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Transition Metal-catalyzed Allylic Substitution Reactions with Unactivated Allylic Substrates

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Abstract

The transition metal-catalyzed allylic substitution of unactivated allylic substrates (allylic alcohols, allylic ethers and allylic amines) is rapidly becoming an important area of research. There are several advantages to using these substrates in allylic substitution reactions: the use of unactivated alcohols minimizes the production of waste by-products and reactions steps; and allylic ethers and allylic amines are useful substrates because of their stability and their presence in numerous biologically active compounds. Research in this field has therefore gained widespread attention for promoting the development of efficient and environmentally benign procedures for the formation of C-C, C-N and C-O bonds.

Keywords

allylic substitution, allylic alcohols, allylic ethers, allylic amines, asymmetric catalysis

About the authors

Dr Nicholas Butt received his Master's degree from the University of Warwick in 2007. From 2007-2011 he carried out PhD research at the University of Nottingham under the supervision of

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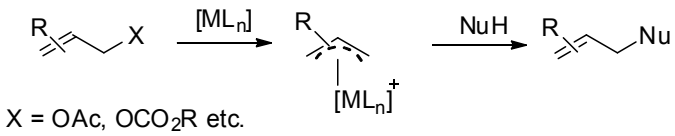
1. Introduction

Transition metal-catalyzed allylic substitution reactions of allylic substrates are some of the most versatile reactions in organic chemistry. Their flexibility and efficiency are just two of the many reasons as to why these reactions are of great interest to the chemical community. Allylic substitution reactions typically utilize an activated allylic substrate (i.e. an allylic alcohol protected as an acetate or ester acting as a leaving group), a transition metal-catalyst (commonly palladium) and a nucleophile (**Scheme 1**)[1–8]



Scheme 1 Transition metal-catalyzed allylic substitution with activated allylic substrates

Significant progress in this area of research has taken place, however procedures involving activated allylic species generate stoichiometric quantities of waste material thus making these procedures environmentally unsuitable. In recent years, the use of allylic alcohol substrates for substitution

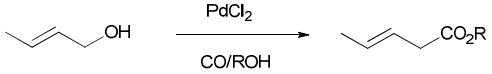
reactions has gained significant traction to counteract this problem.[9–12] These methodologies avoid the generation of unwanted by-products and thus provide more environmentally benign and economical procedures for the synthesis of target compounds. Allylic substitution reactions involving allylic alcohols have been well documented in preceding reviews, in particular by Bruneau and co-workers who have provided a detailed account of the transition metal-catalyzed nucleophilic allylic substitution of allylic alcohols.[11]

In continuation of the above research, transition metal-catalyzed allylic substitution reactions of other unactivated allylic substrates have become increasingly popular. These procedures typically involve the transition metal-catalyzed allylic substitution of allylic ethers (including allylic epoxides) and allylic amines (including allylic aziridine derivatives). Use of such species in allylic substitution reactions has several advantages: allylic ethers and allylic amines are generally stable compounds and are therefore amenable to a variety of reaction conditions; and such species can often be found in important chemical intermediates and natural products, thus allylic substitution reactions which contain these functionalities allow for easier derivatization of complex structures.

Although the transition metal-catalyzed allylic substitution reactions of unactivated allylic substrates has gained increasing prominence within the chemical community, reviews documenting advances in this field are absent. The present review aims to address this glaring omission and provide an up-to-date overview of methodologies for C-C, C-N and C-O bond formation directly from unactivated allylic alcohols, allylic amines and allylic ethers using palladium, iridium and other transition metal-catalysts. In order to prevent overlap with earlier reviews, especially that published by Bruneau et al.,[11] the section pertaining to transition metal-catalyzed allylic substitution reactions of allylic alcohols will mostly concern new methodologies developed since 2011 onwards, although some overlap is inevitable. Additionally, each chapter of the review will be divided into subsections according to the method used to activate the allylic substrate to nucleophilic attack.

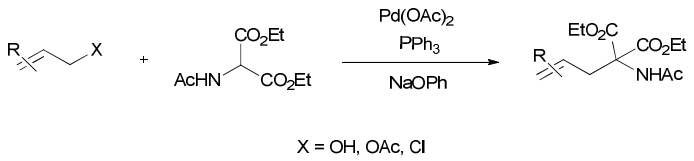
2. Transition metal-catalyzed allylic substitution reactions with allylic alcohols

The most commonly used transition metals for the activation of allylic alcohols to nucleophilic attack are palladium and iridium. The first palladium-catalyzed allylic substitution reactions of allylic alcohols was reported by Tsuji in 1964.[13] A $PdCl_2$ catalyst was utilized for the carbonylation of allylic alcohols (**Scheme 2**). This discovery was closely followed by Atkins et al. who utilized a $Pd(acac)_2$ catalyst in the presence of PPh_3 to effect the allylic substitution of allylic alcohol with carbonucleophiles. A relatively high temperature of 80 ^oC was required for this transformation.[14]

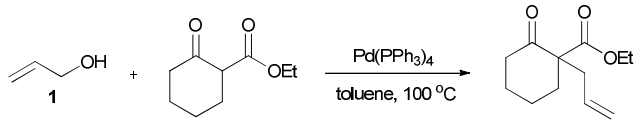


Scheme 2 Carbonylative allylation with allylic alcohols

In 1979 Chauvin and co-workers reported a synthesis of α-amino acids via the alkylation of diethyl acetamidomalonate in the presence of a $Pd(OAc)_2$-PPh_3-PhONa catalyst (**Scheme 3**) and allylic substrates.[15] Allylic alcohol was found to be the most reactive species. In 1989 Bergbreiter and co-workers used a palladium tetrakis catalyst for the alkylation of active methylene compounds with allyl alcohol **1** (**Scheme 4**).[16]



Scheme 3 Synthesis of amino acids



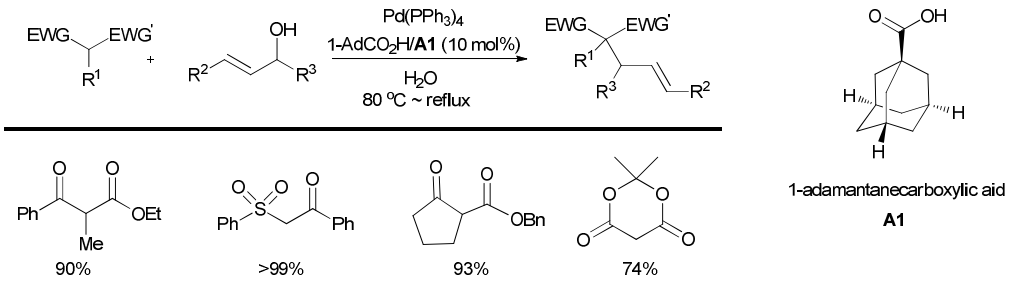
Scheme 4 Alkylation with allyl alcohol

Since these pioneering discoveries, much milder conditions have been developed for substitution reactions with allylic alcohols. Activation of the allylic species using additives such as Lewis acids, Brønsted acids, and ligands allow for reactions at lower temperatures and thus expanded substrate scope. Contrary to other transition metal-catalyzed allylic substitution reactions, those which utilize Pd as the catalytic species predominantly afford linear allylated products.

2.1. Palladium-catalyzed allylic substitution reactions with allylic alcohols

2.1.1. Allylic substitutions with allylic alcohols using protic acids as activators

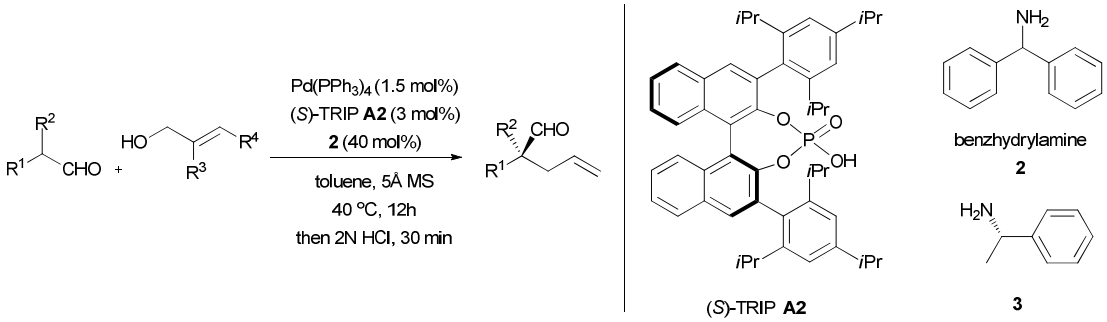
Tsuji-Trost-type allylations using carbonucleophiles are still relatively challenging. Several procedures utilizing protic acids have been developed for substitution reactions with allylic alcohols. In 2003, Mannabe and Kobayashi reported a carboxylic acid-assisted palladium-catalyzed allylation of carbonucleophiles with a number of allylic alcohols using water as a solvent.[17] A catalytic system consisting of $Pd(PPh_3)_4$ and 1-adamantanecarboxylic acid **A1** (10 mol%) in water, was suitable for the allylation of a number of carbonucleophiles (**Scheme 5**). Comparatively high reaction temperatures were required in order to obtain the products in high yield (up to >99% for some substrates). The acidic additive is essential for activation of the allylic species, accelerating the slow process of π-allyl-palladium formation.



Scheme 5 Allylic substitution of allylic alcohols using 1-adamantanecarboxylic acid as an activator

In 2011, List and co-workers reported the first example of a highly enantioselective α-allylation of aldehydes with simple allylic alcohols.[18] Pivotal to the success of this reaction was the introduction of a catalytic amount of the chiral Brønsted acid (*S*)-3,3'-bis(2,4,6-triisopropylphenyl)-2,2'-binaphtholate ((*S*)-TRIP, **A2**), which in combination with a Pd-catalyst and amine additive creates an effective tri-catalyst system (**Table 1**). Previous studies by List et al. had shown that benzhydrylamine **2** was sufficient for the generation of a suitably nucleophilic enamine from the aldehyde substrate. This enamine is able to outperform its corresponding enol intermediate leading to the formation of one predominant enantiomeric product. Benzhydrylamine **2** is required for the reaction to proceed, with low quantities of co-catalyst leading to lower product yields.

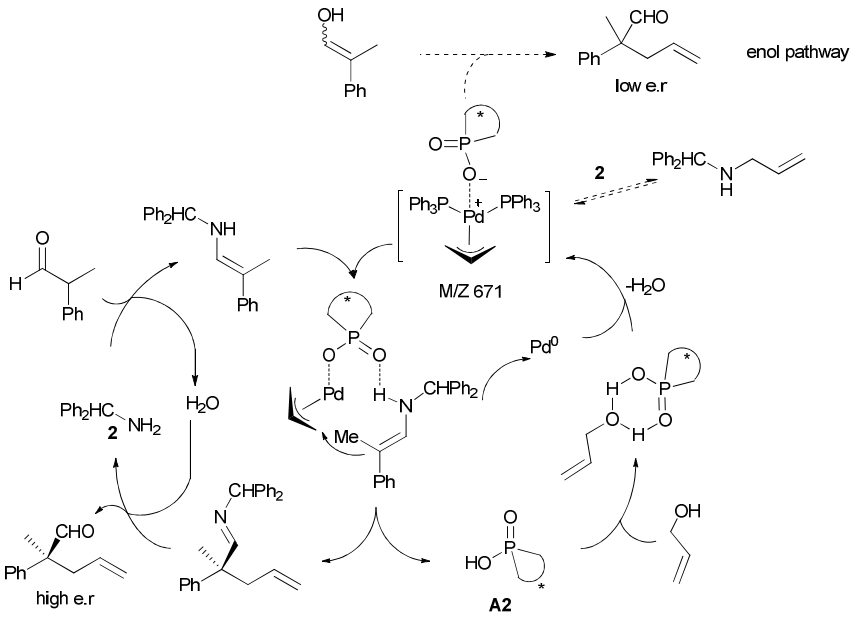
The optimized reaction conditions were found to be amenable to a range of methyl-branched aromatic aldehydes bearing electron-donating and electron-withdrawing groups (**Table 1**). Treating various aldehydes with different allylic alcohols (2 equiv) in the presence of $Pd(PPh_3)_4$ (1.5 mol%), (*S*)-TRIP (**A2**, 3.0 mol%), amine **2** (40 mol%), and 5Å molecular sieves at 40 ^oC in toluene for 12 h, provided the corresponding allylated aldehydes in 94-98% yields and excellent enantioselectivities (up to 99.8:0.2 e.r.; entries 1-9). Aliphatic aldehydes such as cyclohexyl aldehyde failed to give their desired products under these reaction conditions. Interestingly, subjection of the aliphatic aldehyde to reactions conditions in which benzhydrylamine **2** had been replaced with (*S*)-1-phenylethylamine **3** (80 mol%), and carrying out the reaction at 100 ^oC, led to the formation of the desired allylic product (entry 11). Additionally, a range of substituted alcohols could also be subjected to the previously described reaction conditions (entries 13-16).



entry	R^1	R^2	R^3	R^4	yield (%)	e.r.
1	C_6H_5	Me	H	H	97	97:3
2	4-$MeOC_6H_4$	Me	H	H	95	97:3
3	4-MeC_6H_4	Me	H	H	94	99.8:0.2
4	3-MeC_6H_4	Me	H	H	94	96:4
5	4-PhC_6H_4	Me	H	H	98	96:4
6	4-ClC_6H_4	Me	H	H	98	95:5
7	2-FC_6H_4	Me	H	H	94	96:4
8	3-FC_6H_4	Me	H	H	97	96:4
9	6-MeO-2-naph	Me	H	H	96	96:4
10	C_6H_5	Et	H	H	77	81:19
11	Cyclohexyl	Me	H	H	90	84.5:15.5
13	Ph	Me	H	Ph	96	94:6
14	Ph	Me	Ph	H	96	99.3:0.7
15	Ph	Me	H	Me	66	96:4
16	Ph	Me	Me	H	95	94:6

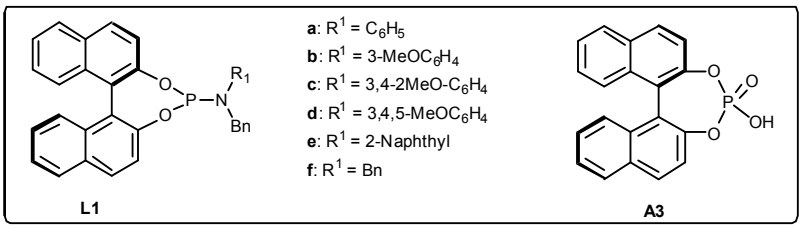
Table 1 Asymmetric allylation of different aldehydes and allylic alcohols using a tri-catalyst system

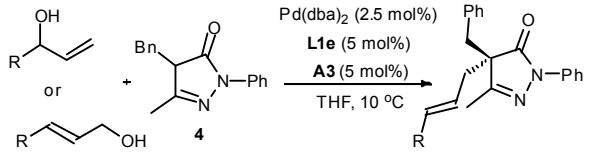
List and co-workers have proposed a mechanism for the above reactions, which involves three catalytic cycles (**Scheme 6**): The first catalyst cycles involves formation of an enamine form reaction of the aldehyde with the primary amine catalyst **2**.[18] The enamine is subsequently allylated by a π-allyl-Pd-phosphate complex to give the product imine, Pd(0), and TRIP **A2**. The second catalyst cycle generates π-allyl-Pd-phosphate complex via oxidation of Pd(0) with the activated allylic alcohol. Finally, the third catalytic cycle comprises Brønsted acid catalysis with TRIP **A2** and activation of the allylic alcohol for Pd insertion. List et al. reported that the π-allyl-Pd cation was observed via mass spectroscopy.



Scheme 6 Mechanism of tri-catalyst system

Gong and co-workers utilized chiral phosphoric acids for the first asymmetric allylic alkylation of pyrazol-5-ones with allylic alcohols.[19] A combination of chiral phosphoric acid **A3**, BINOL-derived chiral phopshoramidite ligands **L1a**-**L1f** bearing axial chirality, and $Pd(dba)_2$, was suitable for the allylic alkylation of pyrazol-5-one **4**. Ligand **L1e** provided the greatest enantioselectivtiy and yield for the alkylation reactions, with the solvent THF proving to be most suitable. The chiral phosphoric acid was required for the reaction, with other acids such as trifluoroacetic acid (TFA) and *p*-toluenesulfonic acid (*p*-TSA) giving rise to inferior results under identical reaction conditions. Electron deficient cinnamyl alcohols gave better stereocontrol than electron rich/neutral substrates (**Table 2**, entries 1-8). Aliphatic allylic alcohols (entries 9-11) and a branched substrate (entry 12) were also amenable to the reaction conditions.

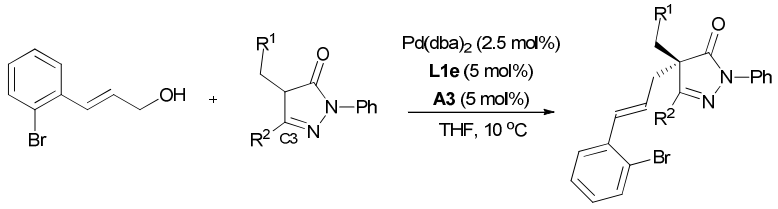




entry	R	yield (%)	ee (%)
1	2-$MeOC_6H_4$	98	91
2	3-$MeOC_6H_4$	95	93
3	4-$MeOC_6H_4$	97	90
4	2-BrC_6H_4	86	96
5	3-$BrOC_6H_4$	99	95
6	4-BrC_6H_4	95	95
7	4-FC_6H_4	95	95
8	2-$NO_2C_6H_4$	99	96
9	$(CH_2)_8CH_3$	81	90
10	Me	81	91
11	*n*-Pr	77	85
12	4-MeC_6H_4	94	91

Table 2 Allylic alkylation of pyrazol-5-ones with allylic alcohols - allylic alcohol substrate scope

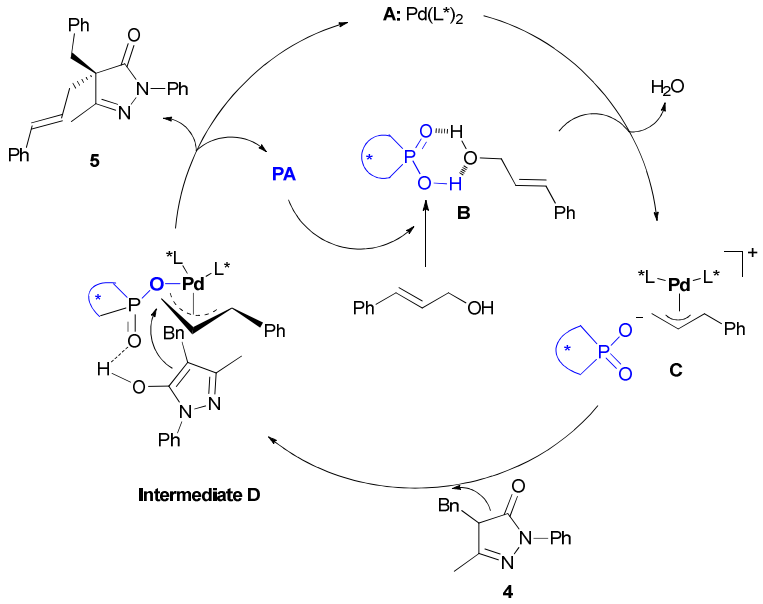
A number of pyrazol-5-ones bearing different substituents could also be reacted under the optimized conditions. The stereocontrol was sensitive to the substituent at the C-3 position of the pyrazol-5-one (**Table 3**). Bulky groups, phenyl groups and hindered isopropyl substituents led to a reduction in enantioselectivity, while linear aliphatic substituents gave high enantioselectivities.[19]



entry	R^1	R^2	yield (%)	ee (%)
1	Ph	Ph	81	66
2	Ph	*n*-Pr	97	95
3	Ph	*i*-Pr	96	88
4	Ph	Et	85	95
5	2-FC_6H_4	Me	98	96
6	2-FC_6H_4	Me	93	95
7	2-FC_6H_4	Me	92	96
8	2-FC_6H_4	Me	99	96
9	2-FC_6H_4	Me	96	95
10	α-Naph	Me	89	94
11	2-thienyl	Me	99	97
12	Me	Me	74	94
13	H	Me	90	97
14	Ph	H	60	92

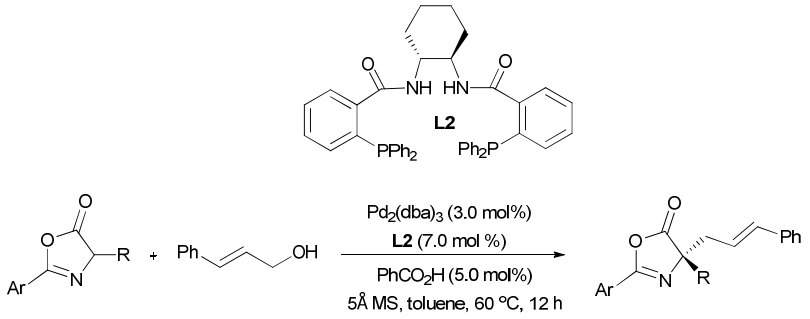
Table 3 Scope of pyrazol-5-one alkylation.

Based on HRMS studies, Gong and co-workers proposed a mechanism to explain the excellent stereocontrol (**Scheme 7**). Two molecules of the chiral ligand **L1e** coordinate to the palladium to give complex $Pd(L^*)_2$ (**A**). Complex **A** reacts with phosphoric acid-activated cinnamic alcohol **B** via the aid of hydrogen bonding, expelling the hydroxyl group and forming the cationic π-allyl-palladium(II) complex **C** and water. The enolizable nucleophile **4** forms hydrogen-bonds with the chiral phosphate counter-ion to give intermediate **D**, which is activated for nucleophilic substitution. The chiral palladium complex and chiral phosphate counteranion work in tandem to activate the substrates and control the stereochemistry of the asymmetric allylic alkylation reaction. Complex **A** is finally regenerated.[19]



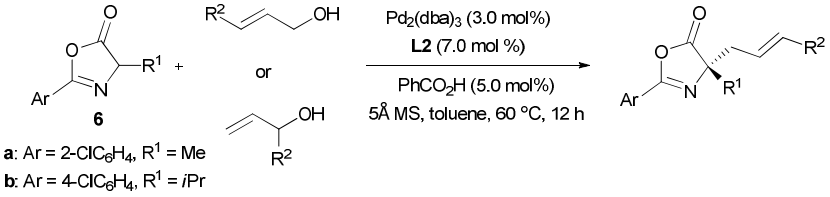
Scheme 7 Proposed catalytic cycle for allylic alcohol substitution with pyrazol-5-ones

Jiang and Xia disclosed a Brønsted acid accelerated Pd-catalyzed asymmetric allylic alkylation of azlactones using a $Pd_2(dba)_3$ catalyst, Trost ligand **L2** and benzoic acid.[20] A range of azlactones were suitable for the reaction conditions. Azlactones bearing electron withdrawing and donating groups on the phenyl ring and aliphatic/aromatic R groups, gave their corresponding products in good yields and enantioselectivities when alkylated with cinnamyl alcohol (**Table 4**). Azlactones **6** were also successfully reacted with a number of linear and branched cinnamyl alcohols bearing electron-donating and electron-withdrawing groups (**Table 5**). Only linear products were detected suggesting a cationic π-allylpalladium(II) intermediate facilitates the regioselective reaction.



Ar	R	yield (%)	ee (%)
Ph	Me	82	77
Ph	Me	85	81
4-MeC_6H_4	C_3H_5	93	88
4-MeC_6H_4	4-$CF_3C_6H_4CH_2$	91	78
2-ClC_6H_4	Me	98	90
4-ClC_6H_4	Bn	80	82

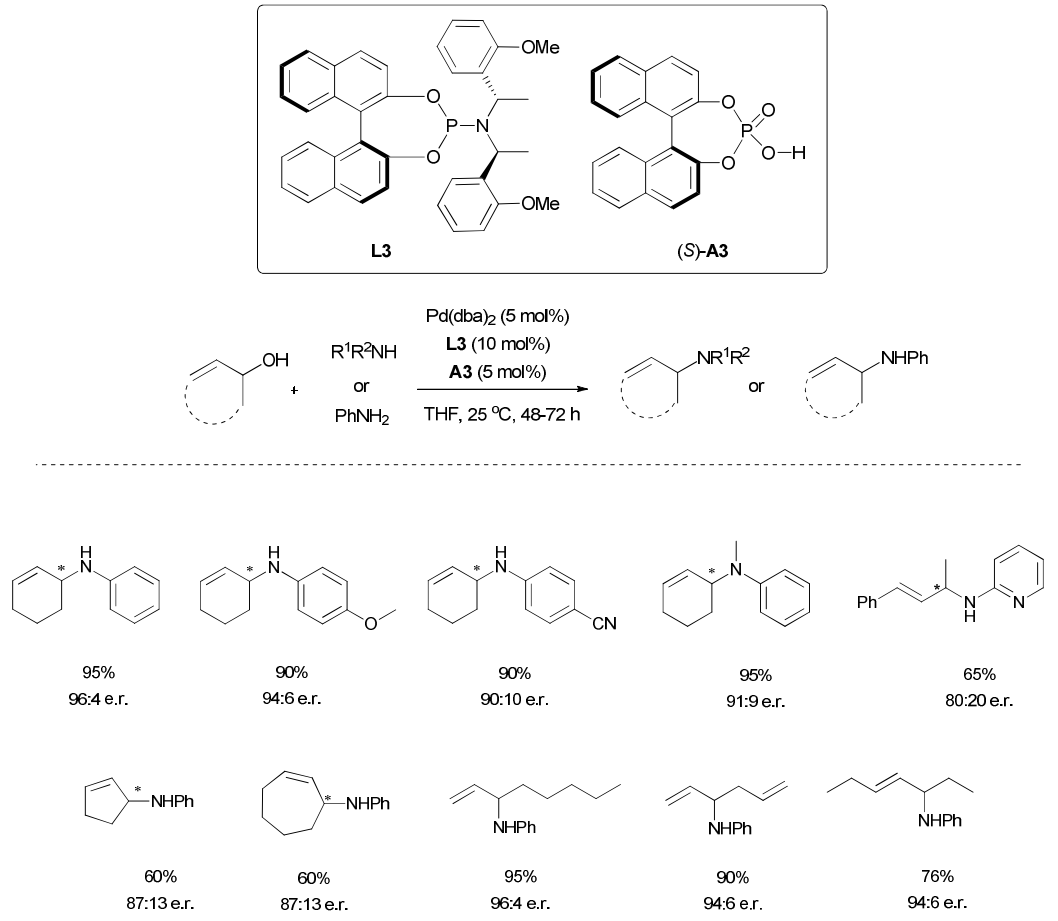
Table 4 Allylic alkylation with azlactones



azlactone	alcohol R^2	yield (%)	ee (%)
6a	4-$MeOC_6H_4$	95	88
6a	4-ClC_6H_4	98	86
6a	4-$CF_3C_6H_4$	89	76
6a	C_6H_5	93	90
6b	4-$MeOC_6H_4$	93	87
6b	4-$MeOC_6H_4$	93	90
6b	4-$CF_3C_6H_4$	88	94

Table 5 Allylic alcohol substrate scope

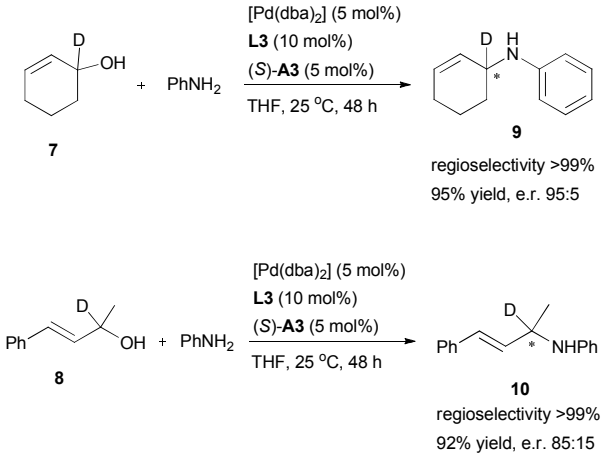
In 2014 Beller and co-workers reported the first palladium-catalyzed enantioselective amination of racemic allylic alcohols using chiral phosphoric acid cooperative catalysis. Phosphoramidite ligand **L3** was found to be the most suitable ligand for the reaction (**Scheme 8**).[21] Following the work of List et al., the stereoselectivity of the reaction could be further improved via the addition of chiral binaphthol-based phosphoric acid derivative **A3**. More sterically demanding ligands proved to be less effective. The optimized reaction conditions are shown in **Scheme 8** and were suitable for the allylic amination of a number of aniline-derived nucleophiles. Substrate scope could be expanded via the reaction of acyclic and cyclic racemic alcohols (including challenging secondary alcohols) with aniline, with the corresponding products being obtained in good yields and enantioselectivities.



Scheme 8 Palladium-catalyzed enantioselective amination of racemic allylic alcohols

Deuterium experiments involving deuterated allylic alcohols **7** and **8** with aniline showed that the reaction was highly regio- and enantioselective (Scheme 9).[21] Beller proposed that the allylic palladium intermediate formed in situ is stabilized by the ligand, and that the rate of isomerization of the two

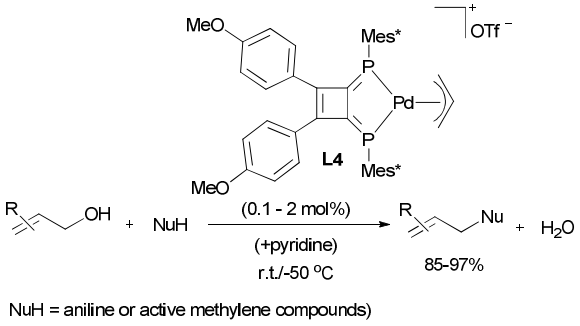
allylic palladium intermediates is slower than the rate of nucleophilic attack. No other regioisomers were observed. Although the mechanism for the reaction is not well understood, the authors believe that the formation of an active palladium-phosphate complex is paramount for reactivity.



Scheme 9 Enantioselective amination of deuterated allylic alcohols

2.1.2. Allylic substitutions with allylic alcohols using ligands and solvents as activators

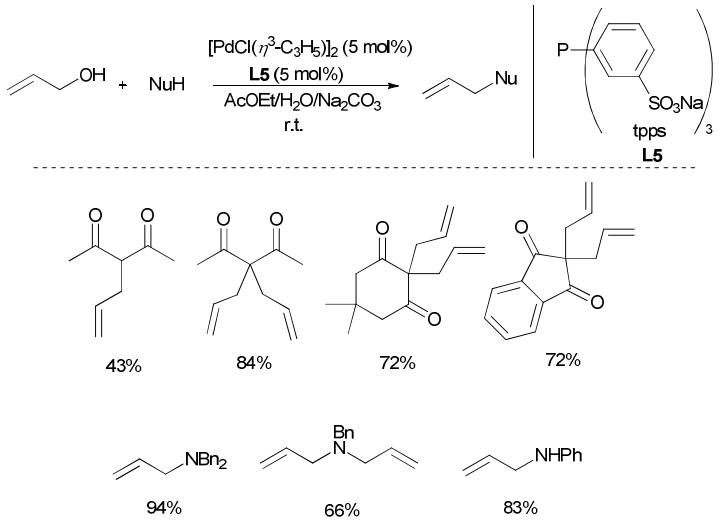
Transition metal-catalyzed reactions involving supramolecular interactions have gained prominence in recent years for a number of chemical transformations. Ozawa and co-workers prepared (π-ally)palladium complexes **L4** bearing a sp^2-hybridized diphosphinidenecyclobutene ligand for the activation of allylic alcohols. No additional additives were required.[22–24] A number of aniline substrates could be alkylated with allyl alcohol to give mono-allylated substrates in good yields (85-95%). Additionally, the C-allylation of active methylene compounds was achieved used a catalytic amount of pyridine as a base and carrying out the reaction at 50 °C (**Scheme 10**).[22]



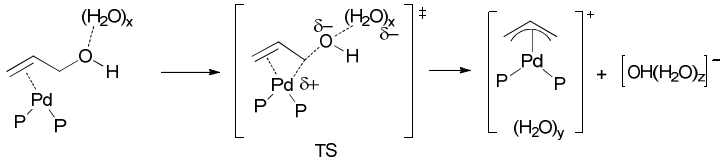
Scheme 10 Activation of allylic alcohols using a diphosphinidenecyclobutene ligand

Oshima and co-workers reported that hydrogen-bonding between water and allylic alcohols is a key process for reducing the activation energy barrier for allylic substitution reactions.[25] A range of active

methylene compounds could be alkylated with allyl alcohol under a biphasic catalyst system consisting of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and **L5** in the presence of a H_2O/EtOAc solvent system. The system was also suitable for the allylation of various aniline species (**Scheme 11**). Water is believed to activate the allyl alcohol via hydration of the hydroxyl group and stabilizes the resulting hydroxide ion by solvation with water (**Scheme 12**).[25]



Scheme 11 Allylic alcohol activation with H_2O

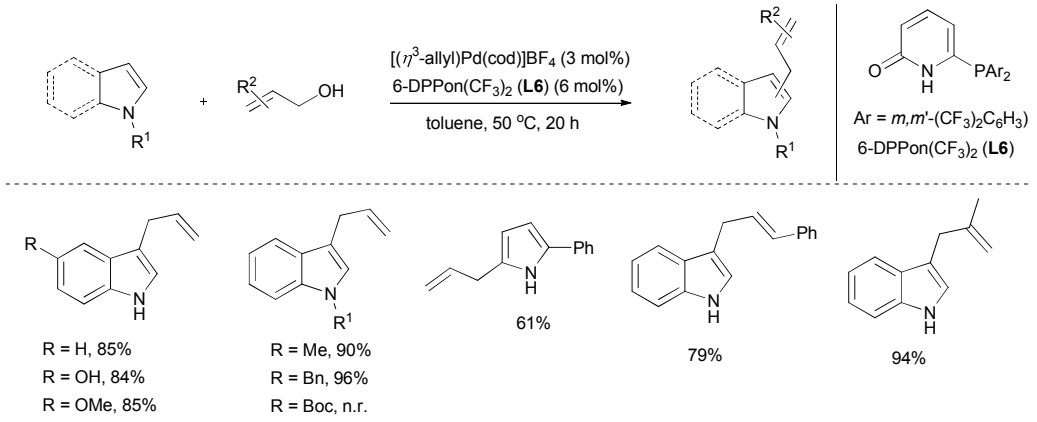


Scheme 12 Proposed mechanism of activation with water

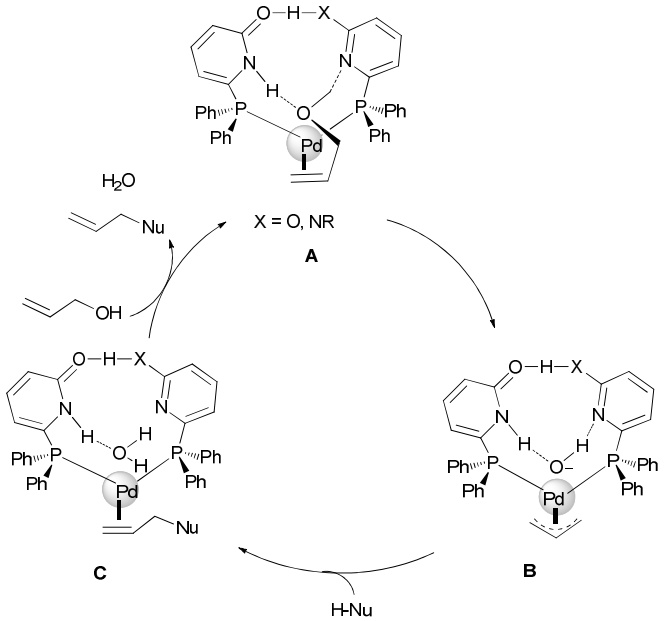
Ikariya and co-workers reported a halide free dehydrative allylation with allylic alcohols by employing a palladium-triphenyl phopshite catalyst. A $Pd[P(OC_6H_5)_3]_4$ complex was suitable for the dehydrative allylation of alcohols and the C- and N-allylation of activated methylene compounds and anilines respectively. Products with yields up to 96% were obtained when the reactions were carried out in toluene at 80 ^oC.[26]

Breit and co-workers designed self-assembling palladium phosphane catalysts for the allylation of *N*-heterocycles with allylic alcohols.[27] *N*-Heterocycles and aniline substrates were allylated using a catalyst system consisting of $[(\eta^3\text{-allyl})Pd(cod)]BF_4$ and the ligand 6-DPPon$(CF_3)_2$ (**L6**) in toluene solvent (**Scheme 13**). Ligand **L6** self-assembles with the Pd-catalyst via hydrogen-bonding to form the

complex shown in **Scheme 14**. It is assumed that the self-assembled catalyst also helps activate the allylic alcohol to nucleophilic attack via hydrogen bonding between the N-H groups of the ligand and the hydroxyl group of the alcohol.



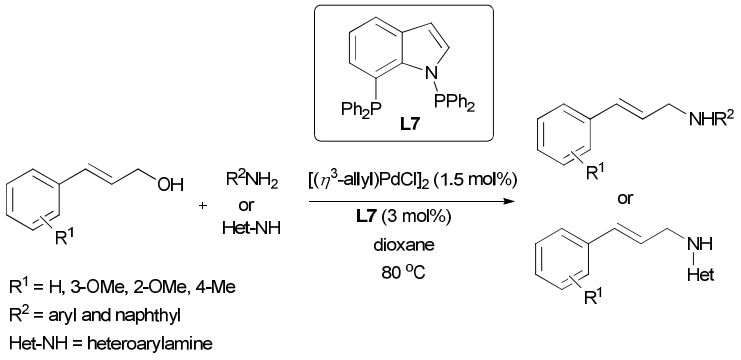
Scheme 13 Allylation via self-assembling palladium phosphane catalysts



Scheme 14 Proposed mechanism for allylation via self-assembling palladium phosphane catalyst[27]

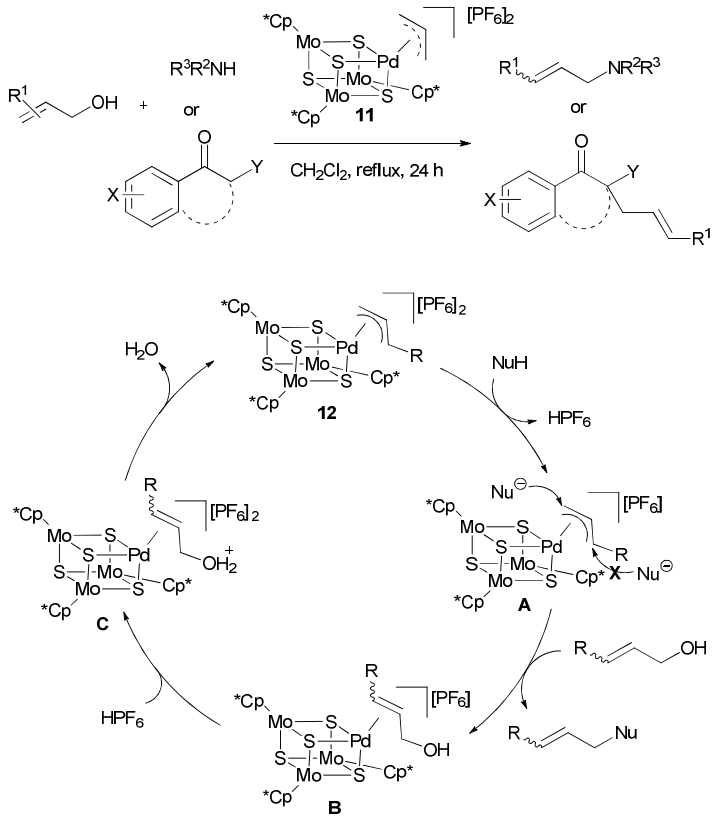
Bis-phosphane ligands have been used for the amination of aryl-substituted allylic alcohols.[28] A catalyst system consisting of a $[(\eta^3\text{-allyl})PdCl]_2$ precursor in the presence of bis-phopshine ligand **L7** was suitable for the reaction of a large number of electronically and structurally diverse allyl alcohols

with substituted arylamines (**Scheme 15**). Substituted cinnamyl alcohols were successfully reacted with aniline, *p*-anisidine, *m*-acetylamine and 2-naphthylamine to give their corresponding mono allylic amine products in good yields. Both *cis*- and *trans*-cinammyl alcohols gave the *trans*-isomer allylated product. Additionally susbtitued allylic alcohols could also undergo amination with heteroarylamines such as imidazole and pyrazole, with the corresponding products being obtained in excellent yields.



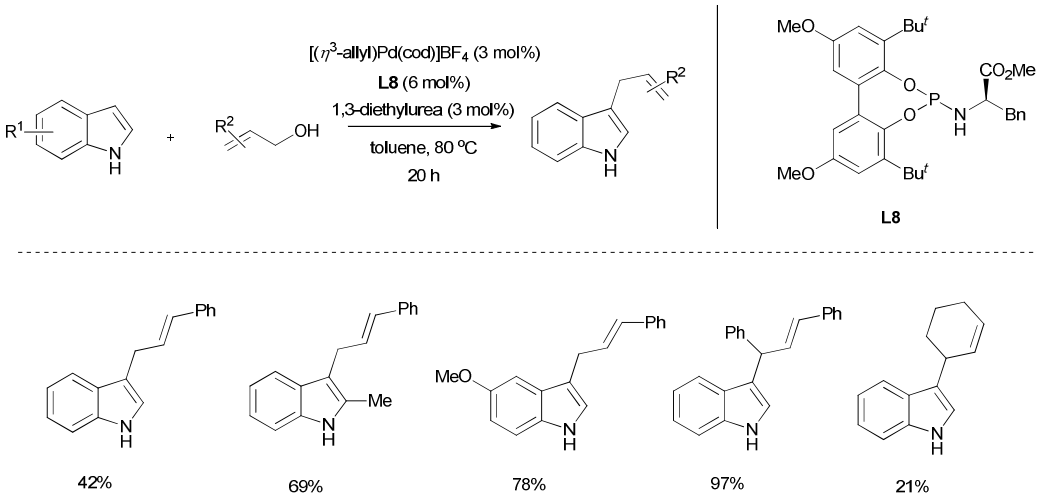
Scheme 15 Pd-catalyzed allylation with bis-phospine ligand **L7**

Qu and co-workers reported the use of a cubane-type sulfido $[(Cp^*Mo)_3(\mu^3\text{-}S)_4Pd(\eta^3\text{-allyl})][PF_6]$ (**11**) cluster for the regioselective allyation of amines and active methylene compounds using allyl- and cinnamyl alcohol (**Scheme 16**).[29] Aniline substrates were directly reacted with allylic alcohols in the absence of any additives, giving the corresponding products in yields ranging from 53-96%. Anilines bearing a free NH_2 group gave rise to diallylated products. Allylation of methylene compounds gave similarly good yields. A proposed mechanism for the reaction is shown in **Scheme 16**. Catalyst **11** is first converted to **12** via reaction with the allylic alcohol. The $(Cp^*Mo)_3S_4$ chelates to the $(\eta^3$-allyl)Pd catalyst through three sulfur atoms as determined by X-ray crystallography. The regioselectivity arises from attack of the nucleophile at the least hindered carbon atom.

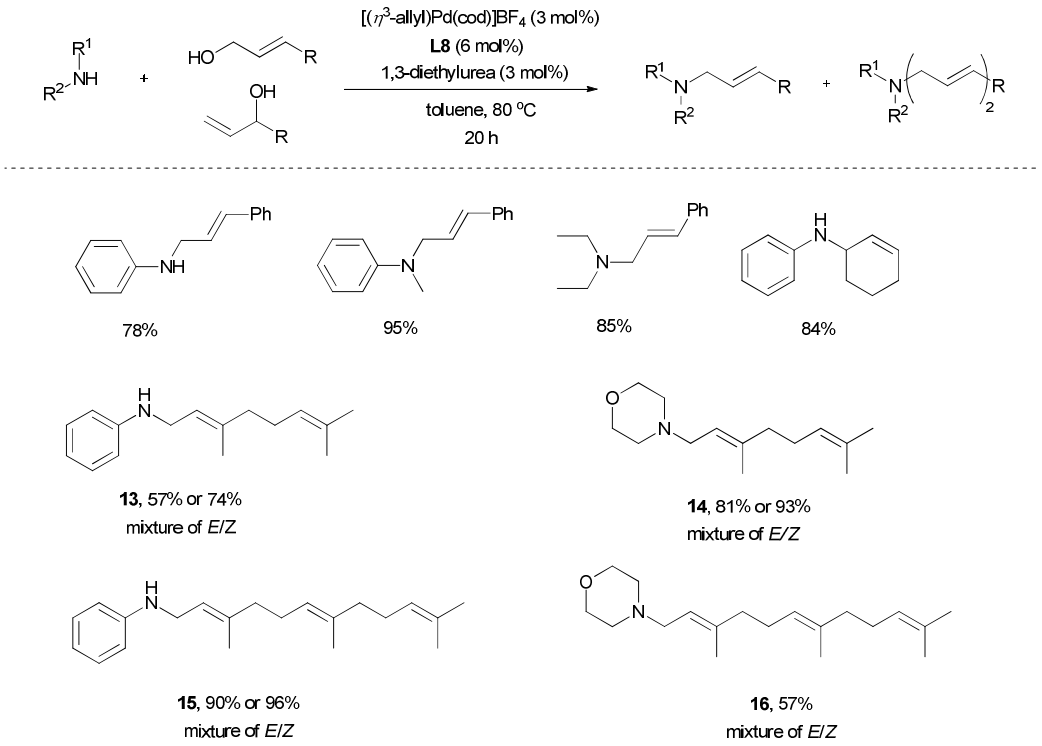


Scheme 16 Proposed mechanism of allylation using a cubane-type sulfido cluster[29]

In a continuation of these initial discoveries, Reek et al. developed a directed activation of allylic alcohols using a hydrogen-bond-assisted palladium catalysis.[30] The catalyst system consists of a functionalized monodentate phosphoramadite ligand (**L8**) and 1,3-diethylurea. The ligand and substrate in combination with a [(η^3-allyl)Pd(cod)]BF_4 catalyst was successful for allylic substitution reactions with indole derivatives (**Scheme 17**) and the amination of primary and secondary amines with allylic alcohols (**Scheme 18**). Most reactions gave acceptable yields depending on the substitution pattern of the indole, with the reaction being selective for the C3 position. C3-methyl substituted indoles did not form any allylation products showing that the reaction is selective for the C3-position. Long chain, linear allylic alcohols such as geraniol, linalool, farnesol, and neralidol reacted with both aniline and morpholine to give their corresponding products **13**, **14**, **15**, and **16** respectively (**Scheme 18**).

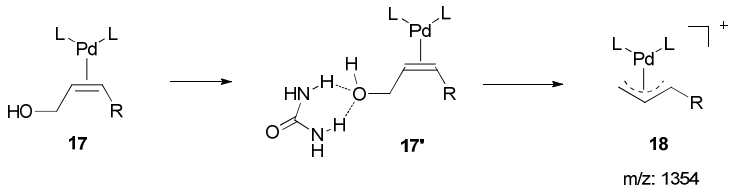


Scheme 17 Allylic alkylation of indole derivatives with allylic alcohols



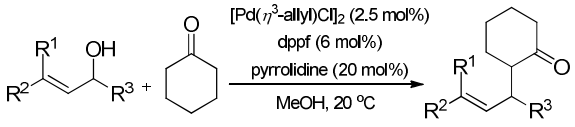
Scheme 18 Allylic amination reactions of primary and secondary amines with allylic alcohols

The addition of a urea additive to the reaction system enables the allylic alcohol to form additional hydrogen bonds with the urea (**Scheme 19**, complex **17'**). These additional hydrogen bonds presumably aid the formation of the reactive Pd-complex **18**, a species observed by mass spectrometry.



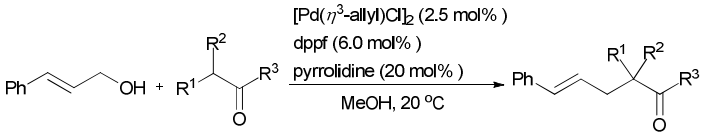
Scheme 19 Proposed mechanism for the amination of allylic alcohols using urea activators

Zhang and co-workers developed a novel approach to activate allylic alcohols using protic solvents. A [Pd(η^3-ally)Cl]$_2$/dppf catalyst in the presence of a pyrrolidine co-catalyst and hydrogen-bonding solvent such as methanol, was suitable for the alkylation of a series of simple ketones with allylic alcohols.[31] The reaction was more effective in the absence of acidic additives. Cyclohexanone was alkylated with a number of terminally-substituted allylic alcohols in good yields, including a tri-substituted allylic species (**Table 6**). The reaction conditions were also effective for the alkylation of a series of other simple cyclic ketones aldehydes (**Table 7**).



entry	R^1	R^2	R^3	time (h)	yield (%)
1	H	H	H	8	93
2	H	Me	H	12	94 (*E*/*Z* = 11/1)
3	H	-$(CH_2)_3$-		24	57
4	Me	Me	H	24	54
5	H	Ph	Me	24	82
6	H	Ph	H	12	97
7	H	3-Me-C_6H_4	H	12	98
8	H	4-Me-C_6H_4	H	12	99
9	H	4-MeO-C_6H_4	H	12	99
10	H	4-Cl-C_6H_4	H	12	98
11	H	Ph	Ph	18	98

Table 6 Allylation of cyclohexanone with allylic alcohols using H-bond activation



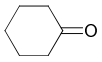
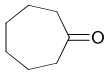
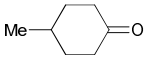
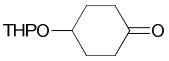
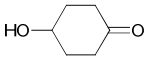
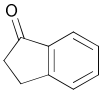
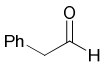
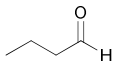
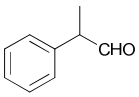
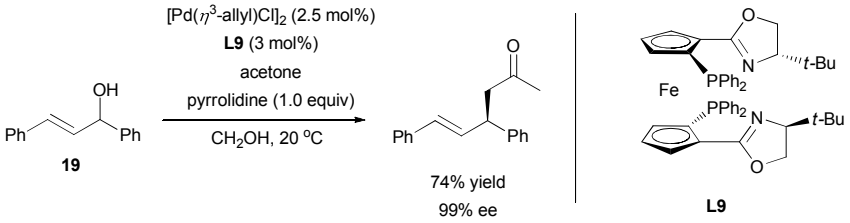
entry	ketones/aldehydes	time (h)	yield (%)
1		10	92
2		12	97
3		24/12[a]	52/97[a]
4		12	98
5		12	98
6		12	97
7		24	92
8		24	66
9		24	70
10		18	92

Table 7 Aldehyde and ketone scope

Application of ferrocene-based phosphinooxazoline ligand **L9** enabled the asymmetric allylation of acetone with allylic alcohol **19** giving the desired product in high yield and high enantioselectivity (**Scheme 20**).[31]



Scheme 20 Asymmetric allylation with ferrocene ligand **L9**

Zhang and co-workers explored the mechanism of the above alkylation reactions by using DFT calculations for the C-O bond cleavage of allyl alcohol in methanol (**Figure 1**). Methanol was shown to be essential for the cleavage of the C-O bond via hydrogen-bond activation. The solvent plays a prominent role in the formation of the π-allylpalladium complex by lowering the activation energy and stabilizing the resulting hydroxide ion. DFT studies shown in **Figure 1** indicate that the ionization of the allylic OH of complex **20** gives the π-allylpalladium complex **21** via $TS_{20\text{-}21}$. The enamine (generated in situ) attacks the π-allypalladium complex **21**, giving complex **22** via $TS_{21\text{-}22}$. Contrary to previous mechanistic investigations, Zhang and co-workers showed that the regenerated Pd catalyst does not require dissociation of the product into a 14-valence-electron Pd complex.[31]

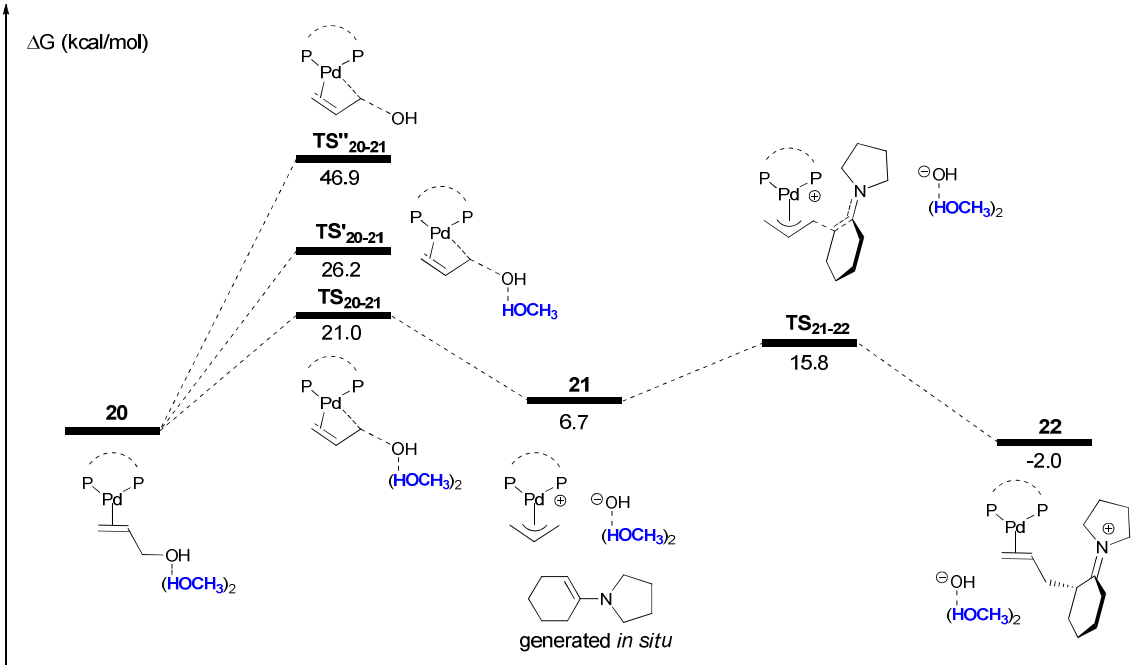
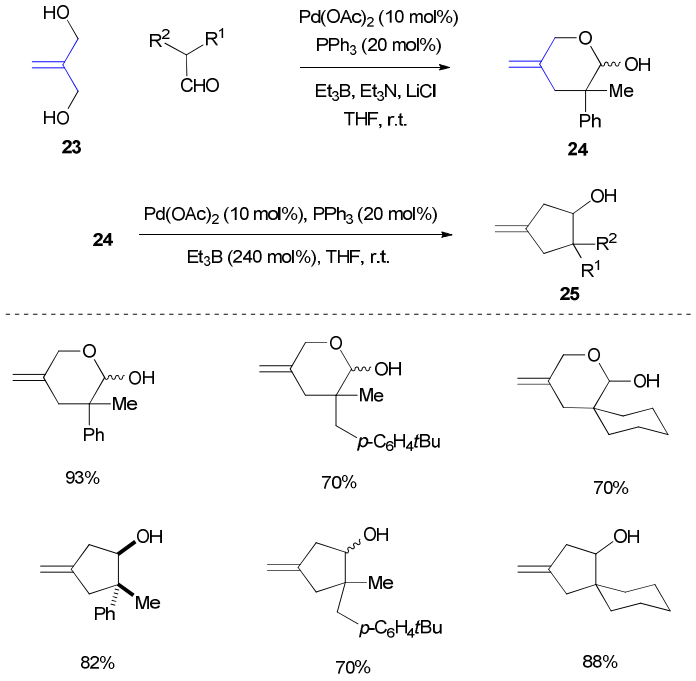


Figure 1 The free energy profile of Pd-catalyzed allylic alkylation of cyclohexanone with allyl alcohol. **L** = 1,2-bis(diphenylphosphino)ethane (dppe).

2.1.3. Allylic substitutions with allylic alcohols using Lewis acids as activators

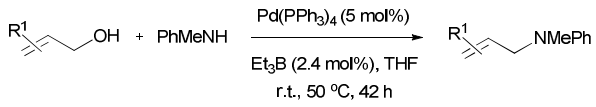
Lewis acids are commonly used activators of allylic alcohols, particularly those based on boron. The first studies involving Lewis acids for allylic alcohol activation required stoichiometric amounts of boron to generate reactive allylic borates.[32–34]

Tamaru et al. have reported the use of stoichiometric amounts of BEt_3 for allylic alcohol activation.[35–38] In 2004, a Pd(0)-catalyzed amphilic activation of bis-allyl alcohol using the reaction conditions shown in **Scheme 21** was developed. The symmetric bis-allyl alcohol, 2-hydroxymethl-2-propen-1-ol **23**, undergoes electrophilic allylation at the α-position of aldehydes to give hemi-acetals **24**, which subsequently act as allylic nucleophiles (in the absence of base) to furnish 3-methylenecyclopentanols **25** in good yields. The reaction is also suitable for aldehydes bearing less acidic α-protons.[39]



Scheme 21 Pd(0)-catalyzed amphiphilic activation of bis-allyl alcohols

A catalytic system consisting of $Pd(PPh_3)_4$ and Et_3B was suitable for the di-alkylation of primary amines and mono-alkylation of secondary aromatic and aliphatic amines with a diverse array of allylic alcohols.[40] *E*-Isomers were formed preferentially in good yields with addition to the least substituted end of the allylic terminus (**Table 8**).



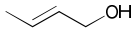
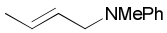
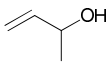
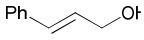
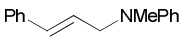
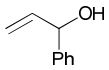
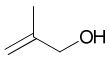
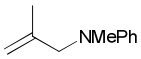
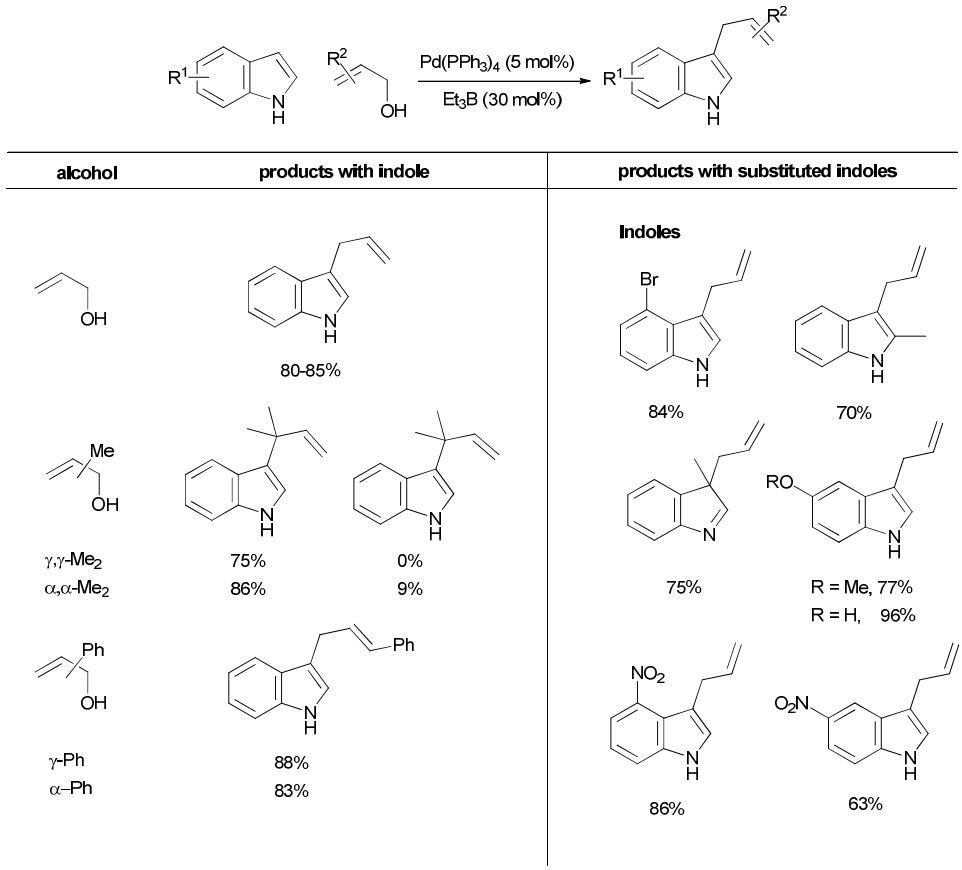
alcohol	Et_3B (mmol)	temp, time	% yield (ratio)
	0.3	r.t., 30 h	 93% [8:1 *E*/*Z*]
	0.3	r.t., 30 h	88% [8:1 *E*/*Z*]
	0.3	r.t., 24 h	 85% *E*
	0.3	r.t., 24 h	82% *E*
	0.6	50 °C, 24 h	 88%

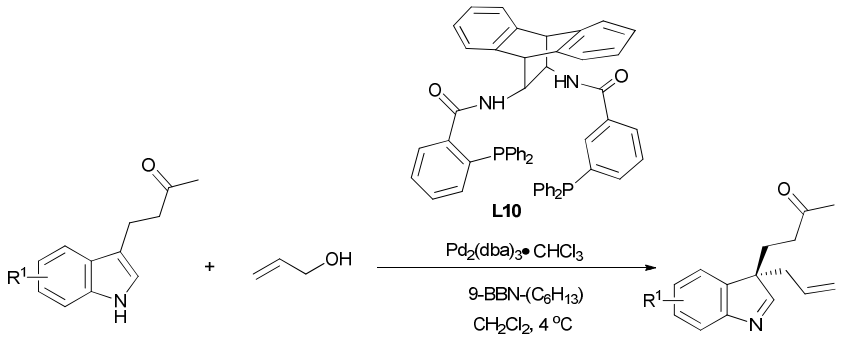
Table 8 Et_3B activated allylation of *N*-methylaniline with allylic alcohols

The reaction conditions mentioned above were also suitable for the Pd-catalyzed C3-selective allylation of indoles and naphthols with allylic alcohols. In the presence of 30 mol% Et_3B and 100 mol% of an allylic alcohol, allylated indoles could be obtained in good yields (**Scheme 22**).[41] Unsymmetrical alcohols showed similar regioselectivities, however an explanation for the differing regioselectivities giving either a straight-chain isomer or a branched-chain isomer is lacking. Perhaps surprisingly, no alkylation at the indole NH is observed with exclusive selectivity for the indole C3.



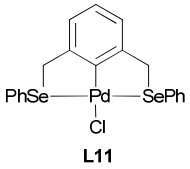
Scheme 22 Allylations of indole with allylic alcohols and substituted indoles with allyl alcohol

Trost and Quancard have also published methodology for the allylic substitution of indoles at the C-3 position. They utilized 9-BBN-(C_6H_{13}) as the activating borane agent and ligand **L10** to induce enantioselectivity (**Scheme 23**).[42] The reaction conditions were tolerable for a range of 3-substituted indoles possessing both electron donating- and electron withdrawing groups, with electron rich indoles providing higher activities. The borane activator is believed to be involved in the enantiodetermining step.

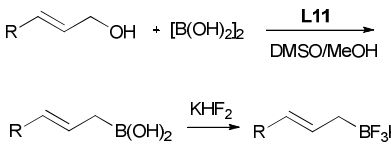


Scheme 23 Pd-catalyzed enantioselective C3 allylation of 3-substituted-1*H*-indoles using 9-BBN-(C_6H_{13}) as an allylic alcohol activator

Szabó and co-workers reported a Pd(II)-catalyzed silylation and boronation of allylic alcohols using relatively mild reaction conditions.[43] Pincer-Pd complex **L11**, in the presence of diboronic acid in DMSO solvent prompted an efficient and facile borylation of a number of allylic alcohols (**Table 9**). Pd(0) sources such as $Pd_2(dba)_3$ and Pd $(PPh_3)_4$ were ineffective as catalysts. Both branched and linear allylic alcohols provided linear allyl boronates respectively, with the reaction conditions also being suitable for the borylation of cyclic allyl alcohols. The allylic boronic acid products were converted to their corresponding trifluoro(allyl)borate derivatives due to the unstable nature of the allylic boronic acids under solvent-free conditions. A DMSO/MeOH solvent mixture was required for high reaction rates and high yields, and the diboronic acid acts as a Lewis acid activator for the allylic group. Additionally, stereodefined allylic alcohols give rise to products with inverted stereochemistry (**Table 9**, entry 5).



L11



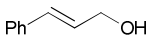
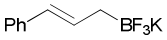
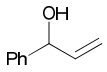
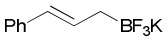
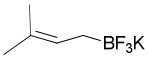
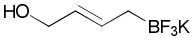
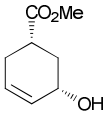
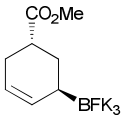
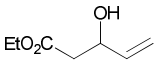
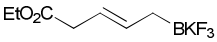
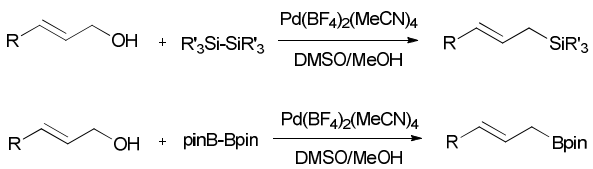
entry	substrates	cond. (°C/h)	products	yield (%)
1		40/16		92
2		40/7		86
3		50/16		98
4		20/16		74
5		50/24		87
6		40/20		77

Table 9 Pd(II)-catalyzed borylation of allylic alcohols using a pincer complex **L11**

Szabó and co-workers discovered that a catalyst system consisting of $Pd(BF_4)_2(MeCN)_4$ (5 mol%) in DMSO/MeOH was suitable for the conversion of a range of allylic alcohols to their corresponding allyl silanes at a lower temperature compared to that described above (**Table 10**).[44] Reaction of various allylic alcohols with disilanes as a silyl source gave the corresponding silane products in good yield. The regio- and stereoselectivity of the reaction was found to be very high with linear allylic products being formed exclusively (entry 4). The double bond geometry was also selectively *trans* even when *cis*-alcohol starting materials were used (entry 6).



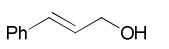
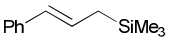
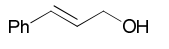
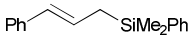
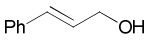
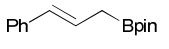
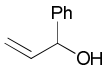
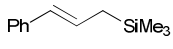
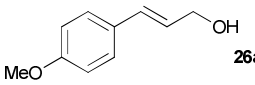
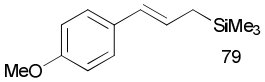
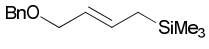
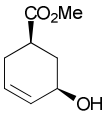
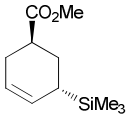
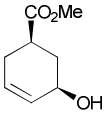
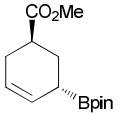
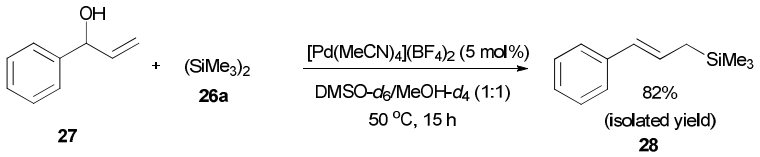
entry	substrates	cond °C/h.	product	yield
1		$(Me_3Si)_2$ **26a** 50/15		84/77
2		$(Me_2PhSi)_2$ **26b** 50/15		79
3		$(Bpin)_2$ 20/1.5		78
4		**26a** 50/15		83
5		**26a** 50/15		79
6		**26a** 50/15		69
7		**26a** 60/15		52
8		$(Bpin)_2$ 20/1.5		70

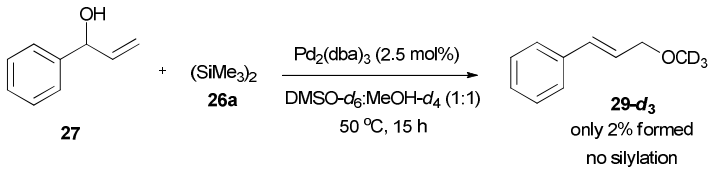
Table 10 Pd(II)-catalyzed silylation and borylation of allylic alcohols

A mechanistic pathway for the Pd-catalyzed synthesis of allylic silanes and boronates from allylic alcohols was elucidated using detailed NMR studies. A model system consisting of allylic alcohol **27** and disilane **26a** was used for the NMR experiments (**Scheme 24**).[45] Several important details were uncovered: 1) the tetrafluoroborate anion releases BF_3, which is able to activate allylic alcohol substrates; 2) (η^3-ally)palladium species are key intermediates; and 3) the transmetalation is the rate-limiting step for the silylation.



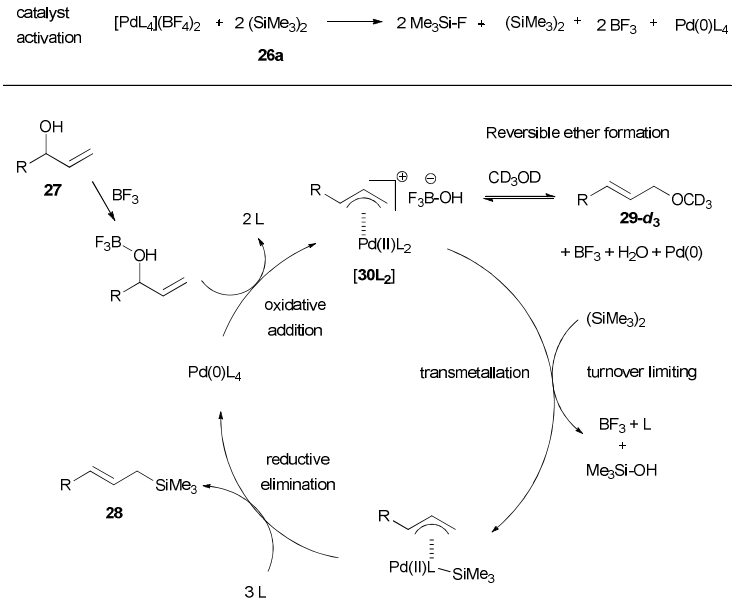
Scheme 24 Model system used to determine mechanism of allyl silane formation

The importance of the BF_3 was determined by replacing the Pd catalyst with $Pd_2(dba)_3$ (**Scheme 25**). In the absence of any Lewis acid, no silylation occurred; the only product obtained was the deuterated allyl ether **29**. However, when the reaction was conducted in the presence of 15 mol% Lewis acid BF_3•OEt_2, the alkylated product was obtained in 72% yield. This suggested that the BF_3 generated throughout the reaction (as observed via ^{19}F NMR spectroscopy) was essential for reaction activity i.e. for the activation of the allylic hydroxyl group.



Scheme 25 Attempted silylation usng $Pd_2(dba)_3$ as catalyst in the absence of BF_3

Szabó and co-workers propose the catalytic cycle shown in **Scheme 26**. The Pd catalyst is activated with 2 equivalents of $(SiMe_3)_2$ to give Me_3Si-F, BF_3 and a Pd(0) complex with loosely coordinated ligands. The allylic alcohol is activated by the newly formed BF_3 and oxidative addition with Pd(0) gives complex $\mathbf{30L_2}$.Transmetallation of $\mathbf{30L_2}$ with $(SiMe_3)_2$ followed by reductive elimination gives the allylic silane **28** and regenerates the Pd(0) catalyst. Interestingly, deuteration experiments showed that allylic ether **29**-d_3 can be generated via reaction of the (η^3-allyl)palladium complex $\mathbf{30}L_2$ with methanol, as well as via alcohol **27** by a BF_3-catalyzed nucleophilic substitution. This ether can also be converted to the silane **28** via the same catalytic mechanism in which allylic alcohol **27** is converted to the allylic silane product.

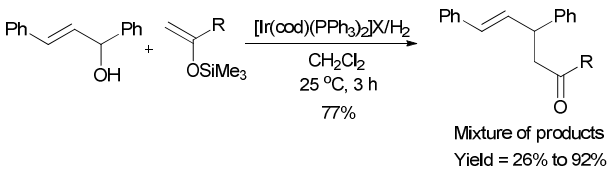


Scheme 26 Mechanism for the palladium-catalyzed allylic silylation reaction as proposed by Szabó and co-workers

2.2. Iridium-catalyzed allylic substitution reactions with allylic alcohols

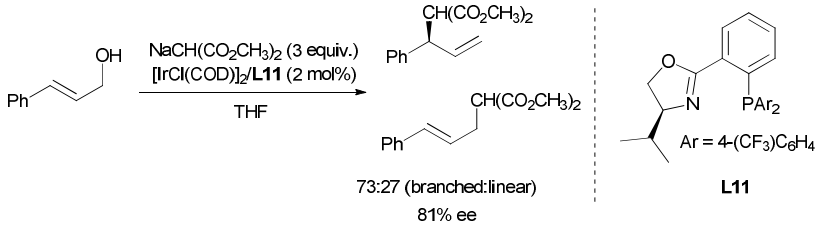
Iridium is a versatile metal which has found use in a number of catalytic systems. One particularly useful application of iridium complexes is their ability to be used as catalysts in asymmetric allylic substitution reactions with a variety of allylic species.[46] A notable feature of Ir-catalyzed allylic substitution reactions is that in contrast to Pd-catalyzed methodologies, branched allylic products are preferentially formed.

In 1997 the first enantioselective Ir-catalyzed allylic substitution reactions with allylic acetates was reported by Helmchen and co-workers.[47] In 1998 the Takeuchi group developed an nn $[Ir(COD)Cl]_2/P(OPh)_3$ catalyst system for the alkylation of simple linear and branched alcohols with sodiomalonate.[48] The reaction was regioselective for the most substituted allylic terminus when non-symmetrical allylic alcohols were used. In 2002 Matsuda and co-workers discovered that an $[Ir(cod)(PPh_3)_2]X$ complex (where X = PF_6, OTf, ClO_4) activated by H_2, was suitable for the allylic substitution of 1,3-diphenylprop-1-ene derivatives with enoxysilanes.[49] Pent-4-en-1-one derivatives could be prepared as a mixture of isomers in up to 94% yield with Ir complexes bearing a triflate counter-ion (**Scheme 27**).



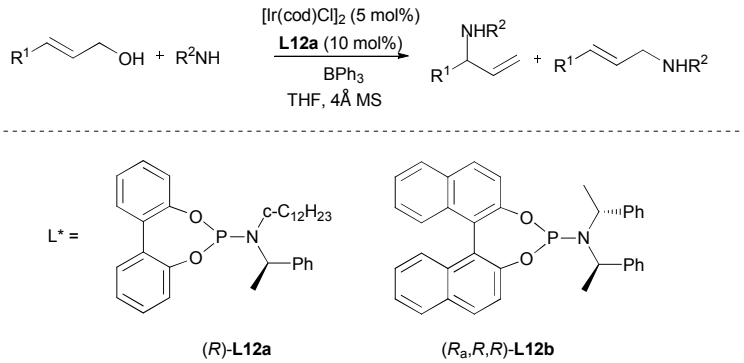
Scheme 27 Ir-catalyzed reaction of enoxysilanes with allylic alcohols

In 2004 Helchem reported an Ir-catalyzed of allylic alkylation of monosubstituted allylic substrates using phosphinooxazolines as ligands.[50] A combination of $[Ir(cod)]_2$ with the P,N ligand **L11** was suitable for the allylic substitution of cinnamyl alcohol with sodiomalonate. The branched product was predominantly formed with 81% ee (**Scheme 28**).



Scheme 28 Ir-catalyzed allylic substitution with a phosphinooxazoline ligand

Hartwig et al. used phosphoramidite ligands in conjunction with stoichiometric quantities of Lewis acid for regio- and enantioselective aminations with substituted aryl alcohols.[51] A catalytic complex generated from phosphoramidite ligands **L12** and $[Ir(cod)Cl]_2$, in the presence of a catalytic amount of BPh_3 in dioxane solvent, was suitable for the preparation of branched allylic amines with excellent regioselectivities and enantioselectivities (**Table 11**). A number of cinnamyl alcohol derivatives were successfully reacted with various anilines giving the corresponding products in acceptable yields when ligand **L12a** was used. The highest yields were obtained with cinnamyl alcohols bearing *p*-substituted electron-donating groups (entries 1 and 2). Anilines bearing *o*-, *m*-, and *p*-substituents reacted without cleavage of the C-Cl bond (entries 6-10). 1.5 Equivalents of alcohol was required to prevent formation of diallyl ethers.

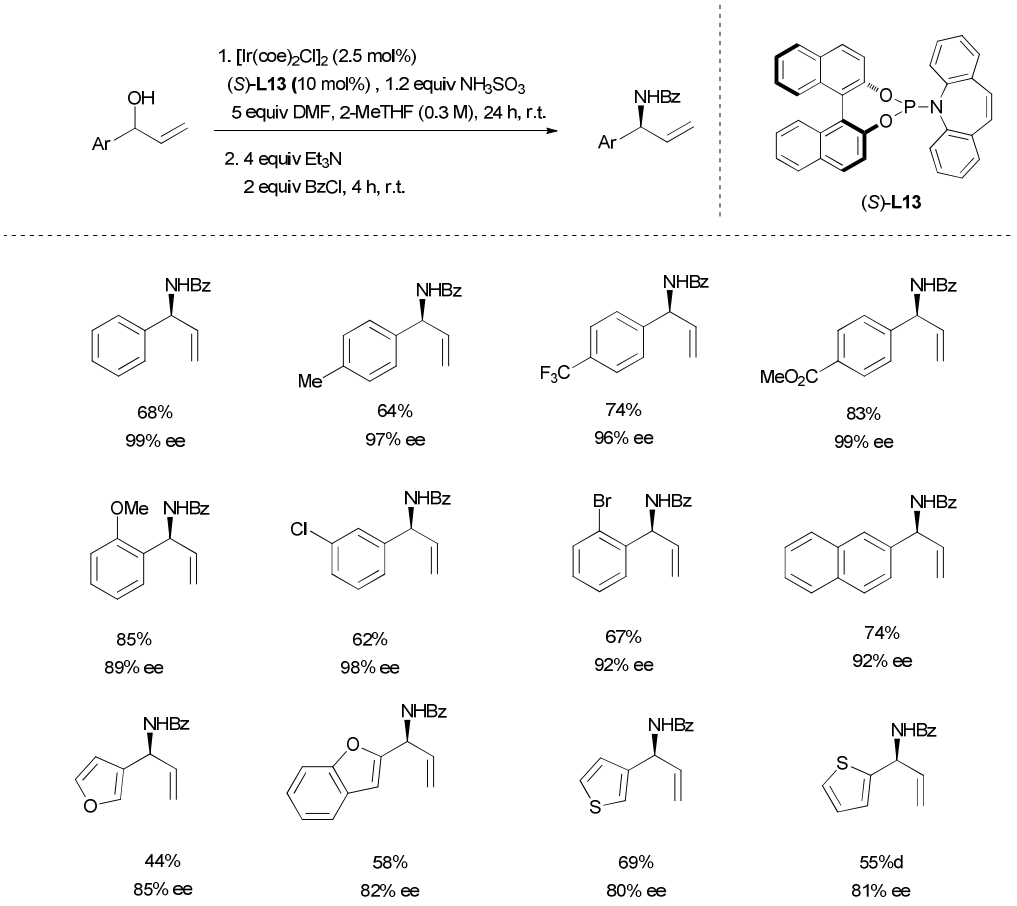


(*R*)-**L12a** (*R*a,*R*,*R*)-**L12b**

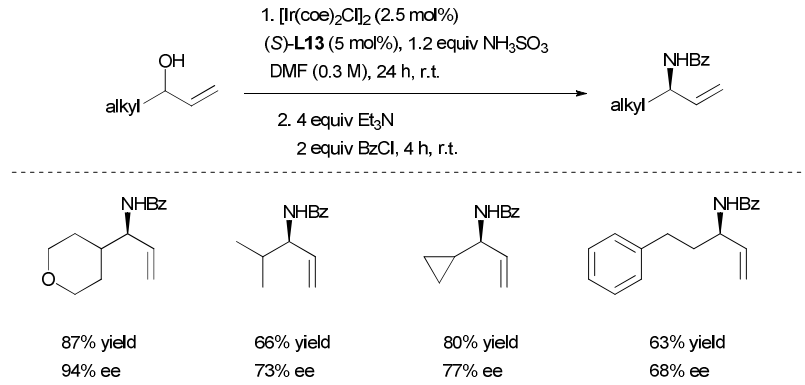
entry	R^1	R^2	yield (%)	branched/linear	ee (%)
1	Ph	*p*-MeC_6H_4	74	97/3	88
2	Ph	*p*-$MeOC_6H_4$	72	94/6	93
4	Ph	*o*-$MeOC_6H_4$	52[d]	95/5	94
5	Ph	*p*-ClC_6H_4	53	>94/<6	92
6	*p*-$MeOC_6H_4$	*p*-MeC_6H_4	72	96/4	92
7	*p*-$MeOC_6H_4$	*m*-$MeOC_6H_4$	61	>97/<3	83
8	*p*-$MeOC_6H_4$	*p*-ClC_6H_4	66	95/5	93
9	*p*-MeC_6H_4	*p*-MeC_6H_4	66[d]	>95/<5	94
10	*p*-BrC_6H_4	*p*-MeC_6H_4	61	>92/<8	87

Table 11 Ir-catalyzed allylic substitution using BPh_3 as an activator[51]

Carreira and co-workers have developed several procedures for the synthesis of primary and secondary allylic amines from racemic allylic alcohols using sulfamic acid as an ammonia equivalent.[52–54] A number of allylic amines could be prepared using an [Ir(coe)Cl_2] catalyst precursor and phosphoramidite-olefin ligand (*S*)-**L13** (**Scheme 29**). A co-solvent system consisting of DMF (5 equivalents) and 2-methyltetrahydrofuran provided the best yields. The reaction conditions were suitable for a range of electron-rich and electron-deficient aromatic allylic alcohols, with the corresponding products being obtained in moderate to good yields and good to high enantioselectivities.[54] For certain substrates the stereoselectivity could be fine-tuned using different co-solvents. Aliphatic racemic allylic alcohols were also amenable to the allylic amination reaction conditions (**Scheme 30**). Interestingly, for aliphatic allylic alcohols, in situ generation of the ligand/Ir complex with a ligand/Ir ratio of 2:1 as used previously provided the aminated products with good ee but comparatively poor yields. A ligand/Ir ratio of 1:1 gave superior results.



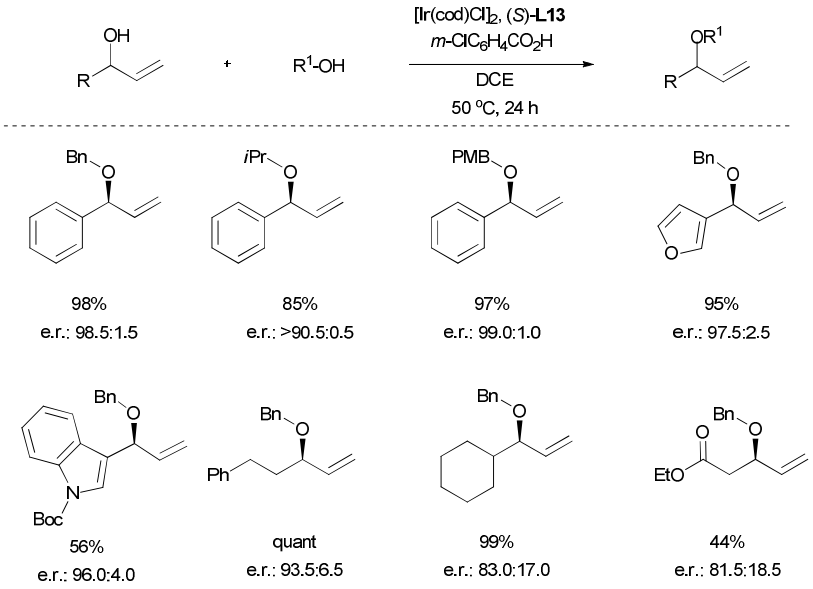
Scheme 29 Ir-catalyzed preparation of allylic amines from aryl allylic alcohols



Scheme 30 Ir-catalyzed amination with aliphatic allylic amines

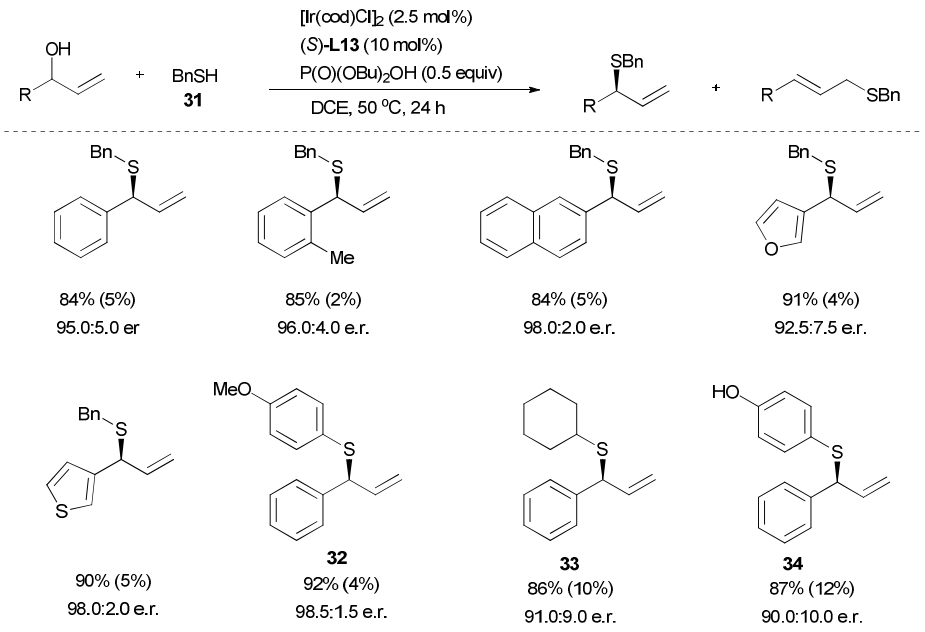
The Ir-ligand (*S*)-**L13**, in conjunction with a Brønsted acid as an activator, was suitable for the preparation of allylic ethers from allylic alcohols.[55] Carreira and co-workers discovered that a range of Brønsted acids with pKa values in the range of 3.4 to 3.9 (aq) could be used to activate allylic alcohols to nucleophilic attack with alcohol nucleophiles. Interestingly, the authors discovered that the structural

features of the Brønsted acid affects the reaction outcome. For example, *m*-chlorobenzioic acid (pKa 3.8) was far more effective than formic acid (pka 3.8) despite having an identical pKa. Carrying out the reaction in 1,2-dichloromethane with 5 equivalents of aliphatic co-reactant (to preclude the formation of symmetrical diallyl ether) gave the allylic ether products in high yields and ees (**Scheme 31**). The reaction conditions proved to be applicable to a wide range of aliphatic and allylic alcohol substrates. The highest yields of product were obtained using arene vinyl carbinols as nucleophiles. Aromatic, heteroaromatic and electron-deficient allylic alcohols could also be used successfully but were not as effective as the aforementioned substrates. Additionally, the same ether enantiomer is formed from both substrate enantiomers.



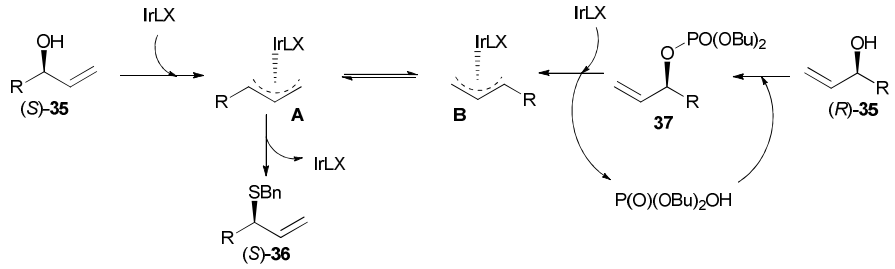
Scheme 31 Ir-catalyzed allylic etherification.

Similar reaction conditions were found to be of use for enantioselective allylic thioetherification reactions.[56] Previous attempts at the synthesis of allylic thioesters have required the use of activated allylic species and reactive sulfur nucleophiles. (*S*)-**L13** in combination with an $[Ir(cod)Cl_2]$ catalyst and $P(O)(OBu)_2OH$ as a phosphate diester activator, was found to be a suitable ligand for the enantioselective allylation of racemic allylic alcohols with BnSH **31** (**Scheme 32**). Electron-rich allylic alcohols underwent thioetherification at 23 °C while electron-deficient substrates required a higher temperature of 80 °C. *p*-Methoxybenzyl mercaptan (**32**), cyclohexanethiol (**33**) and thiopehenol (**34**), were all able to form their respective thioesters.



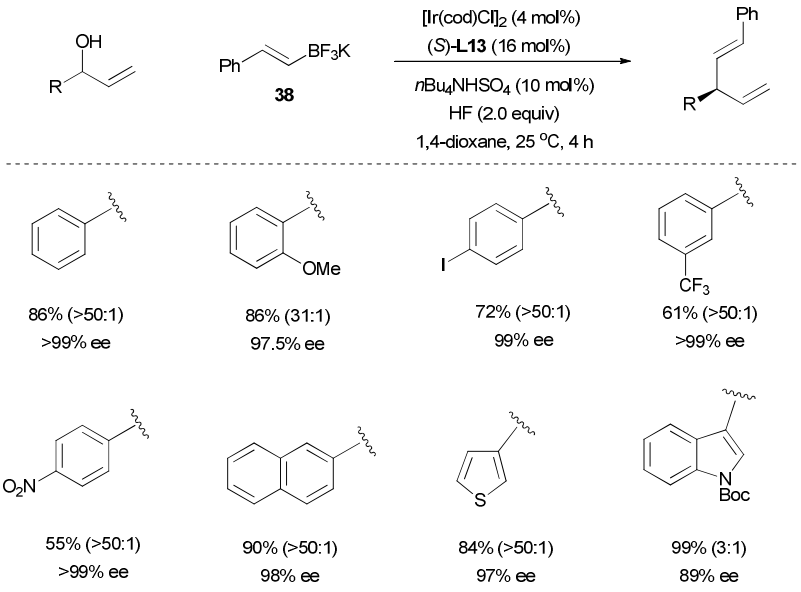
Scheme 32 Ir-catalyzed enantioselective allylic thioetherification

Due to the preferential formation of a single enantiomer from a racemic allylic alcohol mixture, the thioetherification process is thought to occur via an enantioconvergent mechanism i.e. each enantiomeric alcohol undergoes reaction through separate mechanistic pathways (**Scheme 33**).[56] Thus (*S*)-**35** is directly converted to its product enantiomer (*S*)-**36** (with retention of stereochemistry) via allyl-iridium intermediate **A**. The other enantiomer, (*R*)-**35**, is first transformed to allyl phosphoric ester **37**, and then allyl-iridium complex **B**. Complex **B** is likely in equilibrium with **A** and undergoes conversion to thioester (*S*)-**36**. This reaction proceeds with inversion of configuration. Interestingly, aliphatic and electron-poor allylic alcohols did not undergo enantioconvergent thioetherifications, and alternatively underwent a phosphate-promoted kinetic resolution.[56]



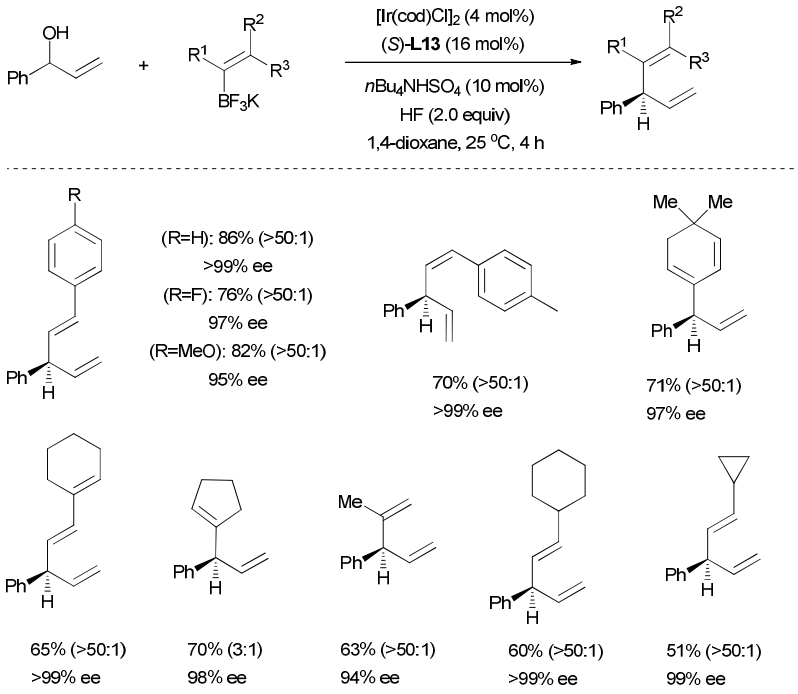
Scheme 33 Proposed mechanism for allylic thioetherication from two enantiomers of the same allylic alcohol

Ligand (*S*)-**L13** further proved its versatility by being successfully used in Ir-catalyzed enantioselective allylic vinylations. Carreira and co-workers utilized vinyl potassium trifluoroborates for the Ir-catalyzed vinylation of allylic alcohols.[57] Due to the poor solubility of potassium trifluoroborates in organic solvents, a phase transfer catalyst system was employed for this reaction. nBu$_4$NHSO$_4$ was essential for high yields and plays two important roles in the reaction; it acts as the phase transfer catalyst for potassium alkenyltrifluoroborates; and secondly, it acts as a Brønsted acid activator (pKa of HSO_4^- = 1.99). Using the optimized reaction conditions shown in **Scheme 34**, a number of alkoxyl, halogenated, ester and aldehyde bearing aromatic allylic alcohols were reacted with styryltrifluoroborate **38** to give their corresponding products in good yields. More electronically challenging substrates (*p*-NO_2 and *m*-CF_3) were also amenable to the reaction conditions albeit giving the corresponding products in slightly lower yields.



Scheme 34 Ir-catalyzed vinylation of allylic alcohols with potassium styryltrifluoroborate **38**

Reaction of different alkylenyltrifluoroborate substrates with α-vinylbenzyl alcohol was also successful (**Scheme 35**). *p*-Fluoro and *p*-methoxy substituted trifluoroborates gave the corresponding products in good yields and high ees (no olefin isomerization was observed). Conjugated dienes, cyclic vinyltrifluoroborates and monosubstituted vinyltrifluoroborates all gave their conjugated products in high yields and enantioselectivities.



Scheme 35 Ir-catalyzed vinylation of allylic alcohols with various potassium trifluoroborates

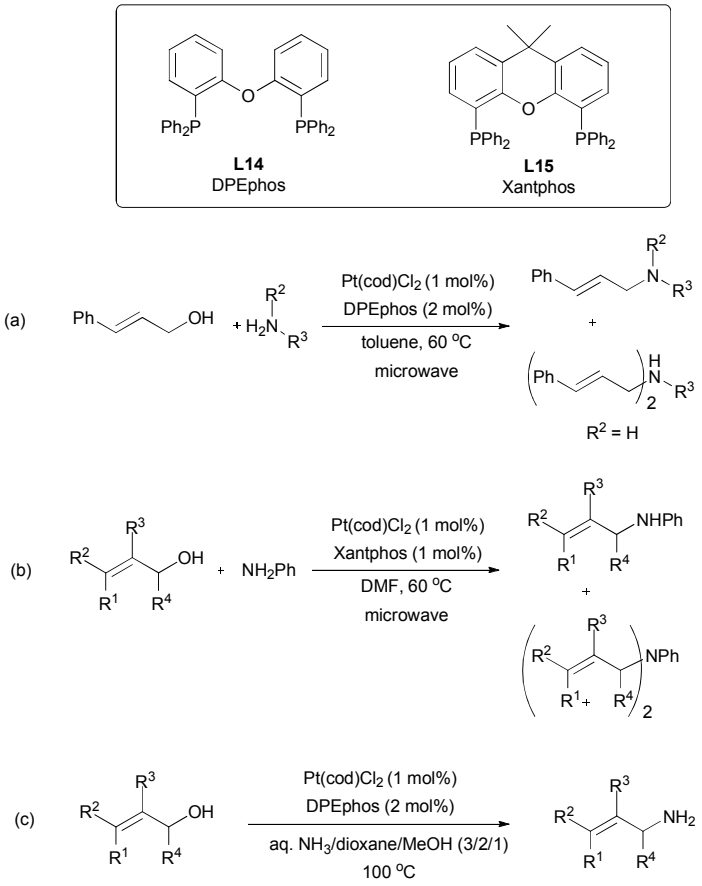
2.3. Allylic substitutions with allylic alcohols using other transition metals

Although the majority of allylic substitution reactions with allylic alcohols use the transition metals Pd and Ir, methodologies using other transition metals such as Ru, Ni, Pt, and Mo have been reported. Such procedures discussed in prior reviews will not be discussed in this report.[11]

Jamison and co-workers utilized a [Ni(COD)$_2$] catalyst and P(*o*-anisyl)$_3$ for the substitution of cinnamyl alcohols with ethylene as a nucleophile.[58] Triethylsilyl trifluoromethanesulofnate (Et_3SiOTf) and a base (Et_3N) were required to effect the transformation. 1-Phenylpent-1,4-diene could be prepared selectively in 56% yield.

Oshima and co-workers reported a catalytic amination of allyl and cinnamyl alcohol using a Pt(cod)Cl$_2$ catalyst and ligands with large bite-angles (DPEphos **L14** and Xantphos **L15**).[59] The reaction conditions were suitable for the synthesis of a number of substituted anilines in good yields. No allylic activating additives were required for the reaction and monoallylated products were prepared selectively. The reaction conditions were further optimized using microwave irradiation and were suitable for the catalytic amination of allylic alcohols with arylamines, and alkyl amines (**Scheme 36a**).[60] Amination of a number of allylic alcohol substrates with aniline was possible when DPEphos was replaced with 4,5-bis(diphenylphopshino)-9.9-dimethylxanthene (Xantphos) (**Scheme 36b**).[60] Carrying out the reaction in DMF solvent under microwave irradiation gave the corresponding aminated products in up to 92% yield (including branched allylic alcohols) with high selectivity for the

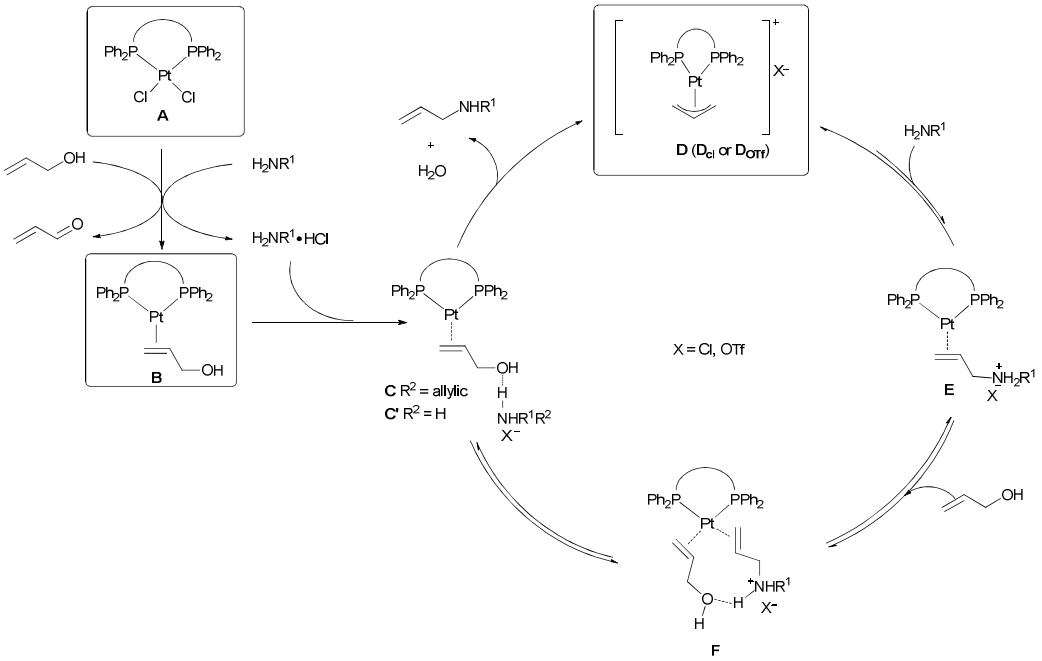
monoallylation products. Similar reaction conditions were suitable for the synthesis of primary allylic amines from a variety of aryl-substituted allylic alcohols using ammonia as a nucleophile. Primary allylic amines were obtained in good yields when the reaction was carried out at 100 °C in dioxane/methanol solvent (**Scheme 36c**).[61]



Scheme 36 Pt-catalyzed allylic amination

A mechanism for the above reactions has been proposed based on ^{1}H and ^{31}P NMR studies, X-ray crystallography studies and cross-over experiments (**Scheme 37**).[60] Pt(cod)Cl_2 complex **A** is reduced with allyl alcohol and the amine H_2NR^1 to give the active Pt(0) species **B** and the accompanying ammonium salt H_2NR^1• HCl and aldehyde. Intermediate [Pt(η^3-allyl)(xantphos)]OTf (**D_{OTf}**) is involved in the catalytic cycle and possesses a higher reactivity than intermediate **B**. This may be because of the generation of the ammonium salts H_2NR^1• HCl and H_2NR^1• HOTf, which act as more efficient activators of the hydroxyl group by accelerating the elimination of the hydroxide through hydrogen bonding of the ammonium salts with the hydroxyl group of the allylic alcohol (**C'→D**).[60] Results suggested that complexes **D**, **E**, **F**, and **C** are in rapid equilibrium, with **D** being the most reactive and

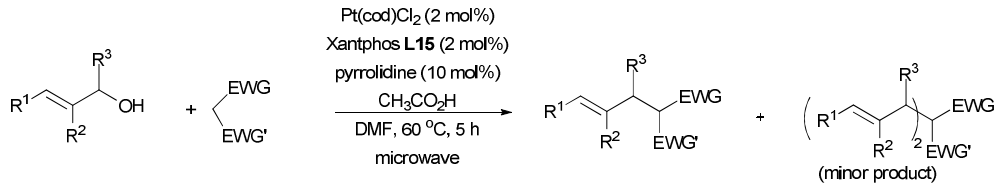
stable species in the presence of excess amounts of nucleophile. Formation of **D** from **C** via elimination of water and the allylic amine was determined to be the rate-limiting (and an irreversible) step and required a reaction temperature of 50 ^{o}C.



Scheme 37 Proposed mechanism for Pt-catalyzed allylic amination

The large bite-angle of the ligands allows for preferential formation of the monoallylation products. Le Floch and co-workers proposed that ligands with a large bite-angle prevent the formation of platinum hydride complexes and therefore the formation of an inactive bicyclic aminopropyl complex.[62] Oshima et al. further proposed that the linker oxygen atom in DPEphos and Xantphos were also important for the high catalyst performance. Interestingly, electronic effects of the ligand do not play a significant role in determining catalytic activity. However, addition of an oxygen atom at the *ortho*-position of the triarylphosphine ligands increased the catalytic activity of the Pt complex, possibly by increasing the leaving ability of the hydroxyl group through hydrogen bonding.[60]

Oshima and co-workers improved the reaction selectivity and reduced the formation of unwanted by-products by adding a catalytic amount of pyrrolidine and acetic acid to the reaction mixture (**Table 12**).[63] Direct alkylation of a number of 1,3-diketone products was successful using a [Pt(cod)Cl_2] catalyst precursor in the presence of Xantphos ligand **L15** in DMF solvent. The Pt-catalysis was also suitable for the alkylation of a range of allylic alcohols using identical reaction conditions, retaining good selectivity for the formation of the monoallylated products.



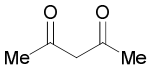
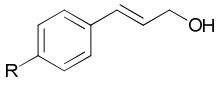
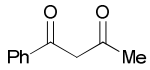
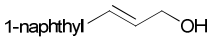
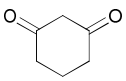
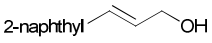
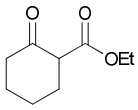
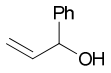
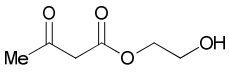
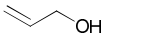
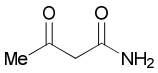
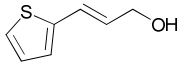
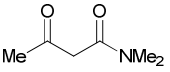
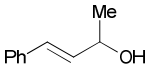
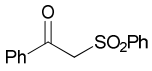
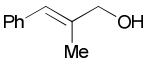
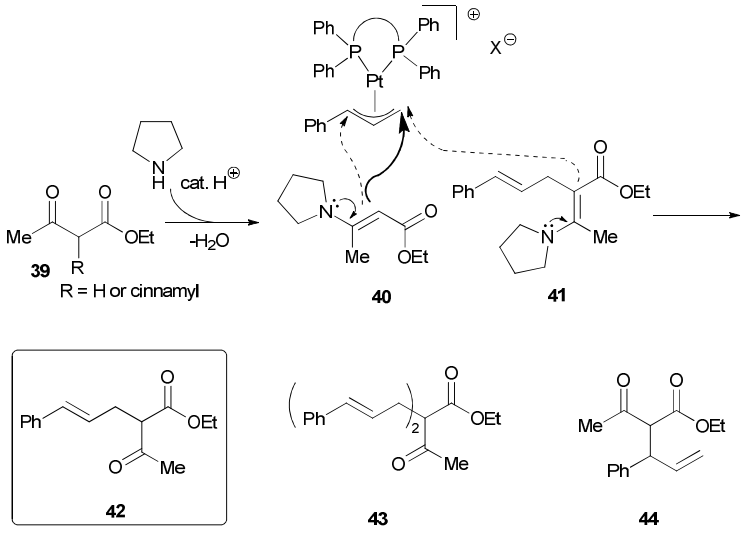
a) nucleophile	yield (%)	ratio	b) allylic alcohol		yield (%)	ratio
	82	93:7		**a** (R = H)	85	95:5
				b (R = Me)	81	92:8
				c (R = Br)	87	94:6
				d (R = OMe)	82	93:7
				e (R = OH)	83	97:3
				f (R = OTBS)	80	95:5
				g (R = OTHP)	84	96:4
	91	>99:1			84	95:5
	86	92:8			82	95:5
	87	-			85	95:5
	83	95:5			86	93:7
	87	93:7			91	97:3
	93	97:3			80	97:3
	91	>99:1			86	96:4

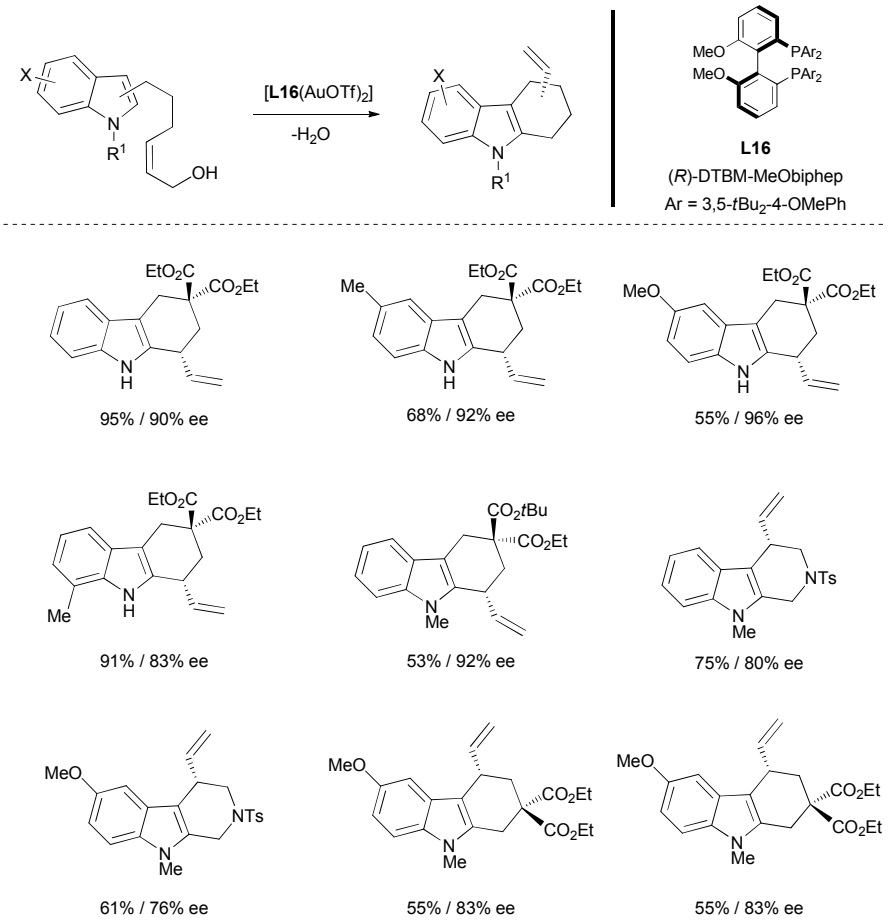
Table 12 Pt-catalyzed direct alkylation of active methylene compounds: a) allylic alcohol = cinnamyl alcohol; b) nucleophile = ethyl acetoacetate

To determine the effects of the pyrrolidine and acetic, an acid-controlled alkylation of cinnamyl alcohol with enamine **40** was carried out (**Scheme 38**). The result was identical to that of the reaction between *β*-keto ester **39** in the presence of catalytic amounts of pyrrolidine and acetic acid.[63] Additionally, direct reaction of a mixture of **39** and a catalytic amount of **40** and acetic acid also produced identical results. Conversely, use of *N*-methylpyrrolidine instead of pyrrolidine gave a mixture of compounds **42**, **43**, and **44**, thus suggesting that the pyrrolidine acts as an organocatalyst to form the intermediate enamine **40**, which then reacts with the activated allyl-Pt complex. The acetic acid promotes the generation of enamine **40** by activating the carbonyl group of the methylene compound **39**.



Scheme 38 Action of pyrrolidine and acetic acid

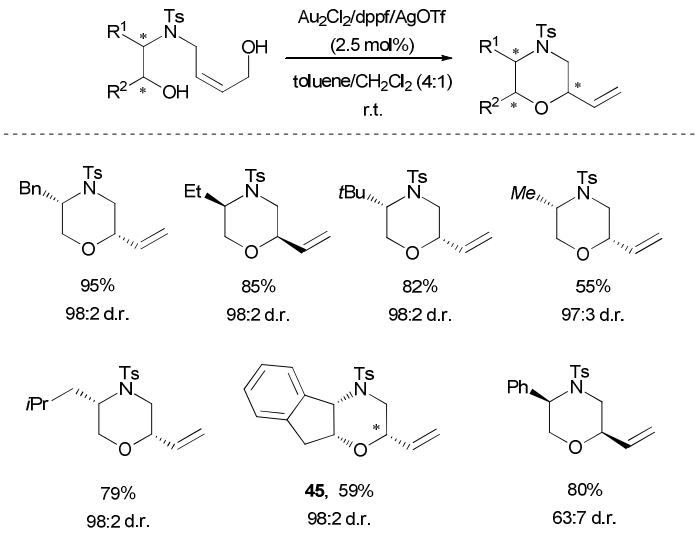
More recently, gold, in addition to its use in a multitude of other asymmetric catalytic reactions, has also been used for substitution reactions with allylic alcohols. Bandini and co-workers developed a gold-catalyzed enantioselective allylic alkylation of indoles with allylic alcohols utilising (*R*)-DBTBM-MeObiphep ligand **L16**.[64–66] [**L16**$(AuOTf)_2$] was used as the active catalyst precursor for these reactions. A range of tricyclic indolyl derivatives could be prepared via an intramolecular allylic alkylation at 0 ^{o}C in toluene solvent (**Scheme 39**). The configuration of the carbon-carbon double bond, the nature of the gold counter-ion, and the leaving hydroxyl group all play an important role in the outcome of the intramolecular alkylation reaction.



Scheme 39 Synthesis of tricyclic indolyl scaffolds via the intramolecular enantioselective allylic alkylation of substituted indoles

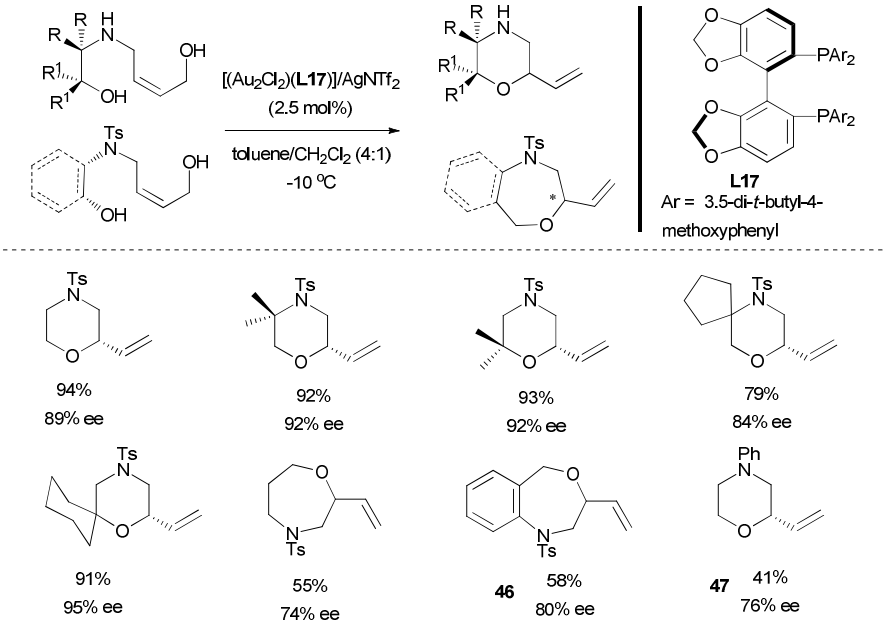
From detailed DFT studies Bandini et al.[65] were able to elucidate that: (1) The favoured mechanism for the reaction is a stepwise indole auration of the C-C double bond via an S_N2' type mechanism; (2) the triflate counter-ion forces the two reactive sites of the starting adducts together (via two strong H-bonds involving the indole NH, allylic hydroxyl group, and the two triflate oxygen atoms) so that they have the correct orientation to react; 3) The electrophilicity of the C2-C3 double bond is enhanced by the gold atom resulting in a low energy barrier; and 4) Attack of the C2 indole carbon atom on the Au(I)-activated olefin is favored.

A co-catalyst system constituting AgOTf and a cationic dinuclear gold complex $[(Au_2Cl_2)(dppf)]$/AgOTf derived from ferrocene ligand dppf, was successfully used for the diastereoselective synthesis of morpholines from diols containing allylic alcohol groups.[67] A series of enantiomerically pure diols were subjected to dehydrative ring closure using the catalyst system shown in **Scheme 40**. *cis*-2,5-Disubstituted morpholines were prepared with excellent yields and > 97:3 d.r., including an enantiomerically pure 2,5,6-trisubstituted-tetrahydro-1,4-oxazine (**45**).



Scheme 40 Diastereoselective gold(I)-catalyzed synthesis of morpholines

Vinylmorpholines could also be prepared with up to 95% ee utilizing a catalyst system consisting of [(Au_2Cl_2){(*R*)-3,5-tBu_2-4-MeO-segphos (**L17**)}] and $AgNTf_2$ (**Scheme 41**).[67] A *p*-methylbenzenesulfonyl substituent (Ts) was paramount for stereocontrol; other sulfonyl protecting groups gave products in high yields but lower ees. Seven-membered 1,4-oxazepanyl rings (**46**) were also synthesized from their diol precursors but required a higher catalyst loading (5 mol%). *N*-phenyl morpholine (**47**) was also prepared but with a relatively low yield of 41% (76% ee).



Scheme 41 Enantioselective gold(I)-catalyzed synthesis of heterocyclic aza-compounds.

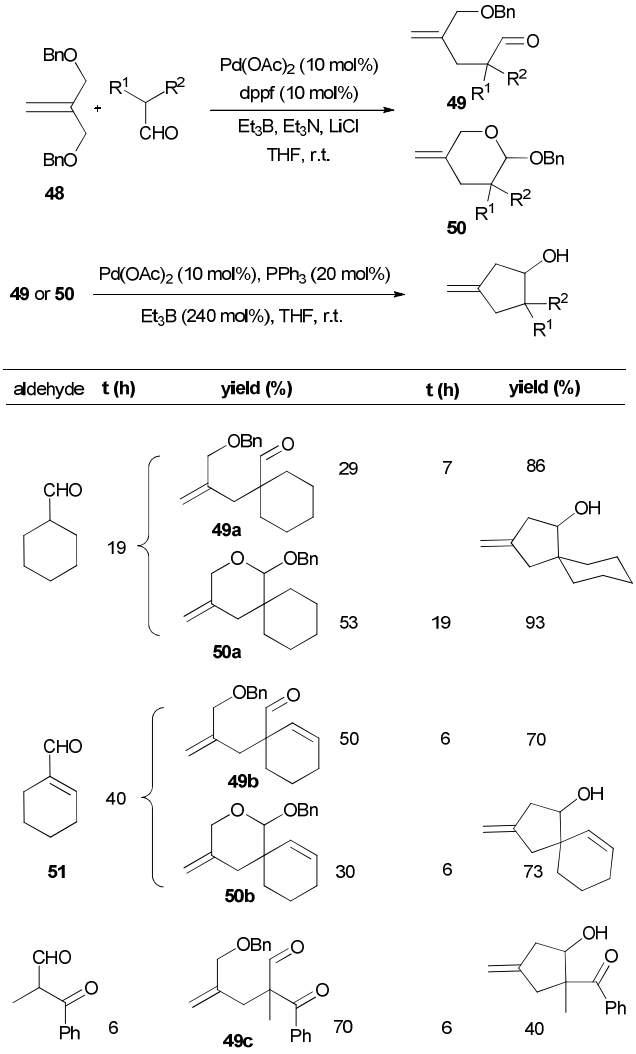
3. Transition metal-catalyzed allylic substitutions with allylic ethers

Allylic ethers, especially alkyl allylic ethers, are challenging substrates for use in allylic substitution reactions. More commonly, allylic ethers tend to be 'masked' as allylic epoxides or strained ring systems in order to increase their reactivity for transition metal-catalyzed substitutions. Due to their stability, metal-catalyzed substitutions involving allylic ethers often involve stoichiometric amounts of strong activating agents such as Lewis acids and powerful Grignard nucleophiles.

3.1. Palladium-catalyzed substitutions with allylic ethers

3.1.1. Palladium-catalyzed substitutions with allylic alkyl ethers

Tamaru and co-workers reported the Pd(0)-catalyzed amphiphilic activation of bis-allyl ethers. Using conditions identical to those described in **Section 2.1.3** for the activation of allylic alcohols. Bis-benzyl ether **48** undergoes electrophilic allylation with aldehydes to yield a mixture of allylated aldehydes **49** and acetals **50** (**Scheme 42**).[39] In the case of aldehyde **51**, allylation occurs at the α-position via the deprotonation of a γ-proton to afford aldehyde intermediate **49b** and acetal **50b**. Intermediates **49** and **50** can subsequently be converted to the corresponding cyclopentanol products using the allylation conditions described, in the absence of Et_3N and LiCl.

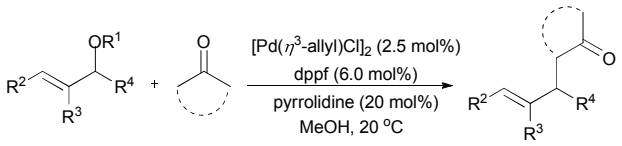


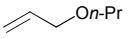
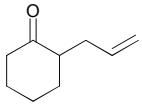
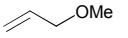
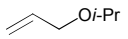
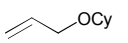
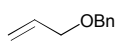
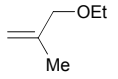
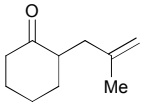
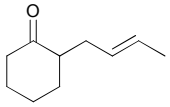
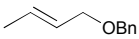
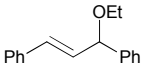
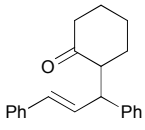
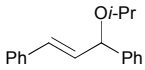
Scheme 42 Pd-catalyzed alkylation with bis-allyl ethers[39]

Zhang and co-workers discovered that a catalyst system consisting of [Pd(η^3-allyl)Cl]$_2$, dppf and pyrrolidine in MeOH was suitable for the hydrogen-bond activation of allylic alkyl ethers.[68] The MeOH plays a crucial role in the formation of the Pd-allyl complex by lowering the activation energy and stabilizing the resulting hydroxide and alkyloxide ion.

Cyclohexanone could be alkylated with a variety of alkyl allylic ethers (**Table 13**). Linear allylic ethers were more reactive than their branched counterparts. Notably, regioisomeric methyl or phenyl-substituted allylic ethers gave identical products (entries 7 and 8). High yields were also obtained when 1,3-disubstituted allylic substrates were used with an equivalent of pyrrolidine. In addition to cyclohexanone, other carbonyl could be alkylated with allylic propyl ether. 5- and 6-membered cyclic ketones were found to be more reactive than cycloheptanone (entry 13). A

substituent at the 4-position of the cyclohexanone ring had no adverse effect on the reaction outcome and even phenyl acetaldehyde could be successfully converted to its allylated product in modest yield.



entry	ether	t (h)	product	yield (%)
1		4		95
2		4		92
3		6		92
4		9		91
5		24		93
6		7		95
7		8		93
8		8		96
9		8		99
10		12		98

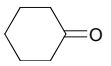
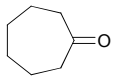
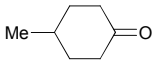
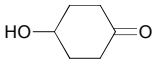
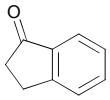
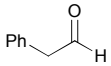
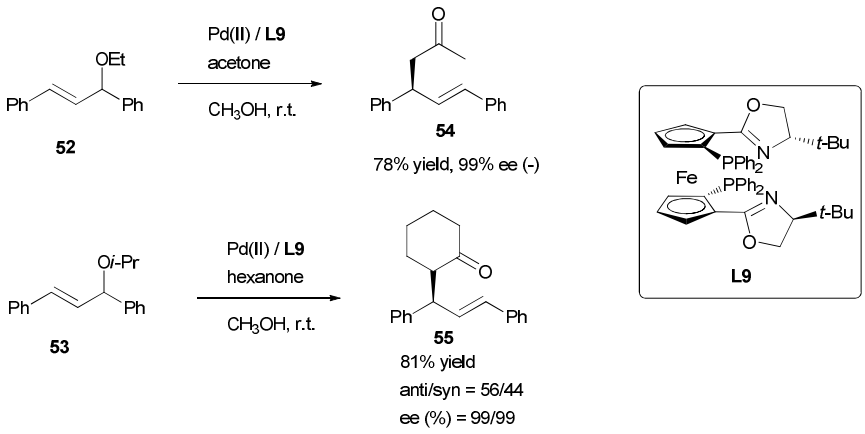
entry	ketone	t (h)	yield (%)
11		2.5	96
12		4	95
13		18	95
14		5	98
15		12	92
16		4	96
17		18	62

Table 13 H-bond activated Pd-catalyzed allylic alkylation of ketones and aldehydes

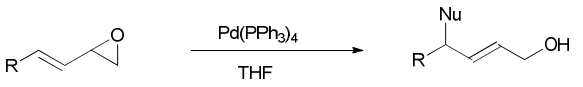
Replacement of dppf with ligand **L9** allowed the reaction to be carried out asymmetrically. Allylic ethers **52** and **53** were reacted with acetone and hexanone respectively, to give the corresponding products **54** and **55** in high yields and excellent enantioselectivities (**Scheme 43**).



Scheme 43 Asymmetric alkylation with allylic alkyl ethers[68]

3.1.2. Allylic substitutions with vinyl epoxides and allylic aryl ethers

Vinyl epoxides and allylic aryl ethers are more commonly used in allylic substitution reactions than allylic ethers. In 1981, Trost et al. reported a regioselective alkylation of vinyl epoxides using $Pd(PPh_3)_4$ as a catalyst with a series of ketone nucleophiles.[69] Acyclic and cyclic vinyl epoxides were alkylated successfully in modest yield, with complete selectivity for the 1,4-addition product (**Table 14**). The reactions proceed with alkylation from the same face as the oxygen of the epoxide and with allyl inversion.



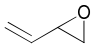
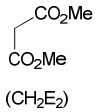
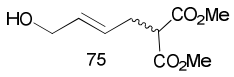
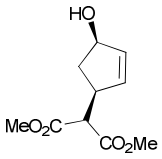
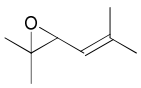
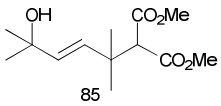
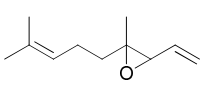
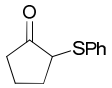
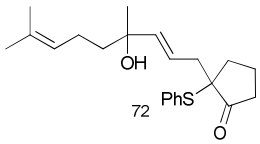
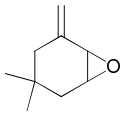
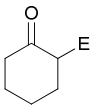
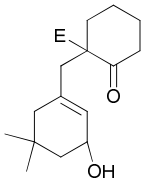
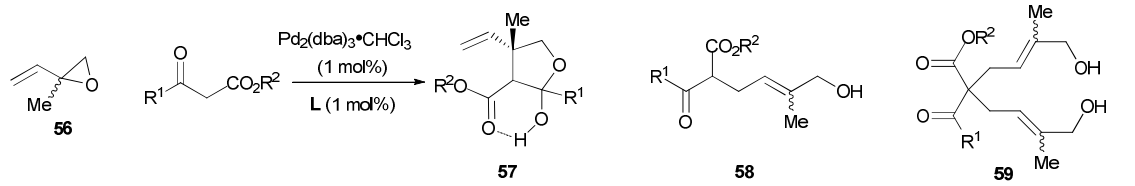
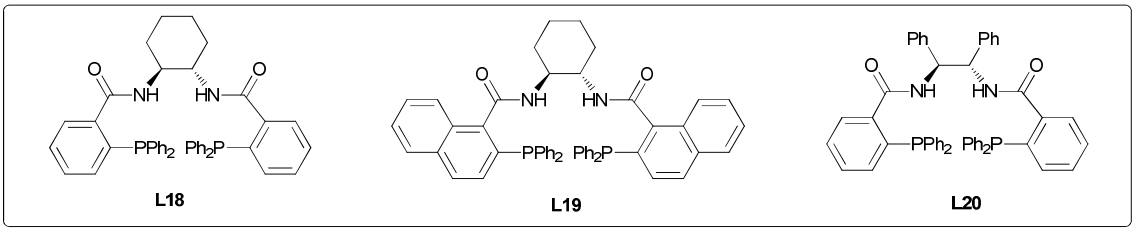
vinyl epoxide	nucleophile	product / yield (%)
	 (CH_2E_2)	 75
	CH_2E_2	 57
	CH_2E_2	 85
		 72
		 79

Table 14 Pd-catalyzed regioselective alkylation of vinyl epoxides

One of the difficulties encountered when using vinyl epoxides for allylic alkylations is selective formation of either the 1,2- or 1,4-addition product. To this end, Trost and co-workers developed a regio- and enantioselective 1,2-nucelophilic addition of *β*-ketoesters with vinyl epoxide **56** using ligands (*S*,*S*)-**L18**-**L20**, in the presence of the catalyst $Pd_2(dba)_3$.[70,71] The more flexible ligand (*S*,*S*)-**L20** gave the best results and only low catalyst loadings were required. A range of *β*-ketoesters were amenable to the reaction conditions all giving their respective products in good yields and high enantioselectivities (93.5 to 99% ee) (**Table 15**). The larger the R^1 group, the greater the regioselectivitiy.





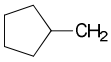
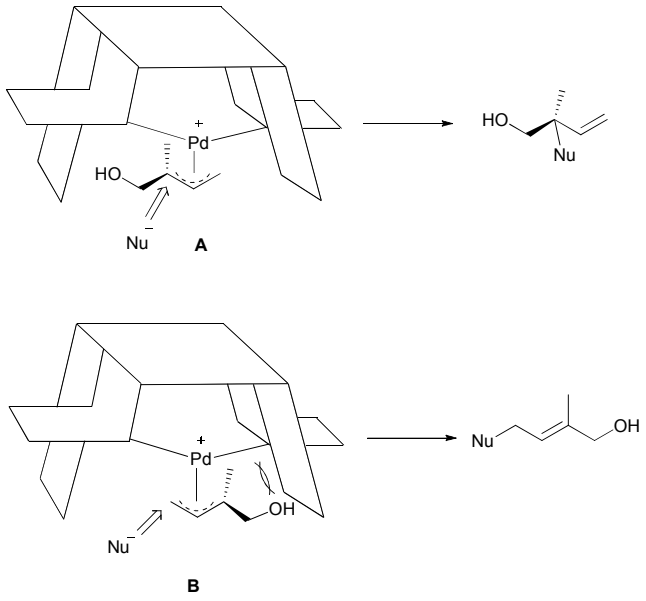
***β*-ketoester**		**ratio**	**yield (%)**	**ee (%)**
R^1	R^2	57:58:59	3	3
Me	C_2H_5	79:17:4	70	96
Me	*n*-C_4H_9	82:14:4	65	97
Me	*t*-C_4H_9	77:17:6	65	95
Me	Bn	72:19:9	61	95
C_2H_5	C_2H_5	80:17:3	71	96.5
CH_2=$CH(CH_2)_8$		80:13:7	71	95
Bn	C_2H_5	n.d.	71	93.5
	C_2H_5	80:13:7	70	98
i-C_3H_7	C_2H_5	81:17:2	74	97
	C_2H_5	90:10	74	99
	C_2H_5	90:10	80	97
Ph	C_2H_5	77:23	59	98.5
p-O_2N-C_6H_4	C_2H_5	n.d.	57	95

Table 15 Regio- and enantioselective alkylation of vinyl epoxides

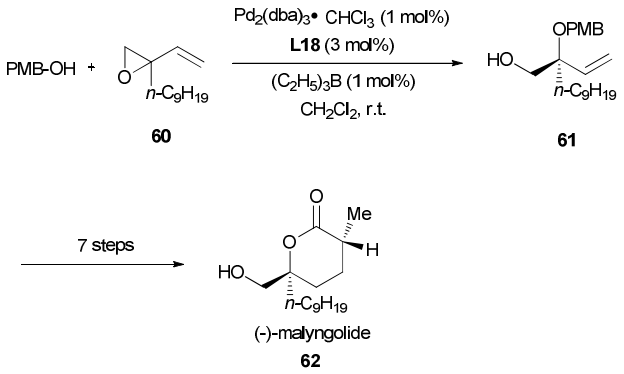
Regioselectivity decreased when the enantiopure ligand (*S*,*S*)-**L18** was used. Trost et al. propose that the reduction in regioselectivity with the enantiopure ligand is a result of kinetic discrimination. Initial ionization of the racemic epoxide and racemic ligand favors formation of enantiomers of the same diastereomer (**Scheme 44**) of the intermediate π-allylpalladium species, **A**.[71] This species has a higher

preference for the addition to the more subsituted allyl terminus. An enantiopure ligand and racemic expoxide give rise to the formation of two different diastereomeric π-allylpalladium intermediates, **A** and **B**. Complex **A** favors formation of the branched product and **B** the formation of the linear product.



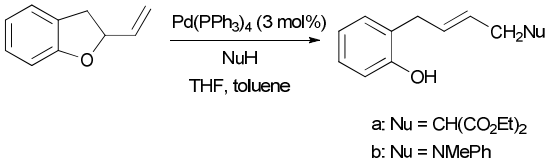
Scheme 44 Explanation of regiocontrol in alkylation of vinyl epoxides with **L18**[71]

Trost and co-workers have utilized the alkylation of monoepoxides for the preparation of key intermediates required for the synthesis of biologically active natural products.[72,73] A deracemization of a vinyl epoxide was required for the synthesis of (-)-malyngolide **62**. Epoxide **60** was treated with *p*-methoxy benzyl alcohol in the presence of 1 mol% $Pd_2(dba)_3 \bullet CHCl_3$ and 3 mol% of the ligand (*S*,*S*)-**L18** to give ether **61** as the exclusive product with 97-99% ee (**Scheme 45**). Through a series of manipulations, ether intermediate **61** was transformed to (-)-malyngolide **62**.



Scheme 45 Synthesis of (-)-malyngolide via alkylation of a vinyl epoxide

Reactions concerning Pd-catalyzed allylic substitution reactions with allylic aryl ethers are rare. Hosokawa and Murahashi reported the synthesis of 2-(2-butenyl)phenols from 2,3-dihydro-2-vinylbenzofuran using $Pd(PPh_3)_4$ and diethyl sodiomalonate or *N*-methyl aniline nuceleophiles (**Scheme 46**).[74]



Scheme 46 Synthesis of 2-(2-butenyl)phenols from 2,3-dihydro-2-vinylbenzofuran

3.2. Allylic substitutions of allylic ethers with other transitions metals

Allylic substitution reactions with allylic ethers more commonly employ other transition metals as catalysts such as Zr, Ni and Cu, in combination with powerful nucleophiles.

Zr-catalysis has found use in a number of C-C bond forming reactions, including allylic substitution reactions. Takahashi and co-workers reported a Zr-catalyzed allylic allylation of allylic ethers using ethyl magnesium bromide as a nucleophile. The reactions are selective for the γ-carbon of the allylic ethers (**Table 16**).[75]

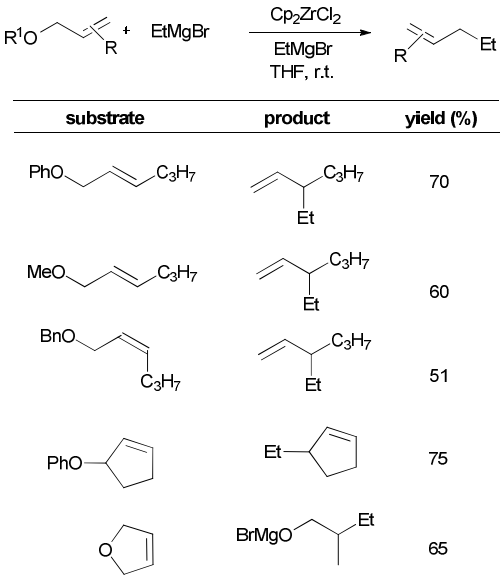
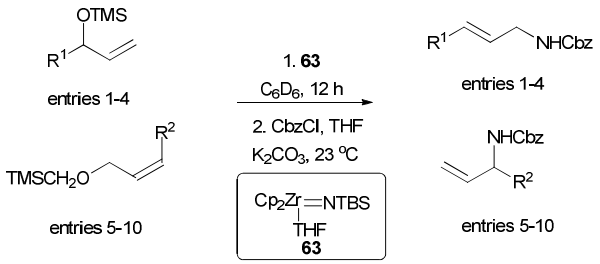


Table 16 Zr-catalyzed allylic substitution with Grignard reagents

A Zr-mediated S_N2' substitution of allylic ethers was developed for the regio- and stereospecific formation of protected allylic amines.[76] Complex **63** reacted with alkyl, aryl and trimethylsilyl (TMS) allyl ethers to afford the substituted products. In situ hydrolysis of the initial zirconium amide adducts and Cbz protection of the free amines gave protected allylic amines (**Table 17**). The size of the α-substituent influenced diastereoselectivity with larger substituents requiring higher temperatures to react (entry 3). No reaction was observed with a bulky *t*-Bu group (entry 4). Electron rich TMS methyl ethers successfully reacted with complex **63** to give their corresponding products via an S_N2' pathway (entries 5 to 10). High chemoselectivity was observed in the presence of other functional groups.



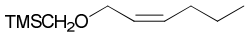
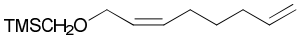
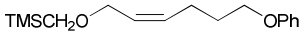
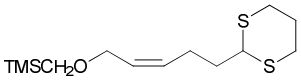
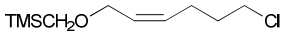
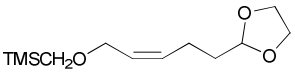
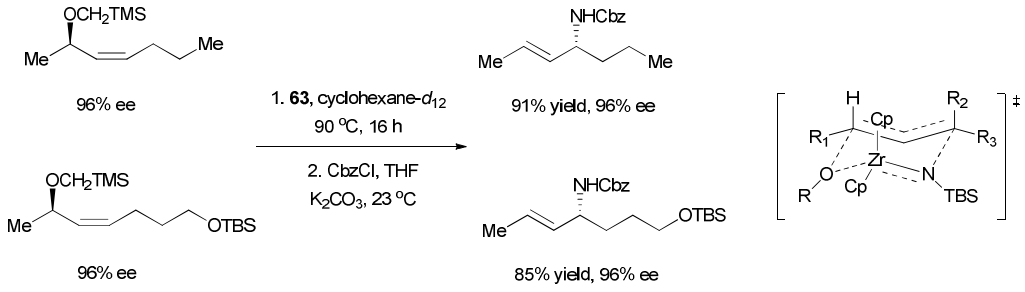
entry	R^1	temp (°C)	dr (*E*:*Z*)	yield (%)
1	H	23		96
2	Et	23	3:1	92
3	*i*-Pr	45	>9:1	89
4	*t*-Bu	90		NR
	Substrates (70 °C, 16 h)			
5				94
6				90
7				92
8				89
9				92
10				77

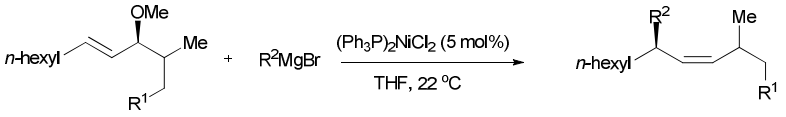
Table 17 Regioselective Zr-mediated S_N2' substitution of allylic ethers

Enantioenriched 1,3-disubstituted ethers reacted with complete chirality transfer allowing for the stereoselective synthesis of allylic amines in high yield and enantioselectivity. The substitutions proceed with *syn* stereochemistry via the transition state shown in **Scheme 47**.[76]



Scheme 47 Asymmetric synthesis of allylic amines[76]

Several examples of nickel-catalyzed allylic substitution reactions with allylic ethers have been reported. Hoveyda developed a Ni-catalyzed addition of PhMgBr and MeMgBr to allylic ethers using the coordinating ability of the phosphorous atom.[77,78] Reaction of various allylic ethers with PhMgBr in the presence of 5 mol % of $(Ph_3P)_2NiCl_2$ yielded the corresponding allylic products. The substrate chirality greatly influences the reactivity and selectivity of the metal-ligand complex. The phosphorous group was essential for reactivity; silyl ether **64** did not undergo any reaction with the Grignard reagents. Several allylic ethers reacted with high regio-, diastereo- and olefin selectivity. *cis-trans* Isomerization of the products occurs with prolonged reaction times (**Table 18**).



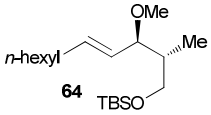
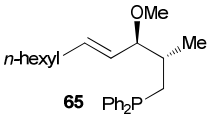
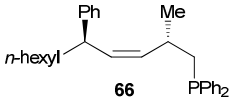
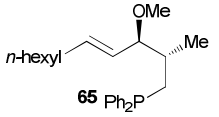
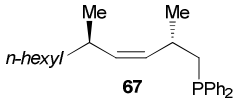
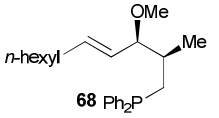
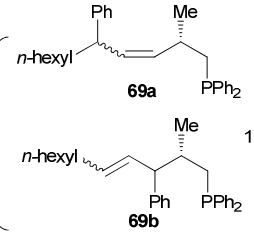
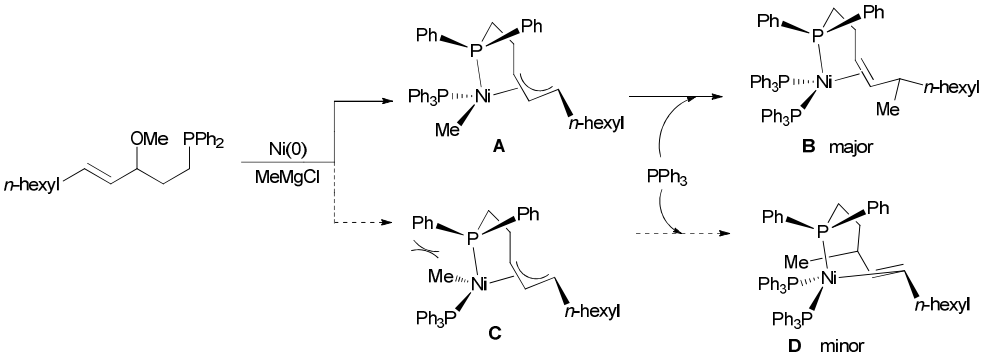
substrate	grignard reagent	product	regioselectivity	c.t	ds	yield (%) time
 **64**	PhMgBr	no reaction				12 h
 **65**	PhMgBr	 **66**	>99:1	>49:1	10:1	85 6 h
 **65**	MeMgBr	 **67**	>99:1	>49:1	>49:1	75 12 h
 **68**	PhMgBr	 **69a** **69b**	1:1		1:1	85 3 h

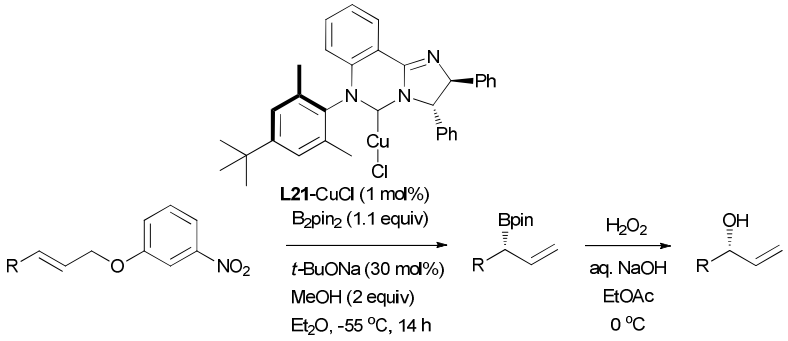
Table 18 Phosphorous-directed Ni-catalyzed allylic substitution

Mechanistic studies indicated that the reaction may proceed through the mechanism shown in **Scheme 48** via a metal-π-allyl complex **A**. The process involves *anti*-insertion of the transition metal into the allylic C-O bond; and *syn*-reductive elimination of the π-allyl-Ni-alkyl complex. The preferential formation of the *cis*-products arises from unfavorable steric interactions in complex **C** between the phenyl groups of the tethered diphenylphosphine substituent and the bound PPh_3 group; these interactions are less apparent in complex **A**, of which leads to the major *cis*-product.



Scheme 48 Mechanism of phosphorous-directed metal-catalyzed allylic alkylation[77]

McQuade and co-workers developed a stereoconvergent synthesis of chiral allylboronates from an *E*/*Z* mixture of allylic ethers using 6-NHC-Cu(I) catalysts.[79] Cu catalyst **L21**-CuCl gave the best yields and regioselectivities for the borylation of allylic aryl ethers with B_2pin_2, in the presence of base (**Table 19**). (*E*)- and (*Z*)-isomers of the same allylic substrate give rise to the same configuration of product. A pure *trans*-substrate with a bulky α-substituent gave the corresponding product with >99% ee (entry 2). The reactions were also chemoselective with various functional groups being tolerable to the reactions conditions shown (entries 5-9).



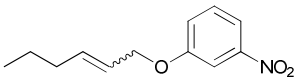
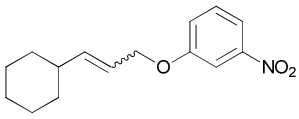
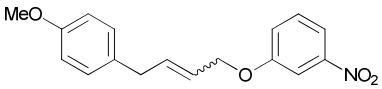
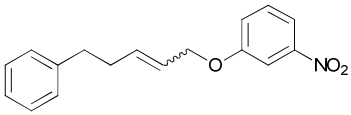
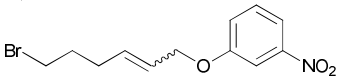
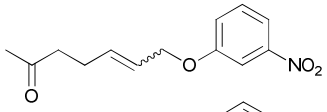
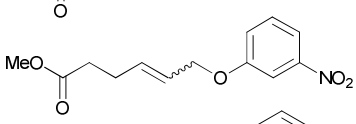
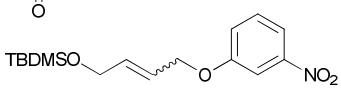
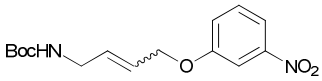
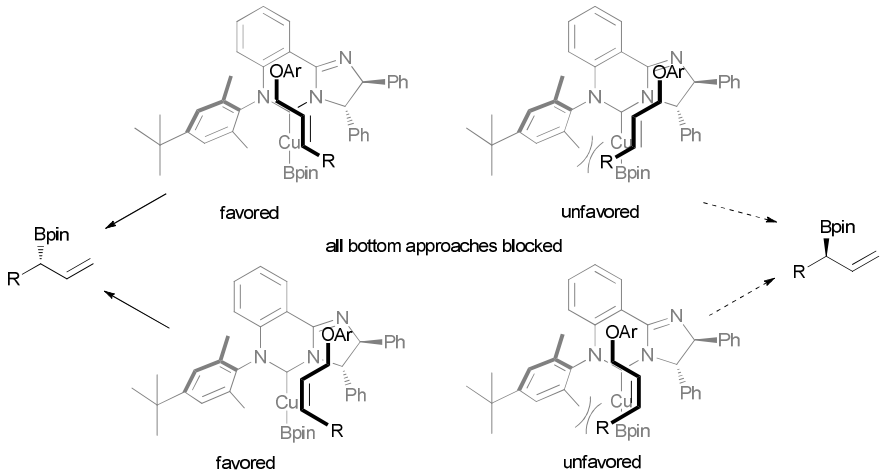
entry	substrate	*trans*/*cis*	yield (%)	ee (%)
1		>30/1 <1/30	90 80	93 (*S*) 96 (*S*)
2		26/1	84	>99 (*R*)
3		5.5/1	87	92
4		6.6/1	95	93 (*S*)
5		3.3/1	92	93
6		3.2/1	50	94
7		1.1/1	>95	94
8		12/1 <1/30	81 91	93 (*S*) 93 (*S*)
9		>30/1	92	90

Table 19 Cu-catalyzed borylation of aryl allylic ethers with B_2pin_2[79]

The preferential formation of the branched products can be explained by the presence of a bulky *t*-butyl group at the *para* position of the N-aryl substituent of the Cu-catalyst. The bulky substituent enhances the energy difference between the favored and unfavored transition states so that the *trans* isomers react faster than the *cis* isomers.[79] The authors postulate that the transition state energy of the

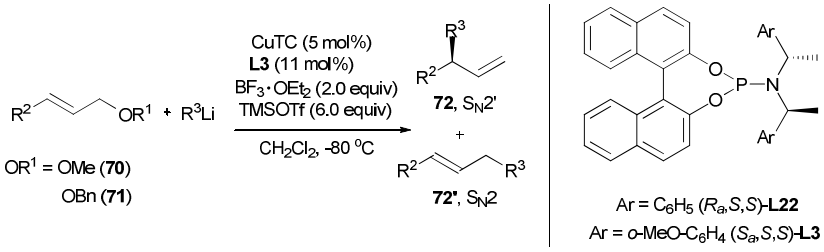
(*Z*)-alkene is higher than that of the (*E*)-alkene and that the catalyst reacts with the same face of both the (*E*)- and (*Z*)-alkenes (**Scheme 49**).



Scheme 49 Reaction of Cu-catalyst with allylic ethers[79]

Enantioselective allylic substitution reactions utilizing allylic ethers are challenging; besides those reported by Hoveyda et al. only a few other procedures have been developed. Several asymmetric reactions have been reported using oxabicyclic alkenes, however their reactivity arises predominantly from their structural properties and lack the diversity of allylic substitution reactions with traditional substrates.[80] Zhang and co-workers reported a Pd-catalyzed asymmetric allylic substitution with allylic alkyl ethers using a ferrocene-based catalyst (see **Section 3.1**).

Feringa and co-workers developed an asymmetric alkylation of allylic ethers with organolithium reagents using phosphoramidite ligand **L3**, a Cu catalyst (CuTC) and Lewis acid activator ($BF_3.OEt_2$).[81] Allylic ethers bearing OMe and OBn groups provided the best results and regioselectivity was improved via the in situ generation of BF_2OTf from $BF_3{\cdot}OEt_2$ and TMSOTf (**Table 20**). Allylic ethers **70** and **71** underwent reaction with *n*BuLi and *n*HexLi and displayed selectivity for the branched S_N2' adduct over the linear S_N2 product. 1-Naphthyl-substituted substrates showed greater regioselectivity with substrate **71** (entries 5-8). Although linear aliphatic substrates were less amenable to the reaction conditions (entries 13 and 14), substrates bearing two ether groups gave their corresponding products in high yields (entries 17 and 18).

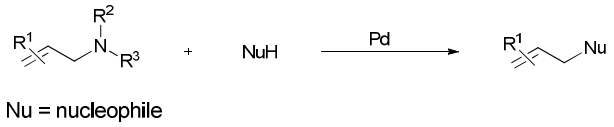


entry	R^2	R^3	yield (%)	72/72'	e.r
1	**70**, Ph	*n*Bu	80	91:9	99:1
2	**70**, Ph	*n*Hex	80	91:9	>99:1
3	**71**, Ph	*n*Bu	86	95:5	99:1
4	**71**, Ph	*n*Hex	92	96:4	>99:1
5	**70**, 1-Np	*n*Bu	80	84:16	96:4
6	**70,** 1-Np	*n*Hex	80	82:18	95:5
7	**71**, 1-Np	*n*Bu	84	>98:2	99:1
8	**71**, 1-Np	*n*Hex	80	>98:2	98:2
9	**70**,4-ClPh	*n*Bu	70	80:20	97:3
10	**70**,4-ClPh	*n*Hex	88	91:9	98:2
11	**71**, 4-ClPh	*n*Bu	81	97:3	99:1
12	**71**, 4-ClPh	*n*Hex	79	90:10	99:1
13	**70**,C_3H_7	*n*Bu	50	70:30	n.d.
14	**70**,C_3H_8	*n*Hex	11	90:10	n.d.
15	**71**, CH_3	*n*Hex	100	97:3	95:5
16	**71**, C_3H_7	*n*Hex	100	95:5	>99:1
17	**70**,CH_2OBn	*n*Bu	60	>99:1	93:7
18	**71**, CH_2OBn	*n*Hex	55	>99:1	98:2

Table 20 Copper-catalyzed allylic substitution with allylic ethers

4. Palladium-catalyzed allylic substitutions with allylic amines

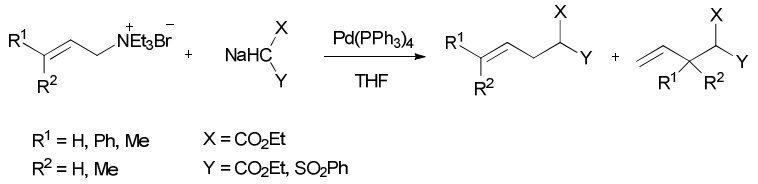
Pd-catalyzed allylic substitution reactions with allylic amines (**Scheme 50**) provide an alternative approach towards the synthesis of allylic containing substrates. Much like their allylic ether counterparts, reactions involving allylic amines represent a challenging, and relatively unexplored area of research due to the stability of the C-N bond.



Scheme 50 Allylic substitution with allylic amines

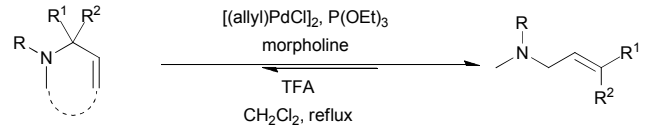
4.1. Palladium-catalyzed allylic substitutions with allylic amines via allylic ammonium intermediates

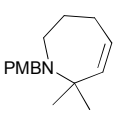
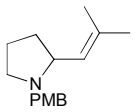
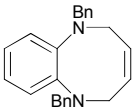
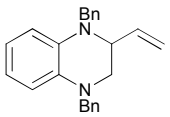
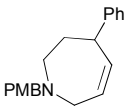
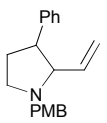
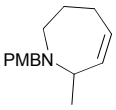
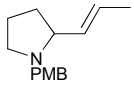
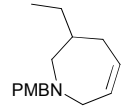
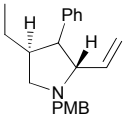
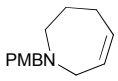
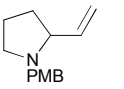
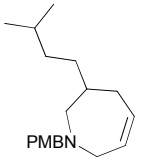
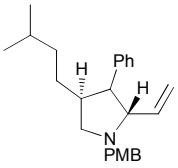
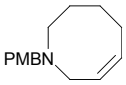
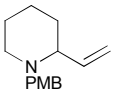
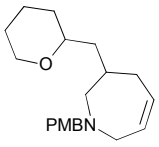
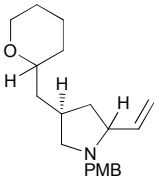
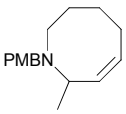
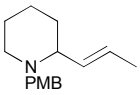
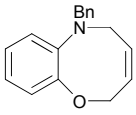
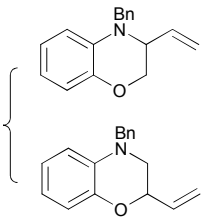
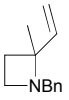
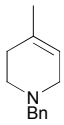
In 1982 Agawa and co-workers reported the first Pd-catalyzed substitution of allylic ammonium bromides with active methylene nucleophiles and enolate substrates (**Scheme 51**).[82] Allylic products were obtained as a mixture of regioisomers.



Scheme 51 Allylic substitution with allylic ammonium bromides

Yudin and co-workers have developed a palladium-catalyzed ring-contraction and ring-expansion reaction of cyclic allylic amines.[83,84] Seven- and eight-membered cyclic allylic amines were contracted using a catalyst system constituting of $[Pd(allyl)Cl]_2$, $P(OEt)_3$ and morpholine in CH_2Cl_2 (**Scheme 52**). TFA was used for activation of the allylic bond. 7-Membered ring systems bearing substituents with a 2,4- and 2,5- relationship gave ring contracted products in modest yields and diastereoselectivities, with reactions proceeding under thermodynamic control. Contraction of 7- and 8-membered rings provided the highest yields whereby the easing of ring strain overcomes the substitution pattern of the olefin as the driving force of the reaction. (*E*)-Alkenes are favored when a disubstituted alkene can be formed.

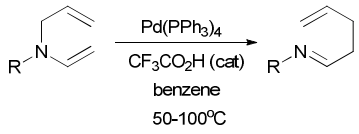


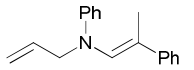
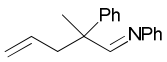
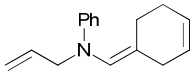
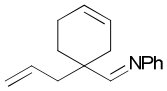
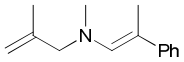
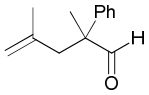
substrate	product	yield (%)	substrate	product	yield (%)
		97			78
		0			94 (*E*/*Z*=3.6:1)
		53 (2:1)			93
		50 (2:1)			97
		69 (2:1)			92 (E/Z=4.6:1)
		83 (1:1)			96

Scheme 52 Pd-catalyzed ring contraction[84]

4.2. Palladium-catalyzed allylic substitutions with allylic amines via allylic enammonium cation intermediates

Several methodologies have been developed in which enammonium cation intermediates are generated during the catalytic cycle. Murahashi et al. established a Pd(0)-catalyzed 3-aza-Cope rearrangement of *N*-allylenamines to the corresponding δ,ε-unsaturated imines or γ,δ-unsaturated carbonyl compounds (after hydrolysis) in the presence of trifluoroacetic acid (**Scheme 53**).[85] The reaction proceeds via an ammonium ion generated via the protonation of the enamine with acid.

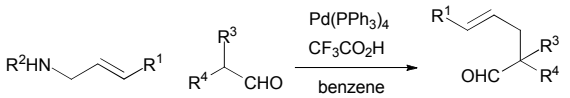


substrate	product	yield (%)
		82
		98
		78

after hydrolysis

Scheme 53 Pd(0)-catalyzed 3-aza-Cope rearrangement of *N*-allylenamines

The same group reported a Pd(0)-catalyzed allylic substitution reaction between secondary allyl amines with carbonyl compounds.[86] A catalyst system consisting of $Pd(PPh_3)_4$ and a stoichiometric amount of acid activator (CF_3CO_2H) was suitable for the synthesis of several allylic substrates in modest to excellent yields (**Table 21**).



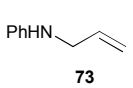
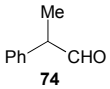
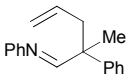
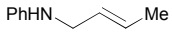
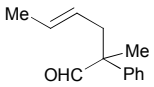
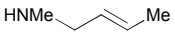
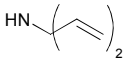
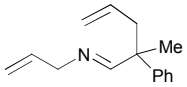
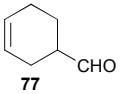
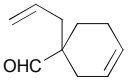
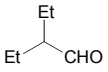
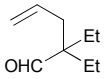
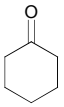
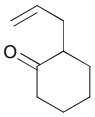
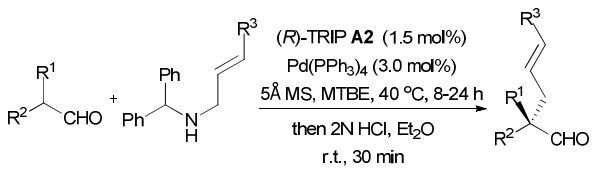
allylamine	carbonyl comound	product	yield (%)
 **73**	 **74**	 **75**	86
	**74**	 **76**	84
	**74**	**76**	63
	**74**		82
73	 **77**		77
73			64
73			61

Table 21 Allylation of secondary allyl amines

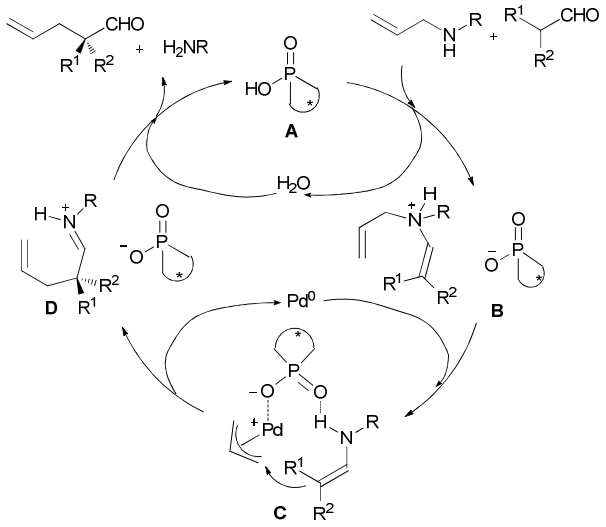
In 2007 List et al. reported an enantioselective Pd/Bronsted acid-catalyzed direct α-allylation of aldehydes.[87] A combination of the chiral phosphoric acid (*R*)-TRIP **A2** (1.5 mol%), $Pd(PPh_3)_4$ (3 mol%) and molecular sieves (5Å), was suitable for the enantioselective alkylation of a range of aldehydes with *N*-benzhydryl allyl amines (**Table 22**). Phenyl substituted aldehydes, bearing electron-donating and electron-withdrawing groups afforded their allylated products in good yields and with high enantiomeric ratios (entries 2 to 6). 2-Naphthyl and 2-thiophenyl derived aldehydes also gave their corresponding products with high ers (entries 7 and 8). 2,3-Dihydro-1-indanone showed modest reactivity as a substrate but afforded its allylated product in high er (entry 9). Alkyl derived aldehydes and substituted allylic amines were also successfully allylated using these reaction conditions (entries 10 to 12).



entry	R^1	R^2	R^3	yield (%)	er
1	Me	Ph	H	85	98.5:1.5
2	Me	4-Me-C_6H_4	H	89	97:3
3	Me	3-Me-C_6H_4	H	84	98:2
4	Me	3-F-C_6H_4	H	85	98:2
5	Me	2-F-C_6H_4	H	74	97:3
6	Me	4-*i*-Bu-C_6H_4	H	76	97.5:2.5
7	Me	2-naph	H	71	97:3
8	Me	2-thiophenyl	H	80	93:7
9	-	2,3-dihydro-1-indanone	H	45	95:5
10	Me	*c*-hex	H	65	85:15
11	Me	Ph	Me	40	96:4
12	Me	Ph	Ph	82	91:9

Table 22 Catalytic asymmetric allylation of aldehydes

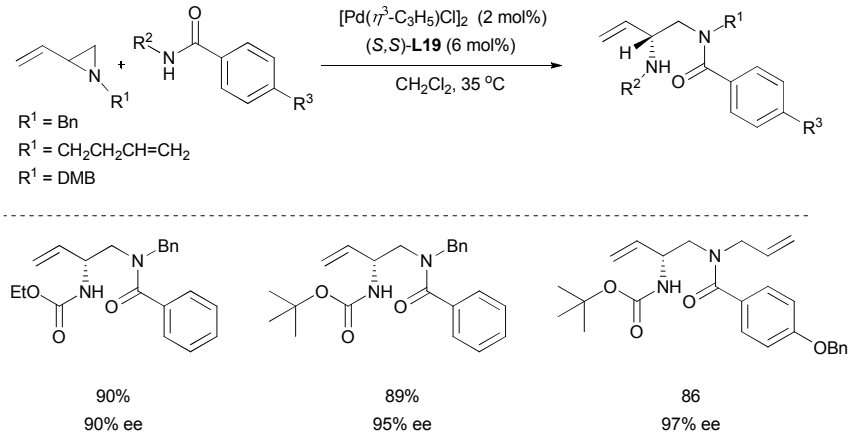
List and co-workers proposed the mechanism shown in **Scheme 54** starting from the chiral phosphoric acid **A**. Enamonium salt **B** is formed via condensation of an allylamine with the aldehyde, which reacts with Pd(0) to form a cationic π-allyl-Pd-complex, an enamine and chiral phosphate counteranion (**C**). Nucleophilic attack of the enamine on to the π-allyl-Pd-complex leads to the α-allylated iminium ion intermediate **D**. This enamonium phopshonate may act as a chiral counteranion inducing asymmetry in the final step.[87]



Scheme 54 Proposed mechanism for allylation of aldehydes using a chiral phosphoric acid

4.3. Palladium-catalyzed allylic substitutions with allylic amines using mini-cyclic tension or hydrogen-bond activation

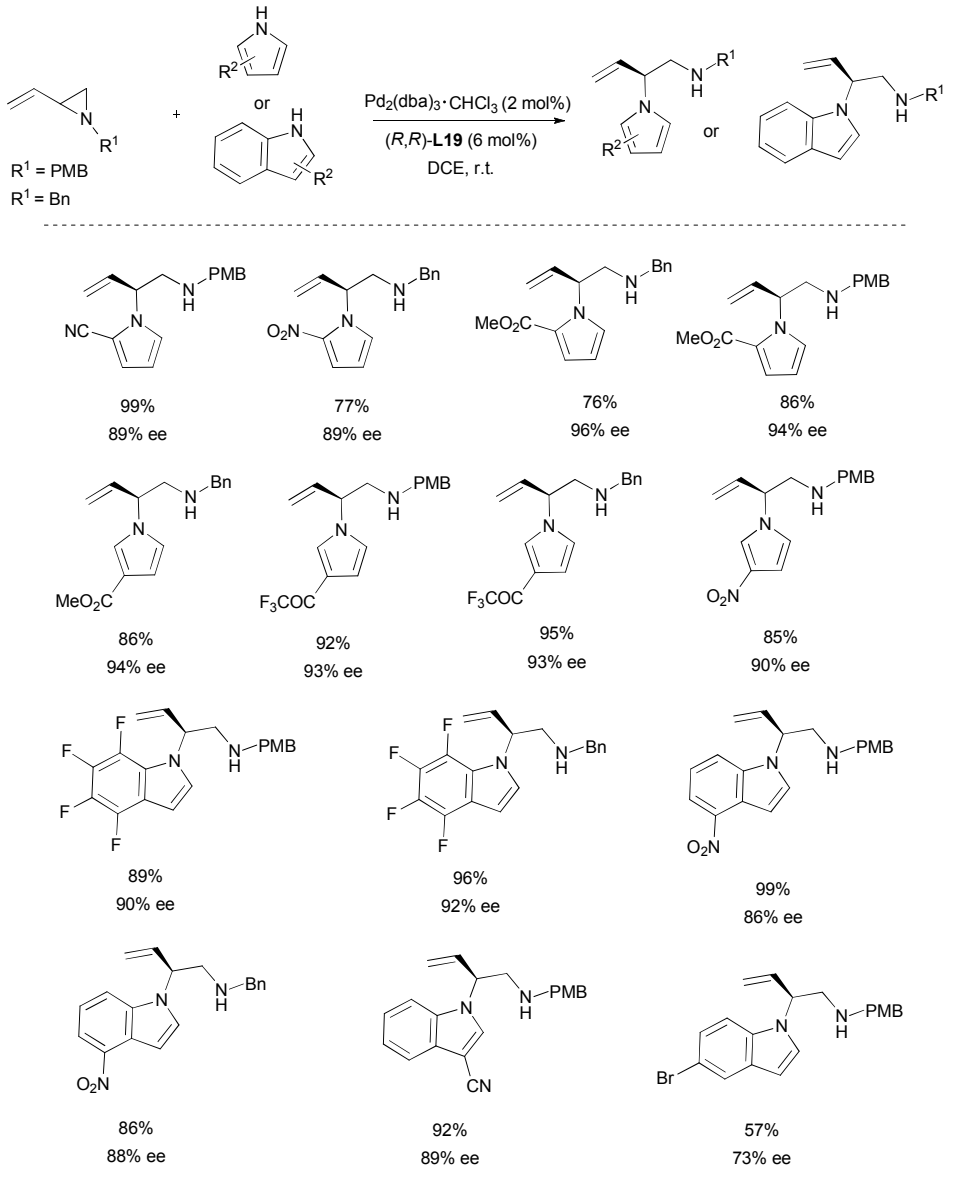
Mini-cyclic tension in species such as vinyl-aziridines can be exploited in allylic substitution reactions. A dymanic kinetic asymmetric allylic amination between aziridines and benzoylimido carboxylates was achieved using a catalytic system consisting of Trost diphosphine ligand **L19** and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (**Scheme 55**). Following the allylic amination, a facile acyl migration occurs to give *N*-benzoyl-*N*-*tert*-butoxycarbonyl vicinal diamines in good yields and high ees.[88]



Scheme 55 Dynamic kinetic asymmetric allylic amination with benzoyl imidocarboxylates

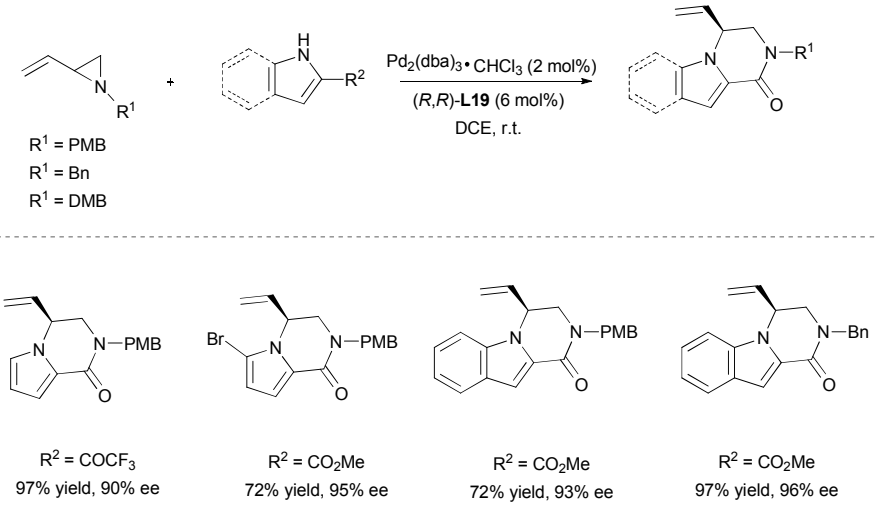
Similar reaction conditions were suitable for the Pd-catalyzed asymmetric alkylation of heterocycles with vinyl aziridines.[89] A number of pyrrole substrates could be alkylated with vinyl aziridines bearing

PMB or Bn groups using the reaction conditions shown in **Scheme 56**. An electron withdrawing substituent attached to the pyrrole substrate at either the C2- or C3-position was required for the reaction to proceed. *N*-Alkylated branched products were prepared exclusively with good yields and high ees. Additionally electron-deficient indoles also reacted smoothly under these reactions conditions. Only *N*-alkylation of the indole was observed. Strong electron-withdrawing groups were required to obtain high reaction activities, with weaker withdrawing groups such as Cl or Br providing lower product yields and ees.



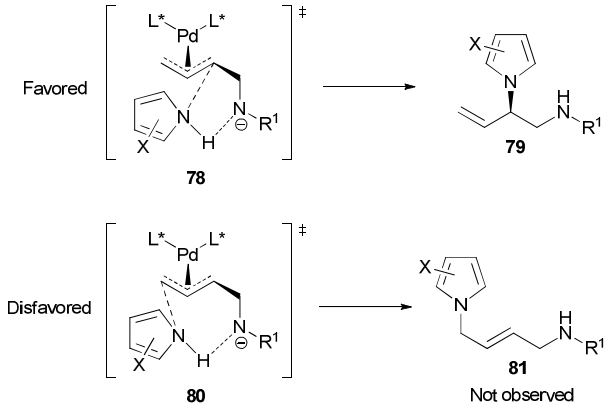
Scheme 56 Pd-catalyzed *N*-alkylation of pyrroles and indoles[89]

The reaction conditions described above were also successful for the synthesis of enantioenriched piperazinones. Pyrroles and indoles could be utilized as nucleophiles for the preparation of pyrrole- and indole-fused piperazinones from vinyl aziridines, in high yields and enantioselectivities (**Scheme 57**).



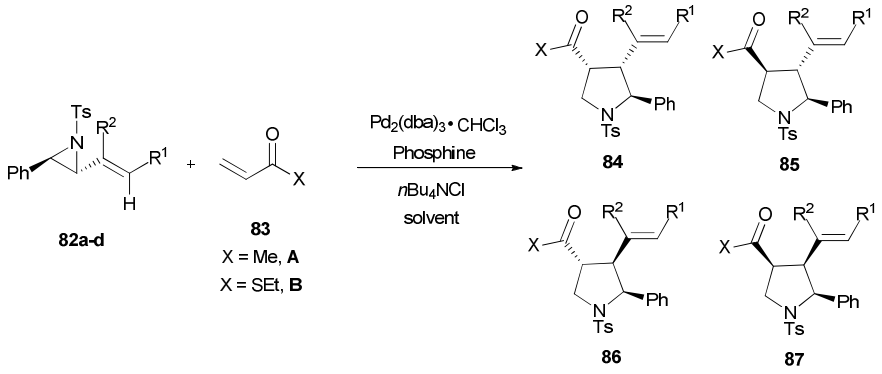
Scheme 57 Synthesis of pyrrole- and indole-fused piperazinones

The preferential formation of one enantiomer over the other can be explained using a "wall and flap" model similar to that used to describe enantioselective alkylations with epoxides (**Scheme 44**).[89] Regioselectivity can be be explained as follows: Monosubstituted π-allyl-Pd intermediates favor formation of achiral linear products, possibly via a 5-memebred transition state (**Scheme 58**). A H-bond directs the pyrrole nucleophile through a hydrogen bond with the pyrrole N-H and amide ion of the vinyl aziridine to the terminal end of the alkene. Nucleophilic attack therefore proceeds through the favored five-membered transition state **78** giving the branched product **79**. A disfavored seven-membered transition state, **80**, is not observed. [89]



Scheme 58 Explanation for observed regiochemistry[89]

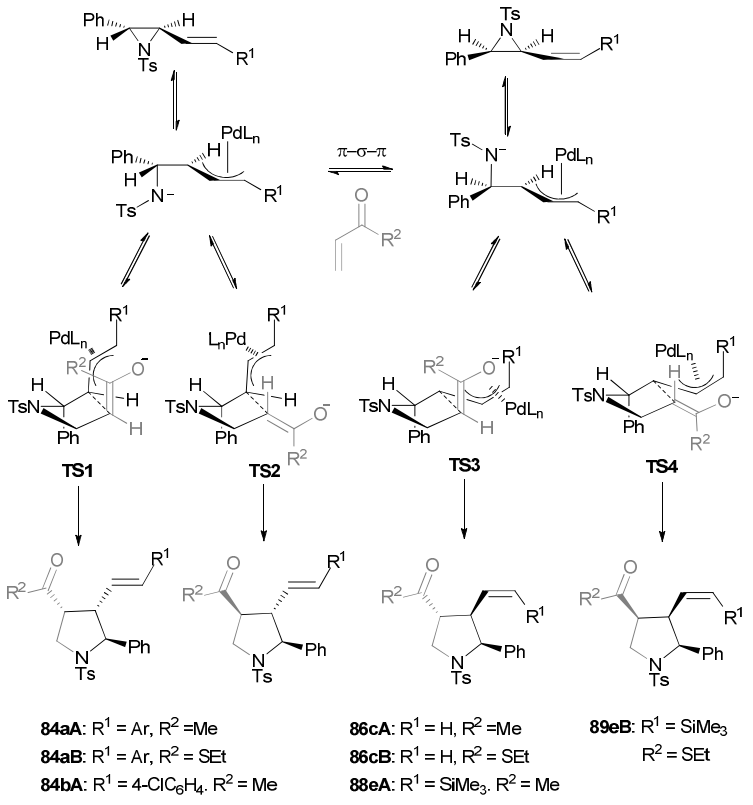
A Pd-catalyzed annulation of vinyl azidirines with α,β-unsaturated carbonyl compounds has been developed for the synthesis of multi-substituted pyrrolidines.[90] Aziridines **82** could be reacted with Michael acceptors **83** in the presence of $Pd_2(dba)_3$•$CHCl_3$, sterically hindered phosphines and *n*-Bu_4NCl, to give pyrrolidines **84** to **87** as a mixture of diastereomers; the e.r. of the aziridine is maintained in the cyclic products (**Table 23**). Diastereoselectivity is dependent on the nature of the aziridine and Michael acceptor. Aryl groups at the terminal position of the vinyl aziridine **82b** gave diastereomers **84** and **85** in modest yields (entries 1 and 2). Vinyl aziridine **82c** gave 2,3-*cis*-3,4-*trans*-substituted pyrrolidine **86cA** as the major diastereomer. 2,3-*trans*-3,4-*trans*-Substituted pyrrolidine **85dA** was prepared from aziridine **82d**. Ethyl thioacrylate **83B** was also a suitable Michael acceptor for reaction with various aziridines giving the corresponding products (entries 5 and 6).[90] Interestingly, reaction of aziridine **82e** with methyl vinyl ketone gave the 2,3-*cis*-3,4-*trans*-pyrrolidine bearing a *Z*-olefin as the major diastereomer, the exact opposite of that obtained from phenyl substituted aziridine **82a**. Use of ethyl thioacrylate gave the all-*cis* isomer **89eB** as the major diastereomer.



entry	aziridine			e.r	83	phosphine	solvent	product type (d.r)				yield (%)
	82	**R^1**	**R^2**					**84**	**85**	**86**	**87**	
1	**82a**	Ph	H	99:1	**A**	(*o*-tolyl)$_3$P	Pent/TBME	93	7	-	-	66
2	**82b**	4-ClC_6H_4	H	99:1	**A**	(*o*-tolyl)$_3$P	Pentane	80	20	-	-	60
3	**82c**	H	H	94:6	**A**	(*o*-tolyl)$_3$P	Pentane	-	-	80	20	52
4	**82d**	H	Me	99:1	**A**	(4-FC_6H_4)$_3$P	Et_2O	14	58	28	-	57
5	**82a**	Ph	H	99:1	**B**	(2-furyl)$_3$P	Pent/TBME	75	25	-	-	50
6	**82c**	H	H	94:6	**B**	(2-furyl)$_3$P	Et_2O	-	-	66	33	59

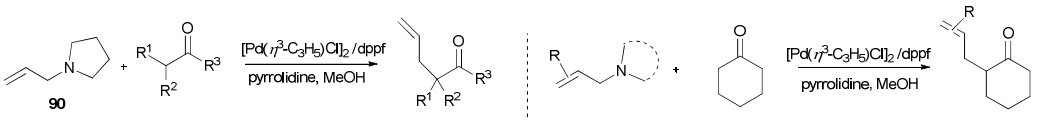
Table 23 Annulation of aziridines with Michael acceptors[90]

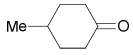
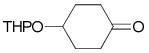
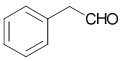
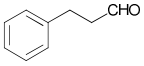
The differences in the stereochemical outcome of the annulation reactions can be explained by the transition states involved in the ring closing step of the enolate onto the π-allyl palladium complex (**Scheme 59**).[90] The phenyl group adopts a pseudoaxial position to minimize steric hindrance with the PdL_n complex. Aryl substituted vinyl aziridines favor the *E* π-allyl palladium complexes leading to **TS1** and **TS2**, of which **TS1** leads to major products **84aA**, **84bA**, and **84aB**. Terminal vinyl aziridine **82c** leads to **86cA** and **86cB** via **TS3**, which bears the least steric hindrance. Vinyl aziridine **82e** (R^1 = $SiMe_3$), allows both *E* and *Z* π-allyl palladium complexes to be accessed, possibly due to the increased bond length of the C-Si bond. Thus, when reaction occurs with methyl vinyl ketone, **TS3** is favored due to lower steric hindrance, giving rise to **88eA**.[90] Conversely, use of a thiosester Michael acceptors leads to an attractive interaction between the soft S atom and the π-allyl palladium complex, thus favoring **TS4** and giving **89eB** as the predominant diastereomer. **TS3** and **TS4** may also be favored because of interactions between the anionic oxygen atom of the enolate and the silyl group.



Scheme 59 Explanation of stereochemical outcome of annulation reactions[90]

Zhang et al. reported a Pd-catalyzed solvent hydrogen-bond-activated alkylation of carbonyl substrates with various allylic amines.[91] The reaction proceeds via in situ generation of an enamine from the carbonyl substrate using a pyrrolidine co-catalyst (**Table 24**). *N*-allylpyrrolidine **90** was successfully reacted with a number of cyclic ketones in good yields, including 4-substituted cyclic ketones (entries 4-6) and several aldehydes (entries 9 and 10). Several *N*-allylamine derivatives could also be utilized as allylic electrophiles for the alkylation of cyclohexanone. Of particular note were the preparation of allylated products from a primary *N*-allylamine (entry 16) and a cyclic *N*-allylamine (entry 18) in high yields.



entry	ketone/aldehyde	t (h)	yield (%)
1		3	95
2		3	95
3		8	93
4		4	90
5		4	88
6		12	92
7		18	79
8		18	73

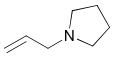
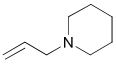
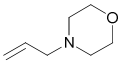
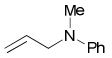
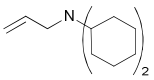
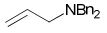
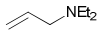
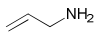
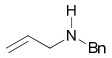
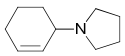
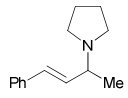
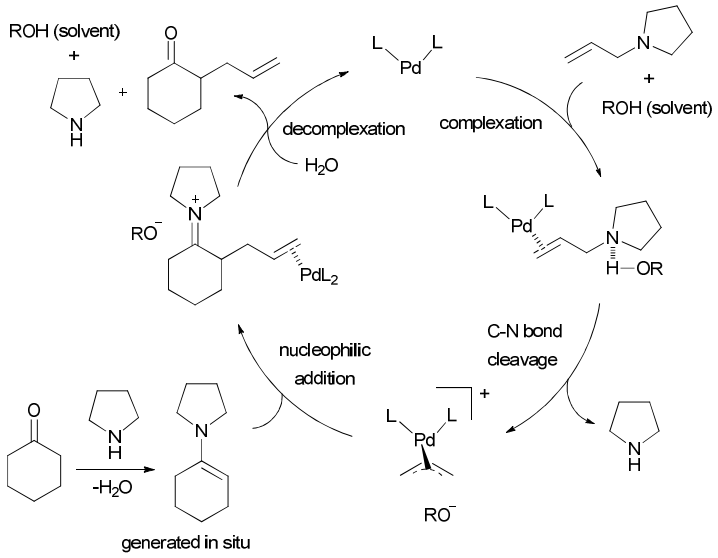
entry	allylamine	t (h)	yield (%)
9		3	98
10		8	92
11		8	91
12		12	88
13		12	78
14		12	90
15		12	93
16		4	94
17		4	92
18		12	96
19		12	95

Table 24 Pd-catalyzed hydrogen-bond-activated α-alkylation of carbonyl substrates with allylic amines[91]

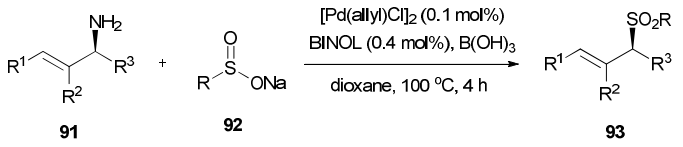
A proposed mechanism for the alkylation reaction is shown in **Scheme 60**. The role of methanol in hydrogen-bond participation was determined via reaction of cyclohexanone with *N*-allylpyrrolidine in methanol and methanol-*d*[1]. After 0.5 h the corresponding products were obtained in 48% and 77% conversions respectively. The difference in reaction activity is presumed to arise from the increased bond strength of the methanol-*d* i.e. the N---D hydrogen-bond is stronger than the N---H hydrogen-bond.[91]



Scheme 60 Proposed mechanism for H-bond activated allylic alkylation

4.4. Palladium-catalyzed substitutions with allylic amines using Lewis acids as activators

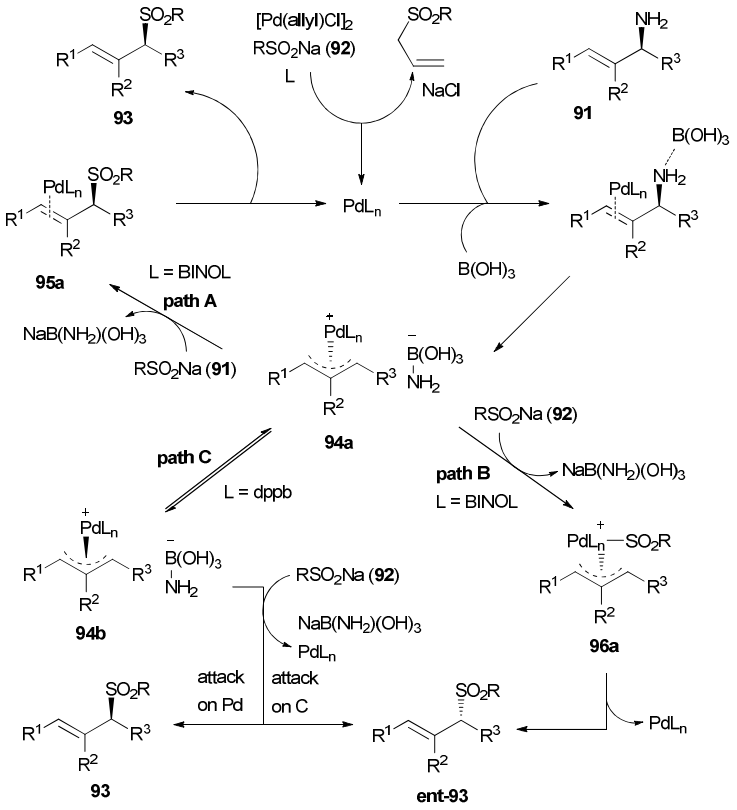
Tian and co-workers developed a substitution of primary allylic amines with sulfonate salts, using $B(OH)_3$ as an allylic activator.[92] A range of α-unbranched primary allylic amines were substituted with sodium sulfonates in the presence of 0.1 mol% $[Pd(allyl)Cl]_2$, 0.4 mol% 1,4-bis(diphenylphosphino)butane (dppb) and excess boric acid. The allylic sulfones were obtained exclusively as *E* isomers in good to excellent yields. Allylic sulfones could be prepared enantioselectively from enantiopure allylic primary amines via the addition of the ligand BINOL (**Table 25**).



91, R^1, R^2, R^3	92, R	91, ee (%)	93, ee (%)	93, yield (%)
Ph, H, Me	4-MeC_6H_4	99	96	93
2-naphthyl, H, Me	4-MeC_6H_4	93	92	86
Cyclohexyl, H,	4-MeC_6H_4	99	99	82
Me	4-MeC_6H_4	98	98	92
Ph, Me, Me	4-MeC_6H_4	96	96	95
Ph, H, Et	Ph	99	99	93
Ph, H, Me	4-ClC_6H_4	99	99	90
Ph, H, Me	Me	99	99	78
Ph, H, Me	$PhCH_2$	99	99	88

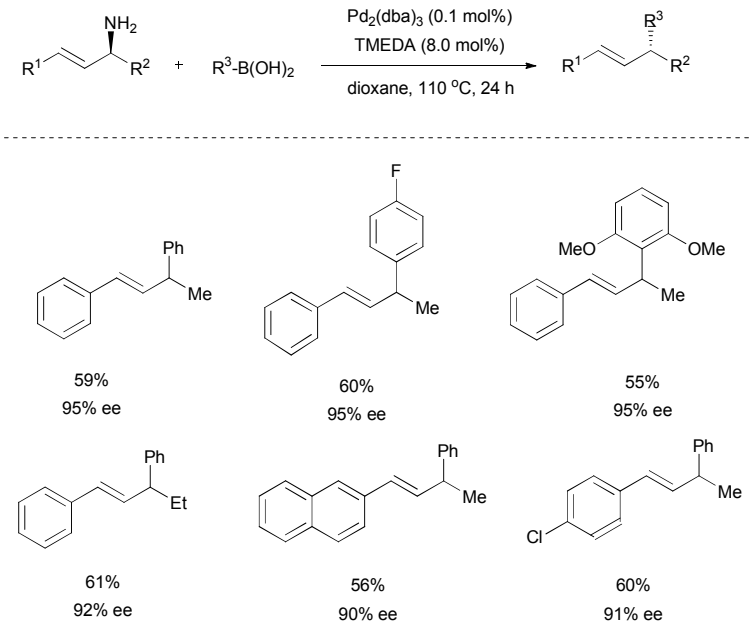
Table 25 Asymmetric substitution of α-chiral primary allylic amines with sodium sulfonates[92]

Tian proposed the reaction pathway shown in **Scheme 61**. Allyl sulfone **93** and Pd(0) catalyst PdL_n are formed from nucleophilic attack of sulfonate **92** on the catalyst precursor.[92] Boric acid activates the NH_2 group of the chiral amine **91** and the allylic C-N bond is cleaved by the Pd(0) catalyst with inversion of configuration to give π-allylpalladium **94a**. Use of BINOL as the ligand results in attack of sulfonate **92** on the allylic carbon of complex **94a** to give chiral sulfone **93** and regeneration of the Pd(0) catalyst (path A). Alternatively, the Pd atom of complex **94a** is attacked by sulfonate **92** to from the Pd-S-sulfinate **96a**, which undergoes reductive elimination to give the minor enantiomer **ent-93** (path B). The steric and electronic properties of the R^1 and R^3 groups in complexes **94a** and **96a** determine the regioselectivity of the reaction.[92]



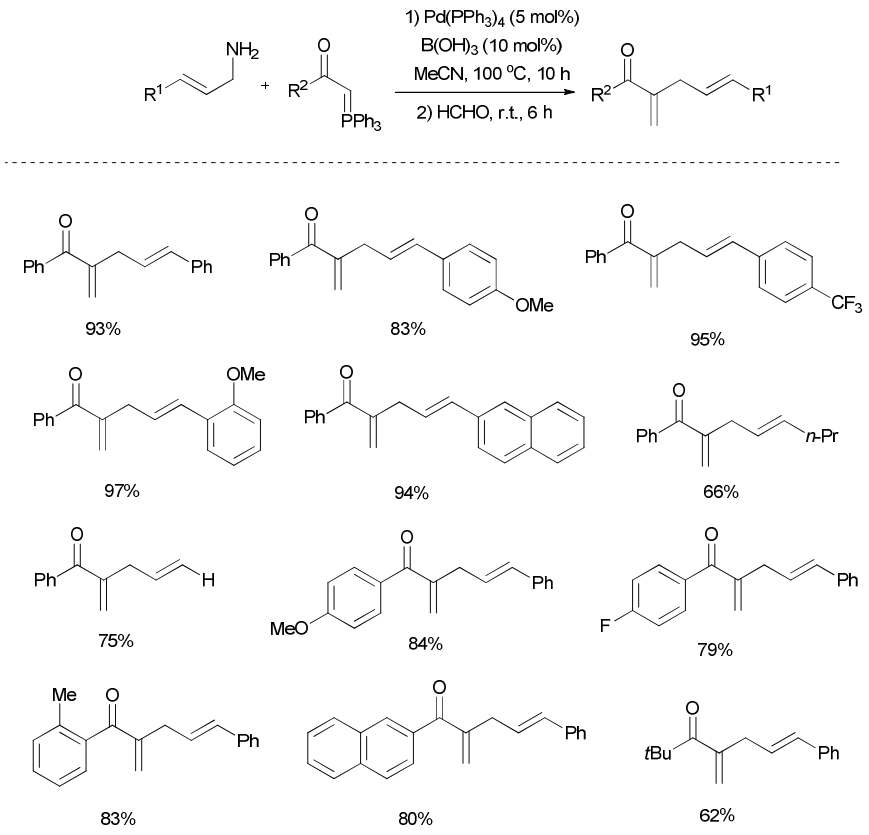
Scheme 61 Proposed reaction pathway[92]

Tian and co-workers have also reported a Pd-catalyzed stereospecific cross-coupling of α-chiral primary allylic amines with aryl boronic acids.[93] The catalyst system shown in **Scheme 62** was sufficient for the coupling of α-chiral primary allylic amines (R^1 = Ar, R^2 = Me, Et) with aryl boronic acids bearing electron-donating and electron-withdrawing groups. The coupled products were obtained in modest yields but with high enantioselectivites.



Scheme 62 Cross coupling of α-chiral primary allylic amines with aryl boronic acids

Activation of primary allylic amines with $B(OH)_3$ has also been successfully employed for the Pd-catalyzed allylation of stabilized phosphonium ylides.[94] A number of ketone-stabilized phosphonium ylides were allylated with high regioselectivity using a catalyst system consisting of 5 mol% $Pd(PPh_3)_4$ and 10 mol% $B(OH)_3$. Subsequent one-pot Wittig olefination gave the corresponding α,β-unsaturated ketones in good to excellent yields. The γ-positions of the primary allylic amines could bear aryl, heteroaryl, and alkyl groups (**Scheme 63**). Phosphonium ylides bearing aromatic groups gave higher yields than those bearing aliphatic substituents.



Scheme 63 Allylation of ketone-stabilized phopshonium ylides with primary allylic amines

5. Conclusion

Great strides have been made in the area of allylic substitution reactions using transition-metal catalysts. The use of allylic alcohols, allylic ethers and allylic amines for use in such reactions has opened up new avenues of research for bond-forming reactions. Countless ligands and activators have been developed to make allylic substitution reactions more efficient and environmentally benign. In particular, allylic alcohols represent substantially more economical substrates compared to their activated counterparts.

Despite the rapid increase in procedures utilizing such species, a number of challenges still remain: 1) Efficient and highly stereoselective allylic substitutions with allylic alcohols are still relatively challenging. Although several chiral ligands and additives have been developed, substrate scope is often limited. For example allylic substitution reactions with tetrasubstituted allylic species are still notoriously difficult to effect; 2) Allylic ethers and allylic amines remain difficult to employ as substrates in allylic substitutions. The majority of reactions involving these species usually require the use of vinyl epoxides and vinyl aziridines, as well as relatively harsh reaction conditions; only a handful of reactions employing alkyl allylic ethers and amines have been reported; 3) Many allylic

substitution reactions still require the use of additives (e.g. Lewis and protic acids) to activate the unreactive allylic species to nucleophilic attack. More effective procedures are therefore required; 4) Reaction conditions that are successful for one group of substrates does not necessarily imply identical conditions can be used for other substrates; reaction conditions (ligands, catalysts etc) which can be used more universally are therefore desirable; and 5) Although several examples of enantioselective allylic substitution reactions have been reported, such reactions still remain challenging, especially for syntheses involving the formation of quaternary centers. Therefore new ligands and reactions must be designed in order to overcome these problems.

Although the challenges mentioned above are numerous, recent advances relating to allylic substitution reactions have shown that they are far from insurmountable. These difficulties provide an excellent opportunity for synthetic chemists to apply their knowledge to this area of exciting and important chemistry.

Acknowledgements

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