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Asymmetric synthesis of allylic compounds *via* hydrofunctionalisation and difunctionalisation of dienes, allenes, and alkynes

Guanlin Li,†[a] Xiaohong Huo,†[a] Xieyang Jiang[a] and Wanbin Zhang *[abc]

Hydrofunctionalisation and difunctionalisation of dienes, allenes, and alkynes are widely utilized in the synthesis of valuable allylic compounds. In the past decades, asymmetric catalysis has emerged as one of the most attractive fields in organic synthesis. Recently, the asymmetric versions of hydrofunctionalisation and difunctionalisation reactions have become powerful and compelling tools to afford enantiopure allylic compounds, appealing to a large range of chemists. Various metal complexes modified with a large number of chiral ligands and several chiral organocatalysts have been developed to promote the hydrofunctionalisation and difunctionalisation reactions and expand substrate scope. This review provides an overview of this field, and aims at summarizing the chiral ligand used in this area of research. A detailed discussion of the development of these reactions and the general reaction mechanisms is provided.

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1. Introduction

Allylic compounds containing a stereogenic centre are important synthetic intermediates, which have been widely applied in the preparation of various natural products, pharmaceuticals and biologically active molecules. Several classic methodologies have been developed and great progress has been made with regards to the construction of these structural motifs, including allylic substitutions,[1–14] allylic C–H functionalisations,[15–18] Keck asymmetric allylations,[19–21] Roush asymmetric allylations,[22–25] Sakurai allylations,[26,27] functionalisation of conjugated dienes (abbreviated as dienes), allenes, and alkynes, *etc.*

In the 21st century, an increasing amount of attention has been directed towards problems associated with the environment, the loss of natural resources and energy consumption. The winner of the 2010 Nobel prize in chemistry, Ryoji Noyori, once said

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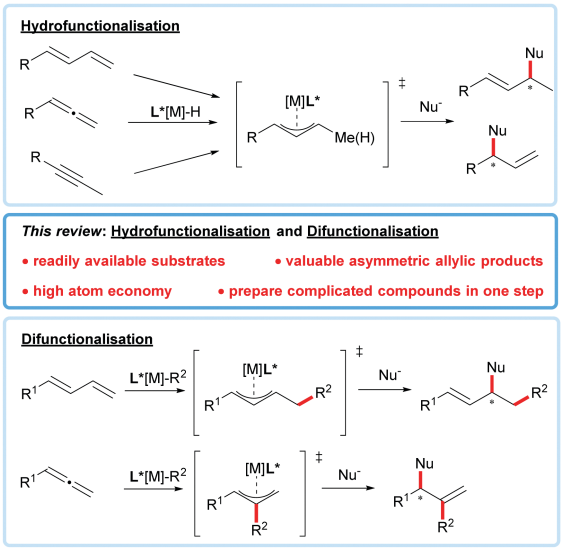
Xiaohong Huo

Dr Xiaohong Huo undertook his PhD studies at Shanghai Jiao Tong University under the supervision of Professor Wanbin Zhang from 2012–2017. After postdoctoral appointments with Professor Wanbin Zhang at SJTU, he was appointed an associate tenure-track professor at SJTU in 2019. His research interests focus on the development and application of synergistic catalysis in organic synthesis, particularly asymmetric allylic substitution reactions.



Scheme 1 Hydrofunctionalisation and difunctionalisation of dienes, allenes, and alkynes.

"Ideally, we should aim at synthesizing target compounds with a 100% yield and 100% selectivity and avoid the production of waste. This process must be economical, safe, resource-efficient, energy-efficient and environmentally benign".[28] Accordingly, chemists have devoted themselves to developing chemical reactions that are environmentally-friendly and atom efficient.[29] Recently, the enantioselective hydrofunctionalisation of dienes, allenes and alkynes with common (pro)nucleophiles has attracted broad attention and has developed rapidly (Scheme 1). This is mainly due to the several advantages of such reactions: (1) dienes, allenes and alkynes are common in the petroleum industry and inexpensive;[30] (2) the inherent atom economy in comparison to allylic oxidation or substitution,[31] which both produce stoichiometric amounts of waste and, in case of substitution reactions, require prefunctionalisation of the starting material; (3) the corresponding products are important synthetic intermediates, which can be readily applied in the preparation of various bioactive molecules (Scheme 2).[32,33]

Enantioselective difunctionalisation of dienes and allenes is also an important and frequently studied strategy to synthesize enantiopure allylic compounds (Scheme 1).[34–37] Compared to hydrofunctionalisation, two different or similar chemical bonds can be constructed from the raw material in one step, including C–C/C–N, C–C/C–O, C–C/C–C, C–N/C–N, C–N/C–O, C–O/C–O, C–C/C–B, and C–B/C–B bonds. Thus, it provides the possibility of preparing a large range of allylic compounds with more complicated structures that are of great importance in organic synthesis in a simple and convenient manner (Scheme 2).

In this review, we will mainly discuss the asymmetric hydrofunctionalisation and difunctionalizaton of dienes, allenes, and alkynes *via* electrophilic allyl–metal intermediates. Some other unique and elegant works involving organocatalyst-catalysed hydrofunctionalisation are also mentioned.[38] Besides electrophiles, the allyl–metal intermediates could also act as nucleophiles, reactions of which have been summarized by Krische,[39–42] Toste,[43,44] Widenhoefer,[45] Marks,[46–48] and others.[49–56] Please note that the reactions involving nucleophilic allylic-metal intermediates will not be included in this review. Cycloaddition[57–60] with multiple bonds, conjugated addition,[61–63] and borohydride reactions[64–67] are also common reactions for these three substrates, but they are not included in this review.

Sporadic but impressive reviews related to this field have been reported, such as the Rh-catalysed hydrofunctionalisation of allenes and alkynes by Breit and co-workers,[32,68] and the difunctionalisation of dienes by Gong and Zhang.[35–37]

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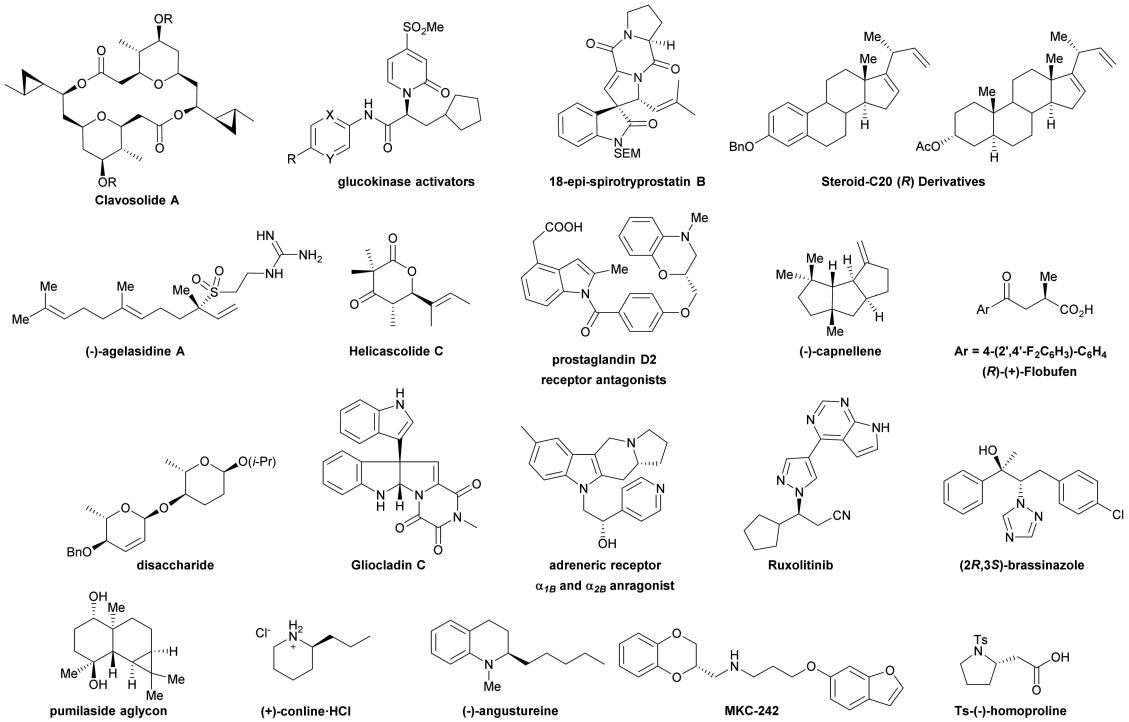
Xieyang Jiang graduated from Qingdao No. 2 high school in 2018 and won the first prize in the 30th National Chemical Olympiad (Provincial competition area). He has been studying in the Shanghai Jiao Tong University Chemistry (Zhiyuan Honors Program) from 2018 and won the Zhiyuan Honors Scholarship in 2018 and Fan Hsu-chi Scholarship in 2019. In 2018, he joined professor Wanbin Zhang group, and has been researching in asymmetric catalysis and organometallic chemistry.

Wanbin Zhang

Professor Wanbin Zhang received his BS and MS degrees from East China University of Science and Technology (ECUST) in 1985 and 1988 respectively. From 1993 to 1997, he undertook PhD studies at Osaka University under the supervision of Professor Isao Ikeda. He then worked as an assistant professor at Osaka University until 2001 and then as a research fellow at the Specialty Chemicals Research Centre of the Mitsubishi Chemical Corporation. Since 2003, he has worked as a professor in the School of Chemistry and Chemical Engineering at Shanghai Jiao Tong University (SJTU). In 2013, he was promoted to the position of distinguished professor. Professor Zhang's current research interests include organometallic chemistry, asymmetric catalysis, and pharmaceutical process chemistry.



Scheme 2 Representative bioactive molecules in this review.

Nevertheless, a comprehensive summary on enantioselective hydrofunctionalisation and difunctionalisation of three substrates catalysed by different metals or organocatalysts is still absent. Additionally, in the last few years, many great advances have been reported with regards to the synthesis of enantiopure allylic compounds from dienes, allenes, and alkynes through these methods. Accordingly, it is necessary to provide an extensive and new review in this field. This review will cover and summarize various catalytic systems, mechanisms, reaction development, and other synthetic applications related to the asymmetric hydrofunctionalisation and difunctionalisation of the three substrates. The significant development established by Hartwig, Malcolmson, Hayashi, Dong, Toste, Shibasaki, Gong, Trost, Breit, Larock, Hiroi, Ma, Yamamoto and many others was involved in this review. The reaction development is divided into three parts according to the three different substrates, and in each section hydrofunctionalisations and difunctionalisations catalysed by palladium, rhodium and other metals or organocatalysts will be demonstrated.

2. Chiral ligands/organocatalysts utilized in the enantioselective hydrofunctionalisation and difunctionalisation of dienes, allenes, and alkynes

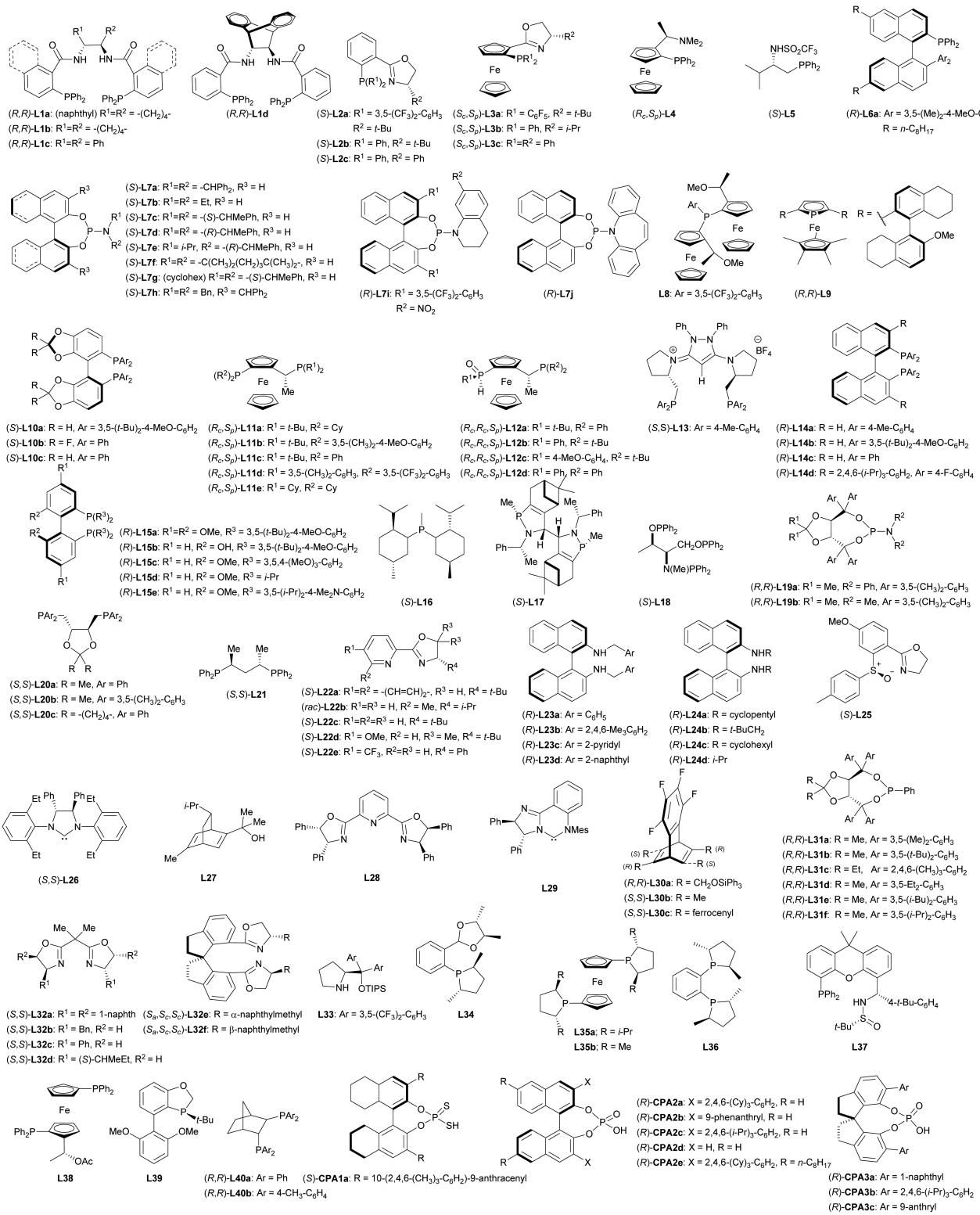
Various chiral ligands/organocatalysts used in the enantioselective hydrofunctionalisation and difunctionalisation of dienes, allenes, and alkynes are summarized in the following scheme (Scheme 3). The metals and types of bond formation that match with an appropriate ligand are illustrated in Table 1.

3. Formation of asymmetric allylic compounds from dienes

Dienes and related derivates can participate in various types of reactions. Cycloadditions are widely used in academia as well as industrial production.[59,60,212] Nevertheless, only dienes bearing activating groups can partake in the addition process with high efficiency, limiting its application scope. Polymerization is also a common process that dienes can undergo,[213,214] and it is mainly utilized in synthesizing organic materials, such as rubber and plastic. In recent years, transition-metal catalysed direct diene additions have emerged and attracted a lot of attentions, since these methodologies can be applied to generally unactivated dienes and possess the potential for asymmetric synthesis. For instance, the hydrofunctionlisation and difunctionalisation of dienes are efficient methods to modify molecules, especially with regards to the constructing C–C bonds, and much significant work has been conducted in this field. In this section, we will give an overview of asymmetric hydrofuntionalization and difunctionalisation of dienes and their derivates.

3.1 Hydrofunctionalisation

The earliest study concerning the asymmetric hydrofunctionalisation of dienes was the nickel-catalysed hydrovinylation of cyclooctadiene reported by Wilke in 1972;[154] this was also the first example of metal-catalysed asymmetric C–C bond formation.



Scheme 3 Chiral ligands/organocatalysts used in the asymmetric hydrofunctionalisation and difunctionalisation of dienes, allenes, and alkynes.

Nevertheless, the enantioselectivity was moderate and only the cyclodiene could be used. To expand the method to vinyl cycloalkenes, RajanBabu utilized chiral monodentate phospholane and diarylphosphinite ligands, providing the desired products in high enantioselectivity (>99% ee).[100] Later, cobalt complexes coordinated with chiral bidentatephosphine ligands (BDPP and DIOP) catalysed hydrovinylation was also developed.[159] In comparison to Ni and Co, palladium could be utilized in

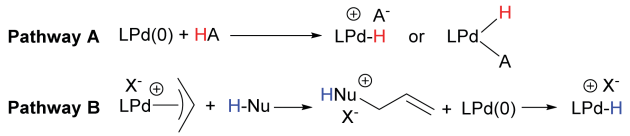
Table 1 Details about the ligands and organocatalysts

Chiral ligand/CPA	Metal(s)	Substrate(s)	New bond(s)	Ref.
L1	Pd	Diene, allene	C–N, C–O, C–C, C–C/C–O	69–81
L2	Pd	Diene	C–N, C–C, C–C/C–N	82–86
L3	Pd, Cu, Ni	Diene, allene	C–N, C–C, C–C/C–N	87–89
L4	Pd	Diene	C–Si	90
L5	Pd	Diene	C–Si	91 and 92
L6	Pd	Diene	C–Si	93–97
L7	Pd, Rh, Ni	Diene, allene	C–N, C–C, C–Si, C–C/C–N, C–C/C–C, C–N/C–N	98–109
L8	Pd	Diene	C–Si	110 and 111
L9	Pd	Diene	C–Si	112
L10	Pd, Rh, Co, Cu, Au	Diene, allene, alkyne	C–N, C–C, C–Si, C–P, C–S, C–N/C–N	113–123
L11	Pd, Rh, Co	Diene, allene	C–N, C–C, C–O, C–S, C–P	88, 113 and 124–132
L12	Rh	Diene, allene, alkyne	C–N	133–139
L13	Rh	Diene	C–C	140
L14	Pd, Rh	Diene	C–N, C–C, C–S, C–C/C–N, C–C/C–O, C–C/C–C	118, 124 and 141–148
L15	Rh, Ni	Diene, allene, alkyne	C–N, C–C, C–S	117, 124 and 149–153
L16	Ni	Diene	C–C	154
L17	Ni	Diene	C–C	155
L18	Ni	Diene	C–C	156
L19	Pd, Ni	Diene, allene	C–C, C–B/C–B	157 and 158
L20	Pd, Rh, Co	Diene, allene, alkyne	C–C, C–O, C–C/C–C	119, 152, 153 and 159–163
L21	Rh, Co	Diene, alkyne	C–C, C–N	159 and 164–166
L22	Pd, Co	Diene	C–Si, C–C/C–N, C–N/C–N	167–169
L23	Li	Diene	C–N	170 and 171
L24	Li	Diene	C–N	170 and 171
L25	Pd	Diene	C–C/C–N	172
L26	Pd	Diene	C–N/C–N	173
L27	Pd	Diene	C–C/C–C	174
L28	Pd	Diene	C–N/C–O, C–O/C–O	175 and 176
L29	Cu	Diene	C–C/C–B	177
L30	Ir	Diene	C–C/C–O, C–C/C–C	178–180
L31	Pt	Diene	C–B/C–B	181–184
L32	Pd, Cu, Fe	Diene, allene	C–C/C–N, C–C/C–O, C–C/C–C, C–N/C–O	185–193
L33	Pd	Allene	C–C	194
L34	Ni	Diene	C–C	100
L35	Rh	Allene	C–N, C–O	195 and 196
L36	Rh	Allene	C–C, C–S	197 and 198
L37	Pd	Allene	C–C/C–N	199
L38	Pd	Allene	C–C	163
L39	Pd	Allene	C–B/C–B	200
L40	Pd	Alkyne	C–N	201–203
CPA1	None	Diene, allene	C–N	38
CPA2	Pd, Cu, none	Diene, allene, alkyne	C–C, C–N/C–N, C–C/C–B	73 and 204–209
CPA3	Pd, none	Diene	C–N, C–C/C–B	210 and 211

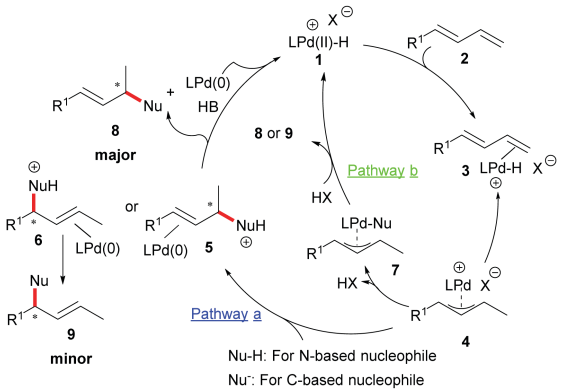
hydrofunctionalisations to construct more kinds of bonds including C–N, C–C, C–Si, C–P. Hartwig initially reported the Pd-catalysed hydroamination of cyclohexadiene with aniline,[69] using the chiral Trost ligand. The nucleophiles were restricted to aryl amine and linear dienes were not compatible. In 2017, Malcolmson utilized the PHOX ligand, which is electron deficient, making the Pd complex more readily insert into the unsaturated bonds of dienes and realized the asymmetric addition of aliphatic amines to linear 1,3-dienes.[82] Hartwig also established the enantioselective hydroalkylation of dienes. Asymmetric hydrosilylation was originally developed by Kumada, Hayashi, Goda, and many others. Pd-Catalysed asymmetric hydrophosphorylation was developed by Dong's group, utilizing the chiral Josiphos ligand.[113] The same group also used a rhodium complex to realize the asymmetric hydroamination and hydrothiolation of dienes. Apart from Pd, Rh, Co, and Ni, other metals and organocatalysts have also been applied in this area by Collin, Toste, and others. Important progress has been made in the past decade for the formation of C–C, C–N, C–Si bonds. The following sections provide a comprehensive and systematic overview of the asymmetric hydrofunctionalisation of dienes.

3.1.1 Catalysed by Pd. Most of the Pd-catalysed asymmetric hydrofunctionalisations of dienes share a similar and typical pathway. The Pd(0)-precatalyst will be initially transformed into the active Pd(II)–H species. The generation of the Pd–H species is complicated, and two major pathways are illustrated in Scheme 4. Pathway A is usually applied in conditions where some Brønsted acids are added, such as phosphate and TFA. The Pd–H species is directly prepared from the oxidative addition of Pd(0) with HA/HNu^+. Pathway B occurs when the precatalyst is the π-allyl–Pd(II) species. The initial substitution with pronucleophile or other co-catalyst produces the activated positive hydrogen, which promotes the oxidative addition of the Pd(0) that was generated from the substitution.

The fundamental catalytic cycle is shown in Scheme 5. The Pd–H species **1** is coordinated to one of the double C–C bonds in the diene **2**. The selectivity between the two double bonds is



Scheme 4 Typical routes of the generation of Pd–H species.



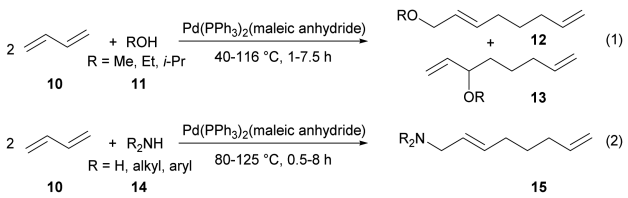
Scheme 5 Typical mechanism for Pd-catalysed hydrofunctionalisation of dienes.

determined by the steric hinderance of the two sides of the diene. For the 1,3-diene, **3** will be the major intermediate, where the binding occurs at the less hinderance olefin. Then, migratory insertion will occur forming the π-allyl–Pd intermediate **4**. Notably, although it is not shown in the figure, there is a σ–π–σ equilibrium between the π-allyl–Pd intermediate and its σ-allyl–Pd form. Isotopic labeling experiments suggested that the migratory insertion is generally reversible.

Later, two pathways are possible. Pathway a (nucleophilic substitution): the (pro)nucleophile attacks the diene in intermediate **4** to give addition intermediate **5**. For the nitrogen-based pronucleophile, the neutral pronucleophile attacks directly since there is a lone pair of electrons on the nitrogen atom. Conversely, carbon-based pronucleophiles must be transformed to an active nucleophile first, usually assisted by a basic additive. Notably, the formation of a C–C single bond in this step is usually irreversible. For the generation of the C–N single bond, transamination experiments proved the reversibility of this step, which may lead to a decrease in enantioselectivity. Pathway b (reductive elimination): in some cases, the pronucleophile may first attack the Pd(II) atom in the intermediate **4**, and at the same time reproduce the acidic additive. Next, the generated intermediate **7** undergoes reductive elimination to give the final product.

For the pathway a, after the attach of (pro)nucleophile to allylic the intermediate **4**, the cationic intermediate **5** is deprotonated by another pronucleophile or additive to give the final product **8** and Pd(0). Pd(0) will then be protonated *via* oxidative addition with the conjugated acid of the pronucleophile or basic additive to reproduce the Pd–H species **1**.

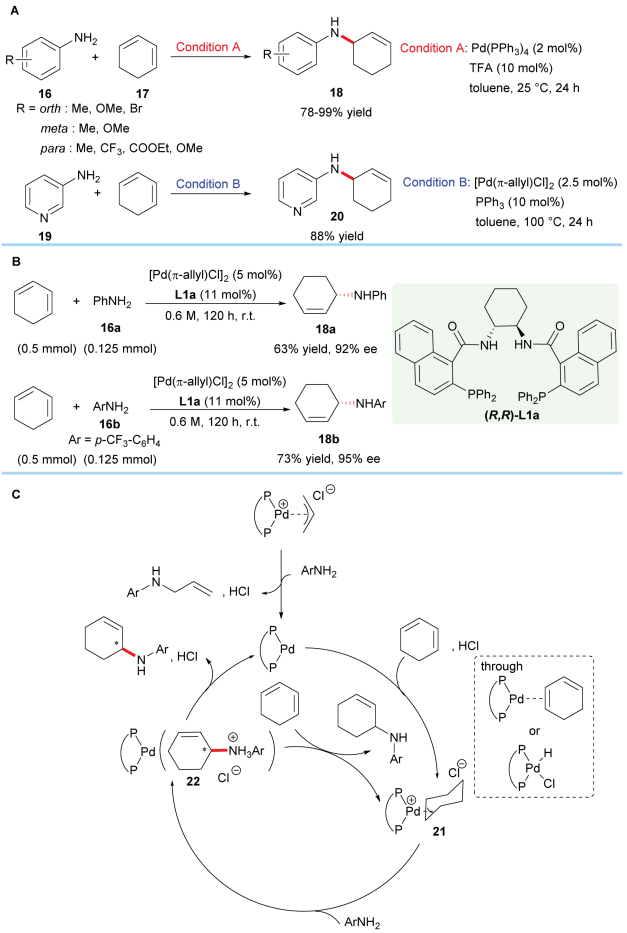
3.1.1.1 Formation of C–N bond. Early studies on hydroamination were reported by Hagihara in 1968. When the



Scheme 6 The dimerization of butadiene by palladium complex catalysts.

Pd-catalysed dimerization of butadiene was conducted in alcohols or amine solvent,[215] they found the butadiene dimer-alcohol or amine adducts were also produced in significant yields (**12**, **13**, **15**) (Scheme 6). These adducts might be the result of the addition of amine to butadiene, which has also been named hydroamination in following years, but the octadienylamines were the major products. The ligands in these reactions are mainly monophosphines, phosphonites, and 1,5-cyclooctadienyl. By using diphosphine ligand such as 1,2-bis(diphenylphosphiro)ethane, the 1+1 adducts can be obtained without dimerization. The 1,2-addition products are the major products. In 1986, Dieck introduced hydroiodide salts to the reaction system,[216] and successfully preparing the 1,4-addition products without dimerization. The hydroiodide salt is critical, since it produces HI to promote the reaction by participating in the oxidative addition of Pd(0). A number of other reactions have also been conducted to broaden the substrate scope and improve the reaction conditions *via* the development of new ligands, such as Trost's ligand and sp^2-hybrided phosphorus ligands.[69,217,218] In addition, Ni-catalysed hydroaminations were also developed during the same period.[219] Although significant progress on the catalytic hydroamination of dienes has been reported, there were still some challenges remaining. These reactions are mostly conducted at high temperature and the regioselectivity is hard to control. More importantly, no highly enantioselective versions of the Pd-catalysed hydroamination have been reported yet.

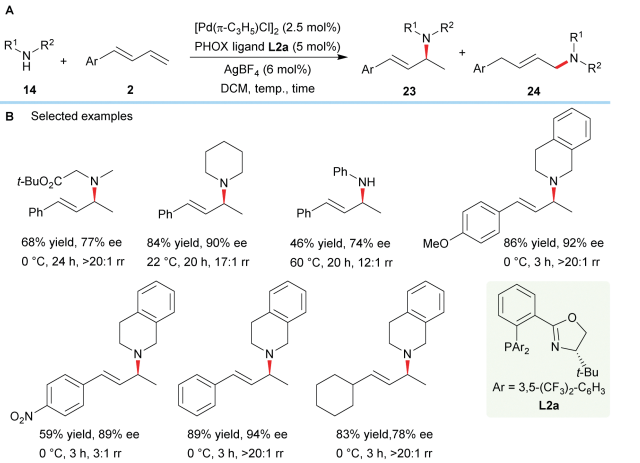
The first example of a highly enantioselective hydroamination of dienes was developed by Hartwig's group in 2001.[69] They developed a catalytic system that can promote the addition of aniline and its derivates to cyclohexadiene **17** and linear dienes at a mild temperature (Scheme 7A). Condition A (2 mol% $Pd(PPh_3)_4$, 10 mol% TFA, toluene, 25 °C, and 24 h) was suitable for most of the tested aryl amines; however, pyridylamines **19** were not amenable to the reaction conditions. Conversely, condition B (2.5 mol% $[Pd(\pi\text{-allyl})Cl]_2$, 10 mol% PPh_3, toluene, 100 °C, and 24 h), could promote the reaction. This might be because the N atom on the aryl ring of the pyridylamines would react with the TFA. Also, condition B suggests that the presence of acid is not necessary. Although adding TFA would increase the reactivity, when the researchers explored the enantioselective version of this reaction by using different chiral ligand, they found the enantioselectivity was poor in the presence of TFA. This was possibly the results of the racemization of the products in the presence of strong acid. Subsequent reactions were therefore conducted without TFA. The chiral Trost ligand **L1a** performed the best among the other chiral



Scheme 7 The enantioselective hydroamination of cyclic dienes.

ligands that were tested, providing the desired products with 92% ee (Scheme 7B). Aniline derivates with an electron withdrawing group on the phenyl ring afforded the products with greater enantiomeric excess. They also proposed a possible catalytic cycle for the hydroamination of cyclic dienes (Scheme 7C).[220]

Previous research has mostly focused on hydroamination with aryl amines, and aliphatic amines were yet to be subjected to the reaction conditions. This may be due to the acidity of the ammonia cation from the aliphatic amine being weaker than that of the aryl amine, which results in difficulty in forming the corresponding Pd–H intermediate. In addition, acyclic dienes remain challenging substrates due to the difficulty in controlling regioselectivity. In 2017, Malcolmson and co-workers reported the enantioselective 1,2-addition of aliphatic amines to unsymmetrical acyclic dienes catalysed by a cationic Pd–PHOX complex (Scheme 8A).[82] They initially utilized the Trost ligand, however, none of the desired product was obtained. Next, the group turned their attention to phosphinooxazoline (PHOX) ligands, which have been widely used in allylic substitution reactions. Encouragingly, they obtained the desired products in good yield with high enantioselectivity. A trend was observed in that the more electron-deficient ligands exhibited higher regioselectivity and enantioselectivity. Generally, the 1,2-addition

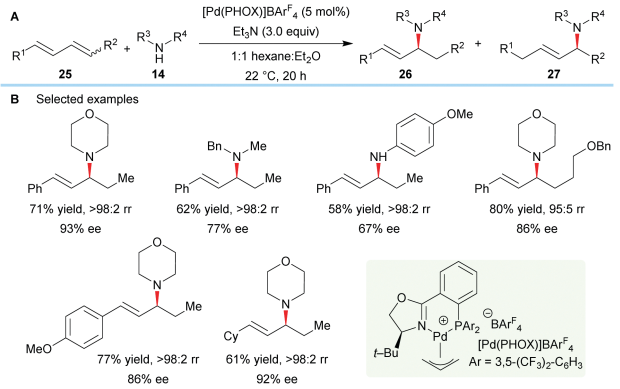


Scheme 8 The enantioselective hydroamination of 1,3-dienes using chiral PHOX-ligand.

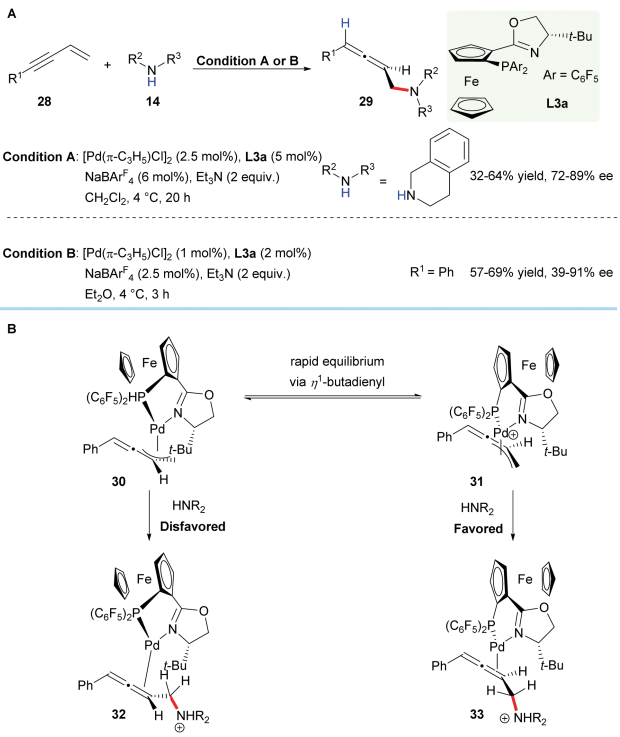
product is favoured because it is a thermodynamically stable isomer. Furthermore, the author used $AgBF_4$ to promote the reaction which improved the yield and enantioselectivity. With the optimized reaction conditions in hand, the group investigated various substrates (Scheme 8B). It was found that as the amine becomes more electron-donating, a higher temperature is required due to increasing competition with the diene for coordination to Pd. They also investigated the electronic variation at the *para*-position of aryl group in the butadienes to prove that the substituted group has a profound effect on the site selectivity. Some alkyl substituted dienes could also afford the corresponding products in good yields and selectivity.

Besides the terminal 1,3-dienes, internal dienes are also studied. They are even more challenging substrates because the different reactivity and hardness to control the regioselectivity. In 2018, Malcolmson's group successfully developed the enantioselective and regioselective hydroamination of internal dienes (Scheme 9A).[83] They adjusted the reaction conditions used in the hydroamination of monosubstituted 1,3-diene: 1:1 hexane/Et_2O displaced DCM as better solvent. Adding the Et_3N was important because it may promote the ionization of ammonia cation. Among the different internal dienes, all the R^2 groups were not conjugated with the dienes, because it would make the regioselectivity more complicated. Furthermore, alkyl/alkyl disubstituted dienes were also investigated, and the yield, regioselectivity, and enantioselectivity were all good (Scheme 9B). Transamination experiment was conducted to study enantiocontrol. It showed that the enantioselectivity was closely relative to the reaction time, which might be the results of the reversal transformation and racemization of enantiopure products.

Very recently, the same group developed a method to synthesize chiral allenes *via* the asymmetric hydroamination of conjugated enynes catalysed by Pd (Scheme 10A).[87] They first developed a non-enantioselective method to furnish racemic allenes *via* the 1,4-hydroamination of enynes with primary and secondary aliphatic and aryl-substituted amines, using DPEphos as a ligand. Then, studies were conducted to develop



Scheme 9 The enantioselective hydroamination of internal dienes using chiral PHOX ligand.

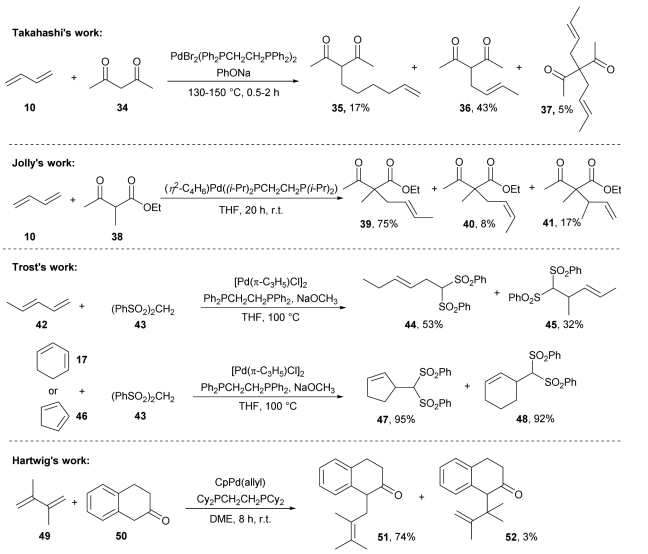


Scheme 10 The enantioselective hydroamination of enynes.

an enantioselective synthesis of chiral allenes by using the PHOX ligand. Although adding Et_3N and a bulky counterion such as BAr^F_4 could improve the yield and enantioselectivity, unfortunately, the enantioselectivity remained moderate and changeable with time. This may be attributed to the reversibility of the produced amino allene, which leads to a decrease in enantioselectivity, as they found in their previous work.[83] The reverse process may occur *via* cleavage of the C–N bond in the product, regenerating the π-allyl–Pd intermediate. To retard this cleavage, a more electron-deficient ligand can be employed, which is less readily able to bind to the allene products and thus prevent cleavage. Although the alkyl substituted enynes could yield the corresponding products under these conditions, the enantioselectivity was poor. This might suggest competition between the ionization of the products and ligand exchange by displacement of the allene for another enyne. They also proposed a stereochemical model for the hydroamination, giving a clear view of the stereo-control in this reaction (Scheme 10B).

3.1.1.2 Formation of C–C bond. The formation of C–C bonds is very important for the assembly of important and valuable compounds in organic synthesis. The hydroalkylation of dienes is one of the most attractive methods to directly construct C–C bonds with advantages of high atom economy and readily available substrates. According to our discussions above, the Pd–H species, which is generated by the oxidative addition of the N–H in the ammonium ion to Pd(0), is crucial to the hydroamination of dienes. However, the acidity of the C–H bond is much lower than that of the N–H of the ammonium ion, which increases the difficulty of the oxidative addition with Pd(0). To overcome this challenge, a number of strategies have been developed: (a) active methylene compounds, such as ethyl acetoacetate and acetylacetone, have been investigated due to the relatively high acidity of the α-H. (b) Some organic amines such as Et_3N were introduced to the catalytic system, since their conjugated acids could easily react with Pd(0), giving the Pd–H species. (c) Using appropriate ligands to promote the reaction and avoid the formation of by-products. Early development was made by Takahashi's group in 1972 (Scheme 11).[221] Bidentate phosphine ligands were applied in order to avoid telomerization.

Jolly,[222,223] Trost,[224] and Hartwig[132] made further developments improving the reactivity and selectivity. In 1990, Jolly's group established a simplified catalytic system which did not require the use of additives, and this system could enlarge the scope of the dienes. The bidentate phosphine ligands were employed to exclusively afford 1+1 adducts from diene and pronucleophile at room temperature. Trost's group reported the intermolecular addition of bis(phenylsulfonyl)methane to linear or cyclic dienes catalysed by the dppp–Pd system. Hartwig's group developed more efficient reaction conditions



Scheme 11 Development of hydroalkylation of dienes.

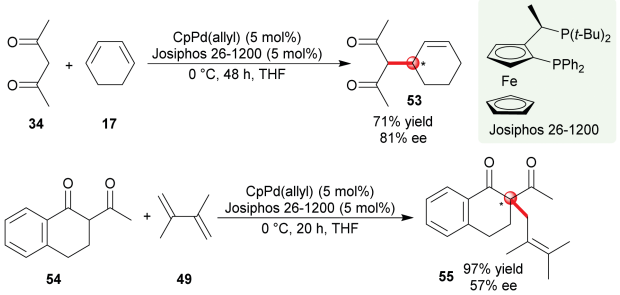
involving the less active methylene compounds as pronucleophiles. A series of bidentate phosphine ligands were systematically investigated, and DCyPP was found to perform the best. Some monocarbonyl compounds such as lactone isochroman-3-one could give the desired products in good yield under mild conditions. Besides Pd, a Ni-catalysed hydroalkylation of diethylmalonate and acetoacetate to 1,3-dienes has been reported by Moberg and co-workers in 1986.[225]

In 2004, Hartwig's group developed the first enantioselective hydroalkylation of dienes with a Josiphos ligand with enantiomeric excess up to 81%.[132] 2,4-Pentadione and 1,3-cyclohexadiene reacted in THF at 0 °C, giving the desired product in a yield of 71% with 81% ee (Scheme 12). Furthermore, prochiral pronucleophiles were also utilized in the addition to 2,3-dimethylbutadiene giving the corresponding products in an excellent yield of 97% with moderate enantioselectivity.

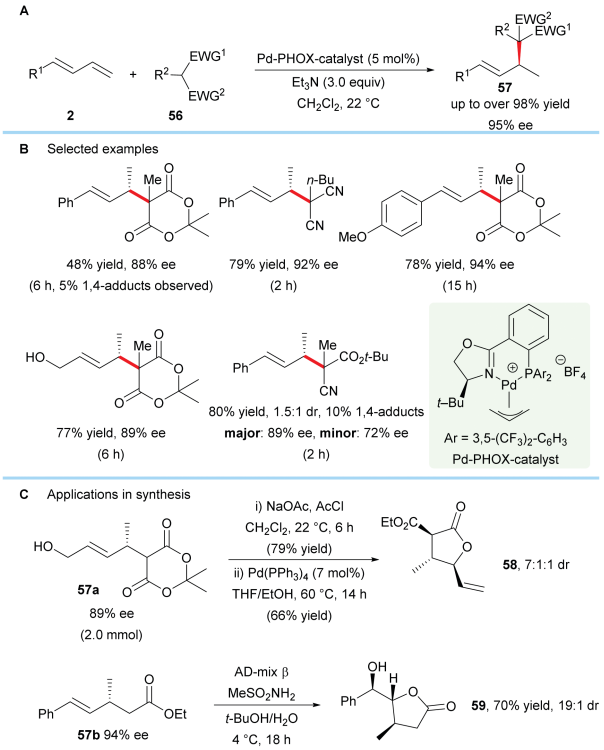
In 2018, the electron deficient PHOX ligand was utilized in the highly enantioselective and efficient addition of activated C-pronucleophiles to various aryl- and alkyl-substituted acyclic dienes by Malcolmson's group (Scheme 13A).[84] 1,3-Dicarbonyl compounds and compounds bearing two electron-withdrawing groups attached to one carbon could be utilized as substrates, giving the corresponding products in moderate to good yield and enantioselectivity. In addition, many 1,3-dienes derivates including aryl- and alkyl-were tolerated (Scheme 13B). This method provides us with a valuable example of extending a carbon chain system, and the enantiopure products bearing a chiral centre were useful for further transformations (Scheme 13C).

Much attention has been paid to the asymmetric hydroalkylation of terminal dienes whereas internal dienes have not been employed widely in hydroalkylation reactions. In 2019, J. Malcolmson reported a Pd–PHOX and Brønsted acid dual-catalysed enantioselective coupling of internal dienes and carbon-based pronucleophiles **56** (Scheme 14A).[85] The enantioselectivity was excellent (>98% ee) as was the yield. Notably, 1,4-dialkyl-dienes were also tolerated with good selectivity if the steric hinderance at the two positions was significantly different. The stereochemistry of the diene has great impact on the activity. The (*E*,*Z*) isomers were much more active than the (*E*,*E*) ones, but both of these could yield the products with high enantioselectivity (Scheme 14B).

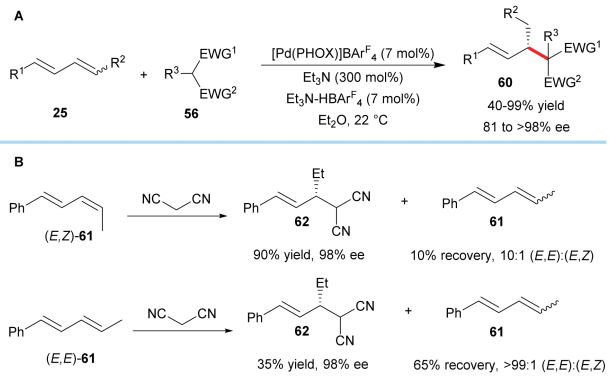
Pd/Cu dual catalysis has attracted attention in the field of asymmetric synthesis.[226–234] Very recently, Zi *et al.* employed this catalyst system in the enantioselective hydroalkylation of dienes with aldimine esters.[88] The synergistic Pd/Cu catalysis allowed for the stereodivergent addition of aldimine esters **63** to 1,3-dienes,[235–239] giving the corresponding products in excellent yield with high enantioselectivity and diastereoselectivity (Scheme 15A). With the help of JosiPhos-derived ligand and PHOX ligand **L3c**, the four stereoisomers could be obtained with excellent enantioselectivity (>99% ee) and good diastereoselectivity (13.6 : 1, 14 : 1, >20 : 1, >20 : 1) (Scheme 15B). Internal dienes were also tolerated, giving the desired products in moderate yield with perfect enantioselectivity. A reaction pathway has been proposed by the authors (Scheme 15C). The insertion of a Pd–H species into the diene substrates would give the π-allyl–Pd



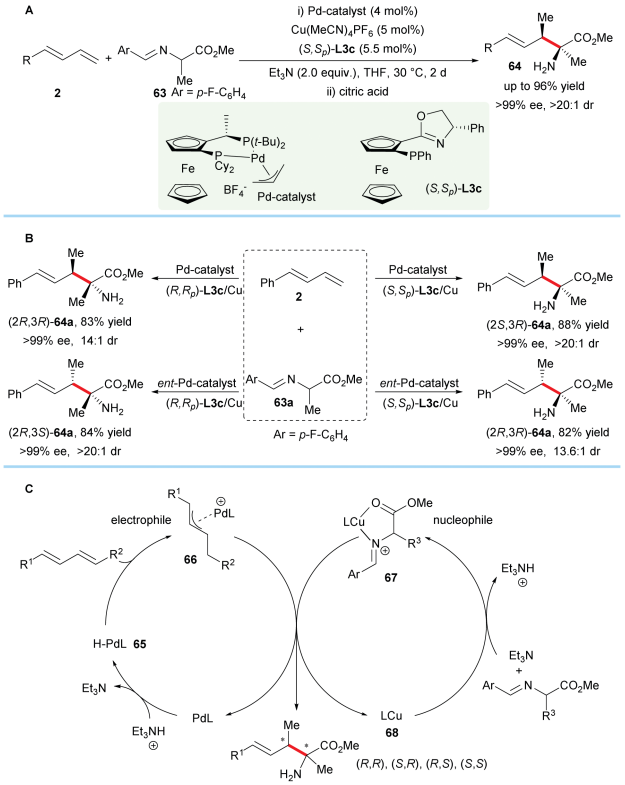
Scheme 12 The first enantioselective hydroalkylation of dienes.



Scheme 13 The enantioselective hydroalkylation of 1,3-dienes using chiral PHOX-ligand.



Scheme 14 The enantioselective hydroalkylation of internal dienes.

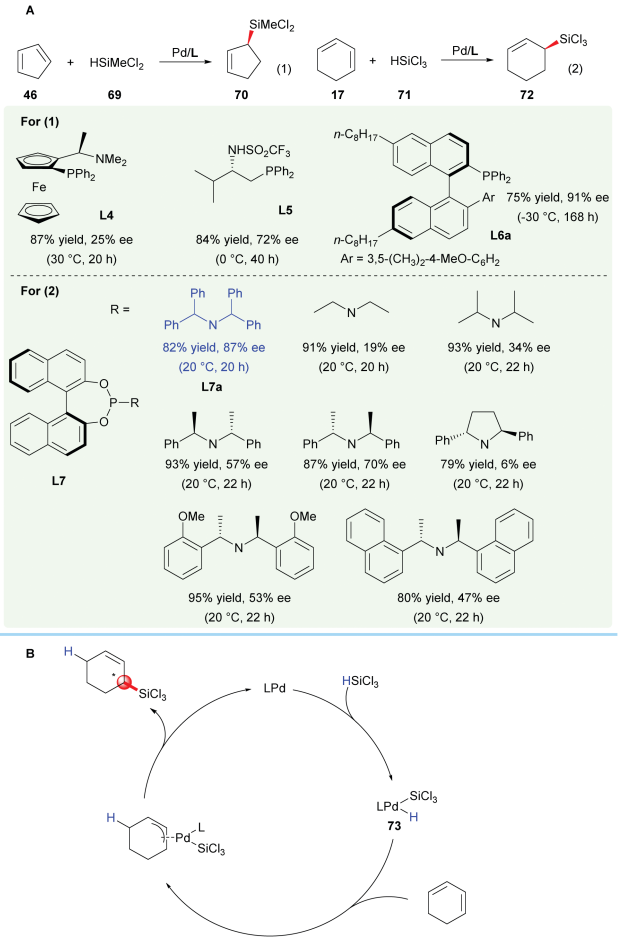


Scheme 15 Pd/Cu synergistic catalysis for the stereodivergent hydroalkylation of dienes.

intermediate **66**. The coordination between the aldimine esters and Cu-catalyst activated the α-H, furnishing the nucleophilic intermediate **67**. Next, the two intermediates generated *in situ* can interact with each other to give the adducts.

3.1.1.3 Formation of C–Si bond. Enantiopure allylsilanes are valuable building blocks in organic synthesis, which can be easily prepared by the hydrosilylation of dienes. Since the seminal example was reported by Hayashi in 1983,[90] great progress has been made in the Pd-catalysed hydrosilylation of dienes. Much effort has been donated to the development of chiral ligands for improving the reactivity and enantioselectivity.[240] Various chiral ligands have been introduced to the catalyst system, including chiral monophosphine ligands with a binaphthyl skeleton, ferrocenylmonophosphine, and monophosphoramidite.

Hayashi first utilized chiral ferrocenylmonophosphine ligands, successfully achieving the asymmetric hydrosilylation of cyclodienes with electron deficient silanes (Scheme 16A). Later, Kazuo and Frejd used chiral amine monophosphines **L5**, greatly improving the reactivity and enantioselectivity (72% ee).[91,92] Hayashi utilized a more efficient ligand Ar-MOP **L6a**, increasing the enantioselectivity to 91% ee.[93–97] In 2013, a series of chiral monophosphramidite ligands were investigated by the same group,[98] and it was shown that sterically hindered **L7a** could catalyse the hydrosilylation of cyclodienes with trichlorosilane, furnishing the desired products in 87% ee (Scheme 16A).

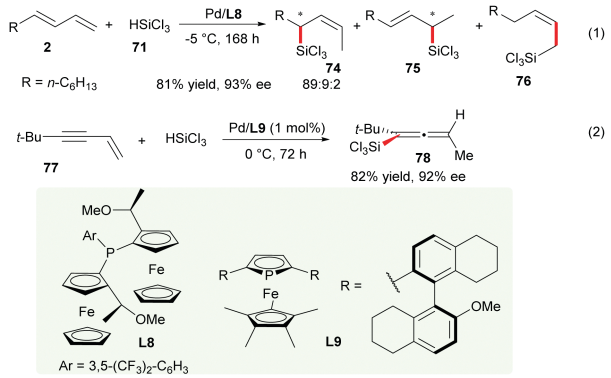


Scheme 16 The enantioselective hydrosilylation of cyclic dienes.

It was revealed that the bulkiness of the substituents on the ligand was critical to the enantioselectivity.

A reaction pathway for the hydrosilylation has ben proposed by Hayashi (Scheme 16B).[94] The Pd–H species **73** were directly generated from the addition of silane to Pd(0), thus the products are furnished through reductive elimination.

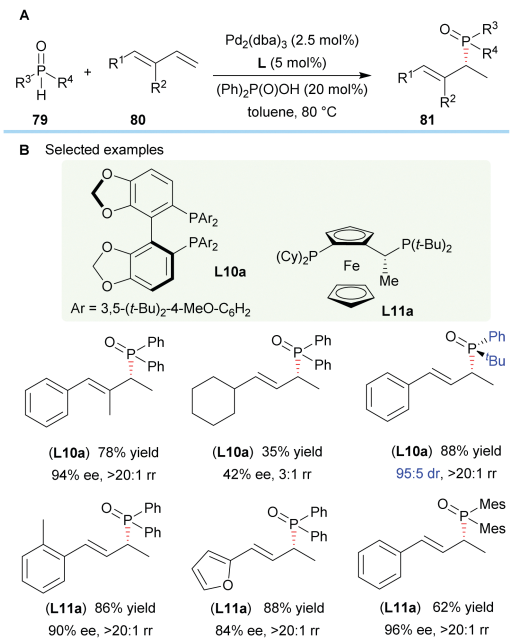
Compared to cyclic dienes, the hydrosilylation of linear 1,3-dienes is more challenging, due to difficulties associated with controlling the regioselectivity. Although a catalyst system using Ar-MOP and dioctylated Ar-MOP ligands favoured the formation of 1,4-addition products with good regioselectivity, the enantioselectivity was moderate.[95] Subsequently, bis(ferrocenyl)-monophosphine ligands **L8** were then introduced by Hayashi's group (Scheme 17).[110] They could promote the hydrosilylation of 1,3-dienes with trichlorosilane, furnishing the desired products in 93% ee and good regioselectivity (Scheme 17, eqn (1)). It was found that the electronic nature of the bis(ferrocenyl)monophosphine ligand had a significant influence on the enantioselectivity, with an increase in ee being observed as the electronic density decreased. The bis(ferrocenyl)monophosphine ligand could also promote the addition of silane to enyne, affording the chiral allenylsilane with good regioselectivity and enantioselectivity.[111] In 2006, another chiral ligand **L9** was developed for this reaction



Scheme 17 The enantioselective hydrosilylation of acyclic dienes.

by Hayashi, giving the corresponding products with high enantioselectivity (Scheme 17, eqn (2)).[112]

3.1.1.4 Formation of C–P bond. Compared to the asymmetric hydroamination and hydrosilylation of dienes, the hydrophosphinylation was developed relatively late. Early work concerning the hydrophosphinylation of isoprenes and dienes was conducted by Hirao[241] and Tanaka,[242] respectively, but either poor efficiency or racemic mixtures were obtained. Recently, Dong reported the method to enantioselectively add phosphine oxides to 1,3-dienes catalysed by a Pd–Josiphos complex (Scheme 18A).[113] The commercially available phosphine oxides have an acidity range between amines and thiols, so it is possible to undergo reactions similar to hydroamination and hydrothiolation. Although both Pd and Rh were tested, it was found that Rh could not promote the reaction. To obtain the optimized conditions, three factors were investigated: (1) ligand bite angle; (2) acidity, and; (3) the type of chiral ligand.

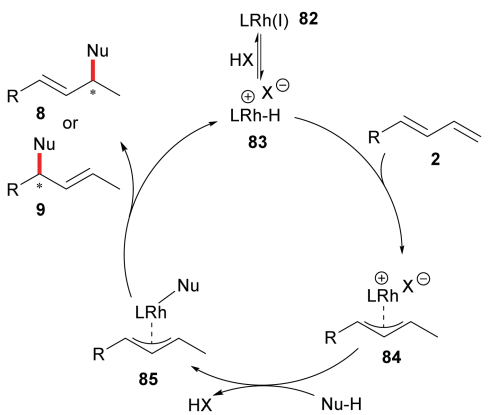


Scheme 18 The enantioselective hydrophosphinylation of dienes.

The results showed that the Josiphos ligand and diphenylphosphinic acid could efficiently catalyse the reaction. Notably, a moderate ligand bite angle and acidity were better for this reaction. The aryl substituted 1,3-dienes performed well under these conditions, although the bromoaryl substituted species showed low yield, probably because of side reactions caused by the oxidative addition into the C–Br bond. Substrates possessing alkyl groups gave moderate results, in particular, the (*S*)-DTBM-SegPhos ligand **L10a** seemed more suitable for cyclohexthyldiene and 1,2-disubstituted diene (Scheme 18B). In addition, various phosphine oxides were tested, giving their corresponding products in up to 88% yield and 96% ee. By using chiral phosphine oxides, a diastereoselectivity hydrophosphinylation was realized with >20:1 dr. According to the author's proposed mechanism, reductive elimination is the favoured reaction process.

3.1.2 Catalysed by Rh. The rhodium-catalysed hydrofunctionalisations of dienes share many similarities with palladium. An abbreviated but representative example is described in (Scheme 19). In general, the Rh–H specie **83** and diene **2** undergo migratory insertion to give the π-allyl–Rh intermediate **84**. Next, the pronucleophile will attack the Rh, furnishing the intermediate **85**. The products are ultimately obtained *via* reductive elimination. It was found that the counterion could influence the regioselectivity. When using a non-coordinated counterion, the 1,2-Markovnikov products are predominantly formed; for coordinated counterions, the 3,4-anti-Markovnikov products are favoured (Scheme 26). Notably, when a tridentate ligand was used, a nucleophilic substitution pathway similar to Pd-catalysed reactions is favoured. In some circumstances.

3.1.2.1 Formation of C–N bond. The Pd-catalysed asymmetric hydroamination of cyclodienes *via* the formation of Pd–H and π-allyl–Pd intermediates was developed at the beginning of this century. While the Rh-catalysed asymmetric hydroamination of asymmetric and linear dienes was reported in 2017 by Dong's group. The asymmetric addition of indoline to 1,3-dienes was catalysed by JoSPOphos–Rh complex and a Brønsted acid co-catalyst, giving the corresponding products



Scheme 19 Typical mechanism for Rh-catalysed hydrofunctionalisation of dienes.

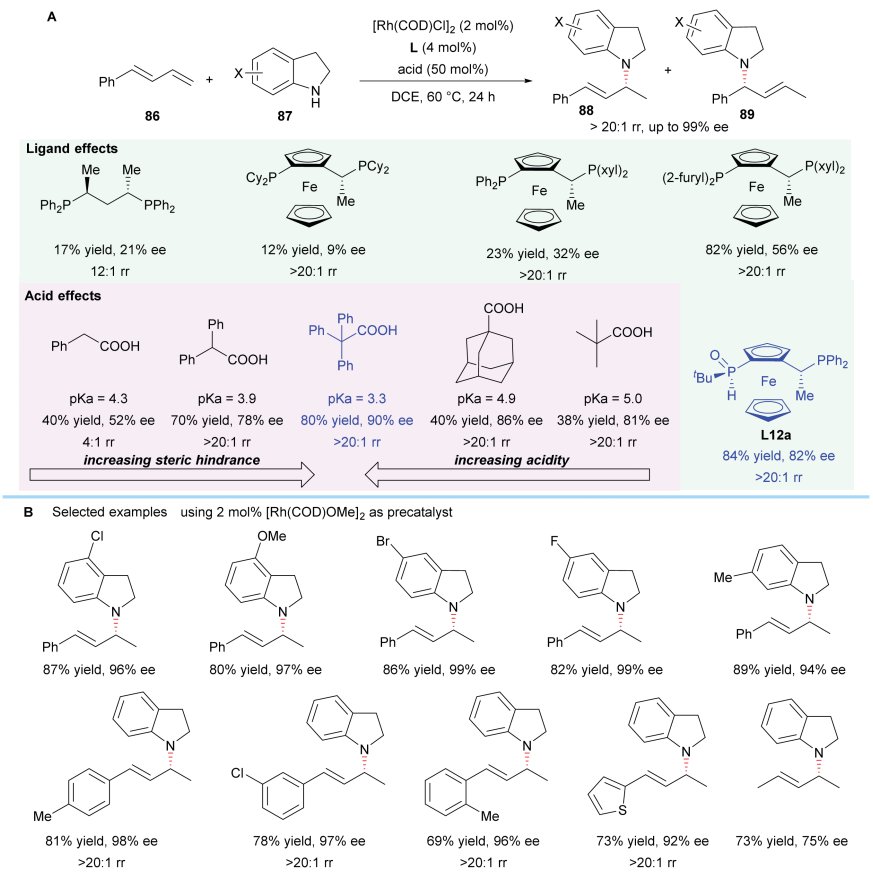
with up to 99% ee (Scheme 20A).[133] Chiral BDDP, Josiphos, and JoSPOphos ligands were tested to optimize the conditions, and JoSPOphos gave the highest reactivity, regioselectivity and enantioselectivity. The acidity and steric hinderance effects of the Brønsted acid were important to both reactivity and enantioselectivity. It was found that by increasing the steric hinderance of the acid, high enantioselectivity could be obtained, and that increasing the acidity lead to higher reactivity. Triphenylacetic acid balanced the steric hinderance and acidic properties well, and gave the best reactivity and enantioselectivity. Notably, $[Rh(COD)OMe]_2$ replaced the $[Rh(COD)Cl]_2$ as the initial precatalyst because the carboxylate and the methoxide can exchange more efficiently, promoting the catalytic cycle.

Next, the authors explored the hydroamination of various 1,3-dienes and various indoline derivatives (Scheme 20B). Many of them could furnish the corresponding products in good yield and excellent ee. In particular, alkyl-substituted 1,3-dienes were also tolerated, although they gave lower regioselectivity and enantioselectivity compared with aryl substituted species.

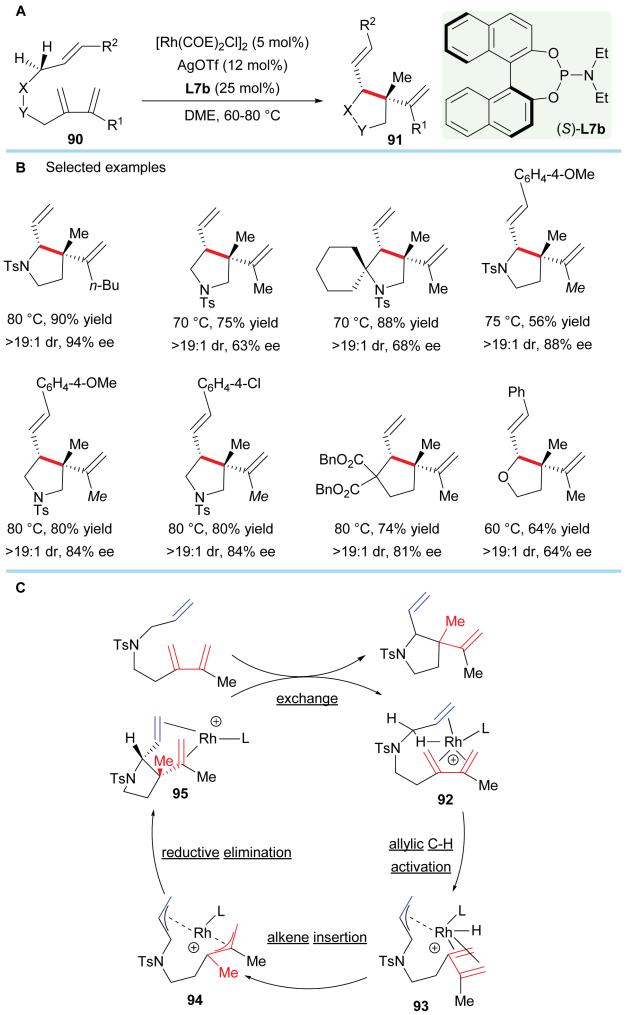
3.1.2.2 Formation of C–C bond. In 2010, Yu developed a Rh-catalysed intramolecular addition of allylic C–H bonds to dienes.[243] The ene-2-diene substrates could be transformed to multi-substituted tetrahydrofurans, tetrahydropyrroles, and cyclopentanes bearing quaternary carbon centers with good selectivity. Later, an enantioselective version was realized by introducing chiral phosphoramidites into the reaction (Scheme 21A).[99] The desired heterocyclic products could be prepared in high yield with good enantioselectivity and diastereoselectivity (Scheme 21B).

A reasonable catalytic cycle was proposed (Scheme 21C).[244] The Rh-catalyst first activates the allylic C–H, generating a Rh–H species **93** bearing a π-allyl–Rh. Next, the Rh–H species underwent migratory insertion to furnish the bis-allyl–Rh intermediate **94**, followed by reductive elimination to give the final products. The DFT calculations revealed that the conjugated diene motif was critical to the addition, since it could prevent double-bond isomerization and promote the final reductive elimination of the bis-allyl–Rh intermediates. The C–H activation and migratory insertion were reversible. In addition, the absence of any [4+2] cyclization is the result of the bridgehead double bond distortion of the cyclized products.

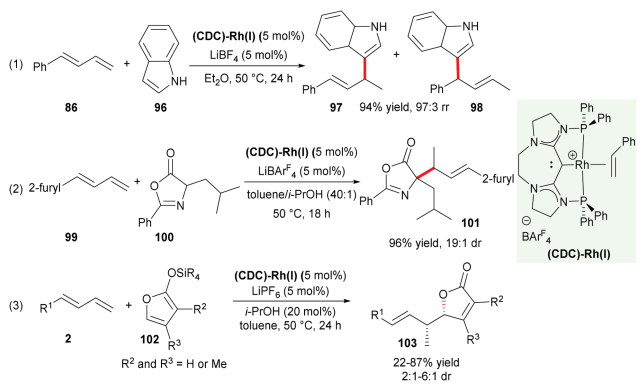
Chiral ligands have profound impact on reaction reactivity and selectivity in asymmetric catalysis. Thus, the development of various ligands is one of the most essential and appealing objectives in asymmetric hydrofunctionalisation. Carbdicarbene (CDC) pincers are a special type of tridentate ligand.[245] They can be used in Rh-catalysed hydroarylations and hydroalkylations of 1,3-dienes. Meek's group reported a CDC–Rh catalysed hydroarylation of 1,3-dienes with indoles in 94% yield with 97 : 3 regioselectivity (Scheme 22(1)).[246] The Lewis acid plays an



Scheme 20 Rh-Catalysed enantioselective hydroamination of 1,3-dienes with indolines.



Scheme 21 Rhodium-catalysed enantioselective allylic C–H activation for the addition to dienes.



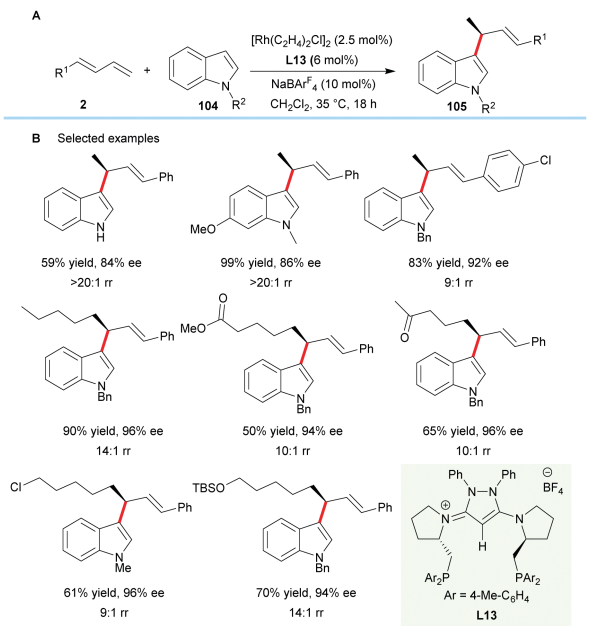
Scheme 22 Rh-Catalysed hydroalkylations of 1,3-dienes with CDC-ligand.

important role in the reaction process, most of which are alkali metal or BI group metal cations. Later, oxazolone was used as the prenucleophile to realize the Rh-catalysed hydroalkylation of dienes assisted by CDC pincer ligands (Scheme 22(2)).[247]

In 2017, the hydroalkylation of 1,3-dienes with enol silanes or carbonyl compounds was reported by the same group (Scheme 22(3)).[248] The corresponding products could be afforded in moderate to good yield and diastereomeric ratio.

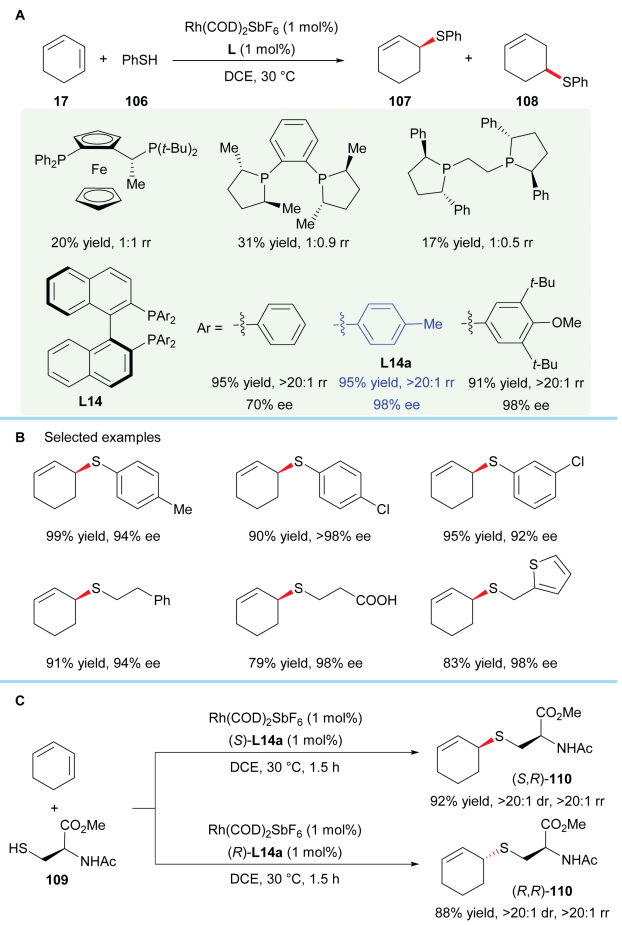
The asymmetric hydroarylation of internal and terminal dienes with indoles was reported by Meek's group in 2017.[140] A chiral CDC ligand **L13** was introduced to the catalytic system, giving the adducts with up to 96% ee (Scheme 23A). Instead of using lithium salts as Lewis acids as they did in their previous work, $NaBAr^F_4$ was utilized in this asymmetric conversion. $NaBF_4$ may impede the reaction because the BF_4^- may coordinate with the Rh, preventing the insertion of the diene. Various indoles were tested as well as internal dienes, giving the corresponding products with moderate to excellent yield and with good enantiomeric excess (Scheme 23B). 1,4-Disubstituted internal dienes bearing alkyl, alkyl halide, ester, ketone, and silyl ether groups are also tolerated. The structure of the π-allyl–Rh intermediate was determined by X-ray diffraction. It was found that the Rh–C distance to the Ph-substituted allylic terminus is longer than the corresponding distance to the Me-substituted terminus, which is caused by the steric hinderance of the phenyl group. According to the author, the reaction pathway favors nucleophilic substitution, in which the pronucleophile attacks at the allylic group rather than the Rh metal.

3.1.2.3 Formation of C–S bond. The coupling of carbon and sulfur is a valuable method for the generation of molecules containing heteroatom,[249] and asymmetric hydrothiolations are one of the powerful tools to realize this possessing excellent atom economy. A typical hydrothiolation of dienes was reported by He in 2007,[250] which was catalysed by an Au complex and afforded racemic products. Some of the Rh-catalysed hydrothiolations were

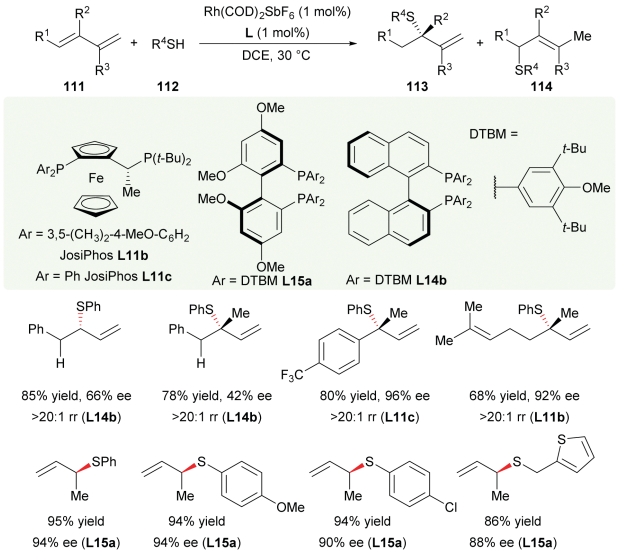


Scheme 23 Rh-Catalysed enantioselective hydroalkylation of 1,3-dienes with chiral CDC-ligand.

for allenes and alkynes, which will be discussed in the next section. A Rh-catalysed asymmetric hydrothiolation of dienes with thiols was developed by Dong's group in 2018 (Scheme 24A).[124] The reaction could proceed under mild conditions and in the absence of additional base or Brønsted acid. This may be because the acidity of thiol is strong enough to undergo oxidative addition with Rh(I). Both cyclic and acyclic dienes were investigated, and different chiral ligands were utilized to suit specific circumstances (Schemes 24B and 25). Chiral Tol-BINAP **L14a** could catalyse the addition of thiol to cyclodienes in excellent yield (up to 99%) and enantioselectivity (over 98% ee). Chiral JosiPhos **L11b** and DTBM-BINAP **L14b** were compatible with the asymmetric acyclic dienes, yielding the adducts with excellent regioselectivity (>20 : 1 rr), and an electron withdrawing substituent could benefit the regioselectivity. Notably, easily available feedstocks such as butadienes were also amenable to the reaction conditions, and the corresponding adducts could be furnished with up to 96% ee. The chiral DTBM-GarPhos **L15a** was used for some of these substrates to maintain high reactivity and enantioselectivity. Diastereomeric products could be generated by the addition of L-cysteine ester **109** to a cyclodiene catalysed by Rh-Tol-BINAP with excellent diastereoselectivity (>20 : 1 dr) (Scheme 24C).



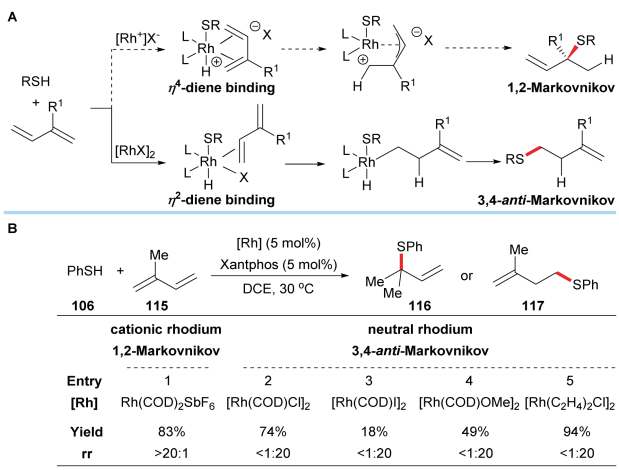
Scheme 24 Rh-Catalysed enantioselective hydrothiolation of cyclic dienes.



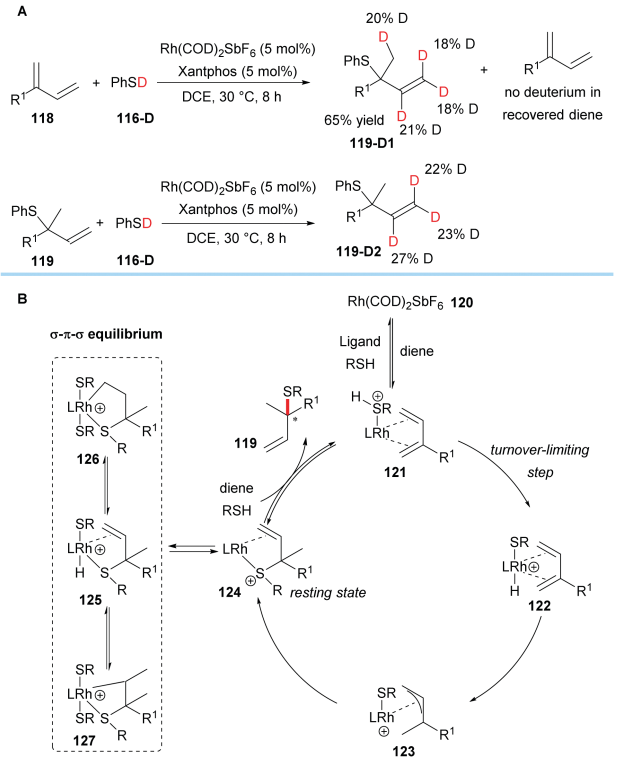
Scheme 25 Rh-Catalysed enantioselective hydrothiolation of acyclic dienes.

More specific details concerning the mechanism and regioselectivity were studied by the same group recently.[251] The correlation between the counterion and regioselectivity was revealed by the proposed mechanisms for the 1,2-Markovnikov addition and the 3,4-anti-Markovnikov addition, (Scheme 26A). A counterion with poorer coordinating ability, such as SbF_6^-, gives the 1,2-Markovnikov addition products, since η^4-diene coordination to Rh is possible. In contrast, stronger coordinating counterions, such as Cl^-, only allow for the η^2-diene coordination, ultimately leading to 3,4-anti-Markovnikov addition (Scheme 26B). According to the mechanism for 1,2-Markovnikov addition, electron rich thiols could accelerate the process by stabilizing the cationic transition state for the oxidative addition.

A plausible catalytic cycle was proposed (Scheme 27B). The generation of Rh–H species **121** proceeds *via* ligand exchange of the precatalyst, which is followed by the turnover-limiting step.



Scheme 26 Counterion-controlled regioselectivity.



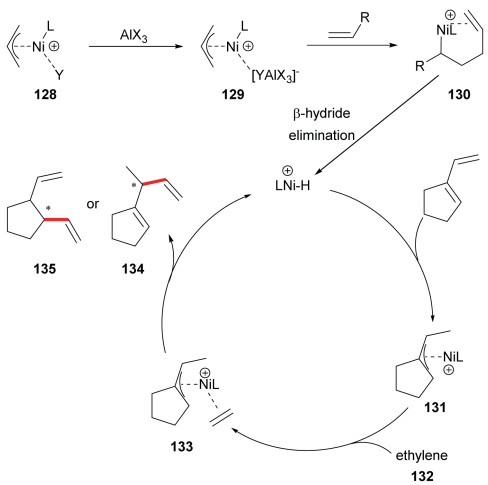
Scheme 27 Proposed mechanism of Rh-catalysed hydrothiolation of dienes.

The final product is more likely to be furnished *via* reductive elimination. Isotopic labelling experiments showed that the migratory insertion of **122** is irreversible since the recovered diene raw material possesses no deuterium incorporation (Scheme 27A). However, deuterium scrambling in the product suggests there may be another transformation resulting in proton exchange. Thus, the oxidative addition of the resting state **124** was proposed as well as a σ–π–σ equilibrium among **125**, **126**, **127**. The regioselectivity was determined jointly by the migratory insertion and reductive elimination.

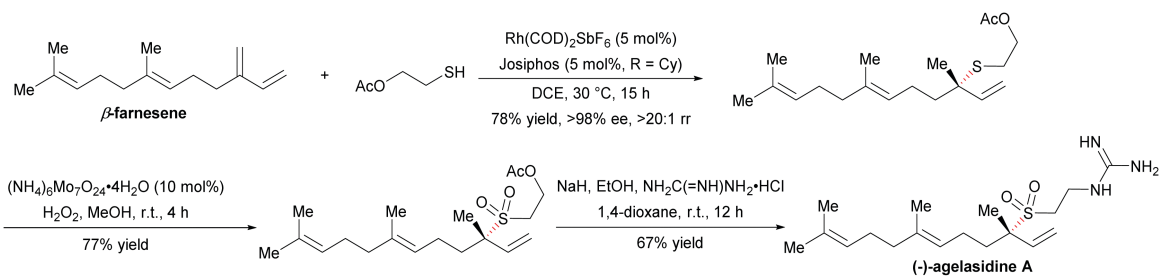
As the stereochemical properties of the thiolate ligand that binds to Rh does not influence the configuration of the newly built chiral center based on the proposed mechanism, a diastereoselective hydrothiolation of cyclodienes was developed with chiral thiols. Utilising the chiral Tol-BINAP ligand, the reaction could be completed with excellent reactivity, regioselectivity and diastereoselectivity. In addition, one method for the enantioselective total synthesis of (−)-agelasidine was developed (Scheme 28).[252]

3.1.3 Catalysed by Ni. The hydrovinylation of dienes is a major reaction for the Ni-based catalytic system, in which the Ni-precatalyst is usually a π-allyl–Ni species. A Lewis acid first removes the ligand from Ni to give the cationic intermediate **129**. Next, the ethylene inserts into the π-allyl–Ni species, and β-elimination gives the Ni–H species. Monodentate rather than bidentate ligands are used in Ni-catalysed hydrovinylations. The general process is shown in (Scheme 29). The Ni–H inserts into the exocyclic olefin, exclusively giving the multiple substituted π-allyl–Ni intermediate **131**. The ethylene then coordinates to the cationic Ni **131** to form **133**, and undergoes insertion. The final products are afforded after β-hydride elimination.

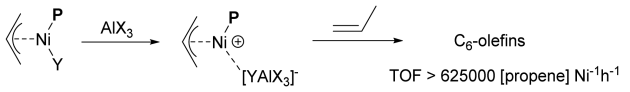
3.1.3.1 Formation of C–C bond. Ni–H catalysed oligomerizations of olefins are environmentally friendly chemical process and possess high economic benefits. As a typical procatalyst, $[\eta^3\text{-(allyl)Ni(PR}_3)]^+[RAlX_3]^-$ has an incredible TOF of over 625 000 $[propene][Ni]^{-1}$ $[h]^{-1}$, making the dimerization reaction a widely applied commercial process (Scheme 30).[253] The hydrovinylation of dienes with simple ethene is one of the most appealing types of oligomerization methods, since both



Scheme 29 Typical mechanism for Ni-catalysed hydrovinylation of dienes.



Scheme 28 Synthesis of (−)-agelasidine A.



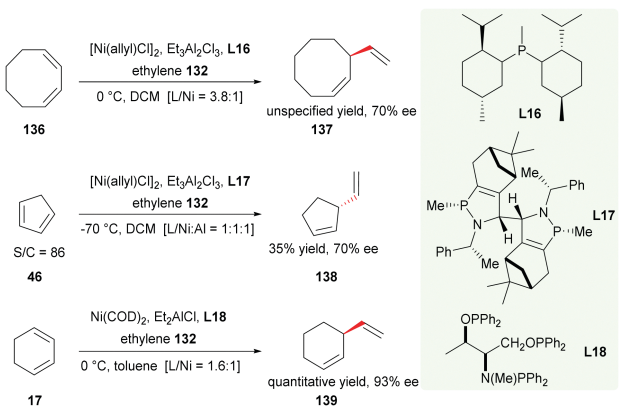
Scheme 30 Ni–H catalysed oligomerizations of olefins.

dienes and ethenes are common products in the oil industry and the adducts of these have a chiral centre as well as extra C–C double bonds, which can provide subsequent access to more plentiful olefin-containing products.[254]

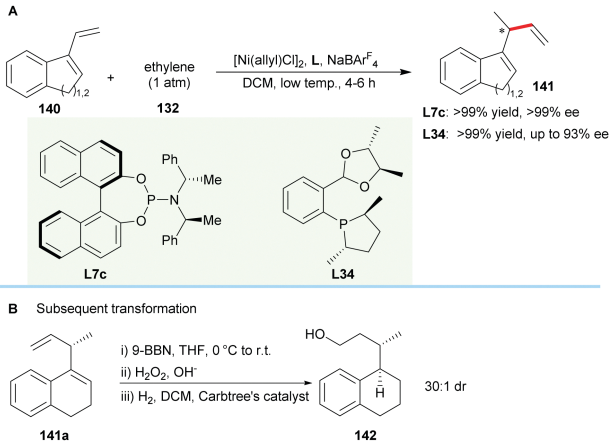
The nickel-catalysed asymmetric hydrovinylation of dienes is one of the earliest reported transition-metal-catalysed asymmetric C–C bond forming reactions, which was reported by Wifke in 1972.[154] The $(\pi\text{-}C_3H_5)Ni(PR_3)X{\cdot}AlX_3$ complex was utilized in the asymmetric hydrovinylation of cyclooctadiene with ethene, giving the corresponding products with up to 70% ee (Scheme 31). Dimenthylmethylphosphane was the most efficient ligand for this reaction. Other ligands such as **L17**, **L18** were also utilized later to promote the asymmetric hydrovinylation of cyclohexadiene and cyclopentadiene, improving the enantioselectivity to 93% ee (Scheme 31).[155,156]

Although significant progress had been reported with regards to the asymmetric hydrovinylation of dienes, there is still significant room for improvement. Methods for acyclic dienes are rare and a strong Lewis acid had to be utilized to promote the reaction. RajanBabu and co-workers developed a highly efficient and enantioselective hydrovinylation of 1,3-dienes in 2006. Both chiral phospholane **L34** and phosphoramidite **L7c** were ideal ligands for this reaction, and the latter even performed better giving the desired product with an enantioselectivity over 99% ee (Scheme 32A).[100] A non-coordinating counterion such as $NaBAr^F{}_4$ proved to be advantageous to high reactivity and enantioselectivity. The enantiopure products could induce another chiral centre in a subsequent transformation, such as *via* direct hydrogenation using Crabtree's catalyst (Scheme 32B).

This catalyst system could be applied to drug post-modification and chiral intermediate preparation, which were reported by the same group. The functionalization of a steroid



Scheme 31 Development of enantioselective Ni-catalysed hydrovinylation of cyclic dienes.

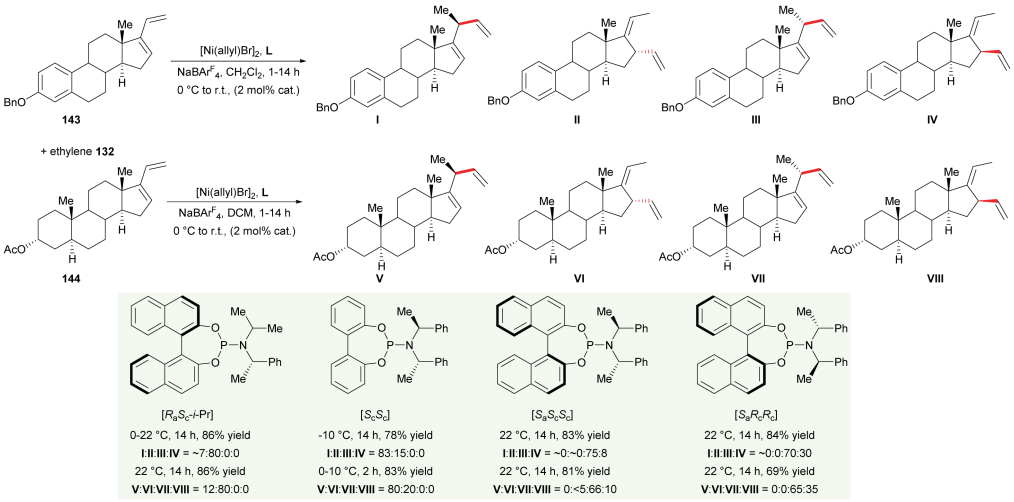


Scheme 32 Ni-Catalysed highly enantioselective hydrovinylation of acyclic dienes.

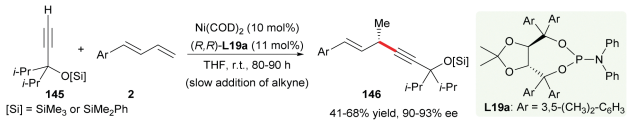
D-ring is an example.[101] To achieve good yield and selectivity, a series of phosphoramidites were investigated (Scheme 33). The chiral phosphoramidite ligand contains three stereochemical elements. It was found that the BINOL unit could induce chirality. In addition, a ligand with an N-i-Pr group and corresponding benzyl group derivates favoured the 1,4-addition products. A proposed mechanism shows that the origin of enantioselectivity may be derived from the different faces of the diene binding to the Ni complex.

In addition to asymmetric hydrovinylation, Ni complexes can also catalyse the enantioselective hydroalkynylation, hydroalkylation, and hydroarylation of 1,3-dienes. In 2010, Suginome developed an enantioselective addition of alkynes **145** to *trans*-dienes in the presence of Taddol-derived phosphorus ligands **L19a**. It was found that the α-siloxy-*sec*-alkyl group on the alkynyl carbon is critical to the reaction (Scheme 34).[157] High enantioselectivity could be achieved with up to 93% ee under mild conditions.

Although significant work had been reported using Pd and Rh as catalysts to achieve the enantioselective coupling of stabilized carbon nucleophiles with 1,3-dienes, a version with unstabilized nucleophiles such as enols or enolates of simple ketones is yet to be divulged. In 2018, Zhou developed a Ni-catalysed enantioselective coupling of simple ketones with 1,3-dienes with good enantioselectivity and excellent regioselectivity (Scheme 35A).[149] Various chiral ligands were tested, among which the (*S*)-DTBM-HO-BIPHEP **L15b** performed best, giving the corresponding products with up to 94% ee. It was found that adding *t*-BuOK could increase the yield. Reaction with aryl-substituted 1,3-dienes and aryl-substituted ketones could afford products in high yields and good enantioselectivity (Scheme 35B). Alkyl-substituted dienes could also react with (*S*)-DTBM-MeO-BIPHEP, giving the corresponding products with in slightly reduced yield and enantioselectivity. Notably, simple aliphatic ketones such as acetone, whose enols are more unstable, could generate the corresponding products with a good enantioselectivity of 88% ee. The enantiopure products could be transformed into other valuable compounds and building blocks for subsequent syntheses (Scheme 35C).



Scheme 33 Ni-Catalysed enantioselective hydrovinylation of steroid D-ring using chiral phosphoramidite ligand.



Scheme 34 Ni-Catalysed enantioselective hydroalkynylation of dienes.

A mechanistic study was conducted. According to deuterium-labelling experiments, the protons of the Ni–H intermediate correspond mainly to the alcohol (Scheme 35D). In addition, the insertion step of the diene into Ni–H bond is reversible, and the addition of enol/enolate is slower than the insertion. A catalytic cycle was proposed. The general route is the same as that of a typical Rh-catalysed hydrofunctionalisation. However, another type of Ni–H formation was proposed. The complexation of Ni(0) might first occur, followed by an LLHT process, giving the Ni–H species.[255]

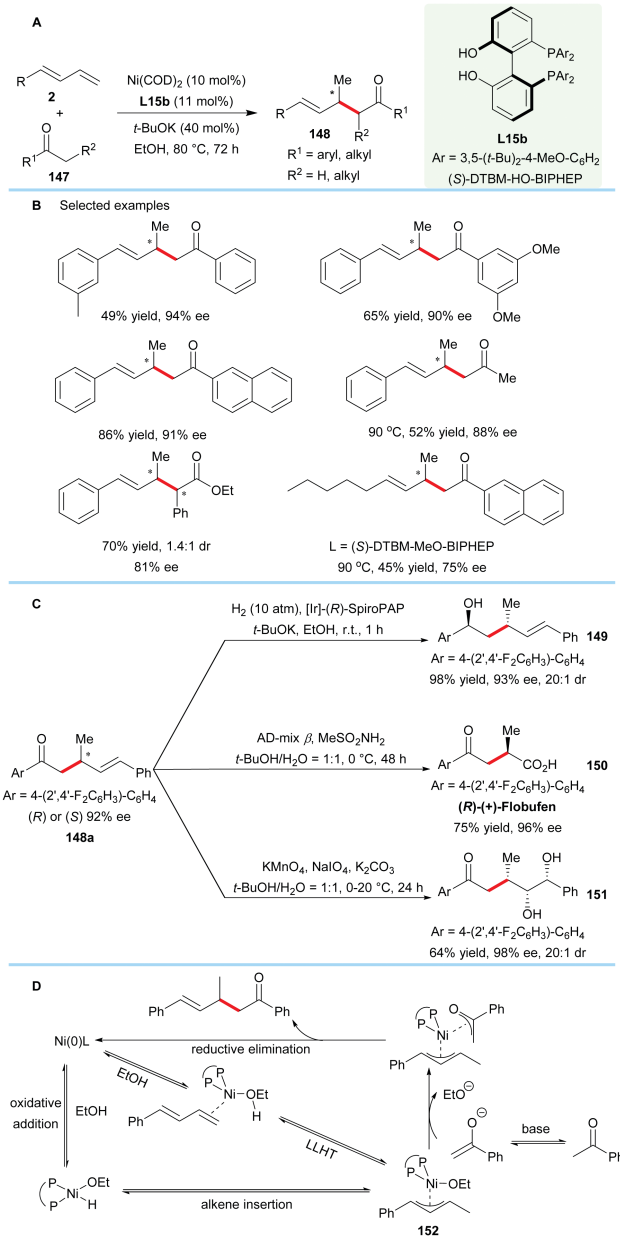
Recently, Zhou established a Ni-catalysed enantioselective hydroarylation of styrenes and dienes with arylboronic acids based on their previous works.[256,257] The desired products could be obtained in high yield and good enantioselectivity (Scheme 36A). Notably, 1,4-disubstituted internal dienes were also investigated, providing promising yield and enantioselectivity (Scheme 36B).

3.1.4 Catalysed by Co. Co-Catalysed hydrovinylation is also important for the hydrofunctionalisation of dienes. The mechanism of this process will be descried in the reaction development section. Additionally, hydrosilylation can also be promoted by a Co-catalyst.

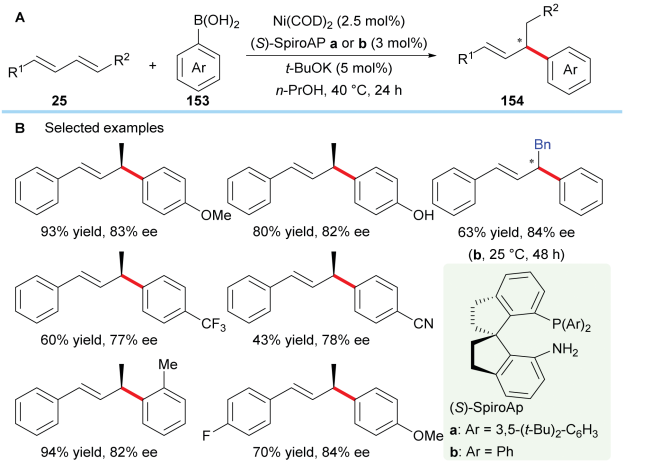
3.1.4.1 Formation of C–C bond. Chelating ligands such as bidentate phosphine ligands are rarely used in Ni-catalysed hydrovinylations, but it is common in cobalt-catalysed hydrovinylations, largely extending the scope of the diene substrates. The Co-catalysed asymmetric hydrovinylation of unactivated linear 1,3-dienes was first reported by RajanBabu's group (Scheme 37).[159] Several chiral ligands were investigated to realize the enantioselective addition, and it was found that the bidentate phosphine ligands DIOP **L20a**, BDPP **L21**, and Josiphos **L11d** were the most compatible in this reaction. The Josiphos ligand was more active although it provided a slight decrease in enantioselectivity. For alkyl substituted dienes, the 1,4-hydrovinylation products are the predominant products. The new C–C bond is more likely to form at the more substituted side of the alkyl-substituted 1,3-dienes **155**, **156**; for aryl substituted dienes, the ethylene adds to the terminal double bond **157**. In addition, it was found that the stereochemical properties of the dienes could influence the reaction: *E*-dienes had higher reactivity than *Z*-dienes.

A possible catalytic cycle was proposed to describe the reaction process (Scheme 38).[125] Compared to Ni, Co can support more flexible geometries for the intermediates in the catalytic cycle, since it can possess a higher coordination number. In this mechanism, the Co–H species **164** is the activated catalyst. It is generated from the β-hydride elimination of **163**, which is furnished from the alkene insertion of the coordinated unsaturated cationic intermediate **162**. The species **164** coordinates with the diene, forming an η^4-complex **165**. There are two pathways for the insertion of Co–H bonds which lead to different regioselectivities. The regioselectivity is also influenced by the stereochemical property of the π-allyl–Co intermediates (**166** and **170**). The enantioselectivity is determined by the migratory insertion of ethylene to the π-allyl–Co intermediate. All the terminal molecules were afforded *via* β-hydride elimination, giving the Co–H species **164** simultaneously.

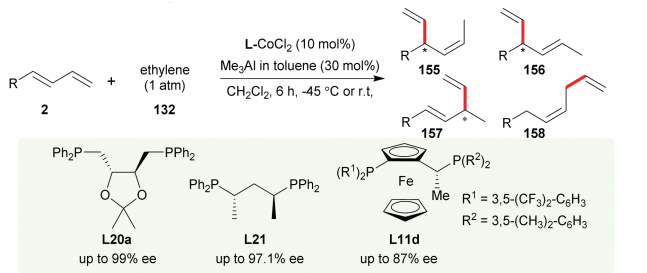
The Ni-catalysed asymmetric 1,2-hydrovinylation of vinylcycloalkenes was achieved by RajanBabu's group, giving the corresponding products in excellent enantioselectivity. Nevertheless, chiral 1,4-adducts of vinylcycloalkenes are also valuable building blocks, so the same group developed a highly selective 1,4-hydrovinylation of vinylcycloalkene catalysed by a Co complex (Scheme 39).[164] Chiral bisphosphine ligand 2,4-bisdiphenylphosphinopentane (BDPP) was utilized in this



Scheme 35 Ni-Catalysed enantioselective hydroalkylation of dienes.



Scheme 36 Ni-Catalysed enantioselective hydroarylation of dienes.



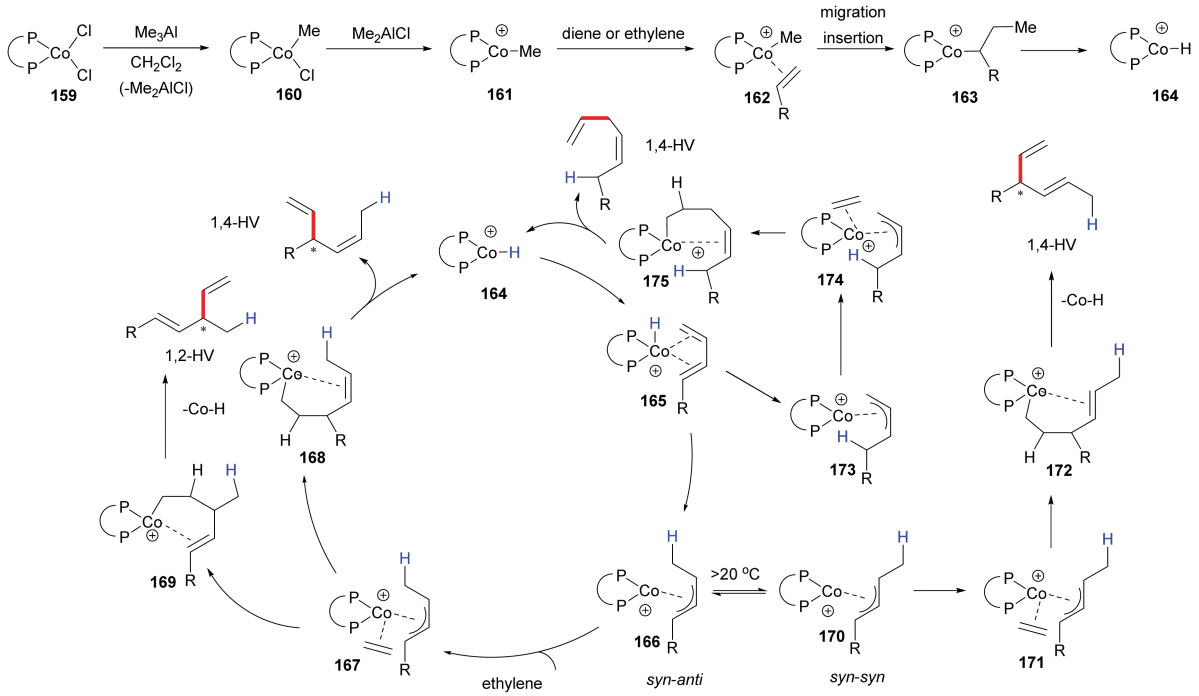
Scheme 37 Co-Catalysed enantioselective hydrovinylation of 1,3-dienes.

method, generating the products bearing a chiral centre on the ring with excellent yield, regioselectivity, and enantioselectivity.

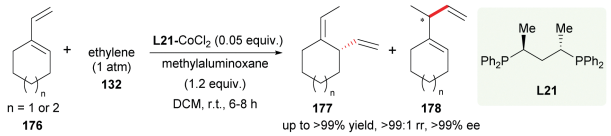
The hydrovinylation of dienes we have discussed mainly use ethylene as the dimerization reagent, since it is the most common and inexpensive raw material. Alkyl acrylates **179** are also readily available compounds bearing a double bond similar to ethylene. However, when applying the catalytic conditions of the hydrovinylation of dienes with ethylene to alkyl acrylates, the reaction was inhibited. In order to solve this challenge, a new catalytic system was developed by RajanBabu's group in 2017,[165] with which they successfully achieved high enantioselective hetero-dimerization of acrylates and 1,3-dienes (Scheme 40A). Chiral BDPP ligands could still work well, but $AlMe_3$ was not compatible in this reaction system due to the presence of the carbonyl group in the alkyl acrylates. Thus, $NaBAr^F_4$ was used in place of $AlMe_3$ to activate the reaction. The precatalyst was Co(II), which could be reduced by Zn or other reducing reagents to participate in the catalytic cycle. Coordinating solvent such as THF were not compatible with reaction conditions, and the hydrocarbon solvents were also incompatible. Many monosubstituted 1,3-dienes could be transformed into the corresponding products with 70–95% yield and 94–99% ee, but the 2 or 3-substituted species could not afford their chiral products (Scheme 40B).

The mechanism of this reactions differs from the one previously discussed (Scheme 40C). The Co(II) precatalyst **181** initially undergoes a reduction process, generating Co(I) complex **182**, which then reacts with $NaBAr^F_4$ to form the active cation **183**. The next step is oxidative dimerization *via* the insertion of acrylate to the Co–C_4 bond, giving the Co(III) intermediate **186**. Another pathway gives the 1,4-anti-Markovnikov adducts **189**, which is the less favoured regioisomer. **186** can undergo β-hydride elimination and then reductive elimination to afford the final products **180**.

3.1.4.2 Formation of C–Si bond. Catalysts based on cobalt could also promote the hydrosilylation of 1,3-dienes, and a lot of work has been performed to optimize the conditions and improve the conversion and selectivity. Nevertheless, in most cases, the 1,4-addition products were predominantly formed, as



Scheme 38 Proposed mechanism for Co-catalysed enantioselective hydrovinylation of 1,3-diene.



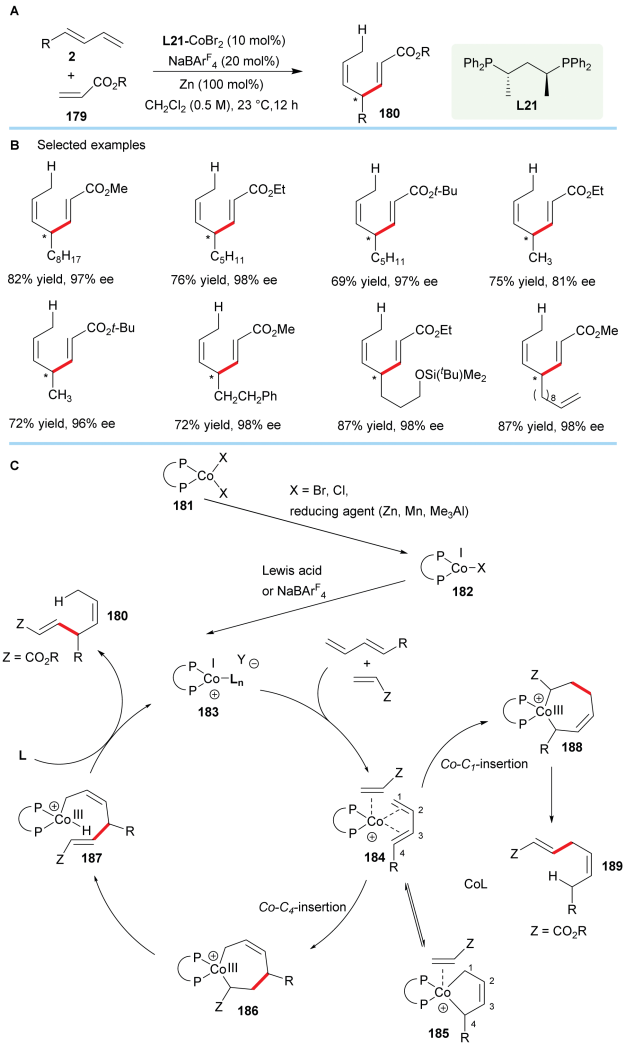
Scheme 39 Co-Catalysed enantioselective hydrovinylation of vinylcycloalkenes.

well as the 1,2-anti-Markovnikov products. The 1,2-Markovnikov selective hydrosilylation of dienes catalysed by Co was developed by Ge's group in 2018 (Scheme 41A).[114] In addition, an enantioselective version of this reaction was also investigated. The Xantphos ligand was utilized to achieve high 1,2-selectivity (>99%). Different chiral ligands were tested to realize the enantioselective hydrosilylation, and the axially chiral ligand Difluorphos **L10b** performed the best, giving the corresponding products with up to 80% ee. The proposed mechanism showed there is a 2,1-migratory insertion of the 1,3-diene to Co–H (Scheme 41B). The generated allyl–cobalt species undergoes σ–π–σ isomerization to afford **195**, which then reacts with $PhSiH_3$ to give the final products.

Recently, Huang's group used QuinOx–Co as a catalyst to realize the highly regio- and enantioselective 1,2-Markovnikov-addition of $PhSiH_3$ to mono- or 1,2-disubstituted 1,3-dienes with aryl or alkyl substituents (Scheme 42A).[167,258] Several bidentate oxazoline derivates were tested to control the stereochemistry of the products and chiral *t*-Bu-QuinOx **L22a** gave the highest regioselectivity (>99 : 1 rr) and enantioselectivity (94% ee). The $NaBEt_3H$ additive was essential to this reaction, and exchanging it with other bases such as MeLi and EtMgBr resulted in a decrease in conversion. Notably, the (*Z*)-diene could not react under these conditions, suggesting that the geometry of the dienes could constrain the reaction. Various aryl-substituted 1,3-dienes were investigated, and it was found that the electronic effect and position of the substituents on the aryl group had little influence on the activity and enantioselectivity. Alkyl-substituted 1,3-dienes, which usually performed poorly in hydrofunctionalisations, were tolerated with this method, giving up to 92% ee. With regards to 1,2-disubstituted dienes, although the yield was lower, the enantioselectivity was as good as that for monosubstituted substrates. Some derivates could be prepared after subsequent reactions (Scheme 42B). The chiral allyl dihydrosilane **196a** is also the raw material for chiral polyorganosiloxane (Scheme 42C). A deuterium-labeling experiment showed that the mechanism of this method was more likely to be a modified Chalk–Harrod mechanism, in which the terminal double bond inserts into the Co–Si bond rather than Co–H (Scheme 42D).

3.1.5 Catalysed by other metals. The main group metal, lithium, has also been widely employed in the construction of chiral catalysts to promote the hydroamination of dienes. Through screening a series of ligands, Collin reported that chiral *N*-substituted binaphthyldiamines were efficient ligands for the cyclohydroamination of conjugated aminodienes, giving the pyrrodine and piperidine with high enantioselectivities (65% and 73% ee, respectively) (Scheme 43).[170,171]

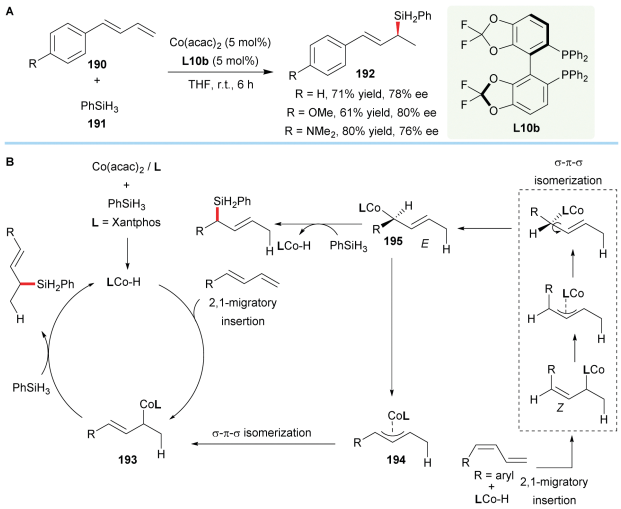
In 2011, Toste developed a new Au-catalysed method for the enantioselective hydroamination of aminodienes. The alcohols were used as Brønsted acids which are activated by the gold complexes, which perform as Lewis acid (Scheme 44A).[115] The chiral DTBM-Segphos **L10a** and $AgBF_4$ were used to obtain the enantiopure products. Initially, CH_2Cl_2 was used as the solvent



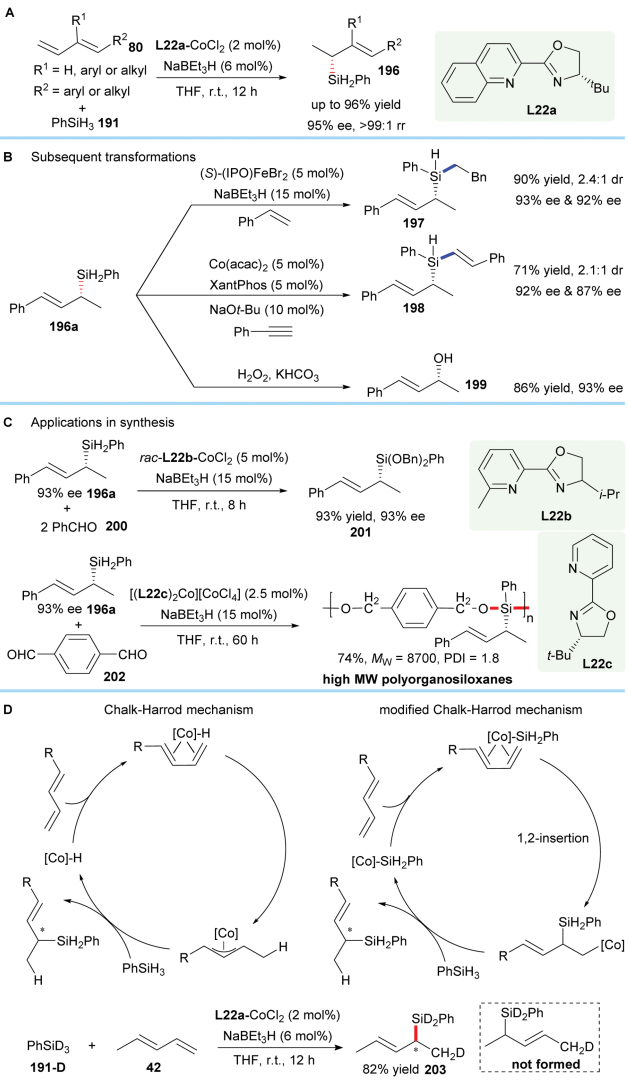
Scheme 40 Co-Catalysed enantioselective hetero-dimerization of acrylates and 1,3-dienes.

rather than alcohol, but the reaction was unsuccessful. By replacing CH_2Cl_2 with i-PrOH, the conversion was significantly increased as well as the enantioselectivity, which shows the importance of the Brønsted acid in this reaction. Other alcohols were tested to optimize the conditions, among which (−)-menthol was able to improve the regioselectivity and enantioselectivity. Many pyrrolidine derivates could be furnished with excellent yield and enantioselectivity, while piperidines could not be synthesized using this method.

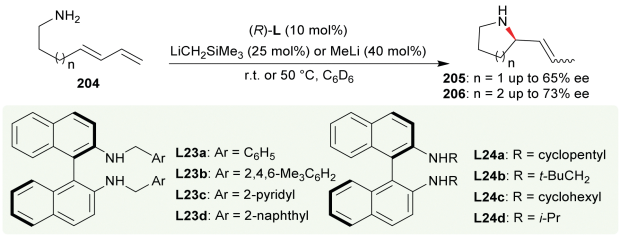
The mechanism was also studied by monitoring the reaction rate under different conditions. For the generation of 1,4-addition products, the addition of menthol could significantly accelerate the reaction; while for the generation of 1,2-addition products, menthol had little impact on the rate (Scheme 44B). This could explain why this reaction is 1,4-regioselective. When a proton sponge was added to the system, all the products were 1,2-addition adducts; whereas if a more acidic Brønsted acid (TfOH) was used in the absence of Au, the 1,4-addition products are the predominant species (Scheme 44C). These results



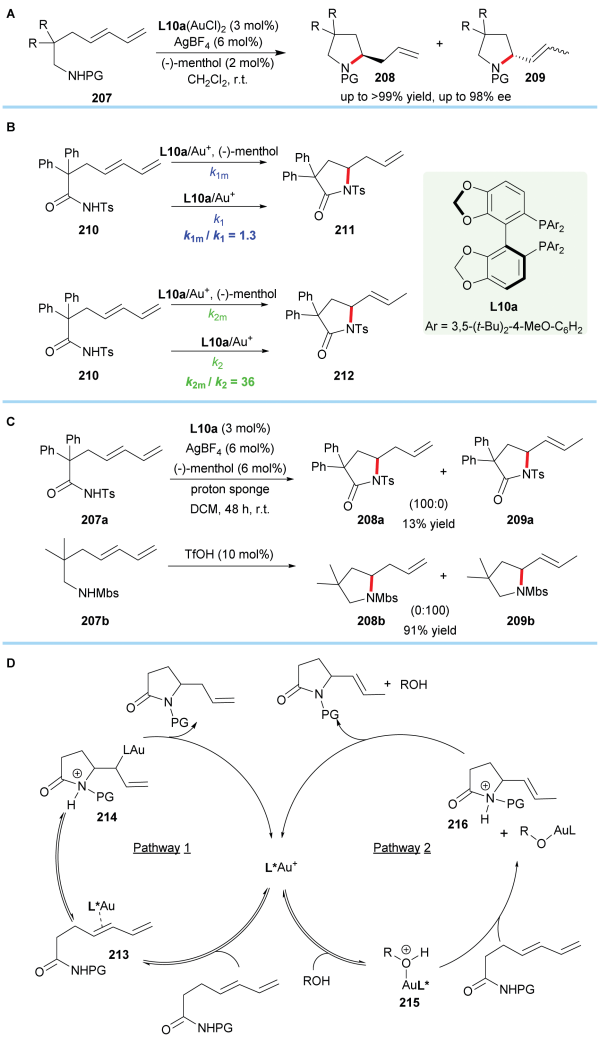
Scheme 41 Co-Catalysed enantioselective hydrosilylation of 1,3-dienes by Ge.



Scheme 42 Co-Catalysed enantioselective Markovnikov 1,2-hydrosilylation of dienes by Huang.



Scheme 43 Intramolecular enantioselective hydroamination of dienes catalysed by chiral lithium binaphthylamino catalysts.

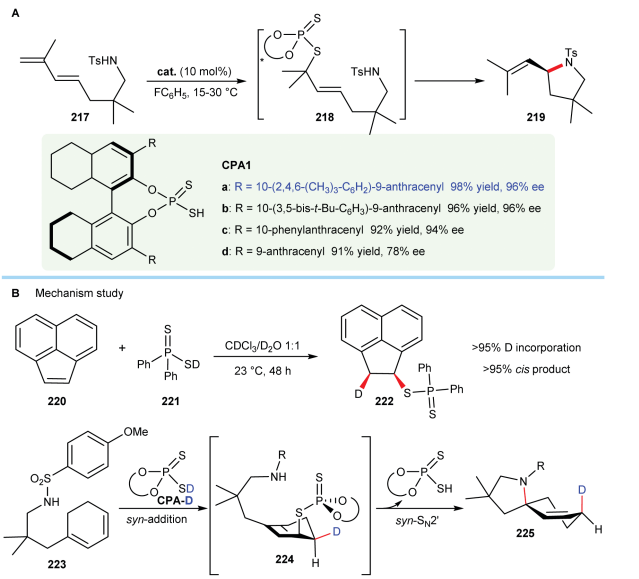


Scheme 44 Au-Catalysed intramolecular enantioselective hydroamination of dienes.

showed that there may be two different reaction pathways for the two regioisomers. A catalytic cycle was proposed by the author (Scheme 44D). In pathway 1, the coordination of the double bond to the Au promotes the addition of N to the double bond, which finally furnishes the 1,2-addition products. In pathway 2, the alcohol coordinates to the Au and allows for the protonation of the diene and cyclization, which ultimately affords the 1,4-addition products. If there is no Au catalysis present, a strong acid such as TfOH can also promote the reaction. The catalytic cycle shows that the generation of the 1,4-addition products is closely related to the alcohol and this is consistent with the reaction rate studies.

3.1.6 Catalysed by chiral organocatalyst. Organometal catalysts have been widely employed in asymmetric synthesis, giving excellent conversion and stereoselectivity. Metal-free enantioselective reactions are also attractive to many scientists due to low contamination and cost. However, the metal-free enantioselective hydrofunctionalisation of alkenes or dienes has not been widely reported. This can be attributed to the fact that Brønsted acid have difficulty in catalysing enantioselective additions to alkenes since the carbocation intermediates generated from the protonation of alkenes are less rigid, leading to poor discrimination between the two enantiotopic faces. This problem could be rectified by applying a strong Brønsted acid with a nucleophilic conjugated base. This strategy takes advantage of the covalent bond associating the conjugated base and carbocation generating a stable intermediate. As a result, the following substitution is in good selectivity. A point of this strategy is discovering an appropriate Brønsted acid with a nucleophilic conjugated base.

In 2011, Toste applied the strategy above to develop an enantioselective intramolecular hydroamination of 1,3-dienes in excellent yield up to 99% and 99% ee under mild reaction conditions (Scheme 45A).[38] As the chiral dithiophosphoric acids **CPA1** possess both strong acidity and a nucleophilic conjugated base, their derivates were investigated to find the most suitable structure. It was found that the bulky group on the phenyl ring played an important role in the enantioselectivity of the reaction. As the S_N2' reaction after the X–H insertion is distant to the dithiophosphate functionality, the more extended catalyst structure results in more efficient enantioselectivity. After optimizing the structure of the dithiophosphoric acid, conducting the reaction in fluorobenzene with 4 Å molecule sieves and reducing



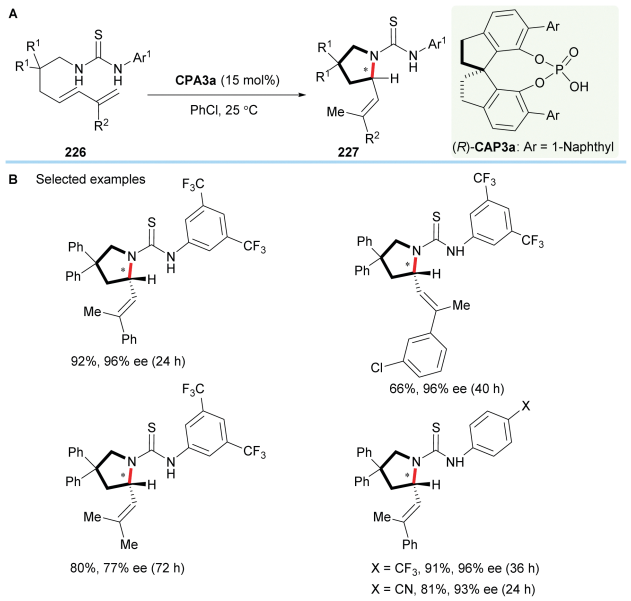
Scheme 45 Chiral dithiophosphoric acid catalysed intramolecular enantioselective hydroamination of dienes.

the temperature could also increase the selectivity. Many substrates were tested, including 1,3-dienes and allenes, and both of these could give the corresponding products in excellent yield and enantioselectivity. By conducting experiments using deuterated dithiophosphoric acid as a catalyst, it was found that both the initial addition and the following substitution undergo *syn* pathways, differing from the metal-catalysed process (Scheme 45B).

Recently, Liu reported a chiral phosphoric catalysed asymmetric hydroamination of *N*-(γ-dienyl) thiourea **226.**[210] The SPINOL-derived **CPA3a** was utilized as a catalyst (Scheme 46A). Various dienes reacted smoothly under mild conditions, giving the corresponding products in good yield and enantioselectivity (Scheme 46B).

3.2 Difunctionalisation

The enantioselective difunctionalisation of dienes has been studied since the end of the last century, providing a powerful method for the synthesis of complicated allylic compounds.[35–37]

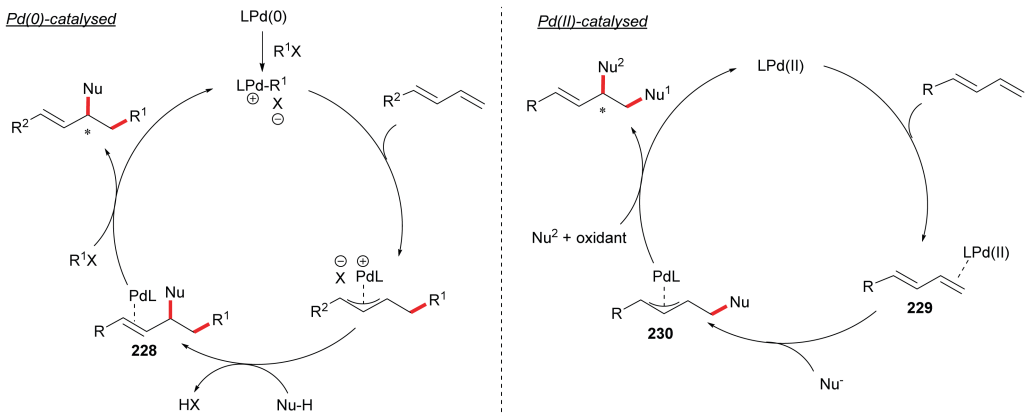


Scheme 46 Chiral phosphoric acid catalysed intramolecular enantioselective hydroamination of dienes.

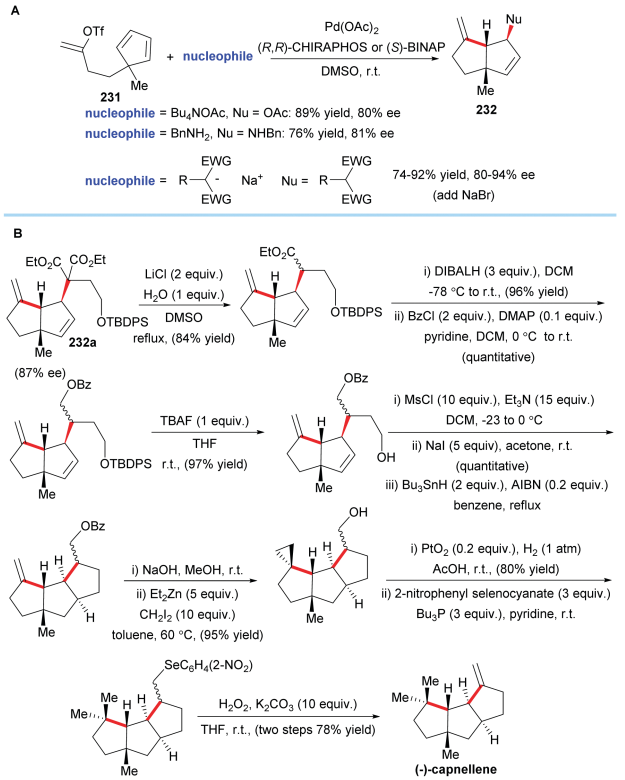
3.2.1 Catalysed by Pd. The general reaction pathway for the Pd-catalysed difunctionalisation shares a number of similarities with hydrofunctionalisation.[37] The biggest difference is that the metal–H species is displaced by aryl-metal, vinyl-metal, or other organometallic species. These reactions can be divided into Pd(0)-catalysed and Pd(II)-catalysed difunctionalisations. The typical catalytic cycles of the two kinds of reactions are shown in Scheme 47. For the Pd(0)-catalysed difunctionalisations, the insertion of the Pd–R^1 into the diene is a Heck-type migratory insertion; while the Pd(II)-catalysed reactions, go through a Wacker-type insertion. Note that for some of the Pd(0)-catalysed reactions, the precatalyst may be the Pd(II) complex, which will be reduced when the catalytic cycle is started. After insertion, the following steps are the same: the nucleophile will attack the π-allyl–Pd intermediates **228** or **230** generated *in situ* to give the final products. An oxidant is needed in the Pd(II)-catalysed reaction to recover the Pd(II)-catalyst from Pd(0)-catalyst. Notably, 1,4-addition compounds are also possible products although they are not drawn in the scheme.

3.2.1.1 Formation of C–C/C–N. In 1991, Shibasaki reported an asymmetric Heck reaction catalysed by Pd,[259] which can be regarded as an intramolecular difunctionalisation of dienes. (*R*,*R*)-Chiraphos was the chiral ligand used in this reaction, with the desired products being obtained with 80% enantiomeric excess (Scheme 48A). Some details concerning this reaction were reported by the same group later.[141] DMSO and (*S*)-BINAP were found to be the most suitable for this reaction. Subsequent work showed that aniline derivates and carbanions could also be added to the olefins.[142] This reaction could be applied to the total synthesis of (−)-capnellene (Scheme 48B).

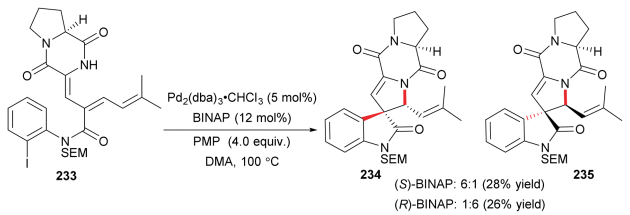
Besides alkenyl group, aryl groups can also serve as coupling reagents for the difunctionalisation of dienes. An elegant method has been reported by Overman to synthesize spirotryprostain B.[260] A (*Z*)-2,4-hexadienamide substrate could undergo asymmetric intramolecular difunctionalisation to give the pentacyclic products (Scheme 49). The chiral BINAP ligand induced the enantioselectivity, and the *R*- and *S*-ligands give the products with opposite configuration in similar conversion.[143]



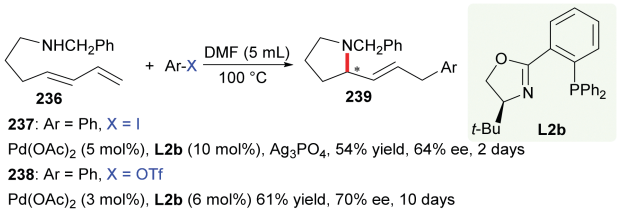
Scheme 47 Typical mechanism for Pd-catalysed difunctionalisation of dienes.



Scheme 48 Pd-Catalysed enantioselective difunctionalisation of dienes involving Heck-coupling.



Scheme 49 Pd-Catalysed enantioselective arylation/amination of dienes.

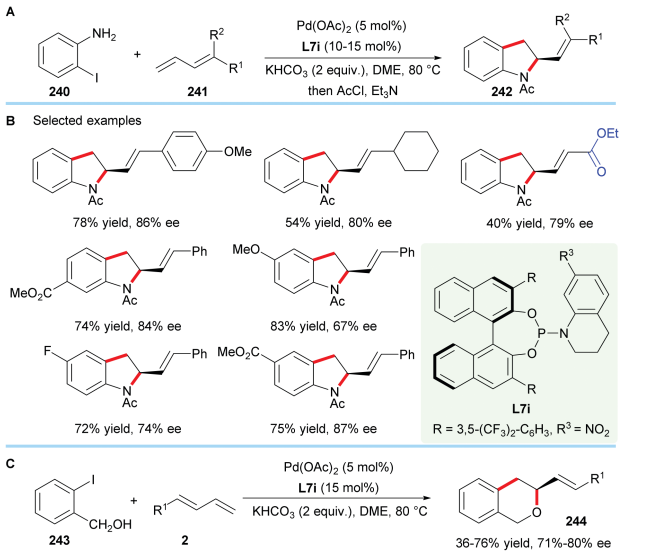


Scheme 50 Pd-Catalysed enantioselective arylation/amination of dienes affording 1,4-addition piperidines.

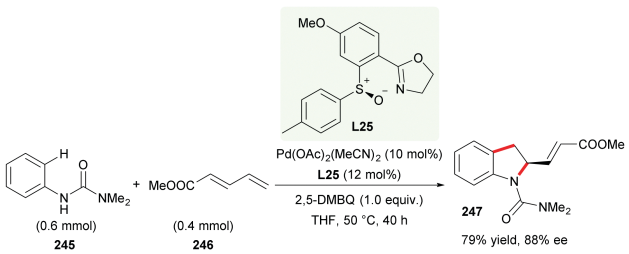
The two-component intermolecular enantioselective Heck reaction was developed by Helmchen in 1999 (Scheme 50).[86] The 1,4-addition of piperidines **239** were the favoured products in this reaction. It was found that the chiral PHOX **L2b** performed well in inducing chirality, but the BINAP ligand exhibits poor enantioselective efficiency in this reaction. In addition, aryl-triflates **238** can give the corresponding products with higher enantioselectivity compared with phenyl iodides **237**, but the reaction time is long (10 days). This might suggest that the counterion has an influence on the enantioselectivity.

In 2016, Han developed an enantioselective addition of *o*-iodoanilines **240** to 1,3-dienes **241** catalysed by a Pd-complex bearing a BINOL-derived phosphoramidite ligand (Scheme 51A).[102] The desired cyclic products could be obtained with up to 87% ee. It was found that the more electron-deficient the ligand, the better the enantioselectivity. Several different aniline derivates and aryl dienes could react smoothly with good yield and enantioselectivity (Scheme 51B). Notably, the dienyl ester was also tolerated in this reaction, giving moderate yield and good enantioselectivity (79% ee). The *o*-iodobenzyl alcohols **243** was also tried under the same reaction conditions, generating the corresponding products **244** with equally high enantioselectivity (Scheme 51C).

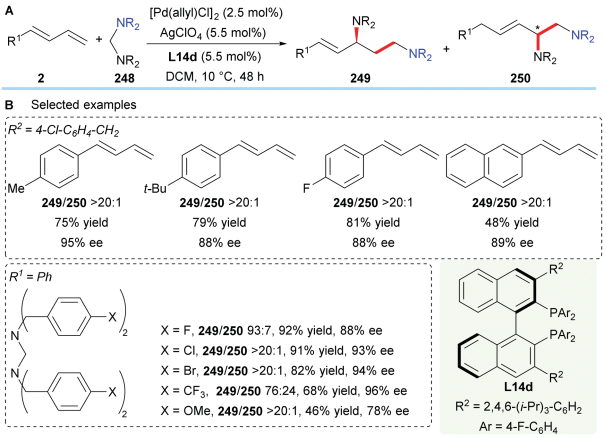
One year later, the same group used aryl anilines as substrates,[172] requiring a catalytic system that could promote the cleavage of the sp^2 C–H bond. A SOX-derived chiral ligand **L25** showed a high level of activity and enantioselectivity, allowing for the desired optical active indolines **247** to be generated in excellent yield and enantioselectivity (79% yield, 88% ee) (Scheme 52).



Scheme 51 Pd-Catalysed enantioselective arylation/amination of dienes.



Scheme 52 Pd-Catalysed enantioselective arylation/amination of dienes with aryl ureas.

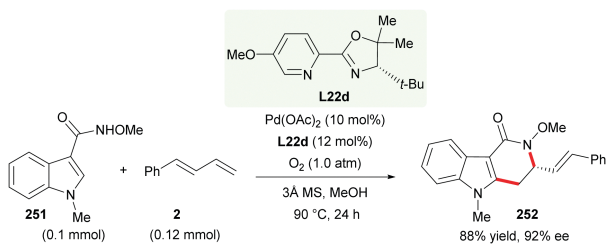


Scheme 53 Pd-Catalysed enantioselective aminomethylation/amination of dienes with aminals.

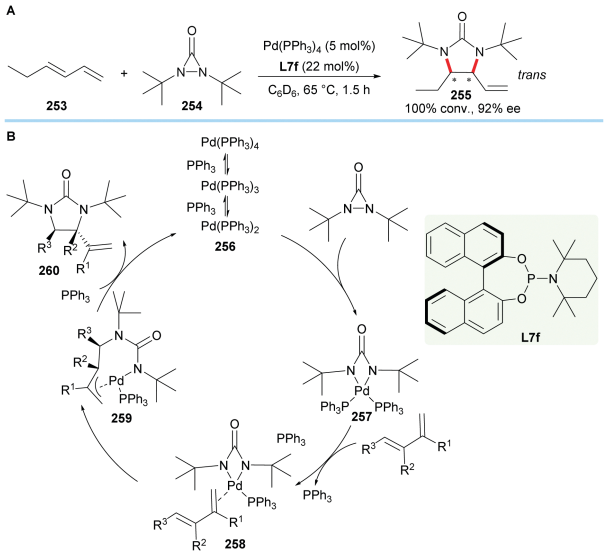
In 2016, Huang reported the highly enantioselective 1,2-aminomethylamination of 1,3-dienes catalysed by Pd (Scheme 53A).[144] They examined a series of BINAP ligands and found that **L14d** was the most effective, affording the desired 1,3-diamine in 84% yield with 84% ee and excellent regioselectivity. Benzyl aminals bearing both EWG and EDG on the phenyl ring were tolerated (Scheme 53B). However, if the EWG is too electron-deficient, the yield and regioselectivity is poor due to the weak nucleophilicity of the corresponding amine. It was found that the reactivity, regio- and enantioselectivity of this reaction were not affected by the (*E*/*Z*) ratio of the dienes.

Recently, Gong and co-workers developed a Pd(II)-catalysed enantioselective addition of arylamides to 1,3-dienes (Scheme 54).[168] Compared with Pd(0)-catalysed difunctionalisation, an oxidant such as O_2 is needed to complete the catalytic cycle, since the final substitution step gives the Pd(0)-catalyst. In addition, harsh reaction conditions were required (90–110 °C) to assist the initial cleavage of the aryl C–H bond, leading to the search for an appropriate chiral ligand whose Pd-complex could withstand high temperatures. Fortunately, it was found that the electron-rich Pyrox-type ligand **L22d** performed with a high level of efficiency and enantioselectivity in this reaction.

3.2.1.2 Formation of C–N/C–N bonds. Vicinal diamines bearing chiral centres are important motifs appearing in many valuable bioactive molecules. The direct diamination of dienes provides an effective method for the preparation of allylic diamines.[261]



Scheme 54 Pd(II)-Catalysed enantioselective arylation/amination of dienes with arylamides.



Scheme 55 Pd-Catalysed enantioselective diamination of dienes with di-*tert*-butyldiaziridinone.

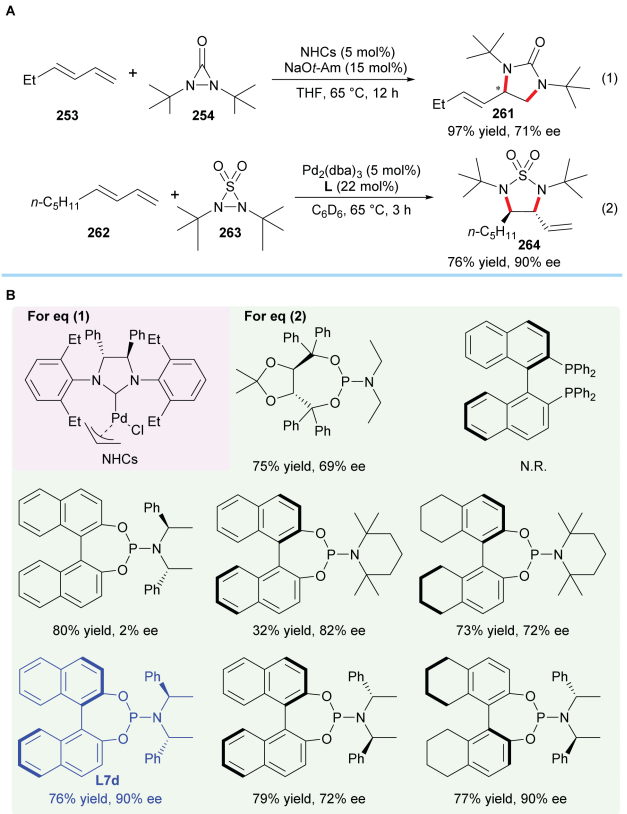
In 2007, Shi developed a Pd-catalysed diamination of dienes with di-*tert*-butyldiaziridinone **254**, giving the imidazolidiones **255**.[262] Later, the same group examined different chiral monodentate phosphine ligands, finding that **L7f** allowed for an asymmetric version of the diamination to be conducted in excellent yield and high enantioselectivity (Scheme 55A).[103] The addition predominantly occurs at the internal olefin of the diene.

The reaction mechanism for the diamination differs from the typical Pd-catalysed difunctionalisation that was mentioned previously. The Pd(0) and diaziridinone first undergo oxidative addition, giving the species **257**, which then inserts into the diene. The generated π-allyl–Pd intermediate **259** then goes through a reductive elimination process to give the products (Scheme 55B).[263]

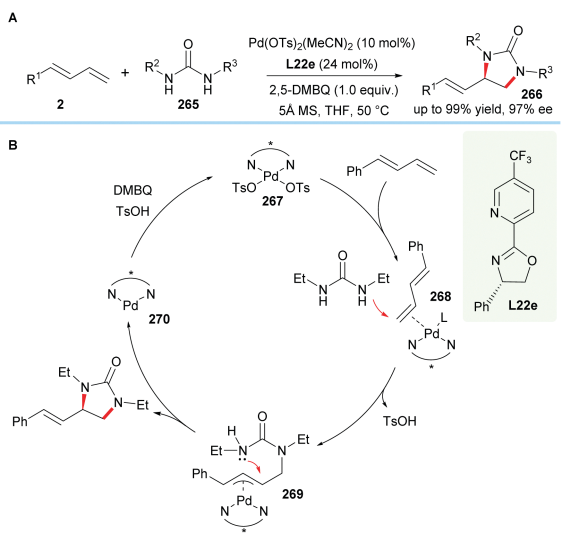
N-Heterocyclic carbenes (NHCs) have also been employed in the enantioselective diamination of dienes by the same group (Scheme 56A).[173] In addition, di-*tert*-butylthiadiaziridine 1,1-dioxide **263** was also used as a N-source (Scheme 56B).[104] Several chiral ligands were tried, and it was shown that the chiral phosphoramidite ligand **L7d** could promote the reaction, giving the desired cyclic sulfamides **264** in 76% yield with 90% ee (Scheme 56B).

In Shi's works, the diamination of dienes was catalysed by a Pd(0)-complex. In 2018, Gong and co-workers reported a Pd(II)-catalysed enantioselective diamination of dienes with ureas (Scheme 57A).[169] Notably, this diamination occurred at the terminal olefin of the diene with excellent regioselectivity. Incorporation with chiral pyridine-oxazoline **L22e** lead to the desired 4-vinylimidazolidin-2-one products **266** in excellent yield with high enantioselectivity (up to 99% yield, 97% ee). Similar to many other Pd(II)-catalysed difunctionalizations, a Wacker type process is involved in the generation of π-allyl–Pd intermediate **269** (Scheme 57B).

3.2.1.3 Formation of C–C/C–C bonds. In 2014, Sigman and co-workers developed an enantioselective route from 1,3-dienes

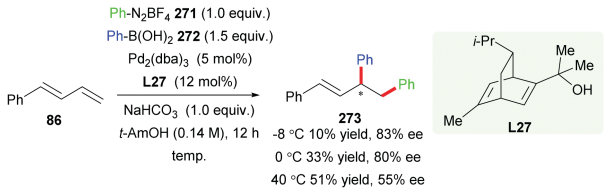


Scheme 56 Further development of Pd-catalysed enantioselective diamination of dienes.

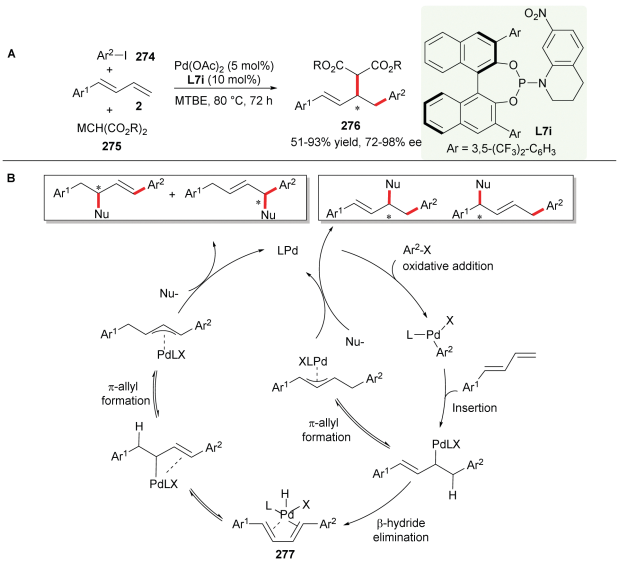


Scheme 57 Pd(II)-Catalysed enantioselective diamination of dienes with ureas.

to diarylation products, a strategy based on their work concerning a three-component diarylation of terminal 1,3-dienes (Scheme 58).[174,264] Aryldiazonium tetrafluoroborates **271** and arylboronic acids **272** served as aryl reagents. Commonly used phosphine ligands in organic catalysis were ineffective since two aryl reagents can couple with each other, leaving the diene unreacted.



Scheme 58 Pd-Catalysed enantioselective diarylation of dienes.

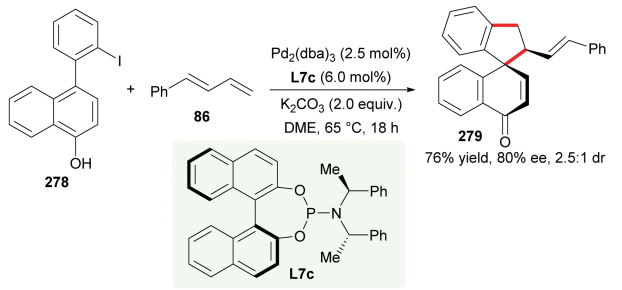


Scheme 59 Pd-Catalysed enantioselective arylation/alkylation of dienes.

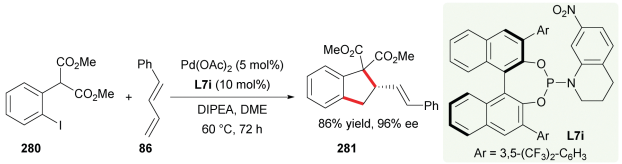
Therefore, the researchers focused on non-nucleophilic ligands—chiral dienes, like bicyclo[2.2.2]octadienyl **L27**, could give the desired diarylation products with a promising enantiomeric excess of up to 83%.

In 2015, Gong and co-workers successfully developed a highly efficient regio- and enantioselective difunctionalisation of 1,3-dienes with aryl iodides and stabilized C-nucleophiles (Scheme 59A).[105] Similar to Sigman's work, common and privileged ligands for asymmetric catalysis including Trost ligands and others, failed to give satisfactory results. Thus, chiral phosphoramidite ligands which performed well in allylic substitutions were tried. Ultimately, the best ligand was found to be H_8-BINOL-based phosphoramidite **L7i**, which afforded the products in up to 93% yield with 98% enantiomeric excess. It was found that the substitution pattern of the aryl groups had an effect on both regio- and stereoselectivities. Isotopic labelling studies proved the presence of a β-hydride elimination and reinsertion reaction to form an allyl–Pd intermediate, and a plausible mechanism was proposed (Scheme 59B).

In 2016, Luan developed an addition of 1,3-dienes with halogenated phenol biaryls **278**, giving the spirocyclohexadienones **279** with promising yield (Scheme 60).[106] For asymmetric naphthol substrate, chemo- and regioselectivity were excellent, and the 1,2-terminal addition products were the predominant adducts. Chiral phosphoramidite ligand **L7c** allowed for an asymmetric version of this reaction with up to 80% ee.



Scheme 60 Pd-Catalysed enantioselective arylation/alkylation of dienes with spirocyclohexadienones.

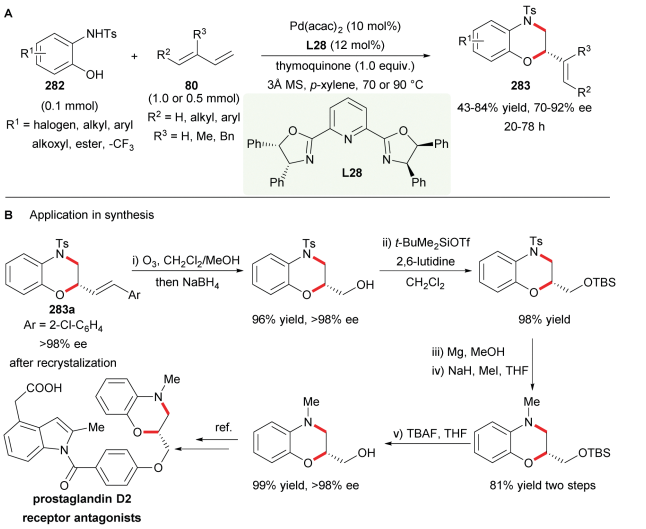


Scheme 61 Pd-Catalysed enantioselective arylation/alkylation of dienes with 2-(2-iodophenyl)malonate.

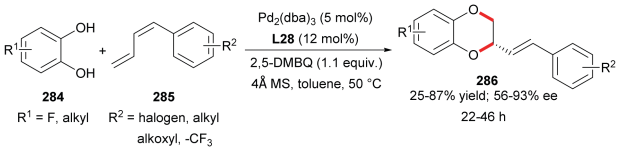
Recently, Gong developed a highly enantioselective addition of 1,3-dienes with 2-(2-iodophenyl)malonate ester **280** (Scheme 61).[107] BINOL-derived phosphoramidite ligands were examined in the optimization of the reaction conditions. The electron-deficient one **L7i** gave the best enantioselectivity. A linear correlation between the ee values of the products and those of the chiral ligands was observed, indicating that one molecule of phosphoramidite ligand is coordinated in Pd-complex, which results in enantiocontrol of the catalytic process.

3.2.1.4 Formation of C–N/C–O bonds. In 2018, the enantioselective aminohydroxylation of 1,3-dienes catalysed by Pd(II) was developed by Gong and co-workers.[175] The main challenge of this kind of reaction was that the ligand would diminish the electron-deficiency of the Pd(II)-complex, leading to poor reactivity of the catalyst; but the chiral ligand is necessary to induce the chirality of the products. In addition, the *N*-tosyl-2-aminophenols **282** were challenging substrates for this reaction since a mixture of two isomers might be afforded. Accordingly, searching for a suitable chiral ligand to provide high enantioselectivity and regioselectivity as well as enough activity was important. It was pleasant that the chiral pyridinebis(oxazoline) ligand **L28** could work well, providing the desired 3,4-dihydro-2*H*-1,4-benzoxazine derivates **283** with good regioselectivity and enantioselectivity (up to 92% ee) (Scheme 62A). This method could be applied to the synthesis of prostaglandin D2 receptor antagonists (Scheme 62B).[265]

3.2.1.5 Formation of C–O/C–O bonds. Recently, Gong and co-workers extended the Pd(II)-catalysed difunctionalisation to dihydroxylation with catechols **284** (Scheme 63).[176] The reaction also went through the similar Wacker type pathway as the aminohydroxylation. Chiral pyridinebis(oxazoline) ligand **L28** was used to provide promising yield and good enantioselectivity.



Scheme 62 Pd-Catalysed enantioselective amination/hydroxylation of dienes with *N*-tosyl-2-aminophenols.



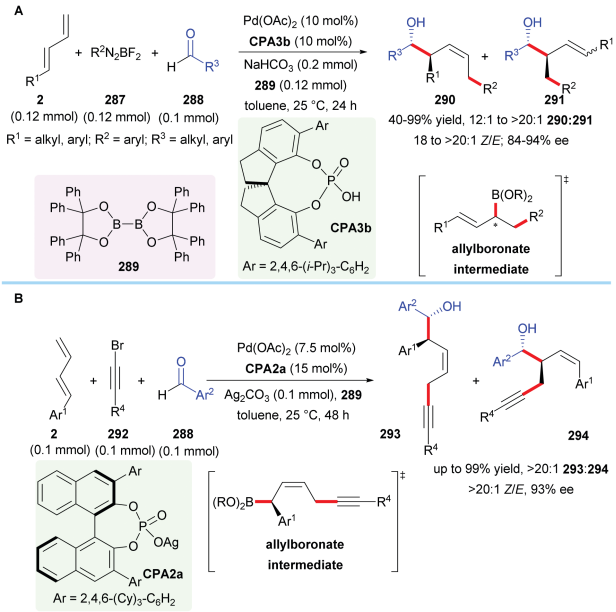
Scheme 63 Pd-Catalysed enantioselective hydroxylation of dienes with catechols.

Some bioactive compounds could be prepared from the products of this method.[266]

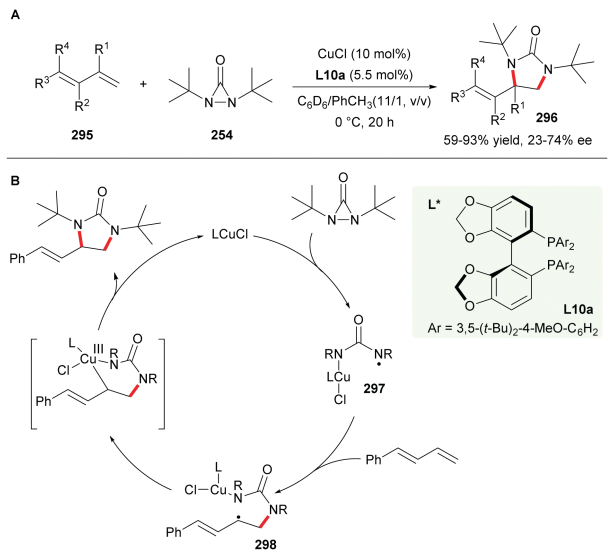
3.2.1.6 Formation of C–C/C–B bonds. Homoallylic alcohols are valuable synthetic motifs widely applied in a range of transformations, making them useful intermediates in organic synthesis. Common methods for the preparation of homoallylic alcohols depend on the attack of an allylic metal species to a carbonyl group. A novel method targeting enantiopure homoallylic alcohols relying on multicomponent carbonyl allylation was developed by Gong in 2016.[211] Octaphenyl-2,2′-bi(1,3,2-dioxaborolane) **287**, $B_2(Pin)_2$ **289**, were utilized to give the allylboronate intermediates, which then reacted with various aldehydes to give the homoallylic alcohols **290** (Scheme 64A). Chiral phosphoric acids served as a chiral anion phase transfer reagent, giving enantioselectivity up to 94% ee. High regioselectivity (1,4-addition) was observed, as well as a privileged *Z*-configuration of the products. Recently, the same group reported the enantioselective carbonyl allylation of aldehydes with alkynyl bromides **292** and dienes (Scheme 64B).[204] The desired products could be obtained in up to 99% yield and 93% ee.

3.2.2 Catalysed by Cu

3.2.2.1 C–N/C–N formation. In addition to the Pd-catalysed diamination of dienes, a Cu-complex could also be utilized in the diamination of dienes with di-*tert*-butyldiaziridinones **254**. In 2008, Shi utilized (*R*)-DTBM-Segphos and CuCl to explore the



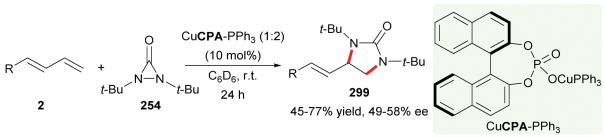
Scheme 64 Synthesis of homoallylic alcohols through diene difunctionalisation.



Scheme 65 Cu-Catalysed diamination of dienes through single-electron pathway.

enantioselective diamination of dienes (Scheme 65A).[116] It was believed that a single electron reaction process occurred in this reaction. Nevertheless, after the optimization of the chiral ligands, (*R*)-DTBM-Segphos **L10a** could improve the enantioselectivity up to 74% ee. A single electron process was proposed by the author (Scheme 65B). Terminal 1,2-addition products were the main products in account of being less sterically hindered and more stabilized single electron intermediate **298**.

Later, the same group tried to apply chiral anions instead of ligands to improve the enantioselectivity (Scheme 66).[205] BINOL-based chiral phosphoric acid **CPA2d** allowed for asymmetric diamination which proved the potential of this methodology;

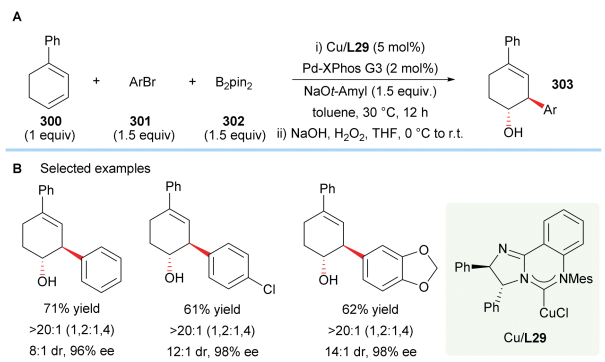


Scheme 66 Cu-Catalysed diamination of dienes using chiral cation.

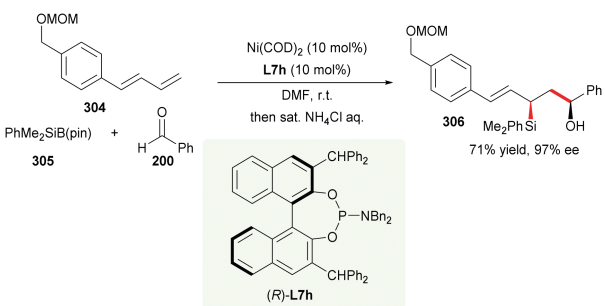
however, the enantioselectivity was slightly inferior compared to the chiral ligand.

3.2.2.2 C–B/C–C formation. A Pd/Cu-catalysed arylboration of dienes was developed by Brown and co-workers in 2017. The reaction initially occurred from the insertion of a Cu–B bond into the diene substrate, followed by cross coupling with an aryl halide catalysed by a Pd-complex (Scheme 67A).[177] It was found that proper matching of the ligand, Pd, and Cu could control the regioselectivity, thus both 1,2- and 1,4-addition products could be exclusively prepared under the same conditions by simply changing the ligand. An asymmetric version was realized by applying chiral Cu–carbene catalyst Cu/**L29**. Cyclic dienes could be enantioselectively transformed into 1,2-addition products in promising yield and with excellent enantioselectivity (96–98% ee) (Scheme 67B).

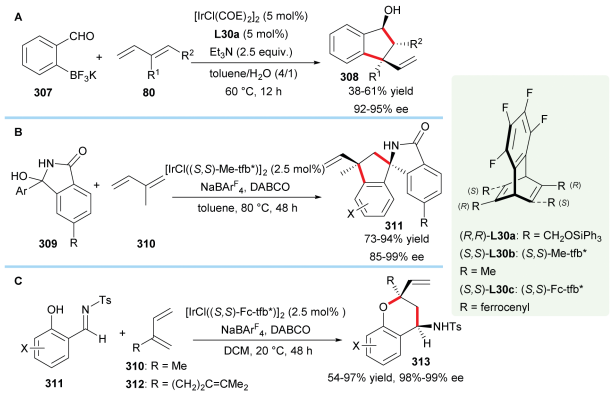
3.2.3 Catalysed by Ni. In 2012, a Ni-catalysed enantioselective three-component coupling of 1,3-dienes, aldehydes, and silylborane **305** was reported by Sato (Scheme 68).[108] Chiral monophosphoramidite **L7h** was utilized, giving the corresponding products in up to 97% ee. It was found that the



Scheme 67 Pd/Cu-Catalysed enantioselective difunctionalisation of dienes.



Scheme 68 Ni-Catalysed three-component enantioselective difunctionalisation of dienes.



Scheme 69 Ir-Catalysed enantioselective difunctionalisation of diene.

conversion was related to the electronic properties of the aldehyde: an electron-withdrawing group on the aryl group of the aldehyde negatively influenced the yield.

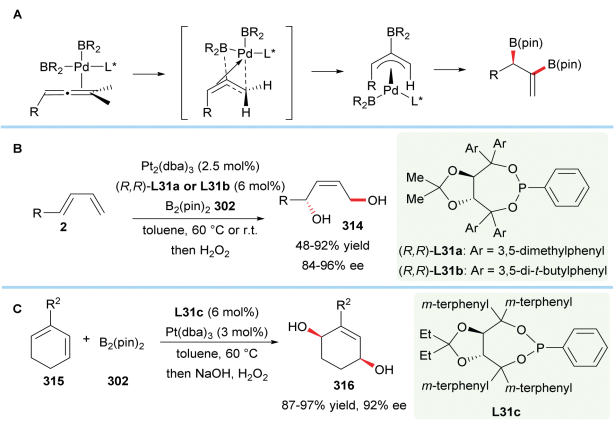
3.2.4 Catalysed by Ir. In 2007, Hayashi introduced C_2-symmetric tetrafluorobenzobarrelene **L30a** into their previous method for the 2-formylphenylboron **307** to 1,3-dienes,[267] realizing the asymmetric synthesis of 1-indanol derivates in good yield with high enantioselectivity (Scheme 69A).[178] In 2013, this catalytic system was applied to the addition of *N*-acyl ketimines **309** to dienes (Scheme 69B).[268] (*S*,*S*)-Me-tfb* **L30b** could allow the cyclisation reaction to occur with excellent enantioselectivity.[179] Later, the same group reported the enantioselective difunctionalisation of simple dienes with salicylimines **311** in combination with (*S*,*S*)-ferrocenyl-tfb* **L30c** (Scheme 69C).[180] The desired 4-aminochromanes **313** could be obtained under mild conditions with excellent yield and enantioselectivity.

3.2.5 Catalysed by Pt. Allylic diols are synthetically useful compounds, but the direct oxidation of 1,3-dienes is difficult. Thus, an indirect pathway *via* diboration of a diene, followed by oxidation has been developed.[34] In 2009, Morken applied the strategy utilized in the enantioselective diboration of allenes to the reaction involving dienes (Scheme 70A).[181] A Pt-complex, instead of a Pd-complex, showed high efficiency in this reaction. A Pt-$(BR_2)_2$ catalyst generated *in situ* initially undergoes migratory insertion to the diene, furnishing the π-allyl–Pt intermediate, which then goes through reductive elimination to give the 1,4-diboration products. Chiral TADDOL-derived ligand **L31** performed with high reactivity and good enantioselectivity for most of the *trans*-1,3-diene substrates (Scheme 70B). Later, Morken's group extended this diboration to cyclic diene substrates **315**.[182] The *syn*-addition products **316** were the predominant adducts with up to 92% enantiomeric excess (Scheme 70C).

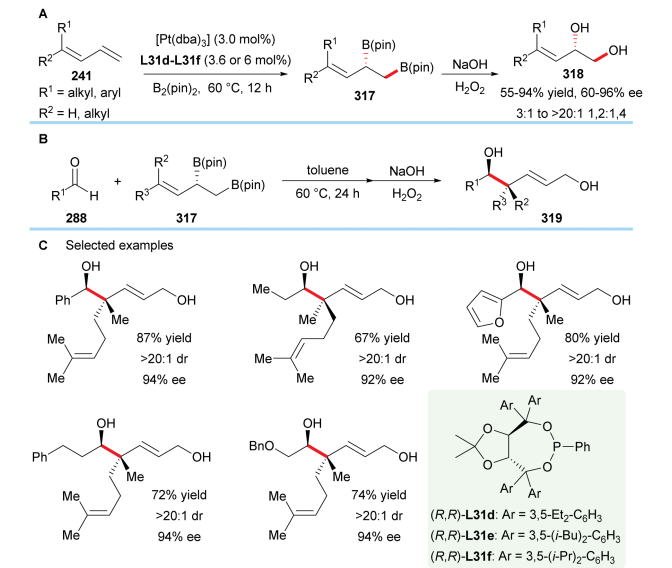
In 2012, the same group developed an enantioselective 1,2-diboration of diene using the same reaction conditions (Scheme 71A).[183] In order to change the regioselectivity, it was found that replacing the *trans*-1,3-dienes with *cis*-1,3-dienes could largely increase the ratio of 1,2-diboration products (3 : 1 to > 20 : 1 1,2/1,4 selectivity). With similar TADDOL-derived ligands **L31**, the enantioselectivity could be increased to 96% ee. In addition to oxidation, the diboration products could also participate in the allylboration of carbonyl compounds **288** (Scheme 71B), giving a large range of useful allylation products **319** (Scheme 71C).

In 2013, the same group applied the enantioselective diboration of 1,3-dienes to the synthesis of carbocyclic reactions *via* allylboration of dicarbonyl compounds with the diboration products (Scheme 72A).[184] Excellent diastereomeric ratio could be obtained using this reaction (> 15 : 1 dr). One of the synthetic uses of this method is illustrated in the synthesis of the pumilaside aglycon (Scheme 72B).

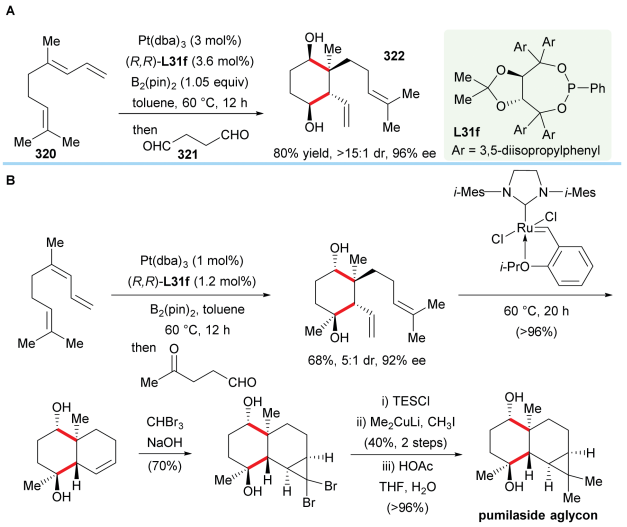
3.2.6 Catalysed by Fe. In 2012, Yoon's group developed a case of Fe-catalysed oxyamination of olefins with good yield and enantioselectivity (Scheme 73A).[185] The chemo-, regio- and enantioselectivity were excellent for the 1,3-diene substrates in the present of the bis(oxazoline) ligand **L32a**. The corresponding oxazolidine products **325a** could be utilized to prepare the enantiopure amino alcohols (Scheme 73B).



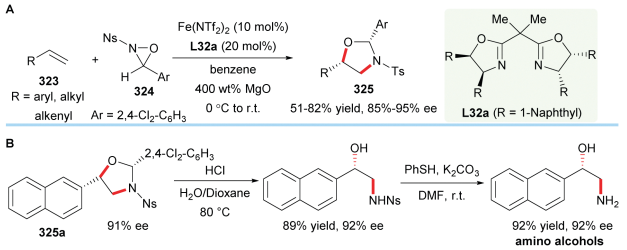
Scheme 70 Pt-Catalysed enantioselective 1,4-diboration of 1,3-dienes and cyclic dienes.



Scheme 71 Pt-Catalysed enantioselective 1,2-diboration of dienes.



Scheme 72 Pt-Catalysed enantioselective 1,2-diboration of 1,3-diene for the synthesis of the pumilaside aglycon.



Scheme 73 Fe-Catalysed enantioselective difunctionalisation of alkene and diene.

4. Formation of asymmetric allylic compounds from allenes

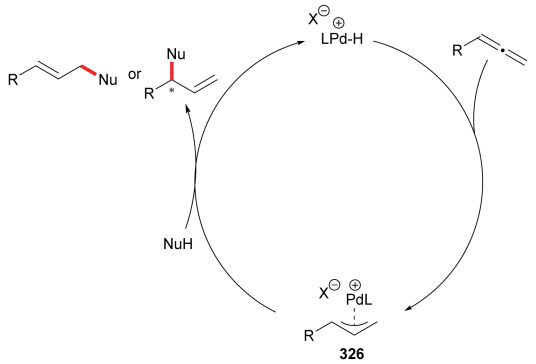
Allenes are highly reactive functional groups possessing two adjacent C–C double bonds. Since the first time allene derivate was prepared in 1887 by Burton and Pechmann,[269] many developments have been made to exploit the additions of allenes with carbon-based reagents and heteroatomic reagents, making it widely used in pharmaceuticals synthesis, polymer synthesis, biochemicals synthesis, *etc.*[33,270] In particular, catalytic hydrofunctionalisation and difunctionalisation of allenes are valuable methodologies, generating the useful and important allyl products. And although these methods were widely studied in the last century, the enantioselective version was rarely reported. At the end of last century, Larock established the enantioselective addition of aniline derivates to allenes *via* defunctionalisation; at the beginning of this century, the Trost's group developed the Pd-catalysed hydroalkylation of alkoxylallene.[70] Then, the enantioselective reactions catalysed by Pd, Rh, Ni and organocatalyst were frequently reported by the groups of Trost, Breit, Ma, Morken and many others. The enantiopure allyl compounds including alcohols, esters, amines, amides, thiols, ketones, nitrile, heterocycles, *etc.* were successfully prepared by this methodology with high yield, regioselectivity, and enantioselectivity.

4.1 Hydrofunctionalisation

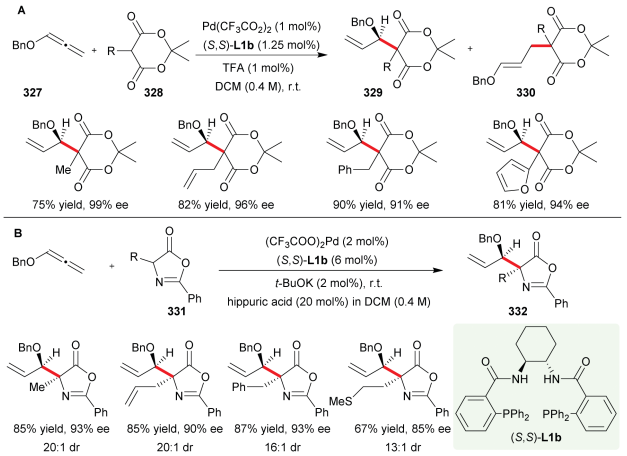
4.1.1 Catalysed by Pd. Palladium-catalysed hydrofunctionalisation of allenes has been demonstrated to be a powerful method for the synthesis of allylic compounds. And a distinct feature is its ability to form multiple kinds of chemical bonds such as C–C and C–X (N, O). These reactions involve the π-allyl–Pd intermediates, which was generated from the insertion of Pd–H to allene. It then undergoes nucleophilic substitution or reductive elimination to give the desired products. Most of the allene substrates are alkoxyl-substituted allenes while alkyl-substituted allenes are also used in some examples. The initial and important progress has been made by Trost's group.[70] A combination of Trost's ligands and control of the pH of the reaction system is largely responsible for the high reactivity and enantioselectivity. Subsequently, a dual catalytic system was introduced by Dixon and Luo.[194,271] The desired products in many cases could be transformed into other valuable building blocks and bioactive motifs, which make this area more attractive.

The general reaction route for the enantioselective hydrofunctionalisation of allenes catalysed by Pd is described in Scheme 74. Pd–H species are also very important in the catalytic cycle. The anionic hydride inserts at the middle carbon of the allene, giving the π-allyl–Pd intermediate **326**. The other part of the mechanism is almost identical to that for the diene. The origin of the regioselectivity and enantioselectivity will be demonstrated in the following reaction development section.

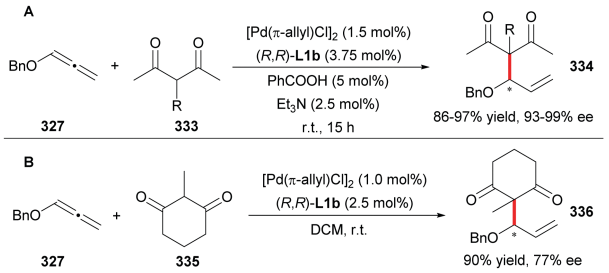
4.1.1.1 Formation of C–C bond. Compared with the alkylation of enolates, one of the most important C–C bond forming methods, the hydroalkylation of allenes represents a simple and convenient process for complex synthesis. This reaction is an atom-economic process where everything else is required only catalytically avoiding a stoichiometric amount of base and use of electrophiles such as organohalides and pseudohalides. In 2003, Trost and co-workers successfully developed an atom-economical process using the Pd-catalysed hydroalkylation of alkoxylallenes **327** with Meldrum's acids **328** and azlactones **331** (Scheme 75).[70] The reaction could be conducted in mild reaction conditions with Trost's ligand **L1b**, giving the desired products with good yield and excellent enantioselectivity. A plausible reaction process in which a



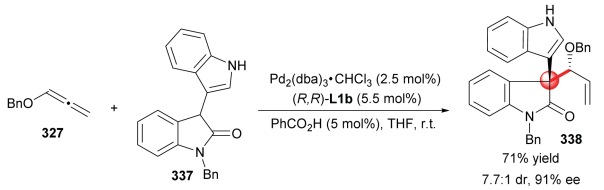
Scheme 74 Typical mechanism for Pd-catalysed hydrofunctionalisation of allenes.



Scheme 75 Pd-Catalysed enantioselective hydroalkylation of alkoxyl-allenes.



Scheme 76 Pd-Catalysed enantioselective hydroalkylation of alkoxyl-allenes with 1,3-diketones or cyclic diketones.



Scheme 77 Pd-Catalysed enantioselective hydroalkylation of alkoxyl-allenes with oxindoles.

π-allyl–Pd intermediate has been proposed. The alkoxy-substituted allenes were examined as substrates, which allow for the formation of branched adducts. Notably, it was found that the match between the pH of the conditions and pK_a of the pronucleophile had a significant impact on reactivity and selectivity. For more acidic pronucleophiles such as Meldrum's acid derivatives (pK_a is about 5), acidic conditions with trifluoroacetic acid were favoured, giving the corresponding products with good yield and up to 99% ee (Scheme 75A). While for the less acidic pronucleophiles like azlactones (pK_a is about 9), a basic environment is better to avoid the lack of nucleophiles which are generated by the enolization of the pronucleophiles (Scheme 75B). Nevertheless, excessively basic conditions are prohibited due to the structure of the ligand. It has been revealed that the deprotonation of the secondary amine in the chiral ligand would diminish enantioselective recognition.

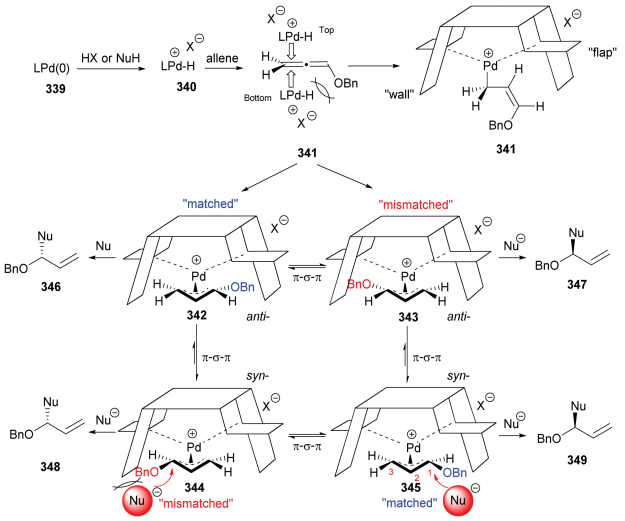
To illustrate the specific role of additives on the reactivity and selectivity, more experiments were conducted by Trost's group.[71] For the reaction of the more acidic Meldrum's acids and allenes, the addition of TFA was essential for good stereoselectivity, suggesting that the enol form of the nucleophiles behaved more stereoselectively than its conjugated base. This phenomenon supported the explanation that the less reactive nucleophiles enhance the selectivity of the two types of π-allyl–Pd intermediates by allowing a more sufficient π–σ–π equilibration. Additionally, acidic additives would react with Pd(0), generating the corresponding Pd(II)–H species, which prevented the oxidative addition of Pd(0) with the products. For the less acidic 1,3-diketones, a buffer system such as $PhCO_2^-$/Et_3NH^+ instead of TFA would be more compatible since it gives consideration to both the required concentration of the nucleophile and maintenance of pH to protonate the Pd(0) (Scheme 76A). With regards to cyclic diketones **335**, neutral conditions were utilized to maintain the enantioselectivity *via* retardation of the nucleophilic substitution of the π-allyl–Pd intermediate (Scheme 76B).

Oxindoles **327** are widely utilized in the construction of biologically relevant natural products, and are also applied to the enantioselective hydroalkylation of allene by Trost's group in 2011 (Scheme 77).[72] The normal Trost' ligand and the pre-catalyst $Pd_2(dba)_3$–$CHCl_3$ suited this reaction best. Although the oxinodole itself is acidic enough to promote this reaction, adding 10 mol% benzoic acid and 10 mol% Et_3N forming a buffer could improve both diastereo- and enantioselectivity. A large range of aryl groups installed on the oxindoles were tolerant to this method, except those that are *ortho*-substitution due to larger steric hindrance. This problem could be solved by introducing solvents with higher polarity such as DMF and MeCN to accelerate nucleophilic attack. Notably, in reactions involving *ortho*-substituents, the opposite diastereomer is favoured. In addition to 3-aryloxindoles, 3-alkyloxindoles were also tested. Due to being less acidic, highly polar solvents could increase the reactivity and employing Bn as a protecting group gave the best results. For almost all the circumstances discussed above, the normal Trost ligand was the most efficient. The products of this reaction could be applied to the synthesis of Gliocladin C.

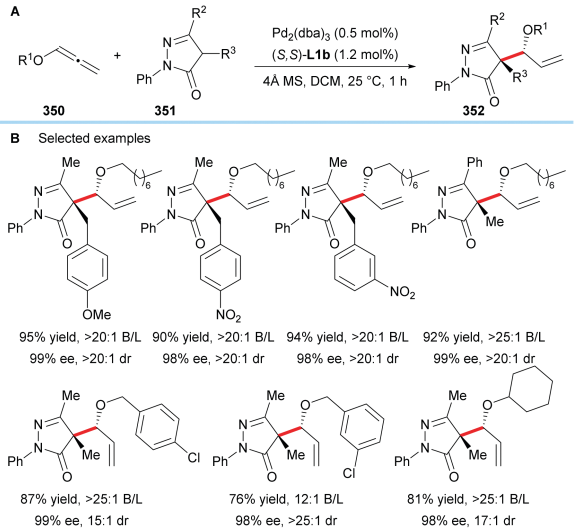
A convenient cartoon mnemonic (''wall and flap'' model) was introduced by Trost to demonstrate the mechanism of this type of reaction,[272] giving a clear explanation of the origin of the enantioselectivity (Scheme 78).

The Pd–H species **340** is furnished by the protonation (oxidative addition) of Pd(0) **339** with an acidic additive or pronucleophile. The co-produced conjugated base then performs as the counterion of the cationic Pd intermediates, forming an ion pair. The Pd–H species generated *in situ* inserts into the allene from the top face to give the *anti*-σ-allyl–Pd complex **341**. The top face is favoured due to the less steric hinderance.

Next, the transformation of the σ-allyl–Pd intermediate to a π-allyl–Pd intermediate occurs. Two pathways are possible, either matched **342** or mismatched **343**, and the latter has a



Scheme 78 The "wall and flap" model.



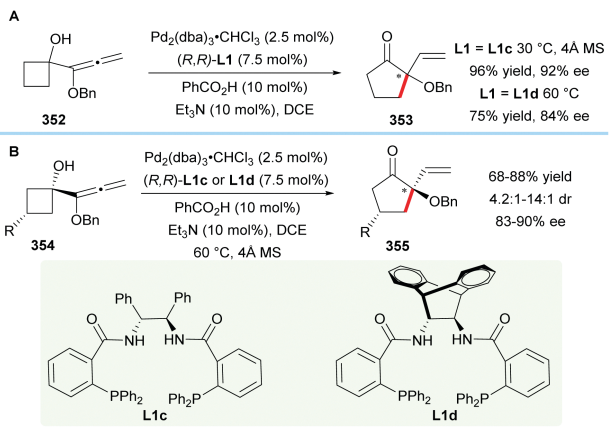
Scheme 79 Pd-Catalysed enantioselective hydroalkylation of alkoxylallenes with pyrazolones.

collision of the benzyloxy group with the "wall" of the ligand (steric hinderance). A π–σ–π conversion of **342** and **343** occurs to give the *syn*-intermediate **344** and **345**. Since the *syn*-π-allyl–Pd intermediate is thermodynamically more stable than the *anti*-one, the equilibrium is expected to prefer the formation of the former. A π–σ–π equilibrium could also occur between **344** and **345**. The nucleophile may attack all of the four π-allyl–Pd intermediates, but the trappings of **342** and **345** are favoured since the nucleophile could approach the intermediates from the "flap" side of the ligand in contrast to crossing the "wall" when approaching **343** and **344**. Furthermore, the *syn*-intermediate is the favoured configuration, thus the trapping of **345** will be the predominant pathway. In general, only the branched products could be obtained, suggesting that C^1 is the favoured position for attack rather than C^3. This may be because the benzyloxy substituent could stabilize the developing electron-positive C^1 in the transition state when the nucleophile is attacking, which increases the probability of the attack at this position.

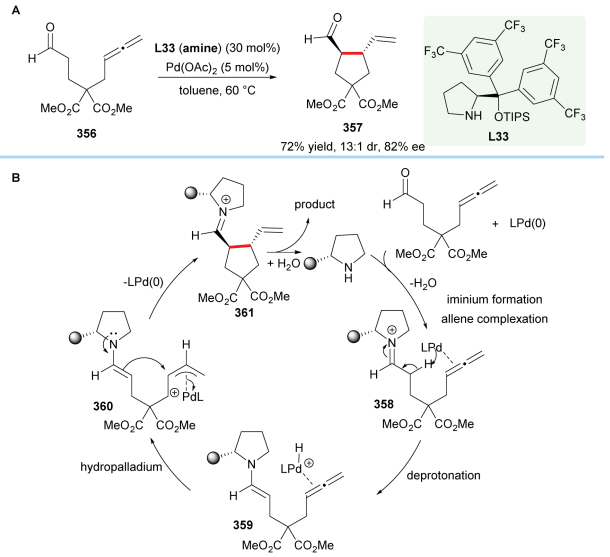
According to the reaction process discussed above, the enantioselectivity is determined by the equilibriums among the four intermediates (**342**, **343**, **344** and **345**). Providing chances for efficient equilibriums is an important way to enhance the enantioselectivity. For example, if it is the pronucleophile that protonates the Pd(0), the closely accompanied counterion will be the anionic nucleophile, which is very active and likely to attack the π-allyl–Pd intermediates as soon as they are generated. Thus, introducing some acid additives into the reaction system could improve the enantioselectivity since the less nucleophilic conjugated bases will displace the active nucleophile to be the counterion. This retards the attack of the nucleophile, leading to a more efficient equilibrium among the intermediates. In addition, nonpolar solvents could hinder the dissociation of the ion pair of the non-nucleophilic counterion and cationic intermediate, which will also slow down the attack, resulting in higher enantioselectivity.

In 2017, Jiang developed a highly stereoselective hydroalkylation of alkoxylallene with pyrazolones **351** derivates using Trost's ligand Pd catalyst (Scheme 79A).[73] In particular, this reaction did not involve other activators such as a buffer. This was possibly because of the inherently high acidity of the pyrazolones derivates. Plenty of reactions were conducted involving various alkoxylallenes and pyrazolones derivates, giving the corresponding products with excellent yield, diastereoselectivity and enantioselectivity (Scheme 79B). Notably, chiral Brønsted acids could also promote this reaction and will be discussed later.

After developing the asymmetric hydroalkylation of allenes in 2003 and 2005, Trost then applied it to the enantioselective version of Wagner–Meerwein's shift (Scheme 80A).[74] The group successfully realized the ring expansion of allenylcyclobutanols **352**, giving the α-alkenyl substituted enantiopure cyclopentanones. It was found that the Trost's ligand derivates **L1c** and **L1d** did best in catalysing the shift. Again, the buffer system $PhCOOH/Et_3N$ worked well in this reaction. The low yield caused by the ready hydrolysis of the substrate could be



Scheme 80 Pd-Catalysed enantioselective Wagner–Meerwein shift of allenylcyclobutanols.

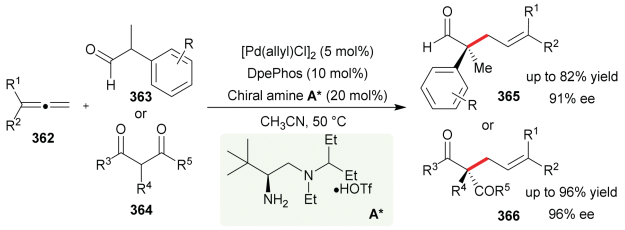


Scheme 81 Pd-Catalysed enantioselective intramolecular hydroalkylation of allenes.

overcome by adding 4 Å molecule sieves. Further investigation included trisubstituted substrates bearing one another group on the ring (Scheme 80B).[273] Several products bearing two chiral centres could be prepared with excellent yield, enantioselectivity and diastereoselectivity.

In 2012, Dixon's group developed an enantioselective intramolecular hydroalkylation of aldehyde-linked allenes **356** to furnish the products bearing vicinal stereocenters (Scheme 81A).[194] A Pd and amine dual catalytic system was essential to reactivity and enantioselectivity. The chiral amine activated the α-H of the carbonyl group by forming an enamine **358**;[274] the Pd complex would coordinate to the allene for generating the π-allyl–Pd intermediate **360** (Scheme 81B). The chiral pyrrolidine derivates were tested to realize an enantioselective version leading to the product with 82% ee. Besides aldehydes, some ketones could also be tolerated, giving excellent diastereoselectivity.

In 2017, Luo reported an enantioselective terminal intermolecular addition to allenes with α-branched β-keto-carbonyls **364** and aldehydes **363** catalysed by a chiral primary amine/achiral palladium system (Scheme 82).[271] It showed that electron-rich phosphine ligands benefit this process, and that the steric hindrance of the chiral amine is critical to the enantioselectivity. Several branched β-keto-carbonyls were tested and many of them gave the desired products with excellent yield



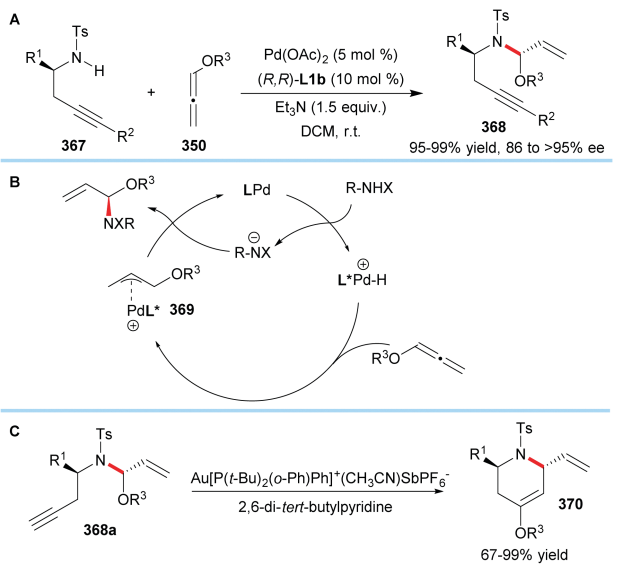
Scheme 82 Pd-Catalysed enantioselective hydroalkylation of allenes.

and enantioselectivity. Allenes bearing alkyl and aryl substituents were all tolerated by this method. Notably, an 1,1′-disubstituted allene could also give its corresponding products with moderate yield and excellent enantioselectivity (58% yield, 90% ee). In addition, several α-branched aldehydes were also examined and they successfully generated the desired adducts with good yield and enantioselectivity.

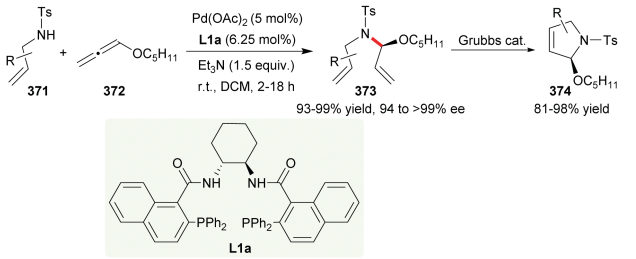
4.1.1.2 Formation of C–N bond. The Pd-catalysed hydroamination of allenes is a common method to construct C–N bonds. In 2012, Rhee's group reported a stereoselective synthesis of *N*,*O*-acetals **368** through the enantioselective hydroamination of alkoxylallenes (Scheme 83A).[75] Trost's ligand was combined with Pd to activate the allene. It was found that bulky allenes were more beneficial to the reactivity and diastereoselectivity. The reaction pathway shares similar properties with the hydroalkylation, in which a π-allyl–Pd intermediate is involved (Scheme 83B). The acyclic *N*,*O*-acetal could undergo cycloisomerization catalysed by a Au complex to generate other useful motifs (Scheme 83C).

Ts-Protected allylic amines could also be utilized in the enantioselective hydroamination of alkoxylallenes, giving the corresponding adducts with excellent yield and enantiomeric excess (Scheme 84).[76] The resulting adducts could be readily transformed into cyclic *N*,*O*-acetals *via* a ring-closing metathesis (RCM) reaction. Trost's ligand derivate was utilized to give enantioselectivity >99% ee. The conversions of the reactions are very high, suggesting the excellent reactivity of this system. For some bulky allylic amines, the yields are still 99%. Chiral allylic amine substrates were also examined to achieve a diastereoselective synthesis. The desired cyclic *N*,*O*-acetal products could undergo subsequent transformations to give many valuable motifs and building blocks.

In addition to N-heterocyclic *N*,*O*-acetals, the O-heterocyclic *N*,*O*-acetals could also be synthesized by a similar strategy. In



Scheme 83 Pd-Catalysed enantioselective intermolecular hydroamination of allenes with chiral homopropargylic amine.

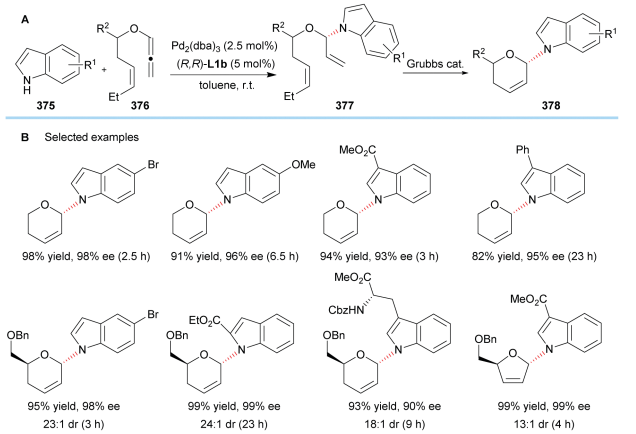


Scheme 84 Pd-Catalysed enantioselective intermolecular hydroamination of allenes with amino olefin.

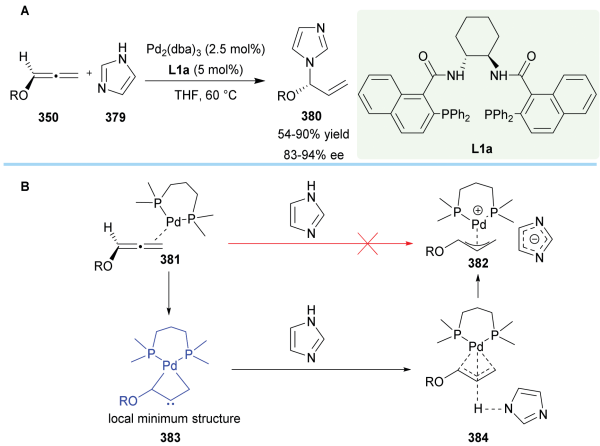
2018, Rhee's group developed a Pd-catalysed enantioselective hydroamination of alkoxyl allenes with indole **375** (Scheme 85A).[77] The subsequent RCM reaction would happen between the alkoxyl group and the residual olefin after addition. Trost's ligand was used and there was no other acid or base additive. Indoles bearing substituents on the phenyl ring or pyrrole ring were tolerated by this reaction with excellent yield and enantioselectivity (Scheme 85B). Some valuable bioactive molecules could be synthesized through this strategy.

In 2017, Rutjes's group reported the asymmetric hydroamination of alkoxylallene with N-heterocycles **379** (Scheme 86A).[78] Based on their DFT calculations, the author proposed an alternative pathway rather than the conventional Pd–H insertion, in which a π-allyl–Pd intermediate **382** is obtained. A carbene-like local minimum **383** that is generated from the coordination of the Pd to the allene is then protonated by the pronucleophile (Scheme 86B).

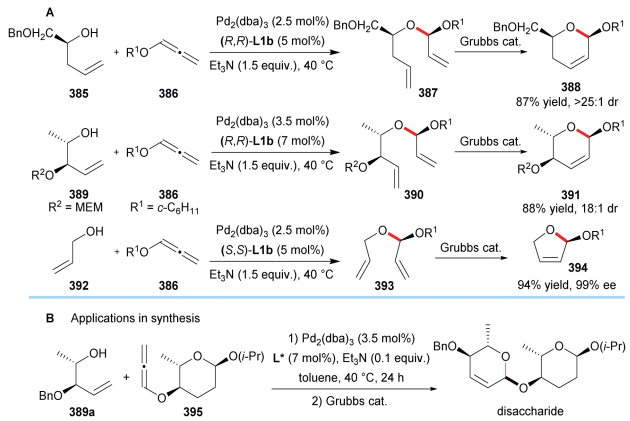
4.1.1.3 Formation of C–O bond. In 2014, the Rhee's group also applied similar strategies to those mentioned above for the formation of C–O bonds. Alkenyl alcohol was utilized for coupling alkoxylallenes to give the corresponding acetals, which could be treated with Grubbs catalyst to furnish the cyclic products (Scheme 87A).[79] Compared to N-based nucleophiles, the alcohols are less active reagents in the hydrofunctionalisation of allenes, but this problem was overcome by optimizing the reaction conditions. It was found that by conducting the reaction in toluene with $Pd_2(dba)_3$ and Trost's



Scheme 85 Pd-Catalysed enantioselective hydroamination of alkoxyl-allenes with indole.



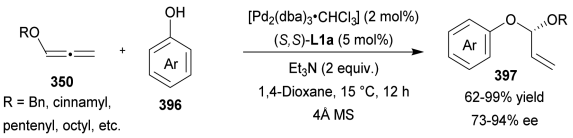
Scheme 86 Pd-Catalysed enantioselective hydroamination of alkoxyl-allenes with imidazole.



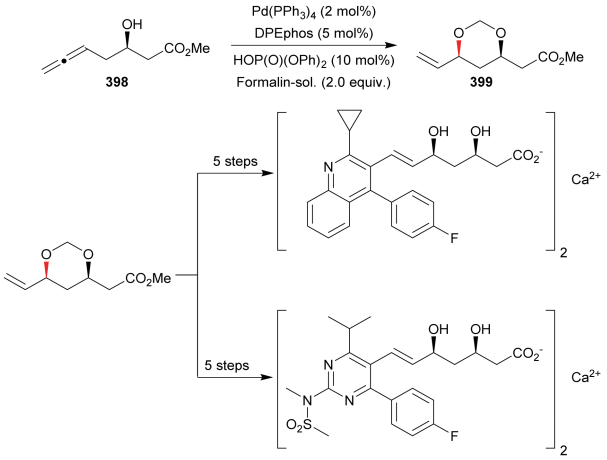
Scheme 87 Pd-Catalysed enantioselective hydroalkoxylation of alkoxyl-allenes.

ligand in the presence of Et_3N, could give the desired products with excellent yield and enantioselectivity. Several alcohols were tested to give the corresponding products with good yield and slightly decreased enantioselectivity. The cyclic acetal products bearing a residual olefin could undergo diastereoselective oxidation to give monosaccharides with excellent selectivity. Furthermore, this method could be applied to the synthesis of disaccharides containing 2,3,6-tri-deoxysugars (Scheme 87B).

Later, Cao's group utilized phenols as pronucleophiles to afford acyclic *O*,*O*-acetals with good yield and excellent enantioselectivity (Scheme 88).[80] Among the chiral ligands (sulfinylphosphine, BINAP, and Trost's ligand) they tested, the Trost's ligand derivates gave the best results in promoting this



Scheme 88 Pd-Catalysed enantioselective hydroalkoxylation of alkoxyl-allenes with phenol.



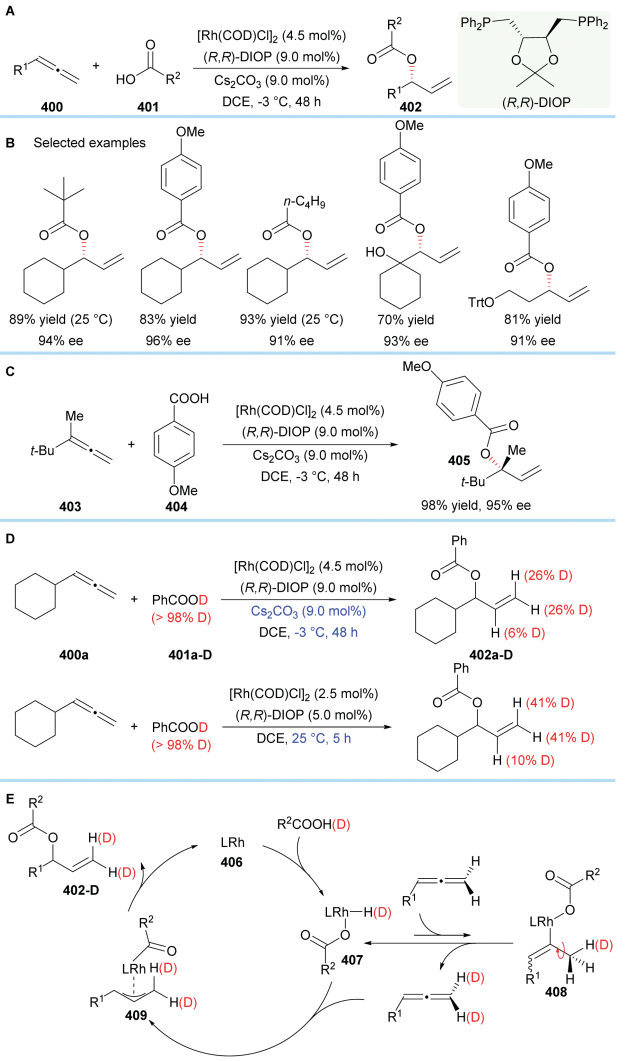
Scheme 89 Pd-Catalysed diastereoselective hydroalkoxylation of allene.

reaction. Various phenol derivates and alkoxylallenes were investigated and the cyclohexylmethyl-, cinnamyl-, and octyloxyallenes could also react successfully to give corresponding products in good yield and enantioselectivity.

One Pd-catalysed diastereoselective intramolecular hydroalkoxylation of allene was reported by Breit in 2018 (Scheme 89).[275] The allenyl alcohol substrate was reacted with Formalin-sol in the presence of $Pd(PPh_3)_4$, DPEPhos, and $HOP(O)(OPh)_2$ to give the 1,3-dioxane. The diastereoselective control experiment showed the reversibility of the reaction. It was hypothesized that the diastereoselectivity was achieved by the *syn*-attack of the semiacetal to the π-allyl–Pd intermediate. The 1,3-dioxane products could be transformed to Rosuvastatin Lactone and Pitavastatin Lactone after several steps of subsequent reactions.

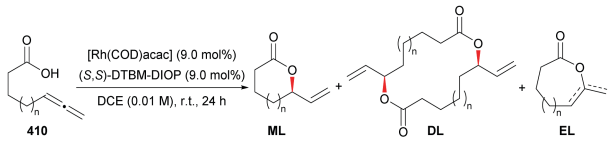
4.1.2 Catalysed by Rh. Most of the Pd-catalysed intermolecular enantioselective hydrofunctionalisations of allenes in the literature are restricted to alkoxylallene. Nevertheless, the inactivated alkyl or aryl substituted allenes are rarely utilized as substrates. In contrast, many of the examples in the Rh-catalysed hydrofunctionalisation of allene involve alkyl or aryl allenes. Breit and others have made great development in this area.[32] Various chemical bonds including C–O, C–S, C–N, and C–C bonds have been successfully constructed with excellent enantioselectivity and regioselectivity. The mechanism study of the Rh-catalysed hydrofunctionalisation of allene will be illustrated in the following section.

4.1.2.1 Formation of C–O bond. In 2011, Breit's group reported the Rh-catalysed hydrocarboxylation of allenes and alkynes. It was found that replacing the previous P,N ligand (2-(diphenylphosphinomethyl)pyridine) with a diphosphine ligand (DPEphos) possessing a bigger bite angle could reverse the regioselectivity from the linear to branched product, which are valuable and provide the possibility of constructing a chiral centre.[152] In the same year, the enantioselective hydrocarboxylation of terminal allenes with carboxylic acids was developed by the same group.[160] This method could be used to prepare the enantiopure branched allylic esters **402** with excellent enantioselectivity (up to 96% ee) (Scheme 90A).



Scheme 90 Rh-Catalysed enantioselective intermolecular hydrocarboxylation of allenes.

Although some chiral diphosphine ligands showed poor reactivity to this reaction, (*R*,*R*)-DIOP performed well with excellent reactivity and enantioselectivity. Reducing the temperature from 60 °C to −3 °C could improve the enantioselectivity, but the reactivity was lower. Adding a catalytic amount of Cs_2CO_3 could significantly increase the reactivity (from 63% to 100% yield). The scope of the substrates was large, and both aryl and alkyl groups on the carboxylate acids could be tolerated (Scheme 90B). Interestingly, more sterically hindered 1,1′-disubstituted terminal allenes could react smoothly, providing the allylic ester with a quaternary centre in high yield and with excellent enantioselectivity (98% yield, 95% ee) (Scheme 90C). A mechanism was proposed taking consideration of the isotopic labelling experiment (Scheme 90D). The reaction started with the oxidative addition of Rh(I) **406** with carboxylate acid **401**. Then, the generated Rh–H species **407** was inserted by the allene, furnishing the π-allyl–Rh intermediate **409**, which would undergo reductive elimination, providing the final products **402** and Rh(I). Notably, Rh–H species could interact with allene



n =	Combined yield	ratio (ML:DL:EL)	ee (ML)
8	47%	74:2:24	93%
10	76%	82:8:10	91%
11	79%	84:8:8	85%
13	62%	83:10:7	82%
16	68%	84:6:10	82%

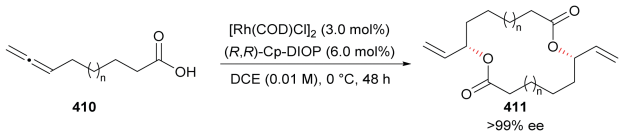
Scheme 91 Rh-Catalysed enantioselective intramolecular hydrocarboxylation of allenes.

to undergo a proton exchange *via* a σ-vinyl–Rh species **408**. This could explain the results of isotopic labeling experiments (Scheme 90E).

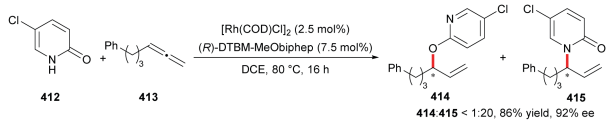
An important application of this method is enantioselective macrolactonization. The same group developed the Rh-catalysed intramolecular hydrocarboxylation of allenyl-substituted carboxylic acids **410** in 2016 (Scheme 91).[161] The modified chiral DIOP ligand, DTBM-DIOP, was utilized to improve the enantioselectivity (91% ee). Although there were some by-products such as enol lactones and diolides, the regioselectivity was generally good. Several lactones with different ring sizes (13, 15, 16, 17, 18, 20, and 21) could be easily furnished under mild reaction conditions with good yield and enantioselectivity.

The diolide was always observed in the enantioselective macrolactonization as a by-product, especially when the desired lactones were of moderate size. Thus, Breit's group then developed a method to synthesize these types of macrodiolides *via* the Rh-catalysed enantioselective dimerization of allenyl-substituted carboxylic acids (Scheme 92).[162] Chiral Cp-DIOP was utilized to facilitate the dimerization. It turned out that the enantioselectivity of this reaction was excellent (>99% ee) albeit the diastereoselectivities were only moderate.

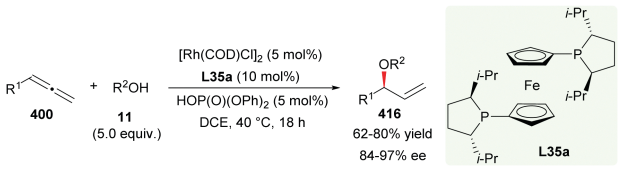
The Rh-catalysed enantioselective hydroalkoxylation of terminal allenes with 2-pyridones **412** using (*R*)-DTBM-MeObiphep as ligand was reported by the same group (Scheme 93).[150] Nevertheless, the *O*-allylated product **414** could be readily transformed to *N*-allylated products **415**, which we will discuss later.



Scheme 92 Rh-Catalysed dimerization of ω-allenyl carboxylic acid.



Scheme 93 Rh-Catalysed enantioselective addition of allenes with 2-pyridones.

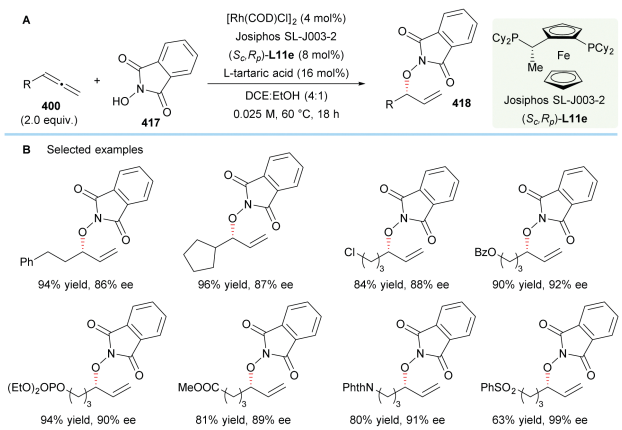


Scheme 94 Rh-Catalysed enantioselective hydroalkoxylation of allenes with alcohols.

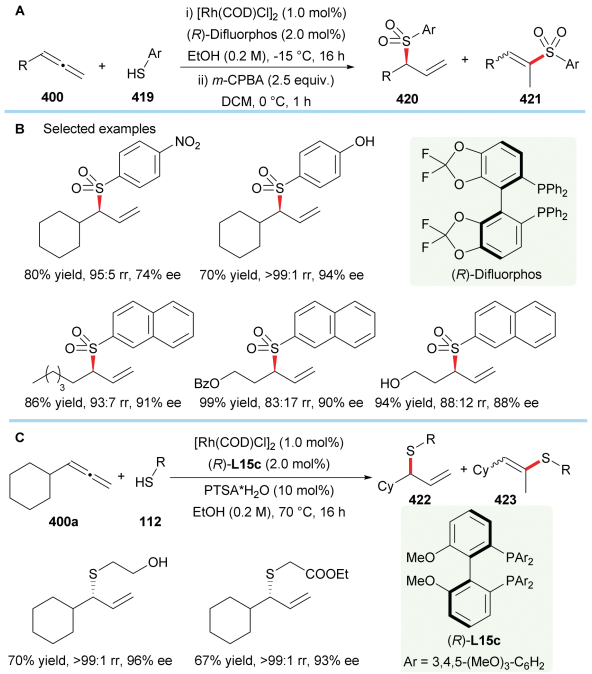
Applying alcohols in the Rh-catalysed hydroalkoxylation of allenes are attractive since alcohols are very common raw materials and the allylic ether products are valuable. However, compared with carboxylate acid, alcohols have poor acidity, which might prevent the initial oxidative addition of Rh(I). Thus, acidic additives must be utilized to facilitate the reaction. In 2016, Breit developed the enantioselective hydroalkoxylation of allenes with various alcohols utilizing chiral ferrocene-type ligand **L35a** to realize the enantio-control (Scheme 94).[195] Acidic diphenyl phosphate was used to promote the reaction. The enantioselective hydroalkoxylation of alkyne was also reported and we will discuss it in the next section. The mechanistic study showed there was a ligand exchange of the π-allyl–Rh intermediate with alcohol, which reproduced the phosphate and generated a similar intermediate to that of the hydrocarboxylation.

In 2018, the same group developed the enantioselective addition of *N*-hydroxyphthalimide **417** to allenes (Scheme 95A).[126] The products of the addition could be transformed to allylic alcohols and hydroxylamine compounds. Chiral Josiphos SL-J003-2 was tested to be the best ligand. A large scope of allenes and phthalimides were investigated and many of them could afford the corresponding products with good yield and enantioselectivity (Scheme 95B). This method could be utilized in the synthesis of Putaminoxin E.[276]

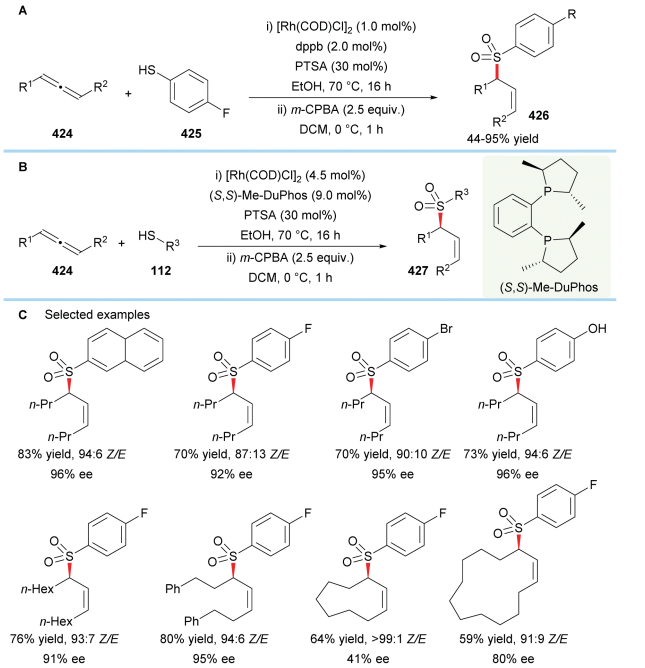
4.1.2.2 Formation of C–S bond. In order to construct more types of carbon–heteroatom bonds, Breit envisioned that thiols may be able undergo addition with allenes for C–S formation *via* the Rh-catalysed enantioselective hydrothiolation reaction (Scheme 96A).[117]



Scheme 95 Rh-Catalysed enantioselective addition of allenes with *N*-hydroxyphthalimide.



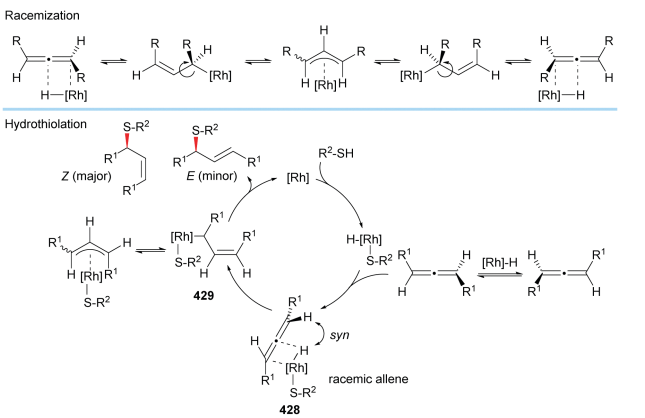
Scheme 96 Rh-Catalysed enantioselective hydrothiolation of terminal allenes.



Scheme 97 Rh-Catalysed enantioselective hydrothiolation of internal allenes.

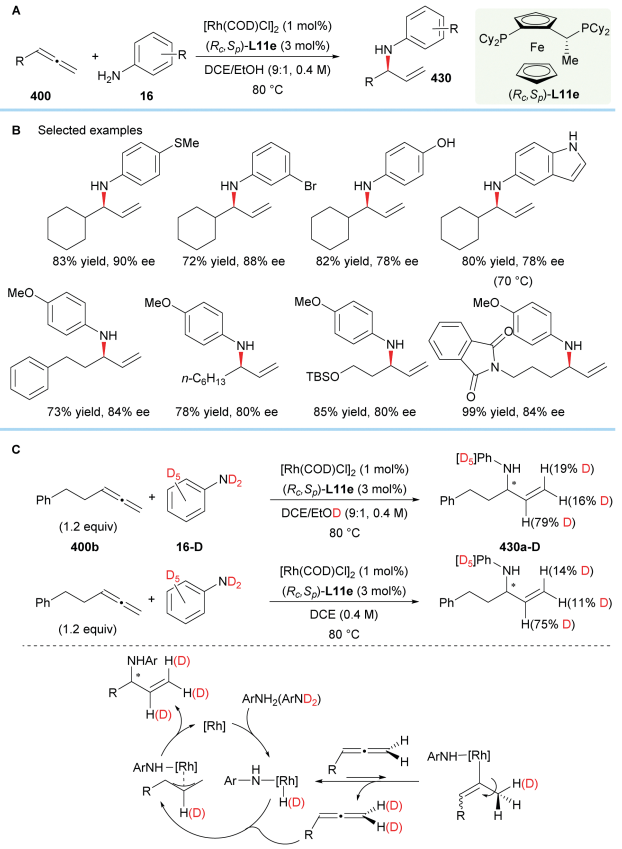
A series of chiral ligands were examined to fulfil this reaction, and it turned out that for the aryl thiols, the (*R*)-Difluorphos was the most suitable, giving excellent yield, regio- and enantioselectivity; while for the aliphatic thiols, (*R*)-3,4,5-(MeO)$_3$-MeOBIPHEP was the best (Scheme 96C). The allylic thioether products could be oxidized by *m*-CPBA to furnish the allylic sulfones, which are common motifs in biochemical molecules. A large range of different thioethers and sulfones could be prepared with excellent yield and selectivity (Scheme 96B). The isotopic labelling experiments gave an unexpected result showing that the deuterium incorporation only appeared at the 2-position, which was different from the results of the hydrocarboxylation.

Later, the same group extended the substrate scope to the more complicated racemic 1,3-disubstituted allenes. Their method could realize the *Z*-selective and enantioselective hydrothiolation of allenes (Scheme 97).[197] High yield and *Z*-selectivity could be achieved on the symmetric 1,3-dipropyl allenes in the presence of dppb and *p*-toluene sulfonic acid (PTSA) (Scheme 97A). While for the asymmetric dienes, most of them showed excellent regioselectivity and *Z*- or *E*-selectivity (Scheme 97B). (*S*,*S*)-Me-DuPhos was utilized to achieve the enantioselective version of this reaction, which led to excellent enantioselectivity (up to 96% ee) (Scheme 97C). The racemization and kinetic experiments suggested that the hydrothiolation was slower than the racemization. A dynamic kinetic resolution mechanism has been proposed (Scheme 98). The selective insertion of the Rh–H species to C–C double bonds of the allene is the origin of the *Z*-selectivity. The intermediate **429** could undergo either reductive elimination or intermolecular substitution to generate the final products.

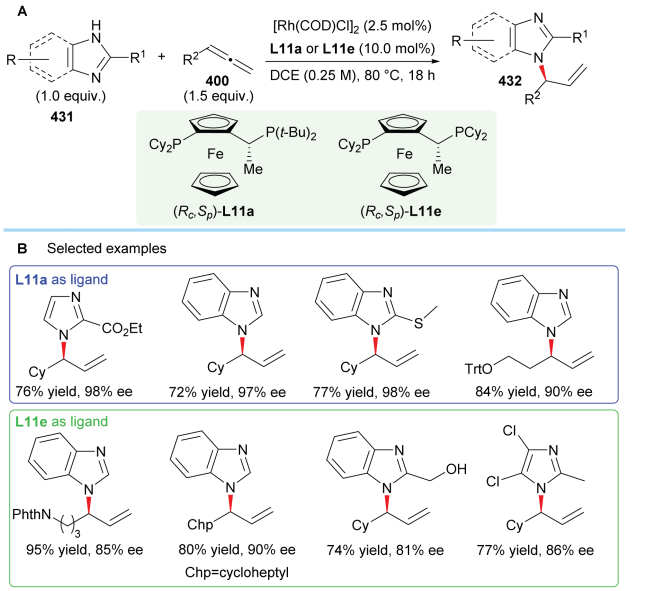


Scheme 98 Proposed mechanism for Rh-catalysed enantioselective hydrothiolation of internal allenes.

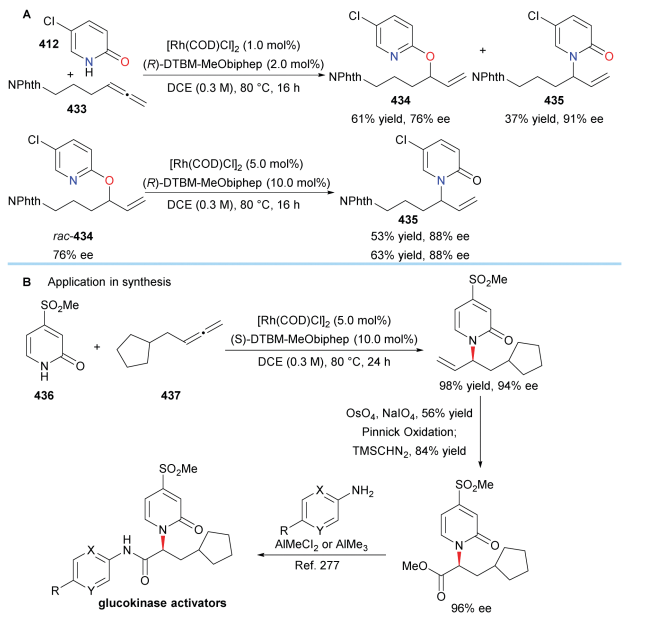
4.1.2.3 Formation of C–N bond. The Rh-catalysed hydroamination of allenes have been intensively investigated and various kinds of N-heterocycles and other N-based pronucleophiles have been developed in this area. In 2012, Breit described the enantioselective hydroamination of allenes with anilines (Scheme 99).[127] Chiral Josiphos **L11e** was used, providing enantioselectivity up to 90% ee. It was found that increasing the ratio of DCE : EtOH from 1 : 2 to 9 : 1 could improve the enantioselectivity (Scheme 99A). Various aniline derivates could all undergo reaction with good reactivity and enantioselectivity, but the alkyl amines could not react at all. Several allenes were also investigated and gave the corresponding products with good reactivity and enantioselectivity (Scheme 99B). The isotopic labelling experiments suggested



Scheme 99 Rh-Catalysed enantioselective hydroamination of allenes with anilines.



Scheme 100 Rh-Catalysed enantioselective hydroamination of allenes with imidazoles.



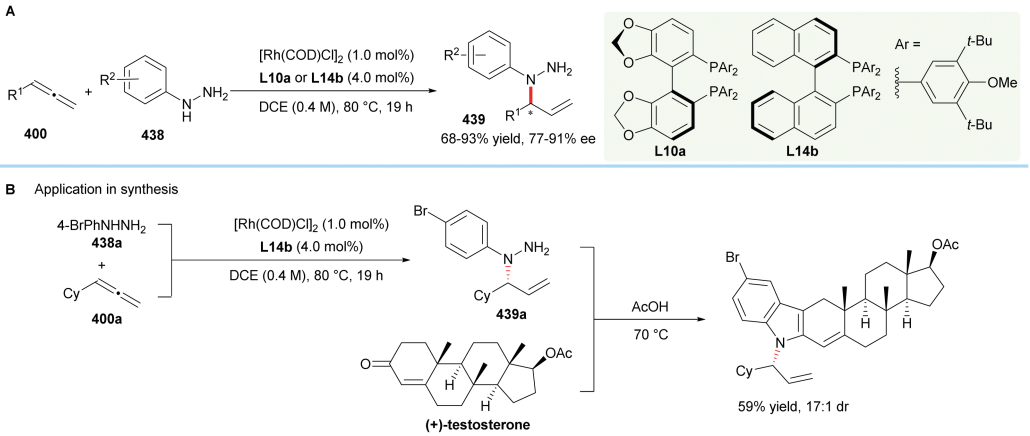
Scheme 101 Rh-Catalysed enantioselective hydroamination of allenes with 2-pyridones.

that the reaction may go through a similar pathway as to that of the hydrocarboxylation, and a reasonable catalytic cycle was proposed (Scheme 99C).

In 2014, Breit developed a regiodivergent and stereoselective hydroamination of terminal allenes and imidazoles (Scheme 100).[128] The regioselectivity was mainly determined by the catalyst: Rh-Josiphos favoured the branched products, while the Pd-dppf provided linear-selectivity. Chiral Josiphos SL-J009-1 **L11a** and Josiphos SL-J003-1 **L11e** were utilized to give the desired enantioselectivity, providing the products with up to 98% ee (Scheme 100A). The symmetric imidazoles were chosen as pronucleophiles in order to avoid the challenge of N^1- and N^2-selectivity. This catalytic system has good functional group tolerance and a variety of substituents (for example, free hydroxyl groups, esters, halides or methylthio groups) on the imidazole were compatible (Scheme 100B).

Later, the same group developed the hydroamination of 2-pyridones **412** to terminal allenes. DTBM-MeObiphep was used as a chiral ligand (Scheme 101).[150] As mentioned earlier, this reaction had high chemoselectivity since the *O*-allylated products would readily transform to *N*-allylated products (Scheme 101A). This could be explained by DFT calculation, which showed the *N*-allylated products were more stable than the *O*-allylated ones. However, *O*-allylated products would be predominant by decreasing the load of catalyst and shortening the reaction time, suggesting that the they were the kinetic products. Notably, it was found that the electron-withdrawing group on the ring promoted the conversion, while the electron-donating group gave a relatively low yield. A catalytic cycle was proposed which was also the typical type for these Rh-catalysed hydrofunctionalisation. This reaction could be utilized in the synthesis of glucokinase activators (Scheme 101B).[277]

The hydroamination with aryl hydrazines **438** was developed by Breit in 2015,[118] affording the corresponding products with high enantioselectivity and perfect N^1-selectivity (Scheme 102A). The chiral DTBM-Segphos **L10a** and DTBM-BINAP **L14b** could be



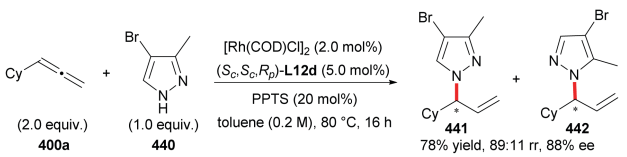
Scheme 102 Rh-Catalysed enantioselective hydroamination of allenes with aryl hydrazines.

used in the catalytic system. Several experiments were conducted to study the mechanism. Control experiment using 1-methyl-1-phenylhydrazine gave only trace amounts of the desired products, suggesting the poor reactivity of N^2. The isotopic labelling experiments showed there might be only one kind of isomer for the hydrometallation as per the example with the hydrothiolation. Notably, the Rh–H species were detected by NMR, which supported the typical mechanism. Some products of this reaction could be used in other valuable transformations such as the indolization of (+)-testosterone acetate (Scheme 102B).

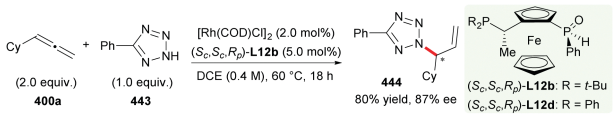
Pyrazoles **440** were also tried as substrates in the hydroamination of allenes by the same group (Scheme 103).[134] The two tautomeric pyrazoles may give different *N*-selective products. However, high N^1-selectivity was obtained in the presence of PPTS and JoSPOphos ligand **L12d**. It was found that the addition of PPTS plays a critical role on the regioselectivity of N^1 and N^2 products. A wide range of monosubstituted terminal allenes could react with different substituted pyrazoles with excellent enantioselectivity and reactivity. Notably, 1,1′-disubstituted allenes were also tested, giving the corresponding products with lower yield and enantioselectivity. (*R*)-Ruxolitnib could be easily prepared based on this reaction.

N-heterocyclic compounds bearing more nitrogen atoms were also investigated by the same group. In 2015, tetrazoles were utilized as pronucleophiles, successfully giving the desired products with good yield and enantioselectivity in the presence of the classic chiral JoSPOphos ligands **L12b** (Scheme 104).[135]

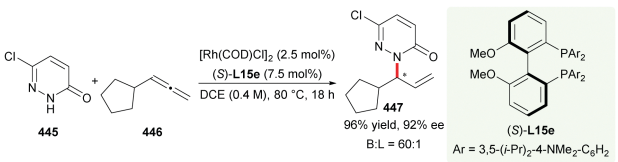
Breit continued their works on the enantioselective addition of terminal allenes with N-heterocycles. In 2017, they developed the enantioselective hydroamination with pyridazinones **445**,



Scheme 103 Rh-Catalysed *N*-selective and enantioselective hydroamination of allenes with pyrazoles.



Scheme 104 Rh-Catalysed *N*-selective and enantioselective hydroamination of allenes with tetrazoles.

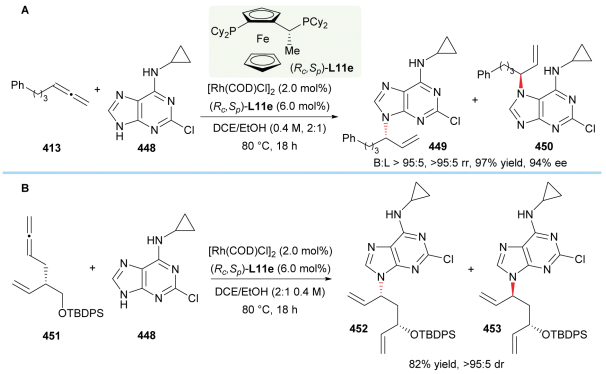


Scheme 105 Rh-Catalysed *N*-selective and enantioselective hydroamination of allenes with pyridazinones.

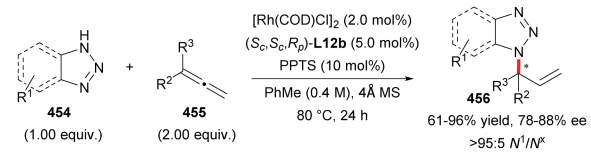
furnishing branched N^2-allylated products in good yields with high regio- and enantioselectivity (Scheme 105).[151] Chiral 3,5-diisoprop4-dimethylamino-substituted MeObiphep **L15e** was used to facilitate the reaction. The regioselectivity was also excellent: the ratios of B : L were up to 99 : 1.

Purine **448** was also utilized as a pronucleophile. In 2016, Breit developed an enantioselective hydroamination of purine and terminal allene (Scheme 106A).[129] With the addition of chiral Josiphos 003-1 **L11e** and Rh precatalyst, the reactions could proceed with good enantioselectivity, N^9-selectivity and regioselectivity (branched). The Pd-dppf system give the linear products as the major isomer. This reaction could be employed in the synthesis of the HIV drug abacavir. The chiral allene substrate could also be used to give the diastereoselective products with up to 98 : 2 dr (Scheme 106B).

Triazoles **454** were also investigated in the enantioselective hydroamination of allenes and alkynes by the same group. In 2014, the JosPOphos ligand was employed in the highly *N*-selective addition of allenes with triazoles.[136] Other chiral JosPOphos derivatives were examined to achieve the enantioselective version, reported in 2018 (Scheme 107).[139] It turned out that **L12b** was the best choice. In addition, adding PPTS



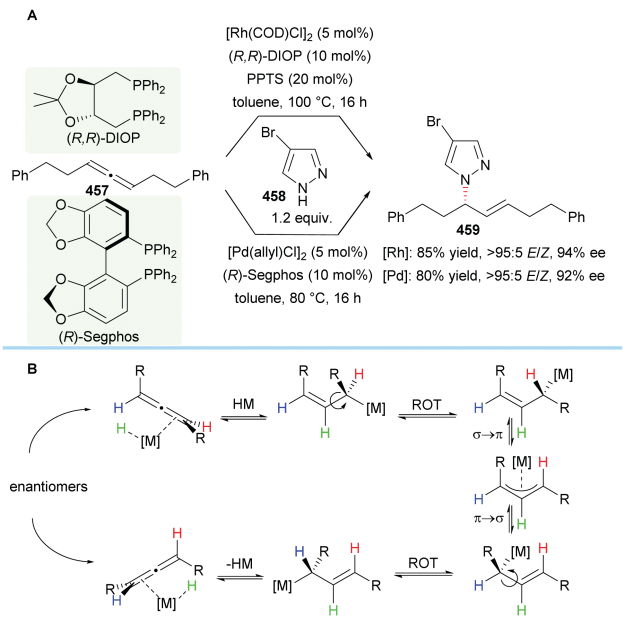
Scheme 106 Rh-Catalysed *N*-selective and enantioselective hydroamination of allenes with purines.



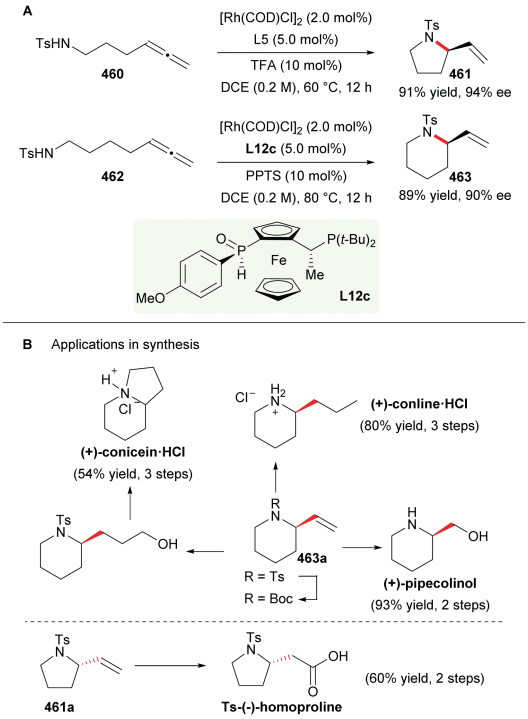
Scheme 107 Rh-Catalysed *N*-selective and enantioselective hydroamination of allenes with triazoles.

and 4 Å molecule sieve could improve the reactivity and enantioselectivity.

Pd- and Rh-catalysed hydroaminations of racemic internal allenes with pyrazoles **458** *via* a dynamic kinetic resolution was recently developed by Breit. It was found that both the (*R*)-Segphos-Pd and (*R*,*R*)-DIOP-Rh system were able to catalyse this reaction with high yield and selectivity. A large scope of allenes and pyrazoles were investigated (Scheme 108A).[119] The reaction



Scheme 108 Rh-Catalysed enantioselective hydroamination of internal allenes with pyrazoles *via* dynamic kinetic resolution.

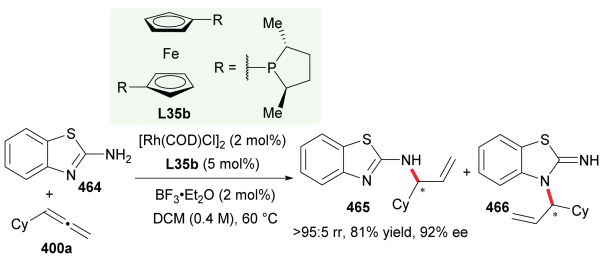


Scheme 109 Rh-Catalysed enantioselective intramolecular hydroamination of allenes.

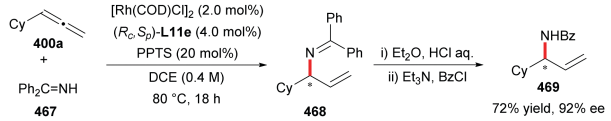
often occurred at the sterically least hindered *N*-atom (N^1). Transformation between two isomers of the racemic raw materials was proposed through the σ–π–σ isomerization (Scheme 108B).

Recently, an enantioselective intramolecular hydroamidation of allenes **460** and **462** catalysed by Rh-**L12c** was reported by the same group (Scheme 109A).[137] Notably, the reaction temperature was slightly lower than the other Rh-catalysed hydrofunctionalization of allenes they had developed before. Many N-heterocyclic compounds were successfully prepared by this method with high yield and enantioselectivity (Scheme 109B). Some products could undergo subsequent reactions to afford other useful molecules.

The N-selective hydroamination of allenes with 2-aminothiazoles **464** was developed by Breit in 2019 (Scheme 110).[196] Chiral **L35b** was utilized to promote the reaction. The allylated products were the predominant, probably due to less steric hinderance. Several monosubstituted allenes were involved in this reaction, while the 1,1′-disubstituted ones showed poor



Scheme 110 Rh-Catalysed enantioselective hydroamination of allenes with 2-aminothiazoles.

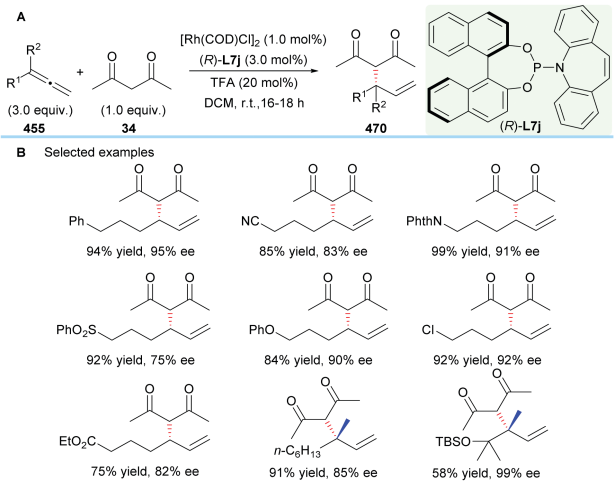


Scheme 111 Rh-Catalysed enantioselective hydroamination of allenes with benzophenone imine.

reactivity but high enantioselectivity. One of the products could be used in the synthesis of chiral isothoureas.

Due to the volatility and toxicity of gaseous NH_3 and the high basicity of the sp^3 hybridized nitrogen atom which deactivates the oxidative addition, there are few examples of the directed enantioselective addition of ammonia to allenes. Thus, Breit took advantage of the relatively stable imine **467**, which served as the succedaneum of ammonia, to furnish the desired products (Scheme 111).[130] Chiral Josiphos ligand **L11e** was suitable for this reaction, giving the adducts in high yield and enantioselectivity.

4.1.2.4 Formation of C–C bond. As we have mentioned before, construction of the C–C bonds *via* the hydrofunctionalisation of allenes has always been challenging, since the low acidity of the C–H retards the initial oxidative addition step in the catalytic cycle. Nevertheless, Breit reported a brilliant development in 2014 to realize the hydroalkylation of allenes using β-keto acids.[278] Next, other 1,3-dicarbonyl compounds were also tried, such as β-keto esters and amides, and 1,3-diketones, forming the allylic C–C bonds with good regioselectivity. The first enantioselective hydroalkylation of allenes was developed later by the same group (Scheme 112A).[109] 1,3-dicarbonyl compounds were utilized as pronucleophiles to remedy the poor acidity of the C–H bond. In addition, TFA was added to offer the acid conditions facilitating the oxidative addition. Chiral phosphoramidite ligand **L7j** coordinated to the Rh allowed for enantiocontrol. The asymmetric 1,3-dicarbonyl compounds could yield the corresponding products bearing two chiral centres but with poor diastereoselectivity. A number of functional groups on the allenes were tolerated such as phenyl ethers, sulfonyl groups, esters, phthalimidoyl, and nitriles (Scheme 112B). Notably, 1,1′-disubstituted allenes were also investigated, giving the corresponding products with excellent yield and enantiomeric excess.

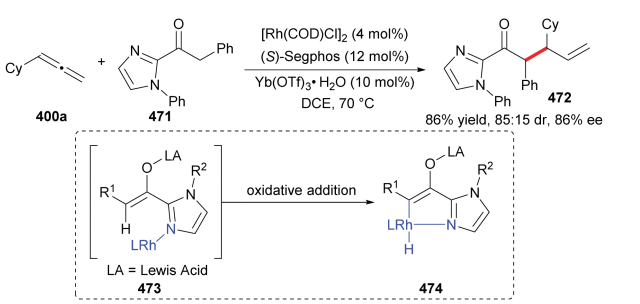


Scheme 112 Rh-Catalysed enantioselective hydroalkylation of allenes with 1,3-diketones.

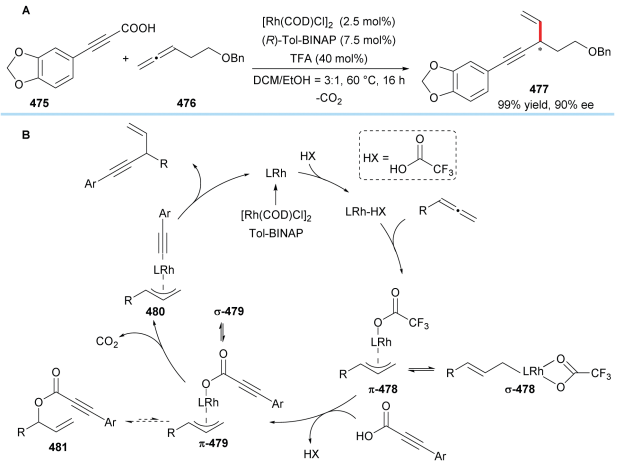
In 2018, Kang's group developed the an enantioselective hydroalkylation of allenes with 2-acyl imidazoles with good to excellent yield, enantioselectivity, and diastereoselectivity (Scheme 113).[120] They used a suitable Lewis acid to enhance the acidity of the α-H of pronucleophiles. The imidazole group attracts the Rh in order to facilitate the oxidative addition of C–H with it by forming a dentate intermediate **474**. (*S*)-SegPhos was chosen to be the best chiral ligand and $Yb(OTf)_3$ served as the suitable Lewis acid. Various allenes and imidazoles were investigated, and many of them underwent reaction smoothly with high selectivity. 1,1′-Disubstituted allenes were tested to construct the all-carbon quaternary centres. Control experiments showed that the absence of either a Lewis acid or imidazole group would halt the reaction. It was found that the hydrogen could be exclusively add to C^2 according to isotopic labelling experiments. Kinetic experiments suggested that the formation of the Rh–H species was the rate-determining step.

In the same year, the enantioselective decarboxylative alkynylation of terminal allenes with arylpropiolic acids was developed by Breit (Scheme 114A).[145] TFA and (*R*)-Tol-BINAP were utilized to provide high reactivity and enantioselectivity. A catalytic cycle was proposed based on mechanistic study (Scheme 114B). The Rh(I) first interacts with TFA to form the Rh–H species, which is inserted into the allene to give the π-allyl–Rh intermediate **π-478**. Then, a ligand exchange occurs between the pronucleophile and the intermediate **π-478**. The generated **π-479** then undergoes decarboxylation to give alkyne complex **480**, which underwent subsequent reductive eliminate affording the final product and Rh(I). There might be an equilibrium between the intermediate **π-479** and ester **481**. According to the crossover experiment, the decarboxylation was more likely to happen if the aryl was more electron-rich. Although it was not a 100% atomic economic method, CO_2 is a nontoxic gas and no by-products remained in the reaction mixture.

Recently, the same group developed the Rh-catalysed intramolecular hydroarylation of allenes **482**. Chiral DTBM-Segphos



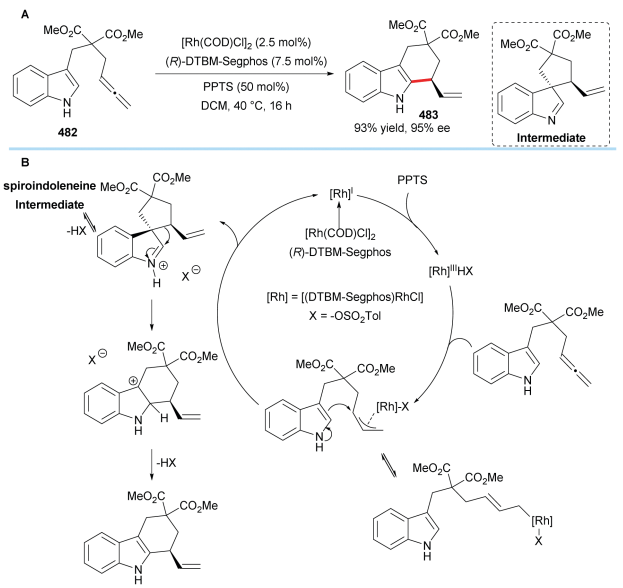
Scheme 113 Rh/Lewis acid catalysed enantioselective hydroalkylation of allenes with 2-acyl imidazoles.



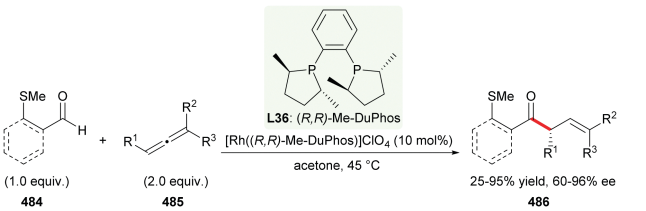
Scheme 114 Rh-Catalysed enantioselective decarboxylative alkynylation of allenes with arylpropiolic acids.

was used to promote the reaction, giving excellent enantioselectivity (Scheme 115A).[121] The reaction pathway was a little bit different from the typical Rh-catalysed hydrofunctionalisation. The π-allyl–Rh intermediate would undergo an intramolecular substitution to generate the spiroindoleneine intermediate, which would soon rearrange to the final 1-vinyltetrahydrocarbazole products **483** (Scheme 115B).

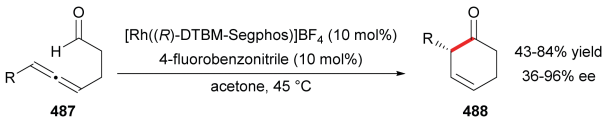
Preparing β,γ-unsaturated carbonyl compounds through the hydrofunctionalisation of allenes is challenging, since the carbons in the carbonyl groups rarely perform as nucleophiles. In 2008, Willis successfully developed the enantioselective intermolecular hydroacylation of internal allenes (Scheme 116).[198] The β,γ-unsaturated ketones **486** could be prepared with high enantioselectivity in the presence of [Rh((*R*,*R*)-Me-DuPhos)]ClO_4. Notably, no Lewis acid or base additive was needed in this reaction.



Scheme 115 Rh-Catalysed enantioselective cyclization of 3-allenyl indoles.



Scheme 116 Rh-Catalysed enantioselective hydroacylation of internal allenes.

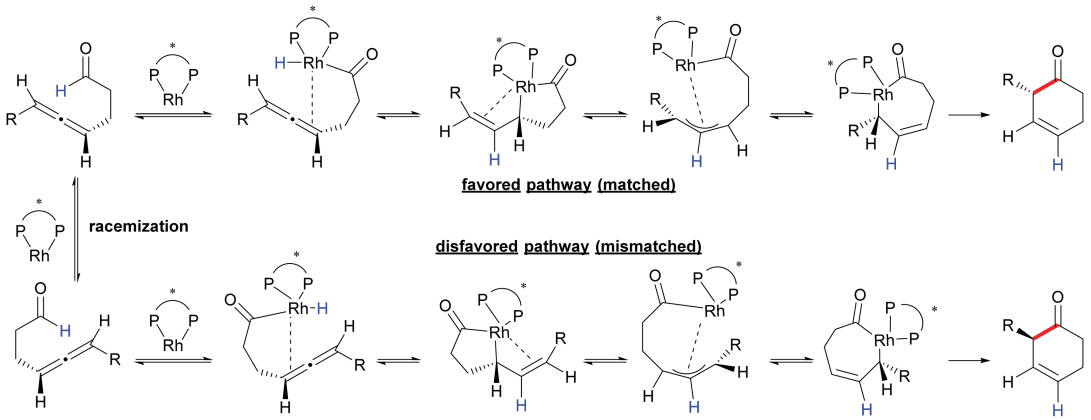


Scheme 117 Rh-Catalysed enantioselective intramolecular hydroacylation/cyclization of allenals.

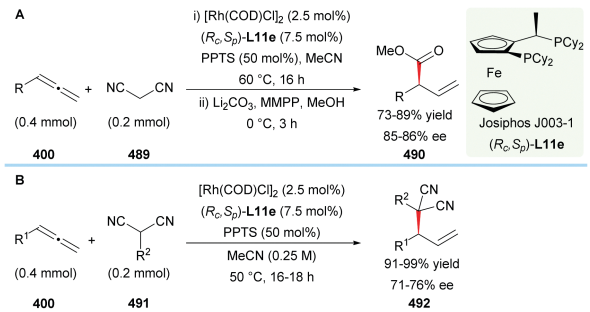
Recently, Sato developed the intramolecular hydroacylation of racemic allenals **487** (Scheme 117).[122] (*R*)-DTBM-Segphos performed well as a chiral ligand. The acetone was chosen as solvent since it could improve the yield and enantioselectivity. In addition, adding a nitrile could improve the efficiency and enantioselectivity of the reaction. The mechanism study suggested that the dynamic kinetic resolution model could explain the enantioselectivity (Scheme 118). The oxidative addition of the carbonyl C–H bond to the Rh(I) catalyst was the initial step of the reaction. And the final products were afforded *via* reductive elimination.

Besides hydroacylation, using malononitriles as pronucleophiles could also prepare the β,γ-unsaturated carbonyl compounds. In 2018, Breit reported the Rh-catalysed hydroalkylation of allenes, followed by the oxidative cleavage, giving the desired β,γ-unsaturated carbonyl products (Scheme 119A).[131] The Josiphos ligand J003-1 **L11e** was introduced to realize the enantioselectivity. α-Substituted malononitriles could also be tolerated in this reaction (Scheme 119B).

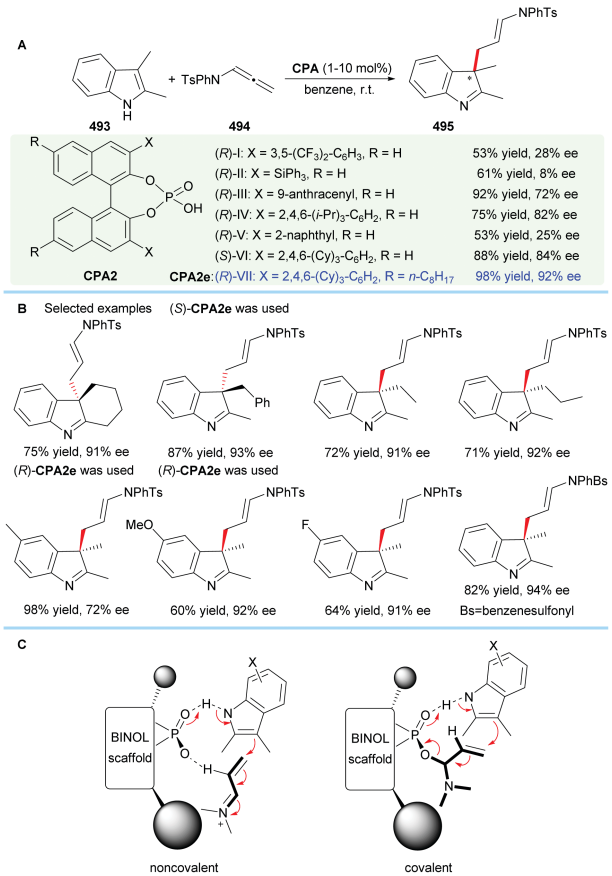
4.1.3 Catalysed by organocatalyst. Since Toste developed the first chiral Brønsted acid catalysed intramolecular hydroamination of 1,3-dienes and allenes in 2011,[38] important progress has been made recently with regard to the metal-free catalysed hydrofunctionalisation of allenes. In 2014, Bandini's group developed a chiral phosphoric acid catalysed intermolecular enantioselective hydroarylation of allenamides **494** with indoles. It was found that the terminal addition product was predominately formed (Scheme 120A).[206] Various 2,3-substituted indoles for dearomatization were investigated under the optimal catalytic reaction conditions. The corresponding dearomatization products were obtained smoothly with high reactivity and excellent enantioselectivity (Scheme 120B). Additionally, two possible activation models were proposed to understand the catalytic reactivity, regioselectivity and enantioselectivity: noncovalent and covalent of CPA–allenamide interactions (Scheme 120C). The former was realized through the hydrogen bond between the transient α,β-unsaturated iminium intermediate and the



Scheme 118 Proposed dynamic kinetic resolution model for Rh-catalysed enantioselective intramolecular hydroacylation/cyclization of allenal.



Scheme 119 Rh-Catalysed enantioselective hydroalkylation of allenes with malononitriles.



Scheme 120 Chiral phosphoric acid catalysed enantioselective hydroarylation of allenamides with indoles.

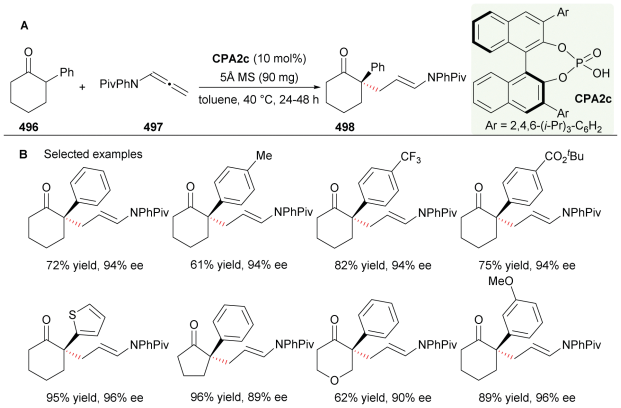
phosphoryl oxygen atom; while the latter was the result of the temporarily generated C–O bond in the intermediate. These proposed models could explain the enantiodiscriminating process.

Subsequently, α-branched ketones were applied in the asymmetric addition of allenamides **497** using the chiral phosphoric acids catalytic system developed by the Toste group (Scheme 121A).[207] A large range of α-branched ketones bearing an aryl or conjugated substituent were investigated and gave the desired products with a chiral quaternary stereocenter (up to 95% yield, 96% ee) (Scheme 121B). The prepared products could be easily transformed to other valuable motifs such as the core structure of amaryllidaceae-type alkaloids.

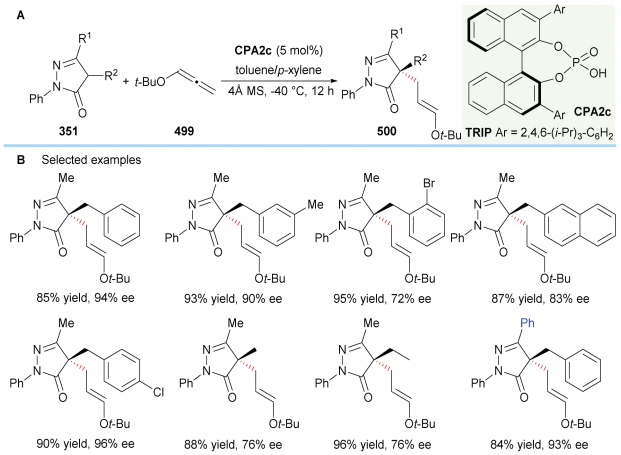
Jiang also described a CPA-catalysed asymmetric hydroalkylation of alkoxylallene **499** and pyrazolones **351** derivates (Scheme 122A).[73] The corresponding products could be afforded with good yield (up to 96%) and enantioselectivity (up to 97% ee) (Scheme 122B). The catalytic cycle the author proposed supported the covalent bond model for the activation of the reaction.

The asymmetric hydroalkylation of allenamides with pyrazolones catalysed by chiral phosphoric acid **CPA2b** were developed by Wang in 2018 (Scheme 123A).[208] Various pyrazolones were investigated and most of them could undergo the reaction successfully with excellent yield and good enantioselectivity (Scheme 123B). Gram-scale synthesis was conducted, and the yield was slightly decreased while the enantioselectivity was maintained. The noncovalent activation model was proposed based on the configuration of products and the reactivity of the allenamides.

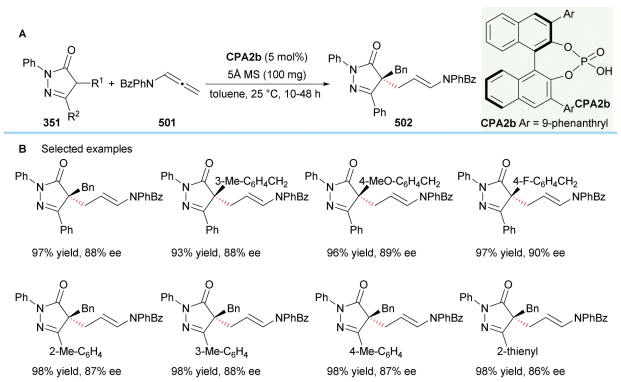
The 1,3,3′-trisubstituted allenes are challenging raw material for the asymmetric hydrofunctionalisation since the stereo-effect of the substrate may influence the enantioselectivity. Dynamic kinetic asymmetric transformations (DyKATs) could turn the racemic raw materials into enantiopure products. The chiral



Scheme 121 Chiral phosphoric acid catalysed enantioselective hydroalkylation of allenamides with α-branched cyclic ketones.

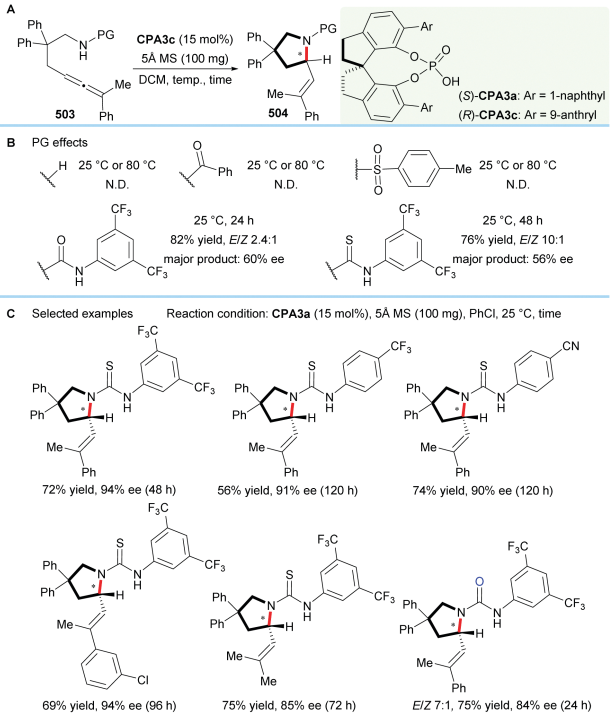


Scheme 122 Chiral phosphoric acid catalysed enantioselective hydroalkylation of alkoxyallenes with pyrazolones.



Scheme 123 Chiral phosphoric acid catalysed enantioselective hydroalkylation of allenamides with pyrazolones.

phosphoric acid catalysed intramolecular DyKATs of allenyl thiourea was recently developed by the Liu group (Scheme 124A).[210] The optimizing experiment showed that the SPINOL-derived **CPA3a** could give the corresponding products with the best *E*/*Z* selectivity and enantioselectivity. Various protecting groups were tried, and



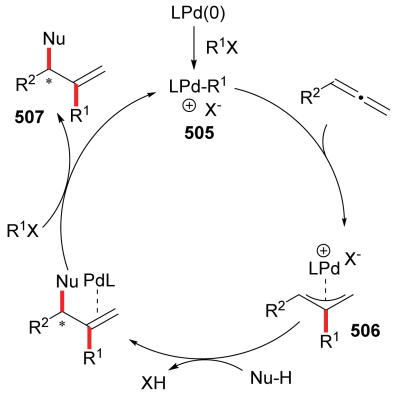
Scheme 124 Chiral phosphoric acid catalysed enantioselective intramolecular hydroamination of allenes.

the thiourea substrates could be transformed with good *E*/*Z* selectivity (Scheme 124B). Several various racemic allenes were tested and most of them gave excellent results (Scheme 124C). A control experiment utilizing the enantiopure allenes as substrates suggested a similar racemization rate for the two enantiomers. And, the stereo-property of the substrates did not affect the enantioselectivity of the reaction. Based on these facts, a mechanistic model involving an allyl cation/N-anion pair was proposed, which revealed a dynamic kinetic asymmetric hydroamination process.

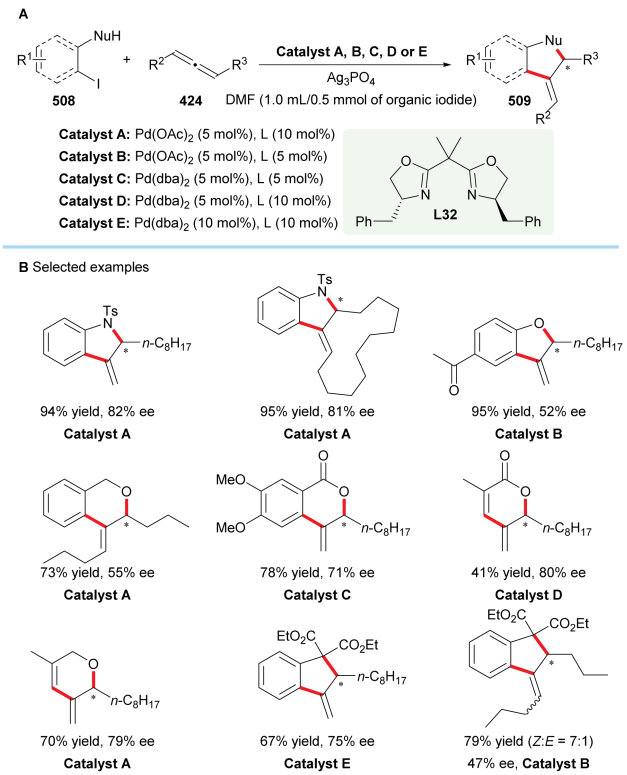
4.2 Difunctionalisation

4.2.1 Catalysed by Pd. Pd-Catalysed difunctionalisation of allenes has been frequently investigated. The typical reaction pathway is similar to the hydrofunctionalisation of allenes (Scheme 125). In general, the Pd(0)-precatalyst first undergoes oxidative addition with an aryl or vinyl halide, generating the Pd(II)–R^1 catalyst **505**. The catalyst then undergoes a migratory insertion with the allene substrate, in which the R group will attach to the middle carbon of the allene, furnishing the multiple substituted π-allyl–Pd intermediate **506**. Next, the (pro)nucleophile attacks the allylic group, giving the Pd(0)-complex. Finally, oxidative addition of Pd(0) occurs again to reproduce the Pd(II)–R^1 catalyst **505**.

4.2.1.1 Formation of C–C/C–N bonds. Based on their previous work concerning the Pd-catalysed hetero- and carboannulation of allenes in 1991,[279] Larock and co-workers developed an enantioselective carboannulation of allenes with *ortho*-substituted aryl halide **508**,[186] which could serve as a complementary method

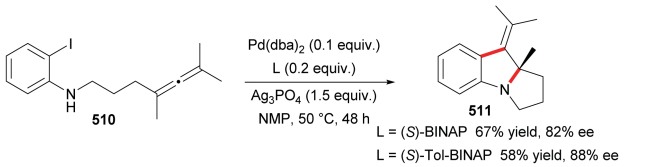


Scheme 125 Typical mechanism for Pd-catalysed difunctionalisation of allene.



Scheme 126 Pd-Catalysed enantioselective difunctionalisation of allenes.

to allylic substitution by taking advantage of the π-allyl–Pd species for chirality induction (Scheme 126). Among the chiral ligands tested in the optimization experiment, the bisoxazoline ligand **L32** gave the best results (Scheme 126A). The Ag_3PO_4 served as an important additive, which could trap the I^- to promote the reaction. It was found that the nucleophile tended to attack at the more substituted carbon of the π-allyl–Pd intermediate due to the electronic properties of the intermediate and the catalyst. Nitrogen-, oxygen-, and carbon-based (pro)nucleophiles are amenable to this method, all of which could give the corresponding products in promising yield and enantioselectivity (Scheme 126B).[187]

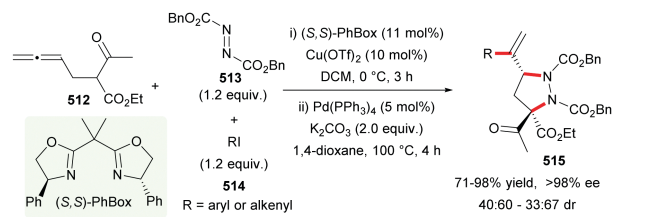


Scheme 127 Pd-Catalysed enantioselective intramolecular arylation/amination of allenes.

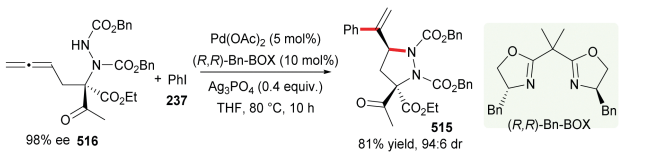
In 2002, Hiroi's group utilized the enantioselective difunctionalisation of allenes in the synthesis of chiral indole derivatives.[146] The allenyl aniline derivatives could undergo intramolecular cyclizations in the presence of Pd-complex. (*S*)-(−)-BINAP and (*S*)-Tol-BINAP were found to be efficient chiral ligands to give moderate yield and good enantioselectivity (Scheme 127).

In 2004, based on their previous works on the difunctionalisation of allenes[280] and the development of enantioselective aminations of 2-keto-esters, Ma's group proposed a novel Pd/Cu-catalysed one pot tandem addition/cyclization of dibenzyl azodicarboxylate **513**, 2-(2′,3′-lkadienyl)-β-keto esters **512**, and phenyl/vinyl halide **514** (Scheme 128).[188] The pyrazolidine products are valuable building blocks that appear in the synthesis of bioactive compounds. The chiral bisoxazoline ligand allowed for the asymmetric addition under mild conditions with excellent yield and enantioselectivity.

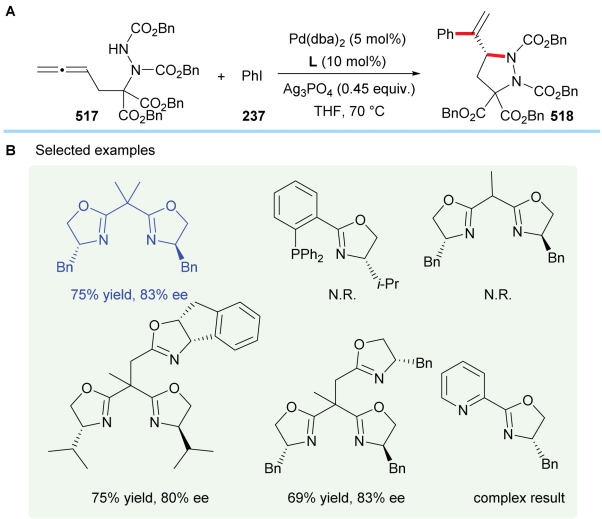
Three years later, the same group used the enantiopure allenylhydrazine **516** as starting materials to prepare pyrazolidine derivatives (Scheme 129).[189] Besides the optically active substrates, the chiral bisoxazoline ligand was another factor that could control the stereo-configuration of the products. Compared to the Pd/Cu-catalysed three-component addition method, the diastereomeric ratios in this method were improved significantly (95 : 5 *vs.* 67 : 33 dr). In addition, the enantioselectivity was up to >99% ee. It was found that the absolute configuration of the newly formed chiral centres relied



Scheme 128 Pd/Cu-Catalysed addition of dibenzyl azodicarboxylate and phenyl halide to allenes.



Scheme 129 Pd-Catalysed enantioselective arylation/amination of enantiopure allenylhydrazine.



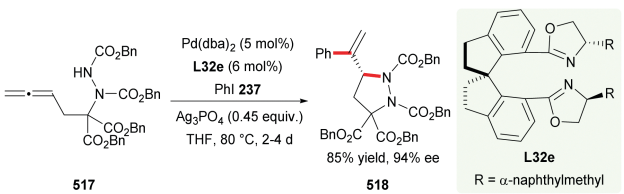
Scheme 130 Pd-Catalysed enantioselective arylation/amination of racemic allenylhydrazines.

on the configuration of the substrates, and the level of diastereo- and enantioselectivity was influenced by both the chiral ligand and substrates.

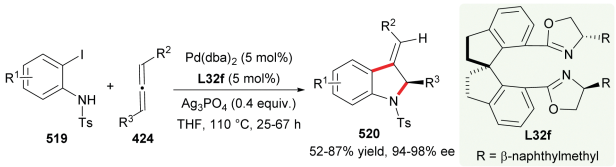
In their previous work, enantiopure substrates were needed to obtain high enantioselectivity. Thus, they reported a method involving racemic 3,4-allenylic hydrazines **517** as substrates, giving the same products in 75% yield and with 83% ee in the presence of Pd/**L** catalyst (Scheme 130).[190]

Although the chiral bisoxazoline ligand Bn-BOX allowed the enantioselective reaction to proceed smoothly, the enantioselectivity of these reactions was moderate (no more than 84% ee was found). This may be attributed to the *syn*/*anti*-complexity caused by the substituent at the 2-position of the π-allyl–Pd intermediate. Thus, new chiral ligands bearing other structural motifs were tried to further improve the enantioselectivity. The author used the BOX ligand bearing a spiro-skeleton due to its excellent performance in previous asymmetric syntheses.[281,282] It was found that both the spiro-skeleton and bulkiness of the substituent on the ligand can influence the enantioselectivity; the bulky α-naphthylmethyl spiro-BOX ligand **L32e** gave the best results (94% ee) (Scheme 131).[191]

The same group also applied the spiro-BOX ligand to the enantioselective cyclization of allenes with 2-iodoaniline (Scheme 132).[283] The bulky (R_a,*S*,*S*)-β-naphthylmethyl spiro-BOX **L32f** gave the indole products enantioselectively with up to 98% ee. A number of terminal and internal allenes were



Scheme 131 Pd-Catalysed highly enantioselective arylation/amination of allenylhydrazines.



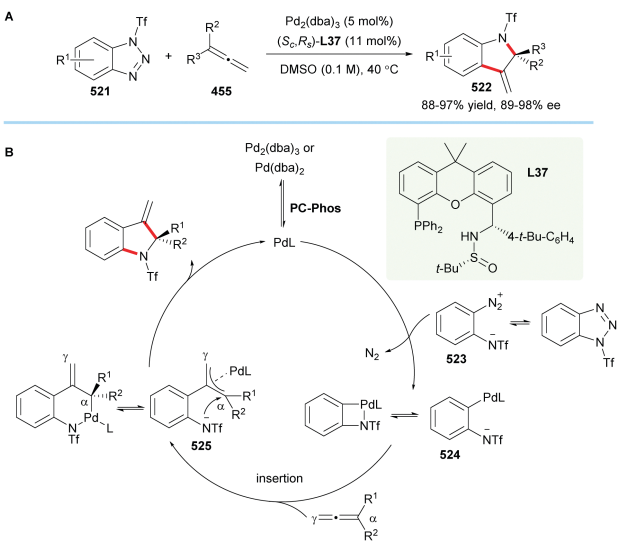
Scheme 132 Pd-Catalysed enantioselective arylation/amination of allenes.

tested and all of them gave their corresponding products with excellent enantioselectivity (94–98% ee).

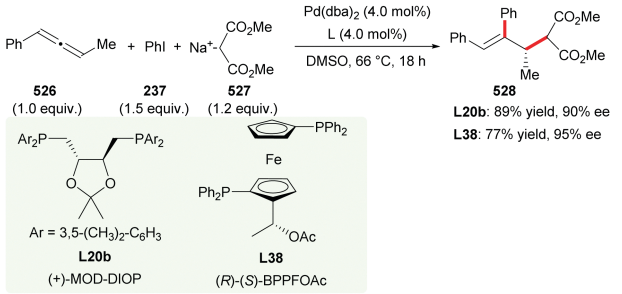
Benzotriazoles can readily undergo denitrogenation, promoting addition to olefins with the help of a transition-metal complex, the products of which are useful. Zhang developed the Pd-catalysed enantioselective difunctionalisation of 1,1′-disubstituted allenes with benzotriazoles **521** (Scheme 133A).[199] The benzotriazoles first isomerized to diazoniums, which then underwent denitrogenation with a Pd(0)-catalyst to give the oxidative addition intermediate; migratory insertion and nucleophilic substitution give the final products (Scheme 133B). PC-Phos ligand **L37** allowed the reactions to proceed smoothly with good yield and enantioselectivity. A gram-scale experiment suggested that this method has the potential for use in various synthetic applications.

4.2.1.2 Formation of C–C/C–C bonds. A three-component enantioselective difunctionalisation of internal allenes was reported by Hiroi and co-workers in 1998 (Scheme 134).[163] Phenyl iodide and enolate salts mixed with allene substrates could give the desired products in good yield with high enantioselectivity in the presence of a Pd catalyst. Chiral phosphine ligand MOD-DIOP **L20b** and chiral ferrocenyl phosphine ligand BPPFOAc **L38** performed with high efficiency and enantioselectivity in this reaction.

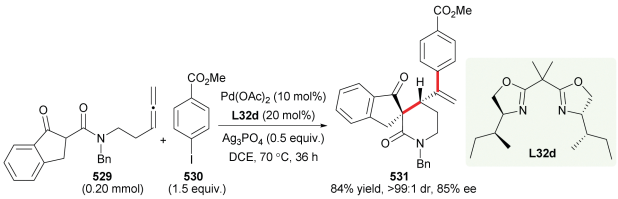
In 2013, Dixon utilized allene-linked ketoamide **529** as a substrate to synthesize enantiopure azaspirocyclic products (Scheme 135).[192]



Scheme 133 Pd-Catalysed enantioselective arylation/amination of allenes *via* denitrogenation.



Scheme 134 Pd-Catalysed enantioselective arylation/alkylation of internal allenes.



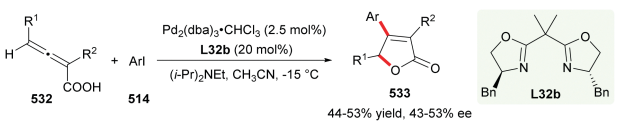
Scheme 135 Pd-Catalysed enantioselective arylation/alkylation of terminal allenes.

Bisoxazoline ligand **L32d** was tested to be the most useful ligand giving excellent diastereoselectivity (>99:1 dr) and good enantioselectivity (85% ee). The enolate form of the dicarbonyl motif of the ketoamide served as the nucleophile in this reaction after the generation of the π-allyl–Pd intermediate.

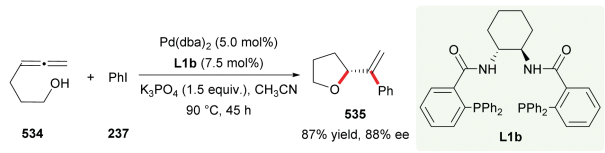
4.2.1.3 Formation of C–C/C–O bonds. In 2001, Ma's group developed the enantioselective addition of aryl iodides to allenic carboxylic acids, serving as a complementary route towards enantiopure β-arylbutenolides **533** (Scheme 136).[193] The bisoxazoline ligand **L32b** allowed the desired products to be furnished with up to 53% ee in moderate yields.

In 2013, the same group utilized Trost's ligands for the difunctionalisation of allenes, which possess different skeletons compared with the bisoxazoline ligands, BINAP-derived ligands, and DOIP-derived ligands, that have previously been employed in these types of reactions. γ-Allenols and phenyl iodide were the substrates for the difunctionalisation, thus a large range of allylic tetrahydrofurans **535** could be prepared with good enantioselectivity (Scheme 137).[284,285] Adding 3 Å molecule sieves slightly improved the yield and enantioselectivity.

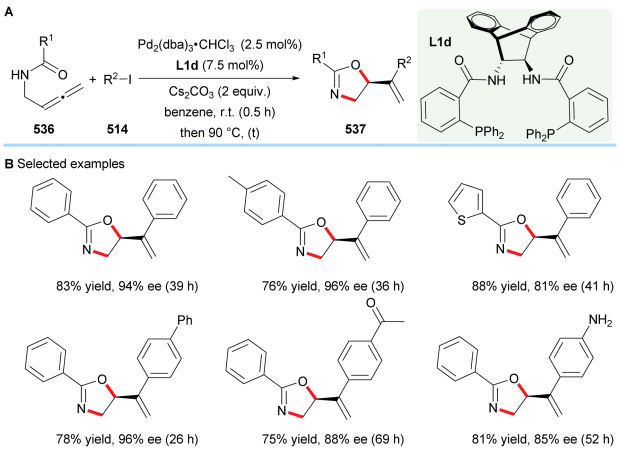
Years later, Ma developed an enantioselective method for the synthesis of oxazolines *via* the difunctionalisation of **536**.[81] Interestingly, the oxygen atom, and not nitrogen atom in the substrate could serve as the pronucleophile, leading to the



Scheme 136 Pd-Catalysed enantioselective arylation/carboxylation of allenes.



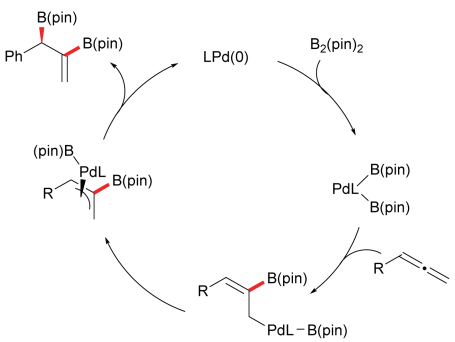
Scheme 137 Pd-Catalysed enantioselective arylation/alkoxylation of allenes.



Scheme 138 Synthesis of substituted oxazoline *via* the Pd-catalysed enantioselective difunctionalisation of allenes.

generation of oxazoline products (Scheme 138A). Trost's ligand **L1d** was found to be the most suitable chiral ligand for this reaction, allowing for the reactions to proceed with high enantioselectivity. Among the carbonates, phosphates, and hydroxides tested in the optimization experiments, Cs_2CO_3 was the best base giving the highest enantiomeric excess. It was found that the aromatic solvent was beneficial to the enantioselectivity. Many terminal allenes could give the desired products in good yield and enantioselectivity, but internal allenes failed to afford the corresponding oxazoline products (Scheme 138B).

4.2.1.4 Formation of C–B/C–B bonds. The diboration of allenes differs slightly from other difunctionalisations of allenes (Scheme 139).[158] The initial oxidative addition will occur between the Pd(0)-catalyst and diboron reagent, giving the Pd(II) species with two B atoms coordinated to one Pd atom. One of the Pd–B



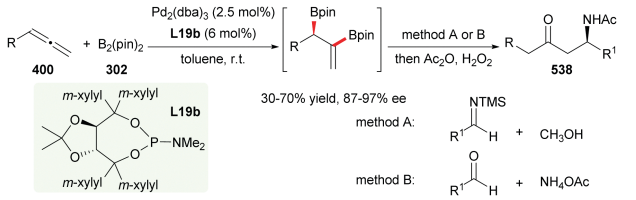
Scheme 139 General mechanism for Pd-catalysed enantioselective diboration of allenes.

bonds then inserts into the C–C double bond of the allene, and the B atom attaches to the middle carbon of the allene. The next step tends to be reductive elimination rather than nucleophilic substitution of the allyl–Pd intermediate.

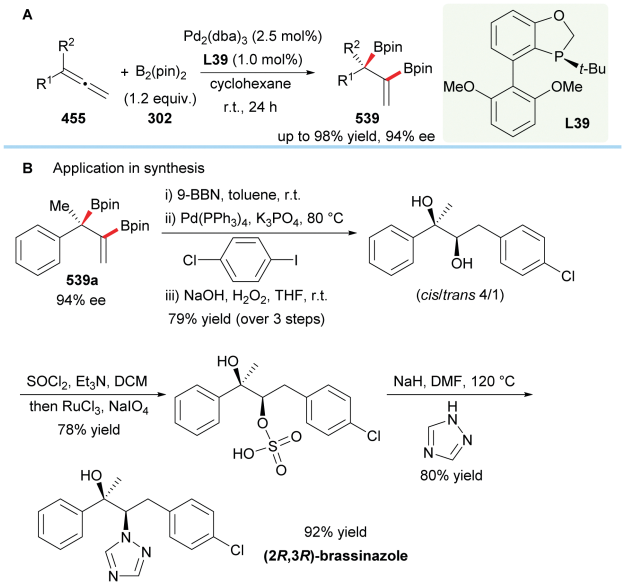
Morken's group has made outstanding progress in the diboration of allenes. In 2004 and 2006, they reported an elegant enantioselective diboration of allenes (Scheme 140).[286,287] I TADDOL-derived phosphoramidite **L19b** gave good chiral induction and yield for most of the allene substrates. Compared with the Pt-catalysed diboration of allenes that gave a mixture of regioisomeric products, the Pd-catalysed version only afforded the internal addition products. The diboron products could be subsequently transformed to β-amidoketones **538** when treated with (silylimine and methanol) or (aldehyde and solid ammonium acetate).

Later, the same group conducted further investigations on ligand development, substrate scope and the mechanism of the reaction.[158] TADDOL-derived **L19b** was the best ligand for excellent enantioselectivity. The electronic properties of the substrates had no significant impact on the enantiocontrol of the reaction, but more forcing conditions were needed for electron-deficient substrates.

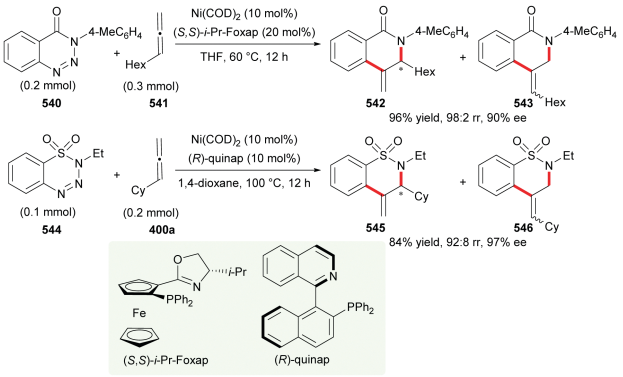
Recently, Ding extended the substrate scope to 1,1′-disubstituted allenes (Scheme 141A).[200] Chiral BI-DIME ligand



Scheme 140 Pd-Catalysed enantioselective diboration of allenes.



Scheme 141 Pd-Catalysed enantioselective diboration of 1,1′-disubstituted allenes.



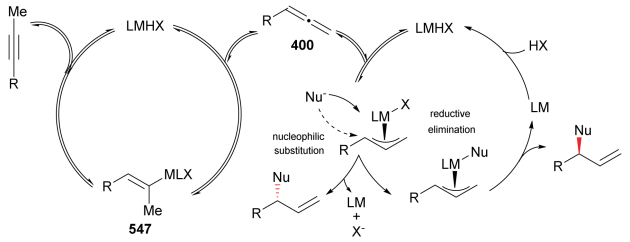
Scheme 142 Ni-Catalysed enantioselective arylation/amination of allenes *via* denitrogenation.

L39 was used to promote the reaction, allowing for up to 96% ee. Notably, the load of Pd-catalyst could be lowered to 0.2 mol% without significantly decreasing the yield and enantioselectivity. This method could be applied to the synthesis of (2*R*,3*R*)-brassinazole (Scheme 141B).

4.2.2 Catalysed by Ni. In 2010, Murakami developed the Ni-catalysed enantioselective difunctionalisation of allenes with 1,2,3-benzotriazin-4(3*H*)-ones **540** *via* denitrogenation (Scheme 142).[89] The addition mainly occurred at the internal olefin of the terminal allenes. Chiral (i-Pr)–FOXAP ligand allowed for an asymmetric version with excellent enantioselectivity. In the same year, the same group utilized 1,2,3,4-benzothiatriazine-1,1(2*H*)-dioxides **544** as one of the substrates, successfully affording the desired products in good yield and high regio- and enantioselectivity.[288,289] (*R*)-Quinap served as the most suitable chiral ligand to give the highest level of enantioselectivity. The reaction process was similar to that of Pd-catalysed difunctionalisation, in which the π-allyl–Ni intermediate can be attacked by the nucleophile to give the cyclization products.

5. Formation of asymmetric allylic compounds from alkynes

The transition-metal-catalysed hydrofunctionalization of alkynes is a large research area in organic synthesis. Most of these transformations are catalysed by Pd, Au, Rh, Pt, Ir, Ru, Ni, *etc.* and can be assigned to classical hydrofunctionalisation procedures[148] in which nucleophilic attack occurs with the help of a metal catalyst.[44,48,290–298] Since the newly formed bond is directly attached to the residual olefin, most of the products are not enantiopure allylic compounds (2-substituted allylic compounds). Although some of the classical hydrofunctionalisation methods can afford enantiopure allylic products, including the Au-catalysed cyclization of enynes and addition of enolates to alkynes, a number of specific and comprehensive reviews summarize these reactions.[44,45,56,293,296] Herein, we mainly focus on a different type of hydrofunctionalisation of alkynes, in which the metal-hydride species and allenes are necessary intermediates in the catalytic process. Yamamoto, Breit, Dong, and others have reported elegant developments in this



Scheme 143 Typical mechanism for transition-metal-catalysed hydrofunctionalisation of alkyne.

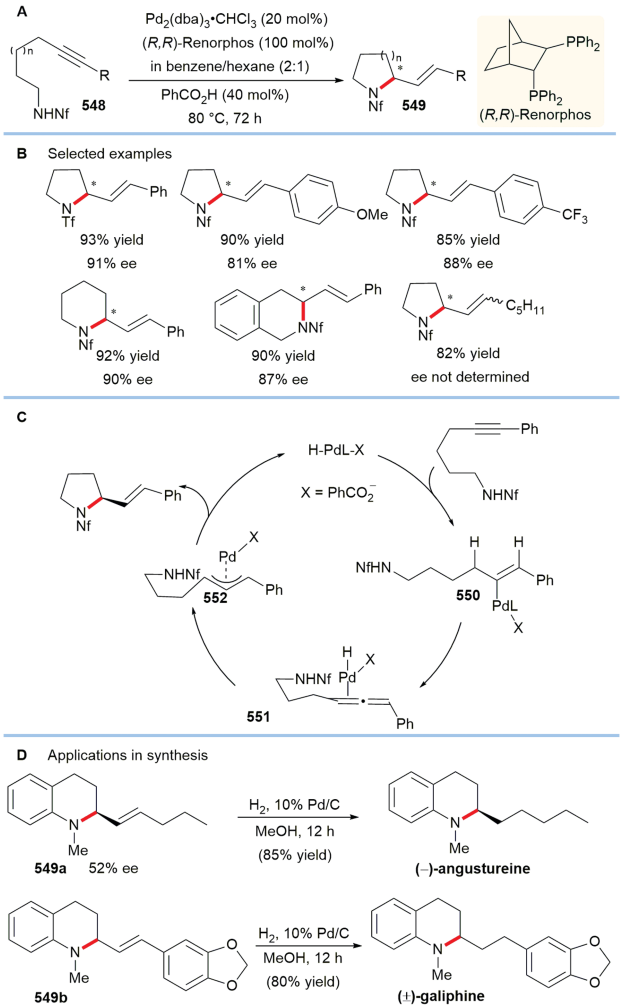
transformation. C–O, C–S, C–N, and C–C bonds can be constructed under the catalysis of Pd and Rh complexes, providing an efficient method to synthesize the enantiopure allylic compounds (1 or 3-substituted allylic compounds). Notably, there have been no examples concerning the enantioselective difunctionalisations that involve an allene intermediate generated to give the allylic adducts.

The reaction process of this special type of alkyne hydrofunctionalisation is interesting (Scheme 143). The alkyne first undergoes hydrometallation with the M–H species, giving the vinylmetallic compounds. Next, β-hydride elimination occurs, and the allene intermediate is generated (isomerization of alkyne to allene). Again, the M–H species inserts into the allene to form the π-allyl–M intermediate, and the final products are furnished through nucleophilic substitution or reductive elimination. Specific mechanism will be illustrated in the following reaction development discussion.

5.1 Catalysed by Pd

5.1.1 Formation of C–N bond. Although there had been a number reports concerning transition-metal complex-catalysed hydrofunctionalisations of alkynes,[48,299,300] reports of the enantioselective addition to alkynes remained rare until the early turn of this century. In 2004, Yamamoto developed an intramolecular enantioselective hydroamination of alkynes catalysed by a Pd-complex (Scheme 144A).[201] Many different bidentate phosphines were tested to find the most suitable chiral ligand, including MOP, BRRFOAc, DIOP, BINAP, BPPM, Pyrphos, Chiraphos, Norphos, and Renorphos. The ligand Renorphos was the most appropriate. In addition, the nonafluorobutanesulfonyl (Nf) group was the most compatible protecting group for the amino substituent rather than benzyl, acetyl, Boc, and tosyl protecting groups. Benzoic acid was added to promote the reaction. Both the reactivity and enantioselectivity increased when the catalyst loading was raised. Several alkynes were investigated: for the aryl substituted alkynes, electron-rich groups on the phenyl ring would accelerate the reaction but slightly diminish the enantioselectivity; while alkyl substituted alkynes could undergo reaction with good reactivity but poor enantioselectivity. In addition, both five- and six-members rings could be furnished using this method (Scheme 144B).

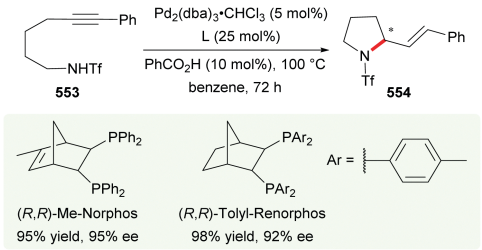
A catalytic cycle was proposed (Scheme 144C). The palladium precatalyst first interacts with benzoic acid to generate the Pd–H species, which is then inserted into the alkyne. The generated vinylpalladium intermediate **550** undergoes β-elimination to give



Scheme 144 Pd-Catalysed enantioselective intramolecular hydroamination of alkynes.

the species **551**, which is then transformed to π-allyl–Pd intermediate **552**. Intramolecular substitution then gives the final N-heterocyclic products. Some applications of this method were reported by the same group in 2007,[301] including the synthesis of 2-substituted tetrahydroquinolines (Scheme 144D). In 2006, the same group enlarged the reaction scope to enantioselective hydroalkoxylation and hydroalkylation, which we will discuss later. Furthermore, the origin of enantioselectivity is discussed based on DFT calculations.[202]

Although the enantioselective hydroamination of alkynes was realized, a stoichiometric amount of expensive chiral ligand (100 mol%) had to be used to give high enantioselectivity. Thus, efforts were made to decrease the loading of the catalyst as well as improve the yield and enantioselectivity, as studied by Yamamoto's group in 2008 (Scheme 145).[203] It was found that a slight change in the framework of the Renorphos and Norphos had a significant impact on the reactivity and enantioselectivity. Thus, a series of derivatives were prepared to test the catalytic efficiency, including chiral Me-Norphos, Tolyl-Norphos, CF_3-Norphos, Me-Renorphos, Tolyl-Renorphos, and CF_3-Renorphos.

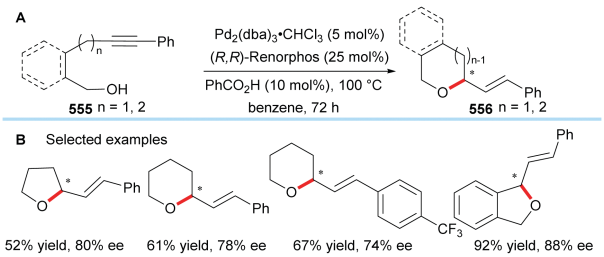


Scheme 145 Ligand effects in the Pd-catalysed enantioselective intramolecular hydroamination of alkynes.

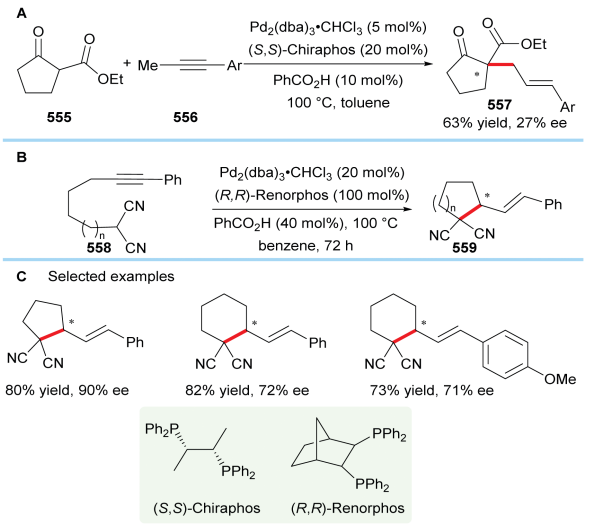
The results of the intramolecular enantioselective hydroamination showed that Me-Norphos and Tolyl-Renorphos were the most efficient ligands for this reaction (95% yield, 95% ee; 98% yield, 92% ee, respectively). The amount of chiral ligand could be lowered to 20 mol% without obviously decreasing the enantioselectivity. Control experiments demonstrated the oxide of the ligand could not promote the reaction. NMR was employed to monitor the presence of the oxide in the reaction mixture. Thus, the oxidation of the ligand and the hydroamination were competing in the catalytic system, suggesting that oxygen was detrimental to the hydroamination. Several alkynes underwent smooth reaction, giving the corresponding products with high yield and enantioselectivity. Unfortunately, the alkyl substituted alkynes gave a racemic mixture.

5.1.2 Formation of C–O bond. Due to the poorer nucleophilic ability of the oxygen nucleophiles, the hydroalkoxylation of alkynes represents a challenging topic in this field. In 2006, Yamamoto reported the Pd-catalysed intramolecular enantioselective hydroalkoxylation of alkynols **555** (Scheme 146A).[202] Chiral Renorphos was utilized as a ligand to promote the reaction. Due to the similarity of the hydroxyl group and the amino group, the hydroalkoxylation performed in an analogous manner to that of hydroamination. The allylic cyclic ethers could be obtained with good enantioselectivity (Scheme 146B).

5.1.3 Formation of C–C bond. In 2004, Yamamoto developed a method to construct quaternary carbon centres *via* the hydroalkylation of alkynes with 1,3-dicarbonyl compounds (Scheme 147A).[302] (*S*,*S*)-Chiraphos was utilized to construct the chiral centre, but the enantioselectivity was poor (27% ee). Later, based on their works on enantioselective hydroamination, it was found that although the carbon-based nucleophiles were usually considered as softer nucleophiles comparing with the



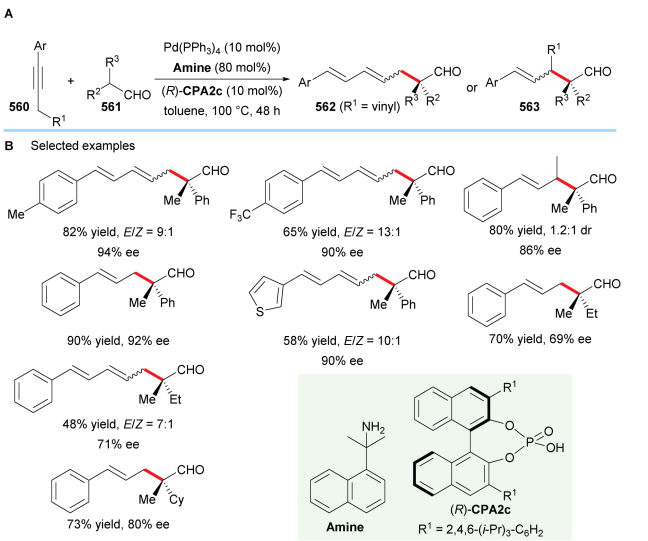
Scheme 146 Pd-Catalysed enantioselective intramolecular hydroalkoxylation of alkynes.



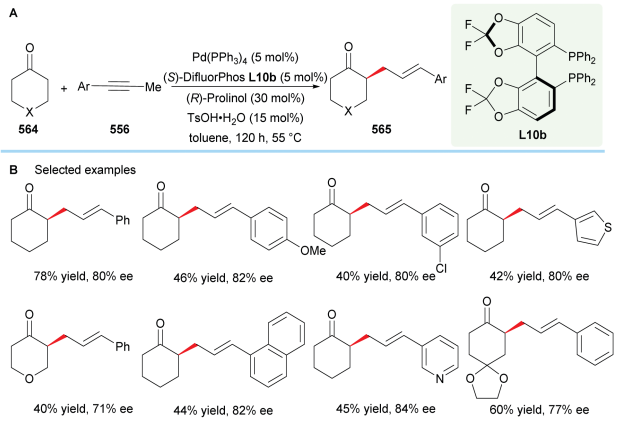
Scheme 147 Pd-Catalysed enantioselective hydroalkylation of alkynes.

nitrogen- and oxygen-based ones, the method Yamamoto used for the intramolecular enantioselective hydroamination of alkynes was also suitable for hydroalkylation.[202] 1,3-Dinitrile compounds were utilized due to the relatively stronger acidity of the C–H bond, which could facilitate the reaction (Scheme 147B and C).

Subsequently, a Pd-catalysed asymmetric intermolecular hydroalkylation of alkynes was developed by Wang and Gong (Scheme 148A).[209] Amine and chiral phosphoric acid **CPA2c** were added as co-catalysts to promote this reaction. It was found that the electronic properties and framework of the phosphine ligand in the precatalyst influences the reaction significantly. Additionally, replacing the $Pd(OAc)_2$ and PPh_3 with $Pd(PPh_3)_4$ could improve the enantioselectivity. The substrate scope of this reaction was large. The skipped enynes were



Scheme 148 Pd-Catalysed enantioselective hydroalkylation of alkynes with aldehydes.



Scheme 149 Pd-Catalysed enantioselective hydroalkylation of alkynes with cyclic ketones.

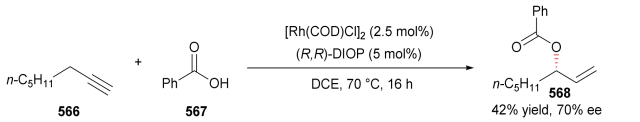
investigated to prepare the valuable diene products. The electron-donating groups and electron-withdrawing groups on the aryl substituents were tolerated (Scheme 148B). The general internal alkynes showed higher reactivity, giving high yield and enantioselectivity (90% yield, 92% ee). Various aldehydes were also tested, and alkyl aldehydes could also give the corresponding products with reduced yield and enantioselectivity. A catalytic cycle was proposed. The Pd-catalyst first interacts with the alkyne in the same manner as that seen in general Pd-catalysed intramolecular hydrofunctionalisations of alkynes, giving the π-allyl–Pd intermediate. The aldehyde undergoes a nucleophilic substitution with the amine to give the enamine intermediate. The two intermediates generated *in situ* then afforded the final products.

In the same year, Zhao's group developed an enantioselective hydroalkylation using cyclic ketones as the pronucleophiles (Scheme 149A).[123] The chiral ligand (*S*)-Difluorphos **L10b** and chiral amine (*R*)-prolinol were used to promote the reaction and induce enantioselectivity. Various substituents on the aryl group of the alkynes were tolerated, giving a good conversion and enantiomeric excess (Scheme 149B).

5.2 Catalysed by Rh

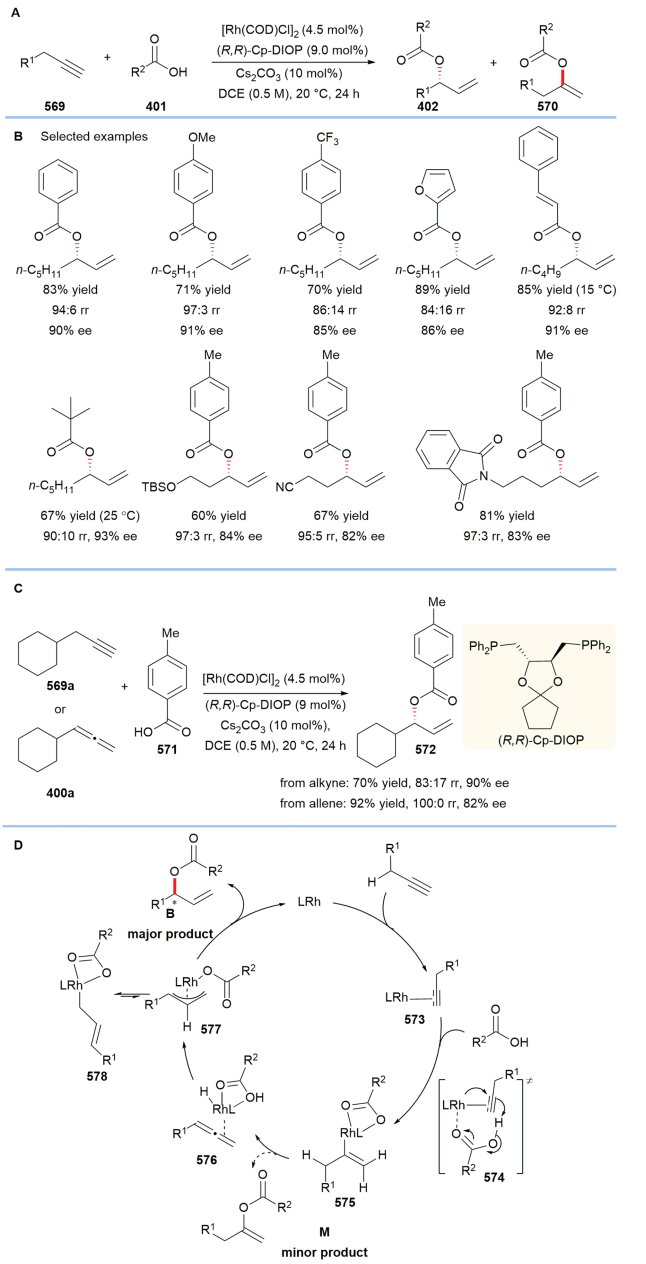
Similar to allenes, much effort has been made with regards to the rhodium-catalysed enantioselective hydrofunctionalization of alkynes.[32,41] Various chemical bonds including C–O, C–N, and C–C bonds could be constructed by this elegant method. In these methods, the isomerization of alkynes to allenes accompanying the formation of Rh–H species was the essential step for the reaction. The oxidation state of the Rh also changed during the reaction like, as in the hydrofunctionalisation of allenes.

5.2.1 Formation of C–O bond. Early studies on the hydrofunctionalisation of alkynes was conducted by Breit. They used a Rh(I)/DPEphos system to realize the hydrocarboxylation of terminal alkynes with carboxylic acids.[152] (*R*,*R*)-DIOP was applied to this system to investigate the enantioselective version of this reaction, and it gave an encouraging enantioselectivity (70% ee), which suggested the feasibility of the Rh-catalysed enantioselective hydrofunctionalisation of alkynes (Scheme 150).



Scheme 150 Early study of the Rh-catalysed enantioselective hydrocarboxylation of alkynes.

Further developments were reported by the same group in 2015. Based on their previous works, it was envisioned that the Rh/DIOP system might be able to give the desired products in high yield and enantioselectivity (Scheme 151A).[153] Optimization experiments were conducted to find suitable conditions.

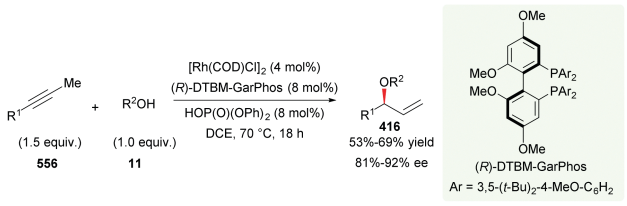


Scheme 151 Rh-Catalysed highly enantioselective hydrocarboxylation of alkynes.

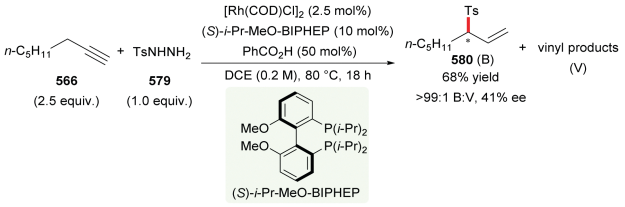
It was found that the enantioselectivity could be improved by lowing the temperature at the cost of reduced reactivity. Nevertheless, the presence of Cs_2CO_3 could compensate this. Various alkyl alkynes and carboxylic acids were investigated, and many of them gave the corresponding products at a mild temperature with good yield (up to 89% yield) and enantioselectivity (up to 93% ee) (Scheme 151B). Comparison experiment between allenes and alkynes were conducted (Scheme 151C). For the allene, no minor **M** product was generated. In addition, the allene reacted faster than the alkyne. These phenomena supported the initially isomerization of the alkyne to an allene and a similar subsequent pathway between the alkyne and allene. A reasonable catalytic cycle was proposed based on mechanistic studies and DFT calculations (Scheme 151D).[303] The Rh catalyst first coordinated to the alkyne to give the intermediate **573**, and **573** then undergoes an intramolecular protonation with carboxylic acids. The generated vinyl–Rh intermediate **575** undergoes β-elimination to give the Rh–H species **576** or direct reductive elimination, furnishing the minor products **M**. Compounds **576** can pass through a similar pathway like that observed in the hydrocarboxylation of allenes to afford the desired branched products **B**. This enantioselective hydrocarboxylation of alkynes can be applied to the synthesis of *trans*-Cognac Lactone and *trans*-Whisky Lactone.

Carboxylic acids are not the only pronucleophiles. In 2016, a Rh-catalysed asymmetric hydroalkoxylation of allenes and alkynes using alcohols as pronucleophiles was developed by Breit (Scheme 152).[195] Based on the reaction conditions for the hydroalkoxylation of allenes, they replaced the ferrocene-type ligand with (*R*)-DTBM-Garphos and increased the temperature, making the conditions compatible with terminal alkynes. Although the yield is moderate, the enantioselectivity was surprisingly high (up to 92%). The mechanism was a little different from the that of the hydrocarboxylation. Because the alcohol has poor acidity, diphenyl phosphate was utilized to assist the reaction. It is the phosphate that initially undergoes oxidative addition with Rh(I). After the isomerization and the generation of the π-allyl–Rh intermediate, a ligand exchange occurs between the alcohol and phosphate, followed by reductive elimination to give the final product.

5.2.2 Formation of C–S bond. In 2014, the hydrosulfination of alkynes with sulfonyl hydrazide **579** catalysed by Rh was developed by Breit (Scheme 153).[304] The Rh(I)/DPEphos system could give good yield and regioselectivity. However, when trying to investigate the asymmetric version of this reaction



Scheme 152 Rh-Catalysed highly enantioselective hydroalkoxylation of alkynes.

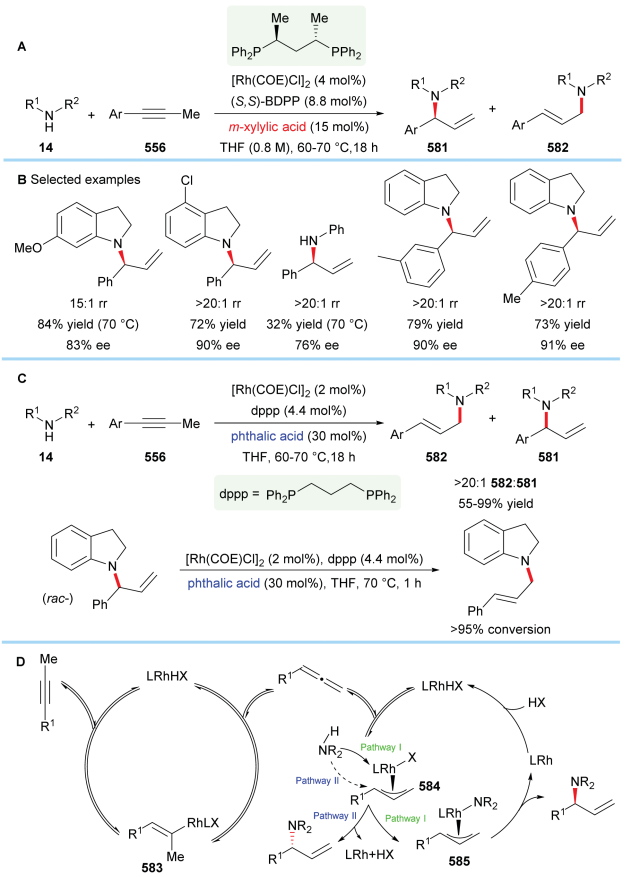


Scheme 153 Rh-Catalysed enantioselective hydrosulfination of alkynes.

by applying (*S*)-i-Pr-MeO-BIPHEP as chiral ligand, the product was obtained with only 41% enantiomeric excess.

5.2.3 Formation of C–N bond. The hydroamination of alkynes has been extensively studied,[290,291,295,305] but enantioselective transformations have not been widely reported. Again, isomerization of the alkyne and generation of the Rh–H species were the critical steps to afford the desired branched allylic amine products.

In 2015, Dong's group developed an enantioselective hydroamination of internal alkynes with indolines (Scheme 154)[166] catalysed by Rh/(*S*,*S*)-BDPP system. *m*-Xylylic acid was added to promote the reaction and improve the enantioselectivity (Scheme 154A). Several indolines were tested and all of them gave good yield, regio- and enantioselectivity (Scheme 154B). Aliphatic amines showed poor reactivity and enantioselectivity. The aryl substituent on the alkyne was necessary to give the



Scheme 154 Rh-Catalysed enantioselective hydroamination of alkynes.

desired product in good yield and enantioselectivity. Terminal alkynes were less reactive substrates for this reaction. Interestingly, when *m*-xylylic acid was replaced with phthalic acid, the linear products became predominant (Scheme 154C). It was also found that the branched products would isomerize to the linear products in the presence of acid, and the stronger acid could even accelerate the isomerization. This phenomenon suggested that the branched products were the kinetic products and could only be prepared in the presence of a relatively weak acid (*m*-xylylic acid). A catalytic cycle similar to that of hydroalkoxylation was proposed (Scheme 154D). Notably, the author believes that there are two competing pathways to afford the final branched products. Pathway I: ligand exchange followed by reductive elimination; pathway II: nucleophilic substitution of the π-allyl–Rh intermediate with the amine. Control experiments suggested the generation of an allene intermediate. The isotopic labelling experiment showed the reversibility of the β-elimination.

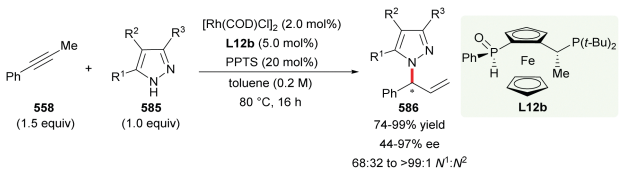
In order to further extend the substrate scope and enhance selectivity, Breit applied another catalyst system to realize the regio- and enantioselective hydroamination of alkynes with pyrazoles **585** (Scheme 155).[138] Chiral JoSPOPhos **L12b** was utilized, since it gave high regio- and enantioselectivity in the hydroamination of allenes. PPTS was also used to realize N^1-selectivity. Surprisingly, most of the substrates could give the branched products with >99 : 1 rr. Some of the benzyl and alkenyl substituted alkynes could afford the corresponding products with good reactivity. The terminal alkynes were also tolerated with reduced reactivity but good enantioselectivity. Besides aryl alkynes, some other alkynes were also tolerated, but only the alkynes with a conjugated system could give satisfactory results.

As we have mentioned in the previous section, in 2018 Breit reported the enantioselective hydroamination of allenes and internal alkynes with triazoles **586** (Scheme 156).[139] A large range of aryl alkynes were compatible with this method and a number of benzyl and alkenyl alkynes were also tolerated.

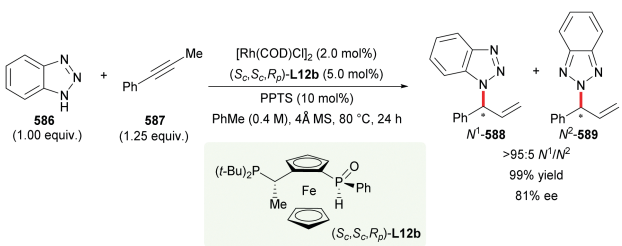
5.2.4 Formation of C–C bond. Hydroalkylations of alkynes with 1,3-dicarbonyl compounds were studied by Breit and Dong, and Rh(I)/DPEphos and Rh(I)/DIOP systems were developed to give the branched products in high yield.[306–308] Nevertheless, although the asymmetric version was tried with a chiral ligand, the enantioselectivity was relatively low (64% ee). Methods for constructing C–C bonds *via* a highly enantioselective Rh-catalysed hydroalkylation and hydroarylation remain undeveloped.

One of the biggest challenges for the formation of C–C bonds is the low reactivity of carbon-based pronucleophiles, such as carbonyl compounds. To cope with this problem, Dong, in 2017, applied the chiral amine to the system (Scheme 157).[147]

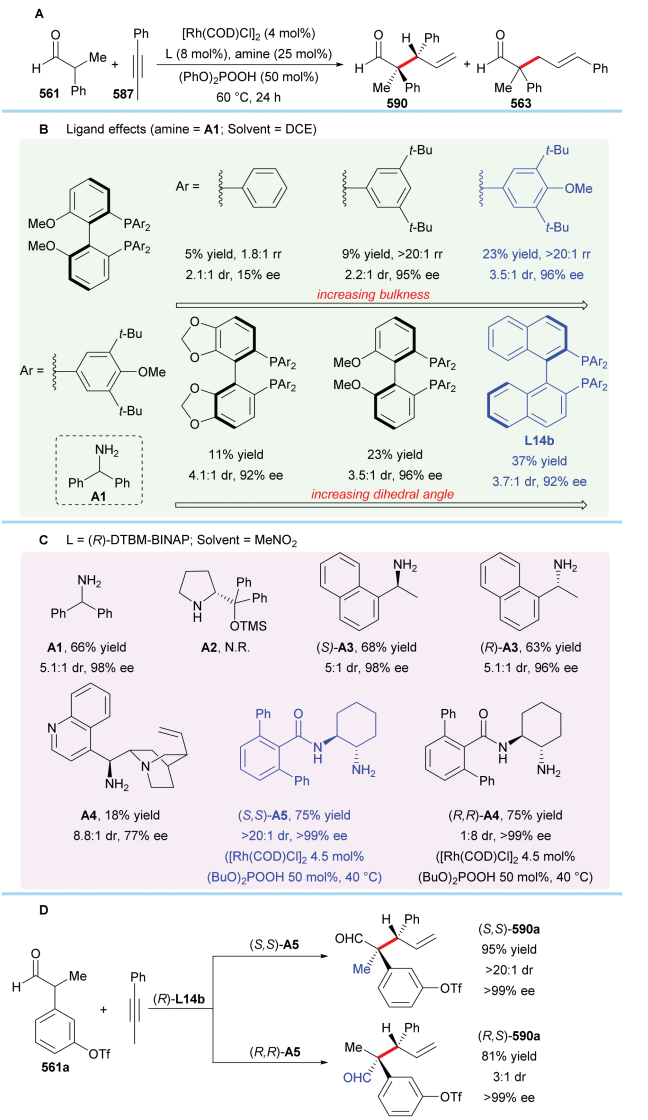
Amines can interact with aldehydes to give the corresponding enamines, which are good nucleophiles, and are able



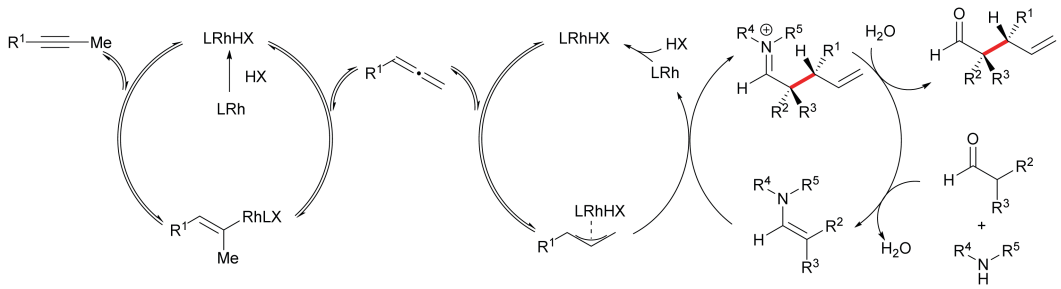
Scheme 155 Rh-Catalysed enantioselective N^1-selective hydroamination of alkynes with pyrazoles.



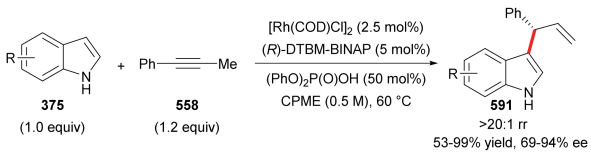
Scheme 156 Rh-Catalysed enantioselective N^1-selective hydroamination of alkynes with triazoles.



Scheme 157 Rh/chiral amine dual catalysed enantioselective hydroalkylation of alkynes with aldehydes.



Scheme 158 Proposed mechanism for the dual catalysed enantioselective hydroalkylation of alkynes with aldehydes.



Scheme 159 Rh-Catalysed enantioselective hydroarylation of alkynes with indoles.

to trap the π-allyl–Rh intermediate to generate the desired adducts (Scheme 157A). To realize this strategy, several chiral amines were tried. Jacobsen's amine was found to be the most efficient (>20:1 dr, >99% ee) (Scheme 157C). (*R*)-DTBM-BINAP **L14b** was a suitable chiral ligand since it has large steric hinderance and large dihedral angle (Scheme 157B). In addition, a phosphate was used to promote the reaction. This dual-catalytic system could allowed for the stereodivergent hydroalkylation of alkynes with aldehydes (Scheme 157D). Various aldehydes and alkynes could be applied to this method with excellent selectivity, and the electronic effect of the substituent on the aryl group of the alkyne does not significantly influence the reaction. The efficiencies for *syn*- and *anti*-selective additions were similar, suggesting that there might be a partial match between the enamine and Rh–allyl species. A catalytic cycle was proposed to demonstrate the dual catalysis system (Scheme 158).

Later, the same group reported an enantioselective hydroarylation of alkynes with indoles (Scheme 159).[148] The chiral DTBM-BINAP was chosen as a chiral ligand. Various indole derivates and alkynes were tolerated using this method, giving the corresponding products in good yield and enantioselectivity. However, the alkyl-substituted alkynes did not react at all under these reaction conditions.

6. Conclusions

Big strides have been made in the area of the asymmetric hydrofunctionalisation and difunctionalisation of dienes, allenes, and alkynes, giving a large range of enantiopure allylic and homoallylic compounds. The significant diversity of these useful compounds prepared by the methods reported in this review can be credited to the abundance of bond forming reactions, including the formation of C–B, C–C, C–N, C–O, C–Si, C–P, and C–S bonds. Numerous chiral ligands, small molecules, and additives have been developed in order to make the reactions run more efficiently and with better selectivity.

Nevertheless, although there have been significant developments, some challenges still remain: (a) the majority of the dienes, allenes, and alkynes are aryl substituted or activated by heteroatoms, whereas alkyl substituted substrates show poorer activity and selectivity. Although several successful examples have been reported with alkyl substituted species, 1,4-disubstituted dienes and 1,1′-disubstituted allenes are difficult to react. Efficient control of enantioselectivity and regioselectivity, as well as providing sufficient reactivity, are significant problems for these substrates; (b) earth-abundant metals are limited to the enantioselective hydrofunctionalisations and difunctionalisations of the three substrates; (c) compared with asymmetric allylic substitution, the enantiocontrol of enantioselective hydrofunctionalisations and difunctionalisations needs further improvement; (d) the diastereoselective hydrofunctionalisation and difunctionalisation of dienes, allenes, and alkynes with prochiral nucleophiles for the construction of compounds bearing vicinal stereocentres remains challenging; (e) the construction of quaternary stereocenters is also challenging but some great progress has been made; (f) although initial difunctionalisation reactions were studied many years ago, enantioselective examples are limited and only began to appear in the recent 20 years. There is therefore room for further development. New catalytic systems and novel concepts are needed to overcome these problems.

Despite the numerous challenges listed above, recent advances concerning enantioselective hydrofunctionalisations and difunctionalisations have shown that such challenges can be overcome. In addition, it has been widely recognized that dienes, allenes, and alkynes are readily available and useful raw materials in the oil industry. Thus, it is undoubtable that the asymmetric hydrofunctionalisation and difunctionalisation of dienes, allenes, and alkynes will provide the organic synthetic community with numerous opportunities to prepare enantiopure allylic compounds.

Conflicts of interest

There are no conflicts to declare.

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