CHEMICAL REVIEWS

REVIEW

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Catalytic Enantioselective Allylation of Carbonyl Compounds and Imines

Miguel Yus,* José C. González-Gómez, and Francisco Foubelo*

Departamento de Química Orgánica, Facultad de Ciencias and Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain

CONTENTS

1. INTRODUCTION

The addition of an organometallic reagent to a carbonyl compound or an imine represents an important process in synthetic organic chemistry because in this reaction, together with a new carbon−carbon bond, a new functionality (an alcohol or an amine, respectively) is formed.[1] This methodology is especially interesting when the electrophilic partner is a ketone or its imine derivative since a functionalized quaternary center is created.[2] A special case for the nucleophilic reagents appears by using an allylic system: in this case, the allylic moiety allows further possible transformations due to the presence of a double bond that can be manipulated synthetically.[3] Remarkably, the asymmetric version of this technology, above all in the catalytic fashion, would produce chiral homoallylic alcohols and amines, which constitute valuable building blocks in organic synthesis for the above-mentioned reasons.[4]

The reaction of simple *N*-H imines with nucleophiles has not been studied because of the instability of these electrophiles. Nucleophilic addition to hydrazones and to *N*-alkyl and *N*-aryl substituted imines, which are considerably less reactive than

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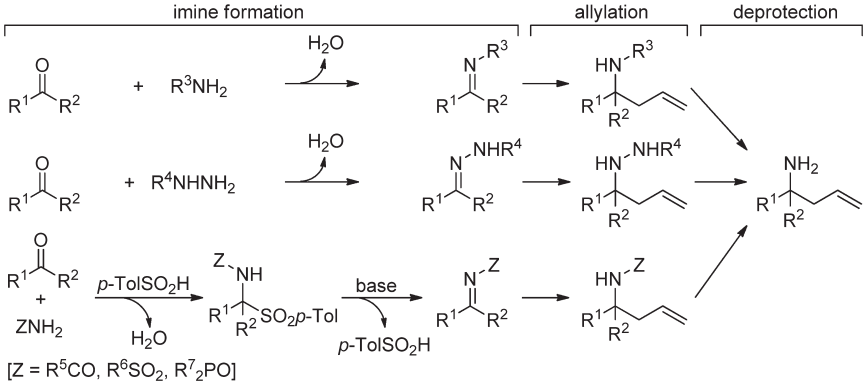
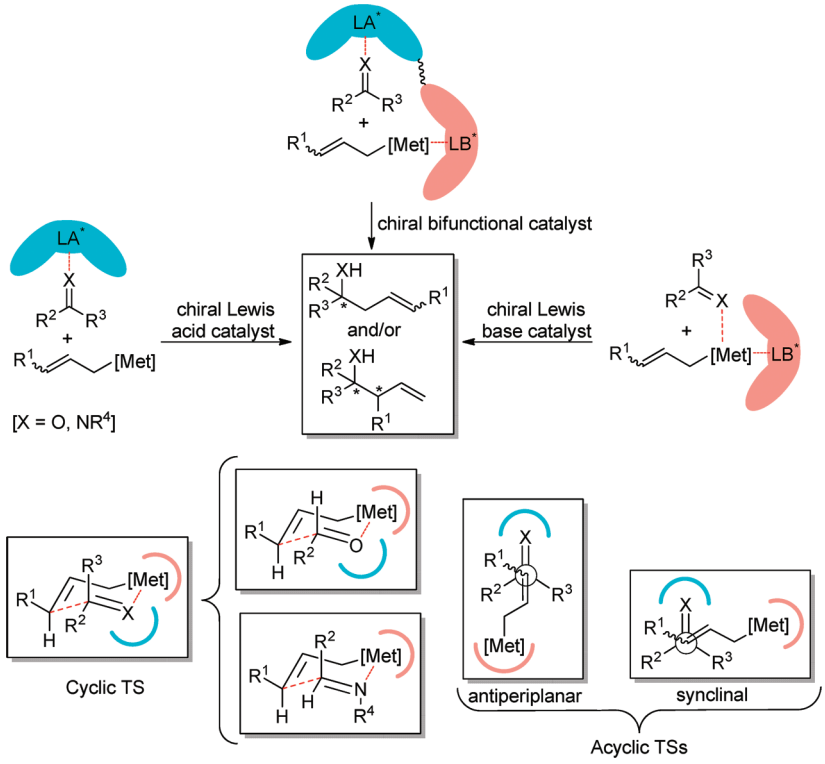
Scheme 1



Scheme 2



carbonyl compounds, takes place easily only when strong nucleophilic reagents are used, such as organolithium and organomagnesium compounds. The electrophilicity of these compounds is considerably increased by coordination of the nitrogen to a Lewis acid, or by using imines *N*-substituted with an electron-withdrawing group (acyl, sulfonyl, or phosphonyl). The hydrazones and most of the imines are easily prepared just by mixing the corresponding amine nucleophile [*N*-substituted hydrazine, aryl or alkyl (benzyl and allyl) amine] and the carbonyl compound in the presence of a dehydrating agent. Importantly, the advantages of hydrazones over imines include a favorable equilibrium in their formation, ease of purification and handling, and resistance to tautomerization. On the contrary, the most effective methodology for the preparation of *N*-acyl, *N*-sulfonyl, or *N*-phosphinoyl imines (usually, aldimines) involves a two-step procedure:[5] (a) formation of the *para*-toluenesulfinic acid adduct of the imine from the carbonyl compound and the corresponding amide, which is a solid that can be recrystallized, and (b) base treatment of the adduct, which leads to the expected imine in high yield (Scheme 1). Because of the instability of the *N*-acyl derivatives, they have to be used in the reaction with nucleophiles without further purification. Because primary homoallylic amines are interesting products from a synthetic point of view, after the allylation step, N−N bond cleavage in the hydrazones or other activated imines is highly desirable under conditions compatible with the alkene moeity. Therefore, benzylic and allylic groups do not accomplish this requirement, because hydrogenolysis is the method of choice to remove the *N*-benzyl group; in the case of *N*-allyl groups removal, an isomerization catalyzed by a transition metal is always involved in the first step.[6] On the other hand, the reductive cleavage of the

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N−N bond in the corresponding homoallylhydrazides can be efficiently produced after *N*-trifluoroacetylation with an excess of SmI_2, without affecting the alkene functionality.[7] Moreover, electron-rich aromatic moieties attached to the nitrogen can be removed by oxidative cleavage with ceric ammonium nitrate;[8] meanwhile acid or base hydrolysis are used to removed acyl, sulfonyl, or phosphonyl groups on the nitrogen.[6] The latest methodologies sometimes require harsh reaction conditions that may damage sensitive functionalities, and this should be taken into account to choose the starting imine or hydrazone (Scheme 1).

The majority of catalytic enantioselective allylations rely on the use of chiral Lewis acids (LA*),[9] which bind to the electrophile, activating it toward nucleophilic attack. The chiral Lewis bases (LB*)[10] catalyzed reactions are conceptually distinct and involve the binding of the ligand to the allylmetal species (enhancing its nucleophilicity), which can further coordinate the electrophile (increasing its electrophilicity). This dual mechanism of activation could provide high reaction rates and excellent transfer of stereochemistry. Double activation could be also achieved by using chiral bifunctional catalysts (LA*−LB*).[11] In this case, the simultaneous activation of both electrophilic and nucleophilic reaction partners occurs ideally through a cooperative action of different functionalities of the ligand(s) (Scheme 2). In addition to the face selectivity under the influence of an external chiral controller, substituted allyl organometallics display also high levels of diastereoselection because they react usually at γ-position through an ordered acyclic or cyclic transition state, depending mainly on the metal of the allylic organometallic nucleophile. For Si and Sn derivatives, the addition is commonly explained using acyclic models where the major approach (antiperiplanar or synclinal) takes place through the conformation where destabilizing gauche interactions are minimized. On the contrary, for Mg, Ti, B, and In allylic derivatives, a cyclic six-membered Zimmerman−Traxler-type[12] transition state is usually invoked. In the cyclic model, it is generally proposed that aldehydes locate the R^2 group in the equatorial position, whereas aldimines with *E*-configuration locate R^2 group in the axial position (Scheme 2).[13] Consequently, opposite relative configurations (anti/syn) are generally observed in the reaction of aldehydes and aldimines with the same γ-substituted allyl organometallic.

Former reviews related to the topic of this overview include the following reports: (a) The domino multicomponent allylation of aldehydes and ketones using allyltrimethyl silane and norpseudoephedrine or mandelic acid as chiral auxiliaries, in the presence of catalytic amounts of trifluoromethanesulfonic acid, gives chiral secondary or tertiary homoallylic silyl ethers, with the obtained asymmetric induction being explained by theoretical calculations (DFT).[4a] (b) The enantio- and diastereoselective addition of allylic silanes and stannanes, mainly to aldehydes, with a chiral Lewis acid (derived from B, Ti, Zr, Ag, Rh, Zn, and Si) as auxiliary, as well as the direct metal-mediated (Cr, Zn, and In) addition of allylic halides to aldehydes afford the expected chiral homoallylic alcohols.[4b] (c) The allylation of chiral imines and related compounds (oximes, hydrazones, nitrones, and iminium ions) using organometallic reagents (derived from Mg, Zn, B, Si, In, Sn, and Cu) gives the expected homoallylic amines in a diastereoselective manner.[4c] (d) Indium metal is an effective promoter for the diastereoselective addition of allylic halides (mainly bromides) to chiral aldehydes and aldimines to afford the corresponding homoallylic derivatives.[4d] (e) The asymmetric allylation of carbonyl compounds with allyltrimethoxysilane mediated by silver fluoride and BINAP is a convenient method for the preparation of chiral homoallylic alcohols.[4e] (f) The combination of copper(I) fluoride and a chiral diphosphane allows the enantioselective addition of allylic boronates to ketones and ketimines, yielding the expected tertiary homoallylic derivatives.[4f] (g) The Lewis or Brønsted catalyzed addition of β-alkoxycarbonyl allylic boronates (or in some cases using Si, Sn, Zn, or In derivatives) to carbonyl compounds is a good method to prepare α-*exo*-alkylidene γ-lactones in a diastereoselective manner.[4g] (h) The asymmetric (mainly diastereoselective) addition of allylic organometallics (derived from Mg, Si, Li, Zn, Sn, B, Sn, and In) to chiral imines generates chiral amines containing several stereocenters.[4h] (i) One part of the study on asymmetric catalytic addition to C=N bonds is devoted to the enantioselective allylation of imines using allyl metal compounds (derived from Si, B, Sn, B, and In) and a chiral auxiliary derived from TADDOL, BINOL, or BINAP.[4i]

In this review, methodologies on the catalytic enantioselective addition of allylic nucleophiles to carbonyl compounds, imines (mostly with *N*-allyl, -aryl, -benzyl, and -sulfonyl substituents), and imine derivatives (hydrazones)[14] will be considered, paying special attention to the most useful reactions from a synthetic point of view. The review is organized according to the different allylic derivatives (derived from Si, Sn, B, halides, alcohols, acetates, and others), dedicating the last parts to the enantioselective propargylation/allenylation, as well as to the application of the catalytic allylation of carbonyl compounds and imines to some selected synthesis of natural products. In these processes, the stereochemical pathway is determined by an external chiral promoter, which should most likely be present in a substoichiometric amount. However, some examples, where an excess of the chiral source was necessary to achieve high stereoselectivities, with the chiral source being not consumed and consequently recovered at the end of the reaction, were also included. Diastereoselective reactions among chiral reactants (with or without chiral auxiliaries) will not be considered in this review. The present work will comprehensively cover the most pertinent contributions to this important research area since 2003 to the second half of 2010, because the excellent reviews of Denmark and Fu[4b] and Merino et al.[4c] covered until 2002 the literature of the enantioselective catalyzed allylation of carbonyl compounds and the stereoselective allylation of imines, respectively.

2. ENANTIOSELECTIVE ADDITION OF ALLYLIC SILANES

2.1. Acid-Catalyzed Allylation Reactions

2.1.1. Allylation of Aldehydes. Many examples of enantioselective allylation of carbonyl compounds under the influence of chiral Lewis acid catalysts, the so-called Sakurai−Hosomi allylation, have been reported. Among them, the combination of chiral bisphosphanes as chiral ligands and silver(I) triflate plays an important role. H. Yamamoto and co-workers found that a catalytic amount of the KF·18-crown-6 complex is effective as a soluble fluoride source to activate an asymmetric Sakurai−Hosomi allylation with BINAP and silver(I) triflate, and using allyltrimethoxysilane as the allylating reagent: it can easily form a pentacoordinate silicate, and it is a preferable reagent compared to allyltin compounds from the standpoint of toxicity. Various BINAP derivatives (**1** and **2**) and other chiral bisphosphanes (**3** and **4**) were screened as chiral ligands under the optimized reaction conditions shown in Scheme 1.[15] The highest enantioselectivity was obtained using (*R*)-*p*-Tol-BINAP [(*R*)-**1b**] as the chiral ligand; meanwhile (*R*)-H_8−BINAP [(*R*)-**2a**] led

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Scheme 3

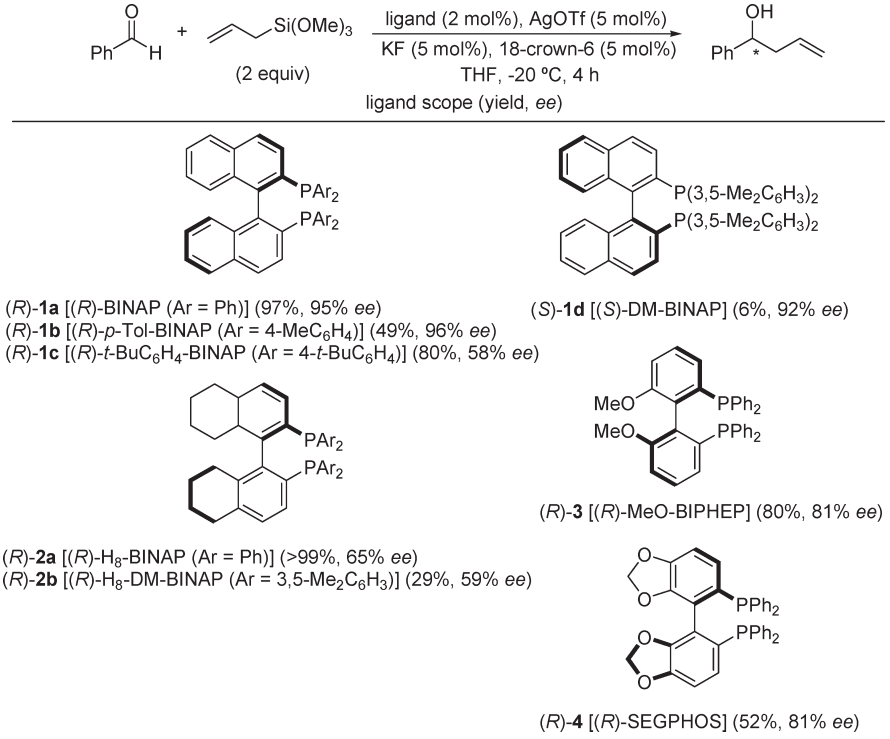
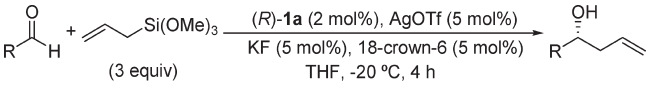


Table 1. Asymmetric Allylation of Aldehydes Catalyzed by (*R*)-1a, AgOTf, KF, and 18-Crown-6



entry	R	yield (%)	ee (%)
1	Ph	97	95
2	(*E*)-PhCH=CH	81	87
3	2-furyl	57	95
4	1-naphthyl	95	92
5	4-$MeOC_6H_4$	61	95
6	4-BrC_6H_4	95	96
7	2-MeC_6H_4	82	97
8[a]	Cy	62	93
9[a]	$PhCH_2CH_2$	76	86

[a] Reaction conditions were different: (*R*)-BINAP (6 mol %), AgOTf (15 mol %), KF (15 mol %), and 18-crown-6 (15 mol %) in THF at −20 °C for 24 h.

to the highest chemical yield. However, taking into account both enantioselectivity and chemical yield, (*R*)-BINAP [(*R*)-**1a**] was the most effective chiral ligand for this transformation (Scheme 3).

The allylation of different aldehydes under the optimized reaction conditions was also studied. Aromatic and α,β-unsaturated aldehydes gave satisfactory yields and good ee values (Table 1, entries 1−7). In contrast, aliphatic aldehydes gave relatively low chemical yield with 2 mol % of (*R*)-BINAP [(*R*)-**1a**] and 5 mol % of other additives, whereas treatment of cyclohexanecarboxaldehyde and 3-phenylpropanal with allyltrimethoxysilane, 6 mol % of (*R*)-BINAP [(*R*)-**1a**], and 15 mol % of the other additives gave the allylated product in 62 and 76% yield, respectively (Table 1, entries 8 and 9, respectively).

Two probable reaction mechanisms for the catalytic asymmetric allylation were proposed and are shown in Figure 1: an acyclic antiperiplanar transition state (Lewis acid mechanism) or a six-membered chairlike transition state (transmetalation mechanism).

A chiral bisoxazoline bearing a phosphane oxide moiety **5**, which has been synthesized from L-serine, has shown to be an effective ligand for the asymmetric allylation of aldehydes in the presence of different metals. The reaction proceeds with the dual activation of both the aldehyde and the allylsilane by the Lewis acid and base of the bisoxazoline complex catalyst. Fujimoto, I. Yamamoto, and co-workers investigated the metal complex catalyzed asymmetric allylations of benzaldehyde with allyltrichlorosilane in the presence of 10 mol % of **5** in CH_2Cl_2 at room temperature.[16] They found that the combination of **5**−ZnI_2 in a coordinating solvent, such as THF, is the best matched one to give the product in up to 74% yield with an 86% ee (Table 2, entry 1). Because the mechanism of allylation with allyltrichlorosilane involves chloride ionization, it is possible that ZnI_2 acts as anion scavenger instead of (or in addition to) as a Lewis acid. The catalytic loading amount of 5 mol % widely decreased the yield, but the ee decreased only slightly (51% yield, 77% ee). When other allylic reagents, such as allyltrimethylsilane and allyltrimethoxysilane, were employed, the homoallylic alocohols were obtained in low yields. The allylations of aldehydes with allyltrichlorosilane in the absence of ZnI_2 in THF at room temperature gave no reaction products. The allylation of the *para*-nitro- and *para*-chlorobenzaldehyde gave similar results as those from benzaldehyde (Table 2, entries 2 and 3); meanwhile, lower chemical yields and enantioselectivities were obtained with *para*-methoxybenzaldehyde, 3-phenylpropanal, and cinnamaldehyde (Table 2,

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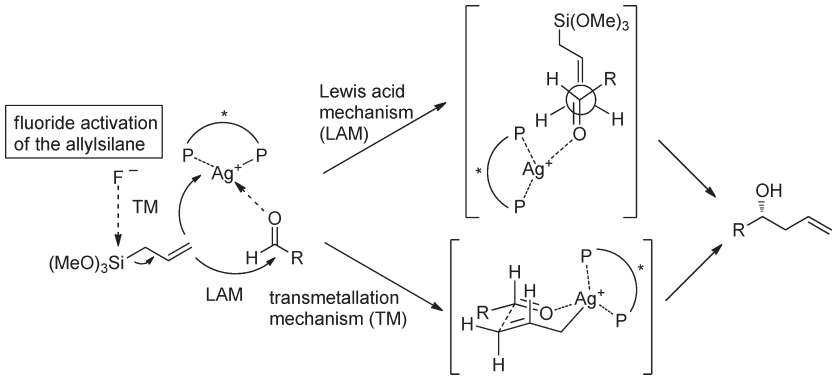
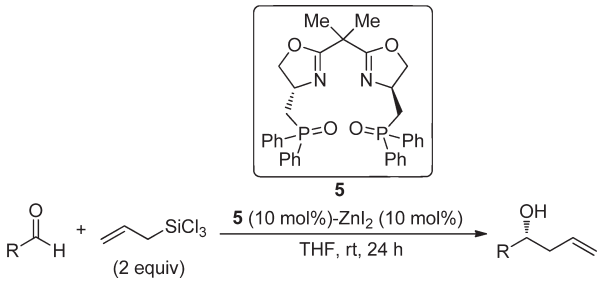


Figure 1. Probable reaction mechanisms of the catalytic asymmetric allylation.

Table 2. Asymmetric Allylation of Aldehydes Catalyzed by 5−ZnI_2 Complex



entry	R	yield (%)	ee (%)	configuration
1	Ph	74	86	*R*
2	4-$NO_2C_6H_4$	73	79	*R*
3	4-ClC_6H_4	65	76	*R*
4	4-$MeOC_6H_4$	52	39	*R*
5	$PhCH_2CH_2$	48	68	*S*
6	(*E*)-PhCH=CH	54	64	*R*

entries 4, 5, and 6, respectively), with 1,2-addition taking place exclusively in the case of cinnamaldehyde.

2.1.2. Allylation of Ketones. There are few effective methodologies for the asymmetric allylation of ketones that allow the access to chiral tertiary homoallylic alcohols. Wadamoto and H. Yamamoto reported the catalytic asymmetric Sakurai−Hosomi allylation of a variety of ketones using allyltrimethoxysilane as nucleophile and 1 equiv of methanol (catalyst turnover was increased by the addition of methanol) in the presence of 5 mol % of AgF and (*R*)-DIFLUORPHOS [(*R*)-**6**] as chiral ligand in THF (Table 3).[17] Good enantioselectivities were obtained in the case of aryl methyl ketones (Table 3, entries 1−4) and cyclic aromatic ketones (Table 3, entries 6−9). With cyclic and acyclic conjugate enones, 1,2-addition took place exclusively and with similar levels of enantioselectivity (Table 3, entries 10−12).

A more challenging process, considering both regio- and stereoselectivity, is the allylation of carbonyl compounds with substituted allylic reagents. This catalytic system was also effective for the allylation of acetophenone with substituted allylic silanes. Branched syn products with the same level of enantioselectivity were obtained from (*E*)- and (*Z*)-crotyltrimethoxysilane, and (but-3-en-2-yl)trimethoxysilane[18] led to the γ-adduct with high syn-selectivity. The same reaction product, with the same level of diastereoselectivity, was also obtained in the case of 2-butenyltrimethoxysilane (Scheme 4). By starting from racemic 3-cyclohexenyltrimethoxysilane, an almost enantiomerically pure compound was obtained (Scheme 4). It seems that the reaction proceeds via a single allylsilver intermediate, generated through a transmetalation process from structurally isomeric allylsilanes, as indicated in Figure 1 for aldehydes.

To investigate the stereochemical aspects of this silver-catalyzed asymmetric Sakurai−Hosomi allylation of ketones, the reaction of acetophenone with (5-phenylcyclohexen-3-yl)trimethoxysilanes was also studied.[18] Surprisingly, only two isomers **7** and **8** with high ee values were obtained in all cases, with compounds **9** and **10** not being detected. It is important to note that diastereo- and enantioselectivity do not depend on the syn/anti ratio of the starting (5-phenylcyclohexen-3-yl)trimethoxysilane (Scheme 5). These results suggest that a single allylsilver intermediate is formed and reacts with ketones to furnish homoallyl alcohols in a highly regio-, diastereo-, and enantioselective fashion. The stereochemical information in the allylsilane does not translate to the product. Thus, under these reaction conditions tedious procedures for the preparation of enantiopure allylsilanes are not necessary to get reaction products with high optical purity.

2.1.3. Allylation of Imines and Imine Derivatives. Fernandes and Y. Yamamoto reported the first allylation of aldimines with the tetraallylsilane−TBAF−MeOH combination with the use of the bis-π-allylpalladium catalyst under catalytic, non-Lewis acid, essentially neutral, and very mild reaction conditions.[19] The use of 1.2 equiv of tetraallylsilane, 25 mol % of TBAF, 1 equiv of MeOH, and 5 mol % of the chiral π-allylpalladium(II) complex **11** in a mixture of THF/hexane (1:2) at 0 °C were found to be the optimum reaction conditions for the allylation of imines. The scope of this allylation protocol was studied for various imines to furnish the corresponding homoallylamines (Table 4) in high yields (up to 98%, Table 4, entry 11) and good to excellent enantioselectivities (up to 92% ee, Table 4, entries 6 and 10).

In the proposed mechanism of the allylation, the reaction was triggered by a dual activation/promotion by TBAF and MeOH. The fluoride anion activated the C−Si bond cleavage and allowed the formation of a chiral bis-π-allyl palladium complex. A coordination of the nitrogen of the imine to the Pd facilitated the intramolecular nucleophilic attack of the η^1-allyl ligand in a chiral environment.[20] Finally, MeOH promoted the facile protonation of the intermediate palladium amide to liberate the final homoallylamine (Scheme 6).

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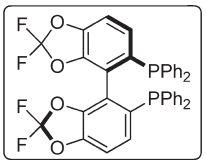
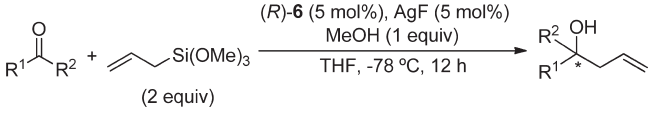
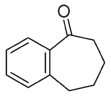
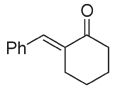
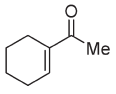
Table 3. Asymmetric Allylation of Ketones Catalyzed by (*R*)-6−AgF Complex



(*R*)-**6** [(*R*)-DIFLUORPHOS]



entry	R^1	R^2	yield (%)	ee (%)
1	3-$CF_3C_6H_4$	Me	92	90
2	4-$MeOC_6H_4$	Me	63	78
3	2-MeC_6H_4	Me	62	92
4	1-naphthyl	Me	98	95
5	$PhCH_2CH_2$	Me	42	65
6			89	91
7			63	93
8			78	92
9			74	92
10			92	96
11			96	84
12			56	95

The asymmetric allylation of acylhydrazono esters in aqueous media has been achieved by using a catalytic amount of ZnF_2 (20 mol %) and the chiral diamine ligand **12** (10 mol %). Kobayashi and co-workers found that a catalytic amount of the fluoride anion is sufficient for the allylation, whereas a stoichiometric amount of the fluoride anion is needed in the Mannich-type reaction of these hydrazones. The diamine **12** accelerated the reaction significantly, with the reaction proceeding with double activation: Zn(II) acts as a Lewis acid to activate the hydrazone as an electrophile and, at the same time, the fluoride anion acts as a Lewis base to attack the silicon atom to activate the allyltrimethoxysilane as nucleophile. It seems that the methoxy group in the chiral diamine ligand **12** plays an essential role for attaining high yields and stereoselectivities. Among the diamines, compounds **12a** and **12h** led to the highest yields and ee values (Table 5, entries 1 and 8).[21]

Some examples of the allylation reactions under the optimized reaction conditions using diamines **12a** and **12h** are shown in Table 6. An improvement in the yield was observed when the reaction was performed with the hydrazone derived from ethyl glyoxylate instead of the methyl glyoxylate (Table 6, compare entries 1, 2 and 3, 4). Yields were slightly lower with 2-substituted allylsilanes (Table 6, entries 5 and 6).[21]

The allylation of *N*-acyliminoglyoxylates with allylsilanes was achieved with reasonable levels of enantioselectivity, by using a copper complex (10 mol %) prepared from $Cu(OTf)_2$ and the diamine **12i** (Table 7, entries 1−11).[22] The addition of 3 Å molecular sieves (3 Å MS) and a slow addition of the substrates were found to improve the yield, selectivity, and reproducibility. Under these reaction conditions, Kobayashi and co-workers also reported the first example of catalytic enantioselective allylations of iminophosphonates for the synthesis of α-aminophosphonate esters (Table 7, entries 12−14). The catalyst turnover frequency was lower in reactions of iminophosphonates than in those of iminoesters; therefore, slow addition of the electrophile was also essential in this allylation reaction.

The first example of a catalytic allylation of a cyclic imine was reported by Itoh et al.: the allylation of 3,4-dihydro-6,7-dimethoxyisoquinoline with allyltrimethoxysilane in the presence of 10 mol % of the complex prepared from CuCl and (*R*)-*p*-Tol-BINAP [(*R*)-**1b**]. Various phosphane derivatives were investigated as chiral ligands, and it was found that (*R*)-**1b** in THF at room temperature afforded the best result (Table 8).[23]

Enantioselective allylation of aldimines was also achieved under Ag(I) catalytic conditions in the presence of chiral mono- and diphosphanes. The results of crotylation of the aldimine derived from benzaldehyde and *ortho*-methoxyaniline with the (*Z*)-crotyltrimethoxysilane under AgF catalysis in the presence of different monophosphane ligands are shown in Scheme 7. Although many ligands exhibited high levels of reactivity, the enantioselectivities observed were unsatisfactory.[24]

Various additives (alcohols and amines) used instead of MeOH, and different solvents or Ag(I) salts, provided no improvement both in the reactivity and the enantioselectivity. However, modification of the substituent on the nitrogen atom of the aldimine had a more drastic effect on the performance of the catalytic system. The imine substrate bearing a 2-phenoxyphenyl group yielded the corresponding homoallylamine in high yield with the monophosphane ligand (*R*)-MOP [(*R*)-**15**] (Table 9, entry 6), and excellent enantioselectivity with the diphosphane ligand (*R*)-DIFLUORPHOS [(*R*)-**6**] (Table 9, entry 7).

2.2. Base-Catalyzed Allylation Reactions

Lewis bases promote the allylation of carbonyl compounds and imines with allyl metal reagents in a different way than Lewis acids. In a pioneering work, Kobayashi and Nishio found that the allylation of aldehydes with substituted allylic trichlorosilanes (with *Z* or *E* configuration) was highly distereoselective in DMF, proposing a close chairlike transition state through activation with DMF as a Lewis base.[25] After formation of the chiral base−allyl metal complex, the metal center should keep the Lewis acidity to coordinate with the electrophile (carbonyl compound or imine derivative). The allylation should take place through a three-component complex in a chiral environment, with the stereoselectivity depending mainly on the nature of the chiral base. Allyltrihalosilanes are typical allyl metal compounds that accomplish these requirements.

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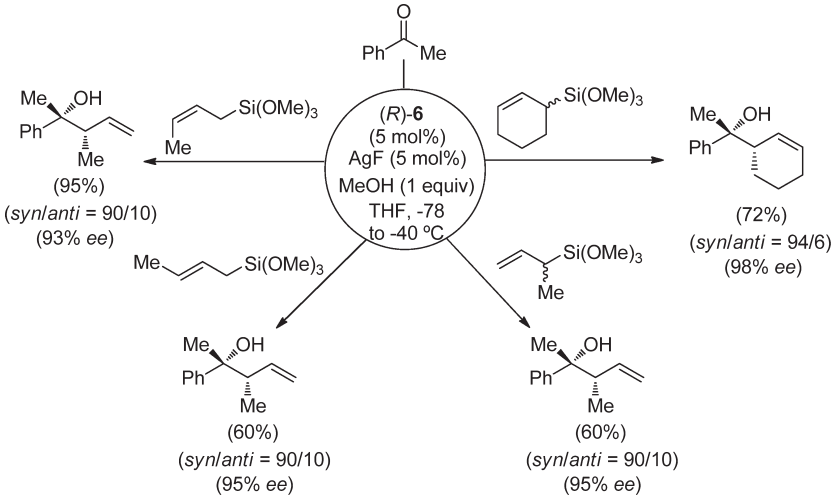
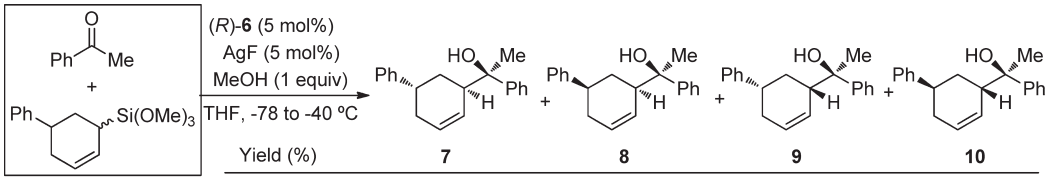
Scheme 4

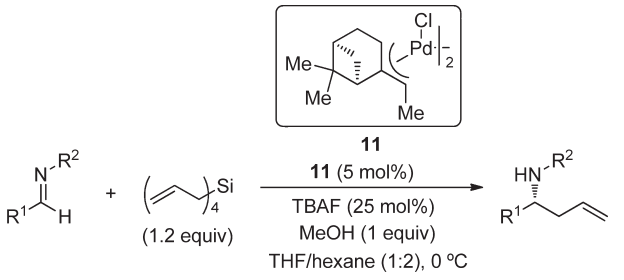


Scheme 5



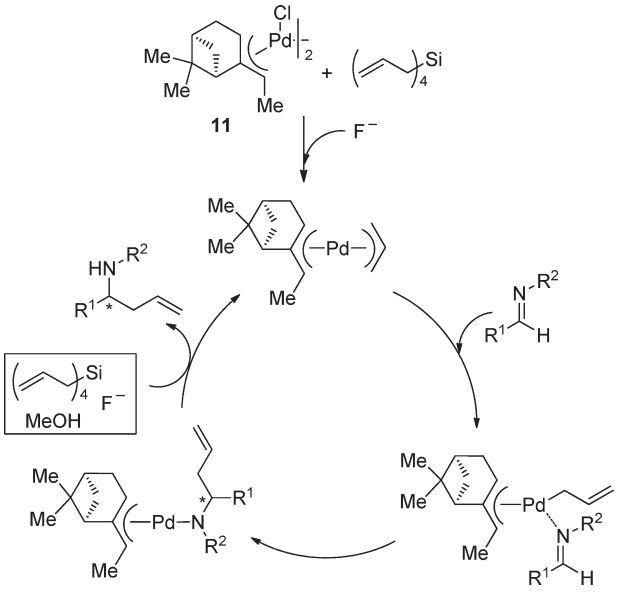
	Yield (%)	7	8	9	10
(*syn*/*anti* = >99:1)	88	65 (86% *ee*)	34 (98% *ee*)	<1	<1
(*syn*/*anti* = <1:99)	>99	65 (88% *ee*)	34 (>99% *ee*)	<1	<1
(*syn*/*anti* = 67:33)	>99	65 (90% *ee*)	34 (>99% *ee*)	<1	<1

Table 4. Catalytic Asymmetric Allylation of Imines



entry	R^1	R^2	*t* (h)	yield (%)	ee (%)
1	Ph	Bn	14	86	91
2	Ph	2-$MeOC_6H_4CH_2$	21	83	88
3	Ph	CH_2=$CHCH_2$	19	83	84
4	(*E*)-PhCH=CH	Bn	20	86	74
5	2-naphthyl	Bn	28	76	91
6	4-MeC_6H_4	Bn	14	92	92
7	Cy	Bn	20	86	52
8	2-furyl	Bn	18	89	76
9	2-thienyl	Bn	18	90	67
10	4-$MeOC_6H_4$	4-$MeOC_6H_4CH_2$	26	80	92
11	3-pyridyl	Me	36	68	55
12	3-pyridyl	Bn	32	98	67

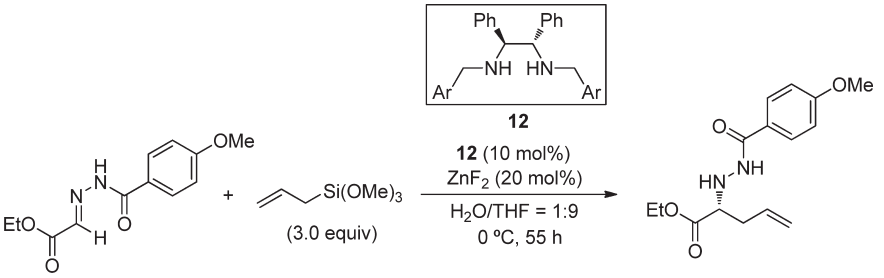
Scheme 6



2.2.1. Allylation of Aldehydes. *2.2.1.1. Chiral Phosphoramides and Phosphonamides as Promoters.* Denmark et al.

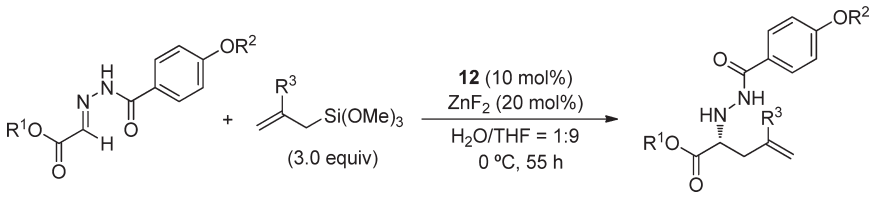
dx.doi.org/10.1021/cr1004474 |*Chem. Rev.* 2011, 111, 7774–7854

Table 5. Effect of Chiral Diamines on the Enantioselective Allylation



entry	Ar	diamine	yield (%)	ee (%)
1	2-MeOC$_6$H$_4$	**12a**	84	81
2	Ph	**12b**	29	48
3	2-MeC$_6$H$_4$	**12c**	26	83
4	2,5-(MeO)$_2$C$_6$H$_3$	**12d**	81	76
5	3,5-(MeO)$_2$C$_6$H$_3$	**12e**	27	31
6	2-MeO-5-*t*-BuC$_6$H$_3$	**12f**	99	64
7	1-MeO-2-naphthyl	**12g**	19	70
8	3-MeO-2-naphthyl	**12h**	59	84

Table 6. Catalytic Asymmetric Allylation of Acylhydrazono Esters



entry	R^1	R^2	R^3	diamine	yield (%)	ee (%)
1	Me	Me	H	**12a**	61	83
2[a]	Me	Me	H	**12h**	60	86
3	Et	Et	H	**12a**	92	81
4	Et	Et	H	**12h**	81	85
5	Et	Et	Me	**12a**	88	65
6[b]	Et	Et	Ph	**12a**	62	78

[a] 96 h. [b] 162 h.

reported the first example of enantioselective allylation of aldehydes promoted by chiral phosphoramides as bases.[26] Numerous chiral phosphoric triamides, among them compounds **21**−**23**, have been evaluated also as activators for the enantioselective allylation of benzaldehyde with allyltrichlorosilane, but modest enantioselectivities were obtained in all cases (Table 10).[27] For a comparative study, 1 equiv of the chiral phosphoric triamide was used in all cases, with yields and stereoselectivities being significantly lower by decreasing the ligand loading.

The allylation of benzaldehyde was performed using **21b** as the promoter and (*E*)- and (*Z*)-crotyltrichlorosilanes as nucleophiles. In contrast with the silver-catalyzed crotylation of acetophenone in the presence of chiral diphosphanes,[13,14] the process is diastereospecific, with the (*E*)-isomer yielding the anti product and the (*Z*)-isomer yielding the syn one (Scheme 8). A chairlike transition state has been proposed to explain the high diastereoselectivity observed, with enantiomeric ratios being similar to that obtained with allyltrichlorosilane.

On the basis of nonlinear effects and kinetics studies, two phosphoramides are supposed to be involved in both the rate- and stereochemistry-determining steps (Figure 2);[28] for that reason, the study of the allylation of benzaldehyde using bidentate chiral phosphoramides was of interest and will be discussed in the following two paragraphs.

Different chiral bisphosphoramides **24**−**29** were synthesized to study their influence as promoters on the yield and the stereoselectivity of the allylation of benzaldehyde with allyltrichlorosilane. All reactions were performed in a 1:1 mixture of CH_2Cl_2 and *i*-Pr_2NEt (DIPEA) at −78 °C. The tether length in the bidentate phosphoramides is important for achieving high enantioselectivities (Table 11, entries 6−8). Among the studied promoters, **27b** with 2,2′-bispyrrolidine skeleton was the most promising one for performing enantioselective allylations of aldehydes in terms of yield, turnover efficiency, and enantioselectivity.[29]

Regarding the enantio- and diastereoselectivity achieved by means of the former promoter, a transition state structure has

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been proposed to explain the preference for the *Si*-face attack. In the chairlike assembly leading to the *Re*-face attack, the benzaldehyde ring is located in a quadrant of the ligand environment that is occupied by a forward-pointing pyrrolidine ring, thereby creating unfavorable steric interactions (Figure 3).[29]

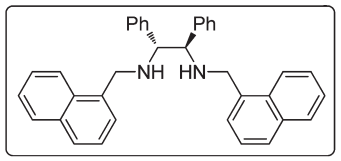
The scope of the allylation reaction with **27b** was examined with substituted allylic trichlorosilanes and other aromatic and α,β-unsaturated aldehydes (Table 12). Importantly, through this methodology it was possible to generate quaternary centers when γ,γ-disubstituted silanes were used (Table 12, entries 16−18). In the case of using unsymmetrical γ,γ-disubstituted silanes, the quaternary stereogenic center was created in a highly stereoselective manner (Table 12, entry 18).

The above-mentioned methodology worked nicely in the case of aromatic and α,β-unsaturated aldehydes but showed to be uneffective with aliphatic aldehydes. As was previously commented, the allylation should take place through a three-component complex: an ionization of a chloride ion from the allyltrichlorosilane−phosphoramide adduct occurs first, and after that the aldehyde binds to the cationic silicon. Aromatic aldehydes undergo allylation leading to the desired product, whereas for aliphatic aldehydes, the collapse of the zwitterion is much faster and only the corresponding α-chloro silyl ether is observed (Scheme 9).[29]

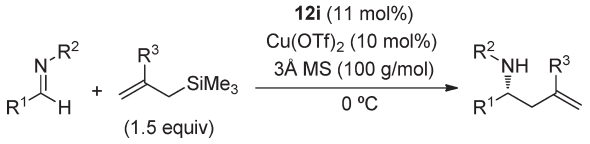
Chiral phenylphosphonamides **30** and **31** were also used as chiral Lewis basic catalysts for the asymmetric allylation of benzaldehyde, providing the corresponding homoallylic alcohol derivatives in good yields and diastereoselectivities, but with modest enantiomeric excesses (Table 13).[30] These results suggest that the catalytic asymmetric reactions proceed via a six-membered chairlike transition state.

2.2.1.2. Chiral Phosphane Oxides as Promoters. Chiral phosphane oxides are readily prepared from the corresponding chiral phosphanes. Along with phosphoramides and phosphonamides, phosphane oxides were also used as promoters in the allylation of aldehydes with allyltrichlorosilanes. For instance, Nakajima and co-workers found that chiral phosphane oxide (*S*)-BINAPO [(*S*)-**32a**] exhibited good catalytic activities in the enantioselective addition of allyltrichlorosilanes to aldehydes. The combination of DIPEA and tetrabutylammonium iodide (TBAI) as additives is crucial for accelerating the catalytic

Table 7. Catalytic Asymmetric Allylation of Iminoesters and Iminophosphonates with Allylsilanes

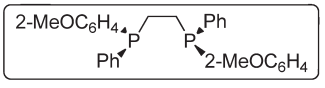


12i

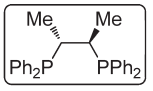


entry	R^1	R^2	R^3	solvent	yield (%)	ee (%)
1	CO_2Et	n-$C_{11}H_{23}CO$	SEt	CH_2Cl_2/PhMe	76	93
2	CO_2Et	n-$C_{11}H_{23}CO$	SPh	CH_2Cl_2/PhMe	84	92
3	CO_2Et	CH_3CO	SEt	CH_2Cl_2	75	90
4	CO_2Et	n-$C_{11}H_{23}CO$	Ph	CH_2Cl_2	68	91
5	CO_2Bn	n-$C_{11}H_{23}CO$	Me	CH_2Cl_2	33	90
6	CO_2Bn	n-$C_{11}H_{23}CO$	H	CH_2Cl_2	trace	
7	CO_2Et	Cbz	Me	CH_2Cl_2	94	63
8	CO_2Et	Cbz	Me	CH_2Cl_2/THF	99	88
9	CO_2Et	Cbz	H	CH_2Cl_2/THF	73	88
10	CO_2Et	Boc	SEt	CH_2Cl_2/PhMe	84	86
11	CO_2Et	Boc	SPh	CH_2Cl_2/PhMe	71	86
12	$PO(OEt)_2$	CCl_3CH_2OCO	Ph	CH_2Cl_2/THF	71	85
13	$PO(OEt)_2$	CCl_3CH_2OCO	Me	CH_2Cl_2/THF	73	89
14	$PO(OEt)_2$	CCl_3CH_2OCO	H	CH_2Cl_2/THF	66	80

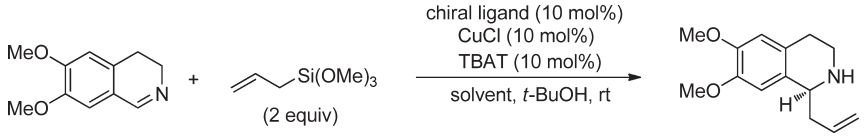
Table 8. Enantioselective Allylation of 3,4-Dihydro-6,7-dimethoxyisoquinoline



(*R*,*R*)-**13** [(*R*,*R*)-DIPAMP]



(*R*,*R*)-**14** [(*R*,*R*)-CHIRAPHOS]



entry	solvent	chiral ligand	t (h)	yield (%)	ee (%)
1	THF		20	72	
2	THF	(*R*)-*p*-Tol-BINAP [(*R*)-**1b**]	24	91	71
3	THF	(*R*)-BINAP [(*R*)-**1a**]	24	35	71
4	THF	(*R*,*R*)-DIPAMP [(*R*,*R*)-**13**]	24	78	5
5	THF	(*R*,*R*)-CHIRAPHOS [(*R*,*R*)-**14**]	24	31	21
6	DMF	(*R*)-*p*-Tol-BINAP [(*R*)-**1b**]	24	21	50
7	Et_2O	(*R*)-*p*-Tol-BINAP [(*R*)-**1b**]	24	37	47
8	dioxane	(*R*)-*p*-Tol-BINAP [(*R*)-**1b**]	24	35	

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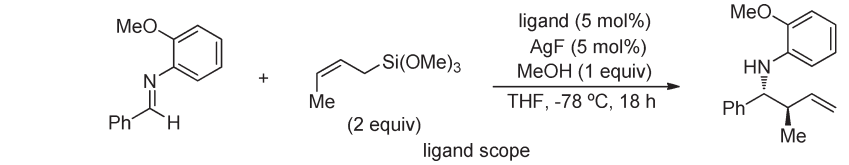
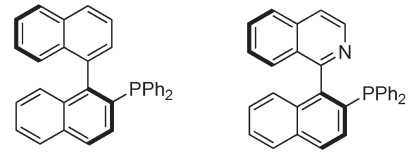
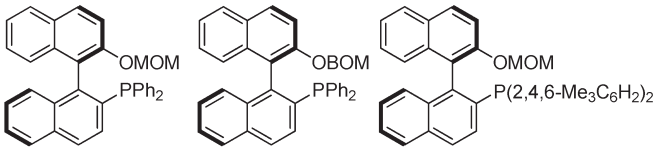
Scheme 7



ligand scope

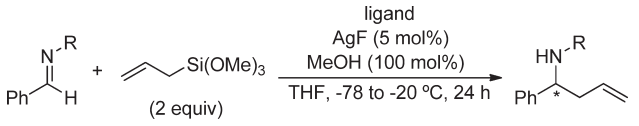


(*R*)-MOP [(*R*)-**15**] (*S*)-QUINAP [(*R*)-**19**] (*S*)-NMDPP [(*S*)-**20**]



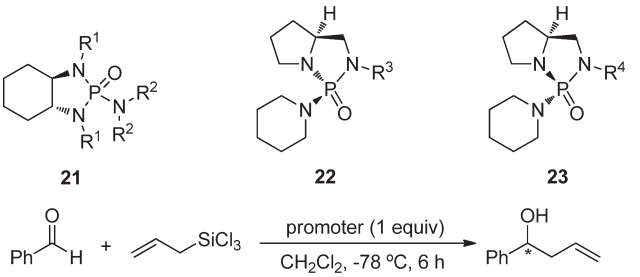
	(*R*)-**15**	(*R*)-**16**	(*R*)-**17**	(*R*)-**18**	(*S*)-**19**	(*S*)-**20**
Yield (%)	99	90	85	93	35	99
dr	90 : 10	80 : 20	89 : 11	89 : 11	77 : 23	89 : 11
(*ee*, %)	(35) (42)	(64) (60)	(79) (73)	(57) (64)	(61) (66)	(57) (64)

Table 9. Enantioselective Allylation of Aldimines Using AgF-Phosphane Catalysts



entry	ligand (mol %)	R	yield (%)	ee (%)
1	(*R*)-**15** (5)	1-naphthyl	>99	77
2	(*R*)-**15** (5)	2-naphthyl	>99	70
3	(*R*)-**6** (2.5)	2-naphthyl	74	62
4	(*R*)-**15** (5)	4-PhOC$_6$H$_4$	>99	60
5	(*R*)-**6** (2.5)	4-PhOC$_6$H$_4$	40	37
6	(*R*)-**15** (5)	2-PhOC$_6$H$_4$	>99	30
7	(*R*)-**6** (2.5)	2-PhOC$_6$H$_4$	70	82

Table 10. Enantioselective Allylation of Benzaldehyde Using Chiral Phosphoric Triamides



entry	promoter	yield (%)	ee (%)
1	**21a** (R^1 = R^2 = Me)	78	60
2	**21b** [R^1 = Me; R^2−R^2= (CH$_2$)$_5$]	81	60
3	**22a** (R^3 = Me)	55	9
4	**22b** (R^3 = Bn)	53	16.6
5	**23a** (R^4 = Me)	72	24
6	**23b** (R^4 = Bn)	nr	

cycle.[31,32] The allylations of benzaldehyde mediated by (*S*)-**32a** are highly diastereoselective because *syn*-homoallylic alcohol was obtained from (*Z*)-crotyltrichlorosilane (Table 14, entry 2) while the corresponding *anti*-alcohol was produced from (*E*)-crotyltrichlorosilane (Table 14, entry 3). The diastereomeric purity of the starting crotylsilanes was reflected in the syn/anti ratio of the resulting homoallylic alcohols. The enantioselectivity strongly depended on the substituent pattern of the allylsilane: (*E*)-crotylsilane (Table 14, entry 3) gave a selectivity similar to that of the parent allylsilane (Table 14, entry 1), while (*Z*)-crotylsilane (Table 14, entry 2) dramatically decreased the enantioselectivity. Regarding the heteroaromatic diphosphane oxide (*S*)-**33**, Simonini, Benaglia, and Benincori found that it efficiently promoted the addition of allyltrichlorosilane to aromatic aldehydes bearing both electron-withdrawing groups (Table 14, entrie 6) and electron-donating groups (Table 14, entry 7), always with enantioselectivities higher than 90%.[33] Electron-poor aldehydes react slower than electron-rich aldehydes, which give the product consistently in yields higher than 90% (Table 14, entry 6 vs entry 7). A mixture of anti and syn diastereomeric alcohols was obtained from crotyltrichlorosilane in 47% yield (Table 14, entry 9). The fact that the anti/syn diastereomeric ratio reflected the (*E*)/(*Z*) ratio of the starting silane supports that a six-membered cyclic chairlike transition state structure is involved in this allylation. Importantly, the allylation of the aliphatic aldehyde 3-phenylpropanal in the presence of catalysts (*S*)-**32a** and (*S*)-**33** proceeded in both cases with low enantioselectivities, but with the chemical yield being considerably higher for (*S*)-**33** (Table 14, entries 4 and 8, respectively).

A plausible reaction mechanism for this Lewis base-catalyzed allylation with allyltrichlorosilanes has been proposed, and it is

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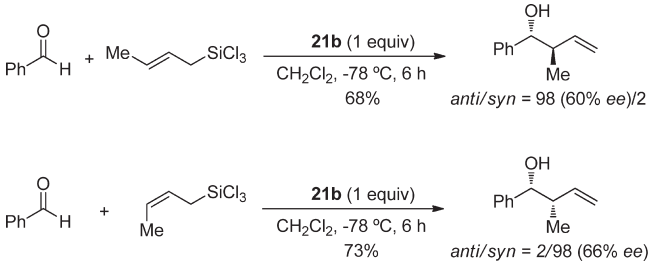
similar to that shown in Scheme 9 for the case of phosphoramides.[32] The binding of the bidentate Lewis base to allyltrichlorosilane affords a pentacoordinate silicon complex. Then the aldehyde attacks the enhanced electrophilic silicon to form a ternary complex, which provides the silylated allylic alcohol via a chairlike transition state and subsequently releases the Lewis base for further turnover. Nakajima suggests that DIPEA promotes the dissociation of phosphane oxide from the silicon atom, and consequently increases the catalytic efficiency.

Kočovský and co-workers studied the diastereoselective allylation of aromatic aldehydes with pure *trans*- and *cis*-γ-bromoallyltrichlorosilanes in the presence of different chiral Lewis basic catalysts.[34] Interestingly, the nucleophilicity of the γ-carbon in bromoallyltrichlorosilanes is significantly reduced (compared to allyltrichlorosilane) due to the electron-withdrawing effect of bromine. However, allylation of benzaldehyde with (*Z*)-γ-bromoallyltrichlorosilane in the presence of the diphosphane dioxide **34** produced the *syn*-bromohydrine, but in low yield (17%) and with only 18% ee (Table 15, entry 1). The diphosphane monoxide **35** and the dioxide **36** exhibited similar levels of reactivity and enantioselectivity (Table 15, entries 2−4). The best results were obtained with (*S*)-BINAPO [(*S*)-**32a**], which catalyzed the formation of *syn*-bromohydrines from (*Z*)-γ-bromoallyltrichlorosilane in 43−50% ee (Table 15, entries 5 and 6). High diastereoselectivities (>95:5) were observed in all cases.

2.2.1.3. Chiral Sulfoxides as Promoters. Chiral sulfoxides have been employed in asymmetric synthesis as chiral auxiliaries in different types of reactions and also as chiral ligands in catalytic processes.[35] The unique properties of this functional group with a sulfur oxygen multiple bond derive from the fact that the sulfur atom adopts a tetrahedral sp^3 hybridization instead of a planar conformation, with a lone pair of electrons as one of the substituents. For that reason, the faces of a sulfoxide are highly differentiated due to the large steric difference between its substituents, which range from an electron lone pair to large

Scheme 8



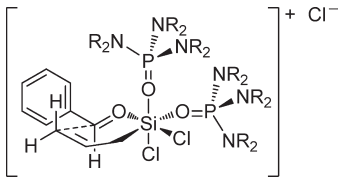
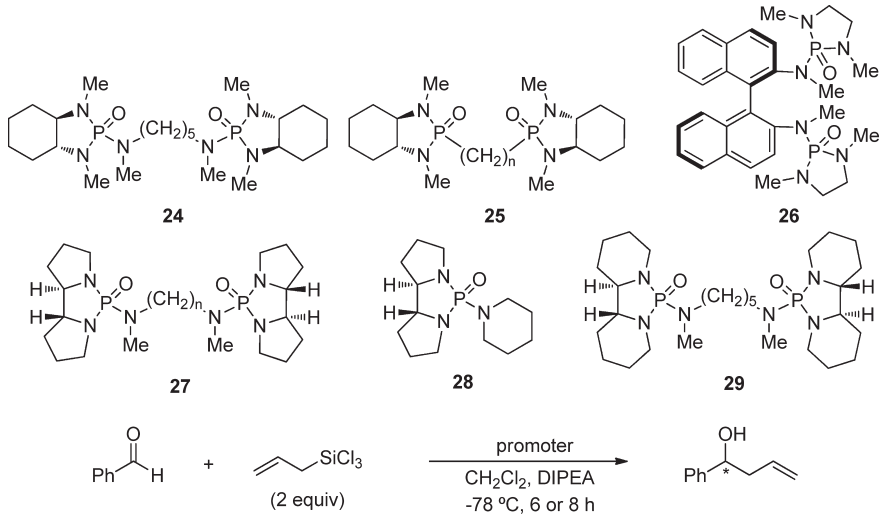


Figure 2. Transition state structure with two phosphoramides.

Table 11. Allylation of Benzaldehyde Catalyzed by Bisphosphoramides and Bidentate Phosphonic Amides



entry	promoter	yield (%)	ee (%)
1	**24** (0.1 equiv)	73	72
2[a]	**25a** (n = 4, 0.1 equiv)	37	54
3[a]	**25b** (n = 5, 0.1 equiv)	42	74
4[a]	**25c** (n = 6, 0.1 equiv)	40	66
5	**26** (0.1 equiv)	67	80
6	**27a** (n = 4, 0.05 equiv)	54	18
7	**27b** (n = 5, 0.05 equiv)	85	87
8	**27c** (n = 6, 0.05 equiv)	58	67
9	**28** (0.05 equiv)	56	56
10	**29** (0.05 equiv)	72	58

[a] The reaction was carried out without DIPEA.

dx.doi.org/10.1021/cr1004474 |*Chem. Rev.* 2011, 111, 7774–7854

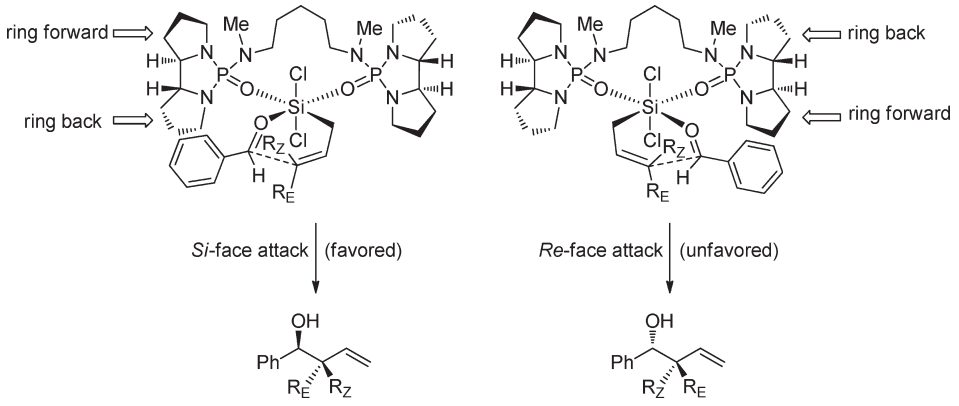
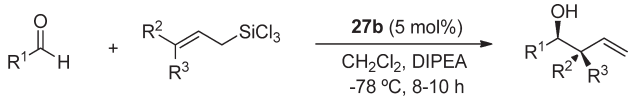


Figure 3. Hypothetical transition state structure for the reaction promoted by **27b**.

Table 12. Addition of Allyltrichlorosilanes to Aldehydes Catalyzed by 27b



entry	R^1	R^2	R^3	yield (%)	syn/anti	ee (%)
1	Ph	H	H	85		87
2	2-naphthyl	H	H	92		87.8
3	4-BrC_6H_4	H	H	84		88
4	4-$CF_3C_6H_4$	H	H	79		80.2
5	(*E*)-PhCH=CH	H	H	84		80.4
6	2-furyl	H	H	59		80.6
7	Ph	Me	H	82	1/99	85.6
8	2-naphthyl	Me	H	83	1/99	80.8
9	(*E*)-PhCH=CH	Me	H	59	1/99	80.8
10	Ph	H	Me	89	99/1	93.4
11	2-naphthyl	H	Me	88	99/1	93.6
12	4-BrC_6H_4	H	Me	91	99/1	94.6
13	4-$CF_3C_6H_4$	H	Me	85	99/1	84.6
14	(*E*)-PhCH=CH	H	Me	78	99/1	88
15	2-furyl	H	Me	82	99/1	95.6
16	Ph	Me	Me	89		96
17	(*E*)-PhCH=CH	Me	Me	71		88.2
18	Ph	Me_2C=CH$(CH)_2$	Me	83	1/99	94

alkyl groups like *tert*-butyl. In addition, both sulfur and oxygen have lone pairs of electrons available to coordinate to Lewis acidic functionality, often promoting highly ordered transition states. Importantly, sulfoxides are conformationally stable at room temperature and racemize at high temperatures (usually over 200 °C) or upon irradiation. Recent advances in transition metal catalyzed asymmetric sulfides oxidations make chiral sulfoxides readily available.[36]

Rowlands and Barnes reported in 2003 the first example of a chiral sulfoxide utilized as a Lewis base promotor of the allylation of benzaldehyde with allyltrichlorosilane. Since then, many other examples appeared in the literature. Moderate yields of the homoallylic alcohol were always obtained with chiral oxazolinyl-sulfoxides **37** (Table 16) in CH_2Cl_2 as solvent at −78 °C, with a major concern in these processes being the low recovery of the sulfoxides. Only 29% of compound (S_S)-**37** was recovered after 6 h at −78 °C (Table 16, entry 1). Lower stereoselectivity was found with (R_S)-**37**, probably due to a mismatch combination (Table 16, entry 2). It proved possible to increase the yield of product, but not the enantioselectivity, by simply employing an excess of the sulfoxide (R_S)-**37** (3 equiv, Table 16, entry 3).[37]

Soon after the pioneering work of Rowlands and Barnes, Massa, Scettri, and co-workers reported that the allylation of aldehydes with allyltrichlorosilane in the presence of 3 equiv of chiral aryl methyl sulfoxides in CH_2Cl_2 at −78 °C resulted in the formation of the corresponding homoallylic alcohols in good yields and moderate enantiomeric excesses. The best results were obtained with (*R*)-methyl *para*-tolylsulfoxide [(*R*)-**38a**].[38] It is noteworthy that, owing to the mild conditions of this procedure, the chiral sulfoxide could be recovered with only a very slightly reduced enantiomeric excess (97%) and in almost quantitative yields (>95%). Later, and taking advantage of the work of Nakajima and co-workers[32] about the beneficial effect exerted by the use of tetrabutylammonium salts on the rate of allylation of aldehydes promoted by *O*-donor ligands, they found that the use of tetrabutylammonium iodide (TBAI), as additive, resulted in an increase of the yields and stereoselectivities. The allylation of different aldehydes with allyltrichlorosilane in the presence of (*R*)-**38a**, DIPEA, and TBAI led to the corresponding homoallylic alcohols (Table 17, entries 1−3). The highest enantioselectivies were obtained in the case of heteroaromatic compounds with electron-withdrawing groups (Table 17, entry 2). Substituted allylic trichlorosilanes performed well in the asymmetric allylation of aldehydes under optimized reaction conditions (Table 17, entries 4−8).[39] These processes occurred with good to high yields, high diastereoselectivities, and moderate to high enantiomeric excesses (up to 97%) with aromatic aldehydes (Table 17, entries 4 and 7), as well as heteroaromatic ones (Table 17, entries 5 and 8). Massa and Scettri also found that a catalytic amount of the chiral bis(iminosulfoxide) **39**,[40] instead of a large excess of monosulfoxides,[38,39] promoted the stereoselective allylation of aldehydes with allyltrichlorosilane. The allylation of benzaldehyde in the presence of 0.2 equiv of **39** yielded the corresponding homoallylic alcohol in moderate yield and enantiomeric excess. Increasing the loading of the catalyst to 0.3 equiv provoked a slight enhancement of both yield and stereoselectivity (Table 17, entry 9).[40] Other imino- and aminosulfoxides **40**−**44**, easily accessible from chiral 2-methylsulfinyl benzaldehyde, were also evaluated as activators for the allylation of benzaldehyde with

dx.doi.org/10.1021/cr1004474 |*Chem. Rev.* 2011, 111, 7774–7854

Scheme 9

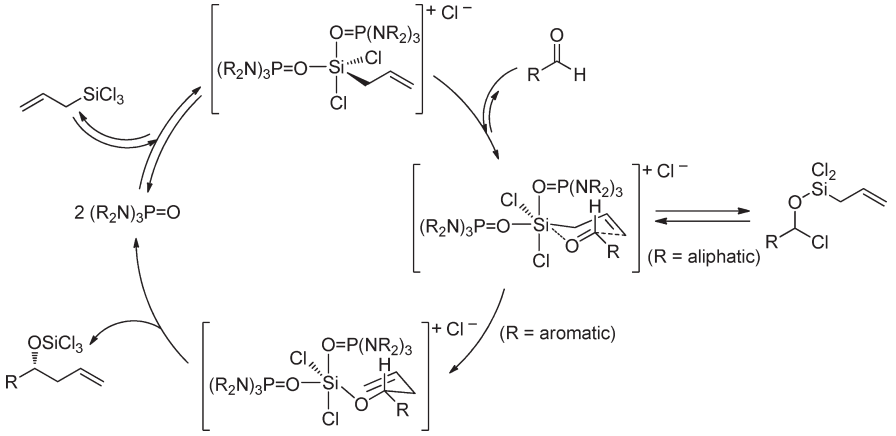
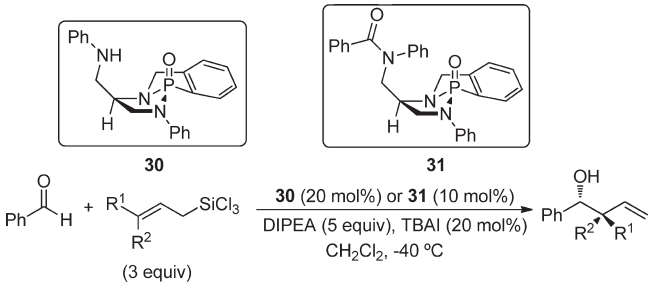


Table 13. Allylation of Benzaldehyde with Allyltrichlorosilanes Catalyzed by 30 and 31



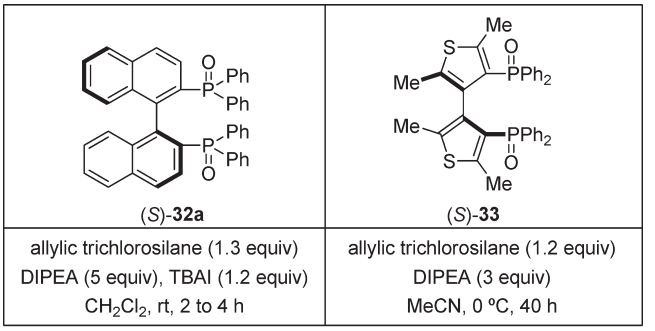
entry	chiral ligand	R^1	R^2	yield (%) (anti/syn)	ee (%)
1	**30**	H	H	69	52
2	**31**	H	H	84	46
3[a]	**30**	Me	H	72 (7/93)	44
4[a]	**31**	Me	H	86 (7/93)	48
5[b]	**30**	H	Me	54 (99/1)	7
6[b]	**31**	H	Me	87 (99/1)	26

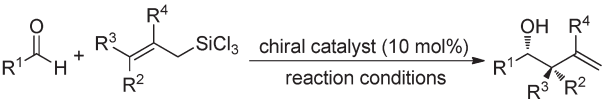
[a] (*E*)-Crotyltrichlorosilane (*E*/*Z* = 95:5). [b] (*Z*)-Crotyltrichlorosilane (*E*/*Z* = 1:99).

allyltrichlorosilane. Moderate yields and stereoselectivities were obtained in all cases (Table 17, entries 10, 12, and 14) except for secondary amines **41** and **43**, due to rapid decomposition of the allyl trichlorosilane (Table 17, entries 11 and 13).[41] A hexacoordinate silicon intermediate in the stereodetermining step has been proposed to occur in a chairlike transition state involving the coordination of two molecules of sulfoxide to the silicon atom.

The enantioselective allylation of aldehydes with allyltrichlorosilane promoted by 1.5 equiv of enantiomerically pure mono- and bisaryl *tert*-butyl sulfoxides, **45** and **46**, respectively, was studied by Liao and co-workers. The promoters can be recovered in almost quantitative yields without affecting their optical purity by diluting with ethyl acetate. Moderate to good yields and modest to high enantioselectivities were achieved with monoaryl *tert*-butyl sulfoxides **45** (Scheme 10). Substituents on the phenyl ring played an important role in the enantioselectivity, so electron-donating substituents at the 2-position of the aromatic ring provided the highest yields and stereoselectivities. Bisaryl

Table 14. Allylation of Aldehydes with Allyltrichlorosilanes Catalyzed by Chiral Phosphane Oxides (*S*)-32a and (*S*)-33





entry	catalyst	R^1	R^2	R^3	R^4	yield (%)	ee (%) (syn/anti)
1	(*S*)-**32a**	Ph	H	H	H	92	43
2[a]	(*S*)-**32a**	Ph	Me	H	H	92	4 (99/1)
3[b]	(*S*)-**32a**	Ph	H	Me	H	87	46 (23/77)
4	(*S*)-**32a**	$PhCH_2CH_2$	H	H	Me	59	29
5	(*S*)-**33**	Ph	H	H	H	85	93
6	(*S*)-**33**	4-$NO_2C_6H_4$	H	H	H	51	93
7	(*S*)-**33**	4-$MeOC_6H_4$	H	H	H	95	91
8	(*S*)-**33**	$PhCH_2CH_2$	H	H	H	98	23[c]
9[d]	(*S*)-**33**	Ph	H	Me	H	47	85 (17/83)

[a] *E*/*Z* = 1/99. [b] *E*/*Z* = 77/23. [c] The enantiomer with opposite configuration to that shown on this table was obtained. [d] *E*/*Z* = 80/20.

tert-butyl sulfoxides **46** with varying tether lengths, from one to three carbons, were also evaluated as allylation promoters. An *ortho*-oxygen was incorporated into the structures of **46** to ensure a better comparison with the most stereoselective monosulfoxides **45**. The bissulfoxide **46b** with a two-carbon tether was the most stereoselective bissulfoxide for the allylation of benzaldehyde with allyltrichlorosilane (Scheme 10). Regarding the mechanism, the absence of nonlinear effect, spacer effect, promoter loading, and concentration

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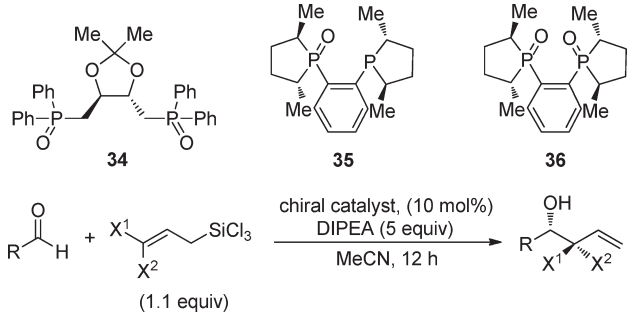
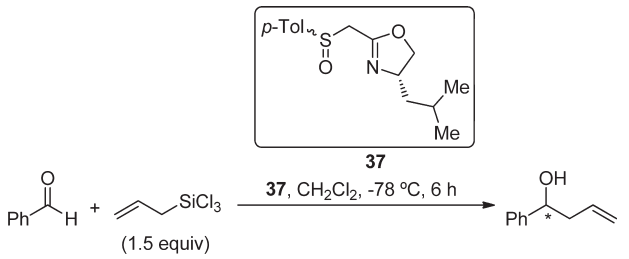
Table 15. Reaction of Aromatic Aldehydes with *trans*- and *cis*-γ-Bromoallyltrichlorosilanes Catalyzed by 32 and 34−36



entry	catalyst	R	X^1	X^2	T (°C)	yield (%)	ee (%)
1	**34**	Ph	H	Br	−20	17	18
2	**35**	Ph	Br	H	−20	23	29
3	**36**	Ph	Br	H	−20	10	15
4	**36**	Ph	H	Br	−20	43	25
5	(*S*)-**32a**	Ph	H	Br	−20	34	50
6	(*S*)-**32a**	4-$CF_3C_6H_4$	H	Br	−10	22	43

Table 16. Allylation of Benzaldehyde with Allyltrichlorosilane in the Presence of (*S*)-37



entry	**37**	yield (%)	ee (%)
1	(S_S)-**37** (1 equiv)	45[a]	57 (*S*)
2	(R_S)-**37** (1 equiv)	49	47 (*R*)
3	(R_S)-**37** (3 equiv)	68	42 (*R*)

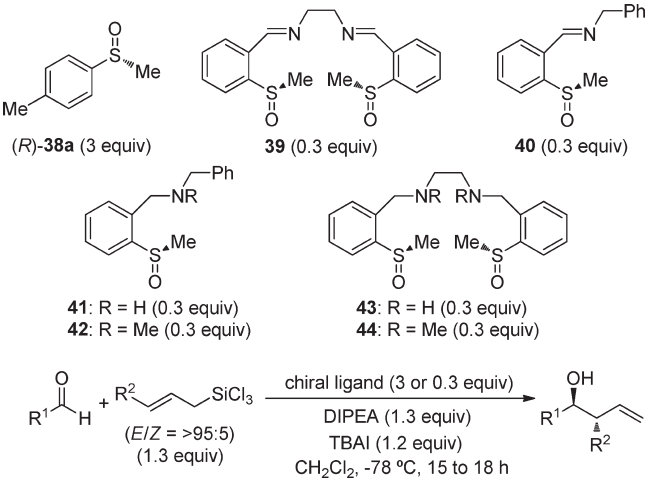
[a] 29% of catalyst was recovered.

effect indicates that only one molecule of aryl *tert*-butyl sulfoxide is involved in the stereodetermining step in these processes.[42]

2.2.1.4. Chiral N-Oxides as Promoters. Several methods allow the preparation of compounds with sp^2 nitrogens showing central, axial, planar, and helical chirality, or any combination of these. The sp^2 nitrogens can be oxidized to the corresponding *N*-oxides, and that not only alters the electronic and steric properties of the system but also allows different modes of coordination. Bipyridine, bisisoquinoline, and terpyridine *N*-oxide derivatives have been successfully used as chiral ligands in enantioselective catalysis.[43] Importantly, the asymmetric allylation of aldehydes with allyltrichlorosilanes has also been performed in the presence of different chiral *N*-oxides as ligands.[44,45]

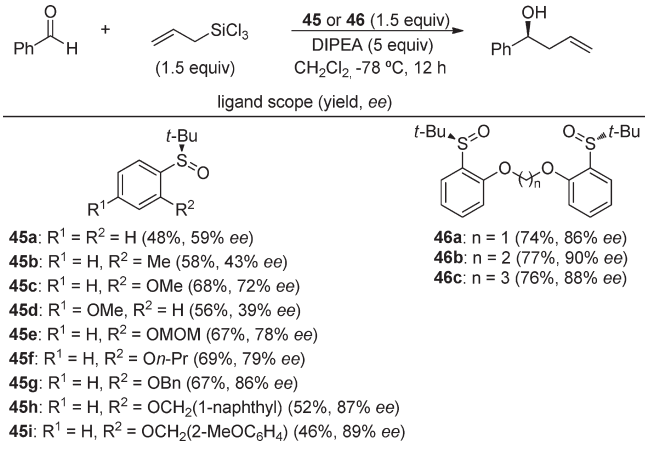
We will comment on the enantioselective allylation of benzaldehyde with allyltrichlorosilane under de influence of chiral *N,N′*-dioxides to compare these compounds as the most valuable promoters for this reaction. Thus, Hayashi and co-workers reported the use of different *N,N′*-dioxides **47** in the Sakurai−Hosomi−Denmark type allylation. Compounds **47** are substituted with aryl

Table 17. Allylation of Aldehydes with Allylic Trichlorosilanes in the Presence of Chiral Sulfoxides 38−44



entry	chiral sulfoxide	R^1	R^2	yield (%)	ee (%) (anti/syn)
1	(*R*)-**38a**	Ph	H	99	60
2	(*R*)-**38a**	5-NO_2-2-furyl	H	99	80
3	(*R*)-**38a**	$PhCH_2CH_2$	H	80	74
4	(*R*)-**38a**	Ph	Me	88	68 (97:3)
5	(*R*)-**38a**	5-NO_2-2-furyl	Me	70	87 (97:3)
6	(*R*)-**38a**	$PhCH_2CH_2$	Me	67	64 (97:3)
7	(*R*)-**38a**	4-$MeOC_6H_4$	Et	58	74 (95:5)
8	(*R*)-**38a**	5-NO_2-2-furyl	Ph	68	97 (>99:1)
9	**39**	Ph	H	57	53
10	**40**	Ph	H	35	44
11	**41**	Ph	H		no reaction
12	**42**	Ph	H	56	46
13	**43**	Ph	H		no reaction
14	**44**	Ph	H	60	56

Scheme 10



groups at the 6 and 6′ positions and were prepared by a palladium-catalyzed cross-coupling of bipyridine *N,N′*-dioxide 6,6′-dichloride with the corresponding aryl Grignard reagent.[46] The allylation proceeded smoothly in acetonitrile at −45 °C in the presence of 0.1 mol % of **47** to give the corresponding homoallyl

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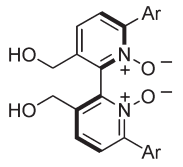
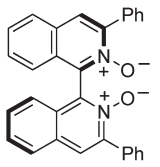
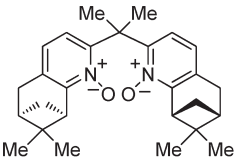
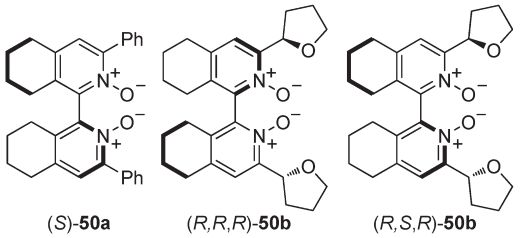
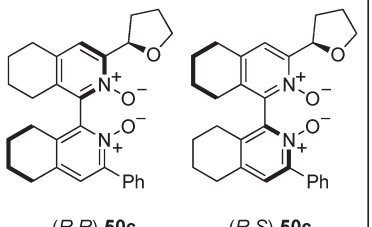
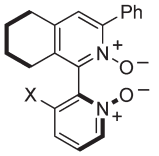
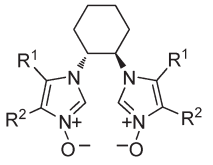
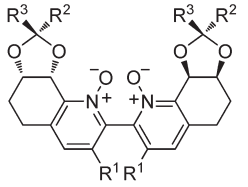
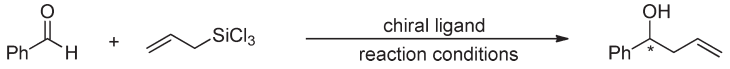
Table 18. Allylation of Benzaldehyde with Allyltrichlorosilane Catalyzed by Chiral *N,N′*-Dioxides

 (*R*)-**47a** (Ar = Ph) (*R*)-**47b** (Ar = 3,5-Me_2-4-$MeOC_6H_2$)	 (*R*)-**48**	 **49**
allyltrichlorosilane (1.3 equiv) chiral ligand (0.1 mol%) DIPEA (3 equiv)	allyltrichlorosilane (1.2 equiv) chiral ligand (5 mol%) DIPEA (1 equiv)	allyltrichlorosilane (1.2 equiv) chiral ligand (5 mol%) DIPEA (3 equiv)
 (*S*)-**50a** (*R,R,R*)-**50b** (*R,S,R*)-**50b**	 (*R,R*)-**50c** (*R,S*)-**50c**	
allyltrichlorosilane (1.2 equiv) chiral ligand (1 mol%) DIPEA (1.2 equiv)	allyltrichlorosilane (1.5 equiv) chiral ligand (1 mol%) DIPEA (1.5 equiv)	
 (*S*)-**51a** (X = Me) (*S*)-**51b** (X = CF_3)	 (*R,R*)-**52a** (R^1 = R^2 = Me) (*R,R*)-**52b** (R^1 = Me, R^2 = Ph) (*R,R*)-**52c** (R^1 = Ph, R^2 = Me) (*R,R*)-**52d** (R^1 = R^2 = Ph)	 **53a** (R^1 = H, R^2 = R^3 = Me) **53b** (R^1 = H, R^2 = R^3 = Et) **53c** [R^1 = H, R^2-R^3 = $(CH_2)_5$]
allyltrichlorosilane (1.3 equiv) chiral ligand (5 mol%) DIPEA (1.3 equiv)	allyltrichlorosilane (1.2 equiv) chiral ligand (5 mol%) DIPEA (3 equiv)	allyltrichlorosilane (1.2 equiv) chiral ligand (10 mol%) DIPEA (5 equiv), TBAI (1.2 equiv)



entry	catalyst	solvent	*T* (°C)	*t* (h)	yield (%)	ee (%)
1	(*R*)-**47a**	MeCN	−45	2.5	95	84 (*S*)
2	(*R*)-**47b**	MeCN	−45	2.5	96	91 (*S*)
3	(*R*)-**48**	CH_2Cl_2	−80	18	≥99	81 (*S*)
4	**49**	MeCN	−40	67	37	85 (*S*)
5	**49**	MeCN	25	67	97	77 (*S*)
6	(*S*)-**50a**	MeCN	−40	24	100	65 (*S*)
7	(*S*)-**50a**	PhCl	−40	24	100	82 (*R*)
8	(*R,R,R*)-**50b**	MeCN	−40	24	100	48 (*S*)
9	(*R,S,R*)-**50b**	PhCl	−40	24	100	62 (*S*)
10	(*R,R*)-**50c**	THF	−78	1	100	93 (*R*)
11	(*R,S*)-**50c**	THF	−78	1	98	96 (*S*)
12	(*S*)-**51a**	CH_2Cl_2	−60	3	87	74 (*R*)
13	(*S*)-**51b**	CH_2Cl_2	−60	3	53	72 (*R*)
14	(*R,R*)-**52a**	CH_2Cl_2	−90	20	55	18 (*R*)
15	(*R,R*)-**52b**	CH_2Cl_2	−60	20	85	43 (*R*)
16	(*R,R*)-**52c**	CH_2Cl_2	−40	20	54	5 (*S*)
17	(*R,R*)-**52d**	CH_2Cl_2	−40	20	86	53 (*S*)
18	**53a**	CH_2Cl_2	−40	24	64	26 (*R*)
19	**53b**	CH_2Cl_2	−20	24	62	16 (*R*)
20	**53c**	CH_2Cl_2	−40	24	28	14 (*R*)

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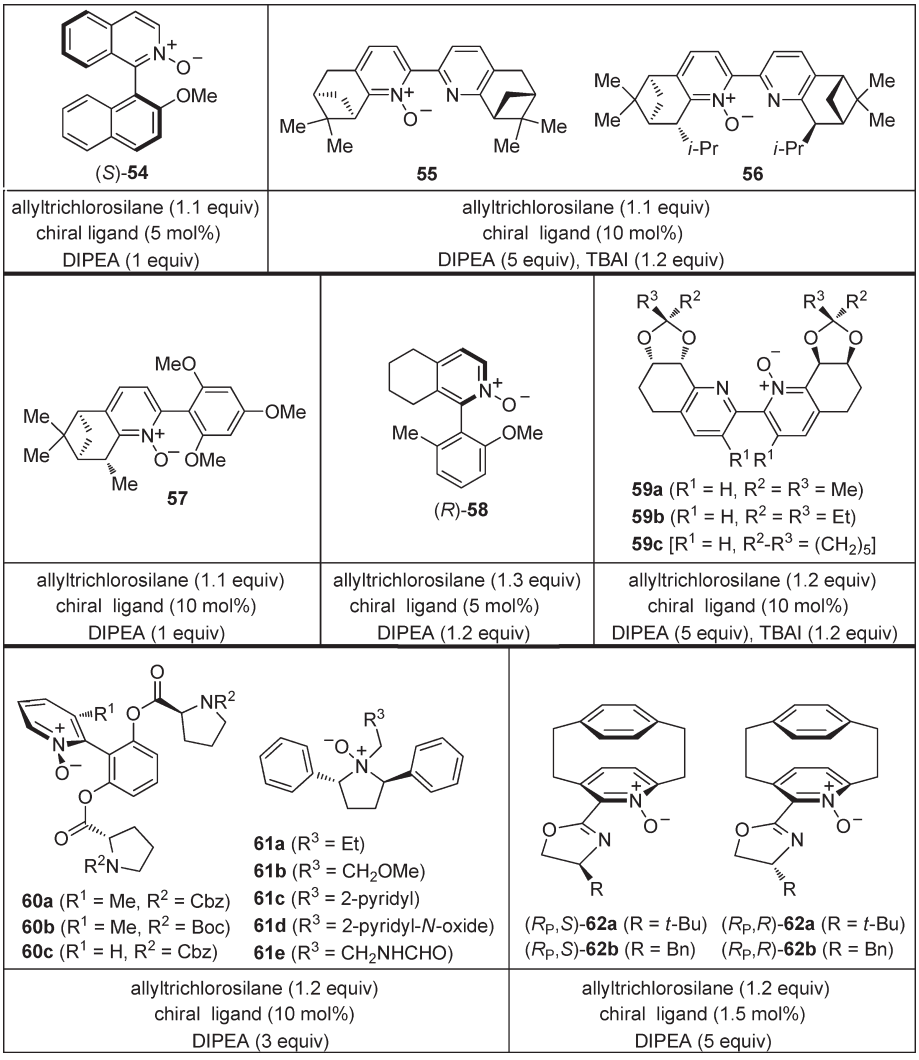
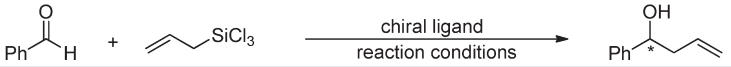
Table 19. Allylation of Benzaldehyde with Allyltrichlorosilane Catalyzed by Chiral *N*-Oxides





entry	catalyst	solvent	T (°C)	t (h)	yield (%)	ee (%)
1	(*R*)-**54**	CH_2Cl_2	−40	12	68	87 (*R*)
2	**55**	CH_2Cl_2	−40	6	65	87 (*S*)
3	**56**	MeCN	−40	18	75	96 (*S*)
4	**57**	MeCN	−20	18	>95	93 (*S*)
5	(*R*)-**58**	CH_2Cl_2	20	72	50	20 (*R*)
6	**59a**	CH_2Cl_2	0	24	60	35 (*R*)
7	**59b**	CH_2Cl_2	−40	24	42	24 (*R*)
8	**59c**	CH_2Cl_2	−40	24	28	30 (*R*)
9	**60a**	MeCN	0	48	45	68 (*S*)
10	**60b**	MeCN	0	48	87	62 (*S*)
11	**60c**	MeCN	0	48	50	60 (*S*)
12	**61a**	MeCN	0	48	no reaction	
13	**61b**	MeCN	0	48	45	11 (*R*)
14	**61c**	MeCN	25	48	55	17 (*R*)
15	**61d**	MeCN	25	48	24	21 (*R*)
16	**61e**	MeCN	0	48	51	81 (*R*)
17	(R_P,*S*)-**62a**	MeCN	−40	6	95	93 (*S*)
18	(R_P,*S*)-**62b**	MeCN	−40	6	90	87 (*S*)
19	(R_P,*R*)-**62a**	MeCN	−20	6	93	47 (*S*)
20	(R_P,*R*)-**62b**	MeCN	−40	6	89	53 (*S*)

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alcohol in high yields (Table 18, entries 1 and 2). The enantioselectivity was higher with aromatic aldehydes bearing electron-donating groups and also with cinnamaldehyde, although aliphatic aldehydes were not good substrates, showing poor reactivity and enantioselectivity.[46,47] Kočovský and co-workers synthesized the C_2-symmetrical *N,N′*-dioxide **48**, and it showed also good enantioselectivity in this reaction with benzaldehyde (Table 18, entry 3), as well as with electron-poor aromatic aldehydes; however, the electron-rich derivatives turned out to give the products with poor selectivity.[48] Chelucci, Benaglia, and co-workers studied the enantioselective addition of allyltrichlorosilane to aldehydes in the presence of dipyridine *N*-monoxides and *N,N′*-dioxides, which possess an isopropylidene backbone between two pyridine rings, that have been prepared from naturally occurring monoterpenes. The bis-(*N*-oxidoquinoline) derivative **49** proved to be the most efficient one for these transformations. Surprisingly, in the reaction with benzaldehyde, the yield increased by raising the temperature from −40 to 0 and 25 °C, with a slight decrease in the enantioselectivity (Table 18, entries 4 and 5). For other aromatic aldehydes, enantioselectivites were always ⩾70% and yields were constantly >58%. Enantioselectivities were considerably lower for cinnamaldehyde and the aliphatic 3-phenylpropanal.[49] Taking advantage of the cobalt-catalyzed heterocyclotrimerization of 1-pyridyl-1,7-octadiynes with nitriles, Kotora and co-workers synthesized a new class of axially chiral bipyridine *N,N′*-dioxides with a bis(tetrahydroisoquinoline) framework **50**, and they were also tested as promoters in the reaction of aliphatic and aromatic aldehydes with allyltrichlorosilane to afford homoallylic alcohols. In the case of aliphatic aldehydes, chloroform, compared with dichloromethane and acetonitrile, was the solvent in which higher yields and enantioselectivities were obtained with the chiral Lewis bases **50a**, **b**.[50] For benzaldehyde, and other aromatic aldehydes, and with the same ligands, a dramatic solvent effect was observed. The use of different solvents induced opposite chiralities of the product with the same enantiomer of the catalyst: in acetonitrile the allylation of benzaldehyde in the presence of (*S*)-**50a** led to the corresponding homoallylic alcohol with 65% ee and (*S*)-configuration (Table 18, entry 6), and in chlorobenzene the reaction product showed (*R*)-configuration with 82% ee (Table 18, entry 7).[51] Reactions with chiral dioxides **50c** led to homoallylic alcohols with higher enantioselectivities and under milder reaction conditions (−78 °C, 1 h) in THF as solvent (Table 18, entries 10 and 11).[52] Kotora and co-workers achieved the synthesis of axially chiral bipyridine *N,N′*-dioxides **51**. The key step of the synthesis is a cobalt-catalyzed heterocyclotrimerization of 1-pyridyl-1,7-octadiynes with nitriles. These compounds were then tested in the enantioselective allylation of aromatic aldehydes with allyltrichlorosilane. The allylation catalyzed by the methyl-substituted bipyridine (*S*)-**51a** proceeded in all cases with good yields of the corresponding (*R*)-homoallylic alcohols and moderate enantioselectivities.[53] The highest ee (74%) was obtained in the reaction with benzaldehyde (Table 18, entry 12). Mlostoń, Jurczak, and co-workers studied the allylation of aromatic aldehydes with allyltrichlorosilane using bisimidazole-*N*-oxides derived from (1*R*,2*R*)-*trans*-1,2-diaminocyclohexane **52** as ligands.[54] The comparison of the results summarized indicated that the best results in the allylation of benzaldehyde in terms of both yield and enantioselectivity were achieved using (*R*,*R*)-**52b** and (*R*,*R*)-**52d** as ligands (Table 18, entries 15 and 17). It is interesting to note that the sense of asymmetric induction was in these two entries just the opposite. The reaction occurred efficiently with different aromatic aldehydes using the catalyst (*R*,*R*)-**52d**. Boyd et al. achieved the synthesis of *N,N′*-dioxide derivatives **53**, derived from 2,2′-bipyridines, including separable atropisomers, and they were used as enantioselective organocatalysts in the asymmetric allylation of aldehydes with allyltrichlorosilane in the presence DIPEA and TBAI, using CH_2Cl_2 as solvent.[55] Moderate yields and low stereoselectivities were obtained with benzaldehyde (Table 18, entries 18−20), but the results were optimal with electron-rich *para*-methoxybenzaldehyde.[55]

Enantioselective allylation of benzaldehyde with allyltrichlorosilane was also carried out with chiral *N*-monoxide ligands. In general, reaction rates are lower than in the case of *N,N′*-dioxides. Kočovský and co-workers have also synthesized several monodentate chiral pyridine *N*-oxides. The most significant chiral Lewis bases regarding yields and stereoselectivities were axially chiral isoquinoline *N*-oxide **54** (QUINOX),[56,57] the terpene-derived bipyridine *N*-monoxides **55** (PINDOX)[58] and **56** (*i*-Pr_2-iso-PINDOX),[58] and the terpene-derived pyridine *N*-oxide **57** (METHOX).[59] The axially chiral isoquinoline *N*-oxide QUINOX (**54**) was a very efficient catalyst with benzaldehyde (Table 19, entry 1) and electron-poor aromatic aldehydes. For terpene-derived bipyridine *N*-monoxides **55** and **56**, the reactions were performed in the presence of TBAI, and MeCN was identified as the optimal solvent for these catalysts (Table 19, entry 2 vs 3). In the absence of TBAI, the reaction was slower and less selective. Regarding METHOX (**57**), it has been found to exhibit the best activity in MeCN (Table 19, entries 4) and also high tolerance to aldehyde substituents. The attempt to carry out the allylation of benzaldehyde in the presence of the 2-arylpyridine *N*-oxide **58** at low temperature was not successful. Kotora and co-workers found that the reaction proceeded only at room temperature, but even then the reaction rate was rather low, with 50% yield of the corresponding alcohol being obtained after 72 h with the modest asymmetric induction of 20% ee (Table 19, entry 5).[60] Boyd et al. also synthesized *N*-oxides **59**[55] and found that the rate of the allylation of benzaldehyde was slower when using monoxides **59** (Table 19, entries 6−8) than in the case of dioxides **53** (Table 18, entries 18−20); meanwhile, yields and stereoselectivities were rather similar. Benaglia and co-workers synthesized new structurally simple axially chiral pyridine *N*-oxides **60** derived from (*S*)-proline, and amine *N*-oxides derived from *trans*-2,5-diphenylpyrrolidine **61** in enantiomerically pure form. These compounds were tested as metal-free catalysts in the reaction of aldehydes with allyltrichlorosilane to afford homoallylic alcohols. Pyridine *N*-oxide derivatives **60** promoted the allylation of benzaldehyde (Table 19, entries 9−11) and other aromatics aldehydes with high stereocontrol in acetonitrile at 0 °C.[61] However, the allylation of heteroaromatic, α,β-unsaturated, and aliphatic aldehydes was less satisfactory. Regarding the catalytic activity of *trans*-(2*R*,5*R*)-2,5-diphenylpyrrolidine-derived *N*-oxides **61**, it seems that the presence of a chelating element on the *N*-alkyl chain was necessary to have a chemically active catalyst (Table 19, entry 12 vs entries 13−16).[62] These findings are in accordance with the general proposed transition state for the reaction involving the coordination of the silicon atom by two binding units. Pyrrolidine derivative **61e** was found to be the most efficient ligand among the pyrrolidine series (Table 19, entry 16). Chiral azaparacyclophane oxazoline *N*-oxides **62** were prepared and explored also as promoters for the asymmetric allylation of aldehydes using trichloroallylsilane, taking advantage of their rigid structure.[63] Andrus and co-workers found that the allylation of benzaldehyde in acetonitrile in the presence of 5 equiv of DIPEA and 1.5 mol % of the *N*-oxide derivatives **62** at −40 °C led always to 1-phenylbut-3-en-1-ol

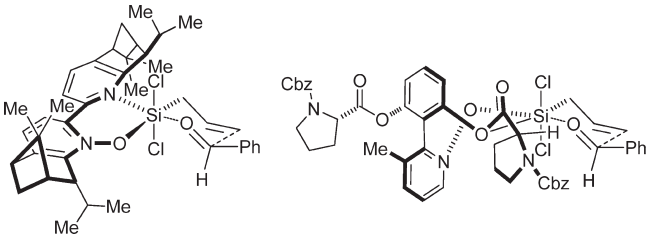
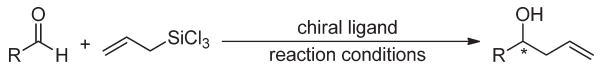


Figure 4. Proposed transition states for allylation of benzaldehyde in the presence of bipyridine *N*-monoxide **56** and quinoline *N*-oxide **60a**.

Table 20. Allylation of Aldehydes with Allyltrichlorosilane Catalyzed by Chiral *N*-Oxides and *N,N′*-Dioxides



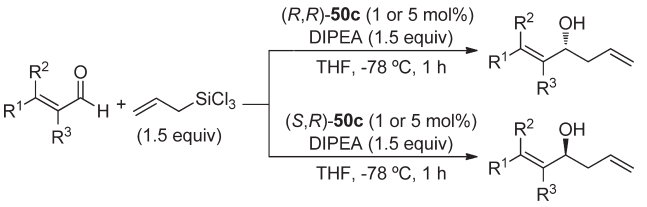
entry	R	ligand	solvent	*T* (°C)	*t* (h)	yield (%)	ee (%)
1[a]	4-$MeOC_6H_4$	(*R*)-**47a**	MeCN	−45	2.5	96	94 (*S*)
2[a]	4-$MeOC_6H_4$	(*R*)-**47b**	MeCN	−45	2.5	98	94 (*S*)
3[b]	4-$MeOC_6H_4$	**57**	MeCN	−40	18	>95	96 (*S*)
4[b]	3,4-$(MeO)_2C_6H_3$	(R_P,*S*)-**62a**	MeCN	−40	6	93	90 (*S*)
5[b]	4-$NO_2C_6H_4$	(*R*)-**54**	CH_2Cl_2	−40	4	73	89 (*R*)
6[b]	4-$CF_3C_6H_4$	(*R*)-**54**	CH_2Cl_2	−40	4	85	96 (*R*)
7[a]	4-$CF_3C_6H_4$	(*R,S*)-**50c**	THF	−78	1	99	94 (*S*)
8[a]	$CH_3(CH_2)_4$	(*S*)-**50a**	$CHCl_3$	−40	24	82	40 (*R*)
9[b]	$PhCH_2CH_2$	**61e**	MeCN	0	48	67	85 (*S*)
10[b]	$PhCH_2CH_2$	(R_P,*S*)-**62b**	MeCN	−40	6	77	85 (*S*)

[a] For specific reaction conditions, see Table 18. [b] For specific reaction conditions, see Table 19.

with high yields (Table 19, entries 17−20). Stereoselectivities for (R_P,*S*)-**62a,b** (Table 19, entries 17 and 18) were notably higher than for (R_P,*R*)-**62a,b** (Table 19, entries 19 and 20) where a mismatch effect was observed. In general, chemical yields for (R_P,*S*)-**62a,b** were similar, and regarding the stereoselectivity, (R_P,*S*)-**62a** proved to be superior to (R_P,*S*)-**62b**, except for the allylation of 3-phenylpropanal.

Concerning the stereochemical pathway of the nucleophilic addition of the allyl unit to the carbonyl group, bipyridine *N*-monoxide **56** (Table 19, entry 3) and *N*-pyridine oxides **60** (Table 19, entries 9−11) showed the same facial stereoselectivity and opposite to that of pyrrolidine derivatives **61** (Table 19, entries 13−16): *Si*-face addition for **56** and **60** and *Re*-face addition in the case of **61**. Malkov, Kočovský, and co-workers proposed a transition state to explain the stereochemical result of the allylation reaction promoted by the catalyst **56** (Figure 4).[58] In this model, the hypervalent silicon atom is coordinated by both the Lewis basic *N*-oxide oxygen (which is positioned trans to the allylic group to enhance its nucleophilicity) and the nitrogen of the second pyridine ring. In the case of catalyst **60a**, and based on conformational analysis of model compounds using molecular mechanics calculations, Benaglia and co-workers proposed that the silicon atom is coordinated by the pyridine *N*-oxide oxygen and the phenolic oxygen of one side arm (Figure 4).[61] The bulky proline residue effectively blocks one side of the adduct and accommodates the aldehyde as its cis substituent, better than the sterically more demanding allyl residue. The proposed

Table 21. Allylation of α,β-Unsaturated Aldehydes with Allyltrichlorosilanes Catalyzed by *N,N′*-Dioxides 50c



				ligand (*R,R*)-**50c**		ligand (*S,R*)-**50c**	
entry	R^1	R^2	R^3	yield (%)	ee (%)	yield (%)	ee (%)
1	Ph	H	H	92	97.4	95	93
2	Ph	H	Me	90	88.6	99	97.2
3	Ph	H	Cl	35	92	35	93.6
4	4-$NO_2C_6H_4$	H	H	60	86.6	60	39.2
5	4-$MeOC_6H_4$	H	H	80	81.6	80	63
6	Et	H	H	85	99	90	96
7	*n*-Bu	H	H	90	99	95	96.2
8	H	H	Me	20	28.6	25	94.6
9	Et	H	Me	70	19.2	90	96.2

models of stereoselection are in agreement with the observed formation of homoallylic alcohols with (*S*)-configuration.

Among the here-described catalysts, and considering the allylation of aromatic aldehydes with electron-donating groups, the bests results in terms of chemical yield and stereoselectivity were obtained with bipyridine *N,N′*-dioxides (*R*)-**47a** and (*R*)-**47b**,[47] terpene-derived pyridine *N*-oxide **57**,[59] and azaparacyclophane oxazoline *N*-oxide (R_P,*S*)-**62a**[63] (Table 20, entries 1−4). With respect to aromatic aldehydes bearing electron-withdrawing groups, chiral isoquinoline *N*-oxide **54** (QUINOX)[56,57] and chiral dioxide (*R,S*)-**50c**[52] were the most efficient ligands in the allylation reaction with allyltrichlorosilane (Table 20, entries 5−7). Yields and stereoselectivities were considerable lower in the catalyzed allylation of aliphatic enolizable aldehydes, and few catalysts performed well with these substrates. With dioxide (*S*)-**50a**, allylation of hexanal took place in 82% yield and 40% ee (Table 20, entry 8).[50] Better yields and stereoselectivities were obtained in the allylation of 3-phenylpropanal in the presence of *N*-oxides **61e**[62] and (R_P,*S*)-**62**[63] (Table 20, entries 9 and 10, respectively).

Interestingly, Kotora and co-workers reported that the allylation of α,β-unsaturated aldehydes with allyltrichlorosilane in the presence of chiral *N,N′*-dioxides **50c** proceeded with enantioselectivities of up to 99% ee (Table 21).[64] Again, THF was the solvent of choice, and surprisingly, the reaction in acetonitrile did not produce any product. Yields, in general, were higher with (*E*)-β-substituted acroleins, with the lower yield being obtained in the case of methacrolein (Table 21, entry 8) for both diastereomers **50c**. Interestingly, because allylation of α,β-unsaturated aldehydes takes place to the *Re*-face with (*R,R*)-**50c** and to the *Si*-face with (*S,R*)-**50c**, this methodology allows access to both optic antipodes allylic−homoallylic alcohols.

The crotylation reaction of benzaldehyde was found to be highly diastereoselective with chiral *N*-oxides **47**,[47] **54**, **55**, and **56**[58] and led only to the corresponding γ-allylated homoallyl alcohol, whose relative configuration was syn from (*Z*)-crotyltrichlorosilane while anti from the (*E*)-crotyl derivative, with the process being totally stereospecific. These results supported a

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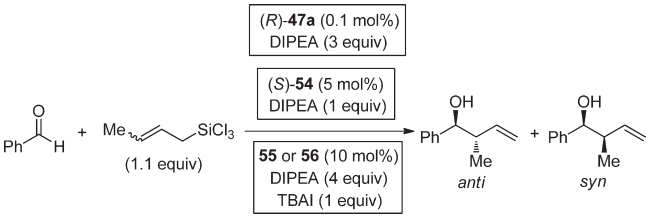
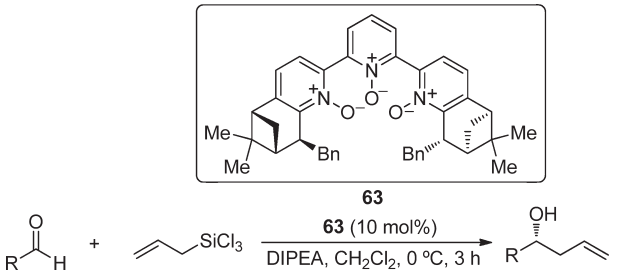
Table 22. Reaction of Benzaldehyde with Crotyltrichlorosilanes Catalyzed by 47, 54, 55, and 56



entry	catalyst	crotyl	solvent	T (°C)	t (h)	yield (%)	anti (% ee)/ syn (% ee)
1	(*R*)-**47a**	(*Z*)	MeCN	−45	2.5	82	1:99 (77)
2	(*R*)-**47a**	(*E*)	MeCN	−45	2.5	84	96 (73):4
3	(*S*)-**54**	(*E*)	CH_2Cl_2	−40	12	65	95 (66):5 (77)
4	(*S*)-**54**	(*Z*)	CH_2Cl_2	−40	12	78	1 (69):99 (79)
5	**55**	(*E*)	CH_2Cl_2	−60	15	44	96 (87):4
6	**56**	(*E*)	MeCN	−40	18	88	98 (98):2
7	**56**	(*Z*)	MeCN	−40	18	37	10:90(87)

Table 23. Allylation of Aldehydes with Allyltrichlorosilane Catalyzed by *N*-Oxides 63



entry	R	yield (%)	ee (%)
1	Ph	89	74
2	4-$MeOC_6H_4$	94	65
3	4-$NO_2C_6H_4$	91	86
4	1-naphthyl	95	74
5	1-naphthyl	86	78
6	5-methylfuryl	82	44
7	$Me(CH_2)_7$	80	20

six-membered ring chairlike transition state. Significantly, (*Z*)-crotyltrichlorosilane exhibited a higher rate of allylation and diastereoselectivity compared to the (*E*)-isomer for QUINOX (**54**), with the (*Z*)-isomer leading to the syn product and the (*E*)-isomer leading to the anti one (Table 22, entries 3 and 4). With PINDOX (**55**), (*E*)-crotyltrichlorosilane in CH_2Cl_2 produced mainly the anti-isomer (Table 22, entry 5). Changing the solvent to acetonitrile for *i*-Pr_2-iso-PINDOX (**56**) and (*E*)-crotyltrichlorosilane resulted in considerable improvement of the conversion rate and diastereoselectivity, producing also the practically enantiopure anti-isomer (Table 22, entry 6). The (*Z*)-crotyl derivative reacted much more slowly than its trans-isomer even in acetonitrile and afforded mainly the corresponding syn-isomer (Table 22, entry 7).

In addition to monoxide and dioxides, chiral terpyridine *N,N′,N″*-trioxides derived from terpenes were also used as promoters for the enantioselective allylation of aldehydes with allyltrichlorosilane.

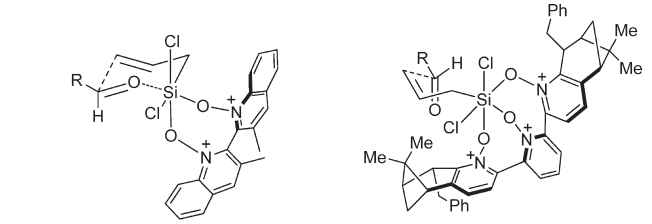
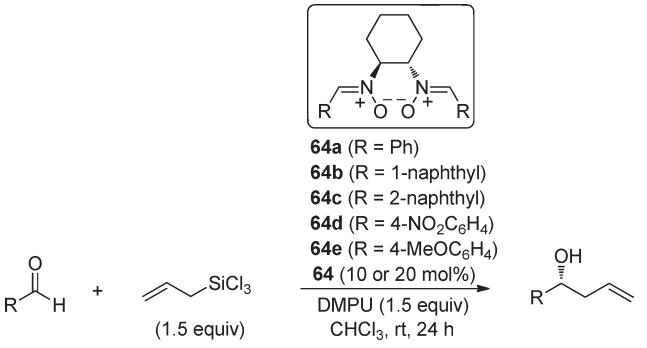


Figure 5. Proposed transition states for allylation with planar quinoline *N,N′*-dioxides and tri-*N*-oxide **63**.

Table 24. Allylation of Aldehydes with Allyltrichlorosilane Catalyzed by Dinitrones 64



entry	chiral dinitrone	R	yield (%)	ee (%)
1[a]	**64a**	Ph	46	45
2[a]	**64b**	Ph	62	35
3[a]	**64c**	Ph	57	60
4[a]	**64d**	Ph	27	0
5[a]	**64e**	Ph	67	71
6[b]	**64e**	Ph	78	73
7[b]	**64e**	$PhCH_2CH_2$	42	8
8[b]	**64e**	4-BrC_6H_4	84	74
9[b]	**64e**	4-$NO_2C_6H_4$	93	64
10[b]	**64e**	4-$MeOC_6H_4$	68	63
11[b]	**64e**	3,4,5-$(MeO)_3C_6H_2$	82	87

[a] Reaction run in the presence of 10 mol % of **64**. [b] Reaction run in the presence of 20 mol % of **64**.

Kwong and co-workers found the compound **63** to be the most effective one considering both yield and enantioselectivity. Optimal results were obtained working in a mixture of DIPEA and CH_2Cl_2 at 0 °C in the presence of 10 mol % of catalyst **63** (Table 23).[65] An electron-donating group at the para-position of benzaldehyde exhibited a negative impact on the enantioselectivity (Table 23, entry 2), whereas the substrate bearing an electron-withdrawing group at the para-position remarkably improved the enantioselectivity to 86% ee with 91% isolated yield (Table 23, entry 3). Again, the aliphatic aldehyde nonanal led to the lowest value of ee (Table 23, entry 7).

In the former case, the cyclic 6-membered chairlike structure, which could be generated via the coordination between the quinoline *N,N′*-dioxide-type ligands and allyltrichlorosilane,[42] may not be favorable for the highly sterically demanding tri-*N*-oxide ligands. Instead of that, Kwong and co-workers suggested

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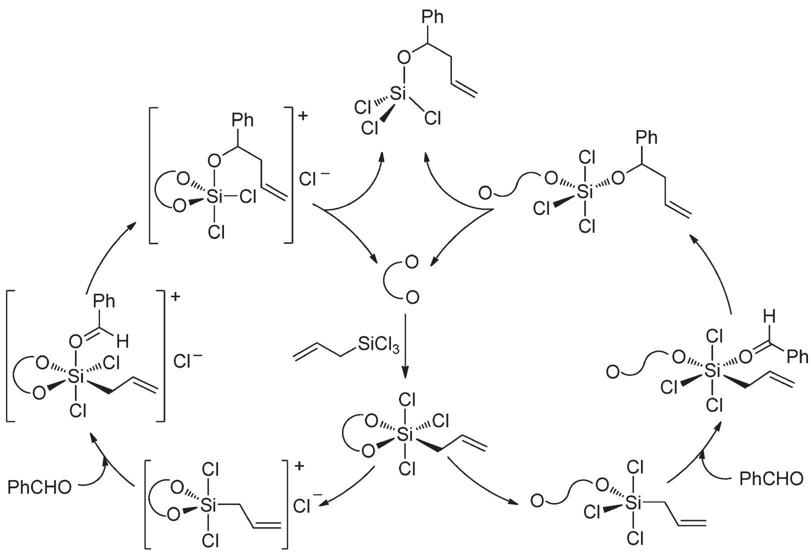
Scheme 11



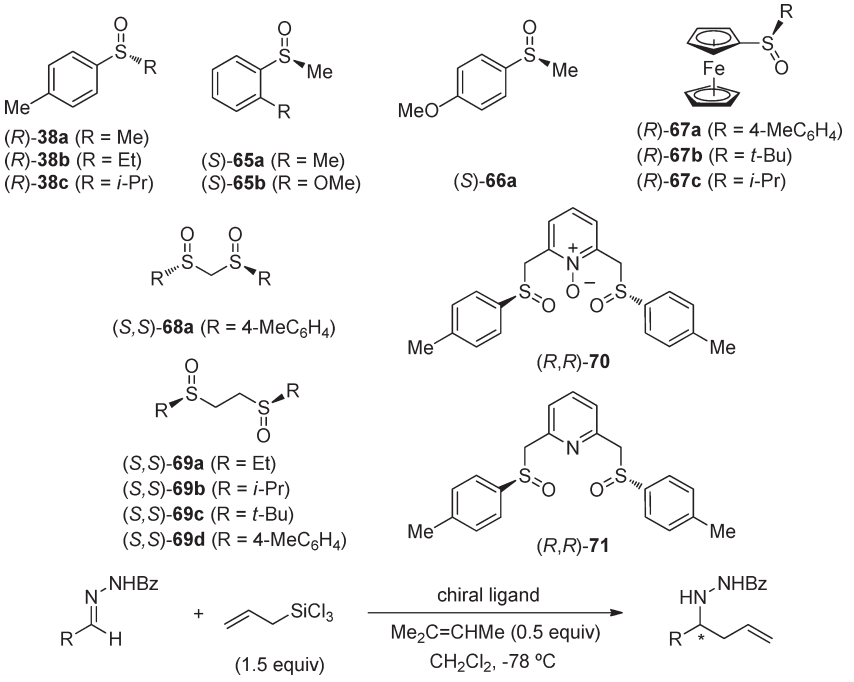
that the reactions could proceed through an acyclic transition state with the tri-*N*-oxide **63** acting as tridentate ligand (Figure 5).[65]

Chiral dinitrones **64** were also tested as base catalysts in the enantioselective allylation of aldehydes with allyltrichlorosilanes. Good yields and stereoselectivities were obtained using DMPU as an additive, in chloroform as solvent at room temperature in the presence of 10 mol % of the catalyst. Sugiura, Nakajima, and co-workers found that compound **64e**, derived from *para*-methoxybenzaldehyde, gave the highest yield and enantioselectivity (Table 24, entry 5 vs entries 1−4).[66] Using **64e**, the yield and the enantioselectivity were improved upon increasing the catalyst loading to 20 mol % (Table 24, entry 6). Under these reaction conditions, a modest yield and very low enantioselectivity was obtained with the aliphatic aldehyde 3-phenylpropanal (Table 24, entry 7). However, benzaldehyde derivatives having electron-withdrawing groups increased the yield but tended to decrease the selectivity (Table 24, entries 8 and 9), and 3,4,5-trimethoxybenzaldehyde provided the highest enantioselectivity among the aldehydes tested (Table 24, entry 11). This methodology was applied to the crotylation of benzaldehyde with (*E*)- and (*Z*)-trichlorocrotylsilanes to produce anti and syn homoallylic alcohols, respectively, with moderate yields and enantioselectivities.

On the basis of experimental as well as theoretical calculations, Kotora and co-workers reported that the allylation of aldehydes catalyzed by bipyridine *N,N*′-dioxides proceeded by two different reaction mechanisms depending on the solvent used. Thus, in polar electrophilic solvents the mechanism proceeded via ionic intermediates; meanwhile, neutral intermediates are involved in less polar and less electrophilic solvents (Scheme 11).[67] The B3LYP model for reaction energy calculations indicated that, in the case of electrophilic solvents, such as acetonitrile and dichloromethane, the energy gained upon formation of the complex between a bipyridine *N,N*′-dioxide and silicon tetrachloride is larger than the energy required for its subsequent dissociation. However, for less electrophilic solvents, such as chlorobenzene and ethyl acetate, the energy gained from the formation of the complex is not sufficient for its subsequent dissociation. The computational study clearly showed that the reactants are ionic in polar solvents, whereas they stay nondissociated in less polar solvents, which was experimentally demonstrated by the measured conductivities of the reaction mixtures.

2.2.2. Allylation of Imines and Imine Derivatives. As previously commented, among nitrogenated compounds with C═N bonds, hydrazones have been the most extensively studied as substrates in nucleophilic additions because they can be easily formed, purified, and handled. In addition, *N*-benzoylhydrazones are of special interest because of the possibility of performing as a bidentate substrate through coordination with both the oxygen and the nitrogen. In this scenario, Kobayashi et al. found that chiral aryl alkyl sulfoxides were effective in the enantioselective allylation of the *N*-benzoylhydrazone derived from 3-phenylpropanal with allyltrichlorosilane.[68] The best result, regarding stereoselectivity, was obtained when 3 equiv of (*R*)-methyl *para*-tolyl sulfoxide [(*R*)-**38a**] were used (Table 25, entry 1). Addition of 2-methyl-2-butene, an acid scavenger, was also found to be key to suppress undesired racemization of (*R*)-**38a**. After the usual workup, (*R*)-**38a** could be recovered in >90% with >97% ee. For chiral sulfoxides **38b**,**c**, the bulkier alkyl group, the lower enantioselectivity was obtained (Table 25, entries 2 and 3). The enantioselectivity also decreased with aryl 2-substituted sulfoxides **65** (Table 25, entries 4 and 5), probably due to the steric hindrance; meanwhile, the sulfoxide (*S*)-**66a** with an electron-donating *para*-methoxyphenyl group increased the yield (Table 25, entry 6). Fernández and Khiar studied the allylation of a *N*-benzoylhydrazone derived from isobutyraldehyde with allyl trichlorosilane using as promoters different chiral monosulfoxides **38a**[69] and **67**,[70] methylene-bridged C_2-symmetric bissulfoxide (*S,S*)-**68a**,[69] and ethylene-bridged C_2-symmetric bissulfoxides **69**.[69] They found that the concentration of the ligand was important in order to achieve high stereoselectivity, as was already observed by Kobayashi et al.,[68] with the best result for (*R*)-**38a** being obtained in a 0.46 M solution in CH_2Cl_2, and any change in this concentration led to a drop of the enantioselectivity (Table 25, entry 7). Chiral alkylsulfinylferrocenes **67** were also good ligands for the allylation of hydrazones, and the highest chemical reactivity and better enantiomeric discrimination were obtained with the isopropylsulfinyl derivative (*S*)-**67c** (Table 25, entries 8−10). Low yield (30%) and stereoselectivity (30% ee) were obtained when the methylene-bridged

Table 25. Allylation of *N*-Benzoylhydrazones with Allyltrichlorosilane Catalyzed by Chiral Aryl Alkyl Sulfoxides and Bissulfoxides



entry	R	chiral ligand (equiv)	*t* (h)	yield (%)	ee (%)
1	$PhCH_2CH_2$	(*R*)-**38a** (3)	1	73	93 (*R*)
2	$PhCH_2CH_2$	(*R*)-**38b** (3)	1	77	50 (*R*)
3	$PhCH_2CH_2$	(*R*)-**38c** (3)	1	74	1 (*S*)
4	$PhCH_2CH_2$	(*S*)-**65a** (3)	1	75	30 (*S*)
5	$PhCH_2CH_2$	(*S*)-**65b** (3)	1	79	42 (*S*)
6	$PhCH_2CH_2$	(*S*)-**66a** (3)	1	91	69 (*S*)
7	*i*-Pr	(*R*)-**38a** (3)	0.5	95	92 (*R*)
8	*i*-Pr	(*R*)-**67a** (3)	1.5	>95	4 (*R*)
9	*i*-Pr	(*R*)-**67b** (3)	1	72	26 (*R*)
10	*i*-Pr	(*R*)-**67c** (3)	1	>95	82 (*S*)
11	*i*-Pr	(*S,S*)-**68a** (3)	18	30	30 (*R*)
12	*i*-Pr	(*S,S*)-**69a** (1)	6	76	80 (*R*)
13	*i*-Pr	(*S,S*)-**69b** (1.5)	0.25	81	30 (*R*)
14	*i*-Pr	(*S,S*)-**69c** (1.5)	0.25	26	0
15	*i*-Pr	(*S,S*)-**69d** (1.5)	0.25	81	82 (*R*)
16	Ph	(*R,R*)-**70** (1.5)	1	89	76 (*R*)
17	Ph	(*R,R*)-**71** (1.5)	1	73	58 (*S*)

bissulfoxide (*S,S*)-**68a** was used (Table 25, entry 11). On the other hand, the use of enantiomerically pure ethylene-bridged bissulfoxide (*R,R*)-**69d** afforded the allylated product in excellent yield and enantioselectivity (Table 25, entry 15). It seems that the enantioselectivity of the process is highly dependent on the spacer between the two sulfur atoms and the concentration of the reaction medium. Fernández, Khiar, and co-workers proposed that the allylation reaction in the presence of these sulfoxides could proceed through two operating pathways. The first one will be highly enantioselective and two sulfoxide molecules will be bonded to the chlorosilane, and on the contrary, in the other less selective pathway, only one sulfoxide unit will be involved in the transition state. The allylation of *N*-benzoyl hydrazones in the presence of the C_2-symmetric bissulfoxide/*N*-oxide (*R,R*)-**70** and the bissulfoxide (*R,R*)-**71** under Kobayashi's protocol was also studied by Juaristi and co-workers.[71] In general, the *N*-oxide derivative (*R,R*)-**70** showed to be quite superior to the bissulfoxide (*R,R*)-**71** under these reaction conditions, considering chemical yields and stereoselectivities (Table 25, entries 16 and 17). Surprisingly, the allylation of the hydrazone resulting from acetophenone proceeded with a higher enantiomeric ratio in the case of bissulfoxide (*R,R*)-**71**, albeit with poor chemical yield. Compounds **70** and **71** may be recovered in 72−87% yields after purification by column chromatography.

Kobayashi et al. found also that the asymmetric allylation of different aliphatic and aromatic *N*-acylhydrazones using (*R*)-**38a** proceeded with high enantioselectivity in all cases (Table 26, entries 1−5), as well as the crotylation with (*Z*)- and (*E*)-crotyltrichlorosilanes (Table 26, entries 6−11). Importantly,

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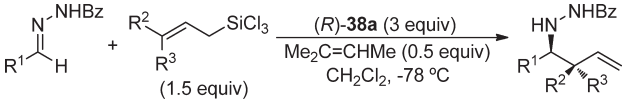
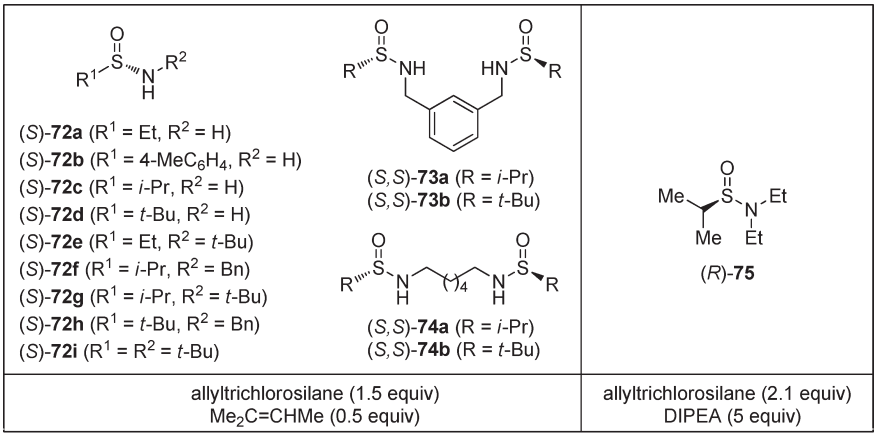
Table 26. Allylation of *N*-Benzoylhydrazones with Allyltrichlorosilanes Catalyzed by (*R*)-38a

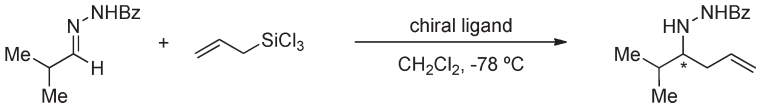


entry	R^1	R^2	R^3	*t* (h)	yield (%)	ee (%)[a] (syn/anti)
1	Me	H	H	17	78	90
2	$CH_3(CH_2)_6$	H	H	1	81	88
3	*i*-Pr	H	H	1	80	98
4	4-$MeOC_6H_4$	H	H	18	82	81
5	PhC≡C	H	H	8	95	70
6	$PhCH_2CH_2$	H	Me	4	60	91 (<1/>99)
7	$PhCH_2CH_2$	Me	H	4	58	89 (99/1)
8	Me	H	Me	17	99	73 (<1/>99)
9	Me	Me	H	17	99	82 (98/2)
10	$CH_3(CH_2)_6$	H	Me	3	83	86 (<1/>99)
11	$CH_3(CH_2)_6$	Me	H	3	82	91 (95/5)

[a] The ee of the major diastereomer is given.

Table 27. Allylation of *N*-Benzoylhydrazones with Allyltrichlorosilane Catalyzed by Chiral Sulfinamides and Bissulfinamides





entry	chiral ligand (equiv)	*t* (h)	yield (%)	ee (%)
1	(*S*)-**72a** (3)	0.5	50	7 (*S*)
2	(*S*)-**72b** (3)	0.5	60	74 (*S*)
3	(*S*)-**72c** (3)	0.6	80	56 (*S*)
4	(*S*)-**72d** (3)	0.7	100	82 (*S*)
5	(*S*)-**72e** (3)	0.5	73	30 (*S*)
6	(*S*)-**72f** (3)	1	76	72 (*S*)
7	(*S*)-**72g** (3)	1.5	92	70 (*S*)
8	(*R*)-**72h** (3)	0.5	90	80 (*R*)
9	(*R*)-**72i** (3)	24	84	84 (*R*)
10	(*S,S*)-**73a** (1)	72	67	46 (*S*)
11	(*S,S*)-**73b** (1)	36	49	74 (*S*)
12	(*S,S*)-**74a** (1)	1	50	50 (*S*)
13	(*R,R*)-**74b** (1)	72	70	90 (*R*)
14	(*R*)-**75** (3)	18	90	8 (*S*)

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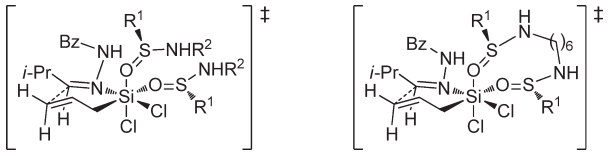


Figure 6. Possible dicoordinate transition states for the organocatalytic allylation of hydrazones with sulfinamides.

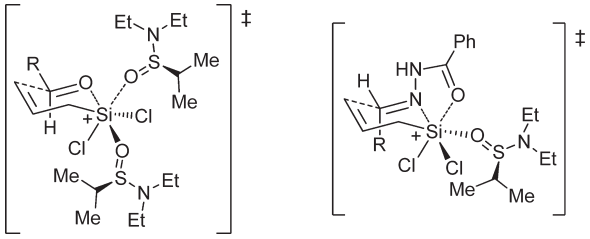


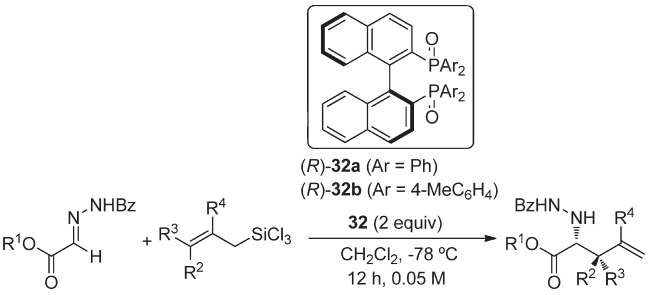
Figure 7. Possible transition states for the organocatalytic allylation of aldehydes and hydrazones with sulfinamide **75**.

the reaction of hydrazones proceeded well at a higher concentration exhibiting high stereospecificity for the crotylation reactions. Thus, (*E*)-crotyltrichlorosilane afforded syn-adducts, while anti-adducts were obtained from the (*Z*)-isomer.[68]

Monosulfinamides **72** and C_2-symmetric bissulfinamides **73** and **74** were also evaluated by Fernández, Khiar, and co-workers as activators in the allylation of acyl hydrazones,[72] with optimal results being obtained using 3 equiv of monosulfinamides **72**. Thus, simple sulfinamides **72a**−**d** were able to promote the reaction affording the corresponding allylated product in moderate to high chemical yields (Table 27, entries 1−4). The size of the alkyl group determined the enantioselectivity: the bulkier the alkyl group, the higher was the enantioselectivity. The same behavior is maintained in the case of *N*-substituted sulfinamides **72e**−**i** (Table 27, entries 5−9), where sterically hindered sulfinamides **72h** and **72i** afforded the best enantioselectivities (Table 27, entries 8 and 9). Regarding the bissulfinamides **73** and **74**, the allylated product was obtained in moderate to good yields using only 1 equiv of ligand (Table 27, entries 12−16), in contrast to monosulfinamides **72** where 3 equiv were necessary. Again, bulkier ligands produced higher enantioselectivities for bissulfinamides **73** with an aromatic spacer, and those with the aliphatic one **74**, the more flexible ligands (bissulfinamides **74** with the aliphatic spacer), gave better results than the aromatic analogues (Table 27, entry 11 vs 13). Rowlands and co-workers investigated also the use of bissulfoxides and sulfinamides as promoters in the allylation of benzaldehyde and *N*-benzoylhydrazones with allyltrichlorosilane.[73] Among the collection of chiral ligands, (*R*)-**75** was found to be the most efficient in the allylation of benzaldehyde [the homoallylic alcohol was obtained in 99% yield and 50% ee (*S*)] and a range of benzoylhydrazones. Although chemical yields were high, enantioselectivities were extremely poor in the case of hydrazones derived from *para*-nitrobenzaldehyde and isobutyraldehyde (Table 27, entry 14). Importantly, the sulfinamide could be recovered in ∼90% yield in all these reactions.

On the basis of the experimental results (the enantioselectivity decreased when the catalyst loading was reduced) and on the observed negative nonlinear effect, Fenández, Khiar, and co-workers proposed that a dicoordinate transition state should be involved in the organocatalytic allylation of hydrazones with neutral sulfinamides. A dicoordinated intermediate could be

Table 28. Allylation of α-Hydrazone Esters with Allyltrichlorosilanes Catalyzed by Phosphane Oxides (*R*)-32



entry	R^1	R^2	R^3	R^4	phosphane oxide	yield (%)	syn/anti	ee (%)
1	Et	H	H	H	(*R*)-**32a**	91		98 (*R*)
2	*i*-Pr	H	H	H	(*R*)-**32a**	70		97
3	Cy	H	H	H	(*R*)-**32a**	28		98
4	Bn	H	H	H	(*R*)-**32a**	12		91
5	Et	H	Me	H	(*R*)-**32a**	92	98/2	>99 (2*R*,3*S*)
6	Et	Me	H	H	(*R*)-**32a**	96	<1/>99	96 (2*R*,3*R*)
7	Et	H	Me	Me	(*R*)-**32b**	80	98/2	96 (2*S*,3*R*)
8	Et	Me	H	Me	(*R*)-**32b**	80	<1/>99	81 (2*S*,3*S*)
9[a]	Et	H	H	Me	(*R*)-**32a**	83		94 (*R*)
10	Et	H	H	Ph	(*R*)-**32b**	50		95

[a] Reaction time was 6 h.

formed intramolecularly more easily in the case of bissulfinamides **74** with the aliphatic spacer (Figure 6).[72]

Comparing aldehydes and hydrazones, Rowlands and co-workers found that the reactions of hydrazones occurred faster and gave higher yields and enantioselectivities. In addition, allylations performed by the same promoter **75** gave the opposite configuration in the homoallylic alcohol and the homoallylic hydrazide. To explain these differences, two transition states were proposed. Aldehydes presumably reacted via a chairlike transition state in which the substituent of the aldehyde adopted the pseudoequatorial position (Figure 7). On the contrary, the substituent of the benzoylhydrazone (potentially bidentate substrates with both the benzoyl carbonyl and the imine-like nitrogen able to coordinate to the silicon) adopted a pseudoaxial position, leading to the opposite configuration in the newly created stereogenic center (Figure 7).[73]

Kobayashi and co-workers studied the allylation of α-hydrazono esters with allyltrichlorosilanes using in this case chiral BINAP dioxides **32** as the source of chirality. The presence of 2 equiv of dioxides **32** (smaller amounts gave lower yields and enantioselectivities) at low concentration (0.05 M) led to the formation of the corresponding homoallylic α-amino esters with high yields and enantio- and diastereoselectivities (Table 28).[74] A drawback of this reaction is the use of 2 equiv of chiral dioxides **32**; however, they could be recovered after the reaction almost in quantitative yields without loss of optical purity. Concerning the ester group, larger substituents gave lower yields (Table 28, entries 1−4). The reactions proceeded stereospecifically in high yields: (*E*)-crotyltrichlorosilane gave the syn adduct, whereas (*Z*)-crotyltrichlorosilane led to the anti diastereomer (Table 28, entries 5 and 6, respectively). Regarding the BINAP dioxide derivatives, better results were obtained in general with (*R*)-**32a** than with the *para*-tolyl derivative (*R*)-**32b**. High yields and enantioselectivities were also observed with other allylating reagents (Table 28, entries 7−10).

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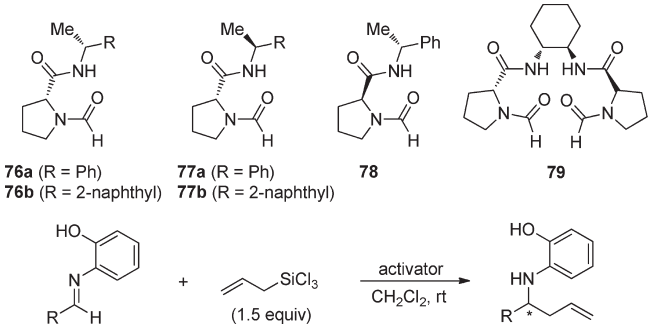
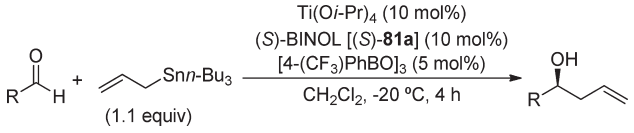
Table 29. Allylation of Aldimines with Allyltrichlorosilane Catalyzed by *N*-Proline Derivatives 76−80



entry	R	activator (equiv)	*t* (h)	conc. (M)	additive (equiv)	yield (%)	ee (%)
1	4-MeOC$_6$H$_4$	**76b** (0.2)	55	0.5		15	37 (*S*)
2	4-MeOC$_6$H$_4$	**76b** (1)	72	0.5		45	40 (*S*)
3	4-MeOC$_6$H$_4$	**77b** (1)	72	0.5		42	48 (*S*)
4	4-MeOC$_6$H$_4$	**76a** (1)	72	0.5		48	47 (*S*)
5	4-MeOC$_6$H$_4$	**77a** (1)	72	0.5		50	57 (*S*)
6	4-MeOC$_6$H$_4$	**78** (1)	72	0.5		52	54 (*R*)
7	4-NO$_2$C$_6$H$_4$	**77a** (1)	72	0.05		60	28 (*S*)
8	4-NO$_2$C$_6$H$_4$	**77a** (1)	72	0.5		54	42 (*S*)
9	4-NO$_2$C$_6$H$_4$	**77a** (1)	72	1		43	50 (*S*)
11	4-NO$_2$C$_6$H$_4$	**79** (2)	48	0.5		93	54 (*S*)
12	4-NO$_2$C$_6$H$_4$	**79** (2)	4	0.5	L-proline (2)	94	83 (*S*)
13	4-BrC$_6$H$_4$	**79** (2)	4	0.5	L-proline (2)	84	79 (*S*)
14	2-naphthyl	**79** (2)	4	0.5	L-proline (2)	91	71 (*S*)
15	4-NO$_2$C$_6$H$_4$	**77a** (2)	72	1	L-proline (2)	84	43 (*S*)

Table 30. Boroxin−Ti-(*S*)-BINOL-Catalyzed Allylation of Aldehydes



entry	R	*t* (h)	yield (%)	ee (%)
1	PhCH$_2$CH$_2$	4	93	94
2	(*E*)-PhCH=CH	8	83	88
3	Cy	8	87	92
4	2-furyl	3	95	97

Instead of using hydrazones, Tsogoeva and co-workers studied the stereoselective addition of allyltrichlorosilane to aldimines derived from aromatic aldehydes and 2-aminophenol in the presence of different chiral *N*-formylproline compounds **76**−**79** (Table 29).[75] In the case of the imine derived from *para*-methoxybenzaldehyde, the use of a stoichiometric amount of formamide **76b** led to a higher yield than with 20 mol % of the ligand, with the enantioselectivity being almost the same in both cases (Table 29, entries 1 and 2). Moderate yields and enantioselectivities were observed with chiral formamides **76a**−**78** under the same reaction conditions (Table 29, entries 3−6). Interestingly, the absolute configuration of the created stereogenic center depends only on the configuration of the proline moiety: (*S*)-proline derivatives (**76** and **77**), independently of the configuration of the arylethyl moiety, led to (*S*)-products and (*R*)-proline derivative **78** gave the (*R*)-enantiomer. In the reaction of the imine derived from *para*-nitrobenzaldehyde in the presence of chiral formamide **77a** (the best activator considering both yield and enantioselectivity, Table 29, entry 5), higher levels of asymmetric induction were observed at higher substrate concentrations; meanwhile, the yields decreased when the concentration was increased (Table 29, entries 7−9). The reaction rate and the enantioselectivity were significantly improved by combination of the chiral bisformamide activator **79** with an L-proline additive in the reaction with different aldimines (Table 29, entries 11−14).[76] However, with 2 equiv of monoformamide **77a**, although the yield improved to 84% also in the presence of 2 equiv of L-proline as an additive, no improvement in the enantioselectivity was observed (Table 29, entry 9 vs 15).

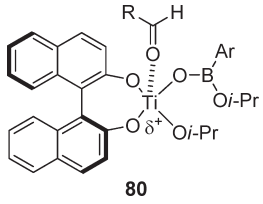


Figure 8. Plausible activation mode of the boroxin−Ti-(*S*)-BINOL-catalyst.

3. ENANTIOSELECTIVE ADDITION OF ALLYLIC STANNANES

3.1. Acid-Catalyzed Allylation Reactions

3.1.1. Group IV (Titanium and Zirconium) Catalysts. Although Ti-BINOL catalyst and allyl-*n*-tributyltin is one of the

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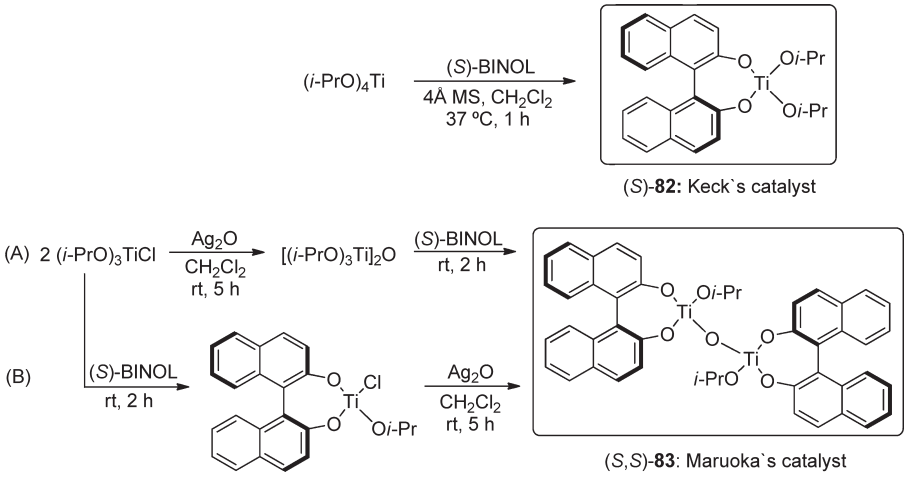
Scheme 12. Preparation of BINOL-Modified Mono-Ti(IV) Catalyst (*S*)-82 and Bis-Ti(IV) Oxide Catalyst (*S,S*)-83



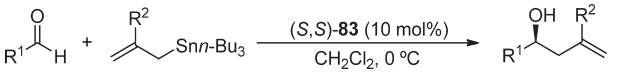
best combinations to generate chiral homoallylic alcohols (the so-called Keck's allylation),[77] there still remain several problems to be solved: catalyst loading, reaction time, reproducible results, and others. In this context, an interesting mode to activate the Ti-BINOL catalyst is the use of an additional Lewis acid [Lewis acid assisted chiral Lewis acid catalysts (LLA)]. H. Yamamoto and co-workers have found a system made up Ti-BINOL and 4-(trifluoromethyl)phenylboroxin that efficiently catalyzed the allylation of a variety of aldehydes in high yield and high asymmetric induction (Table 30).[78]

The exact activation mechanism of this LLA system has not been clarified yet. A plausible interpretation is the formation of a hetero multimetallic complex **80** having a B−O−Ti bond shown in Figure 8. Thus, Lewis acidity of the boron atom would enhance the Lewis acidity of the titanium atom.

Inspired by the strong Lewis acid character of bis(dimethylaluminum) oxide, Maruoka has recently designed a new binaphthoxyl-modified bis-Ti(IV) oxide (L*−Ti−O−Ti−L*) for the enantioselective activation of carbonyl compounds. The chiral catalyst (*S,S*)-**83** can be readily prepared from triisopropoxytitanium chloride, instead of the tetraisopropoxytitanium used for the preparation of Keck's catalyst (*S*)-**82**, either by treatment with Ag_2O followed by (*S*)-BINOL [(*S*)-**81a**], or using the reverse order, as shown in Scheme 12. A positive ESI-MS of the isolated complex (*S,S*)-**83** showed an *m/z* peak at 943 (M·2THF + H^+), which is in accordance with the mono-μ-oxo Ti−O−Ti structure proposed for the catalyst.

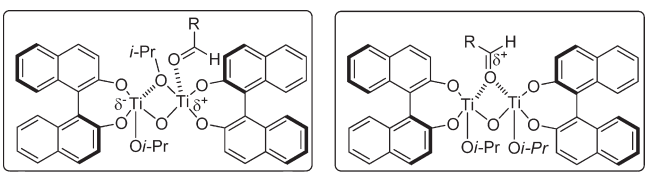
The reactivity and asymmetric induction of the catalyst were tested in the asymmetric allylation of aldehydes with allylic *n*-tributyltin species (Table 31).[79,80] Using 10 mol % of the chiral bis-Ti(IV) oxide (*S,S*)-**82** in CH_2Cl_2 at 0 °C, high asymmetric induction (up to 99% ee) as well as high chemical yields were obtained for a reasonable range of aliphatic and aromatic aldehydes. Notably, the enantioselectivity of this reaction does not change significantly with the temperature, and this catalytic system proved to be more reactive than the corresponding mono-(*S*)-**82**. Closely related, asymmetric methallylation and propargylation of aldehydes were also successfully accomplished with high enantioselectivity using this system. Interestingly, a positive nonlinear effect (chirality amplification) was observed when the catalyst [(*S,S*)-**83**] was prepared from partially resolved (*S*)-BINOL. The latter result was mainly ascribed to a greater

Table 31. Allylation and Methallylation of Aldehydes with Allyl-*n*-tributyltin Catalyzed by the Chiral Bis-Ti(IV) Oxide (*S,S*)-83



entry	R^1	R^2	*t* (h)	yield (%)	ee (%)
1	$Ph(CH_2)_2$	H	4	84	99 (*R*)
2	$Me(CH_2)_6$	H	12	85	99 (*R*)
3	*i*-Pr	H	28	71	>99 (*S*)
4	(*E*)-PhCH=CH	H	15	70	95 (*S*)
5	Ph	H	7	90	96 (*S*)
6	4-BrC_6H_4	H	15	85	98 (*S*)
7	2-furyl	H	18	96	97 (*S*)
8	$Ph(CH_2)_2$	Me	0.5	90	94 (*R*)
9	$Me(CH_2)_6$	Me	20	87	92
10	(*E*)-PhCH=CH	Me	2	63	94 (*S*)
11	Ph	Me	0.5	94	95 (*S*)
12	2-furyl	Me	2	88	91 (*S*)

reactivity of symmetric (*S,S*)-**83** and (*R,R*)-**83** compared to *meso*-(*S,R*)-**83** catalyst. The authors suggested that intramolecular coordination of one isopropoxy oxygen of the catalyst (*S,S*)-**83** to the other titanium should enhance the otherwise weak Lewis acidity of the original titanium(IV) center for the carbonyl activation, as shown in **84**. Alternatively, they proposed that a carbonyl oxygen atom can coordinate simultaneously to two Ti centers, thereby producing strong activation of the aldehyde carbonyl group, such as is depicted in **85**.



84 **85**

Despite the success in the allylation of aldehydes, the search for Ti-based catalysts that exhibit high levels of enantioselectivity in the allylation of ketones, however, remained challenging for almost a decade. By investigating the structure of the (BINOLate)Ti(O*i*-Pr)$_2$

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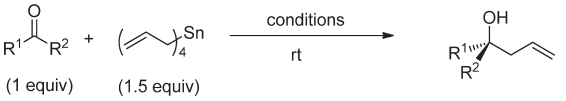
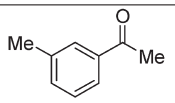
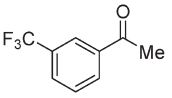
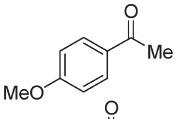
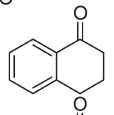
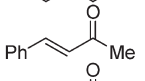
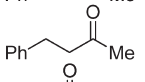
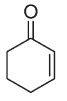
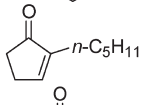
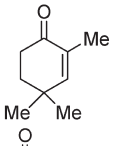
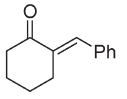
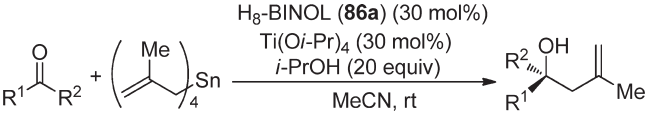
Table 32. Allylation of Ketones Catalyzed by Ti(O*i*-Pr)$_4$/BINOL (81a)



entry	R^1COR^2	BINOL (**81a**) (20-30 mol%) Ti(O*i*-Pr)$_4$ (20-30 mol%) *i*-PrOH (20 equiv), CH_2Cl_2 yield (%)	ee (%)	BINOL (**81a**) (10 mol%) Ti(O*i*-Pr)$_4$ (20 mol%) *i*-PrOH (3 equiv) yield (%)	ee (%)
1		82	96	93	95
2		93	92	87	89
3		99	89	99	88
4		96	95	99	87
5		99	90	--	--
6		96	80	--	--
7		75	11	--	--
8		92	94	85	90
9		84	96	80	91
10		99	96	96	91

introduced by Tagliavini and co-workers[81] for the catalytic asymmetric allylation of ketones with tetrallyltin, a key discovery was made by the group of Walsh.[82] It was found that, when the catalyst was prepared in situ from a 1:1 mixture of titanium tetraisopropoxide and BINOL without removal of the liberated 2-propanol, the enantioselectivity in the allylation of 3-methylacetophenone rose from 51% to 73%. The beneficial effect of 2-propanol was optimum when 20 equiv were used, resulting in 96% ee for the model reaction. This result indicates that the affinity of the BINOL for the titanium is high enough to compete efficiently with a large excess of 2-propanol. With this simple procedure in hand, a variety of ketones were examined (Table 32). The allylation of aryl alkyl ketones proceeded with high enantioselectivity (84−96% ee), whereas conjugated enones gave exclusively 1,2-allylation products in high yields and enantioselectivities. Importantly, the enantioselective allylation of cyclic conjugated enones (entries 7−10) was also evaluated for the first time. In contrast to 2-cyclohexenone, which gave rather poor enantioselection (11% ee) under the catalytic conditions, 2-substituted cyclic

Table 33. Methallylation of Ketones Catalyzed by a H_8-BINOLate-Ti Complex



entry	R^1	R^2	yield (%)	ee (%)
1	Ph	Me	78	75
2	3-$MeOC_6H_4$	Me	99	72
3	3-$CF_3C_6H_4$	Me	95	67
4	2-naphthyl	Me	95	90
5	(*E*)-PhCH=CH	Me	93	72
6	1-tetralone		85	84
7	1-indanone		81	46

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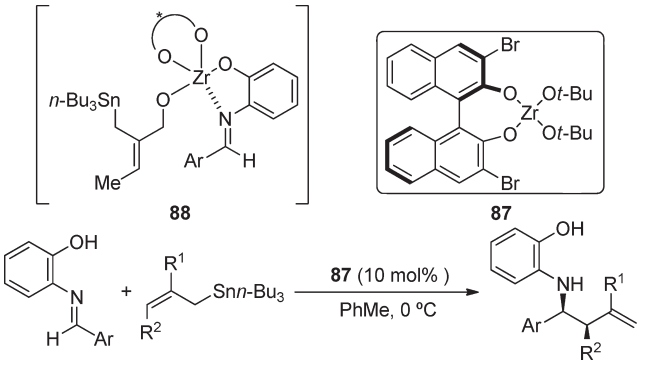
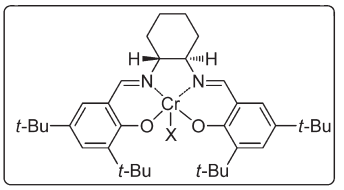
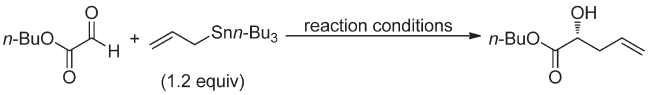
Table 34. Allylation of Imines with Allylstannanes Catalyzed by the Zirconium Complex 87



entry	Ar	R^1	R^2	yield (%)	ee (%)
1	Ph	Me	H	74	55
2	Ph	CH_2OTBS	H	74	54
3	Ph	CH_2OH	H	86	83
4	1-naphthyl	CH_2OH	H	91	68
5	Ph	CH_2OH	Me	84	93
6	1-naphthyl	CH_2OH	Me	81	95
7	3,4-$(OCH_2O)C_6H_3$	CH_2OH	Me	72	91
8	2,3-$(MeO)_2C_6H_3$	CH_2OH	Me	71	94
9	2-furyl	CH_2OH	Me	76	92
10	4-Cl C_6H_4	CH_2OH	Me	78	87

Table 35. Enantioselective Reaction of *n*-Butyl Glyoxylate with Allyltri-*n*-butyltin Catalyzed by Chromium(III) Complexes 89a−c





	reaction conditions					
entry	catalyst (mol %)	solvent	T (°C)	t (h)	yield (%)	ee (%)
1	**89a** (2)	CH_2Cl_2	20	3	82	61
2	**89a** (2) + 4 Å MS	CH_2Cl_2	20	1	82	62
3	**89a** (5)	CH_2Cl_2	20	1	80	61
4	**89a** (5)	CH_2Cl_2	−78 to −20	24	76	36
5	**89a** (2)	CH_2Cl_2	40	0.25	77	58
6	**89a** (2)	$MeNO_2$	20	3	79	70
7	**89a** (0.2)	$MeNO_2$	20	24	61	62
8	**89a** (2)	no solvent	5−29	5	90	65
9	**89b** (2)	CH_2Cl_2	20	3	73	54
10	**89c** (2)	CH_2Cl_2	20	3	90	65

enones exhibited high levels of enantioselectivity. Continuing their work, the group of Walsh reported a modified procedure for the Ti-BINOLate catalyzed allylation of ketones with tetrallylstannane. They have found that, when the catalyst is generated from titanium tetraisopropoxide and BINOL in a 1:2 ratio, the reaction can be conducted under highly concentrated reaction conditions in the presence of only 3 equiv of 2-propanol.[83] The results listed in Table 32 demonstrate a similar degree of enantioselection and comparable isolated yields for both catalytic systems examined for a range of representative substrates. It is noteworthy that the highly concentrated reaction conditions allow for a significant reduction in titanium and BINOL loading, as well as an important decrease in the reaction volume. Because of the tendency of group (IV) alkoxide-based catalysts to oligomerize, detailed mechanistic studies of their reactions are very difficult and the exact role of 2-propanol in this reaction remains elusive at this time. Moreover, the authors developed an attractive chemo- and diasteroselective tandem allylation−epoxidation for some cyclic conjugated enones. After the ketone allylation was conducted in any of the two reaction conditions reported, 1 equiv of anhydrous *tert*-butyl hydroperoxide (TBHP) was added at room temperature, producing a selective epoxidation of the allylic double bond. The representative substrates examined exhibited good yields for this tandem reaction (72−89%), and only a single diastereomer was detected in each case by NMR and GC analysis.

The group of Walsh applied their BINOLate-Ti-based catalyst to study the first enantioselective catalytic methallylation of ketones with tetramethallylstannane.[84] They have observed a significant 25% increase in enantioselectivity of the methallylation reaction when BINOL (**81a**) was substituted for H_8-BINOL (**86a**). On the basis of precedents for other reactions that made use of BINOL-type ligands in the catalyst, they speculate that the bigger O−Ti−O bite angle (~2°) of H_8-BINOL may account for its enhanced performance. The results of the methallylation of a range of ketones in acetonitrile, using 20 equiv of 2-propanol as additive, at room temperature are summarized in Table 33. Aryl methyl ketones were generally good substrates with enantioselectivities up to 90% ee and only marginal electronic influence of the substituents. Conjugated enones were also used as substrates, obtaining the corresponding homomethallylalcohols in good yields and with moderate to good enantioselectivities (46−84% ee). Interestingly, the homomethallyl alcohol obtained from 3′-trifluoromethylacetophenone using this protocol was submitted to ozonolysis, and the corresponding tertiary β-hydroxyketone was obtained without erosion of enantioselectivity. The latter compounds are known precursors to several natural products and are currently accessible only through kinetic resolution of racemic products.

Kobayashi described a highly enantioselective allylation of imines with substituted allylstannanes in the presence of a chiral zirconium catalyst derived from (*R*)-BINOL (Table 34).[85] A key choice in this protocol is the *O*-hydroxyaryl substituent at the imine nitrogen, which facilitates coordination to the catalyst, which is formed in situ by combination of equimolar amounts of $Zr(Ot\text{-}Bu)_4$ and the corresponding BINOL ligand. Interestingly, a remarkable acceleration rate and improved enantioselectivities were observed with the stannane bearing an unprotected alcohol functionality ($R^1 = CH_2OH$, Table 34, entries 3−10). Importantly, the allylstannane with a methyl substituent at the C-3 position furnished the expected homoallylic amines with improved enantioselectivities (87−95% ee) and excellent (>95:5) syn/anti ratios (Table 34, entries 5−10). Moreover, for the less selective C-3 unsubstituted stannane, the enantioselectivities were further improved for all the aromatic imines tested when the catalyst was prepared with MeOH as an additive. The authors

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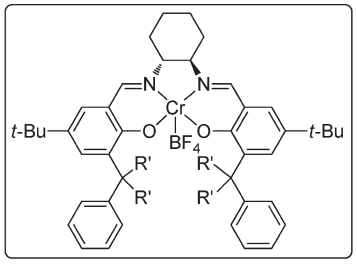
suggest that in the presence of MeOH deoligomerization of the less selective oligomeric catalyst structures might result in the formation of the desired active monomeric catalyst species. Concerning the mechanism, it is proposed that the active catalyst is generated by the bonding of the alcohol functionalities of the imine and the allylstannane to the zirconium center, so the allylstanane attacks the azomethinic carbon in an intramolecular ene-like fashion (see structure **88**).

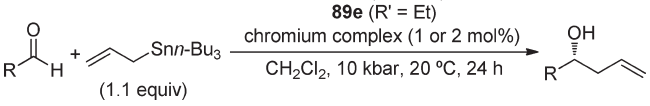
3.1.2. Chromium(III) Catalysts. The first example of enantioselective allylation where a salen−Cr(III)-complex is directly used as a Lewis acid catalyst was recently reported.[86] It was found that the addition of allylstannanes to alkyl glyoxylates proceeded smoothly in the presence of 2 mol % of classic Jacobsen's chromium salen complexes (**89**). Under the above-mentioned conditions, (2*R*)-*n*-butyl-2-hydroxypent-4-enoate was obtained in good yield and enantioselectivity (Table 35). Although the reaction is commonly performed in CH_2Cl_2 or nitromethane, it can also be conveniently conducted without solvent with a similar degree of enantioselectivity. Apart from catalysts **89a** and **89c**, which can be easily prepared from commercially available **89b**, other chiral salen complexes with different metals and ligands were examined with less success. Under these optimized conditions, different alkyl (*i*-Pr, *t*-Bu, Bn) glyoxalates were also used, obtaining similar enantioselectivities to those obtained for *n*-butyl glyoxylate.

When the catalyst **89a** was used for the allylation of furfural with allyltri-*n*-butyltin, under identical conditions to the ones used for glyoxylates, the expected product was obtained with 56% ee, but only in ~10% yield after three days. In 1983 Y. Yamamoto et al. demonstrated that the addition of allylstannanes to aldehydes, as many other reactions where the association of molecules are accompanied by a reduction in volume, is significantly accelerated at high pressure.[87] Following this pioneer work, Isaacs and co-workers determined a large negative activation volume for the addition of allylstannane to chloral, which is consistent with a six-membered cyclic transition state ("Diels-Alder like") involving tin−oxygen coordination.[88] With these precedents, Kwiatkowski and Jurczak decided to use this mode of activation and performed the enantioselective allylation of different aldehydes with allyl-*n*-tributyltin under high pressure (10 kbar) at room temperature.[89] Using this methodology, only 2 mol % of catalyst **89a** was required to afford the corresponding homoallylic alcohols in uniformly good yields and moderate to good enantioselectivities (Table 36). Encouraged by these results, the same authors prepared a new generation of chromium complexes for the high-pressure allylation of aldehydes with allyltri-*n*-butyltin.[90] The salen ligands for catalysts **89d** and **89e** were prepared from readily available precursors and afforded the

Table 36. High-Pressure Enantioselective Allylation of Aldehydes Catalyzed by Complexes 89a, 89d, and 89e

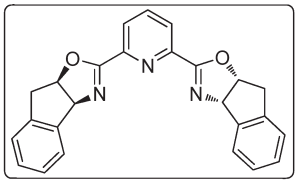


89d (R' = Me)
89e (R' = Et)

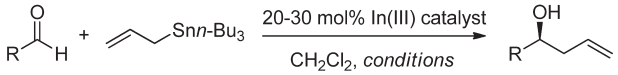


		89a (2 mol %)		**89d** (2 mol %)		**89e** (1 mol %)	
entry	R	yield (%)	ee (%)	yield (%)	ee (%)	yield (%)	ee (%)
1	2-furyl	89	67	85	81	84	90
2	Ph	82	55	87	67	89	86
3	4-ClC_6H_4	81	60	80	77	90	87
4	4-$NO_2C_6H_4$	83	68	90	80	92	83
5	Cy	82	79	90	84	90	92
6	PhCH=CH	84	65	94	85	92	92

Table 37. Enantioselective Allylation of Aldehydes with Chiral Indium(III) Catalysts



90



		90-In(OTf)$_3$, TMSCl (1.2 equiv), 4 Å MS, −60 °C, 30 h		(*S*)-BINOL-$InCl_3$, 4 Å MS, −78 °C, 4 h, rt, 16 h		(*S*)-BINOL-$InCl_3$, H_2O (2.2 equiv), rt, 20 h	
entry	R	yield (%)	ee (%)	yield (%)	ee (%)	yield (%)	ee (%)
1	Ph	65	87	76	92	53	83
2	2-naphthyl	72	85	55	90	51	72
3	$PhCH_2CH_2$	77	60	64	90	57	80
4	PhCH=CH	62	67	72	96	76	85
5	$BnO(CH_2)_3$	72	63	70	94	42	86
6	$CH_3(CH_2)_7$			72	94	75	78

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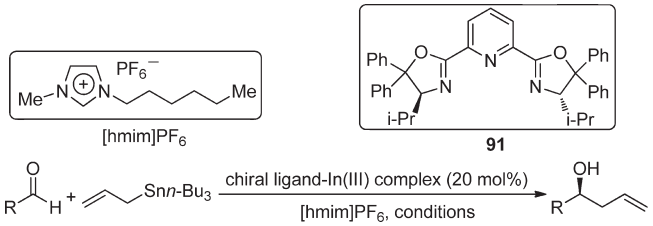
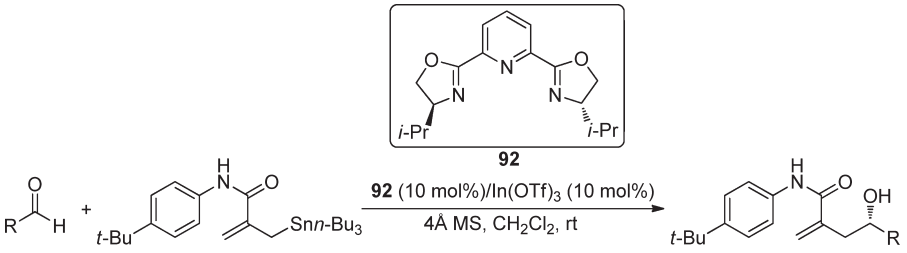
Table 38. Allylation of Aldehydes Catalyzed by Chiral−In(III) Complexes in [hmim]PF_6



		(*S*)-BINOL-$InCl_3$, rt, 40 h		ligand **91**-$In(OTf)_3$, TMSCl, 4 Å MS, −60 °C, 30 h	
entry	R	yield (%)	ee (%)	yield (%)	ee (%)
1	Ph	62	70	72	88
2	4-ClC_6H_4	42	72	68	94
3	2-naphthyl	46	78	88	91
4	(*E*)-PhCH=CH	60	92	89	91
5	$PhCH_2CH_2$	40	74		
6	$Me(CH_2)_7$	72	26	71	86

Table 39. Allylation of Aldehydes with *N*-(4-*tert*-Butylphenyl) Allyltri-*n*-butylstannane Catalyzed by the In(III)−PYBOX-92 Complex



entry	R	yield (%)	ee (%)
1	Ph	78	77 (*S*)
2	*i*-Bu	45	47 (*R*)
3	*t*-Bu	45	58 (*R*)
4	4-$MeOC_6H_4$	79	59 (*S*)
5	3-ClC_6H_4	90	61 (*S*)
6	4-$NO_2C_6H_4$	79	58 (*S*)

corresponding homoallyl alcohols in good yields (usually >80%). More importantly, the catalyst **89e** showed higher enantioselectivity (up to 92%) than the classic Jacobsen's complex (**89a**) for all aldehydes examined (Table 36). Importantly, the method does not require anhydrous solvents or an inert atmosphere. Moreover, this mild protocol might be useful for the allylation of thermally unstable or acid-sensitive aldehydes. In spite of good yield, the enantioselectivity was much lower for methallyltri-*n*-butyltin (up to 38% ee), and the enantioselectivities observed for the syn adducts were similar to those for simple allylation when crotyl-*n*-tributyltin (*E*/*Z* ratio = 65:35) was used.[91] Interestingly, the authors propose a plausible stereochemical model that is in accordance with the absolute configuration observed for the products.

3.1.3. Indium(III) Catalysts. *3.1.3.1. Allylation of Aldehydes Using Indium(III) Catalysts.* Because of their low toxicity, high chemoselectivity, and tolerance to the presence of water, indium complexes are also very attractive to catalyze asymmetric transformations. In this context, the group of Loh examined a chiral indium(III) complex, which was prepared from $In(OTf)_3$ and the ligand PYBOX-**90**, for the allylation of different aldehydes with allyltri-*n*-butyltin.[92] The reaction was conducted in dichloromethane at −60 °C in the presence of powdered, activated 4 Å MS and TMSCl, obtaining good yields and enantioselectivities not only for aromatic but also for aliphatic aldehydes (Table 37). In the reaction with α,β-unsaturated aldehydes, the 1,2-addition reaction proceeded exclusively. It is worthy to be mentioned that chiral PYBOX could be easily recovered after usual workup and reused without loss of enantioselectivity. The same group explored the complex formed from (*S*)-BINOL [(*S*)-**81a**] and $InCl_3$ for the allylation of aldehydes with allyltri-*n*-butyltin.[93] The reaction was performed in dichloromethane at low temperature, using 20 mol % of the catalyst and activated 4 Å MS. As shown in Table 37, good yields and higher enantioselectivities than with ligand PYBOX-**90** (up to 96% ee) were obtained for aromatic and aliphatic aldehydes. Importantly, the chiral ligand [(*S*)-**81a**] can be easily recovered by silica gel chromatography in almost quantitative yield (98%).

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The authors suggest that an (*S*)-BINOL−In−allyl complex, resulting from a transmetalation, should probably act as the actual chiral Lewis acid for the asymmetric allylation reaction. Importantly, when water was added prior to the formation of the chiral indium complex, a racemic product was formed in <10% yield. Apparently, the addition of 4 Å MS is crucial to guarantee a better complexation with the chiral indium catalyst, which is reflected in a better asymmetric induction. On the contrary, when 3.7 equiv of water (relative to $InCl_3$) were added to a stirred solution of the preformed catalyst, prior to the addition of benzaldehyde and allyltri-*n*-butyltin, the corresponding homoallyl alcohol was obtained in 40% yield and 80% ee. Given the latter mentioned result, the authors decided to explore the generality of this moisture-tolerant chiral indium complex with different aldehydes.[94] As shown in Table 37, when the reactions were conducted in the presence of 2.2 equiv of water, the corresponding homoallyl alchohols were obtained in moderate to good yields and good enantioselectivities (72−86% ee).

The group of Loh extended the utility of the asymmetric allylation of aldehydes catalyzed by (*S*)-BINOL/$InCl_3$ complex through the use of ionic liquids as environmentally benign reaction medium.[95] Among the ionic liquids explored, [hmin]PF_6 was shown to give the best chemical yield and enantioselectivity in the allylation of benzaldehyde, whereas the [Cl^-]-type ionic liquids did not exhibit any enantioselectivity. Under these optimized conditions, the allylation of a variety of aldehydes resulted in moderate to good yields (40−62%) and enantioselectivities (70−92% ee), except for nonanal, which afforded the homoallyl alcohol in good yield but poor enantioselectivity (Table 38). Unfortunately, after extraction of organic products with Et_2O, the resulting ionic liquid was unreactive when aldehydes and allyltri-*n*-butyltin were subsequently added. The authors have observed the BINOL ligand in the ^1H NMR spectra of the ether extracts and suggest that deactivation of the chiral complex could be related to a catalyst hydration. Continuing their interest in the recyclability of the catalytic system in the enantioselective allylation of aldehydes in ionic liquids, other chiral indium(III) complexes were explored by the group of Loh. Following their own results, different PYBOX ligands and ionic liquids were screened, resulting in better isolated yields and enantioselectivities when the ligand **91** was used in [hmin]PF_6−CH_2Cl_2 for the allylation of benzaldehyde.[96] In this case, the addition of CH_2Cl_2 as cosolvent was necessary to ensure an efficient stirring of the reaction mixture at −60 °C. More importantly, under the optimized allylation conditions, a variety of aromatic and aliphatic aldehydes afforded the corresponding homoallylic alcohols in uniformly good isolated yields (71−89%) and high enantioselectivities (86−94% ee, Table 38). Notably, the enantioselectivity for the allylation of nonanal was significantly improved with these new conditions (26% vs 86% ee). Importantly, after removing CH_2Cl_2 under vacuum and extracting the ionic liquid with dry hexane, the chiral catalytic system could be reused four times with similar enantioselectivity and yield (benzaldehyde and 2-naphthaldehyde were examined).

The catalytic enantioselective allylation of aldehydes with β-carbonyl allyltri-*n*-butylstannane has also been subject of investigation because the corresponding homoallyl alcohols can be easily converted into α-methylene-γ-butyrolactones, which exhibit a wide range of potent biological activities. In this context, the first example of a catalytic enantioselective allylation of aldehydes with β-amido-functionalized allyltri-*n*-butyltin was recently reported using 10 mol % of In(OTf)$_3$/PYBOX-**92**.[97] The authors have found that the reaction of different aldehydes with *N*-(4-*tert*-butylphenyl) allyltri-*n*-butylstannane proceeded smoothly at room temperature in CH_2Cl_2, using 4 Å MS as additive and giving the expected products in satisfactory ee's and good yields (Table 39).

The authors suggest that the observed stereoselectivity might be related to the strong chelating ability of indium ion, which coordinates with the amide moiety of the allyltin reagent and the oxygen atom of the aldehyde to organize cyclic transition states A and B in Figure 9. Model A, in which the steric interaction between the stannyl group and R^2 of aldehyde is minimized, was considered to be preferred over B. Full experimental details of these reactions, as well as the application to the synthesis of some α-methylene-γ-butyrolactones, and the mechanistic interpretation have been recently reported.[98]

3.1.3.2. Allylation of Ketones Using Indium(III) Catalysts. With the accumulated experience in the asymmetric indium(III)-catalyzed allylation of aldehydes, the group of Loh has also

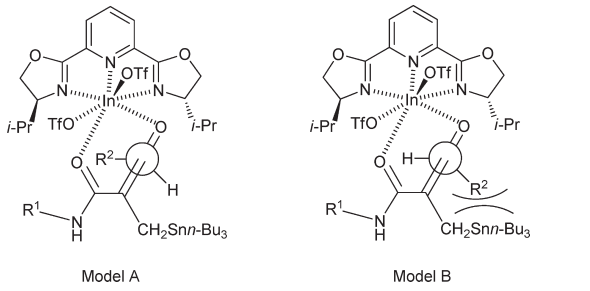
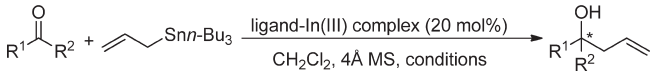


Figure 9. Proposed transition states for the allylation of aldehydes catalyzed by In(III)−PYBOX-**92**.

Table 40. Allylations of Various Ketones Catalyzed by Chiral−In(III) Complex



	(*R*)-BINOL-$InBr_3$, rt, 72 h		PYBOX **91**-In(OTf)$_3$, TMSCl, 0 °C, 72 h		PYBOX **91**-In(OTf)$_3$, [hmim]PF_6, TMSCl, 0 °C	
R^1, R^2	yield (%)	ee (%)	yield (%)	ee (%)	yield (%)	ee (%)
Ph, Me	74	82 (*R*)	80	62 (*R*)	82	65 (*R*)
4-MeC_6H_4, Me	41	84 (*R*)	85	67 (*R*)	78	71 (*R*)
PhCH=CH, Me	82	90 (*R*)	71	54 (*R*)	68	55 (*S*)
$PhCH_2CH_2$, Me	60	80 (*S*)	80	55 (*S*)	74	56 (*S*)
1-indanone	61	90 (*R*)	90	95 (*R*)	82	93 (*R*)
1-tetralone			68	84 (*R*)	74	81 (*R*)

dx.doi.org/10.1021/cr1004474 |*Chem. Rev.* 2011, 111, 7774–7854

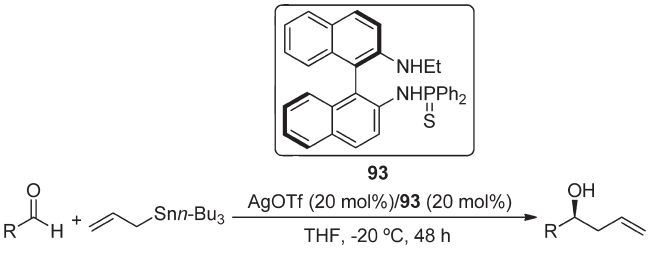
studied the more challenging ketone substrates. To compensate for the reduced reactivity of ketones, the catalyst was prepared using $InBr_3$, due to its higher Lewis acidity compared to $InCl_3$. The chiral catalyst was prepared in situ using 22 mol % of (*R*)-BINOL and 4 Å MS in CH_2Cl_2, with the reaction of a selection of ketones with allyltri-*n*-butyltin being conducted at room temperature.[99] In all cases, the homoallylic alcohols were obtained in good enantioselectivities (up to 92% ee), not only for aromatic but also for aliphatic ketones. It is worth noting that this is the first catalytic system for the asymmetric allylation of ketones using allyltri-*n*-butylstannane, unlike most other systems that require stronger allylation reagents such as tetraallylstannanes. Importantly, the chiral ligand (*R*)-BINOL can be recovered in high yield after conventional column chromatography. Regarding the stereochemical outcome of the reaction, the *Re*-face of the ketone is attacked when the (*R*)-catalyst is used (Table 40). The group of Loh also screened several variants of the PYBOX ligand for the In(III)-catalyzed allylation of ketones with allyltri-*n*-butyltin. The best results were found with PYBOX-**91**, for which a range of ketones afforded the corresponding homoallyl alcohols in moderate to high enantioselectivities (54−95%) and good yields (Table 40).[100] It was found that TMSCl plays a crucial role in this protocol, the absence of which results in a dramatic decrease in enantioselectivity and yield of the product. It is worth noting that practically no attenuation of catalytic efficiency and enantioselectivity was observed by reusing the recovered chiral ligand. Additionally, when this catalytic system was used in a 1:1 mixture of $[hmin]PF_6/CH_2Cl_2$ for the allylation of a similar set of ketones, the corresponding homoallyl alcohols were isolated in similar isolated yields and enantioselectivities to when the reaction was conducted in a solution of dichloromethane.[101] Importantly, the catalyst was easily recovered by simply extracting with hexane and reused with comparable enantioselectivities and yields.

3.1.4. Silver(I) Catalysts. Chiral binaphthylthiophosphoramide **93**, prepared from C_2 symmetric BINAM, was used as a chiral ligand in the silver(I)-catalyzed enantioselective allylation reaction of various aromatic aldehydes with allyltri-*n*-butyltin to furnish the corresponding homoallylic alcohols in high ee (up to 98%) and isolated yields.[102] The results are summarized in Table 41. It is worth noting that the chiral ligand could be recovered after column chromatography and reused in this asymmetric reaction without loss of enantioselectivity. It was also found that the reaction did not proceed at all with the parent binaphthylphosphoramide ligand, what suggests that coordination between the sulfur atom and silver(I) plays an important role in this reaction.

The enantioselective addition of allyltri-*n*-butylstannane to *N*-protected-α-iminoesters was catalyzed by AgOTf in the presence of chiral imine ligands. Several chiral imines derived from 1,2-diaminocyclohexane or binaphthyl diamine (BINAM) were readily prepared and used in this model reaction, with the best results obtained with the diimine **94**. To clarify if mono- or bimetallic species were involved, different ratios of **Ag**/**94** were used. However, quantitative yields and similar enantioselectivities were observed for all cases, and there is no further evidence of the real catalytically active species. Importantly, slightly better enantioselection was achieved at −40 °C (Table 42).[103]

3.1.5. Metals of Group X Catalysts. Several chiral biphosphinite ligands were screened in the Pt-catalyzed allylation of

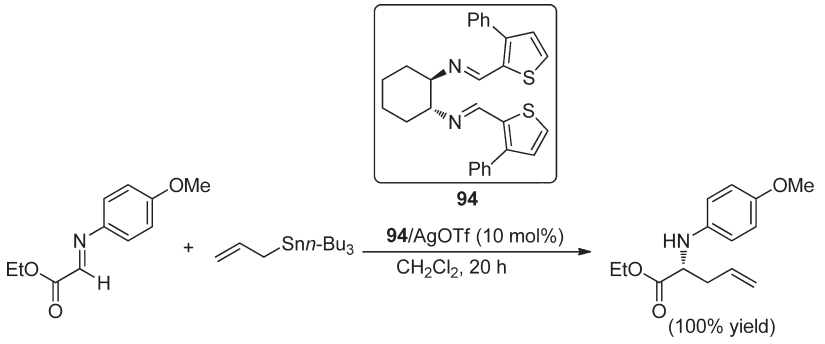
Table 41. Allylation of Arylaldehydes in the Presence of Chiral Ligand 93 and Silver(I) Triflate



entry	R	yield (%)	ee (%)
1	4-MeC_6H_4	75	98 (*S*)
2	4-ClC_6H_4	74	96 (*S*)
3[a]	4-ClC_6H_4	70	96 (*S*)
4	4-$MeOC_6H_4$	56	80 (*S*)
5	(*E*)-PhCH=CH	80	68 (*S*)

[a] Recovered **93** was used as a chiral ligand.

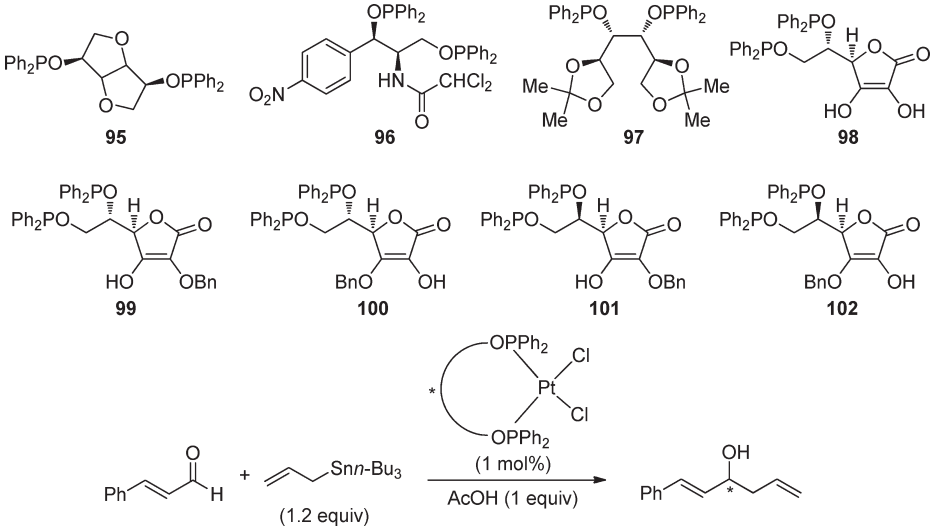
Table 42. Addition of Allyltri-*n*-butyl Stannane to *N*-PMP-α-iminoesters Promoted by Ag(I)



entry	Ag/**94** ratio	*T* (°C)	ee (%)
1	1:1	0	65
2	2:1	0	57
3	1:2	0	67
4	1:2	−40	71

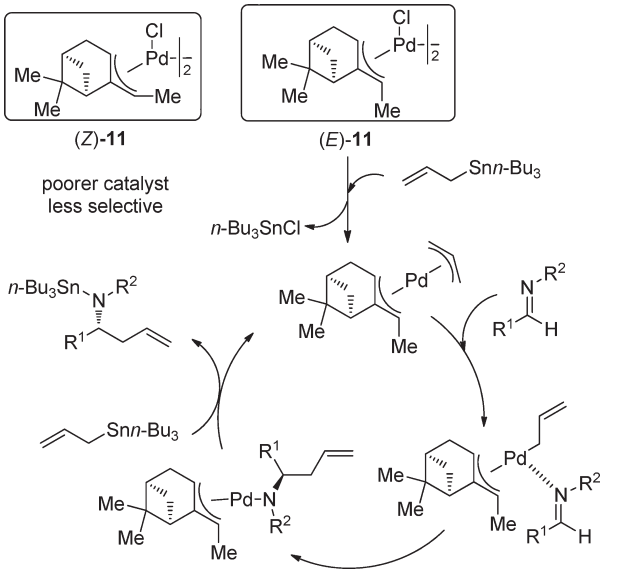
dx.doi.org/10.1021/cr1004474 |*Chem. Rev.* 2011, 111, 7774–7854

Table 43. Allylation of Cinnamaldehyde with Various Platinum Bisphosphinite Complexes



entry	bisphosphinite ligand	*t* (h)	yield (%)	ee (%)
1	**95**	12	91	28 (*R*)
2	**96**	22	88	88 (*R*)
3	**97**	22	81	12 (*R*)
4	**98**	13	90	73 (*R*)
5	**99**	10	89	83 (*R*)
6	**100**	19	77	15 (*R*)
7	**101**	28	81	70 (*S*)
8	**102**	32	70	47 (*S*)

Scheme 13



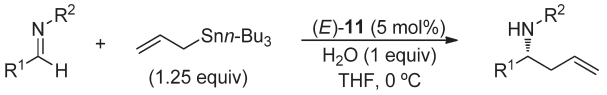
cinnamaldehyde with allyltri-*n*-butyltin.[104] It was found that ligands based on ascorbic acid provide an opportunity for editing the stereochemical elements with hydrogen bond donors and acceptors (ligands **95**−**102**, Table 43). Interestingly, higher selectivity and turnover numbers are achieved in the presence of acetic acid as a promoter.

The first catalytic asymmetric allylation of imines was reported in 1998 by Y. Yamamoto and co-workers,[105] who proposed that the bis-π-allylpalladium complex coordinates the imine, and the subsequent intramolecular allylation would proceed via a six-membered chairlike transition state. Importantly, the bulky π-allyl group acts as a nontransferable chiral π-allyl ligand. As shown in Scheme 13 (similar to Scheme 5 shown prevously), the turnover of the catalyst could be possible by transmetalation with allyltri-*n*-butyltin, producing the corresponding stannyl homoallylamine. The same authors have had problems with reproducing the enantioselectivities and chemical yields for different imines, and attempting to understand and solve these fluctuations, they have recently found that the addition of 1 equiv of water to this catalytic system gives more general and reproducible results.[106] It was proposed that water could accelerate the transmetalation step for the turnover of the active catalytic species, by coordination to the tetravalent stannane, thereby facilitating the C−Sn bond cleavage. Moreover, stereochemical models were proposed for the intramolecular allylation step to account for the better enantioselection observed for the *trans*-imines compared to the poor results for the *cis*-imines used. After some optimization efforts, an initial 1.3:1 mixture of (*E*)-**11** and (*Z*)-**11** was separated after three recrystallizations from propionitrile, to afford the catalyst with (*E*)-**11**/(*Z*)-**11** in >400:1 ratio. Importantly, the catalyst (*E*)-**11** gave the corresponding homoallylic amine in much higher enantioselectivity than (*Z*)-**11**, giving the same major enantiomer and therefore justifying the need to separate both diastereomers. The use of this robust catalytic system over a wide range of imines is summarized in Table 44.

dx.doi.org/10.1021/cr1004474 |*Chem. Rev.* 2011, 111, 7774–7854

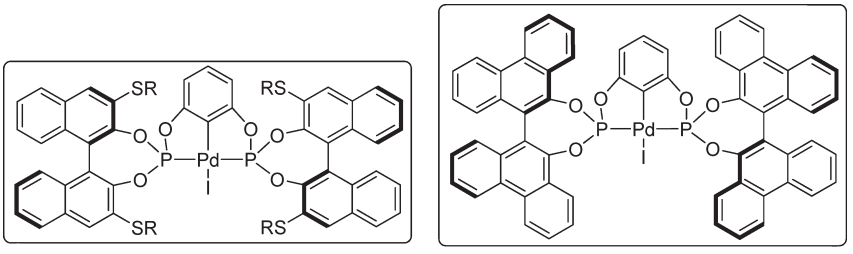
Using pincer complex catalysis, allylation reactions can be performed without formation of bis(allyl)palladium intermediates. In fact, pincer complexes of palladium have been recently examined as catalysts for the enantioselective allylation of sulfonimines.[107] The chiral complexes were prepared from BINOL derivatives or biphenanthrol, using a flexible modular approach that allows for an efficient tuning of the selectivity of the catalysts. The allylation reactions of aryl sulfonyl imines with allyltri-*n*-butyl stannane were conducted under mild conditions (6−20 °C) in dry DMSO without additives. The allylstannane reagent could be successfully replaced with potassium trifluoro(allyl)borate, although with somewhat lower enantioselectivity. From the results listed in Table 45, it is clear that biphenanthrol-based complexes **104** gave higher selectivity than the substituted BINOL-based analogues **103**, probably due to a better well-shaped chiral pocket. Accordingly, aromatic sulfinimines afforded the corresponding homoallylic sulfonamines in high enantioselectivity (80−85% ee, entries 8−11, Table 45). Importantly, the (*R*)-biphenanthrol-based complex **104** provides the homoallylamine products with *R* selectivity, while *ent*-**104** induces (*S*)-configuration at the stereogenic carbon of the product. On the other hand, the higher selectivity of biphenanthrol-based catalysts is accompanied by lower catalytic activity than the BINOL analogues. Therefore, the yield could be improved by increasing the catalyst loadings to 10 mol % (Table 45, entry 11). Moreover, considering the enantioselectivity achieved in this study (up to 85%), a possible palladium(0)-catalyzed process can be ruled out, so it is proposed that the enantioselectivity of the

Table 44. Allylation of Imines with Allyltribuylstannane in the Presence of the Catalyst (*E*)-11



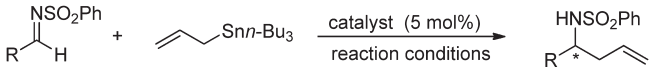
entry	R^1	R^2	*t* (h)	yield (%)	ee (%)
1	Ph	Bn	48	86	85
2	4-MeOC_6H_4	Bn	98	82	85
3	2-MeOC_6H_4	Bn	73	78	88
4	Cy	Bn	74	84	50
5	(*E*)-PhCH=CH	Bn	73	84	69
6	2-furyl	Bn	72	90	67
7	Ph	PMB	73	89	90
8	4-MeOC_6H_4	PMB	88	78	85
9	4-$NO_6C_6H_4$	PMB	70	94	42
10	Ph	CH_2=$CHCH_2$	78	82	78
11	Ph	$PhSO_2$	144	<10	
12	3-pyridyl	Me	168	42	55

Table 45. Allylation of Sulfonimines Catalyzed by P-Chiral Pincer Metal Complexes 103 and 104



103a (R = Me)
103b (R = Et)
103c (R = Ph)

104

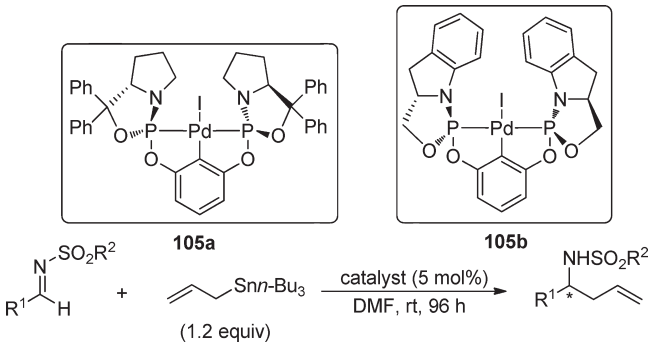


entry	R	catalyst	*T* (°C)/*t* (h)	solvent	config.	yield (%)	ee (%)
1[a]	Ph	**103a**	6/66	DMF	*R*	49	73
2[a]	Ph	**103a**	20/94	DMSO	*R*	57	71
3[a]	Ph	*ent*-**103a**	20/94	DMSO	*S*	53	74
4[a]	Ph	**103b**	20/94	DMSO	*R*	44	67
5[a]	Ph	**103c**	20/94	DMF	*R*	70	48
6[b]	(*E*)-PhCH=CH	*ent*-**103a**	6/66	DMF	*S*	53	59
7[b]	3-$NO_2C_6H_4$	*ent*-**103a**	20/68	DMF	*S*	85	66
8[b]	3-$NO_2C_6H_4$	**104**	20/94	DMF	*R*	71	85
9[a]	3-$NO_2C_6H_4$	**104**	20/68	DMF	*R*	78	82
10[a]	Ph	*ent*-**104**	20/91	DMF	*S*	28	83
11[a,c]	Ph	*ent*-**104**	20/91	DMF	*S*	50	80

[a] Ar = Ph. [b] Ar = 4-MeC_6H_4. [c] 10 mol % of catalyst was used.

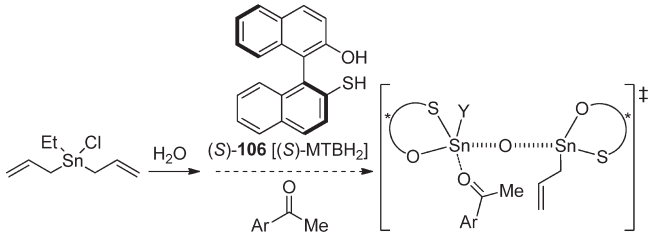
dx.doi.org/10.1021/cr1004474 |*Chem. Rev.* 2011, 111, 7774–7854

Table 46. Allylation of Sulfonimines Catalyzed by P-Chiral Pincer Metal Complexes 105a and 105b



entry	R^1	R^2	catalyst	yield (%)	ee (%)
1	Ph	4-MeC_6H_4	**105a**	60	0
2	Ph	4-MeC_6H_4	**105b**	65	11
3	3-$NO_2C_6H_4$	4-MeC_6H_4	**105b**	75	20
4	4-$NO_2C_6H_4$	4-MeC_6H_4	**105b**	81	12
5	4-$NO_2C_6H_4$	2,4,6-$Me_3C_6H_2$	**105b**	75	14.5
6	4-$NO_2C_6H_4$	2,4,6-(i-Pr)$_3C_6H_2$	**105b**	78	29
7	3-$NO_2C_6H_4$	Me_2N	**105b**	70	28
8	4-$NO_2C_6H_4$	Me_2N	**105b**	78	33

Scheme 14

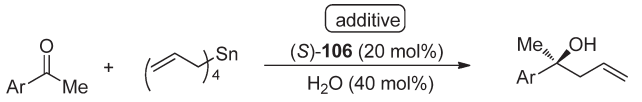


process is determined by the reaction of the corresponding η^1-allyl−palladium pincer complex with the sulfonimine. It is worth noting that, based on previous DFT and experimental studies,[108] the authors suggest that the nitrogen atom of the sulfonylimine unit does not coordinate to palladium because the negative charge is efficiently delocalized toward the sulfonyl group.[109] Therefore, the sulfonylimine substrate does not form a six-membered ring TS with the allyl moiety and palladium, and the stereoselectivity is determined by steric interactions between the sulfonyl group and the chiral pincer ligand.

P-stereogenic bisphosphoramidite pincer palladium complexes **105a** and **105b**, derived from L-proline and (*S*)-2-indoline-2-carboxylic acid, were prepared and examined for the asymmetric allylation of sulfonimines.[110] In this case, the corresponding homoallylic amines were obtained in good yields but with low (up to 33% ee) to no enantioselectivity, as shown in Table 46.

3.1.6. Tin(IV) Catalysts. The first example of asymmetric allylation of ketones catalyzed by tin(IV) species was reported in 2002 by the group of Woodward. It was found that tetraallylstannane with 98% chemical purity was more selective than completely pure samples (>99%) in the allylation of ketones in the presence of 20 mol % of the (*Sa*)-$MTBH_2$ ligand.[111] Subsequent careful studies revealed that impure samples of

Table 47. Tin(IV) Catalyzed Allylation of Aryl Methyl Ketones



		method A[a]		method B[b]	
entry	Ar	yield (%)	ee (%)	yield (%)	ee (%)
1	Ph	97	87	75	86
2	2-naphthyl	>98	87	45	80
3	4-$NO_2C_6H_4$	>98	86	85	94
4	4-BrC_6H_4	97	86	68	76
5	4-ClC_6H_4	94	85	70	81
6	4-MeC_6H_4	78	82	47	66
7	4-$MeOC_6H_4$	62	29	<2	
8	(*E*)-PhCH=CH	96	71	53	55

[a] Method A: 0.3 equiv of $(allyl)_3SnBu$ was used as additive. [b] Method B: 3 mol % of $SnCl_4$ was used.

tetraallyltin contain trace amounts of $EtSnCl(allyl)_2$, which underwent hydrolysis with traces of water to provide bis(diallyldiethyldichlorodistanoxane). Ligation of the distanoxane with (*S*)-$MTBH_2$ [(*S*)-**106**] leads to a very selective catalyst, which is proposed to operate via the working model shown in Scheme 14.

A range of ketones were screened using a 7:3 mixture of tetraallyltin/n-$BuSn(allyl)_3$ [which contained trace amounts of $ClSnBu(allyl)_2$], in the presence of 40 mol % of water and (*S*)-**106** (method A, Table 47).[112] Synthetically useful yields and selectivities were found for aryl methyl ketones using this catalytic system. Similar reactivity was attained by in situ formation of $ClSn(allyl)_3$ from allyltri-n-butyltin and 3 mol % of $SnCl_4$ (method B, Table 47).[113] Using this method, optimal enantioselectivities were achieved after 3−4 h, whereas longer reaction times resulted in lower ee values. Although the reactivity was slightly lower, the fact that tedious preparation of individual components of organotin species is not required makes this an attractive practical alternative. The possibility of using allylsilane as the terminal allyl source was also investigated, but rapid transmetalation to tin could not be attained and the reactions performed poorly.

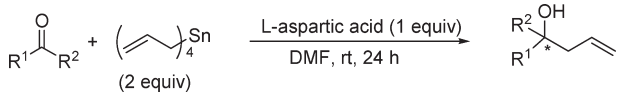
3.1.7. Brønsted Acid Catalysts. The asymmetric allylation of aldehydes with tetraallyltin and other allylstannanes was achieved using different α-amino acids as chiral promoters,[114] with the best results being found using L-aspartic acid in DMF. Importantly, triallyl-n-butyltin showed a similar reactivity and enantioselectivity to those of tetraallyltin, whereas in marked contrast the reaction using allyltri-n-butyltin did not proceed at all. With the optimized conditions in hand, various optically active homoallylic alcohols were obtained in high yields and moderate enantioselectivities up to 40% ee (Table 48). No reaction was observed for acetophenone under the standard conditions.

3.2. Base-Catalyzed Allylation Reactions

Recently, L-proline derivatives and other chiral ligands in conjunction with Lewis bases were used to promote the allylation of aldehydes with allyltin tribromide in CH_2Cl_2.[115] After some optimization efforts, the ligand **107** in combination with DIPEA

dx.doi.org/10.1021/cr1004474 |*Chem. Rev.* 2011, 111, 7774–7854

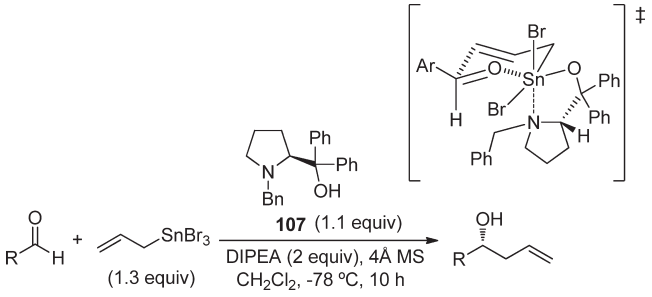
Table 48. Allylation of Aldehydes Promoted by Aspartic Acid



entry	R^1	R^2	yield (%)	ee (%)	configuration
1	Ph	H	88	33	*S*
2	4-BrC_6H_4	H	95	28	*a*
3	4-$NO_2C_6H_4$	H	99	23	*a*
4	4-$MeOC_6H_4$	H	79	40	*S*
5	(*E*)-PhCH=CH	H	74	32	*S*
6	$PhCH_2CH_2$	H	82	20	*a*
7	Ph	Me	<1		

[a] Unknown configuration.

Table 49. Asymmetric Allylation of Aldehydes with Allyltin Tribromide Catalyzed by 107

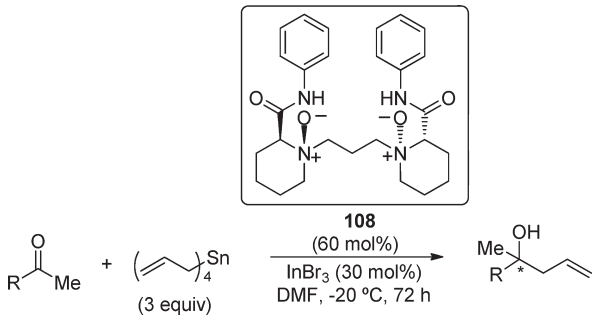


entry	R	yield (%)	ee (%)
1	Ph	75	56
2	4-FC_6H_4	59	33
3	4-ClC_6H_4	78	42
4	4-$MeOC_6H_4$	40	32
5	4-$NO_2C_6H_4$	80	40
6	2-FC_6H_4	54	62
7	2-$NO_2C_6H_4$	65	48
8	(*E*)-PhCH=CH	62	34

resulted in the best chiral promoter. As listed in Table 49, different aromatic aldehydes, as well as cinnamaldehyde, reacted smoothly with moderate enantioselectivity under the optimized conditions. The reaction was considered to proceed via a six-membered transition state where the tin is ligated to the chiral ligand and coordinated to the aldehyde. The proposed working model is in agreement with the observed formation of (*R*)-homoallyl alcohols and the large influence exerted by the presence of the benzyl substituents on the nitrogen atom of the prolinol derivative.

To compensate for the low reactivity of ketones, the concept of bifunctional catalysis was put into practice using different In(III) reagents and chiral *N,N′*-dioxides in the allylation of ketones. Using the allylation of acetophenone with tetraallyltin as the model reaction, the (*S*)-pipecolic acid derivative **108** proved to be the most selective ligand from all *N*-oxides used in combination with $InBr_3$.[116] Importantly the best results were found when the reaction was conducted in DMF at −20 °C and using 30 mol % of In(III) coordinated to 2 equiv of ligand.

Table 50. Asymmetric Allylation of Aldehydes with Tetraallyltin Catalyzed by 108



entry	R	yield (%)	ee (%)
1	Ph	72	80 (*R*)
2	2-$MeOC_6H_4$	69	83
3	4-$MeOC_6H_4$	48	80 (*R*)
4	4-FC_6H_4	61	81
5	4-ClC_6H_4	86	80
6	2-naphthyl	89	73 (*R*)
7	$PhCH_2CH_2$	49	53 (*S*)

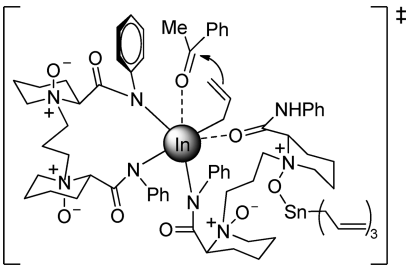


Figure 10. Proposed transition state for the allylation of aldehydes with tetraallyltin catalyzed by **108**.

As shown in Table 50, aryl methyl ketones afforded the corresponding homoallylalcohols with moderate to high yields in good enantioselectivities (70−83% ee). Importantly, substituents on the aromatic ring had a slight influence on the enantioselectivity. However, moderate enantioselectivity was obtained for aliphatic ketones such us 4-phenylbutan-2-one (Table 50, entry 7).

A positive nonlinear effect that fit well with a $MetL_2$ for this reaction was found. Moreover, the ^1H NMR data of a 1:2 mixture of $InBr_3$/ligand **108** revealed that 3 molecules of HBr were removed in the formation of the complex. On the basis of this fact, it was speculated that, in the transition state, 2 molecules of the ligand **108** were tetradentately coordinated to In(III), which was also bound to an allylic group that migrated from a tetraallyltin. The metal center of the chiral allylindium complex still behaved as a Lewis acid, activating the ketone, which suffers an intramolecular transfer of the allylic group (facilitated by coordination to the *N*-oxide ligand) to afford the final product (Figure 10).[116]

Bifunctional catalysts formed from In(III) reagents and *N*-oxides of (*S*)-pipecolic acid derivatives have also been explored for the reaction of tetraallyltin with α-ketoesters.[117] After some optimization, it was found that $In(OTf)_3$ in combination with the ligand **109** gave the most active and selective catalyst for the allylation of methyl α-ketoesters in DMF. Interestingly, a 1:1

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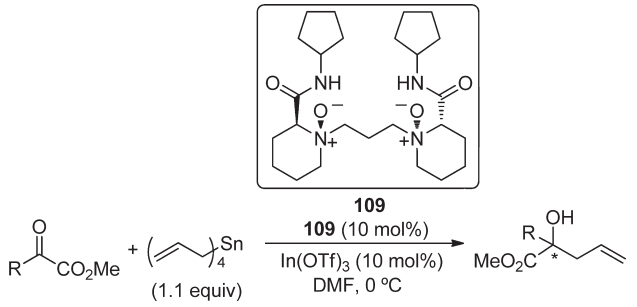
Table 51. Enantioselective Allylation of α-Ketoesters with Tetraallyltin Catalyzed by 109



entry	R	yield (%)	ee (%)
1	Ph	>99	93 (*R*)
2	2-MeC_6H_4	87	77 (*R*)
3	4-FC_6H_4	>99	92 (*R*)
4	2-MeOC_6H_4	97	83
5	4-MeOC_6H_4	89	94 (*R*)
6	2-furyl	98	89
7	2-naphthyl	80	91
8	Cy	90	69

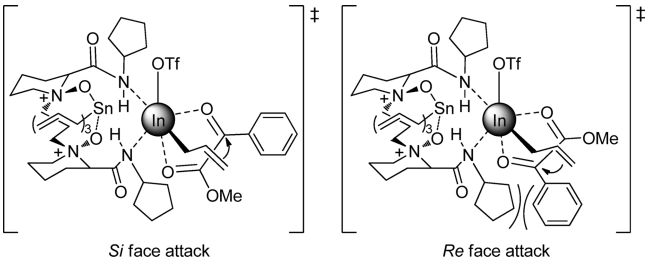


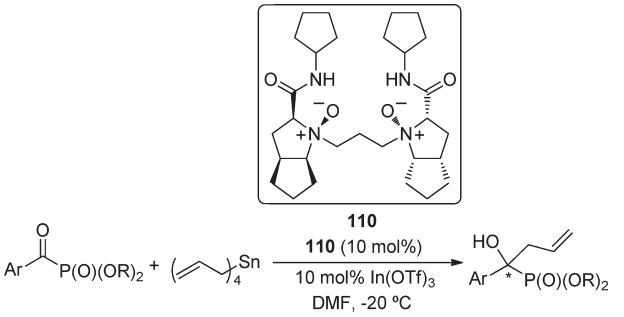
Figure 11. Proposed transition states for *Si*- and *Re*-face attack in the allylation of α-ketoesters with tetraallyltin catalyzed by **109**.

ratio of In/ligand **109** was optimum in this reaction. More importantly, only 10% of $In(OTf)_3$ and 1.1 equiv of tetraallyltin were necessary to achieved good chemical yields and enantioselectivities, which is in accordance with the higher reactivity of α-ketoesters compared to inactivated ketones. As summarized in Table 51, although aromatic α-ketoesters gave excellent yields (up to 99%) and very high enantioselectivities (up to 94%), aliphatic α-ketoesters gave only moderate enantioselectivity (Table 51, entry 8).

Control experiments were performed to ensure that any component of the reaction was necessary to obtain the product in good yields and enantioselectivities. Moreover, ^{1}H NMR and ESI-HRMS studies suggest that the major active precatalyst should be [ligand **109**-InOTf]$^{2+}$. On the bases of these experiments, it was speculated that the reaction proceeds through the transition state shown in Figure 11.[117] Steric repulsions between the phenyl group of α-ketoesters and the cyclopentyl subunit of the catalyst appears in the transition state proposed for the allylation to the *Re*-face of the carbonyl group. Consequently, the *Si*-face attack is more likely and this stereochemical outcome is in accordance with the absolute configuration observed for the products.

Chiral α-hydroxy phosphonic acid derivatives have important biological activity and are widely used for pharmaceutical

Table 52. Enantioselective Allylation of α-Ketophosphonates with Tetraallyltin Catalyzed by 110



entry	Ar	R	yield (%)	ee (%)
1	Ph	Et	95	90
2	Ph	Me	85	90
3	Ph	*i*-Pr	88	86
4	4-ClC_6H_4	Et	84	91
5	4-MeOC_6H_4	Et	86	90
6	4-MeC_6H_4	Et	98	89
7	3-MeOC_6H_4	Me	82	91
8	2,6-$F_2C_6H_3$	Et	82	68

applications.[118] Recently, chiral α-allylic hydroxy phosphonates have been prepared by asymmetric allylation of α-keto phosphonates with tetraallyltin catalyzed by chiral *N,N′*-dioxide–In(III) complexes.[119] The (*S*)-rampiril acid derivative **110** in combination with $In(OTf)_3$ was found to be the most active and selective catalyst from a series of *N,N′*-dioxides used. The reactivity and enantioselectivity was also largely dependent on the central metal and the counteranion. Subsequently, a 1:1 ligand/metal molar ratio and 10 mol % catalyst loading proved to be optimum when the reaction was conducted in DMF at −20 °C. Under the optimal conditions found, a range of aromatic α-keto phosphonates afforded the corresponding products in excellent yields (up to 98%) and uniform high enantioselectivities (up to 91% ee) (Table 52). Although the enantioselectivity is not sensitive to electronic effects of substituents at the para- or meta-position of the aromatic ring, ortho-substituted substrates gave somewhat lower enantioselectivity. On the basis of some control experiments to gain insight into the mechanism, it was proposed that the reaction proceeded through a transition state similar to what was proposed for α-ketoesters (Figure 11). A bifunctional catalyst working model is proposed where the nucleophilicity of the allylic reagent is enhanced by coordination of the tin atom of the tetraallyl stannane to the *N,N′*-dioxide complex (*Lewis base activation*). The transfer of one activated allylic group to the indium atom is followed by coordination of the α-keto phosphonate to the central indium atom (*Lewis acid activation*), and intramolecular allylation occurred through the most stable diastereomeric transition state (a *Si*-face attack is preferred).

A range of C_2-symmetric *N,N′*-dioxide ligands, in combination with different Lewis acids, have been examined as catalysts to develop an attractive multicomponent preparation of optically active homoallylic amines.[120] For the three-component reaction of benzaldehyde, 2-aminophenol, and allyltri-*n*-butyltin as benchmark, and after some optimization efforts, the combination of (*S*)-rampiril acid derivative **111** and $Sc(OTf)_3$ in a 1:1 ratio

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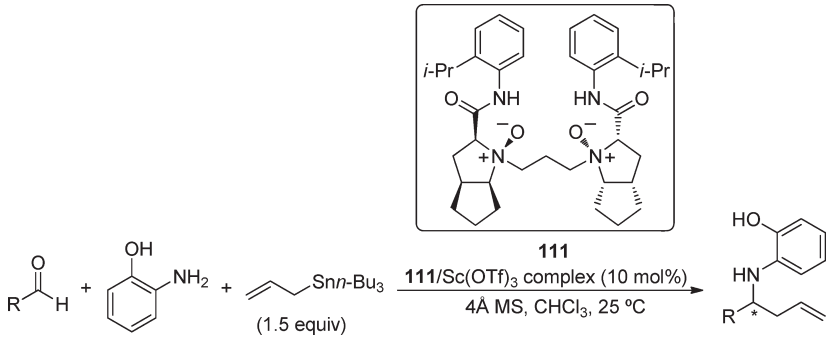
Table 53. Catalytic Asymmetric Three-Component Allylation of Aldimines Catalyzed by 111



entry	R	yield (%)	ee (%)
1	Ph	81	95
2	2-MeC_6H_4	76	95
3	4-MeC_6H_4	74	92
4	4-$NO_2C_6H_4$	84	97 (*S*)
5	3-$MeOC_6H_4$	80	95
6	4-FC_6H_4	75	96
7	2-naphthyl	75	96
8	3-pyridyl	81	96
9	2-thienyl	71	87
10	(*E*)-PhCH═CH	67	71

proved to be superb. Importantly, the multicomponent approach exhibited better enantioselectivity than the allylation of the pure isolated aldimine (95% vs 80% ee), and the addition sequence of benzaldehyde and allyltri-*n*-butyltin had no effect on the ee. Further optimization showed that 10 mol % of catalyst loading with $CHCl_3$ as solvent in the presence of 4 Å MS at 25 °C were optimal conditions. The results for a variety of aldehydes are summarized in Table 53. Neither the electronic influence nor the steric hindrance of the substituents at the aromatic ring had a significant impact on the enantioselectivities achieved for the wide range of aromatic and heteroaromatic aldehydes examined (87−97% ee). Cinnamaldehyde was also a suitable substrate, providing the corresponding product in good yield and moderate enantioselectivity.

4. ENANTIOSELECTIVE ADDITION OF ALLYLIC BORANES

Allylic boranes and boronates add to carbonyl compounds and imines in a highly diastereoselective manner, probably through a chairlike transition state. Diastereoselective allylboration of carbonyl compounds with chiral allylboranes and allylboronates is a well-known procedure to achieve homoallylic alcohols with high optical purity. However, only allylboration using achiral allylboron derivatives in the presence of an external source of chirality will be considered in this section, as previously mentioned in the Introduction (see above). In general, allyldialkylboranes are significantly more reactive than allyldialkoxyboranes, but the reactivity and also the stereoselectivity of the latter can be improved by adding Lewis acid or base catalysts to the reaction medium.

4.1. Allylation of Carbonyl Compounds

On the basis of experimental and kinetic studies, Rauniyar and Hall proposed that the Lewis acid catalyzed allyl boration of aldehydes takes place by coordination of the metal ion to one of

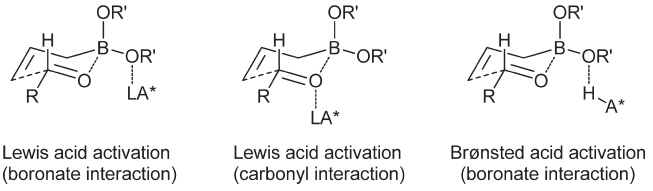


Figure 12. Proposed transition states in the Lewis and Brønsted acid catalyzed allyl boration.

the boronate oxygens, probably the most accessible pseudoequatorial one, instead of to the carbonyl oxygen, in a closed bimolecular six-membered chairlike transition state.[121] Sakata and Fujimoto studied theoretically the allylation of benzaldehyde with allylboronate in the presence of $AlCl_3$.[122] They found through B3LYP calculations a high activation barrier for the reaction in the absence of $AlCl_3$ and that the reaction paths that go through the transition states coordinated by an $AlCl_3$ molecule at one of the two oxygen atoms in the boronate gave significantly lower values of activation energy. The $AlCl_3$ molecule attached to the boronate oxygen atom strengthened the electrophilicity of the boron center and weakened the nucleophilicity of the C═C double bond. In contrast, the reaction path in which $AlCl_3$ is coordinated to the carbonyl oxygen of benzaldehyde shows a higher activation barrier, though the initial reactant complex is more stable than those in other reaction paths. These results supported the electrophilic boronate activation mechanism proposed by Rauniyar and Hall. Similarly, the Brønsted acid catalyzed allylation would take place by protonation of one of the boronate oxygens (Figure 12).[123]

4.1.1. Brønsted Acid Catalyzed Allyl Boration of Aldehydes. Hall found that the combination of C_2-symmetric chiral diols **112** with $SnCl_4$ led to high levels of asymmetric induction in the allylboration of aldehydes by the allylboronic acid pinacol

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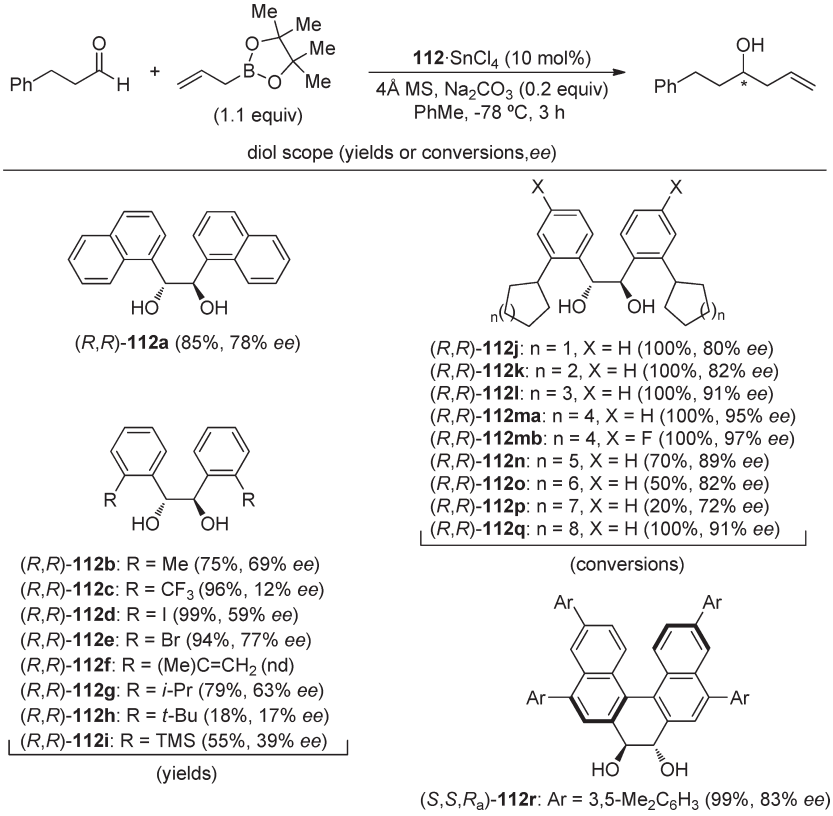
Scheme 15



ester (Scheme 15). After reacting the diol and $SnCl_4$, the resulting complex showed Brønsted acidic character in a highly dissymmetrical environment, making them ideal candidates for catalysis. H. Yamamoto and Futatsugi introduced the concept of Lewis acid assisted Brønsted acid catalysis (LBA) and designed numerous combined acid catalyst systems, which have been shown to be remarkably effective for stereoselective transformations.[124] In this catalyst system, coordination of $SnCl_4$ to the oxygen atoms of the chiral alcohols generated rigid complexes that restrict the directional orientation of the hydroxylic protons, increasing at the same time their acidity (Figure 13). Further controls have ruled out a possible boron transesterification mechanism with the chiral diol and pointed to LBA catalyst-derived activation of the pinacol allylic boronates. Because of slow dissociation of the diol·$SnCl_4$ complex, it was also observed that a small excess of diol with respect to catalyst was required to suppress a competing racemic cycle catalyzed by free $SnCl_4$.

Several diols **112** were tested in the prototypic allylation of 3-phenylpropanal under the reaction conditions shown in Scheme 15. Molecular sieves and Na_2CO_3 were used as precautionary scavengers of adventitious water and HCl, respectively. The addition of allylboronic acid pinacol ester to 3-phenylpropanal under a stoichiometric loading of the **112a**·$SnCl_4$ catalyst system only led to a modest increase in selectivity, namely, 83% vs 78% ee under catalytic conditions.[125] Taking into account electronic and steric factors, different ortho-substituted hydrobenzoin-derived diols (*R*,*R*)-**112b**−**i** were tested in the model allylation in the presence of 10 mol % of the diol·$SnCl_4$ complex. It seemed that large nonpolar substituents had a beneficial effect on the enantioselectivity of the reaction. In addition, slow reaction

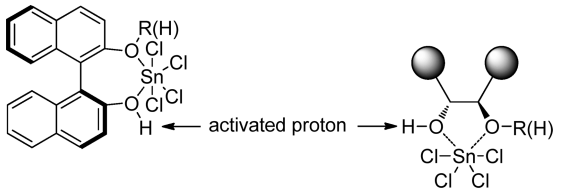


Figure 13. H. Yamamoto and Futatsugi's Lewis acid assisted Brønsted acid (LBA) catalytic system based on chiral diol·$SnCl_4$ complexes.

rates were observed with the hindered catalyst complexes (*R*,*R*)-**112h**·$SnCl_4$ and (*R*,*R*)-**112i**·$SnCl_4$, probably due to an inefficient accessibility of the activated proton. It seemed that there should be at least one benzylic hydrogen in the ortho-substituent of the diol unit for maintaining a desirable level of activity of the LBA catalyst. For that reason, different diols (*R*,*R*)-**112j**−**r** were prepared and subjected to the model allylboration of 3-phenylpropanal under the LBA catalyst system (Scheme 15).[126] The most efficient catalysts were found to be those resulting from diols (*R*,*R*)-**112ma** (Vivol) and (*R*,*R*)-**112mb** (*p*-F-Vivol).[127] Good results were also obtained with the diol (*S*,*S*,*R*$_a$)-**112s** derived from BINOL, which was recovered easily from the final product by silica gel chromatography separation.[128]

The substrate scope of the catalytic enantioselective allylborations was studied with diols (*R*,*R*)-**112a**,[125] (*R*,*R*)-**112ma**,[126,127] and (*R*,*R*)-**112mb**[127] (Table 54). Aliphatic aldehydes gave high enantioselectivities in the allylboration process (Table 54, entries 1−8), whereas aromatic and unsaturated aldehydes gave modest selectivities (Table 54, entries 9−13). The enantiomeric ratio

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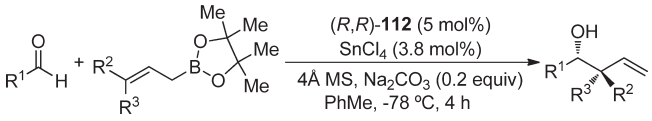
values of prototypic crotylborations were slightly lower than those obtained in the simple allylborations, with the (*E*)-crotyl reagent giving higher selectivities (Table 54, entries 14−17) than with the (*Z*)-isomer (Table 54, entries 18−20).

Rauniyar and Hall studied also the double diastereoselection with the former diols and found that the $SnCl_4$-catalyzed addition of allylboronic acid pinacol ester to *O*-TBS protected (*S*)-2-methyl-3-hydroxypropanal gave minimal selectivity (46:54) favoring the syn-diastereomer (Scheme 16). In the allylation in the presence of (*R*,*R*)-**112a**, the catalyst system improved the intrinsic selectivity preference of the $SnCl_4$-catalyzed reactions to give predominantly the anti-isomer in a 84:16 ratio in the matched combination, and even improved the selectivity of the disfavored diastereomer when using (*S*,*S*)-**112a** (mismatched combination), the antipode of diol (*R*,*R*)-**112a**.[125] Using the (*S*,*S*,R_a)-**112s**·$SnCl_4$ catalyst combination, it was also possible to control the facial selectivity in this model allylation of the mentioned chiral aldehyde (Scheme 16).[128]

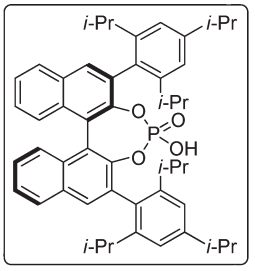
Jain and Antilla developed a simple and highly efficient chiral phosphoric acid-catalyzed allylboration of aldehydes with the allylboronic acid pinacol ester. As chiral phosphoric acid, (*R*)-TRIP-PA [(*R*)-**113**] was found to be a very effective promoter working in toluene at −30 °C, with the substrate scope being extended to electron-rich and electron-poor aromatic aldehydes (Table 55, entries 1−7). Heteroaryl (Table 55, entry 8), α,β-unsaturated (Table 55, entry 9), and aliphatic (Table 55, entries 10−12) aldehydes were also allylated efficiently with high enantioselectivity in the presence of (*R*)-**113** as catalysis.[129] The authors suggested that an activation via protonation of the boronate oxygen by the chiral phosphoric acid catalyst would provide a reasonable explanation for the observed reactivity (see Figure 12).

Table 54. Stereoselective Allylation and Crotylation of Aldehydes Catalyzed by (*R*,*R*)-112a, (*R*,*R*)-112ma·$SnCl_4$, and (*R*,*R*)-112mb·$SnCl_4$ Complexes

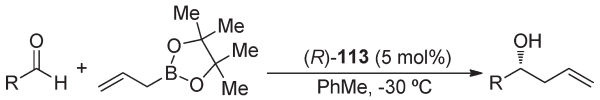


entry	R^1	R^2	R^3	diol	yield (%)	ee (%)
1	$PhCH_2CH_2$	H	H	(*R*,*R*)-**112a**	85	78
2	$CH_3(CH_2)_8$	H	H	(*R*,*R*)-**112a**	76	80
3	$TBDPSO(CH_2)_2$	H	H	(*R*,*R*)-**112a**	90	66
4	$PhCH_2CH_2$	H	H	(*R*,*R*)-**112ma**	99	95
5	$TBSO(CH_2)_2$	H	H	(*R*,*R*)-**112ma**	98	95
6	$CH_3(CH_2)_3$	H	H	(*R*,*R*)-**112ma**	90	95
7	$PhCH_2CH_2$	H	H	(*R*,*R*)-**112mb**	99	97
8	$TBSO(CH_2)_2$	H	H	(*R*,*R*)-**112mb**	99	96
9	Ph	H	H	(*R*,*R*)-**112a**	99	10
10	(*E*)-PhCH=CH	H	H	(*R*,*R*)-**112a**	72	20
11	$CH_3(CH_2)_4C{\equiv}C$	H	H	(*R*,*R*)-**112a**	99	12
12	Ph	H	H	(*R*,*R*)-**112ma**	99	71
13	3,5-$(CF_3)_2C_6H_3$	H	H	(*R*,*R*)-**112ma**	99	94
14	$PhCH_2CH_2$	Me	H	(*R*,*R*)-**112a**	99	72
15	$PhCH_2CH_2$	Me	H	(*R*,*R*)-**112ma**	93	96
16	$TBDPSO(CH_2)_2$	Me	H	(*R*,*R*)-**112ma**	94	93
17	$TBDPSO(CH_2)_2$	Me	H	(*R*,*R*)-**112mb**	95	96
18	$CH_3(CH_2)_8$	H	Me	(*R*,*R*)-**112a**	70	46
19	$PhCH_2CH_2$	H	Me	(*R*,*R*)-**112ma**	78	84
20	$TBDPSO(CH_2)_2$	H	Me	(*R*,*R*)-**112ma**	75	80

Table 55. Enantioselective Allylation and of Aldehydes Catalyzed by (*R*)-TRIP-PA [(*R*)-113]

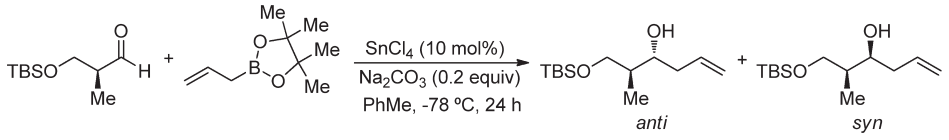


(*R*)-**113** [(*R*)-TRIP-PA]



entry	R	yield (%)	ee (%)
1	Ph	99	98
2	4-BrC_6H_4	99	99
3	4-$NO_2C_6H_4$	98	98
4	4-$MeOC_6H_4$	95	98
5	3-$MeOC_6H_4$	96	97
6	4-$(CO_2Me)C_6H_4$	96	96
7	1-naphthyl	93	98
8	2-thienyl	91	96
9	(*E*)-PhCH=CH	94	96
10	Bn	98	90
11	$BnOCH_2$	96	79
12	Cy	98	73

Scheme 16



$SnCl_4$ alone	46	:	54	(75%)
with (*R*,*R*)-**112a** (11 mol%)	84	:	16	(83%)
with (*S*,*S*)-**112a** (11 mol%)	35	:	64	(60%)
with (*S*,*S*,R_a)-**112s** (11 mol%)	30	:	70	(85%)

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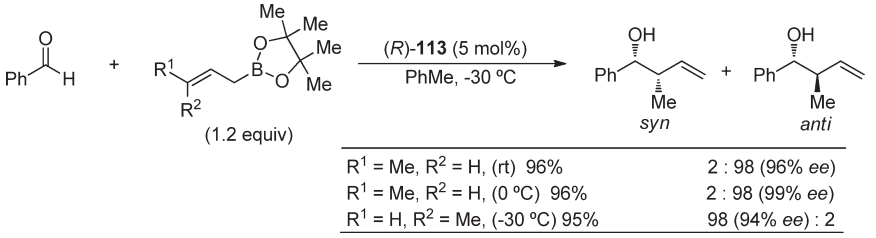
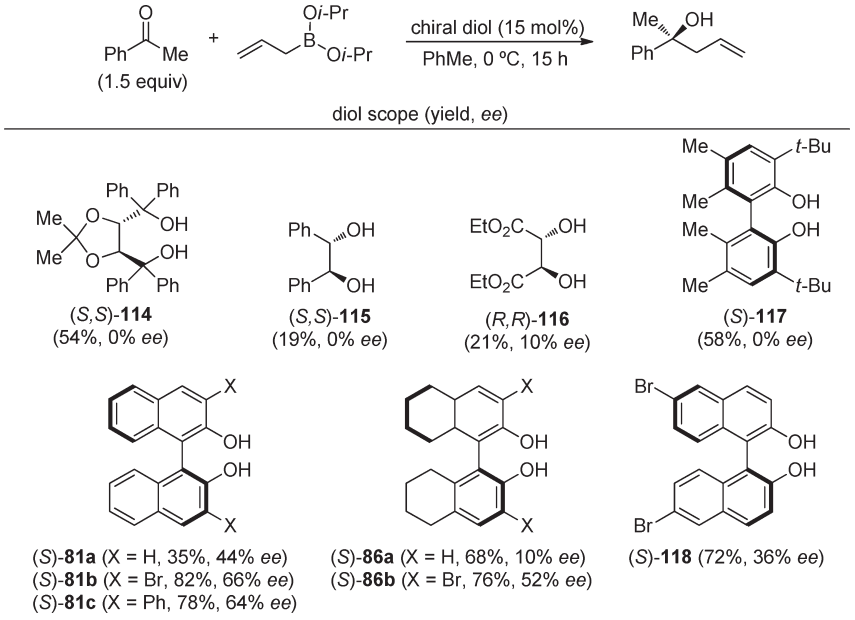
Scheme 17



Scheme 18



The crotylation of benzaldehyde in the presence of (*R*)-**113** occurred with high diastereo- and enantioselectivity. The use of (*E*)-crotylboronate provided the anti isomer with 96% ee at room temperature and >99% ee at 0 °C, whereas (*Z*)-crotylboronate led to the syn isomer almost exclusively with 94% ee at −30 °C (Scheme 17).

4.1.2. Brønsted Acid Catalyzed Allyl Boration of Ketones. Schaus and co-workers investigated the enantioselective allylation of ketones with allyldiisopropoxyborane in the presence of chiral diols. The allylation of acetophenone in toluene at 0 °C was chosen as the model reaction for evaluating the influence of different diols (Scheme 18).[130] The uncatalyzed reaction afforded the racemic homoallylic alcohol in only 13% yield. However, when 15 mol % of (+)-TADDOL [(*S*)-**114**] was added, a higher yield (54%) of the tertiary alcohol was obtained, but in a racemic form. Almost no enantioselectivity was observed with chiral diols **115**−**117**, but better enantioselectivities were obtained with BINOL (**81a**) and 3,3′-disubstituted BINOL derivatives **81b**,**c**, **86b**, and **118**. Among them, the 3,3′-dibromo BINOL derivative (*S*)-**81b** afforded the expected product with the highest enantioselectivity (66% ee). With the organocatalyst (*S*)-**81b** in hand, it was found that a mixture of $PhCF_3$ and toluene (1:3 ratio) was the most effective solvent system at −35 °C, affording the corresponding tertiary homoallylic alcohol in 83% yield and 94% ee. The optimized reaction conditions were effective at promoting the asymmetric allylboration of a variety of ketones with high enantioselectivities (Scheme 18 and Table 56).[130]

Schaus and co-workers studied the mechanism of this reaction, evaluating first the role of both the chiral diol and isopropyl alcohol in the catalytic cycle. The key steps of the proposed mechanism included a crucial ligand-exchange process at the beginning and end of the catalytic cycle (Scheme 19).[131] The allylboronate exchanges a ligand with the chiral diol to afford the catalytic active species, which was detected by direct ESI-MS analysis of the reaction mixture. A crucial intramolecular Brønsted acid activation of the boronate took place in the catalyst, facilitating the carbonyl coordination in the second step. Allylation occurred through a six-membered chairlike transition state leading to the homoallylic boron alcoholate. Finally, the second ligand-exchange process was greatly facilitated when 1 equiv of isopropanol (relative to boronate) was added to the reaction mixture. It was also shown that the rate-determining exchange process was not the initial formation of the active boronate species but the liberation of the chiral diol from the allylation product (Scheme 19).

Cyclic boronates such as dioxaborolanes and dioxaborinanes are substantially more stable than acyclic boronates and can be prepared, purified easily, and stored for longer periods. In addition to the enhancement of stability, cyclic boronates would produce a tethered alcohol upon catalyst exchange, which would

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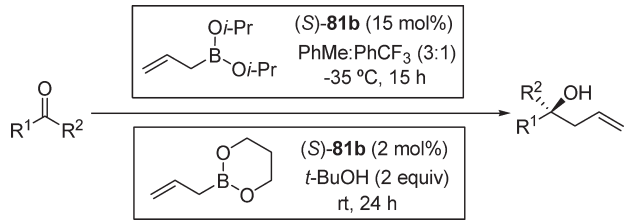
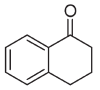
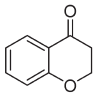
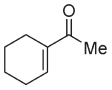
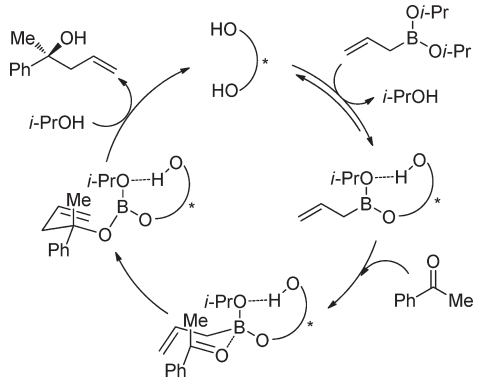
Table 56. Enantioselective Allylation of Ketones with Allylic Boronates Catalyzed by (*S*)-81b



			Oi-Pr B Oi-Pr		O B O	
entry	R^1	R^2	yield (%)	ee (%)	yield (%)	ee (%)
1	Ph	Me	83	94	96	98
3	4-BrC_6H_4	Me	86	99	97	98
5	4-$MeOC_6H_4$	Me	83	99	88	98
7	2-thienyl	Me	87	94	93	>99
8	3-thienyl	Me	88	94	92	98
10	Ph	$ClCH_2$	76	96	95	>99
11			88	93	95	>99
12			87	95	95	>99
13			83	92	95	>99
14			91	93	96	97

Scheme 19



liberate more readily the catalyst at the end of the proposed catalytic cycle shown in Scheme 19. For that reason Schaus studied also the allylation of ketones with allyldioxaborinane in the presence of BINOL derivative (*S*)-**81b**, which was proven to be the most efficient one in the allylation of ketones with allyldiisopropoxyborane. The optimized reaction conditions using allyldioxaborinane required the use of only 2 mol % of (*S*)-**81b** and 2 equiv of *tert*-butanol at room temperature. Excellent yields and enantioselectivies were achieved for a broad range of ketones (>90% yield, >96% ee), as is shown in Table 56.[131]

The catalyst (*S*)-**81b** also promoted the stereoselective crotylboration of acetophenone with both diisopropoxy acyclic boronate[130] and cyclic allyldioxaborinane.[131] The anti-product was obtained with (*E*)-crotyl boronates, whereas (*Z*)-crotyl boronates yielded the syn-product. Chemical yields were higher with allyldioxaborinane (>94%); meanwhile, diastereomeric ratios were always >97:3 (Scheme 20). The observed diastereoselectivities were consistent with a Zimmerman−Traxler transition state model as shown in Scheme 19.

4.1.3. Metal-Mediated Allylation of Carbonyl Compounds with Allylboronates. The stereoselective allylation of carbonyl compounds with allylboronates was also achieved in the presence of metal salts and chiral ligands. Kanai, Shibasaki, and co-workers developed the first catalytic enantioselective allylboration of ketones using the combination of 3 mol % of $CuF_2 \cdot 2H_2O$, 6 mol % of (*R*,*R*)-*i*-Pr-DuPHOS [(*R*,*R*)-**119a**] as a chiral catalyst, and 4.5 mol % of La(O*i*-Pr)$_3$ as a cocatalyst. Under these reaction conditions, the allylboration of aromatic, heteroaromatic, cyclic, and aliphatic ketones proceeded in excellent yields and high enantioselectivities (Table 82),[132,133] with the reaction being completed in 1 h in dichloromethane as solvent at −40 °C. Regarding the reaction mechanism, an allylcopper intermediate was proposed to be the active nucleophile, with the fundamental role of La(O*i*-Pr)$_3$ being to facilitate the dynamic ligand exchange between the boron and copper atoms. More recently, the same authors provided new modular chiral phosphanes that were effective for Cu(I)-catalyzed asymmetric allylation (and propargylation) of ketones. Compound **120** was the most effective catalyst for performing enantioselective allylations in terms of yield and enantioselectivity (Table 57).[134] It was found that a rigid conformation of the core macrocycle, defined by the linker and wing modules, was critical for achieving high stereoselectivities, as well as the introduction of electron-withdrawing substituents at the para-position of the aryl groups at the phosphorus atoms. The reactivity was also enhanced after addition of 1 equiv of isopropanol, allowing the reaction temperature to be decreased to −75 °C. The substrate scope was then studied under the optimized reaction conditions with **120** (Table 57), and in general, the enantioselectivity and catalytic activity were significantly higher than in the reaction using (*R*,*R*)-*i*-Pr-DuPHOS [(*R*,*R*)-**119a**],[132,133] with the only exception being for *tert*-butyl methyl ketone (Table 57, entry 7).

Chiral tetrasubstituted carbon stereocenters were obtained for the first time with high enantioselectivity by crotylation of ketones in the presence of the chiral diphosphane (*R*,*R*)-**119a** (Scheme 21).[132,133] Diastereo- and enantioselectivities were improved when the chiral ligand **120** was used instead of (*R*,*R*)-**119a** (Scheme 21).[134]

Kobayashi and co-workers reported one example of a catalytic asymmetric allylation of acetophenone with the allyl boronic acid pinacol ester in water by means of 5 mol % of In(0) combined with the chiral bis(oxazoline) ligand **121** in a molar ratio of 1:1, with the process taking place probably through a catalytic transmetalation at the In metal surface (Scheme 22).[135] The desired homoallylic alcohol was isolated with 52% ee in 68% yield, which was the best result so far obtained for a catalytic asymmetric allylation of acetophenone in water. Other more effective methods require strict anhydrous conditions.

Regio- (predominantly 1,2-addition) and enantioselective allylation of δ-substituted dienals with allylboronic acid pinacol ester proceeded in the presence of Ni(II) and the chiral

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Scheme 20

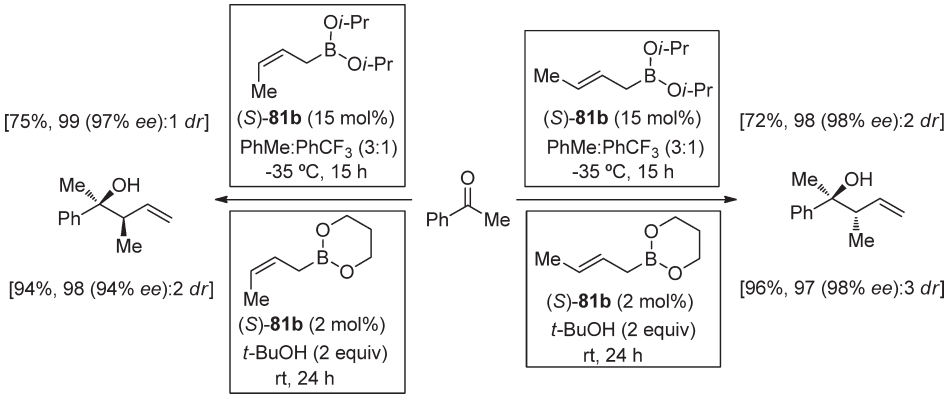
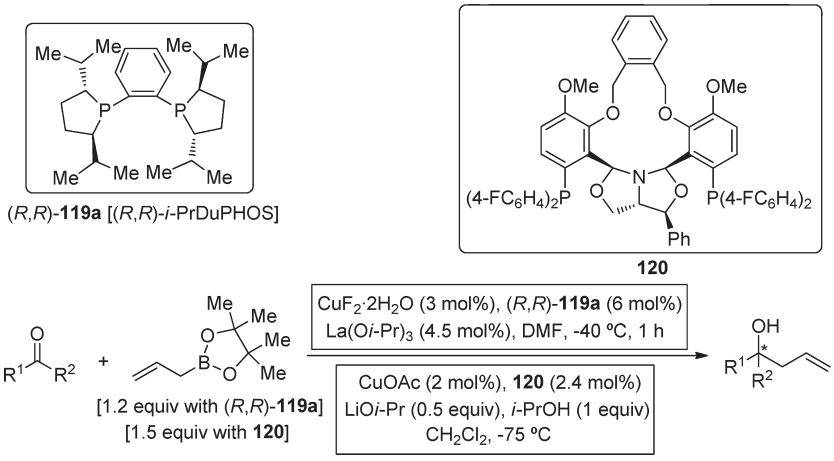
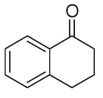


Table 57. Enantioselective Allylboration of Ketones Catalyzed by Cu(I) in the Presence of Chiral Phosphanes



			CuF·(*R*,*R*)-**119a**		CuOAc·**120**	
entry	R^1	R^2	yield (%)	ee (%)	yield (%)	ee (%)
1	Ph	Me	94	82	99	89
2	4-MeC_6H_4	Me	89	84	98	92
3	3-MeC_6H_4	Me	83	83	99	87
4	3-thienyl	Me	84	85	94	93
5			88	84	99	98
6	1-cyclohexenyl	Me	87	90	91	90
7	*t*-Bu	Me	99	91	88	83

phosphonite (*R*,*R*)-**122** at −35 °C in THF. Zhang and Morken found that total conversion occurred after 18 h and that aromatic and aliphatic substituents were tolerated at the δ-carbon and provided products with high enantiomeric purity (Table 58).[136] Concerning the diene moiety, a remarkable inversion of the olefin geometry occurred, so the predominant reaction product was the (*E*,*Z*)-stereoisomer, whereas the (*E*,*E*)-isomer (when observed) was racemic. Importantly, substrates with allylic oxygenated substituents, which are supposed to be labile groups in the presence of late-transition metal catalysts, led also to the expected homoallylic alcohols in good yields and stereoselectivities (Table 58, entries 4 and 5).

Zhang and Morken proposed that the former allylation proceeded by a 3,3′-reductive elimination of a bis(allyl)metal species, which is obtained by boron Lewis acid promoted electron transfer from Ni(0) to the enal, followed by transmetalation of the allyl group from B to Ni (Scheme 23). This mechanism could explain that the stereoselectivity was dependent upon the diene substituents, even when these groups were 5 atoms away from the newly formed stereocenter.

4.2. Allylation of Imines and Imine Derivatives

The first catalytic enantioselective allylation of ketimines was reported by Nakai and Shibasaki, taking as reaction model the

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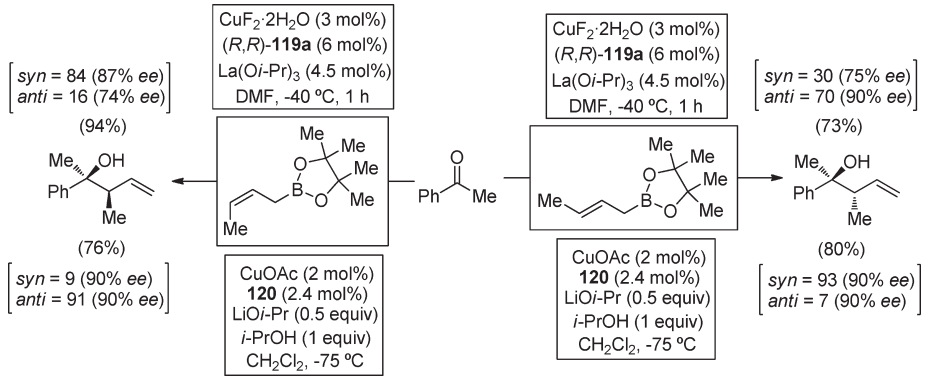
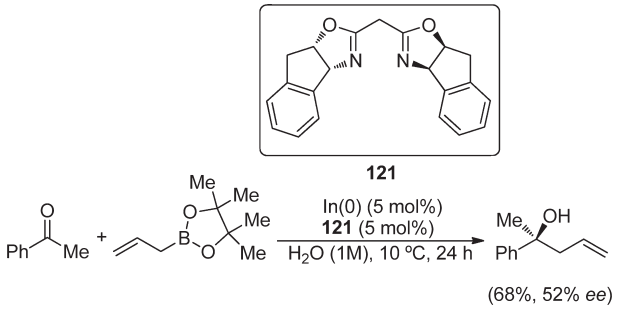
Scheme 21



Scheme 22

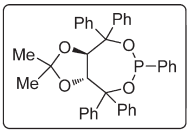


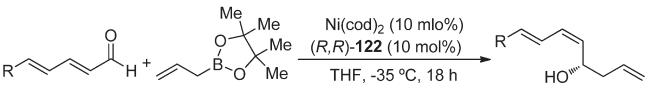
enantioselective allylation of methyl ketones procedure (Scheme 21) that was developed by the same group. Allylation of *N*-benzylketimines with the allylboronic acid pinacol ester proceeded in the presence of CuF combined with a LiO*i*-Pr cocatalyst, with the sterically tuned (*R*,*R*)-cyclopentyl-DuPHOS [(*R*,*R*)-**119b**] being the optimum chiral ligand. The use of LiO*i*-Pr instead of La(O*i*-Pr)$_3$ led to a significant improvement of reaction rates. Although good yields and enantioselectivities were achieved for a broad range of aromatic ketones (Table 59, entries 1−7), aliphatic ketimines gave unsatisfactory enantioselectivity under these reaction conditions (Table 59, entry 8).[137]

On the basis of the different kinetic and NMR studies, Nakai and Shibasaki proposed the catalytic cycle shown in Scheme 24. At the beginning, the addition of LiO*i*-Pr increased the concentration of the allylcopper reagent, which is the active nucleophile, by generating an electron-rich precursor (copper alkoxyallylborate). Addition of the nucleophile to the ketimine produced the copper amide, and the liberation of the homoallyl amine occurred upon its reaction with *t*-BuOH, with concomitant production of CuO*t*-Bu. Finally, the allylcopper nucleophile was regenerated after reaction of the allylboronic acid pinacol ester with CuO*t*Bu. Indeed, the catalytic cycle could be efficiently initiated by CuO*t*-Bu even in the absence of LiO*i*-Pr: using 10 mol % of CuO*t*Bu, the allylation of acetophenone imine proceeded in 3 h, to give the corresponding homoallyl amine in 76% yield.

The allylation of hydrazono esters with dialkoxy allyl boranes in the presence of a catalytic amount of ZnF_2 and the chiral diamine **12a** in a mixture of water and acetone as solvents afforded the allylated products in high yields and good enantioselectivities (Scheme 25). It is worthwhile to note that the reactions proceeded

Table 58. Enantioselective Allylboration of Dienals Catalyzed by Ni(II) in the Presence of the Chiral Phosphonite (*R*,*R*)-122





entry	R	yield (%)	(*E*,*Z*)/(*E*,*E*)	ee (%)
1	Me	84	>20:1	88
2	$Me(CH_2)_4$	84	>20:1	87
3	Ph	68	>20:1	91
4	$BnOCH_2$	86	15:1	73
5	$TBSOCH_2$	81	7:1	85
6	Cy	92	>20:1	93
7	2-furyl	73	15:1	94
8	$TBSOCH_2CH_2$	83	16:1	90

faster than those using allyltrimethoxysilane as the nucleophile source (compare Tables 5 and 6). The reaction did not take place in the absence of water. Regarding the allylating reagent, the allylboronic acid pinacol ester and cyclic boronates, such as allyldioxaborolane and allyldioxaborinane, gave the same levels of yield and enantioselectivity (Scheme 25).[138]

The allylations with (*E*)- and (*Z*)-crotylboronates under the optimal conditions proceeded in low yield (19% and 25%, respectively, after 110 h). Interestingly, α-substituted allylboronates reacted with the methyl hydrazono ester under the optimal conditions to give the expected allylated product in high yields. In all cases, independent of the substituent, only formal α-addition products were obtained with relative anti-configuration with high enantioselectivities (Table 60).[138]

To explain the unprecedented reaction pathway, Kobayashi and co-workers proposed a catalytic cycle (Scheme 26)[138] in which the initial step was the reaction of the allylboronate with ZnF_2 to form the γ-substituted (*Z*)-allylzincate via a six-membered chairlike transition state. The allylzincate may react stereoselectively with the hydrazono ester of methyl oxoacetate

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Scheme 23

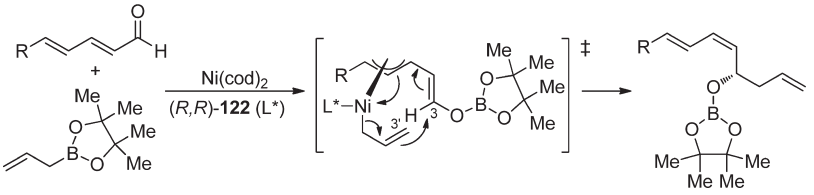
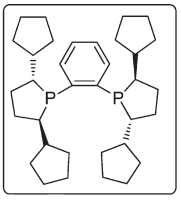
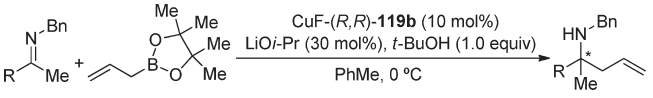


Table 59. Enantioselective Allylation of Ketimines Catalyzed by Cu(I) in the Presence of the Chiral Bisphosphane (*R,R*)-119b



(*R,R*)-**119b** [(*R,R*)-cyclopentyl-DuPHOS]



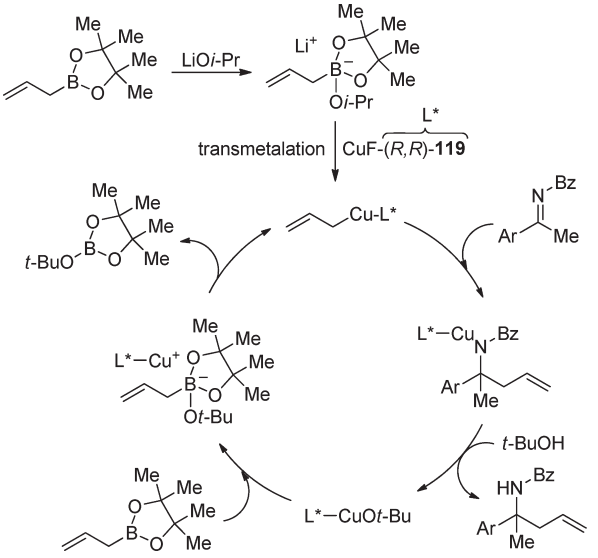
entry	R	*t* (h)	yield (%)	ee (%)
1	Ph	0.5	92	89[a]
2	3-MeC_6H_4	1	96	91
3	3-MeOC_6H_4	1	97	93
4	3-FC_6H_4	1	89	87
5	4-MeOC_6H_4	24	76	85
6	4-ClC_6H_4	24	82	81
7[b]	2-naphthyl	12	88	92
8[c]	Ph$(CH_2)_2$	2	98	23

[a] The absolute configuration was determined to be (*R*). [b] THF was used as solvent. [c] (*R,R*)-**119a** was used as the chiral ligand.

via a γ-addition, giving the adduct with anti-relative configuration, which, after hydrolysis, led to the corresponding reaction product along with Zn(OH)F or other active Zn species.

Excellent allylated product yields and high levels of stereocontrol were obtained in the asymmetric InI catalyzed allylation of hydrazones derived from aromatic aldehydes. Kobayashi and co-workers found the chiral semicorrin ligand **123** to be the best ligand for stabilizing the labile InI, thus creating excellent environments for asymmetric induction. Different aromatic substrates bearing functionalities such as hydroxy, methoxy, tertiary amino, and nitro groups were allylated in high yields with excellent enantioselectivities, using the allylboronic acid pinacol ester under optimized reaction conditions (Table 61, entries 1−7).[139] Lower yield and poorer enantioselectivity were obtained with the aliphatic cyclohexane carbaldehyde imine derivative (Table 61, entry 8). Crotylation of aromatic and heteroaromatic substrates with the racemic α-methylallyl boronic acid pinacol ester under similar reaction conditions and in the presence of the same InI·**123** complex produced exclusively the α-adduct with anti/syn ratios of up to 19:1 and enantioselectivities up to 93% ee (Table 61, entries 9−11). Importantly, α-adducts were also formed with highly reactive α-chloroallyl

Scheme 24



boronate in good yields with excellent anti/syn ratios (up to 99:1) and enantioselectivities (Table 61, entries 12−14).

Different experiments were carried out to clarify the mechanism of the former catalytic asymmetric allylation. Kobayashi and co-workers detected through MALDITOF-MS analysis the formation a metal−ligand complex in a 1:1 ratio (InI·**123**). Transmetalation was not observed after addition of the allylic boronate to a toluene/methanol solution of the InI·**123** complex. However, upon addition of the hydrazone, the asymmetric allylation occurred smoothly. It could be possible that hydrazone acted as a Lewis base to activate the allylic boronate for the transmetalation to take place, and then, the resulting chiral allylindium complex will participate in the nucleophilic addition to the imine derivative through a cyclic transition state (Scheme 27).[139]

5. ENANTIOSELECTIVE ADDITION OF ALLYLIC HALIDES

The enantioselective allylation of carbonyl compounds and imine derivatives with allylic halides using metals as mediating reagents under Barbier-type reaction conditions (metalation in the presence of the electrophile) is of great interest. This strategy circumvents the need of isolating allyl metal species (the real nucleophiles), which usually are sensitive and in many cases also toxic. Chromium and indium are the metals that have been more commonly used in these transformations, with zinc being used to a lesser extension.

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Scheme 25

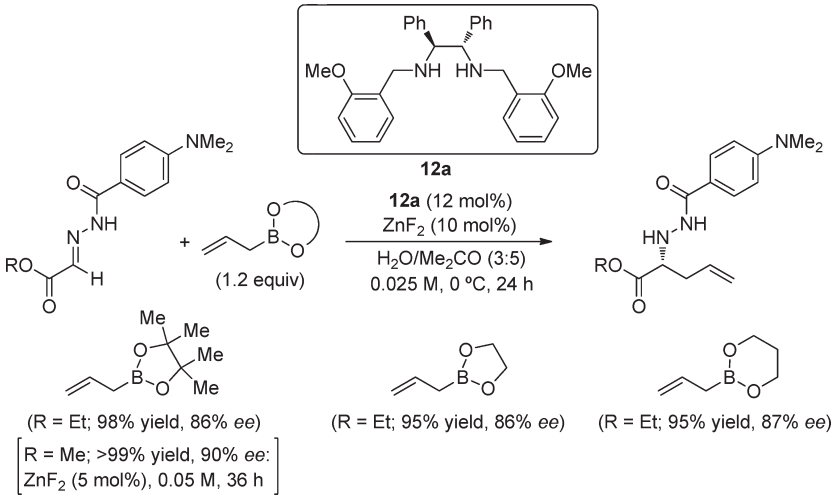
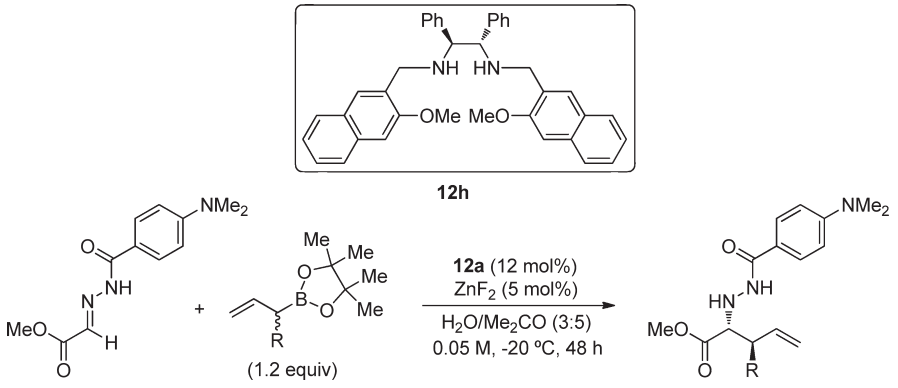


Table 60. Enantioselective Allylation of Hydrazono Ester Catalyzed by Zn(II) in the Presence of Chiral Diamines 12



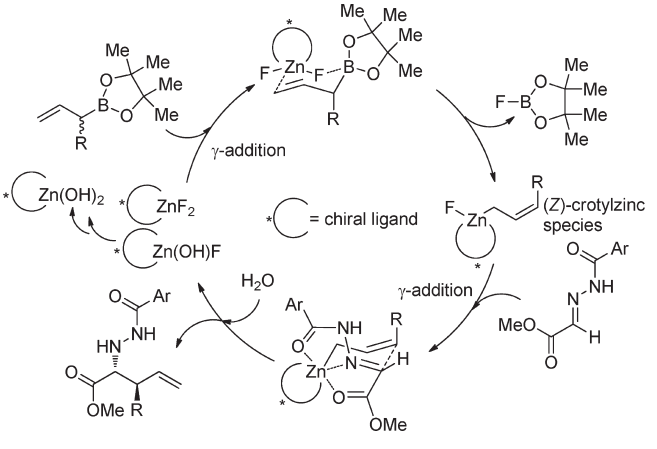
entry	R	yield (%)	α/γ	syn/anti	ee (%)
1	Me	>99	>99/<1	<1/>99	88
2	Et	98	>99/<1	<1/>99	87
3	*n*-Bu	88	>99/<1	<1/>99	87
4	$(CH_3)_2CHCH_2$	76	>99/<1	<1/>99	87
5[a]	OBn	65	>99/<1	<1/>99	82

[a] **12h** was used instead of **12a**.

5.1. Allylations Mediated by Chromium

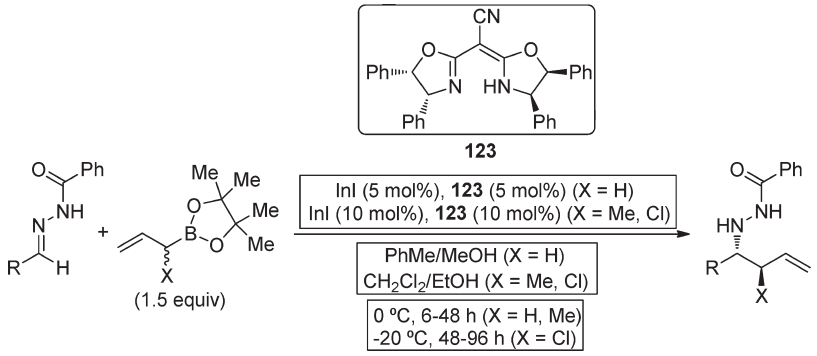
The coupling between allylic halides and aldehydes mediated by Cr(II) was reported for the first time by Nozaki, Hiyama, and co-workers in 1977.[140] The reaction proved to be highly chemoselective toward aldehydes, but with the disadvantage of the use of an excess of toxic chromium salts. Fürstner and Shi provided a methodology that allowed the allylation of aldehydes with allyl bromide in the presence of a catalytic amount of $CrCl_2$ and stoichiometric amounts of manganese and TMSCl, with both salts acting as the bulk reducing reagent, and as the quenching and turnover reagent, respectively.[141] On the bases of these findings, Cozzi, Umani-Ronchi, and co-workers reported the first enantioselective version of the chromium-mediated allylation of aldehydes using a chiral chromium salen catalyst derived from ligand **124**.[142] After that, modest to high enantioselectivities in the allylation of aldehydes were also obtained by Berkessel et al.[143] using an

Scheme 26



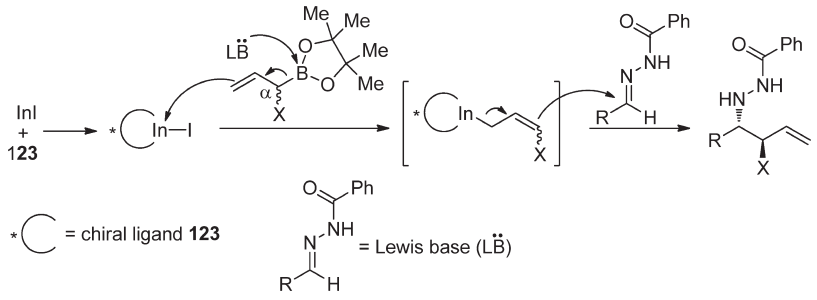
dx.doi.org/10.1021/cr1004474 |*Chem. Rev.* 2011, 111, 7774–7854

Table 61. Enantioselective Allylation of *N*-Benzoylhydrazones Catalyzed by In(I) in the Presence of the Chiral Semicorrin Ligand 123



entry	R	X	yield (%)	anti/syn	ee (%) (anti)
1	Ph	H	99		96
2	4-MeOC$_6$H$_4$	H	97		96
3	3-MeOC$_6$H$_4$	H	>99		95
4	4-Me$_2$NC$_6$H$_4$	H	88		99
5	4-NO$_2$C$_6$H$_4$	H	95		84
6	4-PhC$_6$H$_4$	H	98		96
7	2-thienyl	H	99		95
8	Cy	H	87		30
9	Ph	Me	85	19:1	94
10	4-MeOC$_6$H$_4$	Me	86	19:1	93
11	2-thienyl	Me	>99	15:1	88
12	Ph	Cl	84	99:1	84
13	2-naphthyl	Cl	71	33:1	81
14	2-thienyl	Cl	89	99:1	86

Scheme 27



analogous catalyst derived from **125** under rather similar reaction conditions, and by Nakada and co-workers[144] with a bis(oxazolinyl)carbazole ligand. For instance, allylation of benzaldehyde with allyl bromide under Cozzi/Umani-Ronchi conditions led to the homoallylic alcohol in 65% yield and 65% ee (Table 62, entry 1). Both yield and stereoselectivity were improved using the Berkessel protocol (Table 62, entry 2). Sigman and co-workers studied also the Cr-catalyzed allylation of aldehydes with allylic halides in the presence of chiral oxazoline ligands derived from simple amino acids. Therefore, a complete set of diastereomers of the ligand **126a** derived from phenylalanine, valine, and proline were synthesized and evaluated for the allylation of benzaldehyde. The ligand (*R*,*S*,*S*)-**126a** gave the highest yield (95%) and enantioselectivity (92% ee) in the addition of allyl bromide to benzaldehyde (Table 62, entry 6), with allyl chloride and allyl iodide yielding poorer results with the same ligand. Changing the catalyst diastereomer had a profound effect on the reaction outcome regarding both yield and stereoselectivity, with facial selection being completely reversed in some cases (Table 62, entry 5 vs 6).[145] The optimal diastereomer (*R*,*S*,*S*)-**126a** for the benzaldehyde allylation was chosen as a starting ligand structure for carbamate modifications to investigate their effect on the enantioselective outcome of the reaction. Different ligands (*R*,*S*,*S*)-**126** were synthesized from a common precursor by varying the size of the carbamate substituent on the nitrogen from a small group [methyl, (*R*,*S*,*S*)-**126c**] to a medium group [isopropyl, (*R*,*S*,*S*)-**126b**] and to a large group (adamantyl, not shown in Table 62) and were evaluated for the benzaldehyde allylation. A trend

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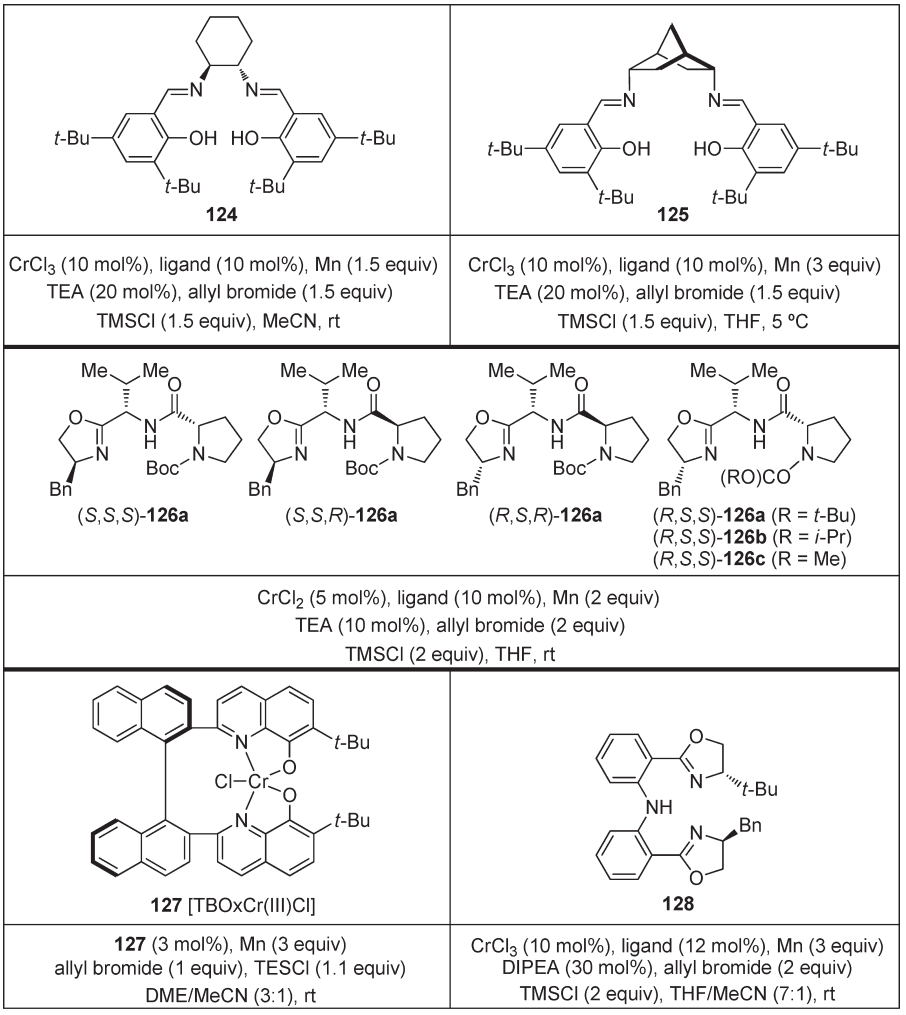
Table 62. Enantioselective Allylation of Benzaldehyde Mediated by Chiral Chromium Catalysts

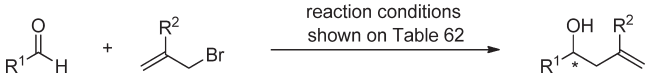


entry	chiral ligand or complex	yield (%)	ee (%)
1	**124**	65	65 (*R*)
2	**125**	72	90 (*R*)
3	(*S*,*S*,*S*)-**126a**	75	76 (*S*)
4	(*S*,*S*,*R*)-**126a**	88	36 (*R*)
5	(*R*,*S*,*R*)-**126a**	22	89 (*S*)
6	(*R*,*S*,*S*)-**126a**	95	92 (*R*)
7	(*R*,*S*,*S*)-**126b**	nd	66 (*R*)
8	(*R*,*S*,*S*)-**126c**	nd	20 (*R*)
9	**127**	93	98 (*R*)
10	**128**	88	87 (*R*)

between the relative size of the carbamate substituents and the ee of the product was observed. The methyl carbamate derivative (*R*,*S*,*S*)-**126c** led to a 20% ee (Table 62, entry 8); meanwhile, the isopropyl derivative (*R*,*S*,*S*)-**126b** led to a 66% ee (Table 62, entry 7). Enantioselectivity was the same for the largest groups, the *t*-butyl (*R*,*S*,*S*)-**126a** and the 1-adamantyl chiral ligands. A correlation between the size of the group and the enantiomeric ratio was also observed in the case of allylation of 3-phenylpropanal and acetophenone.[146] A chiral tethered bis-(8-quinolinolato) (TBOx) chromium catalyst **127** developed and synthesized by H. Yamamoto and co-workers was used in the enantio- and diastereoselective pinacol coupling reaction of aldehydes.[147] Somewhat expected, when this catalyst was used in the allylation of benzaldehyde with allyl chloride under typical Nozaki−Hiyama reaction conditions, the pinacol was the major reaction product instead of the homoallylic alcohol. The homoallylic alcohol turned out to be

dx.doi.org/10.1021/cr1004474 |*Chem. Rev.* 2011, 111, 7774–7854

Table 63. Enantioselective Allylation of Aldehydes Mediated by Chiral Chromium Catalysts



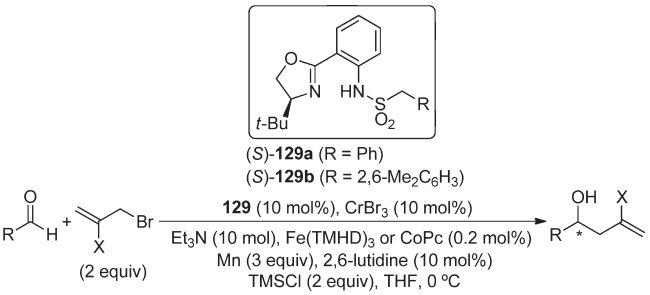
entry	R^1	R^2	chiral ligand or complex	yield (%)	ee (%)
1	4-$MeOC_6H_4$	H	(*R*,*S*,*S*)-**126a**	95	89 (*R*)
2	2-furyl	H	(*R*,*S*,*S*)-**126a**	73	92 (*R*)
3	PhCH=CH	H	(*R*,*S*,*S*)-**126a**	79	89 (*R*)
4	$PhCH_2CH_2$	H	(*R*,*S*,*S*)-**126a**	94	46 (*S*)
5	2-MeC_6H_4	H	**127**	83	83 (*R*)
6	1-naphthyl	H	**127**	81	93 (*R*)
7	2-furyl	H	**127**	87	97 (*R*)
8	$CH_3(CH_2)_6$	H	**127**	89	97 (*S*)
9	*t*-Bu	H	**127**	68	97 (*R*)
10	4-ClC_6H_4	H	**128**	98	86 (*R*)
11	$CH_3(CH_2)_5$	H	**128**	69	91 (*S*)
12	4-$MeOC_6H_4$	Me	**128**	69	59 (*R*)
13	$CH_3(CH_2)_5$	Me	**128**	71	89 (*S*)

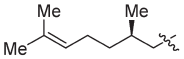
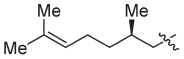
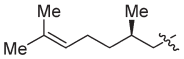
the major product when the allylation was performed with more reactive allyl bromide. Optimal yield (93%) and enantioselectivity (98% ee) were obtained in the allylation of benzaldehyde when the catalyst **127** was mixed with Mn in MeCN and DME under an Ar atmosphere at room temperature, followed by addition first of allyl bromide and, after 30 min, of benzaldehyde and TESCl (Table 62, entry 9).[148] Guiry and co-workers found that the nonsymmetric *tert*-butyl/benzyl-substituted bis(oxazoline) ligand **128** proved to be also the optimal ligand, in a series of symmetric and nonsymmetric bis(oxazolines), for the Nozaki–Hiyama stereoselective allylation of benzaldehyde (Table 62, entry 10).[149] Other nonsymmetrical bis(oxazoline)-containing ligands possessing an *N*-thienylaniline unit were also synthesized and subsequently applied in the chromium-catalyzed enantioselective Nozaki–Hiyama–Kishi allylation of benzaldehyde, but enantioselectivities were always lower than those obtained with **128**.[150]

The scope of the allylation reaction was studied using the previously mentioned procedures. For chiral ligand (*R*,*S*,*S*)-**126a**, high yields and excellent enantioselectivities were obtained with aryl, heteroaryl, and α,β-unsaturated aldehydes (Table 63, entries 1–3); meanwhile, the aliphatic aldehyde 3-phenylpropanal led to the poorest enantiomeric excess (Table 63, entry 4).[145] Higher enantioselectivities were obtained in the allylation of all kinds of aldehydes using catalyst **127** (Table 63, entries 5–9).[148] Ligand **128** performed well also in the allylation of aromatic and aliphatic aldehydes (Table 63, entries 10 and 11).[149] However, lower enantioselectivities were obtained in the methallylation of these aldehydes (Table 63, entries 12 and 13).[151]

Kishi and co-workers also achieved excellent yields and enantioselectivities in the allylation of aldehydes using a Cr–ligand complex generated from the sulphonamide (*S*)-**129a** and $CrCl_3\cdot 3THF$ in the presence of Et_3N, Mn, and TMSCl. However, all attempts to perform the allylation with 2,3-dibromopropene under the previous optimized reaction conditions failed.[152] It has been pointed out that the reactivity of this dibromide against the reducing metals was electronically and sterically attenuated by the bromine at the β-position. The reactivity of the ligand (*S*)-**129a**–Cr complex was enhanced by replacing

Table 64. Enantioselective Allylation of Aldehydes Mediated by Chromium and Chiral Ligands 129



entry	R	X	chiral ligand	yield (%)	ee or de (%)
1[a]	$Me(CH_2)_5$	Br	(*S*)-**129a**	75	93 (*R*)
2[a]	$TBDPSO(CH_2)_3$	Br	(*S*)-**129a**	75	92 (*R*)
3[a]	$(EtS)_2CH(CH_2)_2$	Br	(*S*)-**129a**	70	90 (*R*)
4[a]	$Me(CH_2)_2CH=CH$	Br	(*S*)-**129a**	75	87 (*S*)
5[a]	PhCH=CH	Br	(*S*)-**129a**	75	83 (*S*)
6[a]	Ph	Br	(*S*)-**129a**	86	84 (*S*)
7[b]	$TBDPSO(CH_2)_3$	I	(*S*)-**129a**	63	93 (*R*)
8[b]		I	(*S*)-**129b**	70	94 (*R*)
9[b]	$TBDPSO(CH_2)_3$	Br	(*S*)-**129b**	82	93 (*R*)
10[b]		Br	(*R*)-**129b**	73	97 (*S*)
11[b]	$TBDPSO(CH_2)_3$	Cl	(*S*)-**129b**	71	92 (*R*)
12[b]		Cl	(*S*)-**129b**	75	93 (*R*)

[a] $Fe(TMHD)_3$ was used. [b] CoPc was used.

$CrCl_3$ with $CrBr_3$ in the presence of iron tris-(2,2,6,6-tetramethyl-3,5-heptanedione) [$Fe(TMHD)_3$]. Fortunately, 2-bromoallylation of saturated aldehydes in the presence of 10 mol % of the complex generated from (*S*)-**129a**, $Fe(TMHD)_3$, $CrBr_3$, Mn, Et_3N, TMSCl, and 2,6-lutidine in THF afforded, after selective TMS-desilylation, the desired products in high yields and excellent stereoselectivities (Table 64, entries 1–3). However, α,β-unsaturated and aromatic aldehydes gave slightly lower ee's (83–87%) (Table 64, entries 4–6). It was demonstrated that $CrBr_3$ is a chromium source superior to $CrCl_3\cdot 3THF$ in terms of reaction rate, chemical yield, asymmetric induction, and cost. Kishi and co-workers noticed that an active chromium–bromide complex was formed via cobalt phthalocyanine (CoPc) and that the Co/Cr-mediated system enhanced the reaction rate (Table 64, entry 7). Kishi and co-workers reported also that sulfonamide **129b** performed well as a ligand for Cr-mediated catalytic asymmetric 2-haloallylation and allylation and that the high crystallinity of ligand **129b** allowed its effective recovery from the reaction in a pure form, with the latter being an advantage over ligand **129a**. Under the optimized conditions, 2-iodoallyl, 2-bromoallyl, and 2-chloroallyl bromides were coupled with different aldehydes (Table 64, entries 8–12).[153]

Regarding the mechanism of the chromium-mediated allylation of aldehydes, low-valent Co and Fe species are known to facilitate radical formation from alkyl halides. First, the **129**/Cr(II) complex is formed from Fe(III) or Co(II)/$CrBr_3$/Mn/

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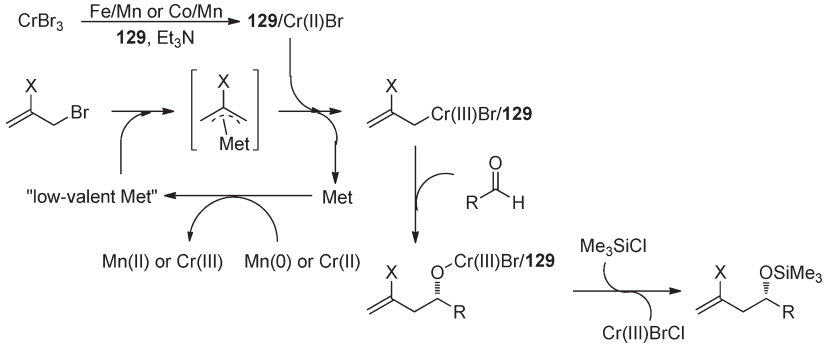
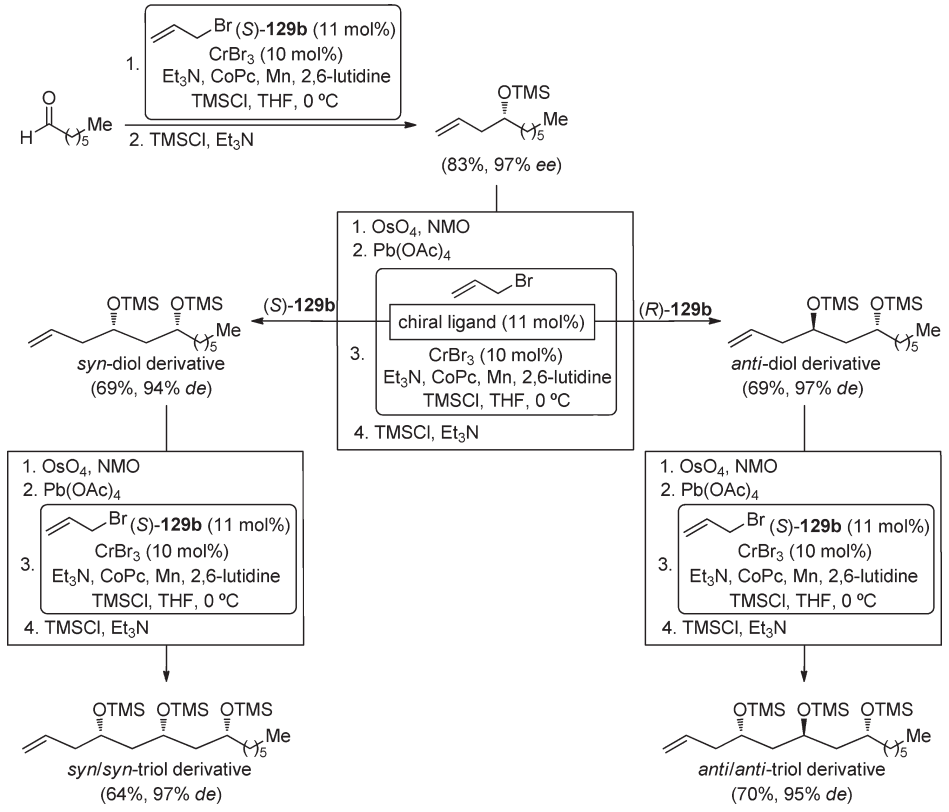
Scheme 28



Scheme 29



Et_3N. A transmetalation between the **129**/Cr(II) complex and the metalloallyl species should result in the **129**/allyl−Cr(III) complex. This complex would then undergo the addition to aldehydes through a cyclic six-membered transition state to give de Cr(III) alcoholate, which by reaction with TMSCl would liberate the Cr(III) salt (Scheme 28).[152]

The iterative use of the Kishi's Cr-mediated catalytic asymmetric allylation of aldehydes allowed access to 1,3-polyols[154] with total stereochemical control, making it possible to prepare *syn/syn*- and *anti/anti*-1,3,5-triols. Regarding the protecting groups of the hydroxy groups, the sterically least demanding TMS was found to give the most satisfactory results on both asymmetric induction and yield. After the first chromium-mediated allylation in the presence of (*S*)-**129b**, the TMS-protected homoallylic alcohol was submitted to oxidative cleavage and subsequent Cr-mediated catalytic asymmetric allylation in the presence of sulfonamide ligand (*S*)-**129b** or its enantiomer (*R*)-**129b**, followed by TMS protection. After that, the second cycle of iteration in the presence of sulphonamide (*S*)-**129b** led to *O*-TMS protected *syn/syn*- and *anti/anti*-1,3,5-triol derivatives, respectively (Scheme 29).[155]

Allylation of different kinds of aldehydes with γ-substituted allyl bromides has also been studied under the here-mentioned asymmetric variants of the Nozaki−Hiyama allylation. Sigman and coworkers found that the crotylation of benzaldehyde with (*E*)-crotyl bromide in the presence of (*R,S,S*)-**126a** led to an anti/syn ratio of 2.3:1. This low diastereoselectivity was similar to all reported asymmetric crotylations using Fürstner/Nozaki−Hiyama conditions. In contrast to these reports, this crotylation led to high enantiomeric

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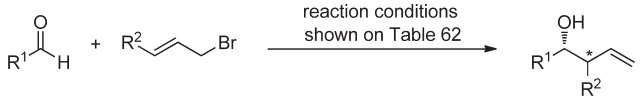
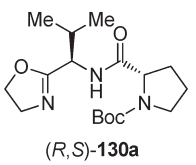
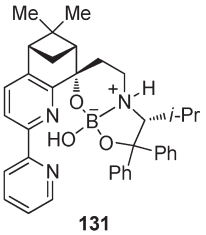
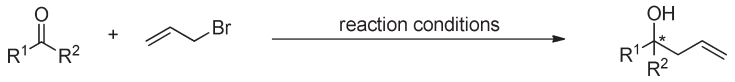
Table 65. Enantioselective Allylation of Aldehydes with γ-Substituted Allyl Bromides Mediated by Chiral Chromium Catalysts

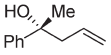
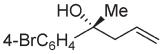
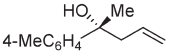
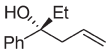
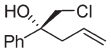
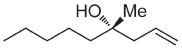
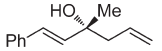


entry	R^1	R^2	chiral ligand or complex	yield (%)	anti/syn	ee (%) anti/syn
1	Ph	Me	(*R*,*S*,*S*)-**126a**	88	2.3:1	91/95
2	Ph	Me	**127**	84	4.4:1	97/97
3	Ph	*n*-Pr	**127**	71	8.4:1	91/91
4	Ph	$CH_3(CH_2)_4$	**127**	65	10.3:1	90/87
5	Cy	Me	**127**	73	6.3:1	96/97
6	Ph	Me	**128**	77	77:23	82/90
7	4-$MeOC_6H_4$	Me	**128**	87	80:20	71/80
8	$CH_3(CH_2)_4$	Me	**128**	60	74:26	83/90

Table 66. Enantioselective Allylation of Ketones Mediated by Chiral Chromium Catalysts

 (*R*,*S*)-**130a**	 **131**
$CrCl_3$ (10 mol%), (*R*,*S*)-**130a** (10 mol%), Mn (2 equiv) TEA (20 mol%), allyl bromide (2 equiv) TMSCl (4 equiv), THF, 0 °C	$CrBr_3$ (5 mol%), **131** (5 mol%), Mn (1.5 equiv) TEA (10 mol%), allyl bromide (1.5 equiv) TMSCl (1.5 equiv), THF, rt



		(*R*,*S*)-**130a**		**131**	
entry	product	yield (%)	ee (%)	yield (%)	ee (%)
1		82	92	75	73
2		73	90	82	81
3		94	86	82	57
4		64	59	--	--
5		77	93	76	60
6		56	90	--	--
7		--	--	75	73
8		--	--	77	77

excess for both diastereomers with 95% ee for the syn- and 91% ee for the anti-diastereomer (Table 65, entry 1).[145] On the other hand, a mixture of the anti- and syn-diastereomers, favoring always the anti-product, was obtained by allylation of benzaldehyde with γ-substituted allyl bromides under the reaction conditions developed by Xia and H. Yamamoto with the chromium catalyst **127**.

When the size of the substituent at the γ-position was decreased, lower diastereoselectivities were observed with higher yields and similar enantioselectivities (Table 65, entries 2−4).[148] Similarly, Guiry and co-workers found that the crotylation of aromatic and aliphatic aldehydes with crotyl bromide, under identical reaction conditions shown in Table 65 with chiral ligand **128**, proceeded

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Scheme 30

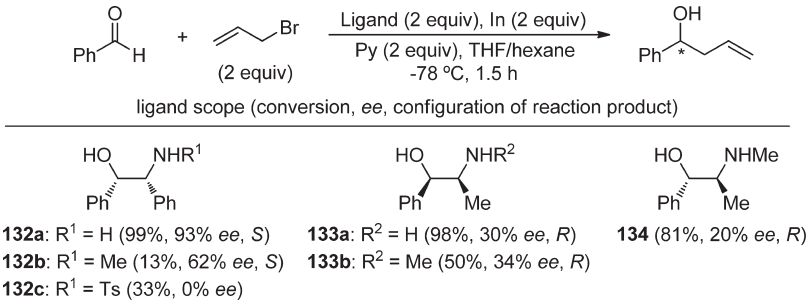
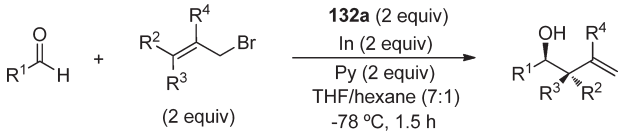


Table 67. Indium-Promoted Stereoselective Allylation of Aldehydes with Allylic Bromides in the Presence of the Amino Alcohol 132a



entry	R^1	R^2	R^3	R^4	yield (%)	ee (%) (anti/syn)
1	Ph	H	H	H	90	93
2	4-$MeOC_6H_4$	H	H	H	92	89
3	2-MeC_6H_4	H	H	H	94	88
4	4-$(CO_2Me)C_6H_4$	H	H	H	94	76
5	4-CNC_6H_4	H	H	H	99	80
6	Cy	H	H	H	93	93
7	Ph	Me	H	H	99	72 (57:43)
8	Ph	H	H	Me	70	45
9	Ph	Me	Me	H	54	56
10	Ph	Ph	H	H	50	56 (>95:5)

with total regioselectivity, leading to the corresponding homoallyl alcohols with moderate diastereoselectivity (up to 80:20 anti/syn) and good isolated yields (Table 65, entries 6−8).[149] Interestingly, the enantioselectivity of the minor syn-diastereomer was higher than that of the anti-diastereomer for the majority of substrates.

Miller and Sigman investigated also the stereoselective allylation of ketones using oxazoline ligands **126** without modifying the previously reported aldehyde allylation conditions. Allylation of acetophenone with allyl bromide using ligand (*R*,*S*,*S*)-**126a** led to the corresponding tertiary homoallylic alcohol in 40% yield and 66% ee. However, an increase in the enantioselectivity (82% ee) and in the yield (69%) of the acetophenone allylation product was obtained with the most simple ligand (*R*,*S*)-**130a**. Optimization of the catalytic system using the ligand (*R*,*S*)-**130a** and acetophenone led to the use of 4 equiv of TMSCl, which increased the isolated yield with no detrimental effects on the ee. Lowering the reaction temperature from room temperature to 0 °C enhanced the stereoselectivity (92% ee, Table 66, entry 1). Aryl ketones were excellent substrates under the optimized reaction conditions (Table 66, entries 1−6).[156] The enantioselective allylation of alkyl and aryl ketones using allyl bromide was also studied by Chen and co-workers, but in this case in the presence of Cr(III) salts and different rigid chiral spirocyclic borate ligands. The best enantioselectivity was obtained with $CrBr_3$ and chiral borate **131**. Aryl

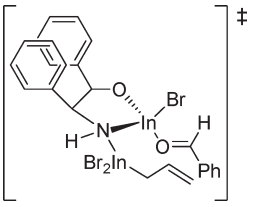


Figure 14. Proposed transition state for the indium-mediated allylation of benzaldehyde in the presence of **132a**.

ketones with a wide range of functional groups were excellent substrates for the transformation. Notably, similarly high levels of reactivity and enantioselectivity were observed for aliphatic ketones and α,β-unsaturated methyl ketones under identical reaction conditions (Table 66, entries 7 and 8).[157]

5.2. Allylations Mediated by Indium

Indium-mediated allylation of carbonyl compounds and imines with allyl halides are of great interest because of the low toxicity of the metal and the high tolerance to a wide range of functional groups, aqueous solvents, and exposure to air.[158]

5.2.1. Allylation of Carbonyl Compounds. The indium-mediated enantioselective allylation of both aromatic and aliphatic aldehydes using commercially available amino alcohols as chiral ligands under Barbier-type reaction conditions was reported by Singaram and co-workers . Two equiv each of indium, allyl bromide, aminoalcohol, and pyridine, with respect to the aldehyde in a mixture of THF and hexane in a 7:1 ratio, were the optimized reaction conditions used. Importantly, chiral aminoalcohols are recovered via a simple acid−base extraction in high yields. The highest enantioselectivity was obtained with (1*S*,2*R*)-2-amino-1,2-diphenylethanol (**132a**). Other structurally similar ligands under the optimized reaction conditions, such as amino alcohols **132b,c**, norephedrine (**133a**), ephedrine (**133b**), and pseudoephedrine (**134**), were found to be significantly less effective as chiral promoters (Scheme 30).[159]

Aromatic and aliphatic aldehydes were allylated with allyl bromide in the presence of **132a** to give the corresponding homoallylic alcohols in excellent yields (up to 99%) and enantioselectivities (up to 93% ee) (Table 67, entries 1−5). This method demonstrated to be highly chemoselective, so the allylation of the aldehyde took place in the presence of ester and nitrile functionalities (Table 67, entries 4 and 5). Additionally, these results showed that the para-substituted aldehydes containing electron-donating groups (Table 67, entry 2) gave a higher enantiomeric excess than those with an electron-withdrawing

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Scheme 31

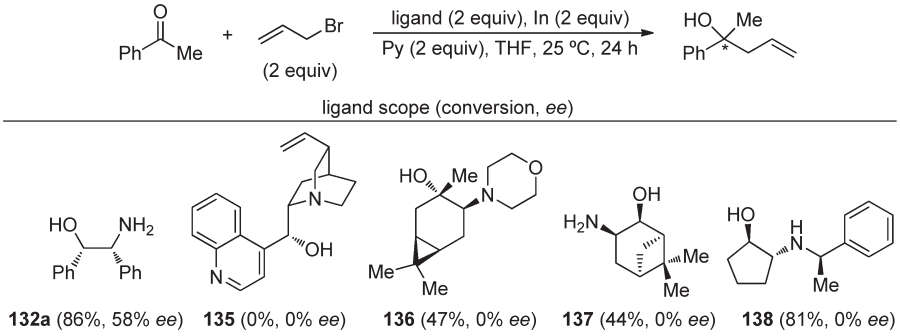
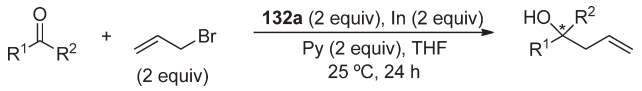


Table 68. Indium-Promoted Stereoselective Allylation of Ketones with Allyl Bromide in the Presence of Amino Alcohol 132a



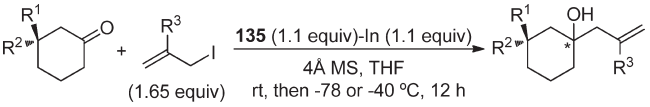
entry	R^1	R^2	ligand	conversion (%)	ee (%)
1	Ph	Me	**132a**	87	58 (*S*)
2	Ph	Me	*ent*-**132a**	72	57 (*R*)
3	4-CNC_6H_4	Me	**132a**	92	48 (*S*)
4	4-$(CO_2Me)C_6H_4$	Me	**132a**	74	48 (*S*)
5	4-HOC_6H_4	Me	**132a**	77	41 (*S*)
6	2-furyl	Me	**132a**	>99	44 (*S*)
7	*n*-Bu	Me	**132a**	77	45 (*S*)
8	Cy	Me	**132a**	46	42 (*S*)
9	*t*-Bu	Me	**132a**	81	64 (*S*)
10	Ph	CF_3	**132a**	94	80 (*S*)
11	Ph	CF_3	*ent*-**132a**	>99	78 (*R*)

group in the para-position (Table 67, entries 4 and 5). Good enantioselectivity and poor diastereoselectivity were obtained in the allylation of benzaldehyde under optimized reaction conditions with (*E*)-crotyl bromide (Table 67, entry 7); meanwhile, allylation with cinnamyl bromide led to poor enantioselectivity and good diastereoselectivity (Table 67, entry 10). Other substituted allylic bromides provided low yields and enantiomeric excesses (Table 67, entries 8 and 9).[160]

On the basis of experimental data, Singaram and co-workers proposed a possible transition state for the indium-mediated allylation of benzaldehyde in the presence of the chiral amino alcohol **132a**, which is shown in Figure 14.[160] From this model, an attack to the *Si*-face of the aldehyde occurred, which was in agreement with the fact that the (*S*)-homoallylic alcohol was obtained when aminoalcohol **132a** was used.

Singaram studied also the enantioselective allylation of both aromatic and aliphatic ketones under indium-mediated Barbier-type conditions in the presence of chiral amino alcohols. Allylation of acetophenone with allyl bromide under the previously reported optimized reaction conditions for the allylation of aldehydes did not take place at −78 °C. Fortunately, allylation of ketones occurred at 25 °C after 24 h because ketones are generally less reactive than aldehydes. Different chiral amino alcohols were screened for their efficiency in the allylation of ketones. The chiral amino

Table 69. Indium-Promoted Stereoselective Allylation of 3-Substituted Cyclohexanones with Allylic Bromides in the Presence of (−)-Cinchonidine (135)



entry	R^1	R^2	R^3	*T* (°C)	yield (%)	ee (%)
1	OCH_2CH_2O		H	−78	79	87
2	OCH_2CH_2O		Me	−40	71	58
3	SCH_2CH_2S		H	−40	54	64
4	SCH_2CH_2S		Me	−40	23	30
5	Me	Me	H	−40	37	40
6	Me	Me	Me	−40	38	31

alcohol **132a** was also found to be the most effective ligand in the addition of allyl bromide to acetophenone. The addition did not occur with (−)-cinchonidine (**135**); amino alcohols **136**−**138** provided moderate conversion of acetophenone (47%, 44%, and 81%), and the product was racemic (Scheme 31).[161]

High conversions and moderate enantioselectivities were obtained in the allylation of aryl and alkyl methyl ketones with allyl bromide in the presence of **132a** and/or *ent*-**132a** (Table 68), thus permitting access to both homoallylic tertiary enantiomeric alcohols (Table 68, compare entries 1 and 2). The reaction with the more sterically demanding *tert*-butyl methyl ketone afforded the product with a higher enantiomeric excess of 64% (Table 68, entry 9). Similarly, α,α,α-trifluoroacetophenone produced the corresponding homoallylic alcohol in 80% ee, the highest observed for this ketone under indium-mediated Barbier reaction (Table 68, entry 10).[161]

Monodioxolane protected 1,3-cyclohexadione was converted into bridgehead hydroxyl bicyclo[2.2.2]octane derivative through a three-step process: first, an enantioselective indium-mediated allylation, followed by ozonolysis and intramolecular aldol addition. Frejd and co-workers studied the asymmetric allylation of 3,3-disubstituted derivatives of cyclohexanone with different allylic bromides in the presence of indium metal and (−)-cinchonidine (**135**).[162] Remarkably, 1.1 equiv of chiral ligand were used instead of 2 equiv as previously reported in similar processes. The highest yield and enantioselectivity was obtained in the case of the spiro dioxolane derivative at −78 °C

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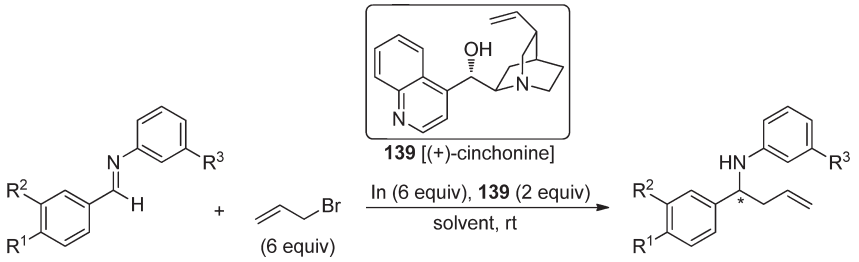
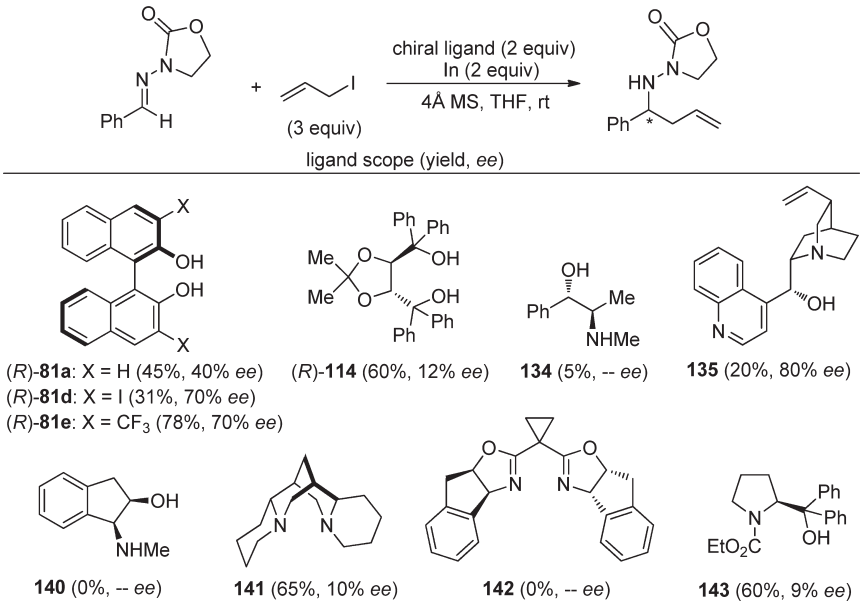
Table 70. Indium-Promoted Stereoselective Allylation of Aryl Aldimines with Allyl Bromide in the Presence of (+)-Cinchonine (139)



entry	R^1	R^2	R^3	solvent	*t* (h)	yield (%)	ee (%)
1	H	H	H	THF	20	76	28
2	H	H	H	THF/hexane (3/1)	26	89	33
3	Cl	H	H	THF	17	86	28
4	Cl	H	H	THF/hexane (3/1)	25	91	30
5	EtO	H	H	THF	26	84	24
6	EtO	H	H	THF/hexane (3/1)	22	68	44
7	H	Br	H	THF	26	88	20
8	Me	H	H	THF	22	84	26
9	*i*-Pr	H	H	THF	20	83	24
10	H	Cl	H	THF	22	93	24
11	H	H	MeO	THF	22	70	34

Scheme 32



(Table 69, entry 1). The yields and enantioselectivities obtained from the allylation of dithiolane and dimethyl derivatives (Table 69, entries 3 and 5, respectively) were lower compared to the dioxolane one. Additionally, allylation with the bulkier methallyl bromide resulted in products of both lower yields and enantiomeric excesses in all cases (Table 69, entries 2, 4, and 6).

5.2.2. Allylation of Imine and Imine Derivatives. The indium-promoted allylation of *N*-aryl substituted aldimines derived from aromatic aldehydes in the presence of 2 equiv of (+)-cinchonine (**139**) yielded homoallyl amines with excellent yields and moderate enantiomeric excesses (22−44%). The yields and stereoselectivities were not significantly affected by the substituents attached to the aromatic rings, regardless of whether the substituent was electron-withdrawing or -donating. A slight improvent of the enantioselectivity was achieved by using a THF/hexane (3/1) mixture as solvent, instead of THF (Table 70, compare entries 1, 3, and 5 to entries 2, 4, and 6, respectively).[163]

On the basis of the excellent success obtained in the addition of allylindium reagents to chiral hydrazones,[164] Cook et al. investigated the enantioselective variation of this reaction. The influence of

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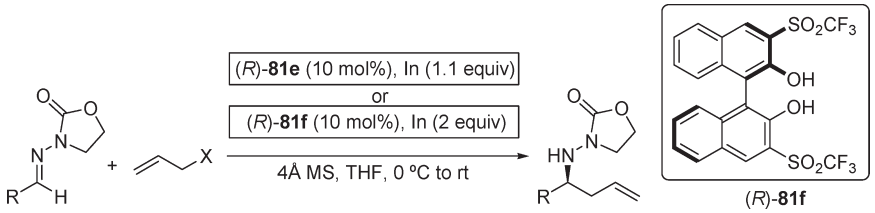
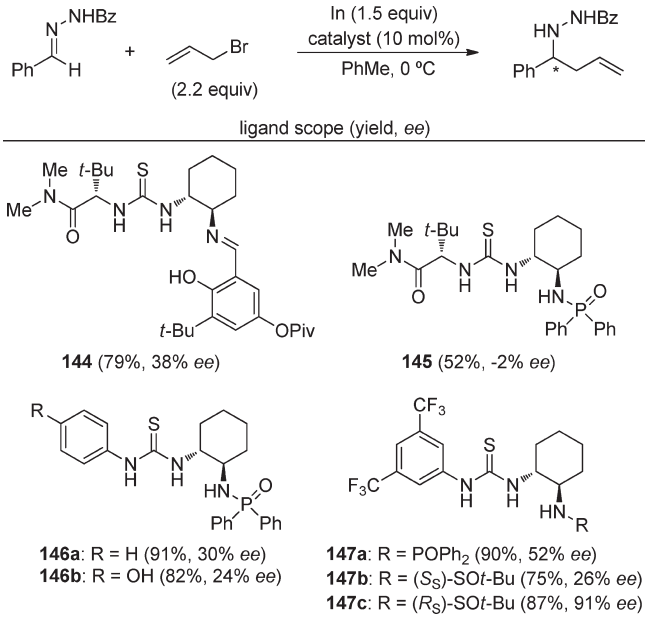
Table 71. Indium-Promoted Stereoselective Allylation of Hydrazones with Allyl Iodide in the Presence of BINOLs (*R*)-81e and (*R*)-81f



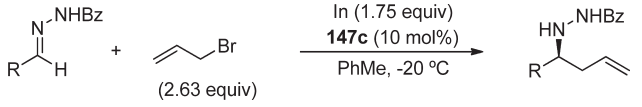
		(*R*)-81e		(*R*)-81f	
entry	R	yield (%)	ee (%)	yield (%)	ee (%)
1	Ph	77	70	82	90
2	4-MeC_6H_4	60	70	98	87
3	4-$MeOC_6H_4$	74	77	96	95
4	4-ClC_6H_4	78	82	96	92
5	2-BrC_6H_4	76	85	96	99
6	2-ClC_6H_4	67	91	99	99
7	1-naphthyl	65	70	96	98
8	2-furyl	70	70	94	92
9	(*E*)-PhCH=CH	79	34	87	97
10	$Ph(CH_2)_2$	73	34	88	70

Scheme 33



different chiral ligands on the stereochemical outcome of the allylation of achiral hydrazone derived from benzaldehyde and *N*-amino oxazolidinone with 3 equiv of allyl iodide in the presence of 2 equiv of indium metal and 2 equiv of a chiral ligand was studied (Scheme 32). The use of (−)-cinchonidine (**135**) afforded the expected homoallyl amine derivative in good enantioselectivity (80% ee) but very poor yield (20%). Allylation did not take place with the aminoindanol derivative **140** and bisoxazoline **142**; meanwhile, pseudoephedrine (**134**) led to the reaction product in 5% yield in racemic form. Other ligands such as (−)-sparteine

Table 72. Indium-Promoted Stereoselective Allylation of Hydrazones with Allyl Bromide in the Presence of the Chiral Sulfinamide 147c



entry	R	yield (%)	ee (%)
1	Ph	87	92
2	4-ClC_6H_4	83	92
3	2-furyl	90	87
4	2-thienyl	82	93
5	4-$(CO_2Me)C_6H_4$	92	76
6	2-BrC_6H_4	78	93
7	2-MeC_6H_4	89	95
8	1-naphthyl	89	95
9	4-$MeOC_6H_4$	79	93

(**141**), the pyrrolidine **143**, and the (−)-TADDOL (*R*)-**114** afforded moderate yields and very poor stereoselectivities. Whereas modest yield and stereoselectivity were also obtained with the (*R*)-BINOL (*R*)-**81a**, the 3,3′-diiodo BINOL (*R*)-**81d** resulted in an improvement in selectivity, and the 3,3′-bistrifluoromethyl-BINOL (*R*)-**81e** performed the best, affording a 78% yield of the allylated product in 70% ee (Scheme 32).[163]

Surprisingly, the allylation of the hydrazone derived from benzaldehyde was also carried out with good selectivity, employing only 10 mol % of (*R*)-**81e**, 1.1 equiv of In, and 1.5 equiv of allyl iodide, giving the expected reaction product in 77% yield and 70% ee (Table 71, entry 1). The method showed to be general for aromatic, heteroaromatic, aliphatic, and α,β-unsaturated aldehyde derived hydrazones and represented the first successful example

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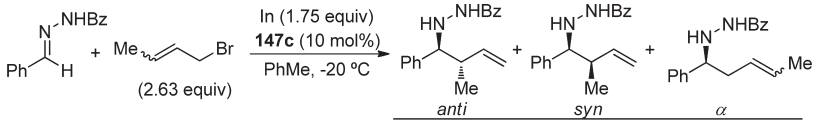
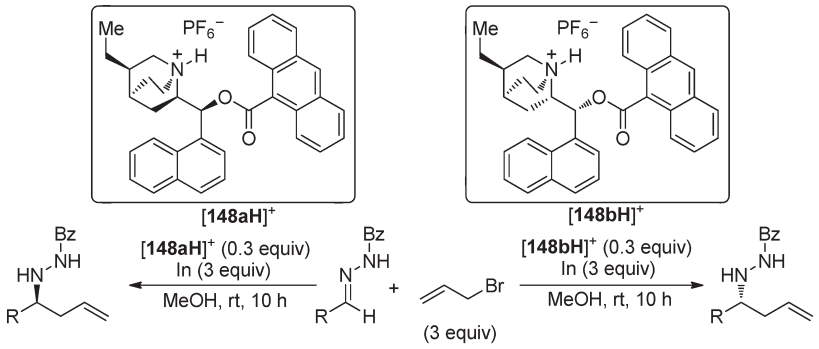
Scheme 34



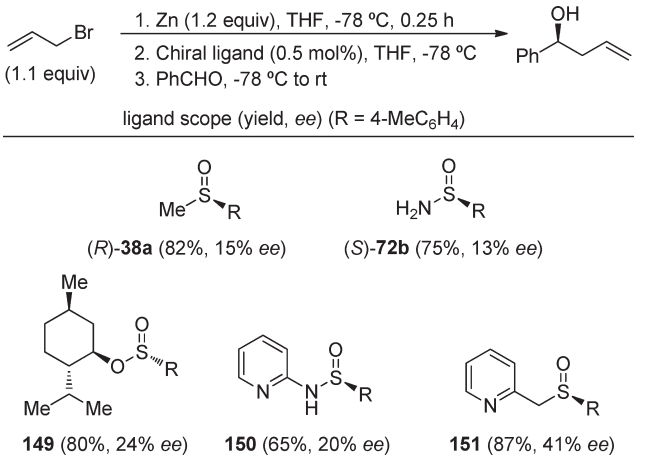
	anti	*syn*	α
(*E*)-crotyl bromide (70%)	1.10 (90% *ee*)	1.00 (85% *ee*)	0.40 (>90% *ee*)
(*Z*)-crotyl bromide (71%)	1.57 (95% *ee*)	1.00 (86% *ee*)	0.38 (90% *ee*)

Scheme 35



yield (%)	ee (%)	R	yield (%)	ee (%)
90	99	4-FC_6H_4	94	99
89	99	4-$NO_2C_6H_4$	92	99
90	99	4-(MeCO)C_6H_4	90	99
90	96	4-EtC_6H_4	88	99
88	99	4-$MeOC_6H_4$	90	99
81	78	$CH_3(CH_2)_6$	80	80

Scheme 36



of the use of catalytic amounts of a chiral additive in an addition reaction with allylindium.[165] More recently, Cook, Lloyd-Jones, and co-workers reported a more efficient sulfone BINOL ligand (*R*)-**81f**.[166] Although aliphatic substrates were commonly problematic for the asymmetric allylation reaction, possibly because of their greater reactivity, (*R*)-**81f** afforded significantly improved enantioselectivity (Table 71, entries 9−10) as compared to the chiral ligand (*R*)-**81e** (34% ee).

Tan and Jacobsen studied the indium-mediated allylation of acylhydrazones catalyzed by different chiral thiourea derivatives. The first-generation thiourea catalyst **144** was found to mediate the addition of allylindium to the *N*-benzoylhydrazone of benzaldehyde in 79% yield but with only 38% ee (Scheme 33). Replacement of the imine portion of catalyst **144** with a phosphinic amide (**145**) yielded almost racemic product. However, when the *tert*-leucine portion of the catalyst was replaced by an aryl group (**146a,b**), moderate enantioselectivity was restored (Scheme 33). Better results were obtained with diastereomeric sulfinamides **147b** and **147c**, which promoted the allylation with 26% and 91% ee, respectively (Scheme 33).[167]

The bifunctional nature of **147c**, in which a hydrogen-bond donor and a Lewis base are positioned properly and in close proximity, was found to be crucial for the attainment of high ee values in the allylation of acylhydrazones derived from aromatic or heteroaromatic aldehydes (Table 72). Substrates bearing ortho-substituents on the aromatic ring were particularly effective, giving enantioselectivities between 93 and 95% ee (Table 72, entries 6 and 7). Aryl halides and ester groups were compatible with the reaction conditions (Table 72, entries 2, 5, and 6), and acylhydrazones derived from aliphatic aldehydes underwent allylation with substantially lower ee values (generally <50% ee).[167]

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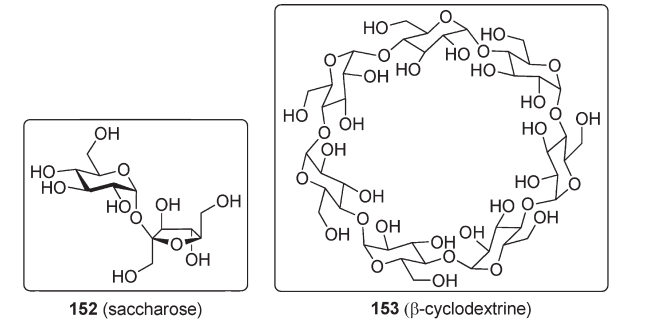
Crotylation of the *N*-benzoylhydrazone of benzaldehyde using the ligand **147c** led to the syn- and anti-diastereomeric products with high ee values but with very poor diastereoselectivities. This fact proved that the allylindium reagent was not geometrically stable, as the reactions of both (*Z*)- and (*E*)-crotyl bromide afforded similar product mixtures (Scheme 34).[167]

Kim and Jang developed a catalytic enantioselective indium-mediated allylation of *N*-benzoylhydrazones in conjunction with protonated chiral amines $[\mathbf{148aH}]^+$ and $[\mathbf{148bH}]^+$ to afford enantioenriched homoallylic amines with a high level of enantioselectivity and chemical yield. Benzoylhydrazones derived from aliphatic aldehydes underwent allylation at room temperature with relatively lower ee values and yields than aromatic aldehyde-derived *N*-benzoylhydrazones. Functional groups such as halogens, nitro, carbonyl, and methoxy groups were tolerated under the optimized reaction conditions shown in Scheme 35.[168] Chiral promoters $[\mathbf{148aH}]^+$ and its pseudoenantiomer $[\mathbf{148bH}]^+$ worked with similar levels of chemical efficiency and stereoselectivity, providing allylated products with opposite configuration. Importantly, the two chiral promoters were readily recovered after a simple aqueous workup in >95% yield.

Table 73. Zinc- and Tin-Promoted Stereoselective Allylation of Aromatic Aldehydes with Allyl Bromide in the Presence of Saccharose (152) and β-Cyclodextrine (153)

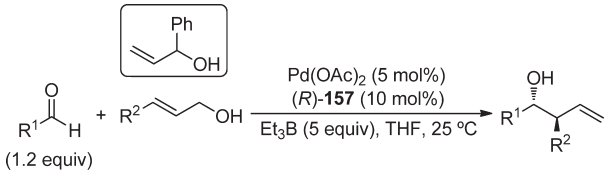


entry	chiral polyol	metal	R	yield (%)	ee (%)
1	**152**	Zn	H	23	21
2	**152**	Zn	MeO	60	87
3	**152**	Zn	Me	70	75
4	**152**	Zn	Cl	88	85
5	**152**	Sn	H	19	71
6	**152**	Sn	MeO	67	16
7	**152**	Sn	Me	61	66
8	**152**	Sn	Cl	81	68
9	**153**	Zn	MeO	91	93
10	**153**	Zn	Me	67	72
11	**153**	Zn	Cl	75	63

5.3. Allylations Mediated by Zinc and Tin

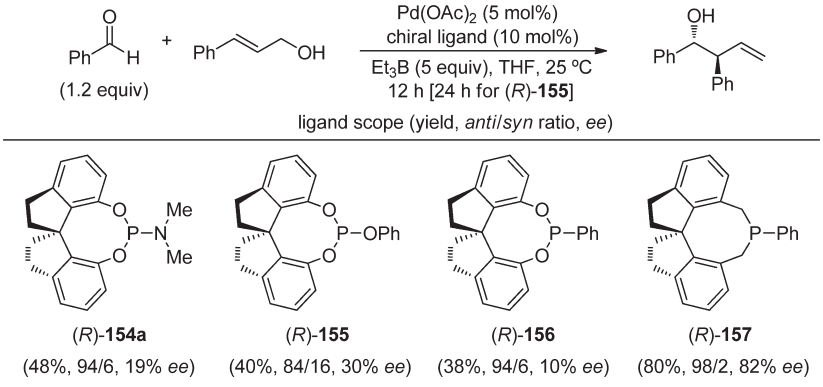
The enantioselective addition of allylzinc bromide to benzaldehyde in the presence of a catalytic amount (0.5 mol %) of chiral sulfur containing compounds (*R*)-**38a**, (*S*)-**72b**, **149**−**151** was also studied by Menezes and co-workers. The conversion was completed in 15 min at −78 °C in THF, and 1-phenylbut-3-en-1-ol was obtained in good yields in all cases but with modest enantioselectivities (Scheme 36).[169] The best results were obtained with the 2-pyridylmethyl sulfoxide **151**. Substrate scope was also investigated using **151**, with aromatic and aliphatic aldehydes yielding the homoallylic alcohols in good yields in all

Table 74. Pd-Catalyzed Et_3B-Promoted Asymmetric Allylation of Aldehydes with Allylic Alcohols in the Presence of the Spiro Phenylphospholane (*R*)-157



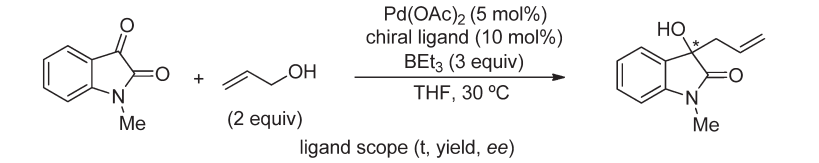
entry	R^1	R^2	*t* (h)	yield (%)	anti/syn	ee (%)
1	Ph	Ph	12	80	98/2	82
2	4-$MeOC_6H_4$	Ph	48	97	99/1	74
3	2-$MeOC_6H_4$	Ph	17	91	95/5	69
4	4-$CF_3C_6H_4$	Ph	12	81	97/3	58
5	1-naphthyl	Ph	12	99	99/1	79
6	2-naphthyl	Ph	12	95	99/1	73
7	2-furyl	Ph	12	73	99/1	78
8	Cy	Ph	32	50	99/1	83
9	Ph	H	24	80		80

Scheme 37



dx.doi.org/10.1021/cr1004474 |*Chem. Rev.* 2011, 111, 7774–7854

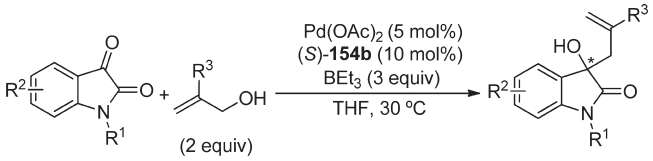
Scheme 38



(*R*)-**154a**: $R^1 = R^2 = Me$, $R^3 = H$ (48 h, <1%, -- *ee*)
(*S*)-**154b**: $R^1 = Me$, $R^2 = Ph$, $R^3 = H$ (4 h, 97%, 71% *ee*)
(*R*)-**154c**: $R^1 = Et$, $R^2 = Ph$, $R^3 = H$ (2 h, 96%, 60% *ee*)
(*S*)-**154d**: $R^1 = R^2 = Ph$, $R^3 = H$ (24 h, 75%, 65% *ee*)
(*S*)-**154e**: $R^1 = H$, $R^2 = Ph$, $R^3 = H$ (48 h, <1%, -- *ee*)
(*S*)-**154f**: $R^1 = Me$, $R^2 = 4\text{-}MeOC_6H_4$, $R^3 = H$ (3 h, 99%, 67% *ee*)
(*S*)-**154g**: $R^1 = Me$, $R^2 = 4\text{-}ClC_6H_4$, $R^3 = H$ (3 h, 99%, 70% *ee*)
(*S*)-**154h**: $R^1 = Me$, $R^2 = 2,6\text{-}Me_2C_6H_3$, $R^3 = H$ (16 h, 89%, 47% *ee*)
(*R*)-**154i**: $R^1 = Me$, $R^2 = Ph$, $R^3 = Me$ (6 h, 95%, 30% *ee*)

(*R*)-**155** (48 h, 18%, 38% *ee*) (*R*)-**156** (48 h, <1%, -- *ee*) (*R*)-**157** (12 h, 85%, 35% *ee*)

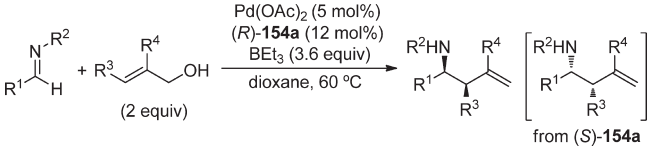
Table 75. Pd-Catalyzed Et_3B-Promoted Asymmetric Allylation of Isatins with Allylic Alcohols in the Presence of Spiro Phosphoramidite (*S*)-154b



entry	R^1	R^2	R^3	*t* (h)	yield (%)	ee (%)
1	Me	H	H	4	97	71
2	H	H	H	20	90[a]	63
3	$(CH_3)_3CCH_2$	H	H	4	85	62
4	Bn	H	H	12	99	56
5	Ph	H	H	5	93	62
6	Ts	H	H	20	74	47
7	Me	5-Cl	H	2	98	46
8	Me	5-MeO	H	3	96	53
9	Me	5-Me	H	3	99	54
10	Me	7-Cl	H	2	89	52
11	Me	7-Me	H	2	98	64
12	Me	H	Me	3	99	48
13	Me	H	Ph	5	93	57
14	Me	H	$4\text{-}MeOC_6H_4$	5	88	50
15	Me	H	$4\text{-}CF_3C_6H_4$	3	99	60
16	Me	H	Bn	4	98	48

[a] The main reaction product was 1,3-diallyl-3-hydroxyindolin-2-one.

Table 76. Pd-Catalyzed Et_3B-Promoted Asymmetric Allylation of Imines with Allylic Alcohols in the Presence of the Spiro Phosphoramidite 154a



entry	R^1	R^2	R^3	R^4	yield (%)	ee (%)	syn/anti
1	Ph	Ts	H	H	86	67	
2[a]	$4\text{-}FC_6H_4$	Ts	H	H	88	77	
3	$4\text{-}ClC_6H_4$	Ts	H	H	95	80	
4	$4\text{-}MeOC_6H_4$	Ts	H	H	94	74	
5	$2\text{-}ClC_6H_4$	Ts	H	H	93	65	
6	$2\text{-}MeOC_6H_4$	Ts	H	H	86	64	
7	2-furyl	Ts	H	H	71	75	
8	(*E*)-PhCH=CH	Ts	H	H	60	76	
9[a]	$CH_3(CH_2)_5$	Ts	H	H	75	77	
10[a,b]	Ph	$4\text{-}CF_3C_6H_4SO_2$	H	H	62	60	
11[a,b]	Ph	$4\text{-}MeOC_6H_4SO_2$	H	H	92	67	
12[a]	Ph	Ts	Me	H	65	69	10:1
13[a]	Ph	Ts	Ph	H	67	65	>99:1
14[a]	Ph	Ts	H	Me	85	81	

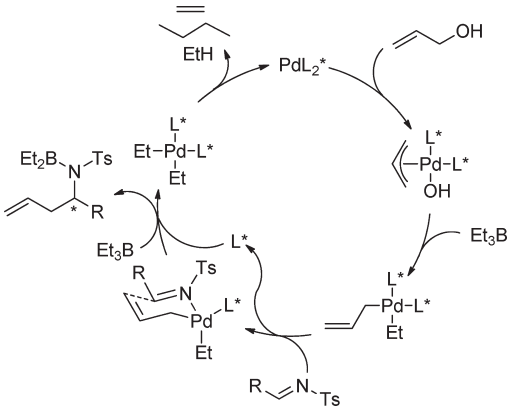
[a] (*S*)-**154a** was used instead of (*R*)-**154a**. [b] The reaction was performed in THF.

cases but with modest or nil enantioselectivities (*n*-butanal and *n*-heptanal gave the corresponding racemic alcohol).

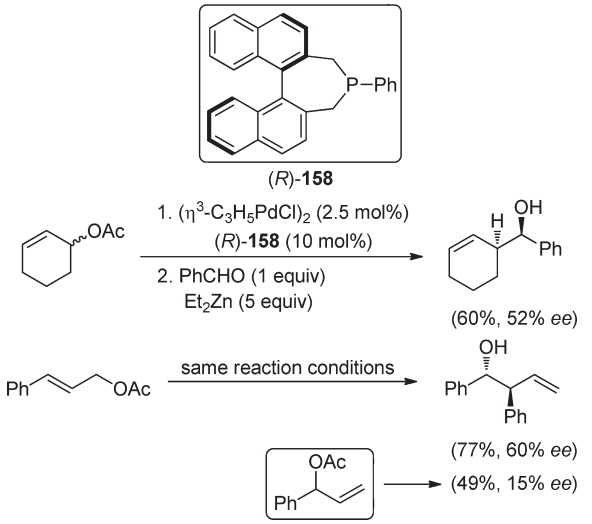
Easily accessible carbohydrates saccharose (**152**) and β-cyclodextrin (**153**) were used as chiral promoters in the enantioselective metal-mediated addition of allyl bromide to aromatic aldehydes.[170] Braga and co-workers found that by using zinc as the metal in the presence of 1.2 equiv of saccharose (**152**), high levels of enantioselection were achieved with para-substituted benzaldehydes (Table 73, entries 2−4), although the yield for *para*-anisaldehyde was only moderate, whereas for *para*-chlorobenzaldehyde very good conversion was observed (Table 73, entries 2 and 4). By changing zinc to tin, only moderate yields and enantioselectivities were observed for all aldehydes tested (Table 73, entries 5−8). On the other hand, using 1 equiv of β-cyclodextrin (**153**) as the chiral agent and zinc as metal, a very high ee of 93% was achieved by reaction with *para*-anisaldehyde, in 91% yield (Table 73, entry 9). Lower levels of enantioselectivity were achieved with *para*-chloro- and *para*-tolualdehyde (72% and 63%, respectively; Table 73, entries 8 and 9).

dx.doi.org/10.1021/cr1004474 |*Chem. Rev.* 2011, 111, 7774–7854

Scheme 39



Scheme 40



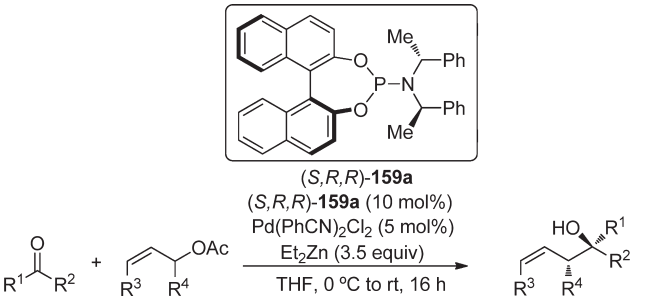
6. ENANTIOSELECTIVE ADDITION OF ALLYLIC ALCOHOLS

Allylic alcohols have been also used as allylating reagents for carbonyl compounds and imines under Pd catalysis.[171] Zhou and co-workers studied the influence of different monodentate chiral ligands on the stereochemical outcome and chose the allylation of benzaldehyde with cinnamyl alcohol as a model reaction. The reactions were performed in THF at room temperature using palladium acetate and triethylborane as reducing agent. Low yields and poor enantioselectivities were obtained with phosphoramidite (*R*)-**154a**, phosphite (*R*)-**155**, and phosphinite (*R*)-**156** (Scheme 37). However, the monodentate spiro phenylphospholane ligand (*R*)-**157** led to 1,1-diphenylbut-3-en-1-ol in high yield (80%) and with good levels of stereocontrol (98/2 anti/syn ratio, 82% ee).[172]

Under the optimal conditions, high yields and good stereoselectivities were obtained in the allylation of various aromatic aldehydes with cinnamyl alcohol (Table 74, entries 1−8). Lower yield (50%) and the highest value of ee was obtained in the case of cyclohexanecarbaldehyde (Table 74, entry 8). Interestingly, when racemic 1-phenylprop-2-en-1-ol was used as the allylic reagent in the reaction with benzaldehyde, the same reaction product was obtained as when cinnamyl aldohol was used, in 60% yield, 79% ee, and a 98:2 anti/syn ratio. Probably, the same π-allyl palladium complex intermediate is formed from 1-phenylprop-2-en-1-ol and its regioisomer cinnamyl alcohol. Simple allylic alcohol also reacted with benzaldehyde under the standard conditions, giving 1-phenylbut-3-en-1-ol in good yield and enantioselectivity (Table 74, entry 9).

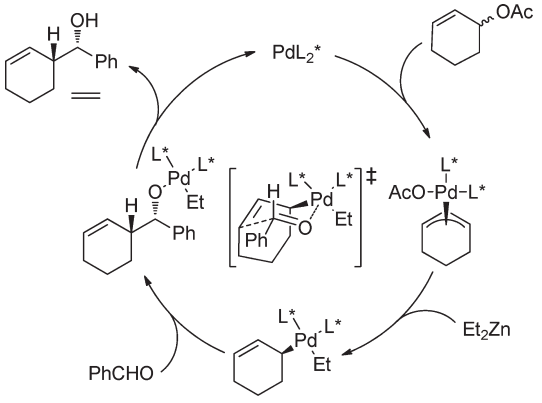
Zhou and co-workers reported also the first catalytic asymmetric allylation of ketones with allylic alcohol as the allylating agent. Various chiral spiro ligands **154**−**157** were evaluated in the palladium-catalyzed asymmetric allylation of 1-methylindoline-2,3-dione with allylic alcohol (Scheme 38).[173] Reaction conditions were similar to those used in the allylation of aldehydes with allylic alcohols (vide supra). The phosphite ligand (*R*)-**155** and the

Table 77. Pd-Catalyzed Et_2Zn-Promoted Asymmetric Allylation of Carbonyl Compounds with Allylic Acetates in the Presence of the Phosphoramidite (*S,R,R*)-159a



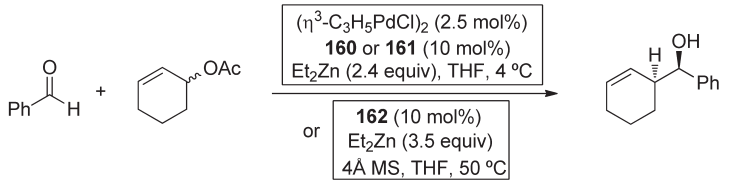
entry	R^1	R^2	R^3 R^4	yield (%)	syn/anti	ee (%)
1	H	Ph	$(CH_2)_3$	77	>20:1	81
2	H	4-$MeOC_6H_4$	$(CH_2)_3$	73	>20:1	71
3	H	4-$(CO_2Me)C_6H_4$	$(CH_2)_3$	73	>20:1	80
4	H	4-MeC_6H_4	$(CH_2)_3$	82	>20:1	72
5	H	2-MeC_6H_4	$(CH_2)_3$	79	>20:1	68
6	H	2-furyl	$(CH_2)_3$	80	>20:1	60
7	H	Et	$(CH_2)_3$	<5		
8	H	*i*-Pr	$(CH_2)_3$	<5		
9	Me	Me	$(CH_2)_3$	<5		
10	Me	Ph	$(CH_2)_3$	<5		
11	H	Ph	$(CH_2)_2$	66	>20:1	45
12	H	Ph	H H	73		37

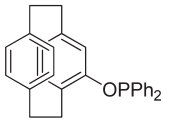
Scheme 41



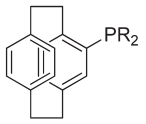
dx.doi.org/10.1021/cr1004474 |*Chem. Rev.* 2011, 111, 7774–7854

Scheme 42

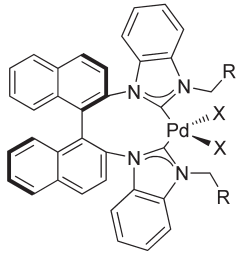




(*R*)-**160** (45%, 95:5, 21% *ee*)

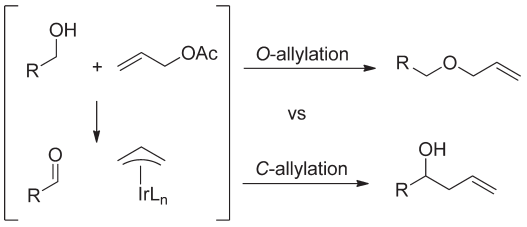


(*S*)-**161a**: R = Ph (90%, 99:1, 56% *ee*)
(*S*)-**161b**: R = 4-MeOC$_6$H$_4$ (92%, 99:1, 58% *ee*)
(*S*)-**161c**: R = 4-CF$_3$C$_6$H$_4$ (80%, 92:8, 27% *ee*)
(*S*)-**161d**: R = 3,5-Me$_2$C$_6$H$_3$ (82%, 92:8, 35% *ee*)
(*S*)-**161e**: R = Cy (52%, 90:10, 15% *ee*)



162a: R = H, X = I (13%, >99:1, 42% *ee*)
162b: R = Ph, X = I (21%, >99:1, 70% *ee*)
162c: R = Ph, X = Cl (85%, 93:7, 41% *ee*)
162d: R = Ph, X = Br (80%, >99:1, 53% *ee*)
162e: R = 2,6-Me$_2$C$_6$H$_3$, X = Br (93%, 87:13, 50% *ee*)

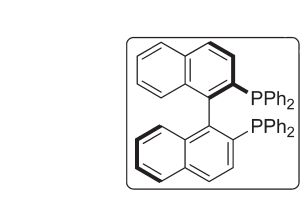
Scheme 43



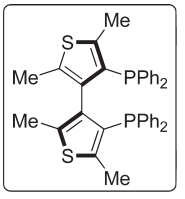
phosphinite ligand (*R*)-**156** were very unreactive in the allylation reaction, giving very low yields (<20%) after long reaction times (Scheme 38). The phosphane ligand (*R*)-**157**, which was the best in the palladium-catalyzed allylation of aldehydes with allylic alcohols, gave the desired product in high yield (85%), while the enantioselectivity (35% ee) was low (Scheme 38). Meanwhile, the reactivity and enantioselectivity of phosphoramidite ligands **154** were quite different depending on the amine substituent. The ligand **154a** with a dimethylamino group was inert for the reaction. Interestingly, ligand **154b**, produced by a simple replacement of one methyl group of ligand **154a** by a phenyl, afforded the allylation product in an almost quantitative yield with 71% ee (Scheme 38). The combination of a methyl and a phenyl group at the nitrogen atom of the ligand was necessary for achieving good results (compare ligands **154b**−**154h**). The enantioselectivity of the reaction decreased from 71 to 30% ee when the ligand **154b** was modified by introducing two methyl groups onto the 6,6′-position of the spiro backbone (ligand **154i**, Scheme 38).

The allylation of various isatin derivatives with allylic alcohols under the optimal reaction conditions, in the presence of chiral phosphoramidite (*S*)-**154b**, was examined considering the effect on the yield and stereoselectivity of the substituents on the isatin. With no *N*-protecting group, the isatin facilitated the allylation at both nitrogen and carbonyl group to generate bisallylation product 1,3-diallyl-3-hydroxyindolin-2-one in 90% yield and 63% ee (Table 75, entry 2). A tosyl group on the nitrogen increased the reaction time and lowered the enantioselectivity (Table 75, entry 6). Almost quantitative yields and moderate enantioselectivities were obtained

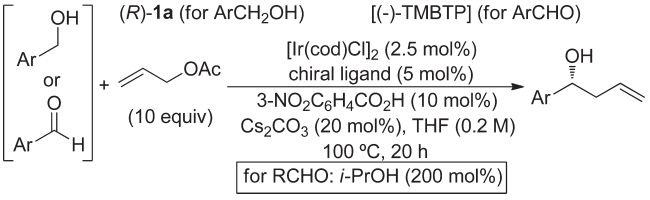
Table 78. Ir-Catalyzed Transfer Hydrogenative Allylation of Benzylic Alcohols and Aromatic Aldehydes



(*R*)-**1a** (for ArCH$_2$OH)



[(-)-TMBTP] (for ArCHO)



Ar	from alcohols		from aldehydes	
	yield (%)	ee (%)	yield (%)	ee (%)
4-NO$_2$C$_6$H$_4$	72	91	78	97
4-(CO$_2$Me)C$_6$H$_4$	77	93	85	97
Ph	62	93	76	96
4-BrC$_6$H$_4$	74	93	77	97
2-MeOC$_6$H$_4$	80	92	86	95
4-MeOC$_6$H$_4$	73	93	75	94
3,5-Cl$_2$C$_6$H$_3$	61	92	76	98
2-(*N*-methylindolyl)	55	90	82	94

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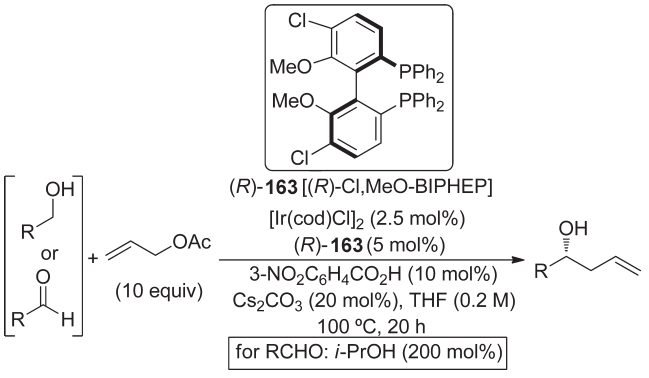
with *N*-alkyl and aryl substituted isatins using simple allylic alcohol and 2-substituted allylic alcohols (Table 75).

Palladium-catalyzed asymmetric allylation of imines with allylic alcohols under the influence of chiral spiro ligands **154**−**157** was also studied by Zhou and co-workers, with phosphoramidite (*R*)-**154a** being the best ligand in these reactions. The allylation of *N*-tosyl-protected aromatic aldimines was accomplished with high yields and good enantioselectivities (Table 76, entries 1−6).[174] The same levels of stereocontrol were obtained with imines derived from heteroaromatic, α,β-unsaturated, and aliphatic aldehydes (Table 76, entries 7−9). The protecting group of the imine strongly affected the reactivity of the allylation reaction, so the *para*-trifluoromethyl and *para*-methoxyphenyl sulfonyl-protected imines exhibited lower enantioselectivities (Table 76, entries 10 and 11). Homoallylic amines were produced with excellent diastereoselectivities when 3-substituted alcohols, such as (*E*)-crotyl and (*E*)-cinnamyl alcohols (syn/anti 10:1 and >99:1, respectively), were used in the allylation of the *N*-tosyl-protected imine derived from benzaldehyde (Table 76, entries 12 and 13). Moreover, methallyl alcohol achieved the highest level of enantioselectivity (81% ee) in the allylation of the same starting material (Table 76, entry 14).

A mechanism was proposed to rationalize the umpolung of the π-allylpalladium (Scheme 39), which was inspired by the mechanism proposed by Feringa and co-workers for the allylation of aldehydes (vide infra).[175] In this mechanism, after oxidative addition of the allylic alcohol to form the η^3-allylpalladium complex, a transfer of the electron-rich ethyl group from boron to palladium was thought to be essential to change the electronic property of the palladium center, and to enhance the nucleophilicity of the resulting η^1-allyl ligand toward the imine. Thus, the nucleophilic addition would take place through a chairlike cyclic transition state.

Table 79. Ir-Catalyzed Transfer Hydrogenative Allylation of Aliphatic Alcohols and the Corresponding Aldehyde



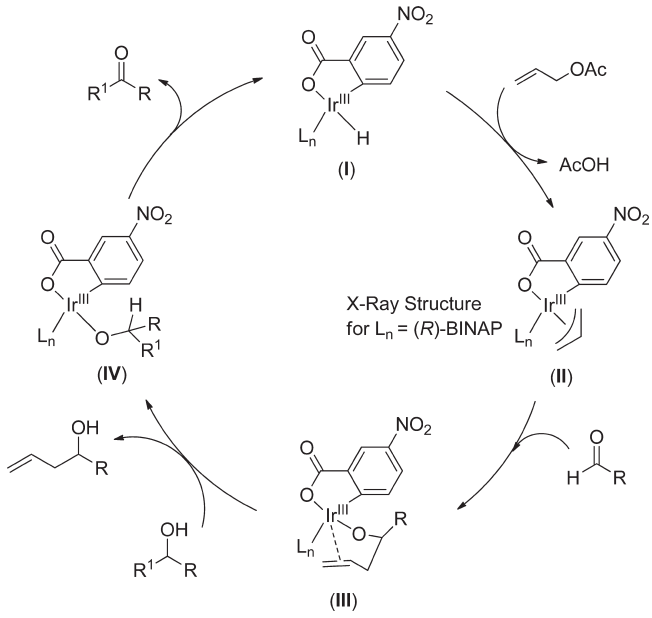
	from alcohols		from aldehydes	
R	yield (%)	ee (%)	yield (%)	ee (%)
(*E*)-PhCH=CH	72	91	73	94
(*E*)-$CH_3(CH_2)_5CH$=CH	72	91	71	93
$Ph(CH_2)_3$	81	95	83	96
$CH_3(CH_2)_7$	78	95	77	97
i-Pr	83	94	74	95
$BnOCH_2C(CH_3)_2$	63	93	81	94
$BnOCH_2$	68	88	41	92
$BnO(CH_2)_2$	63	94	45	96
$BnO(CH_2)_3$	78	95	88	97

7. ENANTIOSELECTIVE ADDITION OF ALLYLIC ACETATES

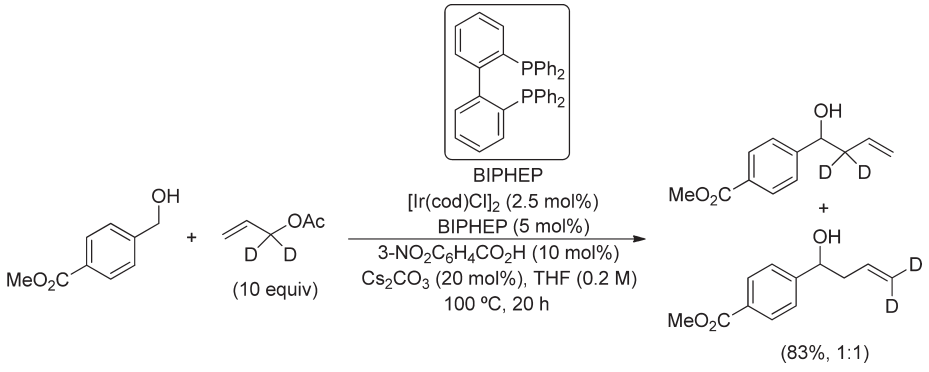
7.1. Allylations Mediated by Palladium

The first enantioselective allylation of carbonyl compounds by the umpolung π-allyl palladium complexes was reported by

Scheme 45



Scheme 44



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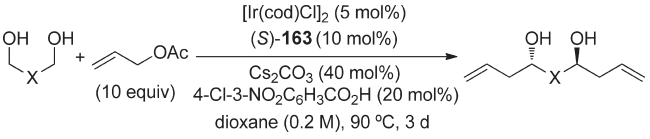
Zanoni et al. in 2004.[176] In a model reaction, to a THF solution of 3-cyclohexenyl acetate in the presence of 10 mol % of a chiral ligand and 2.5 mol % of complex $(\eta^3\text{-}C_3H_5PdCl)_2$, was sequentially added benzaldehyde and 5 equiv of diethylzinc at 4 °C. Several chiral ligands were tested, and the best ligand was the phosphepine (*R*)-**158**, which provided the addition product in 60% yield and 52% ee (Scheme 40). Cinnamyl acetate performed even better as a substrate, with a faster and more stereoselective reaction being observed to produce the anti-addition product in a 77% yield and 60% ee. Meanwhile, isomeric racemic 1-phenylallyl acetate, which is expected to originate the same intermediate π-allyl palladium complex as cinnamyl acetate, led to the anti-product in a 49% yield and a poor 15% ee (Scheme 40), probably due to the intervention of memory effects.

Enantioselective palladium-catalyzed dialkylzinc-mediated allylation of aldehydes with allylic acetates was also achieved using monodentate phosphoramidite ligands. Among different combinations of reactants, Feringa and co-workers found that bisbenzonitrile palladium dichloride, diethylzinc, and phosphoramidite (*S*,*R*,*R*)-**159a** in THF proved to be optimal in the allylation of benzaldehyde with 3-cyclohexenyl acetate (Table 77, entry 1).[175] This protocol worked efficiently for a range of aromatic aldehydes (Table 77, entries 1−6), with good yields and enantioselectivities, along with very high syn-selectivity. However, almost no conversion was observed with aliphatic aldehydes and ketones (Table 77, entries 7−10).

Szabó found, after experimental observations and computational calculations, that the presence of electron-releasing substituents on palladium promoted the change from η^3- to η^1-allylpalladium species, and that η^1-allylpalladium species allylated aldehydes.[177] On the basis of this information, Feringa and co-workers proposed that the role of diethylzinc was to alkylate the η^3-allylpalladium species and to promote the formation of the corresponding η^1-allylpalladium species, which reacted with benzaldehyde through a cyclic chairlike transition state in a stereoselective fashion to give the expected homoallylic alcohol (Scheme 41).

More recently, planar chiral [2.2]paracyclophane phosphinite **160** and phosphanes **161** were used as ligands in the umpolung allylation of benzaldehyde with cyclohexenyl acetate, giving the corresponding homoallyl alcohol in high diastereoselectivity and

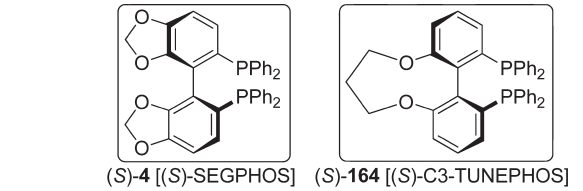
Table 80. Enantioselective Allylation of Diols



X	yield (%)	ee (%) (configuration)	dr
CH_2	70	>99 (*S*,*S*)	>30:1
CH(Me)	51	>99 (*S*,*S*)	>30:1
$C(Me)_2$	48	>99 (*R*,*R*)[a]	20:1
$C(CH_2CH_2)$	65	>99 (*S*,*S*)	18:1
$C{=}CH_2$	66	>99 (*S*,*S*)	19:1
CH_2CH_2	68	>99 (*S*,*S*)	>30:1
$CH_2CH_2CH_2$	56	>99 (*S*,*S*)	>30:1

[a] (*R*)-Cl,MeO-BIPHEP was used as chiral ligand.

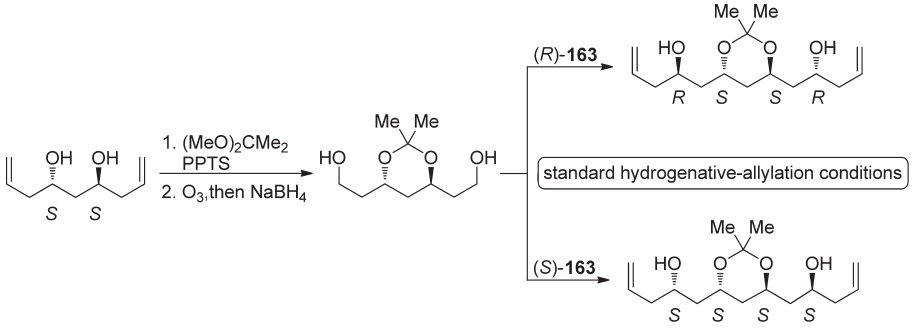
Table 81. Ir-Catalyzed Transfer Hydrogenative Crotylation of Alcohols and Aldehydes



	from alcohols			from aldehydes		
R	yield (%)	anti/syn	ee (%)	yield (%)	anti/syn	ee (%)
Ph	65	6:1	95	77	9:1	98
$3\text{-}MeOC_6H_4$	70	6:1	95	74	9:1	98
$4\text{-}MeOC_6H_4$	67	5:1	90	75	7:1	96
	73	4:1[a]	92	77	6:1[a]	98
$4\text{-}BrC_6H_4$	73	8:1	95	78	11:1	97
$4\text{-}(CO_2Me)C_6H_4$	70	7:1	95	80	11:1	96
	77	8:1[a]	97	82	13:1[a]	97
PhCH=CH	61	7:1	86	66	7:1	98
	63	6:1[a]	90	68	8:1[a]	98
$PhCH_2CH_2$	69	7:1	97	71	11:1	97
$BzO(CH_2)_3$	68	7:1	97	68	11:1	97
$CH_3(CH_2)_7$	69	7:1	97	75	11:1	97

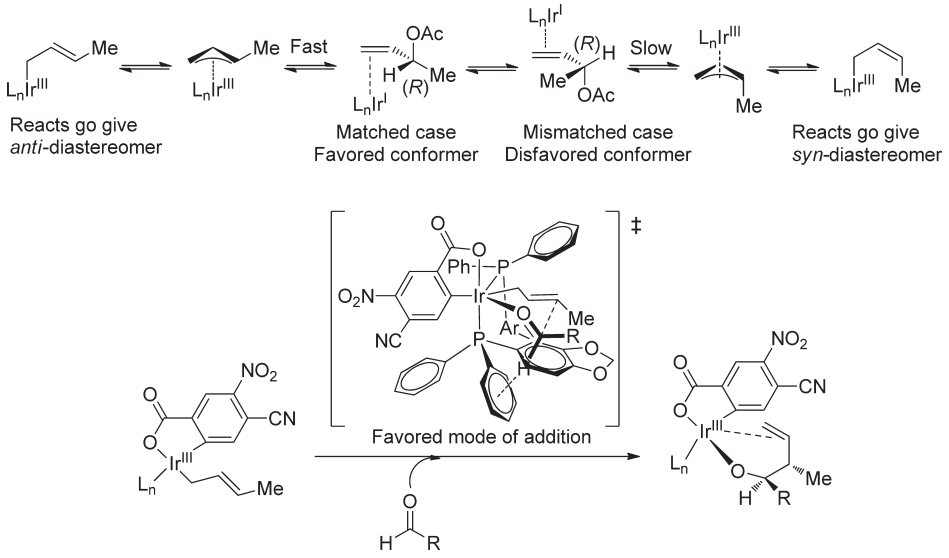
[a] (*S*)-C3-TUNEPHOS [(*S*)-**164**] was used as chiral ligand.

Scheme 46

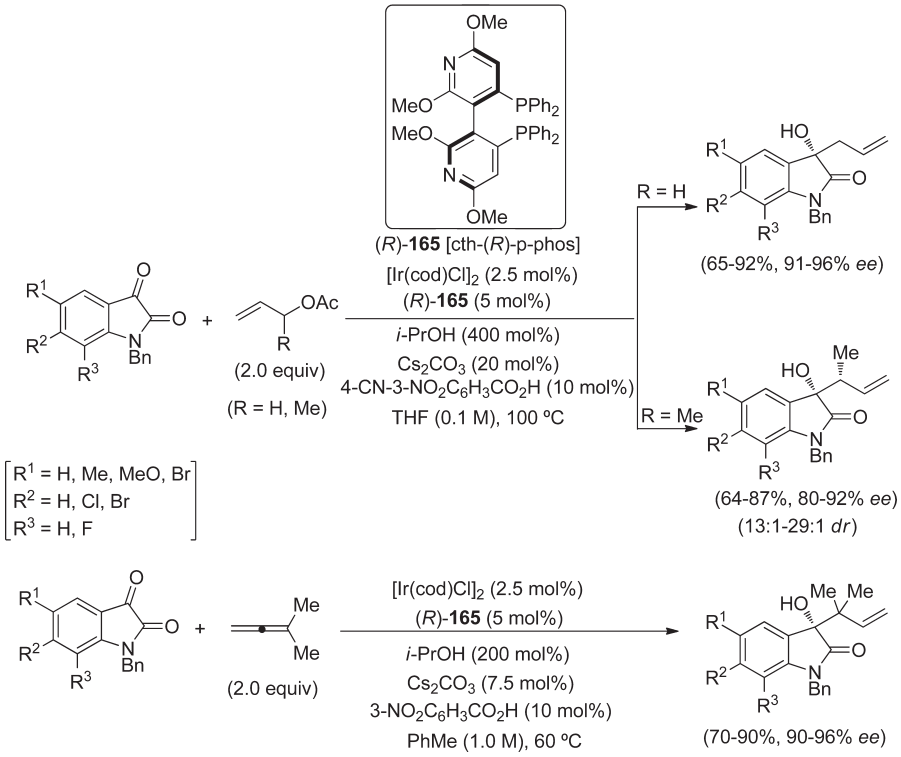


dx.doi.org/10.1021/cr1004474 |*Chem. Rev.* 2011, 111, 7774–7854

Scheme 47



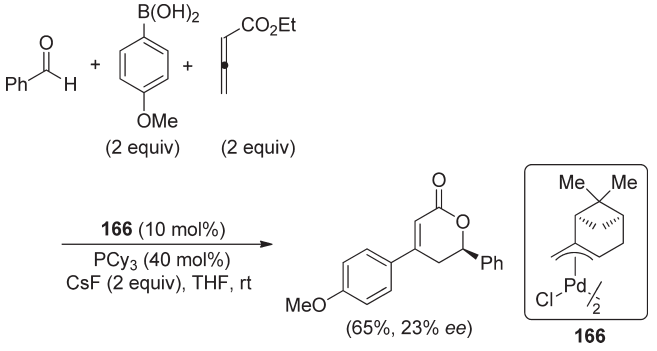
Scheme 48



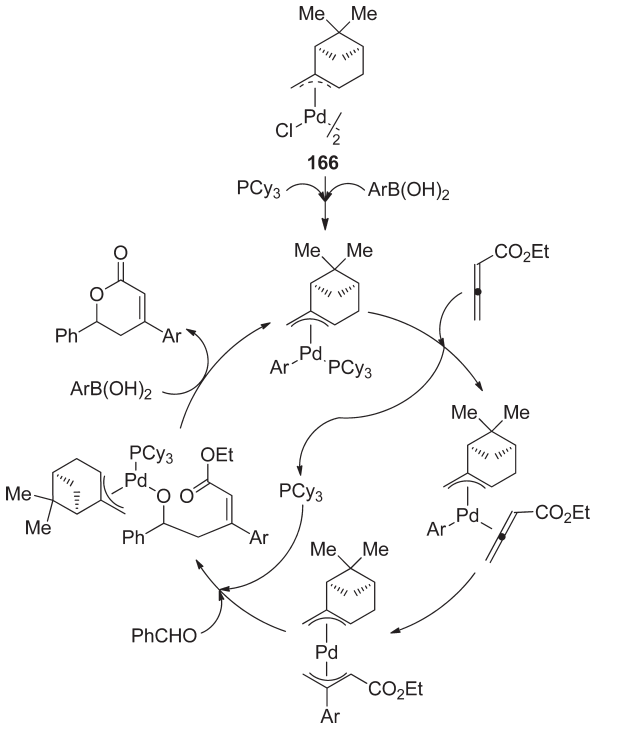
in moderate to good enantioselectivity (Sheme 42).[178] Similarly, a series of chiral bis(NHC)−Pd(II) complexes **162**, bearing different coordinating counterions, have been prepared and applied in the same transformation, affording the same homoallylic alcohol in moderate to excellent yields (up to 96%), modest enantioselectivities (54−66% ee), and good to excellent syn diastereoselectivities (up to 99:1 dr) (Scheme 42).[179] The scope of the aldehyde allylation with cyclohexenyl acetate was studied using the paracyclophane phosphane (*S*)-**161b** and the biscarbene−palladium complex **162b**, and the reactions demonstrated good to excellent diastereoselectivities for all the substrates. Importantly, aliphatic aldehydes led to high levels of enantioselectivities, albeit the yields were lower than for aromatic aldehydes. Suprisingly, the reaction of (*E*)-cinnamyl acetate and benzaldehyde in the presence of the complex **162b**, under the same conditions shown in Table 77, afforded the allylation product 1,2-diphenylbut-3-en-1-ol in 72% yield (anti/syn 55:45), but almost as a racemic mixture.

dx.doi.org/10.1021/cr1004474 |*Chem. Rev.* 2011, 111, 7774–7854

Scheme 49



Scheme 50



7.2. Iridium-Catalyzed Transfer Hydrogenative Allylation

In the course of developing hydrogen-mediated C−C couplings,[180] the group of Krische has recently examined the allylation of carbonyl compounds under transfer hydrogenative conditions employing iridium catalysts. Interestingly, allyl acetate was used as a convenient surrogate of allylmetal reagents in the enantioselective carbonyl allylation of alcohols or the corresponding aldehydes.[181] Considering that closely related systems are reported for the iridium-catalyzed allylic substitution using alcohols as nucleophiles (*O*-allylation), the reactivity of the intermediate allyl iridium as nucleophile is remarkable (Scheme 43).

A range of benzylic alcohols reacted with allyl acetate (10 equiv) in the presence of the commercially available iridium complex $[Ir(cod)Cl]_2$ (2.5 mol %) in combination with (*R*)-BINAP [(*R*)-**1a**] (5 mol %) as ligand, along with Cs_2CO_3 (20 mol %) and 3-$NO_2C_6H_4CO_2H$ (10 mol %) as additives. The reactions were conducted in THF at 100 °C in a sealed tube, furnishing the corresponding *C*-allylated products in good yield and excellent enantioselectivity. Under otherwise identical reaction conditions, the allylation of the corresponding aldehydes was explored using isopropanol as the terminal reductant and (−)-TMBTP as ligand. As shown in Table 78, the homoallyl alcohols were obtained in good to excellent isolated yields and with somewhat higher enantioselectivity. A salient feature of this methodology is that regardless of the oxidation level, benzylic alcohols and the corresponding aldehydes are both excellent substrates.

The scope of the iridium-catalyzed transfer hydrogenative allylation with allyl acetates was expanded to use aliphatic alcohols. In this case, (*R*)-Cl,MeO-BIPHEP [(*R*)-**163**] was the most active and selective ligand from several chiral phosphanes screened. The same set of homoallyl alcohols was generated from aliphatic alcohols or the corresponding aldehydes, using the previously optimized conditions for benzylic alcohols. Importantly, linear, branched, α,β-unsaturated, and heteroatom-substituted aliphatic alcohols provided the homoallylic alcohols in good yields and enantioselectivities generally above 90% ee. Moreover, the corresponding aldehyde partners provide slightly higher enantioselectivities, using the same chiral ligand and isopropanol as hydrogen donor (Table 79).[182]

Some experiments were performed to gain insight on the mechanism; transfer hydrogenative allylation of a benzylic alcohol with isotopically labeled allyl acetate using BIPHEP as ligand was consistent with the intervention of symmetric iridium π-allyl intermediates (Scheme 44). Moreover, competition experiments demonstrated rapid and reversible hydrogenation−dehydrogenation of the carbonyl partner prior to the C−C coupling.

When a THF solution of $[Ir(cod)Cl]_2$, (*R*)-BINAP [(*R*)-**1a**], and 3-$NO_2C_6H_4CO_2H$ was heated at 80 °C, in the presence of Cs_2CO_3, a compound was isolated and crystallized from THF−ether. Single-crystal X-ray diffraction analysis revealed the ortho-cyclometalated iridium(III)−π-allyl complex **II** (Scheme 45), which serves as active catalyst in the transfer hydrogenative allylation under standard conditions. A plausible mechanism involves the formation of the active catalytic species **II** from ortho-cyclometalated complex **I** by mechanisms not shown in this simplified version. Allyl transfer through a closed chairlike transition state furnishes the homoallyl iridium complex **III**, in which the remaining coordination site of the iridium is occupied by the olefin moiety, disabling β-hydride elimination pathways. Upon exchange of the homoallylic alcohol by isopropanol or a reactant alcohol, the intermediate **IV** is formed, where a coordination site becomes available at the iridium center. β-Hydride elimination regenerates the complex **I**, accompanied by the reactive aldehyde or acetone when isopropanol is used (Scheme 45). A stereochemical model to account for the observed absolute stereoinduction has also been proposed.

Although asymmetric iterative allylmetalation of aldehydes has found broad applicability, the low stability of malondialdehyde derivatives limits the use of this approach to prepare synthetically attractive 1,3-polyol substructures. In this context, the group of Krische has examined 1,*n*-glycols as dialdehyde equivalents in the enantioselective iridium-catalyzed hydrogenative allylation with allyl acetate.[183] As shown in Table 80, a range of glycols furnished the corresponding C_2-symmetric homoallylic diols in good isolated yields and excellent diastero-and enantioselectivities. Remarkably, good results were also obtained for 1,4-butanediol

dx.doi.org/10.1021/cr1004474 |*Chem. Rev.* 2011, 111, 7774–7854

Scheme 51

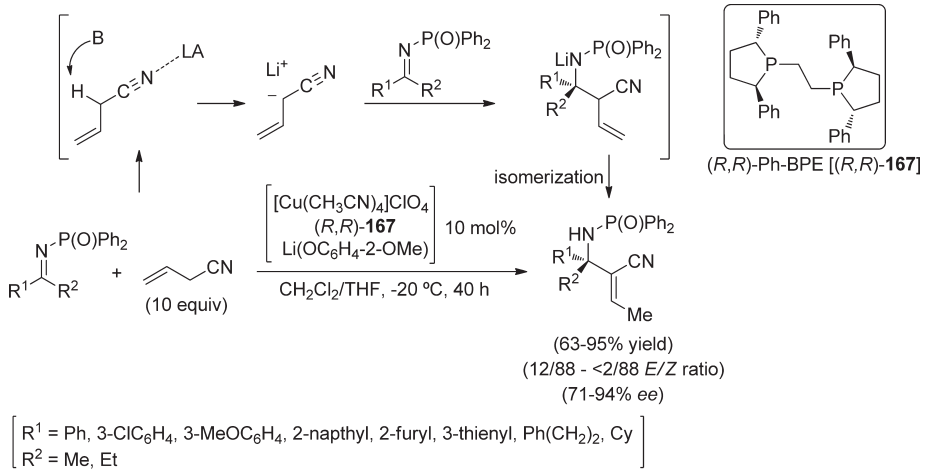
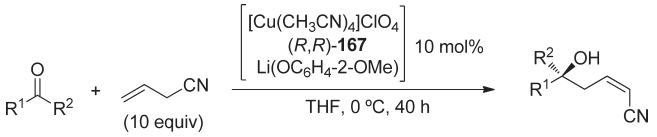


Table 82. Catalytic Asymmetric Addition of Allyl Cyanide to Ketones under Proton-Transfer Conditions



entry	R^1	R^2	yield (%)	ee (%)
1	Ph	Me	81	97
2	2-naphthyl	Me	88	96
3	3-$MeOC_6H_4$	Me	92	94
4	3-ClC_6H_4	Me	76	95
5	2-furyl	Me	80	84
6	3-thienyl	Me	73	94
7[a]	Ph	Et	48	87
8[a]	Ph	*n*-Pr	41	7
9	(*E*)-PhCH=CH	Me	79	78
10	(*E*)-CH_3CH=CCH_3	Me	54	88

[a] LiO*t*-Bu was used instead of Li(OC_6H_4-2-OMe).

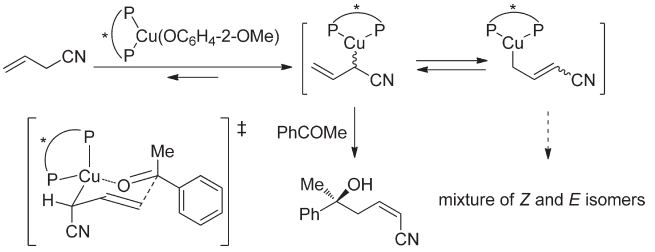
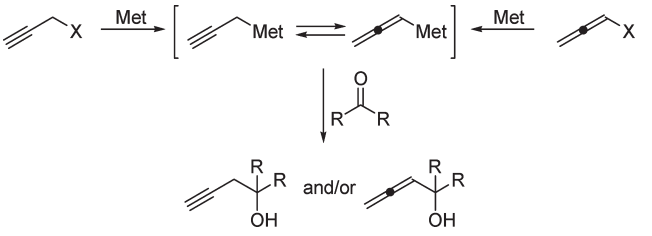


Figure 15. Proposed mechanism for γ- and *Z*-selectivity.

Scheme 52



and 1,5-pentanediol, which are transformed into γ-butyrolactone and δ-valerolactone, respectively, under transfer hydrogenative conditions.

To further illustrate the utility of the method, a C_2-symmetric homoallyl diol was converted into the acetonide and submitted to ozonolysis with reductive quenching ($NaBH_4$). The diol obtained was then subjected to standard transfer hydrogenative−allylation conditions. Notably, C_2-symmetric tetraols (*R,S,S,R*)- or (*S,S,S,S*)- can be obtained as single stereoisomers by simply choosing the chiral ligand of the iridium catalyst (Scheme 46).

When α-methyl allyl acetate was used in the allylation of different alcohols (or aldehydes) with the iridium catalyst generated in situ from $[Ir(cod)Cl]_2$, 3-$NO_2C_6H_4CO_2H$, and different chiral phosphane ligands, poor anti-diastereoselection was observed regardless of the ligand used. Accordingly, further optimization of the catalytic system was necessary to achieve good levels of anti-diastereoselectivity.[184] After screening a survey of 4-substituted-3-nitrobenzoic acids, it was found that the catalyst prepared from 4-cyano-3-nitrobenzoic acid and the BIPHEP ligand **163** provided the homoallyl alcohol in 3.0:1 anti/syn ratio. Remarkably, the diastereoselection was improved up to 7.5:1 dr using the same catalytic system, but performing the reaction with only 2 equiv of α-methyl allyl acetate, at 90 °C and 1.0 M concentration of benzylic alcohol. Moreover, when BIPHEP was replaced by chiral (*S*)-SEGPHOS [(*S*)-**4**] or (*S*)-C3-TUNEPHOS [(*S*)-**164**], similar levels of diastereoselection and excellent enantioselectivities (95% and 97% ee, respectively) were achieved. A range of alcohols were submitted to the optimized conditions providing the corresponding homoallyl alcohols in good isolated yields, good anti-diastereoselection, and excellent enantioselection, for the major anti products. Benzylic, allylic, as well as aliphatic alcohols were good substrates for this methodology and in most cases the catalyst modified by (*S*)-SEGPHOS [(*S*)-**4**] gave better results. By using 2 equiv of isopropanol as the terminal reductant, under otherwise identical

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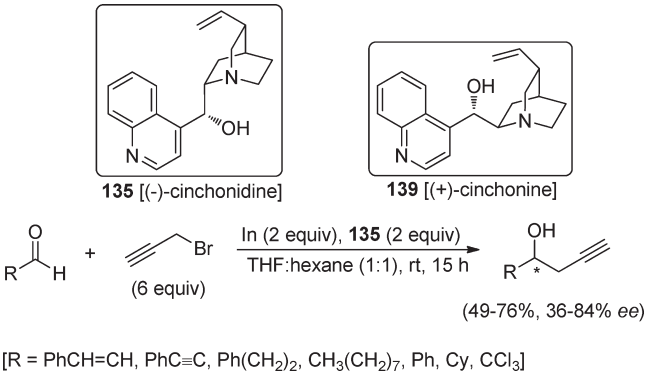
Scheme 53



Scheme 54

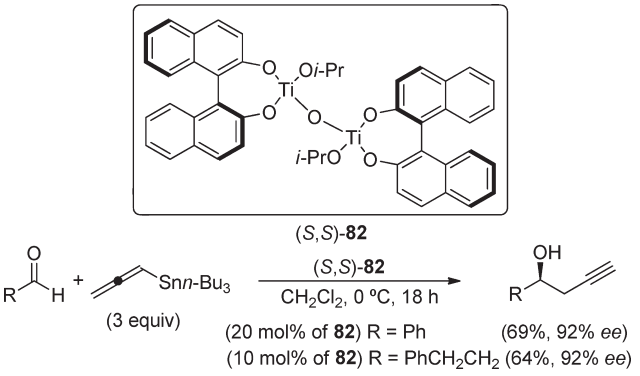
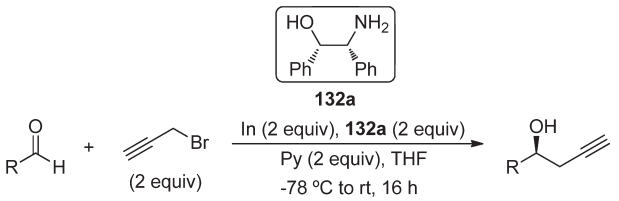


Table 83. Indium-Promoted Stereoselective Propargylation of Aldehydes with Propargyl Bromide in the Presence of the Chiral Aminoalcohol 132a



entry	R	yield (%)	ee (%)
1	Ph	90	88
2	4-ClC_6H_4	89	84
3	4-$MeOC_6H_4$	82	88
4	4-CNC_6H_4	75	83
5	3-HOC_6H_4	90	85
6	2-furyl	78	78
7	3-furyl	69	78
8	*n*-Pr	63	74
9	Et_2CH	60	83
10	*t*-Bu	53	95
11	(*E*)-PhCH=CH	71	75

conditions, the crotylation of the corresponding aldehydes furnished the same set of homoallylic alcohols in uniformly better levels of relative and absolute stereocontrol (Table 81). To evaluate the origin of the stereoselection, optically enriched α-methyl allyl acetate (98% ee) was used under standard conditions employing achiral BIPHEP ligand (**163**). The homoallyl alcohol is produced in only 14% ee, suggested that racemization via π-facial interconversion of the crotyl iridium complex takes place at a rate similar to the carbonyl addition rate. Further kinetic studies developed by the authors suggest that consumption of the (*R*)-α-methyl allyl acetate from the racemic mixture by the (S)-SEGPHOS [(*S*)-**4**]-modified iridium catalyst is a more rapid reaction pathway (stereochemically matched combination). Upon these observations, anti-diastereoselectivity presumably arises via kinetic formation of an (*E*)-crotyl iridium intermediate. Following the working model originally proposed for the iridium-catalyzed transfer hydrogenative allylation of alcohols, it was reasoned that the intermediate (*E*)-σ-crotyliridium complex is coordinated to the aldehyde and the crotyl group is transferred through a closed chairlike transition state. The observed stereochemistry is explained by a favored mode of addition where the aldehyde is bound in a way that the aldehydic C−H bond projects into the π-face of the ligand, giving rise to a weakly attractive C−H π-interaction. In the disfavored mode of addition, the aldehyde is bound with the alkyl/aryl group, giving rise to severe nonbonded interaction with the ligand (Scheme 47).

Substituted isatins have been evaluated as substrates for the allylation using the transfer hydrogenation protocol with allyl acetate.[185] In this case, 4-cyano-3-nitrobenzoic acid and cth-(*R*)-p-phos ligand [(*R*)-**165**] emerged from a large set of optimization experiments as the best choices to form the iridium catalyst. Importantly, it was necessary to increase the loading of isopropanol up to 400 mol % to achieve good levels of conversion. Under the optimized conditions, a selection of substituted isatins afforded the corresponding homoallyl alcohols in good yields and excellent enantioselection. The crotylation of the same substrates using α-methyl allyl acetate as the crotyl donor required longer reaction times, under identical conditions, to furnish the desired products with good to excellent enantioselectivities. Finally, the reverse prenylation was also accomplished using 1,1-dimethylallene under similar conditions to give the expected products in high yields and high optical enrichment. Interestingly, the enantiofacial selectivity of the carbonyl addition is opposite to that observed in the allylation and crotylation, and a stereochemical model was proposed to account for this inversion (Scheme 48).

8. OTHER ENANTIOSELECTIVE ALLYLATIONS

8.1. From Allenes

Hopkins and Malinakova reported a palladium-mediated three-component coupling of an aldehyde, a boronic acid, and an alkyl allene to afford highly substituted homoallyl alcohols with excellent regio- and diastereoselectivity, but very low enantioselectivity.[186] When an allenyl ester was used in this coupling, instead of the alkyl derivative, a 2-pyranone was the reaction product.[187] For instance, the coupling of *para*-methoxybenzene boronic acid and benzaldehyde with ethyl buta-2,3-dienoate catalyzed by the palladium complex **166** (10 mol %) in the presence of PCy_3 and CsF in THF afforded the corresponding lactone in 65% yield and 23% ee (Scheme 49).

dx.doi.org/10.1021/cr1004474 |*Chem. Rev.* 2011, 111, 7774–7854

Scheme 55

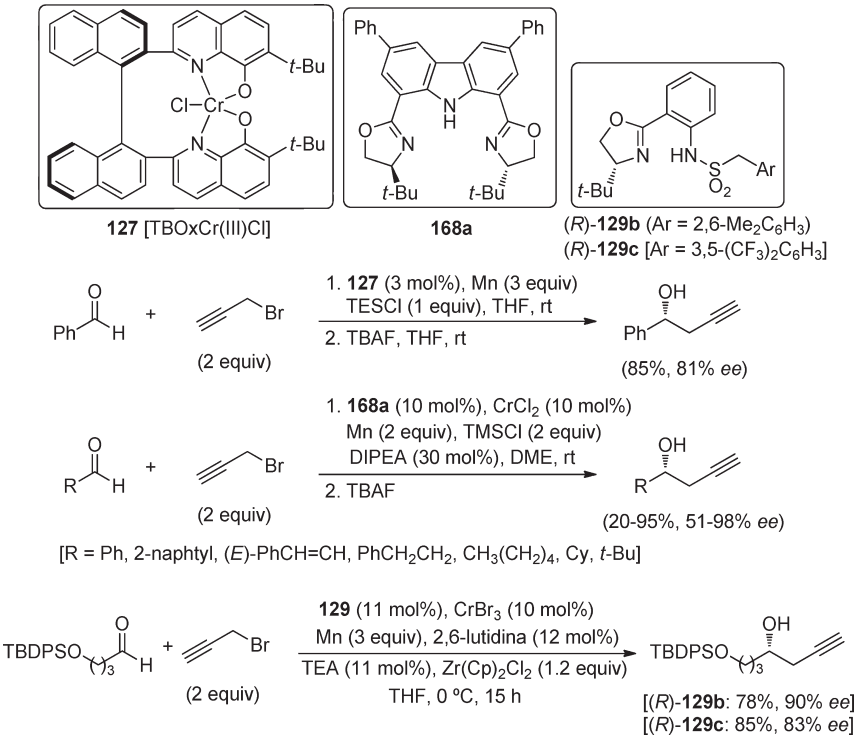
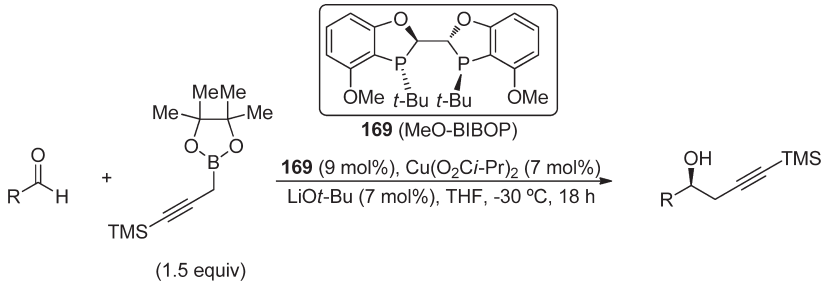


Table 84. Copper-Catalyzed Enantioselective Propargylation of Aldehydes with Propargyl Borolane in the Presence of the Chiral Diphosphane 169



entry	R	yield (%)	ee (%)
1	Ph	99	97
2	4-MeOC$_6$H$_4$	97	98
3	3-(EtO$_2$CCH$_2$O)C$_6$H$_4$	95	99
4	2-F-3-CN-4-NMe$_2$C$_6$H$_2$	94	96
5	4-MeO-2-naphthyl	98	97
6	6-MeO-3-pyridyl	93	97
7	2-benzofuryl	77	93
8	*N*-Me-2-indolyl	86	97
9	(*E*)-PhCH=C(Me)	96	97
10	CbzNHCH$_2$CH$_2$	95	90

The proposed catalytic cycle for the reaction mediated by complex **166** involved transmetalation, ligand exchange equilibrium, followed by migratory insertion of the allene to yield an unsymmetrical bis-π-allylpalladium intermediate,[188] which reacted with the aldehyde, providing the homoallylic product. Finally, the arylallylpalladium(II) complex was regenerated via transmetalation upon reaction with the boronic acid, liberating the lactone at the same time (Scheme 50).

8.2. From Nitriles

The asymmetric addition of allyl cyanide to ketimines under proton-transfer conditions was performed using a catalytic

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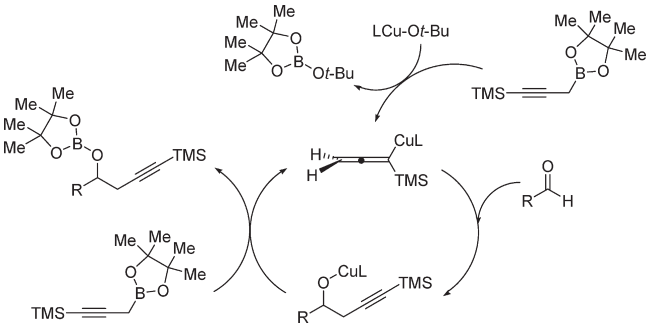
system comprising $[Cu(CH_3CN)_4]ClO_4$, the chiral ligand (*R*,*R*)-Ph-BPE [(*R*,*R*)-**167**], and $Li(OC_6H_4$-2-OMe) as a base. Kumagai, Shibasaki, and co-workers found that the combination of a soft Lewis acid (Cu^+) and a base (the alkali metal aryloxide) enabled the catalytic generation of an active nitrile nucleophile and the subsequent α-addition to ketoimines, affording first a β,γ-unsaturated nitrile, which isomerized to give the final α,β-unsaturated derivative with high *E*-selectivity (Scheme 51).[189]

Yazaki, Kumagai, and Shibasaki extended also this methodology to the allylation of aryl methyl ketones including heteroaromatic substrates. Regarding the regiochemistry, γ-addition took place exclusively with excellent enantioselectivity and complete *Z*-selectivity (Table 82, entries 1−6). In the case of ketones bearing ethyl or *n*-propyl substituents, a stronger base [LiO*t*-Bu instead of $Li(OC_6H_4$-2-OMe)] was required (Table 82, entries 7 and 8). Exclusive 1,2-addition was observed with enones bearing either aromatic or aliphatic substituents (Table 82, entries 9 and 10).[190]

The exclusive γ-addition of allyl cyanide could be explained considering that the combination of the chiral ligand (*R*,*R*)-**167** and $[Cu(CH_3CN)_4]ClO_4$ furnished a monomeric (*R*,*R*)-**167**/Cu complex, which would give (*R*,*R*)-**167**/$Cu(OC_6H_4$-2-OMe) and $LiClO_4$ upon anion exchange with $Li(OC_6H_4$-2-OMe). A soft−soft interaction of Cu^+ and allyl nitrile was immediately followed by deprotonation with the neighboring base to give an α-*C*-copper active nucleophile. The initially formed α-*C*-copper species could interconvert into a γ-*C*-copper nucleophile, which should provide an *E*,*Z*-mixture of the γ-addition product in the 1,2-addition to ketones. However, the exclusive formation of a *Z*-olefin would be indicative of the involvement of a six-membered cyclic transition state where the reaction proceeded through an α-*C*-copper species with the nitrile group occupying the pseudoaxial position, thus avoiding the steric repulsion with the phenyl group of (*R*,*R*)-**167**, affording the corresponding (*S*)-*Z*-adduct (Figure 15).

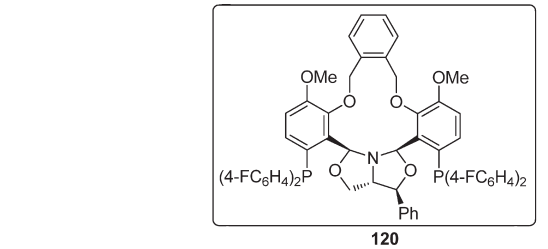
Scheme 56

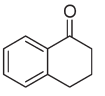


9. ENANTIOSELECTIVE PROPARGYLATION AND ALLENYLATION OF CARBONYL COMPOUNDS

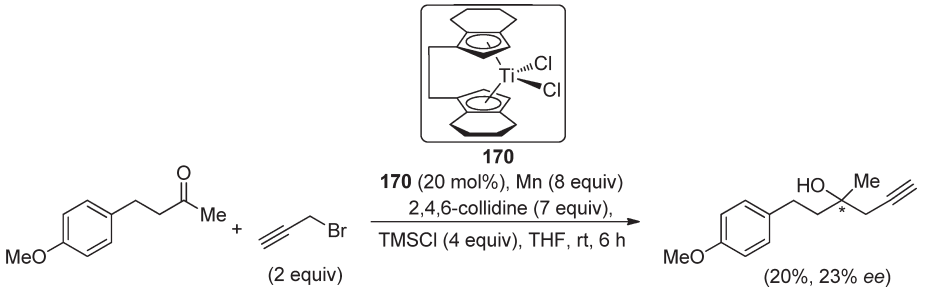
Chiral homopropargylic and allenylic alcohols are also versatile building blocks for the enantioselective synthesis of complex molecules. In addition to the stereogenic center, the triple bond or the cumulene moiety allows further transformations including the generation of new carbon−carbon and carbon−heteroatom bonds. Most of the methods that have been developed for the preparation of these compounds involve the stereoselective addition of propargylic or allenylic metals to carbonyl compounds. Depending on the metal and also on the reaction conditions, homopropargylic and allenylic alcohols are accessible in a pure form or as a mixture because propargylic or allenylic metals could interconvert easily. Thus, methodologies for the

Table 85. Copper-Catalyzed Enantioselective Propargylation of Ketones with Allenyl Borolane in the Presence of the Chiral Ligand 120



Entry	R^1	R^2	Yield (%)	*ee* (%)
1	Ph	Me	93	95
2	4-BrC_6H_4	Me	85	90
3	4-$MeOC_6H_4$	Me	82	93
4	Ph	Et	94	42
5	2-naphthyl	Me	93	88
6	2-thienyl	Me	83	95
7			84	98
8	(*E*)-PhCH=CH	Me	90	86
9	1-cyclohexenyl	Me	67	86
10	*i*-Pr	Me	65	81

Scheme 57



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regio- and stereoselective addition of propargyl or allenyl metals to carbonyl compounds are of synthetic interest (Scheme 52).

9.1. Propargylation of Carbonyl Compounds

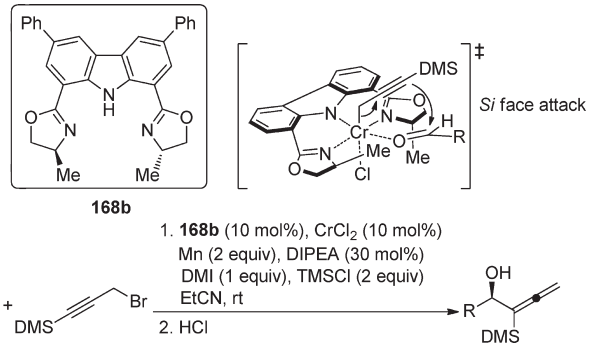
Loh et al. investigated the indium-mediated propargylation of aldehydes with propargylic bromide in the presence of (−)-cinchonidine (**135**). The reactions proceeded smoothly to afford the corresponding homopropargylic alcohols in good yields, and no detectable amount of the corresponding allenic alcohol was observed. Contrary to the normal indium-mediated propargylation addition to carbonyl compounds, this system was sensitive to water, with the best results being obtained using a 3:1 THF/hexane mixture of solvents (Scheme 53). Interestingly, even the commercially available trifluoroacetaldehyde hemiacetal (not represented in Scheme 53) was used directly without the need to use the unstable and volatile trifluoroacetaldehyde.[191]

An indium-promoted enantioselective propargylation of both aromatic and aliphatic aldehydes using commercially available (1*S*,2*R*)-2-amino-1,2-diphenylethanol (**132a**) as a chiral auxiliary was also reported by Singaram and co-workers. Importantly, the addition of a stoichiometric amount of pyridine not only improved the yield of the reaction but also increased the ee of the resulting alcohol,[159] and only 2 equiv of propargyl bromide were used. Aromatic aldehydes (Table 83, entries 1−5) provided homopropargylic alcohol products in higher yield than the aliphatic derivatives. Regarding the enantioselectivity, sterically demanding pivalaldehyde led to the reaction product with the highest value of ee (95%, Table 83, entry 10).[192] It is worthy to note that although 2 equiv of the amino alcohol ligand (commercially available in either enantiomer) were necessary, it was recovered via a simple acid−base extraction. In addition, (−)-cinchonidine (**135**) and chiral aminoalcohol **132a** showed opposite facial stereoselectivity in the indium-mediated propargylation of benzaldehyde: *Re*-face addition for **135** and *Si*-face addition in the case of **132a**.

The enantioselective propargylation with allenyl *n*-tributyltin was also carried out using Maruoka's catalyst and the chiral bis-Ti oxide (*S*,*S*)-**82** in CH_2Cl_2 at 0 °C. Compared to the allylation process with the same catalytic system, in this case, yields were improved using a larger excess of the propargylation reagent (3 equiv). In addition, 10−20 mol % catalyst loading was required in order to get high enantiomeric excesses (92% ee). Regarding the regiochemistry, the expected homopropargyl alcohol was accompanied by a small amount of the isomeric allenyl derivative in a 10:1 ratio for benzaldehyde and 15:1 ratio for 3-phenylpropanal (Scheme 54).[80]

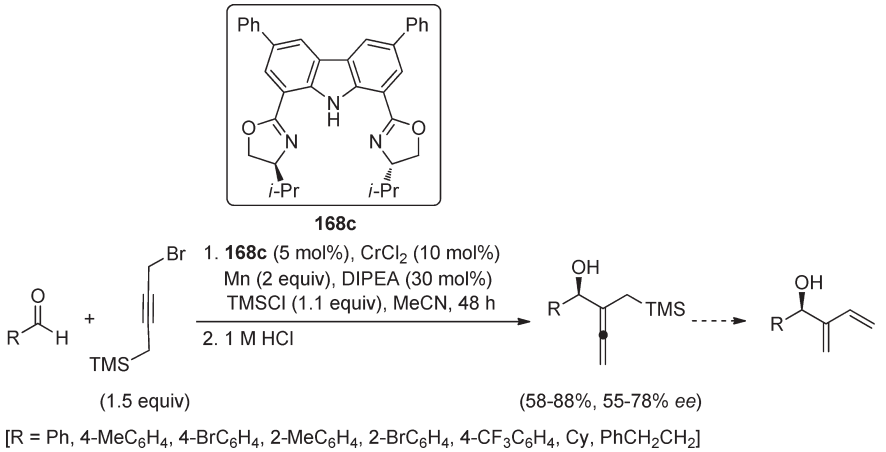
Chiral bis-(8-quinolinolato) (TBOx) chromium catalyst **127**, which has also been used by H. Yamamoto in enantioselective allylation of carbonyl compounds, was effectively employed in the enantioselective propargylation of benzaldehyde with propargyl bromide, leading exclusively to the formation of (*R*)-homopropargyl alcohols (Scheme 55).[193] Inoue and Nakada found that catalytic asymmetric Nozaki−Hiyama propargylation of various aldehydes with propargyl bromide in the presence of tridentate ligand **168a**, under optimized reaction conditions, proceeded with good to excellent enantioselectivity (Scheme 55).[194] Although Inoue and Nakadas's conditions worked well for aromatic and α,β-unsaturated compounds (>90% yield and >73% ee), the propargylation product derived from 3-phenylpropanal was isolated in 20% yield with 51% ee; meanwhile, sterically demanded pivalaldehyde led to the highest level of enantiocontrol (98% ee). Kishi and co-workers studied also the catalytic enantioselective propargylation of *O*-TBDPS-protected 4-hydroxybutanal with propargyl bromide

Table 86. Chromium-Catalyzed Enantioselective Allenylation of Aldehydes in the Presence of Chiral Ligand 168b



entry	R	*t* (h)	yield (%)	ee (%)
1	4-$MeOC_6H_4$	36	90	80
2	4-ClC_6H_4	24	91	82
3	$PhCH_2CH_2$	24	99	72
4	Cy	24	95	74
5	$CH_3(CH_2)_4$	24	81	75

Scheme 58



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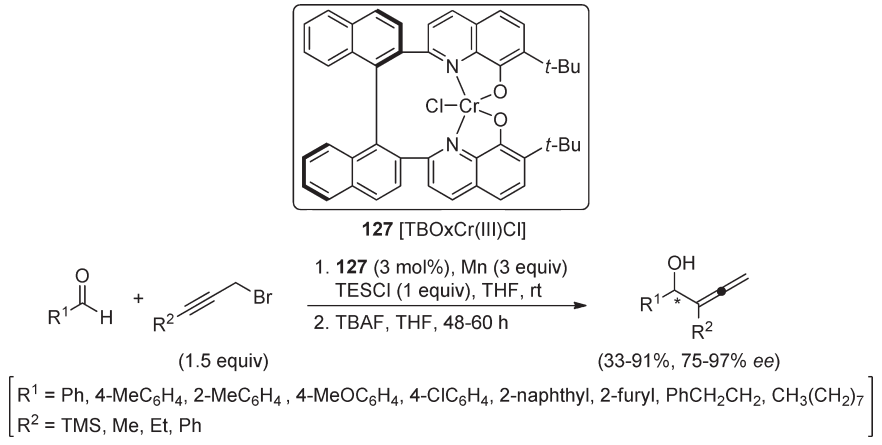
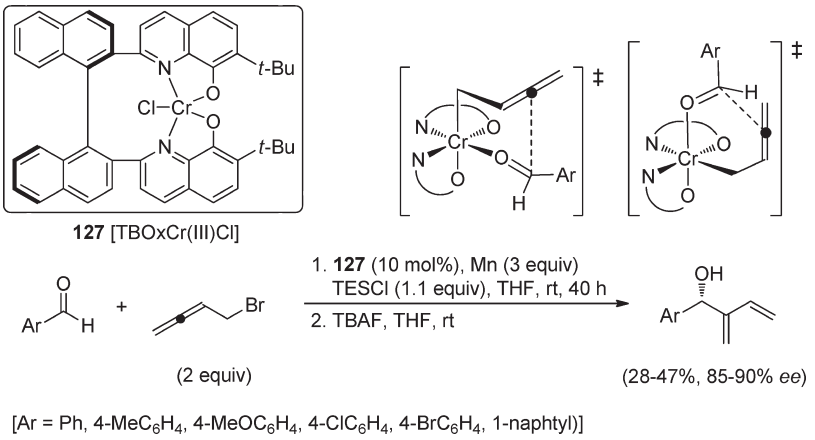
Scheme 59



Scheme 60



in the presence of 10 mol % of a Cr catalyst prepared from $CrBr_3$ and (*R*)-sulfonamides **129b**,**c**. The reaction proceeded with higher yields (85 and 78%) in the case of (*R*)-**129c**; however, higher enantioselectivities (90 and 83% ee) were obtained using (*R*)-**129b** (Scheme 55).[195] The resulting homopropargyl alcohol was converted into a building block of the C14−C15 fragment of natural products halichondrins. Importantly, the above-presented H. Yamamoto's, Nakada's, and Kishi's propargylation protocols showed the same face selectivity.

Chiral homopropargylic alcohols were prepared by Fandrick et al. through a highly enantioselective copper-catalyzed propargylation of aldehydes with a propargyl borolane reagent. Whereas moderate site selectivity for the alkynyl over the allenyl product was obtained when a catalytic amount of Cu(I)-*tert*-butoxide was exclusively used, the site selectivity for the homopropargylic alcohol was considerably improved in the presence of phosphane ligands. Regarding the enantioselectivity of the process, the most efficient chiral phosphane ligand was MeO-BIBOP (**169**). High enantioselectivities (93−99% ee) and yields were achieved for aromatic and heteroaromatic aldehydes (Table 84, entries 1−8). For the aliphatic aldehyde, a slight decrease in the enantioselectivity (90% ee) was observed (Table 84, entry 10). Interestingly, the presence of different functional groups such as esters, nitriles, an aryl fluoride, and a carbamate showed no impact on the asymmetric propargylation.[196]

A plausible catalytic cycle based on two key steps was proposed. First, reaction of copper−alkoxide with the propargyl borolane would lead to an allenyl copper intermediate through a B/Cu exchange. The addition of the allenyl copper to the aldehyde would produce the homopropargyl copper alcoholate, which after reaction with the propargyl borolane would regenerate an allenyl copper intermediate to establish the catalytic cycle (Scheme 56).

Justicia, Cuerva, and co-workers described recently a novel method for the propargylation of aldehydes and ketones with propargyl bromide using titanocene complexes as catalysts. Importantly, homopropargylic alcohols were obtained as the sole products even when ketones are used as starting materials, which is unusual in Barbier-type propargylations. A first approach to achieve enantioselective propargylation using this methodology consisted in the reaction of 4-(4-methoxyphenyl)butan-2-one with propargyl bromide in the presence of the commercially available Brintzinger complex **170**, with the expected propargyl alcohol being obtained in 20% yield and a 23% ee (Scheme 57).[197]

Homopropargyl tertiary alcohols were produced with high enantioselectivity by propargylation of ketones with the allenyl borolane derived from pinacol in the presence of the CuOAc-**120**

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catalyst. This catalytic system developed by Kanai, Shibasaki, and co-workers was also used in the enantioselective allylation of ketones (Table 85). It is worth noting that the reaction proceeded with total regioselectivity through a γ-addition without detecting in any case the isomeric allenyl tertiary alcohols resulting from a α-addition. High enantioselectivities (88−95% ee) were achieved for aryl and heteroaryl methyl ketones (Table 85, entries 1−3, 5, and 6), but the highest value (98% ee) was obtained for α-tetralone (Table 85, entry 7).[133]

9.2. Allenylation of Carbonyl Compounds

The asymmetric catalysis for the Nozaki−Hiyama allenylation of aldehydes was achieved by Inoue and Nakada using terminally substituted propargyl halides with different silyl groups.[198] Surprisingly, the reactions afforded always the allenyl alcohol in good yields as the sole reaction product. Regarding the stereoselectivity of the process, the most effective ligand was the tridentate carbazole **168b**. Inoue and Nakada found that the silyl group of the propargyl halide affected the enantioselectivity, so while silyl groups bulkier than the TMS group did not improve the enantioselectivity, the smaller DMS group afforded the best results. In addition, a polar additive such as DMI improved both the yield and the enantioselectivity. Under the optimized reaction conditions shown in Table 86, various aromatic (Table 86, entries 1 and 2) and aliphatic aldehydes (Table 86, entries 3−5) were successfully allenylated with high enantioselectivity and excellent yield. The aldehydes were allenylated predominantly at the *Si*-face. Thus, compared to the previously reported Nakadas's catalytic asymmetric propargylation (Scheme 55)[194] in which aldehydes showed *Re*-face selectivity, the enantioface selectivity in the allenylation is reversed. This result could be explained considering the transition state shown in Table 86, in which the terminally silylated propargyl group was positioned at the less-hindered apical position of the asymmetric catalyst; meanwhile, the aldehyde was coordinated at the equatorial position, leading under these circumstances to a *Si*-face attack.

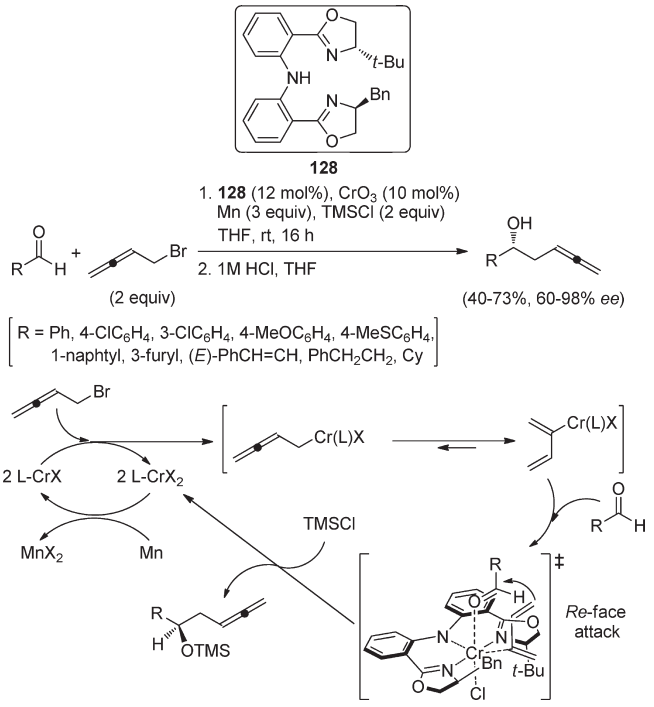
Applying similar reaction conditions to those of Nakada, Durán-Galván and Connell performed the enantioselective allenylation of aldehydes with (4-bromobut-2-ynyl)trimethylsilane.[199] Among different chiral carbazole tridentate ligands, the isopropyl derivative **168c** provided the highest yield and enantioselectivity. The allenylation was successful for both aromatic and aliphatic substrates affording [1-(silylmethyl)allenyl]methanols (Scheme 58). These compounds are of interest because they are precursors of chiral 2-hydroxyalkyl-1,3-dienes after desilylation and isomerization.

Xia and H. Yamamoto applied also the chiral chromium catalyst **127** to the asymmetric allenylation of aldehydes with commercially available terminally substituted (TMS, methyl, ethyl, and phenyl group) propargylic bromides. Excellent enantioselectivities (up to 97% ee, R^1 = 2-furyl, R^2 = TMS) for the allenylation reaction of aromatic and aliphatic aldehydes were obtained. Regarding the chemoselectivity, the isomeric homopropargyl alcohol was formed always in <5% yield (Scheme 59).[200]

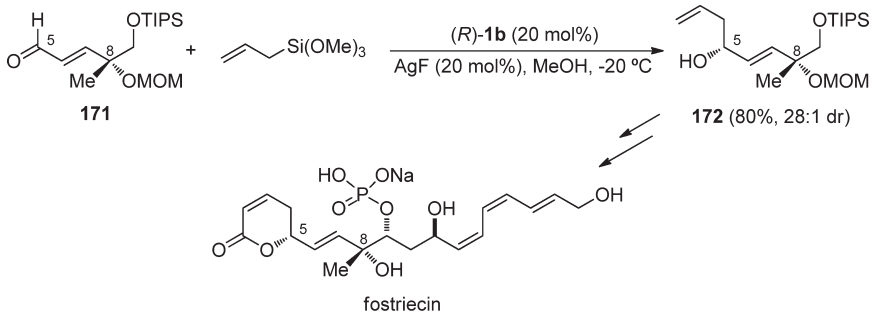
9.3. Chromium-Mediated Addition of Homoallenyl Bromide to Aldehydes

H. Yamamoto and co-workers explored also the reactivity of 4-bromobuta-1,2-diene with aromatic aldehydes in a process catalyzed by **127**, and surprisingly, only the 1,3-butadiene product was obtained as reaction product. The reaction proceeded well under the optimized conditions shown in Scheme 60, providing the expected adducts with moderate yields and high enantioselectivities.[201] Electron-rich *para*-methoxybenzaldehyde afforded 2-substituted 1,3-butadienes with the highest yield (47%), in contrast to electron-poor aldehydes that exhibited decreased reactivity (32 and 34% yield for *para*-bromo and *para*-chlorobenzaldehyde, respectively). Generally, high levels of enantioselectivity were maintained for all of the carbonyl substrates used. Reaction products had (*R*)-absolute configuration, and two plausible transition states were proposed by the authors

Scheme 61



Scheme 62



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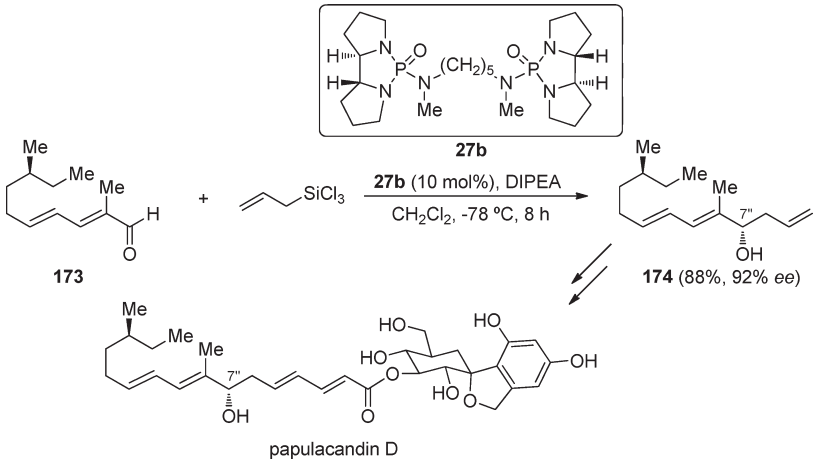
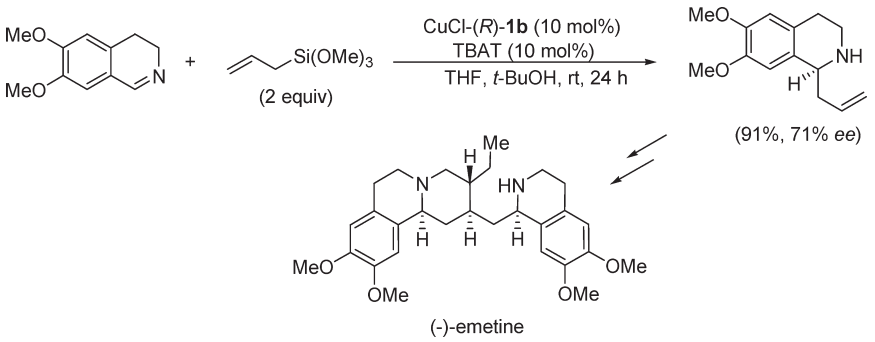
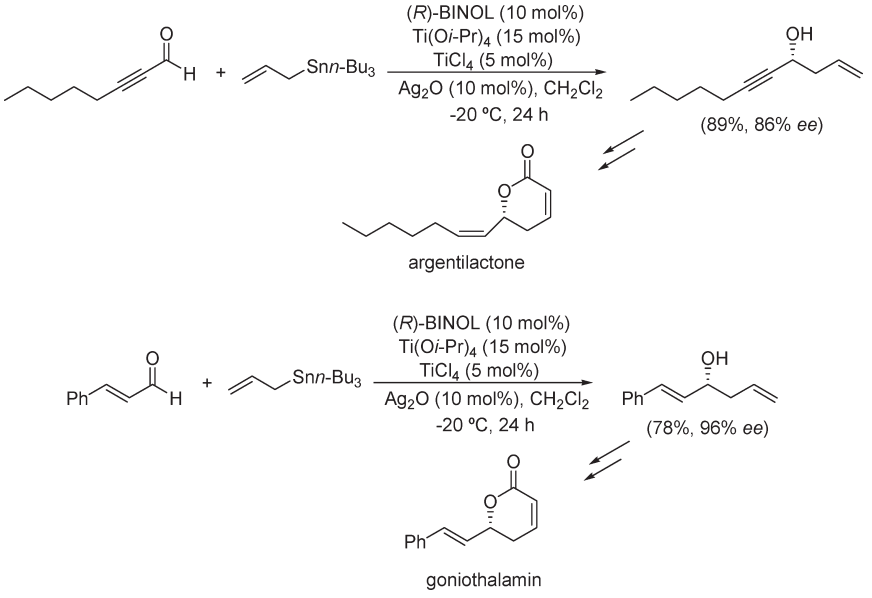
Scheme 63



Scheme 64



Scheme 65



to explain this result. In one transition state, the allenyl moiety was bonded axially to chromium in octahedral coordination geometry while the aldehyde adopted an equatorial orientation. The other transition state involved opposite coordination of the

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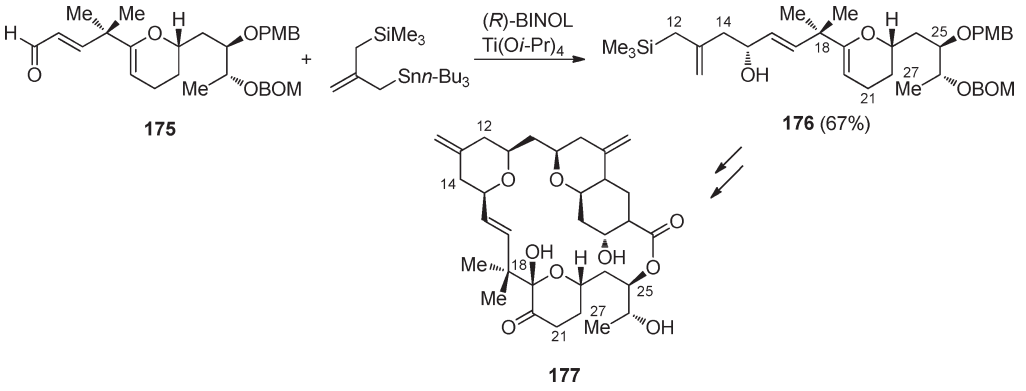
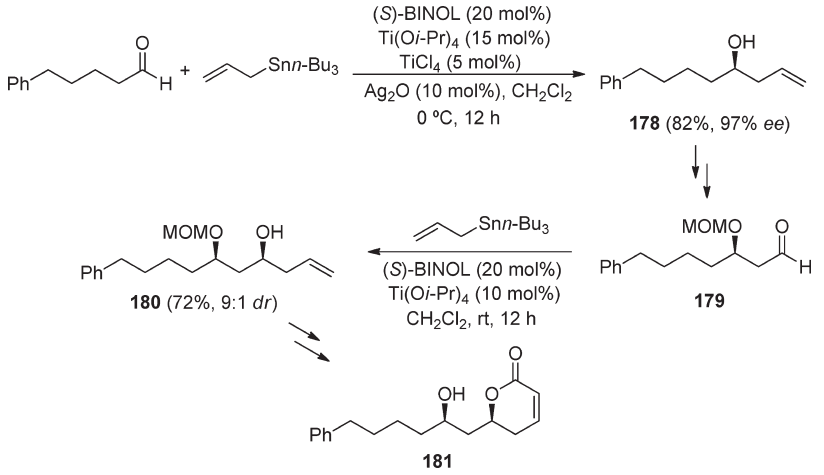
Scheme 66



Scheme 67



substrates. In both cases, nucleophilic attack of the dienyl moiety occurred at the *Re*-face of the aldehyde to deliver the corresponding (*R*)-alcohol (Scheme 60).

The ligand **128** was also used in the chromium-catalyzed addition of 4-bromobuta-1,2-diene to aldehydes. Interestingly, opposite regiochemistry to that found in the allylation catalyzed by ligand **127** was observed. In this case, the corresponding β-allenol was almost exclusively obtained with good enantiocontrol for cyclohexanecarbaldehyde (60% ee) and excellent enantiocontrol (>90% ee) for the rest of the aromatic, aliphatic, and α,β-unsaturated aldehydes (Scheme 61).[202] In terms of enantiodiscrimination, the reaction of 4-bromobuta-1,2-diene with aromatic and heteroaromatic aldehydes gave rise to (*R*)-β-allenols. This is the same sense of induction as previously observed for the allylation, methallylation, and crotylation of benzaldehyde using **128** as the ligand.[149,151] Guiry proposed a mechanism to explain the regiochemistry and the stereochemical outcome of the reaction. In this mechanism the homoallenyl bromide reacts with 2 equiv of the ligand—chromium complex (L—CrX) to form homoallenyl and 1,3-butadien-2-yl chromium(III) intermediates. The 1,3-butadien-2-yl chromium(III) species is more favored and was proposed to add to the aldehyde via the transition state shown in Scheme 61, in which the 1,3-butadien-2-yl moiety would be bonded to chromium in the equatorial position while the aldehyde would coordinate at the apical position through an anti-geometry to minimize the steric interactions between the alkyl group and the oxazoline ring. Therefore, *Re*-face attack should be favored through this transition state (Scheme 61).

10. SYNTHESIS OF NATURAL PRODUCTS

Some of the previously presented methodologies for the catalytic enantioselective allylation of carbonyl compounds and imines have been used in the synthesis of natural products or pharmaceutical drugs, displaying the usefulness and versatility of these transformations. Allylic silanes, stannanes, and boranes are the precursors most commonly used in these allylations, and some recent examples of synthesis of complex molecules, which include as a key step a catalytic enantioselective allylation, are commented below.

10.1. Allylic Silanes

Kanai, Shibasaki, and co-workers reported the asymmetric synthesis of the natural antibiotic fostriecin[203,204] and its analogue 8-epifostriecin[205] (its epimer at C-8). Fostriecin is a structurally interesting novel metabolite isolated from *Streptomyces pulveraceus*,[205] which displays in vitro antitumor activity against a broad range of cancerous cell lines. One of the key steps of the proposed synthesis was the stereoselective allylation of enal **171**. Unfortunately, Keck allylation using 2 equiv of

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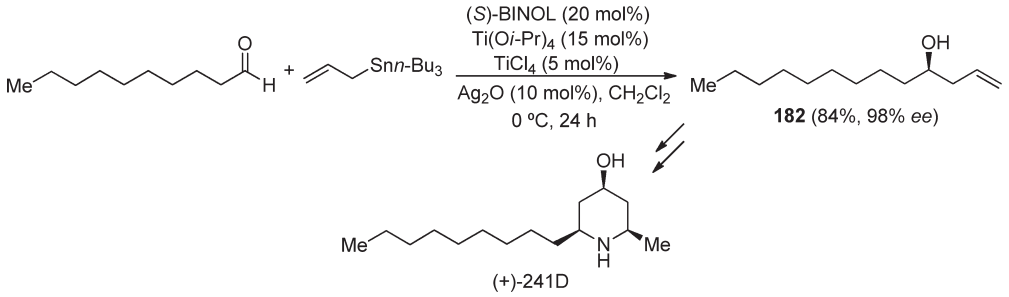
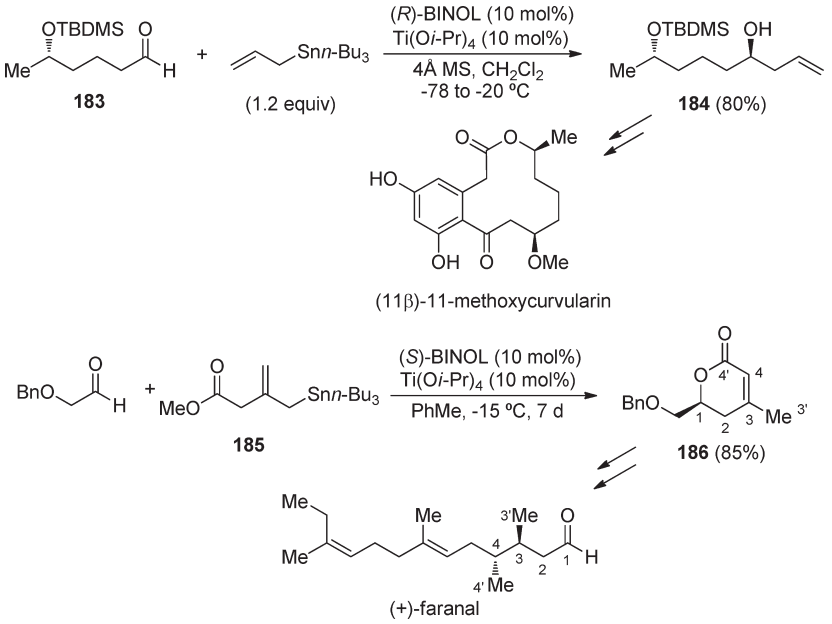
Scheme 68



Scheme 69



allyltri-*n*-butyltin and 20 mol % catalyst prepared from Ti(O*i*-Pr)$_4$ and (*R*)-BINOL did not proceed well, and led to **172** in only 39% yield with a diastereomeric ratio of 7:1. By contrary, H. Yamamoto's AgF-catalyzed allylation of the enal **171** with allyltrimethoxysilane in the presence of (*R*)-*p*-tol-BINAP [(*R*)-**1b**] proved to be superior. In this case, diastereoselectivity was as high as 28:1 in favor of the isomer with (*R*)-configuration at C-5 **172**, being consistent with H. Yamamoto's transition state model (Scheme 62).

Papulacandins have shown potent in vitro antifungal activity against *Candida albicans*, *C. tropicalis*, *Pneumocystis carinii*, and related microorganisms.[206] Denmark reported the synthesis of papulacandin D through a convergent synthetic strategy that features a silicon-based, cross-coupling reaction to construct the key spirocyclic *C*-aryl glycopyranoside, and an enantioselective allylation reaction. For that reason, different asymmetric allylation reactions of a model dienal (similar to compound **173**) were evaluated. Keck allylation conditions[77c−e] provided the homoallylic alcohol with excellent enantioselectivity (92% ee), albeit in only 30% yield. Treatment of the dienal with allyl bis(isopinocampheyl)borane developed by Brown and co-workers [207] afforded an improved yield (around 70−75%), and the enantiomeric ratio reflected the purity of the reagent. A major drawback of Brown-type allylation is the need to synthesize stoichiometric amounts of a chiral reagent. Fortunately, the enantioselective allylation with allyltrichlorosilane catalyzed by a chiral bisphosphoramide developed by Denmark proved to be superior to the other methodologies on the model dienal. Thus, allylation of the dienal **173** with allyltrichlorosilane using chiral bisphosphoramide **27b** provided **174** in good yield and excellent stereoselectivity (88%, 92% ee) with the expected (*S*)-configuration at C-7″ (Scheme 63).[208]

Itoh et al. studied the catalytic asymmetric allylation of 3,4-dihydro-6,7-dimethoxyisoquinoline with allyltrimethoxysilane in the presence of Cu(I) and (*R*)-*p*-tol-BINAP [(*R*)-**1b**] to give 1-allyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline in 91% yield and 71% ee. The enantiomeric excess was further increased by recrystallization in the presence of dibenzoyl tartaric acid to afford a pure enantiomer. The allylic adduct thus obtained was transformed into a key intermediate for the total synthesis of (−)-emetine (Scheme 64).[23]

10.2. Allylic Stannanes

Keck and Maruoka reported highly efficient methods for the enantioselective allylation of carbonyl compounds with allyltri-*n*-butylstannane catalyzed by BINOL/Ti(IV) complexes. These

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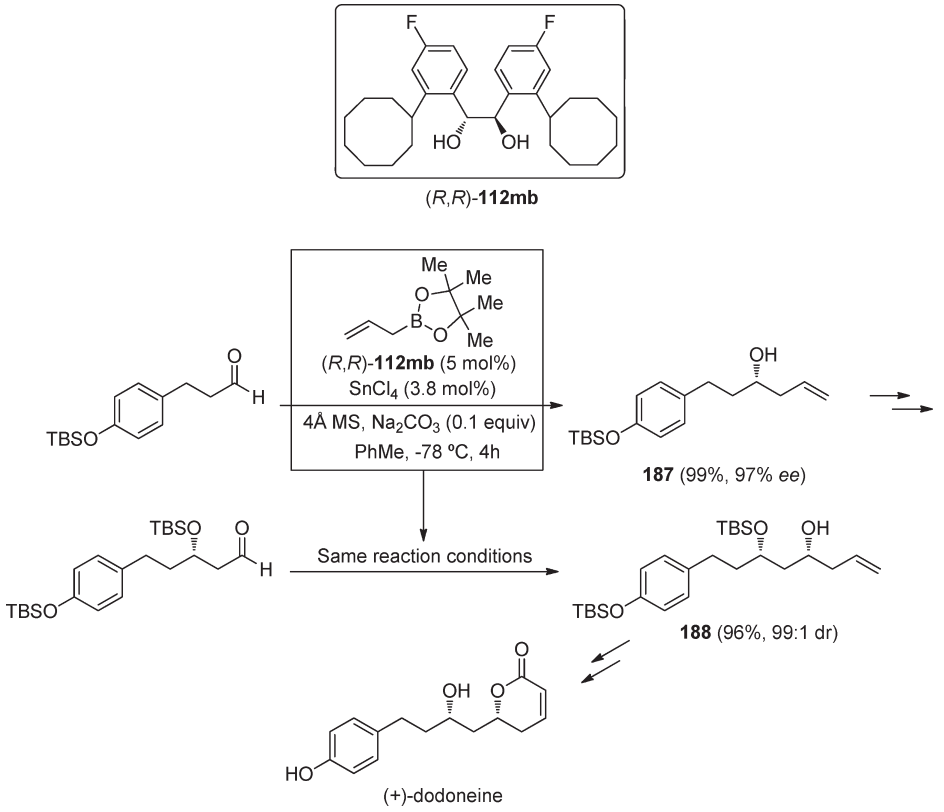
Scheme 70



methodologies have the broadest substrate scope, because the allylation of aliphatic, aromatic, and α,β-unsaturated aldehydes proceeded in high yields and excellent enantioselectivities. For example, enantioselective Maruoka allylation and ring-closing metathesis were the key steps in the synthesis of argentilactone and goniothalamin reported by de Fátima and Pilli.[209] The addition of allyltri-*n*-butyltin to oct-2-ynal proceeded in 89% yield and 86% ee in the first step of the synthesis of argentilactone. In the case of goniothalamin, the allylation of *trans*-cinnamaldehyde under the same reaction conditions provided the corresponding homoallylic alcohol in 78% yield and 96% ee (Scheme 65).

Another interesting example is the synthesis of a bryostatin analogue (**177**) reported by Keck and Truong. In this case, the α,β-unsaturated aldehyde **175** was converted into the alcohol **176**, using 2-(trimethylsilylmethyl)allyltin in the presence of a large excess of the BINOL/Ti(O*i*-Pr)$_4$ (Scheme 66).[210] The product **176** was obtained in modest (67%) yield due to some decomposition during the reaction.

Chandrasekhar et al. applied iterative Maruoka and Keck asymmetric allylations and ring-closing metathesis in the first stereoselective total synthesis of (6*S*)-5,6-dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one (**181**), a novel α,β-unsaturated δ-lactone having antifungal activity, isolated from *Ravensara crassifolia*.[211] The Maruoka asymmetric allylation of 5-phenylpentanal with allyltri-*n*-butyltin gave the homoallyl alcohol **178** in 82% yield and 97% ee. The MOM protection played a crucial role in the asymmetric Keck allylation of aldehyde **179**, leading to the homoallyl alcohol **180** in an overall yield of 72% with a 9:1 syn/anti diastereomeric ratio. Other protecting groups, such as TBDMS and PMB, gave unsatisfactory results in this asymmetric Keck allylation (Scheme 67).[212]

An efficient stereoselective synthesis of the dendrobate alkaloid (+)-241D reported by Rao and co-workers started also with a Maruoka asymmetric allylation of decanal with allyltri-*n*-butyltin in the presence of (*S*)-BINOL. The resulting homoallyl alcohol **182** was obtained in 84% yield with an excellent enantioselectivity of 98% ee (Scheme 68).[213] Dendrobate alkaloid 241D was isolated from methanolic skin extracts of Panamanian poison frogs *Dendrobates speciosus* and *Dendrobates pumilio* and possesses a potent biological activity.[214]

Keck asymmetric allylations were also key steps in the synthesis of (11β)-11-methoxycurvularin and (+)-faranal. Venkateswarlu and co-workers performed the diastereoselective allylation of the functionalized aldehyde **183** to give alcohol **184**, in 80% yield with an excellent diastereoselectivity of 95% de, a precursor of (11β)-11-methoxycurvularin (Scheme 69).[215] In the synthesis of (+)-faranal, the trail pheromone of the pharaon ant, *Monomorium pharaonis*, developed by Mineyeva and Kulinkovich, the allylation of (benzyloxy)acetaldehyde with the allylstannane **185** in dichloromethane, under typical Keck reaction conditions, led to a complex mixture of products. However, the allylation proceeded faster when toluene was used as the solvent. In this case, the reaction was accompanied by lactonization of the intermediate homoallylic alcohol and subsequent migration of the carbon−carbon double bond to a position conjugated to the carbonyl group to afford the lactone **186** in 85% yield, a direct precursor of the natural product (Scheme 69).[216]

10.3. Allylic Boranes

Rauniyar and Hall synthesized (+)-dodoneine, a naturally occurring dihydropyranone recently isolated from a parasitic plant in Burkina Faso,[217] taking advantage of the efficiency of the

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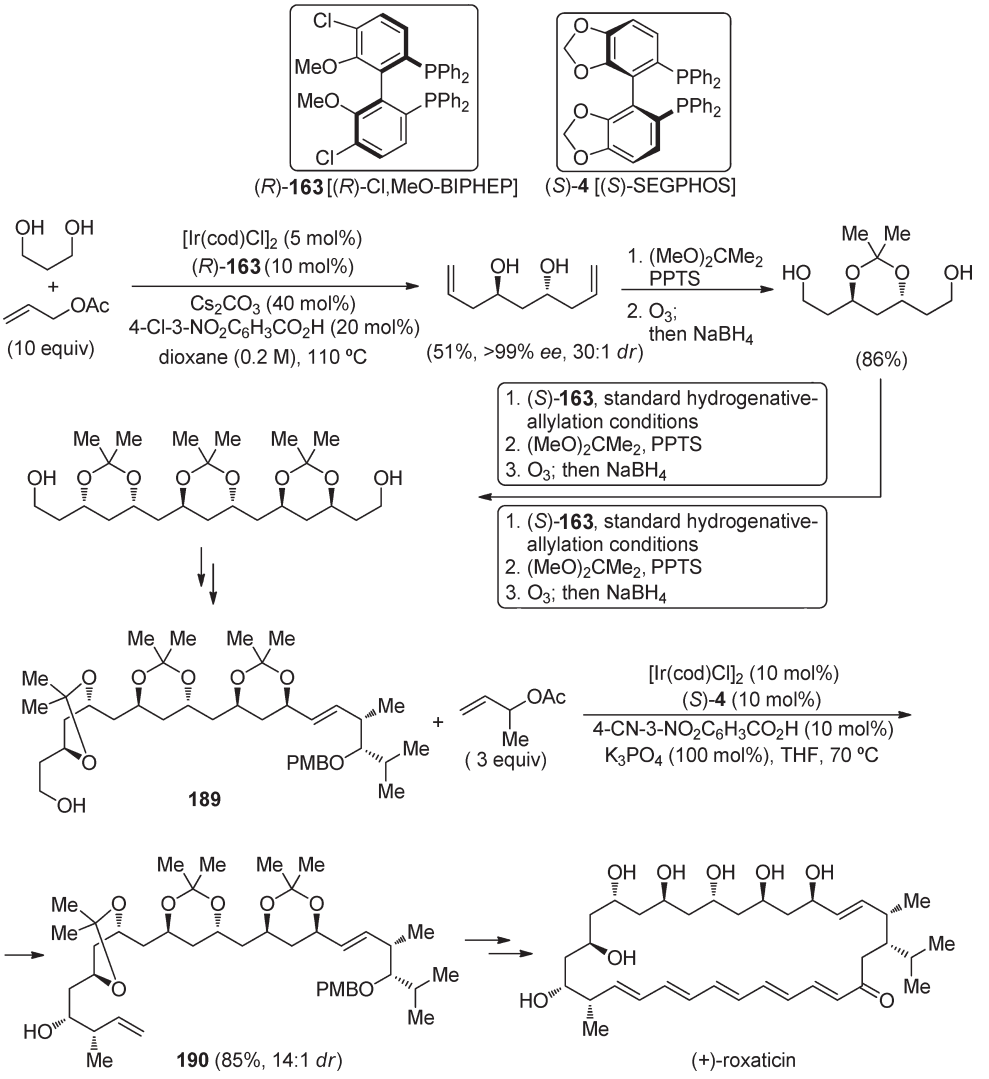
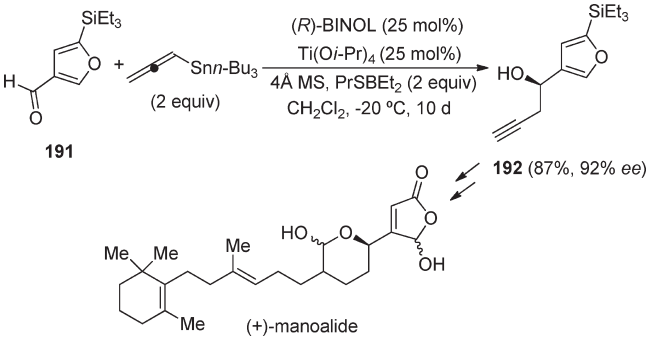
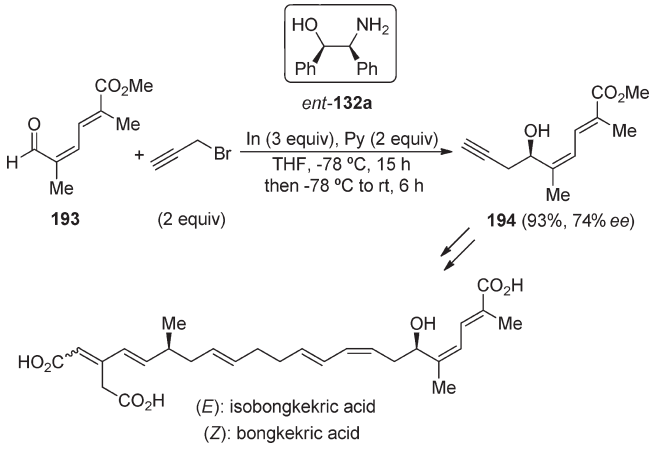
Scheme 71



Scheme 72



Scheme 73



enantioselective allylation on aldehydes with pinacol allyl boronate in the presence of chiral diol *p*-F-Vivol [(*R*,*R*)-**112mb**)]. Two subsequent aldehyde allylations were performed leading to homoallyl alcohols **187** and **188** in almost quantitative chemical yields and high stereoselectivities (Scheme 70),[127] with this methodology performing better than other allylation processes acting over the same substrates. For instance, Falomir, Marco, and co-workers reported that alcohol **187** was obtained

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through a Brown allylation in a significantly lower ee of 90%.[218] In addition, Keck allylation of the same aldehyde was reported to provide 95% ee, however, in a lower yield (77%).[219] Final steps toward (+)-dodoneine from alcohol **188** included *O*-acylation with acryloyl chloride, ring-closing metathesis, and desilylation.

10.4. Allylic Acetates

Krische and co-workers provided the synthesis of the oxopolyene macrolide (+)-roxaticin[220] in 20 steps from 1,3-propanediol.[221] In this approach, 7 of 10 C−C bonds were formed using iterative enantioselective iridium-catalyzed hydrogenative allylation of alcohols with allylic acetates.[183] The synthesis started with double allylation of 1,3-propanediol leading to the corresponding C_2-symmetric homoallylic diol in moderate yield and excellent diastero- and enantioselectivities. The diol was further converted into the acetonide and, after ozonolysis with reductive quenching, into a tetraol derivative. This compound was then subjected to two cycles of standard transfer hydrogenative allylation, acetonide formation, and ozonolysis, providing a C_2-symmetric octaol derivative as a single stereoisomer, with the configuration of the created stereogenic centers being determined by the chiral ligand BIPHEP derivative **163** of the iridium catalyst (Scheme 71). Enantio- and diastereoselctive crotylation of **189** with but-3-en-2-yl acetate under iridium catalysis in the presence of chiral ligand (*S*)-SEGPHOS [(*S*)-**4**] led to compound **190** in high yield. (+)-Roxaticin was prepared from compound **190** in seven steps (Scheme 71).

10.5. Enantioselective Propargylations

The phospholipase A_2 inhibitor (+)-manoalide is a sesterterpenoid metabolite isolated from the Pacific sponge *Luffariella variabilis*.[222] The key step of the synthesis of the (+)-manoalide reported by Kocienski and co-workers was an asymmetric Keck propargylation with an allenyl stannane of the aldehyde **191** to give the alcohol **192** with excellent stereoselectivity (92% ee) and high yield (87%, based on recovered starting material). A major drawback of this step was the long reaction times (ca. 10 days) at the low temperature required to achieve high ee (Scheme 72). Addition of allenyl/propargylzinc reagents in the presence of chiral aminoalcohols or chiral allenylboron derivatives led always to lower yields and stereoselectivities.[223]

Isobongkrekic acid and its isomer bongkrekic acid form a small family of toxic antibiotics with potent antiapoptotic activity. Ley and co-workers achieved the synthesis of these natural products through a convergent strategy using in one step an indium-mediated propargylation of thermally unstable $\alpha,\beta,\gamma,\delta$-unsaturated aldehdye **193** with propargyl bromide in the presence of aminoalcohol *ent*-**132a**, according to the methodology developed by Singaram and co-workers.[192] In this way, homopropargylic alcohol **194** was formed in good yield (93%) and acceptable enantioselectivity (74% ee, Scheme 73).[224]

11. CONCLUSIONS AND OUTLOOK

The catalytic enantioselective allylation of carbonyl compounds and imine derivatives has considerably matured in the past decade. The advancements in the field are a logical consequence of the efforts made by organic chemists to improve this valuable tool to generate C−C bonds. Important progress has been made in the use of nontoxic allylic reagents as well as in the atom economy of the global process. Moreover, more complex substrates like aliphatic aldehydes, ketones, and their corresponding imine derivatives can now be used in this reaction with significantly better results in terms of reactivity and enantioselection. The incorporation of catalytic transfer hydrogenation protocols has also allowed the use of alcohols as substrates of different allylic systems. Despite the incredibly rapid evolution of this topic, there is always room for improvement. Transition from *plausible mechanisms* to *detailed mechanisms*, better supported models by experimental and theoretical data, is still highly desirable to develop fully predictable catalytic enantioselective allylation processes. Furthermore, the catalytic activation of the allylic C−H bond of common alkenes would be a very interesting area to study the use of nonactivated alkenes as allylic reagents.

AUTHOR INFORMATION

Corresponding Author

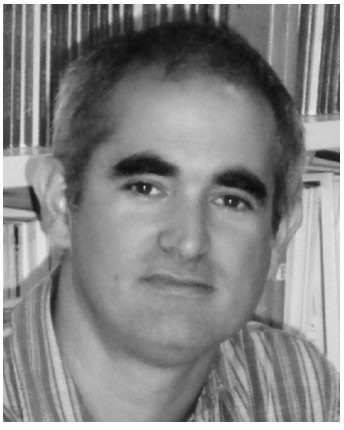
*Fax: +34 6 5903549. E-mail: yus@ua.es, josecarlos.gonzalez@ua.es, foubelo@ua.es.

BIOGRAPHIES

Miguel Yus was born in Zaragoza (Spain) in 1947 and received his B.Sc. (1969), M.Sc. (1971), and Ph.D. (1973) degrees from the University of Zaragoza. After spending two years as a postdoctoral fellow at the Max Planck Institut für Kohlenforschung in Mülheim a.d. Ruhr, he returned to Spain to the University of Oviedo where he became associate professor in 1977, being promoted to full professor in 1987 at the same university. In 1988 he moved to a chair in Organic Chemistry at the University of Alicante, where he is currently the head of the newly created Organic Synthesis Institute (ISO). Professor Yus has been visiting professor at different institutions and universities such as ETH-Zentrum, Oxford, Harvard, Uppsala, Marseille, Tucson, Okayama, Paris, Strasbourg, Sassari, Bologna, Tokyo, and Kyoto. He is coauthor of more than 500 papers mainly in the field of the development of new methodologies involving organometallic intermediates. Professor Yus has delivered around 150 lectures, most of them abroad. Among others, he has received the Spanish−French Prize (1999), twice the Japan Society for the Promotion of Science Prize (Okayama 2000, Kyoto 2007), the Stiefvater Memorial Lectureship Award (Lincoln 2001), the Nagase Science and Technology Foundation fellowship (Kyoto 2003), the Cellchem Lectureship (Sheffield 2005), the Singenta Lectureship (Basel 2007), the Fundeun-Iberdrola Prize (Alicante 2007), and the Serratosa Lectureship (Barcelona, 2010). Professor Yus has been in the Advisory Board of around 20 international journals, among others, *Tetrahedron*, *Tetrahedron Letters*, *European Journal of Organic Chemistry*,

Chemistry Letters, *Current Organic Chemistry*, *Current Chemical Biology*, *Jordan Journal of Chemistry*, and *Trends in Organic Chemistry*, being also Regional Editor of *Letters in Organic Chemistry* and *The World Journal of Chemistry*. His current research interest is focused on the preparation of very reactive functionalized organometallic compounds and their use in synthetic organic chemistry, arene-catalyzed activation of different metals, preparation of new metal-based catalysts, including metallic nanoparticles, for homogeneous and heterogeneous selective reactions and asymmetric catalysis. Professor Yus and other members of the ISO founded the new chemical company MEDALCHEMY S.L. to commercialize fine chemicals.

Francisco Foubelo was born in 1961 and grew up in Eastern Asturias. He studied chemistry at the University of Oviedo from which he received B.S. (1984), M.S. (1986), and Ph.D. (1989) degrees. After a postdoctoral stay (1989−1991) as a Fulbright fellow at Princeton University, he moved to the University of Alicante where he became Associate Professor in 1995 and Full Professor in 2002. Dr. Foubelo has coauthored more than 100 papers, and his current research interests are focused on the development of new synthetic methodologies involving chiral sulfinimines and on metal-promoted functionalization of alkenes and alkynes.



José Carlos González Gómez was born in 1971 and grew up in Havana, Cuba. He obtained his B.S. (1994) and M.S (1998) in chemistry at Havana University. In 1999 he moved to the University of Santiago de Compostela (Spain), where he got his Ph.D degree (2003) working on the synthesis of bioactive psoralen derivatives. After a postdoctoral stay (2005−2007) at the ETH in Zurich, he started as "Juan de la Cierva" researcher at the University of Alicante, where he became Assistant Professor in 2008. Dr. González-Gómez has coauthored about 30 papers, and his research interest is currently focused on the development and application of stereoselective reactions for the synthesis of bioactive compounds, mainly involving chiral sulfinimines.

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ABBREVIATIONS

Ac	acetyl
BIBOP	bisdihydrobenzooxaphosphole
BINAM	1,1′-binaphthyl-2,2′-diamine
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BINAPO	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl dioxide
BINOL	1,1′-bi-2-naphthol
BIPHEP	2,2′-bis(diphenylphosphino)biphenyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOM	benzyloxymethyl
Bz	benzoyl
ca.	circa
Cbz	carbobenzyloxy
CHIRAPHOS	butane-2,3-diylbis(diphenylphosphane)
cod	1,5-cyclooctadiene
Conc.	concentration
Config.	configuration
Cp	cyclopentadienyl
cth-(*R*)-p-phos	(*R*)-(+)-2,2′,6,6′-tetramethoxy-4,4′-bis-(diphenylphosphino)-3,3′-(bipyridine)
Cy	cyclohexyl
d	days
dba	dibenzylideneacetone
de	diastereomeric excess
DFT	density functional theory
DIFLUORPHOS	(2,2,2′,2′-tetrafluoro-4,4′-bibenzo[*d*]-[1,3]dioxole-5,5′-diyl)bis-(diphenylphosphane)
DIPAMP	1,2-bis(diphenylphosphino)-1,2-bis-(2-methoxyphenyl)ethane
DIPEA	diisopropylethylamine
DM-BINAP	2,2′-bis[bis(3,5-dimethylphenyl)phosphino]-1,1′-binaphthyl
DME	dimethoxyethane
DMF	dimethylformamide
DMI	1,2-dimethylimidazole
DMPU	*N*,*N*′-dimethyl-*N*,*N*′-propylene urea
DMS	dimethylsilyl
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
DuPHOS	1,2-di(phospholan-1-yl)benzene
ee	enantiomeric excess
equiv	equivalents
er	enantiomeric ratio
ESI-HRMS	electrospray ionization−high-resolution mass spectrometry

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ESI-MS	electrospray ionization−mass spectrometry
fod	6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedienoate
G	protecting group
h	hours
hmin	1-hexyl-3-methylimidazolium
HPLC	high-performance liquid chromatography
L	ligand
LA	Lewis acid
LAM	Lewis acid mechanism
LB	Lewis base
LBA	Lewis acid assisted chiral Brønsted acid catalysts
LLA	Lewis acid assisted chiral Lewis acid catalysts
M	molar
MALDITOF	matrix-assisted laser desorption ionization time-of-flight
Met	metal
METHOX	pinene-derived 2-(2,4,6-trimethoxiphenyl)pyridine *N*-oxide
MOM	methoxymethyl
MOP	1,1′-binaphthyl-2-yldiphenylphosphane
MS	mass spectrum or molecular sieves
$MTBH_2$	2′-mercapto-1,1′-binaphthyl-2-ol
na	not analyzed
nd	not determined
NHC	*N*-heterocyclic carbene
NMDPP	(2-isopropyl-5-methylcyclohexyl)diphenylphosphane
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
nr	not reported
Pc	phthalocyanine
Ph-BPE	1,2-bis(2,5-diphenylphospholan-1-yl)ethane
PIBOX	2,6-bis(8,8a-dihydro-3a*H*-indeno[1,2-d]oxazol-2-yl)pyridine
PINDOX	pinene-derived bipiridine *N*-monoxide
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
PPTS	pyridinium *para*-toluene sulfonate
Py	pyridine
QUINAP	1-[2-(diphenylphosphino)naphthalen-1-yl]isoquinoline
QUINOX	1-(2-methoxynaphthalen-1-yl)isoquinoline *N*-oxide
quinoxP*	2,3-bis[*tert*-butyl-(methyl)phosphino]quinoxaline
rt	room temperature
SEGPHOS	5,5′-bis(diphenylphosphino)-4,4′-bibenzo[*d*]-[1,3]dioxole
t	time
T	temperature
TADDOL	2,2-dimethyl-α,α,α′,α′-tetraphenyldioxolane-4,5-dimethanol
TANIAPHOS	(S_P)-1-[(*S*)-α-(dimethylamino)-2-(diphenylphosphino)benzyl]-2-diphenylphosphinoferrocene
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBAT	tetrabutylammonium difluorotriphenylsilicate
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBOX	2,2′-(1,1′-binaphthyl-2,2′-diyl)bis-(7-*tert*-butylquinolin-8-ol)
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TES	triethylsilyl
Tf	triflyl
THF	tetrahydrofuran
TM	transmetalation mechanism
TMBPT	(2,2′,5,5′-tetramethyl-3,3′-bithiophene-4,4′-diyl)bis(diphenylphosphane)
TMHD	tris-(2,2,6,6-tetramethyl-3,5-heptanedione
TMM	trimethylenemethane
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
Tol	4-methylphenyl
TRIP-PA	3,3′-di-(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diylhydrogen phosphate
TS	transition state
TUNEPHOS	1,13-bis-(diphenylphosphino)-7,8-dihydro-6*H*-dibenzo[*f*,*h*][1,5]dioxonin
Vivol	1,2-bis-(2-cyclooctylphenyl)propan-1-ol
vs	versus
μW	microwaves

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