselective pyrrolidine-2-ones with a tertiary alcohol at C3. Wang and co-

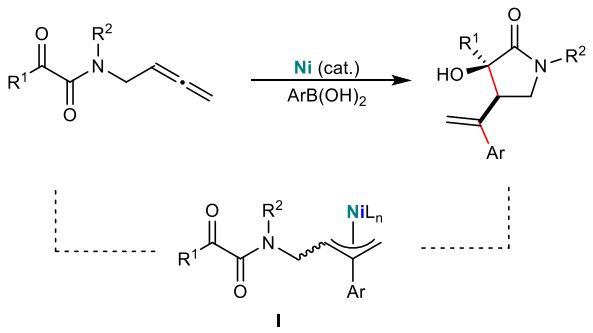
workers used a chiral chromium-salen-catalyzed asymmetric cyclization with an activated carbonyl moiety of α-keto tertiary enamides to furnish enriched enantioselective monocyclic and fused pyrrolidones.[134] The enamides undergo enantioselective intramolecular nucleophilic addition to a carbonyl group to give functionalized *N*-substituted 2-pyrrolidones derivatives bearing a hydroxylated quaternary carbon center (Scheme 126).



Scheme 126. Chiral chromium-salen-catalyzed an asymmetric intramolecular cyclization

3.2. Aims and objectives

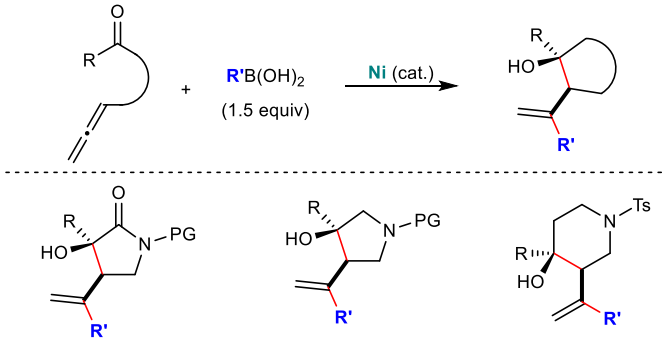
Our group reported enantioselective nickel-catalyzed intermolecular arylative cyclizations (Section 1.3.3, Scheme 83) and intramolecular arylative allylations (Chapter 2) using allenes.[106,135] In these processes, nickel(II)-catalyzed addition of an arylboronic acid to an allenyl-tethered electrophile would give nucleophilic nickelallyl intermediates which undergo intramolecular allylation to form the cyclized product. Therefore, we question whether a chiral pyrrolidine-2-one with a C3 tertiary alcohol can be synthesized *via* a chiral nucleophilic allylmetal species (Scheme 127). Nickel-catalyzed arylnickelation of allene and arylboronic acid would form intermediate allylnickel species **I**.[106,135] These could undergo the diastereo- and enantioselective nucleophilic allylation [90,91] of the ketone to provide pyrroldin-2-ones.



Scheme 127. Possible approach for enantioselective domino arylative 1,2-allylation

To our knowledge, only the Tsukamoto group [99] and Lu group [101] have reported such similar processes for asymmetric cascade arylative-intramolecular cyclizations of allenyl tethered electrophiles using palladium catalysis to give other types of hetero- and carbocycles (Section 1.3.1). Tsukamoto et. al used $Pd(OAc)_2$-SEGPHOS for reactions of allenyl aldehydes and arylboronic acids to give *cis*-fused five- and six-membered cyclic homoallylic alcohols in excellent diastereo- and enantioselectivities (Scheme 70, Section 1.3.1). However, they demonstrated only one example using ketone in moderate enantioselectivity (51% ee). Lu et. al developed a highly enantioselective cationic Pd(II)-catalyzed cyclization of *N*-tosyl-aniline tethered allenyl aldehydes and arylboronic acids (Scheme 74, Section 1.3.1), but no allenyl ketones were used in this chemistry.

Therefore, our aim was to investigate the first enantioselective domino arylative 1,2-allylation-cyclization of allenyl ketones to give a chiral pyrrolidine-2-one with a C3 tertiary alcohol by using nickel catalysts *via* nucleophilic allylnickel intermediates (Scheme 127). In addition, we questioned whether the scope of substrates could be broadened for the formation of not only 3-hydroxypyrrolidinones but also 3-hydroxypyrrolidines and 4-hydroxypiperidines (Scheme 128).

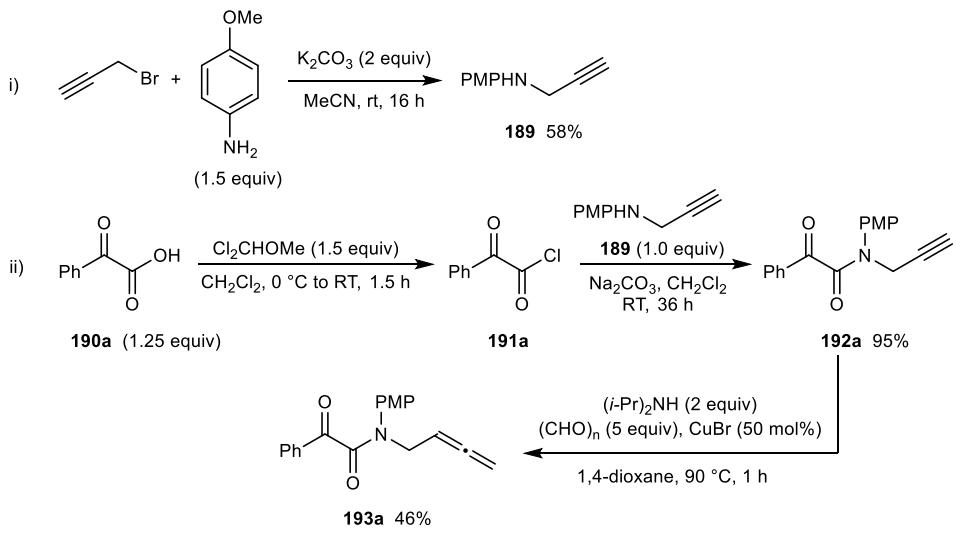


Scheme 128. The scope of substrates

This successful realization of this work would be of significance as it would be an example of an enantioselective cascade arylative/alkenylative intramolecular 1,2-allylation with the formation of chiral pyrrolidine-2-ones, pyrrolidines or piperidines with tertiary alcohols. In addition, using nickel, which is an earth-abundant and inexpensive first-row transition metals would be more beneficial in terms of cost. This project would contribute to transition-metal-catalyzed enantioselective nucleophilic allylation chemistry, without the need for a reducing agent.

3.3. Reaction development

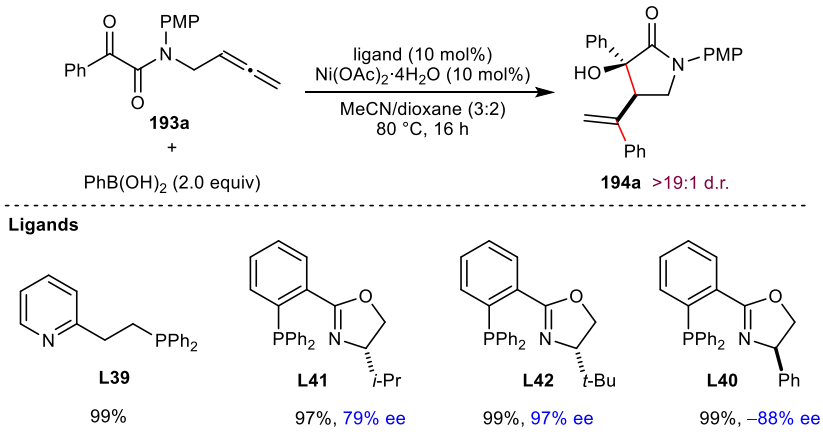
This study began with the synthesis of allenyl ketone **193a** to serve as a test substrate for reaction development (Scheme 129). Propargylamine **189** was prepared by reaction between propargyl bromide and *p-anisidine* using K_2CO_3 as a base and acetonitrile as solvent.[136] The propargylamine **189** was then reacted with acyl chloride **191a**, which was prepared *in situ* from phenylglyoxylic acid **190a** and dichloromethyl methyl ether, to afford alkynyl ketone **192a**. Finally, the allenyl ketone was prepared through a Crabbé homologation of the alkyne using formaldehyde, (*i*-Pr)$_2$NH and CuBr in dioxane.



Scheme 129. Preparation of allenyl ketone 193a

In previous projects, the Lam group showed that chiral phosphinooxazolines are good ligands for nickel-catalyzed asymmetric carbometallative cyclizations (Section 2.2, Scheme 94) [112] and arylative 1,4-allylation of allenyl electrophiles (Chapter 2). [135] Therefore, our reaction screening was initiated with the reation of the allenyl

ketone **193a** and $PhB(OH)_2$ (2.0 equiv) in MeCN/1,4-dioxane (3:2) at 80 °C for 16 h in the present of various ligands **L39**−**L42**. Pleasingly, the reactions went smoothly in excellent yields (79−97%) and using the ligand *t*-BuPHOX **L42** gave pyrrolidine-2-one **194a** in 97% ee (Scheme 130).



Scheme 130. Initial investigation of ligands

The relative and absolute configuration of **194a** was determined by X-ray crystallography. The structure of **194a** was verified in Figure 12.

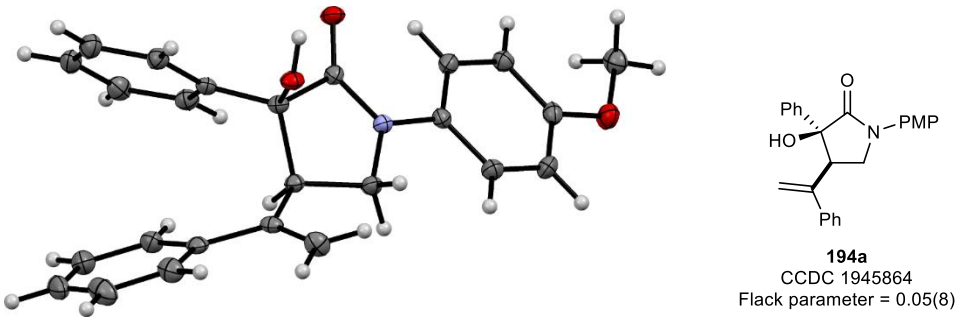
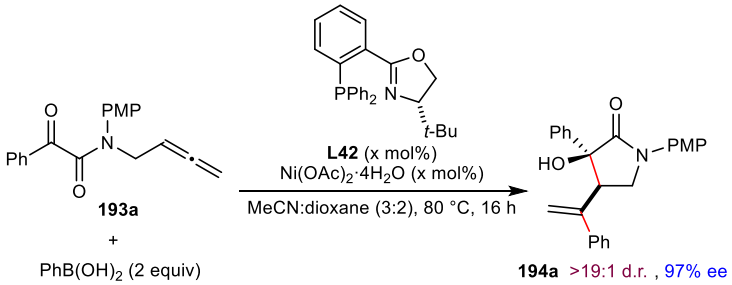


Figure 12. X-ray crystal structure of 194a. X-ray crystallography carried out by Dr. W. Lewis

To improve the practicality and efficiency of this reaction, we tested lower quantities of catalysts, and equivalents of boronic acid in different solvents.

Reducing the amount of catalyst from 10 mol% (entry 1) to 5 mol% and 3 mol% in the reaction, using ligand **L42**, were shown in Table 9. The results illustrated that decreasing quantity of catalyst to 5 mol% was well-tolerated to give a single diastereomer in excellent yield (98%) and enantioselectivity (97% ee) (entry 2). Decreasing the catalyst loading to 3 mol% was detrimental (33−38%) (entries 3 and 4).

Table 9. Investigation of catalyst loading



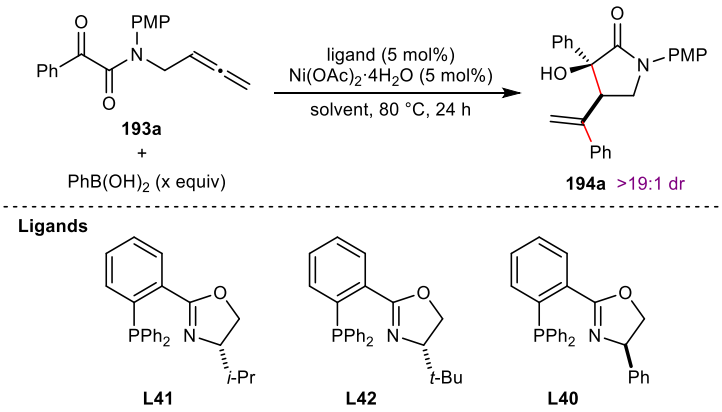
Entry [a]	Catalyst loading (mol%)	Concentration (M)	Yield [%][b]
1	10	0.1	99
2	5	0.1	98
3	3	0.1	38
4	3	0.2	33

[a] Reactions were conducted with 0.1 mmol of **193a**. [b] Determined by ^{1}H NMR analysis of the crude reactions using 1,3,5-trimethoxybenzene as an internal standard.

Lower quantities of $PhB(OH)_2$ were tested with different ligands and solvents and the results are shown in Table 10. When the amount of $PhB(OH)_2$ was decreased from 2 equivalents (entry 1) to 1.5 equivalents (entry 2) in a mixture of MeCN/1,4-dioxane (3:2) with ligand **L42**, the yield decreased from 99% to 78% but excellent enantioselectivity was observed (98% ee).

Interestingly, the pyrrolidine-2-one **194a** was obtained as a single diastereomer in all cases. The reation of allenyl ketone **193a**, $PhB(OH)_2$ (1.5 equiv) and $Ni(OAc)_2{\cdot}4H_2O$ in MeCN/1,4-dioxane (3:2) without ligand gave the racemic product **194a** in only 32% yield (entry 3). Then the reactions were repeated under these conditions with different chiral ligands. The chiral phosphinooxazoline (*S*)-*i*-Pr-PHOX **L41** decreased the yield of **194a** to 55% and the enantiomeric excess was 90% ee (entry 4). (*R*)-Ph-PHOX **L40** gave 61% yield and -91% ee (entry 5). Overall, in MeCN/1,4-dioxane (3:2), ligand **L42** gave the best yield (78%) and enantioselectivity (98% ee) (entry 2).

Table 10. Further development of reaction conditions



Entry[a]	Ligand	$PhB(OH)_2$ (equiv)	Solvent(s)	Yield (%)[b]	ee (%)[c]
1	**L42**	2	MeCN/1,4-dioxane (3:2)	99	97
2	**L42**	1.5	MeCN/1,4-dioxane (3:2)	78	98
3	–	1.5	MeCN/1,4-dioxane (3:2)	32	–
4	**L41**	1.5	MeCN/1,4-dioxane (3:2)	55	90
5	**L40**	1.5	MeCN/1,4-dioxane (3:2)	61	–91[d]
6	**L42**	1.5	MeCN	78	98
7	**L42**	1.5	1,4-dioxane	59	98
8	**L42**	1.5	TFE	>99	96

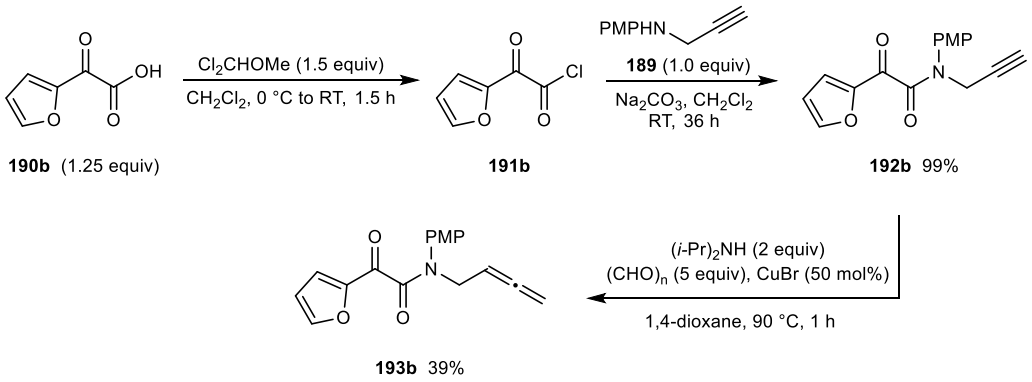
[a] Reactions were conducted using 0.10 mmol of **193a**. [b] Determined by 1H NMR analysis of the crude reactions using 1,3,5-dimethoxybenzene as an internal standard. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The major product was the enantiomer of **194a**. PMP = para-methoxyphenyl.

Further experiments were conducted by replacing the mixture of solvents to single solvents with **L42** as the ligand. Using MeCN or 1,4-dioxane alone gave no improvement (78% yield and 59% yield, respectively, entries 6 and 7). Changing the solvent to TFE (entry 9) gave full conversion and **194a** was obtained in >99% yield with only a slight decrease in enantioselectivity (96% ee). Although the use of TFE as the reaction solvent was not desirable on the basis of cost, it offered the best conditions to generate products in quantitive yield and excellent enantioselectivity.

Therefore, the conditions of Table 10, entry 8 which use $PhB(OH)_2$ (1.5 equiv), $Ni(OAc)_2 \cdot 4H_2O$ (5 mol%), ligand **L42** (*S*)-*t*-Bu-PHOX (5 mol%) in TFE were adopted for investigating the reaction scope.

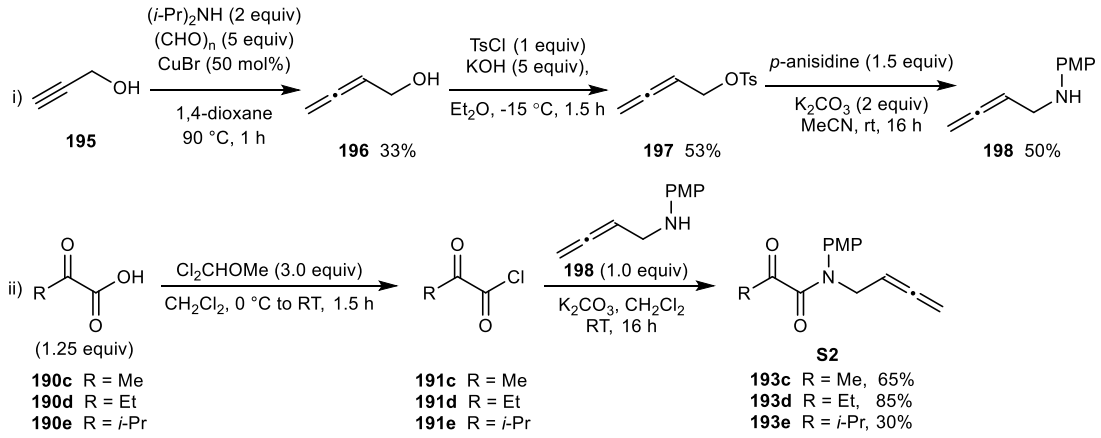
3.4. Synthesis of substrates

The allenyl ketone **192b** with a 2-furyl substituent was prepared as shown in Scheme 131. α-Oxo-2-furanacetic acid **190b** was reacted with dichloromethyl methyl ether to form acyl chloride **191b** *in situ*. To this solution was added propargylamine **189** to afford alkynyl ketone **192b**. The allenyl ketone **193b** was then prepared through a Crabbé homologation reaction of alkyne using formaldehyde, $(i\text{-Pr})_2NH$ and CuBr in dioxane.



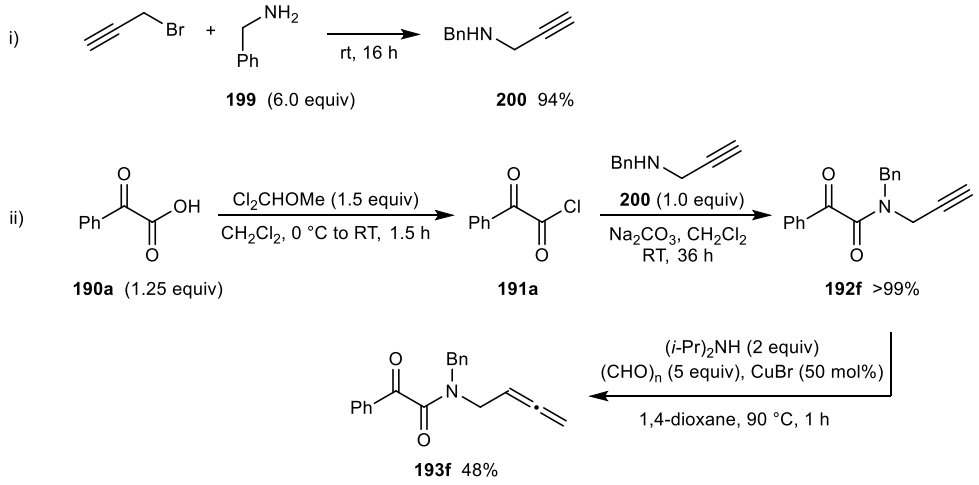
Scheme 131. Preparation of allenyl ketone with 2-furyl substituent ketone

A variety of allenyl ketones with various substituents including simple alkyl (**192c** and **192b**) and branched alkyl (**192e**) groups were also synthesized (Scheme 132). The buta-2,3-dien-1-ol **196** was synthesized from propargyl alcohol **195** by a Crabbé homologation reaction. Then, buta-2,3-dien-1-ol **196** was reacted with TsCl to furnish allylic tosylate **197**, which was subjected to a solution of *p*-anisidine and K_2CO_3 in MeCN to give allene **198** (Scheme 132i). The alkylglyoxylic acids **190c**, **190d** and **190e** were reacted with dichloromethyl methyl ether to form acyl chlorides **191c**, **191d** and **191e,** respectively. Subsequently, the allenyl ketones **193c**, **193d**, and **193e** were prepared from these acyl chlorides and allenyl amines **198** (Scheme 132ii).



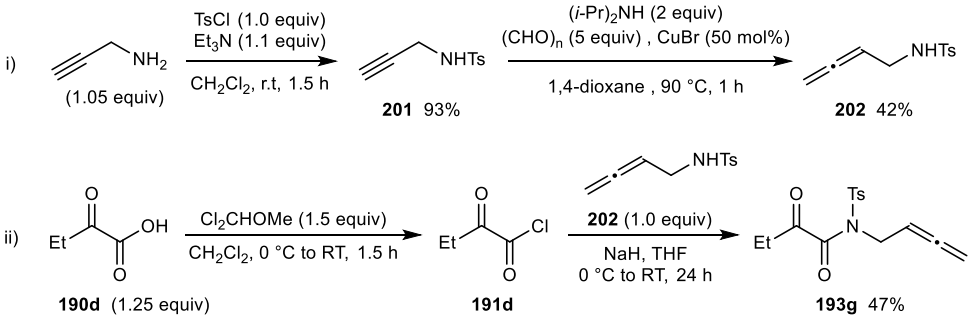
Scheme 132. Preparation of allenyl ketones with alkyl substituents

The allenyl phenyl-substitued ketone **193f** with an *N*-benzyl group was prepared as shown in Scheme 133. Propargylamine **200** was formed by propargyl bromide and amine **199**. Phenylglyoxylic acid (**190a**) was reacted with dichloromethyl methyl ether to form acyl chloride **191a** *in situ*. To this solution was added the propargylamine **200** to afford alkynyl ketone **192f**. The allenyl ketone **193f** was then prepared through a Crabbé homologation reaction.



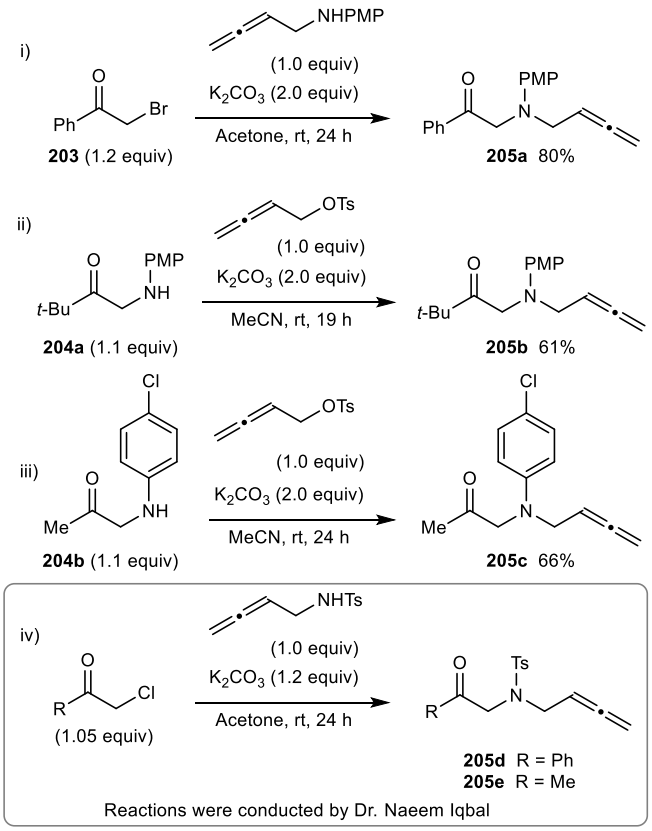
Scheme 133. Preparation of allenyl ketone with phenyl substituent ketone

The alkynyl sulfonamide **201**, formed by the reaction of propargylamine and TsCl, was subjected to a Crabbé homologation reaction of alkyne using formaldehyde, (*i*-Pr)$_2$NH and CuBr in dioxane to furnish allene **202** (Scheme 134i). α-Ketobutyric acid **190g** was reacted with dichloromethyl methyl ether to form acyl chloride **191d** *in situ*. Subsequently, the addition of allene **202** gave the allenyl ketone **193g** (Scheme 134ii).



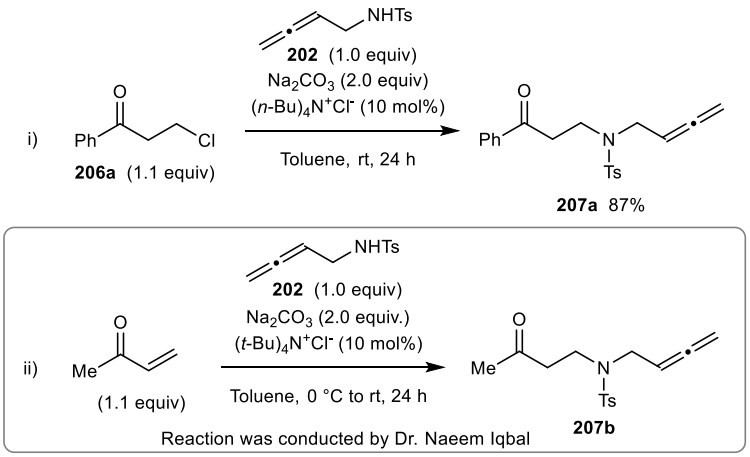
Scheme 134. Preparation of allenyl ketones with *N*-sulfonyl tethered

The preparation of allenyl ketones with different substituents and *N*-protecting groups are shown in Scheme 135. Substrates **205a** were prepared from α-haloketones **230** by reaction with the allenyl amines **198** (Scheme 135i). The allenyl ketones **205b** and **205c** with different substituents on nitrogen were synthesized from ketones **204a, 204b** and tosylate **197** under basic conditions (Scheme 135ii and iii). The *N*-tosyl-protected allenyl ketones **205d**, **205e** were prepared by Dr. Naeem Iqbal (Scheme 135iv).



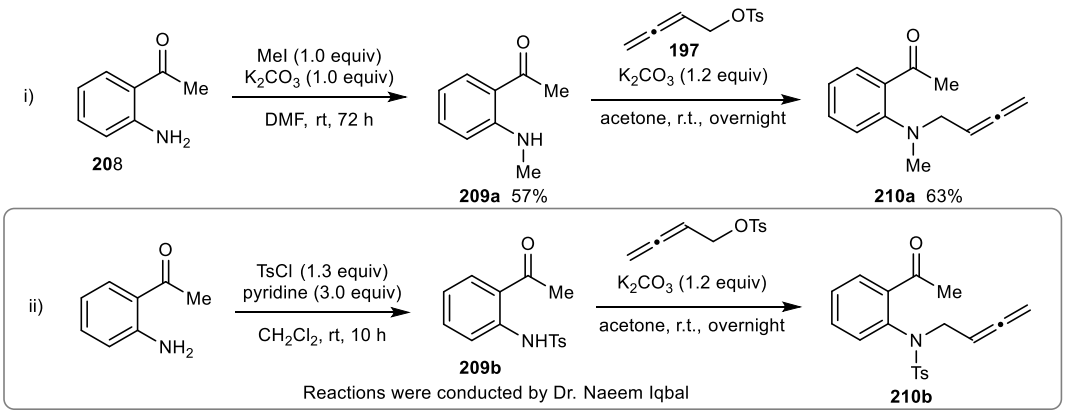
Scheme 135. Preparation of allenyl ketones with different substituents and *N*-protecting groups

The reaction of 3-chloropropiophenone **206a** with sulfonamide **202** using *n*-Bu_4NCl and Na_2CO_3 in toluene gave allene **207a** (Scheme 136i). In addition, the allenyl ketone **207b** was prepared by Dr. Naeem Iqbal (Scheme 136ii).



Scheme 136. Preparation of allenyl ketones with *N*-sulfonyl tether

Allenyl ketone **210a** was synthesized by methylation of 2'-aminoacetophenone **208** with MeI and K_2CO_3 in DMF, followed by the allenylation reaction with allenyl tosylate **197** (Scheme 137i). The allenyl ketone **210b** was prepared by Dr. Naeem Iqbal where tosylation of 2'-aminoacetophenone and *p*-toluenesulfonyl chloride using pyridine afforded benzenesulfonamide **209b**, which was then subjected to tosylate **197** to furnish allenyl ketone **210b** (Scheme 137ii).



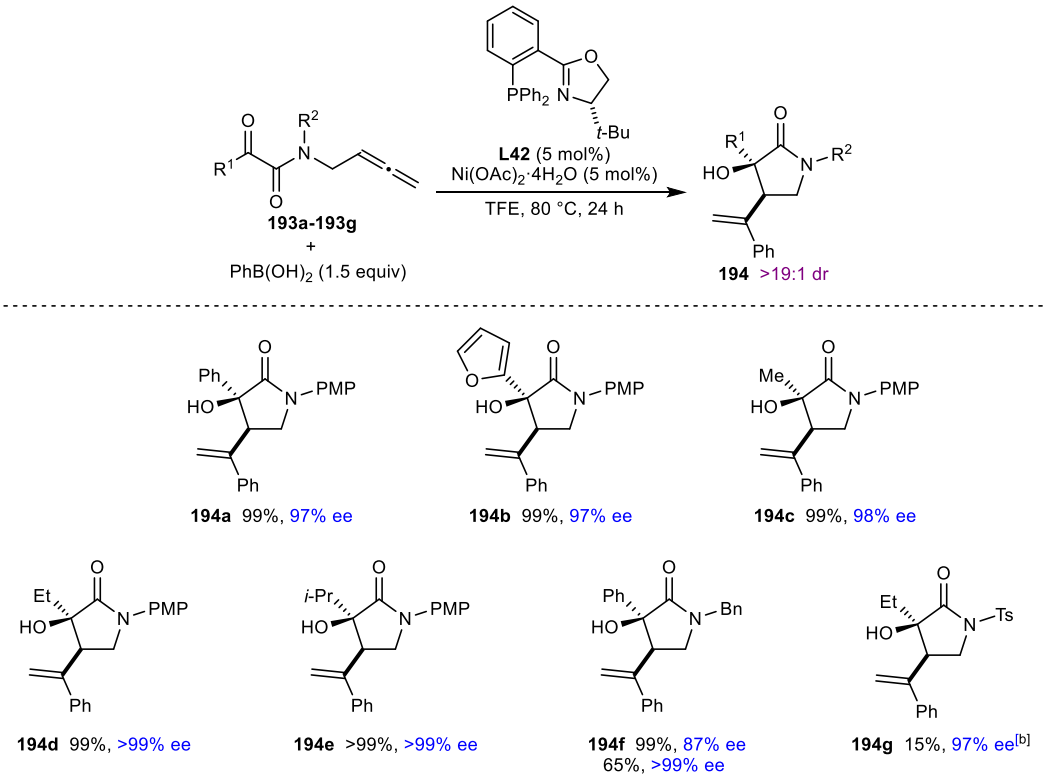
Scheme 137. Preparation of allenyl ketones 210a, 210b

3.5. Exploration of substrate scope

With the optimal conditions and a series of allenyl ketones in hand, we investigated the generality of our procedure with regard to the scope of substrates.

The reaction of various allenyl ketones, $PhB(OH)_2$ (1.5 equiv), $Ni(OAc)_2 \cdot 4H_2O$ (5 mol%) and ligand **L42** (*S*)-*t*-Bu-PHOX in TFE at 80 °C for 24 h were carried out and the results are shown in Table 11. Pleasingly, the chiral pyrrolidine-2-ones were successfully formed in most cases in excellent yield and enantioselectivities except for the *N*-tosyl-protected product (**194g**). The ketone substituents of *N*-PMP-protected allenes could be changed from phenyl (**194a**), 2-furyl (**194b**), simple alkyl (**194c** and **194d**) and branched alkyl (**194e**) to give pyrrolidine-2-ones in almost quantitative yields and high enantioselectivities. (96−99% ee). Changing to an *N*-benzyl tether, the reaction occurred in quantitative yield and 87% ee, however; the product **194f** was obtained with higher enantioselectivity (>97% ee) but in a lower yield (65%) when replacing TFE with MeCN as the solvent. In the case of the *N*-sulfonyl tethered substrate, the yield dramatically dropped to only 15% but the enantioselectivity of the product was high (97% ee). The relative and absolute configuration of the products were assigned by analogy with **194a** (Figure 12, section 3.3).

Table 11. Scope of allenyl substrates [a]

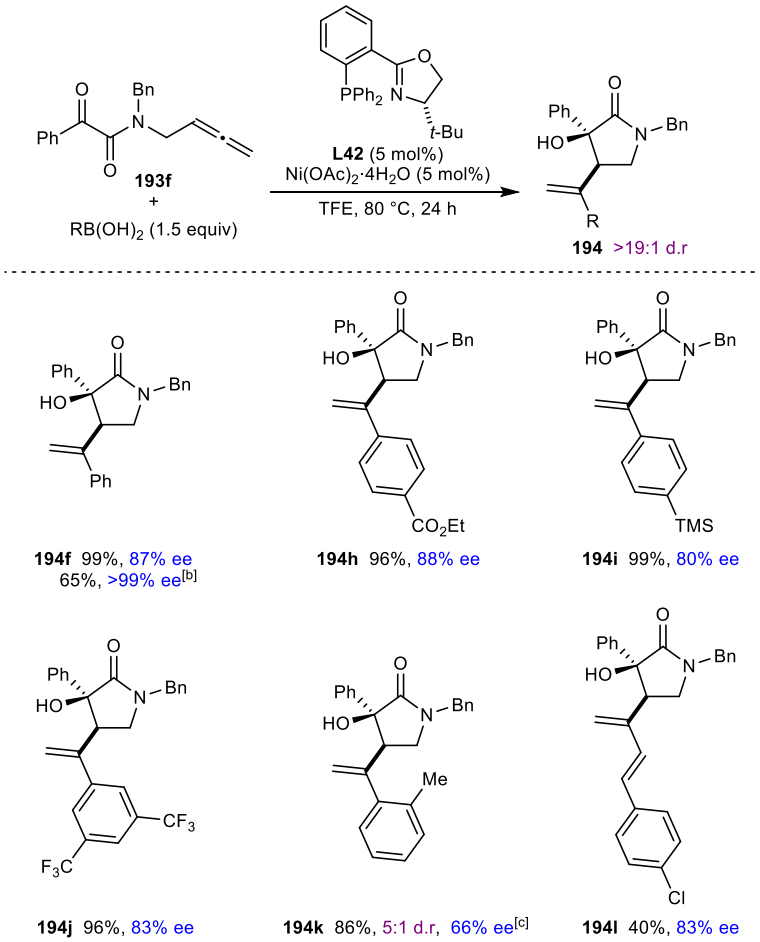


[a] Reactions were conducted with 0.3 mmol of **193**, enantioselectivities were determined by chiral HPLC analysis. [b] Reaction was conducted in MeCN**.** [c] Reaction was conducted with 0.1 mmol of **193g**.

3.6. Exploration of boronic acid scope

The investigation of various boronic acids was then explored using substrate **193f** (Table 12). The reaction tolerated other boronic acids. Arylboronic acids with substituents on the *para*- position such as carboethoxy and trimethylsilylphenyl-boronic acid gave excellent yields (96−99%) and good enantioselectivities (80−88% ee) in TFE as a solvent. A *meta*-disubstituted aryboronic acid was also examined and gave chiral pyrrolidine-2-one **194j** in excellent yield (96%) and good enantioselectivity (83% ee). Then, use of *ortho*-substituted arylboronic acid was also explored and furnished the product **194k** in 86% yield but moderate enantioselectivity of 66% ee. In addition, *trans*-2-(4-chlorophenyl)vinylboronic acid was also subjected to the optimized conditions and successfully gave **194l** in 40% and 83% ee.

Table 12. Scope of boronic acids [a]



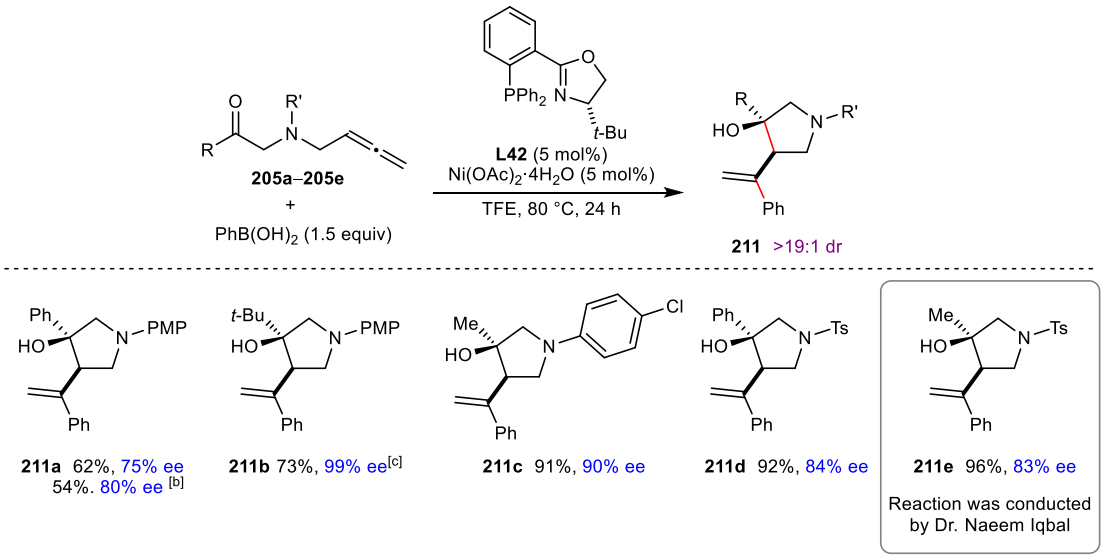
[a] Reactions were conducted with 0.3 mmol of **193f**, enantioselectivities were determined by chiral HPLC analysis. [b] Reaction was conducted in MeCN. [c] The diastereomer ratio of the crude reaction mixture was 5:1. Isolated as a 5:1 mixture of inseparable diastereomers.

3.7. Further exploration to form pyrrolidines, piperidine and tetrahydroquinolines

Inspired by the formation of chiral pyrrolidin-2-ones, we were interested in applying this method for the synthesis of other types of azacycles such as pyrrolidine, piperidine or quinoline-one.

Pleasingly, a series of allenyl ketones **205a**-**205e** can react to form pyrrolidines (Table 13). Moreover, it was compatible with *N*-tosyl tethers and **211** was obtained in 92−96% yield and 83−84% ee. The reactions were well-tolerated regarding the phenyl- (**211d**) and methyl- (**211e**) substituents on the ketone. Reactions of *N*-4-methoxyphenyl tethers occurred generating pyrrolidines in high enantioselectivites. Replacing TFE by MeCN as the solvent gave products **211a** in higher enantioselectivities (80% ee) but lower yields (54%). *t*-Butyl substituted ketone **211b** gave 73% yield and excellent enantioselectivity (99% ee). It was suggested that increasing the steric bulk on the ketone moiety would have a favourable effect on the enantioselectivity. In addition, a substrate with a *N*-4-chlorophenyl tether (**211c**) also furnished a chiral pyrrolidine in 91% and 90% ee.

Table 13. Formation of pyrrolidine [a]



[a] Reactions were conducted with 0.3 mmol of **205**, enantioselectivities were determined by chiral HPLC analysis. [b] Reaction was conducted in MeCN. [c] A 7.7:1 inseparable mixture of **211b** and starting allene **205b** was obtained (the yield of **211b** has been adjusted accordingly).

The absolute stereochemistry of product **211b** and **211d** obtained from *N*-PMP tethered and *N*-tosyl tethered substrates were determined by X-ray crystallography (Figure 13). The single crystals were prepared by slow diffusion of petroleum ether into a solution of **211b**, **211d** in EtOAc.

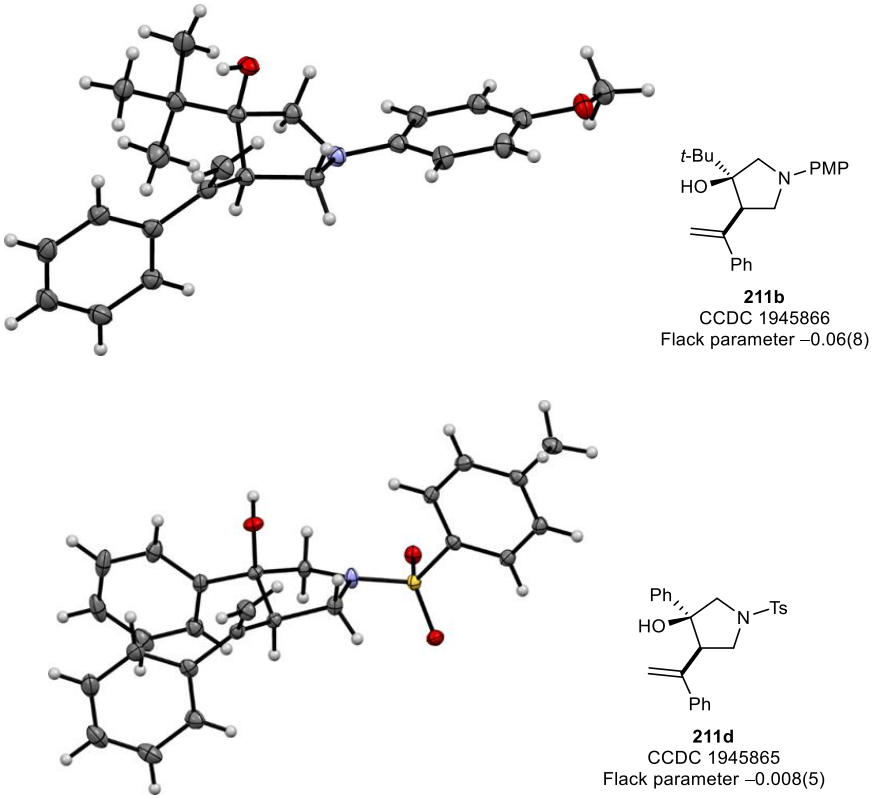
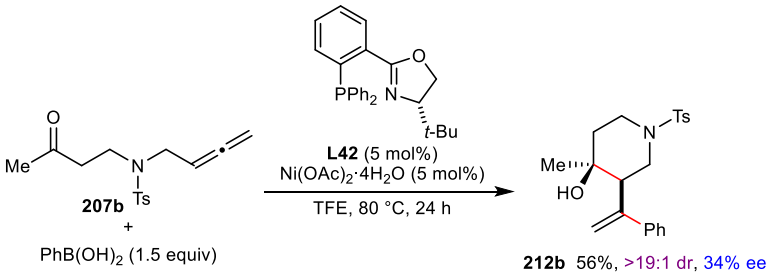


Figure 13. Xray structure of 211b, 211d. X-ray crystallography carried out by Dr. S. P. Argent

Allenyl ketone **207b** was subjected to the optimized conditions. Unfortunately, the reaction only gave product **212b** in 56% yield and 34% ee (Scheme 138).

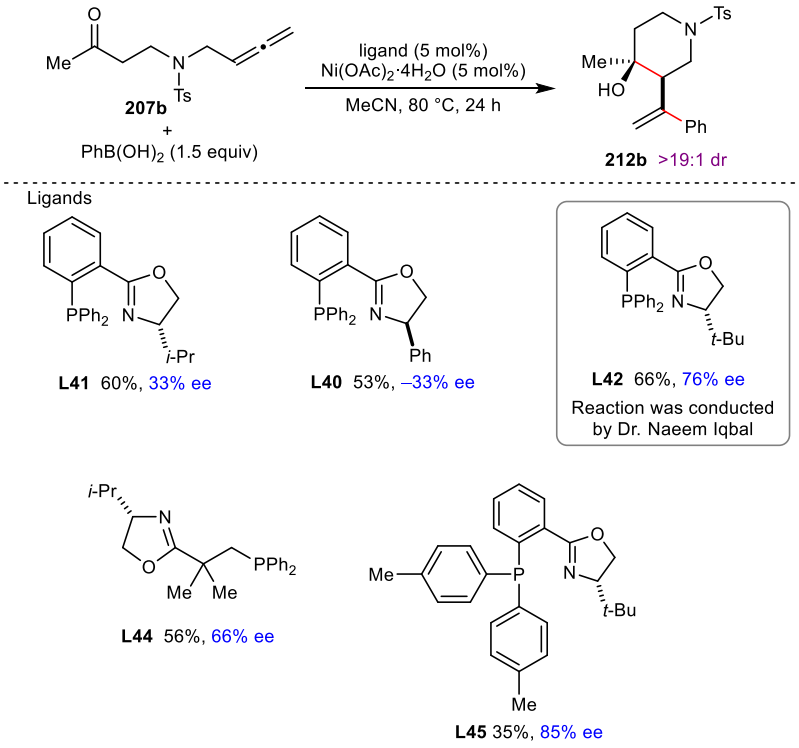


Scheme 138. Initial preparation of piperidine [a]

[a] Reactions were conducted with 0.05 mmol of **207b**; yield was determined by ^{1}H NMR analysis of the crude reacions using 1,3,5-trimethoxybenzene; enantioselectivities was determined by chiral HPLC analysis.

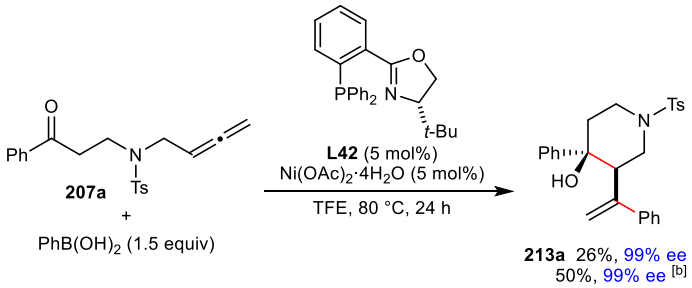
To explore the formation of piperidine, the reaction of allenyl ketone **207b** was carried out in MeCN as a solvent with $PhB(OH)_2$ (5 mol%), $Ni(OAc)_2{\cdot}4H_2O$, ligand **L42** (*S*)-*t*-Bu-PHOX at 80 °C for 24 h (Table 14). The enantioselectivity of product **212b** was improved to 76% ee. We tried to improve the enantioselectivity of product **212b** using different ligands (Table 14). The chiral phosphinooxazolines with phenyl (**L40**) and *i*-propyl (**L41**) substituents were detrimental to the enantioselectivity (33% ee). Using a (*S*)-neo-PHOX **L44** gave 66% ee. The using of phosphinooxazoline **L45** afforded higher enantioselectivity (85% ee); however, the yield decreased to 35%.

Table 14. Formation of piperidines with different chiral ligands [a]



[a] Reactions were conducted with 0.05 mmol of **207b**; yield was determined by ^1H NMR analysis of the crude reacions using 1,3,5-trimethoxybenzene; enantioselectivities was determined by chiral HPLC analysis.

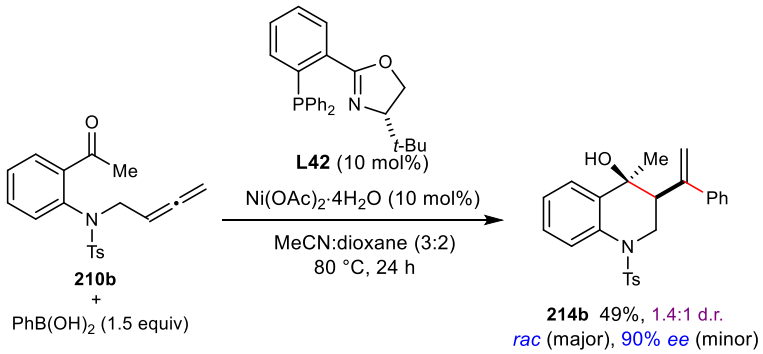
An allene with a phenyl substituent on the ketone **207b** moiety was investigated. The product **213a** was obtained in only 26% yield but excellent enantioselectivity (99% ee). Increasing the reaction time to 48 h enhanced the yield to 50% and the enantioselectivity remained at 99% ee (Scheme 139).



Scheme 139. Formation of 213a [a]

[a] Reactions were conducted with 0.3 mmol of **207a**. [b] Reaction was conducted in 48 h. Enantioselectivities were determined by chiral HPLC analysis.

Encouraged by the previous results, we questioned whether the reaction could give the benzannulated product. The reaction was carried out with 0.1 mmol allenyl ketone **210b**, $PhB(OH)_2$ (1.5 equiv), and $Ni(OAc)_2 \cdot 4H_2O$ (10 mol%) and ligand **L42** (*R*)-*t*-Bu-PHOX (10 mol%) in MeCN/1,4-dioxane (3:2) at 80 °C for 24 h (Scheme 140). We were pleased to observe that quinoline-ol **241b** was obtained in 49% ^{1}H NMR yield as a 1.4:1 ratio of diastereomers. However, the major diastereomer was obtained as a racemate and the minor diastereomer was formed in high enantioselectivity (90% ee). The absolute configuration was not determined.



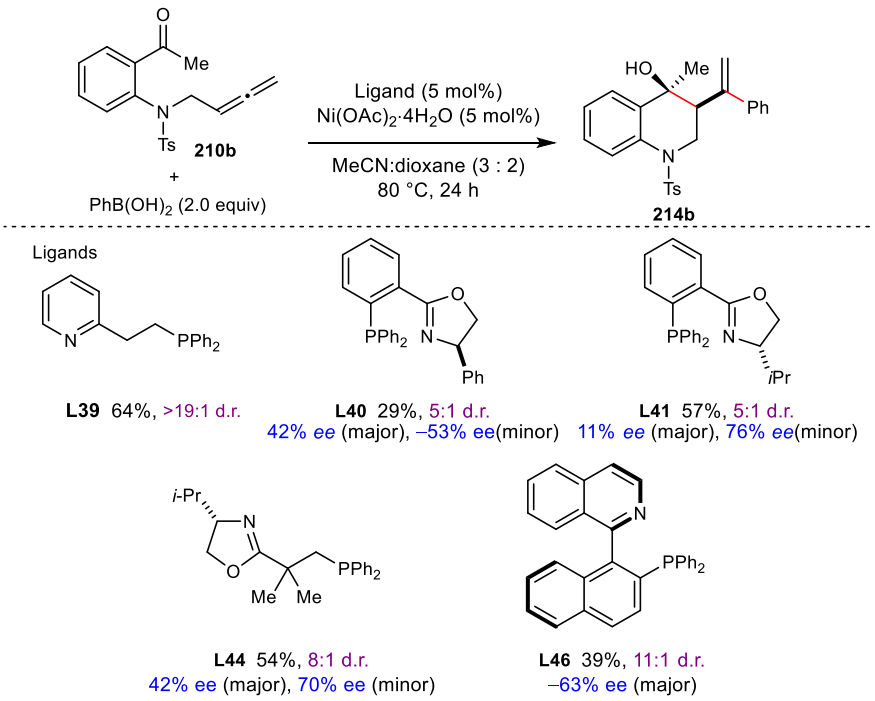
Scheme 140. Initial preparation of tetrahydroquinoline [a]

[a] Reactions were conducted with 0.1 mmol of **210b** in 0.1 M; yield was determined by ^{1}H NMR analysis of the crude reacions using 1,3,5-trimethoxybenzene; enantioselectivities were determined by chiral HPLC analysis.

To improve the diastereo- and enantioselectivity of the reaction, different ligands were examined (Table 15). The reaction using *P*,*N*-ligand **L39** increased the yield of **214b** to 64% as a single diastereomer. Various PHOX ligands gave increased diastereoselectivities but the products were low yielding (29-57%). (*R*)-QUINAP

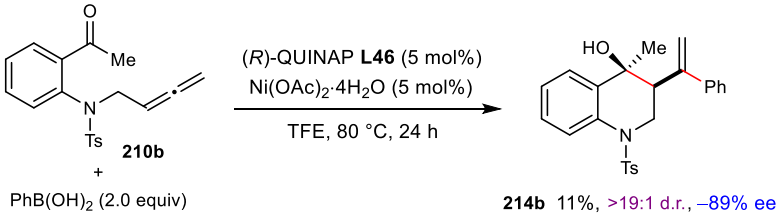
L46 gave product **214b** in a 11:1 ratio of diastereomers and 63% ee of the major diastereomer but only 39% yield.

Table 15. Formation of tetrahydroquinoline with different chiral ligands [a]



[a] Reactions were conducted with 0.1 mmol of **210b**; yield was determined by ^{1}H NMR analysis of the crude reacions using 1,3,5-trimethoxybenzene; enantioselectivities were determined by chiral HPLC analysis.

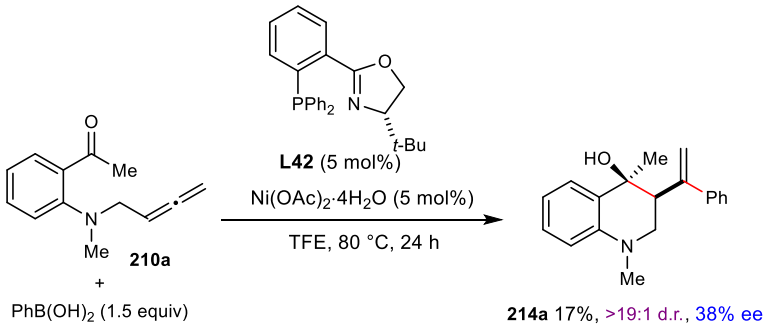
The reaction was then carried out in TFE as the solvent (Scheme 141). The quinoline-ol was obtained in a single diastereomer (>19:1 d.r) and high enantioselectivity (89% ee) but in low yield (11%).



Scheme 141. Formation of tetrahydroquinoline 214b [a]

[a] Reactions were conducted with 0.3 mmol of **210b**; enantioselectivities were determined by chiral HPLC analysis.

Subsequently, allenyl ketone **210a** was subjected to the reaction conditions with $PhB(OH)_2$ (1.5 equiv), $Ni(OAc)_2 \cdot 4H_2O$ (5 mol%) and ligand **L42** (*R*)-*t*-Bu-PHOX (5 mol%) in TFE at 80 °C for 24 h. The reaction afforded **214a** in 17% yield as a single diastereomer and 38% ee (Scheme 142).

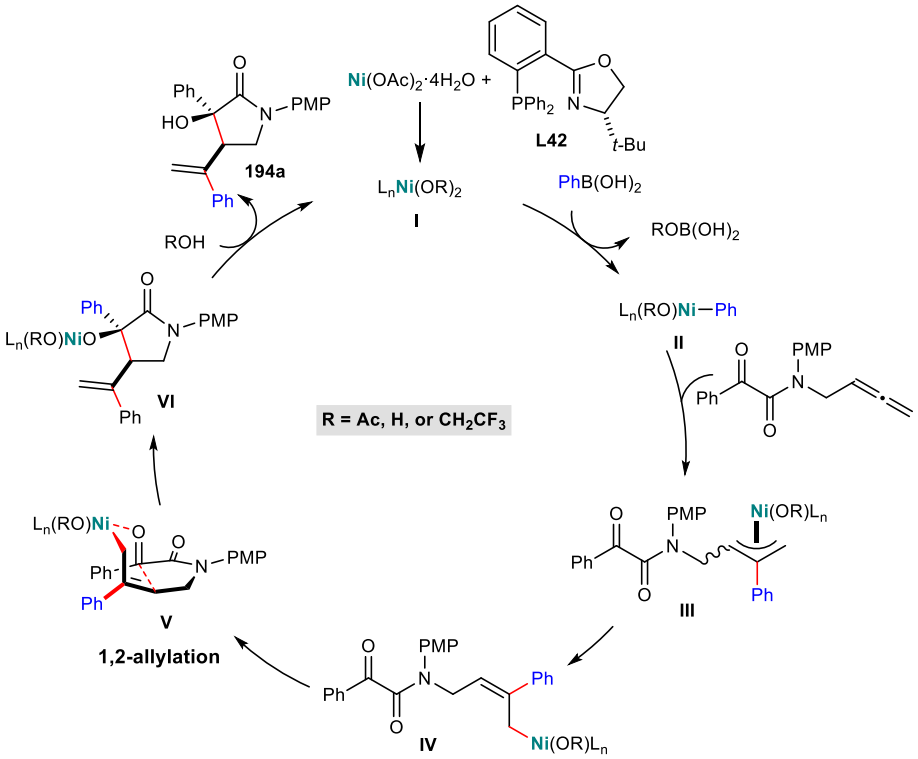


Scheme 142. [a] Formation of quinoline-ol 214a

[a] Reactions were conducted with 0.1 mmol of **210a**; yield was determined by ^1H NMR analysis of the crude reacions using 1,3,5-trimethoxybenzene; enantioselectivities were determined by chiral HPLC analysis.

3.8. Proposed mechanism

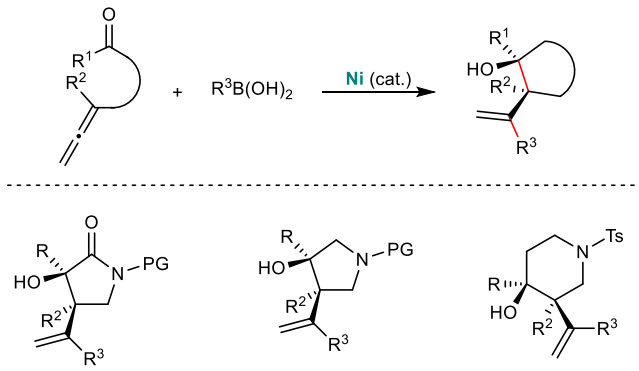
A proposed mechanism for the nickel-catalyzed arylative intramolecular 1,2-allylation, using allenyl ketone **193a** and phenylboronic acid as representative substrates, is shown in Scheme 143. The reaction is initiated with the formation of nickel complex **I** between $Ni(OAc)_2 \cdot 4H_2O$ and chiral ligand **L42**. Subsequently, transmetallation with $PhB(OH)_2$ gives phenylnickel species **II**, followed by migratory insertion of allenyl ketone **193a** to afford the nucleophilic allylnickel species **III**. Phenylnickelation of the less-substituted terminal double bond of the allene of **193a** from the least hindered face would give *Z*-allylnickel species **IV**. An intramolecular nucleophilic allylation of the ketone would furnish nickel alkoxide **VI** *via* a cyclic six-membered chair-like conformation of **V**. Protonolysis of this nickel alkoxide **VI** would release a pyrroldin-2-one and regenerate the active nickel(II) complex **I** to finish the catalytic cycle.



Scheme 143. Proposed mechanism for nickel-catalyzed intramolecular 1,2-allylations

3.9. Future work

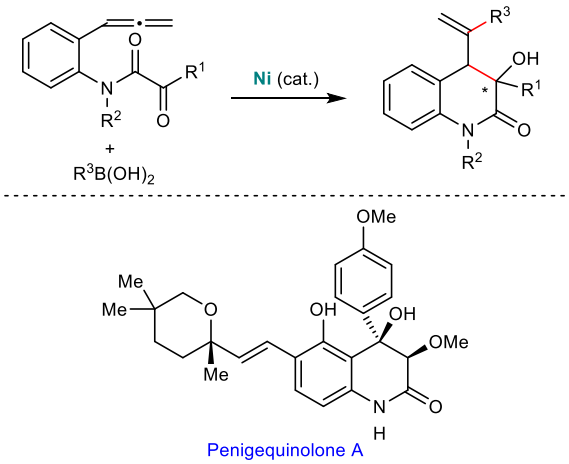
Our method enables the preparation of not only a variety of chiral pyrrolidine-2-ones but also various chiral pyrrolidines and piperidines which are common frameworks that appear in many natural products and bioactive molecules. In this study, the process was explored with only terminal allenes. Therefore, exploration of different substituted allenes would afford two continuous quarternary centers (Scheme 144).



Scheme 144. Examples of further investigation

On the other hand, the reaction has limited success in forming quinolinols. Therefore, further exploration of the substrates and conditions to furnish these core structures is

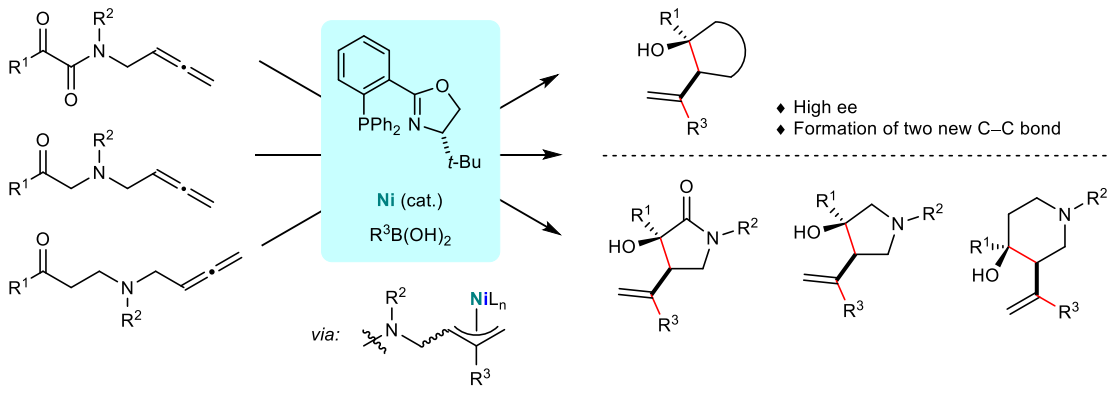
also valuable. The framework also appears in bioactive molecules such as penigequinolone A (Scheme 145).[137]



Scheme 145.

3.10. Conclusion

In summary, a new nickel-catalyzed arylative and alkenylative intramolecular 1,2-allylation has been described through nucleophilic allylnickel intermediates. The carbonickelation of an allene generates the allylnickel intermediate, which cyclizes onto a tethered ketone. This method gives access to prepare a range of pyrrolidine-2-ones with tertiary alcohols in high diastereo- (>19:1) and enantioselectivites (80−99% ee). In addition, it is also broadened to the synthesis of pyrrolidines and piperidines, of those containing a tertiary-alcohol in high diastereo- (>19:1) and up to 99% ee.



Scheme 146. Summary of enantioselective nickel-catalyzed arylative intramolecular 1,2-allylations *via* nucleophilic allylnickel species

4. Experimental: Enantioselective nickel-catalyzed arylative intramolecular 1,4-allylations

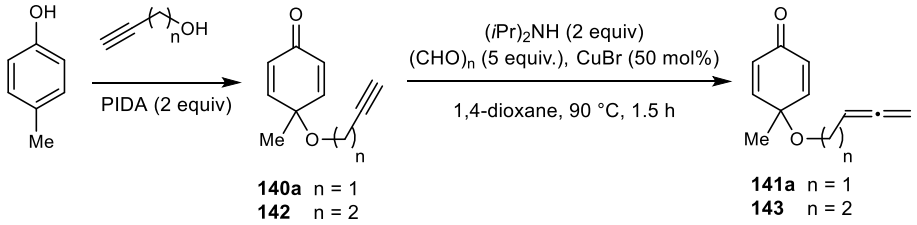
4.1. General information

All air-sensitive reactions were carried out under a nitrogen atmosphere using oven-dried apparatus. Unless stated otherwise, all solvents used in reactions were anhydrous. THF, DMF and MeCN were dried and purified by passage through activated alumina columns using a solvent purification system. Anhydrous 1,4-dioxane was obtained from commercial sources. All commercially available reagents were used as received unless otherwise stated. Arylboronic acids were used as received unless the sample contained >10% boroxine as determined by ^{1}H NMR analysis. In this case, the boronic acid was stirred in a mixture of Et_2O and water for 30 minutes. The organic phase was separated, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give the corresponding boronic acid which was used without further purification. Petroleum ether refers to 40–60 °C petroleum ether. Flash column chromatography was carried out using silica gel (Fisher Scientific 60Å particle size 35–70 micron) or using a Interchim Puriflash 430 series purification system with IR-50SI 50μm pre-packed columns. 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 either a Shimadzu IRAffinity-1 or a Nicolet Avatar 360 FT instrument on the neat compound. ^{1}H and ^{13}C NMR spectra were referenced to external tetramethylsilane *via* the residual protonated solvent (^{1}H) or the solvent itself (^{13}C). All chemical shifts are reported in parts per million (ppm). For $CDCl_3$, the shifts are referenced to 7.27 ppm for ^{1}H NMR spectroscopy and 77.0 ppm for ^{13}C NMR spectroscopy. Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. High-resolution mass spectra were recorded using electrospray ionization (ESI). X-ray diffraction data were collected by Dr. W. Lewis at 120 K on either an Agilent SuperNova diffractometer using MoKα radiation at 0.71 Å or on an Agilent GV1000 using CuKα radiation, and refined in SHELXTL. Chiral HPLC analysis was performed on an Agilent 1290 series or Agilent 1260 series instrument using 4.6 × 250 mm columns. 2-[2-

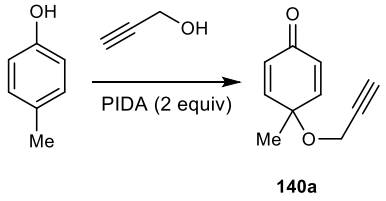
(Diphenylphosphino)ethyl]pyridine (**L39**, Sigma-Aldrich product 695599) was used as an achiral ligand to obtain authentic racemic compounds.

4.2. Preparation of allenyl cyclohexa-2,5-dienones

Preparation of allenyl cyclohexa-2,5-dienone with *O*-tethers

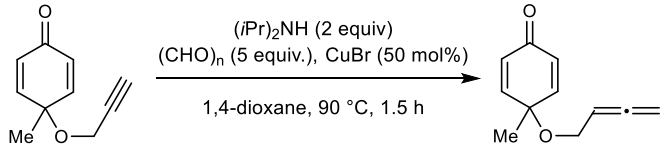


4-Methyl-4-(prop-2-yn-1-yloxy)cyclohexa-2,5-dien-1-one (140a).



To a well-stirred solution of *p*-cresol (2.00 g, 18.5 mmol) in propargyl alcohol (24.7 mL, 42.4 mmol) was added PIDA (11.9 g, 37.0 mmol) at 0 °C. The reaction was stirred at 0 °C for 30 min. The reaction was then diluted with CH_2Cl_2 (20 mL), washed with solution NaOH 2 M (2 x 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The mixture was purified by column chromatography (20% EtOAc/petroleum ether) to give alkyne **140a** (1.51 g, 50 %) as a yellow sticky oil.[109] R_f = 0.38 (20% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86−6.78 (2H, m, 2 × O=CCH=C**H**), 6.34−6.27 (2H, m, 2 × O=CC**H**), 3.99 (2H, d, *J* = 2.5 Hz, C**H₂**), 2.47 (1H, t, *J* = 2.4 Hz, ≡C**H**). 1.49 (3H, s, C**H₃**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.9 (C), 150.6 (2 × CH), 130.6 (2 × CH), 80.2 (C), 74.9 (CH), 73.3 (C), 53.7 (CH_2), 26.3 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{10}H_{11}O_2]^+$ $[M+H]^+$: 163.0754, found: 163.0744. Spectroscopic data consistent with those reported previously. [138]

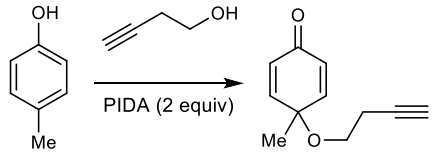
4-(Buta-2,3-dien-1-yloxy)-4-methylcyclohexa-2,5-dien-1-one (141a).



140a **141a**

To a solution of alkyne **140a** [138] (1.78 g, 12.0 mmol) in 1,4-dioxane (40 mL) at room temperature under inert atmosphere was added paraformaldehyde (1.82 g, 61.0 mmol), CuBr (871 mg, 6.0 mmol), and diisopropylamine (3.41 mL, 24.3 mmol). The reaction was heated at 90 °C for 1.5 h, cooled to room temperature, filtered through a pad of celite using EtOAc as eluent, and concentrated under reduced pressure. The mixture was purified by column chromatography (20% EtOAc/petroleum ether) to give allene **141a** (589 mg, 30%) as a pale yellow oil. R_f = 0.60 (40% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85−6.79 (2H, m, 2 × O=CCH=C**H**), 6.34−6.26 (2H, m, 2 × O=CC**H**), 5.22 (1H, quin, *J* = 6.8 Hz, C**H**=C=CH_2), 4.78 (2H, dt, *J* = 6.5, 2.4 Hz, =C**H**$_2$), 3.88 (2H, dt, *J* = 7.1, 2.4 Hz, OC**H**$_2$), 1.46 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.2 (C), 185.1 (C), 151.7 (2 × CH), 129.9 (2 × CH), 88.4 (CH), 76.0 (CH_2), 72.6 (C), 63.9 (CH_2), 26.3 (CH_3). Spectroscopic data consistent with those reported previously.[109]

4-(But-3-yn-1-yloxy)-4-methylcyclohexa-2,5-dien-1-one (142)

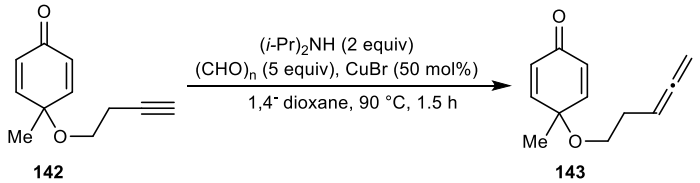


142

To a well-stirred solution of *p*-cresol (6.00 g, 55.5 mmol) in propargyl alcohol (50 mL) was added PIDA (21.5 g, 66.6 mmol) at 0 °C. The reaction was stirred at 0 °C for 45 min. The reaction was then diluted with CH_2Cl_2 (2 × 50 mL), washed with solution saturated of $NaHCO_3$ (2 x 50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The mixture was purified by column chromatography (20% EtOAc/petroleum ether) to give alkyne **142** (1.97 g, 20%) as a colorless oil. R_f = 0.40 (20% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83−6.79 (2H, m, 2 × O=CCH=C**H**), 6.32−6.29 (2H, m, 2 × O=CC**H**), 3.43 (2H, t, *J* = 6.8 Hz, OC**H**$_2$), 2.43

(2H, td, J = 6.8, 2.7 Hz, C**H**$_2$C≡), 1.99 (1H, t, J = 2.7 Hz, ≡C**H**), 1.46 (3H, s, C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.1 (C), 151.6 (2 × CH), 130.2 (2 × CH), 80.9 (C), 72.6 (C), 69.5 (CH), 63.8 (CH_2), 26.3 (CH_3), 20.5 (CH_2). Spectroscopic data consistent with those reported previously.[138]

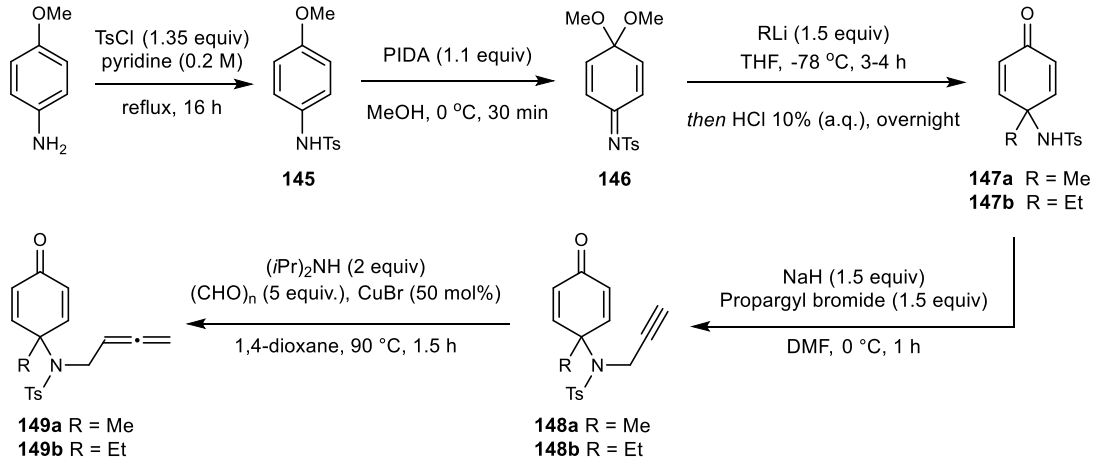
4-Methyl-4-(penta-3,4-dien-1-yloxy)cyclohexa-2,5-dien-1-one (143)



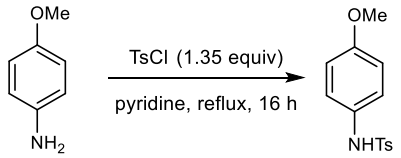
142 143

To a solution of alkyne **142**[138] (1.34 g, 7.60 mmol) in 1,4-dioxane (38 mL) at room temperature under inert atmosphere was added paraformaldehyde (1.14 g, 38.0 mmol), CuBr (546 mg, 3.80 mmol), and diisopropylamine (2.13 mL, 15.2 mmol). The reaction was heated at 90 °C for 1.5 h, cooled to room temperature, filtered through a pad of celite using EtOAc as eluent, and concentrated under reduced pressure. The mixture was purified by column chromatography (20% EtOAc/petroleum ether) to give *allene* **143** (252 mg, 17%) as a yellow oil. R_f = 0.57 (20% EtOAc/petroleum ether); IR 2981, 2928, 2967, 1956 (C=C=C), 1669 (C=O), 1631, 1515, 1438, 1382, 1178, 1084, 858, 727, 702, 541, 509, 461 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83−6.77 (2H, m, 2 × O=CCH=C**H**), 6.31−6.25 (2H, m, 2 × O=CC**H**), 5.09 (1H, quin, J = 6.8 Hz, C**H**=C=CH_2), 4.68 (2H, dt, J = 6.5, 3.1 Hz, =C**H**$_2$), 3.37 (2H, t, J = 6.7 Hz, OC**H**$_2$), 2.25−2.20 (2H, m, C**H**$_2$CH=), 1.43 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.9 (C), 185.2 (C), 152.2 (2 × CH), 130.0 (2 × CH), 86.3 (CH), 75.1 (CH_2), 72.4 (C), 65.0 (CH_2), 29.3 (CH_2), 26.4 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{12}H_{14}NaO_2]^+$ $[M+Na]^+$: 213.0886, found: 213.0885.

Preparation of allenyl cyclohexa-2,5-dienone with *N*-tethers 149a and 149b

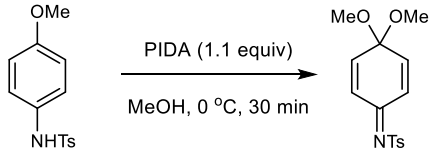


***N*-(4-methoxyphenyl)-4-methylbenzenesulfonamide (145)**



To a solution of *p*-anisidine (5.00 g, 40.6 mmol) in pyridine (200 mL) was added tosylchloride (10.5 g, 54.8 mmol). The reaction was refluxed for 16 h and cooled to room temperature. The solvent was removed under reduced pressure and the crude residue was extracted with EtOAc (2 x 100 mL) and washed with HCl 1 M (2 x 100 mL), water and brine. The organic layer was dried over $MgSO_4$ and concentrated under the pressure. The crude residue was purified by column chromatography (30% EtOAc/petreoleum ether) to give amine **145** as a pale yellow solid (10.8, 96%). R_f = 0.44 (30% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62−7.57 (2H, m, Ar**H**), 7.25−7.18 (2H, m, Ar**H**), 7.00−6.95 (2H, m, Ar**H**), 6.78−6.72 (2H, m, Ar**H**), 6.55 (1H, s, N**H**), 3.76 (3H, s, OC**H**$_3$), 2.39 (3H, s, ArC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0 (C), 143.6 (C), 136.0 (C), 129.5 (2 × CH), 128.8 (C), 127.3 (2 × CH), 125.5 (2 × CH), 114.4 (2 × CH), 55.4 (CH_3), 21.5 (CH_3). Spectroscopic data consistent with those reported previously. [139]

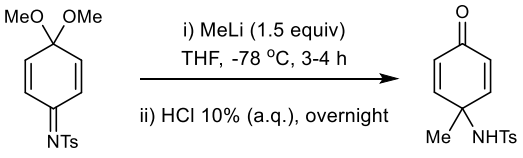
***N*-(4,4-dimethoxycyclohexa-2,5-dien-1-ylidene)-4-methylbenzenesulfonamide (146)**



145 **146**

To a solution of tosyl amine **145** (10.5 g, 40.4 mmol) in methanol (133 mL) was added PIDA (14.3 g, 44.4 mmol) at 0 °C. The reaction was stirred at 0 °C for 30 min and the suspension solution was formed. The white solid was filtered and washed with cold MeOH (2 × 50 mL), dried under reduced pressure to give imine **146** (11.1 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (2H, d, *J* = 8.4 Hz, Ar**H**), 7.63 (1H, dd, *J* = 10.6, 2.2 Hz, O=CCH=C**H**), 7.35 (2H, d, *J* = 8.0 Hz, Ar**H**), 6.75 (2H, ddd, *J* = 25.5, 10.4, 2.8 Hz, 2 × O=CC**H**), 6.36 (1H, dd, *J* = 10.2, 2.2 Hz, O=CCH=C**H**), 3.37 (6H, s, 2 × OC**H**$_3$), 2.45 (3H, s, ArC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1 (C), 144.1 (C), 143.3 (C), 142.1 (CH), 137.1 (CH), 130.7 (CH), 129.6 (2 × CH), 127.3 (2 × CH), 123.3 (CH), 91.9 (C), 50.4 (CH_3), 21.6 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{15}H_{18}NO_4S]^+$ $[M+H]^+$: 308.0951, found: 308.0958. Spectroscopic data consistent with those reported previously.[140]

4-methyl-*N*-(1-methyl-4-oxocyclohexa-2,5-dien-1-yl)benzenesulfonamide (147a)

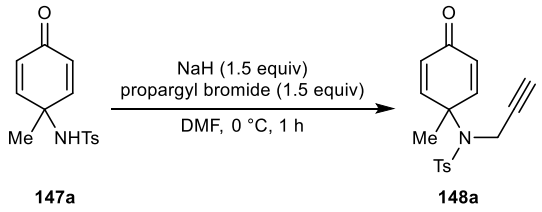


146 **147a**

To a solution of imine **146** [140] (5.51 g, 18.0 mmol) in THF (90 mL) was added MeLi (16.8 mL, 26.9 mmol, 1.6 M in hexane) dropwise at -78 °C, then the reaction was stirred for 2.5 h. The reaction was monitored by TLC and then added HCl 10% (90 mL). The mixture was spontaneously warmed up to room temperature and stirred overnight. Then the volatiles were removed under reduced pressure. The crude mixture was washed with $NaHCO_3$ (250 mL), extracted with Et_2O (200 mL). The combined organics were washed with brine (2 × 75 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The mixture was purified by column

chromatography (55% EtOAc/petroleum ether) to furnish a sulfoamide **147a** as a white solid (3.47 g, 70%). R_f = 0.20 (20% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (2H, d, *J* = 8.3 Hz, Ar**H**), 7.29−7.27 (3H, m, Ar**H**), 6.67−6.63 (2H, m, 2 × O=CCH=C**H**), 6.07−6.03 (2H, m, 2 × O=CC**H**), 5.03 (1H, s, N**H**), 2.43 (3H, s, ArC**H$_3$**), 1.45 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.6 (C), 150.5 (2 × CH), 144.2 (C), 137.3 (C), 129.6 (2 × CH), 128.10 (2 × CH), 127.7 (2 × CH), 54.4 (C), 27.7 (CH_3), 21.6 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{14}H_{15}NNaO_3S]^+$ $[M+Na]^+$: 300.0665, found: 300.0670. Spectroscopic data consistent with those reported previously.[141]

4-Methyl-*N*-(1-methyl-4-oxocyclohexa-2,5-dien-1-yl)-*N*-(prop-2-yn-1-yl)benzene-1-sulfonamide (148a)

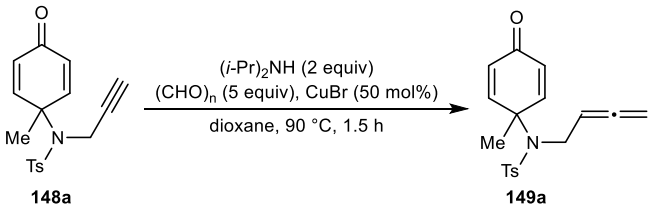


147a **148a**

To a solution of sulfonamide **147a**[141] (2.77 g, 10.0 mmol) in DMF (20 mL) at 0 °C under inert atmosphere was added NaH (60% dispersion in mineral oil, 0.60 g, 15 mmol) portionwise. Propargyl bromide (80% in toluene, 1.68 mL, 15.0 mmol) was added and the mixture was stirred for 1 h. The reaction was diluted with EtOAc (30 mL), washed with saturated aqueous NH_4Cl solution (25 mL) and brine/H_2O (1:1, 40 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The mixture was purified by column chromatography (40% EtOAc/petroleum ether) to give *alkyne* **148a** (2.70 g, 87%) as a white solid. R_f = 0.43 (40% EtOAc/petroleum ether); m.p. 123-124 °C (Et_2O); IR 3312, 3222, 3051, 2974, 2919, 2112 (C≡C), 1670 (C=O), 1629, 1314, 1148, 1088, 1030, 861, 815, 695, 547 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (2H, d, *J* = 8.0 Hz, Ar**H**), 7.30 (2H, d, *J* = 8.0 Hz, Ar**H**), 7.03 (2H, d, *J* = 10.4 Hz, 2 × O=CCH=C**H**), 6.17 (2H, d, *J* = 10.0 Hz, 2 × O=CC**H**), 4.27 (2H, d, *J* = 2.4 Hz, C**H$_2$**), 2.44 (3H, s, ArC**H**$_3$), 2.36 (1H, t, *J* = 2.4 Hz, ≡C**H**), 1.61 (3H, s, NCC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.3 (C), 151.1 (2 × CH), 144.0 (C), 138.5 (C), 129.6 (2 × CH), 128.0 (2 × CH), 127.7 (2 × CH), 80.3 (C), 73.7 (CH),

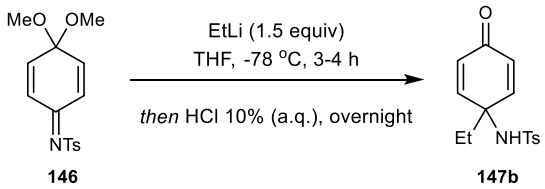
60.1 (C), 36.3 (CH_2), 25.8 (CH_3), 21.6 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{17}H_{17}NNaO_3S]^+$ $[M + Na]^+$: 338.0821, found: 338.0824.

_N_-(Buta-2,3-dien-1-yl)-4-methyl-_N_-(1-methyl-4-oxocyclohexa-2,5-dien-1-yl)benzene-1-sulfonamide (149a)



To a solution of sulfonamide **148a** (2.90 g, 8.50 mmol) in 1,4-dioxane (45 mL) at room temperature under inert atmosphere was added paraformaldehyde (1.30 g, 42.5 mmol), CuBr (0.61 g, 4.27 mmol), and diisopropylamine (2.4 mL, 17 mmol). The reaction was heated at 90 °C for 1.5 h, cooled to room temperature, filtered through a pad of celite using EtOAc as eluent, and concentrated under reduced pressure. The mixture was purified by column chromatography (40% EtOAc/petroleum ether) to give *allene* **149a** (1.30 g, 45%) as a pale yellow solid. R_f = 0.63 (40% EtOAc/petroleum ether); m.p. 118-120 °C (Et_2O); IR 2979, 2924, 1956 (C=C=C), 1670 (C=O), 1629, 1445, 1309, 1183, 1146, 1085, 864, 812, 699, 648, 330, 529, 513 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (2H, d, *J* = 8.4 Hz, Ar**H**), 7.32 (2H, d, *J* = 8.4 Hz, Ar**H**), 6.94 (2H, d, *J* = 10.0 Hz, 2 × O=CCH=C**H**), 6.17 (2H, d, *J* = 10.0 Hz, 2 × O=CC**H**), 5.31 (1H, quin, *J* = 6.4 Hz, C**H**=C=CH_2), 4.76 (2H, dt, *J* = 6.8, 2.4 Hz, =C**H**$_2$), 4.01 (2H, dt, *J* = 6.8, 2.8 Hz, NC**H**$_2$), 2.44 (3H, s, ArC**H**$_3$), 1.57 (3H, s, NCC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.1 (C), 184.5 (C), 151.5 (2 × CH), 143.8 (C), 139.3 (C), 129.7 (2 × CH), 127.8 (2 × CH), 127.3 (2 × CH), 89.4 (CH), 76.7 (C), 60.0 (CH_2), 46.8 (CH_2), 26.0 (CH_3), 21.5 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{18}H_{19}NNaO_3S]^+$ $[M+Na]^+$: 352.0978, found: 352.0978.

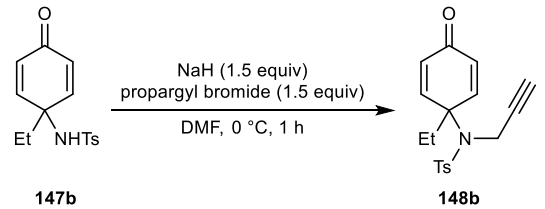
***N*-(1-ethyl-4-oxocyclohexa-2,5-dien-1-yl)-4-methylbenzenesulfonamide (147b)**



146 **147b**

To a solution of imine **146** [140] (3.69 g, 12.0 mmol) in THF (40 mL) was added EtLi (0.5 M in benzene, 36.0 mL, 18.0 mmol) dropwise at -78 °C, then the reaction was stirred for 3.0 h. The reaction was monitored by TLC and then added HCl 10% (60 mL). The mixture was spontaneously warmed up to room temperature and stirred overnight. Then the volatiles were removed under reduced pressure. The crude mixture was washed with $NaHCO_3$ (200 mL), extracted with Et_2O (250 mL). The combined organics were washed with brine (2 × 75 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The mixture was purified by column chromatography (60% EtOAc/petroleum ether) to furnish a sulfoamide **147b** as a white solid (1.06 g, 30%). R_f = 0.20 (20% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69−7.63 (2H, m, Ar**H**), 7.30−7.22 (3H, m, Ar**H**), 6.56−6.50 (2H, m, 2 × O=CCH=C**H**), 6.14−6.06 (2H, m, 2 × O=CC**H**), 5.02 (1H, s, N**H**), 2.43 (3H, s, ArC**H$_3$**), 1.76 (2H, q, *J* = 7.5 Hz, C**H$_2$**CH$_3$), 0.80 (3H, t, *J* = 7.5 Hz, CH$_2$C**H$_3$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.0 (C), 149.2 (2 × CH), 144.2 (C), 137.4 (C), 129.60 (2 × CH), 129.58 (2 × CH), 127.8 (2 × CH), 58.1 (C), 33.4 (CH_2), 21.6 (CH_3), 7.5 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{15}H_{17}NNaO_3S]^+$ $[M+Na]^+$: 314.0821, found: 314.0831. Spectroscopic data consistent with those reported previously.[141]

***N*-(1-Ethyl-4-oxocyclohexa-2,5-dien-1-yl)-4-methyl-*N*-(prop-2-yn-1-yl)benzene-1-sulfonamide (148b)**

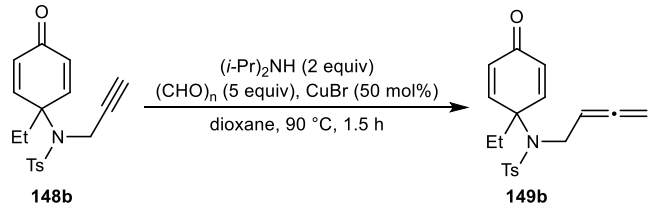


147b **148b**

To a solution of sulfonamide **147b**[141] (1.06 g, 3.64 mmol) in DMF (7.5 mL) at 0 °C under inert atmosphere was added NaH (60% dispersion in mineral oil, 0.22 g, 5.46 mmol) was added portionwise. Propargyl bromide (80% in toluene, 0.60 mL, 5.46

mmol) was added and the mixture was stirred for 1 h. The mixture was diluted with EtOAc (15 mL), washed with saturated aqueous NH_4Cl solution (20 mL) and brine/H_2O (1:1, 20 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The mixture was purified by column chromatography (30% EtOAc/petroleum ether) to give *alkyne* **148b** (920 mg, 77%) as a pale yellow solid. R_f = 0.37 (30% EtOAc/petroleum ether); m.p. 92-94 °C (Et_2O); IR 3273, 2970, 2939, 2882, 2118 (C≡C), 1665 (C=O), 1628, 1337, 1156, 1088, 904, 811, 649, 543 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (2H, d, *J* = 8.2 Hz, Ar**H**), 7.29 (2H, d, *J* = 8.2 Hz, Ar**H**), 6.93 (2H, d, *J* = 10.2 Hz, 2 × O=CCH=C**H**), 6.24 (2H, d, *J* = 10.2 Hz, 2 × O=CC**H**), 4.32 (2H, d, *J* = 2.4 Hz, NC$\mathbf{H}_2$), 2.44 (3H, s, ArC$\mathbf{H}_3$), 2.36 (1H, t, *J* = 2.4 Hz, ≡C**H**), 2.05 (2H, q, *J* = 7.2 Hz, C$\mathbf{H}_2CH_3$), 0.74 (3H, t, *J* = 7.2 Hz, $CH_2C\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.9 (C), 149.1 (2 × CH), 144.0 (C), 138.5 (C), 129.8 (2 × CH), 129.5 (2 × CH), 127.8 (2 × CH), 80.4 (C), 73.7 (CH), 64.5 (C), 36.0 (CH_2), 29.4 (CH_2), 21.6 (CH_3), 8.4 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{18}H_{19}NNaO_3S]^+$ $[M+Na]^+$: 352.0978, found: 352.0976.

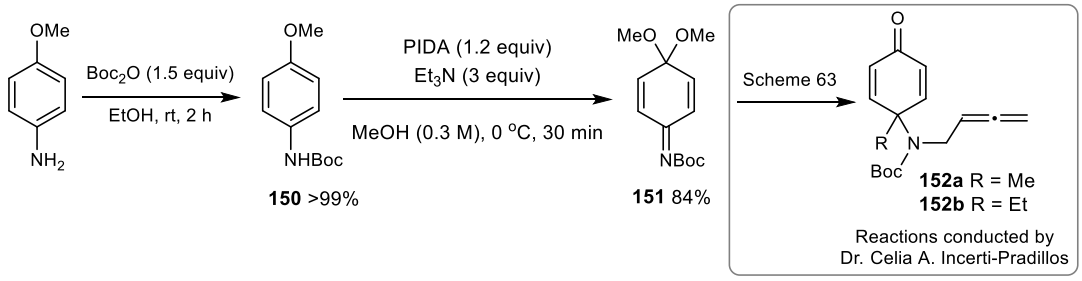
_N_-(Buta-2,3-dien-1-yl)-_N_-(1-ethyl-4-oxocyclohexa-2,5-dien-1-yl)-4-methylbenzene -1-sulfonamide (149b)



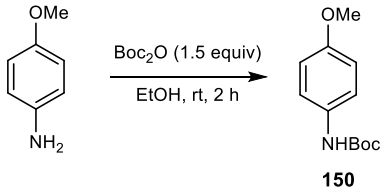
To a solution of alkyne **148b** (861 mg, 2.62 mmol) in 1,4-dioxane (13 mL) at room temperature under inert atmosphere was added paraformaldehyde (398 mg, 13.1 mmol), CuBr (188 mg, 1.30 mmol), and diisopropylamine (0.74 mL, 5.25 mmol). The reaction was heated at 90 °C for 1.5 h, cooled to room temperature, filtered through a pad of celite using EtOAc as eluent, and concentrated under reduced pressure. The mixture was purified by column chromatography (40% EtOAc/petroleum ether) to give *allene* **149b** (295 mg, 33%) as a yellow solid. R_f = 0.56 (40% EtOAc, 60% petroleum ether); m.p. 110-112 °C (Et_2O); IR 2968, 2934, 2925, 1952 (C=C=C), 1670 (C=O), 1632, 1437, 1305, 1144, 1091, 860, 814, 701, 647, 551, 517 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (2H, d, *J* = 8.4 Hz, Ar**H**),

7.28 (2H, d, *J* = 8.4 Hz, Ar**H**), 6.82 (2H, d, *J* = 10.4 Hz, 2 × O=CCH=C**H**), 6.24 (2H, d, *J* = 10.4 Hz, 2 × O=CC**H**), 5.31 (1H, quin, *J* = 6.8 Hz, C**H**=C=CH_2), 4.75 (2H, dt, *J* = 6.4, 2.8 Hz, =C**H**$_2$), 4.03 (2H, dt, *J* = 6.8, 2.4 Hz, NC**H**$_2$), 2.42 (3H, s, ArC**H**$_3$), 2.01 (2H, q, *J* = 7.6 Hz, C**H**$_2$$CH_3$), 0.70 (3H, t, *J* = 7.2 Hz, CH_2C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.8 (C), 185.0 (C), 149.2 (2 × CH), 143.7 (C), 139.2 (C), 129.62 (2 × CH), 129.56 (2 × CH), 127.2 (2 × CH), 89.5 (CH), 76.7 (C), 64.5 (CH_2), 46.6 (CH_2), 29.5 (CH_2), 21.5 (CH_3), 8.4 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{19}H_{21}NNaO_3S]^+$ $[M+Na]^+$: 366.1134, found: 366.1132.

Preparation of allenyl cyclohexa-2,5-dienone with *N*-tethers

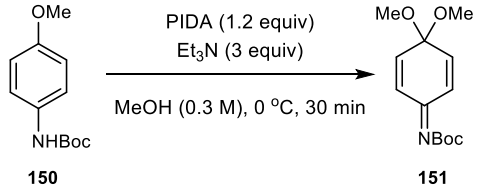


***tert*-butyl (4-methoxyphenyl)carbamate (150)**



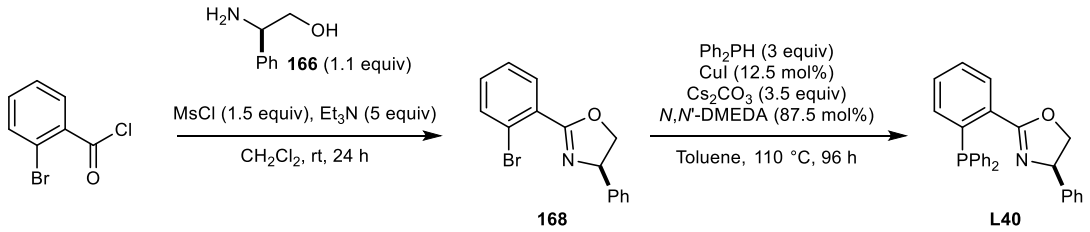
To a solution of *p*-anisidine (4.93 g, 40.0 mmol) in ethanol (84 mL) was added di-*tert*-butyl dicarbonate (13.3 g, 60.0 mmol). The reaction was left to stir for 2 h at room temperature. The solvent was removed under reduced pressure. The crude residue was purified by column chromatography (20% EtOAc/petreoleum ether) and then recrystallized by dissolving in a minimum amount of EtOAc and adding petreoleum ether until achieving a 9:1 ratio to give amine **150** as white needle crystals (10.5, >99%). R_f = 0.48 (30% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.26 (2H, m, Ar**H**), 6.86−6.82 (2H, m, Ar**H**), 6.34 (1H, s, N**H**), 3.79 (3H, s, OC**H**$_3$), 1.52 (9H, s, (C**H**$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7 (C), 153.2 (C), 131.4 (C), 120.6 (2 × CH), 114.2 (2 × CH), 80.2 (C), 55.5 (CH_3), 28.4 (3 × CH_3). Spectroscopic data consistent with those reported previously.[142]

***tert*-butyl (4,4-dimethoxycyclohexa-2,5-dien-1-ylidene)carbamate (151)**

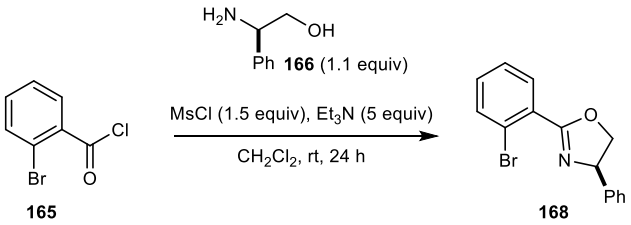


A solution of PIDA (7.73 g, 24.0 mmol) in methanol (110 mL) was added to a solution of amine **150** [142] (4.47 g, 20.0 mmol), Et_3N (8.40 mL, 60.0 mmol) in methanol (50 mL) at 0 °C. The reaction was left to warm up to room temperature sponstaneouly and stirred for 16 h. The reaction was quenched with saturated solution of $NaHCO_3$ (100 mL). The solution was filtered off and extracted with EtOAc (2 × 100 mL). The organic phase was combined, washed with brine (5 × 70 mL), dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude was then purified by column chromatography on silica gel (ratio of EtOAc/petroleum ether/Et_3N in 19:80:1) to give imine **151** (4.27 g, 84%). R_f = 0.63 (30% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60−6.47 (2H, m, 2 × N=CCH=C**H**), 6.47−6.40 (2H, m, 2 × N=CC**H**), 3.34 (6H, s, 2 × OC**H₃**), 1.57 (9H, s, (C**H₃**)**₃**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.2 (C), 156.4 (C), 139.6 (CH), 138.8 (CH), 130.8 (CH), 122.9 (CH), 93.1 (C), 82.9 (C), 50.3 (2 × CH_3), 28.1 (3 × CH_3). Spectroscopic data consistent with those reported previously.[142]

Preparation of ligand *(R)*-Ph-PHOX

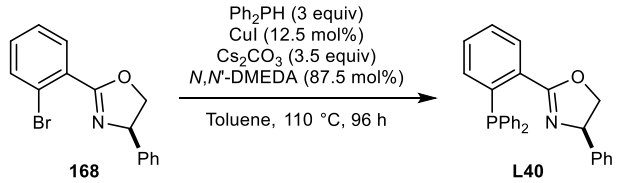


***(R)*-2-(2-bromophenyl)-4-phenyl-4,5-dihydrooxazole (168)**



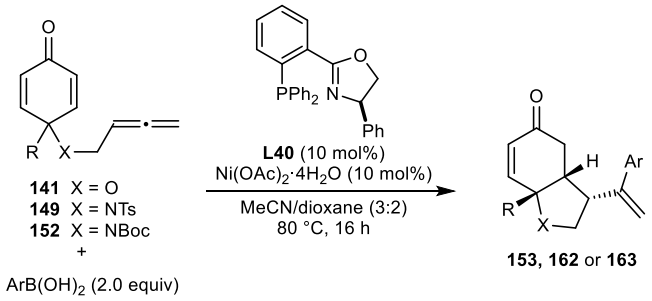
To an aminoalcohol **166** (5.00 g, 36.4 mmol) suspended in dried CH_2Cl_2 (150 mL) was added Et_3N (20.3 mL, 146 mmol). The solution was cooled to 0 °C and 2-bromobenzoylchloride **165** (5.68 mL, 40.1 mmol) was added dropwise. Then the mixture was left to warm gradually to room temperature for 16 h. The reaction was cooled to 0°C and MsCl was added dropwise and monitored by TLC. On completion, the solution was quenched with saturated NH_4Cl solution (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL), dried over Na_2SO_4, concentrated under reduced pressure. The crude was purified by column chromatography (30% EtOAc/petroleum ether) to give the title compound **168** (3.80 g, 35%). R_f = 0.60 (30% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (1H, dd, *J* = 7.6, 1.9 Hz, Ar**H**), 7.69 (1H, dd, *J* = 7.9, 1.3 Hz, Ar**H**), 7.41−7.29 (7H, m, Ar**H**), 5.46 (1H, dd, *J* = 10.2, 8.4 Hz, NC**H**Ph), 4.84 (1H, dd, *J* = 10.2, 8.4 Hz, OC**H**$_2$), 4.31 (1H, app t, *J* = 8.4 Hz, OC**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2 (C), 142.0 (C), 133.9 (CH), 131.8 (CH), 131.5 (CH), 129.7 (C), 128.7 (2 × CH), 127.6 (CH), 127.1 (CH), 126.7 (2 × CH), 121.9 (C), 75.0 (CH_2), 70.5 (CH). Spectroscopic data consistent with those reported previously.[143]

(*R*)-2-(2-(diphenylphosphaneyl)phenyl)-4-phenyl-4,5-dihydrooxazole (L40)



To a mixture of *N*,*N*'-DMEDA (0.32 mL, 2.90 mmol), CuI (79 mg, 0.41 mmol), Ph_2PH (1.73 mL, 9.93 mmol) in toluene (25 mL) under inert atmosphere was added a solution of oxazoline **168** (1.00 g, 3.31 mmol) in toluene (5 mL) dropwise. Then Cs_2CO_3 (3.77 g, 11.6 mmol) was added to solution and the reaction was stirred at 110 °C for 96 h. The reaction was cooled and filtered over celite and concentrated under reduced pressure. The crude was purified by column chromatography (10% EtOAc/petroleum ether) to give phosphinooxazoline **L40** (751 mg, 56%). R_f = 0.24 (10% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) 8.04−7.98 (1H, m, Ar**H**), 7.41−7.19 (15H, m, Ar**H**), 6.95−6.91 (3H, m, Ar**H**), 5.23 (1H, dd, *J* = 10.1, 9.1 Hz, NC**H**), 4.57 (1H, dd, *J* = 10.2, 8.3 Hz, OC**H**$_2$), 3.95 (1H, dd, *J* = 9.0, 8.3 Hz, OC**H**$_2$); ^{31}P NMR (162 MHz, $CDCl_3$) δ -5.42. Spectroscopic data consistent with those reported previously.[143]

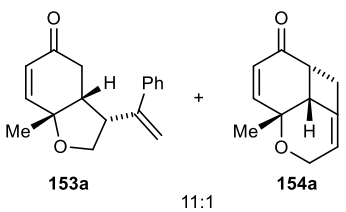
4.3. Enantioselective nickel-catalyzed arylative intramolecular 1,4-allylations: General procedure



An oven-dried microwave vial fitted with a stirrer bar was charged with $Ni(OAc)_2{\cdot}4H_2O$ (7.5 mg, 0.03 mmol) and (*R*)-Ph-PHOX (**L40**, 12.2 mg, 0.03 mmol). The vial was capped with a crimp cap PTFE seal and purged with a stream of N_2. MeCN (0.9 mL) and 1,4-dioxane (0.6 mL) were added and the mixture was stirred at 80 °C for 15 min. In a separate vial, the allenyl cyclohexa-2,5-dienone **141, 149** or **152** (0.30 mmol) and the arylboronic acid (0.60 mmol) were weighed out and the vial was purged with a stream of N_2. MeCN (0.45 mL) and 1,4-dioxane (0.3 mL) were added. The resulting solution was then transferred to the first microwave vial *via* syringe. The vial originally containing the substrate was rinsed with additional MeCN (0.45 mL) and 1,4-dioxane (0.3 mL), and the rinsing solution was transferred to the first microwave vial *via* syringe. The reaction was stirred at 80 °C for 18 h, cooled to room temperature, filtered through a plug of silica, and concentrated under reduced pressure. The residue was purified by flash column chromatography to give the title compound **153** or **162** or **163**. The relative and absolute configurations of **162a-d**, **162g-h** were determined by X-ray crystallography, and those of the remaining products were assigned by analogy.

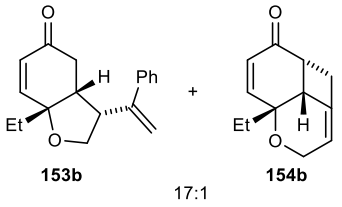
4.4. Exploration of allenyl substrate scope

4.4.1. Hexahydrobenzofuran-5-ones



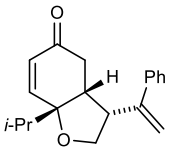
(3*R*,3a*R*,7a*R*)-7a-Methyl-3-(1-phenylethenyl)-2,3,3a,4,5,7a-hexahydro-1-benzofuran-5-one (153a). The General Procedure was followed using allenyl cyclohexa-2,5-dienone **141a** (52.8 mg, 0.30 mmol) and phenylboronic acid (73.1 mg, 0.60 mmol), and purified

by column chromatography (30% EtOAc/petroleum ether) to give an 11:1 inseparable mixture of *arylative cyclization product* **153a** and *cyclobutane* **154b** as a colorless oil (59.7 mg, 74%, adjusted yield of **153a**). R_f = 0.23 (20% EtOAc/petroleum ether); $[\alpha]_D^{25}$ −77.8 (*c* 0.72, $CHCl_3$); IR 2970, 2927, 1681 (C=O), 1495, 1371, 1049, 901, 779, 705, 531 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.30 (5H, m, Ar**H**), 6.60 (1H, dd, *J* = 10.4 Hz, O=CCH=C**H**), 5.97 (1H, dd, *J* = 10.4 Hz, O=CC**H**=), 5.42 (1H, s, =C$\mathbf{H}_2$), 4.95 (1H, s, =C$\mathbf{H}_2$), 4.24 (1H, app t, *J* = 8.4 Hz, OC$\mathbf{H}_2$), 4.05 (1H, app t, *J* = 10.0 Hz, OC$\mathbf{H}_2$), 3.89 (1H, app q, *J* = 17.2, 8.5 Hz, $OCH_2C\mathbf{H}$), 2.61 (1H, q, *J* = 8.0 Hz, $O{=}CCH_2C\mathbf{H}$), 2.26 (1H, dd, *J* = 16.8, 8.4 Hz, O=CC$\mathbf{H}_2$), 2.08 (1H, dd, *J* = 16.8, 6.8 Hz, O=CC$\mathbf{H}_2$), 1.49 (3H, s, C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.5 (C), 150.1 (CH), 144.0 (C), 141.4 (C), 128.7 (CH), 128.6 (2 × CH), 127.9 (CH), 125.9 (2 × CH), 115.0 (CH_2), 78.6 (C), 69.5 (CH_2), 45.5 (CH), 44.0 (CH), 35.2 (CH_2), 27.3 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{17}H_{18}NaO_2]^+$ $[M+Na]^+$: 277.1199, found: 277.1193. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (major) = 7.2 min, t_r (minor) = 8.4 min, 91% ee.



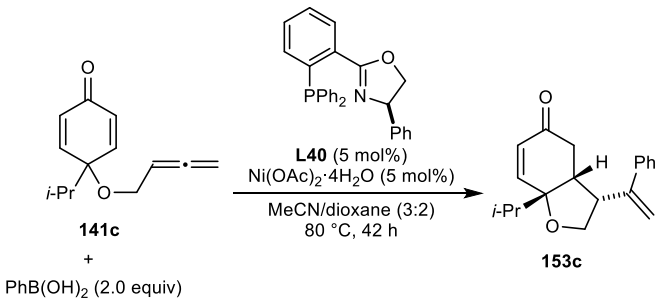
(3*R*,3a*R*,7a*R*)-7a-Ethyl-3-(1-phenylethenyl)-2,3,3a,4,5,7a-hexahydro-1-benzofuran-5-one (153b). The General Procedure was followed using allenyl cyclohexa-2,5-dienone **141b** (57.1 mg, 0.30 mmol) and phenylboronic acid (73.1 mg, 0.60 mmol), and purified by column chromatography (30% EtOAc/petroleum ether) to give a 17:1 inseparable mixture of *arylative cyclization product* **153b** and *cyclobutane* **154b** as a colorless oil (65.2 mg, 78%, adjusted yield of **153b**). R_f = 0.29 (20% EtOAc/petroleum ether); $[\alpha]_D^{25}$ −68.8 (*c* 0.64, $CHCl_3$); IR 2965, 2932, 1682 (C=O), 1494, 1380, 1052, 906, 777, 703, 634 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.30 (5H, m, Ar**H**), 6.58 (1H, dd, *J* = 10.4 Hz, O=CCH=C**H**), 6.06 (1H, dd, *J* = 10.4 Hz, O=CC**H**=), 5.43 (1H, s, =C$\mathbf{H}_2$), 4.94 (1H, s, =C$\mathbf{H}_2$), 4.20 (1H, app t, *J* = 7.2 Hz, OC$\mathbf{H}_2$), 4.00 (1H, app t, *J* = 10.0 Hz, OC$\mathbf{H}_2$), 3.80 (1H, app q, *J* = 8.5 Hz, $OCH_2C\mathbf{H}$), 2.67 (1H, app q, *J* = 7.8 Hz, $O{=}CCH_2C\mathbf{H}$), 2.27 (1H, dd, *J* = 16.8, 7.6 Hz, O=CC$\mathbf{H}_2$), 2.07 (1H, dd, *J* = 16.8, 6.8 Hz, O=CC$\mathbf{H}_2$), 1.88-1.71 (2H, m, C$\mathbf{H}_2CH_3$), 0.95 (3H, *J* = 7.6 Hz, $CH_2C\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.7 (C), 149.2 (CH), 144.1 (C), 141.4 (C), 129.8 (CH), 128.6 (2 × CH),

127.9 (CH), 125.9 (2 × CH), 115.0 (CH_2), 81.6 (C), 69.1 (CH_2), 45.9 (CH), 41.1 (CH), 35.6 (CH_2), 33.1 (CH_2), 8.6 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{18}H_{21}O_2]^+$ $[M+H]^+$: 269.1536, found: 269.1527. Enantiomeric excess was determined by HPLC with a Chiralpak IA-3 column (98:2 *iso*-hexane:*i*-PrOH, 1 mL/min, 230 nm, 25 °C); t_r (major) = 21.6 min, t_r (minor) = 27.6 min, 92% ee.



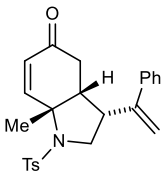
(3*R*,3a*R*,7a*R*)-3-(1-Phenylethenyl)-7a-(propan-2-yl)-2,3,3a,4,5,7a-hexahydro-1-benzofuran-5-one (153c). The title compound was prepared according to the General Procedure using allenyl cyclohexa-2,5-dienone **141c** (61.3 mg, 0.30 mmol) and phenylboronic acid (73.1 mg, 0.60 mmol), and purified by column chromatography (20% EtOAc/petroleum ether) to give **153c** as a colorless oil (65.0 mg, 77%). R_f = 0.36 (20% EtOAc/petroleum ether); $[\alpha]_D^{25}$ −83.0 (*c* 0.53, $CHCl_3$); IR 2961, 2877, 1683 (C=O), 1495, 1385, 1256, 1041, 934, 906, 778, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27−7.16 (5H, m, Ar**H**), 6.46 (1H, d, *J* = 10.2 Hz, O=CCH=C**H**), 6.02 (1H, d, *J* = 10.2 Hz, O=CC**H**=), 5.33 (1H, s, =C**H**$_2$), 4.82 (1H, s, =C**H**$_2$) 4.04 (1H, app t, *J* = 8.2 Hz, OC**H**$_2$), 3.78 (1H, app t, *J* = 8.2 Hz, OC**H**$_2$), 3.58 (1H, q, *J* = 8.8 Hz, OCH_2C**H**), 2.62 (1H, q, *J* = 7.6 Hz, $O{=}CCH_2C$**H**) 2.17 (1H, dd, *J* = 16.8, 6.1 Hz, O=CC**H**$_2$), 2.01−1.88 (2H, m, O=CC**H**$_2$ and C**H**$(CH_3)_2$), 0.91 (3H, d, *J* = 6.8 Hz, C**H**$_3$), 0.87 (3H, d, *J* = 6.8 Hz, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.7 (C), 148.1 (CH), 144.1 (C), 141.4 (C), 130.7 (CH), 128.6 (2 × CH), 127.9 (CH), 125.8 (2 × CH), 115.0 (CH_2), 83.9 (C), 68.7 (CH_2), 46.7 (CH), 39.2 (CH), 36.6 (CH), 36.4 (CH_2), 17.35 (CH_3), 17.31 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{19}H_{23}O_2]^+$ $[M+H]^+$: 283.1693, found: 283.1689. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (98:2 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (major) = 9.4 min, t_r (minor) = 11.9 min, 94% ee.

Reaction Conducted on 2.00 mmol Scale:



An oven-dried microwave vial fitted with a stirrer bar was charged with $Ni(OAc)_2 \cdot 4H_2O$ (24.8 mg, 0.10 mmol) and (*R*)-Ph-PHOX (**L40**, 40.7 mg, 0.10 mmol). The vial was capped with a crimp cap PTFE seal and purged with a stream of N_2. Deoxygenated MeCN (1.5 mL) and 1,4-dioxane (1.0 mL) were added and the mixture was stirred at 80 °C for 15 min. In a separate vial, the allenyl cyclohexa-2,5-dienone **141c** (408.6 mg, 2.00 mmol) and phenylboronic acid (487.2 mg, 4.00 mmol) were weighed out and the vial was purged with a stream of N_2. Deoxygenated MeCN (0.75 mL) and 1,4-dioxane (0.5 mL) were added. The resulting solution was then transferred to the first microwave vial *via* syringe. The vial originally containing the substrate was rinsed with additional deoxygenated MeCN (0.75 mL) and 1,4-dioxane (0.5 mL), and the rinsing solution was transferred to the first microwave vial *via* syringe. The reaction was stirred at 80 °C for 42 h, cooled to room temperature, filtered through a plug of silica, and concentrated under reduced pressure. The residue was purified by column chromatography to give the title compound **153c** as a colorless oil (355.0 mg, 63%). Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (98:2 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (major) = 9.4 min, t_r (minor) = 11.9 min, 94% ee.

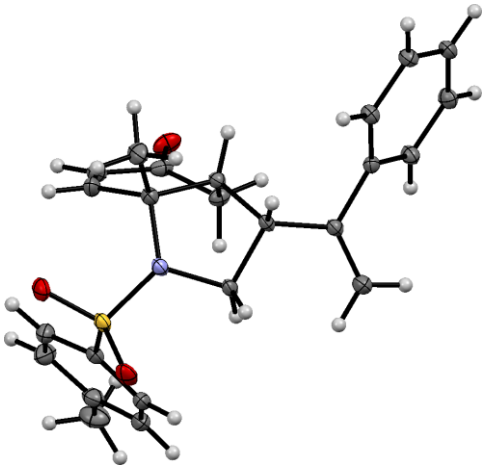
4.4.2. Hexahydroindol-5-ones

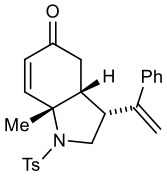


(3*R*,3a*R*,7a*R*)-7a-Methyl-1-(4-methylbenzenesulfonyl)-3-(1-phenylethenyl)-2,3,3a,4,5,7a-hexahydro-1*H*-indol-5-one (162a). The title compound was prepared according to the General Procedure using allenyl cyclohexa-2,5-dienone **149a** (98.8 mg, 0.30 mmol) and phenylboronic acid (73.1 mg, 0.60 mmol), and purified by column chromatography (20% EtOAc/petroleum ether) to give **162a** as a colorless solid (93.7 mg, 77%). R_f = 0.36 (20% EtOAc/petroleum ether); m.p. 113−118 °C (Et_2O); $[\alpha]_D^{25}$ +88.9 (*c* 0.54, $CHCl_3$); IR 2929, 1679 (C=O), 1337, 1038, 1267, 1168, 1149, 1130, 1105, 1066, 898, 775, 581, 542 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74−7.71 (2H, m, Ar**H**), 7.51-7.28 (7H, m, Ar**H**), 7.20 (1H, d, *J* = 10.3 Hz, O=CCH=C**H**), 5.89 (1H, dd, *J* = 10.3, 0.8 Hz, O=CC**H**=), 5.35 (1H, d, *J* = 1.6 Hz, =C**H**$_2$), 4.90 (1H, d, *J* = 1.6 Hz, =C**H**$_2$), 3.94−3.87 (2H, m, NC**H**$_2$), 3.59−3.52 (1H, m, NCH_2C**H**), 2.48−2.42 (1H, m, O=CCH_2C**H**), 2.43 (3H, s, ArC**H**$_3$), 1.91-1.81 (2H, m, O=CC**H**$_2$), 1.74 (3H, s, NCC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.0 (C), 149.0 (CH), 144.0 (C), 143.5

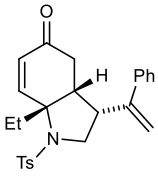
(C), 140.2 (C), 136.8 (C), 129.6 (2 × CH), 128.7 (2 × CH), 128.2 (CH), 128.1 (CH), 127.1 (2 × CH), 126.0 (2 × CH), 114.9 (CH_2), 63.7 (C), 49.5 (CH_2), 47.3 (CH), 41.7 (CH), 34.1 (CH_2), 28.7 (CH_3), 21.5 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{24}H_{25}NNaO_3S]^+$ $[M+Na]^+$: 430.1447, found: 430.1444. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (minor) = 16.2 min, t_r (major) = 18.4 min, 90% ee.

Slow diffusion of petroleum ether into a solution of **162a** in EtOAc gave crystals that were suitable for X-ray crystallography:





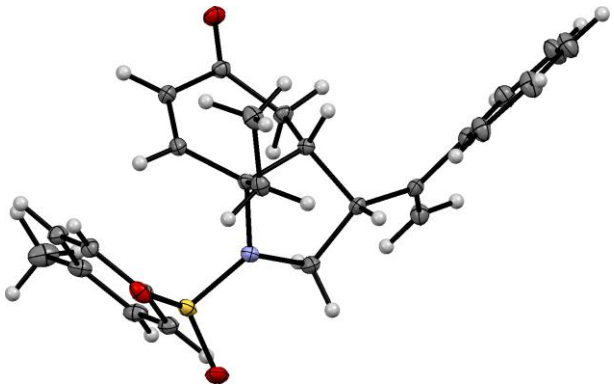
162a
CCDC 1584893
Flack parameter = 0.05(14)

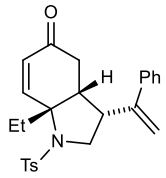


(3*R*,3a*R*,7a*R*)-7a-Ethyl-1-(4-methylbenzenesulfonyl)-3-(1-phenylethenyl)-2,3,3a,4,5,7a-hexahydro-1*H*-indol-5-one (162b). The title compound was prepared according to the General Procedure using allenyl cyclohexa-2,5-dienone **149b** (102.9 mg, 0.30 mmol) and phenylboronic acid (73.1 mg, 0.60 mmol), and purified by column chromatography (30% EtOAc/petroleum ether) to give **162b** a colorless solid (98.6 mg, 78%). R_f = 0.55 (30% EtOAc/petroleum ether); m.p. 173−175 °C (Et_2O); $[\alpha]_D^{25}$ +71.0 (*c* 0.62, $CHCl_3$); IR 2959, 2929, 2851, 1672 (C=O), 1496, 1385, 1342, 1165, 1105, 1064, 904, 773, 679, 589, 545 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74−7.70 (2H, m, Ar**H**), 7.37−7.28 (7H, m, Ar**H**), 7.15 (1H, d, *J* = 10.4 Hz, O=CCH=C**H**), 5.99 (1H, dd, *J* = 10.4, 0.8 Hz, O=CC**H**=), 5.34 (1H, d, *J* = 1.6 Hz, =C$\mathbf{H}_2$), 4.88 (1H, d, *J* = 1.6 Hz, =C$\mathbf{H}_2$), 3.88−3.81 (2H, m, NC$\mathbf{H}_2$), 3.56-3.49 (1H, m, $NCH_2C\mathbf{H}$), 2.61 (1H, dt, *J* = 12.8, 5.6 Hz, $O=CCH_2C\mathbf{H}$), 2.42 (3H, s, $ArC\mathbf{H}_3$), 2.39-2.29 (1H, m, O=CC$\mathbf{H}_2$), 2.07 (1H, dq, *J* = 14.0, 7.6 Hz, O=CC$\mathbf{H}_2$), 1.84 (1H, ddd, *J* = 16.4, 5.7, 1.0 Hz, C$\mathbf{H}_2CH_3$), 1.72 (1H, dd, *J* = 16.4, 12.8 Hz, C$\mathbf{H}_2CH_3$), 0.86 (3H, t, *J* = 7.6 Hz,

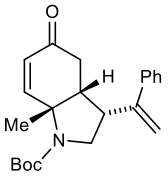
$CH_2C\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.1 (C), 148.3 (CH), 144.0 (C), 143.5 (C), 140.3 (C), 136.6 (C), 130.0 (CH), 129.6 (2 × CH), 128.8 (2 × CH), 128.2 (CH), 127.2 (2 × CH), 125.9 (2 × CH), 114.8 (CH_2), 67.9 (C), 49.2 (CH_2), 42.1 (CH), 41.5 (CH), 34.1 (CH_2), 33.2 (CH_2), 21.5 (CH_3), 9.9 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{25}H_{27}NNaO_3S]^+$ $[M+Na]^+$: 444.1604, found: 444.1589. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (minor) = 13.9 min, t_r (major) = 17.6 min, 92% ee.

Slow diffusion of petroleum ether into a solution of **162b** in EtOAc gave crystals that were suitable for X-ray crystallography:



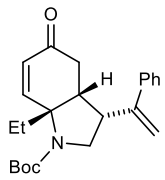


162b
CCDC 1584894
Flack parameter = 0.008(10)



***tert*-butyl (3R,3aR,7aR)-7a-methyl-5-oxo-3-(1-phenylvinyl)-2,3,3a,4,5,7a-hexahydro-1H-indole-1-carboxylate (163a).** The title compound **163a** was prepared according to the General Procedure using allenyl electrophile **152a** (82.6 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol). Purification by column chromatography (6% EtOAc/dichloromethane) gave **163a** (71.8 mg, 68%) as a 1.3:1 mixture of rotamers as a colorless liquid. R_f = 0.48 (6% EtOAc, 94% dichloromethane); $[\alpha]_D^{25}$ –64.3 (*c* 0.56, $CHCl_3$); IR 2974, 1679 (C=O), 1365, 1163, 1123, 1063, 1040, 905, 878, 776, 729, 698, 599 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *major rotamer*: δ 7.43−7.31 (6H, m, Ar**H** and O=CCH=C**H**), 5.89 (1H, d, *J* = 10.3 Hz, O=CC**H**=), 5.40 (1H, s, =C$\mathbf{H}_2$), 5.02 (1H, s, =C$\mathbf{H}_2$), 4.00−3.69 (3H, m, NC$\mathbf{H}_2$ and $NCH_2C\mathbf{H}$), 2.52−2.41 (1H, m, $O{=}CCH_2C\mathbf{H}$), 2.28−2.13 (1H, m, O=CC$\mathbf{H}_2$), 2.00−1.93 (1H, m, O=CC$\mathbf{H}_2$), 1.60 (3H, d, *J* = 12.6 Hz, C$\mathbf{H}_3$), 1.53 (9H, d, *J* = 13.8 Hz, C(C$\mathbf{H_3}$)$_3$); *minor rotamer*: δ 7.43−7.31 (5H, m, Ar**H**), 7.05 (1H, d, *J* = 10.4 Hz, O=CCH=C**H**), 5.89 (1H, d, *J* = 10.3 Hz, O=CC**H**=), 5.40 (1H, s, =C$\mathbf{H}_2$), 5.04 (1H, s, =C$\mathbf{H}_2$),

4.00−3.69 (3H, m, NC**H**$_2$ and NCH$_2$C**H**), 2.52−2.41 (1H, m, O=CCH$_2$C**H**), 2.28−2.13 (1H, m, O=CC**H**$_2$), 2.00−1.93 (1H, m, O=CC**H**$_2$), 1.60 (3H, d, *J* = 12.6 Hz, C**H**$_3$), 1.53 (9H, d, *J* = 13.8 Hz, C(C**H**$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) *major rotamer*: δ 199.2 (C), 153.4 (C), 150.5 (CH), 144.6 (C), 140.7 (C), 128.7 (2 × CH), 128.05 (CH), 127.0 (CH), 126.1 (2 × CH), 114.61 (CH_2), 79.9 (C), 59.9 (C), 45.5 (CH_2), 46.1 (CH), 41.2 (CH), 34.47 (CH_2), 28.57 (3 × CH_3), 25.2 (CH_3); *minor rotamer*: δ 199.9 (C), 153.6 (C), 150.2 (CH), 144.4 (C), 140.7 (C), 128.7 (2 × CH), 128.02 (CH), 127.2 (CH), 126.1 (2 × CH), 115.0 (CH_2), 80.7 (C), 59.3 (C), 48.7 (CH_2), 47.2 (CH), 40.6 (CH), 34.45 (CH_2), 28.59 (3 × CH_3), 26.3 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{22}H_{28}NO_3]^+$ $[M+H]^+$: 354.2064, found: 354.2060. Enantiomeric excess was determined by HPLC with a Chiralpak IC column (90:10 *iso*-hexane:*i*PrOH, 1 mL/min, 254 nm, 25 °C); t_r (minor) = 17.2 min, t_r (major) = 24.4 min, 89% ee.

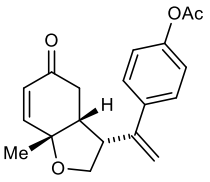


***tert*-butyl (3R,3aR,7aR)-7a-ethyl-5-oxo-3-(1-phenylvinyl)-2,3,3a,4,5,7a-hexahydro-1H-indole-1-carboxylate (163b).** The title compound **163b** was prepared according to the General Procedure using allenyl electrophile **152b** (86.8 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.60 mmol). Purification by column chromatography (6% EtOAc/dichloromethane) gave **163b** (54.6 mg, 50%) as a 1.4:1 mixture of rotamers as a colorless liquid. R_f = 0.63 (6% EtOAc, 94% dichloromethane); $[\alpha]_D^{25}$ −57.1 (*c* 0.63, $CHCl_3$); IR 2971, 1679 (C=O), 1314, 1164, 1114, 908, 775, 729, 698, 580 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *major rotamer*: δ 7.45−7.26 (6H, m, Ar**H** and O=CCH=C**H**, one rotamer), 5.96 (1H, d, *J* = 10.4, O=CC**H**=), 5.39 (1H, s, =C**H**$_2$), 5.00 (1H, s, =C**H**$_2$), 3.96−3.68 (3H, m, NC**H**$_2$ and NCH$_2$C**H**), 2.67−2.55 (1H, m, O=CCH$_2$C**H**), 2.36−2.27 (1H, m, C**H**$_2$CH$_3$), 2.23−2.07 (1H, m, O=CC**H**$_2$), 2.01−1.93 (1H, m, O=CC**H**$_2$), 1.90−1.79 (1H, m, C**H**$_2$CH$_3$), 1.49 (9H, s, C(C**H**$_3$)$_3$), 0.84 (3H, t, *J* = 7.8 Hz, CH$_2$C**H**$_3$); *minor rotamer*: δ 7.45−7.26 (5H, m, Ar**H**), 6.99 (1H, d, *J* = 10.4 Hz, O=CCH=C**H**), 5.95 (1H, d, *J* = 10.3 Hz, O=CC**H**=), 5.37 (1H, s, =C**H**$_2$), 5.01 (1H, s, =C**H**$_2$), 3.96−3.68 (3H, m, NC**H**$_2$ and NCH$_2$C**H**), 2.64−2.56 (1H, m, O=CCH$_2$C**H**), 2.36−2.27 (1H, m, C**H**$_2$CH$_3$), 2.23−2.07 (1H, m, O=CC**H**$_2$), 2.01−1.93 (1H, m, O=CC**H**$_2$), 1.90−1.79 (1H, m, C**H**$_2$CH$_3$), 1.51 (9H, s, C(C**H**$_3$)$_3$), 0.82 (3H, t, *J* = 7.7 Hz, CH$_2$C**H**$_3$); ^{13}C

NMR (101 MHz, $CDCl_3$) *major rotamer*: δ 199.2 (C), 153.5 (C), 150.0 (CH), 144.7 (C), 140.7 (C), 128.8 (CH), 128.72 (2 × CH), 128.08 (CH), 126.0 (2 × CH), 114.6 (CH_2), 79.9 (C), 63.8 (C), 48.40 (CH_2), 41.2 (CH), 41.1 (CH), 34.50 (CH_2), 30.5 (CH_2), 28.6 (3 × CH_3), 9.8 (CH_3); *minor rotamer*: δ 198.9 (C), 153.7 (C), 149.8 (CH), 144.5 (C), 140.7 (C), 128.8 (CH), 128.68 (2 × CH), 128.05 (CH), 126.0 (2 × CH), 115.0 (CH_2), 80.7 (C), 63.2 (C), 48.5 (CH_2), 42.4 (CH), 40.4 (CH), 34.46 (CH_2), 29.40 (CH_2), 28.6 (CH_3), 9.8 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{23}H_{30}NO_3]^+$ $[M+H]^+$: 368.2220, found: 368.2225. Enantiomeric excess was determined by HPLC with a Chiralpak IC column (90:10 *iso*-hexane:*i*PrOH, 0.4 mL/min, 254 nm, 25 °C); t_r (minor) = 36.7 min, t_r (major) = 44.1 min, 90% ee.

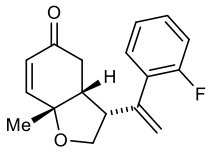
4.5. Exploration of boronic acid scope

4.5.1. Hexahydrobenzofuran-5-ones



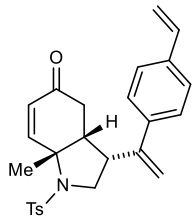
(3*R*,3a*R*,7a*R*)-4-[1-(7a-Methyl-5-oxo-2,3,3a,4,5,7a-hexahydro-1-benzofuran-3-yl)ethenyl]phenyl acetate (153e). The title compound was prepared according to the General Procedure using allenyl cyclohexa-2,5-dienone **141a** (52.8 mg, 0.30 mmol) and 4-acetoxyphenylboronic acid (108.0 mg, 0.60 mmol), and purified by column chromatography (30% EtOAc/petroleum ether) to give **153e** as a colorless solid (64.1 mg, 68%). R_f = 0.25 (30% EtOAc/petroleum ether); m.p. 88−93 °C (Et_2O); $[\alpha]_D^{25}$ −87.2 (*c* 0.78, $CHCl_3$); IR 2969, 2928, 2881, 1747 (C=O), 1681 (C=O), 1506, 1370, 1196, 1170, 1014, 911, 855, 790, 655 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41−7.38 (2H, m, Ar**H**), 7.10−7.07 (2H, m, Ar**H**), 6.61 (1H, d, *J* = 10.2 Hz, O=CCH=C**H**), 5.97 (1H, d, *J* = 10.2 Hz, O=CC**H**=), 5.41 (1H, d, *J* = 0.8 Hz, =C$\mathbf{H}_2$), 4.97 (1H, d, *J* = 1.6 Hz, =C$\mathbf{H}_2$), 4.24 (1H, dd, *J* = 8.8, 7.6 Hz, OC$\mathbf{H}_2$), 4.03 (1H, dd, *J* = 10.4, 9.2 Hz, OC$\mathbf{H}_2$), 3.83 (1H, dd, *J* = 17.6, 8.8 Hz, $OCH_2C\mathbf{H}$), 2.63 (1H, td, *J* = 8.4, 6.8 Hz, $O{=}CCH_2C\mathbf{H}$), 2.32 (3H, s, O=CC$\mathbf{H}_3$), 2.27 (1H, dd, *J* = 16.9, 7.9 Hz, O=CC$\mathbf{H}_2$), 2.10 (1H, d, *J* = 16.9, 6.8 Hz, O=CC$\mathbf{H}_2$), 1.50 (3H, s, C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.4 (C), 169.3 (C), 150.4 (CH), 150.2 (C), 143.2 (C), 139.2 (C), 128.9 (CH), 127.0 (2 x CH), 121.7 (2 x CH), 115.5 (CH_2), 78.8 (C), 69.6 (CH_2), 45.7 (CH), 44.1 (CH), 35.4 (CH_2), 27.2 (CH_3), 21.1 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{19}H_{20}NaO_4]^+$ $[M+Na]^+$: 335.1254, found: 335.1253. Enantiomeric excess was

determined by HPLC with a Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH), 1 mL/min, 254 nm, 25 °C); t_r (major) = 13.9 min, t_r (minor) = 24.1 min, 92% ee.



(3*R*,3a*R*,7a*R*)-3-[1-(2-Fluorophenyl)ethenyl]-7a-methyl-2,3,3a,4,5,7a-hexahydro-1-benzofuran-5-one (153f). The title compound was prepared according to the General Procedure using allenyl cyclohexa-2,5-dienone **141a** (52.8 mg, 0.30 mmol) and 2-fluorophenylboronic acid (83.9 mg, 0.60 mmol), and purified by column chromatography (20% EtOAc/petroleum ether) to give **153f** as a colorless oil (47.4 mg, 58%). R_f = 0.34 (20% EtOAc/petroleum ether); $[\alpha]_D^{25}$ –84.6 (*c* 0.52, $CHCl_3$); IR 2971, 2929, 1682 (C=O), 1630, 1486, 1448, 1371, 1268, 1209, 1153, 1118, 1088, 1033, 906, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.26 (2H, m, Ar**H**), 7.16−7.12 (1H, m, Ar**H**), 7.09-7.03 (1H, m, Ar**H**), 6.62 (1H, d, *J* = 10.2 Hz, O=CCH=C**H**), 5.98 (1H, d, *J* = 10.2 Hz, O=CC**H**=), 5.37 (1H, d, *J* = 1.2 Hz, =C$\mathbf{H}_2$), 5.11 (1H, d, *J* = 1.6 Hz, =C$\mathbf{H}_2$), 4.27 (1H, dd, *J* = 8.4, 6.8 Hz, OC$\mathbf{H}_2$), 4.03 (1H, ddd, *J* = 10.4, 8.4, 1.2 Hz, OC$\mathbf{H}_2$), 3.98-3.91 (1H, m, $OCH_2C\mathbf{H}$), 2.56 (1H, dt, *J* = 8.4, 6.8 Hz, $O{=}CCH_2C\mathbf{H}$), 2.37 (1H, dd, *J* = 16.8, 8.8 Hz, O=CC$\mathbf{H}_2$), 2.18 (1H, dd, *J* = 16.8, 6.8 Hz, O=CC$\mathbf{H}_2$), 1.46 (3H, s, C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.8 (C), 159.6 (C, d, J^1 = 252.5 Hz), 150.2 (CH), 140.9 (C), 129.9 (CH, d, J^3 = 4 Hz), 129.7 (C, d, J^3 = 13.1 Hz), 129.4 (CH, d, J^3 = 8.1 Hz), 128.6 (CH), 124.5 (CH, d, J^4 = 4.0 Hz), 118.5 (CH_2, d, J^4 = 1.0 Hz), 116.0 (CH, d, J^2 = 23.2 Hz), 78.6 (C), 69.9 (CH_2), 46.2 (CH, d, J^4 = 2.0 Hz), 44.2 (CH), 35.4 (CH_2), 27.5 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{17}H_{17}FNaO_2]^+$ $[M+Na]^+$: 295.1105, found: 295.1109. Enantiomeric excess was determined by HPLC with a Chiralpak IC-3 column (90:10 *iso*-hexane:*i*-PrOH), 1 mL/min, 254 nm, 25 °C); t_r (major) = 12.9 min, t_r (minor) = 24.2 min, 89% ee.

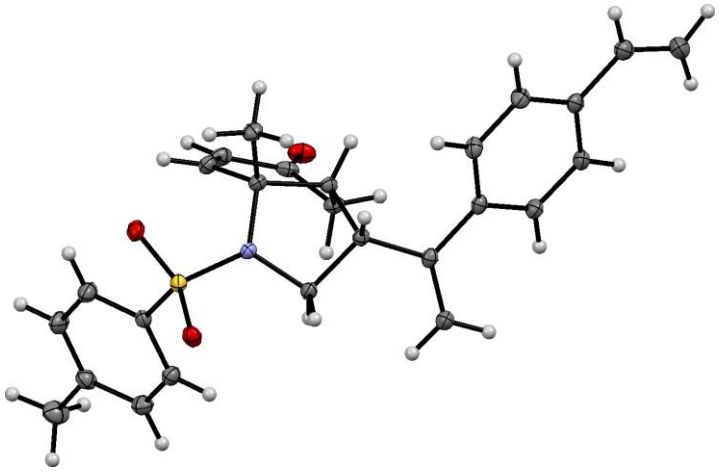
4.5.2. Hexahydroindol-5-ones



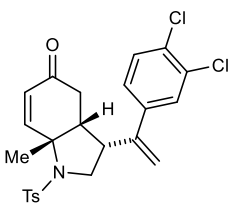
(3*R*,3a*R*,7a*R*)-3-[1-(4-Ethenylphenyl)ethenyl]-7a-methyl-1-(4-methylbenzenesulfonyl)-2,3,3a,4,5,7a-hexahydro-1*H*-indol-5-one (162c). The title compound was prepared according to the General Procedure using allenyl cyclohexa-2,5-dienone **149a** (98.8 mg, 0.30 mmol) and 4-vinylphenylboronic acid (88.8 mg, 0.60 mmol), and purified by column chromatography (30% EtOAc/petroleum ether) to give **162c** as a

colorless solid (82.2 mg, 63%). R_f = 0.44 (30% EtOAc/petroleum ether); m.p. 163-165 °C (Et_2O); $[\alpha]_D^{25}$ −81.4 (*c* 0.59, $CHCl_3$); IR 3008, 2972, 1679 (C=O), 1332, 1148, 1133, 1114, 1071, 1056, 989, 906, 849, 681, 583 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (2H, d, *J* = 8.2 Hz, Ar**H**), 7.38 (2H, d, *J* = 8.2 Hz, Ar**H**), 7.30−7.27 (4H, m, Ar**H**), 7.20 (1H, d, *J* = 10.0 Hz, O=CCH=C**H**), 6.70 (1H, dd, *J* = 17.6, 10.8 Hz, C**H**=CH_2), 5.89 (1H, d, *J* = 10.0 Hz, O=CC**H**=), 5.75 (1H, dd, *J* = 17.6, 0.6 Hz, CH=C**H**$_2$), 5.37 (1H, d, *J* = 1.4 Hz, C=C**H**$_2$), 5.27 (1H, dd, *J* = 10.8, 0.6 Hz, CH=C**H**$_2$), 4.89 (1H, d, *J* = 1.4 Hz, C=C**H**$_2$), 3.92−3.87 (2H, m, NC**H**$_2$), 3.58−3.52 (1H, m, NCH_2C**H**), 2.49−2.44 (1H, m, O=CCH_2C**H**), 2.43 (3H, s, ArC**H**$_3$), 1.89−1.80 (2H, m, O=CC**H**$_2$), 1.74 (3H, s, NCC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.0 (C), 149.0 (CH), 143.6 (2 × C), 139.6 (C), 137.6 (C), 136.8 (C), 136.0 (CH), 129.6 (2 × CH), 128.1 (CH), 127.1 (2 × CH), 126.5 (2 × CH), 126.2 (2 × CH), 114.7 (CH_2), 114.5 (CH_2), 63.7 (C), 49.5 (CH_2), 47.4 (CH), 41.6 (CH), 34.1 (CH_2), 28.7 (CH_3), 21.5 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{26}H_{27}NNaO_3S]^+$ $[M+Na]^+$: 456.1604, found: 456.1595. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH, 0.2 mL/min, 254 nm, 25 °C); t_r (major) = 90.9 min, t_r (minor) = 94.7 min, 99% ee.

Slow diffusion of petroleum ether into a solution of **162c** in EtOAc gave crystals that were suitable for X-ray crystallography:



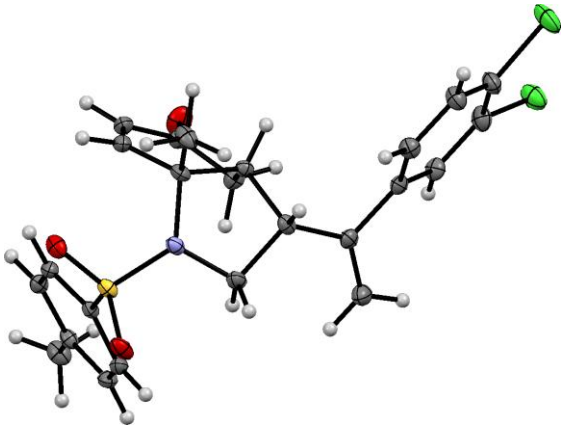
162c
CCDC 1584895
Flack parameter = 0.002(8)



(3*R*,3a*R*,7a*R*)-3-[1-(3,4-Dichlorophenyl)ethenyl]-7a-methyl-1-(4-methylbenzenesulfonyl)-2,3,3a,4,5,7a-hexahydro-1*H*-indol-5-one (162d). The title compound was prepared according to the General Procedure using allenyl cyclohexa-2,5-dienone

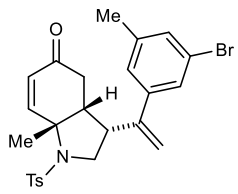
149a (98.8 mg, 0.30 mmol) and 3,4-dichlorophenylboronic acid (114.5 mg, 0.60 mmol), and purified by column chromatography (30% EtOAc/petroleum ether) to give **162d** as a colorless solid (73.2 mg, 51%). R_f = 0.46 (30% EtOAc/petroleum ether); m.p. 179-181 °C (Et_2O); $[\alpha]_D^{25}$ –61.5 (*c* 0.78, $CHCl_3$); IR 2957, 2852, 1679 (C=O), 1472, 1307, 1169, 1150, 1066, 893, 862, 663, 580 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (2H, d, *J* = 8.4 Hz, Ar**H**), 7.42 (1H, d, *J* = 8.4 Hz, Ar**H**), 7.39 (1H, d, *J* = 2.4 Hz, Ar**H**), 7.30 (2H, d, *J* = 8.0 Hz, Ar**H**), 7.20 (1H, d, *J* = 10.2 Hz, O=CCH=C**H**), 7.14 (1H, dd, *J* = 8.0, 2.4 Hz, Ar**H**), 5.91 (1H, d, *J* = 10.2 Hz, O=CC**H**=), 5.38 (1H, d, *J* = 1.2 Hz, =C$\mathbf{H}_2$), 4.97 (1H, d, *J* = 2.0 Hz, =C$\mathbf{H}_2$), 3.87 (1H, dd, *J* = 8.9, 7.3 Hz, NC$\mathbf{H}_2$), 3.82−3.77 (1H, m, NC$\mathbf{H}_2$), 3.56−3.51 (1H, m, $NCH_2C\mathbf{H}$), 2.47−2.41 (4H, m, $O{=}CCH_2C\mathbf{H}$ and Ar$C\mathbf{H}_3$), 1.82 (2H, d, *J* = 9.3 Hz, O=CC$\mathbf{H}_2$), 1.74 (3H, s, NCC$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.5 (C), 148.9 (CH), 143.7 (C), 142.0 (C), 140.3 (C), 136.7 (C), 133.1 (C), 132.4 (C), 130.7 (CH), 129.7 (2 × CH), 128.1 (CH), 127.9 (CH), 127.1 (2 × CH), 125.3 (CH), 116.6 (CH_2), 63.8 (C), 49.4 (CH_2), 47.3 (CH), 41.6 (CH), 34.2 (CH_2), 28.7 (CH_3), 21.5 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{24}H_{24}Cl_2NO_3S]^+$ $[M+H]^+$: 476.0848, found: 476.0842. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (minor) = 18.7 min, t_r (major) = 23.7 min, 87% ee.

Slow diffusion of petroleum ether into a solution of **162d** in EtOAc gave crystals that were suitable for X-ray crystallography:

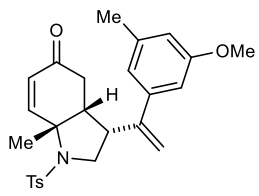


162d
CCDC 1584896
Flack parameter = –0.01(2)

Note: The *meta*-chloro group is disordered over two possible positions. The occupancies of the two components were refined competitively, converging to a ratio of 0.95:0.05. This disorder is not shown above, for clarity.

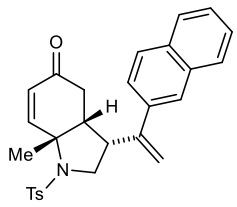


(3*R*,3a*R*,7a*R*)-3-[1-(3-Bromo-5-methylphenyl)ethenyl]-7a-methyl-1-(4-methylbenzenesulfonyl)-2,3,3a,4,5,7a-hexahydro-1*H*-indol-5-one (162e). The title compound was prepared according to the General Procedure using allenyl cyclohexa-2,5-dienone **149a** (98.8 mg, 0.30 mmol) and 3-bromo-5-methylphenylboronic acid (128.9 mg, 0.60 mmol), and purified by column chromatography (30% EtOAc/petroleum ether) to give **162e** as a colorless solid (84.0 mg, 56%). R_f = 0.49 (30% EtOAc/petroleum ether); m.p. 139−142 °C (Et_2O); $[\alpha]_D^{25}$ −70.6 (*c* 0.51, $CHCl_3$); IR 2963, 2923, 2863, 1682 (C=O), 1597, 1563, 1337, 1306, 1163, 1133, 1106, 1058, 985, 889, 852, 808, 682, 658, 581, 544 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (2H, d, *J* = 8.3 Hz, Ar**H**), 7.32-7.27 (3H, m, Ar**H**), 7.23 (1H, s, Ar**H**), 7.21 (1H, d, *J* = 10.3 Hz, O=CCH=C**H**), 7.02 (1H, s, Ar**H**), 5.91 (1H, d, *J* = 10.3 Hz, O=CC**H**=), 5.34 (1H, d, *J* = 1.6 Hz, =C$\mathbf{H}_2$), 4.91 (1H, d, *J* = 1.6 Hz, =C$\mathbf{H}_2$), 3.94−3.74 (2H, m, NC$\mathbf{H}_2$), 3.61-3.41 (1H, m, NCH_2C**H**), 2.51−2.40 (4H, m, O=CCH_2C**H** and ArC$\mathbf{H}_3$), 2.33 (3H, m, ArC$\mathbf{H}_3$), 1.92−1.79 (2H, m, O=CC$\mathbf{H}_2$), 1.74 (3H, s, NCC$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.9 (C), 149.0 (CH), 143.6 (C), 142.9 (C), 142.2 (C), 140.5 (C), 136.7 (C), 131.9 (CH), 129.6 (2 × CH), 128.1 (C), 127.1 (2 × CH), 126.1 (CH), 125.6 (CH), 122.6 (C), 116.0 (CH_2), 63.7 (C), 49.4 (CH_2), 47.3 (CH), 41.6 (CH), 34.2 (CH_2), 28.6 (CH_3), 21.5 (CH_3), 21.2 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{25}H_{26}BrNNaO_3S]^+$ $[M+Na]^+$: 522.0709, found: 522.0713. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (minor) = 12.7 min, t_r (major) = 16.7 min, 88% ee.



(3*R*,3a*R*,7a*R*)-3-[1-(3-Methoxy-5-methylphenyl)ethenyl]-7a-methyl-1-(4-methylbenzenesulfonyl)-2,3,3a,4,5,7a-hexahydro-1*H*-indol-5-one (162f). The title compound was prepared according to the General Procedure using allenyl cyclohexa-2,5-dienone **149a** (98.8 mg, 0.30 mmol) and 3-methoxy-5-bromophenylboronic acid (99.6 mg, 0.60 mmol), and purified by column

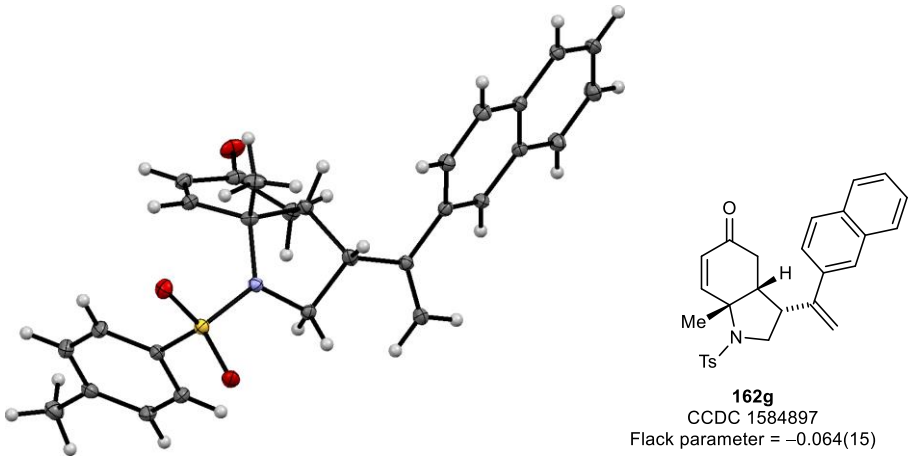
chromatography (30% EtOAc/petroleum ether) to give **162f** as a colorless solid (97.1 mg, 72%). R_f = 0.48 (30% EtOAc/petroleum ether); m.p. 55−60 °C (Et_2O); $[\alpha]_D^{25}$ –92.3 (*c* 0.39, $CHCl_3$); IR 2935, 2253, 1681 (C=O), 1589, 1333, 1292, 1150, 1111, 1059, 985, 907, 728, 662, 582 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (2H, d, *J* = 8.0 Hz, Ar**H**), 7.29 (2H, d, *J* = 8.0 Hz, Ar**H**), 7.20 (1H, d, *J* = 10.4 Hz, O=CCH=C**H**), 6.70 (1H, s, Ar**H**), 6.65 (2H, dd, *J* = 10.0, 2.0 Hz, Ar**H**), 5.90 (1H, d, *J* = 10.4 Hz, O=CC**H**=), 5.34 (1H, d, *J* = 1.2 Hz, =C**H**$_2$), 4.86 (1H, d, *J* = 1.6 Hz, =C**H**$_2$), 3.89−3.82 (2H, m, NC**H**$_2$), 3.79 (3H, s, OC**H**$_3$), 3.57−3.50 (1H, m, NCH_2C**H**), 2.52−2.46 (1H, m, $O{=}CCH_2C$**H**), 2.43 (3H, s, ArC**H**$_3$), 2.33 (3H, s, ArC**H**$_3$), 1.91 (1H, dd, *J* = 16.4, 5.6 Hz, O=CC**H**$_2$), 1.81 (1H, dd, *J* = 16.4, 12.4 Hz, O=CC**H**$_2$), 1.73 (3H, s, NCC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.2 (C), 159.7 (C), 149.0 (CH), 144.0 (C), 143.5 (C), 141.6 (C), 139.8 (C), 136.8 (C), 129.6 (2 × CH_2), 128.1 (CH), 127.1 (2 × CH_2), 119.4 (CH), 114.8 (CH_2), 113.8 (CH), 109.5 (CH), 63.7 (C), 55.2 (CH_3), 49.5 (CH_2), 47.4 (CH), 41.7 (CH), 34.2 (CH_2), 28.7 (CH_3), 21.7 (CH_3), 21.5 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{26}H_{29}NNaO_4S]^+$ $[M+Na]^+$: 474.1710, found: 474.1690. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.5 mL/min, 210 nm, 25 °C); t_r (minor) = 16.5 min, t_r (major) = 26.1 min, 90% ee.



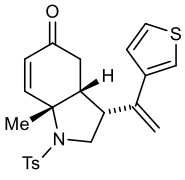
(3*R*,3a*R*,7a*R*)-7a-Methyl-1-(4-methylbenzenesulfonyl)-3-[1-(naphthalen-2-yl)ethenyl]-2,3,3a,4,5,7a-hexahydro-1*H*-indol-5-one (162g). The title compound was prepared according to the General Procedure using allenyl cyclohexa-2,5-dienone **149a** (98.8 mg, 0.30 mmol) and 2-naphthylboronic acid (103.2 mg, 0.60 mmol), and purified by column chromatography (20% EtOAc/petroleum ether) to give **162g** as a colorless solid (109.7 mg, 80%). R_f = 0.51 (30% EtOAc/petroleum ether); m.p. 174−177 °C (Et_2O); $[\alpha]_D^{25}$ –65.8 (*c* 0.79, $CHCl_3$); IR 2921, 1678 (C=O), 1391, 1151, 1057, 864, 788, 707, 676, 647, 623, 585, 550 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84−7.80 (3H, m, Ar**H**), 7.76−7.73 (3H, m, Ar**H**), 7.51-7.43 (3H, m, Ar**H**), 7.32−7.30 (2H, m, Ar**H**), 7.20 (1H, d, *J* = 10.4 Hz, O=CCH=C**H**), 5.88 (1H, dd, *J* = 10.4, 0.8 Hz, O=CC**H**=), 5.49 (1H, d, *J* = 1.6 Hz, =C**H**$_2$), 5.00 (1H, d, *J* = 2.0 Hz, =C**H**$_2$), 4.08−4.02 (1H, m, NC**H**$_2$), 3.95 (1H, dd, *J* = 9.2, 7.2 Hz, NC**H**$_2$), 3.61 (1H, dd, *J* = 10.8, 9.2 Hz, NCH_2C**H**), 2.53−2.46 (1H, m, $O{=}CCH_2C$**H**), 2.44 (3H, m,

ArC**H**$_3$), 1.96−1.83 (2H, m, O=CC**H**$_2$), 1.77 (3H, s, NCHC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.9 (C), 149.0 (CH), 144.0 (C), 143.6 (C), 137.6 (C), 136.8 (C), 133.2 (C), 133.0 (C), 129.6 (2 × CH), 128.5 (CH), 128.1 (2 × CH), 127.6 (CH), 127.1 (2 × CH), 126.5 (CH), 126.3 (CH), 124.9 (CH), 124.2 (CH), 115.4 (CH_2), 63.8 (C), 49.5 (CH_2), 47.4 (CH), 41.8 (CH), 34.2 (CH_2), 28.7 (CH_3), 21.5 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{28}H_{28}NO_3S]^+$ $[M+H]^+$: 458.1784, found: 458.1773. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (95:5 *iso*-hexane:EtOH, 1.0 mL/min, 254 nm, 25 °C); t_r (major) = 46.5 min, t_r (minor) = 54.1 min, 87% ee.

Slow diffusion of petroleum ether into a solution of **162g** in EtOAc gave crystals that were suitable for X-ray crystallography:



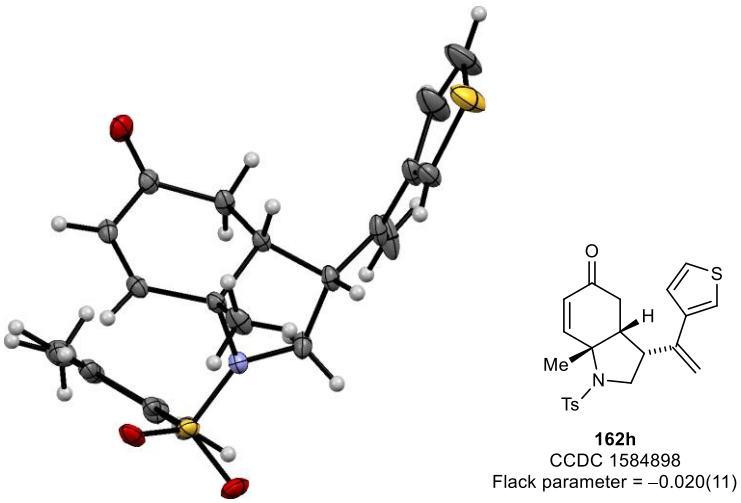
Note: The alkene-naphthyl group is disordered over two positions. The occupancies of the two components was refined competitively, converging to a ratio of 0.84:0.16. This disorder is not shown above, for clarity.



(3*R*,3a*R*,7a*R*)-7a-Methyl-1-(4-methylbenzenesulfonyl)-3-[1-(thiophen-3-yl)ethenyl]-2,3,3a,4,5,7a-hexahydro-1*H*-indol-5-one (162h). The title compound was prepared according to the General Procedure using allenyl cyclohexa-2,5-dienone **149a** (98.8 mg, 0.30 mmol) and 3-thienylboronic acid (76.8 mg, 0.60 mmol), and purified by column chromatography (20% EtOAc/petroleum ether) to give **162h** as a yellow solid (86.8 mg, 70%). R_f = 0.50 (30% EtOAc/petroleum ether); m.p. 118−121 °C (Et_2O); $[\alpha]_D^{25}$ –67.7 (*c* 0.65, $CHCl_3$); IR 2969, 2927, 1678 (C=O), 1337, 1150, 1131, 1111,

1068, 794, 670, 582, 547 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (2H, d, *J* = 8.3 Hz, Ar**H**), 7.31−7.29 (3H, m, Ar**H**), 7.22 (1H, d, *J* = 10.3 Hz, O=CCH=C**H**), 7.18 (1H, dd, *J* = 2.9, 1.4 Hz, Ar**H**), 7.13 (1H, dd, *J* = 5.1, 1.4 Hz, Ar**H**), 5.92 (1H, dd, *J* = 10.3, 0.8 Hz, O=CC**H**=), 5.45 (1H, d, *J* = 0.8 Hz, =C**H**$_2$), 4.87 (1H, s, =C**H**$_2$), 3.85-3.77 (2H, m, NC**H**$_2$), 3.60−3.55 (1H, m, NCH$_2$C**H**), 2.64−2.58 (1H, m, O=CCH$_2$C**H**), 2.42 (3H, s, ArC**H**$_3$), 1.90 (1H, dd, *J* = 16.6, 6.0 Hz, O=CC**H**$_2$), 1.82 (1H, dd, *J* = 16.6, 12.3 Hz, O=CC**H**$_2$), 1.76 (3H, s, NCC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.1 (C), 148.9 (CH), 143.6 (C), 141.4 (C), 138.2 (C), 136.8 (C), 129.6 (2 × CH), 128.1 (CH), 127.1 (2 × CH), 126.3 (CH), 125.6 (CH), 120.6 (CH), 113.3 (CH_2), 63.8 (C), 49.2 (CH_2), 47.7 (CH), 42.0 (CH), 34.3 (CH_2), 28.7 (CH_3), 21.5 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{22}H_{23}NNaO_3S_2]^+$ $[M+Na]^+$: 436.1012, found: 436.0987. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (minor) = 23.8 min, t_r (major) = 25.6 min, 92% ee.

Slow diffusion of petroleum ether into a solution of **162h** in EtOAc gave crystals that were suitable for X-ray crystallography:



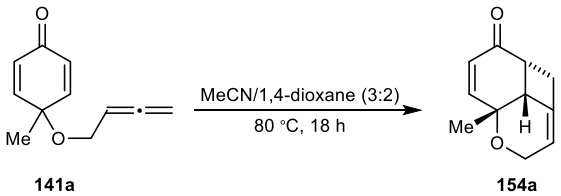
162h
CCDC 1584898
Flack parameter = –0.020(11)

Note: The thiophene ring of the molecule starting from S31 is disordered over two orientations, resulting in split positions for the sulfur and one of the carbon atoms of this ring. The occupancies of the disordered atoms were refined competitively, converging to a ratio of 0.63:0.37. This disorder is not shown above, for clarity.

4.6. [2+2] cycloaddition products

Independent Formation of the [2+2] Cycloaddition Products

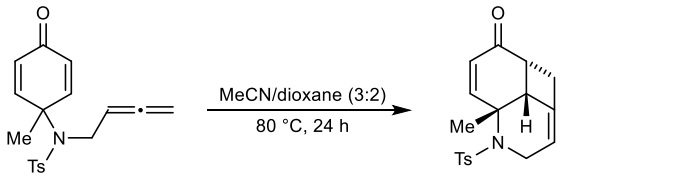
(±)-(3a1*R*,4a*R*,7a*R*)-7a-Methyl-3a1,4,4a,7a-tetrahydrocyclobuta[de]chromen-5(2*H*)-one (154a)



141a **154a**

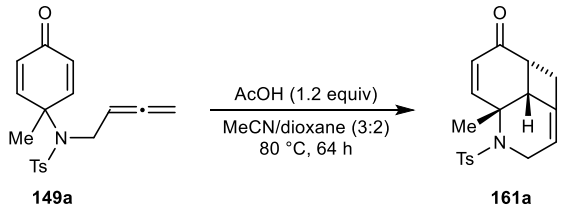
An oven-dried microwave vial fitted with a stirrer bar was charged with allenyl cyclohexa-2,5-dienone **141a** (17.6 mg, 0.10 mmol), then capped with a crimp cap PTFE seal and purged with a stream of N_2. MeCN (0.6 mL) and 1,4-dioxane (0.4 mL) were added and the mixture was stirred at 80 °C for 18 h. The reaction was cooled to room temperature, filtered through a plug of silica using EtOAc as eluent, and concentrated under reduced pressure. The residue was purified by column chromatography to give the *cyclobutane* **154b** as a colorless oil (4 mg, 25%). R_f = 0.21 (20% EtOAc/petroleum ether); IR 2962, 2926, 1714, 1669 (C=O), 1258, 1081, 1015, 863, 791, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.62 (1H, dd, *J* = 10.6, 1.8 Hz, O=CCH=C**H**), 6.05 (1H, dd, *J* = 10.6, 0.6 Hz, O=CC**H**=), 5.38−5.35 (1H, m, OCH_2C**H**=), 4.37−4.32 (1H, m, OC$\mathbf{H}_2$), 4.19−4.14 (1H, m, OC$\mathbf{H}_2$), 3.45−3.36 (1H, m, O=CCHC$\mathbf{H}_2$), 3.34−3.31 (1H, m, O=CCHC**H**), 3.15−3.10 (1H, m, O=CC**H**), 2.72−2.67 (1H, m, O=CCHC$\mathbf{H}_2$), 1.36 (3H, s, C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.2 (C), 152.0 (CH), 134.7 (C), 130.9 (CH), 113.3 (CH), 67.6 (C), 63.8 (CH_2), 46.7 (CH), 40.8 (CH), 39.8 (CH_2), 27.2 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{11}H_{12}NaO_2]^+$ $[M+Na]^+$: 199.0730, found: 199.0730.

(±)-(3a1*R*,4a*R*,7a*R*)-7a-Methyl-1-tosyl-1,2,3a1,4,4a,7a-hexahydro-5*H*-cyclobuta[de]quinolin-5-one (161a)



149a **161a** 44% (by ^1H NMR analysis)

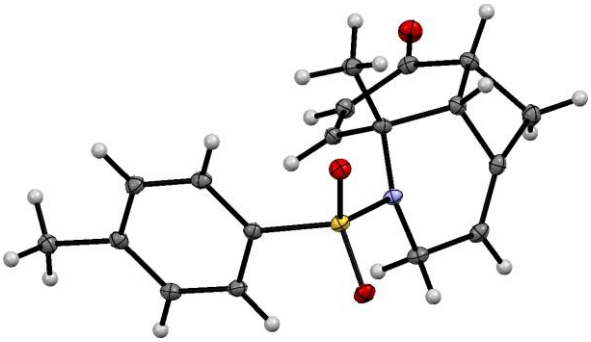
An oven-dried microwave vial fitted with a stirrer bar was charged with allenyl cyclohexa-2,5-dienone **149a** (98.8 mg, 0.30 mmol) and the vial was capped and purged with a stream of N_2. MeCN (1.8 mL) and 1,4-dioxane (1.2 mL) were added. The reaction was stirred at 80 °C for 24 h, cooled to room temperature, filtered through a plug of silica using EtOAc as eluent, and concentrated under reduced pressure. ^{1}H NMR analysis of the residue using an internal standard showed **161a** was formed in 44% yield. Full experimental characterization of **161a** was performed on material obtained by the procedure described below:

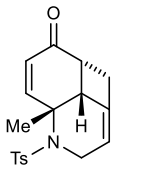


149a **161a**

An oven-dried microwave vial fitted with a stirrer bar was charged with allenyl cyclohexa-2,5-dienone **149a** (98.8 mg, 0.30 mmol) and the vial was capped and purged with a stream of N_2. MeCN (1.8 mL) and 1,4-dioxane (1.2 mL) were added followed by AcOH (28 μL). The reaction was stirred at 80 °C for 64 h, cooled to room temperature, filtered through a plug of silica using EtOAc as eluent, and concentrated under reduced pressure. The residue was purified by column chromatography (30% EtAc/petroleum ether) to give the *cyclobutane* **161a** as a colorless solid (43.4 mg, 44%). R_f = 0.30 (30% EtOAc/petroleum ether); m.p. 110−112 °C (Et_2O); IR 2919, 2850, 1664 (C=O), 1595, 1450, 1339, 1167, 1154, 1143, 928, 850, 813, 749, 720, 675, 617, 544 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76−7.73 (2H, m, Ar**H**), 7.33-7.30 (2H, m, Ar**H**), 6.57 (1H, dd, *J* = 10.8, 2.0 Hz, O=CCH=C**H**), 5.93 (1H, d, *J* = 10.4 Hz, O=CC**H**=), 5.36 (1H, quin d, *J* = 2.4, 0.8 Hz, NCH_2C**H=**), 4.74−4.68 (1H, m, NC**H**$_2$), 3.75−3.69 (1H, m, NC**H**$_2$), 3.27-3.21 (2H, m, CHC**H**$_2$C=CH), 3.05−3.01 (1H, m, O=CC**H**CH_2), 2.64−2.59 (1H, m, O=CCHC**H**), 2.45 (3H, s, ArC**H**$_3$), 1.55 (3H, s, NCC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.1 (C), 151.4 (CH), 143.5 (C), 139.8 (C), 135.1 (C), 129.7 (2 × CH), 129.3 (CH), 126.9 (2 × CH), 112.0 (CH), 55.8 (C), 48.7 (CH), 46.5 (CH_2), 40.4 (CH), 38.7 (CH_2), 25.9 (CH_3), 21.6 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{18}H_{20}NO_3S]^+$ $[M+H]^+$: 330.1158, found: 330.1160.

Slow diffusion of petroleum ether into a solution of **161a** in EtOAc gave crystals that were suitable for X-ray crystallography:

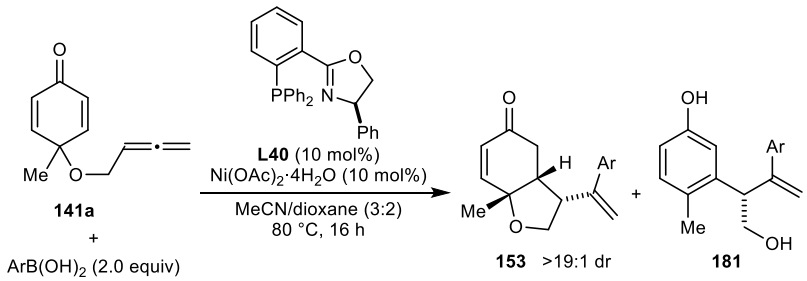




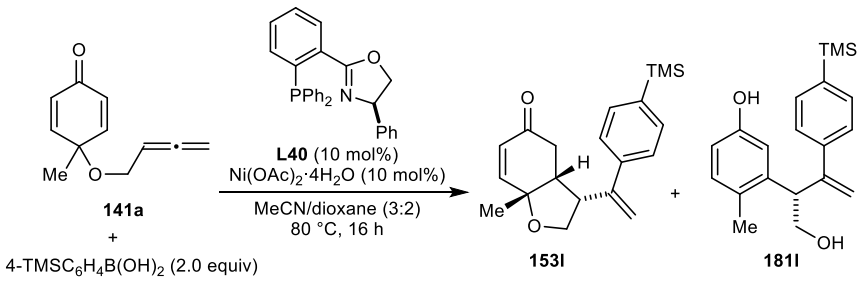
3a
CCDC 1584899

4.7. Reactions producing phenols

Formation of side products phenol



(3*R*,3a*R*,7a*R*)-7a-Methyl-3-(1-[4-(trimethylsilyl)phenyl]ethenyl)-2,3,3a,4,5,7a-hexahydro-1-benzofuran-5-one (153l) and 3-[(*S*)-1-hydroxy-3-[4-(trimethylsilyl)phenyl]but-3-en-2-yl]-4-methylphenol (181l)

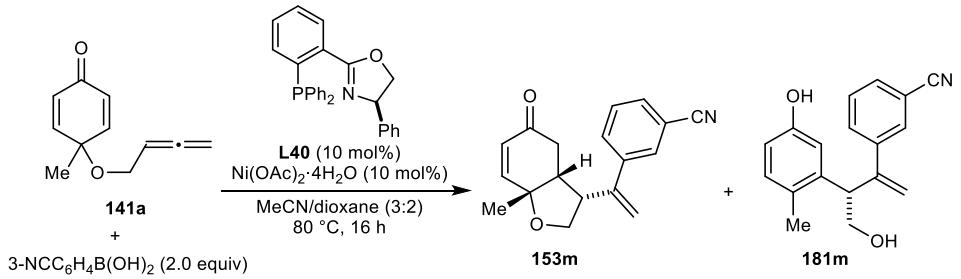


The General Procedure was followed using allenyl cyclohexa-2,5-dienone **141a** (52.8 mg, 0.30 mmol) and 4-(trimethylsilyl)phenylboronic acid (116.5 mg, 0.60 mmol). Purification by column chromatography (30% EtOAc/petroleum ether) gave **153l** as a colorless solid (33.8 mg, 35%) followed by **181l** as a white amorphous solid (14.1 mg, 14%).

Data for **153l**: R_f = 0.44 (30% EtOAc/petroleum ether); m.p. 90-93 °C (Et_2O); $[\alpha]_D^{25}$ −63.2 (*c* 0.76, $CHCl_3$); IR 2955, 1683 (C=O), 1387, 1248, 1154, 1117, 1035, 828, 733, 701, 664 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (2H, d, *J* = 8.2 Hz, Ar**H**), 7.37 (2H, d, *J* = 8.2 Hz, Ar**H**), 6.61 (1H, d, *J* = 10.2 Hz, O=CCH=C**H**), 5.58 (1H, d, *J* = 10.2 Hz, O=CC**H**=), 5.44 (1H, d, *J* = 0.5 Hz, =C$\mathbf{H}_2$), 4.95 (1H, d, *J* = 1.5 Hz, =C$\mathbf{H}_2$), 4.25 (1H, dd, *J* = 8.8, 7.3 Hz, OC$\mathbf{H}_2$), 4.06 (1H, dd, *J* = 10.3, 8.8 Hz, OC$\mathbf{H}_2$), 3.91 (1H, dd, *J* = 17.4, 8.4 Hz, $OCH_2C\mathbf{H}$), 2.63 (1H, td, *J* = 8.4, 6.8 Hz, $O{=}CCH_2C\mathbf{H}$), 2.27 (1H, dd, *J* = 16.8, 8.4 Hz, O=CC$\mathbf{H}_2$), 2.08 (1H, dd, *J* = 16.8, 6.8 Hz, O=CC$\mathbf{H}_2$), 1.50 (3H, s, C$\mathbf{H}_3$), 0.28 (9H, s, Si(C$\mathbf{H}_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.7 (C), 150.1 (CH), 144.1 (C), 141.7 (C), 140.3 (C), 133.7 (2 × CH), 128.8 (CH), 125.3 (2 × CH), 115.0 (CH_2), 78.7 (C), 69.6 (CH_2), 45.5 (CH), 44.0 (CH), 35.3 (CH_2), 27.4 (CH_3), −1.2 (3 × CH_3); HRMS (ESI) Exact mass calcd for $[C_{20}H_{27}O_2Si]^+$ $[M+H]^+$: 327.1775, found: 327.1756. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (major) = 7.2 min, t_r (minor) = 11.7 min, 93% ee.

Data for **181l**: R_f = 0.32 (40% EtOAc/petroleum ether); $[\alpha]_D^{25}$ −28.6 (*c* 0.14, $CHCl_3$); IR 3382 (OH), 2957, 2926, 1723, 1462, 1381, 1264, 1248, 1124, 1075, 840, 829, 735, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (2H, d, *J* = 8.3 Hz, Ar**H**), 7.34 (2H, d, *J* = 8.3 Hz, Ar**H**), 7.05 (1H, d, *J* = 8.0 Hz, Ar**H**), 6.87 (1H, d, *J* = 3.0 Hz, Ar**H**), 6.63 (1H, dd, *J* = 8.0, 2.5 Hz, Ar**H**), 5.59 (1H, s, =C$\mathbf{H}_2$), 5.13 (1H, s, =C$\mathbf{H}_2$), 4.97 (1H, br s, O**H**), 4.32 (1H, t, *J* = 6.5 Hz, ArC**H**), 3.98 (1H, dd, *J* = 11.5, 6.5 Hz, C$\mathbf{H}_2$OH), 3.89 (1H, dd, *J* = 11.5, 6.5 Hz, C$\mathbf{H}_2$OH), 2.31 (3H, s, ArC$\mathbf{H_3}$), 0.25 (9H, s, Si(C$\mathbf{H}_3$)$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.0 (C), 147.8 (C), 141.9 (C), 139.9 (C), 139.5 (C), 133.4 (2 × CH), 131.7 (CH), 128.7 (C), 125.5 (2 × CH), 114.8 (CH_2), 114.1 (CH), 113.6 (CH), 64.4 (CH_2), 48.2 (CH), 18.2 (CH_3), −1.2 (3 × CH_3); HRMS (ESI) Exact mass calcd for $[C_{20}H_{26}NaO_2Si]^+$ $[M+Na]^+$: 349.1594, found: 349.1599. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH), 1 mL/min, 280 nm, 25 °C); t_r (major) = 8.8 min, t_r (minor) = 13.5 min, 94% ee.

(3*R*,3a*R*,7a*R*)-3-[1-(7a-Methyl-5-oxo-2,3,3a,4,5,7a-hexahydro-1-benzofuran-3-yl)ethenyl]benzonitrile (153m) and 3-[(*S*)-4-hydroxy-3-(5-hydroxy-2-methylphenyl)but-1-en-2-yl]benzonitrile (181m)

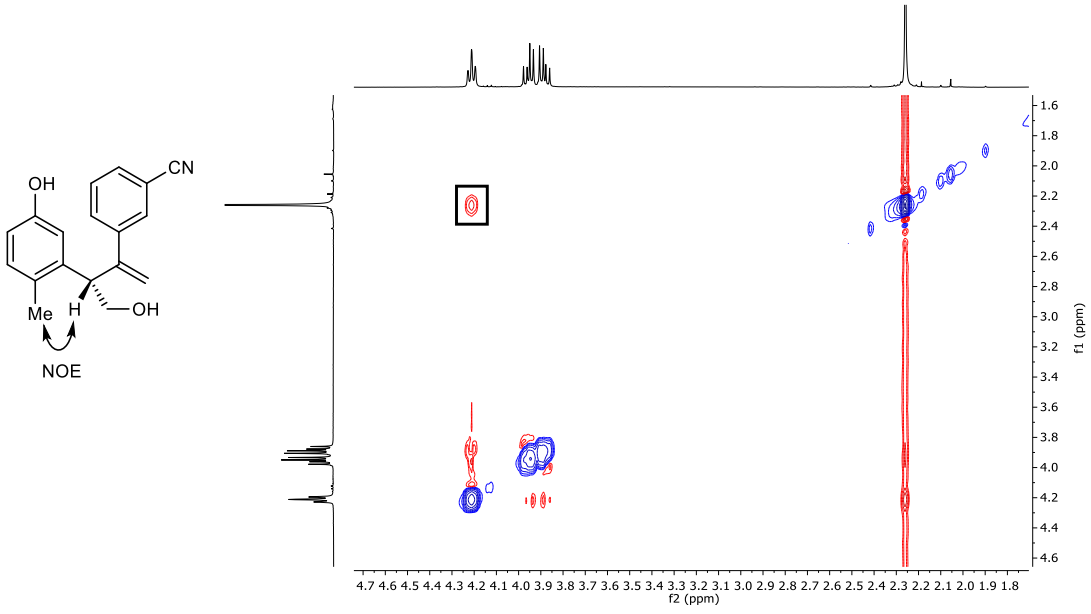


The General Procedure was followed using allenyl cyclohexa-2,5-dienone **141a** (105.6 mg, 0.60 mmol) and 3-cyanophenylboronic acid (176.3 mg, 1.20 mmol). Purification by column chromatography (40% EtOAc/petroleum ether) gave **153m** as a colorless oil (46.9 mg, 28%) followed by **181m** as a white amorphous solid (99.3 mg, 59%).

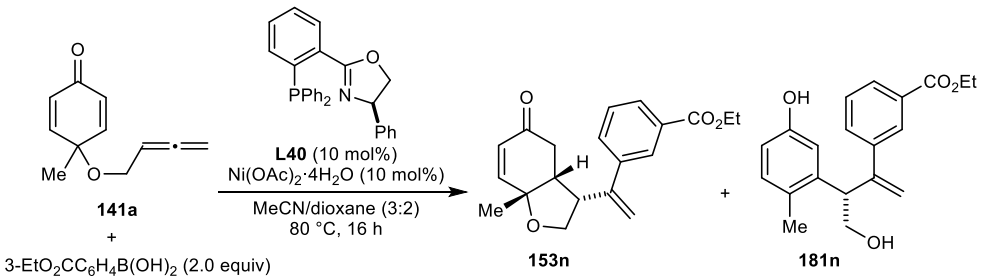
Data for **153m**: R_f = 0.23 (40% EtOAc/petroleum ether); $[\alpha]_D^{25}$ −80.0 (*c* 0.35, $CHCl_3$); IR 3058, 2972, 2230 (C≡N), 1681 (C=O), 1482, 1373, 1266, 1119, 1036, 904, 805, 732, 703, 671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66−7.59 (3H, m, Ar**H**), 7.49 (1H, t, *J* = 8.0 Hz, Ar**H**), 6.61 (1H, d, *J* = 10.0 Hz, O=CCH=C**H**), 6.00 (1H, d, *J* = 10.0 Hz, O=CC**H**=), 5.49 (1H, s, =C$\mathbf{H}_2$), 5.10 (1H, d, *J* = 1.6 Hz, =C$\mathbf{H}_2$), 4.25 (1H, dd, *J* = 8.8, 7.2 Hz, OC$\mathbf{H}_2$), 4.02 (1H, t, *J* = 9.6 Hz, OC$\mathbf{H}_2$), 3.80 (1H, q, *J* = 8.8 Hz, $OCH_2C\mathbf{H}$), 2.63 (1H, dt, *J* = 8.4, 7.2 Hz, $O{=}CCH_2C\mathbf{H}$), 2.21 (1H, dd, *J* = 16.8, 7.6 Hz, O=CC$\mathbf{H}_2$), 2.09 (1H, dd, *J* = 16.8, 6.8 Hz, O=CC$\mathbf{H}_2$), 1.51 (3H, s, OCC$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.8 (C), 150.2 (CH), 142.7 (C), 142.4 (C), 131.4 (CH), 130.5 (CH), 129.6 (CH), 129.3 (CH), 128.9 (CH), 118.5 (C), 117.5 (CH_2), 112.9 (C), 78.9 (C), 69.5 (CH_2), 45.4 (CH), 44.2 (CH), 35.5 (CH_2), 27.0 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{18}H_{17}NNaO_2]^+$ $[M+Na]^+$: 302.1151, found: 302.1149. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH), 1 mL/min, 254 nm, 25 °C); t_r (major) = 16.9 min, t_r (minor) = 28.0 min, 89% ee.

Data for **181m**: R_f = 0.16 (40% EtOAc/petroleum ether); $[\alpha]_D^{25}$ −4.7 (*c* 0.86, $CHCl_3$); IR 3436 (OH), 2926, 2230, 1667, 1620, 1587, 1501, 1292, 1265, 1056, 1015, 907, 808, 735, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (1H, td, *J* = 1.8, 0.5 Hz, Ar**H**), 7.51 (1H, d, *J* = 1.7 Hz, Ar**H**), 7.49 (1H, d, *J* = 1.7 Hz, Ar**H**), 7.37−7.34 (1H, m, Ar**H**), 7.01 (1H, dd, *J* = 8.2, 0.8 Hz, Ar**H**), 6.76 (1H, d, *J* = 2.7 Hz, Ar**H**), 6.62 (1H, dd, *J* = 8.2, 2.7 Hz, Ar**H**), 5.51 (1H, s, =C**H**$_2$), 5.25 (1H, d, *J* = 0.9 Hz, =C**H**$_2$), 4.21 (1H, td, *J* = 6.6, 1.2 Hz, ArC**H**), 3.98−3.86 (2H, m, C**H**$_2$OH), 2.26 (3H, s, ArC**H**$_3$), the two O**H** protons were not observed clearly); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3 (C), 146.3 (C), 143.1 (C), 138.4 (C), 131.9 (CH), 131.0 (CH), 130.8 (CH), 130.1 (CH), 129.2 (CH), 128.4 (C), 118.7 (C), 116.5 (CH_2), 114.04 (CH), 114.02 (CH), 112.3 (C), 64.3 (CH_2), 48.0 (CH), 18.7 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{18}H_{17}NNaO_2]^+$ $[M+Na]^+$: 302.1151, found: 302.1146. Enantiomeric excess was determined by HPLC with a Chiralpak IC-3 column (90:10 *iso*-hexane:*i*-PrOH), 1.5 mL/min, 254 nm, 25 °C); t_r (minor) = 34.0 min, t_r (major) = 41.5 min, 91% ee.

NOE spectrum of **181m**



(3*R*,3a*R*,7a*R*)-3-[1-(7a-Methyl-5-oxo-2,3,3a,4,5,7a-hexahydro-1-benzofuran-3-yl)ethenyl]benzoate (153n) and ethyl 3-[(*S*)-4-hydroxy-3-(5-hydroxy-2-methylphenyl)but-1-en-2-yl]benzoate (181n)



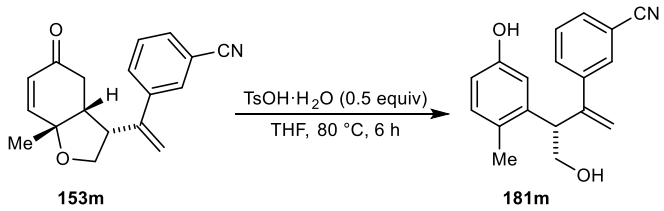
The General Procedure was followed using allenyl cyclohexa-2,5-dienone **141a** (52.8 mg, 0.30 mmol) and 3-ethoxycarbonylphenylboronic acid (116.4 mg, 0.60 mmol). Purification by column chromatography (30% EtOAc/petroleum ether) gave **153n** as pale yellow oil (62.7 mg, 64%) followed by **181n** as a white amorphous (21.2 mg, 22%).

Data for **153n**: R_f = 0.23 (30% EtOAc/petroleum ether); $[\alpha]_D^{25}$ –58.7 (*c* 0.75, $CHCl_3$); IR 3055, 2980, 1715 (C=O), 1684 (C=O), 1289, 1265, 1024, 906, 875, 732, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (1H, t, *J* = 1.9 Hz, Ar**H**), 7.99 (1H, dt, *J* = 7.7, 1.4 Hz, Ar**H**), 7.59 (1H, ddd, *J* = 7.8, 2.0, 1.2 Hz, Ar**H**), 7.44 (1H, td, *J* = 8.0, 0.4 Hz, Ar**H**), 6.61 (1H, d, *J* = 10.0 Hz, O=CCH=C**H**), 5.98 (1H, d, *J* = 10.4 Hz, O=CC**H**=), 5.50 (1H, d, *J* = 1.2 Hz, =C$\mathbf{H}_2$), 5.03 (1H, d, *J* = 1.6 Hz, =C$\mathbf{H}_2$), 4.40 (2H, q, *J* = 7.2 Hz, C$\mathbf{H}_2$CH$_3$), 4.26 (1H, dd, *J* = 8.8, 7.2 Hz, OC$\mathbf{H}_2$), 4.05 (1H, dd, *J* = 10.4, 8.8 Hz, OC$\mathbf{H}_2$), 3.91 (1H, dd, *J* = 17.2, 8.8 Hz, OCH$_2$C**H**), 2.63 (1H, td, *J* = 8.4, 6.8 Hz, O=CCH$_2$C**H**), 2.24 (1H, dd, *J* = 16.8, 8.0 Hz, O=CC$\mathbf{H}_2$), 2.07 (1H, dd, *J* = 16.8, 6.8 Hz, O=CC$\mathbf{H}_2$), 1.50 (3H, s, OCC$\mathbf{H}_3$), 1.42 (3H, t, *J* = 7.2 Hz, CH$_2$C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.3 (C), 166.3 (C), 150.2 (CH), 143.3 (C), 141.6 (C), 130.9 (C), 130.4 (CH), 129.0 (CH), 128.8 (CH), 128.8 (CH), 126.8 (CH), 116.1 (CH_2), 78.8 (C), 69.6 (CH_2), 61.1 (CH_2), 45.5 (CH), 44.0 (CH), 35.4 (CH_2), 27.3 (CH_3), 14.3 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{20}H_{22}NaO_4]^+$ $[M+Na]^+$: 349.1410, found: 349.1409. Enantiomeric excess was determined by HPLC with a

Chiralpak IA-3 column (98:2 *iso*-hexane:*i*-PrOH, 0.5 mL/min, 230 nm, 25 °C); t_r (major) = 103.5 min, t_r (minor) = 121.8 min, 91% ee.

Data for **181n**: R_f = 0.21 (40% EtOAc/petroleum ether); $[\alpha]_D^{25}$ +36.4 (*c* 0.33, $CHCl_3$); IR 3369 (OH), 2925, 2855, 1715 (C=O), 1462, 1368, 1290, 1264, 1020, 907, 735, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (1H, t, *J* = 2.0 Hz, Ar**H**), 7.91 (1H, dt, *J* = 7.6, 1.2 Hz, Ar**H**), 7.50 (1H, ddd, *J* = 6.8, 2.0, 0.8 Hz, Ar**H**), 7.34 (1H, t, *J* = 7.6 Hz, Ar**H**), 7.03 (1H, d, *J* = 8.0 Hz, Ar**H**), 6.81 (1H, d, *J* = 2.8 Hz, Ar**H**), 6.62 (1H, dd, *J* = 8.4, 2.8 Hz, Ar**H**), 5.60 (1H, s, =C**H**$_2$), 5.23 (1H, s, =C**H**$_2$), 4.39−4.30 (3H, m, C**H**$_2$CH$_3$ and CH$_2$O**H)**, 4.00 (1H, dd, *J* = 11.2, 6.8 Hz, C**H**$_2$OH), 3.90 (1H, dd, *J* = 11.6, 6.4 Hz, C**H**$_2$OH), 2.32 (3H, s, ArC**H**$_3$), 1.72 (1H, br s, O**H**), 1.39 (3H, t, *J* = 6.8 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6 (C), 154.1 (C), 147.2 (C), 141.9 (C), 139.1 (C), 131.8 (CH), 130.6 (CH), 130.5 (C), 128.7 (CH), 128.6 (C), 128.4 (CH), 127.5 (CH), 115.2 (CH_2), 114.1 (CH), 113.8 (CH), 64.6 (CH_2), 61.1 (CH_2), 48.1 (CH), 18.8 (CH_3), 14.3 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{20}H_{23}O_4]^+$ $[M+H]^+$: 327.1591, found: 327.1598. Enantiomeric excess was determined by HPLC with OD-H (90:10 *iso*-hexane:*i*-PrOH), 1 mL/min, 280 nm, 25 °C); t_r (major) = 18.2 min, t_r (minor) = 37.0 min, 91% ee.

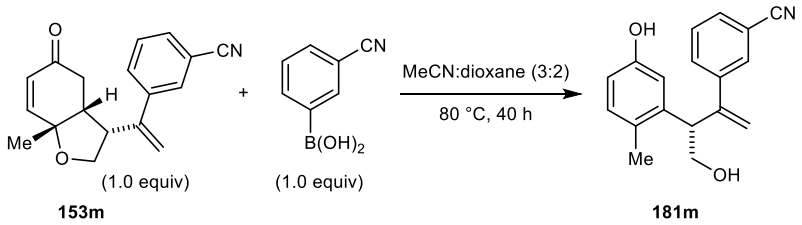
Acid-Catalyzed of Hexahydrobenzofuran-5-one 153m into Phenol 181m



153m **181m**

An oven-dried microwave vial fitted with a stirrer bar was charged with 6,5-bicycle **153m** (14.0 mg, 0.05 mmol) and *p*-toluenesulfonic acid monohydrate (4.8 mg, 0.025 mmol), then capped with a crimp cap PTFE seal and purged with a stream of N_2. THF (0.5 mL) was added and the mixture was stirred at 80 °C for 6 h. The reaction was cooled to room temperature, filtered through a plug of silica and concentrated under reduced pressure. The residue was purified by column chromatography to give phenol **181m** as a colorless oil (9.1 mg, 65%).

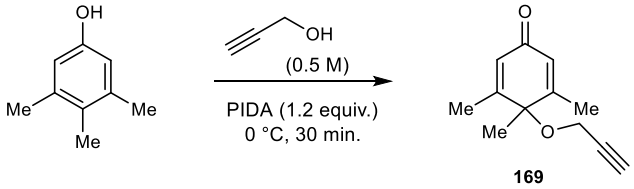
Transformation of hexahydrobenzofuran-5-one 153m into phenol 181m



An oven-dried microwave vial fitted with a stirrer bar was charged with 6,5-bicycle **153m** (3.4 mg, 0.012 mmol) and 3-cyanophenylboronic acid (1.8 mg, 0.012 mmol), then capped with a crimp cap PTFE seal and purged with a stream of N_2. Mixture of MeCN/1,4-dioxane (3:2) (0.125 mL) was added and the mixture was stirred at 80 °C for 40 h. The reaction was cooled to room temperature, filtered through a plug of silica and concentrated under reduced pressure. The yield (31%) was determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-dimethoxybenzene as an internal standard.

4.8. Further exploration of allenyl substrates scope

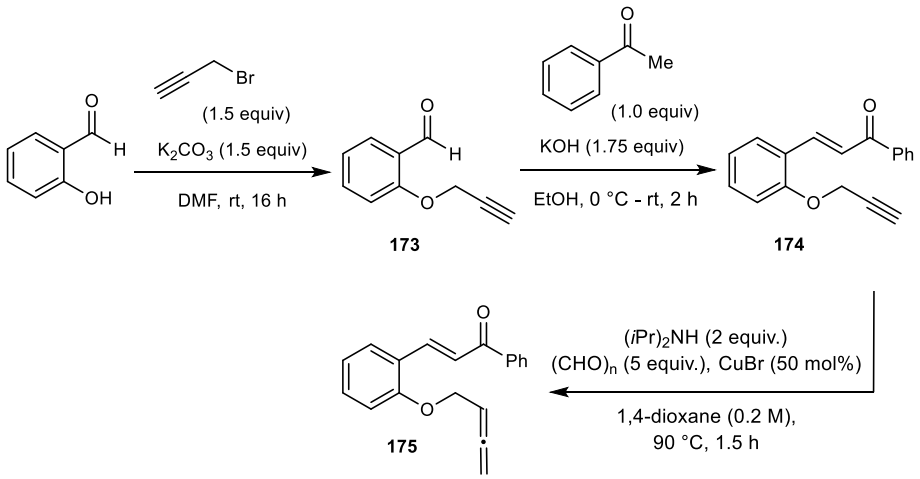
3,4,5-trimethyl-4-(prop-2-yn-1-yloxy)cyclohexa-2,5-dien-1-one (169)



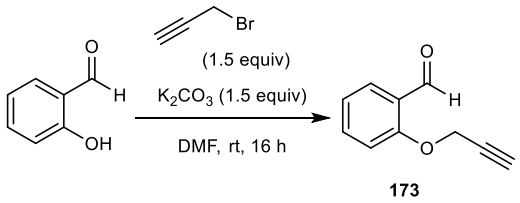
To a solution of 3,4,5-trimethoxyphenol (272 mg, 2.00 mmol, 1 equiv) in propargyl alcohol (4 mL), (diacetoxyiodo)benzene (773 mg, 4.80 mmol, 1.2 equiv) was added in one portion at 0 ^{o}C. The reaction mixture was then allowed to stir at 0 ^{o}C for 30 min. The resulting solution was diluted with dichloromethane (5 mL), washed with aqueous saturated solution of $NaHCO_3$ (2 × 5 mL) and brine (2 × 5 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The mixture was purified by column chromatography (20% EtOAc/pet. ether) to give *alkyne* **169** (229 mg, 60%) as an off-white solid. R_f = 0.37 (20% EtOAc/pet. ether); m.p: 74–76 ^{o}C

(Et_2O); IR 3255, 2991, 2124, 1669 (C=O), 1631, 1438, 1380, 1301, 1168, 1081, 1045, 893, 666, 625, 475 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.18 (2H, d, *J* = 1.3 Hz, COCH=C**H**), 3.70 (2H, d, *J* = 2.5 Hz, C**H₂**C≡), 2.46 (1H, t, *J* = 2.5 Hz, ≡C**H**), 2.06 (6H, s, 2 × CH=CC**H₃**), 1.46 (3H, s, C**H₃**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.9 (C), 159.6 (2 × C), 129.4 (2 × CH), 79.1 (C), 77.2 (C), 74.7 (CH), 52.9 (CH_2), 28.8 (CH_3), 17.9 (2 × CH_3); HRMS (ESI) Exact mass calcd for $[C_{12}H_{15}NaO_2]^+$ $[M + Na]^+$: 213.0886, found: 213.0884.

Preparation of allenyl ketone 175



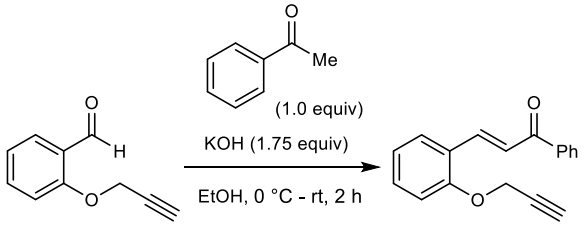
2-(prop-2-yn-1-yloxy)benzaldehyde (173)



To a salicylaldehyde (1.5 mL, 14.0 mmol) in DMF (5 mL) was added K2CO3 (2.92 g, 21.1 mmol), propargyl bromide (2.25 mL, 21.1 mmol, 80% in toluene) at 0 °C. The resulting mixture was stirred for 16 h at room temperature. Ice-cold water (5 mL) was added to the mixture to quench reaction. The precipitate solid was filtered, washed with water and recrystalized from MeOH to furnish **173** as a pure pale yellow solid (1.95 g, 86%). The product was pure and carried out for next step without purification. R_f = 0.72 (30% EtOAc/petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) 10.50 (1H, d, *J* = 0.8 Hz, O=C**H**), 7.87 (1H, dd, *J* = 7.7, 1.9 Hz, Ar**H**), 7.58 (1H, ddd, *J* = 8.5, 7.3, 1.9 Hz, Ar**H**), 7.16–7.06 (2H, m, Ar**H**), 4.84 (2H, d, *J* = 2.4

Hz, OC**H**$_2$), 2.58 (1H, t, *J* = 2.4 Hz, ≡C**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.5 (O=CH), 159.7 (C), 135.7 (CH), 128.6 (CH), 125.5 (C), 121.7 (CH), 113.2 (CH), 77.7 (C), 76.5 (CH), 56.4 (CH_2). Spectroscopic data consistent with those reported previously.[144]

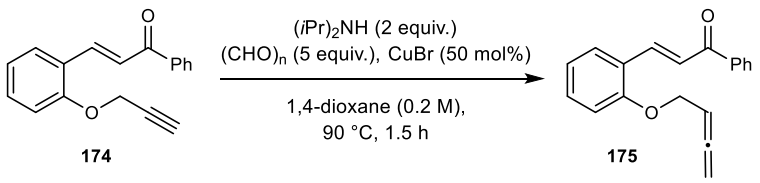
(*E*)-1-phenyl-3-(2-(prop-2-yn-1-yloxy)phenyl)prop-2-en-1-one (174)



173 174

To a 2-(prop-2-yn-1-yloxy)benzaldehyde (**173**) (801 mg, 5.00 mmol) and KOH (490 mg, 8.75 mmol) in ethanol (5 mL) was added slowly a solution of acetophenone (0.58 mL, 5.00 mmol) in ethanol (0.40 mL) within 10 min. The reaction was stirred for 2 h at room temperature and quenched with ice-cold water to form yellow solid. The solid was filtered, washed with water (2 × 5 mL), wash with ethanol (2 × 5 mL) to afford the alkyne **174** (1.02 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (1H, d, *J* = 15.9 Hz, O=CCH=C**H**), 8.06–8.02 (2H, m, Ar**H**), 7.72–7.64 (2H, m, Ar**H** and O=CC**H**), 7.63–7.56 (1H, m, Ar**H**), 7.55–7.47 (2H, m, Ar**H**), 7.40 (1H, ddd, *J* = 8.4, 7.3, 1.7 Hz, Ar**H**), 7.11–7.03 (2H, m, Ar**H**), 4.82 (2H, d, *J* = 2.4 Hz, OC**H**$_2$), 2.56 (1H, t, *J* = 2.4 Hz, ≡C**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.0 (C), 156.7 (C), 140.0 (CH), 138.4 (C), 132.6 (CH), 131.5 (CH), 129.5 (CH), 128.6 (2 × CH), 128.5 (2 × CH), 124.6 (C), 123.4 (CH), 121.7 (CH), 112.8 (CH), 78.2 (C), 76.0 (CH), 56.2 (CH_2); HRMS (ESI) Exact mass calcd for $[C_{18}H_{14}NaO_2]^+$ $[M+Na]^+$: 285.0886, found: 285.0884. Spectroscopic data consistent with those reported previously.[123]

(*E*)-3-(2-(buta-2,3-dien-1-yloxy)phenyl)-1-phenylprop-2-en-1-one (175)

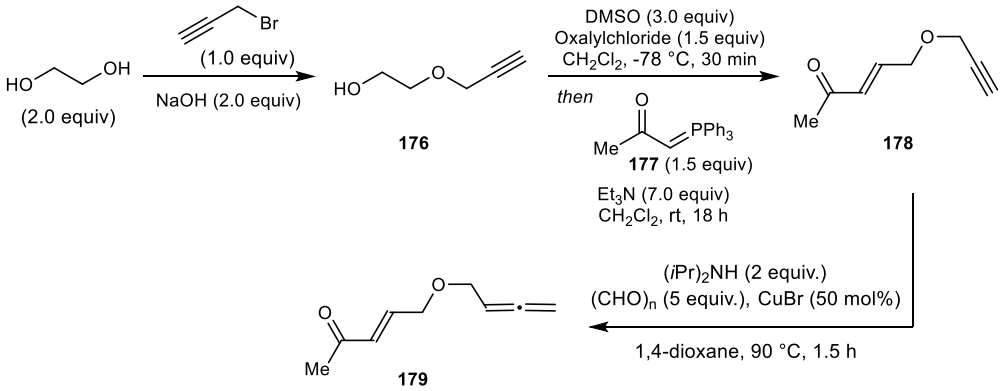


174 175

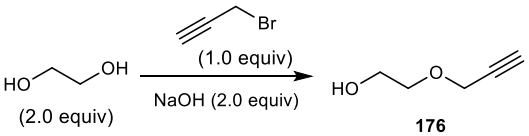
To a solution of alkyne (*E*)-1-phenyl-3-(2-(prop-2-yn-1-yloxy)phenyl)prop-2-en-1-one (**174**) [123] (500 mg, 1.90 mmol) in anhydrous 1,4-dioxane (9.5 mL) under inert

atmosphere, paraformaldehyde (285 mg, 9.5 mmol), CuBr (136 mg, 0.95 mmol) and diisopropylamine (0.53 mL, 3.80 mmol) were added subsequently and the mixture was allowed to react at 90 °C for 1.5 h. The reaction mixture was allowed to cool at room temperature, filtered through a pad of celite, and concentrated under reduce pressure. The mixture was purified by column chromatography (20% EtOAc/petroleum ether) to give *allene* **175** (257 mg, 49%) as a pale-yellow oil. R_f = 0.29 (10% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (1H, d, *J* = 15.9 Hz, O=CCH=C**H**), 8.07–7.98 (2H, m, Ar**H**), 7.73–7.63 (2H, m, Ar**H** and O=CC**H**), 7.62–7.55 (1H, m, Ar**H**), 7.55–7.46 (2H, m, Ar**H**), 7.37 (1H, ddd, *J* = 8.3, 7.3, 1.7 Hz, Ar**H**), 7.08–6.92 (2H, m, Ar**H**), 5.46 (1H, quin, *J* = 6.6 Hz, CH_2C**H**), 4.89 (2H, dt, *J* = 6.6, 2.6 Hz, =C**H$_2$**), 4.68 (2H, dt, *J* = 6.7, 2.6 Hz, OC**H$_2$**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.5 (C), 191.2 (C), 157.6 (C), 140.4 (CH), 138.5 (C), 132.5 (CH), 131.5 (CH), 129.5 (CH), 128.5 (4 × CH), 124.4 (C), 123.1 (CH), 121.0 (CH), 112.7 (CH), 86.9 (CH), 76.9 (CH_2), 66.2 (CH_2); HRMS (ESI) Exact mass calcd for $[C_{19}H_{16}NaO_2]^+$ $[M+Na]^+$: 299.1043 , found: 299.1043. Spectroscopic data consistent with those reported previously.[124]

Preparation of allenyl ketone 179



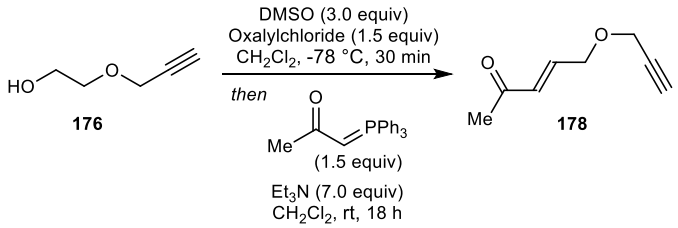
2-(prop-2-yn-1-yloxy)ethan-1-ol (176)



To a solution of propargyl bromide (80% in toluene, 2.50 mL, 22.5 mmol) and ethylene glycol (2.5 mL) at 0 °C was added NaOH (1.80 g, 45.0 mmol). Reaction mixture was stirred at 45 °C for 3 h. The precipitate was filtered and washed with

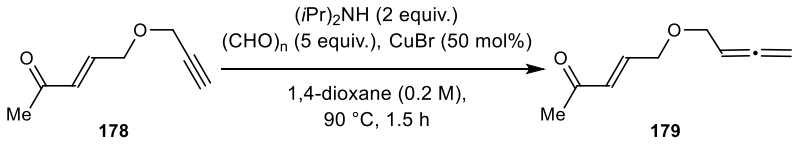
CH_2Cl_2 (2 × 10 mL). The organic layer was dried over Na_2SO_4, concentrated under vacuo. The crude was purified by silica gel chromatography (20% EtOAc/petroleum ether) to give the alkyne **176** (1.12 g, 50%). R_f = 0.25 (20% EtOAc/petroleum ether; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (2H, dd, *J* = 2.9, 1.5 Hz, OC**H₂**C≡), 3.82–3.74 (2H, m, HOC**H₂**), 3.71–3.62 (2H, m, CH_2C**H₂**O), 2.46 (1H, td, *J* = 2.4, 1.0 Hz, ≡C**H**), 2.09 (1H, s, O**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 79.4 (C), 74.7 (CH), 71.2 (CH_2), 61.7 (CH_2), 58.4 (CH_2). Spectroscopic data consistent with those reported previously.[145]

(*E*)-5-(prop-2-yn-1-yloxy)pent-3-en-2-one (178)



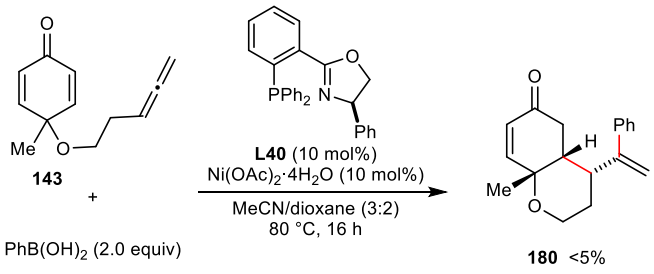
To a solution of DMSO (2.39 mL, 33.7 mmol) in CH_2Cl_2 at 0 °C was added oxalyl chloride (1.42 mL, 16.8 mmol) dropwise, the reaction was stirred for 15 min. Then alkyne 2-(prop-2-yn-1-yloxy)ethan-1-ol **176** (1.12 g, 11.2 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise at -78 °C, the reaction was stirred for 30 min. The mixture was alloed to warm to -50 °C, Et_3N (11.0 mL, 78.6 mmol) was added by syringe to form white suspension. The reaction was stirred for 2 h at room temperature. The mixture was quenched with 0.1 N HCl (50 mL). The organic layer was separated, extracted with CH_2Cl_2 (3 x 10 mL) dried over $MgSO_4$. Ph_3P=CHC(O)CH_3 (5.35 g, 16.8 mmol) was added to the obtained solution and stirred for 15 h at room temperature. The solvent was removed under reduced pressure and the crude was purified by column chromatography (33% EtOAc/petroleum ether) to give **178** as a colorless oil (400 mg, 26%). R_f = 0.51 (30% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (1H, dt, *J* = 16.1, 4.5 Hz, O=CCH=C**H**), 6.33 (1H, dt, *J* = 16.0, 1.9 Hz, O=CC**H**), 4.27 (2H, ddd, *J* = 4.6, 1.9, 0.6 Hz, CHC**H₂**O), 4.22 (2H, dd, *J* = 2.4, 0.6 Hz, OC**H₂**C≡), 2.48 (1H, t, *J* = 2.4 Hz, ≡C**H**,), 2.28 (3H, s, C**H₃**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.0 (C), 141.9 (CH), 130.6 (CH), 79.0 (C), 75.1 (CH), 68.3 (CH_2), 58.0 (CH_2), 27.4 (CH_3); HRMS (ESI) Exact mass calcd for $[C_8H_{11}O_2]^+$ $[M+H]^+$: 139.0754 , found: 139.0740. Spectroscopic data consistent with those reported previously.[146]

(3E)-5-(buta-2,3-dien-1-yloxy)pent-3-en-2-one (179)

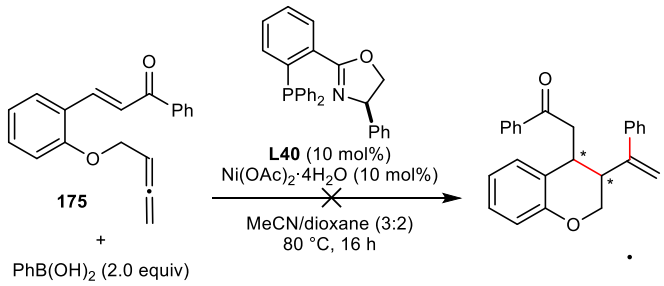


To a solution of alkyne (*3E*)-5-(prop-2-yn-1-yloxy)pent-3-en-2-one (**178**) [146] (400 mg, 2.90 mmol, 1 equiv) in anhydrous 1,4-dioxane (14 mL) under inert atmosphere, paraformaldehyde (435 mg, 14.47 mmol, 5 equiv), CuBr (208 mg, 1.45 mmol, 50 mol%), and diisopropylamine (0.81 mL, 5.79 mmol) were added subsequently and the mixture was allowed to react at 90 ^{o}C for 1.5 h. The reaction mixture was allowed to cool at room temperature, filtered through a pad of celite, and concentrated under reduce pressure. The mixture was purified by column chromatography (20% EtOAc, 80% petroleum ether) to give *allene* **179** (119 mg, 27%) as a pale-yellow oil. R_f = 0.37 (20% EtOAc, 80% petroleum ether); IR 2914, 2854, 1955 (C=C=C), 1674 (C=O), 1634, 1427, 1358, 1252, 1116, 1084, 1033, 970, 848, 543, 473 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (1H, dtd, *J* = 16.0, 4.5, 0.9 Hz, O=CCH=C**H**), 6.35–6.28 (1H, m, O=CC**H**), 5.24 (1H, quin, *J* = 6.8 Hz, CH_2C**H**C), 4.88–4.80 (2H, m, =C**H**$_2$), 4.24–4.17 (2H, m, CH=CHC**H**$_2$O), 4.07 (2H, dtd, *J* = 6.9, 2.4, 1.0 Hz, C**H**$_2$CHC), 2.27 (3H, d, *J* = 1.0 Hz, CH_3); ^{13}C NMR (101 MHZ, $CDCl_3$) δ 209.4 (C), 198.2 (C), 142.8 (CH), 130.3 (CH), 87.2 (CH), 75.9 (CH_2), 68.6 (CH_2), 68.4 (CH_2), 27.3 (CH_3); HRMS (ESI) Exact mass calcd for $[C_9H_{12}NaO_2]^+$ [M+Na]$^+$: 175.0730 , found: 175.0738.

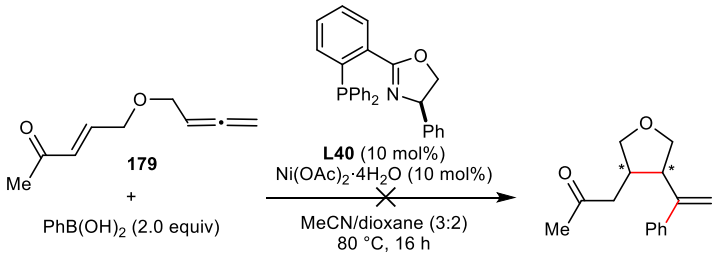
Further investigation of different substrates



The General Procedure (section 4.3) was followed using allenyl cyclohexa-2,5-dienone **143** (57.0 mg, 0.30 mmol) and phenylboronic acid (73.2 mg, 0.6 mmol). The product was obtained in less 5% NMR yield, determined by ^{1}H NMR analysis of the crude reaction using 1,3,5-dimethoxybenzene as internal standard. NMR spectrum was taken in a Bruker 400MHz instrument. The evidence of signals of CH=C**H**$_2$ was obtained from the spectrum at the chemical shifts 5.28 and 5.10 ppm.



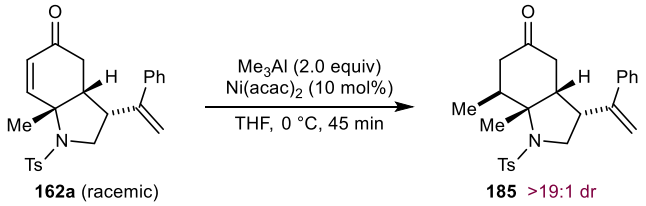
The General Procedure (section 4.3) was followed using allenyl electrophile **175** (27.6 mg, 0.10 mmol) and phenylboronic acid (24.4 mg, 0.2 mmol). A messy crude reaction resulting from a mixturebof unidentified products was observed.



The General Procedure (section 4.3) was followed using allenyl electrophile **179** (15.0 mg, 0.10 mmol) and phenylboronic acid (24.4 mg, 0.2 mmol). A messy crude reaction resulting from a mixturebof unidentified products was observed.

4.9. Further transformation

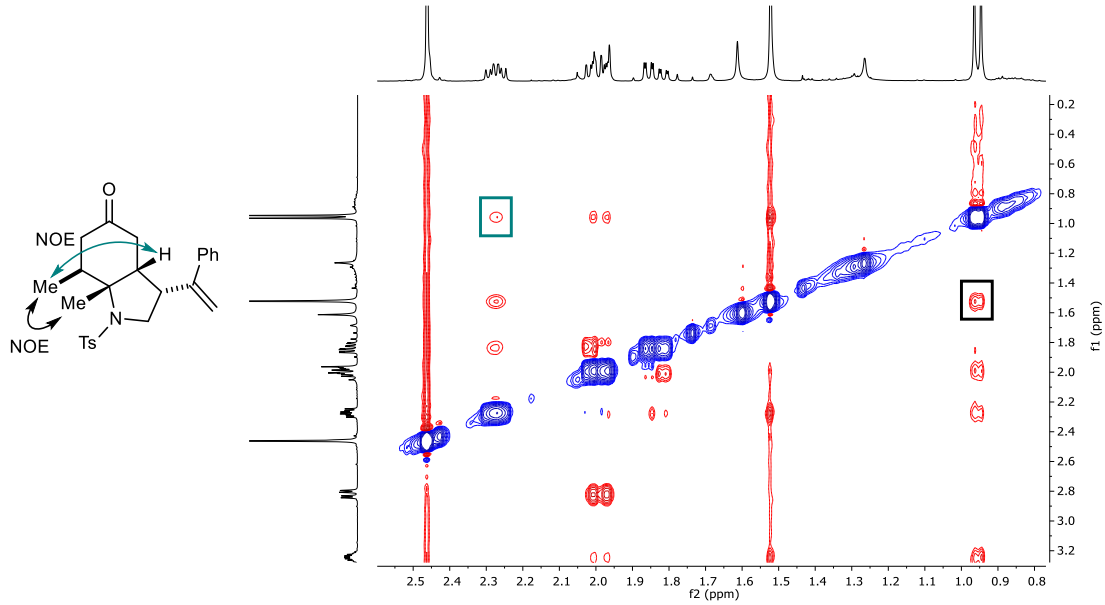
(±)-(3*R*,3a*R*,7*S*,7a*R*)-7,7a-Dimethyl-3-(1-phenylethenyl)-1-(4-methylbenzenesulfonyl)-octahydro-5*H*-indol-5-one (185)



162a (racemic) **185** >19:1 dr

Using **162a** *(racemic)*: An oven-dried microwave vial fitted with a stirrer bar was charged with *rac*-**162a** (40.7 mg, 0.10 mmol) and $Ni(acac)_2$ (2.6 mg, 0.01 mmol). The vial was capped with a crimp cap PTTE seal and purged with a stream of nitrogen. THF (1 mL) was added and the mixture was stirred at 0 °C for 20 min. A solution of Me_3Al (2.0 M in hexane, 0.1 mL, 0.2 mmol) was then added and the reaction was stirred at 0 °C for 45 min. The reaction was diluted with EtOAc (5 mL) and washed with saturated aqueous Rochelle salt solution (1 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The mixture was purified by column chromatography (30% EtOAc/pentane) to give the *title compound* **185** (32.2 mg, 76%) as a colorless solid. R_f = 0.53 (30% EtOAc/pentane); m.p. 160-163 °C (Et_2O); IR 2957, 2925, 1709 (C=O), 1323, 1158, 1097, 907, 778, 728, 676, 584, 547 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (2H, d, *J* = 8.0 Hz, Ar**H**), 7.36-7.29 (5H, m, Ar**H**), 7.26-7.24 (2H, m, Ar**H**), 5.34 (1H, d, *J* = 1.6 Hz, =C**H**$_2$), 4.94 (1H, d, *J* = 1.9 Hz, =C**H**$_2$), 3.88 (1H, dd, *J* = 8.8, 6.4 Hz, NC**H**$_2$), 3.69-3.65 (1H, m, NCH_2C**H**), 3.64-3.59 (1H, m, NC**H**$_2$), 3.28-3.21 (1H, m, CH_3C**H**), 2.82 (1H, dd, *J* = 14.8, 4.8 Hz, CH_3CHC**H**$_2$), 2.46 (3H, s, ArC**H**$_3$), 2.30-2.25 (1H, m, $O{=}CCH_2C$**H**CH), 2.03-1.96 (2H, m, O=CC**H**$_2$CHCH and CH_3CHC**H**$_2$), 1.84 (1H, ddd, *J* = 16.4, 7.8, 1.9 Hz, O=CC**H**$_2$CHCH), 1.52 (3H, s, NCC**H**$_3$), 0.96 (3H, d, *J* = 7.6 Hz, C**H**$_3$CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.0 (C), 144.7 (C), 143.5 (C), 140.5 (C), 137.7 (C), 129.7 (2 x CH), 128.7 (2 x CH), 128.1 (CH), 127.4 (2 x CH), 126.0 (2 x CH), 115.1 (CH_2), 71.4 (C), 49.3 (CH_2), 46.3 (CH), 44.1 (CH_2), 42.3 (CH), 38.0 (CH), 37.2 (CH_2), 24.8 (CH_3), 21.5 (CH_3), 17.5 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{25}H_{30}NO_3S]^+$ $[M+H]^+$: 424.1941, found: 424.1951.

Using **162a** *(90% ee)*: The previous procedure was followed using allene **162a** (40.7 mg, 0.1 mmol) and Me_3Al (2.0 M in hexane, 0.1 mL, 0.2 mmol). Purification by column chromatography (30% EtOAc/pentane) to give the title compound **185** (28.7 mg, 68%) as a colourless oil. $[\alpha]_D^{25}$ −35.3 (*c* 0.34, $CHCl_3$); Enantiomeric excess was determined by HPLC with AD-H (90:10 *iso*-hexane:*i*-PrOH), 1 mL/min, 254 nm, 25 °C); t_r (major) = 16.9 min, t_r (minor) = 19.6 min, 93% ee. An NOE spectrum obtained for **185** is given as following.



(3*R*,3a*R*,7a*R*)-3-[1-(3-Bromo-5-methylphenyl)ethenyl]-7a-methyl-1-(4-methylbenzenesulfonyl)-2,3,3a,4,5,7a-hexahydro-1*H*-indol-5-ol (186)

162e (88% *ee*) **186** >19:1 dr

To a solution of ketone **162e** (49.9 mg, 0.10 mmol) in undried MeOH (1 mL) at –10 °C was added $CeCl_3 \cdot 7H_2O$ (44.7 mg, 0.12 mmol), followed by $NaBH_4$ (20.1 mg, 0.53 mmol) portionwise. The reaction was stirred at –10 °C for 50 min, quenched carefully with 1 M aqueous HCl solution (0.5 mL), diluted with H_2O (5 mL), and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The mixture was purified by column chromatography (30% EtOAc/petroleum ether) to give the *allylic alcohol* **186** (49.8 mg, 99%) as a white solid. R_f = 0.26 (30% EtOAc/petroleum ether); m.p. 74-77 °C (Et_2O); $[\alpha]_D^{25}$ –30.8 (*c* 0.52, $CHCl_3$); IR 3490 (OH), 2924, 1596, 1561, 1443, 1326, 1145, 1111, 1090, 962, 853, 759, 707, 678, 582, 546 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (2H, d, *J* = 8.4 Hz, Ar**H**), 7.32-7.25 (5H, m, Ar**H**), 7.06-

7.05 (1H, m, Ar**H**), 6.24 (1H, dd, *J* = 10.2, 2.0 Hz, HOCHCH=C**H**), 5.69 (1H, dt, *J* = 10.2, 1.5 Hz, HOCHC**H**=), 5.32 (1H, d, *J* = 1.5 Hz, =C**H**$_2$), 4.90 (1H, d, *J* = 1.8 Hz, =C**H**$_2$), 3.95-3.92 (1H, m, HOC**H**), 3.81-3.77 (1H, m, NC**H**$_2$), 3.75-3.68 (1H, m, NCH$_2$C**H**), 3.41 (1H, dd, *J* = 10.8, 8.4 Hz, NC**H**$_2$), 2.43 (3H, s, ArC**H**$_3$), 2.34 (3H, s, ArC**H**$_3$), 1.98-1.92 (1H, m, HOCHCH$_2$C**H**), 1.61 (3H, s, NCC**H**$_3$), 1.46-1.40 (1H, m, HOCHC**H**$_2$), 1.12 (1H, d, *J* = 7.2 Hz, O**H**), 0.71 (1H, ddd, *J* = 13.6, 12.4, 10.4 Hz, HOCHC**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5 (C), 143.0 (C), 142.7 (C), 140.3 (C), 137.2 (C), 132.8 (CH), 131.6 (CH), 130.5 (CH), 129.3 (2 x CH), 127.4 (2 x CH), 126.2 (CH), 125.6 (CH), 122.5 (C), 115.4 (CH_2), 66.7 (CH), 65.0 (C), 48.8 (CH_2), 45.9 (CH), 41.2 (CH), 29.7 (CH_2), 29.6 (CH_3), 21.5 (CH_3), 21.2 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{25}H_{29}BrNO_3S]^+$ $[M+H]^+$: 502.1046, found: 502.1028.

5. Experimental: Enantioselective nickel-catalyzed arylative cyclization intramolecular 1,2-allylations

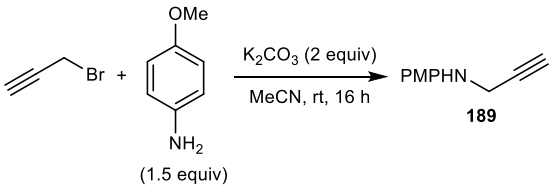
5.1. General information

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. 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). ^{19}F NMR spectra were referenced through the solvent lock (^{2}H) signal according to the IUPAC-recommended secondary referencing method following Bruker protocols. 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). X-ray diffraction data were collected at 120 K on an Agilent SuperNova diffractometer using CuKα radiation. Chiral HPLC

analysis was performed on an Agilent 1290 series instrument using 4.6 × 250 mm columns. 2-[2-(Diphenylphosphino)ethyl]pyridine was used as an achiral ligand to obtain authentic racemic compounds.

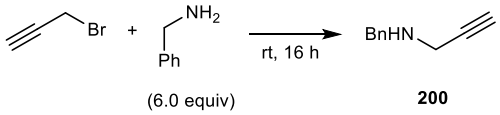
5.2. Synthesis of allenyl ketones

4-methoxy-N-(prop-2-yn-1-yl) aniline (189)



To a solution of *p*-anisidine (14.8 g, 240 mmol) in dried MeCN (45 mL) was added propargyl bromide (6.70 mL, 60 mmol, 80% in toluene) and K_2CO_3 (16.6 g, 120 mmol). The mixture was stirred for 24 h at room temperature. After filtering through celite, the solvent was evaporated under reduced pressure. The crude was purified by a silica gel column chromatography (20% EtOAc/petroleum ether) to furnish the title alkyne **189** (8.20 g, 58%) as a white solid. R_f = 0.41 (20% EtOAc/petroleum ether; IR 3261, 2918, 2361, 1508 (C=O), 1465, 1304, 1234, 1180, 1116, 1063, 824, 686, 654, 516 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.84–6.80 (2H, m, Ar**H**), 6.70–6.65 (2H, m, Ar**H**), 3.90 (2H, d, *J* = 2.4 Hz, NC**H₂**), 3.76 (3H, s, OC**H₃**), 2.21 (1H, t, *J* = 2.4 Hz, ≡C**H**), 2.07 (1H, s, N**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.1 (C), 141.0 (C), 115.2 (2 × CH), 114.9 (2 × CH), 81.5 (C), 71.4 (CH), 55.9 (CH_3), 34.7 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{10}H_{12}NO]^+$ $[M + H]^+$: 162.0913, found: 162.0918. Spectroscopic data consistent with those reported previously.[136]

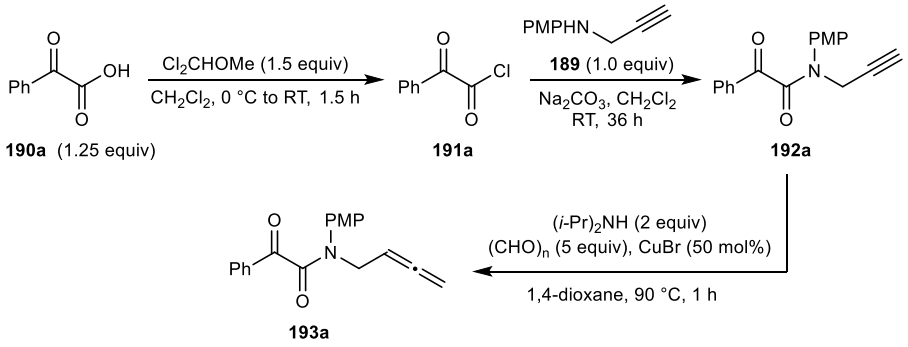
N-benzylprop-2-yn-1-amine (200)



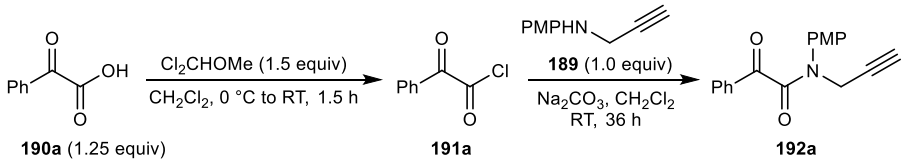
To a solution of benzylamine (40 mL, 360 mmol) was added propargyl bromide (6.70 mL, 60 mmol, 80% in toluene). The mixture was stirred for 16 h at room temperature. The reaction was partitionated with 2M aqueous NaOH (50 mL) and Et_2O (50 mL). The organic phase was washed with Et_2O (2 × 50 mL) and the

combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude was purified by a silica gel column chromatography (30% EtOAc/petroleum ether) to furnish the title alkyne **200** (8.21 g, 94%) as a yellow liquid. R_f = 0.36 (30% EtOAc/petroleum ether; IR 3291, 2839, 1494, 1453, 1360, 1328, 1103, 1028, 905, 733, 697, 636, 468 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28–7.21 (4H, m, Ar**H**), 7.21–7.15 (1H, m, Ar**H**), 3.80 (2H, s, C**H**$_2$Ph), 3.34 (2H, d, *J* = 2.4 Hz, NC**H**$_2$), 2.18 (1H, t, *J* = 2.4 Hz, ≡C**H**), 1.43 (1H, s, O**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.5 (C), 128.49 (2 × CH), 128.46 (2 × CH), 127.2 (CH), 82.2 (C), 71.6 (CH), 52.3 (CH_2), 37.4 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{10}H_{12}N]^+$ [M + H]$^+$: 146.0964, found: 146.0966. Spectroscopic data consistent with those reported previously.[147]

Preparation of allenyl ketone 193a



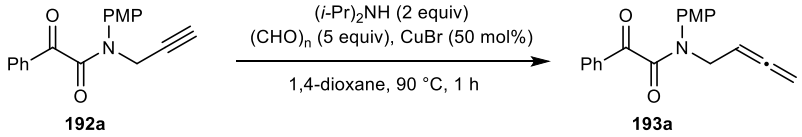
***N*-(4-Methoxyphenyl)-2-oxo-2-phenyl-*N*-(prop-2-yn-1-yl)acetamide (192a).**



To a solution of phenylglyoxylic acid (4.69 g, 31.3 mmol) in CH_2Cl_2 (25 mL) at 0 °C under inert atmosphere was added dichloromethyl methyl ether (3.39 mL, 37.5 mmol) dropwise. The mixture was stirred at room temperature for 1.5 h and then diluted with CH_2Cl_2 (80 mL). Na_2CO_3 (26.3 g, 250 mmol) was added, followed by a solution of propargylamine **189**[136] (4.03 g, 25.0 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at room temperature for 36 h, quenched with H_2O (100 mL), and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column

chromatography (30% EtOAc/petroleum ether) gave *alkyne* **192a** (6.99 g, 95%) as a white solid. R_f = 0.36 (30% EtOAc/petroleum ether); m.p. 83–85 °C (Et_2O); IR 3309, 3275, 2975, 2840, 1651 (C=O), 1508, 1434, 1255, 1240, 1216, 1167, 1020, 944, 837, 713, 619, 582, 540 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85–7.82 (2H, m, Ar**H**), 7.60–7.55 (1H, m, Ar**H**), 7.46–7.41 (2H, m, Ar**H**), 7.17–7.13 (2H, m, Ar**H**), 6.76–6.72 (2H, m, Ar**H**), 4.63 (2H, d, *J* = 2.5 Hz, NC**H**$_2$), 3.73 (3H, s, OC**H**$_3$), 2.31 (1H, t, *J* = 2.5 Hz, ≡C**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.5 (C), 166.9 (C), 159.7 (C), 134.5 (CH), 133.5 (C), 131.4 (C), 129.9 (2 × CH), 129.5 (2 × CH), 128.9 (2 × CH), 114.7 (CH), 78.1 (C), 73.2 (CH), 55.5 (CH_3), 38.2 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{18}H_{16}NO_3]^+$ $[M + H]^+$: 294.1125, found: 294.1132.

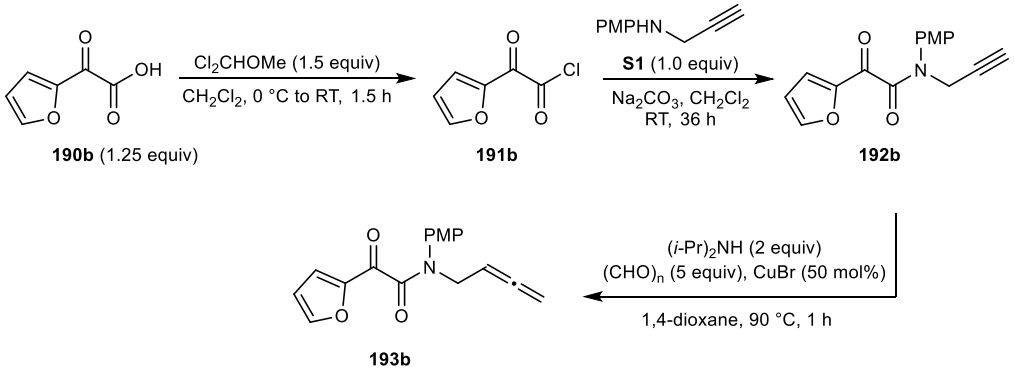
***N*-(Buta-2,3-dien-1-yl)-*N*-(4-methoxyphenyl)-2-oxo-2-phenylacetamide (193a).**



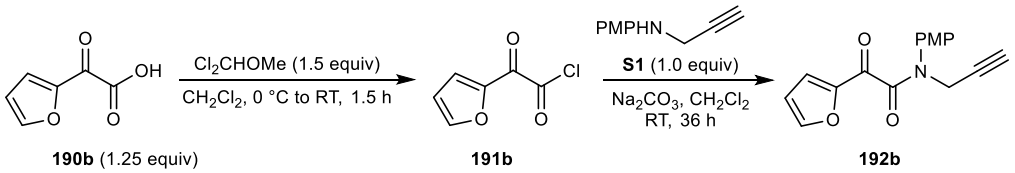
To a solution of alkyne **192a** (5.86 g, 20.0 mmol) in 1,4-dioxane (100 mL) at room temperature under inert atmosphere was added paraformaldehyde (3.00 g, 100 mmol), CuBr (1.43 g, 10.0 mmol), and diisopropylamine (5.61 mL, 40.0 mmol). The reaction was heated at 90 °C for 1 h, cooled to room temperature, filtered through a pad of celite using EtOAc as eluent, and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/petroleum ether) gave *allene* **193a** (2.82 g, 46%) as a 10:1 mixture of rotamers as a pale yellow solid. R_f = 0.42 (30% EtOAc/petroleum ether); m.p. 50–53 °C (EtOAc); IR 2958, 2926, 1960, 1656 (C=O), 1592, 1509, 1450, 1427, 1297, 1242, 1211, 1169, 1025, 945, 838, 814, 756, 732, 717, 688, 656, 550, 445 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *major rotamer*: δ 7.87–7.84 (2H, m, Ar**H**), 7.59–7.55 (1H, m, Ar**H**), 7.46–7.41 (2H, m, Ar**H**), 7.08–7.04 (2H, m, Ar**H**), 6.74–6.70 (2H, m, Ar**H**), 5.32 (1H, quin, *J* = 6.6 Hz, CH_2C**H**=), 4.81 (2H, dt, *J* = 6.6, 2.7 Hz, =C**H**$_2$), 4.45 (2H, dt, *J* = 6.6, 2.7 Hz, NC**H**$_2$), 3.72 (3H, s, OC**H**$_3$); *minor rotamer*: δ 8.07–8.05 (2H, m, Ar**H**), 7.69–7.64 (1H, m, Ar**H**), 7.54–7.52 (2H, m, Ar**H**), 7.33–7.30 (2H, m, Ar**H**), 7.00–6.96 (2H, m, Ar**H**), 5.14 (1H, quin, *J* = 6.5 Hz, NCH_2C**H**), 4.59 (2H, dt, *J* = 6.6, 2.7 Hz, =C**H**$_2$), 4.20 (2H, dt, *J* = 6.5, 2.7 Hz, NC**H**$_2$CH), 3.84 (3H, s, OC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) *major rotamer*: δ 209.8 (C), 191.0 (C), 167.1 (C), 159.4 (C), 134.3 (CH), 133.6 (C), 132.1 (C), 129.8

(2 × CH), 129.5 (2 × CH), 128.9 (2 × CH), 114.6 (2 × CH), 85.9 (CH), 77.0 (CH_2), 55.5 (CH_3), 47.9 (CH_2); *observable signals of minor rotamer*: δ 130.1 (2 × CH), 129.1 (2 × CH), 128.3 (2 × CH), 114.8 (CH); HRMS (ESI) Exact mass calculated for $[C_{19}H_{18}NO_3]^+$ $[M+H]^+$: 308.1281, found: 308.1278.

Preparation of allenyl ketone 193b



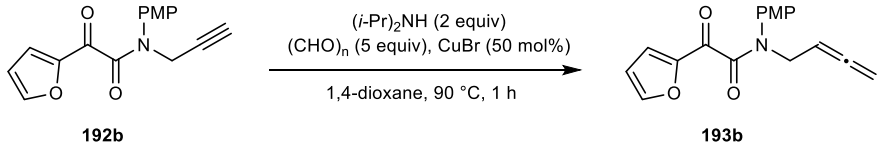
2-(Furan-2-yl)-*N*-(4-methoxyphenyl)-2-oxo-*N*-(prop-2-yn-1-yl)acetamide (192b).



To a solution of α-oxo-2-furanacetic acid (1.09 g, 7.76 mmol) in CH_2Cl_2 (15 mL) at 0 °C under inert atmosphere was added dichloromethyl methyl ether (0.84 mL, 9.31 mmol) dropwise. The mixture was stirred at room temperature for 2 h and then diluted with CH_2Cl_2 (5 mL). Na_2CO_3 (6.58 g, 62.1 mmol) was added, followed by a solution of propargylamine **189**[136] (1.00 g, 6.21 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at room temperature for 24 h, quenched with H_2O (20 mL), and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (30% EtOAc/petroleum ether) gave *alkyne* **192b** (1.74 g, 99%) as a pale yellow solid. R_f = 0.29 (30% EtOAc/petroleum ether); m.p. 55–59 °C (Et_2O); IR 3283, 3125, 2835, 1640 (C=O), 1509, 1459, 1390, 1214, 1164, 1023, 928, 881, 801, 768, 724, 617, 585, 540, 408 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (1H, dd, *J* = 1.7, 0.8 Hz, Ar**H**), 7.27–7.26 (1H, m, Ar**H**), 7.21–7.17 (2H, m, Ar**H**), 6.81–6.77 (2H, m, Ar**H**), 6.54 (1H, dd, *J* = 3.6, 1.7 Hz, Ar**H**), 4.58 (2H, d, *J* = 2.5 Hz, NC**H**$_2$),

3.75 (3H, s, OC**H**$_3$), 2.28 (1H, t, *J* = 2.5 Hz, ≡C**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.4 (C), 159.8 (C), 150.3 (C), 148.4 (2 × CH), 131.4 (C), 129.6 (2 × CH), 121.4 (C), 114.7 (2 × CH), 112.9 (CH), 77.9 (C), 73.2 (CH), 55.5 (CH_3), 38.4 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{16}H_{13}NNaO_4]^+$ $[M+Na]^+$: 306.0737, found: 306.0740.

***N*-(Buta-2,3-dien-1-yl)-2-(furan-2-yl)-N-(4-methoxyphenyl)-2-oxoacetamide (193b).**

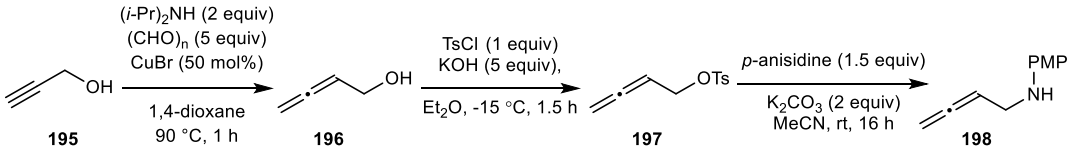


192b **193b**

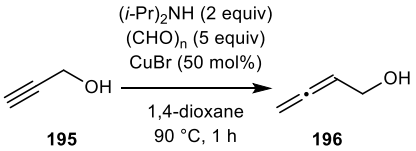
To a solution of alkyne **193b** (708 mg, 2.50 mmol) in 1,4-dioxane (12.5 mL) at room temperature under inert atmosphere was added paraformaldehyde (375 mg, 12.5 mmol), CuBr (287 mg, 2.00 mmol), and diisopropylamine (0.70 mL, 5.0 mmol). The reaction was heated at 90 °C for 1 h, cooled to room temperature, filtered through a pad of celite using EtOAc as eluent, and concentrated *in vacuo*. Purification of the residue by column chromatography (40% EtOAc/petroleum ether) gave *allene* **193b** (293 mg, 39%) as a 10:1 mixture of rotamers as a pale yellow solid. R_f = 0.41 (40% EtOAc/petroleum ether); m.p. 79–81 °C (Et_2O); IR 3116, 1967, 1650 (C=O), 1557, 1456, 1436, 1388, 1248, 1165, 1023, 960, 839, 805, 751, 670, 622, 592, 548, 437 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *major rotamer*: δ 7.61 (1H, dd, *J* = 1.6, 0.7 Hz, Ar**H**), 7.28–7.25 (1H, m, Ar**H**), 7.12–7.08 (2H, m, Ar**H**), 6.79–6.75 (2H, m, Ar**H**), 6.53 (1H, dd, *J* = 3.6, 1.7 Hz, Ar**H**), 5.28 (1H, quin, *J* = 6.7 Hz, CH_2C**H**=), 4.78 (2H, dt, *J* = 6.6, 2.6 Hz, =C**H**$_2$), 4.40 (2H, dt, *J* = 6.6, 2.6 Hz, NC**H**$_2$), 3.75 (3H, s, OC**H**$_3$); *minor rotamer*: δ 7.75 (1H, dd, *J* = 1.7, 0.7 Hz, Ar**H**), 7.43 (1H, dd, *J* = 3.6, 0.8 Hz, Ar**H**), 7.28–7.27 (2H, m, Ar**H**), 6.98–6.94 (2H, m, Ar**H**), 6.63 (1H, dd, *J* = 3.6, 1.6 Hz, ArC**H**), 5.20 (1H, quin, *J* = 6.5 Hz, CH_2C**H**=), 4.66 (2H, dt, *J* = 6.6, 2.7 Hz, =C**H**$_2$), 4.29 (2H, dt, *J* = 6.4, 2.7 Hz, NC**H**$_2$), 3.83 (3H, s, OC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) *major rotamer*: δ 209.8 (C), 178.3 (C), 165.7 (C), 159.5 (C), 150.5 (C), 148.2 (CH), 132.2 (C), 129.6 (2 × CH), 121.1 (CH), 114.7 (2 × CH), 112.8 (CH), 85.7 (CH), 76.9 (CH_2), 55.5 (CH_3), 48.1 (CH_2); *observable signals of minor rotamer*: δ 148.9 (CH), 128.1 (CH), 114.7 (CH), 113.1 (CH), 110.1 (CH), 87.2 (CH),

55.6 (CH_3), 50.4 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{17}H_{16}NO_4]^+$ $[M+H]^+$: 298.1074, found: 298.1077.

Preparation of allenes 198

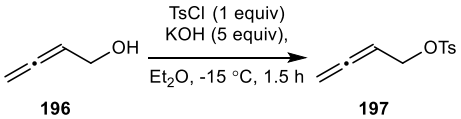


Buta-2,3-dien-1-ol (196)



To a solution of CuI (19.0 g, 100 mmol), paraformaldehyde (9.61 g, 320 mmol) in dried THF (400 mL) was added diisopropylamine (39.2 mL, 280 mmol) dropwise, and propargyl alcohol (11.6 mL, 200 mmol). The reaction was refluxed for 16 h. The solution was quenched with solution of HCl 10 mol% (150 mL) to reach pH 2-4. The solid was filtered on a mixture of sand and celite, washed with petroleum ether. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to obtain the product **196** (4.68 g, 33%). The product was pure and carried out for next step without purification. IR 3308 (OH), 2934, 2873, 1954, 1415, 1362, 1213, 1044, 1006, 842, 687, 595, 532 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.35–5.25 (1H, m, $CH_2C\mathbf{H}$=), 4.81 (2H, dt, *J* = 6.6, 2.9 Hz, =C$\mathbf{H}_2$), 4.11 (2H, dt, *J* = 6.2, 2.9 Hz, OC$\mathbf{H}_2$), 2.42−2.16 (1H, m, O**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.0 (C), 90.9 (CH), 77.0 (CH_2), 60.3 (CH_2); HRMS (ESI) Exact mass calculated for $[C_4H_{10}NO]^+$ $[M+H]^+$: 88.0757, found: 88.0756. Spectroscopic data consistent with those reported previously.[148]

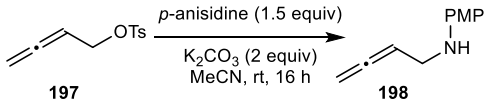
Buta-2,3-dien-1-yl 4-methylbenzenesulfonate (197)



To a solution of buta-2,3-dien-1-ol **196** (1.05 g, 15.0 mmol), *p*-toluenesulfonylchloride (1.91 g, 10 mmol) in Et_2O (25 mL) was added crushed KOH

(2.80 g, 50.0 mmol) in portions over 30 min at -14 °C. The resulting mixture was stirred for additional 45 min. Ice water (24 mL) was added to reaction and the resulting mixture was extracted with Et_2O (4 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to obtain the residue. The crude was triturated with petroleum ether (15 mL) and cooled to -78 °C to cause a solidification of product. The pertroleum ether was got rid of from the mixture (4 × 20 mL). The title allene **197** was formed as a waxy solid (1.77 g, 53%). IR 2955, 1955, 1598, 1494, 1355, 1172, 1095, 921, 811, 769, 664, 546 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (2H, dd, *J* = 8.4, 1.6 Hz, Ar**H**), 7.34 (2H, d, *J* = 8.4 Hz, Ar**H**), 5.24–5.14 (1H, m, CH_2C**H**=), 4.82 (2H, dt, *J* = 6.6, 1.8 Hz, =C**H**$_2$), 4.56 (2H, dt, *J* = 7.4, 2.0 Hz, C**H**$_2$CH=), 2.44 (3H, s, ArC**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.5 (C), 144.9 (C), 133.5 (C), 129.9 (2 × CH), 128.0 (2 × CH), 85.3 (CH), 77.3 (CH_2), 68.5 (CH_2), 21.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{11}H_{16}NO_3S]^+$ $[M+NH_4]^+$: 242.0845, found: 242.0848. Spectroscopic data consistent with those reported previously.[149]

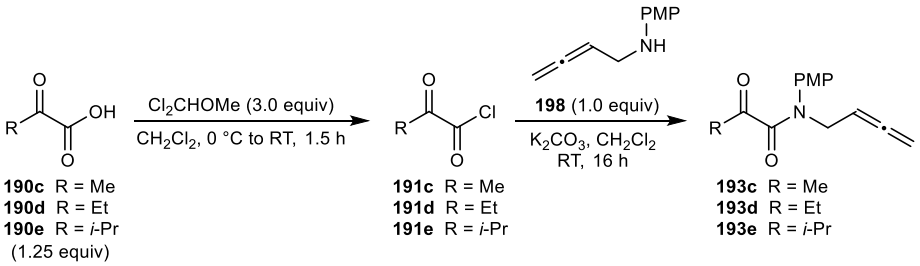
***N*-(Buta-2,3-dien-1-yl)-4-methoxyaniline (198)**



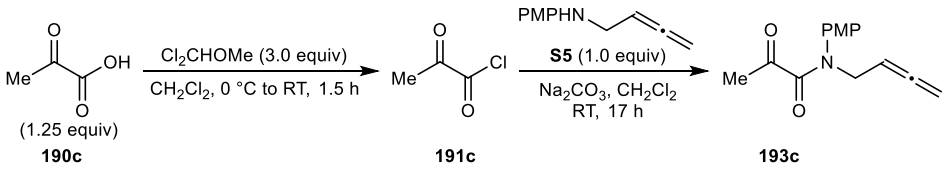
To a solution of *p*-anisidine (3.14 g, 25.5 mmol) in MeCN (68 mL) at room temperature under inert atmosphere was added allylic tosylate **197** (3.82 g, 17.0 mmol) and K_2CO_3 (4.70 g, 34.0 mmol), and the mixture was stirred at room temperature for 16 h. The mixture was partitioned between Et_2O (50 mL) and saturated aqueous $NaHCO_3$ solution (50 mL), and the organic layer was separated and washed with saturated aqueous $NaHCO_3$ solution (2 × 30 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/petroleum ether) gave *allene* **198** (1.50 g, 50%) as a pale yellow oil. R_f = 0.48 (20% EtOAc/petroleum ether); IR 3387 (NH), 2831, 1954, 1617, 1509, 1463, 1407, 1294, 1232, 1178, 1116, 1034, 847, 817, 517 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.83–6.78 (2H, m, Ar**H**), 6.64–6.60 (2H, m, Ar**H**), 5.33–5.25 (1H, m, NCH_2C**H**), 4.83 (2H, dt, *J* = 6.6, 3.3 Hz, =C**H**$_2$), 3.76 (3H, s, OC**H**$_3$), 3.73 (2H, dt, *J* = 6.2, 3.2 Hz, NC**H**$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.3 (C), 152.4 (C), 142.0 (C), 114.9 (2 × CH), 114.7 (2 × CH), 88.9 (CH), 77.0 (CH_2), 55.9 (CH_3),

43.3 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{11}H_{14}NO]^+$ $[M+H]^+$: 176.1070, found: 176.1071.

Preparation of allenes with alkyl substituents on ketone



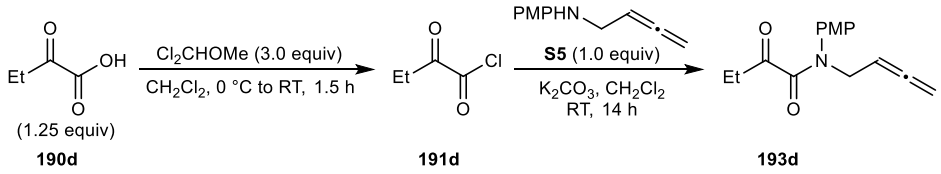
***N*-(Buta-2,3-dien-1-yl)-*N*-(4-methoxyphenyl)-2-oxopropanamide (193c)**



To a solution of pyruvic acid (95.1 mg, 1.08 mmol) in CH_2Cl_2 (1 mL) at 0 °C under inert atmosphere was added dichloromethyl methyl ether (117 μL, 1.30 mmol) dropwise. The mixture was stirred at room temperature for 1.5 h and then diluted with CH_2Cl_2 (3.5 mL). Na_2CO_3 (922 mg, 8.70 mmol) was added, followed by a solution of allenylamine **198** (152 mg, 0.87 mmol) in CH_2Cl_2 (0.5 mL). The mixture was stirred at room temperature for 17 h, quenched with H_2O (5 mL), and extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (40% EtOAc/petroleum ether) gave *allene* **193c** (139 mg, 65%) as a 14:1 mixture of rotamers as a white solid. R_f = 0.42 (40% EtOAc/petroleum ether); m.p. 38–39 °C (Et_2O); IR 3010, 2923, 1955, 1707, 1641 (C=O), 1509, 1433, 1364, 1302, 1248, 1228, 1164, 1053, 1028, 945, 845, 731, 629, 580, 549, 497, 461, 428 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *major rotamer*: δ 7.13–7.09 (2H, m, Ar**H**), 6.89–6.85 (2H, m, Ar**H**), 5.21 (1H, quin, *J* = 6.6 Hz, $CH_2C\mathbf{H}$=), 4.76 (2H, dt, *J* = 6.6, 2.7 Hz, =C$\mathbf{H}_2$), 4.30 (2H, dtd, *J* = 6.6, 2.7 Hz, NC$\mathbf{H}_2$), 3.80 (3H, s, OC$\mathbf{H}_3$), 2.17 (3H, s, C$\mathbf{H}_3$C=O); *minor rotamer*: δ 7.19 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.92 (2H, d, *J* = 8.9 Hz, Ar**H**), 5.28–5.26 (1H, m, $CH_2C\mathbf{H}$=), 4.82–4.81 (2H, m, =C$\mathbf{H}_2$), 4.27–4.26 (2H, m, NC$\mathbf{H}_2$), 3.80 (3H, s, OC$\mathbf{H}_3$), 2.49 (3H, s, C$\mathbf{H}_3$C=O); ^{13}C NMR (101 MHz, $CDCl_3$) *major rotamer*:

δ 209.7 (C), 198.2 (C), 167.3 (C), 159.6 (C), 132.4 (C), 129.2 (2 × CH), 114.8 (2 × CH), 85.7 (CH), 76.9 (CH_2), 55.6 (CH_3), 47.9 (CH_2), 28.0 (CH_3); *observable signals of minor rotamer*: δ 128.0 (2 × CH), 114.6 (2 × CH), 88.0 (CH), 78.0 (CH_2), 49.9 (CH_2), 27.7 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{14}H_{16}NO_3]^+$ $[M+H]^+$: 246.1125, found: 246.1127.

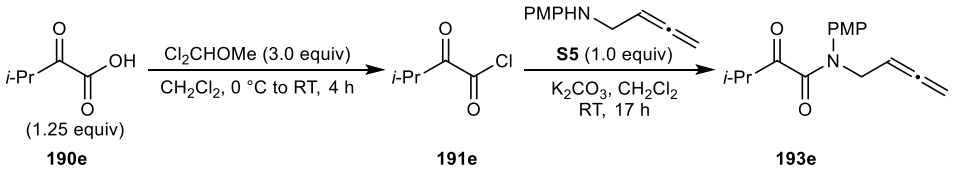
_N_-(Buta-2,3-dien-1-yl)-N-(4-methoxyphenyl)-2-oxobutanamide (193d)



To a solution of 2-ketobutyric acid (383 mg, 3.75 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C under inert atmosphere was added dichloromethyl methyl ether (0.41 mL, 4.5 mmol) dropwise. The mixture was stirred for 5 h at room temperature and then diluted with CH_2Cl_2 (8 mL). K_2CO_3 (2.07 g, 15.0 mmol) was added followed by a solution of allenylamine **198** (263 mg, 1.5 mmol) in CH_2Cl_2 (0.5 mL). The mixture was stirred at room temperature for 14 h, quenched with H_2O (50 mL), and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/petroleum ether) gave *allene* **193d** (332 mg, 85%) as a 14:1 mixture of rotamers as a pale yellow amorphous solid. R_f = 0.30 (20% EtOAc/petroleum ether); IR 2981, 1955, 1714, 1645 (C=O), 1509, 1441, 1404, 1295, 1248, 1217, 1171, 1116, 1028, 835, 725, 613, 544 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *major rotamer*: δ 7.13-7.08 (2H, m, Ar**H**), 6.88-6.84 (2H, m, Ar**H**), 5.21 (1H, quin, *J* = 6.6 Hz, $CH_2C\mathbf{H}$=), 4.75 (2H, dt, *J* = 6.7, 2.7 Hz, =C$\mathbf{H}_2$), 4.29 (2H, dt, *J* = 6.6, 2.7 Hz, NC$\mathbf{H}_2$), 3.80 (3H, s, OC$\mathbf{H}_3$), 2.52 (2H, q, *J* = 7.3 Hz, $CH_3C\mathbf{H}_2$), 0.91 (3H, t, *J* = 7.3 Hz, C$\mathbf{H}_3CH_2$); *minor rotamer*: δ 7.19–7.11 (2H, m, Ar**H**), 6.93–6.91 (2H, m, Ar**H**), 5.24–5.20 (1H, m, $CH_2C\mathbf{H}$=), 4.79 (2H, dt, *J* = 6.4, 2.8 Hz, =C$\mathbf{H}_2$), 4.23 (2H, dt, *J* = 6.0, 2.8 Hz, NC$\mathbf{H}_2$), 3.81 (3H, s, OC$\mathbf{H}_3$), 2.89 (2H, q, *J* = 7.2 Hz, $CH_3C\mathbf{H}_2$), 1.18 (3H, t, *J* = 7.2 Hz, C$\mathbf{H}_3CH_2$); ^{13}C NMR (101 MHz, $CDCl_3$) *major rotamer*: δ 209.7 (C), 201.6 (C), 167.7 (C), 159.5 (C), 132.4 (C), 129.3 (2 × CH), 114.7 (2 × CH), 85.7 (CH), 76.9 (CH_2), 55.6 (CH_3), 47.9 (CH_2), 33.8 (CH_2), 6.9 (CH_3); *observable signals of minor rotamer*: δ 209.1 (C), 128.1 (2 × CH), 114.6 (2 × CH), 87.7 (CH), 77.8 (CH_2), 55.6

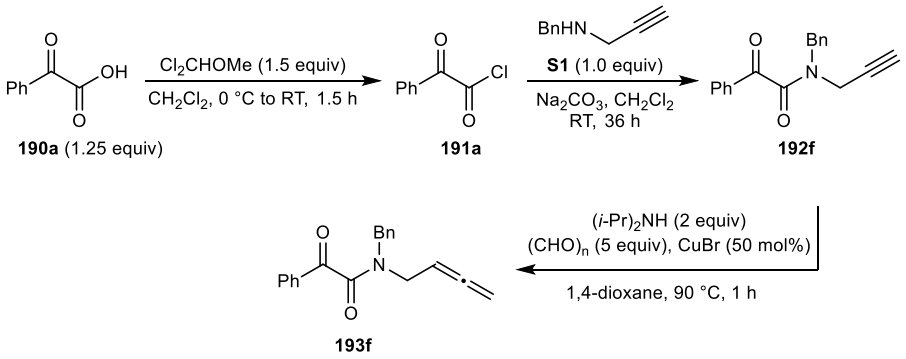
(CH_3), 50.0 (CH_2), 33.4 (CH_2), 7.1 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{15}H_{18}NO_3]^+$ $[M+H]^+$: 260.1281, found: 260.1286.

***N*-(Buta-2,3-dien-1-yl)-N-(4-methoxyphenyl)-3-methyl-2-oxobutanamide (193e)**

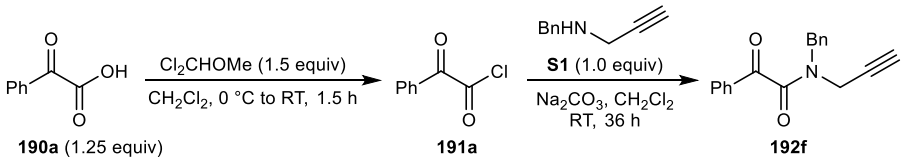


To a solution of 3-methyl-2-oxobutyryl acid (730 mg, 6.29 mmol) in CH_2Cl_2 (6.5 mL) at 0 °C under inert atmosphere was added dichloromethyl methyl ether (0.68 mL, 7.5 mmol) dropwise. The mixture was stirred at room temperature for 4 h and then diluted with CH_2Cl_2 (10 mL). K_2CO_3 (3.46 g, 25.0 mmol) was added followed by a solution of allenylamine **198** (438 mg, 2.50 mmol) in CH_2Cl_2 (0.5 mL). The mixture was stirred at room temperature for 17 h, quenched with H_2O (10 mL), and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/petroleum ether) gave *allene* **193e** (205 mg, 30%) as a 14:1 mixture of rotamers as a pale yellow oil. R_f = 0.39 (20% EtOAc/petroleum ether); IR 2971, 1956, 1712, 1644 (C=O), 1510, 1463, 1441, 1296, 1248, 1217, 1027, 836, 730, 619, 554 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *major rotamer*: δ 7.14–7.10 (2H, m, Ar**H**), 6.87–6.83 (2H, m, Ar**H**), 5.22 (1H, quin, *J* = 6.6 Hz, $CH_2C\mathbf{H}$=), 4.75 (2H, dt, *J* = 6.7, 2.6 Hz, =C$\mathbf{H}_2$), 4.30 (2H, dt, *J* = 6.7, 2.7 Hz, NC$\mathbf{H}_2$), 3.80 (3H, s, OC$\mathbf{H}_3$), 2.78 (1H, sept, *J* = 6.9 Hz, $(CH_3)_2C\mathbf{H}$), 0.98 (6H, d, *J* = 7.0 Hz, $(C\mathbf{H}_3)_2CH$); *minor rotamer*: δ 7.18–7.16 (2H, m, Ar**H**), 6.94–6.92 (2H, m, Ar**H**), 5.22 (1H, quin, *J* = 6.6 Hz, $CH_2C\mathbf{H}$=), 4.74–4.72 (2H, m, =C$\mathbf{H}_2$), 4.19–4.17 (2H, m, NC$\mathbf{H}_2$), 3.81 (3H, s, OC$\mathbf{H}_3$), 3.27 (1H, sept, *J* = 7.0 Hz, $(CH_3)_2C\mathbf{H}$), 1.23 (6H, d, *J* = 7.0 Hz, $(C\mathbf{H}_3)_2CH$); ^{13}C NMR (101 MHz, $CDCl_3$) *major rotamer*: δ 209.7 (C), 204.5 (C), 167.4 (C), 159.4 (C), 132.4 (C), 129.7 (2 × CH), 114.5 (2 × CH), 85.8 (CH), 76.9 (CH_2), 55.55 (CH_3), 48.1 (CH_2), 38.1 (CH), 17.3 (2 × CH_3); *observable signals of minor rotamer*: δ 209.4 (C), 128.3 (2 × CH), 114.7 (2 × CH), 87.1 (CH), 77.4 (CH_2), 55.59 (CH_3), 50.0 (CH_2), 37.8 (CH), 17.2 (2 × CH_3); HRMS (ESI) Exact mass calculated for $[C_{16}H_{20}NO_3]^+$ $[M+H]^+$: 274.1438, found: 274.1442.

Preparation of Allenyl Ketone 193f



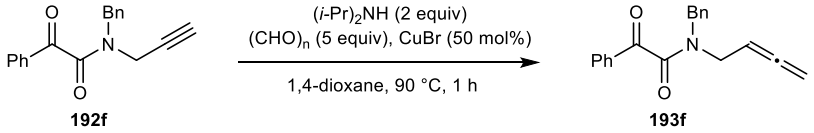
***N*-Benzyl-2-oxo-2-phenyl-*N*-(prop-2-yn-1-yl) acetamide (192f).**



To a solution of phenylglyoxylic acid (2.82 g, 18.8 mmol) in CH_2Cl_2 (20 mL) at 0 °C under inert atmosphere was added dichloromethyl methyl ether (2.04 mL, 22.5 mmol) dropwise. The mixture was stirred at room temperature for 1.5 h and then diluted with CH_2Cl_2 (50 mL). Na_2CO_3 (15.9 g, 150 mmol) was added followed by a solution of propargylamine **200**[147] (2.18 g, 15.0 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred at room temperature for 47 h, quenched with H_2O (30 mL), and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to leave *alkyne* **192f** (4.15 g, >99%) as a 1.7:1 mixture of rotamers as a pale yellow oil. R_f = 0.46 (30% EtOAc/petroleum ether); IR 3287, 2978, 1817, 1678, 1643 (C=O), 1440, 1256, 1203, 1175, 947, 722, 696, 660, 596, 460 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *major rotamer*: δ 8.00-7.98 (2H, m, Ar**H**), 7.67-7.63 (2H, m, Ar**H**), 7.54-7.49 (3H, m, Ar**H**), 7.34-7.31 (3H, m, Ar**H**), 4.53 (2H, s, C**H**$_2$Ph), 4.24 (2H, d, *J* = 2.5 Hz, C**H**$_2$C≡), 2.35 (1H, t, *J* = 2.5 Hz, ≡C**H**); *minor rotamer*; δ 8.14-8.12 (1H, m, Ar**H**), 8.00-7.98 (2H, m, Ar**H**), 7.54-7.49 (1H, m, Ar**H**), 7.48-7.46 (1H, m, Ar**H**), 7.41-7.37 (4H, m, Ar**H**), 7.34-7.31 (1H, m, Ar**H**), 4.89 (2H, s, C**H**$_2$Ph), 3.91 (2H, d, *J* = 2.5 Hz, C**H**$_2$C≡), 2.27 (1H, t, *J* = 2.5 Hz, ≡C**H**); ^{13}C NMR (101 MHz, $CDCl_3$) *major rotamer*: δ 190.8 (C), 166.9 (C), 135.1 (CH), 134.2 (C), 133.1 (C), 130.0 (CH), 129.8 (2 × CH), 129.2 (2 × CH), 128.9 (2 × CH), 128.4 (2 × CH), 77.4 (C), 73.1 (CH), 50.3

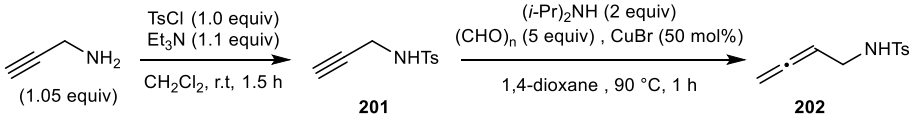
(CH_2), 32.2 (CH_2); *minor rotamer*: δ 190.7 (C), 167.0 (C), 135.2 (C), 135.0 (CH), 133.0 (C), 130.7 (CH), 129.1 (2 × CH), 129.0 (CH), 128.9 (CH), 128.7 (2 × CH), 128.5 (CH), 128.2 (CH), 77.0 (C), 74.1 (CH), 46.8 (CH_2), 36.3 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{18}H_{16}NO_2]^+$ $[M+H]^+$: 278.1176, found: 278.1176.

_N_-Benzyl-_N_-(buta-2,3-dien-1-yl)-2-oxo-2-phenylacetamide (193f).

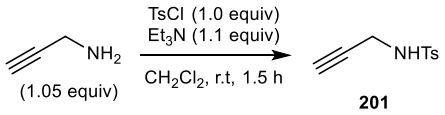


To a solution of alkyne **192f** (693 mg, 2.50 mmol) in 1,4-dioxane (12.5 mL) at room temperature under inert atmosphere was added paraformaldehyde (375 mg, 12.5 mmol), CuBr (287 mg, 2.00 mmol), and diisopropylamine (0.70 mL, 5.0 mmol). The reaction was heated at 90 °C for 1 h, cooled to room temperature, filtered through a pad of celite using EtOAc as eluent, and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/petroleum ether) gave *allene* **193f** (348 mg, 48%) as a 1.3:1 mixture of rotamers as a colorless oil. R_f = 0.52 (30% EtOAc/petroleum ether); IR 3063, 2929, 1955, 1677, 1637 (C=O), 1595, 1446, 1360, 1316, 1259, 1202, 1175, 950, 850, 722, 699, 613, 519, 459 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *major rotamer*: δ 8.02–7.97 (2H, m, Ar**H**), 7.67–7.62 (2H, m, Ar**H**), 7.53–7.49 (2H, m, Ar**H**), 7.39–7.25 (4H, m, Ar**H**), 5.04 (1H, quin, *J* = 6.6 Hz, $CH_2C\mathbf{H}$=), 4.77 (2H, s, C$\mathbf{H}_2$Ph), 4.74 (2H, dt, *J* = 6.6, 2.7 Hz, =C$\mathbf{H}_2$), 3.74 (2H, dt, *J* = 6.6, 2.7 Hz, C$\mathbf{H}_2$CH=); *minor rotamer*: δ 8.02-7.97 (2H, m, Ar**H**), 7.53–7.49 (2H, m, Ar**H**), 7.39–7.25 (6H, m, Ar**H**), 5.23 (1H, quin, *J* = 6.5 Hz, $CH_2C\mathbf{H}$=), 4.87 (2H, dt, *J* = 6.6, 2.8 Hz, =C$\mathbf{H}_2$), 4.42 (2H, s, C$\mathbf{H}_2$Ph), 4.04 (2H, dt, *J* = 6.5, 2.8 Hz, C$\mathbf{H}_2$CH=); ^{13}C NMR (101 MHz, $CDCl_3$) *major rotamer*: δ 209.6 (C), 191.2 (C), 167.3 (C), 135.0 (C), 134.8 (CH), 133.3 (C), 129.9 (2 × CH), 129.1 (2 × CH), 129.0 (2 × CH), 128.8 (2 × CH), 128.3 (CH), 86.1 (CH), 77.2 (CH_2), 46.9 (CH_2), 45.7 (CH_2); *observable signals of minor rotamer*: δ 209.7 (C), 191.4 (C), 167.2 (C), 136.1 (C), 135.0 (CH), 129.9 (2 × CH), 129.1 (2 × CH), 128.9 (2 × CH), 128.3 (2 × CH), 128.0 (CH), 110.1 (C), 85.6 (CH), 77.4 (CH_2), 50.7 (CH_2), 41.8 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{19}H_{18}NO_2]^+$ $[M+H]^+$: 292.1332, found: 292.1333.

Preparation of allene 202

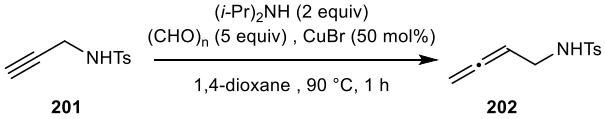


4-methyl-*N*-(prop-2-yn-1-yl) benzenesulfonamide (**201**).



To a solution of p-toluenesulfonyl chloride (10.1 g, 52.9 mmol) and triethylamine (8.0 mL, 57.4 mmol) in CH_2Cl_2 (200 mL) was added propargylamine (3.50 mL, 54.7 mmol) slowly at room temperature. The reaction was stirred for 1.5 h and quenched with HCl 1M (3 × 10 mL), saturated aqueous solution of $NaHCO_3$ (3 × 10 mL) and distilled water (3 × 10 mL). The organic layers were dried with anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure to afford the title alkyne **201** (10.2 g, 93%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.74 (2H, m, Ar**H**), 7.32 (2H, d, *J* = 8.2 Hz, Ar**H**), 4.57 (1H, s, N**H**), 3.83 (1H, ddd, *J* = 6.0, 2.5, 0.6 Hz, C**H**$_2$C≡), 2.43 (3H, s, ArC**H**$_3$), 2.11 (1H, t, *J* = 2.6 Hz, ≡C**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.0 (C), 136.7 (C), 129.9 (2 × CH), 127.6 (2 × CH), 78.1 (C), 73.2 (CH), 33.1 (CH_2), 21.7 (CH_3). Spectroscopic data consistent with those reported previously.[150]

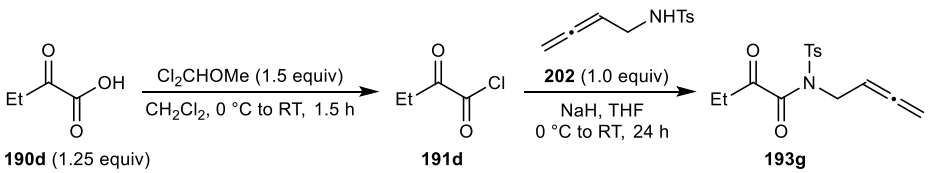
***N*-(buta-2,3-dien-1-yl)-4-methylbenzenesulfonamide (202)**



To a solution of alkyne **201** (4.18 g, 20.0 mmol) in 1,4-dioxane (125 mL) at room temperature under inert atmosphere was added paraformaldehyde (1.50 g, 50.0 mmol), CuBr (1.52 g, 8.00 mmol), and diisopropylamine (5.60 mL, 40.0 mmol). The reaction was heated at 100 ^{o}C for 3 h, cooled to room temperature, filtered through a pad of celite using EtOAc as eluent, and concentrated under reduced pressure. The mixture was purified by column chromatography (20% EtOAc/petroleum ether) to give allene **202** (1.76 g, 42%) as a yellow solid. R_f = 0.24 (20% EtOAc/petroleum

ether); ^{1}H NMR (400 MHz, $CDCl_3$) xx 7.78–7.71 (2H, m, Ar**H**), 7.34–7.28 (2H, m, Ar**H**), 5.06 (1H, quin, *J* = 6.3 Hz, $NCH_2C\mathbf{H}$), 4.77 (2H, dt, *J* = 6.6, 3.3 Hz, $=C\mathbf{H}_2$), 3.59 (2H, tt, *J* = 6.2, 3.2 Hz, $NC\mathbf{H}_2$), 2.43 (3H, s, $Ar\mathbf{CH_3}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.1 (C), 143.7 (C), 137.2 (C), 129.9 (2 × CH), 127.3 (2 × CH), 87.3 (CH), 78.3 (CH_2), 41.5 (CH_2), 21.7 (CH_3). HRMS (ESI) Exact mass calculated for $[C_{11}H_{13}NNaO_2S]^+$ $[M+Na]^+$: 246.0559, found: 246.0562. Spectroscopic data consistent with those reported previously.[151]

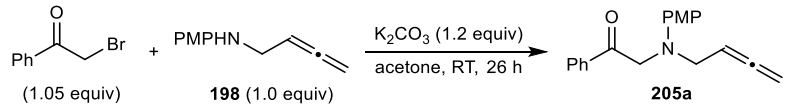
Preparation of *N*-(buta-2,3-dien-1-yl)-2-oxo-*N*-tosylbutanamide (193g)



To a solution of 2-ketobutyric acid (383 mg, 3.75 mmol) in CH_2Cl_2 (1.50 mL) at 0 °C under inert atmosphere, dichloromethyl methyl ether (0.41 mL, 4.50 mmol) was added dropwise. The mixture was stirred for 5 h at room temperature to yield a quantitative amount of 2-oxobutanoyl chloride. In another separate round bottom flask, to a solution of *N*-(buta-2,3-dien-1-yl)-4-methylbenzene sulfonamide **202**[151] (335 mg, 1.50 mmol) in THF (15 mL) was added NaH (60% dispersion in mineral oil, 240 mg, 6 mmol) at 0 °C and then the mixture was allowed to stir at room temperature for 5 h. The obtained acyl chloride solution was then added slowly to allenyl sulfonamide solution at 0 °C. The reaction mixture was stirred at room temperature for 18 h, then quenched with deionized water (20 mL), extracted with Et_2O (2 x 20 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The mixture was purified by column chromatography (20% EtOAc/petroleum ether) to give *allene* **193g** (217 mg, 47%) as a colorless oil. R_f = 0.47 (20% EtOAc/petroleum ether); IR 2980, 1954, 1719, 1673 (C=O), 1595, 1434, 1406, 1291, 1163, 1088, 966, 912, 860, 836, 803, 667, 590, 538 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86–7.83 (2H, m, Ar**H**), 7.38–7.35 (2H, m, Ar**H**), 5.02 (1H, quin, *J* = 6.4 Hz, $NCH_2C\mathbf{H}$), 4.65 (2H, dt, *J* = 6.6, 2.8 Hz, $=C\mathbf{H_2}$), 4.25 (2H, dt, *J* = 6.3, 2.8 Hz, $NC\mathbf{H_2}$), 2.86 (2H, q, *J* = 7.2 Hz, $C\mathbf{H_2}CH_3$), 2.46 (3H, s, $ArC\mathbf{H_3}$), 1.23 (3H, t, *J* = 7.2 Hz, $CH_2C\mathbf{H_3}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.2 (C), 198.7 (C), 168.1 (C), 145.9 (C), 134.8 (C), 130.1 (2 × CH), 128.7 (2 × CH), 85.3 (CH), 77.6 (CH_2), 43.5

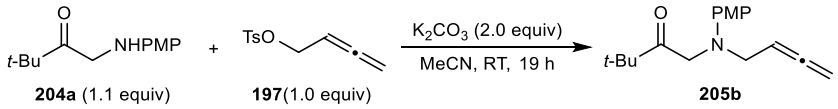
(CH_2), 32.9 (CH_2), 21.9 (CH_3), 7.0 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{15}H_{18}NO_4S]^+$ $[M+H]^+$: 308.0951, found: 308.0952.

2-[Buta-2,3-dien-1-yl(4-methoxyphenyl)amino]-1-phenylethan-1-one (205a)



To a solution of allenylamine **198** (351 mg, 2.00 mmol) in acetone (10 mL) was added K_2CO_3 (553 mg, 4.00 mmol) followed by bromoacetophenone (478 mg, 2.40 mmol), and the resulting suspension was stirred at room temperature for 26 h. The reaction was quenched with H_2O (10 mL) and the acetone was removed under reduced pressure. The resulting aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/petroleum ether) gave *allene* **205a** (469 mg, 80%) as a colorless oil. R_f = 0.41 (10% EtOAc/petroleum ether); IR 2930, 2827, 1954 (C=C=C), 1693 (C=O), 1515, 1263, 1219, 1177, 1033, 966, 846, 805, 757, 721, 692, 519, 504 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02–8.00 (2H, m, Ar**H**), 7.63–7.58 (1H, m, Ar**H**), 7.51–7.47 (2H, m, Ar**H**), 6.82–6.78 (2H, m, Ar**H**), 6.69–6.65 (2H, m, Ar**H**), 5.24 (1H, quin, *J* = 6.5 Hz, $CH_2C\mathbf{H}$=), 4.74 (2H, dt, *J* = 6.8, 2.8 Hz, =C$\mathbf{H}_2$), 4.71 (2H, s, O=CC$\mathbf{H}_2$), 4.03 (2H, dt, *J* = 6.1, 2.8 Hz, NC$\mathbf{H}_2$CH), 3.74 (3H, s, OC$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.2 (C), 196.9 (C), 152.4 (C), 143.0 (C), 135.7 (C), 133.6 (CH), 128.9 (2 × CH), 128.0 (2 × CH), 115.2 (2 × CH), 114.9 (2 × CH), 87.2 (CH), 76.1 (CH_2), 57.7 (CH_2), 55.8 (CH_3), 51.6 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{19}H_{20}NO_2]^+$ $[M+H]^+$: 294.1489, found: 294.1495.

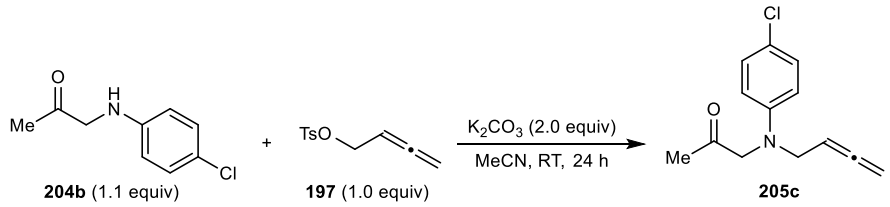
1-[Buta-2,3-dien-1-yl(4-methoxyphenyl)amino]-3,3-dimethylbutan-2-one (205b)



To a solution of aniline **204a**[152] (487 mg, 2.20 mmol) in MeCN (8 mL) was added K_2CO_3 (553 mg, 4.00 mmol) followed by allenyl tosylate **197**[149] (448 mg, 2.00 mmol), and the resulting suspension was stirred at room temperature for 19 h. The reaction was partitioned between Et_2O (10 mL) and saturated aqueous $NaHCO_3$

solution (10 mL). The aqueous layer was separated and extracted with Et_2O (3 × 10 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (2 × 10 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/petroleum ether) gave *allene* **205b** (333 mg, 61%) as a pale yellow oil. R_f = 0.47 (20% EtOAc/petroleum ether); IR 2968, 1954 (C=C=C), 1716, 1673 (C=O), 1511, 1463, 1364, 1243, 1178, 1032, 835, 812, 730, 549 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.79–6.77 (2H, m, Ar**H**), 6.60–6.58 (2H, m, Ar**H**), 5.17 (1H, quin, *J* = 6.6 Hz, $CH_2C\mathbf{H}$=), 4.73 (2H, dt, *J* = 6.6, 2.8 Hz, =C$\mathbf{H}_2$), 4.27 (2H, s, O=CC$\mathbf{H}_2$), 3.90 (2H, dt, *J* = 6.6, 2.8 Hz, NC$\mathbf{H}_2$CH), 3.73 (3H, s, OC$\mathbf{H}_3$), 1.22 (9H, s, C(C$\mathbf{H}_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.4 (C), 209.2 (C), 152.2 (C), 143.2 (C), 114.9 (2 × CH), 114.8 (2 × CH), 87.4 (CH), 75.9 (CH_2), 55.8 (CH_3), 55.5 (CH_2), 51.2 (CH_2), 43.5 (C), 26.7 (3 × CH_3); HRMS (ESI) Exact mass calculated for $[C_{17}H_{23}NNaO_2]^+$ $[M+Na]^+$: 296.1621, found: 296.1619.

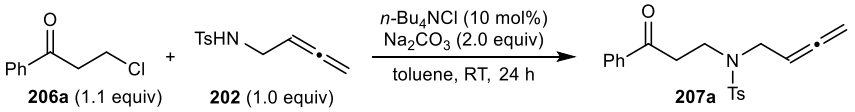
1-[Buta-2,3-dien-1-yl(4-chlorophenyl)amino]propan-2-one (205c)



To a solution of aniline **204b**[152] (302 mg, 1.65 mmol) in MeCN (6 mL) was added K_2CO_3 (415 mg, 3.00 mmol) followed by allenyl tosylate **197**[149] (336 mg, 1.50 mmol), and the resulting suspension was stirred at room temperature for 24 h. The reaction was partitioned between Et_2O (5 mL) and saturated aqueous $NaHCO_3$ solution (5 mL). The aqueous layer was separated and extracted with Et_2O (3 × 5 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (2 × 5 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/petroleum ether) gave *allene* **205c** (234 mg, 66%) as a yellow oil. R_f = 0.36 (20% EtOAc/petroleum ether); IR 2961, 1954 (C=C=C), 1727 (C=O), 1596, 1497, 1352, 1226, 1160, 1097, 961, 847, 808, 655, 508 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.17–7.13 (2H, m, Ar**H**), 6.54–6.50 (2H, m, Ar**H**), 5.17 (1H, quin, *J* = 6.6 Hz, $CH_2C\mathbf{H}$=), 4.78 (2H, dt, *J* = 6.6, 2.9 Hz, =C$\mathbf{H}_2$), 4.00-3.98 (4H, m, O=CC$\mathbf{H}_2$ and NC$\mathbf{H}_2$CH), 2.16 (3H, s, C$\mathbf{H}_3$); ^{13}C NMR

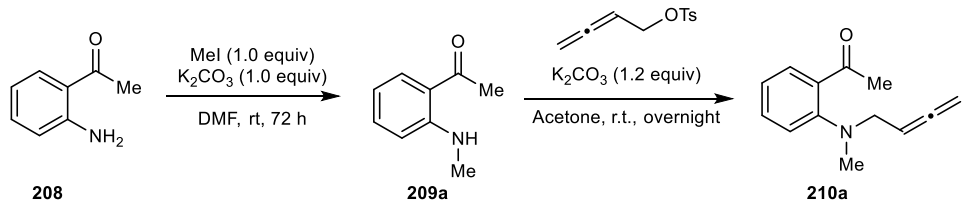
(101 MHz, $CDCl_3$) δ 209.2 (C), 207.7 (C), 146.6 (C), 129.2 (2 × CH), 122.6 (C), 113.9 (2 × CH), 86.4 (CH), 76.9 (CH_2), 61.4 (CH_2), 51.1 (CH_2), 27.2 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{13}H_{15}ClNO]^+$ $[M+H]^+$: 236.0837, found: 236.0836.

_N_-(Buta-2,3-dien-1-yl)-4-methyl-_N_-(3-oxo-3-phenylpropyl)benzenesulfonamide (207a)

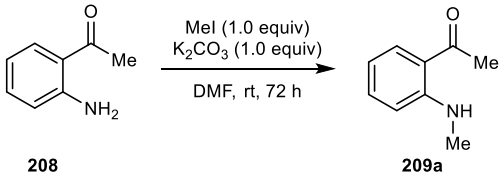


To a suspension of sulfonamide **202**[151] (446 mg, 2.00 mmol), *n*-Bu_4NCl (59 mg, 0.21 mmol), and Na_2CO_3 (424 mg, 4.00 mmol) in toluene (16 mL) at 0 °C and was added 3-chloropropiophenone (371 mg, 2.20 mmol) portionwise and the mixture was stirred at room temperature for 24 h. The reaction was quenched with saturated aqueous NH_4Cl solution (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/petroleum ether to 20% EtOAc/petroleum ether) gave *allene* **207a** (618 mg, 87%) as a white solid. R_f = 0.59 (20% EtOAc/petroleum ether); m.p 73–75 °C (Et_2O); IR 2983, 1965, 1680 (C=O), 1596, 1429, 1321, 1209, 1149, 1092, 995, 936, 861, 838, 808, 740, 685, 538, 509, 426 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96–7.94 (2H, m, Ar**H**), 7.73–7.70 (2H, m, Ar**H**), 7.61–7.56 (1H, m, Ar**H**), 7.50-7.45 (2H, m, Ar**H**), 7.32–7.28 (2H, m, Ar**H**), 4.97 (1H, quin, *J* = 6.9 Hz, $CH_2C\mathbf{H}$=), 4.70 (2H, dt, *J* = 6.6, 2.5 Hz, =C$\mathbf{H}_2$), 3.90 (2H, dt, *J* = 7.1, 2.5 Hz, NC$\mathbf{H}_2$CH), 3.59–3.56 (2H, m, $CH_2C\mathbf{H}_2N$), 3.41–3.37 (2H, m, O=CC$\mathbf{H}_2$), 2.42 (3H, s, ArC$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.6 (C), 198.5 (C), 143.6 (C), 136.7 (C), 136.6 (C), 133.6 (CH), 129.9 (2 × CH), 128.8 (2 × CH), 128.2 (2 × CH), 127.4 (2 ×CH), 86.3 (CH), 76.7 (CH_2), 48.3 (CH_2), 43.2 (CH_2), 39.0 (CH_2), 21.7 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{20}H_{22}NO_3S]^+$ $[M+H]^+$: 356.1315, found: 356.1316.

Preparation of allenyl ketone 210a

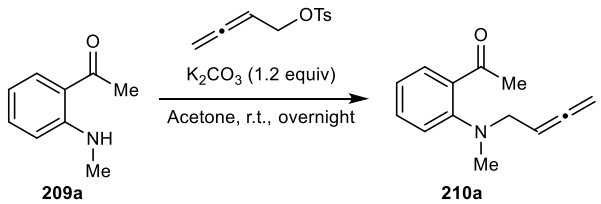


1-(2-(methylamino)phenyl)ethan-1-one (209a)



To a solution of K_2CO_3 (3.46 g, 25 mmol) in DMF (15 mL) was added 2'-aminoacetophenone (3.04 mL, 25 mmol). The reaction was stirred at room temperature for 15 min at room temperature. A solution of MeI (1.56 mL, 25 mmol) was added dropwise to the reaction mixture. The reaction was stirred for 3 days at room temperature. The reaction was diluted water (60 mL) and extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with water (40 mL) and brine (50 mL), dried over anhydrous Na_2SO_4. The filter solution was concentrated and purified by column chromatography (3-5% EtOAc/petreoleum ether) to furnish the title compound **209a** (2.14 g, 57%) as a greenish-yellow solid. R_f = 0.37 (10% EtOAc/petroleum ether); IR 3320, 3075, 2906, 2813, 1631, 1562, 1516, 1410, 1231, 1165, 950, 741, 655, 614, 519 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.78 (1H, s, N**H**), 7.74 (1H, dd, *J* = 8.1, 1.6 Hz, Ar**H**), 7.38 (1H, ddd, *J* = 8.5, 7.0, 1.6 Hz, Ar**H**), 6.69 (1H, dd, *J* = 8.6, 1.1 Hz, Ar**H**), 6.59 (1H, ddd, *J* = 8.1, 7.0, 1.1 Hz, Ar**H**), 2.91 (3H, d, *J* = 5.0 Hz, NHC**H₃**), 2.58 (3H, s, O=CC**H₃**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.9 (C), 152.1 (C), 135.2 (CH), 132.8 (CH), 117.7 (C), 114.0 (CH), 111.4 (CH), 29.4 (CH_3), 28.0 (CH_3) ; HRMS (ESI) Exact mass calculated for $[C_9H_{12}NO]^+$ $[M+H]^+$: 150.0913, found: 150.0917. Spectroscopic data consistent with those reported previously.[153]

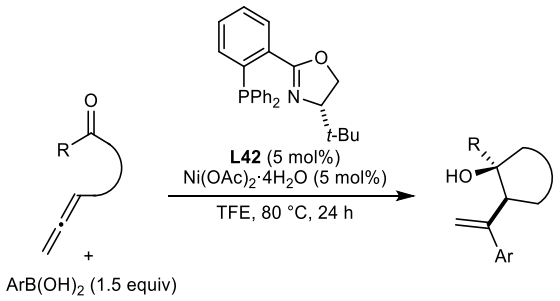
1-(2-(buta-2,3-dien-1-yl(methyl)amino)phenyl)ethan-1-one (210a)



To a solution of aniline **209a** (298 mg, 2.00 mmol) in MeCN (8 mL) was added K_2CO_3 (553 mg, 4.00 mmol) followed by allenyl tosylate (493 mg, 2.20 mmol), and the resulting suspension was stirred at room temperature for 19 h. The reaction was partitioned between Et_2O (10 mL) and saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous layer was separated and extracted with Et_2O (3 × 10 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (2 × 10 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/petroleum ether) gave *allene* **210a** (252 mg, 63%) as a pale yellow liquid. R_f = 0.59 (20% EtOAc/petroleum ether); IR 2944, 2801, 1953, 1675, 1593, 1484, 1447, 1350, 1280, 1240, 1098, 944, 844, 750, 597, 547 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.40 (1H, m, Ar**H**), 7.36 (1H, ddd, *J* = 8.2, 7.3, 1.7 Hz, Ar**H**), 7.04 (1H, dd, *J* = 8.3, 1.0 Hz, Ar**H**), 6.98 (1H, td, *J* = 7.4, 1.1 Hz, Ar**H**), 5.10 (1H, quin, *J* = 6.7 Hz, $CH_2C\mathbf{H}$=), 4.73 (2H, dt, *J* = 6.6, 2.6 Hz, =C$\mathbf{H}_2$), 3.65 (2H, dt, *J* = 6.9, 2.6 Hz, NC$\mathbf{H}_2$), 2.80 (3H, s, NHC$\mathbf{H}_3$), 2.60 (3H, s, O=CC$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.5 (C), 204.1 (C), 150.9 (C), 134.2 (C), 131.8 (CH), 129.5 (CH), 121.4 (CH), 119.3 (CH), 86.3 (CH), 75.8 (CH_2), 56.3 (CH_2), 40.9 (CH_3), 29.2 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{13}H_{16}NO]^+$ $[M+H]^+$: 202.1226, found: 202.1224.

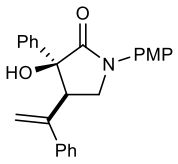
5.3. Enantioselective Nickel-Catalyzed Arylative and Alkenylative Intramolecular Allylations: General procedure

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 (**L42**, 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.

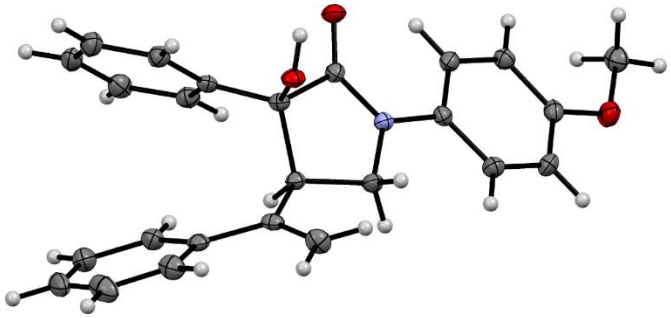
5.3.1. Exploration of substrate scope

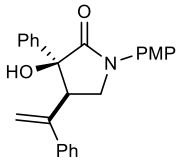


(3*S*,4*R*)-3-Hydroxy-1-(4-methoxyphenyl)-3-phenyl-4-(1-phenylvinyl)pyrrolidin-2-one (194a). The General Procedure was followed using allene **193a** (92.2 mg, 0.300 mmol) and phenylboronic acid (54.9 mg, 0.450 mmol). Filtration through a silica pad without purification by column chromatography gave the title compound **194a** (115 mg, 99%) 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,

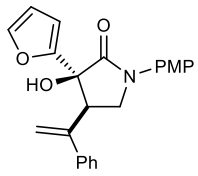
1057, 828 cm^{-1}; $[\alpha]_D^{20}$ +16.0 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.61–7.55 (2H, m, Ar**H**), 7.41–7.37 (2H, m, Ar**H**), 7.36–7.20 (8H, m, Ar**H**), 6.98–6.92 (2H, m, Ar**H**), 5.51 (1H, s, =C**H**$_2$), 5.35 (1H, s, =C**H**$_2$), 4.03–3.92 (2H, m, C**H**$_2$N), 3.83 (3H, s, OC**H**$_3$), 3.79–3.73 (1H, m, C**H**CH_2), 3.20 (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 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C) t_r (minor) = 25.9 min, t_r (major) = 33.3 min, 96% ee.

Slow diffusion of petroleum ether into a solution of **194a** in EtOAc gave crystals that were suitable for X-ray crystallography:



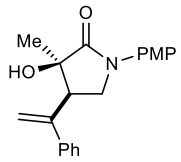


194a
CCDC 1945864
Flack parameter = 0.05(8)

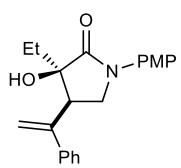


(3*S*,4*R*)-3-(Furan-2-yl)-3-hydroxy-1-(4-methoxyphenyl)-4-(1-phenylvinyl)pyrrolidine-2-one (194b). The General Procedure was followed using allene **193b** (89.2 mg, 0.300 mmol) and phenylboronic acid (54.9 mg, 0.450 mmol). Filtration through a silica pad without purification by column chromatography gave the title compound **194b** (112 mg, 99%) as a white amorphous solid. R_f = 0.41 (40% EtOAc/petroleum ether); $[\alpha]_D^{25}$ +14.8 (*c* 0.27, $CHCl_3$); IR 3366 (OH), 2955, 1681 (C=O), 1509, 1440, 1399, 1298, 1245, 1150, 1057, 1029, 1005, 886, 828, 776, 735, 699, 595, 567, 522 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54–7.52 (2H, m, Ar**H**), 7.39–7.35 (3H, m, Ar**H**), 7.31–7.24 (3H, m, Ar**H**), 6.93–6.90 (2H, m, Ar**H**), 6.36 (1H, dd, *J* = 3.3, 0.9 Hz, Ar**H**), 6.29 (1H, dd, *J* = 3.3, 1.8 Hz, ArC**H**), 5.53 (1H, s, =C**H**$_2$), 5.31 (1H, s,

=C**H**$_2$), 4.11–4.04 (2H, m, C**H**$_2$N), 3.94 (1H, dd, *J* = 8.7, 3.1 Hz, C**H**CH$_2$), 3.80 (3H, s, OC**H**$_3$), 3.54 (1H, s, O**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8 (C), 157.2 (C), 153.5 (C), 145.7 (C), 142.8 (CH), 141.7 (C), 131.9 (C), 128.3 (2 × CH), 127.6 (CH), 126.7 (2 × CH), 121.8 (2 × CH), 115.5 (CH_2), 114.3 (2 × CH), 110.6 (CH), 107.8 (CH), 77.4 (C), 55.6 (CH_3), 51.3 (CH_2), 46.2 (CH); 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 AD-H column (60:40 *iso*-hexane:*i*-PrOH, 1.5 mL/min, 254 nm, 25 °C) t_r (major) = 25.2 min, t_r (minor) = 35.5 min, 97% ee.

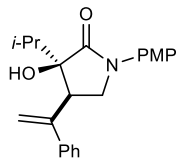


(3*R*,4*R*)-3-Hydroxy-1-(4-methoxyphenyl)-3-methyl-4-(1-phenylvinyl)pyrrolidin-2-one (194c). The General Procedure was followed using allene **193c** (73.6 mg, 0.300 mmol) and phenylboronic acid (54.9 mg, 0.450 mmol). Filtration through a silica pad without purification by column chromatography gave the title compound **194c** (96 mg, 99%) as a colorless solid. R_f = 0.21 (30% EtOAc/petroleum ether); m.p. 122–125 °C (Et_2O); $[\alpha]_D^{25}$ +7.41 (*c* 0.54, $CHCl_3$); IR 3348 (OH), 2979, 1688 (C=O), 1510, 1469, 1391, 1288, 1244, 1175, 1097, 1030, 944, 889, 827, 774, 700, 596, 555, 524 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.49 (2H, m, Ar**H**), 7.43–7.40 (2H, m, Ar**H**), 7.37–7.26 (3H, m, Ar**H**), 6.92–6.88 (2H, m, Ar**H**), 5.48 (1H, s, =C**H**$_2$), 5.32 (1H, s, =C**H**$_2$), 3.92 (2H, app d, *J* = 6.4 Hz, C**H**$_2$N), 3.80 (3H, s, OC**H**$_3$), 3.44–3.40 (1H, m, C**H**CH$_2$), 3.00 (1H, s, O**H**), 1.41 (3H, s, C**H**$_3$C); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0 (C), 156.9 (C), 145.9 (C), 142.4 (C), 132.1 (C), 128.4 (2 × CH), 127.7 (CH), 126.9 (2 × CH), 121.7 (2 × CH), 115.5 (CH_2), 114.2 (2 × CH), 76.4 (C), 55.5 (CH_3), 51.0 (CH_2), 48.1 (CH), 24.4 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{20}H_{22}NO_3]^+$ $[M+H]^+$: 324.1594, found: 324.1597; Enantiomeric excess was determined by HPLC with a Chiralpak IC column (80:20 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C) t_r (major) = 26.7 min, t_r (minor) = 31.3 min, 98% ee.



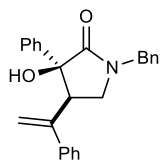
(3*R*,4*R*)-3-Ethyl-3-hydroxy-1-(4-methoxyphenyl)-4-(1-phenylvinyl)pyrrolidin-2-one (194d). The General Procedure was followed using allene **193d** (77.8 mg, 0.300 mmol) and phenylboronic acid (54.9 mg, 0.450 mmol). Filtration through a silica pad without purification by column chromatography gave the title compound **194d**

(101 mg, >99%) as a colorless oil. R_f = 0.10 (20% EtOAc/petroleum ether); $[\alpha]_D^{25}$ +18.6 (*c* 0.43, $CHCl_3$); IR 3550 (OH), 2964, 1682 (C=O), 1514, 1488, 1404, 1253, 1157, 1031, 1018, 909, 873, 823, 781, 746, 695, 575, 526, 463 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54–7.50 (2H, m, Ar**H**), 7.44–7.41 (2H, m, Ar**H**), 7.36–7.26 (3H, m, Ar**H**), 6.93–6.89 (2H, m, Ar**H**), 5.45 (1H, s, =C**H**$_2$), 5.27 (1H, s, =C**H**$_2$), 4.00–3.95 (1H, m, C**H**$_2$N), 3.86 (1H, dd, *J* = 10.0, 4.0 Hz, C**H**$_2$N), 3.80 (3H, s, OC**H**$_3$), 3.52 (1H, dd, *J* = 7.0, 4.0 Hz, C**H**CH_2), 2.93 (1H, br m, O**H**), 1.85 (1H, dt, *J* = 14.8, 7.5 Hz, CH_3C**H**$_2$), 1.71 (1H, dt, *J* = 14.5, 7.4 Hz, CH_3C**H**$_2$), 1.00 (3H, t, *J* = 7.4 Hz, C**H**$_3CH_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8 (C), 156.9 (C), 147.0 (C), 142.4 (C), 132.1 (C), 128.3 (2 × CH), 127.7 (CH), 126.8 (2 × CH), 121.7 (2 × CH), 115.2 (CH_2), 114.2 (2 × CH), 79.4 (C), 55.5 (CH_3), 51.4 (CH_2), 45.0 (CH), 30.3 (CH_2), 8.3 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{21}H_{24}NO_3]^+$ $[M+H]^+$: 338.1751, found: 338.1751; Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C) t_r (major) = 32.1 min, t_r (minor) = 49.1 min, >99% ee.



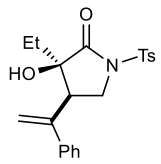
(3*R*,4*R*)-3-Hydroxy-3-isopropyl-1-(4-methoxyphenyl)-4-(1-phenylvinyl)pyrrolidin-2-one (194e). The General Procedure was followed using allene **193e** (82.0 mg, 0.300 mmol) and phenylboronic acid (54.9 mg, 0.450 mmol). Filtration through a silica pad without purification by column chromatography gave the title compound **194e** (105 mg, >99%) as a colorless oil. R_f = 0.23 (20% EtOAc/petroleum ether); $[\alpha]_D^{25}$ +14.3 (*c* 0.84, $CHCl_3$); IR 3422 (OH), 2960, 1681 (C=O), 1510, 1465, 1440, 1401, 1291, 1245, 1178, 1159, 1031, 906, 828, 796, 729, 701, 566, 527 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53–7.49 (2H, m, Ar**H**), 7.44–7.41 (2H, m, Ar**H**), 7.36–7.26 (3H, m, Ar**H**), 6.94–6.89 (2H, m, Ar**H**), 5.43 (1H, s, =C**H**$_2$), 5.24 (1H, s, =C**H**$_2$), 4.00 (1H, dd, *J* = 10.3, 7.3 Hz, C**H**$_2$N), 3.80 (3H, s, OC**H**$_3$), 3.79–3.65 (1H, m, C**H**$_2$N), 3.60 (1H, dd, *J* = 7.3, 2.6 Hz, C**H**CH_2), 2.80 (1H, s, O**H**), 2.11 (1H, hept, *J* = 6.8 Hz, $(CH_3)_2$C**H**), 1.06 (3H, d, *J* = 6.9 Hz, (C**H**$_3)_2$CH), 1.01 (3H, d, *J* = 6.8 Hz, (C**H**$_3)_2$CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1 (C), 157.0 (C), 148.3 (C), 142.4 (C), 131.9 (C), 128.3 (2 × CH), 127.6 (CH), 127.0 (2 × CH), 121.8 (2 × CH), 115.3 (CH_2), 114.2 (2 × CH), 81.6 (C), 55.5 (CH_3), 52.3 (CH_2), 43.4 (CH), 35.0 (CH), 17.4 (CH_3), 16.7 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{22}H_{26}NO_3]^+$ $[M+H]^+$: 352.1907,

found: 352.1909; Enantiomeric excess was determined by HPLC with a Chiralpak IC column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C) t_r (major) = 31.0 min, t_r (minor) = 33.9 min, >99% ee.



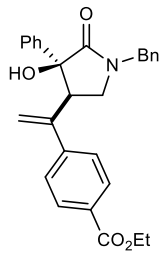
(3*S*,4*R*)-1-Benzyl-3-hydroxy-3-phenyl-4-(1-phenylvinyl)pyrrolidin-2-one (194f). *Using TFE as the solvent:* The General Procedure was followed using allene **193f** (87.4 mg, 0.300 mmol) and phenylboronic acid (54.9 mg, 0.450 mmol). Purification by passing the compound through a short pad of silica using pentane as eluent gave the title compound **194f** (110 mg, 99%) as a colorless solid. R_f = 0.29 (30% EtOAc/petroleum ether); m.p. 158–162 °C (Et_2O); $[\alpha]_D^{25}$ –31.6 (*c* 0.38, $CHCl_3$); IR 3326 (OH), 3060, 2912, 1683 (C=O), 1483, 1436, 1340, 1258, 1024, 950, 895, 741, 695, 659, 589, 510, 465 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.31 (5H, m, Ar**H**), 7.30–7.23 (5H, m, Ar**H**), 7.17–7.12 (3H, m, Ar**H**), 7.10–7.07 (2H, m, Ar**H**), 5.43 (1H, d, *J* = 0.3 Hz, =C**H**$_2$), 5.17 (1H, s, =C**H**$_2$), 4.70 (1H, d, *J* = 14.5 Hz, C**H**$_2$Ph), 4.51 (1H, d, *J* = 14.5 Hz, C**H**$_2$Ph), 3.61 (1H, td, *J* = 6.5, 0.9 Hz, C**H**CH$_2$), 3.47 (2H, app dd, *J* = 6.4, 1.2 Hz, CHC**H**$_2$), 2.88 (1H, s, O**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2 (C), 145.1 (C), 142.0 (C), 141.8 (C), 135.8 (C), 128.9 (2 × CH), 128.5 (2 × CH), 128.2 (2 × CH), 128.0 (2 × CH), 127.9 (CH), 127.6 (CH), 127.3 (CH), 126.8 (2 × CH), 125.5 (2 × CH), 116.3 (CH_2), 80.2 (C), 50.5 (CH), 49.0 (CH_2), 47.3 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{25}H_{24}NO_2]^+$ $[M+H]^+$: 370.1802, found: 370.1803; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C) t_r (major) = 19.4 min, t_r (minor) = 22.2 min, 87% ee.

Using MeCN as the solvent: A modification of the General Procedure was followed using allene **193f** (87.4 mg, 0.30 mmol) and phenylboronic acid (54.9 mg, 0.45 mmol) but using MeCN in place of TFE as the solvent. Purification by column chromatography (20% EtOAc/petroleum ether) gave the title compound **194f** (71.8 mg, 65%) as a colorless solid. $[\alpha]_D^{25}$ –34.8 (*c* 0.46, $CHCl_3$); Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (major) = 19.8 min, t_r (minor) = 22.8 min, 99% ee.



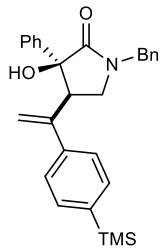
(*3R,4R*)-3-ethyl-3-hydroxy-4-(1-phenylvinyl)-1-tosylpyrrolidin-2-one (194g). The General Procedure was followed using the allene **193g** (15.4 mg, 0.05 mmol) and phenylboronic acid (9.1 mg, 0.075 mmol) and purified by column chromatography (20% EtOAc/petroleum ether) to give the title compound **194g** (2.8 mg, 15%) as a colorless solid. R_f = 0.20 (20% EtOAc/petroleum ether); m.p. 73–75 °C (Et_2O); $[\alpha]_D^{25}$ –100.0 (*c* 0.04, $CHCl_3$); IR 3425 (OH), 2923, 1735, 1725 (C=O), 1355, 1167, 1089, 1028, 949, 913, 831, 814, 777, 701, 659, 577, 544, 413 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97–7.92 (2H, m, Ar**H**), 7.39–7.33 (2H, m, Ar**H**), 7.31–7.27 (5H, m, Ar**H**), 5.33 (1H, s, =C**H**$_2$), 4.97 (1H, d, *J* = 0.4 Hz, =C**H**$_2$), 4.07 (1H, dd, *J* = 10.2, 7.1 Hz, NC**H**$_2$CH), 3.88 (1H, dd, *J* = 10.2, 4.7 Hz, C**H**$_2$N), 3.43–3.37 (1H, m, C**H**CH_2), 2.46 (3H, s, ArC**H**$_3$), 2.20 (1H, s, O**H**), 1.73–1.61 (2H, m, C**H**$_2$$CH_3$), 0.85 (3H, t, *J* = 7.4 Hz, CH_2C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.4 (C), 145.73 (C), 145.67 (C), 141.9 (C), 134.8 (C), 130.0 (2 × CH), 128.6 (2 × CH), 128.2 (2 × CH), 128.1 (CH), 126.7 (2 × CH), 115.7 (CH_2), 79.4 (C), 49.4 (CH_2), 44.6 (CH), 29.8 (CH_2), 21.9 (CH_3), 7.9 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{21}H_{24}NO_4S]^+$ $[M+H]^+$: 386.1421, found: 386.1422. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (minor) = 33.5 min, t_r (major) = 42.5 min, 97% ee.

5.3.2. Exploration of boronic acid scope

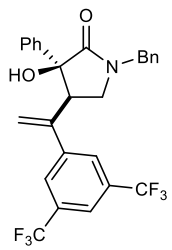


Ethyl 4-(1-((*3R,4S*)-1-benzyl-4-hydroxy-5-oxo-4-phenylpyrrolidin-3-yl)vinyl) benzoate (194h). The General Procedure was followed using the allene **193f** (87.4 mg, 0.30 mmol) and 4-ethoxycarbonylphenylboronic acid (87.3 mg, 0.45 mmol). Filtration through a silica pad without purification by column chromatography gave the title compound **194h** (126.6 mg, 96%) as a colorless solid. R_f = 0.07 (20% EtOAc/petroleum ether); m.p. 147–150 °C (Et_2O); $[\alpha]_D^{25}$ –30.8 (*c* 0.78, $CHCl_3$); IR 3308 (OH), 2978, 1706 (C=O), 1682 (C=O), 1606, 1435, 1404, 1365, 1273, 1193, 1112, 1020, 949, 857, 781, 745, 698, 644, 536, 457 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81–7.75 (2H, m, Ar**H**), 7.39–7.28 (5H, m, Ar**H**), 7.21–7.15 (5H, m,

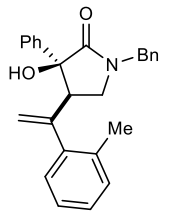
Ar**H**), 7.08–7.05 (2H, m, Ar**H**), 5.44 (1H, s, =C**H**$_2$), 5.25 (1H, s, =C**H**$_2$), 4.66 (1H, d, *J* = 14.6 Hz, C**H**$_2$N), 4.50 (1H, d, *J* = 14.5 Hz, C**H**$_2$N), 4.33 (2H, q, *J* = 7.1 Hz, C**H**$_2$CH$_3$), 3.94 (1H, s, O**H**), 3.58–3.38 (3H, m, C**H**$_2$Ph and C**H**CH$_2$), 1.36 (3H, t, *J* = 7.1 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1 (C), 166.4 (C), 146.4 (C), 144.1 (C), 141.8 (C), 135.7 (C), 129.2 (2 × CH), 129.0 (C), 128.9 (2 × CH), 128.4 (2 × CH), 128.2 (2 × CH), 127.9 (CH), 127.6 (CH), 126.7 (2 × CH), 125.4 (2 × CH), 117.8 (CH_2), 80.1 (C), 60.9 (CH_2), 50.5 (CH), 48.7 (CH_2), 47.2 (CH_2), 14.3 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{28}H_{28}NO_4]^+$ $[M+H]^+$: 442.2013, found: 442.2012. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (major) = 35.0 min, t_r (minor) = 41.8 min, 88% ee.



(*3S*,*4R*)-1-benzyl-3-hydroxy-3-phenyl-4-(1-(4-(trimethylsilyl)phenyl)vinyl) pyrrolidin-2-one (194i). The General Procedure was followed using the allene **193f** (87.4 mg, 0.30 mmol) and 4-(trimethylsilyl)phenylboronic acid (87.3 mg, 0.45 mmol). Filtration through silica pad without purification by column chromatography gave title compound **194i** (132.0 mg, >99%) as a colorless solid. R_f = 0.21 (20% EtOAc/petroleum ether); m.p. 160–162 °C (Et_2O); $[\alpha]_D^{25}$ –29.9 (*c* 0.67, $CHCl_3$); IR 3316 (OH), 2954, 1682 (C=O), 1493, 1434, 1245, 1123, 1093, 915, 826, 745, 696, 659, 514 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.34 (5H, m, Ar**H**), 7.32 (2H, d, *J* = 7.8 Hz, Ar**H**), 7.29–7.22 (5H, m, Ar**H**), 7.06 (2H, d, *J* = 7.8 Hz, Ar**H**), 5.48 (1H, s, =C**H**$_2$), 5.22 (1H, s, =C**H**$_2$), 4.74 (1H, d, *J* = 14.5 Hz, C**H**$_2$N), 4.55 (1H, d, *J* = 14.5 Hz, C**H**$_2$N), 3.62 (1H, t, *J* = 6.8 Hz, C**H**CH$_2$), 3.55–3.47 (2H, m, C**H**$_2$Ph), 3.33 (1H, s, O**H**), 0.27 (9H, s, Si(C**H**$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2 (C), 145.2 (C), 142.1 (C), 142.0 (C), 139.5 (C), 135.8 (C), 133.1 (2 × CH), 129.0 (2 × CH), 128.5 (2 × CH), 128.3 (2 × CH), 128.0 (CH), 127.7 (CH), 126.0 (2 × CH), 125.5 (2 × CH), 116.1 (CH_2), 80.3 (C), 50.4 (CH), 49.0 (CH_2), 47.4 (CH_2), –1.1 (3 × CH_3); HRMS (ESI) Exact mass calcd for $[C_{28}H_{32}NO_2Si]^+$ $[M+H]^+$: 442.2197, found: 442.2201. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (minor) = 11.9 min, t_r (major) = 32.4 min, 80% ee.

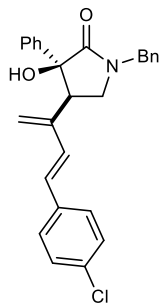


(*3S,4R*)-1-benzyl-4-(1-(3,5-bis(trifluoromethyl)phenyl)vinyl)-3-hydroxy-3-phenylpyrrolidin-2-one (194j). The General Procedure was followed using the allene **193f** (87.4 mg, 0.30 mmol) and 3,5-bis(trifluoromethyl)phenylboronic acid (116.1 mg, 0.45 mmol) and purified by column chromatography (20% EtOAc/petroleum ether) to give the title compound **194j** (130 mg, 96%) as a colorless solid. R_f = 0.26 (20% EtOAc/petroleum ether); m.p. 120–123 °C (Et_2O); $[\alpha]_D^{25}$ –29.3 (*c* 0.41, $CHCl_3$); IR 3315 (OH), 2978, 1686 (C=O), 1436, 1369, 1273, 1174, 1126, 1062, 948, 897, 846, 748, 698, 680, 627, 541, 446 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63–7.61 (1H, m, Ar**H**), 7.44–7.33 (7H, m, Ar**H**), 7.21–7.18 (3H, m, Ar**H**), 7.15–7.12 (2H, m, Ar**H**), 5.47 (1H, s, =C**H**$_2$), 5.28 (1H, s, =C**H**$_2$), 4.69 (1H, d, *J* = 14.5 Hz, C**H**$_2$N), 4.59 (1H, d, *J* = 14.5 Hz, C**H**$_2$N), 3.56-3.49 (3H, m, C**H**$_2$Ph and C**H**CH$_2$), 3.00 (1H, br, O**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4 (C), 144.0 (C), 142.2 (C), 141.0 (C), 135.6 (C), 131.1 (2 x C, q, J^2 = 33.3 Hz), 129.0 (2 × CH), 128.4 (2 × CH), 128.2 (2 × CH), 128.1 (CH), 127.8 (CH), 127.1 (2 × CH, d, J^3 = 4.0 Hz), 125.3 (2 × CH), 123.2 (2 × C-F_3, q, J^1 = 273.8 Hz) , 120.8 (CH, dq, J^3 = 7.3, 3.5 Hz), 119.2 (CH_2), 80.0 (C), 51.2 (CH), 48.1 (CH_2), 47.3 (CH_2); HRMS (ESI) Exact mass calcd for $[C_{27}H_{22}F_6NO_2]^+$ $[M+H]^+$: 506.1549, found: 506.1546. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (95:05 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (minor) = 10.1 min, t_r (major) = 12.3 min, 83% ee.



(*3S,4R*)-1-benzyl-3-hydroxy-3-phenyl-4-(1-(o-tolyl)vinyl)pyrrolidin-2-one (194k). The General Procedure was followed using the allene **193f** (87.4 mg, 0.30 mmol) and o-tolylboronic acid (61.2 mg, 0.45 mmol), and purified by column chromatography (20% EtOAc/petroleum ether) to give the title compound **194k** (99.2 mg, 86%) as a 5:1 mixture of diastereomers as a colorless solid. R_f = 0.18 (20% EtOAc/petroleum ether); m.p. 167–171 °C (Et_2O); $[\alpha]_D^{25}$ –70.6 (*c* 0.34, $CHCl_3$); IR 3348 (OH), 2917, 1681 (C=O), 1482, 1432, 1257, 1159, 950, 908, 741, 697, 624, 543, 462 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *major diastereomer*: δ 7.41–7.26 (5H, m, Ar**H**), 7.22–7.14 (5H, m, Ar**H**), 7.07–6.91 (4H, m, Ar**H**), 5.35 (1H, s, =C**H**$_2$), 5.11 (1H, d, *J* = 0.9 Hz, =C**H**$_2$), 4.67 (1H, d, *J* = 14.6 Hz, C**H**$_2$N), 4.45 (1H, d, *J* = 14.6 Hz, C**H**$_2$N), 3.57 (1H, s, O**H**), 3.49–3.36 (3H, m, C**H**CH$_2$ and C**H**$_2$Ph), 2.14 (3H, s, ArC**H**$_3$); *minor diastereomer*: δ 7.41–7.26 (5H, m, Ar**H**), 7.22–

7.14 (5H, m, Ar**H**), 7.07–6.91 (4H, m, Ar**H**), 5.33 (1H, s, =C**H**$_2$), 5.10 (1H, d, *J* = 1.0 Hz, =C**H**$_2$), 4.64 (1H, d, *J* = 14.8 Hz, C**H**$_2$N), 4.40 (1H, d, *J* = 14.7 Hz, C**H**$_2$N), 3.77 (1H, s, O**H**), 3.49–3.36 (3H, m, C**H**CH$_2$ and NC**H$_2$**Ph), 2.14 (3H, s, ArC**H$_3$**); ^{13}C NMR (101 MHz, $CDCl_3$) *major diastereomer*: δ 174.5 (C), 144.7 (C), 141.8 (C), 141.6 (C), 135.9 (C), 134.7 (C), 130.0 (CH), 128.9 (2 × CH), 128.85 (CH), 128.37 (2 × CH), 128.0 (2 × CH), 127.88 (CH), 127.43 (CH), 127.01 (CH), 125.6 (2 × CH), 125.3 (CH), 117.84 (CH_2), 80.48 (C), 51.56 (CH), 48.36 (CH_2), 47.3 (CH_2), 20.0 (CH_3); *observable signals of minor diastereomer* δ 174.6 (C), 144.6 (C), 141.9 (C), 141.7 (C), 129.9 (CH), 128.9 (2 × CH), 128.86 (CH), 128.0 (2 × CH), 127.86 (CH), 127.40 (CH), 126.97 (CH), 125.7 (2 × CH), 125.2 (CH), 117.87 (CH_2), 80.50 (C), 51.64 (CH), 47.2 (CH_2); HRMS (ESI) Exact mass calcd for $[C_{26}H_{26}NO_2]^+$ $[M+H]^+$: 384.1958, found: 384.1957. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (95:05 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (minor) = 12.5 min, t_r (major) = 17.1 min, 66% ee.

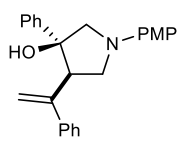


(*3S,4R*)-1-benzyl-4-((*E*)-4-(4-chlorophenyl)buta-1,3-dien-2-yl)-3-hydroxy-3-phenylpyrrolidin-2-one (194l). The title compound was prepared according to the General Procedure using the allene **193f** (87.4 mg, 0.30 mmol) and trans-2-(4-chlorophenyl)vinylboronic acid (82.1 mg, 0.45 mmol), and purified by column chromatography (20% EtOAc/petroleum ether) to give a colorless solid **194l** (51.5 mg, 40%). R_f = 0.12 (20% EtOAc/petroleum ether); m.p. 166-168 °C (Et_2O); $[\alpha]_D^{25}$ –16.7 (*c* 0.24, $CHCl_3$); IR 3320, 2924, 1686, 1487, 1445, 1431, 1366, 1074, 1010, 964, 720, 695, 660, 595, 567, 516 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 7.41–7.27 (10H, m, Ar**H**), 7.22–7.18 (2H, m, Ar**H**), 7.04–7.00 (2H, m, Ar**H**), 6.58 (1H, dd, *J* = 16.3, 0.8 Hz, C**H**=CHAr), 5.93 (1H, d, *J* = 16.3 Hz, CH=C**H**Ar), 5.43 (1H, s, =C**H**$_2$), 5.11 (1H, s, =C**H**$_2$), 4.71 (1H, d, *J* = 14.5 Hz, C**H**$_2$N), 4.58 (1H, d, *J* = 14.4 Hz, C**H**$_2$N), 3.47–3.40 (3H, m, C**H$_2$**Ph and C**H**CH$_2$), 3.21 (1H, s, O**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0 (C), 142.4 (C), 141.5 (C), 135.8 (C), 135.4 (C), 133.3 (C), 130.9 (CH), 129.0 (2 × CH), 128.7 (2 × CH), 128.61 (2 × CH), 128.59 (2 × CH), 128.4 (CH), 128.1 (CH), 128.08 (CH), 127.8 (2 × CH), 125.6 (2 × CH), 118.3 (CH_2), 79.8 (C), 48.5 (CH_2), 48.2 (CH), 47.4 (CH_2); HRMS (ESI) Exact mass calcd for $[C_{27}H_{25}ClNO_2]^+$ $[M+H]^+$: 430.1568, found: 430.1566. Enantiomeric excess was

determined by HPLC with a Chiralpak AD-H column (80:20 *iso*-hexane:*i*-PrOH, 1.5 mL/min, 254 nm, 25 °C); t_r (major) = 11.0 min, t_r (minor) = 31.7 min, 83% ee.

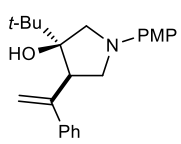
5.4. Exploration to form pyrrolidines, piperidines and tetrahydroquinolines

5.4.1. Pyrrolidines



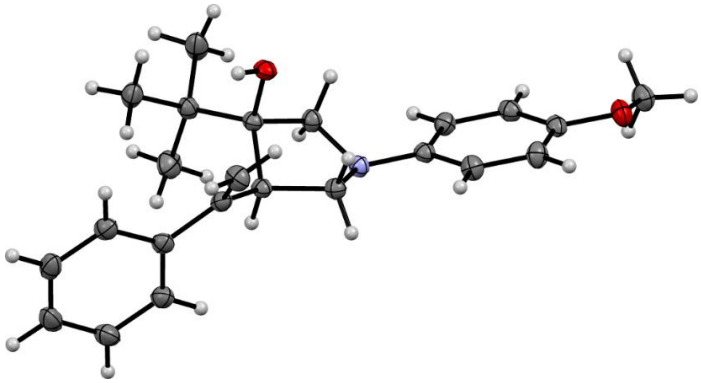
(3*S*,4*R*)-1-(4-Methoxyphenyl)-3-phenyl-4-(1-phenylvinyl)pyrrolidin-3-ol (211a). The General Procedure was followed using allene **205a** (87.9 mg, 0.300 mmol) and phenylboronic acid (54.9 mg, 0.450 mmol). Purification by column chromatography (10% EtOAc/pentane) gave the title compound **211a** (69.1 mg, 62%) as a pale yellow solid. R_f = 0.47 (20% EtOAc/petroleum ether); m.p. 170–174 °C (Et_2O); $[\alpha]_D^{25}$ –21.1 (*c* 0.19, $CHCl_3$); IR 3529 (OH), 2906, 1620, 1511, 1471, 1445, 1371, 1346, 1270, 1238, 1178, 1109, 1038, 898, 815, 766, 664, 596, 511, 410 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.37 (2H, m, Ar**H**), 7.21–7.16 (2H, m, Ar**H**), 7.15–7.10 (4H, m, Ar**H**), 7.07–7.03 (2H, m, Ar**H**), 6.90–6.86 (2H, m, Ar**H**), 6.58–6.53 (2H, m, Ar**H**), 5.46 (1H, d, *J* = 0.8 Hz, =C**H**$_2$), 5.41 (1H, s, =C**H**$_2$), 4.01–3.96 (1H, m, C**H**CH_2), 3.83 (1H, d, *J* = 10.0 Hz, CC**H**$_2$N), 3.80–3.74 (1H, m, CHC**H**$_2$), 3.78 (3H, s, OC**H**$_3$), 3.68 (1H, dd, *J* = 10.1, 9.0 Hz, CHC**H**$_2$), 3.63 (1H, d, *J* = 10.4 Hz, CC**H**$_2$N), 2.49 (1H, s, O**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4 (C), 145.8 (C), 142.8 (C), 142.5 (C), 142.4 (C), 128.1 (4 × CH), 127.4 (CH), 127.1 (CH), 126.8 (2 × CH), 125.4 (2 × CH), 116.8 (CH_2), 115.2 (2 × CH), 112.6 (2 × CH), 80.7 (C), 64.5 (CH_2), 56.1 (CH_3), 53.8 (CH), 52.6 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{25}H_{26}NO_2]^+$ $[M+H]^+$: 372.1958, found: 372.1962; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C) t_r (major) = 28.8 min, t_r (minor) = 37.0 min, 75% ee.

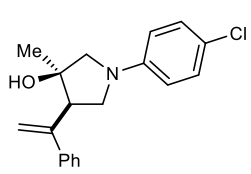
Using MeCN as the solvent: A modification of the General Procedure was followed using allene **205a** (87.9 mg, 0.30 mmol) and phenylboronic acid (54.9 mg, 0.45 mmol) but using MeCN in place of TFE as the solvent. Purification by column chromatography (20% EtOAc/petroleum ether) gave the title compound **211a** (60.4 mg, 54%) as a pale yellow solid. $[\alpha]_D^{25}$ –28.6 (*c* 0.28, $CHCl_3$); Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (major) = 29.1 min, t_r (minor) = 37.3 min, 80% ee.



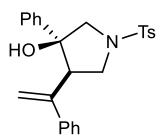
(3*S*,4*R*)-3-(*tert*-Butyl)-1-(4-methoxyphenyl)-4-(1-phenylvinyl)pyrrolidin-3-ol (211b). The General Procedure was followed using allene **205b** (81.9 mg, 0.300 mmol) and phenylboronic acid (54.9 mg, 0.450 mmol). Purification by column chromatography (1% EtOAc/CH_2Cl_2) gave a 7.7:1 inseparable mixture of the title compound **211b** and unreacted allene **205b** (85.2 mg, 73% yield of **211b**, adjusted for the presence of unreacted **205b**), as a colorless oil. R_f = 0.50 (20% EtOAc/petroleum ether); $[\alpha]_D^{25}$ –47.1 (*c* 0.68, $CHCl_3$); IR 2965, 1953, 1716, 1673, 1511, 1465, 1365, 1240, 1179, 1036, 974, 905, 812, 775, 710, 547 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42–7.26 (5H, m, Ar**H**), 6.88–6.86 (2H, m, Ar**H**), 6.61–6.54 (2H, m, Ar**H**), 5.55 (1H, s, =C**H**$_2$), 5.54 (1H, s, =C**H**$_2$), 3.78–3.74 (1H, m, one of CHC**H**$_2$), 3.77 (3H, s, OC**H**$_3$), 3.67–3.53 (3H, m, CC**H**$_2$N and two of C**H**C**H**$_2$), 3.27 (1H, d, *J* = 10.3 Hz, CC**H**$_2$N), 2.12 (1H, s, O**H**), 0.86 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.3 (C), 147.4 (C), 143.5 (C), 142.8 (C), 128.7 (2 × CH), 127.7 (CH), 126.8 (2 × CH), 117.4 (CH_2), 115.2 (2 × CH), 112.6 (2 × CH), 85.0 (C), 58.7 (CH_2), 56.7 (CH_2), 56.1 (CH_3), 46.8 (CH), 37.3 (C), 26.2 (3 × CH_3); HRMS (ESI) Exact mass calculated for $[C_{23}H_{30}NO_2]^+$ $[M+H]^+$: 352.2271, found: 352.2272; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C) t_r (major) = 11.5 min, t_r (minor) = 12.9 min, 99% ee.

Recrystallization of **211b** from EtOAc gave crystals that were suitable for X-ray crystallography:





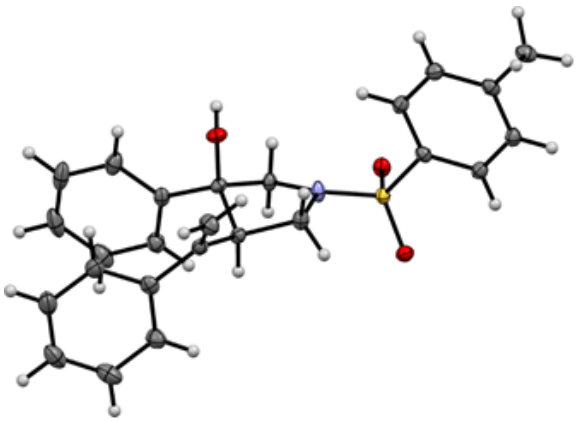
(3*R*,4*R*)-1-(4-Chlorophenyl)-3-methyl-4-(1-phenylvinyl)pyrrolidin-3-ol (211c). The General Procedure was followed using allene **205c** (70.7 mg, 0.300 mmol) and phenylboronic acid (54.9 mg, 0.450 mmol). Purification by column chromatography (10% EtOAc/pentane) gave the title compound **211c** (89.3 mg, 91%) as a pale yellow solid. R_f = 0.43 (20% EtOAc/petroleum ether); m.p. 90–94 °C (Et_2O); $[\alpha]_D^{25}$ –53.3 (*c* 0.30, $CHCl_3$); IR 3546 (OH), 2974, 2845, 1629, 1596, 1498, 1471, 1376, 1324, 1184, 1120, 939, 908, 813, 778, 703, 647, 600, 509, 458 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44–7.32 (5H, m, Ar**H**), 7.21–7.17 (2H, m, Ar**H**), 6.49–6.45 (2H, m, Ar**H**), 5.60 (1H, d, *J* = 0.6 Hz, =C**H**$_2$), 5.41 (1H, s, =C**H**$_2$), 3.68–3.59 (2H, m, CHC**H**$_2$), 3.49–3.38 (3H, m, CC**H**$_2$N and C**H**CH$_2$), 1.94 (1H, s, O**H**), 1.17 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.1 (C), 145.2 (C), 143.1 (C), 129.0 (2 × CH), 128.7 (2 × CH), 127.9 (CH), 126.7 (2 × CH), 120.6 (C), 116.4 (CH_2), 112.4 (2 × CH), 77.1 (C), 61.4 (CH_2), 52.1 (CH), 51.9 (CH_2), 25.4 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{19}H_{21}ClNO]^+$ $[M+H]^+$: 314.1306, found: 314.1302; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C) t_r (major) = 11.0 min, t_r (minor) = 25.1 min, 90% ee.



(3*S*,4*R*)-3-Phenyl-4-(1-phenylvinyl)-1-tosylpyrrolidin-3-ol (211d). The General Procedure was followed using allene **205d** (102 mg, 0.300 mmol) and phenylboronic acid (54.9 mg, 0.450 mmol). Purification by column chromatography (20% EtOAc/petroleum ether) gave the title compound **211d** (116 mg, 92%) as a colorless amorphous solid. R_f = 0.33 (20% EtOAc/petroleum ether); $[\alpha]_D^{25}$ –36.4 (*c* 0.33, $CHCl_3$); IR 3486 (OH), 2894, 1632, 1595, 1489, 1446, 1292, 1137, 1102, 907, 818, 752, 682, 639, 595, 544, 516, 470 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81–7.78 (2H, m, Ar**H**), 7.38–7.35 (2H, m, Ar**H**), 7.17–7.13 (2H, m, Ar**H**), 7.11–7.01 (6H, m, Ar**H**), 6.88–6.84 (2H, m, Ar**H**), 5.32 (1H, s, =C**H**$_2$), 5.15 (1H, s, =C**H**$_2$), 3.92 (1H, dd, *J* = 9.3, 7.2 Hz, CHC**H**$_2$), 3.76 (1H, d, *J* = 11.4 Hz, CC**H**$_2$N), 3.75–3.70 (1H, m, C**H**CH$_2$), 3.64 (1H, d, *J* = 11.4 Hz, CC**H**$_2$N), 3.54 (1H, dd, *J* = 11.4, 9.3 Hz, CHC**H**$_2$), 2.47 (3H, s, ArC**H**$_3$), 2.26 (1H, s, O**H**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9 (C), 143.7 (C), 141.6 (C), 140.8 (C), 134.0 (C), 129.8 (2 × CH), 128.1 (2 × CH), 128.0 (2 × CH), 127.7 (2 × CH), 127.4 (CH), 127.3 (CH), 126.6 (2 × CH), 125.1 (2 × CH), 117.3 (CH_2), 80.4 (C), 62.8

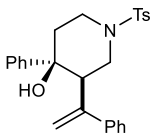
(CH_2), 53.6 (CH), 51.4 (CH_2), 21.7 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{25}H_{26}NO_3S]^+$ $[M+H]^+$: 420.1628, found: 420.1631; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C) t_r (minor) = 23.0 min, t_r (major) = 31.9 min, 84% ee.

Slow diffusion of petroleum ether into a solution of **211d** in EtOAc gave crystals that were suitable for X-ray crystallography:



211d
CCDC 1945865
Flack parameter –0.008(5)

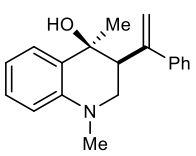
5.4.2. Piperidine



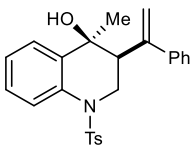
(3*R*,4*S*)-4-Phenyl-4-(1-phenylvinyl)-1-tosylpiperidin-4-ol (213a). The General Procedure was followed using allene **207a** (107 mg, 0.300 mmol) and phenylboronic acid (54.9 mg, 0.450 mmol). Purification by column chromatography (10% EtOAc/pentane) gave the title compound **213a** (65.6 mg, 50%) as a colorless solid. R_f = 0.18 (20% EtOAc/petroleum ether); m.p. 151–152 °C (Et_2O); $[\alpha]_D^{25}$ +107 (*c* 0.15, $CHCl_3$); IR 3548 (OH), 2980, 1599, 1444, 1341, 1159, 1091, 1043, 988, 917, 846, 814, 742, 693, 659, 573, 547, 434 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76–7.72 (2H, m, Ar**H**), 7.39–7.37 (2H, m, Ar**H**), 7.07–6.95 (8H, m, Ar**H**), 6.75–6.73 (2H, m, Ar**H**), 5.14 (1H, s, =C**H**$_2$), 5.03 (1H, s, =C**H**$_2$), 3.91 (1H, ddd, *J* = 11.5, 4.1, 1.9 Hz, C**H**$_2$N), 3.78 (1H, ddt, *J* = 11.6, 4.5, 2.0 Hz, C**H**$_2$N), 3.53 (1H, dd, *J* = 12.1, 4.0 Hz, C**H**$_2$N), 2.93–2.81 (2H, m, C**H**$_2$N and C**H**CH$_2$), 2.48 (3H, s, ArC**H**$_3$), 2.24–2.19 (1H, m, C**H**$_2$CH$_2$N), 2.15 (1H, d, *J* = 2.2 Hz, O**H**), 1.80 (1H, dt, *J* = 13.8, 2.5 Hz, C**H**$_2$CH$_2$N); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.9 (C), 144.9 (C), 143.8 (C), 143.6 (C), 133.8 (C), 130.0 (2 × CH), 127.92 (2 × CH), 127.87 (2 × CH), 127.8 (2 × CH), 127.0 (CH),

126.9 (CH), 126.4 (2 × CH), 124.7 (2 × CH), 116.0 (CH_2), 72.5 (C), 49.9 (CH), 47.2 (CH_2), 42.5 (CH_2), 39.0 (CH_2), 21.7 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{26}H_{28}NO_3S]^+$ $[M+H]^+$: 434.1784, found: 434.1792; Enantiomeric excess was determined by HPLC with a Chiralpak IC column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C) t_r (major) = 33.3 min, t_r (minor) = 36.0 min, 99% ee.

5.4.3. Tetrahydroquinolines



(3S,4S)-1,4-dimethyl-3-(1-phenylvinyl)-1,2,3,4-tetrahydroquinolin-4-ol (214a). The title compound was prepared according to the General Procedure using the allene **210a** (10.0 mg, 0.05 mmol) and phenylboronic acid (9.1 mg, 0.075 mmol), $Ni(OAc)_2{\cdot}4H_2O$ (0.6 mg, 0.0025 mmol), (*S*)-*t*-Bu-PHOX (**L42**, 1.0 mg, 0.0025 mmol) in TFE (0.5 mL) and purified by column chromatography (10% EtOAc/petroleum ether) to give **214a** as a colorless liquid (2.4 mg, 17%). R_f = 0.60 (10% EtOAc/petroleum ether); $[\alpha]_D^{25}$ –10 (*c* 0.40, $CHCl_3$); IR 3656, 2980, 1603, 1504, 1462, 1382, 1154, 1073, 954, 896, 777, 748, 706, 483 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.29 (5H, m, Ar**H**), 7.09 (1H, ddd, *J* = 8.5, 7.2, 1.7 Hz, Ar**H**), 6.89 (1H, dd, *J* = 7.3, 1.6 Hz, Ar**H**), 6.64 (1H, dd, *J* = 8.2, 1.1 Hz, Ar**H**), 6.59 (1H, td, J = 7.3, 1.1 Hz, Ar**H**), 5.32 (1H, s, =C**H**$_2$), 4.93 (1H, d, *J* = 0.6 Hz, =C**H**$_2$), 3.50 (1H, t, *J* = 10.9 Hz, C**H**$_2$N), 3.41–3.29 (2H, m, C**H**CH_2 and C**H**$_2$N), 3.01 (3H, s, NC**H**$_3$), 2.80 (1H, m, O**H**), 0.96 (3H, d, *J* = 7.1 Hz, C**H**$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.0 (C), 149.3 (C), 145.4 (C), 141.8 (C), 129.3 (CH), 128.6 (2 × CH), 128.4 (C), 127.7 (CH), 127.4 (CH), 126.9 (2 × CH), 116.2 (CH), 112.2 (CH_2), 111.1 (CH), 77.3 (C), 49.7 (CH_2), 39.5 (CH), 39.3 (CH_3), 18.9 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{19}H_{22}NO]^+$ $[M+H]^+$: 280.1696, found: 280.1680. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (minor) = 4.9 min, t_r (major) = 5.6 min, 38% ee.



(3S,4S)-4-methyl-3-(1-phenylvinyl)-1-tosyl-1,2,3,4-tetrahydroquinolin-4-ol (214b). The General Procedure was followed using the allene **210b** (102.4 mg, 0.30 mmol), phenylboronic acid (73.2 mg, 0.60 mmol), $Ni(OAc)_2{\cdot}4H_2O$ (3.7 mg, 0.015 mmol), (*R*)–QUINAP (**L46**, 6.6 mg, 0.015 mmol) in TFE (3 mL) and purified by column chromatography (20% EtOAc/petroleum ether) to give **214b** as a colorless oil (14.1

mg, 11%). R_f = 0.30 (20% EtOAc/petroleum ether); $[\alpha]_D^{25}$ –92.3 (*c* 0.13, $CHCl_3$); IR 3064, 2944, 1953, 1675, 1593, 1484, 1447, 1350, 1280, 1240, 1218, 1176, 1098, 1041, 944, 844, 751, 597, 547 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (1H, dd, *J* = 8.4, 1.3 Hz, Ar**H**), 7.61–7.58 (2H, m, Ar**H**), 7.53 (1H, dd, *J* = 7.9, 1.7 Hz, Ar**H**), 5.51 (1H, s, =C**H**$_2$), 5.14 (1H, s, =C**H**$_2$), 4.22 (1H, dd, *J* = 13.5, 3.4 Hz, C**H**$_2$N), 3.76 (1H, dd, *J* = 13.5, 11.6 Hz, C**H**CH_2), 2.96 (1H, dd, *J* = 11.6, 3.4 Hz, C**H**$_2$N), 2.42 (3H, s, ArC**H**$_3$), 1.86 (1H, s, O**H**), 1.13 (3H, s, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.8 (C), 144.0 (C), 143.3 (C), 137.5 (C), 135.7 (C), 134.7 (C), 130.0 (2 x CH), 128.6 (2 x CH), 128.5 (CH), 128.0 (CH), 127.5 (CH), 127.3 (2 x CH), 126.6 (2 x CH), 125.4 (CH), 124.1 (CH), 117.5 (CH_2), 69.7 (C), 47.8 (CH), 47.4 (CH_2), 29.2 (CH_3), 21.7 (CH_3); HRMS (ESI) Exact mass calcd for $[C_{25}H_{29}N_2O_3S]^+$ $[M+NH_4]^+$: 437.1893, found: 437.1889. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_r (major) = 29.3 min, t_r (minor) = 40.1 min, 89% ee.

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