ORGANIC CHEMISTRY
FRONTIERS

REVIEW

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Catalytic asymmetric allylation of carbonyl compounds and imines with allylic boronates

Cite this: *Org. Chem. Front.*, 2014, **1**, 303

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Received 25th December 2013,
Accepted 27th February 2014

DOI: 10.1039/c3qo00081h

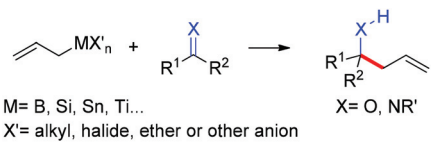
rsc.li/frontiers-organic

Enantioselective allylation is a highly used organic reaction to prepare chiral homoallylic alcohols and amines, which serve as important building blocks in the synthesis of a variety of natural products and pharmaceuticals. In particular, catalytic asymmetric allylation of carbonyl compounds and imines with organoboronates has seen rapid development in the past decade and is the focus of this review.

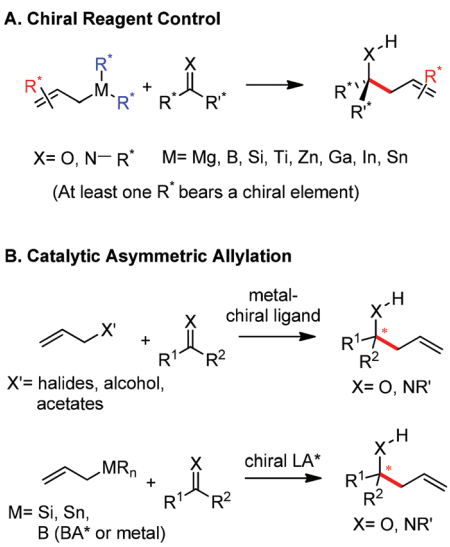
1. Background

The allylation reaction is widely applied to prepare homoallylic alcohols and amines, which serve as common building blocks for the synthesis of a variety of natural products and pharmaceutically relevant compounds (Scheme 1).[1] In this reaction, besides the alcohol or amine being introduced, the carbon–carbon double bond serves as a versatile motif and is readily transformed into other functional groups or used in a a carbon chain elongation.[2] When a ketone or its imine derivative is chosen as the electrophile, asymmetric allylation results in a chiral tetrasubstituted carbon, a long standing challenge in synthetic organic chemistry.[3] For these reasons, this field has attracted wide interest in the last decade. A lot of effort and some impressive progress have been made in the development of stereoselective allylation of carbonyl compounds or imines.[1,2,4] The use of stoichiometric chiral inducing reagents (including substrate control and reagent control) is a common approach to access key intermediates in the synthesis of natural products (Scheme 2).[4d] The major diastereoisomer in most of these examples can be rationalized through the existing working models.

Allylboration was originally documented in a 1964 paper contributed by Mikhailov and Bubnov.[5,6] Triallylborane reacted with aldehydes or ketones to give homoallylic alcohols. In 1966, Gaudemar and co-workers utilized allylic boronate for the allylation of aldehydes.[7] In the late 1970s, the regio- and diastereospecific addition of crotylboronate with aldehydes was rationalized by Hoffmann's model.[8] In 1983, Denmark and co-workers classified two modes of addition for different



Scheme 1 Allylation reaction.



Scheme 2 Enantioselective allylation reaction.

allylation reagents (Scheme 3).[9] In the Type I class, allylic boron reagents can activate the carbonyl to form a closed six-membered chair-like transition state which yields a γ-allylation (Scheme 3).[10] On the other hand, as shown in the Type II class, allyl trialkylsilanes and allyl trialkylstannanes generally react with aldehydes under the activation of an external Lewis acid through an open transition state (Scheme 3). The regioselectivity and diastereoselectivity are generally higher *via* the Type I mechanism than *via* Type II.

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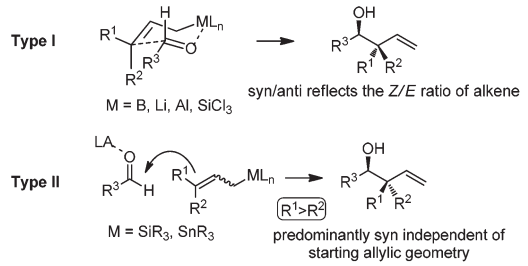
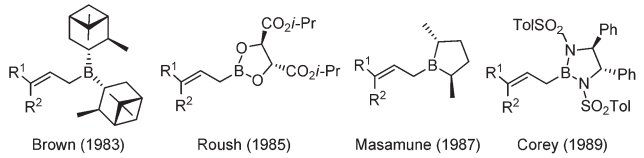
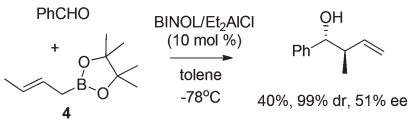


Scheme 3 Mechanistic models for allyl reagents.



Scheme 4 Representative chiral borane reagents for enantioselective allylboration.

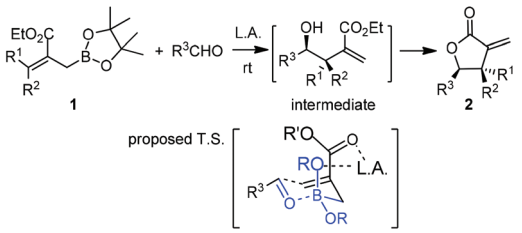


Scheme 5 Early example of catalytic enantioselective allylation.

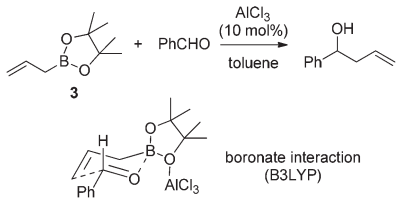
In the 1980s, highly efficient allylboration reactions were reported with excellent enantioselectivity by introducing chiral boron reagents. In the first twenty years of development, several C_2 symmetric chiral boron reagents were disclosed and received wide appreciation in this field.[11] Representative examples of the advancements include pinane-derived borane (Brown),[12] tartrate boronates (Roush),[13] borolane derivatives (Masamune),[14] and bis(sulfonamide) derivatives (Corey)[15] (Scheme 4).

Unfortunately, the development of enantioselective allylboration has long been restricted to chiral auxiliary approaches, requiring stoichiometric amounts of chiral reagent which are difficult to recycle. Lewis acids which potentially induce a changeover from a Type I mechanism toward the open transition structures (Type II) was considered unfeasible for the catalytic approach. One of the early examples to address this challenge was disclosed by Miyaura and co-workers in 2002. They reported the catalytic enantioselective allylation of an aldehyde with allylic boronates by using a catalytic amount of Et_2AlCl/BINOL complex.[16] The corresponding homoallylic alcohols were obtained in excellent diastereoselectivity albeit in moderate yield and enantioselectivity (Scheme 5). Since the continuing research was not followed, it is still not certain whether optimized conditions for higher enantioselectivity could be achieved.

Hall and co-workers reported a comprehensive study on Lewis acid-catalyzed addition of 2-alkoxycarbonyl allylboronates **1** to aldehydes with high diastereocontrol (Scheme 6).[17a] Based on extensive experimental and kinetic studies,[17b] Hall and co-workers subsequently suggested that the Lewis acid most likely coordinated to one of the boronate oxygens, probably the most accessible pseudo-axial one, instead of to the carbonyl oxygen of the aldehyde as generally proposed. The transition state still follows Denmark's classification of a closed chair-like transition state. This model was further refined by Sakata's computational study (B3LYP level),[18] whereas $AlCl_3$ chelates to the boronate oxygen atom, strengthening the electrophilicity of the boron center to accelerate the allylboration of the aldehyde (Scheme 7).



Scheme 6 Lewis acid-catalyzed allylborations.



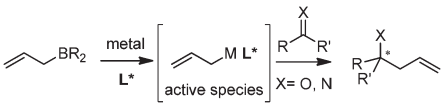
Scheme 7 Theoretical study of Lewis acid-catalyzed allylboration.

Due to their ease of preparation, functional group tolerance, stability, low toxicity, and overall operational simplicity of the addition reaction, allylboronate has been intensively studied in recent years. In this review, we are not intending to cover all allylations since several excellent reviews have appeared in recent years.[1,4] The achievement related to the nature of the boronate–Lewis acid complex which leads to the rapid development of a catalytic enantioselective allylation is discussed. There is no doubt that the catalytic asymmetric version is the focus of current research due to its sustainability and application.[19]

In the following sections, according to the catalyst applied, we will introduce enantioselective catalysis of allylation in three categories including metal complex-catalyzed asymmetric allylation, acid-catalyzed asymmetric allylation by activating boronates and catalyzed asymmetric allylation by ligand exchange of boronate.

2. Metal complex-catalyzed allylation

In this category, the stereoselective allylation with allylboronates is carried out in the presence of metal salts and chiral ligands. The reaction mode involves the critical ligand



Scheme 8 General reaction model for metal-mediated allylboration.

exchange (allyl group) from boron to the metal and the stereoselectivity is controlled by chiral ligands associated with the metal (Scheme 8). Because of the rapid transmetallation to form the active species and the fast regeneration of catalyst, asymmetric allylation proceeds efficiently with a broad substrate scope including aldehydes, ketones, and imines. However, the aldehyde is prone to react with allylboronates even without a catalyst, which therefore decreases the enantioselectivity of allylation. As a result, the reaction with aldehydes is always performed with a relatively higher catalyst loading within a shorter time.

2.1 Cu-mediated system

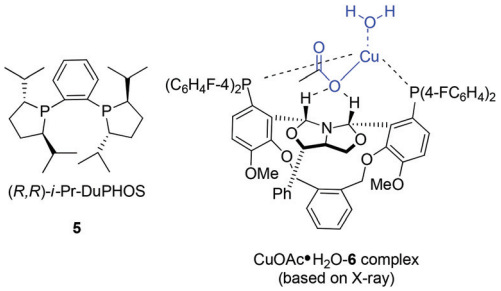
In 2004, Kanai, Shibasaki, and co-workers found that combination of 3 mol% of $CuF_2{\cdot}2H_2O$, 6 mol% of (*R*,*R*)-i-Pr-DuPHOS (**5**) as a chiral ligand and 4.5 mol% of La(Oi-Pr)$_3$ as a co-catalyst was able to catalyze enantioselective allylboration of ketones.[20,21] Substrates bearing aromatic, heteroaromatic, cyclic, and aliphatic ketones were investigated, and they all proceeded in a short reaction time (1 h) resulting in excellent yields and high enantioselectivities (condition A in Table 1). The preliminary mechanistic study indicated that La(Oi-Pr)$_3$ facilitates the transmetallation rather than acting as Lewis acid to activate allylboronates.

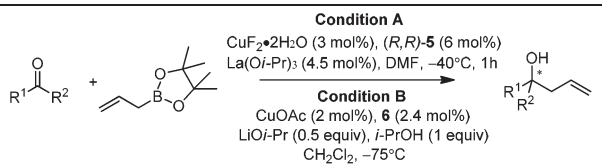
In 2010, they further synthesized a new chiral phosphine **6** for CuOAc-catalyzed allylation of ketones.[22] Under the optimized conditions, enantioselective allylation proceeded in better yield and enantioselectivity (condition B *versus* A in Table 1). To gain preliminary insight into the origin of the high catalytic activity and enantioselectivity, a single crystal of the CuOAc–**6** complex was collected, and the corresponding X-ray structure revealed a rigid folded conformation of the core macrocycle. This chiral space provided by the linker and wing modules may be responsible for the high stereoselectivities.[22] Experiments also showed that chiral ligand **6** offered better diastereo- and enantioselectivities in spite of *E*- or *Z*-allylboronate being utilized as the allyl transfer reagent (Scheme 9).[20,22]

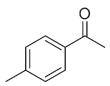
In addition to carbonyl compounds as substrates, Shibasaki and co-workers also disclosed the first catalytic enantioselective allylation of ketimines,[23] where *N*-benzylketimines reacted with allylboronate in the presence of CuF, LiOi-Pr, and the ligand, (*R*,*R*)-cyclopentyl-DuPHOS (**7**). LiOi-Pr was found to accelerate the reaction rate better than La(Oi-Pr)$_3$. Good yields and enantioselectivities were generally obtained for a series of aromatic ketimines, but aliphatic ketimines were not optimal substrates under the reaction conditions (entry 8, Table 2).

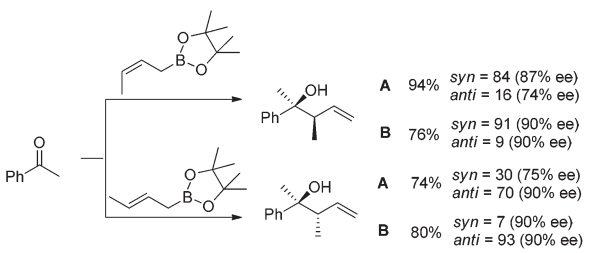
Based on kinetic and NMR studies, the following reaction mechanism was proposed (Scheme 10). First, LiOi-Pr facilitates

Table 1 Enantioselective allylboration of ketones catalyzed by Cu(I)-complex





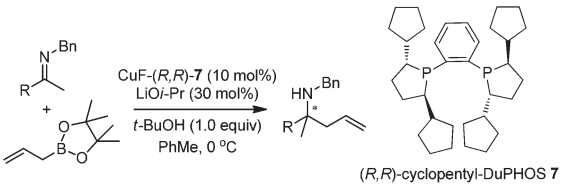
		Condition A		Condition B	
Entry	Substrate	Yield (%)	ee (%)	Yield (%)	ee (%)
1		94	82	99	89
2		89	84	98	92
3		84	85	94	93
4		88	84	99	98
5		87	90	91	90
6		99	91	88	83

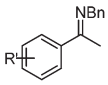
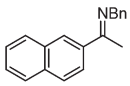
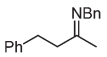


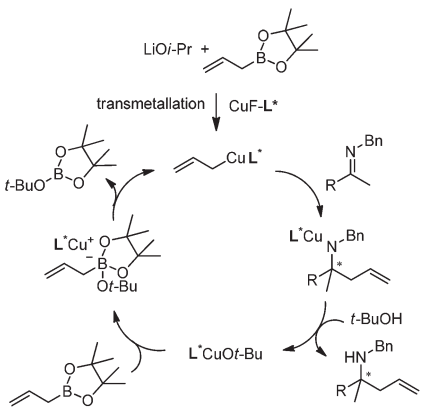
Scheme 9 Catalytic enantioselective crotylation of ketone.

the transmetalation to generate a reactive allylcopper species, which further reacts with ketamine to deliver a copper amide intermediate. After the ligand exchange, the homoallyl amine

Table 2 Allylation of ketimines catalyzed by Cu(I)-complex



Entry	Substrate	R′	t (h)	Yield (%)	ee (%)
1		Ph	0.5	92	89
2		3-MeC_6H_4	1	96	91
3		3-$MeOC_6H_4$	1	97	93
4		3-FC_6H_4	1	89	87
5		4-$MeOC_6H_4$	24	76	85
6		4-ClC_6H_4	24	82	81
7			12	88	92
8			2	98	23



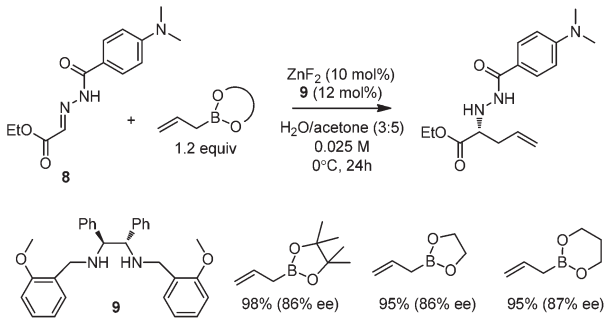
Scheme 10 Proposed catalytic cycle.

was released and the ^{t}BuO anion then associates with allylboronate to form an active boronate species which rapidly transmetallates to regenerate the allylcopper nucleophile in the catalytic cycle.[23]

2.2 Zn-mediated system

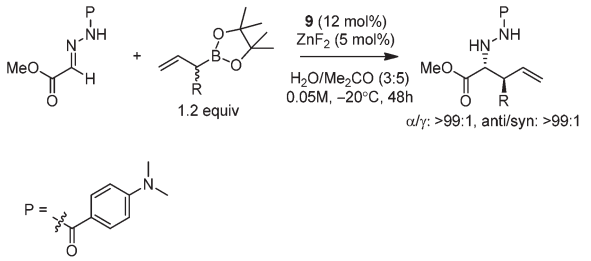
Kobayashi and co-workers developed a ZnF_2/chiral diamine (**9**)-catalyzed allylboration of hydrazono ester **8** in 2008.[24] Using water and acetone as co-solvents, the products were obtained in high yields and good enantioselectivities (Scheme 11). Water was found to be crucial to maintain high conversion and enantioselectivity. Using either allylboronic acid pinacol ester or cyclic boronates, similar yield and enantioselectivity were achieved.

However, under the optimal conditions, crotylboronation of hydrazono ester with (*Z*)-crotylboronate only afforded the adduct in 25% yield and 14% ee. Interestingly, when α-branched allylboronates were employed, the allylboration

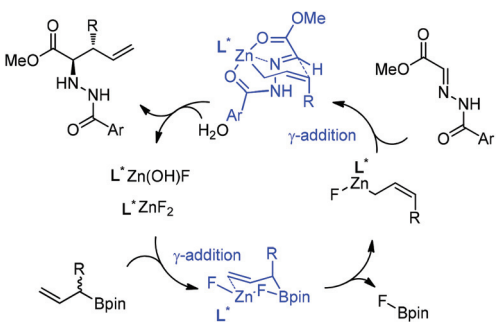


Scheme 11 Allylboration of hydrazono esters **8**.

Table 3 Enantioselective allylation of hydrazono ester



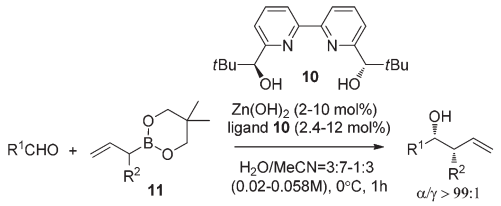
Entry	R	Yield (%)	ee (%)
1	Me	>99	88
2	Et	98	87
3	*n*-Bu	88	87
4	$(CH_3)_2CHCH_2$	76	87



Scheme 12 Proposed catalytic cycle.

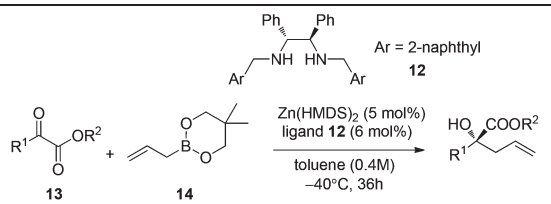
proceeded in high yields. In all cases, only α-addition products were found with high *anti*-selectivity (>99 : 1) and high enantioselectivities (Table 3).[24] Kobayashi and co-workers proposed a double γ-allylation to afford the α-addition product (Scheme 12). The γ-substituted (*Z*)-allylzincate (confirmed by NMR when R = H) was formed by reacting allylboronate with [L*ZnF_2] through a six-membered chair-like transition state. The allylzincate species then underwent the allylation of the hydrazono ester with *anti*-selectivity to yield the adduct *via* another chair-like transition state. Finally, the corresponding α-addition product was formed after hydrolysis.[24]

Table 4 $Zn(OH)_2$/**10**-catalyzed allylation of aldehydes



Entry	R^1	R^2	Loading (mol%)	Yield (%)	ee (%) (*syn*)	*syn*/*anti*
1	Ph	Me	10	92	81	10/1
2	$PhCH_2CH_2$	Me	10	94	88	6/1
3	$CH_3(CH_2)_8$	Me	3	94	82	7/1
4	$PhCH_2CH_2$	Et	5	96	91	3/1
5	$PhCH_2CH_2$	*n*Bu	5	97	90	3/1
6	Ph	OBn	10	82	88	24/1
7	Ph	Cl	5	92	88	24/1
8	$CH_3(CH_2)_{10}$	Cl	2	92	91	13/1

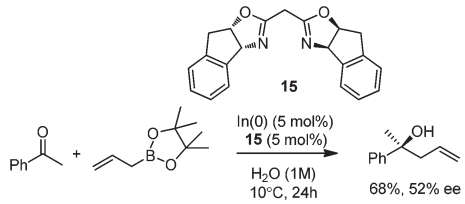
Table 5 Zn-catalyzed allylboration of α-keto esters **13**



Entry	R^1	R^2	Yield (%)	ee (%)
1	Ph	Me	86	97
2	Ph	Bn	78	83
3	Me	Bn	72	89

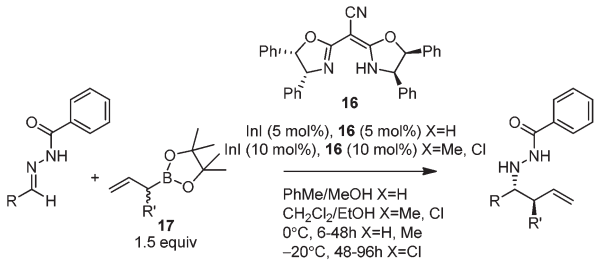
Kobayashi and co-workers further investigated the catalytic asymmetric allylation of aldehydes. They found that the catalytic system of $Zn(OH)_2$ and chiral bipyridine ligand **10** promoted the addition of allylboronic acid 2,2-dimethyl-1,3-propanediol ester (**11**) with aldehydes to give excellent results under the optimized reaction conditions.[25] Similar to allylation of hydrazono esters, the α-addition products were afforded and the favorable *syn*-adduct was generated with good enantioselectivity (Table 4). This catalytic system was also applied to α-methylallylation and other α-alkylallylations, giving moderate to excellent *syn*-selectivities and high to excellent enantioselectivities for both aromatic and aliphatic aldehydes.[25]

Further progress of enantioselective allylation of ketones required intense screening of zinc salts and chiral ligands.[26] A 1,2-diphenylethylene-diamine derived chiral ligand **12** and $Zn(HMDS)_2$ were identified for realizing the allylation of a few α-keto esters in high enantioselectivities under the optimal reaction conditions (Table 5).



Scheme 13 Asymmetric In(0)-catalysis in water.

Table 6 In-complex catalyzed allylation of hydrazones



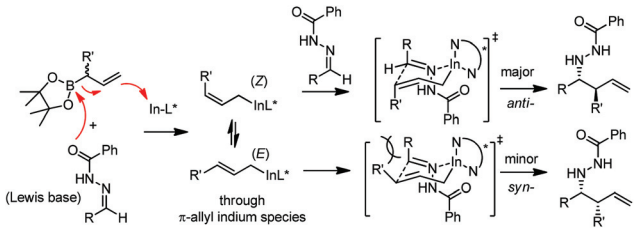
Entry	R	R′	Yield (%)	ee (%)
1	Ph	H	99	96
2	4-MeOC_6H_4	H	97	96
3	2-Thienyl	H	99	95
4	Cy	H	87	30
5[a]	Ph	Me	85	94
6[a]	4-MeOC_6H_4	Me	86	93
7[b]	Ph	Cl	84	84
8[b]	2-Thienyl	Cl	89	86

[a] *anti*/*syn* = 19 : 1. [b] *anti*/*syn* = 99 : 1.

2.3 In-mediated system

In 2008, Kobayashi and co-workers reported a catalytic asymmetric allylation of acetophenone with allylboronate in the presence of 5 mol% In(0)-chiral bis(oxazoline) ligand **15** in water.[27] Although it was the first example of In-mediated asymmetric allylboronation in water, the 68% yield and 52% ee are far from satisfactory (Scheme 13).

Kobayashi and co-workers later disclosed another example of applying indium catalysis in enantioselective allylation, crotylation, and α-chloroallylation of hydrazones with boronates.[28] An *in situ* generated chiral indium(I)–semicorrin catalyst **16** could give high yields and excellent enantioselectivities when different aryl hydrazone substrates were used. The reaction tolerates functionalities at the arene, such as hydroxy, methoxy, tertiary amino, and nitro groups (Table 6). Crotylation of racemic α-methyl or α-chloroallyl boronic acid pinacol ester (**17**) produced exclusively an α-adduct with excellent *anti*/*syn* ratios and good enantioselectivities. However, reaction conditions were not suitable for cyclohexane or other aliphatic carbaldehyde imine derivatives (entry 4). Mechanistically, it was assumed that hydrazone acts as a Lewis base to activate the allylic boronate for transmetallation, and the resulting active species, a chiral allylindium reagent, undergoes the nucleo-



Scheme 14 Proposed mechanism.

philic addition to the imine derivatives *via* a cyclic chair-like transition state. Because of the *gauche* interaction between R and R′ in the transition state when the (*E*)-isomer was employed, the *anti*-product afforded by the allylation of (*Z*)-allyl indium species was predominant. The authors also concluded that an equilibrium between (*E*) and (*Z*)-isomers through π-allyl indium species existed (Scheme 14).

2.4 Ni-mediated system

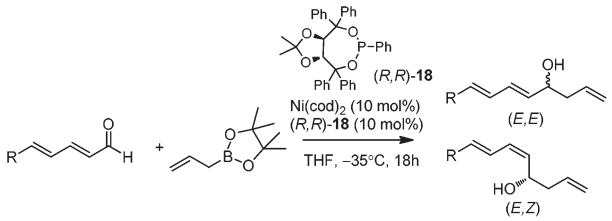
In 2009, Morken and co-workers reported a unique catalytic enantioselective allylation of dienals, which was proposed to occur by 3,3′-reductive elimination in the presence of $Ni(cod)_2$ and chiral phosphonite (*R*,*R*)-**18**.[29] Both *δ*-aromatic and aliphatic substituted dienals gave the predominant *E*,*Z*-adducts in high enantioselectivities (Table 7). Interestingly, the minor *E*,*E*-adduct was determined to be racemic and assumed to arise from a non-catalyzed reaction that occurs at room-temperature. Morken *et al.* further suggested that the following transmetallation consists of the boron Lewis acid-promoted electron transfer from Ni(0) to the dienal, which subsequently forms an allyl nickel species. At last a 3,3′-reductive elimination leads to the *E*,*Z*-allylation product (Scheme 15).

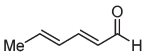
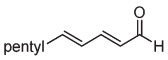
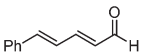
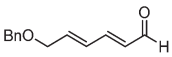
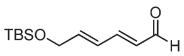
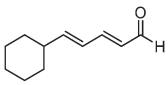
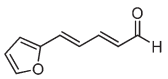
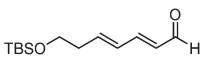
2.5 Rh-mediated system

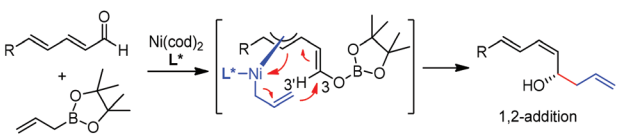
Very recently, Lam and co-workers reported an enantioselective allylation of cyclic aldimines and ketimines with potassium allyltrifluoroborates by using a chiral diene-ligated rhodium complex.[30] In this study, only cyclic imines are effective substrates for allylation. Under the optimized reaction conditions, using diene **19** as the chiral ligand, high enantioselectivities (90–99% ee) and generally good yields were obtained for a wide range of cyclic imines (Table 8). Both benzoxathiazine-2,2-dioxides **20** bearing methyl, methoxy, halogen, cyano, and dioxole groups and other cyclic aldimines and ketimines delivered excellent results.

The crotylation of cyclic imine **21** was realized with high diastereo- and enantioselectivity (Table 9). *E*-Crotyltrifluoroborate **22** and *Z*-crotyltrifluoroborate **23** afforded *anti*-product and *syn*-product, respectively.[30] To gain insights into the mechanism, ketimine **21** was subjected to the allylation with bis-deuterated potassium allyltrifluoroborate **24** (Scheme 16). A mixture of products **25** and **26** (ratio 1/1) suggested that a rapid interconversion between two σ-allyl haptomers might be feasible when allylrhodium(I) species **27a**/**27b** were generated after transmetallation (Schemes 16 and 17). The subsequent

Table 7 Allylboration of dienals catalyzed by Ni(II)-complex



Entry	Substrate	(*E*,*Z*)/(*E*,*E*)	Yield (%)	ee (%)
1		>20 : 1	84	88
2		>20 : 1	84	87
3		>20 : 1	68	91
4		15 : 1	86	73
5		7 : 1	81	85
6		>20 : 1	92	93
7		15 : 1	73	94
8		16 : 1	83	90



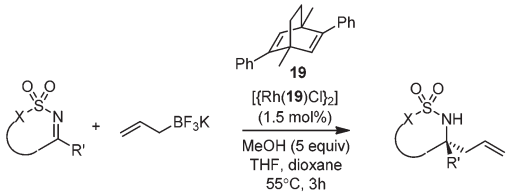
Scheme 15 Proposed mechanism.

allylation proceeded with excellent stereocontrol *via* a cyclic chair-like transition state. After the protonation with HX (X = Cl, F, or OMe) of the rhodium amide, the corresponding product is released and the active species **28** was re-generated to complete the catalytic cycle (Scheme 17).

3. Brønsted acid-catalyzed asymmetric allylation

Recently, organocatalysis has served impressively in many asymmetric transformations. The reaction modes mainly lie in hydrogen bonding and covalent bond formation which differ from the major interaction in metal-catalyzed reactions. The unique interactions between substrates and organocatalysts offer new reactivities and novel transformations. In the

Table 8 Rh-catalyzed allylation of cyclic imines



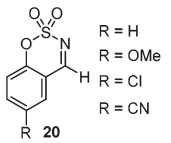
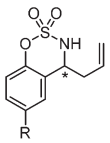
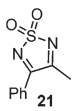
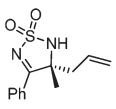
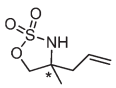
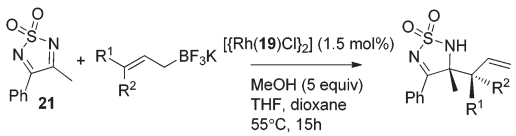
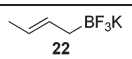
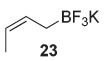
Entry	Starting material	Product	Yield (%)	ee (%)
1	 R = H, R = OMe, R = Cl, R = CN; 20		87	96
2			92	91
3			96	96
4			97	98
5	 21		88	97
6			83	93

Table 9 Allylation of cyclic imines with crotyltrifluoroborates

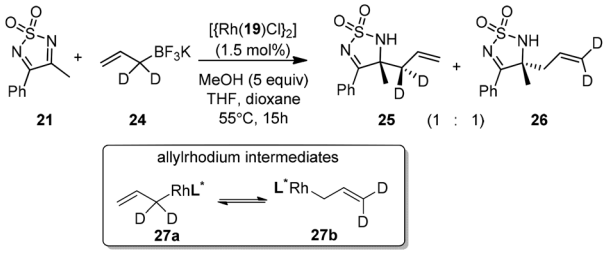


Entry	Allyltrifluoroborate	*syn*/*anti*	Yield (%)	ee (%)
1	 22	<1 : 19	68	97
2	 23	>19 : 1	89	99

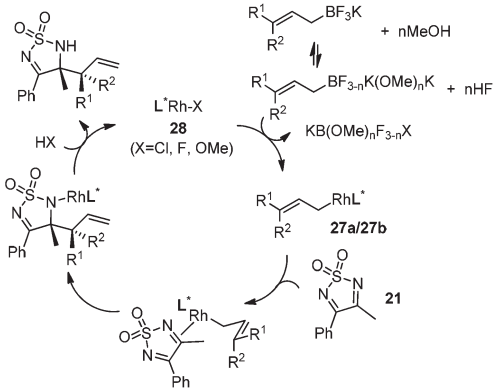
presence of Brønsted acids, allylboronate reacts with aldehydes in a highly diastereoselective and enantioselective manner. Although Lewis acid-assisted Brønsted acid catalysis (LBA) is a metal catalysis, its mode of action is reminiscent of a hydrogen-bond donor like organocatalyst. The chiral acid activates one of the boronate oxygens and accelerates the subsequent enantioselective allylation *via* a pre-organized transition state (Scheme 18). With the proper acid or LBA in hand, the asymmetric allylation proceeds in high yield and enantioselectivity. Concerning phosphoric acid catalyzed allylation, the Lewis base center of the phosphoryl oxygen in the catalyst interacts with the formyl hydrogen of aldehyde (the Lewis acid center) which may be critical for the well-organized transition state.[31]

3.1 Lewis acid-assisted Brønsted acid catalysis (LBA) system

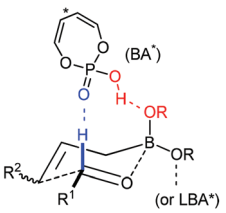
Lewis acid-assisted Brønsted acid catalysis (LBA) was generally conceptualized by Yamamoto and co-workers. In the original



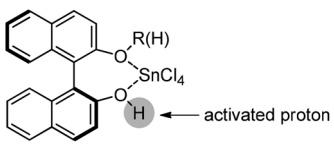
Scheme 16 Deuterium-labeling experiment.



Scheme 17 Possible catalytic cycle.



Scheme 18 Interaction mode of acid-catalyzed asymmetric allylboration.



Scheme 19 Yamamoto's LBA catalytic system.

catalyst system, tin chloride coordinates with the oxygen atoms of BINOL to increase the acidity of the hydroxylic proton, which is oriented in a particular direction.[32] The catalyst system has been shown to be a particularly useful tool for asymmetric transformations (Scheme 19).[33]

Following previous work on Lewis acid-catalyzed allylboration,[15–17] Hall and co-workers screened several chiral ligand systems including scandium, copper, and many other metals as Lewis acids in the asymmetric allylation.

Table 10 Chiral diols evaluated in allylboration

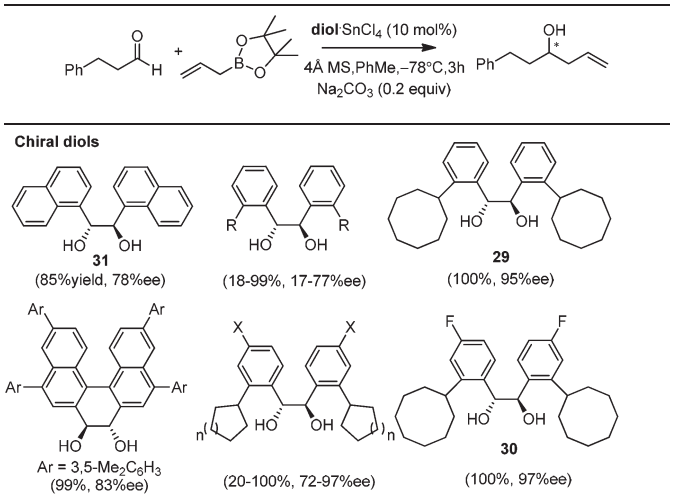
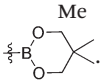


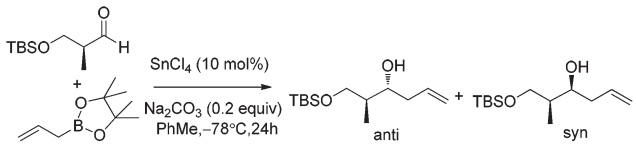
Table 11 Stereoselective allylboration with the LBA approach

Entry	R^1	R^2	R^3	Diol	Yield (%)	ee (%)
1	Ph	H	H	29	99	71
2	$PhCH_2CH_2$	H	H	29	99	95
3	$TBSO(CH_2)_2$	H	H	29	98	95
4	$PhCH_2CH_2$	H	H	30	99	97
5	$TBSO(CH_2)_2$	H	H	30	99	96
6	$3,5\text{-}(CF_3)_2C_6H_3$	H	H	29	99	94
7[b]	$PhCH_2CH_2$	Me	H	29	93	96
8[b]	$PhCH_2CH_2$	H	Me	29	78	84
9[a]	$C_4H_9C{\equiv}C$	H	H	30	84	71
10[a]	$PhC{\equiv}C$	H	H	30	80	69
11[a,b]	$Ph(CH_2)_2C{\equiv}C$	Me	H	30	88	91
12[a,b]	$TMSC{\equiv}C$	Me	H	30	83	82

[a] Boronate = [a] Boronate=  . [b] dr > 98 : 2.

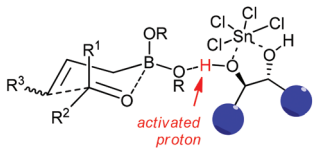
Unfortunately, all of these attempts only provided either low ee values or no rate acceleration over the background reaction. It was assumed that these chiral metal complexes were simply too sterically bulky to coordinate effectively to the hindered boronic ester.[34a] Interestingly, when different C_2-symmetric chiral diols combined with $SnCl_4$ were screened, good to excellent asymmetric induction was obtained in the allylboration of aldehydes by the allylboronic acid pinacol.[32] After extensive experiments, catalysts derived from diols (*R*,*R*)-**29** and (*R*,*R*)-**30**[34c] were identified as the most efficient (Table 10).

With catalytic allylboration, aliphatic aldehydes usually proceed in high enantioselectivities while aromatic aldehydes and enals show moderate enantioselectivity (Table 11).[34a–e] Under the optimized conditions, the crotylation of aldehydes with *E*-crotyl boronate was superior to the reaction with the (*Z*)-isomer (entry 7 *vs.* 8). This catalyst system was also efficient



	anti	:	syn	yield
$SnCl_4$ alone	46	:	54	75%
with (*R*,*R*)-**31** (11 mol%)	84	:	16	83%
with (*S*,*S*)-**31** (11 mol%)	35	:	64	60%

Scheme 20 Double diastereoselection of allylboration to chiral substrate.



Scheme 21 Proposed asymmetric allylation intermediate.

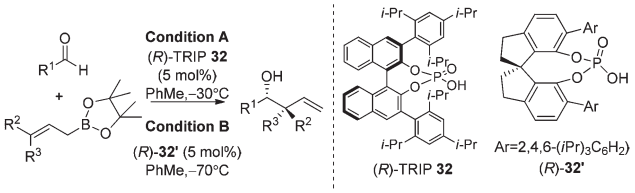
for the catalytic allylation of propargylic aldehydes (entries 9–12).[34f] Hall *et al.* also investigated the double diastereoselection of allylboration to chiral aldehyde[34a] (Scheme 20). In the presence of diol (*R*,*R*)-**31**, the allylboration resulted in a ratio of 84 : 16 favoring the *anti*-isomer (*matched*) while the usage of diol (*S*,*S*)-**31** led to a lower selectivity (*anti* : *syn* = 35 : 64, *mismatched*). The moderate discrimination effect for chiral substances requires further optimization to explore the LBA approach.

Concerning the mechanistic proposal of LBA-catalyzed allylation, the function of the diol·$SnCl_4$ system is much more complex than a Brønsted acid or bisalkoxy-dichlorotin species alone.[34c] Based on the previous concerns of mechanism on Lewis acid-catalyzed allylborations and several controlled experiments,[15–17] it was proposed that allylboration of aldehydes occurred by the coordination of one of the boronate oxygens with the "super" acidic proton which was formed from the combination of diols with $SnCl_4$. The chiral diols determined the facial selectivity for the addition to aldehyde through a closed six-membered chair-like transition state with high levels of asymmetric induction (Scheme 21).

3.2 Brønsted acid catalysis system

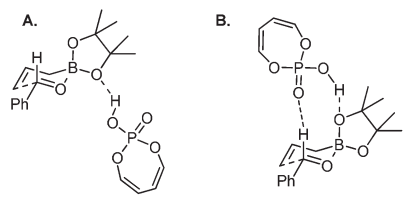
Organocatalysis always devises elegant solutions for the most challenging problems in modern asymmetric synthesis.[35] In 2010, Antilla and co-workers reported the first high-yielding and highly enantioselective chiral phosphoric acid-catalyzed allylboration of aldehydes.[36a] The stability and availability of allylic boronates as well as chiral catalysts was astonishing for the organocatalytic allylation reaction. The reaction was proved to be highly general with a broad substrate scope covering aryl, heteroaryl, α,β-unsaturated, and aliphatic aldehydes. With the catalysts screened, the authors found that phosphoric acid

Table 12 Allylation of aldehydes catalyzed by (R)-TRIP 32

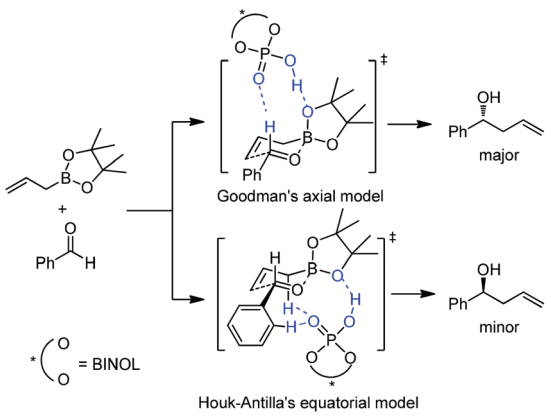


				Condition A		Condition B	
Entry	R^1	R^2	R^3	Yield (%)	ee (%)	Yield (%)	ee (%)
1	Ph	H	H	99	98	97	99
2	4-$MeOC_6H_4$	H	H	95	98	95	99
3	4-$CO_2MeC_6H_4$	H	H	96	96	96	99
4	Cy	H	H	98	73	90	91
5	$PhCH_2$	H	H	96	90	86	98
6	9-Anthracene	H	H	94	91	92	97
7[a]	Ph	Me	H	96 (*anti* : *syn* = 98 : 2)	99	98 (*anti* : *syn* = 99 : 1)	99
8	Ph	H	Me	95 (*anti* : *syn* = 2 : 98)	94	99 (*anti* : *syn* = 1 : 99)	99

[a] Reaction was run at 0 °C.



Scheme 22 Optimized transition states with buta-1,3-diene-1,4-diol-phosphoric acid (the simpler model for TRIP).



Scheme 23 Transition state of chiral BINOL-phosphoric acid catalyzed allylboration.

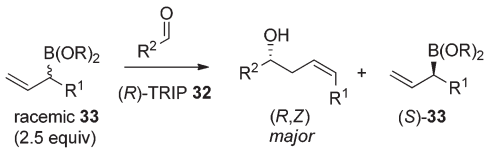
(*R*)-TRIP **32** was the best catalyst for allylation of aldehydes (condition A in Table 12).

Further work by Hu and co-workers found that the SPINOL-based phosphoric acid (*R*)-**32′** is a superior catalyst to achieve higher enantioselectivities on substrates used in Antilla's original report (condition B in Table 12). The new catalyst clearly maintains a high reactivity at lower temperature.[36b]

The reaction conditions were also shown to be effective for the enantioselective crotylation of aldehydes with high diastereoselectivities (entries 7 and 8). It indicates that the allylboration proceeds *via* a Type I mechanism involving a six-membered chair-like transition state. Similar to previous work on allylboration,[15–17,34] Antilla *et al.* believed that activation *via* the protonation of the pseudo-equatorial oxygen in boronate by the chiral phosphoric acid catalyst is the most plausible transition state (Model A, Scheme 22).[36a]

However, Goodman's group utilized DFT and QM/MM hybrid calculations to comment that the reaction actually adopts a transition state involving two crucial hydrogen-bonding interactions (Model B, Scheme 22). One is from the hydroxyl group in PA to the pseudo-axial oxygen of the cyclic boronate; another is a stabilizing interaction between the phosphoryl oxygen of the catalyst (Lewis base site) to the formyl hydrogen of the aldehyde (Lewis acid site).[31] This alternative transition state has the lowest energy and extra rigidity accounting for the excellent asymmetric control.

Subsequently, Antilla and Houk reinvestigated the original TRIP-catalyzed allylboration with density functional theory (B3LYP and B3LYP-D3) besides several levels of DFT calculations in 2013.[37] The lowest energy transition state of chiral BINOL-phosphoric acid catalyzed allylboration is indeed following Goodman's axial model. Moreover, the equatorial model originally proposed by Antilla accounted for the generation of the minor enantiomer (Scheme 23).



Scheme 24 Kinetic allylboration of aldehydes.

In 2013, Malkov *et al.* developed a chiral phosphoric acid-catalyzed kinetic resolution of racemic allylboronates **33** in a face- and *Z*-selective allylation of aldehydes (Scheme 24).[38] The *R*-enantiomer of **33** was found to readily react with aldehydes to deliver adducts in good enantioselectivity, while the *S*-enantiomer remained behind. The enantioselective process was again interpreted by Goodman's axial model.

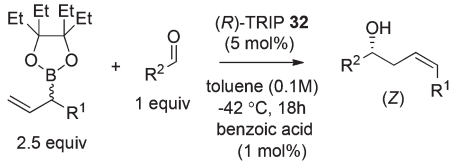
Hoffmann,[39] Pietruszka and Schone[40] illustrated that the *E*/*Z* ratio of the homoallylic alcohol products in the allylation with secondary alkyl allyl boronates was determined by the steric hindrance of the boronate fragment. The *Z*-isomer was more likely generated with larger groups, such as pinacolate or benzopinacolate in the boronate were used. Malkov *et al.* also performed DFT level calculations to understand the influence of the steric size of the cyclic boronate moiety on the *E*/*Z* ratio in the corresponding products.[38] The computation revealed that the transition states involved a two-point activation mode in accord with Goodman's work. Importantly, the calculation also predicted that the tetraethylethylene glycol derivative (Epin) should give a better *Z*/*E* ratio, which indeed guided the authors to locate the optimal boronates. Under the optimal conditions, the allylation of both aromatic aldehydes and aliphatic aldehydes proceeded in high yields and enantioselectivities with an impressive *Z* selectivity of >25 : 1 (Table 13).[38]

In 2013, Murakami and co-workers reported a highly diastereo- and enantioselective synthesis of *anti*-homoallylic alcohols from terminal alkynes and aldehydes with a cationic iridium(I) complex/chiral phosphoric acid relay system (Scheme 25).[41] The cationic iridium(I) complex-catalyzed olefin transposition of (*E*)-1-alkenylboronates, generated from hydroboration of the corresponding terminal alkynes, afforded (*E*)-2-alkenylboronates which further participated in the enantioselective allylboration of aldehydes catalyzed by (*R*)-TRIP **32** (Scheme 25). The iridium(I) catalyst system does not interfere with (*R*)-TRIP **32**, which is used for the asymmetric allylation. While screening the scope of aldehydes, it was discovered that an electronically and sterically diverse array of aromatic aldehydes and aliphatic aldehydes generally proceeded in 85–99% yield with excellent diastereoselectivities and high enantioselectivities (except entry 5, Table 14).[41]

4. Catalytic asymmetric allylation by ligand exchange

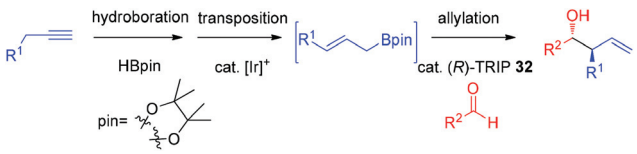
Catalytic asymmetric allylation of ketones and imines can be realized through a crucial ligand-exchange step involving the

Table 13 Scope of the kinetic resolution of racemic secondary allylboronates



Entry	R^1	R^2	Yield (%)	ee[a] (%)
1	Me	Ph	96	97
2	Me	PhCH=CH	84	97
3	Me	4-FC_6H_4	80	85
4	Me	*c*-C_6H_{11}	72	88
5	Me	$PhCH_2CH_2$	81	91[b]
6	*n*Pr	Ph	90	94
7	*n*Pr	PhCH=CH	97[d]	93
8	*n*Pr	$PhCH_2CH_2$	80[d]	87[b,c]

[a] The *Z*/*E* ratio was >25 : 1. [b] The product was assigned as *S*-configuration as a result of the change in the preference of the substituents in the Cahn–Ingold–Prelog system. [c] The *Z*/*E* ratio was 13 : 1. [d] Reaction time was 60 h.



Scheme 25 Allylboration with Ir(I)-complex/TRIP relay system.

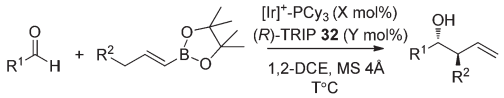
allylboronate. After the ligand exchange on the borane, the corresponding chiral boronate proceeds through the allylation and regenerates the chiral ligand which participates in the subsequent ligand-exchange process (Scheme 26). Restricted to the speed of ligand exchange, this approach may not be feasible for aldehydes since the background reaction is highly prone to occur before the requisite ligand-exchange process.

4.1 Exchange of chiral diols system

In 2006, Schaus and co-workers reported a class of chiral diols which catalyzes an enantioselective and diastereoselective allylboration of ketones with allyldiisopropoxyborane **34**.[42] It was found that 3,3′-Br_2-BINOL **35** was the most effective catalyst to promote the asymmetric reaction of a variety of ketones with high enantioselectivities in $PhCF_3$–toluene (1 : 3 ratio) at −35 °C (condition 1, Table 15). All electron-rich and electron-deficient aromatic ketones and heteroaromatic ketones proceeded with good results. Enones **36** and **37** also underwent 1,2-addition as the regioselective products. Allylboronate **38** was comparable under the standard allylation conditions.

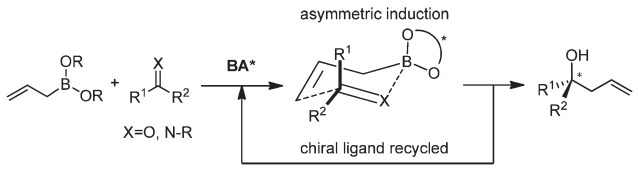
Preliminary mechanistic experiments revealed that the ligand exchange process between one isopropoxy ligand of boronate and chiral diol was observed by ^{1}H NMR and ESI-MS analysis during the reaction of **34** with **35**. The catalyst-associated boronate complex reacts with ketones *via* a six-membered chair-like transition state which is responsible for the high

Table 14 Allylation with (*E*)-1-alkenylboronates[a]



Entry	R^1	R^2	*X*	*Y*	*T* (°C)	Yield (%) (*anti* : *syn*)	ee (%)
1	Ph	Et	5.0	10	28	90 (>98 : 2)	93
2	Ph	Ph	10	20	−15	83 (>98 : 2)	88
3	Ph	$(CH_2)_3OTBS$	7.5	20	28	85 (>98 : 2)	90
4	Ph	$(CH_2)_3CO_2Me$	7.5	20	28	86 (98 : 2)	93
5	Ph	OTBS	7.5	10	28	97 (92 : 8)	17
6	4-$MeOC_6H_4$	Et	7.5	15	28	99 (>98 : 2)	92
7	4-$NO_2C_6H_4$	Et	5.0	10	28	85 (>98 : 2)	95
8	2-Furyl	Et	5.0	10	28	91 (>98 : 2)	92
9	$PhCH_2CH_2$	Et	10	20	5	88 (>98 : 2)	91
10	Cy	Et	10	20	5	82 (97 : 3)	88

[a] Conditions: aldehydes (0.40 mmol), (*E*)-alkenylboronates (0.80 mmol), $[Ir(cod)_2]BF_4$–PCy_3 (Ir : P = 2 : 5), MS 4 Å (50 mg) in 1,2-DCE (1 mL).



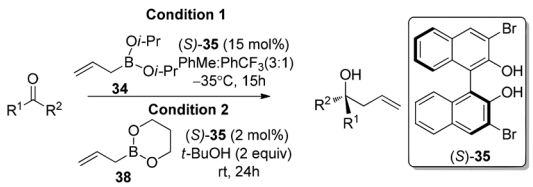
Scheme 26 General reaction mode of ligand-exchange of boronates.

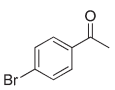
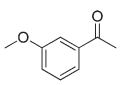
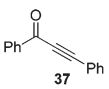
enantioselectivity. Finally, another ligand-exchange process takes place to liberate the chiral diol and allylic alcohol (Scheme 27).[42]

Cyclic boronates such as dioxaborolane and dioxaborinane were further identified as better boronate resources since they are easier to prepare, stable during purification and can be stored for longer than acyclic boronates. In addition to the enhancement of stability, the tethered diol used to generate the cyclic boronate also facilitates ligand exchange at the end of a reaction cycle. As a result, Schaus *et al.* alternatively employed allyldioxaborinane **38** for the allylation of ketones with chiral 3,3′-Br_2-BINOL **35**.[43] Under the optimized reaction conditions, allylation of ketones proceeded in excellent yields and enantioselectivities at room temperature (condition 2, Table 15). Moreover, the crotylboration of acetophenone with both diisopropoxy acyclic boronate and cyclic allyldioxaborinane was performed to give high yields, diastereoselectivities and enantioselectivities (Scheme 28).

In 2007, Schaus and co-workers further explored the concept of ligand-exchange to allylboration of acyl imines.[44] Gratifyingly, allylation of imines was achieved in good yields (75–94%) and high enantioselectivities (90–99% ee) with 15 mol% of **39** and allyldiisopropoxyborane **34**. The reaction can tolerate both aromatic and aliphatic imines with examples such as aryl, cinnamoyl, and cyclohexyl carboxamide imine proceeding in good yield and enantioselectivity (Table 16). However, methyl and methoxyl carbamoyl imine (entries 8 and 10, Table 16) were exceptions to this broad substrate scope. Interestingly, either (*E*)-crotylboronate or (*Z*)-crotylboronate in

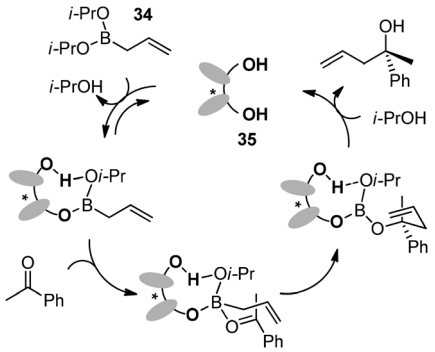
Table 15 Allylation of ketones catalyzed by chiral diol **35**



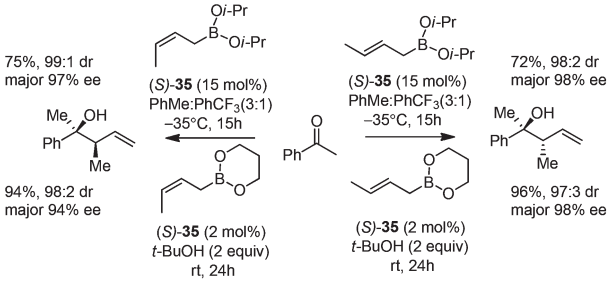
Entry	Substrate	Condition 1 Yield (%)	Condition 1 ee (%)	Condition 2 Yield (%)	Condition 2 ee (%)
1		83	94	96	98
2		86	99	97	98
3		83	99	88	98
4		88	94	92	98
5		87	95	95	>99
6	 **36**	91	93	96	97
7	 **37**	93	90	—[a]	—

[a] Ketone **37** was not examined in condition 2.

the reaction resulted in the *anti*-addition product **41** (Scheme 29). The high degree of *anti*-selectivity afforded by (*E*)-crotylboronate can be rationalized by a chair-like transition

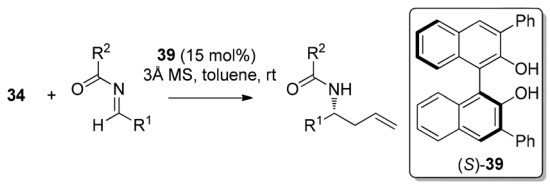


Scheme 27 Possible catalytic cycle.



Scheme 28 Crotylboration of acetophenone with diisopropoxy acyclic boronate and cyclic allyldioxaborinane.

Table 16 Allylation of imines catalyzed by chiral diol **39**

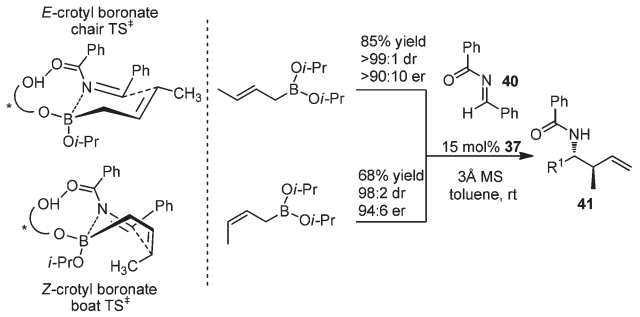


Entry	R^1	R^2	Yield (%)	ee (%)
1	Ph	Ph	87	98
2	4-BrC_6H_4	Ph	86	95
3[a]	4-FC_6H_4	Ph	94	96
4	2-Thienyl	Ph	81	90
5	$BnOCH_2$	Ph	84	93
6	*c*-C_6H_{11}	Ph	80	96
7	*t*-Bu	Ph	81	99
8	Ph	CH_3O	13	14
9	Ph	*c*-C_6H_{11}	83	94
10	Ph	CH_3	52	40

[a] Reaction was run at 10 °C for 48 h.

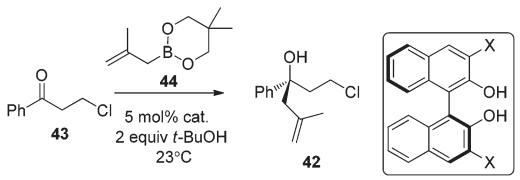
state. For (*Z*)-crotylboronate, a boat-like transition state may be adopted to deliver the same product. A preferred conformer is organized by the pseudo-*trans*-diaxial interaction of the methyl group of the (*Z*)-boronate and the acyl substituent of the imine arising from the chair transition state.[44]

Following Schaus's seminal work, Zhang *et al.* reported asymmetric allylboration of ketones to prepare chiral tertiary alcohol **42**, a precursor for the synthesis of a pharmaceutical



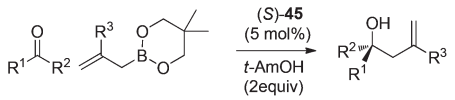
Scheme 29 Crotylboration of imine **40** and proposed transition states.

Table 17 Asymmetric methallylation of ketone **43**



Entry	X	*t* (h)	Conv. (%)	ee (%)
1	Br (**35**)	10	61	78
2	CO_2Me	16	84	2
3	SO_2CF_3	20	88	0
4	CF_3	16	82	4
5	Cl	10	70	82
6	F (**45**)	10	98	74

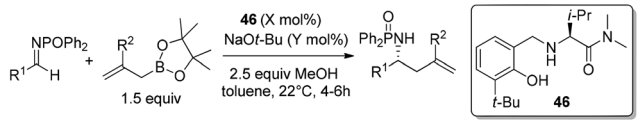
Table 18 Asymmetric alkylallylation of ketones

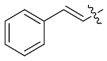


Entry	R^1	R^2	R^3	*T* (°C)	Yield (%)	ee (%)
1	Ph	CH_2Ph	Me	40	98	86
2	4-ClC_6H_4	CH_2Ph	Me	40	97	92
3	2-Thienyl	CH_2Ph	Me	23	97	94
4	Ph	$(CH_2)_3Ph$	Me	40	96	80
5	Ph	Me	Me	23	96	56
6	Ph	CH_2Ph	Et	23	93	90
7	Ph	CH_2Ph	Bu	23	95	86

agent.[45] By using 3,3′-Br_2-BINOL **35**, moderate enantioselectivity and conversion were obtained for the allylation of ketone **43** with cyclic boronate **44** (entry 1, Table 17). When catalyst 3,3′-F_2-BINOL **45** was used, the reaction could reach 98% conversion with 74% ee in 10 h (entry 6). To further explore the scope of reaction using **45**, a variety of ketones were examined and good results were achieved under the optimized reaction conditions (Table 18). Most notably, the sterically hindered boronates (R^3 = Et, Bu) were also tolerated to afford the corresponding adducts in high yields and enantioselectivities (entries 6 and 7 in Table 18).

Table 19 Enantioselective allylation of imines



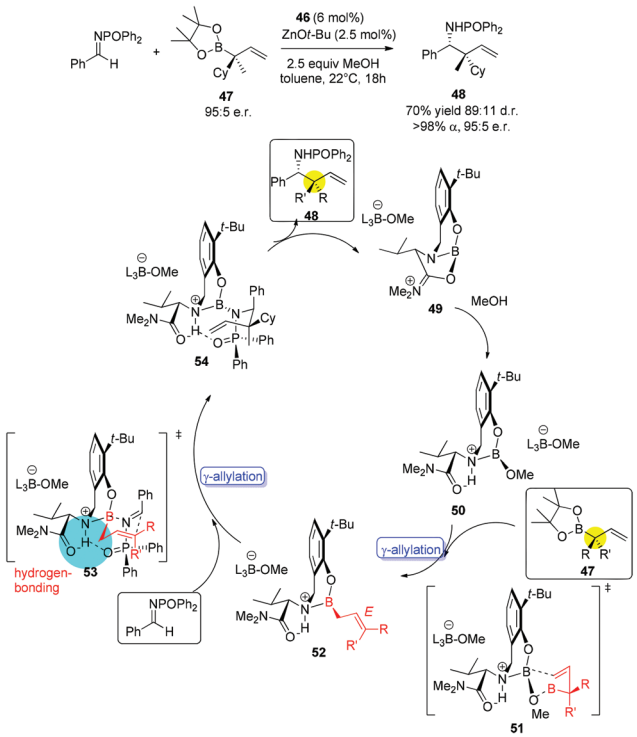
Entry	R^1	R^2	X	Y	Yield (%)	ee (%)
1	Ph	H	3.0	2.5	95	93
2	2-FC_6H_4	H	3.0	2.5	91	96
3	4-$MeOC_6H_4$	H	3.0	2.5	98	93
4		H	3.0	2.5	84	>98
5	*n*-Pr	H	2.5	2.5	96	96
6	Ph—	H	3.0	2.5	95	76
7	*i*-Pr	H	6.0	5.0	50	>98
8		H	6.0	8.5	51	>98
9	Ph	Me	2.5	2.5	96	95
10	Ph	Ph	2.5	2.5	98	95

4.2 Exchange of boron–valine derivative system

In 2013, the Hoveyda group made truly ground-breaking progress in this field. They reported a class of small organic molecules that could catalyze asymmetric allylation of imines and carbonyls.[46] The reactions were conducted with as little as 0.25–0.3 mol% of catalyst to generate products in more than 85% yield and ≥97 : 3 enantiomeric ratio. Furthermore, the catalysts, which were derived from abundant valine, were stable to air and moisture and could be easily prepared in large quantities in four steps.

With catalysts screened, aminophenol **46** was identified as the best candidate to promote the allylation reaction of *N*-phosphinoylimine with allylboronic acid pinacol ester. They used a phosphorus-based protecting group due to its facile preparation and products that were likely to be crystalline (chromatography avoided). Another reason was the inexpensive and mild conditions for removal of the protecting group. Under the optimized conditions, a vast array of aromatic imines was examined to provide excellent yields and enantioselectivities (Table 19). Even alkenyl-, alkynyl- and alkyl-substituted aldimines were tolerated. Moreover, 2-substituted allylboronate proceeded smoothly with equally good yields and enantioselectivities.[46a]

Interestingly, when 1-substituted allylboron reagents were examined, α-selectivity of allylation was found for all the reactions. Allylboronate **47** bearing an α-stereogenic quaternary carbon (95 : 5 er) gave product **48** with the chiral center reversed in 70% yield (for pure diastereomer), 89 : 11 dr and 95 : 5 er (for major isomer) (Scheme 30).[46a] No γ-addition was observed and the reversal in the stereochemistry implicated that the reactions involved double γ-allylation to afford the final α-addition products. To gain further insight into the



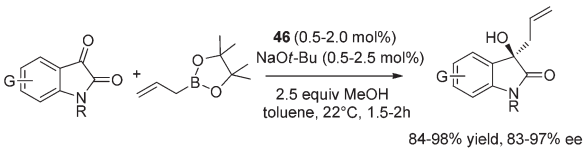
Scheme 30 The proposed mechanism.

mechanism, they carried out kinetic studies which concluded the rate determining step was the C–C bond forming step. They also found MeOH and NaO*t*-Bu or other bases were necessary to complete the transformation and phenol deprotonation of **46** respectively. Based on this evidence, the mechanism (allylboronate **47** as an example) was proposed with the formation of **49** which was derived from product **48**, where the Lewis basic amide group stabilized the boron centre (*e.g.*, **54**). After ligand exchange with MeOH to release active boronate **50**, the following step used substrate **47** to form chiral allylboron species **52** through a synclinal (cyclic) transition state **51**. The γ-allylated species **52** participates in a stereoselective γ-allylation of the imine through the six-membered chair-like transition **53**. The key proton embedded within its structure was crucial to form the rigid intermediate ensuring a high selectivity. The critical hydrogen-bonding interaction was also verified by computational studies.

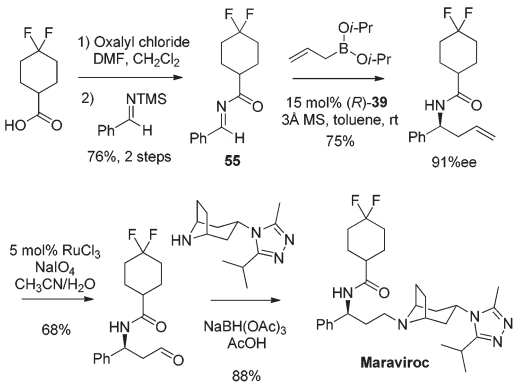
The catalytic strategy was also effective for carbonyl-containing substrates.[46a] Asymmetric allylation of N-protected isatins proceeded smoothly at 22 °C within 2 hours in the presence of 0.5–2.0 mol% **46** and 1.5 equiv. of allylboronic acid pinacol ester. Homoallylic alcohols[47] were obtained in 84–98% yield and 91.5 : 8.5–98.5 : 1.5 er (Scheme 31).

5. Applications in total synthesis

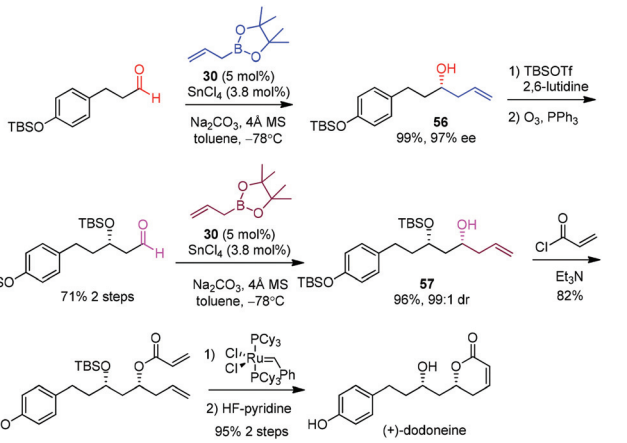
Catalytic asymmetric allylation of carbonyl compounds and imines with organoboronates has been used in the synthesis of a number of pharmaceutical drugs and natural products.



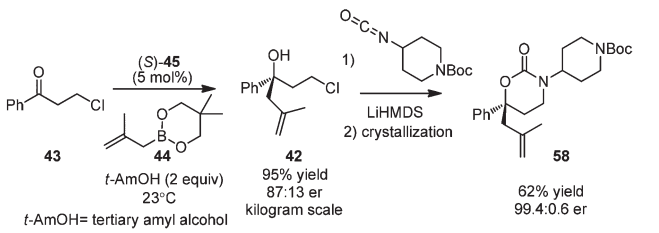
Scheme 31 Allylation of N-protected isatins.



Scheme 32 Synthesis of Maraviroc (Schaus, 2005).



Scheme 33 Synthesis of (+)-dodoneine (Hall, 2009).



Scheme 34 Synthesis of pharmaceutical intermediate **58** (Zhang, 2013).

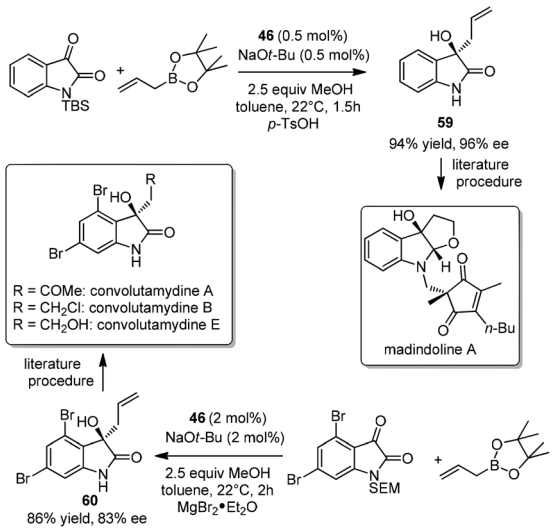
Selected examples presented here are focused on the synthesis of complex molecules employing catalytic enantioselective allylation as a key step. In principle, those allylboration steps enabled by the chiral auxiliary can be developed catalytically as illustrated in this review.

In 2005, Maraviroc, a new CCR5 entry inhibitor, had been fast-tracked through clinical trials as a new compound class in HIV therapy.[48] Schaus *et al.* applied the asymmetric allylation of difluorocyclohexane carboximide imine **55** as the key step to accomplish the synthesis of Maraviroc (Scheme 32).[44] The enantioselective allylation proceeds efficiently under standard reaction conditions. This route featured fewer steps than Price's approach in which β-phenylalanine acid was introduced as the source of chirality for the synthesis,[49] and advantageously diminished the manipulation of the amine protecting group.

Hall *et al.* selected (+)-dodoneine as a target to demonstrate the efficiency of a catalytic asymmetric allylation in the presence of a chiral diol catalyst developed by his group.[53] Dodoneine was isolated from a parasitic plant in Burkina Faso and displays a vasorelaxant effect on preconstricted rat aortic rings, thus suggesting a potential treatment toward cardiovascular disorders.[50] (+)-Dodoneine has been synthesized by Marco[51] and Cossy[52] using an established allylation of an aldehyde. Hall devised similar routes to allow a direct comparison with the *p*-F-vivol (**30**)·$SnCl_4$-catalyzed allylboration.[53] Two subsequent aldehyde allylations were designed to afford homoallyl alcohols **56** and **57** respectively in almost quantitative yields and high enantioselectivities (Scheme 33). In comparison, Marco carried out a Brown allylation, albeit in lower ee (90%).[51] The Keck allylation of the same aldehyde in Cossy's work also proceeded in a lower yield (77%).[52] The following steps involving O-acylation with acryloyl chloride, ring-closing metathesis, and desilylation were carried out to complete the synthesis of (+)-dodoneine.

In 2013, Zhang and co-workers applied Schaus's method in the allylation of ketone **43**.[45] The corresponding chiral tertiary alcohol **42** could be further converted to the key chiral building block **58**, an intermediate for a pharmaceutical agent. They utilized 3,3′-F_2-BINOL as a highly active organocatalyst for the first time. The process of asymmetric allylation was successfully carried out on a kilogram scale in 95% yield with 74% ee after simple workup. Cyclic carbamate product **58** was obtained by reacting with isocyanate in 62% yield after crystallization. After another crystallization process, the enantiomeric purity of **58** was readily enriched to 99.4 : 0.6 (Scheme 34).

Isolated from the fermentation broth of *Streptomyces nitrosporeus* K93-0711 by Omura *et al.*, madindoline A was found as a selective inhibitor of interleukin-6.[54] In 2013, Hoveyda *et al.* employed the organocatalytic enantioselective allylation to construct homoallyl carbinol **59**, the key intermediate for madindoline A.[46a] The allylation proceeded efficiently under the optimized conditions with as little as 0.5 mol% catalyst in 1.5 hours at room temperature. Homoallyl carbinol **59** was achieved in 94% yield and 96% ee[46a] and was readily converted to madindoline A in several steps through a previously reported sequence (Scheme 35).[55] The same protocol was applied to prepare compound **60**,[46a] an important intermediate to convolutamydines.[56] The catalytic asymmetric reaction



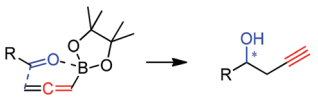
Scheme 35 Formal syntheses of madindoline A and convolutamydines (Hoveyda, 2013).

had a good enantioselectivity, while avoiding the use of chiral auxiliary in Palmisano's route (Scheme 35).[56]

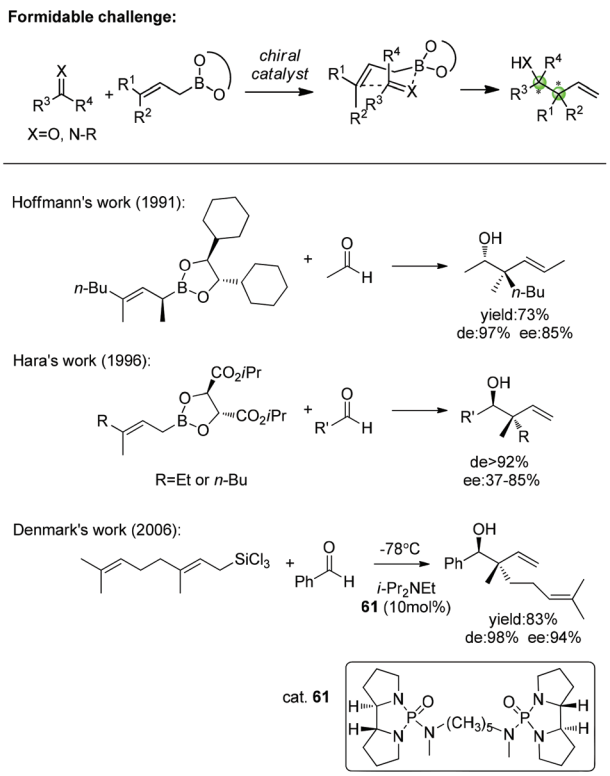
6. Conclusions and outlook

Catalytic asymmetric allylation of carbonyl compounds and imines with allylic boronates has witnessed a rapid development in the past decade. The achievements in this field have made it a powerful tool for constructing homoallylic alcohols or amines, which serve as common building blocks and important precursors for the synthesis of a variety of different pharmaceutically relevant compounds and natural products.

According to the activation mode, enantioselective catalysis of allylation is divided into three categories including metal-mediated asymmetric allylation, acid catalyzed asymmetric allylation by activating boronates and catalytic asymmetric allylation by ligand exchange of boronate. Among them, metal mediated allylation is most exhaustively explored. With the facile transmetallation, swift ligand exchange and catalyst regeneration, this asymmetric allylation proceeds efficiently and covers a broad range of substrates such as ketones, imines, and aldehydes. Of course, under the growing concerns of environmental impact and atom-economy, decreasing the catalyst loading or a metal-free approach is more likely to expand in future developments, and the most recent asymmetric organocatalysis arouses a wide appreciation. As an example, BINOL-derived compounds and chiral phosphorus acid were first developed as simple and highly efficient catalysts which already have had an impact in process chemistry, although they both are restricted in substrate scope (only for aldehydes or ketones, imines respectively). Hoveyda and co-workers devised a novel class of easily prepared and low cost catalysts to promote the allylation smoothly and efficiently



Scheme 36 Propargylation with allenylboronate.



Scheme 37 Allylation with 3,3′-disubstituted allylic boronates or trichlorosilane.

under very mild conditions. This protocol will find a wide application in organic synthesis.

Moreover, catalytic asymmetric approaches discussed in this review can be extended to propargylation when allenyl boronates are used (Scheme 36). The activation mode of propargylation is similar to the allylboration with a substrate derived from allylboronate to allenylboronate. The recent progress was beautifully exemplified[57–60] and surveyed in a recent review.[61] Although so far sporadic examples and only selected aldehydes and ketones have been investigated, this field is expected to have a promising future ahead.

In addition, catalytic asymmetric allylation of carbonyl compounds and imines with 3,3′-disubstituted allylic boronates affording two continuous quaternary/tertiary chiral centers remains a formidable challenge for catalyst development (Scheme 37). So far, there are only a few works on allylation with 3,3′-disubstituted allylboronates or trichlorosilane to construct the chiral quaternary carbon in homoallylic alcohols. Hoffmann and Hara both used chiral allylboronates to accomplish the stereocontrolled allylation of aldehydes. Hoffmann found that the homoallylic alcohol was achieved with good

enantioselectivity with a chiral α-branched boronate while α-unsubstituted ones gave racemic products.[62] Hara applied Roush's boronate to obtain a moderate enantioselectivity.[63] Denmark disclosed the only enantioselective addition of trisubstituted allyltrichlorosilane to benzaldehyde with catalytic chiral phosphoramide.[64] This field is primed for further exploration in terms of the challenge of constructing vicinal quaternary/tertiary chiral centers.

In short, significant advancements in catalytic asymmetric allylation of carbonyl compounds and imines with allylic boronates have occurred over the past decade. The continuing focus on method development will strengthen the field of research and build the confidence of chemists looking to construct chiral homoallyl alcohols and imines in a highly enantioselective manner.

Addendum (March 2014)

After this manuscript was accepted, Hoveyda and co-workers further explored the asymmetric allylation of imines with allenyl boronate.[65] The use of Boc-imines resulted in α-selectivity for the allylation reaction, which afforded homoallenylamide as the major product. With 0.1–3.0 mol% of chiral catalyst **46**, enantioselective allyl additions proceeded in 66–91% yield and 68–99% ee at ambient temperature. The substrate scope covers aryl-, heteroaryl-, and alkylsubstituted imines. In addition, they utilized this method to use enantiopure homoallenylamides (up to 94% ee) as key chiral intermediates to accomplish the synthesis of anisomycin and epi-cytoxazone efficiently on a significant laboratory scale. Overall they offered an efficient, practical, and enantioselective method for the synthesis of homoallenylamides.

Acknowledgements

Financial support from the National Natural Science Foundation of China (no. 21290184 and 21172236), the National Basic Research Program of China (2010CB833200), and Chinese Academy of Sciences is highly appreciated. We also thank Mr Xianwei Mi for helpful discussions during the manuscript preparation.

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