CHEMICAL REVIEWS

Review

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Diastereoselective Allylation of Carbonyl Compounds and Imines: Application to the Synthesis of Natural Products

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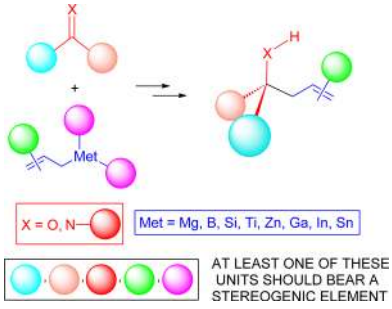

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1. INTRODUCTION

The addition of an allylic organometallic compound to a carbonyl compound or an imine is of great synthetic interest because in this reaction together with a new functionality (hydroxyl or amino group, respectively), a carbon−carbon bond is formed. In addition, the double bond of the allylic moiety can participate in a number of further synthetically useful transformations: cycloaddition, dihydroxylation, epoxidation, hydroboration, hydroformylation, hydrogenation, hydration, olefin metathesis, ozonolysis, etc.[1] Importantly, if the allylations are carried out in a stereoselective fashion, enantioenriched homoallylic alcohols and amines would be produced, which are valuable building blocks.[2] Among the stereoselective methodologies, the catalytic enantioselective

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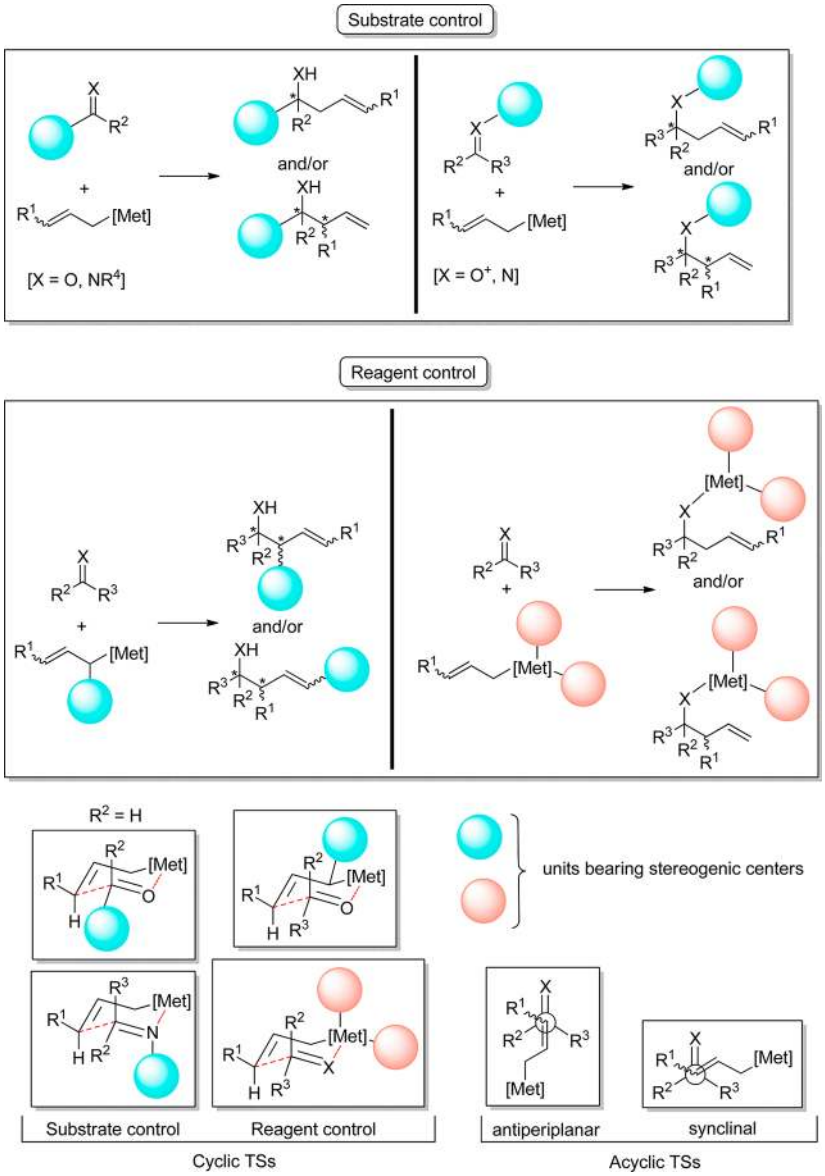
Scheme 1



allylations[3] rely on the use of both chiral Lewis acids,[4] which bind to the electrophile activating it toward nucleophilic attack, and chiral Lewis bases.[5] Double activation could be also achieved by using chiral bifunctional catalysts.[6] 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. Although the development of catalytic enantioselective allylation reactions is a very attractive growing field, it is not always straightforward to find an efficient and practical protocol for any synthetic application. Some challenges that still limit the applicability of catalytic enantioselective allylation are as follows: (a) some of the reported catalytic methods make use of large excess of reagents to ensure the turnover of the catalyst, which are not always cheap and *green*; (b) when the activation mode does not significantly increase the reaction speed, the noncatalytic allylation causes a lower enantioselection; (c) the "plausible mechanisms" reported for the existing catalytic methods do not always allow good predictions of the stereochemical results of new substrates; (d) in the construction of complex molecules, the allylation step is often performed on chiral substrates (chiral pool or advanced intermediates) that can override the chiral induction of the catalyst. Some of these reasons are behind of the fact that in the synthesis of complex organic molecules, including natural products, the stereoselective allylations are more commonly performed with stoichiometric amounts of chiral reagents. In these reactions, the stereochemical information can be transferred by substrate diastereocontrol (substrate control), including chiral auxiliaries, or through the use of chiral reagents (reagent control). Sometimes a double induction could be involved in the process, a match/mismatch effect being possible (Scheme 1).

In addition to the face selectivity under the influence of a chiral substrate or reagent, substituted allyl organometallics display high levels of diastereoselection because they react usually at the 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

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through the conformation where destabilizing gauche interactions are minimized. In contrast, for Mg, Ti, B, and In allylic derivatives, a cyclic six-membered Zimmerman−Traxler[7] type transition state is usually invoked. In the cyclic model, it is generally proposed that aldehydes locate the H (R^2 = H) in the axial position, while aldimines with *E*-configuration place the H (R^2 = H) in the equatorial position (Scheme 1),[8] consequently, opposite relative configurations (*anti*/*syn*) are generally observed in the reaction of aldehydes and aldimines with the same γ-substituted allyl organometallic.

The goal of this review is to highlight diastereoselective allylations involving the use of chiral reagents, emphasizing recent developments of synthetic interest. The review is organized according to the source of stereocontrol: first substrate control and after that reagent control allylations will be studied [stereogenic center(s) could be in the allyl unit or in a ligand bonded to the metal atom]. The last section of this review will be dedicated to related propargylation/allenylation processes, and to the application of these methodologies to some selected synthesis of natural products. Diastereoselective allylations leading to racemic products will not be considered in this review. The present work will comprehensively cover the most pertinent contributions to this important research area from 2003 to the end of 2011. We regret in advance that some contributions are excluded in order to maintain a concise format, especially concerning the natural product synthesis section.

2. SUBSTRATE CONTROL

Nucleophilic addition to chiral carbonyl compounds and imines is governed by steric and electronic factors and occurs predominantly to the less hindered face of the prostereogenic unit. Efficiency, regarding the stereoselectivity, depends strongly on the bulkiness of the reactants and the nature of the nucleophilic species. Felkin−Anh and Cram-chelate models[9] have been recurrently used in order to explain the stereochemical outcomes of these processes, and in many cases, the configuration of the newly created stereogenic center could be successfully predicted.

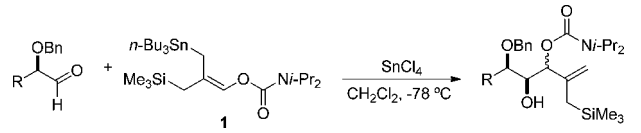
2.1. Chiral Carbonyl Compounds

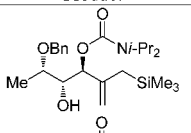
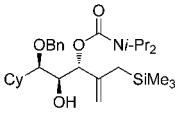
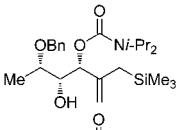
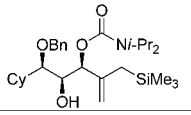
2.1.1. Allyl Stannanes. Allylic stannanes are not reactive enough to add to aldehydes, and for that reason the allylation of carbonyl compounds with these nucleophiles must be performed in the presence of a Lewis or a Brønsted acid in order to increase the reactivity of the electrophile.

Markó and co-workers found that the reaction of α-benzyloxyaldehydes with the functionalized stannane **1** in the presence of $SnCl_4$ proceeded with remarkable levels of stereocontrol producing *syn*−*anti* and *syn*−*syn* configured triol units in almost enantiomerically pure form.[10] The reactions were performed in dichloromethane at −78 °C. Importantly, the stoichiometry of the Lewis acid determined the relative configuration of the three stereogenic centers. Thus, when 1 equiv of $SnCl_4$ was used *syn*−*anti* triols were obtained (Table 1, entries 1 and 2). However, the allylation in the presence of 2 equiv of the Lewis acid afforded *syn*−*syn* triols (Table 1, entries 3 and 4) in good to excellent yields and with high diastereoselectivities in all cases. It was also observed that under these reaction conditions racemization at the chiral aldehyde did not take place.

Two different transition states have been proposed in order to rationalize the observed diastereoselectivities. A bicyclic

Table 1. Allylation of α-Benzyloxyaldehydes with Stannane 1 in the Presence of $SnCl_4$



Entry	$SnCl_4$	Aldehyde	Product	Yield (%)	dr	ee (%)
1	1 equiv			96	96:4	>95
2	1 equiv			81	96:4	>95
3	2 equiv			83	98:2	>95
4	2 equiv			81	95:5	>95

transition state, which is formed after transmetalation, operates when 1 equiv of $SnCl_4$ is used. The tin atom would be chelated to the benzyl ether and to the carbonyl oxygen of the aldehyde, and the carbamate would thus adopt a pseudoaxial orientation in order to interact with the tin. The *syn*−*anti* triols would be produced after allyl transfer through this transition state (Figure 1). On the other hand, an open transition state would operate

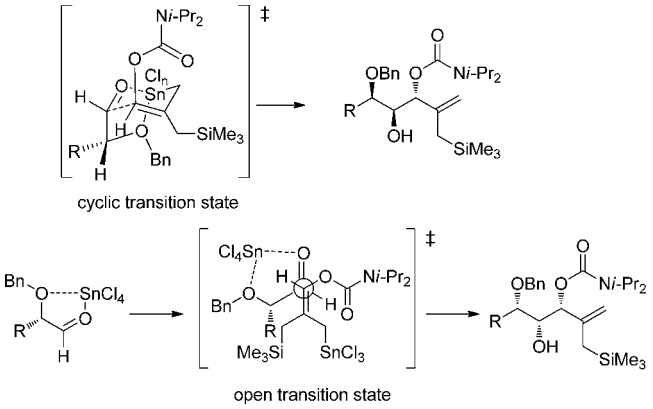


Figure 1. Hypothetical transition state structures for the allylation of α-benzyloxyaldehydes with **1** in the presence of $SnCl_4$.

when the reaction is performed in the presence of 2 equiv of $SnCl_4$: 1 equiv reacts with the aldehyde to form the chelate and the second one transmetallates the allylating agent, generating a more reactive nucleophile. The allyl transfer in this open transition state leads to the *syn*−*syn* triols (Figure 1).

High levels of stereoselection were also achieved in the reaction of functionalized 2-propenylstannane **2** with different chiral α-substituted aldehydes. The allylation reagent **2** was prepared by distannylation of the corresponding allene. Williams and Fultz found that optimal results were obtained working in dichloromethane as solvent at −78 °C in the presence of 2 equiv of $MgBr_2$·etherate.[11] Destannylation is prevented working at low temperature, otherwise acid-catalyzed

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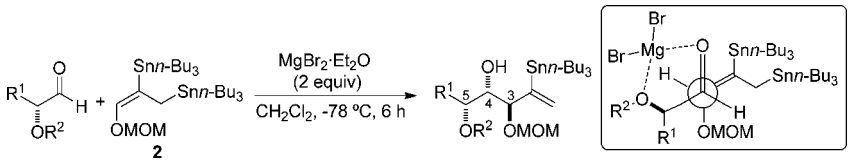
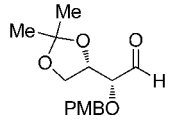
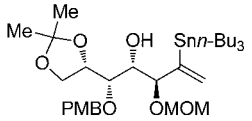
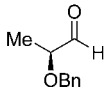
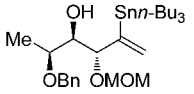
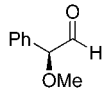
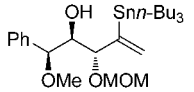
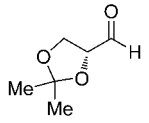
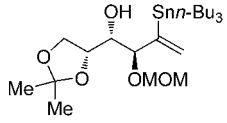
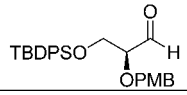
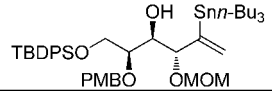
Table 2. Allylation of α-Substituted Aldehydes with Stannane 2 in the Presence of $MgBr_2$·Etherate



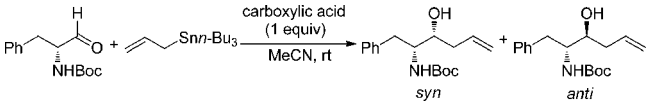
Entry	Aldehyde	Reaction product: Structure	Ratio	Yield (%)
1			>95:5	85
2			>95:5	82
3			>95:5	81
4			90:10	81
5			>95:5	82

decomposition of compound **2** could occur. The allylation of chiral α-alkoxyaldehydes under these reaction conditions provided excellent yields with high stereoselectivity, a single diastereomer being observed in many cases by NMR analyses of the crude reaction product (Table 2, entries 1−3 and 5). Regarding the relative configuration of the created stereogenic centers, the 3,4-*anti*-4,5-*syn*-relationship was always found. This stereochemical outcome could be rationalized by considering a S_E2' reaction in an open chelated transition state as depicted in Table 2.

Allylation of carbonyl compounds with allylic stannanes could also be promoted using carboxylic acids. Li and Zhao demonstrated that the reaction of a wide range of aldehydes with allyltributyltin in different solvents, in the presence of 1 equiv of a carboxylic acid at room temperature, provided the homopropargyl alcohol.[12] They also studied the allylation of chiral (*R*)-*N*-Boc-2-amino-3-phenylpropanal in acetonitrile under the influence of different carboxylic acids. In all cases, the allylation gave high to quantitative yields with moderate diastereoselectivity, the *anti* diastereomer being always the major product (Table 3).

Diastereoselective Lewis acid promoted allylation of ketones with allylic stannanes has also been studied. In this way, optically enriched quarternary α-hydroxy amides **4** and **5** were prepared from chiral α-ketoamides bearing a camphorpyrazolidinone unit **3**. Allylation did not take place in the absence of a Lewis acid. Taking phenylketoamide **3** (R = Ph) as the model compound, Chen and co-workers found that the allylation using 1 equiv of $Eu(OTf)_3$ in acetonitrile at room temperature provided the allylated products in 50% yield and moderate diastereoselectivity (Table 4, entry 1).[13] Both, chemical yield and diastereoselectivity were significantly improved when $Zn(OTf)_2$ was used (Table 4, entry 2). However, the allylation proceeded in a totally stereoselective fashion in almost quantitative yield using $Sn(OTf)_2$ in acetonitrile, after 4 min

Table 3. Diastereoselective Allylation of (*R*)-*N*-Boc-2-Amino-3-phenylpropanal with Allyltributyltin Promoted by Carboxylic Acids



entry	carboxylic acid	*t* (h)	*syn*/*anti*[a]	yield (%)[b]
1	$4\text{-}NO_2C_6H_4CO_2H$	4.5	27/73	98
2	maleic acid	0.25	27/73	88
3	$1,2\text{-}(CO_2H)_2C_6H_4$	4	27/73	100
4	salicylic acid	4	15/75	89

[a]Determined by ^1H NMR. [b]Combined isolated yield.

at room temperature (Table 4, entry 3). This result was not improved by using other solvents under the same reaction conditions. Similar results in terms of yield and stereoselectivity were obtained in the case of other α-ketoamides **3** (Table 4, entries 4−6).

The stereochemical outcome of this study was rationalized by considering the conformational preference of α-ketoamides **3** in the transition state. The pseudoplanar *s-trans* conformation of the α-dicarbonyl group in **3** is electronically favored over its *s-cis* conformer due to the dipole repulsion of the two carbonyl functionalities. However, in the presence of a Lewis acid, the coordination of the metal ion to the dicarbonyl oxygen atoms resulted in the formation of the preferred *s-cis* conformation. The equilibrium of different conformational states is highly dependent upon the type and amount of Lewis acid used in the reaction. Strong Lewis acids, such as $Sn(OTf)_2$, would favor the *s-cis* over the *s-trans* conformer making predominant the *Si*-face attack of the allylic nucleophile leading to compounds **4** (Figure 2).

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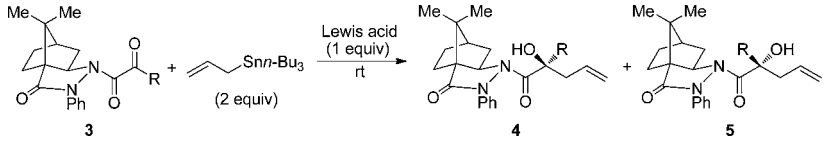
Table 4. Diastereoselective Allylation of Camphorpyrazolidinone Derived α-Ketoamides 3 with Allyltributyltin



entry	R	solvent	Lewis acid	*t*	yield (%)[a]	dr (**4**:**5**)[b]
1	Ph	MeCN	Eu(OTf)$_3$	72 h	50	72:28
2	Ph	MeCN	Zn(OTf)$_2$	40 min	93	96:4
3	Ph	MeCN	Sn(OTf)$_2$	5 min	95	99:1
4	Me	MeCN	Sn(OTf)$_2$	5 min	89	77:23
5	Et	MeCN	Sn(OTf)$_2$	5 min	91	83:17
6	2-thienyl	MeCN	Sn(OTf)$_2$	5 min	92	99:1

[a]Total isolated yield (**4** + **5**). [b]Determined by ^{1}H NMR and chiral HPLC.

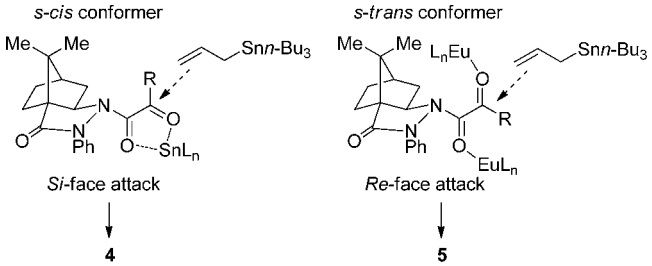
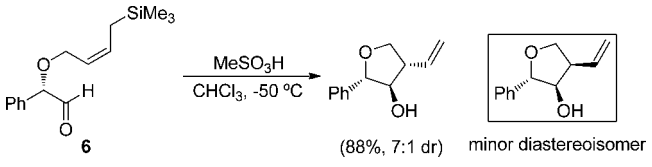


Figure 2. Proposed conformational structures of reacting α-ketoamides **3** with allyltributyltin in the presence of a Lewis acid.

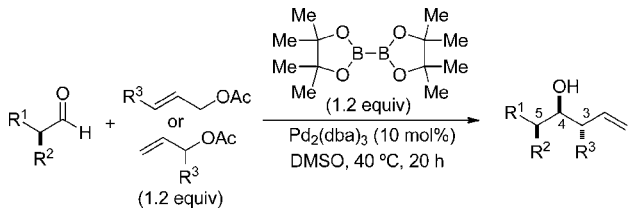
2.1.2. Allyl Silanes and Boranes. Similarly to allylic stannanes, the allylation of carbonyl compounds with allylic silanes must be carried out in the presence of an activating reagent. A diastereoselective synthesis of 2,3,4-trisubstituted tetrahydrofurans has been reported by Cox and co-workers. In these processes, an allyl silane and a carbonyl group of an aldehyde are involved in an intramolecular allylation promoted by a Brønsted acid. When the optimized reaction conditions were applied to the polyfunctionalized enantiomerically pure aldehyde **6**, derived from (*S*)-ethyl mandelate, a trisubstituted tetrahydrofuran was produced with good 1,2-stereoinduction (Scheme 2).[14]

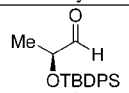
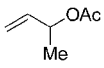
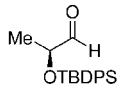
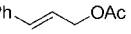
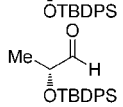
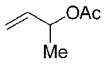
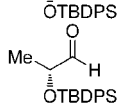
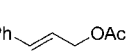
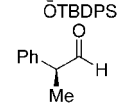
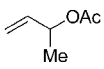
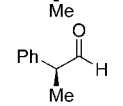
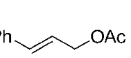
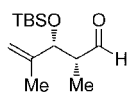
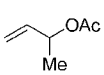
Scheme 2



Allylic acetates have been also used as allylating reagents for carbonyl compounds under Pd catalysis.[15] The character of the initially formed palladium allyl complex can be reversed from electrophilic to nucleophilic in the presence, for instance, of trialkylboron species. Kirschning and co-workers described a stereocontrolled palladium-catalyzed umpolung allylation of aldehydes with allyl acetates in the presence of bis(pinacolato)-diboron. The reactions were performed in DMSO at 40 °C (Table 5).[16] They found that higher yields and levels of stereocontrol were achieved when chiral aldehydes (substrate control) were used instead of chiral allyl boronates (reagent control). The reactions of different chiral α-substituted aldehydes with cinnamyl acetate or racemic 1-methylallyl

Table 5. Pd-Catalyzed Stereoselective Allylation of Chiral Aldehydes with Allylic Acetates in the Presence of Bis(pinacolato)diboron



Entry	Aldehyde	Allylic acetate	Yield (%)[a]	dr[b]
1			73	10:1
2			80	5:1
3			65	7:1
4			60	>20:1
5			54	5:1
6			58	>20:1
7			60	12:1

[a]Isolated yield. [b]Determined by ^{1}H NMR.

acetate, under the optimized reaction conditions depicted in Table 5, proceeded with moderate to good yields and with remarkably high 3,4-*anti*-4,5-*syn* selectivities. Importantly, the here observed 4,5-*syn* selectivity in these palladium-catalyzed reactions of chiral α-substituted aldehydes with (*E*)-crotylboronates, which are the reaction intermediates, is unprecedented. Hoffmann and Roush previously noted that α-alkoxy-substituted aldehydes show a moderate 4,5-*anti* selectivity in the reaction with (*E*)-crotylboronates.[17]

Hall studied also the allylation and crotylation of *O*-TBS-protected (*S*)-2-methyl-3-hydroxypropanal with allyl- and

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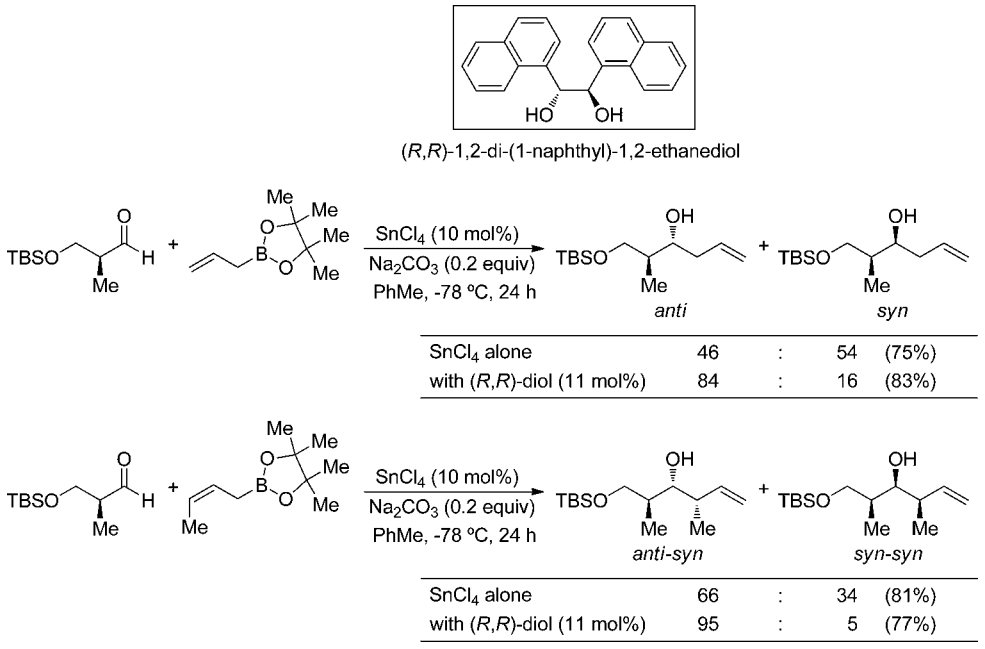
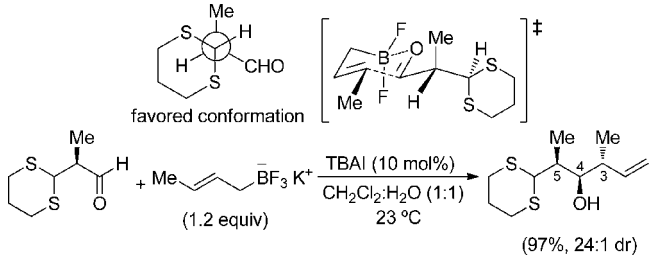
Scheme 3



crotylboropinacolate, respectively. The reactions should be performed in the presence of a Lewis acid. Thus, the $SnCl_4$ catalyzed addition of allylboropinacolate to the chiral aldehyde gave minimal selectivity (46:54) favoring the *syn*-diastereomer. However, better diastereoselectivity was obtained when the reaction was carried out in the presence of a combination of $SnCl_4$ and a chiral diol, such as (*R*,*R*)-1,2-di(1-naphthyl)-1,2-ethanodiol. The new catalyst system improved the intrinsic selectivity preference of the $SnCl_4$-catalyzed reaction to give predominantly the *anti*-isomer in a 84:16 ratio. On the other hand, in the crotylation with (*Z*)-crotylboropinacolate, the selectivity in favor of the *anti*−*syn* isomer was improved from a modest 2:1 ratio with $SnCl_4$ alone to 19:1 using the $SnCl_4$-(*R*,*R*)-1,2-(1-naphthyl)-1,2-ethanodiol catalyst combination (Scheme 3).[18] Poor substrate control was observed in these reactions, a chiral external ligand being extremely beneficial for obtaining high diastereoselectivities.

Saikawa, Nakata, and co-workers reported a substrate-controlled crotylation of β-branched α-methylaldehydes with air- and moisture-stable potassium crotyltrifluoroborates, which provided the diastereoselective construction of stereotriads having consecutive methyl, hydroxy, and methyl substituents in a racemic form. It was found that diastereoselectivities were higher for the (*E*)-crotyl derivative. In addition, they provide a single example of crotylation with potassium (*E*)-crotyltrifluoroborate of enantiomerically pure (*S*)-2-(1,3-dithian-2-yl)propanal, easily prepared from (*S*)-3-hydroxy-2-methylpropionate (Roche ester), leading to the corresponding homoallylic alcohol in 97% yield and high 3,4-*anti*-4,5-*syn* selectivity (24:1 dr, the minor isomer having the 3,4-*anti*-4,5-*anti* configuration). In order to explain the observed diastereoselectivity, a chairlike transition state was proposed in the most favorable conformation regarding steric interactions (β-substituent effects), meanwhile face selectivity (*Re*-face addition) was governed by the aldehyde α-carbon configuration as depicted in Scheme 4.[19]

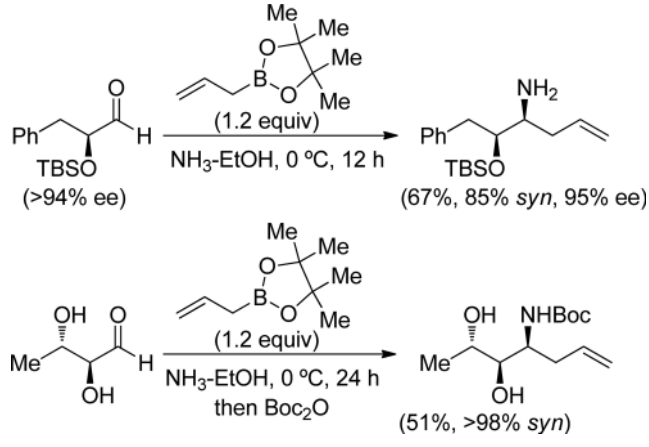
Scheme 4



2.2. Chiral Imines and Imine Derivatives

2.2.1. Imines and Imine Derivatives from Chiral Carbonyl Compounds. Chiral α-oxysubstituted aldehydes were used by Kobayashi and co-workers in a three-component reaction with allylboropinacolate and ammonia in ethanol. The corresponding homoallylic primary amines were obtained with good to high *syn* diastereofacial selectivities (Scheme 5).[20] The precise reaction mechanism was unclear. Preformation of N-

Scheme 5

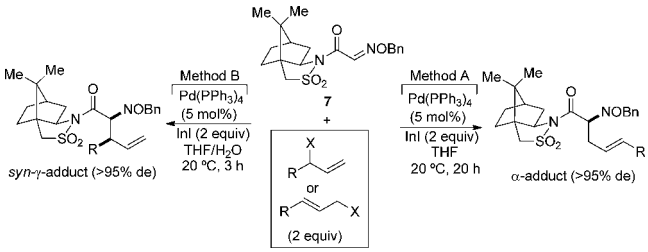


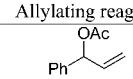
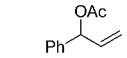
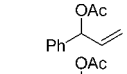
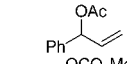
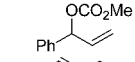
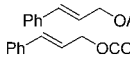
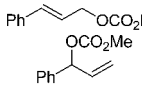
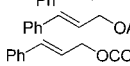
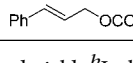
dx.doi.org/10.1021/cr400008h | Chem. Rev. 2013, 113, 5595−5698

unsubstituted imines from aldehydes and ammonia followed by allylation with allylboronates could be a possible reaction pathway. However, formation of a novel aminoallylating agent from the allylboronate and ammonia could not be ruled out, because premixing the allylboronate and ammonia led to higher chemoselectivity for reactions with aliphatic aldehydes.

The palladium-catalyzed allylation of chiral electron-deficient glyoxylic oxime ether 7 derived from Oppolzer's camphorsultam with allylic acetates and carbonates, in the presence of InI, was studied by Takemoto and co-workers.[21] They observed that the reaction of 7 with 1-phenylallyl acetate in the presence of 5 mol % of $Pd(PPh_3)_4$ and 2 equiv of InI at room temperature in THF produced the expected *syn*-γ- and α-adducts in good yields and excellent diastereoselectivities. Surprisingly, the ratio of these regioisomers was dependent on the reaction time and the reaction conditions. When the reaction was carried out in anhydrous THF (method A) for 30 min, a 1:2 mixture of the *syn*-γ-adduct and the α-adduct was obtained in 74% combined yield (Table 6, entry 1). However,

Table 6. Pd-Catalyzed Stereoselective Allylation of Chiral Glyoxylic Oxime Ether 7 with Allylic Acetates and Carbonates in the Presence of InI



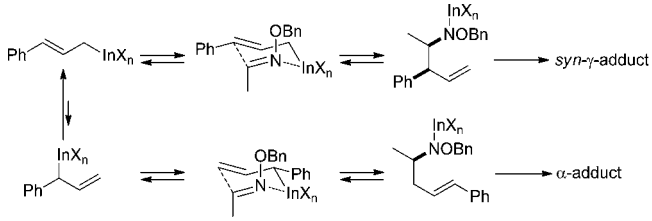
Entry	Allylating reagent	Method	t (h)	Product	Yield (%)[a]
1		A	0.5	*syn*-γ-adduct/ α-adduct (1:2)	74[b]
2		A	20	α-adduct	95
3		B	3	*syn*-γ-adduct	90
4		B	20	*syn*-γ-adduct	89
5		B	3	*syn*-γ-adduct	95
6		B	3	*syn*-γ-adduct	94
7		B	3	*syn*-γ-adduct	95
8		A	20	α-adduct	93
9		A	20	α-adduct	85
10		A	20	α-adduct	87

[a]Isolated yield. [b]Isolated combined yield.

prolonged reaction times led exclusively to the α-adduct (Table 6, entry 2). On the other hand, when the allylation was performed in the presence of water (method B), the *syn*-γ-adduct was the only reaction product isolated, independently of the reaction time (Table 6, entries 3 and 4). The same results were obtained when cinnamyl acetate was used instead of 1-phenylallylacetate, which indicates that both regioisomers generate the same organometallic intermediate under palladium catalysis in the presence of InI (Table 6, compare entries 2 and 9, and 3 and 6). Allylic carbonates were also efficient allylating reagents under the same reaction conditions (Table 6, entries 5, 7, 8, and 10).

The water effect on the regioselectivity of these processes remains unclear. A possible explanation for that based on the reversibility of the allylation was proposed by the authors. Thus, under anhydrous reaction conditions (method A), the prolonged reaction time would allow the reversibility between the *syn*-γ-adduct and the linear indium reagent, giving the branched indium reagent via a metallatropic rearrangement of the indium atom.[22] In this way, the kinetically formed *syn*-γ-adduct isomerized to the thermodynamically most stable α-adduct (Scheme 6).

Scheme 6



Quing and co-workers found also that the indium-mediated allylation of (*R*)-*N*-benzyl-2,3-*O*-isopropylideneglyceraldimine with 4-bromo-1,1,1-trifluoro-2-butene in DMF at room temperature took place in high diastereoselectivity (>95% de) with moderate yield (Scheme 7).[23] The highly stereoselective generation of the *syn* isomer was rationalized by assuming that the benzyl group and the isopropylidenyl moiety in the imine must adopt orthogonal positions so that indium could efficiently chelate with both the nitrogen atom of the imine and the oxygen atom of the isopropylidenyl moiety, forming a six-membered and a five-membered ring, respectively (Scheme 7). The adduct was a precursor of (2*R*,3*S*)- and (2*S*,3*R*)-4,4,4-trifluoroisoleucines and (2*R*,3*S*)-4,4,4-trifluorovaline.

Good levels of stereocontrol have been achieved in the addition of allyllithium and allylmagnesium bromide to chiral α-alkoxy and α-amino nitrones. Merino and co-workers found that the use of a Lewis acid as an activator is highly beneficial for the allylation of α-alkoxy nitrones to occur diastereoselectively.[24] By contrast, the Lewis acid has almost no influence in the allylation of α-amino nitrones, the substituent on the amino group being more determinant on the stereochemical outcome of the reaction. For instance, the reaction of *N*-benzyl-2,3-*O*-isopropylidene-D-glyceraldehyde nitrone with allyllithium led to the formation of *syn* and *anti* compounds with poor stereoselectivity. However, the *syn* isomer was obtained preferentially when the same reaction was performed in the presence of $ZnBr_2$ (Table 7, entries 1 and 2). Interestingly, the allylation with allylmagnesium bromide depended more strongly on the reaction conditions. Thus, in the absence of any additive, the reaction proceeded smoothly to give mixtures of adducts in which the *syn* isomer slightly predominated over the *anti* one (Table 7, entry 3). The addition of $ZnBr_2$ notably increased the amount of the *syn* isomer, and at low temperature, almost total *syn* selectivity was obtained in quantitative yield after 8 h (Table 3, entry 4). To evaluate the influence of the protecting groups in the substrate, the allylation of 2,3-di-(*O*-benzyl)-*N*-benzyl-D-glyceraldehyde nitrone was also studied, but poorer yields in terms of diastereoselectivity were obtained for this acyclic nitrone

dx.doi.org/10.1021/cr400008h | *Chem. Rev.* 2013, 113, 5595−5698

Scheme 7

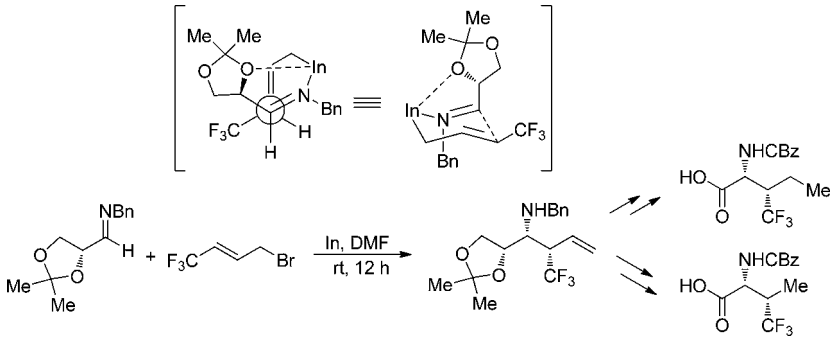
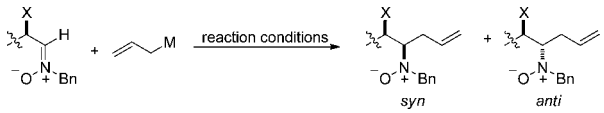
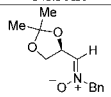
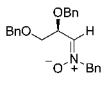
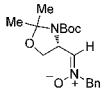
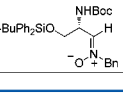


Table 7. Diastereoselective Allylation of α-Alkoxy and α-Amino Nitrones with Allyllithium and Allylmagnesium Bromide



Entry	Nitrone	M	Additive	Reaction conditions	*syn*:*anti*	Yield (%)
1		Li	--	THF, -80 °C, 1 h	55:45	86
2		Li	$ZnBr_2$	Et_2O, -80 °C, 1 h	90:10	75
3		MgBr	--	THF, 0 °C, 2 h	53:47	100
4		MgBr	$ZnBr_2$	Et_2O, -50 °C, 8 h	>96:4	100
5		Li	--	THF, -80 °C, 1 h	60:40	90
6		Li	$ZnBr_2$	Et_2O, -80 °C, 1 h	61:39	80
7		MgBr	--	Et_2O, 0 °C, 2 h	62:38	100
8		MgBr	$ZnBr_2$	Et_2O, -50 °C, 8 h	69:31	90
9		Li	--	Et_2O, -80 °C, 1 h	>95:5	89
10		MgBr	--	Et_2O, 0 °C, 2 h	>95:5	100
11		Li	--	Et_2O, -80 °C, 1 h	20:80	75
12		MgBr	--	Et_2O, 0 °C, 2 h	10:90	81

(Table 7, entries 5−8). Totally different results were achieved in the allylation of chiral α-amino nitrones with allylmetals. The selectivity of nucleophilic additions to these nitrones depended on the protection of the amino group whether or not a Lewis acid is present in the process. Thus, the allylation of the *N*-Boc-protected cyclic *N*-benzyl nitrone derived from (*S*)-*N*-Boc-*N*,*O*-isopropylideneserinal led to the *syn* isomer in excellent yields (Table 7, entries 9 and 10). However, reverse stereoselectivity was achieved under the same reaction conditions in the case of an acyclic N-monoprotected nitrone (Table 7, entries 11 and 12).

2.2.2. Imines and Imine Derivatives with a Chiral Framework Attached to the Nitrogen. *2.2.2.1. Imines from Chiral Amino Alcohols.* The stereochemistry in the addition of allylic organometallic reagents to imines can also be controlled by a chiral moiety attached to the nitrogen atom. Thus, a chelation-controlled model, where one magnesium cation is coordinated by the hydroxyl group and the nitrogen atom, was proposed to operate in the addition of allylmagnesium bromide to a chiral imino alcohol.[25] Based on this model, the *Si*-face of the imine seems to be blocked by the bulky styryl group, while addition to the *Re*-face favored the *trans*-product. The required chiral amino alcohol was prepared from Garner's aldehyde using a Horner−Wadsworth−Emmons reaction, and the imines were prepared by condensation with the corresponding aldehydes in the presence of $MgSO_4$. When benzaldehyde was used, the crude solution of the imine, after filtration of the magnesium salts, was treated with various allyl metals to obtain the best results with allylmagnesium bromide. When the addition was performed at −78 °C and after 1 h the reaction mixture was allowed to warm to −10 °C over 5 h, all aldehydes used gave moderate to good *trans*-selectivity for the corresponding adduct (Table 8).

Due to its low first ionization potential (5.8 eV), indium can easily participate in single electron transfer (SET) processes such as the formation of allylindium species from allyl halides. Compared with other metals, indium is relatively stable in air, nontoxic, and compatible with protic solvents and substrates. Given these characteristics it is not surprising that indium is nowadays considered an attractive metal to be used in organic synthesis. In this context, Paquette et al. have reported that indium-mediated allylation of carbonyl compounds possessing a hydroxyl group proceeds with high diastereoselectivity.[26] With these precedents, the indium-mediated allylation of benzaldimine bearing (*S*)-valinol as chiral auxiliary was studied.[27] When the reaction was carried out in DMF at room temperature under Barbier conditions, good yields and diastereoselectivities were obtained using allyl bromide or allyl iodide (Table 9, entries 1 and 2). Using allyl chloride, under otherwise identical conditions, almost no conversion was observed (entry 3). Similar allylations with a selection of substituted allylic bromides took place regioselectively at the γ-position of the allylindium reagent and with high diastereoselectivity at C-1′ (entries 4−7 and 9). Notably, an aliphatic alkyl substituent at the γ-position of the allylic bromide causes a decrease in the chemical yield (entries 6, 7, and 9), giving no reaction for a disubstituted reagent at this position (entry 10). Moreover, when (*E*)-cinammyl bromide was used, a mixture of four diastereomers was observed. To explain the stereoselectivity of the reaction, a chairlike transition state was proposed where the substituents of the (*E*)-aldimine are placed in axial positions and the indium metal is coordinated to both the nitrogen atom and the hydroxyl group. In this chelation-controlled model, the reactive conformation is locked with the *Re*-face of the imine shielded by the bulky isopropyl group. The coordination of indium to the nitrogen atom enhances the electrophilicity of the imine making this pathway more competitive than other possible ones.

The addition of allyl indium reagents to imines can also be performed in alcoholic solvents, which sometimes produce an acceleration of the reaction. In this context, the indium-mediated allylation of chiral aldimines in methanol at room temperature was examined.[28] From the different chiral benzaldimines examined, the best results in terms of isolated

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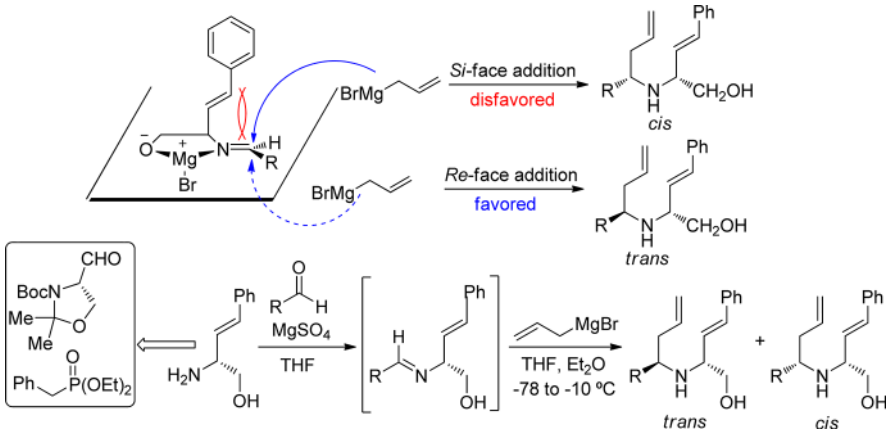
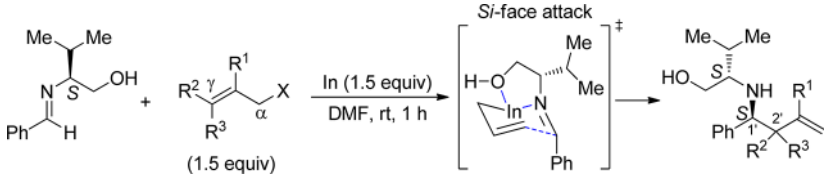
Table 8. Diastereoselective Addition of Allylmagnesium Bromide over Chiral Imino Alcohols



entry	R	*trans*/*cis*[a]	*trans*/*cis*[b]
1	Ph	86:14	73:12
2	$Ph(CH_2)_2$	89:11	62:8
3	$Me(CH_2)_5$	90:10	62:8
4	Cy	90:10	66:7
5	*i*-Pr	90:10	68:8
6	$Me(CH_2)_{11}$	87:13	56:nd

[a]Ratios of diastereomers measured by ^{1}H NMR spectroscopy. [b]Percent yield of isolated product.

Table 9. Indium-Mediated Diastereoselective Allylation of Chiral Benzaldimine



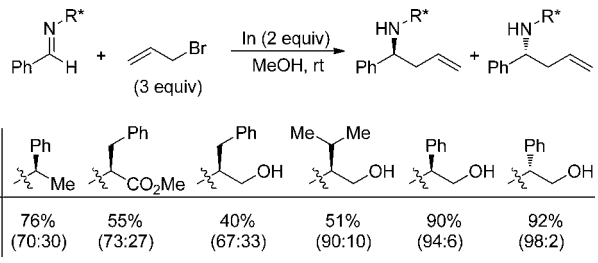
entry	R^1	R^2	R^3	X	*t* (h)	yield (%)	dr (C1′)	dr (C2′)[a]
1	H	H	H	Br	1	95	>99:1	
2	H	H	H	I	1	95	>99:1	
3	H	H	H	Cl	24	*b*		
4	Me	H	H	Br	1	91	>99:1	
5	CO_2Me	H	H	Br	3	48	94:6	
6	H	Me	H	Br	24	79	>99:1	5:1
7	H	Et	H	Br	24	47	>99:1	5:1
8	H	Ph	H	Br	24	60	*c*	*b*
9	H	H	Et	Br	24	21	>99:1	4:1
10	H	Me	Me	Br	24	0		

[a]Diastereomeric ratios at C2′ were determined by ^{1}H NMR spectroscopy. [b]Trace amount. [c]The ratio of the products by ^{1}H NMR was 82:6:4:8.

yields and diastereoselectivities were obtained for (*S*)- and (*R*)-phenylglycinol derivatives (Scheme 8). Although the reactions can be also conducted in ethanol or isopropanol with similar diastereoselectivities, the reaction rate was significantly lower than in methanol.

Having established the most suitable conditions, other aldimines derived from (*R*)-phenylglycinol were examined. As shown in Table 10, aromatic aldimines afforded the corresponding homoallylic amines with good yield and diastereoselectivity, without a significant influence of the electronic nature of the substituent and the substitution pattern (entries 1−8). Notably, easily enolizable aliphatic aldimines gave the expected product in good yield and excellent diastereoselectivity (entries 9−12). Moreover, conjugated aldimines were also well tolerated in this protocol (entry 13). The assignment of the absolute configuration of the products

Scheme 8



was made by NMR spectroscopy, and a cyclic chelation-controlled model was proposed to explain the stereochemical outcome of the reaction.

To remove the chiral auxiliary without reducing the C═C bond, catalytic hydrogenation cannot be used. Among different

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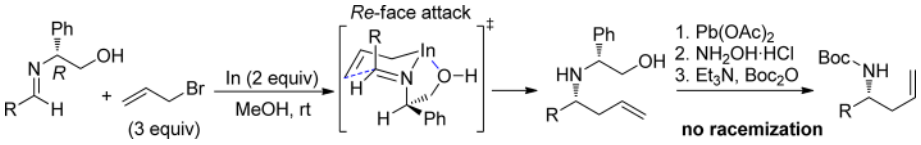
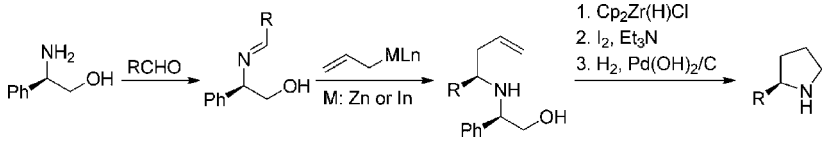
Table 10. Diastereoselective Addition of Allylindium in MeOH to Chiral Aldimines



entry	R	yield[a] (%)	dr[b]
1	4-MeC_6H_4	94	93:7
2	2-$MeOC_6H_4$	82	87:13
3	4-$MeOC_6H_4$	93	92:8
4	2-HOC_6H_4	49	89:11
5	3-HOC_6H_4	88	92:8
6	4-ClC_6H_4	95	98:2
7	2-pyridyl	91	94:6
8	2-furyl	90	>98:2
9	*i*-Pr	96	>98:2
10	*t*-Bu	84	>98:2
11	*n*-Pr	80	>98:2
12	$CH_3(CH_2)_5$	73	>98:2
13	(*E*)-PhCH=CH	90	96:4

[a]Isolated yield for the allylation step. [b]Determined by ^1H NMR.

Scheme 9

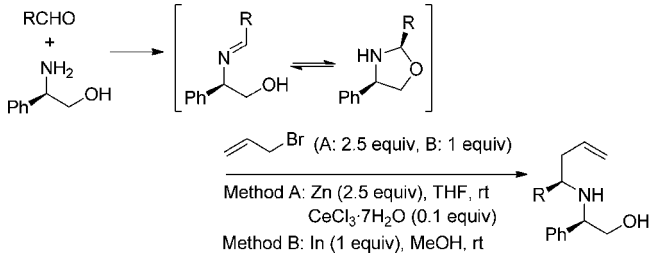


alternatives examined to remove the auxiliary, oxidative cleavage with $Pb(OAc)_2$ followed by acid hydrolysis was the only successful protocol, although the products were obtained in poor yields and low enantiomerical purity. After some experimentation, it was determined that the oxidative cleavage leads initially to the corresponding benzaldimine that is implied in an aza-Cope rearrangement. To overcome this problem, the protocol was modified by only adding hydroxylamine hydrochloride after the oxidative cleavage to catch the Shiff base and to avoid the [3,3]-rearrangement. Under these new conditions, the auxiliary was removed for a number of substrates without observing any racemization.

A versatile new entry to chiral pyrrolidines implies the addition of allylic metal reagents to aldimines with (*R*)-phenylglycinol as chiral inductor, followed by a one-pot hydrozirconation/iodination and hydrogenolysis of the auxiliary (Scheme 9).[29] Importantly, in this work it was demonstrated that the Schwartz reagent was compatible with secondary amines and the use of two equivalents of the reagent avoided the protection of the hydroxyl group, furnishing the corresponding pyrrolidines in good overall yields.

Concerning the stereodetermining step, two different Barbier-type protocols were chosen for the preparation of the homoallylic amine. For aromatic aldehydes, the best results were obtained by adding a mixture of the aldimine and allylbromide to a suspension of zinc and catalytic amounts of $CeCl_3{\cdot}7H_2O$ in THF at room temperature. With this protocol, aromatic and heteroaromatic products were obtained in good yields as single isomers after column chromatography (Table 11, entries 1−3). With aliphatic aldehydes, the chemical yields dropped due to the formation of *N*-alkyl products. This side reaction was associated with a greater stability of the oxazoline species in equilibrium with the imines when condensing

Table 11. Diastereoselective Addition of Allyl Bromide to Chiral Aldimines Mediated by Indium and Zinc



entry	R	method	yield (%)
1	Ph	A	79
2	2-BrC_6H_4	A	72
3	3-furyl	A	71
4	C_5H_6CH=CH	B	78
5	*n*-Pr	B	81
6	2-pyridyl	B	87
7	ferrocenyl	B	91

phenylglycinol and aliphatic aldehydes. For these aliphatic substrates, the use of indium in methanol was clearly a superior method that afforded the corresponding homoallylic amines in good isolated yields as single isomers (entries 4 and 5). Importantly, this method was also applied by the same authors to prepare chiral pyrrolidines to be used as ligands in asymmetric catalysis (entries 6 and 7).[30]

The group of Vasse and Szymokiak expanded their work to prepare enantiopure 2,3-disubstituted pyrrolidines using the allylation of phenylglycinol-derived imines with different γ-substituted allylic bromides as a key step.[31] Again, the protocol that made use of zinc and catalytic amounts of $CeCl_3{\cdot}7H_2O$ in

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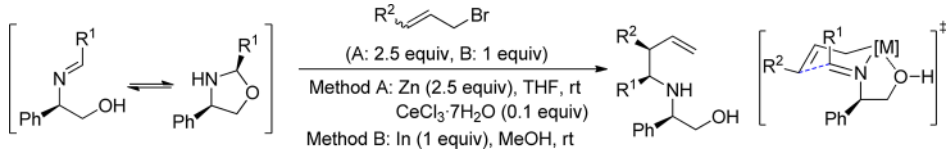
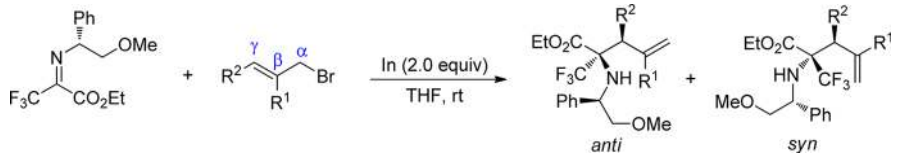
Table 12. Diastereoselective Addition of Crotyl Bromides to Chiral Aldimines Mediated by Indium and Zinc



entry	R^1	R^2	allylic bromide configuration	method	yield (%)[a]	dr
1	2-furyl	Ph	*E*	A	86	11:1
2	3-pyridyl	Ph	*E*	A	91[b]	9.7:1
3	2-furyl	$TBSOCH_2$	*E*	A	75	10.7:1
4	(*E*)-PhCH=CH	$TBSOCH_2$	*Z*	B	83	13:1
5	$BnOCH_2$	Ph	*Z*	B	37	2:1
6	$BnOCH_2$	$CH_3(CH_2)_4$	*Z*	B	74	5:1
7	*i*-Bu	$BnOCH_2$	*Z*	B	54[b]	11:1
8	$TBSO(CH_2)_3$	$BnOCH_2$	*Z*	B	71	8:1
9	$TBSO(CH_2)_3$	$BnOCH_2$	*E*	B	75	9:1

[a]Isolated yield of the major diastereomer as a single isomer. [b]Isolated as a 20:1 mixture of diastereomers.

Table 13. Indium-Mediated Diastereoselective Allylation of Chiral Imines from Trifluoropyruvate



entry	R^1	R^2	*t* (h)	yield (%)	*anti*/*syn*[a]
1	H	H	19	98	*b*
2	Me	H	21	96	*b*
3	CO_2Et	H	48	88	*b*
4	H	Me	72	82	7.4:1 (1.3:1)[c]
5	H	Ph	72	92	>20:1
6	H	CO_2Et	48	60	>20:1

[a]Determined by ^{19}F NMR. [b]Relative to the chiral auxiliary, >20:1 dr. [c]*Syn* isomers with different configurations relative to the chiral auxiliary.

THF (method A) was optimum for aromatic aldehydes, while the use of indium in methanol (method B) was more suitable for aliphatic substrates. Using either method A or method B, the corresponding homoallylic amines bearing aromatic, alkyl, or alkenyl groups were isolated, in most cases, as single diastereomers after chromatography purification (Table 12). The method tolerates well the presence of protected alcohol moieties (OTBS and OBn) and the addition of the allylic bromide occurred always by the γ-position, regardless the protocol used. Importantly, only *syn* isomers were obtained (including the minor isomer) irrespective of the configuration of the allylic bromide (entries 8 vs 9). The preferential formation of *syn* isomers can be explained using a chairlike transition state where the substituents of the (*E*)-imines adopt a pseudoaxial position, while the allylmetal substituent prefers an equatorial orientation. Since (*Z*)-allylic metal reagents need to isomerize to adopt this orientation, this model also explains the slightly better results obtained with (*E*)-allylic bromides (entries 8 vs 9). Moreover, coordination of the metal to both the nitrogen and oxygen atoms locks a conformation that favors the allylation over the *Re*-face of the (*R*)-phenylglycinol imine derivative, thus explaining absolute stereochemistry of the major diastereomer formed.

Quaternary α-trifluoromethyl-α-amino acids have considerably attracted the attention of medicinal chemists since they can improve the bioavailability of peptides and enhance permeability through the body barriers. However, the stereoselective construction of quaternary chiral centers with a CF_3 group still remains as an important synthetic challenge. In this context, the indium-mediated allylation of chiral imines derived from trifluoropyruvate was recently studied.[32] In this study, (*R*)-phenylglycinol methyl ether was used as chiral auxiliary of the imine, and the reaction was conveniently conducted at room temperature (Table 13). The addition of allyl bromide or β-substituted allylic bromides (including the less reactive 2-ethoxycarbonyl derivative) took place with excellent diastereoselectivity affording the products in very good isolated yields (entries 1−3). Notably, the reaction with γ-substituted allylic bromides also took place with excellent (entries 5 and 6) to good (entry 4) diastereoselectivity and perfect regioselectivity at the γ-position. To explain the diastereoselection, the authors propose a rigid chairlike transition state where the indium is coordinated to the iminic nitrogen atom, to the methoxy group of the chiral auxiliary, and also to the ethoxy carbonyl moiety.

2.2.2.2. Chiral Hydrazones. The indium-mediated allylation of chiral hydrazones was examined for different oxazolidinones as chiral auxiliaries.[33] From this study, the valinol-derived oxazolidinone emerged as the most convenient chiral auxiliary. Moreover, while allylic bromides were problematic for the reaction, allyl iodide in the presence of indium gave complete conversion at room temperature in most cases. Under the previously mentioned conditions, all aromatic substrates gave excellent isolated yields and diastereoselection, except two examples (Table 14, entries 1−4). The *p*-nitro derivative (entry

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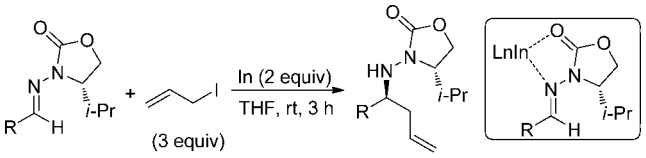
Table 14. Indium-Mediated Allylation of Chiral Hydrazones



entry	R	yield (%)[a]	dr[b]
1	Ph	99	>99:1
2	2-FC_6H_4	97 (90)[c]	97:3 (97:3)[c]
3	4-$NO_2C_6H_4$	50 (95)[c]	>99:1 (>99:1)[c]
4	4-$MeOC_6H_4$	96 (95)[c]	86:14 (>99:1)[c]
5	(*E*)-PhCH=CH	99 (90)[c]	55:45 (97:3)[c]
6	*i*-Pr	99 (90)[c]	66:33 (>95:5)[c]
7	Et	95 (90)[c]	78:22 (>95:5)[c]

[a]Isolated yield. [b]Diastereomeric ratios were determined by ^1H NMR analysis. [c]$In(OTf)_3$ (1.3 equiv) was added, and the reaction was run for 1 h.

3) gave only 50% yield (97% based on recovered starting materials), and for the *p*-methoxy substrate (entry 4), the diastereoselectivity dropped to 86:14. Alkenyl and aliphatic substrates have given near quantitative yields but with poor stereoselectivity (entries 5−7). It was reasoned that an additional Lewis acid could improve the reactivity and stereoselectivity of the more problematic hydrazones forming a chelate that enhances the electrophilic character of the imine and restricts the mobility around the N−N bond. With this idea in mind, $In(OTf)_3$ was used, and the expected improvements were observed. In all cases, the reaction was completed after only 1 h, and the diastereoselectivity was dramatically improved for aliphatic and alkenyl substrates (entries 4−8), while the isolated yield for the *p*-nitro derivative was significantly better (entry 3).

Intramolecular indium-mediated allylations are not straightforward since they are inherently restricted to 1 equiv of the allyl halide, and most of the indium-mediated allylations are optimal with 3 equiv of allyl halide and 2 equiv of indium. This required stoichiometric has been associated to the implication of an allylindium(III) dimer species that can be broken-up with protic acid additives. Following these precedents, the synthesis of chromanes by indium-mediated intramolecular allylation of aromatic chiral hydrazones tethered to an allylic bromide was examined.[34] From different additives assayed, the best chemical yields and diastereoselectivities were obtained with trifluoroacetic acid (6 equiv) or *N*-Boc-glycine (2 equiv). Under optimal conditions, different chromanes were prepared in good yields with excellent diastereoselectivities (Scheme 10). Given that both simple protic acids and carboxylate salts were ineffective as additives, it was speculated that the carboxylic acid triggers the hydrazone and the allylic indium species in a way that resembles the action of bifunctional catalysts.

The fluoride-promoted addition of trialkylallyl silanes to chiral *N*-acylhydrazones (aza-Sakurai reaction) was studied by the group of Friestad.[35] In an initial experiment, the addition of allyltrimethylsilane to an enantiopure hydrazone was promoted by TBAF and the corresponding homoallylic hydrazine was obtained in a moderate yield with moderate diastereoselectivity (Table 15, entry 1). It was anticipated that chelation of the chiral *N*-acylhydrazone to a Lewis acid would increase the electrophilicity of the imine and restrict the rotamer populations exposing the *Si*-face to addition. The success of this dual activation concept required finding an effective Lewis acid compatible with the fluoride donor. Unfortunately, when different Lewis acids were used in combination with TBAF, the products were obtained in poor yields (e.g., entry 2). It was eventually found that soluble, air-stable, and nonhygroscopic tetrabutylammonium triphenyldifluorosilicate (TBAT) resulted in a more effective fluoride source, which in combination with $In(OTf)_3$ provided the expected product in good yield and very good diastereoselectivity (entry 3). In this reagent, the basicity of the fluoride ion should be moderated by the covalent Si−F linkage, and this could minimize the fluoride transfer to the Lewis acid. Moreover, further optimization experiments highlighted the importance of a nonnucleophilic counterion for the Lewis acid (entry 4), and tetraallylsilane proved to be a superior allyl donor in terms of reactivity and stereoselectivity (entry 5). The better performance of the tetraallylsilane compared with allyltrimethyl silane was associated with a slightly more electrophilic silicon atom with greater fluoride ion affinity in the first case. Under these reaction conditions, aromatic chiral hydrazones gave homoallylic amines in good yields with excellent diastereoselectivity (entries 5−7). The (*E*)-cinnamaldehyde derivative gave chemoselective addition to the C=N bond in good yield with very good diastereoselectivity. Although the propionaldehyde derivative was also a suitable substrate under these reaction conditions, the yields and diastereoselectivity were significantly lower.

Importantly, N-trifluoroacetylation followed by treatment with SmI_2 allowed N−N bond cleavage, while the chiral oxazolidinone component is recovered in high yield. This procedure preserves the synthetically useful alkene functionality in the adduct (in contrast to hydrogenolysis) upon providing a TFA-protected amine that can be liberated under mild basic conditions.

Control experiments showed that the addition of allylmagnesium bromide in the presence of $In(OTf)_3$ took place with significant lower stereoselectivity, which is not consistent with a hypothetical addition of allylindium nucleophile formed by transmetalation. All the mechanistic studies confirmed the initial working hypothesis of a dual activation for this reaction:

Scheme 10

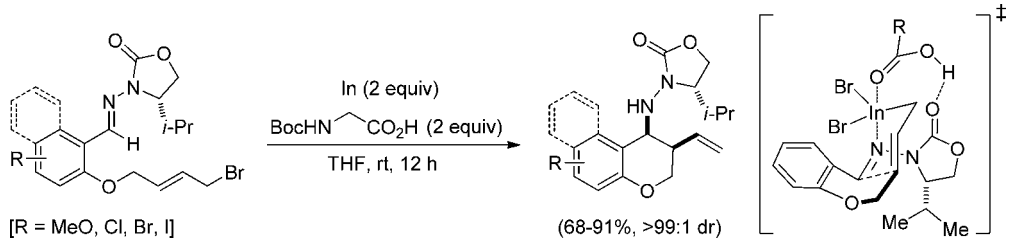


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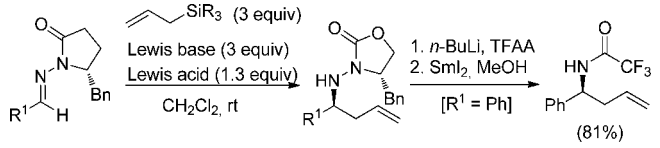
Table 15. Lewis Base/Lewis Acid Promoted Addition of Trialkylallyl Silanes to Chiral *N*-Acylhydrazones

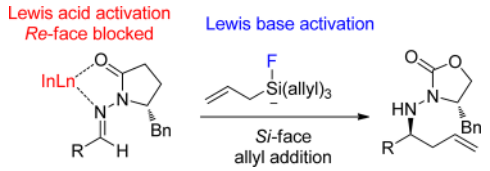


entry	R^1	R	Lewis base	Lewis acid	yield (%)[a]	dr[b]
1	Ph	Me	TBAF		40	5:1
2	Ph	Me	TBAF	$In(OTf)_3$	14	*c*
3	Ph	Me	TBAT	$In(OTf)_3$	58	94:6
4	Ph	Me	TBAT	$InCl_3$	17	33:67
5	Ph	allyl	TBAT	$In(OTf)_3$	78	>99:1
6	4-$MeOC_6H_4$	allyl	TBAT	$In(OTf)_3$	94	98:2
7	3-$NO_2C_6H_4$	allyl	TBAT	$In(OTf)_3$	71	>99:1
8	(*E*)-PhCH=CH	allyl	TBAT	$In(OTf)_3$	60	95:5
9	Et	allyl	TBAT	$In(OTf)_3$	51	82:18

[a]Isolated yields. [b]Determined by HPLC. [c]Not determined.

addition of hypervalent allylsilicate to an indium-chelated chiral *N*-acylhydrazone. The stereochemical outcome is also consistent with this model (Scheme 11).

Scheme 11

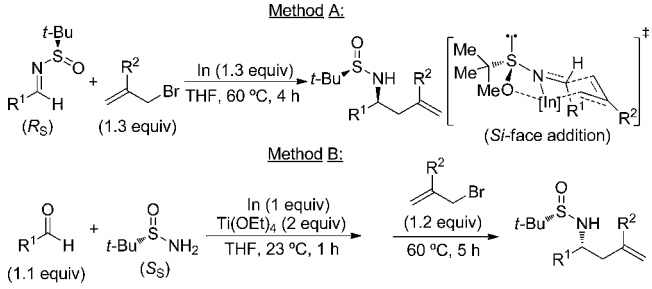


2.2.2.3. Chiral Sulfinyl Imines. Over the past decade chiral imines derived from *tert*-butanesulfinamide have been extensively used as electrophiles in a wide range of synthetic applications. The ready availability of both enantiomers of *tert*-butanesulfinamide in large-scale processes, the easy deprotection of the amine under mild acidic conditions, and a practical procedure for recycling the chiral auxiliary have undoubtedly contributed to the widespread use of this approach.[36] Although the addition of several allylic metal species to these chiral imines has been examined, the most commonly used reagents in latest years are allylzinc and allylindium reagents.[37] Recent selected examples of zinc/indium promoted allylation of chiral *N*-*tert*-butylsulfinyl imines (*t*-BS imines) will be presented in this section.

2.2.2.3.1. Indium-Promoted Allylation. The low toxicity of indium, the high tolerance to aqueous solvents and air exposure, and no need for specific activation are some of the advantages of this metal over others. The reaction of allyl bromides with indium(0) gives a mixture of allylindium species, which have been generally referred as *sesqui*allylindium bromides, regarding the overall stoichiometry of the reaction. Recently, the formation of monoallylindium(III) and diallylindium(III) species has been detected in THF solution by ^{1}H NMR studies. Both species were isolated after complexation with pyridine-type Lewis bases and analyzed by X-ray crystallography.[38] Moreover, in the presence of water (or alkoxides), a new oxygen-bridged binuclear species of In(III) (μ-oxide) was identified as the preferred configuration.

The indium-mediated allylation of different chiral *t*-BS aldimines was examined in THF.[39] The reaction took place smoothly at 60 °C affording the homoallylamine derivatives in good yields and diastereoselectivities when both allyl- and methallyl bromides were used (Table 16, method A). Notably,

Table 16. Indium-Mediated Allylation of *t*-BS Aldimines with and without Imine Isolation



			method A		method B	
entry	R^1	R^2	yield (%)[a]	dr[b]	yield (%)[c]	dr[b]
1	*i*-Pr	H	84	92:8	85	>98:2
2	*i*-Pr	Me	82	88:12		
3	$CH_3(CH_2)_7$	H	91	96:4	81	95:5
4	$CH_3(CH_2)_7$	Me	86	95:5		
5	$Ph(CH_2)_2$	H	79	91:9	92	91:9
6	$Ph(CH_2)_2$	Me	83	90:10	82	90:10
7	$PhCH_2$	H			81	98:2
8	(*E*)-PhCH=CH	H			82	98:2
9	Ph	H	94	94:6	77	89:11

[a]Isolated yield. [b]Determined by ^{1}H NMR analysis of isolated products after column chromatography. [c]Isolated yield over two steps.

the low basicity of allylindium species has made possible the successful allylation of easily enolizable aliphatic aldimines (entries 1−6, method A). These substrates are commonly problematic because the favorite pathway for other allylic metal reagents is the α-deprotonation to form the metalloenamines instead of the expected nucleophilic attack. A chairlike chelation model is consistent with the stereochemical outcome of the reaction. The coordination of indium to the nitrogen atom increases the reactivity of the electrophilic imine carbon, while the coordination of the metal to the oxygen of the sulfinyl group is responsible for the face selectivity. Synthetic applications of homoallylic amine derivatives prepared by this methodology have been conveniently exploited.[40]

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Aimed to develop a more straightforward access to enantioenriched homoallylic amine derivatives, the above mentioned protocol was conveniently modified to avoid the isolation/purification of the *t*-BS aldimines.[41] After different Lewis acids were screened in the α-aminoallylation of aldehydes with *tert*-butylsulfinamide, it was found that $Ti(OEt)_4$ not only allows the formation of the aldimine but also was compatible with *in situ* formation of the allylindium reagent. Under optimized conditions, the allylic bromide was added 1 h after the other reagents were made to react at room temperature, and the reaction mixture was heated to 60 °C over 5 h. The corresponding homoallylic amines were obtained in overall good yields from *tert*-butylsulfinamide (Table 16, method B). Importantly, similar diastereoselectivities were obtained in comparison with the allylation of isolated *t*-BS aldimines (method A vs method B). The chemoselectivity of this one-pot procedure was notorious. Homoallylic alcohols were only obtained in trace quantities, while very easily enolizable substrates (entry 7) and α,β-unsaturated aldehydes (entry 8) were also suitable. Since the stereoinduction was the same as that observed for the allylation of isolated *t*-BS imines, a similar working model was invoked for the transition state. Alternatively, another chelation model was proposed where titanium ethoxide served as a bridge between the indium atom and the sulfinyl group forming another six-membered ring.

Moreover, prenyl bromide and cyclohexenyl bromide were also examined in this one-pot protocol, obtaining very good chemo- and stereoselectivities in both cases (Figure 3).

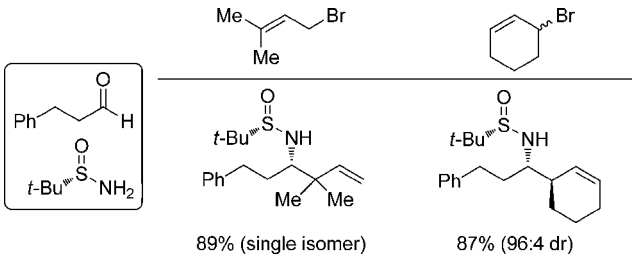


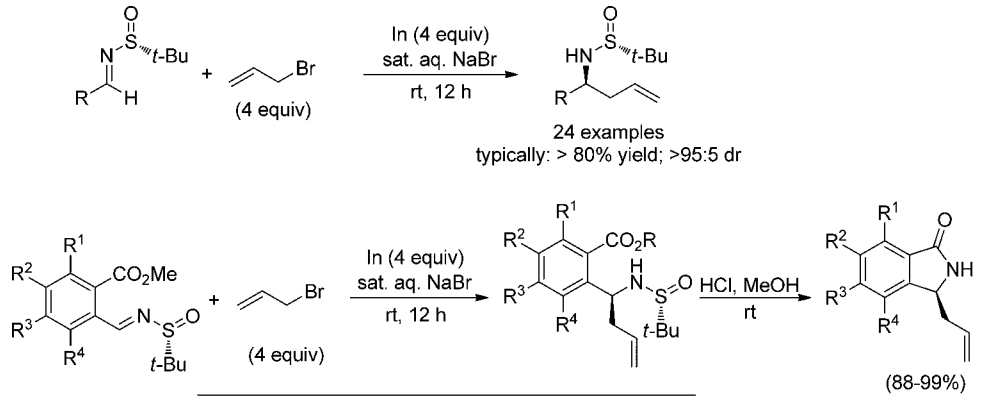
Figure 3. One-pot aminoallylation of 3-phenylpropanal with prenyl bromide and 3-bromocyclohexene.

Importantly, high γ-selectivity was observed for the addition of the prenyl moiety, and excellent *anti* addition selectivity was observed in the reaction of *rac*-cyclohexenyl bromide.

The first practical preparation of enantioenriched homoallylic amines in aqueous media was performed by indium-mediated allylation of *t*-BS imines.[42] Importantly, after the reaction was screened in different electrolyte-rich aqueous solutions at room temperature, it was found that a saturated NaBr solution provided the best diastereomeric ratios and isolated yields for the homoallylic amine derivatives. Notably, the use of 4 equiv of indium was found to be essential to achieve good yields. A wide range of sulfinyl aldimines were suitable substrates under these optimized conditions, providing the products in high yields with good diastereoselection (Scheme 12). In all cases, the major diastereomer was opposite of the one obtained in THF, which is consistent with the allylation over the *Re*-face of the R_S imine. This stereochemical outcome was not mentioned by the authors, but further work developed by the same group and others suggests an open transition state where an *s-cis*-like conformation of the sulfinylimine is involved (e.g., Tables 11 and 12). Remarkably, the allylation of aromatic imines with an alkoxycarbonyl substituent in the *ortho*-position took place smoothly with excellent chemo- and stereoselectivity. *N*-Sulfinyl cleavage of the allyl adducts under acidic conditions occurred with concomitant formation of the corresponding 3-allyl-isoindolinones in good yields. Since the allyl moiety can be synthetically modified, this strategy allows the rapid construction of 3-substituted-isoindolinones, which are considered to be valuable pharmacological compounds.

The indium-mediated addition of 2-(bromomethyl)acrylates to *N*-*tert*-butylsulfinyl aldimines in THF takes place under more forced conditions compared with other common allylic reagents (48 h at 100 °C vs 5 h at 60 °C, typically).[43] Interestingly, the weaker nucleophilicity of the indium allyl reagent derived from 2-(bromomethyl)acrylates was not a limitation to carry out the addition at room temperature, when a saturated aqueous solution of NaBr was used as reaction media.[44] As observed previously by other authors, 4 equiv of indium was required for complete conversion. Under these mild conditions, the corresponding aminoesters were obtained

Scheme 12



$R^1 = R^2 = R^3 = R^4 = H$	94%, >99:1 dr
$R^1 = R^4 = H$, $R^2 = R^3 = Cl$	98%, >99:1 dr
$R^1 = R^3 = H$, $R^2 = R^4 = MeO$	42%, >99:1 dr
$R^1 = R^2 = R^4 = H$, $R^3 = F$	95%, >99:1 dr
R^1-$R^2 = C_4H_4$, $R^3 = R^4 = H$	92%, >99:1 dr
$R^1 = R^4 = H$, R^2-$R^3 = C_4H_4$	98%, >99:1 dr

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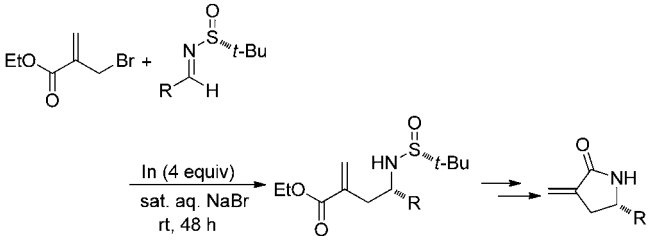
with good diastereoselection in high yields (Table 17). Importantly, the major diastereomers were easily isolated by

Table 17. Diastereoselective Indium-Mediated Addition of Ethyl 2-(Bromomethyl)acrylate to *t*-BS Aldimines in Aqueous Media



	aldimine			
entry	R	configuration	yield (%)[a]	dr[b]
1	$CH_3(CH_2)_7$	R_S	80	95:5
2	*i*-Pr	R_S	73	86:14
3	$Ph(CH_2)_2$	R_S	82	93:7
4	Ph	R_S	72	91:9
5	$CH_3(CH_2)_7$	S_S	79	89:11
6	*i*-Pr	S_S	77	91:9
7	$Ph(CH_2)_2$	S_S	77	88:12
8	Ph	S_S	75	93:7

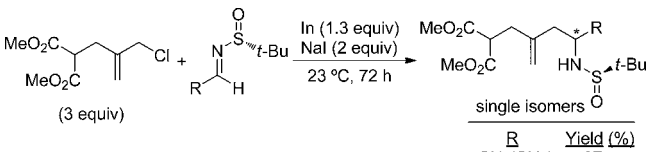
[a]Isolated yield. [b]Determined by ^{1}H NMR analysis of isolated products after column chromatography.

column chromatography and submitted to acidic deprotection followed by treatment with sodium methoxide, in a one-pot process, to afford the corresponding enantioenriched (ee >95%) butyrolactams. Notably, the stereochemical pathway under these aqueous reaction conditions is the opposite of that obtained when the reaction is performed in THF at 100 °C. To explain the addition of the allyl indium reagent to the *Si*-face of the R_S sulfinimine, the authors invoked a chelation control model similar to the one depicted in Table 16.

Recently, the indium-promoted allylation of *t*-BS aldimines with dimethyl-2[2-(chloromethyl)allyl]malonate was examined.[45] The best results in this case were found under neat conditions, when the reaction was carried out in the presence of sodium iodide to facilitate the formation of the more reactive allylic iodide. The products were isolated in high yields as single diastereomers (Scheme 13). However, the configuration of the newly created stereogenic center was not assigned.

2.2.2.3.2. Zinc-Promoted Allylation. Efficient methods for the Zn-mediated allylation of *t*-BS aldimines have been also developed.[46] Notably, the products were obtained in high yields with excellent diastereoselectivities when the reaction was conducted in THF and $In(OTf)_3$ (1.1 equiv) was used as additive. Moreover, the opposite stereocontrol was achieved

Scheme 13



R	Yield (%)
$CH_3(CH_2)_7$	87
i-Pr	87
$Ph(CH_2)_2$	90
Ph	71

using HMPA as solvent and H_2O as additive. A wide range of aliphatic and aromatic substrates were suitable for each set of conditions with very good results in terms of isolated yields and diastereoselection (Table 18). It was reasoned that the $In(OTf)_3$ chelates the sulfinyl group, favoring an *s-trans*-like conformation for the sulfinylimine, thus facilitating the allyl attack over the sterically unblocked *Si*-face (method A). On the other hand, when the HMPA/H_2O system is used (method B), the sulfinimine adopts the more stable *s-cis*-like conformation where the attack of the allylzinc reagent is favored over the *Re*-face. It is noteworthy that methyl aryl ketimines were also suitable substrates for the THF/$In(OTf)_3$ system, and despite their poorer reactivity compared with aldimines, the products were obtained in good yields with high diastereoselectivities (Scheme 14).

The γ-addition of 3,3-disubstituted allylzinc reagents to chiral sulfinimines is much less frequent, probably because the stereocontrolled preparation of the required allylic reagents is not always straightforward. In this context, the carbocupration of 1-octyne allows an efficient stereocontrolled preparation of vinyl iodides that can be transformed into the corresponding vinyl copper derivatives. The homologation of diastereomerically pure vinyl copper reagents by treatment with the zinc carbenoid formed *in situ* from diethyl zinc and diiodomethane offers a convenient approach to 3,3-disubstituted allyl zinc species. Recently, the group of Marek used this strategy to prepare the allyl zinc reagents and examined the addition at −30 °C to (*R*)-*t*-BS aldimines, with all the operations accomplished in a single-pot.[47] The expected homoallylic sulfinylamines were obtained in high overall yields and excellent diastereoselectivities for all aromatic imines used (Table 19, method A). Only the use of aliphatic sulfinylamines leads to a poor diastereomeric ratio (results not reported in Table 19). Additionally, the vinylcopper reagent was prepared by direct carbocupration of 1-octyne with $RCu/MgBr_2$ (prepared from RMgBr/CuI) and treated with the same zinc carbenoid in the presence of (*R*)-*t*-BS imines. Under these new conditions, the homoallylic amines were obtained in high yields and diastereoselectivities (Table 19, method B) but with opposite configurations in the newly created stereogenic centers. Moreover, this protocol also works with aliphatic sulfinylimines with excellent diastereoselection (entry 6).

To explain the stereochemical course of the reaction, a chairlike transition state was invoked where the zinc is coordinated by the nitrogen atom, and the substituent of the sulfinylimine occupies a pseudoaxial position. When the vinyl copper reagent is formed from a vinyl iodide (method A), the sulfinylimine should adopt a conformation where the lone pair on the nitrogen and the S=O bond are *antiperiplanar*. This *s-cis*-like conformation has been reported as the most stable for *t*-BS aldimines with an estimated rotational barrier of 9.9 kcal·mol^{-1}, mainly as a result of a significant $n_N \rightarrow \sigma^*_{S=O}$ negative hyperconjugation interaction.[48] However, when the addition of the vinyl copper reagent to the chiral sulfinylimine is accomplished in the presence of MgX_2 (method B), this Lewis acid can be coordinated to the sulfinyl group and to the zinc atom. This chelation mode stabilizes the *s-trans*-like conformation of the sulfinimine in the transition state, accounting for the stereochemical outcome observed.

The addition of racemic 2-cyclohexenylzinc chloride to (*S*)-*t*-BS imines has also been recently examined. The reaction took place smoothly at −78 °C, either with aldimines or ketimines, the corresponding *anti*-homoallylic amines being obtained with

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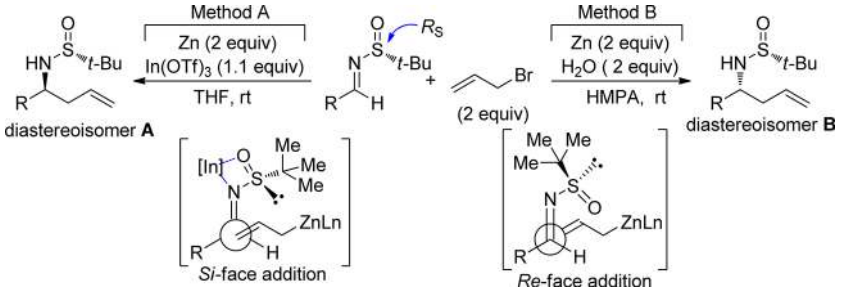
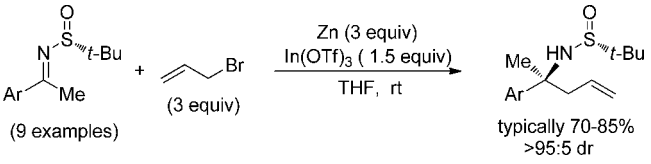
Table 18. . Diastereoselective Allylation of (*R*)-*t*-BS Aldimines with Two Different Reaction Systems



		method A		method B	
entry	R	yield (%)[a]	A/B[b]	yield (%)[a]	A/B[b]
1	Ph	93	98:2	97	1:99
2	4-ClC_6H_4	98	98:2	96	3:97
3	4-$MeOC_6H_4$	91	95:5	81	2:98
4	2-MeC_6H_4	95	98:2	89	3:97
5	*c*-(C_3H_5)	98	86:14	97	4:96
6	Cy	99	97:3	94	3:97
7	Et	93	88:12	92	5:95
8	$PhCH_2CH_2$	92	90:10	93	4:96

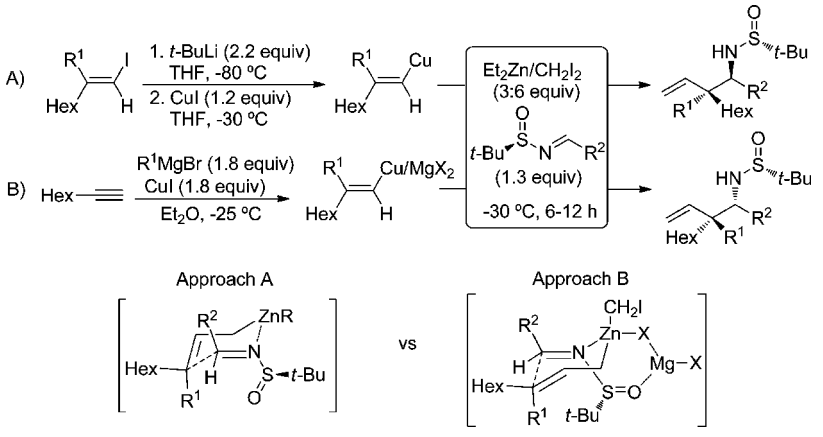
[a]Isolated yield. [b]Determined by ^{1}H NMR from the crude reaction mixture.

Scheme 14



excellent diastereoselectivities (Scheme 15).[49] Notably, 3-methyl-2-cyclohexenylzinc chloride was also suitable for this protocol, allowing the preparation of the corresponding homoallylic amine in good yield with excellent stereocontrol over the two adjacent quaternary centers. Moreover, the preprepared cinnamylzinc chloride also displayed high *syn* diastereoselectivity in the addition to *t*-BS aldimines. Surprisingly, X-ray diffraction analysis showed opposite absolute configurations at the carbon stereocenters to what

Table 19. Diastereodivergent Allylation of (*R*)-*t*-BS Aldimines with *in Situ* Formed 3,3-Disubstituted Allylzinc Reagents



			method A		method B	
entry	R^1	R^2	yield (%)[a]	dr[b]	yield (%)[a]	dr[b]
1	Et	Ph	85	>98:2		
2	Me	Ph	65	>98:2		
3	*i*-Pr	Ph	87	>98:2		
4	Et	*p*-BrC_6H_4	81	>98:2	75	>98:2
5	Et	*p*-AcC_6H_4	77	>98:2	67	>98:2
6	Et	*n*-Bu			67	>98:2
7	*i*-Pr	*p*-BrC_6H_4			62	>98:2
8	*n*-Bu	*p*-BrC_6H_4			70	97:3

[a]Isolated yield. [b]Determined by ^{1}H and ^{13}C NMR analysis of crude products.

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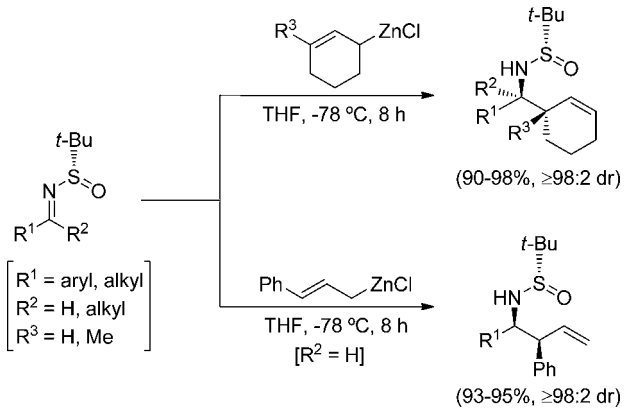
Scheme 15



would be expected under THF conditions. To explain this stereochemistry, the authors proposed a chairlike transition state model that involve a very unusual (*Z*)-imine. The same result can be explained using an acyclic model similar to the one depicted in Table 18.

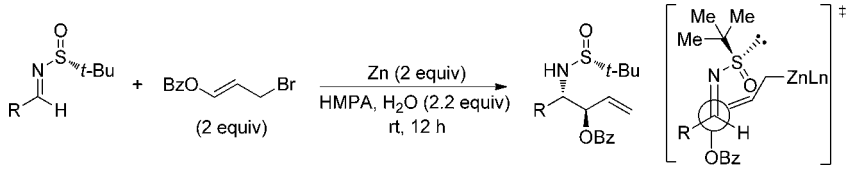
The benzoyloxyallylation of (*R*)-*t*-BS imines was examined in order to facilitate a convenient stereocontrolled access to *β*-amino-*α*-vinyl alcohols.[50] After several conditions were screened, the zinc-promoted addition of (*E*)-3-benzoyloxyallyl bromide was undertaken in HMPA using H_2O as additive. Under these conditions, the reaction took place at room temperature with a range of substrates to furnish the corresponding products in good yields with high diastereoselectivities (Table 20). Substituted aromatic aldimines provided excellent *anti*/*syn* selectivity for the stereocenters created, as well as high enantioselectivity after removal of the sulfinyl group (entries 1−5). Unhindered aliphatic substrates gave significantly lower diastereo- and enantioselectivity (entries 6, 7), while greater *anti*/*syn* selectivity was obtained for bulkier aliphatic substrates (entry 8). To explain the stereochemical outcome of the reaction, an acyclic transition state was invoked, in which the zinc atom is coordinated to the Lewis base (HMPA) rather than to the sulfinyl oxygen. In this model, the addition of the benzoyloxyallylzinc reagent is directed to the less sterically hindered *Re*-face of the more stable *s*-*cis*-like conformation (see above) of the (*R*)-imine.

Following their own results in the Zn/HMPA allylation of *t*-BS-imines, the group of Xu and Lin decided to substitute the unpleasant and carcinogenic HMPA by other Lewis bases. In this context, the observation that different stereochemical outcomes were observed for the addition of cinnamyl zinc reagents prepared *in situ* vs preformed reagents using the Knochel method was crucial. It was reasoned that the excess of LiCl used to mediate the zinc insertion in the Knochel method could be behind this reversal of stereocontrol. To test this hypothesis, the Zn-mediated cinnamylation of (*R*)-*N*-*tert*-butylsulfinyl imines was carried out under Barbier conditions using different amounts of LiCl in THF or DMF.[51] As expected, the reaction proceeded smoothly at room temperature to give a major *syn* product with opposite stereochemistry at the carbon centers than that obtained in the absence of LiCl. The best results were obtained using DMF with small amounts of H_2O as solvent and 1 equiv of LiCl. Under these conditions, the cinnamylation of different *t*-BS imines afforded the corresponding products in very good isolated yields and excellent diastereo- and enantioselectivity (Scheme 16a). The same reaction conditions were applied in the allylation and benzoyloxyallylation reaction of a *t*-BS imine to obtain the corresponding products with excellent selectivity after only 30 min at room temperature (Scheme 16b).

The LiCl/DMF system was also used in the Zn-mediated addition of 2-(bromomethyl)acrylates to *t*-BS imines.[52] As mentioned above, the indium-mediated addition of these challenging allylic systems occurs at higher temperature under anhydrous conditions (100 °C)[43] or after long reaction times at room temperature (48 h) using aqueous saturated solution of NaBr.[44] Under the new set of conditions, the reaction took place at room temperature after only 8 h for a range of *t*-BS imines, with excellent diastereoselectivity for the two newly formed stereogenic centers (Scheme 16c). In this case, the use of 5 equiv of LiCl proved to be optimum. Moreover, acidic removal of the sulfinyl group allowed the one-pot preparation of enantioenriched *α*-methylene-*γ*-lactams in good yields, a common scaffold of bioactive natural and synthetic products.

The addition of allylmagnesium bromide to chiral *t*-BS aldimines is catalyzed by substoichiometric amounts of dimethyl zinc.[53] Notably, a significant improvement in the enantioselectivity was observed when the reaction temperature was increased from −40 to 20 °C. The authors proposed that

Table 20. Diastereoselective Benzoyloxyallylation of (*R*)-*t*-BS Imines in HMPA



entry	R	yield (%)[a]	*anti*/*syn*[b]	ee (%)[b]
1	Ph	95	99:1	96
2	4-ClC_6H_4	99	98:2	95
3	2-MeC_6H_4	98	99:1	90
4	4-MeC_6H_4	96	99:1	98
5	4-$MeOC_6H_4$	99	99:1	93
6	$PhCH_2CH_2$	98	79:21	87
7	*i*-Bu	89	78:22	85
8	Cy	94	98:2	81

[a]Isolated yield. [b]Determined for the *N*-acetyl derivative after removal of the sulfinyl group.

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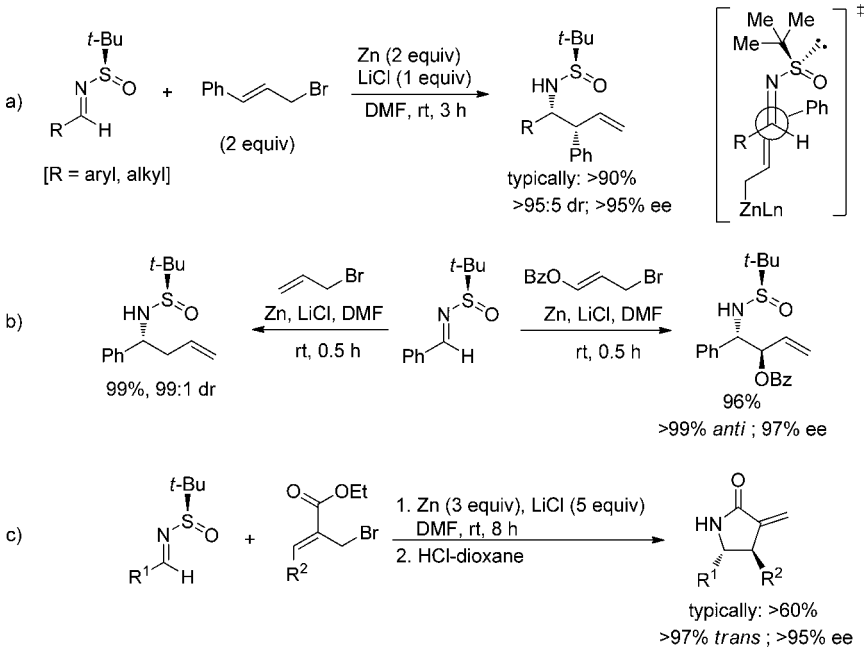
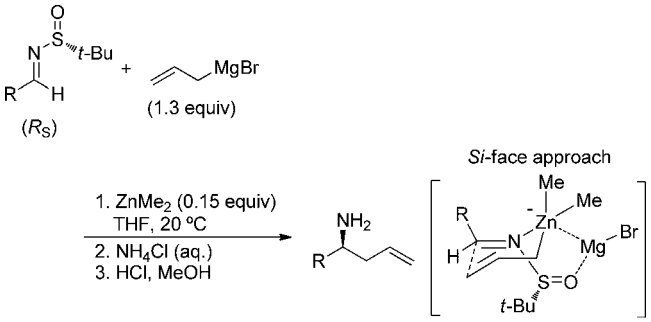
Scheme 16



the reaction should take place by addition of the corresponding triorganozincate to the *Si*-face of the (R_S)-*t*-BS imine, most likely through a chairlike transition state. Good isolated yields and very good stereoselectivities were obtained for aromatic aldimines (Table 21, entries 1−3). Moreover, aliphatic aldimines reacted also smoothly, albeit with moderate diastereoselectivity (entries 4,5).

Table 21. Diastereoselective Allylation of *t*-BS Imines Using Triorganozincates



entry	R	yield (%)[a]	ee (%)[b]
1	Ph	74	90
2	4-ClC_6H_4	69	92
3	4-$MeOC_6H_4$	81	94
4	$PhCH_2CH_2$	64	70
5	$CH_3(CH_2)_7$	74	72

[a]Isolated yield. [b]Determined by chiral HPLC after N-benzoylation.

2.3. Carbonyl Compounds with Chiral Auxiliaries Attached to the Oxygen Atom

The group of Tietze has demonstrated that trimethyl silyl ether of norpseudoephedrine derivatives (NPED) can be efficiently used as chiral inductor in the allylation of carbonyl compounds with allyltrimethylsilane. The reaction is usually performed in a multicomponent fashion, in the presence of substoichiometric amounts of acids, to give the corresponding homoallylic ethers that can be cleaved under reductive conditions (Scheme 17). Importantly, not only aldehydes but also aliphatic methyl ketones can be allylated in excellent yields and stereoselectivities.[54] Notably, opposite induced stereoselectivity has been found when going from aldehydes to ketones. To explain this difference, it was postulated that aldehydes reacts through the corresponding oxazolidines that are intercepted by the allyltrimethylsilane,[55] while oxocarbenium ions are the electrophilic species in the stereogenic step of ketone allylation.[56]

A clear limitation of the former methodology resides on the fact that only one enantiomer of norpseudoephedrine is commercially available. In this context, a modified auxiliary that can be conveniently prepared from both enantiomeric forms of mandelic acid was also evaluated.[57] The preparation of the auxiliary requires only four steps from (*R*)- or (*S*)-mandelic acid and a simple column chromatography separation. As shown in Table 22, aliphatic methyl ketones are suitable substrates for the allylation reaction with the new auxiliary. The good stereoselectivities obtained for the homoallylic ethers proved that the 2-methyl group in the NPED auxiliary is not crucial in these cases. In general, the procedure was not suitable for aromatic, α,β-unsaturated, and free hydroxy ketones. Importantly, 2 equiv of the ketone and the allyl silane is necessary to obtain good yields of the reaction, although the reasons are not clear yet. Moreover, the auxiliary was cleaved in good yields without reduction of the allylic double bond using lithium in THF with DBBP.

Computational study of the allylation of butanone in the presence of a chiral NPED auxiliary supports an S_N1-type attack of the allyltrimethylsilane to an *in situ* formed oxocarbenium ion.[58] The screening of 288 possible transition states (TSs) using semiempirical AM1 method led to the identification of 264 TSs. The number of potential TSs was narrowed down to 61 based on B3LYP//AM1 energies before final calculations were performed at the DFT level in the gas phase. Due to an overestimation of the predicted stereoselectivity using gas-phase calculations, the authors decided to include the solvent of the reaction (DCM) in their calculations. From these new high

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Scheme 17

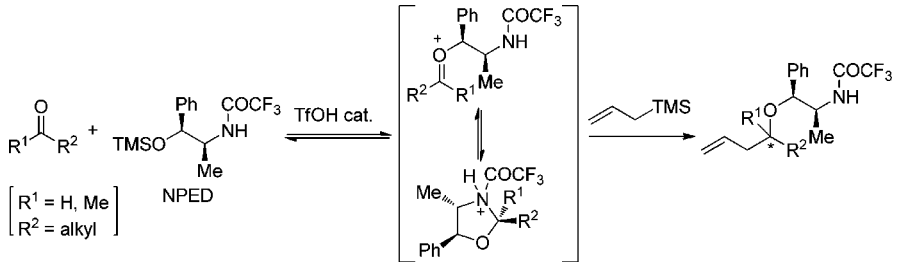
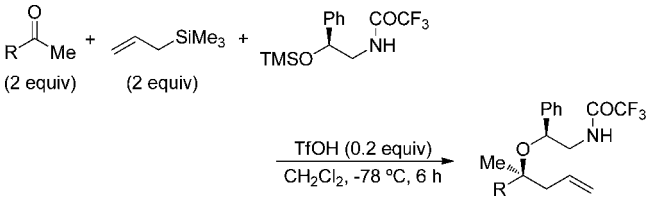


Table 22. Synthesis of Tertiary Homoallylic Ethers from Aliphatic Methyl Ketones in the Presence of a Mandelic Acid Derivative



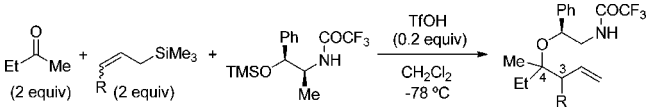
entry	R	yield (%)	dr
1	Et	89	8.8:1
2	*i*-Pr	82	13.6:1
3	$PhCH_2CH_2$	68	10.7:1
4	$TBDPSOCH_2CH_2$	87	>20:1

-level DFT calculations (B3LYP-PCM-large//B3LYP-PCM) a subset of 14 relevant TSs with $E^{\ddagger}_{rel.} \leq 6$ kJ·mol^{-1} was found. According to this calculation, the formation of the major isomer (4*R*) was explained by the attack of allyltrimethylsilane to the *Si*-face of the (*E*)-oxocarbenium ion, while attack to the *Re*-face explained the formation of the minor isomer. Scheme 18 illustrates the relevant attack trajectories calculated, which lead to the predicted selectivity of 85:15, in good agreement with the experimental value of 90:10.

The NPED-mediated allylation of ketones was expanded to use γ-substituted allyl silanes.[59] In this study, the major and minor isomers obtained were always 3,4-*anti*-configured regardless the double bond geometry of the silane (Table 23). Furthermore, the absolute stereochemistry of the isomers obtained was also independent of the silane geometry (*E*/*Z*). Notably, the configurations of major and minor products switch from crotyl silane to pentenyl and other longer chained silanes (entries 1 and 2 vs 3 and 4).

The above-mentioned results were supported using a computational approach to identify the relevants TSs. Following a similar strategy to that used for the allylation case, the TSs with $E^{\ddagger}_{rel} \leq 6$ kJ mol^{-1} were submitted to geometry optimization and frecuency calculation at the B3LYP/6-31+G(d)/PCM/UAKS level of theory. From these calculations emerged three main trajectories for the attack of

Table 23. NPED-Mediated Crotylation and Pentenylation of Butanone with Silanes

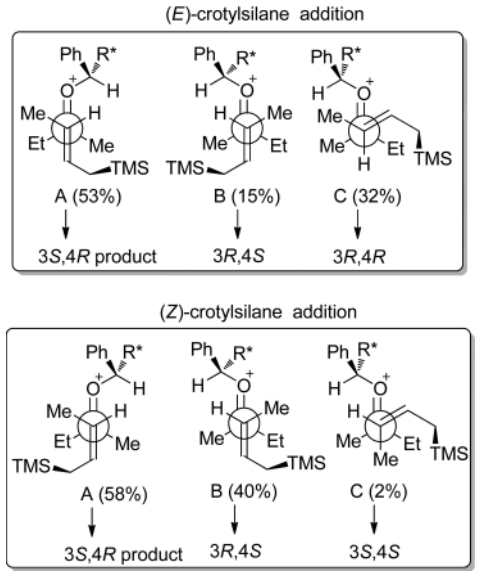


entry	R	configuration of allyl silane	dr[a]	main isomer[b]	minor isomer
1	Me	*E*	90:10	3*S*,4*R*	3*R*,4*S*
2	Me	*Z*	75:25	3*S*,4*R*	3*R*,4*S*
3	Et	*E*	70:30	3*R*,4*S*	3*S*,4*R*
4	Et	*Z*	86:14	3*R*,4*S*	3*S*,4*R*

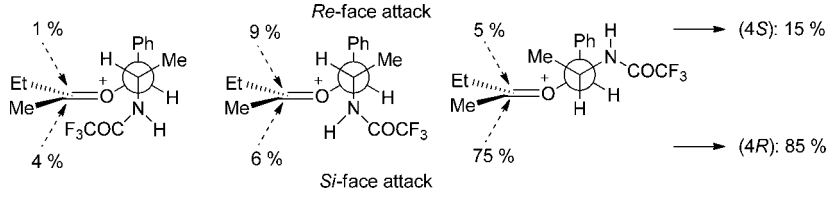
[a]Determined by ^{13}C NMR analysis. [b]Configuration was assigned based on X-ray crystallographic analyses.

the (*E*)-crotylsilane (A, B, and C in Scheme 19). The first two trajectories with antiperiplanar orientation of the double bonds

Scheme 19



Scheme 18

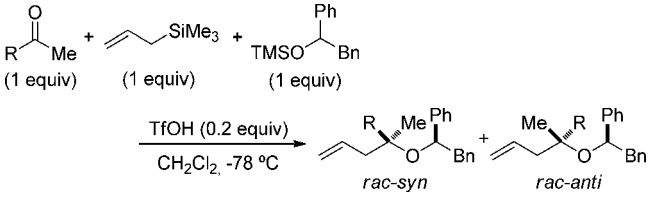


dx.doi.org/10.1021/cr400008h | Chem. Rev. 2013, 113, 5595−5698

(A and B) accounted for the formation of the major and minor isomer, respectively, while trajectory C predicted the formation of the *syn* isomer, 3*R*,4*R*, which is not experimentally detected. Taking into account the relative contribution of trajectories A and B, the calculations predicted a ratio of 78:22 for the *anti* isomers observed, which is in agreement with the experimental results (90:10, 3*S*,4*R*/3*R*,4*S*). For (*Z*)-crotylsilane, similar calculations predicted a 98:2 *anti*/*syn* ratio of products, the *anti* isomers 3*S*,4*R*/3*R*,4*S* being formed in a 59:41 ratio (vs 75:25 experimental ratio). Importantly, in comparison with (*E*)-crotylsilane, the addition of (*Z*)-crotylsilane is predicted to be less selective, but the same major and minor isomers are expected to be formed. When the same computational approach was applied to the pentenylation with (*Z*)-pentenylsilane, only TSs A and B [similar to the (*Z*)-crotylsilane case] were identified as relevant. In contrast to the crotylation, the attack at the *Re*-face of the oxocarbenium ion was then expected to be favored, which correctly predicted the inversion in the stereoselectivity.

Despite the success achieved in the NPED-mediated allylation of ketones with allyltrimethyl silane, the group of Tietze decided to search for new suitable chiral auxiliaries. In order to improve the applicability as protecting group, it was desirable to find an auxiliary with higher stability under basic conditions. Another drawback that prompted the search for new auxiliaries was the necessity of 2 equiv of ketone to obtain good yields with the NPED auxiliary. In this context, different chiral phenyl carbinols were prepared, and their induction in the addition of allyltrimethyl silane to butanone was examined.[60] Among the screened auxiliaries, the simple benzylphenylcarbinol trimethylsilyl ether emerged as the most convenient candidate due to its ready availability in enantiomeric forms and high stereoinduction. Importantly, similar yields were obtained in the reaction using either 1 or 2 equiv of ketone. Moreover, good isolated yields and high *syn*/*anti* selectivities were also obtained for other aliphatic methyl ketones (Table 24, entries 1−6). On the other hand, very sterically hindered pinacolone and aromatic acetophenone gave the products in unsuitably poor yields (entries 7 and 8). The cleavage of the auxiliary was found to be effective under Birch conditions or under conventional catalytic hydrogenation.

Table 24. Allylation of Methyl Ketones with Allylsilanes Mediated by a Chiral Benzylphenyl Carbinol Derivative

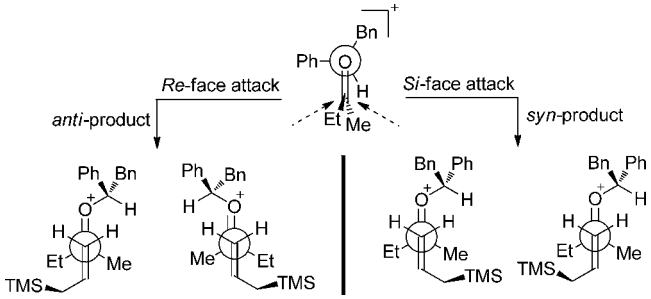


entry	R	yield (%)[a]	*rac-syn*/*rac-anti*
1	Et	93	90:10
2	$CH_3(CH_2)_4$	93	88:12
3	*i*-Pr	91	96:4
4	Cy	89	96:4
5	Bn	86	91:9
6	$PhCH_2CH_2$	76	86:14
7	Ph	9	97:3
8	*t*-Bu	8	72:28

[a]Yield for ketone/allylsilane/auxiliary ratio 1:1:1.

The selectivity of the reaction was studied using quantum-chemical calculations to identify possible TSs of the stereogenic step for the allylation of butanone. After an exhaustive computational screening, only four relevant TSs emerged with (*E*)-configuration for the oxocarbenium ion and antiperiplanar orientations of the double bonds (Scheme 20).

Scheme 20



In all relevant TSs, the phenyl group is fixed in orthogonal position with respect to the carbonyl group by a stereoelectronic effect. Since the attack to the *Re*-face of the oxocarbenium ion is hindered by the phenyl group, it can be easily rationalized that TSs derived from a *Si*-face approach are the most stable. The selectivity predicted from the contribution of all relevant TSs was 91:9 in favor of the *syn* product, which is in perfect agreement with the experimental selectivity of 90:10.

3. REAGENT CONTROL

3.1. Chiral Nucleophiles with Stereogenic Centers in the Transferred Hydrocarbon Backbone

3.1.1. α-Substituted Allyl Boranes. The group of Aggarwal has recently described a straightforward synthesis of chiral α-substituted allylboranes that add to aldehydes with almost complete stereoinduction.[61] The method is based on the reaction of chiral sulfur ylides with readily available vinyl boranes and the selective stereospecific 1,2-migration of the vinyl group (Scheme 21). Importantly, the chiral sulfur auxiliary can be efficiently recovered, and the kinetic chiral α-substituted allylboranes rearranges to the more stable conjugate isomer at a higher temperature (from −100 to 0 °C).

The reaction of chiral allylboranes obtained by this method at −100 °C with benzaldehyde at the same temperature furnished the corresponding homoallylic alcohol with high *Z* selectivity (method A, Table 25). To explain the major *Z* isomer obtained, a chairlike transition state is proposed where the α-allylic substituent is placed in axial position to avoid severe steric interactions with the bulky 9-BBN moiety. Consequently, the disfavored chairlike transition state leads to the minor *E* isomer with the opposite absolute configuration at the carbinol center. Moreover, it was also found that warming the chiral allylborane to 0 °C followed by recooling to −78 °C and trapping with benzaldehyde at the same temperature furnished another isomeric homoallylic alcohol (method B). Again, almost complete enantio- and diastereoselection was observed with high Z selectivity. These results were explained by invoking a highly stereoselective suprafacial [1,3]-borotropic rearrangement that proceeds through the conformation with minimum A strain. Importantly, this study provides the first experimental evidence, in accordance with previous theoretical

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Scheme 21

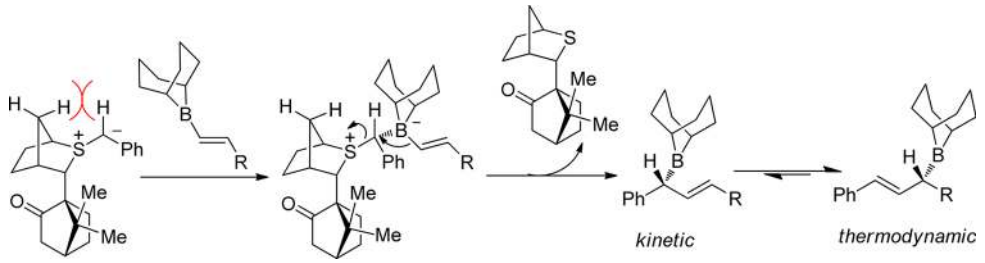
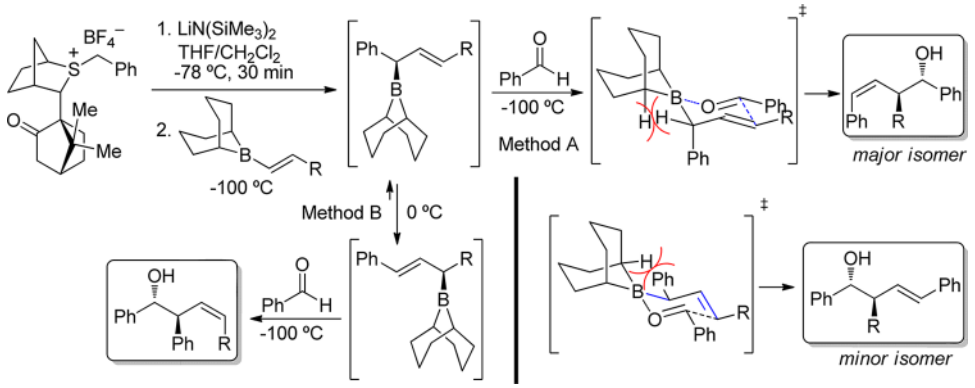


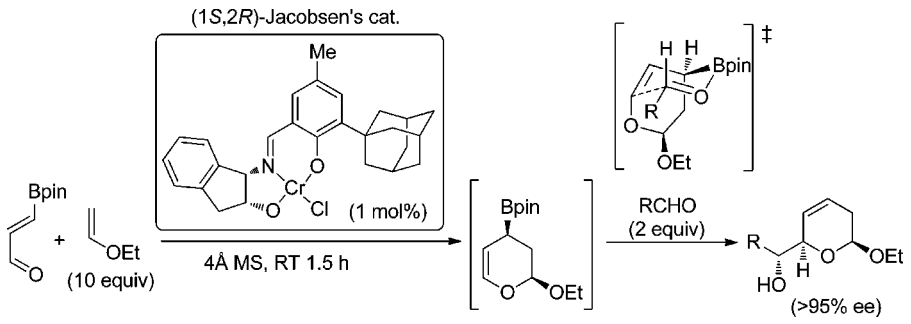
Table 25. Stereoselective Formation and Addition to Aldehydes of Chiral α-Substituted Allylboranes



entry	R	method	yield (%)[a]	Z/E[b]	dr[c]	ee (%)[c]
1	*n*-Bu	A	79	15:1	>95:5	>99
2	$TMSOCH_2$	A	61	>40:1	>95:5	>99
3	$AcOCH_2CH_2$	A	72	>40:1	>95:5	>99
4	*n*-Bu	B	81	10:1	>95:5	>99
5	$TMSOCH_2$	B	49	>30:1	>95:5	>99
6	$AcOCH_2CH_2$	B	56	13:1	>95:5	>99

[a]Isolated yield. [b]Determined by ^1H NMR. [c]Data for the *Z* isomers only.

Table 26. Enantioselective Three-Component Hetero-[4 + 2] Cycloaddition/Allylboration Reaction among 3-Boronoacrolein, Ethyl Vinyl Ether, and Aldehydes



entry	R	*T* (°C)	*t* (h)	yield (%)
1	Ph	40	24	82
2	$4\text{-}MeOC_6H_4$	45	24	81
3	$4\text{-}ClC_6H_4$	40	24	77
4	$PhCH_2$	45	24	82
5	$TBDMSOCH_2$	45	24	82
6[a]	*i*-Pr	50	18	78
7[a]	$(E)\text{-}CH_3CH{=}C(CH_3)$	50	48	76
8[a]	$CH_2{=}CH$	25	24	73

[a]Ethyl vinyl ether was removed after the cyclization step and replaced with CH_2Cl_2.

calculations, suggesting that this rearrangement takes place through a pseudopericyclic transition state.

3.1.2. Cyclic α-Substituted Allyl Boronates. In a preliminary communication, Carreaux reported the three-

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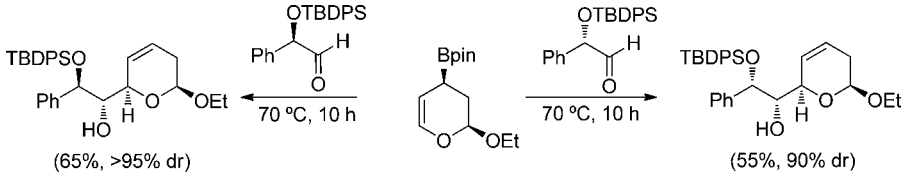
Scheme 22



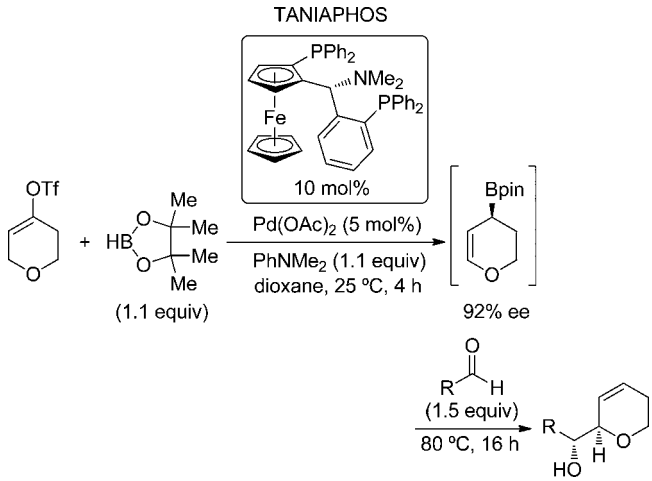
component assembly of 3-boroacrolein pinacolate, ethyl vinyl ether and aldehydes in the presence of $Yb(fod)_3$ as catalyst (5 mol %). The reaction was completed in refluxing dichloromethane after 12 h, obtaining the corresponding α-hydroxyalkyl-3,4-dihydro-2*H*-pyrans with high diastereoselectivities.[62] The tandem process implied a faster inverse electron demand hetero-Diels–Alder reaction that occurs with high endo selectivity followed by the allylboration of aldehydes, which most likely takes place through a chairlike transition state. Significantly, by using 5 mol % of (1*S*,2*R*)-Jacobsen's Cr(III) catalyst[63] the Diels–Alder adduct of 3-boroacrolein pinacolate and ethyl vinyl ether was obtained in high yield and with over 95% enantioselectivity. Subsequent reaction of the purified adduct with aldehydes in toluene at 70 °C took place with almost complete diastereoselection to afford enantioenriched dihydropyrans.[64] Under these conditions, the authors were not able to carry out the two steps, cycloaddition and allylboration, in the same pot with satisfactory results. However, in an independent work, the group of Hall discovered that similar results in the Diels–Alder reaction of 3-boroacrolein pinacolate and ethyl vinyl ether could be obtained using 1 mol % of the Jacobsen's Cr(III) catalyst. More importantly, under these conditions the tandem Diels–Alder/allylboration process took place with different aldehydes, at 40 °C, and using ethyl vinyl ether as solvent, furnishing the desired compounds in good yields and with excellent transfer of chirality.[65]

The contributions of the groups of Carreaux and Hall to this field were summarized in a joint full account.[66] The tandem process was suitable for electron-rich and electron-deficient aromatic aldehydes as well as functionalized aliphatic aldehydes (Table 26). Reactions with α,β-unsaturated aldehydes required a change of solvent to dichloromethane in order to avoid a competing hetero-[4 + 2] cycloaddition reaction with ethyl vinyl ether. The relative configuration of the stereogenic centers is in full agreement with a cyclic chairlike transition state with the alkyl or aryl group of the aldehyde in an equatorial position, as already observed for the racemic version of this allylboration. In contrast to previous reports describing the acceleration of allylborations by Lewis acids,[67] control experiments in this study showed no acceleration nor retardation in the allylboration step promoted by the Cr(III) complex.

Particularly attractive in the context of natural product synthesis was the reaction with aldehydes with a stereogenic center at the α-position of the carbonyl group. The stereochemistry in the addition of (*S*)-allylboronate to both enantiomers of *O*-TBDPS-protected mandelaldehyde was controlled by the allylboronate. Yield and diastereoselectivity were higher for the (*R*)-enantiomer of the substrate (matched combination), as predicted by the Felkin–Anh model, than for the (*S*)-one (Scheme 22).[66]

It was also possible to perform a one-pot *in situ* preparation of a chiral allylic boronate followed by allylboration of aldehydes through a different strategy. Hall found that the palladium-catalyzed borylation of a vinylic dihydropyranyl triflate, followed by isomerization in the presence of TANIAPHOS, led to a chiral cyclic allylic boronate with excellent enantioselectivity. Subsequent reaction of this boronate with aldehydes at 80 °C furnished the corresponding enantioenriched α-hydroxyalkyl-3,4-dihydro-2*H*-pyrans in acceptable isolated yields as single diastereoisomers (Table 27).[68]

Table 27. Allylboration of Aldehydes with a Cyclic Chiral Allylic Boronate Formed by Borylation/Isomerization of a Vinylic Cyclic Dihydropyranyl Triflate



entry	R	yield (%)	ee (%)
1	$PhCH_2CH_2$	54	91
2	$BnOCH_2CH_2$	61	91
3	Ph	59	93
4	$CH_3(CH_2)_4C{\equiv}C$	57	88
5	(*E*)-PhCH=CH	56	89

The former catalytic enantioselective process was also applied to the synthesis of α-hydroxyalkyl-substituted 1,2,3,6-tetrahydropyridines starting from the corresponding *N*-Boc-protected vinylic triflate. The isomerization process was not as effective in this case. Compared with the pyran analogue, the intermediate allylboronate was formed together with the corresponding alkenylboronate in a low 4:1 ratio. Stronger reaction conditions (microwave heating, 130 °C) were also necessary in order to achieve the allylation of the aldehyde in the second step (Scheme 23).[68]

Chiral cyclic allylic boronates were also prepared by a Cu(I)-catalyzed desymmetrization of *meso*-2-alkene-1,4-diol carbonate derivatives and bis(pinacolato)diboron in the presence of (*R*,*R*)-QuinoxP*.[69] The reaction was completed within 4 h in toluene at −20 °C, and the resulting chiral allylic boronate was made to react, without being isolated, with different aldehydes to obtain the homoallylic alcohols in high yields and with excellent control over the three new stereocenters formed. The high diastereo- and enantioselectivities obtained for the final products evidenced the stereoselective formation of the allylic

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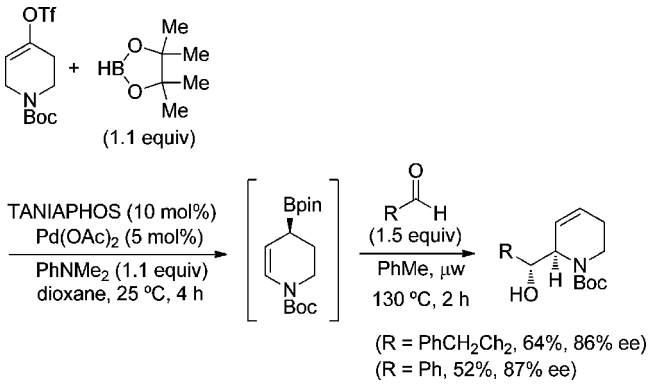
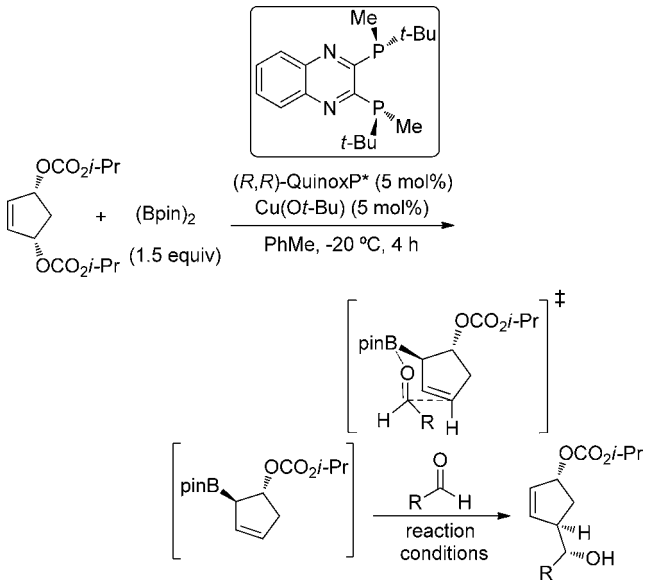
Scheme 23

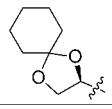


boronate and its excellent transfer of chirality. Similar yields and enantiomeric excesses were obtained with aromatic, aliphatic, and α,β-unsaturated aldehydes (Table 28). Regarding the stereochemical pathway of the allylation, Ito suggested that the carbonyl addition proceeds through a chairlike transition state so that the alkyl group of the aldehyde takes the equatorial position to give the reaction product after the hydrolysis.

Interestingly, in this work the authors demonstrated that the enantioenriched allylic carbonates obtained by the above-mentioned protocol could be submitted to a subsequent borylation/aldehyde allylation process in a stereospecific manner. When TBS-protected substrates were subjected to the borylation using an achiral Xantphos ligand, followed by Lewis acid catalyzed addition to aldehydes, the products were obtained with good yields and excellent transfer of chirality (Scheme 24). Importantly, the combination of these two borylation/allylation processes allows the rapid and modular construction of 3,5-disubstituted cyclopentenes with four new stereodefined stereocenters from *meso*-cyclopent-4-ene-1,4-diol carbonates.

Table 28. Asymmetric Synthesis of Homoallylic Alcohols through Desymmetrization of *meso*-Carbonates and Subsequent Allylation of Aldehydes



Entry	R	Conditions	Yield (%)	dr	ee (%)
1	Ph	0 °C, 4 h	87	>99:1	97
2	4-(CO_2Me)C_6H_4	0 °C, 23 h	85	>99:1	96
3	$PhCH_2CH_2$	0 °C, 20 h	85	97:3	95
4	*i*-Pr	0 °C, 96 h	93	92:8	97
5	$CH_3(CH_2)_5$	0 °C, 25 h	81	98:2	97
6	(*E*)-PhCH=CH	0 °C, 15 h rt, 3 h	64	>99:1	96
7		rt, 3 h	85	>95:5	--

3.1.3. Acyclic α-Substituted Allyl Boronates. A very attractive method to prepare chiral α-substituted allylic boronates is the enantioselective diboration of prochiral allenes. The group of Morken has found that the palladium-catalyzed diboration of allenes with bis(pinacolato)diboron is greatly accelerated by monodentate phosphine ligands. Mechanistic studies suggest that this reaction proceeds by oxidative addition of the diboron to palladium, followed by migratory insertion of the terminal alkene into a Pd−B bond to give an η^3-allyl palladium complex that suffers reductive elimination (Scheme 25).[70] The acceleration effect of phosphine ligands motivated the search for related chiral ligands to prepare enantioenriched allyl-vinyl diboronates that could add to aldehydes in an stereospecific manner. It was reasoned that of the two possible chairlike transition states, the one with the aldehyde alkyl group (R^1) sitting in a pseudoequatorial position would be energetically less favorable due to a nonbinding 1,2-interaction. Importantly, the allylation product of this process contains a versatile vinyl boronate moiety that could be used in a variety of synthetic transformations.

In their initial communication, the group of Morken reported that chiral TADDOL-derived phosporamidite **L1** allowed the preparation of a diboron intermediate in 88% ee, which upon addition of benzaldehyde and oxidative workup, afforded the corresponding β-hydroxyketone in moderate yield and 82% ee (entry 1, Table 29).[71] Further optimization efforts afforded the ligand **L2**, which uniformly gave better levels of enantioselection for the diboron intermediates and excellent transfer of chirality to the β-hydroxyketones. This one-pot diboration/allylboration/oxidation sequence was compatible with alkyl- and aryl-substituted allenes and aldehydes (Table 29).[72] Interestingly, when this protocol was applied with (*R*)-glyceraldehyde ketals and both enantiomers of allene diboration adduct, *syn* or *anti* products were obtained almost exclusively depending on the ligand enantiomer employed. This result shows that the stereoinduction of the chiral allylboron intermediate dominates over the Felkin preference of the chiral aldehyde. Moreover, the synthetic application of the vinylboronate intermediates was illustrated with subsequent transformations like iodo-deboration, proto-deboration, and Suzuki−Miyaura coupling with PhI (Scheme 26).

The reactivity of chiral allyl-vinyl-bisboronates was also used in the synthesis of enantioenriched β-aminoketones by *in situ* trapping of these intermediates with imine derivatives.[73] Eventually, the allylation step did not take place with *N*-substituted silyl, benzyl, and sulfonyl imines, presumably due to the steric demand imposed by the pinacol groups. However, unsubstituted imines were superb substrates in this sequence. Thus, after treating the allene diboration reaction mixture with a silylimine in MeOH (to cleave the N−Si bond), complete consumption of the starting materials was observed in less than 15 min at room temperature (method A). Alternatively, similar results were observed with an α-aminoallylation protocol

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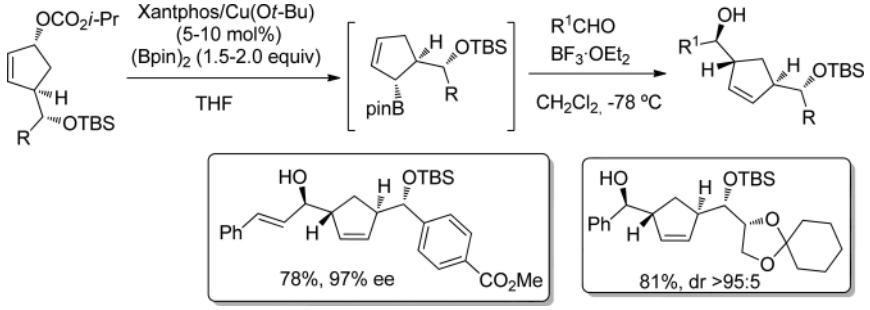
Scheme 24



Scheme 25

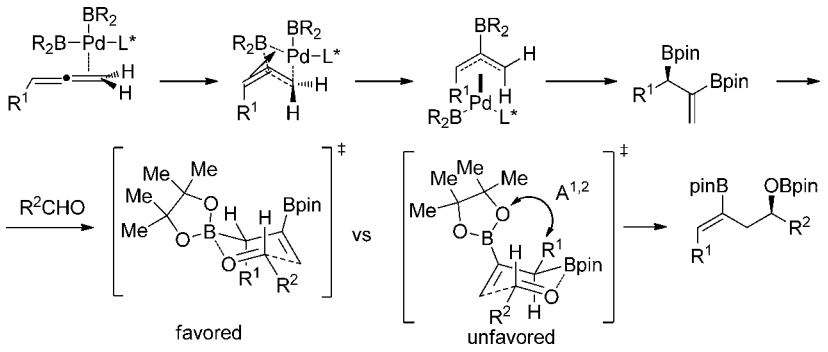
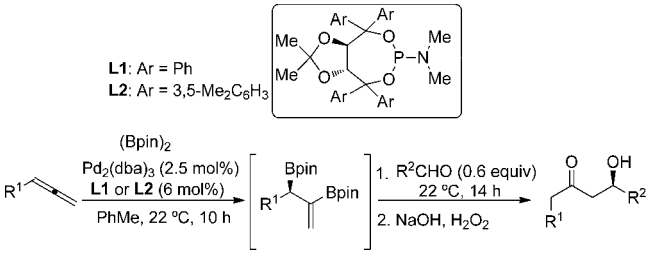


Table 29. Enantioselective Synthesis of β-Hydroxyketones through a Sequential Diboration/Allylboration/Oxidation Reaction



entry	R^1	R^2	yield (%)	e (%)
1	Ph	Ph	56[a] (81)[b]	82[a] (93)[b]
2	Ph	*n*-Pr	85[b]	94[b]
3	Ph	*i*-Pr	89[b]	95[b]
4	$CH_3(CH_2)_9$	*n*-Pr	88[b]	91[b]
5	$CH_3(CH_2)_9$	*i*-Pr	96[b]	91[b]
6	$CH_3(CH_2)_9$	Ph	96[b]	87[b]
7	Cy	*n*-Pr	89[b]	86[b]
8	Cy	*i*-Pr	83[b]	87[b]
9	Cy	Ph	83[b]	84[b]

[a] **L1** was used. [b] **L2** was used.

(method B) upon adding an aldehyde and solid ammonium acetate. After protection with Ac_2O and oxidation with H_2O_2, the corresponding β-aminoketones were obtained in similar yields and enantioselectivities using either method A or method B (Table 30). The levels of chirality transfer were excellent for all substrates examined (>98% ee), being slightly diminished for α,β-unsaturated imines and 2-phenethyl-allene. The enantioselectity in the diboration step was also excellent for all allenes used, being the cyclohexyl allene the poorest sustrate in this regard (93% ee).

The formation of chiral η^3-allyl metal complexes from 1,3-dienes and their reactivity were also examined by the group of Morken.[74] It was found that the catalyst prepared from $Pt_2(dba)_3$ and ligand **L2** allowed the 1,4-addition of bis(pinacolato)diboron for a range of conjugate dienes in good yields and high enantioselectivities. The resulting allylic diboronates were precursors of chiral 2-buten-1,4-diols, but they could also be used in the stereoselective allylation of carbonyl compounds. Thus, when benzaldehyde was added to an unquenched platinum-catalyzed diboration reaction of (*E*)-decane-1,3-diene with $(Bpin)_2$ in the presence of ligand **L2**, an oxidative workup after 12 h of reaction furnished a single isomer with near-perfect chirality transfer. The product structure suggests that this transformation proceeds through a chairlike transition state that minimizes 1,3-interactions (Scheme 27).

A different approach to obtain α-chiral allylboronates was adopted by the group of Ito.[75] In this work, the Cu(I)-catalyzed enantioselective substitution of allylic carbonates with bis(pinacolato)diboron was explored. After some Cu(I)-phosphine chiral catalysts were examined in this reaction, the best results in terms of yields and enantioselection were obtained with the (*R*,*R*)-QuinoxP ligand. Importantly, the enantioselectivity of the reaction was greatly influenced by the *E*/*Z* configuration of the allylic carbonate, being superior for *Z* substrates. The protocol was useful for a range of functionalized *Z*-allylic carbonates, and the synthetic utility of the resulting chiral allylboronates was confirmed in a Lewis acid mediated allylation of benzaldehyde with perfect chiral induction (Scheme 28). A reasonable mechanism that explains the better performance of Z-allylic carbonates is provided by the authors.

Another related approach to enantioenriched α-chiral allylic boronates was the enantioselective Cu(I)-catalyzed S_N2' allylic alkylation of 3-chloropropenylboronates. After checking different chiral ligands and boronate substrates, the group of Hall

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Scheme 26

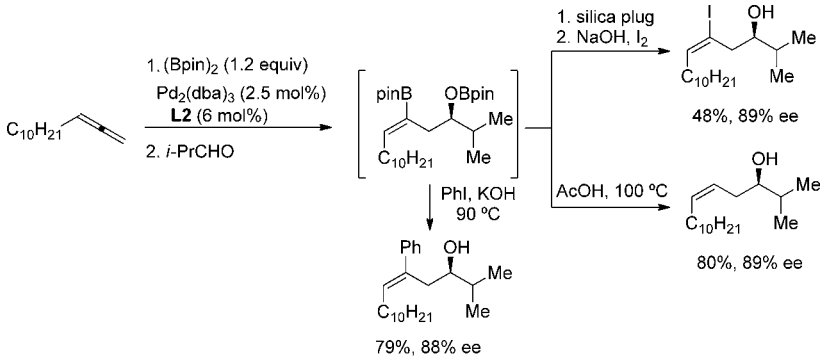
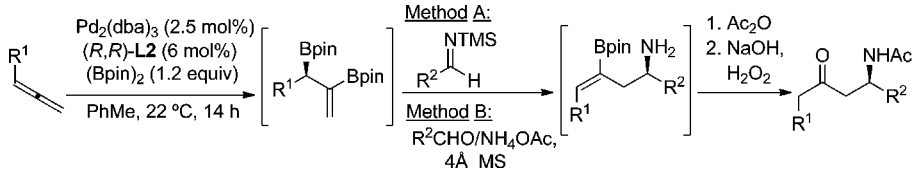
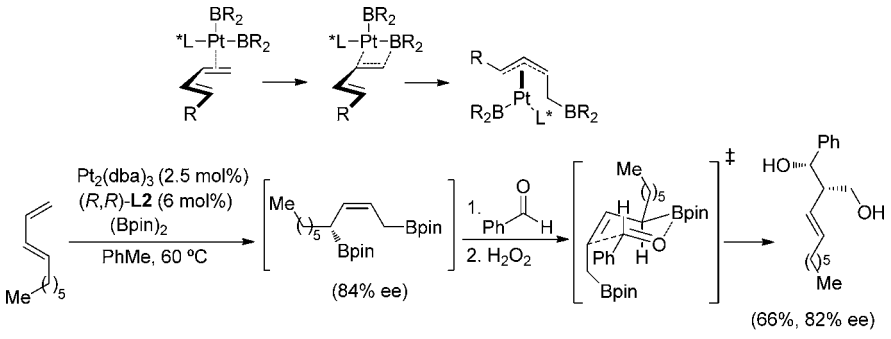


Table 30. Enantioselective Synthesis of β-Aminoketones through a Sequential Diboration/Allylboration/Oxidation Reaction

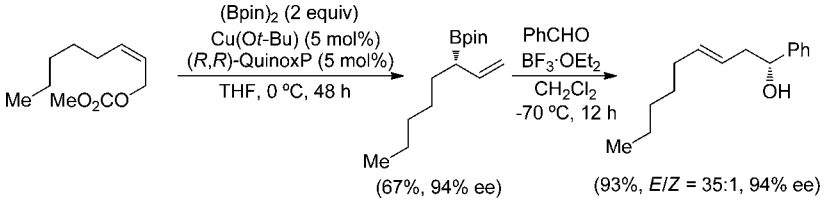


entry	R^1	R^2	method	yield (%)	ee (%)
1	Ph	Ph	A	68	97
2			B	59	96
3	Ph	2-furyl	A	68	97
4			B	69	96
5	Ph	(E)-$CH_3(CH_2)_3CH{=}CH$	A	70	92
6	$PhCH_2CH_2$	Ph	A	64	93
7			B	59	92
8	Cy	Ph	A	46	91
9			B	30	91
10	Cy	(E)-$CH_3(CH_2)_3CH{=}CH$	A	59	87

Scheme 27



Scheme 28



achieved the enantioselective addition of Grignard reagents with high selectivity.[76] The resulting enantioenriched α-substituted allyl boronates were used, without purification, in the Lewis acid promoted addition to aldehydes at low temperature. For all aldehydes used, a near perfect chirality transfer from the allyl boronate was observed. Compared with the corresponding pinacolate, the higher E/Z selectivity may be explained by minimal nonbonded interactions between the pseudoequatorial ethyl group and the boronate group in the transition state. Moreover, it was found that chiral α-substituted

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Scheme 29

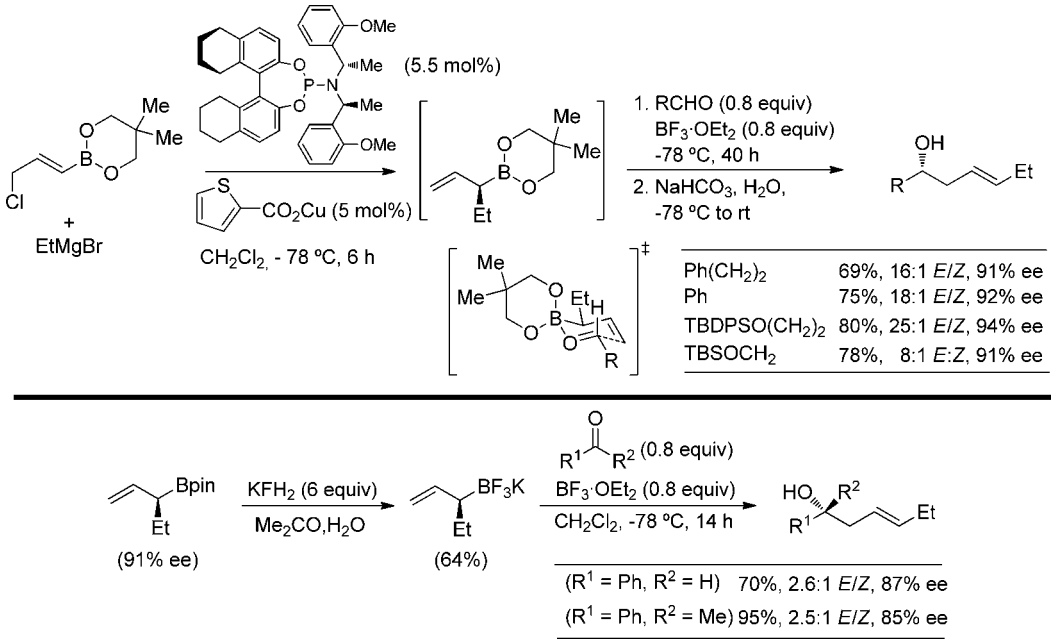
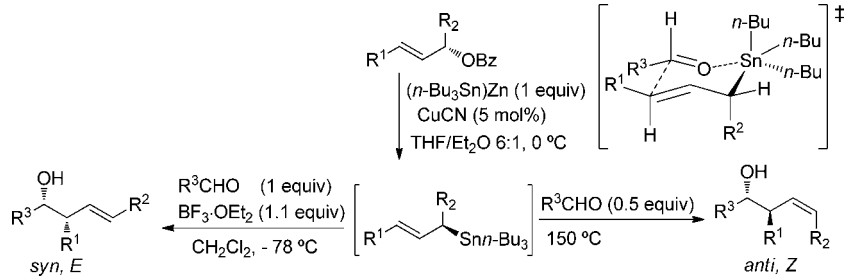


Table 31. Enantiospecific and Diastereoselective Reactions of α-Chiral Allylic Stannanes with Aldehydes under Thermal Conditions or Promoted by BF_3·OEt_2



yield (%)[a]	dr[b]	ee (%)[c]	R^1	R^2	R^3	yield (%)[a]	dr[b]	ee (%)[c]
56	>95:5	100	Ph	Et	Ph	76	90:10	99
62	>95:5	99	Ph	Et	Cy	35	>95:5	93
46	>95:5	98	Ph	Et	*i*-Pr	32	>95:5	83

[a]Isolated yield. [b]Determined by ^{1}H NMR. [c]Determined by chiral HPLC.

allylic boronates could be transformed into the corresponding trifluoroborate salts, which were subsequently added to aldehydes or ketones with moderate *E*/*Z* selectivity and excellent enantioselectivity (Scheme 29).

3.1.4. α-Substituted Allyl Stannanes. The absence of efficient methods to prepare α-chiral allylic stannanes has considerably limited their application in synthetic organic chemistry. Recently, it was found that the substitution of enantioenriched allylic benzoates with $(Bu_3Sn)_2Zn$, in the presence of substoichiometric amounts of CuCN, proceeded cleanly in almost quantitative yield.[77] Importantly, nonsymmetrical allylic benzoates reacted regioselectively at the α-carbon with complete inversion of the absolute configuration. Moreover, when crude (*E*)-allylic stannanes were made to react with aldehydes under thermal conditions, the corresponding *anti*-homoallylic alcohols with *Z*-alkene configuration were obtained in moderate chemical yields but with very good to excellent diastereo- and enantioselectivity (Table 31). Eventually it was found that the allylic transposition was slow at 150 °C, and the stereochemistry observed was rationalized using a cyclic transition state with the substituent at the α-carbon atom in an axial position. On the other hand, when the addition to aldehydes was promoted by BF_3·OEt_2, the reaction was conducted at low temperature and the corresponding *syn*,*E*-homoallylic alcohols were obtained with excellent enantioselectivity and high diastereoselection (Table 31). The relative *syn* configuration of the products is proposed to arise from an acyclic transition state in these Lewis acid promoted allylations.

3.1.5. Allyl Zinc Reagents. The diastereoselective addition of chiral 3,3-disubstituted allyl metal reagents to aldehydes allows the creation of chiral quaternary centers in the allylic position of the corresponding homoallylalcohol. This approach is often limited by tedious preparation of the chiral allyl metal reagents through a multistep sequence and also by the stability of these species that are prone to 1,3-metallotropic rearrangements with the consequent loss of stereochemical information. In this context, the group of Marek developed some straightforward preparations of 3,3-disubstituted allylic zinc reagents with a chiral sulfoxide group at the β-position that enhance the configurational stability of these reagents by

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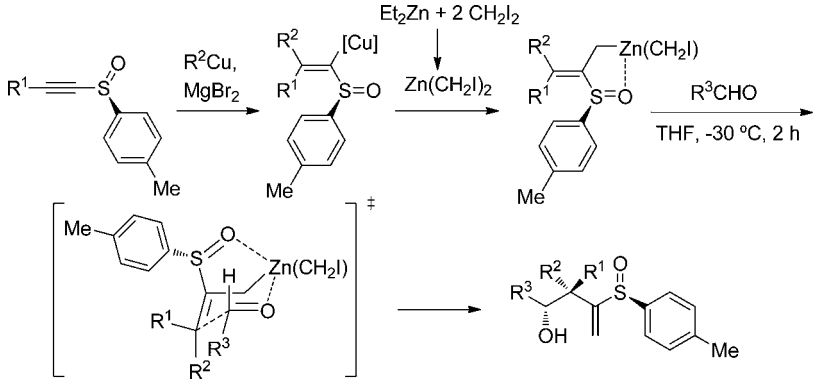
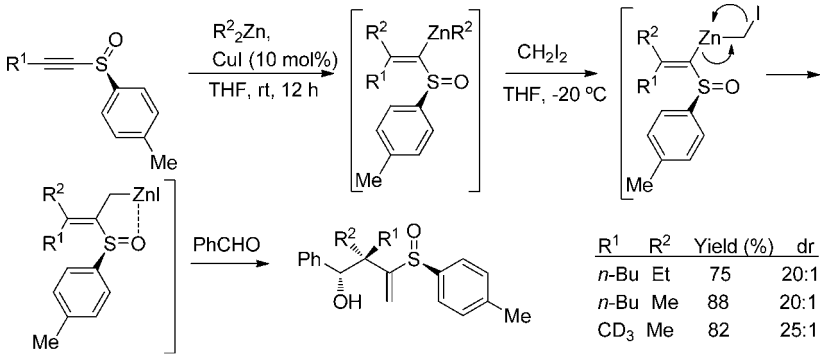
Table 32. Sequential Carbocupration of Chiral Alkynyl Sulfoxides Followed by Homologation and Allylation of Aldehydes



entry	R^1	R^2	R^3	yield (%)	dr
1	*n*-Bu	Et	Ph	78	>99:1
2	*n*-Bu	Et	*n*-Bu	60	>30:1
3	Et	*n*-Bu	Ph	68	>99:1
4	*n*-Bu	Me	Ph	66	>99:1
5	Et	Me	Ph	66	>99:1
6	Et	Me	*n*-Bu	58	>30:1
7	H	Et	Ph	78	80:20

Scheme 30



R^1	R^2	Yield (%)	dr
n-Bu	Et	75	20:1
n-Bu	Me	88	20:1
CD_3	Me	82	25:1

intramolecular chelation. The first method developed was based on the regioselective addition of organocopper reagents to easily prepared (*S*)-1-alkynyl-*p*-tolylsulfoxide, followed by *in situ* homologation of the vinylic copper reagent by addition of preformed bis(iodomethyl)zinc carbenoid in the presence of aldehydes (or aldimines).[78] Importantly, the vinyl copper intermediates as well as the zinc carbenoid were not reactive enough to add to aldehydes; however a faster homologation led to the desired chiral allylic zinc reagents that add instantaneously to the aldehydes. The scope of the reaction was studied using different 1-alkynylsulfoxides, organocopper reagents, and aldehydes obtaining good isolated yields and excellent diastereoselectivities for most of the homoallylic alcohols prepared (Table 32). Interestingly, the worst diastereoselectivity was obtained for 1-unsubstituted alkynylsulfoxide (Table 32, entry 7), which suggests that 1,3-allylic strain of R^1 with the *p*-tolyl group helps to fix the reactive conformation in combination with the intramolecular chelation. The stereochemistry of the products was rationalized using a Zimmerman−Traxler transition state model where one face of the allyl reagent is shielded by the *p*-tolyl group at the sulfur and the bulkier substituent of the aldehyde (R^3) is placed at the pseudoequatorial position.

Alternatively, the same group has found that copper-catalyzed carbozincation of chiral alkynyl sulfoxides proceeds nearly quantitatively with dialkylzinc reagents, facilitating the *in situ* formation of the zinc carbenoid by only adding diiodomethane, which readily rearranges and adds to the present aldehyde (Scheme 30). By use of this improved procedure, it was possible to build a chiral quaternary center with CD_3/CH_3 substituents at the allylic position with excellent diastereoselectivity (25:1).

In a complementary protocol, aldehydes, diethylzinc, and diiodomethane were all added to the *in situ* prepared vinyl copper intermediate, obtaining similar diastereoselectivities as those when preformed bis(iodomethyl)zinc carbenoid is used but slightly better yields (Table 33).[79] These results showed that the zinc carbenoid can be formed *in situ* without any observed addition of diethylzinc to aldehydes. Indeed, a real four-component reaction gave similar good results when alkynyl sulfoxide, benzaldehyde, dialkylzinc, and CH_2I_2 were simultaneously added to the alkyl copper derivative, showing that each component reacts with the right partner in the appropriate order. Moreover, the sulfoxide chiral auxiliary was removed from the products via sulfoxide−lithium exchange with MeLi/*t*-BuLi, followed by acidic hydrolysis without any racemization. Quenching of the same vinyl lithium intermediate

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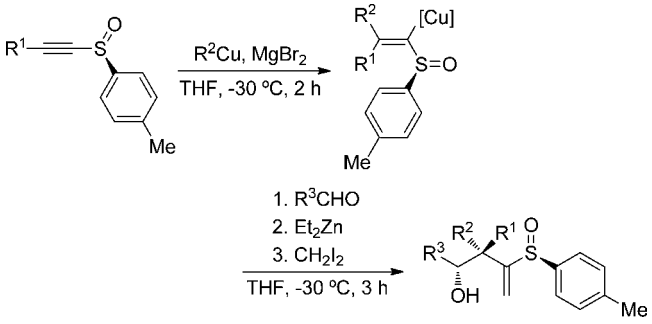
Table 33. Allylation Reaction with *in Situ* Preparation of a Zinc Carbenoid



entry	R^1	R^2	R^3	yield (%)	dr
1	*n*-Bu	Et	Ph	81	99:1
2	$CH_3(CH_2)_5$	Et	Ph	82	99:1
3	$CH_3(CH_2)_5$	Me	Ph	78	99:1
4	Me	Me	4-$(MeO_2C)C_6H_4$	60	97:3
5	*n*-Bu	Et	2-thienyl	83	99:1
6	Me	Me	2-furyl	75	99:1

with iodine allowed the preparation of the corresponding vinyl iodide in good yield.

3.2. Chiral Nucleophiles with Stereogenic Centers in Nontransferred Ligands Bonded to the Metal Center

3.2.1. Allyl Boron Reagents. In the last three decades, allylic boron reagents with a chiral auxiliary on the boron atom have been successfully used for the formation of carbon−carbon bonds with a remarkable transfer of chirality. The popularity of these nontoxic reagents is related to their highly diastereoselective addition to carbonyl compounds and imines that can be easily predicted using a chairlike transition state model. Hoffmann and co-workers reported the first asymmetric allylboration utilizing a camphor-derived auxiliary in 1981.[80] Soon after, isopropyl tartrate was used as a chiral auxiliary for allyl-[81] and crotylborations[82] by Roush and co-workers, and they later found that tartramidoallylboronates provided better selectivity in allylborations than tartrate esters.[83] Simmilarly, the group of Corey performed stereoselective allylations of carbonyl compounds with a chiral diazaborolane.[84] Dialkylallylboranes performed even better than allylboronates in these kinds of stereoselective allylations. In this context, it is worth saying that pinane-derived reagents developed by Brown,[85] as well as other related reagents developed in the group of Masamune,[86] still remain the reagents of choice for many synthetic organic chemists (Figure 4).

3.2.1.1. Allylboronates. Allylboronates are an important class of air-stable reagents used in allylation chemistry. Compared with allylic dialkylboranes, their reactivity is poorer since the electrophilic character of the boron atom is diminished and consequently, the required activation of the carbonyl compound in the transition state is affected. Recently, the groups of Miyaura[87] and Hall[67] have found that in the presence of substoichiometric amounts of certain Lewis acids the addition of allylboronates to carbonyl compounds is significantly accelerated. It is proposed that electrophilic activation of the boron atom through a selective coordination to one of the boronate oxygens is responsible for this reactivity enhancement. The selectivity achieved with $Sc(OTf)_3$ is remarkable since Lewis acids could compete with the boron atom to coordinate the carbonyl oxygen, deactivating the

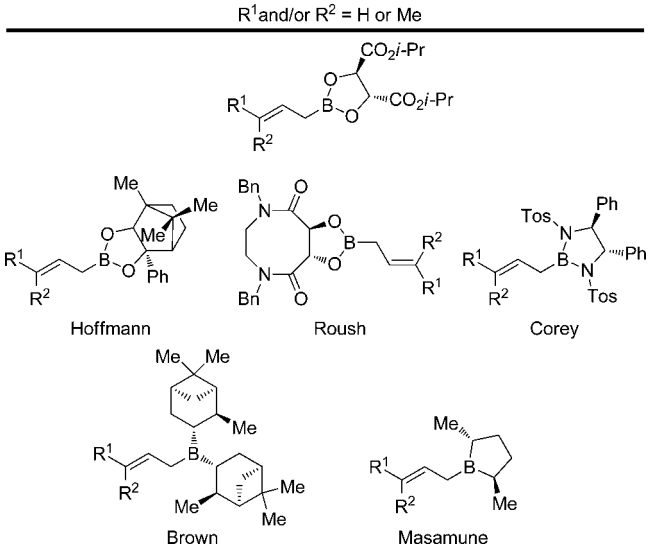


Figure 4. Chiral allyl boron reagents.

substrates in the allylation reaction. Following the track of this finding, the group of Hall revisited the addition of known chiral allyl boronates to aldehydes in the presence of 10 mol % $Sc(OTf)_3$.[88] After solvent optimization and the screening of some 1,2-diols as chiral auxiliaries, it was found that the Hoffmann camphor-based allylboronates **8** gave consistently the highest enantioselectivities under $Sc(OTf)_3$ catalysis in CH_2Cl_2 at −78 °C. Importantly, these allylboronates were the first chiral allyl boron reagents ever reported.[89] However, in the absence of the catalyst, they are unreactive at −78 °C and afford modest enantiomeric excesses (<75%) at higher temperatures.[80a] Under optimized Sc(III)-catalyzed reaction conditions, Hoffmann allyl and methallyl boronates added to aromatic and aliphatic aldehydes furnishing the corresponding homoallylic alcohols in very good yields and excellent enantioselectivities (Table 34, entries 1−8). Moreover, addition of *E*- and *Z*-crotylboronates also gave good yields and good to excellent enantioselectivities (Table 1, entries 9−16). Significantly, it was found that propargylic aldehydes are exceptionally good substrates for this allylation protocol (Table 34, entries 4, 8, 12, and 16).

Since the diastereospecificity of the uncatalyzed reaction is preserved, the allylboration is proposed to proceed via the usual cyclic transition state involving electrophilic activation by metal coordination to a boronate oxygen. From the accepted stereoinduction model based on a $\pi_{phenyl}-\pi^*_{C=O}$ attraction,[90] the proposed transition state (Figure 5) implies Sc(III) coordination to the least hindered lone pair of the pseudoequatorial oxygen, thereby suppressing nO−pB conjugation and maximizing boron−carbonyl bonding. Compared with allyl- and methallylboronates, the corresponding crotyl boronates react slower and provide only low yields for α-branched aldehydes. This limitation can be rationalized on the basis of nonbonding steric interactions between the methyl group (R^1 or R^2) and the aldehyde substituent (R) in the proposed transition state. The worst enantioselectivity was obtained in the addition of the *Z*-crotyl boronate reagent to benzaldehyde (Table 34, entry 13). To explain this result, the authors proposed that the steric bulk of benzaldehyde forced a deformation in the chairlike transition state to minimize a *syn*-pentane interaction, leading to a lower stereoinduction. In terms of practicability, the Hoffmann allylboronates are stable

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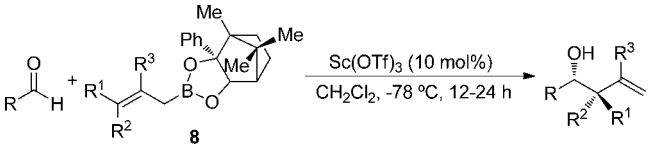
Table 34. Sc(III)-Catalyzed Addition of Hoffmann Allylboronates to Aldehydes



entry	R	R^1	R^2	R^3	yield (%)[a]	ee (%)[b,c]
1	Ph	H	H	H	85	92
2	$PhCH_2CH_2$	H	H	H	64	97
3	$TBDPSOCH_2CH_2$	H	H	H	86	93
4	$CH_3(CH_2)_4C{\equiv}C$	H	H	H	87	95
5[c]	Ph	H	H	Me	64	98
6[c]	$PhCH_2CH_2$	H	H	Me	76	97
7[c]	$TBDPSOCH_2CH_2$	H	H	Me	77	97
8[c]	$CH_3(CH_2)_4C{\equiv}C$	H	H	Me	95	97
9[c]	Ph	Me	H	H	60	97
10[c]	$PhCH_2CH_2$	Me	H	H	71	96
11[c]	$TBDPSOCH_2CH_2$	Me	H	H	63	94
12[c]	$CH_3(CH_2)_4C{\equiv}C$	Me	H	H	78	97
13[c]	Ph	H	Me	H	53	59
14[c]	$PhCH_2CH_2$	H	Me	H	52	96
15[c]	$TBDPSOCH_2CH_2$	H	Me	H	57	96
16[c]	$CH_3(CH_2)_4C{\equiv}C$	H	Me	H	61	95

[a]Isolated yield. [b]Determined by chiral HPLC. [c]The dr was always over 49:1.

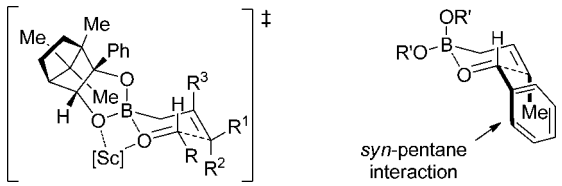


Figure 5. Proposed transition state for Sc(III)-catalyzed addition of allyl boronates to aldehydes.

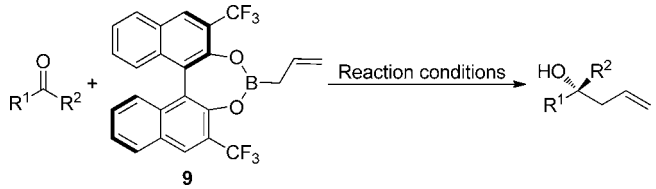
and can be easily handled. The chiral diols used can be prepared in four steps from camphorquinone, which is commercially available in both enantiomeric forms. Moreover, the Sc(III)-catalyzed allylboration procedure works well on a gram scale, and the chiral diol auxiliary can be recovered in good yields when the reaction mixture is quenched with DIBAL-H followed by the addition of 1 M NaOH.

Stereoselective allylation of carbonyl compounds was also achieved using allylboronate derived from 3,3′-disubstituted 2,2′-binaphthols. Chong and co-workers found that aldehydes reacted rapidly with these boronates in THF at −78 °C to give the expected homoallylic alcohols.[91] Among the studied allylboronates, that derived from 3,3′-$(CF_3)_2$BINOL, **9**, proved to be the most efficient one in terms of conversion and stereoselectivity. Aromatic aldehydes worked with **9** nicely (Table 35, entries 1−3), but slightly lower selectivities were found with cinnamaldehyde and cyclohexanecarbaldehyde (Table 35, entries 4 and 5, respectively). Ketones were also allylated with **9**, but the reactions proceeded much more slowly than with aldehydes. Thus, whereas aldehydes usually showed complete reaction with **9** within 5 min at −78 °C, acetophenone was only partially consumed after 6 h at −78 °C to give the expected homoallylic alcohol in 60% yield, although with excellent enantioselectivity. For ketones, yields were improved by allowing the reaction to warm to −40 °C and switching from THF to toluene as solvent, with only a small drop in enantioselectivity (Table 35, entries 5−10).

It was found that the (*R*)-BINOL allylboronate derivative **9** transferred the allyl moiety from the *Re*-face of the carbonyl compound. The sense of asymmetric induction using allylboronate **9** may be explained using a six-membered chair transition state model (Figure 6). In this model, the larger or aryl group occupies an equatorial position in either of two possible transition states.

In order to avoid manipulation and storage of thermal and moisture sensitive chiral allylboronates, Szabó and Sebelius reported a method for the stereoselective allylation of aldehydes using allyl acetates and chiral diboronate reagents **10** in the presence of catalytic amounts of palladium (Table 36).[92] A wide range of functional groups, such as acetate, amido and nitro groups, halogens, nitro, carbonyl, and methoxy groups were tolerated under the optimized reaction conditions (room temperature in a toluene/DMSO, 1:1). The mechanistic

Table 35. Allylation of Carbonyl Compounds with BINOL Boronate Derivative 9



entry	R^1	R^2	reaction conditions	yield (%)[a]	er (*R*/*S*)[b]
1	Ph	H	THF, −78 °C, 1 h	90	98:2
2	4-$MeOC_6H_4$	H	THF, −78 °C, 1 h	93	97:3
3	4-$NO_2C_6H_4$	H	THF, −78 °C, 1 h	96	96:4
4	(*E*)-PhCH=CH	H	THF, −78 °C, 1 h	98	88:12
5	Cy	H	THF, −78 °C, 1 h	90	88:12
6	Ph	Me	PhMe, −78 to −40 °C, 48 h	60	98:2
7	Ph	CH_2Br	PhMe, −78 to −40 °C, 48 h	87	97:3
8	4-$MeOC_6H_4$	Me	PhMe, −78 to −40 °C, 48 h	95	99:1
9	(*E*)-PhCH=CH	Me	PhMe, −78 to −40 °C, 48 h	91	88:12
10	*t*-Bu	Me	PhMe, −78 to −40 °C, 48 h	75	95:5

[a]Isolated yield. [b]Determined by chiral HPLC.

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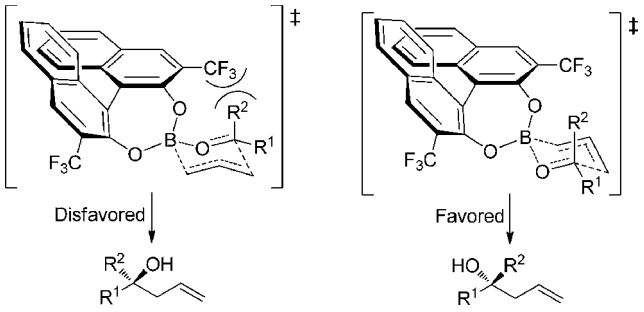
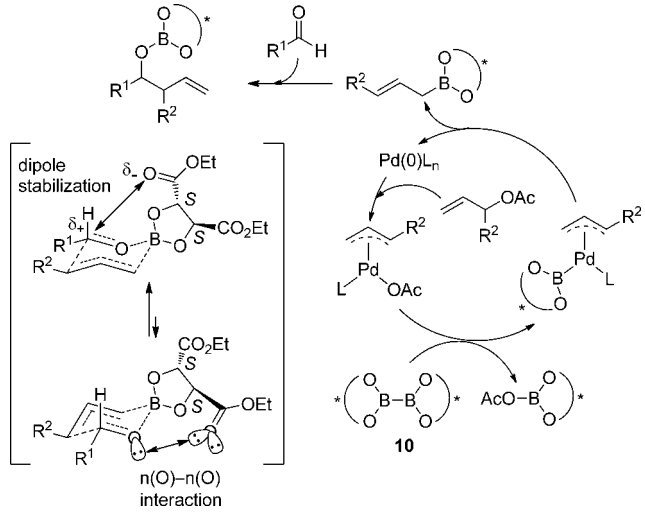


Figure 6. Proposed transition state for the stereoselective allylation of carbonyl compounds with (*R*)-BINOL allylboronate derivative **9**.

studies revealed that the *in situ* generated allylboronates reacted directly with the aldehyde substrates with excellent regioselectivity when α- or γ-substituted allylacetates were involved (Table 36, entries 7−12), providing always the *anti*-branched products (in many cases a single diastereomer was obtained), although with moderate enantiomeric excesses (up to 53% ee). Tartrate-based diborates **10a−c** gave better results in the reaction with 4-nitrobenzaldehyde considering yields and stereoselectivities (Table 36, entries 1−3) compared with tartaramide derivative **10d** or pinane derivative **10e**. These diboronates were found to be ineffective in chiral induction giving a nearly racemic product (Table 36, entries 4 and 5, respectively). Importantly, the ethyl ester derivative **10a** performed even better than the more stable and more expensive isopropyl derivative **10c**. Concerning the stereochemical pathway of the allylation, diborates **10a** and **10c** derived from D-tartrate reacted with 4-nitrobenzaldehyde to give the (*R*)-enantiomer of the homoallylic alcohol as the major product. Opposite configuration was obtained with L-tartrate derivative **10b**.

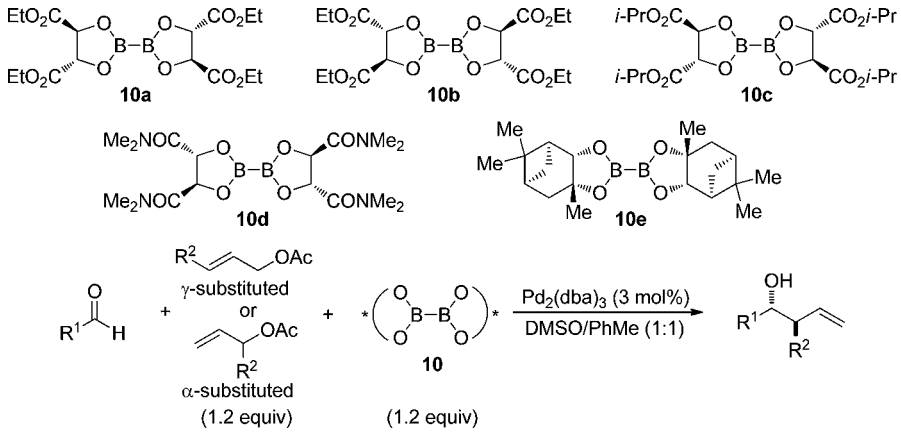
A plausible reaction mechanism for the allylation of aldehydes with allyl acetates and chiral diboronates is shown in Scheme 31. The first step is the oxidative addition of the

Scheme 31



palladium(0) catalyst to the corresponding allyl acetate to form an (η^3-allyl)palladium complex, followed by transmetalation

Table 36. Allylation of Aldehydes by Catalytically Generated Allylboronates



entry	R^1	R^2	diboronate	*T* (°C)	*t* (h)	yield (%)[a]	ee (%)
1	4-$NO_2C_6H_4$	H	**10a**	20	19	83	53
2	4-$NO_2C_6H_4$	H	**10b**	20	22	92	49
3	4-$NO_2C_6H_4$	H	**10c**	20	20	76	45
4	4-$NO_2C_6H_4$	H	**10d**	20	21	73	3
5	4-$NO_2C_6H_4$	H	**10e**	20	21	62	1
6	Ph	H	**10a**	20	63	83	45
7	4-$NO_2C_6H_4$	Me (γ)	**10a**	20	93	64	34
8	Ph	Me (γ)	**10a**	20	96	76	33
9	Ph	Ph (γ)	**10a**	20	21	83	43
10	4-$NO_2C_6H_4$	OAc (α)	**10a**	20	21	67	50
11	Ph	OAc (α)	**10a**	20	21	59	45
12	Cy	Ph (α)	**10a**	20	69	77	53

[a]Isolated yield.

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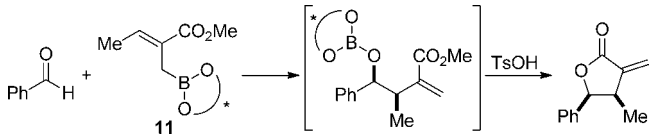
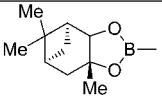
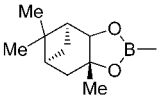
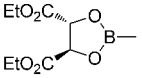
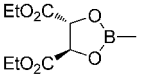
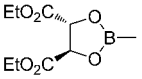
Table 37. Asymmetric Allylboration of Benzaldehyde with Allylboronates Derived via S_N2'-Borylation



Entry	O–B–O	Reaction conditions: Solvent	T (°C)	t (d)	Yield (%)	*cis*/*trans*	ee (%)[a]
1		THF	25	7	75	84:16	10
2		PhMe	100	3	80	83:17	8
3		DMF	25	2	80	94:6	26
4		THF	0	2	75	98:2	22
5		PhMe	0	2	74	98:2	25

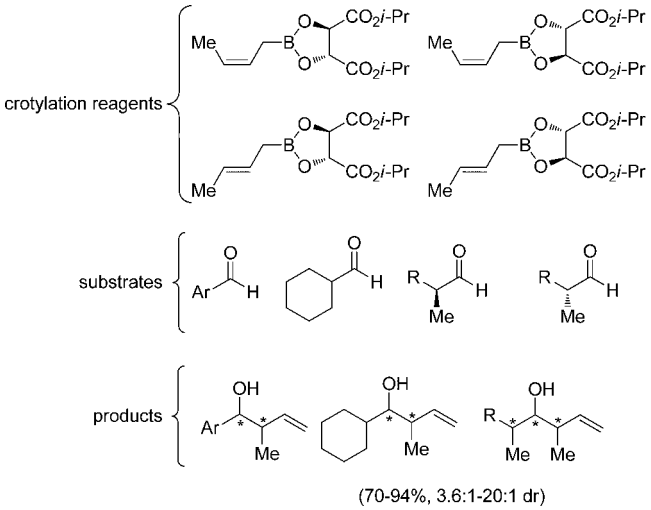
[a]Determined by HPLC; absolute configuration was not determined.

with the diboronate **10** and reductive elimination leading to the allylboronate, which reacts with the aldehyde. This reaction takes place via a six-membered cyclic transition state, in which the substituents occupy equatorial positions, producing the homoallylic alcohols with a high *anti* diastereoselectivity. The face selectivity with diboronate **10a** was explained considering the model proposed by Roush and co-workers.[81,93] According to this model, the addition took place predominantly to the *Re*-face of the aldehyde through a stabilized transition state due to attractive interactions between the carbon (δ^+) of the aldehyde group and the oxygen (δ^-) of an ester group. On the other hand, four-electron interactions induced by the close proximity of the lone-pair electrons in the aldehyde carbonyl and in one of the ester carbonyls of the tartrate unit would destabilize *Si*-face approach (Scheme 31).

The reaction of chiral functionalized allylboronates **11** with benzaldehyde was studied by Ramachandran and co-workers.[94] Starting allylboration reagents were synthesized from allyl acetates and the corresponding chiral diboronate through an S_N2' process. They found that allylboronate **11** derived from pinanediolate reacted very slowly with benzaldehyde at room temperature. The reaction took 7 days to be completed, and after removal of the solvent and further treatment with the *p*-toluenesulfonic acid at 40 °C, a β-substituted α-methylene-γ-butyrolactone was formed as an 84:16 (*cis*/*trans*) diastereomeric mixture (Table 37, entry 1). Reaction time was shortened from 7 to 3 days by performing the reaction in toluene at 100 °C without changes in the stereoselectivity (Table 37, entry 2). Reactions were faster with allylboronate **11** derived from tartrate in different solvents at 25 and 0 °C, a β-substituted α-methylene-γ-butyrolactone being isolated with high diastereoselectivity in all cases (Table 37, entries 3–5). Unfortunately, enantiomeric excesses were always modest, which was attributed to interference from copper salts present in the reaction medium, which were involved in the formation of the chiral functionalized allylboronate **11** via the S_N2' process displacement.

Stereoselective crotylation reactions at low temperature have also been achieved using flow-chemistry technology by Ley and co-workers.[95] They developed reliable flow procedures for the Roush crotylation[82,96] with chiral (*Z*)- and (*E*)-crotylboronates derived from D- and L-tartrate (Chart 1). Taking advantage of this technology, complex target molecules could be accessed in a much shorter time period than by using the corresponding batch reactions.

Chart 1



Hoffmann camphor-derived allylboronate[80] was also used by Kobayashi and co-workers in the enantioselective α-aminoallylation of benzaldehyde through a three-component reaction. The homoallylic amine 4-amino-4-phenylbut-1-eno was obtained with moderate enantioselectivity and high yield (Scheme 32).[20]

3.2.1.2. Allyl Boranes. As previously mentioned, dialkylallylboranes derived from pinane developed by Brown[85] performed

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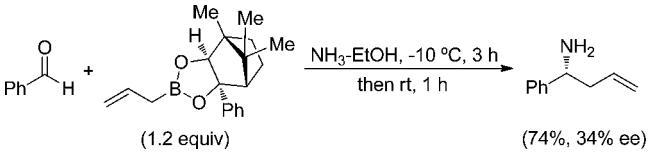
Scheme 32

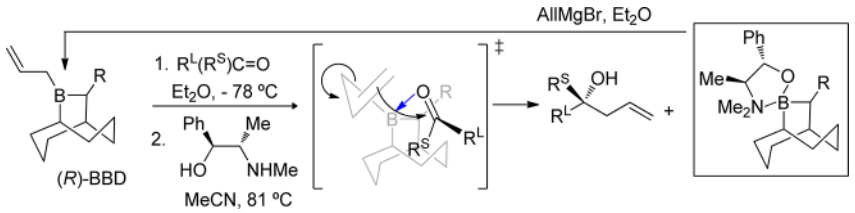


extremely well in the stereoselective allylboration of aldehydes. More recently the group of Soderquist has developed another class of highly efficient and robust dialkylboranes. Both enantiomeric borabicyclo[3.3.2]decanes (BBDs) are easily prepared in only three steps from *B*-MeO-9-BBN using chiral pseudoephedrine as resolving agent. A common limitation to the use of dialkylborane reagents is their poor air stability. Remarkably, the resulting *B*-allyl-10-TMS-9-BBDs are stable and can be storage under N_2 at 25 °C for weeks. Moreover, the reagents can be *in situ* generated quantitatively by simply adding AllMgBr to the corresponding pseudoephedrine-*N*,*O*-boronates, which are air-stable and can be stored indefinitely.[97] The addition of chiral *B*-allyl-10-TMS-9-BBDs to aliphatic or aromatic aldehydes takes place in less than 3 h at −78 °C to furnish the desired homoallyl alcohols in good yields with excellent enantioselection (Table 38, entries 1−4).[97] Importantly, the protocol allows an efficient recovery (68−80%) of the chiral allyl reagent by quenching the reaction with pseudoephedrine and treating the corresponding *N*,*O*-boronate with AllMgBr. The addition of these chiral allyl reagents to ketones was very slow and far less selective, probably because the bulky TMS group makes the chiral pocket of the reagent too small to accommodate groups larger than hydrogen. However, similar 10-Ph derivatives react rapidly with ketones to obtain the homoallylalcohols in very good yields and outstanding enantioselection (Table 38, entries 5−8).[98] Particulary noteworthy is the excellent enantioselectivity obtained in the addition to ketones with groups of similar steric demand (Table 38, entry 8). As occurs for aldehydes, quenching the reaction with pseudoephedrine allows the recovery of the chiral reagent. Alternatively, an oxidative workup procedure can be used. Importantly, the absolute stereochemistry of the products can be easily predicted using a model proposed by the authors that is supported by MM calculations. The model suggests that 10-(*R*)-substituted 9-BBDs define a chiral pocket that accommodates the smaller group when it is coordinated to the carbonyl compound in the pretransition state, favoring the allylation over the *Re*-face.

From optically pure *B*-MeO-10-TMS-9-BBDs, all four possible stereoisomers of *B*-crotyl-10-TMS-9-BBDs were efficiently prepared using a procedure similar to the one used by Brown in the preparation of his terpene-derived crotyl boranes. Eventually it was determined by NMR that the *E* and *Z* isomer slowly isomerize at 25 °C via 1,3-boratropic rearrangement. Given their configurational instability and high reactivity, they were generated and used immediately. The crotylation of representative aldehydes took place with high stereospecificity at −78 °C, and highly enantioenriched *β*-methyl homoallylic alcohols were obtained in good yields (Table 39).[97] Importantly, a judicious choice of the chiral crotyl borane allows the preparation of any of the four possible stereoisomers of the products in <3 h. The stereochemistry of the products can be also anticipated using the same predicted model mentioned above.

Soderquist and co-workers studied also the reactivity of new mixed borabicyclodecane-derived 1,3-diborylpropenes. These compounds were found to function as the equivalent of 1,1-bimetallic allylic reagents, adding sequentially first to ketones and second to aldehydes with total stereoselectivity.[99] They were prepared by hydroboration, for instance, of the corresponding *B*-allenyl-10-TMS-9-BBD with 10-Ph-9-BBD as depicted in Scheme 33, leading to a ∼60:40 mixture of regioisomeric *trans*-1,3-diborylpropene adducts, which rapidly interconverted by consecutive 1,3-borotropic rearrangements. It was found that the 10-Ph-9-BBD moiety underwent 1,3-borotropic shifts much faster than its 10-TMS counterpart, and consequently, the reaction of this mixture of regioisomers with a ketone took place chemoselectively with the 10-Ph-9-BBD component. After that, the steric congestion in the resulting homoallylic boronate forced a 1,3-borotropic rearrangement, leading to a more stable *trans*-crotyl borane, which did not react with ketones. Only after addition of an aldehyde, a second allylboration occurred with total stereoselectivity, fixing, consequently, the two new stereogenic centers in the resulting diols. In summary, this methodology allowed the synthesis of highly functionalized molecules with up to three consecutive

Table 38. Allylation of Aldehydes and Ketones with Chiral *B*-Allyl-BBDs



entry	R	R^L	R^S	yield (%)	ee (%)
1	TMS	*n*-Pr	H	79	≥99
2	TMS	*t*-Bu	H	79	≥98
3	TMS	4-$MeOC_6H_4$	H	90	96
4	TMS	4-$NO_2C_6H_4$	H	87	97
5	Ph	Ph	Me	92	96
6	Ph	*t*-Bu	Me	70	99
7[a]	Ph	*i*-Pr	Me	74	92
8[a]	Ph	Et	Me	80	87

[a](*S*)-BBD was used as reagent.

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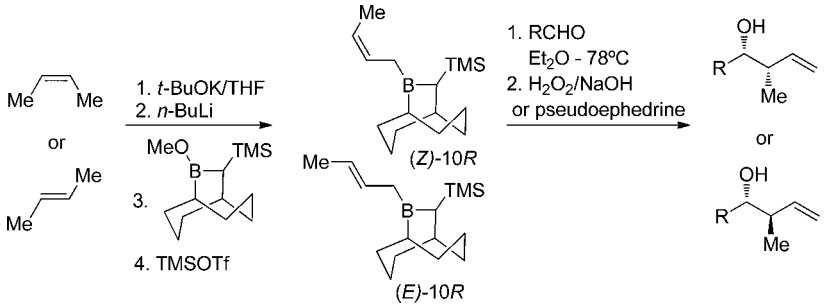
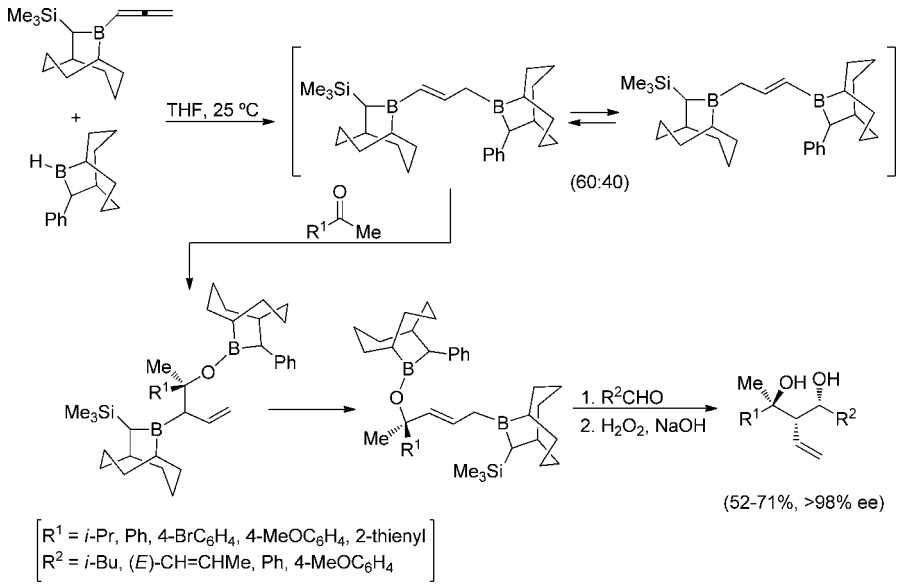
Table 39. Crotylation of Aldehydes with Chiral *B*-Allyl-10-TMS-9-BBDs



entry	R	reagent	yield (%)	dr *syn*/*anti*	ee (%)
1	Me	(*Z*)-10*R*	68	≥98:2	95
2	*n*-Pr	(*Z*)-10*R*	91	≥98:2	94
3	*n*-Pr	(*E*)-10*R*	94	2:98	96
4	*t*-Bu	(*E*)-10*R*	69	2:98	99
5	Ph	(*Z*)-10*S*	72	≥98:2	98
6	Ph	(*E*)-10*S*	82	2:98	97

Scheme 33



stereogenic centers in a single operation. Amino alcohols were also accessed following the here mentioned strategy by combining ketimines and aldehydes or ketones and aldimines.

Soto-Cairoli and Soderquist reported on the stereoselective allylation of enantiomerically pure *N*-triisopropylsilyl-α-amino aldehydes with both enantiomeric *B*-allyl-10-trimethylsilyl-9-borabicyclo[3.3.2]decanes (*B*-allyl-10-TMS-9-BBDs).[100] They found that the reaction proceeded cleanly at −78 °C and exhibited complete reagent control. Face selectivity is exclusively governed by the configuration of the *B*-allyl-10-TMS-9-BBD, independently of the configuration of the substrate (Table 40, compare entries 1 and 2, 3 and 4, 5 and 6, and 7 and 8). After an oxidative workup, an HOAc-mediated *N*−*O*-TIPS rearrangement occurred, the corresponding stable *O*-TIPS-protected α-amino alcohol derivatives being isolated in 60−83% yields, in >96% de, and >99% ee (Table 40). Through this methodology, it is possible to predict the configuration of the reaction products by choosing the appropriate couple of *B*-allyl-10-TMS-9-BBD and *N*-triisopropylsilyl-α-amino aldehyde, without being affected by match−mismatch considerantions.

Chiral planar ferrocene-derived allylboranes **12** and **13** have been used for the stereoselective allylation of ketones. These compounds were accessed in enantiomerically pure form upon resolution of the corresponding methoxyboranes with *N*-methylpseudoephedrine. Surprisingly, Jäkle and co-workers found that allylation using chiral planar boranes **12** and **13** proceeded with poor stereoselectivity in the case of aldehydes (8% ee for benzaldehyde). By contrast, allylation of ketones in dichloromethane at room temperature led to homoallylic alcohols in up to 80% ee after 30 min (Table 41).[101] The enantioselectivity was affected by substituents at the tin atom. Thus, allylation of acetophenone with (S_p)-**12** produced the corresponding homoallylic alcohol in 60% ee, and in 80% ee, if (R_p)-**13** was used as the allylation reagent (Table 41, entries 2 and 3). Compound (S_p)-**12**, with a chlorine substituent attached to tin, can easily extend its coordination sphere from tetrahedral to trigonal bipyramidal through coordination of a nucleophile *trans* to chlorine, leading to a poorer stereoselectivity.

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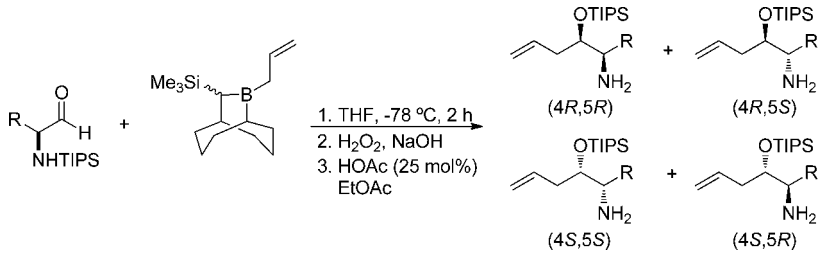
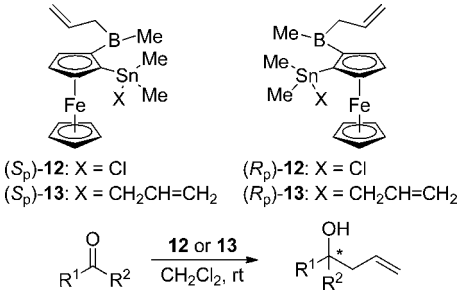
Table 40. Asymmetric Allylboration of Amino Aldehydes with *B*-Allyl-10-TMS-9-BBDs



entry	allyl borane config	R (config)	*syn*/*anti*[a]	ee (%)[b]	yield (%)[c]	abs config
1	(*S*)	*i*-Bu (*S*)	>99:1	99	83	4*S*,5*S*
2	(*S*)	*i*-Bu (*R*)	<1:99	99	73	4*S*,5*R*
3	(*R*)	*i*-Bu (*R*)	>99:1	99	83	4*R*,5*R*
4	(*R*)	*i*-Bu (*S*)	<1:99	99	66	4*R*,5*S*
5	(*S*)	*n*-Pr (*S*)	99:1	99	71	4*S*,5*S*
6	(*S*)	*n*-Pr (*R*)	1:99	99	62	4*S*,5*R*
7	(*R*)	*n*-Pr (*R*)	99:1	99	70	4*R*,5*R*
8	(*R*)	*n*-Pr (*S*)	1:99	99	64	4*R*,5*S*
9	(*S*)	$MeS(CH_2)_2$ (*S*)	98:2	99	80	4*S*,5*S*
10	(*R*)	$MeS(CH_2)_2$ (*S*)	2:98	99	60	4*S*,5*R*
11	(*S*)	$BnOCH_2$ (*S*)	98:2	99	76	4*S*,5*S*
12	(*R*)	$BnOCH_2$ (*S*)	2:98	99	70	4*S*,5*R*

[a]Determined by ^{13}C NMR analysis. [b]Calculated by examination of the Mosher amide derivatives. [c]Isolated yield.

Table 41. Allylboration of Ketones with Chiral Planar Ferrocenylallylboranes



entry	R^1	R^2	chiral reagent	yield (%)[a]	*S*/*R*[b]
1	$CH_3(CH_2)_4$	Me	(R_p)-**12**	80	70:30
2	Ph	Me	(S_p)-**12**	96	20:80
3	Ph	Me	(R_p)-**13**	86	90:10
4	Ph	$CH_3(CH_2)_4$	(R_p)-**13**	97	90:10

[a]Determined by GC. [b]Determined by chiral GC.

Chiral allylboron reagents, such as *B*-allylbis(isopinocampheyl)borane (^{d}Ipc$_2$B-allyl), *B*-allylbis(2-isocaranyl)borane (2-^{l}Icr$_2$B-allyl) and (−)-*B*-allyl-(diisopropyltartrate)boronate (^{l}DIPT-B-allyl) have also been used by Waldmann and co-workers for the stereoselective allylation of aldehydes on solid support.[102] The immobilized aldehyde resulting from esterification of a polystyrene resin and undec-10-enoic acid, followed by ozonolysis of the double bond, was chosen as a model compound. The reactions of this aldehyde with 5 equiv of the corresponding chiral allylborane were performed in THF at temperatures ranging from −78 to 0 °C, and after oxidative workup in a buffered medium, followed by release from the resin by treatment with sodium methoxide, the expected homoallylic alcohols were isolated in high yields and good diastereoselectivities (Table 42, entries 1−3). The crotylation of aldehydes on solid support employing (*Z*)- and (*E*)-^{d}Ipc$_2$B-crotyl also proceeded with very high levels of stereoinduction and in high yields (Table 42, entries 4−7). This methodology was applied to the synthesis of collections of γ- and δ-lactones.

Based on a previous report by Brown regarding the diastereo- and enantioselective synthesis of *anti*-1,2-diols by a sequence involving the hydroboration of an allenylboronate with bis(isopinocampheyl)borane (Ipc$_2$BH),[103] Roush and co-workers found that the hydroboration of 1-methylallenylboronate with bis(isopinocampheyl)borane (^{d}Ipc$_2$BH) in toluene at 0 °C for 2 h, followed by aldehyde allylboration at −78 °C (4 h) and oxidative workup, provided, surprisingly, the synthesis of 1,2-*syn*-diols, bearing a quaternary center in 69−82% yield with >20:1 diastereoselectivity and 85−92% ee (Table 43, entries 1−4).[104] In order to explain this unexpected experimental result and assuming that the allylboration reaction proceeded by way of the usual chairlike transition state, it seemed that the intermediate initially produced in the hydroboration of the 1-methylallenylboronate is a γ-boryl-(*Z*)-allylic borane (kinetic product) and that this intermediate did not isomerize at 0 °C to the most stable γ-boryl-(*E*)-allylic borane (Table 43). Importantly, *anti*-1,2-diols were the major component of the reaction mixture when the hydroboration of 1-methylallenylboronate was performed at 85 °C in toluene for 1.5 h, followed by addition of the aldehyde at −78 °C. Under these reaction conditions, the γ-boryl-(*E*)-allylic borane (thermodynamic product) is formed upon isomerization of the (*Z*)-isomer and reacted then with the aldehyde. In all cases, the 1,2-*anti*-diols were obtained in good yield in a highly diastereoselective fashion (Table 43, entries 5−8).

In general, conventional substituted allylmetal chemistry provided homoallylic alcohols with a terminal olefin unit. However, Roush and co-workers reported the synthesis of (*E*)-δ-stannyl homoallylic alcohols by means of a stannylallylboration reaction of aldehydes.[105] Thus, treatment of allenyltributylstannane with ^{d}Ipc$_2$BH in diethyl ether at temperatures ranging from −40 to −20 °C, followed by treatment of the resulting allylborane with a wide range of aldehydes at −78 °C

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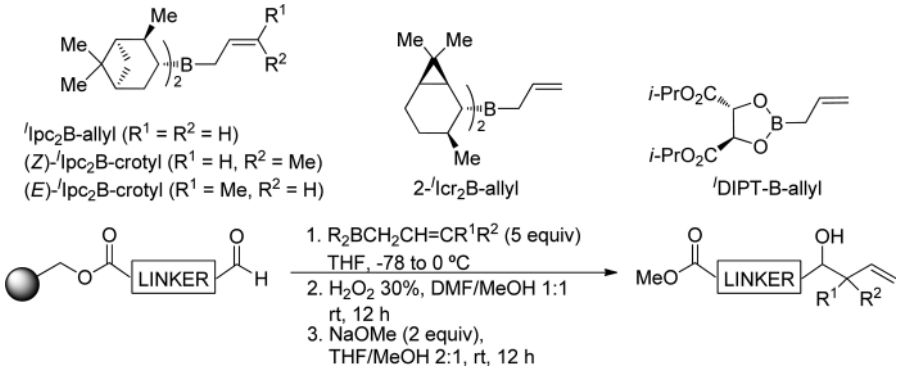
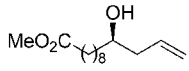
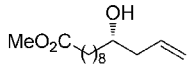
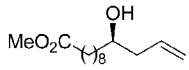
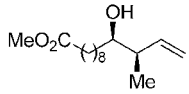
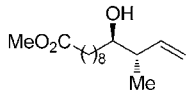
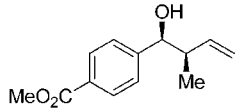
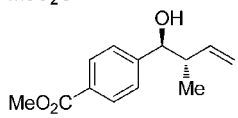
Table 42. Stereoselective Allylation of Aldehydes on Solid Support



Entry	Linker	Allylborane	Product	Yield (%)[a]	dr (er)[b]
1	$(CH_2)_8$	^{d}Ipc$_2$B-allyl		71	(94.5:5.5)
2	$(CH_2)_8$	2-^{i}Icr$_2$B-allyl		95	(90.5:9.5)
3	$(CH_2)_8$	^{i}DIPT-B-allyl		95	(88.5:11.5)
4	$(CH_2)_8$	(*Z*)-^{d}Ipc$_2$B-crotyl		78	96 (95:5):5
5	$(CH_2)_8$	(*E*)-^{d}Ipc$_2$B-crotyl		95	93 (88:12):7
6	1,4-C_6H_4	(*Z*)-^{d}Ipc$_2$B-crotyl		94	96 (94:6):4
7	1,4-C_6H_4	(*E*)-^{d}Ipc$_2$B-crotyl		91	96 (83:17):4

[a]Yield of isolated product. [b]Diastereomer ratios were determined by ^{1}H NMR analysis and enantiomer ratios of the main diastereomers by Mosher ester derivatization.

led to the formation of homoallylic alcohols in 51−78% yield and 92% to >95% ee (Table 44). The configuration of the reaction products was unambiguously assigned. The olefin geometry was always *E*; meanwhile the allylic transfer to the carbonyl group took place from the *Si*-face, which was fully consistent with the normal sense of asymmetric induction by the -^{d}BIpc$_2$ unit. Importantly, *Z*-olefin isomers as well as other possible isomeric homoallylic alcohols were not detected in any of the experiments performed under these conditions. This methodology is of great synthetic value since the here prepared homoallylic alcohols with a functionalized olefin unit are suitable for use in subsequent C−C bond formations.

Regarding this allylation mechanism, it was proposed that the reaction of allenyltributylstannane with ^{d}Ipc$_2$BH would provide (*Z*)-γ-stannylallylborane as the kinetic product (Scheme 34). After that, this allylborane would undergo a kinetically controlled and highly diastereoselective 1,3-boratropic shift at temperatures below −20 °C to give the (*S*)-α-stannylallylborane, which upon reaction with the aldehyde at −78 °C would provide the (*E*)-δ-stannyl homoallylic alcohols via a chairlike transition state, with the α-stannyl unit in a pseudoequatorial position. It was assumed that isomeric (*R*)-α-stannylallylborane resulting from the other possible 1,3-boratropic shift is not formed or, if so, it did not react with the aldehyde, since the (*E*)-δ-stannyl homoallylic alcohols that resulted from *Re*-addition (opposite sense of asymmetric induction by the -^{d}BIpc$_2$ unit) and the (*Z*)-δ-stannyl derivatives were not formed (Scheme 34).

3.2.2. Allyl Silanes. *3.2.2.1. Allylation of Carbonyl Compounds.* Leighton and co-workers reported in 2002 on the uncatalyzed allylation of aldehydes at room temperature with a five-membered sylacycle allylsilane derived from pinacol and allyltrichlorosilane.[106] Since then, a family of other related chiral allylating reagents derived from 1,2-diamines and amino alcohols has been developed in order to pursuit allylations in a stereoselective fashion. Whereas reagent (*S,S*)-**14a**, easily accessible from pseudoephedrine, reacted with aliphatic aldehydes in toluene at −10 °C to give good enantioselectivities of the corresponding homoallylic alcohols (see, for instance, Table 45, entry 1), it performed poorly with aromatic and conjugated aldehydes.[106] On the other hand, the N-benzylated diamine derivative (*R,R*)-**15** provided improved enantioselectivity but also low reactivity upon reaction with 3-phenylpropanal under rather similar reaction conditions (Table 45,

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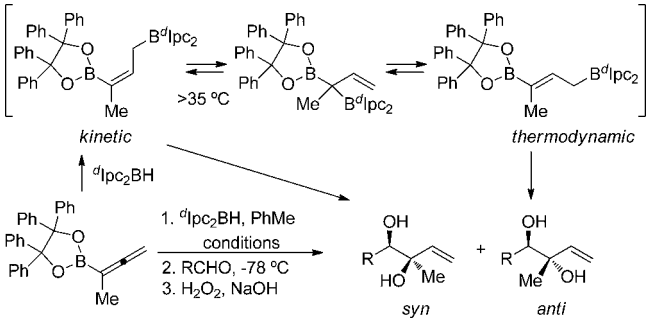
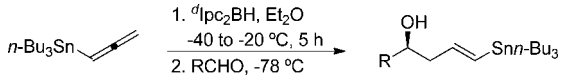
Table 43. Synthesis of 1,2-*syn*- and -*anti*-Diols by Sequential Selective Allylboration-Oxidation of Aldehydes



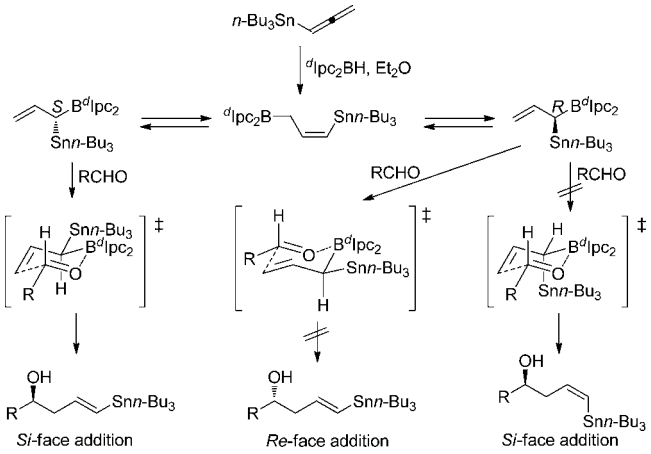
entry	R	conditions	yield (%)	*syn*/*anti*	ee (%)
1	$PhCH_2CH_2$	0 °C, 2 h	72	20:1	92
2	$PhCH_2$	0 °C, 2 h	71	20:1	85
3	Ph	0 °C, 2 h	82	20:1	86
4	$BnO(CH_2)_2$	0 °C, 2 h	69	20:1	89
5	$PhCH_2CH_2$	85 °C, 1.5 h	76	1:17	89
6	$PhCH_2$	85 °C, 1.5 h	67	1:12	87
7	Ph	85 °C, 1.5 h	76	1:15	84
8	$BnO(CH_2)_2$	85 °C, 1.5 h	66	1:14	85

Table 44. Synthesis of δ-Stannyl Homoallylic Alcohols by Hydroboration of Aldehydes with a Double-Chiral Allylborane



entry	R	yield (%)	ee (%)
1	$PhCH_2CH_2$	64	>95
2	$PhCH_2$	67	>95
3	Ph	78	93
4	$BnO(CH_2)_2$	68	>95
5	$BnOCH_2$	71	>95
6	(*E*)-PhCH=CH	73	>95
7	Cy	55	92
8	*t*-Bu	51	94

Scheme 34



entry 2).[106] Fortunately, the bis-(*p*-bromobenzyl)diamine derivative (*R*,*R*)-**16a** was the most effective in terms of yield and enantioselectivity (Table 45, entry 3). The scope of the allylation reaction with (*R*,*R*)-**16a** was examined with a range of aliphatic, aromatic, and α,β-unsaturated aldehydes, and conditions were carefully optimized to maximize yield and enantioselectivity (Table 45, entries 3−10).[107] Importantly, the reactions were only slightly less selective at room temperature, but the yields were significantly lower because of partial decomposition of (*R*,*R*)-**16a**. Interestingly, the electron-rich aromatic aldehyde *p*-anisaldehyde required 60 h to give a similar yield to that obtained with benzaldehyde (Table 45, entries 8 and 9), meanwhile cinnamaldehyde performed poorly under standard reaction conditions. However, good yield and excellent enantioselectivity were obtained when the reaction was carried out at 8 °C for 72 h (Table 45, entry 10).

It is worth mentioning that silicon became a stereogenic center in reagents **14**−**16**, and they were isolated as a mixture of diastereomers [in a 2:1 ratio for (*S*,*S*)-**14a**], which could not separated. Surprisingly, the observed absolute stereoinduction was identical for reagents **14**−**16**, and allylation occurred preferably to the *Si*-face when benzaldehyde was used, and it was assumed that the same happened to the rest of aldehydes. In order to get insight into the origin of the stereoselectivity in these allylations, Zhang, Houk, and Leighton located the corresponding transition states after computational calculations. They proposed a model based on these transition states with the oxygen located on an apical position of the silicon center and *anti* to one of the nitrogens. There was also an antiperiplanar arrangement of an oxygen lone-pair and the silicon−chlorine bond in the chair transition state, and the chlorine was located with the lone pair *anti* to the lone pair of apical nitrogen (Figure 7).[108]

The enantioselective crotylation of aldehydes has also been achieved with two new crystalline solid and storable reagents, **16b** and **16c**, easily accessible by reaction of the corresponding chiral diamine with known *cis*- and *trans*-crotyltrichlorosilanes, respectively, in the presence of DBU. Both reagents reacted with aliphatic, aromatic, and α,β-unsaturated aldehydes in CH_2Cl_2 at 0 °C for 2 h (method A) to produce the corresponding homoallylic alcohols with excellent diastereoselectivity in most cases (>25:1).[109] Regarding the stereoinduction of these processes, the *cis*-crotyl derivative **16b** yielded the *syn* diastereomer, meanwhile the *anti* one was achieved from the *trans*-isomer **16c**. Yields were generally good for aliphatic aldehydes (Table 46, entries 1 and 2) and somewhat lower with aromatic and α,β-unsaturated aldehydes (Table 46, entries 3−6). However, pivalaldehyde was not successfully crotylated by reagents **16b** and **16c**, establishing that these reagents have limited tolerance for steric hindrance. In order to expand the substrate scope for these crotylations, the influence of different Lewis and Brønsted acids on the process was studied. Leighton and co-workers found that $Sc(OTf)_3$ (method B) provided the best combination of high enantioselectivity and effective catalysis (Table 46, compare entries 1−6 and 7−12).[110] Importantly, the reactions carried out without $Sc(OTf)_3$ required significantly longer reaction times. Taking into account atom economy, it was found that the bis-(*p*-bromobenzyl)-diamine could be readily recovered in high yield after chromatographic purification of the expected reaction product [the column was flushed with EtOAc/hexanes/Et_3N (1:1:0.1)]. When 3-phenylpropanal with (*R*,*R*)-**16b** was used on a 15 mmol scale, the chiral diamine was recovered in 90% yield.[109]

Interestingly, the enantioselective crotylation of α-substituted aldehydes, such as Roche ester-derived aldehydes[111] (Scheme 35), with **16b** and **16c** using the standard conditions in the

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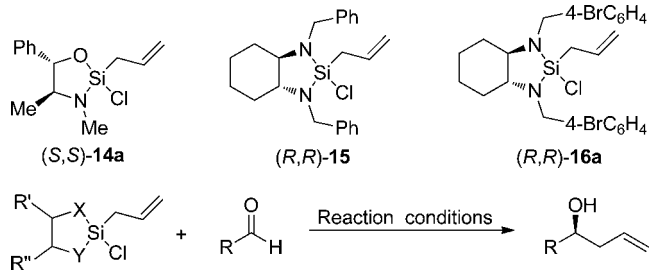
Table 45. Stereoselective Allylation of Aldehydes with Chiral Five-Membered Silacycle Allylsilanes



entry	reagent	R	reaction conditions	yield (%)	ee (%)
1	(*S*,*S*)-**14a**	$PhCH_2CH_2$	PhMe, −10 °C, 2 h	84	88
2	(*R*,*R*)-**15**	$PhCH_2CH_2$	PhMe, rt, 72 h	58	95
3	(*R*,*R*)-**16a**	$PhCH_2CH_2$	CH_2Cl_2, −10 °C, 20 h	93	96
4	(*R*,*R*)-**16a**	Cy	CH_2Cl_2, −10 °C, 20 h	93	96
5	(*R*,*R*)-**16a**	$(CH_3)_2CHCH_2$	CH_2Cl_2, −10 °C, 20 h	80	96
6	(*R*,*R*)-**16a**	$PhCH_2OCH_2CH_2$	CH_2Cl_2, −10 °C, 20 h	87	98
7	(*R*,*R*)-**16a**	*t*-$BuMe_2SiOCH_2$	CH_2Cl_2, −10 °C, 20 h	61	98
8	(*R*,*R*)-**16a**	Ph	CH_2Cl_2, −10 °C, 20 h	69	98
9	(*R*,*R*)-**16a**	4-$MeOC_6H_4$	CH_2Cl_2, −10 °C, 60 h	62	96
10	(*R*,*R*)-**16a**	(*E*)-PhCH═CH	CH_2Cl_2, 8 °C, 72 h	75	96

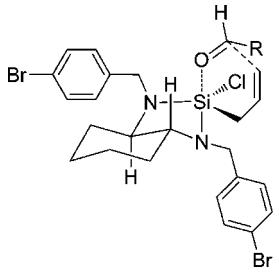
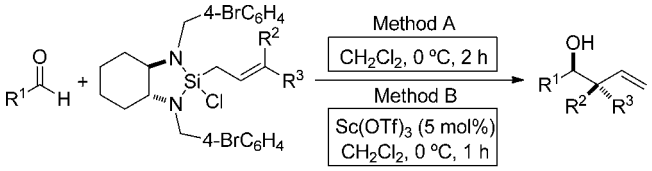


Figure 7. Proposed transition state model for allylation of aldehydes with chiral silacycle allylsilanes.

Table 46. Stereoselective Allylation of Aldehydes with Chiral Crotylsilanes 16b and 16c

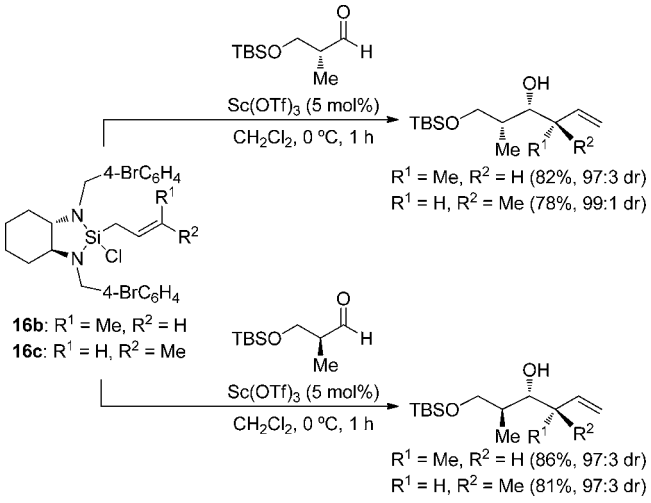


16b: R^2 = Me, R^3 = H
16c: R^2 = H, R^3 = Me

entry	R^1	crotyl silane	method	yield (%)	ee (%)[a]
1	$PhCH_2CH_2$	(*R*,*R*)-**16b**	A	83	97
2	$PhCH_2CH_2$	(*R*,*R*)-**16c**	A	81	98
3	Ph	(*R*,*R*)-**16b**	A	67	95
4	Ph	(*R*,*R*)-**16c**	A	54	93
5	(*E*)-PhCH═CH	(*R*,*R*)-**16b**	A	67	95
6	(*E*)-PhCH═CH	(*R*,*R*)-**16c**	A	52	94
7	$PhCH_2CH_2$	(*S*,*S*)-**16b**	B	96	96
8	$PhCH_2CH_2$	(*S*,*S*)-**16c**	B	96	97
9	Ph	(*S*,*S*)-**16b**	B	94	93
10	Ph	(*S*,*S*)-**16c**	B	96	91
11	(*E*)-PhCH═CH	(*S*,*S*)-**16b**	B	96	95
12	(*E*)-PhCH═CH	(*S*,*S*)-**16c**	B	93	91

[a]Determined by chiral GC and HPLC.

Scheme 35



presence of $Sc(OTf)_3$ outlined above occurred with excellent diastereoselectivity (>97:3 dr) resulting exclusively from a reagent control, independently of the configuration of α-substituted aldehyde (substrate control).[110]

The stereoselective allylation of ketones with five-membered silacycle allylsilane derived from 1,2-diamines and amino alcohols was also studied by Leighton. It was found that the chiral allylation reagent, either (*S*,*S*)-**14a** or (*R*,*R*)-**16a**, did not react with acetophenone under a variety of conditions. On the basis of the success of the acylhydrazone allylations with these reagents (which was attributed both to their intramolecular reaction pathway and to the presumably significant increase in Lewis acidity of the silane because of the protonation of the amino group[112]), Leighton and co-workers reasoned that a suitable nucleophile attached to the ketone substrates might mechanistically mimic the acylhydrazones and proposed 2′-hydroxyacetophenone as a model compound that accomplished these requirements. The reaction of (*S*,*S*)-**14a** with 2′-hydroxyacetophenone failed to give the allylated product. By contrast, (*R*,*R*)-**16a** produced the expected homoallylic tertiary

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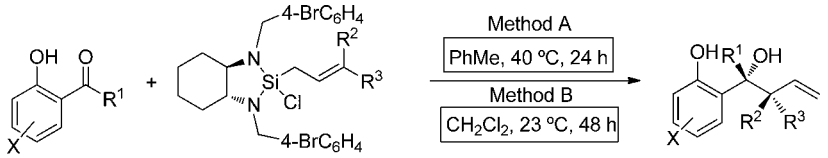
Table 47. Enantioselective Allylation of 2′-Hydroxyphenylketones



(*R*,*R*)-**16a**: $R^2 = R^3 = H$
(*R*,*R*)-**16b**: $R^2 = Me$, $R^3 = H$
(*R*,*R*)-**16c**: $R^2 = H$, $R^3 = Me$

entry	R^1	X	chiral silane	method	yield (%)	ee (%)
1	Me	H	(*R*,*R*)-**16a**	A	75	83
2	Me	5-Cl	(*R*,*R*)-**16a**	A	65	81
3	Me	5-MeO	(*R*,*R*)-**16a**	A	64	82
4[a]	*i*-Pr	H	(*R*,*R*)-**16a**	A	67	88
5[a]	*t*-Bu	H	(*R*,*R*)-**16a**	A	63	93
6	Ph	H	(*R*,*R*)-**16a**	B	62	93
7	Ph	H	(*R*,*R*)-**16b**	B	63	95[b]
8	Ph	H	(*R*,*R*)-**16c**	B	58	92[b]

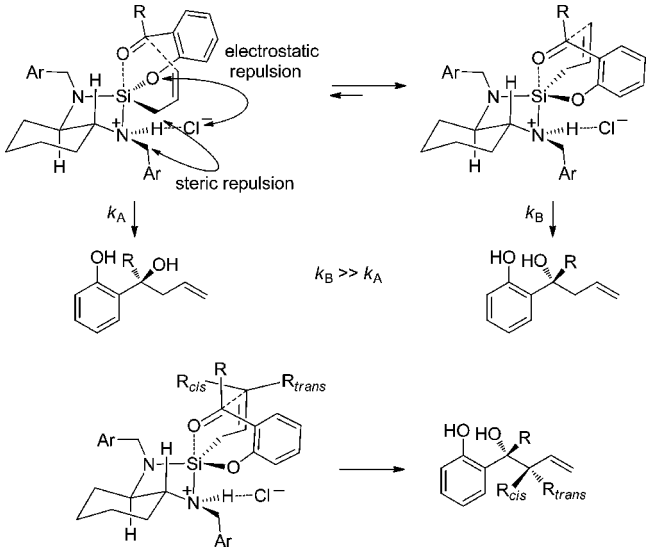
[a]Reaction time = 48 h. [b]>20:1 dr.

carbinol in good yield and high level of stereocontrol under optimized reaction conditions (Table 47, entry 1).[113] Interestingly, no allylation products were observed in the reactions of 3- and 4′-hydroxyacetophenone treated with (*R*,*R*)-**16a**. That result was consistent with the proposed mechanistic hypothesis. On the other hand, the stereoselective allylation was almost not affected by substituents on the aromatic ring (Table 47, entries 2 and 3), meanwhile sterically hindered alkyl phenyl ketones were smoothly allylated with improved enantioselectivity when dichloromethane was used as solvent at room temperature for 2 days (Table 47, entries 4 and 5). Importantly, *cis*- and *trans*-crotyl derivatives **16b** and **16c**, respectively, were found to crotylate 2′-hydroxybenzophenone to give the homoallylic tertiary carbinols in 63% and 57% yield, respectively, with excellent diastereo- and enantioselectivities (Table 47, entries 7 and 8).

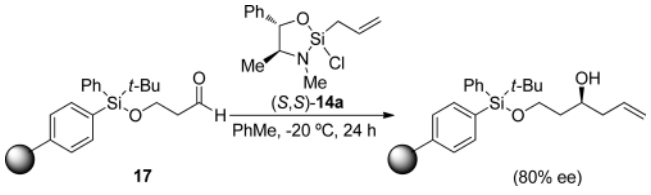
A stereochemical model was proposed for these reactions. In this model, upon reaction of α-hydroxyacetophenone with chiral allylsilanes **16**, the phenol displaces the chloride from the silane, and the HCl thus generated protonates one of the amino groups. Two trigonal bipyramidal intermediates are possible; the most stable one, which lacks steric and electronic repulsions, correctly predicted the observed major enantiomer by considering a chairlike transition state. This model is also consistent with the diastereoselectivity observed in the crotylation reactions with chiral *cis*-and *trans*-crotyl derivatives **16b** and **16c**, respectively (Scheme 36).

The chiral allylsilane reagent (*S*,*S*)-**14a** was also effective in the stereoselective allylation of a supported aldehyde with a robust *tert*-butyldiarylsilyl (TBDAS) linker coupled to polystyrene. Despite the silicon atom of the linker becoming a stereogenic center, the reaction of aldehyde **17** with (*S*,*S*)-**14a** produced the corresponding homoallylic alcohol with high level of stereocontrol (Scheme 37).[114] The resulting alcohol was cleaved from the resin, and the primary hydroxyl group was selectively protected with TBDPSCl. On the other hand, the same reaction product was also synthesized in solution from the TBDPS-protected aldehyde and the chiral alllylsilane (*S*,*S*)-**14a**. Importantly, identical levels of enantiomeric excess were found after Mosher ester analysis of both the solid- and solution-phase-synthesis-derived homoallylic alcohols.

Scheme 36



Scheme 37



3.2.2.2. Allylation of Imines and Imine Derivatives. The chiral allylating reagent (*S*,*S*)-**14a** derived from pseudoephedrine was successfully used in the stereoselective allylation of aldehyde derived acetyl hydrazones. Optimal results were obtained working in CH_2Cl_2 at 10 °C (method A, Table 48, entries 1−6).[115] The substrate scope was then studied under the optimized reaction conditions, and in general, yields and enantioselectivities were high for aromatic, heteroaromatic, and aliphatic aldehyde derived hydrazones. The only exception was the 3-pyridyl acetylhydrazone, which was allylated in only 23% ee (Table 48, entry 5). Compound (*S*,*S*)-**14a** also reacted with

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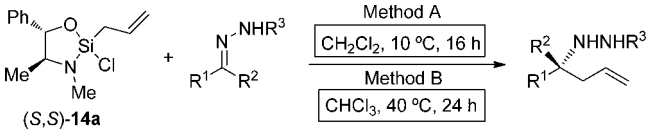
Table 48. Enantioselective Allylation of Acylhydrazones



(*S*,*S*)-**14a**

entry	R^1	R^2	R^3	method	yield (%)	ee (%)
1	Ph	H	Ac	A	86	88
2	2-MeC_6H_4	H	Ac	A	75	85
3	4-BrC_6H_4	H	Ac	A	88	85
4	4-$MeOC_6H_4$	H	Ac	A	82	86
5	3-pyridyl	H	Ac	A	89	23
6	*t*-Bu	H	Ac	A	88	97
7	Ph	Me	Bz	B	86	90
8	Ph	*i*-Pr	Bz	B[a]	80	97
9	4-$MeOC_6H_4$	Me	Bz	B	70	85
10	3-$NO_2C_6H_4$	Me	Bz	B[b]	79	88
11[c]	$PhCH_2CH_2$	Me	Bz	B[b]	87	87

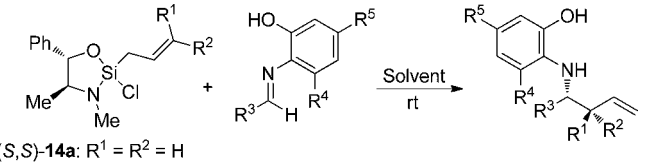
[a]Reaction was run at 57 °C. [b]Reaction was run at 23 °C. [c]The hydrazone starting material was a 3.8:1 *E*/*Z* mixture.

ketone-derived acylhydrazones. In the case of acetophenone, the benzoylhydrazone derivative performed better than the acetyl one, and $CHCl_3$ as solvent at 40 °C represented the optimal conditions (Table 48, entry 7).[112] Even the sterically hindered isobutyrophenone-derived benzoylhydrazone produced the allylated product in 97% ee (Table 48, entry 8). Importantly, all hydrazones were obtained as single (*E*)-isomers after recrystallization. However, identical results were obtained when the allylation of dialiphatic 3-phenylbutanone-derived benzoylhydrazone was performed using the single (*E*)-isomer or a 3.8:1 (*E*/*Z*) mixture of diastereomers (Table 48, entry 11). It seemed that under the optimized reaction conditions one of the isomers preferentially underwent allylation concomitant with rapid hydrazone isomer equilibration, a kind of dynamic kinetic resolution taking place.

It was found that *N*-methylbenzoylhydrazones did not react with (*S*,*S*)-**14a** and that allylation did not proceed by combining benzoylhydrazones and the allylic silane resulting from (*S*,*S*)-**14a** by replacing the chlorine atom by a methoxy group. Based on these experimental results, Leighton and co-workers proposed a mechanism for this transformation in which the imine nitrogen is coordinated to the Lewis acidic silane reagent, meanwhile the acyl oxygen is covalently attached to the silicon by chloride displacement. Only when the reagents reached this scenario did the allylation take place (Scheme 38).[112]

As was previously mentioned, phenols were effective directing and activating groups for these allylchlorosilane reagents.[113] Leighton and co-workers also reported the stereoselective allylation of both aliphatic and aromatic aldimines derived from *ortho*-aminophenols with chiral allylsilanes **14**.[116] The reactions proceeded smoothly at room temperature with (*S*,*S*)-**14a** and aromatic aldimines to give high yields and good levels of enantioselectivity (Table 49, entries 1−3). Similar results were found for the aliphatic aldimine derived from cyclohexanecarbaldehyde (Table 49, entry 4). However, in the case of less hindered aliphatic aldimines, such as that derived from 3-phenylpropanal and 2-amino-3-methylphenol, the allylation proved to be highly stereoselective but it proceeded with poor efficiency (Table 49, entry 5). This result was attributed to imine instability and as a proof of this assumption, they found that yield and stereoselectivity were significantly improved when the imine derived from 2-amino-3,5-di-*tert*-butylphenol was used (Table 49, entry 6). Importantly, when *cis*- and *trans*-crotylsilanes (*S*,*S*)-**14b** and (*S*,*S*)-**14c** were used, it was found that both the aromatic and

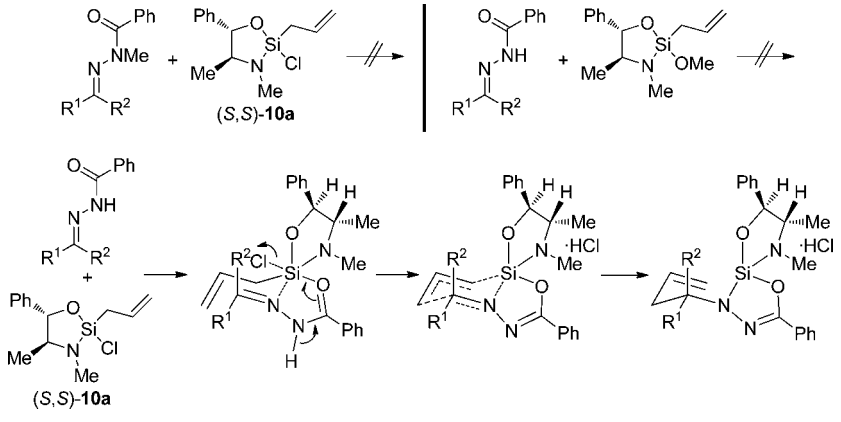
Table 49. Enantioselective Allylation of *N*-(2-Hydroxyaryl)imines



(*S*,*S*)-**14a**: $R^1 = R^2 = H$
(*S*,*S*)-**14b**: $R^1 = Me$, $R^2 = H$
(*S*,*S*)-**14c**: $R^1 = H$, $R^2 = Me$

entry	chiral silane	R^3	R^4	R^5	solvent	yield (%)	ee (%)
1	(*S*,*S*)-**14a**	Ph	H	H	CH_2Cl_2	83	96
2	(*S*,*S*)-**14a**	2-MeC_6H_4	H	H	CH_2Cl_2	89	96
3	(*S*,*S*)-**14a**	2-furyl	H	H	CH_2Cl_2	71	90
4	(*S*,*S*)-**14a**	Cy	Me	H	Et_2O	85	92
5	(*S*,*S*)-**14a**	$Ph(CH_2)_2$	Me	H	Et_2O	40	87
6	(*S*,*S*)-**14a**	$Ph(CH_2)_2$	*t*-Bu	*t*-Bu	CH_2Cl_2	82	98
7	(*S*,*S*)-**14b**	Ph	H	H	CH_2Cl_2	64	98
8	(*S*,*S*)-**14c**	Ph	H	H	CH_2Cl_2	74	99
9	(*S*,*S*)-**14b**	Cy	Me	H	Et_2O	64	93

Scheme 38



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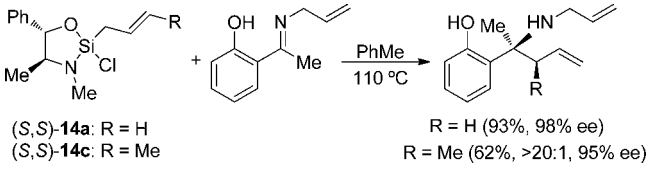
aliphatic aldehyde-derived imines could be crotylated with excellent diastereo- and enantioselectivity (Table 49, entries 7–9).

The phenol unit also facilitated the stereoselective allylation of the simple *N*-allyl ketimine of *ortho*-hydroxyacetophenone with (*S*,*S*)-**14a**. In this case, the phenol unit is part of the imine provided by the carbonyl compound, instead of being a part of the amine as above. Although the reaction was performed in refluxing toluene for 6 h, the allylation proceeded with excellent enantioselectivity (98% ee) and high yield (93%) (Scheme 39).

Scheme 39

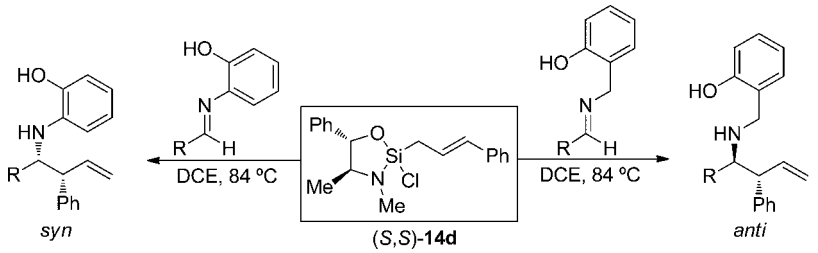


This ketimine was also successfully crotylated with *trans*-crotylsilane (*S*,*S*)-**14c** to provide the expected homoallylamine derivative as a single diastereomer in 62% yield and 95% ee (Scheme 39).

Cinnamylation of aldimines is of synthetic interest because two vicinal stereocenters, one bearing a nitrogen atom and the other with both benzylic and allylic character, are generated. According to the previously mentioned model (Table 49), the reaction of an *N*-(2-hydroxyphenyl)aldimine with a chiral *trans*- or *cis*-cinnamylsilane would produce the corresponding *syn* and *anti* diastereomers, respectively. Leighton and co-workers studied the cinnamylation of the imine derived from benzaldehyde and 2-aminophenol with *trans*-cinnamylsilane (*S*,*S*)-**14d**.[117] The best results were obtained when the reaction was conducted in refluxing 1,2-dichloroethane (Table 50, entry 1 and Scheme 38). Other aromatic and aliphatic imines performed even better considering efficiency and diastereo- and enantioselectivity (Table 50, entries 2–6). In all cases, *trans*-cinnamylsilane (*S*,*S*)-**14d** led to the *syn*-diastereomer as the major reaction product. On the other hand, the *anti*-product was obtained when the imine derived from benzaldehyde reacted with the corresponding chiral *cis*-cinnamylsilane. However, large-scale synthesis of chiral *cis*-cinnamylsilane is more complex and tedious than for the *trans*-isomer (*S*,*S*)-**14d**, this being a major drawback when the *anti*-diastereomers are the target products. This limitation was overcome by changing the substituent on the nitrogen of the imine. Thus, it was possible to synthesize the *anti* isomers with the more easily available *trans*-cinnamylsilane (*S*,*S*)-**14d** when it was reacted with phenolic *N*-benzyl imine derivatives. Yields were similar to those obtained for the *syn* isomers, but stereoselectivities were higher (Table 50, entries 7–12).

A mechanistic model based on the trigonal bipyramidal complex, which resulted upon reaction of chiral cinnamylsilane with the imine, was proposed.[117] In this complex, the phenolic oxygen is covalently bonded to the silicon atom, and the imine nitrogen and the protonated pseudoephedrine nitrogen occupy the apical positions, similarly to those mentioned for related systems in Schemes 36 and 38. For *trans*-cinnamylsilane (*S*,*S*)-**14d** and the imine derived from benzaldehyde and *ortho*-aminophenol, two trigonal bipyramidal intermediates are possible, which differ from the configuration of the imine. The most stable one has an (*E*)-configuration, which correctly rationalizes the *syn* product (Scheme 40). On the other hand, the (*E*)-complex initially formed with the imine resulting from benzaldehyde and *ortho*-hydroxybenzylamine isomerizes to the (*Z*)-complex, which would place the imine phenyl group in a more favored pseudoequatorial position, leading in this case to the *anti* product (Scheme 40). Imine *E*/*Z* isomerization has been previously observed in related systems.[112] The isomerization is presumably produced by chloride ion addition to and elimination from the imine. Importantly, through this strategy, either diastereomer of the product may be accessed from the

Table 50. Enantioselective Cinnamylation of Imines



entry	imine derivative	R	product	yield (%)	dr	ee (%)
1	*N*-(2-HOC$_6$H$_4$)	Ph	*syn*	87	7:1	99
2[a]	*N*-(2-HOC$_6$H$_4$)	4-BrC$_6$H$_4$	*syn*	79	13:1	97
3	*N*-(2-HOC$_6$H$_4$)	4-CNC$_6$H$_4$	*syn*	66	18:1	90
4	*N*-(2-HOC$_6$H$_4$)	2-thienyl	*syn*	69	11:1	96
5[b]	*N*-(2-HOC$_6$H$_4$)	Cy	*syn*	60	>20:1	95
6[c]	*N*-(2-HOC$_6$H$_4$)	PhCH$_2$CH$_2$	*syn*	53	>20:1	98
7	*N*-(2-HOC$_6$H$_4$CH$_2$)	4-NO$_2$C$_6$H$_4$	*anti*	70	>20:1	95
8	*N*-(2-HOC$_6$H$_4$CH$_2$)	4-CNC$_6$H$_4$	*anti*	73	>20:1	96
9	*N*-(2-HOC$_6$H$_4$CH$_2$)	4-MeOC$_6$H$_4$	*anti*	89	>20:1	94
10	*N*-(2-HOC$_6$H$_4$CH$_2$)	2-thienyl	*anti*	77	>20:1	93
11	*N*-(2-HOC$_6$H$_4$CH$_2$)	2-MeOC$_6$H$_4$	*anti*	77	>20:1	99
12[a]	*N*-(2-HOC$_6$H$_4$CH$_2$)	*N*-Boc-2-indolyl	*anti*	51	>20:1	98

[a]Reaction carried out at 60 °C. [b]Reaction carried out in CH_2Cl_2 at 50 °C. [c]Reaction carried out in $CHCl_3$ at reflux.

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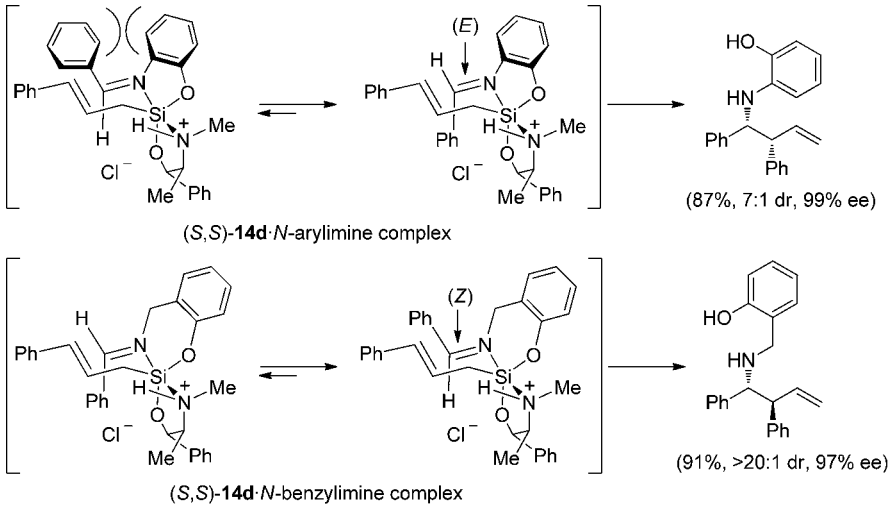
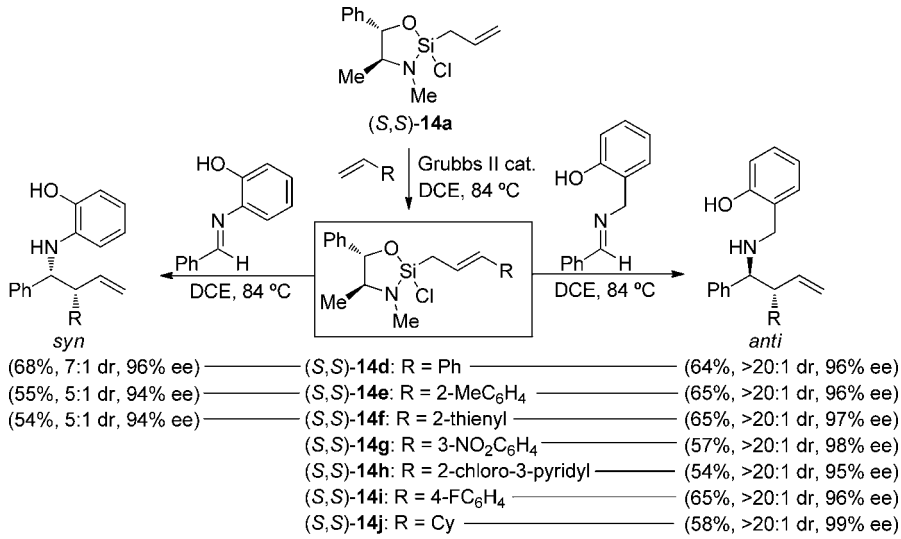
Scheme 40



Scheme 41



same easily affordable in large amounts *trans*-cinnamylsilane (*S*,*S*)-**14d**, just by choosing the appropriate substituent on the nitrogen of the imine.

Based on this strategy, a wide variety of homoallylamine derivatives bearing an aryl, heteroaryl, or alkyl substituent at the benzylic position were synthesized with total control of the stereochemistry. Leighton and co-workers approached the starting substituted chiral allylsilanes **14d−j** by performing a cross-metathesis of easily available chiral allylsilanes (*S*,*S*)-**14a** and the corresponding vinylic compound.[118] They observed that the second-generation Grubbs catalyst[119] was effective for this reaction and that the *trans* isomer was always produced with excellent selectivity (>20:1). Further addition of the imine derived from benzaldehyde and 2-hydroxyaniline- or 2-hydroxybenzylamine to the reaction flask led to *syn* and *anti* products, respectively, with good efficiency and excellent diastereo- and enantioselectivity (Scheme 41). Interestingly, it was not necessary to isolate *trans* chiral allylsilanes **14d−j** in this tandem cross-metathesis/imine cinnamylation.

New chiral allylchlorosilanes derived from (1*R*,2*S*)-1-amino-2-indanol **18** have been developed by Leighton and Perl and successfully used in the stereoselective allylation and crotylation of 2-imidazolylaldimines.[120] The allylation proceeded well in toluene at room temperature and a variety of imine N-substituents are tolerated (Table 51, compare entries 1−3). Surprisingly, ketimines were also allylated under the same mild reaction conditions yielding tertiary carbinamines (Table 51, entries 4−6). Importantly, the imine derived from 2-imidazolyl phenyl ketone, and allylamine was smoothly allylated to provide the corresponding tertiary carbinamide in 79% yield and 70% ee (Table 51, entry 6). This type of compound is not easily available in an enantioselective fashion through conventional methodologies. Moreover, crotylation of the simple imine derived from imidazole-2-carbaldehyde and allylamine yielded always almost a single diastereomer (>20:1). Thus, *cis*-crotylsilane (1*R*,2*S*)-**18b** led to the *syn* product, and *trans*-crotylsilane (1*R*,2*S*)-**20c** to the *anti* product (Table 51, entries 7 and 8).

New easily accessible *N*-heteroaryl hydrazones were developed as an alternative to known *N*-acylhydrazones and 2-aminophenol-derived imines in these stereoselective allylation reactions.[121] Thus, benzoxazole-derived hydrazone (R^2 = $PhCH_2CH_2$) reacted with allylsilane (*S*,*S*)-**14a** in refluxing dichloromethane to give the corresponding hydrazine in 64%

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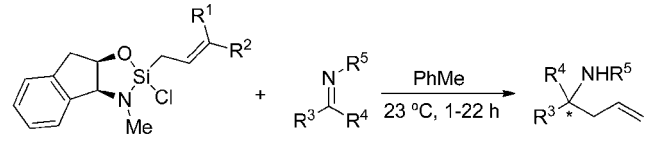
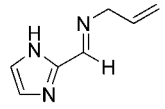
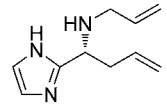
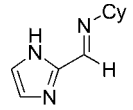
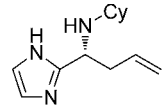
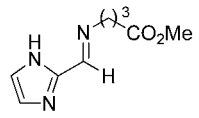
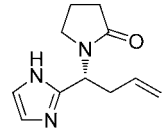
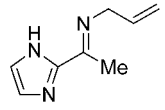
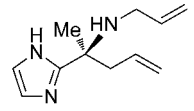
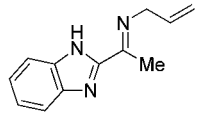
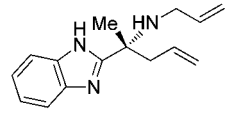
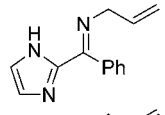
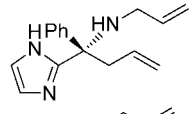
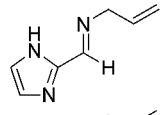
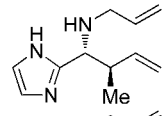
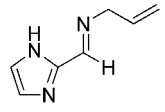
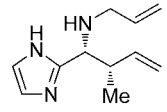
Table 51. Enantioselective Allylation of 2-Imidazolylimines

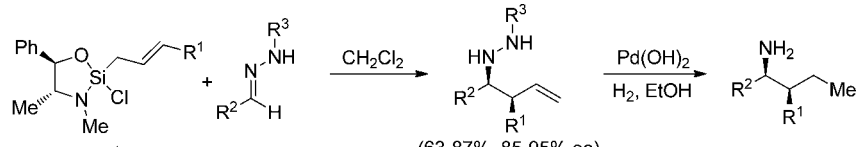


(1*S*,2*R*)-**18a**: $R^1 = R^2 = H$
(1*S*,2*R*)-**18a**: $R^1 = Me$, $R^2 = H$
(1*S*,2*R*)-**18a**: $R^1 = H$, $R^2 = Me$

Entry	Chiral silane	Imine	Product	Yield (%)	ee (%)
1	(1*S*,2*R*)-**18a**			80	87
2	(1*S*,2*R*)-**18a**			85	95
3[a]	(1*S*,2*R*)-**18a**			71	88
4	(1*R*,2*S*)-**18a**			85	91
5	(1*S*,2*R*)-**18a**			86	91
6[b]	(1*S*,2*R*)-**18a**			79	70
7	(1*S*,2*R*)-**18b**			66	86
8	(1*S*,2*R*)-**18c**			74	89

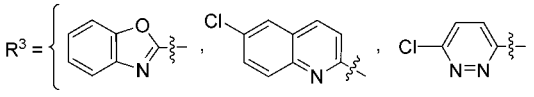
[a]After 1 h, the reaction was heated at 45 °C for 1 h to effect lactamization. [b]This reaction was conducted at 10 °C for 38 h.

Scheme 42



(*R*,*R*)-**14a**: $R^1 = H$
(*R*,*R*)-**14c**: $R^1 = Me$
(*R*,*R*)-**14d**: $R^1 = Ph$

[$R^2 = CH_3(CH_2)_4$, $(CH_3)_2CH(CH_2)_2$, $CyCH_2$, $PhCH_2$, $Ph(CH_2)_2$]

$R^3 =$ 

yield and 91% ee (Scheme 42). On the other hand, 6-chloroquinoline-derived hydrazones proved to be more reactive because crotylations with chiral *trans* crotylsilane (*S*,*S*)-**14c** were carried out in dichloromethane at room temperature. In this case, the corresponding hydrazines were always isolated as a single diastereomer with high enantioselectivity (Scheme 42).

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Scheme 43

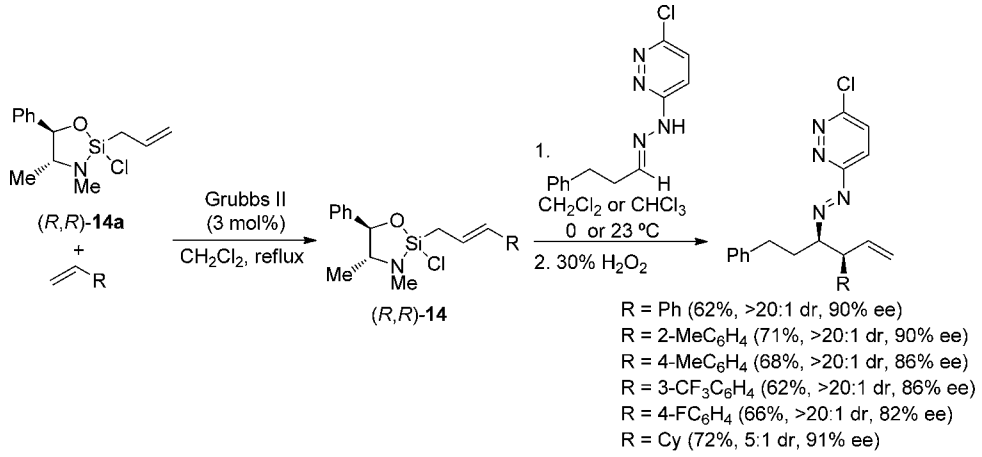
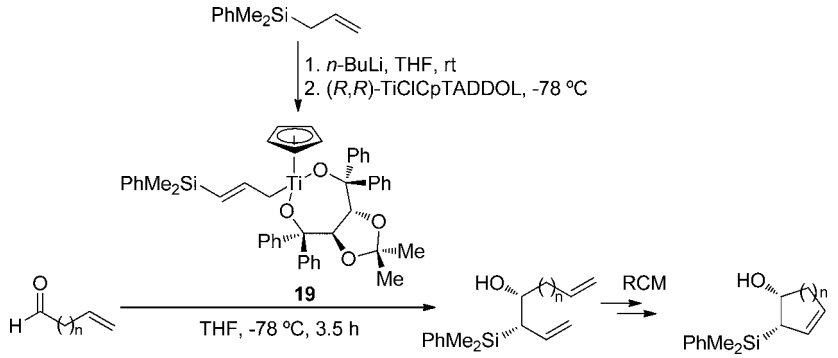


Table 52. Asymmetric Allylmetallation of Unsaturated Aldehydes with the Chiral Allyltitanium Reagent 19



entry	n	yield (%)	ee (%)
1	1	68	96
2	2	68	92
3	3	75	90
4	4	67	94
5	8	71	91

Moreover, 6-chloro-3-pyridazine-derived hydrazone (R^2 = $PhCH_2CH_2$) performed also well with *trans*-cinnamylsilane (*S*,*S*)-**14d** at 0 °C, yielding the expected hydrazine in 82% yield (12:1 dr) and 85% ee. It is worth mentioning that these *N*-heteroaryl hydrazines were smoothly reduced by $Pd(OH)_2$-catalyzed hydrogenation to yield the corresponding primary amines in almost quantitative yields.

The hydrazone resulting from 6-chloro-3-pyridazinylhydrazine and 3-phenylpropanal was chosen as a model compound to investigate the performance of the pyridazine activator in the one-pot cross-metathesis/cinnamylation procedure, which has been previously mentioned in Scheme 39. Upon optimization, this procedure allowed the one-pot synthesis of different hydrazines with two consecutive stereogenic centers showing *syn* diastereoselectivity (Scheme 43). The reaction was tolerant of a range of vinylarenes as well as vinylcyclohexane.

3.2.3. Allyl Titanium Reagents. Similarly to allylboranes and allylsilanes, excellent enantioface control could be achieved in the nucleophilic allyl transfer from a chiral allyltitanium reagent to a prostereogenic carbonyl group.[122] Six-membered cyclic transition states with chair conformation were proposed to explain the regio- and diastereoselectivity. Ghosez and co-workers reported the synthesis of highly enantioenriched cyclic *β*-hydroxyallylsilanes via enantioselective allylation of unsaturated aldehydes using the chiral allyltitanium reagent **19**, followed by a ring-closing metathesis.[123] The (*E*)-*γ*-dimethylphenylsilyl-substituted titanium reagent **19** was prepared by deprotonation of allyldimethylphenylsilane with *n*-BuLi followed by reaction with (*R*,*R*)-TiClCpTADDOL. The chiral allyltitanium reagent **19** was not isolated and reacted *in situ* with neat aldehyde at −78 °C for 3.5 h. This type of allylmetal reagent was known to give the *anti*-*β*-hydroxyallylsilanes, and in this case, they were isolated in good yields and high enantiomeric purities (Table 52).

3.3. Double Stereoselection

Pietruszka and Schöne studied the reaction of new chiral allylboronic esters **20**, which were obtained through Johnson and Eschenmoser rearrangements, with carbonyl compounds.[124] The absolute configuration of the new reagents was assigned by means of chemical correlation or X-ray structure analysis. The reaction of diastereomers (3*S*)- and (3*R*)-**20** with benzaldehyde was performed in good yield (78−91%) and enantiomeric excess (>94% ee). However, a reagent-controlled addition was not observed when aldehydes with an additional stereogenic center were introduced. For instance, a mismatched interaction occurred in the reaction of 2,3-*O*-isopropylidene-D-glyceraldehyde with (3*R*)-**20** to give the *syn*

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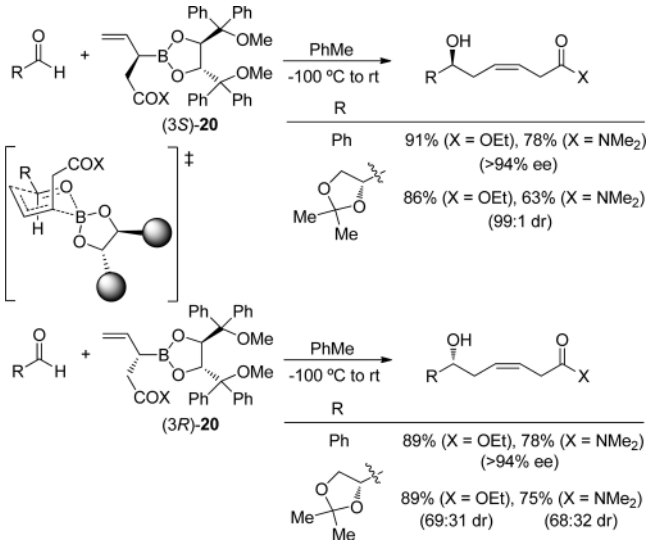
product as around 70:30 dr, meanwhile with (3*S*)-**20**, the *anti* product was exclusively isolated (99:1 dr, matched interaction). Importantly, in all cases, the olefin with *Z* configuration was also formed exclusively, and no traces of the other diastereomer were detected in the crude product. This result was in agreement with a chairlike transition state model depicted in Scheme 44.

Scheme 44



The addition of 2-carboxyester 3,3-disubstituted allylboronates to aldehydes yielded *exo*-methylene butyrolactones with a quaternary carbon center. The stereochemical course of the reaction could be effectively directed by carboxyester-based chiral auxiliaries. Unfortunately, enantioselectivities greater than 82% were not achieved, despite the use of a large number of different chiral alcohols. Interestingly, Kennedy and Hall found that allylboronate **21**, which bore chiral auxiliaries on both the carboxyester and boronic ester, provided high levels of selectivity.[125] The reactions were carried out in toluene at room temperature for 14 days, followed by acid-catalyzed ring closure. Both model aliphatic and aromatic aldehydes were effective in this reaction. Although the requirement for two different auxiliaries might appear excessive, the enantioselectivities obtained were excellent. Furthermore, the auxiliaries were easily removed from the product. Indeed, both auxiliaries were simultaneously removed in the ensuing lactonization, alleviating the need for separate cleavage steps (Scheme 45).

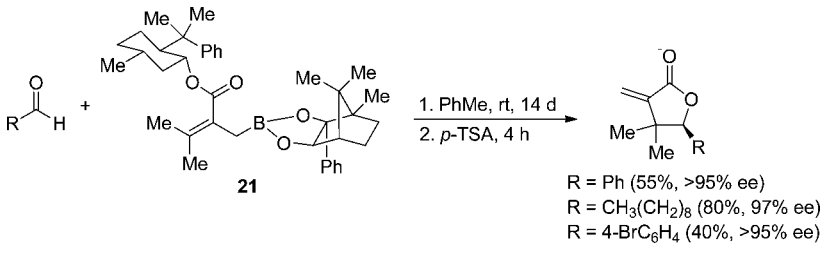
3.4. Chiral Donors in Allyl-Transfer Reactions

3.4.1. Chiral Homoallyl Alcohols. Efficient methods to transfer the allyl moiety from a chiral homoallylic alcohol to an aldehyde without the intervention of allylic organometallic reagents have been developed recently. This unusual allylation reaction seems to take place through a 2-oxonium-[3,3]-sigmatropic rearrangement, as shown in Scheme 46. The formation of the oxonium ion is usually acid-catalyzed, and the sigmatropic rearrangement proceed via the most stable chairlike transition state in a highly stereospecific manner. Importantly, tertiary alcohols are commonly used as allyl donors to shift the equilibrium for the formation of a more stable oxonium ion.[126]

An important synthetic application of this method is the preparation of linear homoallylic alcohols (*E* or *Z*) from branched substrates, easily prepared by addition of organometallic allylic reagents to aldehydes. In this context, the group of Nokami has described the preparation of linear (*E*)-homoallylic alcohols from chiral donors conveniently prepared from cheap and readily available (−)- or (+)-menthone.[127] The equatorial approach of allylic metal reagents (i.e., Grignard reagents) to the chiral menthone afforded the expected diastereomeric mixture of γ-adducts as major products in good overall yields. Importantly, when both crotyl adducts were separated and independently made to react with phenylpropanal, in the presence of *p*-toluenesulfonic acid monohydrate as catalyst, only the major isomer with the *R* configuration at the allylic position reacted. The reaction was examined using the reactive isomer of different allyl donors with a variety of aromatic and aliphatic aldehydes. In all cases, linear enantiopure (*E*)-homoallyl alcohols were obtained in good yields (Table 53). Interestingly, when diallylic substrates are used (Table 53, entries 8 and 9), only one diastereotopic group is transferred allowing a highly enantioselective 2,4-pentadienylation of aldehydes. Notably, two allyl-transfer reactions were tested with a diastereomeric mixture of γ-adducts, and the corresponding products were obtained in similar good yields and excellent enantioselectivities. The stereochemical outcome of the reaction was rationalized on the basis of the generally accepted mechanism (Scheme 46). It was reasoned that in the oxonium ion derived from the (*S*)-allylic γ-adduct, there is a steric hindrance between isopropyl and R^1 groups that is absent in the more reactive (*R*)-allylic isomer (see equation of Table 53).

The major homoallylalcohol resulting from γ-addition of 1,3-dimethylallylic metal reagents to (−)-menthone was also used to transfer the pentenyl group to different aldehydes.[128] The allyl transfer to aliphatic aldehydes took place in good yields with high stereoselectivities to obtain the major isomers with *E*-geometry and 4,5-*syn*-stereochemistry (Scheme 47). The reaction was conducted with 2 equiv of the pentenyl donor to minimize the competing Prins reaction. Although the reaction works well for a variety of aliphatic aldehydes, α-branched aldehydes react slower and more sterically hindered substrates (e.g., pivaraldehyde), α,β-unsaturated and aromatic

Scheme 45



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Scheme 46

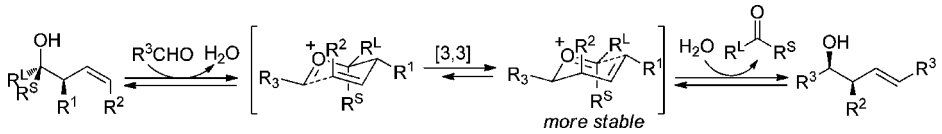
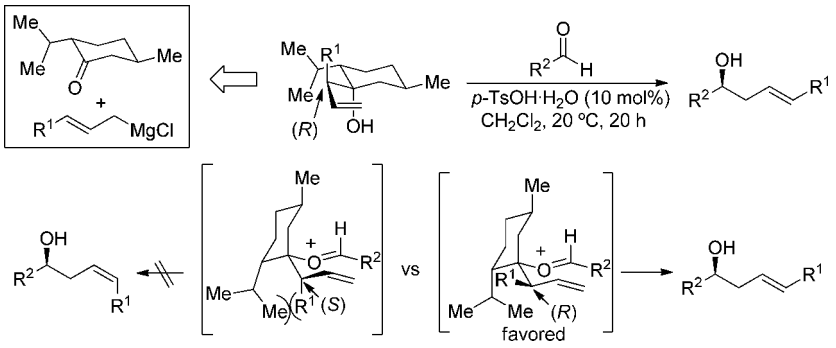


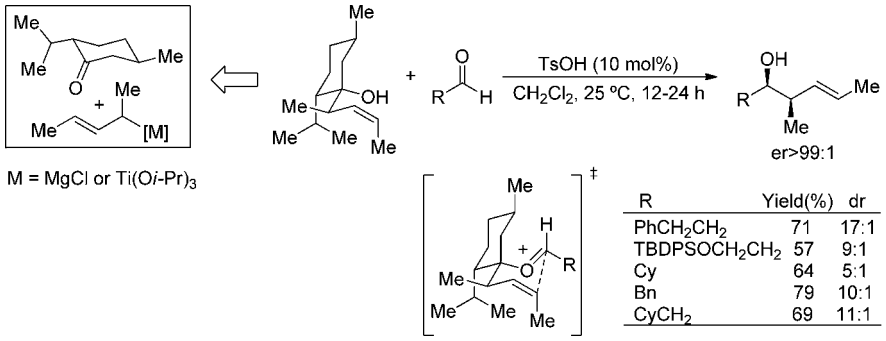
Table 53. Menthone-Derived Homoallylic Alcohols as Chiral Allyl Donors



entry	R^1	R^2	yield (%)	ee (%)
1	Et[a]	$PhCH_2CH_2$	85	>99
2	Et[b]	Ph	61	>99
3	Et[a]	$BnO(CH_2)_5$	88	>99
4	Et[b]	PhCHMe	68	>99
5	Et[a]	$PhSCH_2CH_2$	90	>99
6	Et[b]	Et_2CH	71	>99
7	Et[a]	$CH_2{=}CH(CH_2)_8$	75	>99
8	$CH_2{=}CH$[b]	$PhCH_2CH_2$	83	>99
9	$CH_2{=}CH$[b]	$PhSCH_2CH_2$	63	>99

[a]One equivalent of allylating agent was used. [b]Two equivalents of allylating agent were used.

Scheme 47



aldehydes, are not well suited for the reaction. The stereochemistry observed for the main product, as well as the reactivity of aldehydes, was explained through the generally accepted mechanism involving the oxonia-Cope process through the most stable chairlike transition state (Scheme 47).

The addition of alk-2-enylmetallic reagents to (+)-isomenthone allowed the formation of an easily separable diastereomeric mixture of γ-adducts. The major isomer of this mixture was examined as an allyl donor to a selection of aldehydes, in the presence of *p*-toluenesulfonic acid monohydrate as catalyst.[129] Importantly, it was found that the major isomer furnished only the (*Z*)-olefin of the corresponding α-adduct, while the other isomer gave the corresponding (*E*)-olefin. The transfer of chirality was perfect, obtaining enantiopure homoallylic alcohols in good yields for the aldehydes used. The use of 2 equiv of the allyl donor was required in some cases to improve the yield, and 40 mol % of the Lewis acid was optimum when benzaldehyde was the acceptor. The stereospecificity of the reaction was explained through the generally accepted model (Scheme 48).

A practical crotyl transfer protocol was developed in the group of Loh, using camphor as chiral auxiliary.[130] A diastereomeric mixture (*syn*/*anti* 7:3) of branched homoallylic alcohols, prepared from the addition of crotylmagnesium bromide to (1*R*)-camphor, was treated with a survey of aldehydes in the presence of CSA as catalyst. With different unhindered aliphatic aldehydes and 3 equiv of the crotyl donor, the corresponding linear homoallylic alcohols were obtained in excellent yields and enantio- and (*Z*)-selectivity. The reaction was tolerant to different functionalities, but hindered aldehydes gave poor conversion, and aromatic ones were even less reactive. This difference in reactivity allowed a selective transfer

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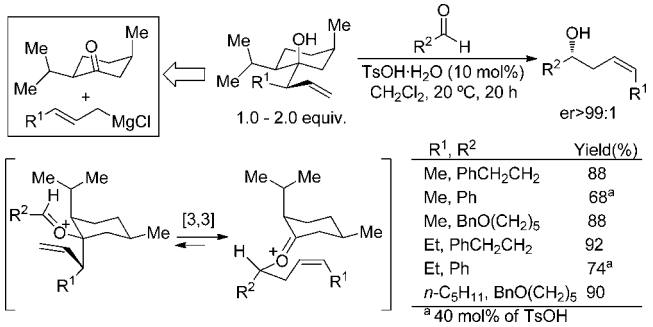
Scheme 48



R^1, R^2	Yield(%)
Me, $PhCH_2CH_2$	88
Me, Ph	68[a]
Me, $BnO(CH_2)_5$	88
Et, $PhCH_2CH_2$	92
Et, Ph	74[a]
n-C_5H_{11}, $BnO(CH_2)_5$	90

[a] 40 mol% of TsOH

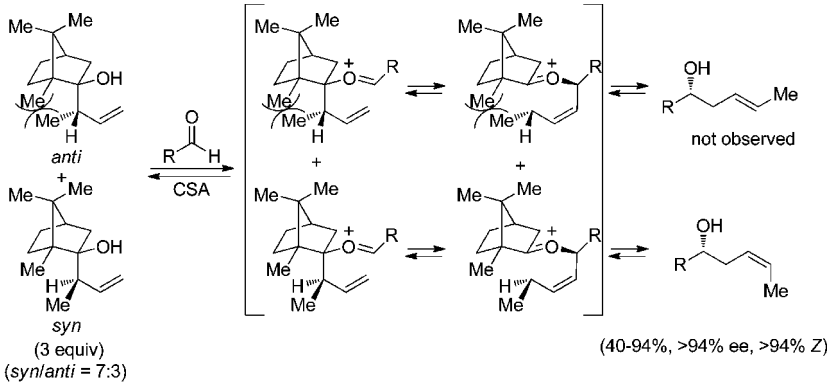
of the crotyl group to an aliphatic aldehyde in the presence of aromatic acceptors. The selectivity obtained from the diastereomeric α-adduct mixture was explained as the result of a kinetic resolution. Due to a severe steric repulsion in the *anti*-oxonium ion, it was reasoned that the [3,3]-rearrangement of the *syn*-oxonium isomer occurs faster to furnish the thermodynamically preferred linear regioisomers (Scheme 49). The stereospecificity of the process is apparent in the high *Z*-selectivity obtained as well as in the efficiency of chirality transfer. Importantly, the excess of chiral camphor-derived crotyl donor used and the camphor generated from the reaction can be recovered and reused.

A chiral allyl donor was prepared from 3-methylbut-2-en-1-ol, using the Sharpless asymmetric epoxidation and the stereospecific addition of vinylmagnesium chloride in the presence of CuBr as key steps. The allyl transfer from this donor to different aldehydes allowed the stereoselective preparation of 5-benzyloxyhomoallylic alcohols.[131] As shown in Scheme 50, the transfer of chirality was excellent when different aliphatic aldehydes were used in the presence of triflic acid as catalyst, including the sterically hindered pivalaldehyde. Importantly, when the (*R*)-allyl donor was used, the major product has (*S*,*E*)-configurations, the (*R*,*Z*)-product being detected as the minor isomer. The preferred stereochemical pathway was explained using the different conformational stabilities of the oxonium ions that could be involved in the [3,3]-rearrangements through a chairlike transition state.

Chiral bispropionate subunits, a common moiety in many bioactive compounds, were also transferred to different aldehydes under acid catalysis.[132] The reductive coupling of a substituted allylic benzoate with *ortho*-silyloxymethylbenzaldehyde afforded a mixture of diastereoisomers, which, after separation, were submitted to a kinetic resolution to obtain all four possible enantioenriched chiral allyl donors. The reaction of (*S*,*R*)-chiral bispropionate donor with aldehydes was promoted by $Sn(OTf)_2$ to obtain a cyclic acetal that upon treatment with $SnCl_4$ and Ag_2CO_3, efficiently transfer the allylic unit (Scheme 51). The *E*-alkene geometry and *anti*-relationship of the two new stereocenters can be explained using the more stable chairlike transition state in the [3,3]-sigmatropic rearrangement. When chiral (*R*)-2-methylpentanal was evaluated in this methodology with (*S*,*R*)- and (*R*,*S*)-allylic donors, the bispropionate transfer reaction occurred without appreciable double diastereoselection. However, matched and mismatched cases were detected for other α-chiral aldehydes. On the other hand, the reaction of the (*S*,*S*)-allyl reagent with aldehydes under identical conditions took place with *in situ* cyclization furnishing the corresponding chiral lactones in good isolated yields. The performance of α-chiral aldehydes was also evaluated with (*S*,*S*)- and (*R*,*R*)-allylic donors, observing double diastereoselection in some cases.

The addition of (*E*)-crotyltrichlorosilane derivatives to aldehydes using (−)-METHOX as Lewis base catalyst, allowed the enantioselective preparation of the γ-adduct homoallylic alcohols.[133] Interestingly, in the presence of this ligand, the reaction of the (*E*)-crotyltrichlorosilane is faster than that of the (*Z*)-isomer, which makes it possible to obtain excellent enantioselectivities using a technical grade crotyl reagent (*E*/*Z* 6:1). The homoallylic alcohols obtained were used as chiral crotyl donors in an acid-catalyzed γ to α rearrangement with other aldehydes. After a brief survey of Lewis acids and crotyl donor substrates, $(TfO)_2Sn$ and the tolyl crotyl donor proved to be optimum. A range of aromatic and aliphatic aldehydes was evaluated under these conditions, obtaining the linear homoallylic alcohols with excellent *E*-selectivity and enantioselectivities and in good isolated yields (Table 54). Importantly, the reaction is not restricted to the crotylation products, but other γ-adducts prepared from (*E*)-3-alkylallyltrichlorosilanes were also suitable with similar good results. According to the generally accepted mechanism, the better performance of the tolyl donors was attributed to their capacity to stabilize the positive charge in the benzylic position, driving the equilibrium to the products. Additionaly, the reduced electrophilicity of the released *p*-tolualdehyde minimizes the competition with the desired receptor aldehyde.

Scheme 49



[R = $Ph(CH_2)_2$, $CH_3(CH_2)_4$, $CH_3(CH_2)_7$, Cy, $BnO(CH_2)_2$, $BnO(CH_2)_3$, $BnO(CH_2)_4$, $(EtO_2C)CH{=}CH(CH_2)_3$]

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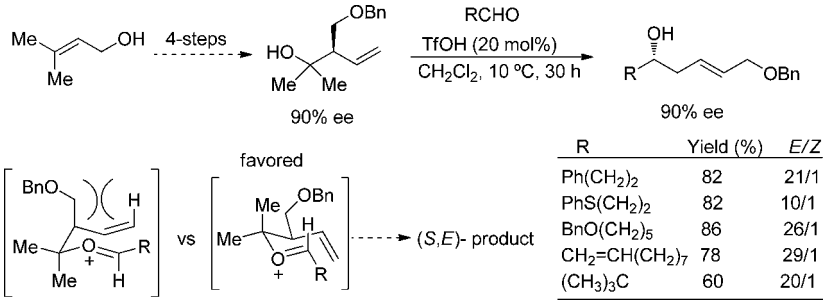
Scheme 50



R	Yield (%)	*E*/*Z*
$Ph(CH_2)_2$	82	21/1
$PhS(CH_2)_2$	82	10/1
$BnO(CH_2)_5$	86	26/1
$CH_2{=}CH(CH_2)_7$	78	29/1
$(CH_3)_3C$	60	20/1

Scheme 51

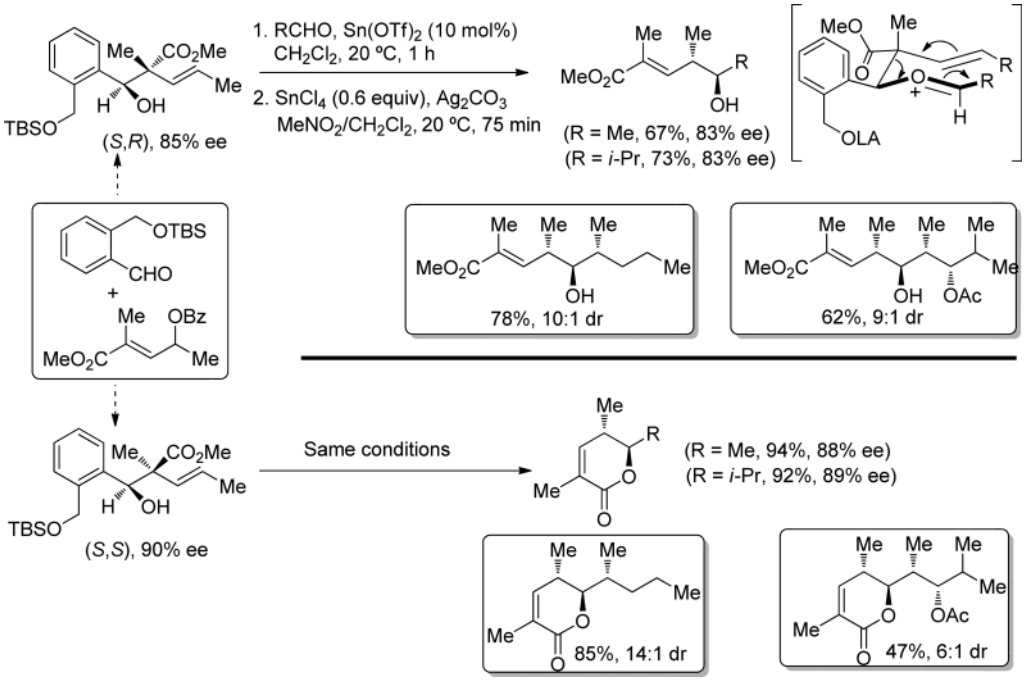
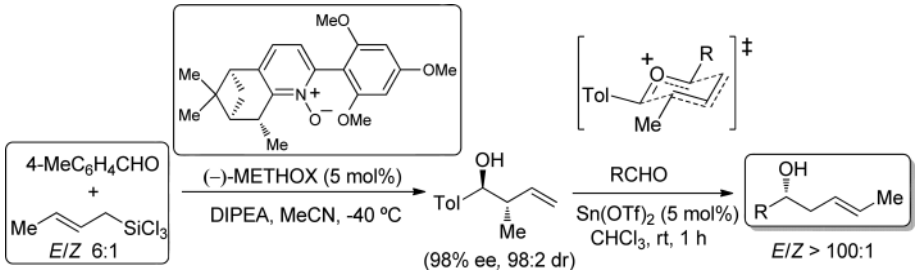


Table 54. Enantioselective α-Crotylation of Aldehydes Followed by Diastereoselective Crotyl Transfer



R	yield (%)	ee (%)
$PhCH_2CH_2$	95	97
4-$NO_2C_6H_4$	75	98
Bn	82	96
t-Bu	60	93
Cy	80	97
$MeSCH_2CH_2$	72	≥97

3.4.2. Chiral Homoallyl Amines. The concept of transfer allylation of aldehydes using a chiral donor has also been expanded to homoallylic amines. With this in mind, the group of Kobayashi prepared an enantiopure amine by amino-allylation of (1*R*)-camphorquinone with ammonia and allylboronic acid pinacol ester.[134] The best results obtained in the transfer aminoallylation of aldehydes were in the presence of substoichiometric amounts of camphorsulfonic acid, using dichloroethane as solvent. Different aldehydes with a wide range of functionalities were suitable for this methodology

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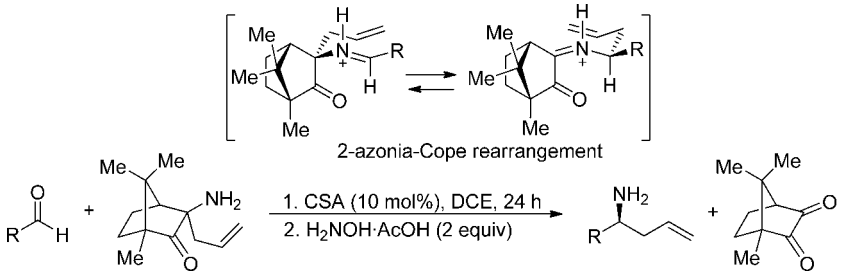
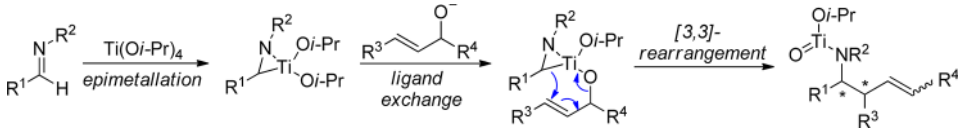
Table 55. Diastereoselective Transfer Aminoallylation of Aldehydes Using (1*R*)-Camphorquinone

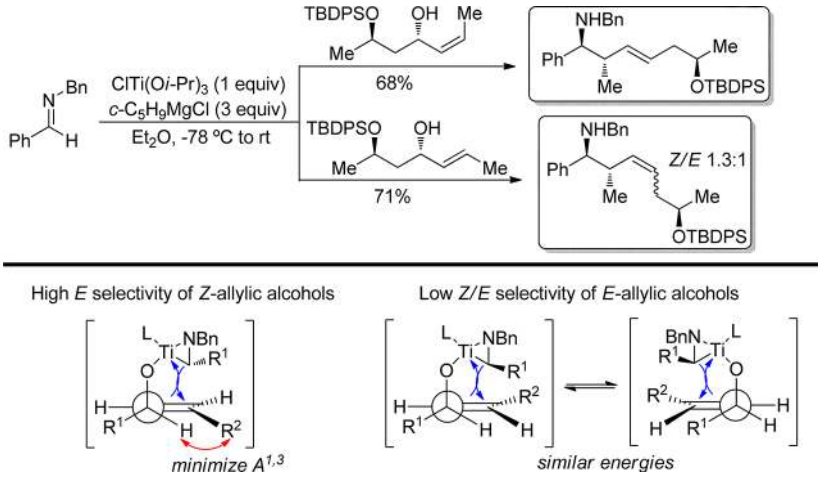


entry	R	*T* (°C)	yield (%)	ee (%)
1	4-$NO_2C_6H_4$	50	92	98
2	4-$MeOC_6H_4$	50	72	97
3	2-furyl	50	60	97
4	3-pyridyl	50	91	98
5	$PhCH_2$	0	77	96
6	$CH_3(CH_2)_6$	0	81	97
7	Cy	0	73	95
8	$BnOCH_2$	0	87	95

Scheme 52



Scheme 53



(Table 55). The homoallylic primary amines were obtained with excellent enantioselectivities and the sense of the chiral induction was rationalized using the most stable chairlike transition state in the 2-azonia-Cope rearrangement. In comparison with aromatic aldehydes, aliphatic substrates, even though being enolizable, were more reactive and their reactions proceed smoothly at 0 °C (Table 55, entries 5−8). Moreover, when chiral aldehydes were used, the new stereogenic center was independently controlled by the camphor moiety. Importantly, the quenching of the reaction with hydroxylamine allowed the recovery of (1*R*)-camphorquinone as the 3-oxime derivative in high yield.

The use of the Kulinkovich reagent in the coupling of allylic alcohols with aldimines provides an alternative approach to regio- and stereodefined homoallylic amines. The reaction is based on the ability of Ti(IV) alkoxides to generate azametallacyclopropanes with imines, via *in situ* formation of low-valent titanium species, which can exchange ligands incorporating the allyl alkoxide as a temporary linker. A formal metallo-[3,3]-rearrangement furnishes, after hydrolysis, the desired homoallylic amine in a regio- and stereoselective manner, imposed by an organized cyclic transition state (Scheme 52). Particularly noteworthy is the direct coupling of allylic alcohols, avoiding the use of preformed allylic organometallic reagents. This versatile coupling reaction was exploited by the groups of Cha[135] and Micalizio.[136]

The group of Cha examined the reaction using aromatic imines and chiral geometrically defined allylic alcohols.[135] Complete transfer of chirality and stereoselectivity was observed for chiral *Z*-alkenes, while *E*-allylic alcohols produced a diastereomeric mixture with low *Z*/*E* selectivity (Scheme 53). The stereochemical outcome of the reaction was rationalized

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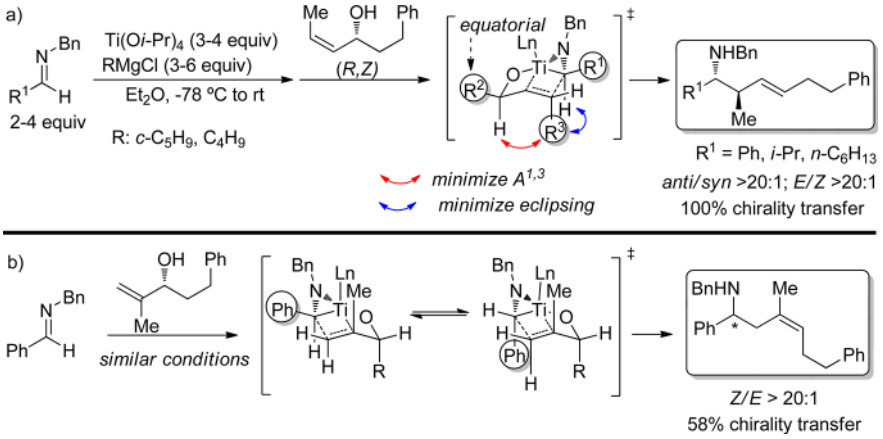
Scheme 54



using the working model mentioned above, where subsequent intramolecular *syn* carbometalation followed by *syn* β-elimination account for the formal metallo-[3,3]-rearrangement. The high diastereoselectivity displayed by *Z*-allylic alcohols is in accordance with the involvement of a conformer where the 1,3-allylic strain is significantly lower with respect to the other possible reactive conformer. On the other hand, the 1,3-allylic strain is similar for both possible reactive isomers of *E*-allylic alcohols, which is consistent with the lack of selectivity in this case. Similar differences in diastereoselectivities were reported in an independent study that also includes more densely substituted allylic alcohols.[136] Remarkably, functionalized allylic alcohols and nonactivated imines are suitable for this protocol. Aliphatic imines were also amenable to this coupling reaction, although the products were obtained in lower yields, mainly for α-branched imines that suffered from direct addition of cyclopentenyl Grignard reagent as an important side reaction. In an attempt to overcome these limitations, the group of Micalizio identified *n*-BuLi as an efficient reductant of Ti(O*i*-Pr)$_4$ that can be used for the reductive cross-coupling of allylic alcohols with aliphatic imines. Under these new conditions, aliphatic imines lead to the corresponding homoallylic amines in synthetically useful yields.[137]

A full account of their efforts in this area was recently reported by the group of Micalizio.[138] In this study, they illustrate through numerous examples the versatility of this cross-coupling reaction, which can accommodate aromatic or aliphatic imines and diversely substituted allylic alcohols. They also propose an empirical model based on the minimization of nonbonded steric interactions in a boat-like transition state of the *syn* carbometalation step, which explains the stereochemical course of the reaction. The high *anti*-selectivities observed in the reactions of racemic *Z*- or *E*-allylic alcohols with racemic Ti−imine complexes were explained as a result of a dynamic kinetic resolution. It was proposed that a rapid interconversion of azatitanacyclopropane enantiomers takes place in order to minimize eclipsing interactions around the developing C−C bond in the kinetically controlled carbometalation. Moreover, the reaction of *Z*-allylic alcohols were expected to produce *E*-homoallylic amines via a boat-like transition state where minimization of 1,3-allylic strain placed the allylic substituent in pseudoequatorial position (Scheme 54a). As expected, the use of of enantioenriched *Z*-allylic alcohols resulted in an effective translation of the stereochemical information to the homoallylic amines. However, when an enantioenriched terminal alkene was used as the allylic alcohol component, a poor chirality transfer was observed in the cross-coupling reaction (Scheme 54b). In this case, the low stereocontrol at the allylic position was related to the ability of the boat-like transition state to accommodate the phenyl ring in pseudoaxial or pseudoequatorial orientations without suffering important eclipsing interactions in the developing C−C bond. The lack of stereoselection observed in the coupling reaction of *E*-disubstituted allylic alcohols was also supported by the boat-like transition state that can place the allylic substituent in pseudoequatorial or pseudoaxial positions without significant A-1,2- or A-1,3-strains. For those cases where the translation of the stereochemical information from the allylic alcohol was not efficient, chiral imines were used and excellent selectivities were obtained for the matched combination of chiral reagents.

4. PROPARGYLATION AND ALLENYLATION REACTIONS

Mechanistically related to the allylation of carbonyl compounds and imines are the corresponding allenylation and propargylation. The resulting allenic and homopropargyl alcohols and amines are also versatile building blocks for the synthesis of complex organic molecules since, in addition to the stereogenic center, the triple bond or the cumulene moiety allow further transformations, including the generation of new carbon−carbon and carbon−heteroatom bonds. The stereochemical pathway of these reactions is determined by the configuration of either the chiral nucleophilic or the electrophilic partners. The propargylic or allenylic metal intermediates should be prepared from appropriate precursors, usually propargyl or allenyl halides upon metalation. However, lack of selectivity is a major drawback of this methodology, because propargylic or allenylic metals undergo metallotropic rearrangement and could be interconverted easily. Furthermore, competitive α- and γ-addition take place considering the regiochemistry in the nucleophile. Thus, methodologies for the regio- and stereoselective addition of propargyl or allenyl metals to carbonyl compounds and imines are of great interest in order to gain synthetic utility (Scheme 55).

4.1. Propargylation Reactions

4.1.1. Substrate Control. *4.1.1.1. Chiral Sulfinyl Imines.* In searching for new methodologies to access to alkynylaziridines in a stereoselective manner, Ferreira and Chemla reported the first examples of addition of an allenylzinc

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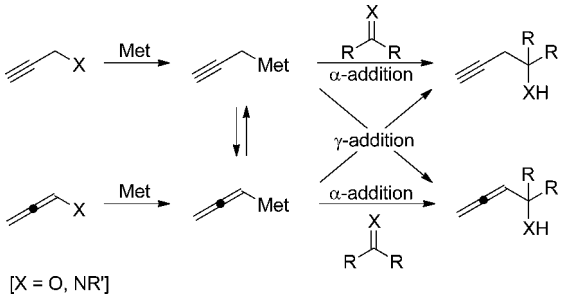
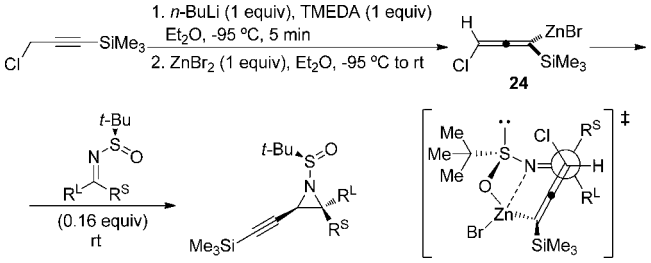
Scheme 55



compound[139] to *t*-BS imines.[140] The allenylzinc compound **24** was generated *in situ* as a racemic mixture from 3-chloro-1-trimethylsilylpropyne by sequential deprotonation and reaction with $ZnBr_2$ at low temperature. Chiral *t*-BS imines undergo *γ*-addition when reacting with **24**,[141] leading first to a *β*-chloroamine derivative, which rapidly undergoes intramolecular cyclization affording the alkynylaziridine. The highest conversions were achieved performing the reactions in Et_2O at room temperature. The reaction works well for a series of alkyl, alkenyl, and aryl aldimines, and also for ketimines derived from acetophenone and 6-undecanone, *trans*-alkynyl aziridines being the major reaction product in all cases. Importantly, facial selectivity was also very high [(R_S)-*t*-BS imines undergo *Si*-face addition], because only one major *trans*-isomer was detected (Table 56, dr >98:2).[142] A large excess of partially configurationally stable racemic allenylzinc compound **24** is necessary in order to get high stereoselectivity through a kinetic resolution. It has been postulated that this resolution results from a chelate transition state in which the zinc atom of **24** is coordinated by both the nitrogen and the oxygen atoms of the imine in a four-membered metallacycle.

Table 56. Synthesis of *trans*-Alkynylaziridines from Racemic 24 and *t*-BS Imines



entry	R^S	R^L	yield (%)	*trans*/*cis*	dr[a]
1	H	*n*-Pr	61	89:11	>98:2
2	H	*i*-Pr	69	94:6	>98:2
3	H	Cy	58	90:10	>98:2
4	H	(*E*)-$CH_3CH{=}CH$	64	90:10	>98:2
5	H	Ph	50	86:14	>98:2
6	Me	Ph	69	90:10	>98:2
7	$CH_3(CH_2)_4$	$CH_3(CH_2)_4$	87		>98:2

[a]The given dr value corresponds to the major isomer.

Relative configuration of racemic **24** and enantioenriched *t*-BS imines in the aziridination reaction was reversed by working in the presence of HMPA. Now the major reaction product was *cis*-alkynylaziridines. The amount of HMPA had a strong influence on the stereoselectivity, the best results being obtained when 60 equiv were used (10 equiv with respect to the allenylzinc **24**). The reaction is limited to imines derived from primary alkyl, alkenyl, and alkynyl aldehydes, and product was not observed when *α*-branched imines were used. Regarding the stereoselectivity, *cis*/*trans* ratio values ranged from 71:29 to 89:11, and *cis*-isomers were always isolated as single stereoisomers (Table 57).[143] Concerning facial selectivity, it was found that (R_S)-*t*-BS imines underwent *Re*-face addition, which is the opposite for that observed when the reaction was performed in the absence of HMPA (Table 56).[142] The observed stereochemistry for the *cis*-aziridines was better rationalized by synclinal models through either suprafacial or antarafacial S_E2' processes (Table 57). In these models, no coordination of zinc atom by the nitrogen and the oxygen atoms takes place, which is responsible for the face selectivity.

The addition of 3-alkoxy allenylzinc compounds to *t*-BS imines was also studied by Ferreira and Chemla. The organometallic nucleophile **25** was prepared *in situ* from the methoxymethyl ether of 3-trimethylsilylprop-2-yn-1-ol through a sequential deprotonation and reaction with $ZnBr_2$. The reaction of racemic **25** with *t*-BS imines at low temperature in Et_2O provided chiral acetylenic *anti*-1,2-amino alcohols via a kinetic resolution (Table 58).[144] The best results considering yield and stereoselectivity were found when the reactions were performed at −80 °C in the presence of 4 equiv of racemic allenylzinc compound **25** and a catalytic amount of TMEDA. Importantly, for highly reactive umbranched *t*-BS aldimines, slow addition of the imine to the reaction mixture was required in order to achieve high levels of diastereoselection. On the other side, slow addition was not necessary for less reactive secondary or unsaturated *t*-BS aldimines. The observed *anti*-stereoselectivity could be explained considering a model where the zinc is exclusively coordinated to the nitrogen of the *t*-BS group, the addition of the nucleophile taking place from the less hindered *Si*-face of the imine with (S_S)-configuration. Removal of the *t*-BS group from the nitrogen and the methoxymethyl unit from the oxygen under acidic conditions yielded *trans*-1,2-amino alcohols without racemization taking place at any extension.[145]

Enantiopure *anti*,*anti* and *syn*,*anti* acetylenic 2-amino-1,3-diol stereotriads were accessible when *α*-alkoxy *t*-BS imines reacted with allenylzinc **25** under the previously mentioned reaction conditions (Table 59).[146] The stereoselectivity was found to be controlled only by the configuration of the *t*-BS group, independently of the configuration of the carbon adjacent to the imino group, thus operating a model similar to that shown in Table 58.

Chemla and co-workers tried also to achieve the stereoselective synthesis of chiral acetylenic *syn*-1,2-amino alcohols from the racemic allenylzinc compound **25** and *t*-BS imines via a kinetic resolution. They anticipated that *syn*-1,2-amino alcohols would be obtained if chelation of the lithium cation by the oxygen atoms of both the *t*-BS imine and the methoxymethyl ether moiety is prevented. In order to do that, different additives were used in the coupling reaction without any success. For that reason, they switched to the corresponding copper analogues **26**. These copper reagents **26** were generated by deprotonation of the methoxymethyl ether of 3-trimethylsilylprop-2-yn-1-ol with *t*-BuLi at −95 °C, followed by transmetalation with the appropriate copper salt (Table 60).[147] They found that the reaction of 2 equiv of lithio cuprates **26** with chiral *t*-BS imines in THF and in the presence of HMPA resulted in the formation of two isomeric *syn* and *anti*

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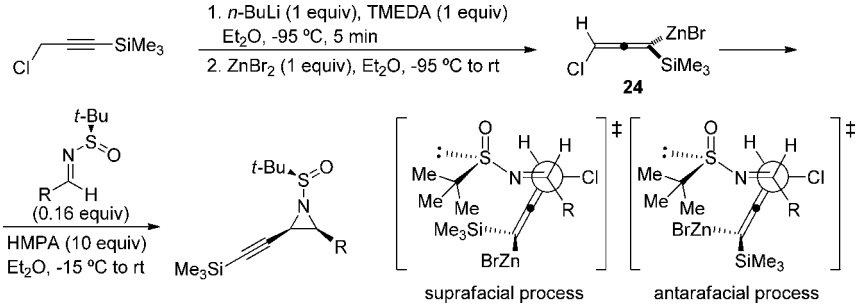
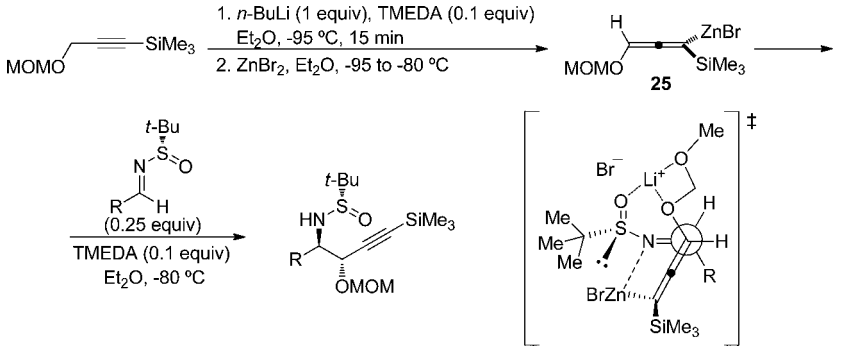
Table 57. Synthesis of *cis*-Alkynylaziridines from Racemic 24 and *t*-BS Imines



entry	R	yield (%)	*cis*/*trans*	dr[a]
1	Me	64	89:11	>98:2
2	*n*-Pr	54	84:16	>98:2
3	(*E*)-PhCH=CH	56	87:13	>98:2
4	$PhCH_2CH_2$	60	71:29	>98:2

[a]The given dr value corresponds to the major isomer.

Table 58. Synthesis of *anti*-(S_S,1*R*,2*S*)-*β*-Amino Propargylic Ethers



entry	R	yield (%)	*anti*/*syn*	dr[a]
1	*n*-Pr	82	>20:1	>20:1
2	*i*-Pr	83	>20:1	>20:1
3	Cy	81	>20:1	>20:1
4	$PhCH_2CH_2$	78	>20:1	>20:1
5	(*E*)-CH_3CH=CH	77	20:1	>20:1
6	Ph	87	>20:1	>20:1

[a]The given dr value corresponds to the major isomer.

adducts. Importantly, the desired *syn*-*β*-amino propargylic ether was always formed as the major isomer. Regarding the cuprate **26**, the best results were attained when cyano (**26**, X = CN) and mesityl cuprates (**26**, X = Mes) were used. By contrast, high-order cuprates led to a significantly lower yield and selectivity. The optimized reaction conditions with both the cyano- and the mesityl cuprates **26** are depicted in Table 60. The reaction of both cuprates with functionalized chiral imines provided the desired *syn*-*β*-amino propargylic ethers in high yields with reasonable levels of *syn*/*anti* selectivity (Table 60, entries 1−4). On the other hand, mesitylcuprate **26** proved to be superior to the cyano derivative in the reaction with aromatic and *α*,*β*-unsaturated imines (Table 60, entries 5−8). Facial selectivity was also determined in these reactions by the configuration of the *t*-BS unit, *Si*-face addition taking place for (S_S)-derivatives.

Chemla and co-workers reported more recently the diastereoselective synthesis of enantiopure homopropargylic amines by propargylation of *t*-BS imines with 1-trimethylsilyl allenylzinc bromide **27**.[148] This organozinc intermediate was generated in THF by metalation of 1-trimethylsilylpropyne with *sec*-butyllithium at −20 °C and subsequent transmetalation with $ZnBr_2$ at −35 °C. Considering the stoichiometry of the process, 2 equiv of **27** were necessary in order to achieve full conversion. The reaction with the imine derived from benzaldehyde in THF at −78 °C led to the homopropargylic amine as a single isomer in 79% yield in a totally regioselective manner (Table 61, entry 1). However, a lower level of diastereocontrol occurred when the same reaction was performed at room temperature, although regioselectivity was maintained (Table 61, entry 2). Surprisingly, at −78 °C, the propargylation of imine derived from *n*-butanal was not completely regioselective, since an 82:18 mixture of homopropargylic and *α*-allenylic amines was obtained; nevertheless, an excellent diastereomeric ratio was achieved (Table 61, entry 3). By contrast, a better result was obtained when the reaction was performed at room temperature, homopropargylic amine being now exclusively formed in 98% yield and dr >98:2 (Table 61, entry 4). Good levels of regio- and stereocontrol were also

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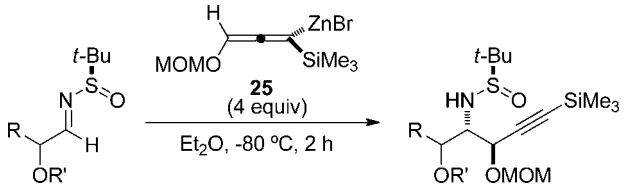
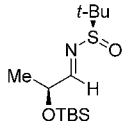
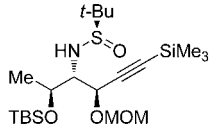
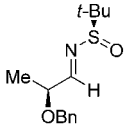
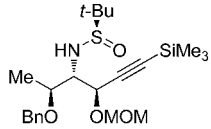
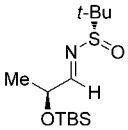
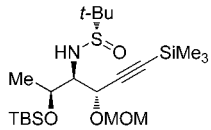
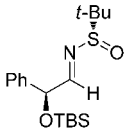
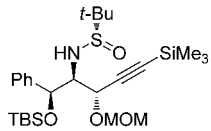
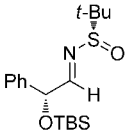
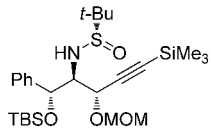
Table 59. Propargylation of α-Substituted Aldimines

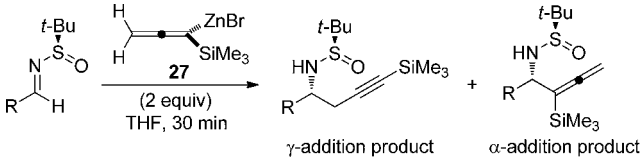


Entry	Aldimine	Product	Yield (%)	dr[a]
1			81	>20:1
2			87	>20:1
3			77	>20:1
4			75	>20:1
5			91	>20:1

[a]The given dr value corresponds to the major isomer.

obtained in the propargylation of other α,β-unsaturated and functionalized imines (Table 61, entries 5−7).

Table 61. Synthesis of Homopropargylamines from Allenylzinc 27 and *t*-BS Imines



entry	R	*T* (°C)	γ-addition/α-addition	yield (%)	dr[a]
1	Ph	−78	>98:2	79	>98:2
2	Ph	rt	>98:2	79	84:16
3	*n*-Pr	−78	82:18	90	>98:2
4	*n*-Pr	rt	>98:2	98	>98:2
5	*i*-Pr	rt	>98:2	70	96:4
6	(*E*)-PhCH=CH	rt	>98:2	98	>98:2
7	$TBSOCH_2$	rt	>98:2	81	>98:2

[a]The given dr value corresponds to the major isomer.

A six-membered transition-state model has been postulated in which the zinc atom of **27** is coordinated only to the nitrogen atom of the imine that adopts the most stable like *s-cis*-conformation (Figure 8). In this case, *Re*-face nucleophilic addition takes place for (R_S)-imines.

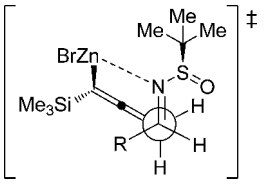
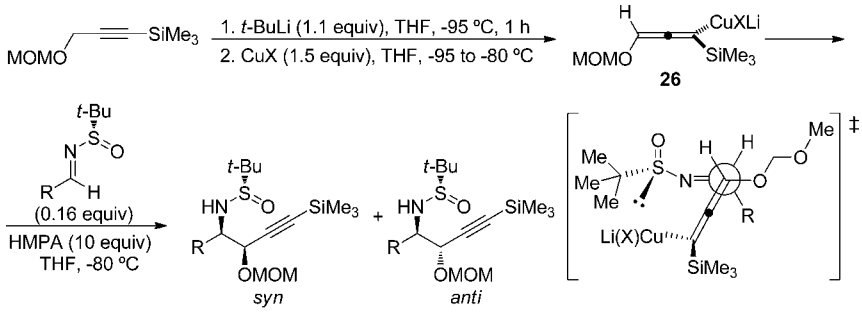


Figure 8. Transition state model for the propargylation of *t*-BS aldimines with allenyl zinc **27**.

4.1.1.2. Chiral Glyoxylic Oximes. Takemoto and co-workers found that the palladium(0)−indium(I) iodide combination was effective for the diastereoselective propargylation of the chiral glyoxylic oxime ether derived from Oppolzer's

Table 60. Synthesis of *syn*-(S_S,1*R*,2*S*)-β-Amino Propargylic Ethers



entry	R	X	yield (%)	*syn*/*anti*
1	$Cl(CH_2)_4$	CN	81	87:13
2	$Cl(CH_2)_4$	Mes	72	91:9
3	$(CH_2{=}CHCH_2)N(Cbz)CH_2$	CN	80	80:20
4	$(CH_2{=}CHCH_2)N(Cbz)CH_2$	Mes	81	90:10
5	Ph	CN	83	40:60
6	Ph	Mes	90	60:40
7	(*E*)-PhCH=CH	CN	72	50:50
8	(*E*)-PhCH=CH	Mes	68	77:23

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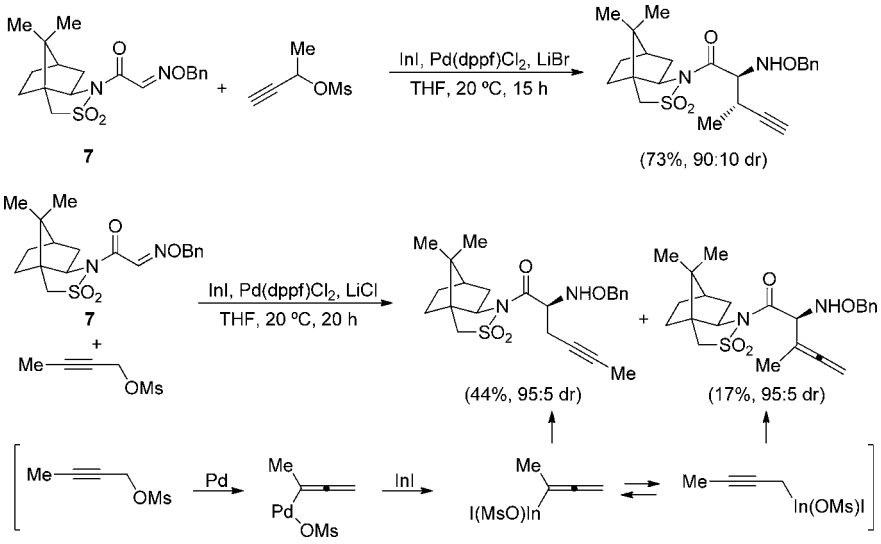
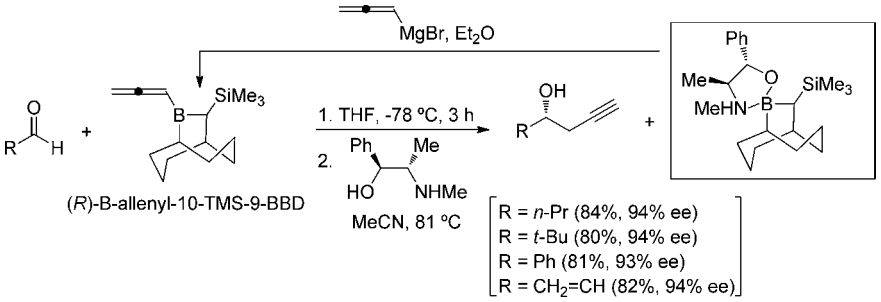
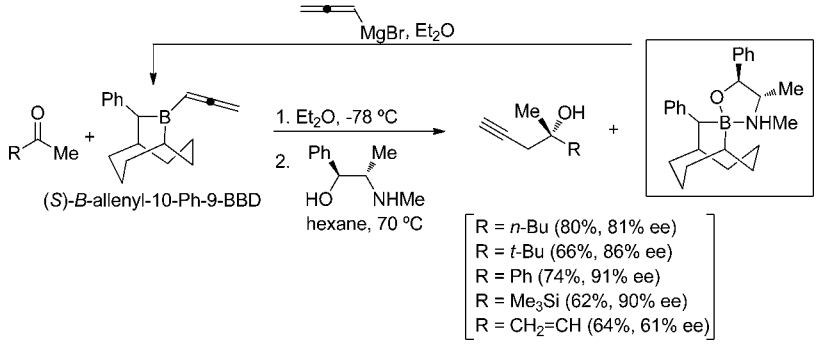
Scheme 56



Scheme 57



Scheme 58



camphorsultam **7** with propargylic alcohol derivatives in the presence of LiBr or LiCl.[149] Among several palladium catalysts, the highest yields and diastereoselectivities were obtained using $Pd(dppf)Cl_2$ in the presence of LiBr. Thus, the reaction of but-3-yn-2-yl mesylate with **7** in THF at 20 °C for 15 h in the presence of catalytic amounts of $Pd(dppf)Cl_2$ and LiBr led to the corresponding *anti*-homopropargylic amine derivative in 73% yield (Scheme 56). On the other hand, the palladium−indium iodide mediated reaction of chiral oxime ether **7** with but-2-yn-1-yl mesylate proceeded smoothly to give a mixture of homopropargylic (44% yield) and allenic (17% yield) amine derivatives. These results indicated that an allenic organometallic isomer and a propargylic organometallic isomer are involved in the process and interconvert to each other, and after reaction with the oxime derivative, **7** would lead to the propargylic product and the allenic product (Scheme 56).

4.1.2. Reagent Control. *4.1.2.1. Allenyl Boranes.* Highly diastereoselective allenylboration of carbonyl compounds has been achieved using chiral allenyl boranes. Soderquist found that the reaction of stable and storable *B*-allenyl-10-trimethylsilyl-9-borabicyclo[3.3.2]decane [*B*-allenyl-10-TMS-9-BBD] with a wide range of aldehydes at −78 °C provided the corresponding stable intermediate borinates in quantitative yields, which after addition of pseudoephedrine led to homopropargylic alcohols and an air-stable crystalline pseudoephedrine−boron complex. Importantly, starting allenylborane (*R*)-*B*-allenyl-10-TMS-9-BBD can be regenerated upon treatment of the crystalline pseudoephedrine−boron complex

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with allenylmagnesium bromide, pseudoephedrine being efficiently recovered in this step (Scheme 57).[150]

Allylboration of ketones took also place with high levels of stereocontrol using (*S*)-*B*-allenyl-10-phenyl-9-borabicyclo-[3.3.2]decane [(*S*)-*B*-allenyl-10-Ph-9-BBD]. The reactions proceeded at −78 °C in reasonable reaction times for methyl ketones, among them challenging substrates, such as 2-butanone and methyl vinyl ketone (Scheme 58).[151] By contrast, the reaction with propiophenone was much slower and took place at 25 °C for 2 days leading to the reaction product in 76% ee.

For the prediction of the product stereochemistry, pretransition state complexes have been proposed based on molecular mechanics calculations. The most favored conformations are the *B*-chiral *anti*-carbonyl complex that forms *cis* to the 10-substituent in the boat−chair form of (*R*)-*B*-allenyl-10-TMS-9-BBD and (*S*)-*B*-allenyl-10-Ph-9-BBD. In this way, selective allenylation of the *Re*-face of the aldehyde with (*R*)-*B*-allenyl-10-TMS-9-BBD and of the *Si*-face of the methyl ketone with (*S*)-*B*-allenyl-10-Ph-9-BBD takes place (Figure 9).

Re-face addition model with (*R*)-*B*-allenyl-10-TMS-9-BBD

Si-face addition model with (*S*)-*B*-allenyl-10-Ph-9-BBD

Figure 9. Proposed pretransition state complexes for stereoselective propargylation of carbonyl compounds with (*R*)-*B*-allenyl-10-TMS-9-BBD and (*S*)-*B*-allenyl-10-Ph-9-BBD.

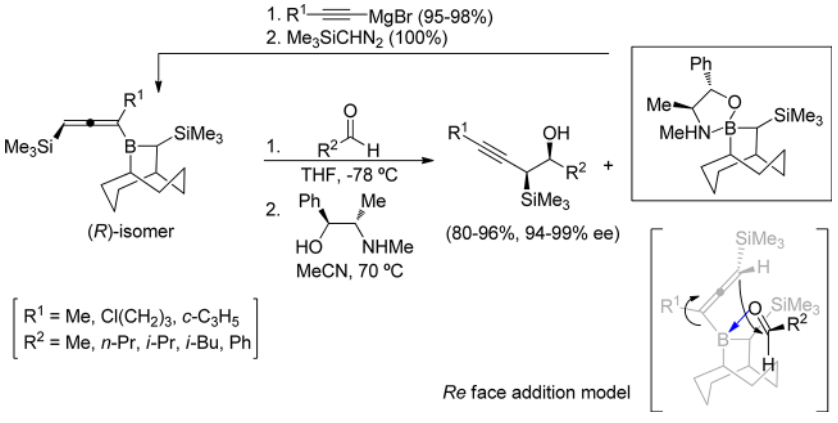
More sophisticated *B*-allenyl-10-trimethylsilyl-9-borabicyclo-[3.3.2]decanes were prepared in enantiomerically and diastereomerically pure form starting from a pseudoephedrine−9-BBD complex by reaction first with alkynyl organomagnesium compounds and then with trimethylsilyldiazomethane. In this second step, a formal insertion of the trimethylsilylmethylene group into the acetylenic carbon−boron bond occurred with concomitant evolution of nitrogen, followed by a suprafacial 1,3-borotropic rearrangement. Allenylboration of aldehydes with chiral α-borylallenes at −78 °C for 3 h provided, after addition of pseudoephedrine, *syn*-β-trimethylsilyl homopropargylic alcohols in high yields, diastereomeric ratios (99:1), and enantioselectivities, along with the starting pseudoephedrine−9-BBD complex (Scheme 59).[152] This process is more enantioselective than allenylboration with (*R*)-*B*-allenyl-10-TMS-9-BBD (Scheme 57).[150] The enhanced enantioselectivity can be attributed to the additional α-substituent, which increases the effective size of the allenyl group relative to that of the aldehyde. It is important to mention that only a modest diminution in enantioselectivity was observed when the reactions were conducted at room temperature (from 94−99% at −78 °C to 91−98% ee at 25 °C). In this case, the pretransition state complex shown in Scheme 59 has been proposed in order to explain the *syn* diastereoselectivity, and the nucleophilic addition to the carbonyl unit occurs on the *Re*-face of the aldehyde with (*R*)-isomers.

These chiral α-borylallenes have also been used for the allenylation of *N*-H imines derived from either *N*-TMS or *N*-DIBAL aldimines. The allenylboration process was triggered upon addition of 1 equiv of methanol to the reaction mixture at low temperature. When allenylboration was completed, transesterification using the appropriate enantiomer of pseudoephedrine in refluxing acetonitrile was carried out in order to get the corresponding homopropargylic amines in high yields (51−85%) and excellent selectivity (>99% *syn*, 92−99% ee). Importantly, the higher the size of R^1 in chiral α-borylallenes and R^2 in the aldimine, the higher the enantioselectivity (Scheme 60).[153] For instance, the lowest ee was obtained when $R^1 = R^2 = Me$ (92% ee).

Regarding the pretransition state complexes *anti-cis* and *anti-trans* (Figure 10), the first one is favored over the second one, due to the unfavorable steric interactions of the allenyl moiety with the trimethylsilyl group at 10 position in the *anti*/*trans* system. The model also anticipates the *syn* diastereoselectivity and the transfer to the *Re*-face of the imine of the allenyl unit from the (*R*)-isomers.

4.1.2.2. Allenyl Stannanes and Silanes. Hegedus and coworkers found that the reaction of optically active α-oxazolidinonylallenylstannanes, prepared through a sequential lithiation−stannylation of *N*-propargyloxazolidinones with aldehydes in the presence of a Lewis acid, such as $BF_3{\cdot}OEt_2$, led to β-hydroxypropargylamines. The process proved to be highly stereoselective, the *syn*-diastereomers always being the major reaction products in high ee (Table 62).[154] When $SnCl_2$ was used instead of $BF_3{\cdot}OEt_2$, yields and diastereomeric ratios were considerably lower (compare entries 4 and 5 in Table 62). The absolute configuration of these compounds was determined by single-crystal X-ray diffraction. A wide range

Scheme 59



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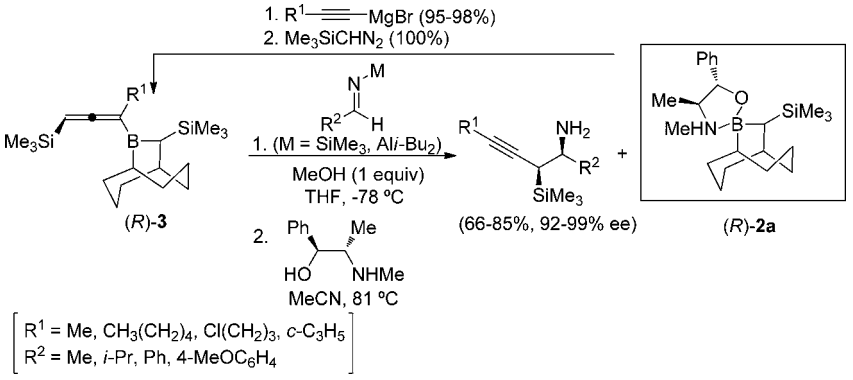
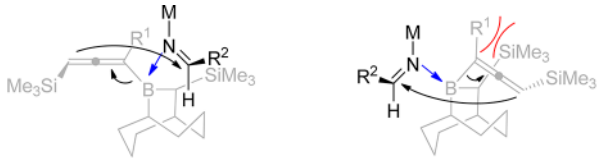
Scheme 60



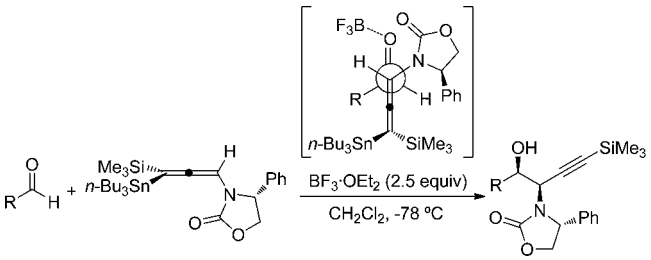


anti-cis complex (favorable)
Re face addition with (*R*)-isomers

anti-trans complex (unfavorable)
Si face addition with (*R*)-isomers

Figure 10. Proposed pretransition state complexes for stereoselective propargylation of carbonyl compounds with α-substituted (*R*)-*B*-allenyl-10-TMS-9-BBDs.

Table 62. Synthesis of β-Hydroxypropargylamine Derivatives from Aldehydes and Chiral α-Oxazolidinonylallenylstannanes



entry	R	yield (%)	dr (*syn*/*anti*)
1	*n*-Pr	93	>95:5
2	*i*-Pr	95	>95:5
3	(*E*)-$CH_3CH{=}CH$	80	>95:5
4	Ph	95	90:10
5[a]	Ph	71	66:34
6	(*S*)-$CH_3CH(OBn)$	87	92:8

[a] $SnCl_2$ was used instead of $BF_3{\cdot}OEt_2$.

of aldehydes (straight and branched chain aliphatic, aromatic, and α,β-unsaturated) underwent the reaction in high yield and diastereoselectivity. However, the electron-rich 4-formylimidazole was unreactive. The stereochemical outcome of the condensation of these α-oxazolidinonylallenylstannanes with aldehydes is consistent with the Felkin−Ahn transition state model proposed by Marshall[155] in the $BF_3{\cdot}OEt_2$-catalyzed reactions of aldehydes with allenylstannanes. According to this model, the aldehyde approaches from the face opposite the tributyltin group with the large oxazolidinone *anti* to the large R group of the aldehyde (Table 62).

Low-temperature flow-chemistry technology has also been used for performing Marshall homopropargylation reactions[156] with chiral allenylstannane (Chart 2).[95] In this way, as previously mentioned in section 3.2.1.1, through this technology, the common starting materials used in complex molecule assembly could be afforded in a much shorter period time than the corresponding batch reactions (Chart 2).

A reliable protocol for the production of enantioenriched allenylsilanes was established by Panek and Brawn, taking advantage of the highly diastereoselective Johnson orthoester Claisen rearrangement of an enantioenriched 1-silyl propargylic alcohol in refluxing xylenes in the presence of propionic acid. The ee of the allene was determined by HPLC and, as anticipated, was nearly identical to the ee of the starting propargylic alcohol. The chiral silane was used in a Lewis acid catalyzed three-component S_E2' reaction of aldehydes and trimethylsilyl ethers to form homopropargylic ethers with higly predominant *syn* stereochemistry. The optimal reaction conditions involved the use of $BF_3{\cdot}OEt_2$ as catalyst in acetonitrile at −20 °C (Table 63).[157] The highest yields and selectivities were achieved with aromatic aldehydes (Table 63, entries 1−3). The homopropargylic ether was obtained in high

Chart 2

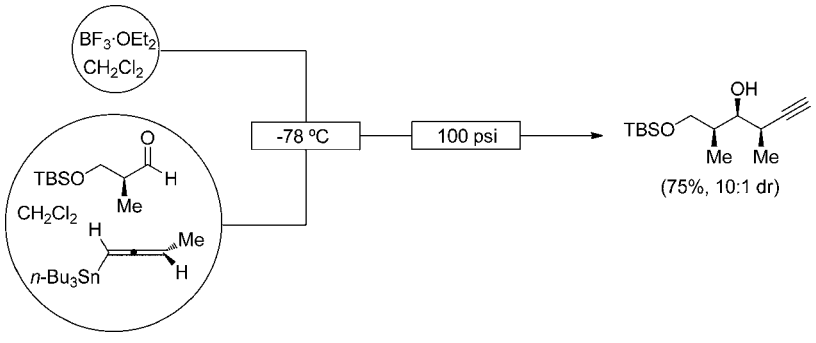


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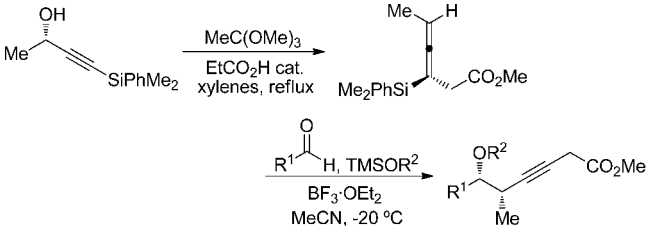
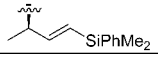
Table 63. Synthesis of *syn* Homopropargylic Ethers from Aldehydes, Trimethylsilyl Ethers, and a Chiral Allenylsilane

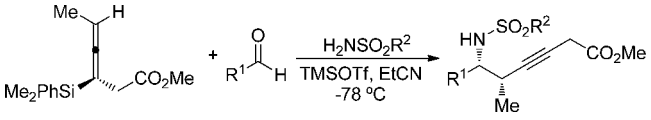


Entry	R^1	R^2	Yield (%)	dr
1	2,5-$(MeO)_2C_6H_3$	Me	69	>20:1
2	Ph	Me	54	6:1
3	2-BrC_6H_4	Me	78	>20:1
4	*i*-Pr	Me	42	>20:1
5	$CH_3(CH_2)_3$	Me	43	1.8:1
6	2-BrC_6H_4	CH_2=$CHCH_2$	78	>20:1
7	2-BrC_6H_4	$PhCH_2$	60	>20:1
8	2-BrC_6H_4		49	10:1

selectivity, albeit in moderate yield, with branched aliphatic aldehydes (Table 63, entry 4). However, straight aliphatic aldehydes gave low yields and stereoselectivities (Table 63, entry 5). Other more complex trimethylsilyl ethers different than TMSOMe were also effective in generating oxonium ions for these reactions (Table 63, entries 6−8).

Enantioenriched allenylsilanes have also been used as carbon nucleophiles in three-component reactions with *in situ* generated *N*-sulfonylimines to selectively form *syn*-homopropargylic sulfonamides. Panek and Brawn reported also that the result of the reaction of iminium ions, which were formed *in situ* by combining aliphatic aldehydes and methanesulfonamide in the presence of trimethylsilyltriflate (TMSOTf), with a chiral allenylsilane was nearly exclusive formation of *syn*-homopropargylic sulfonamides (Table 64).[158] This reaction was effective

Table 64. Synthesis of *syn*-Homopropargylic Sulfonamides from Aldehydes, Sulfonamides, and a Chiral Allenylsilane



entry	R^1	R^2	yield (%)	dr
1	*i*-Pr	Me	81	>20:1
2	$PhCH_2CH_2$	Me	81	10:1
3	$BnO(CH_2)_2$	Me	65	9:1
4	*t*-Bu	Me	82	>20:1
5	Cy	4-MeC_6H_4	80	>20:1
6	*t*-Bu	4-$NO_2C_6H_4$	74	>20:1
7	Ph	Me	47	10:1
8	2-BrC_6H_4	Me	59	13:1
9	4-$NO_2C_6H_4$	Me	28	10:1
10	2,3-$(MeO)_2C_6H_3$	Me	33	6:1

for a variety of aldehyde partners, including secondary aliphatic aldehydes, which formed the product as a single diastereomer (Table 64, entry 1). Primary aliphatic aldehydes (Table 64, entries 1 and 2) gave moderate to high yields and lower but still useful levels of diastereoselectivity. Tertiary aliphatic aldehydes (Table 64, entry 4) also gave high yield of a single diastereomer, although the reactions required slightly higher temperatures to reach completion. Propargylation reactions with aliphatic aldehydes were also tolerant of a number of different sulfonamides, in each case exclusively forming the homopropargylic sulfonamide (Table 64, entries 5 and 6). By contrast, aromatic aldehydes gave always lower yields and diastereoselectivities (Table 64, entries 7−10).

The observed *syn* stereochemistry in the synthesis of both homopropargyl ethers and amines can be rationalized by open transition states using antiperiplanar or synclinal orientations of reaction partners (Figure 11), where the chiral (*R*)-allenylsilane

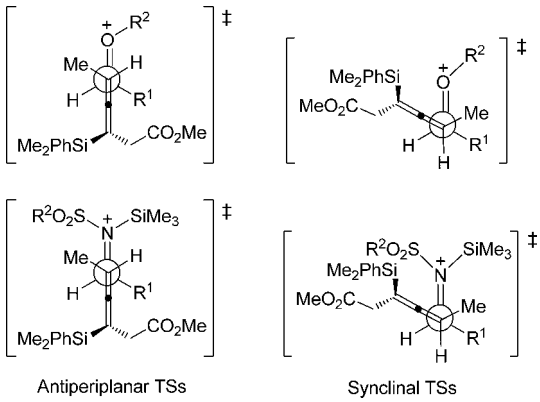


Figure 11. Transition states for the synthesis of homopropargylic ethers and for the aminopropargylation of aldehydes with a chiral (*R*)-allenylsilane.

is shown to add to the *Re*-face of the oxonium or the iminium ion, respectively. While either transition state nicely illustrates the stereochemical course of the reaction, probably the antiperiplanar transition state, where the interaction between the R^2 group on the oxonium ion and the methyl on the allene is minimized, may be the best illustration of this reaction in the case of *syn*-homopropargylic ethers.

4.1.2.3. Allenyl Zinc Derivatives. Marshall developed a methodology for the conversion of chiral propargylic mesylates to chiral allenylzinc or indium reagents upon reaction with Et_2Zn or InI, respectively, in the presence of $Pd(OAc)_2$ and Ph_3P.[155a,159] The reaction of an *in situ* generated chiral allenylzinc reagent with various aldehydes afforded homopropargylic alcohols of high enantiomeric purity (Scheme 61).[160] Additions of the chiral allenylzinc to α-methyl- or silyloxy-substituted aldehydes were highly diastereoselective favoring the *anti* isomer with negligible mismatching. However, additions to unsubstituted conjugated enals led to significant quantities of 1,4-adduct arising from the diethylzinc component of the reaction. This side reaction was avoided through use of the related allenylindium reagent.

4.1.2.4. Allenyl Alcohols. Loh reported a new and efficient method of obtaining homopropargylic alcohols via homopropargylic transfer from the allenic alcohol to various aldehydes in the presence of Lewis acid catalysts. The reaction of an enantiomerically enriched α-trimethylsilyl cyclohexyl allenic alcohol (92% ee) with different aldehydes under the optimized reaction conditions [CH_2Cl_2 in the presence of 1 mol % $In(OTf)_3$] afforded the expected homopropargylic alcohols in high yields and enantioselectivities (88−97% ee, corrected based on 92% ee of the starting material). Mechanistically, an unprecedented oxonium [3,3]-sigmatropic rearrangement of the allenic alcohol in the presence of the aldehyde and the

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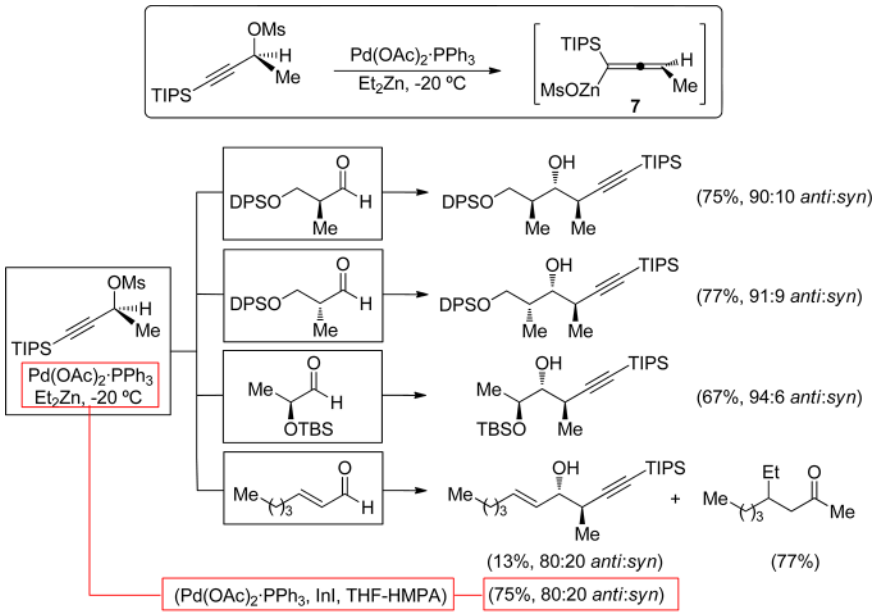
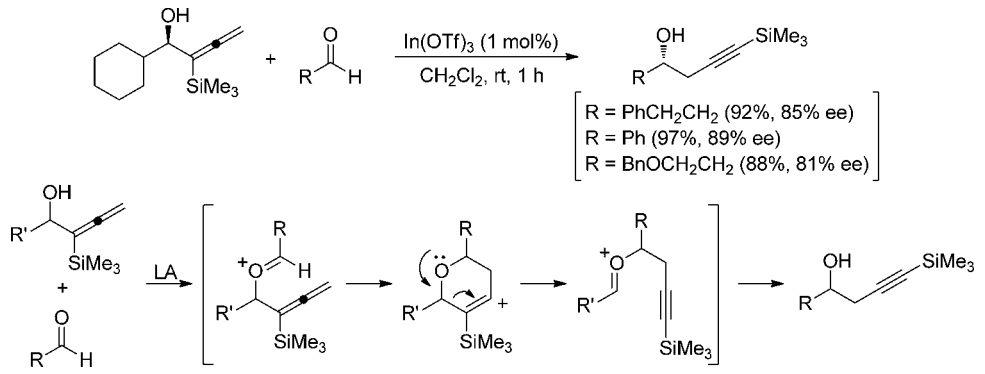
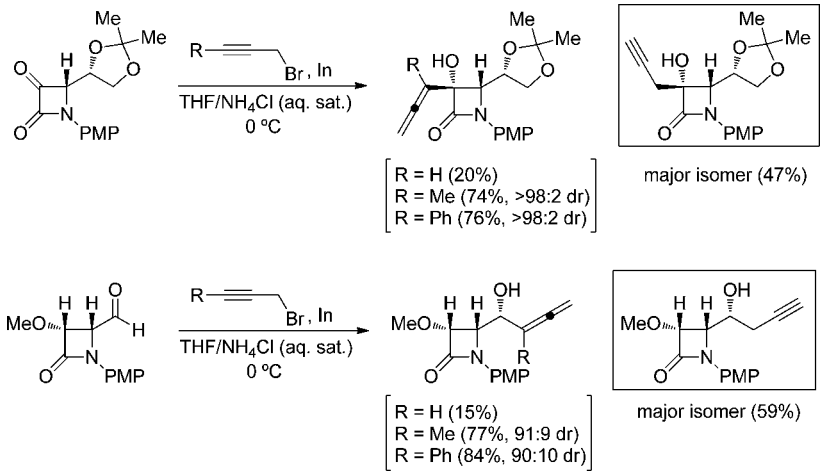
Scheme 61



Scheme 62



Scheme 63



Lewis acid catalyst has been proposed to occur, and consequently, the products were obtained with the opposite configuration compared with the starting material (Scheme 62).[161]

4.2. Allenylation Reactions

4.2.1. Substrate Control. *4.2.1.1. Chiral Carbonyl Compounds.* Chiral carbonyl compounds with prostereogenic centers undergo stereoselective allenylation upon reaction with appropriate propargylic metal intermediates. Alcaide and

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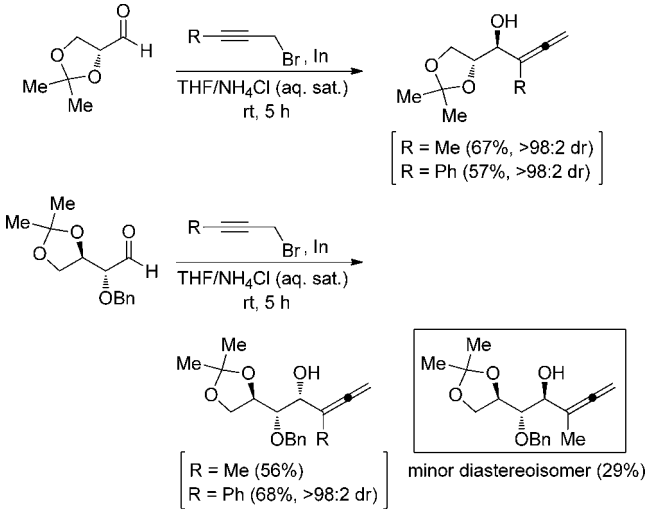
Almendros reported that the indium-mediated addition of propargyl bromide to a chiral azetidine-2,3-dione occurred with poor regioselectivity in aqueous THF. An almost 1:1 mixture of allenyl and homopropargyl derivatives were obtained, the allenyl compound being the major component. Surprisingly, the regiochemical preference was reversed on the indium-promoted reaction just by changing the solvent system from aqueous THF to a saturated aqueous solution of NH_4Cl in THF. Now, the homopropargyl alcohol was predominant in the reaction mixture (Scheme 63).[162] Fortunately, the allenylation reaction proceeded in a totally regioselective fashion when 3-substituted (methyl or phenyl) prop-2-ynyl bromides were used in a saturated aqueous solution of NH_4Cl in THF. The resulting allenyl carbinols were isolated as essentially regio- and diastereoisomerically pure products (Scheme 63). On the other hand, the indium-promoted reaction of a chiral azetidin-2-one-4-carbaldehyde with propargyl bromide proceeded with total diastereocontrol but poor regiocontrol. In a similar way as for the azetidine-2,3-dione, allenyl carbinols were exclusively formed from the azetidin-2-one-4-carbaldehyde when the allenylation was performed with 3-substituted prop-2-ynyl bromides (Scheme 63). Importantly, the resulting *syn*/*anti* alcohols were easily separated by column chromatography.

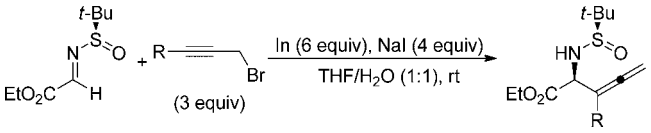
Alcaide and Almendros also studied the stereoselective indium-mediated allenylation of isopropylidene-protected aldehydes derived from D-glyceraldehyde and D-erythrose in aqueous media. They found that the regiochemistry of the process was strongly dependent on both the aldehyde and the propargylic bromide. The indium-mediated Barbier-type carbonyl allenylation of aldehyde derived from D-glyceraldehyde with 1-bromobut-2-yne occurred with complete diastereoselectivity. However, for the aldehyde derived from D-erythrose, an almost 2:1 mixture of *syn*/*anti* diastereomeric diols was obtained. On the other hand, both chiral aldehydes reacted with the organoindium reagent, generated *in situ* from indium and 1-phenyl-3-bromoprop-1-yne, in a totally diastereoselective fashion to generate the corresponding allenylcarbinols as single isomers (Scheme 64).[163] The absolute configurations of the newly created stereocenters were assigned upon esterification of the resulting alcohols with (*S*)- and (*R*)-*O*-methylmandelic acids, according to the empirical model developed by Trost.[164] The here prepared allenylcarbinols have been transformed into functionalized enantiopure tetrahydrofurans, dihydropyrans, and tetrahydrooxepines, after selective removal of the O-protecting groups, through chemo-, regio-, and stereocontrolled metal-catalyzed oxycyclization reactions. An intramolecular version of this indium-mediated Barbier carbonyl allenylation has been used in the construction of a seven-membered ring in a diastereoselective synthesis of the alkaloid (±)-stemoamide.[165]

Scheme 64



4.2.1.2. Chiral Sulfinyl Imines. Xu and Jin developed practical reaction conditions to perform the selective allenylation of *t*-BS imine derived from ethyl glyoxylate. The best results, after extensive screening, are shown in Table 65.[166]

Table 65. Indium-Mediated Allenylation of a *t*-BS Imino Ester

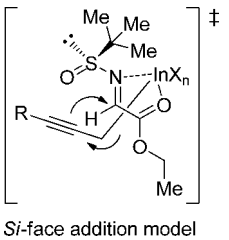


entry	R	yield (%)	dr
1	Ph	94	99:1
2	4-MeC_6H_4	87	>99:1
3	4-$MeOC_6H_4$	80	>99:1
4	4-BrC_6H_4	84	99:1
5	*n*-Bu	84	99:1
6	Me_3Si	54	97.5:2.5

The use of iodide additives was crucial to obtain higher yields. It is supposed that bromine−iodine indium exchange occurred in aqueous solution and facilitates the formation of the propargylindium intermediate. The allenylation reaction took place under these conditions with a variety of propargylic bromides with diverse steric and electronic properties. Different α-allenylglycine ethyl ester derivatives were obtained in good yields and excellent diastereoselectivities (Table 65). When TMS-substituted propargyl bromide was subjected to the same reaction, a 16% yield of propargylamino acid was isolated (Table 65, entry 6).

A five-membered chelation transition state model has been proposed for this asymmetric allenylation, in order to explain the observed facial diastereoselectivity, in which the uncoordinated *N*-sulfinyl group adopts an approximate *syn*-periplanar configuration (Figure 12). Because of the bulky *tert*-butyl group, the addition of the allenyl group took place from the sterically less hindered *Si*-face of the C=N bond in the (R_S)-imine conformation, thus facilitating the formation of the corresponding (*S*)-amino acid derivatives.

4.2.2. Reagent Control. *4.2.2.1. Propargyl Boranes.* The reaction of chiral propargyl boranes derived from 9-



Si-face addition model

Figure 12. Proposed transition state for indium-mediated allenylation of the *t*-BS imine of ethyl glyoxylate.

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Scheme 65

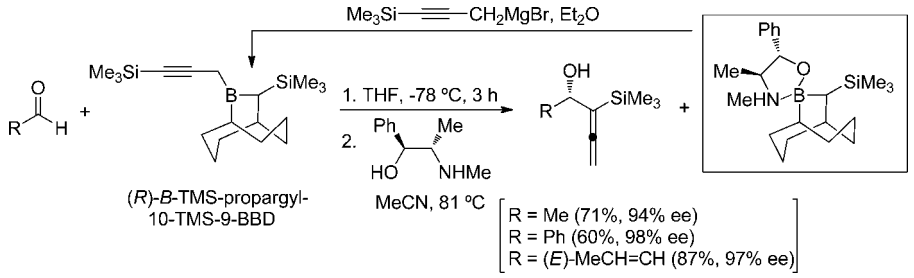
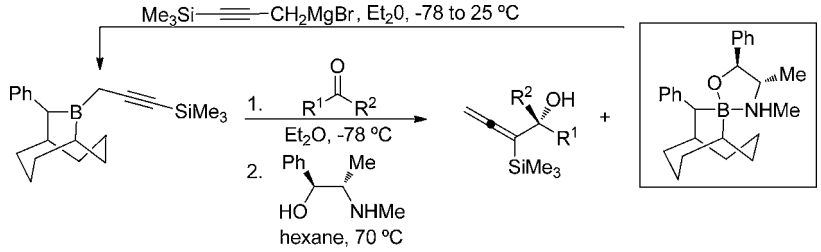


Table 66. Synthesis of Tertiary α-Allenyl Carbinols from Ketones and (*S*)-*B*-TMS-Propargyl-10-Ph-9-BBD



			allenyl alcohol	
entry	R^1	R^2	yield (%)	ee (%) (configuration)
1	Ph	Me	81	97 (*R*)
2	*n*-Bu	Me	62	84 (*R*)
3	Cy	Me	67	91 (*R*)
4	4-BrC_6H_4	Me	80	98 (*R*)
5	4-$NO_2C_6H_4$	Me	79	98 (*R*)
6	2-furyl	Me	82	80 (*R*)
7	Ph	Et	73	64 (*R*)

borabicyclo[3.3.2]decane (9-BBD) with carbonyl compounds produces allenyl carbinols in a stereoselective manner. Applying the methodology developed by Soderquist, chiral propargyl borane derivatives can be easily prepared by reaction of, for instance, 3-trimethylsilylprop-2-ynyl magnesium bromide with a pseudoephedrine−boron complex. This methodology allows easy access to both enantiomers. Soderquist and Hernandez found that the reaction of (*R*)-*B*-TMS-propargyl-10-TMS-9-BBD with different aliphatic, aromatic, and α,β-unsaturated aldehydes at −78 °C for 3 h, followed by addition of pseudoephedrine, yielded the corresponding silylated α-allenyl carbinols and a boron complex (Scheme 65).[167] The reaction proceeded in moderate to high yields (60−87%) and excellent stereoselectivities (94−98% ee). Reaction of this boron complex with trimethylsilylpropargyl magnesium bromide regenerated the starting propargyl borane in quantitative yield, as in the case of other chiral allyl and allenyl 9-borabicyclo[3.3.2]decane derivatives.

Stereoselective allenylation of ketones was also efficiently accomplished with (*S*)-*B*-TMS-propargyl-10-Ph-9-BBD. On the basis of previous experiences, Soderquist and co-workers performed the reaction of this chiral propargyl borane with representative ketones in THF at −78 °C. The expected tertiary α-allenyl carbinols were obtained in high yields and excellent enantioselectivities for methyl ketones (Table 66).[151] Compared with aldehydes, reaction times were considerably longer for methyl ketones, ranging between 3 and 36 h at −78 °C, especially for aryl methyl ketones bearing electron-withdrawing groups (Table 66, entries 4 and 5). Even less reactive was propiophenone, whose allenylation required 52 h at −78 °C (Table 66, entry 7).

The configuration of the resulting α-allenyl carbinols was assigned on the basis of values reported in literature.[168] It has been proposed that addition to the *Re*-face of aldehydes took place with (*R*)-*B*-TMS-propargyl-10-TMS-9-BBD and to the *Si*-face with its (*S*)-enantiomer, through the most energetically favorable pretransition state complex shown in Figure 13. In the case of the allenylation of ketones with (*S*)-*B*-TMS-propargyl-10-Ph-9-BBD, the nucleophilic addition took place to the *Si*-face leading to tertiary carbinols with (*R*)-configuration through a similar pretransiton state complex shown also in Figure 13.

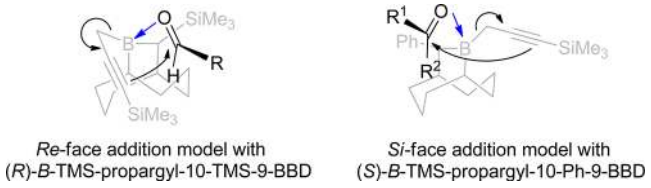


Figure 13. Proposed pretransition state complexes for stereoselective allenylation of carbonyl compounds with (*R*)-*B*-TMS-propargyl-10-TMS-9-BBD and (*S*)-*B*-TMS-propargyl-10-Ph-9-BBD.

4.2.2.2. Propargyltitanium Reagents. Hoppe investigated the enantioselective deprotonation of a propargylic thiocarbamate using *n*-BuLi and (−)-sparteine in pentane at −30 °C. The resulting organolithium compound precipitated, providing suitable crystals for X-ray analysis. Treatment of this organolithium compound with $ClTi(O\textit{i}\text{-}Pr)_3$ yielded a chiral

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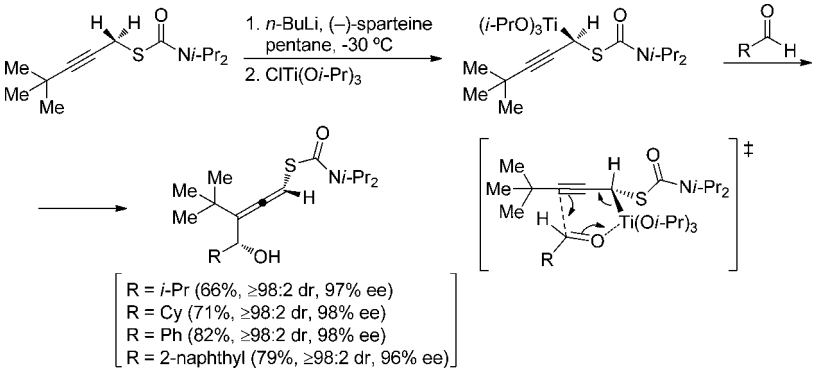
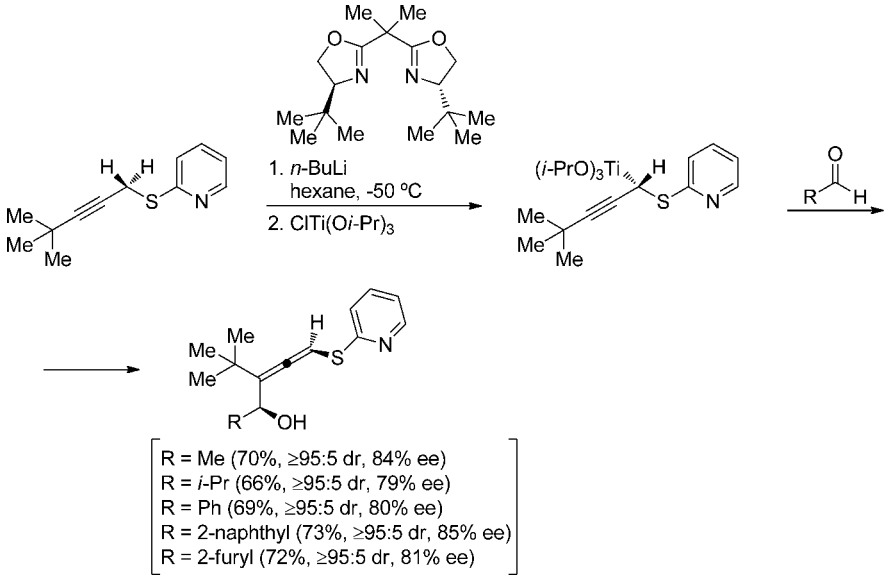
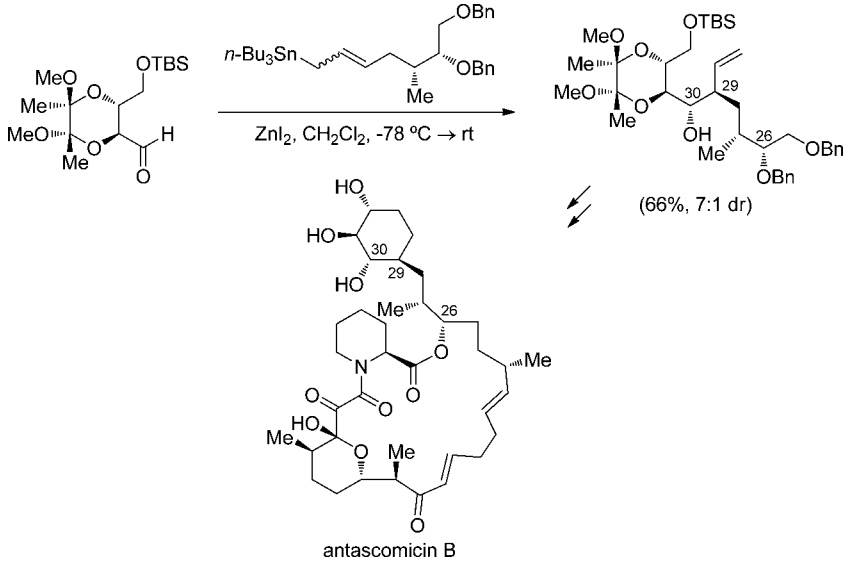
Scheme 66



Scheme 67



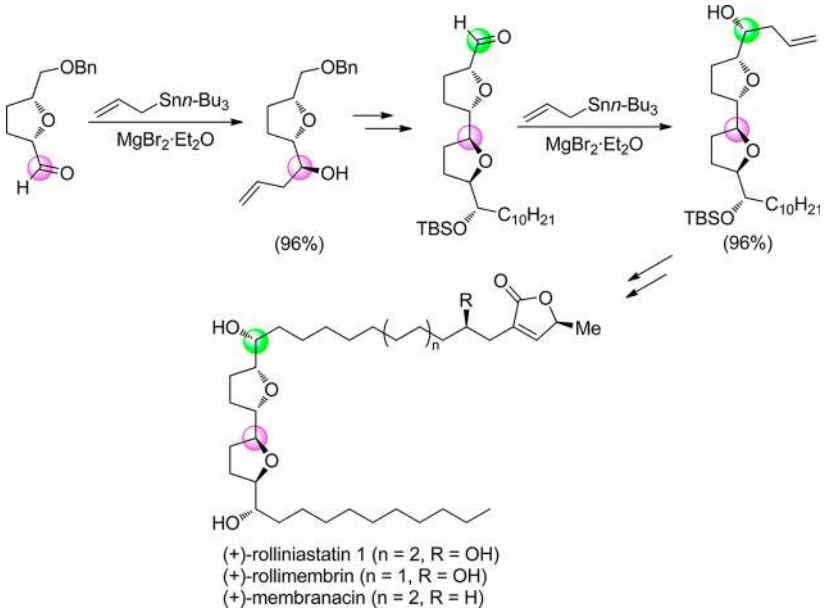
Scheme 68



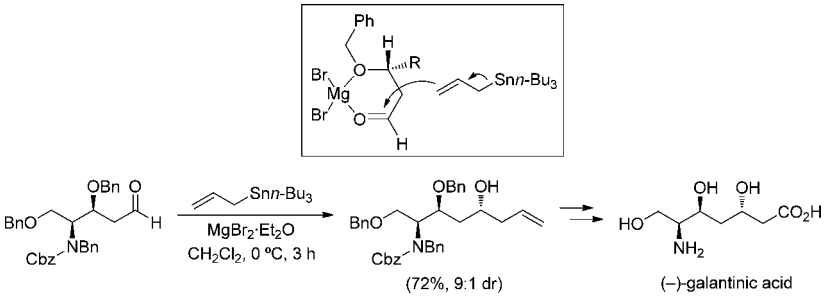
propargyltitanium intermediate. Based on previous experience, it was assumed that the lithium−titanium transmetalation process took place with stereoinversion.[169] Reaction of this chiral propargyltitanium intermediate with different aldehydes led to enantioenriched 1-thio-substituted 4-hydroxy-1,2-alkadienes in high yields, with a stereodefined configuration at the carbinol center and also at the allene moiety. A Zimmerman−Traxler-type transition state has been proposed to rationalize

dx.doi.org/10.1021/cr400008h | Chem. Rev. 2013, 113, 5595−5698

Scheme 69



Scheme 70



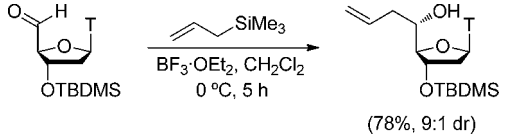
the observed reaction products through a suprafacial nucleophilic addition process (Scheme 66).[170]

The asymmetric lithiation of 2-alkynyl aryl sulfides was faced in a collaborative project by the groups of Toru and Hoppe. Good results in terms of stereoselectivity and further synthetic applications were obtained in the deprotonation of 2-alkynyl aryl sulfides, the 2-pyridyl derivative performing better than the phenyl derivative. Better than using (−)-sparteine, enantioselective deprotonation of the starting 2-alkynyl sulfide was carried out in the presence of a chiral *tert*-butyl-substituted bis(oxazoline) ligand. With this ligand, the intermediate lithium complexes can be reached in up to 85% ee after a dynamic thermodynamic resolution by selective crystallization. Particularly, the best result was obtained for the deprotonation and crystallization in *n*-hexane at −50 °C. Subsequent reaction with ClTi(OiPr)$_3$ at −96 °C led to chiral propargyltitanium intermediate (transmetalation with stereoinversion is also proposed to occur), which after final addition to alkyl, aryl, and heteroaryl aldehydes afforded the expected diastereomerically pure allenyl carbinols in high yields and good levels of enantioselectivity (Scheme 67).[171] The operating mechanism could be similar to that proposed for the thiocarbamate derivatives in Scheme 66.

5. SYNTHESIS OF NATURAL PRODUCTS

The synthetic utility of the here presented methodologies is demonstrated by the total synthesis of a large number of natural

Scheme 71



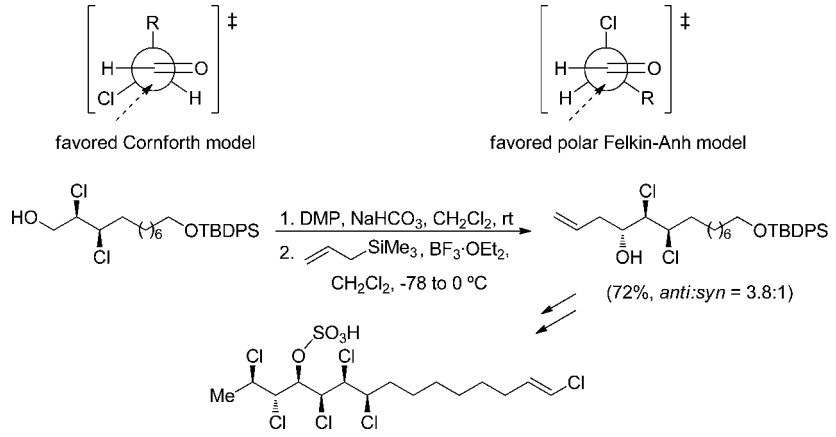
products. Importantly, natural product synthesis played a key role in the development of many synthetic methods, and diastereoselective allylations seem to be preferred to enantioselective allylations when large amounts of homoallylic alcohols or amines are required as synthetic intermediates in a multistep synthesis. Chiral allylboranes, allylsilanes, and titanates are the most commoly used reagents in these allylations, and some recent examples of synthesis of complex molecules, which include as a key step a diastereoselective allylation, are included below.

5.1. Substrate Control

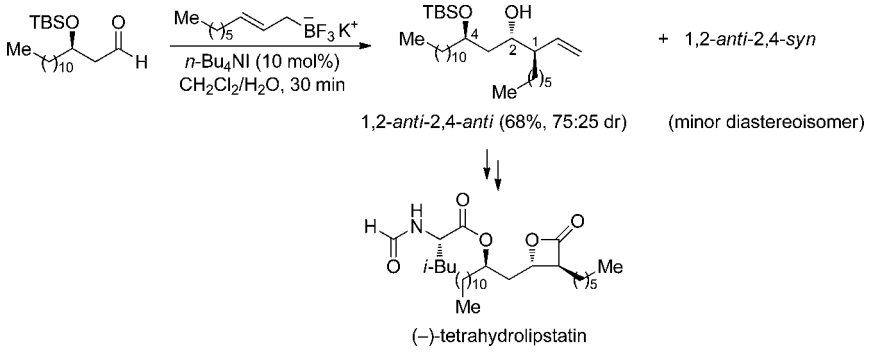
5.1.1. Chiral Carbonyl Compounds. *5.1.1.1. Allyl Stannanes.* A total and stereoselective synthesis of antascomicin B, a macrolide isolated from a strain of *Micromonospora* that possesses structural similarities to FK506 and rapamycin and exhibits potent binding ability to FKBP12, was reported by Ley and co-workers.[172] In one step of the synthesis, the allylation of a threose-derived aldehyde was performed with an allylstannane compound using zinc iodide in CH_2Cl_2. The selectivity was

dx.doi.org/10.1021/cr400008h | *Chem. Rev.* 2013, 113, 5595−5698

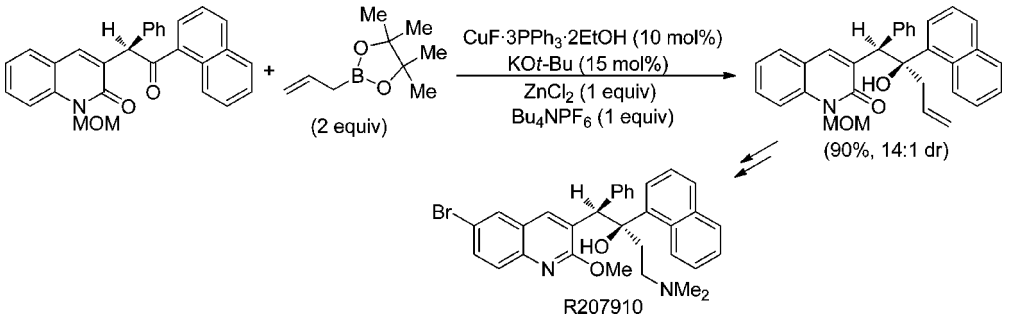
Scheme 72



Scheme 73



Scheme 74



optimum to give the expected product with near total diastereoselectivity at C-30 and in a 7:1 ratio at C-29 in favor of the desired isomer (Scheme 68). It was found that the *E*/*Z* ratio of the stannane had only a minor effect on the diastereoselectivity of the subsequent addition.

Rolliniastatin 1, rollimembrin, and membranacin are annonaceous acetogenins isolated from the seeds of *Rollinia mucosa* and *Rollinia membranacea*.[173] Annonaceous acetogenins are a large family of natural products that have been described as potent *in vitro* inhibitors of the mitochondrial respiratory chain complex I. Lee and co-workers provided a stereoselective synthesis of these natural products performing two stereoselective allylations of chiral α-oxygen-substituted aldehydes in the presence of magnesium bromide etherate (Scheme 69).[174] The corresponding homoallylic alcohols were obtained in high yield and stereoselectivity (>99:1 dr).

The synthesis of (−)-galantinic acid reported by Nagaiah et al. included as a key step the chelation-controlled diastereoselective allylation of a chiral *β*,*γ*,*δ*-trisubstituted aldehyde with allyl(tributyl)stannane in the presence of magnesium bromide at 0 °C. The corresponding homoallylic alcohol was obtained as a mixture of isomers in 72% overall yield, the desired major 1,3-*anti*-addition product being easily separated by column chromatography (Scheme 70).[175] Galantinic acid is an unusual amino acid with dense functionalization and exhibits excellent antibacterial activity.[176]

5.1.1.2. Diastereoselective Addition of Allylic Silanes and Boranes. In order to synthesize dinucleotides with two 5′-*C*-allyl groups, Nielsen and co-workers performed the allylation of a 3-*O*-TBDMS thymidine derivative with allyltrimethylsilane in the presence of boron trifluoride etherate. The allylated product with 5′-(*S*)-configuration was isolated as a 9:1 epimeric mixture in 78% yield (Scheme 71).[177]

An efficient synthesis of (+)-hexachlorosulfolipid, a cytotoxin found in the Adriatic mussel *Mytilus galloprovincialis*, has been achieved recently by Yoshimitsu et al. Key steps in the synthesis

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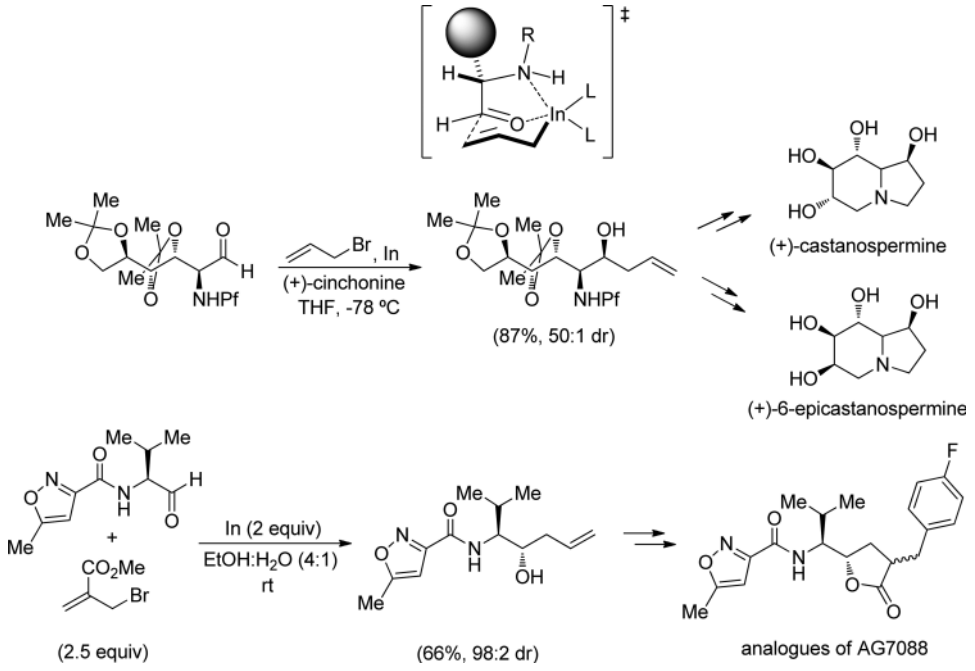
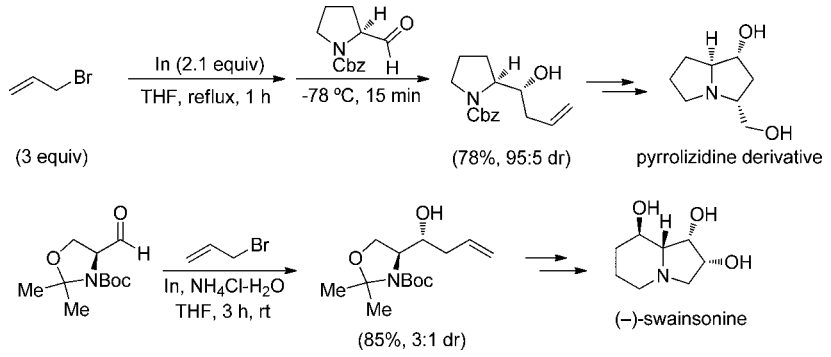
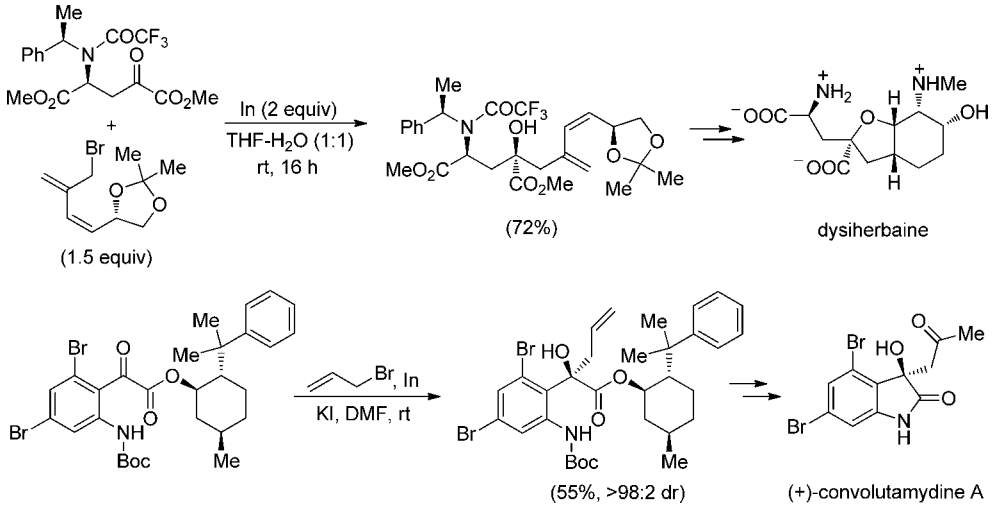
Scheme 75



Scheme 76



Scheme 77



of this hexachlorinated compound are the successive dichlorination of chiral epoxides and the diastereoselective allylation of a chiral α,β-dichloroaldehyde.[178] This aldehyde was quite unstable and decomposed upon thin-layer silica gel chromatography. Consequently, it was prepared *in situ* from the corresponding alcohol with Dess–Martin periodinane and

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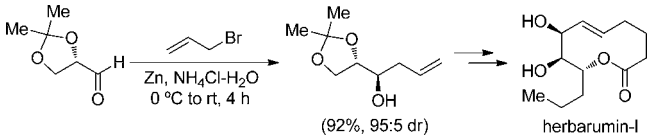
Scheme 78



reacted without purification with allyltrimethylsilane in the presence of boron trifluoride etherate. The corresponding *anti*-chlorohydrin was the major diastereomer. This *anti* selectivity could be rationalized by considering either the Cornforth or the polar Felkin–Anh transition-state model that preferentially undergoes allylation reaction with allyltrimethylsilane to provide *anti*-alcohol (Scheme 72).

Thadani and Batey applied a biphasic allylation methodology in one of the steps of the synthesis of (−)-tetrahydrolipstatin.[179] This compound was isolated from *Streptomyces toxytricini*[180] and is a potent and irreversible inhibitor of pancreatic lipase. They found that the reaction of *O*-TBS-protected (*R*)-3-hydroxytetradecanal with (*E*)-non-2-enyltrifluoroborate in the presence of 10 mol % *n*-Bu_4NI in a biphasic medium (CH_2Cl_2/H_2O) provided a 3:1 mixture of 1,2-*anti*-2,4-*anti* and 1,2-*anti*-2,4-*syn* diastereomers (Scheme 73). The 1,2-*anti* stereochemical relationship was rationalized considering a closed Zimmerman–Traxler-like transition state.

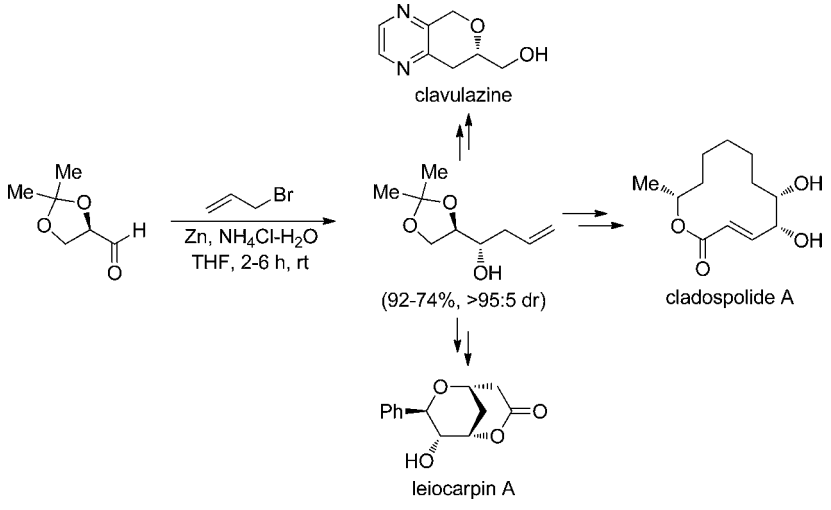
A new antituberculosis drug candidate (R207910) that selectively inhibits the ATP synthase proton pump of both drug-sensitive and drug-resistant *Mycobacterium tuberculosis* was discovered by the Johnson & Johnson pharmaceutical company. Kanai and Shibasaki provided a synthesis of R207910 performing a diastereoselective allylation of a chiral 1-naphthyl ketone with allylboronic acid pinacol ester.[181] The diastereoselectivity was improved when a seven-membered chelate was formed, with the addition of the allyl group taking place from the less hindered *Re*-face of the ketone. Using 10 mol % CuF·$3PPh_3$·2EtOH, 15 mol % KO*t*-Bu, 1 equiv of $ZnCl_2$, and 1 equiv of *n*-Bu_4PBF_4, the reaction was completed after 1 h at room temperature, affording the product in quantitative yield with a diastereomeric ratio of 14/1 (Scheme 74).

5.1.1.3. Indium-Promoted Allylation. As previously mentioned, high diastereoselectivity is usually achieved in the indium-mediated allylation of chiral α-amino-substituted aldehydes with allylic halides, and it might be explained considering a Felkin–Anh chelation model for compounds with N–H bonds. The configuration of the newly created stereogenic center is consequently determined by the configuration of the stereocenter contiguous to the carbonyl group. This methodology was applied in one of the steps of the syntheses of (+)-castanospermine and (+)-6-epicastanospermine,[182] natural indolizidine alkaloids isolated from *Castanospermum australe*[183] and *Alexa leiopetala*.[184] The optimal reaction conditions involved the use of (+)-cinchonine as a chiral promoter in THF, because in the absence of cinchonine, diastereoselectivity dropped from 50:1 to a modest 2:1 *syn*/*anti* ratio (Scheme 75). Similarly, different analogues of AG7088, an inhibitor for the severe acute respiratory syndrome coronavirus main proteinase, were synthesized following the same strategy. In this case, indium-promoted allylation of an L-valine methyl ester derivative proceeded with high diastereoselectivity to produce the *syn* isomer with 98:2 dr (Scheme 75).[185]

By contrast, the indium-mediated allylation of chiral α-amino-substituted aldehydes without N–H bonds with allylic halides leads to the *anti* product as the major diastereomer and, in general, with lower diastereoselectivities. For instance, the indium-mediated allylation of *N*-Cbz-L-prolinal, under Grignard conditions (formation of the allylindium derivative prior the addition of the aldehyde), afforded the *anti* product in high yield and diastereoselectivity, a precursor of 3-hydroxymethylpyrrolizidin-1-ol (Scheme 76).[186] The diastereoselectivity was considerably lower in the allylation of Garner's L-serine-derived oxazolidine aldehyde with allyl bromide in the presence of indium. A mixture of *anti*/*syn* diastereomers was obtained in a 3:1 ratio. The *anti* isomer was used as a synthetic precursor in the synthesis of polyhydroxylated indolizidine alkaloid (−)-swainsonine (Scheme 76).[187]

Chiral α-ketoesters have also been successfully allylated stereoselectively with allyl bromides in the presence of indium. This methodology was used in one of the steps of the synthesis of dysiherbaine,[188] a neurotoxic amino acid isolated from the Micronesian sponge *Dysidea herbacea*,[189] leading to a single diastereomer in 72% yield (Scheme 77). Similarly, (+)-convolutamydine A, a promising antileukemia drug isolated from *Amathia convoluta*, with a 4,6-dibromo-3-hydroxyindoline motif

Scheme 79



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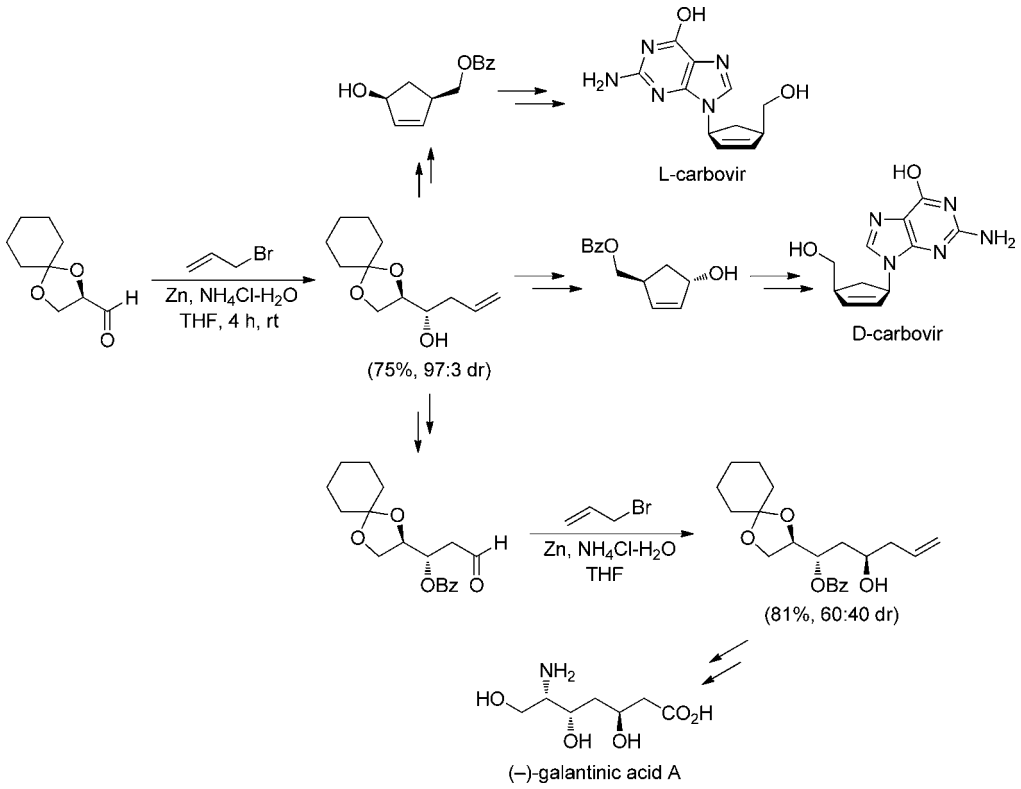
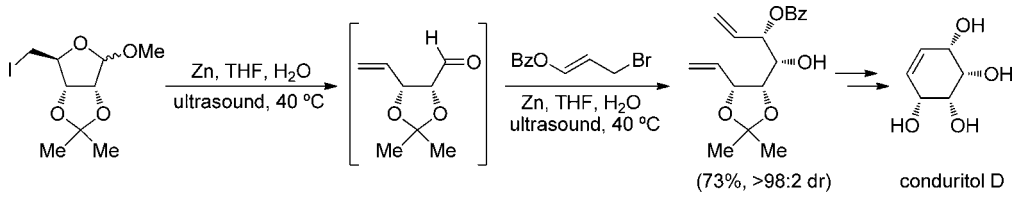
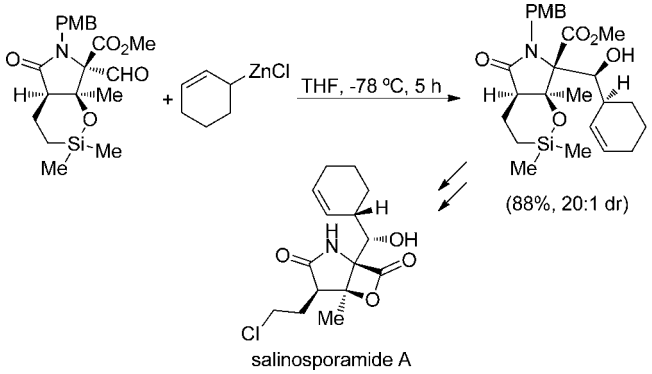
Scheme 80



Scheme 81



Scheme 82



that bears a quaternary stereocenter at C-3 was synthesized by Palmisano and co-workers.[190] The key step of the synthesis was a diastereoselective indium-mediated allylation of a chiral α-ketoesters derived from (1*R*,2*S*,5*R*)-8-phenylmenthol with allyl bromide (Scheme 77).

5.1.1.4. Zinc-Promoted Allylation. The stereoselective zinc-mediated allylation of glyceraldehyde derivatives has been widely used in the synthesis of polyoxygenated natural products. Specially, the addition of allyl bromide to 2,3-*O*-isopropylidene glyceraldehyde in the presence of zinc in an ammonium chloride saturated aqueous solution (Luche's procedure)[191] proceeds in high yield and excellent diastereoselectivity. Yadav and co-workers reported the synthesis of herbarumin-I,[192] a nonenolide isolated from fungus *Phoma herbarum* with phytotoxic activity. The zinc-mediated allylation of L-ascorbic acid derived (*S*)-2,3-*O*-ispropylideneglyceraldehyde furnished a 95:5 *anti*/*syn* mixture of diastereomers in 92% overall yield, which was separated by silica gel chromatography (Scheme 78). After allylation, macrolactonization followed by a ring-closing metathesis were the key steps.

On the other hand, the homoallylic alcohol resulting from the zinc-mediated allylation of (*R*)-2,3-*O*-ispropylideneglyceraldehyde, derived from D-mannitol, was a common synthetic intermediate in the synthesis of (*S*)-clavulazine[193] (isolated from the Okinawan soft coral *Clavularia viridis*[194]), cytotoxic styryl lactones leiocarpin A[175] (isolated from the ethanolic extract of the stem bark of *Goniothalamus leiocarpus*), and polyketide cladospolide A[195] (isolated from fungus *Cladosporium cladosporioides*), which inhibits root growth in lettuce seedlings (Scheme 79). The diastereoselectivity of the allylation was coincident with that previously reported for the (*S*)-isomer.

Luche's procedure was also applied to (*R*)-2,3-*O*-cyclohexylideneglyceraldehyde in the synthesis of different natural

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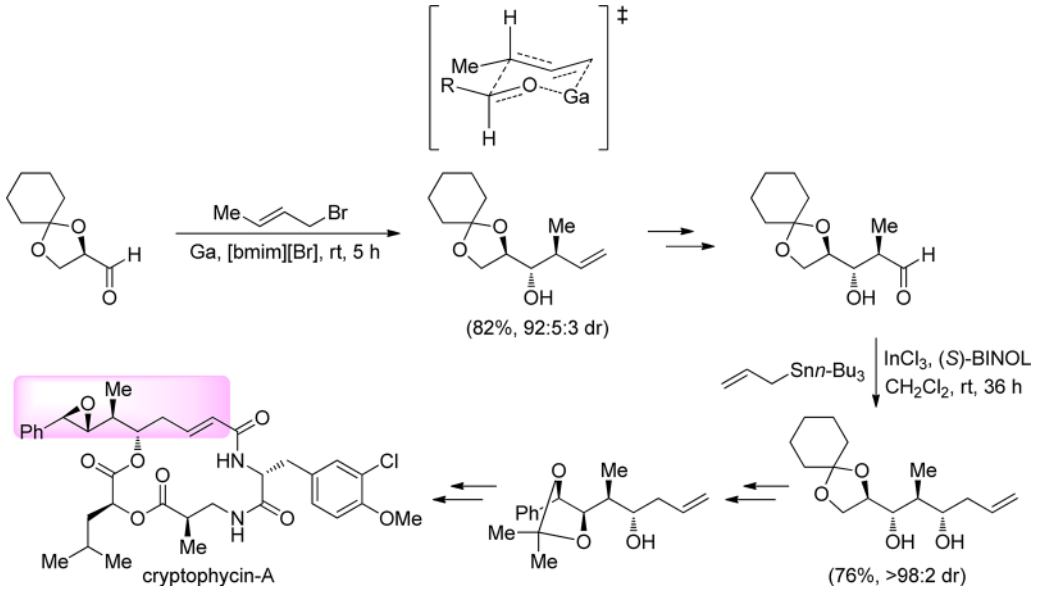
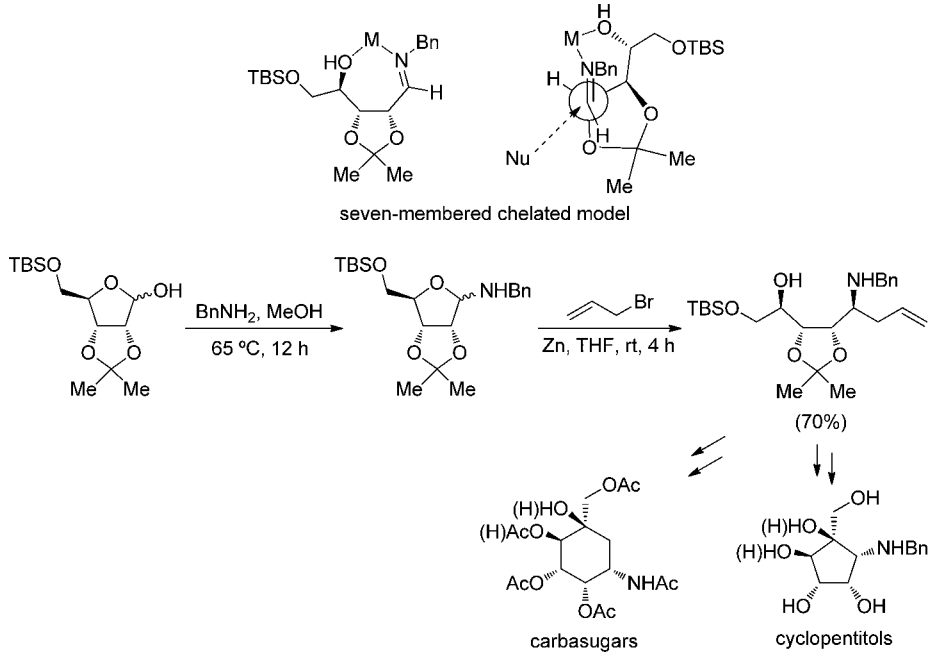
Scheme 83



Scheme 84



products. This cyclohexylidene derivative has some operational advantages over the isopropylidene one, mainly because it is less volatile and also less water-soluble. Chattopadhyay and Tripathy found that this chiral aldehyde reacted completely using excess of both allyl bromide and commercially available Zn dust, yielding the corresponding homoallylic alcohol in good yield and high *anti* diastereoselectivity (97:3 dr), which is an intermediate in the synthesis of potential precursors of (L)-(+)- and (D)-(−)-carbovirs (Scheme 80).[196] The chiral homoallylic alcohol was converted into a *β*-*O*-protected chiral aldehyde and submitted to a new allylation under Luche's conditions, yielding a 3:2 *anti*/*syn* mixture of diastereomers, which were easily separated. The *anti* isomer was subsequently used in the synthesis of (−)-galantinic acid A (Scheme 80).[197]

Keinicke and Madsen reported a concise synthesis of conduritol D. Conduritols are tetrahydroxycyclohexenes and have been used as key intermediates in the preparation of natural products and other biologically important molecules. The key step of the synthesis employed a zinc-mediated fragmentation of protected methyl 5-deoxy-5-iodo-D-pentofuranoside derived from D-ribose followed by allylation of the intermediate aldehyde in the same pot with 3-bromopropenyl benzoate. The process occurred in high yield and excellent diastereoselectivity (Scheme 81).[198] Following the same synthetic strategy but starting from a methyl iodofuranoside derived from D-xylose, (+)-conduritol C was also prepared.

Salinosporamide A is a potent inhibitor of proteasome function that was isolated from a marine microorganism that is widely distributed in ocean sediments.[199] Corey and co-workers

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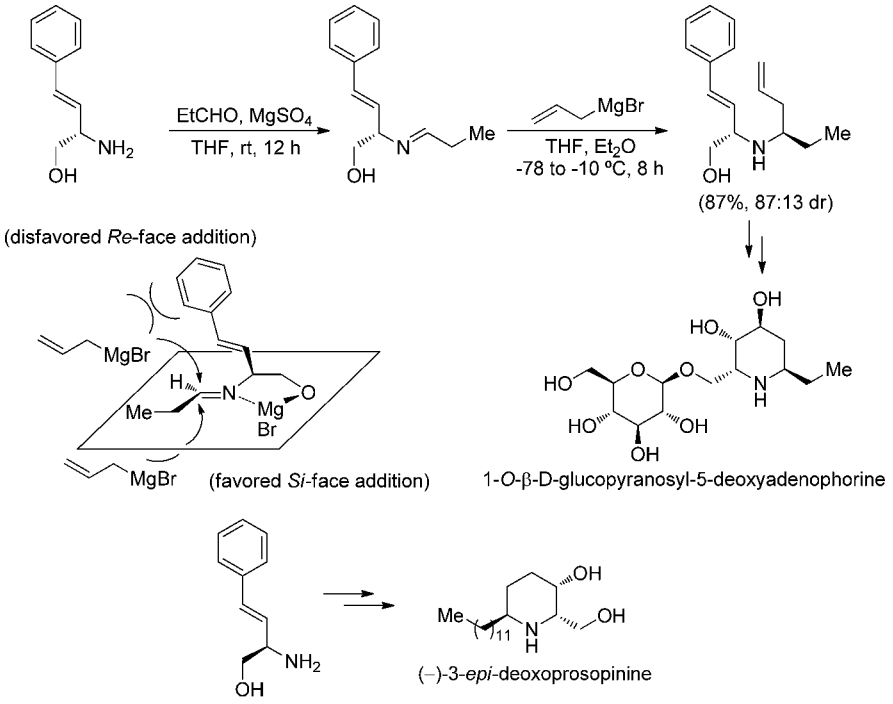
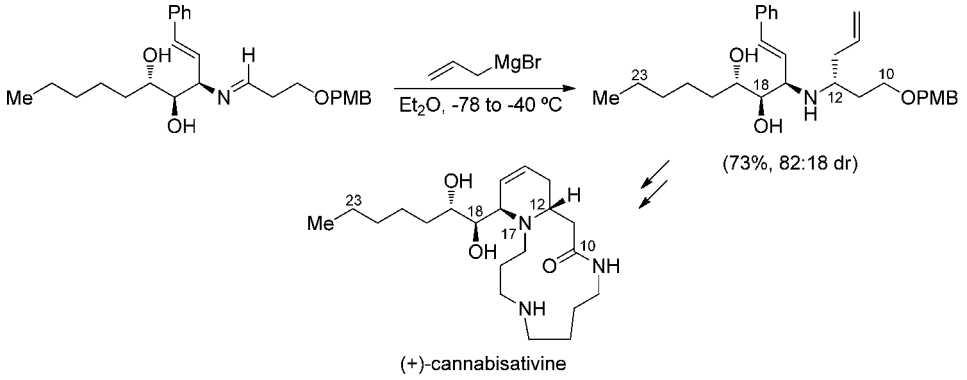
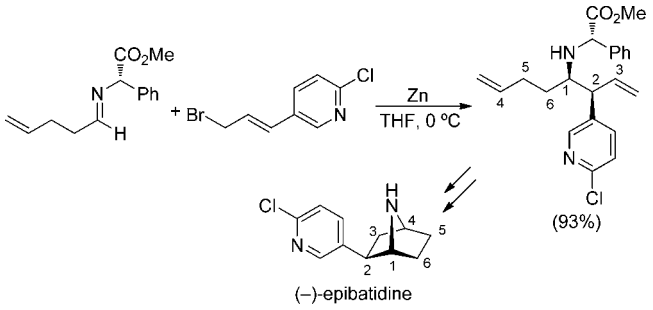
Scheme 85



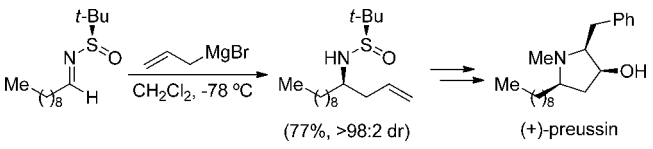
Scheme 86



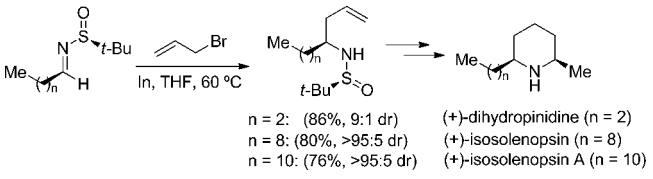
Scheme 87



Scheme 88



Scheme 89



reported a synthesis of this densely functionalized molecule, which contains five stereogenic centers. A key step of the synthesis was the reaction of racemic 2-cyclohexenylzinc chloride with a chiral aldehyde bearing three stereogenic centers. In the process, two stereogenic centers were formed stereoselectively (20:1 dr) with the right configuration in 88% yield (Scheme 82).[200]

5.1.1.5. Gallium-Promoted Crotylation. Cryptophycin-A was first isolated from the blue-green algae *Nostoc* sp. ATCC 537893[201] and is an effective inhibitor of tubulin polymerization. Chattopadhyay and co-workers reported an asymmetric synthesis of the octadienoic acid unit of cryptophycins. The key step of the synthesis was a gallium-mediated crotylation of (*R*)-

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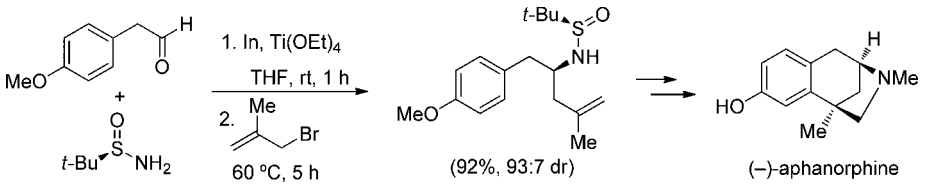
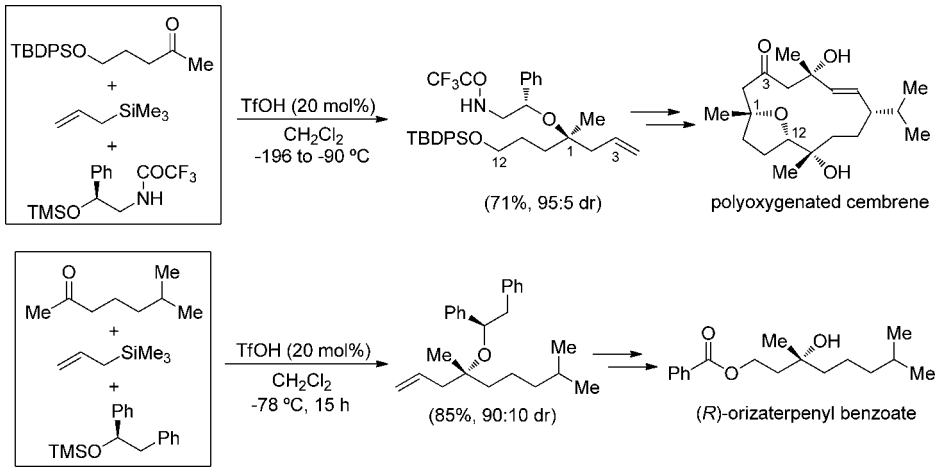
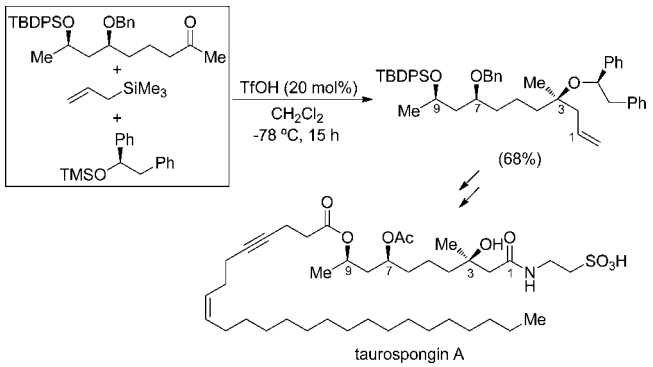
Scheme 90



Scheme 91



Scheme 92



2,3-*O*-cyclohexylideneglyceraldehyde in [bmim][Br] (Scheme 83).[202] The diastereoselectivity of the Barbier-type crotylation of the chiral aldehyde could be tuned by changing the metal atom and solvent. The gallium-mediated reaction in [bmim][Br] produced the best diastereoselectivity, furnishing the all-*anti* product in good yield.[203] A transition state with the substituents adopting equatorial positions was proposed in order to explain the 3,4-*anti* adduct. Another key step of the synthesis involved a stereoselective allylation with allyltributylstannane of a chiral α-methyl-substituted aldehyde. All attempts to perform a diastereoselective allylation with allyl bromide using different metal–solvent combinations led to a nonseparable diastereomeric mixture of homoallylic alcohols. However, when the allylation was carried out with allyltributylstannane in the presence of (*S*)-BINOL,[204] the expected diol was obtained with excellent diastereoselectivity (>98:2 dr) (Scheme 83). Opposite configuration of the newly created stereogenic center was reached using (*R*)-BINOL. This suggested that the stereochemistry of the reaction was dictated exclusively by the reagent, without a significant contribution from the substrate chirality.

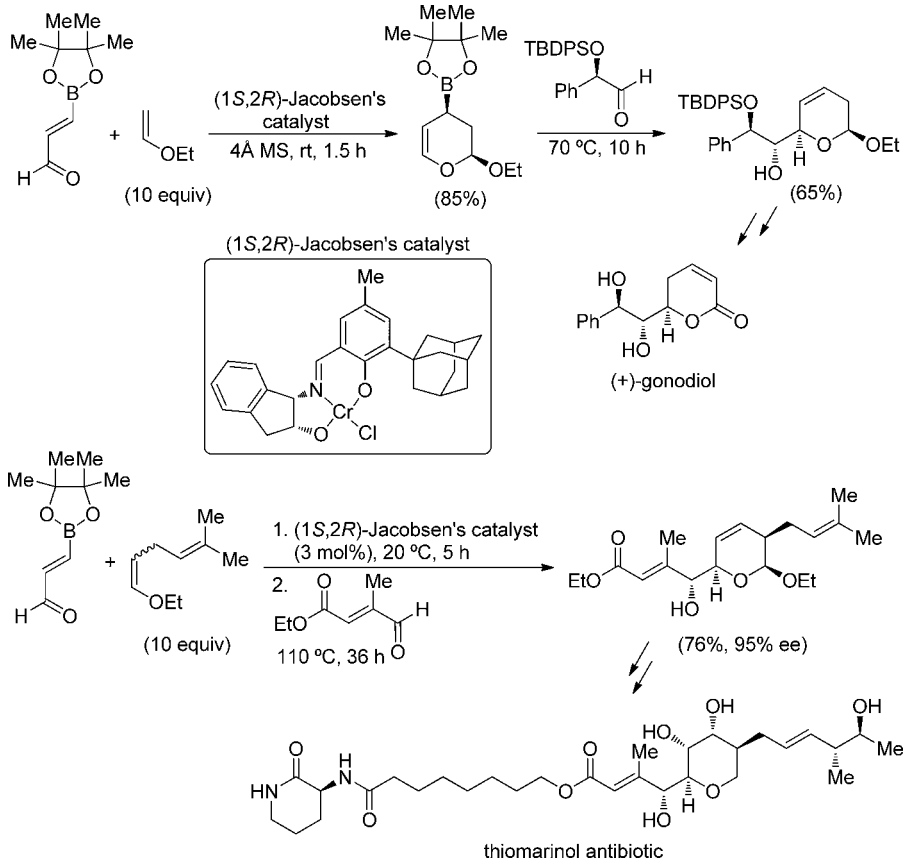
5.1.2. Chiral Imines and Imine Derivatives.

5.1.2.1. Imines and Imine Derivatives from Chiral Carbonyl Compounds. Cyclopentitols and carbasugars (analogues of monosaccharides, in which the ring oxygen is replaced with a methylene group) exhibit glycosidase inhibitory activities.[205] For that reason, aminocyclopentitols and aminocarbasugars have drawn considerable attention as potential glycosidase inhibitors. B. V. Rao and co-workers reported a stereoselective approach for the synthesis of these compounds by using a stereoselective zinc-mediated allylation with allylbromide of a chiral ribosylamine derivative. The starting material, 5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-D-ribofuranose, reacted with benzylamine to give a ribosylamine which reacted *in situ* with allylbromide and zinc, leading to the *erythro*-homoallylamine derivative, a precursor of both targets, aminocyclopentitols[206] and aminocarbasugars[207] (Scheme 84). It has been proposed that the selectivity was due to the formation of a seven-membered transition state resulting from the chelation of hydroxyl and an imine or a Felkin–Anh model, the nucleophilic addition taking place onto the less hindered face of the imine (Scheme 84).

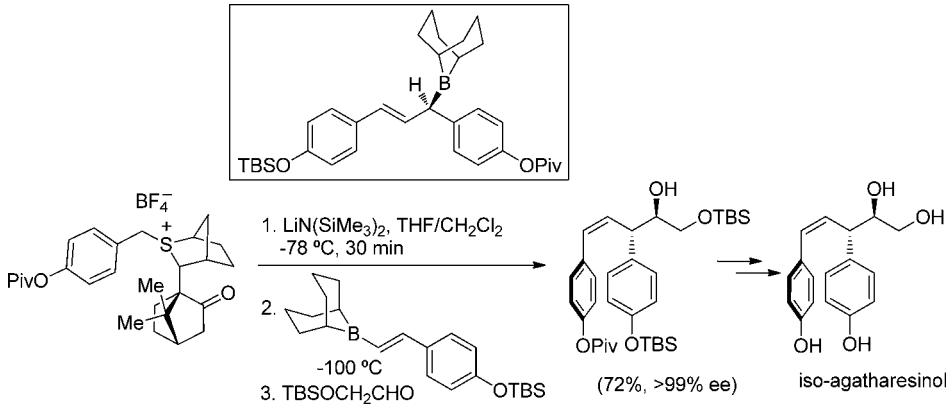
5.1.2.2. Imines and Imine Derivatives with a Chiral Framework Attached to the Nitrogen. 5.1.2.2.1. Imines from Chiral Amino Alcohols. Diastereoselective allylation of the imine resulting from the condensation of propanal and (*E*,*S*)-2-amino-4-phenylbut-3-en-1-ol [easily accessible in two steps from (*R*)-Garner aldehyde] with allylmagnesium bromide led to the corresponding amino alcohol in high yield as an 87:13 mixture of diastereomers (Scheme 85). This amino alcohol is a precursor of the potent glycosidase inhibitor 1-*O*-β-D-glucopyranosyl-5-deoxyadenophorine. Lebreton and co-workers developed the first total synthesis of this glycosidase inhibitor and proposed that the Grignard reagent addition occurs via a chelation model transition state with a transient five-membered ring, leading to the desired adduct contami-

dx.doi.org/10.1021/cr400008h | *Chem. Rev.* 2013, 113, 5595–5698

Scheme 93



Scheme 94



nated by less than 13% of the undesired isomer. Thus, the Grignard reagent attacks the less hindered *Si*-face of the imine (Scheme 85).[208] Starting from (*E*,*R*)-2-amino-4-phenylbut-3-en-1-ol and following the same synthetic strategy, the same group reported the synthesis of (−)-3-*epi*-deoxoprosopinine (Scheme 85).[25]

The diastereoselective allylation of a chiral imine with allylmagnesium bromide was also one of the key steps of the stereoselective synthesis of the C10−C24 fragment of (+)-cannabisativine developed by Chandrasekhar and Tiwari. This natural product is a macrocyclic spermidine alkaloid containing a *trans*-2,6-disubstituted 1,2,5,6-tetrahydropyridine ring annulated to a 13-membered lactam ring and was isolated from *Cannabis sativa* L.[209] The chiral imine was prepared by condensation of the corresponding aminodiol [derived also from (*R*)-Garner aldehyde] and an aldehyde in anhydrous Et_2O in the presence of anhydrous $MgSO_4$ and reacted without further purification with a freshly prepared solution of allylmagnesium bromide in Et_2O at −78 °C, leading to an 82:12 mixture of diastereomers in 73% yield over two steps (Scheme 86).[210]

A gram-scale synthesis of the scantily present in nature (−)-epibatidine alkaloid (isolated from the skin of the Ecuadorian poison frog, *Epipedobates tricolor*)[211] was reported by Lee and Loh. In one step of the synthesis, the allylation of a chiral imine [derived from (*S*)-phenylglycine methyl ester and pent-4-enal] with a pyridyl allyl bromide derivative in the presence of zinc was carried out to produce the desired *syn*-

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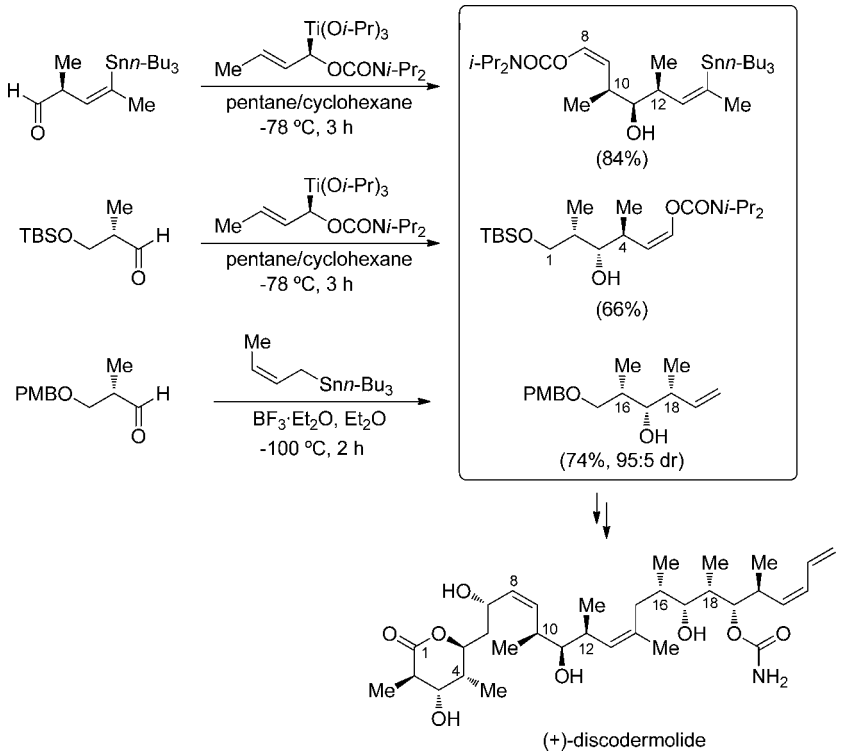
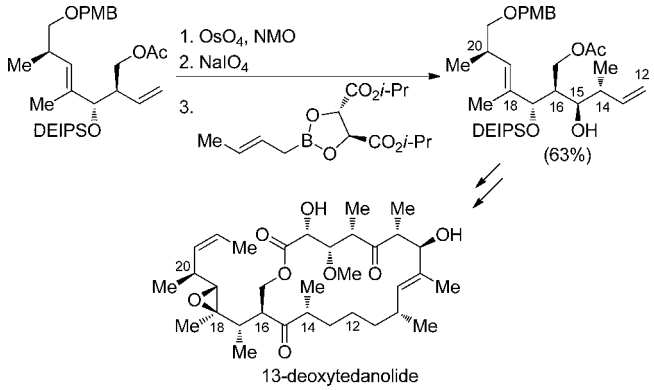
Scheme 95



Scheme 96



homoallylic amine in 93% yield as a single isomer (Scheme 87).[212]

5.1.2.2.2. Chiral Sulfinyl Imines. Chiral imines derived from *tert*-butanesulfinamide are increasingly being applied in asymmetric synthesis, particularly of natural products and biologically active compounds. As previously mentioned, there are many factors that have led to the popularity of this chiral auxiliary. For instance, Bertrand and Wolfe performed a diastereoselective allylation of the (R_S)-*t*-BS imine derived from decanal with allylmagnesium bromide in dichloromethane at −78 °C (Ellman's conditions)[213] to produce the expected homoallyl amine derivative as a single diastereomer in 77% yield (Scheme 88).[214] This compound was further transformed into (+)-preussin, an antifungal and antitumor agent isolated from the fermentation extracts of *Preussia sp.* and *Aspergillus ochraceus*.[215]

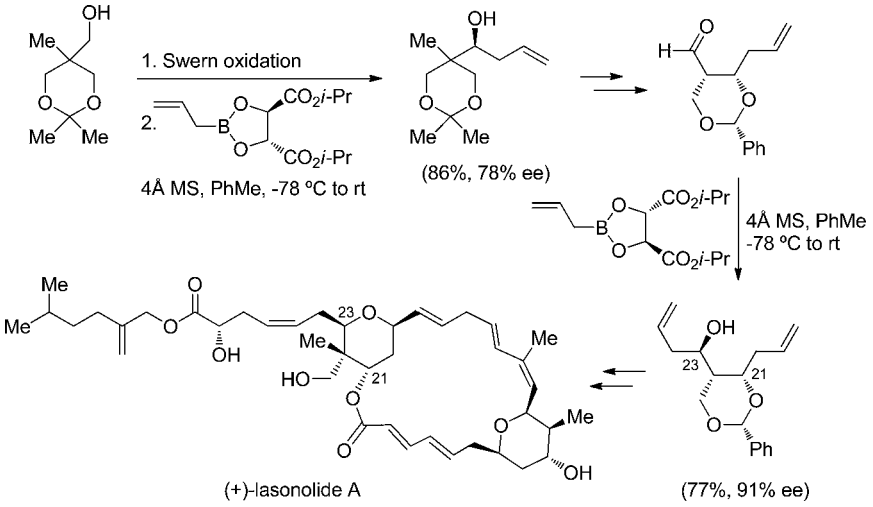
Taking advantage of the expeditious access to chiral homoallylic amine derivatives by diastereoselective indium-mediated allylation with allyl bromides of *t*-BS imines,[39] a concise synthesis of *cis*-2,3-disubstituted piperidinic alkaloids (+)-dihydropinidine, (+)-isosolenopsin, and (+)-isosolenopsin A was reported by González-Gómez et al. The allylation step proceeded in high yields and excellent diastereoselectivities in all cases (Scheme 89).[40a] Starting homoallylic amine derivatives could be also prepared in a one-pot procedure by combination of an aldehyde, an allylic bromide, and *tert*-butanesulfinamide in the presence of indium metal and titanium tetraethoxide.[41] Further transformations of the homoallylic amines toward the target piperidines include cross-metathesis with methyl vinyl ketone in the presence of the Hoveyda−Bletchert ruthenium catalyst, hydrogenation of the enone intermediates in the presence of Wilkinson's catalyst and final reductive amination.

The same research group also provided the synthesis of naturally occurring (−)-aphanorphine, isolated from the fresh-water blue-green alga *Aphanizomenon flos-aquae*.[216] The first step of the synthesis involved an indium-mediated stereoselective α-aminoallylation of *p*-methoxyacetaldehyde with methallyl bromide and (*R*)-*tert*-butanesulfinamide in the presence of indium and titanium tetraethoxide. The homoallyl amine derivative was obtained in 92% yield and 93:7 dr. The major diastereomer was purified by column chromatography to continue the synthesis. The second was the epoxidation, followed by regioselective opening of the epoxide to afford 2-substituted 3-pyrrolidinols. The synthesis was completed by using a reported Friedel−Crafts alkylation and conventional functional-group manipulation (Scheme 90).[217] According to the same route, the *O*-methyl derivative of unnatural (+)-aphanorphine was prepared from (*S*)-*tert*-butanesulfinamide.

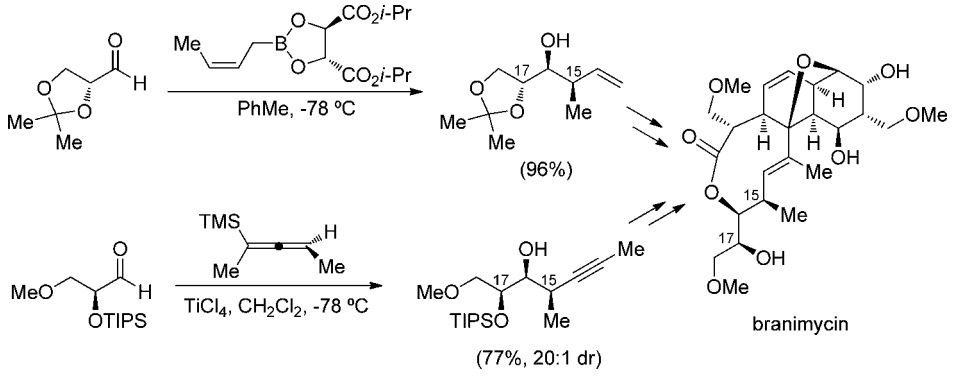
5.1.3. Carbonyl Compounds with Chiral Auxiliaries Attached to the Oxygen Atom. Tietze asymmetric allylation has been applied to the synthesis of complex organic molecules. This multicomponent domino allylation reaction of a prochiral ketone with allyltrimethyl silane and the enantiopure silyl ether

dx.doi.org/10.1021/cr400008h | *Chem. Rev.* 2013, 113, 5595−5698

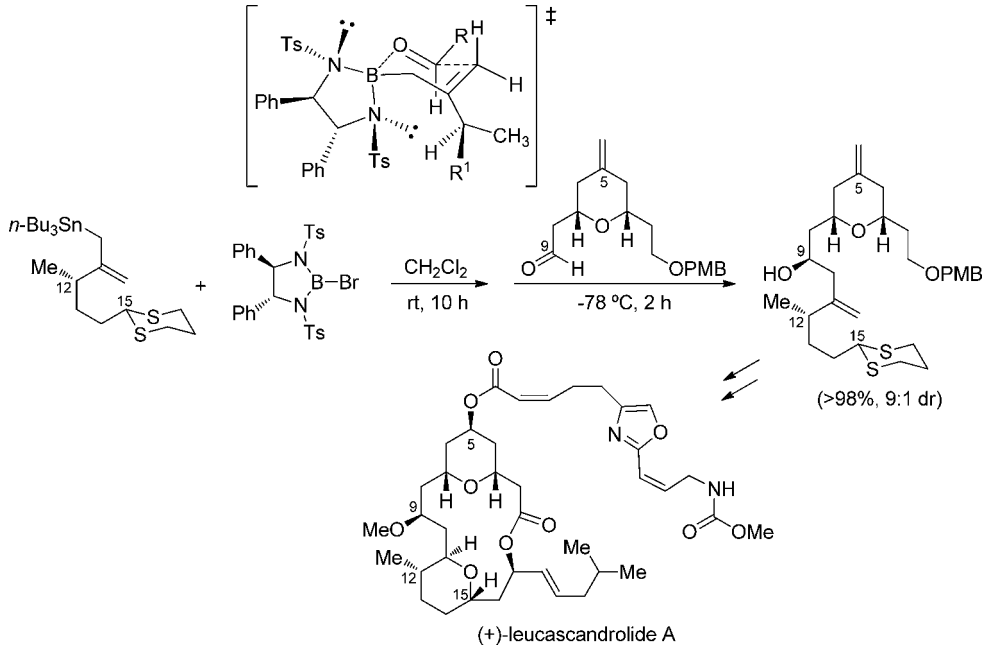
Scheme 97



Scheme 98



Scheme 99



of benzyl phenyl carbinol in the presence of catalytic amounts of TfOH allows the formation of quaternary stereocenters in a highly stereoselective fashion, specially in the case of methyl ketones. Tietze and co-workers reported the synthesis of a polyoxygenated cembrane, which is structurally related to polyoxygenated cembranes occurring in Greek tobacco plants.

dx.doi.org/10.1021/cr400008h | Chem. Rev. 2013, 113, 5595−5698

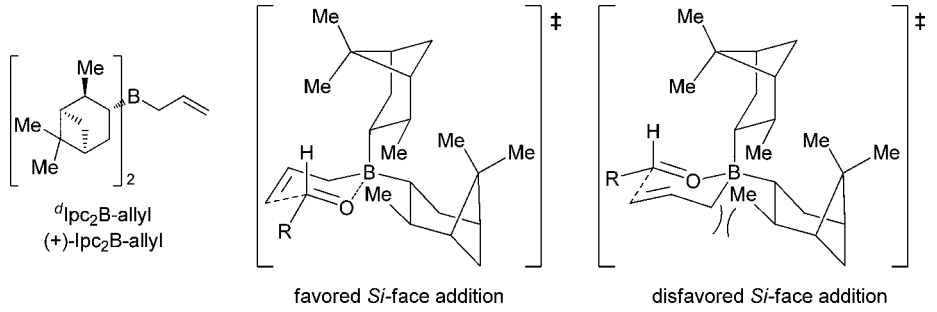
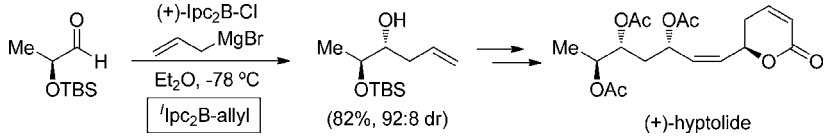
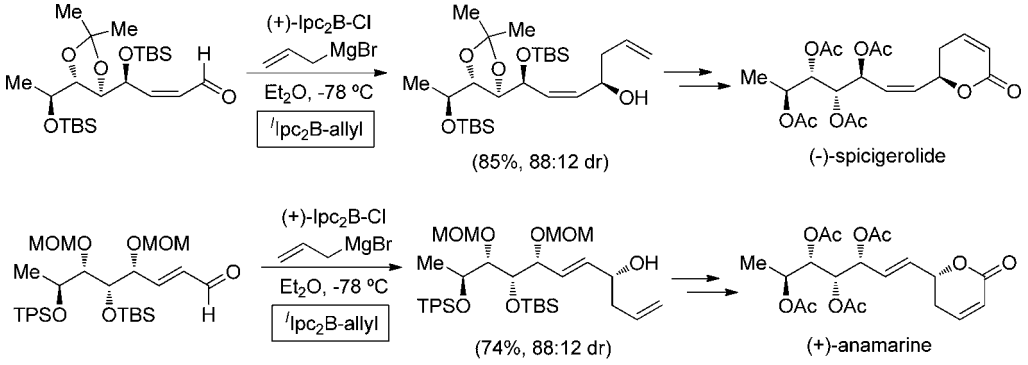


Figure 14. Zimmerman–Traxler-type transition states for the stereoselective allylation of aldehydes with $^{d}Ipc_2B$-allyl.

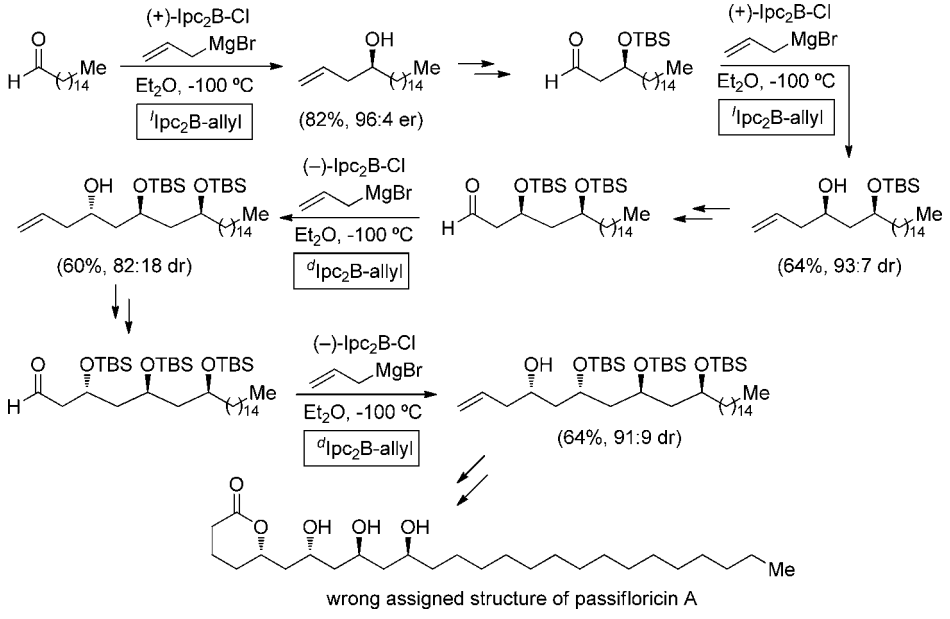
Scheme 100



Scheme 101



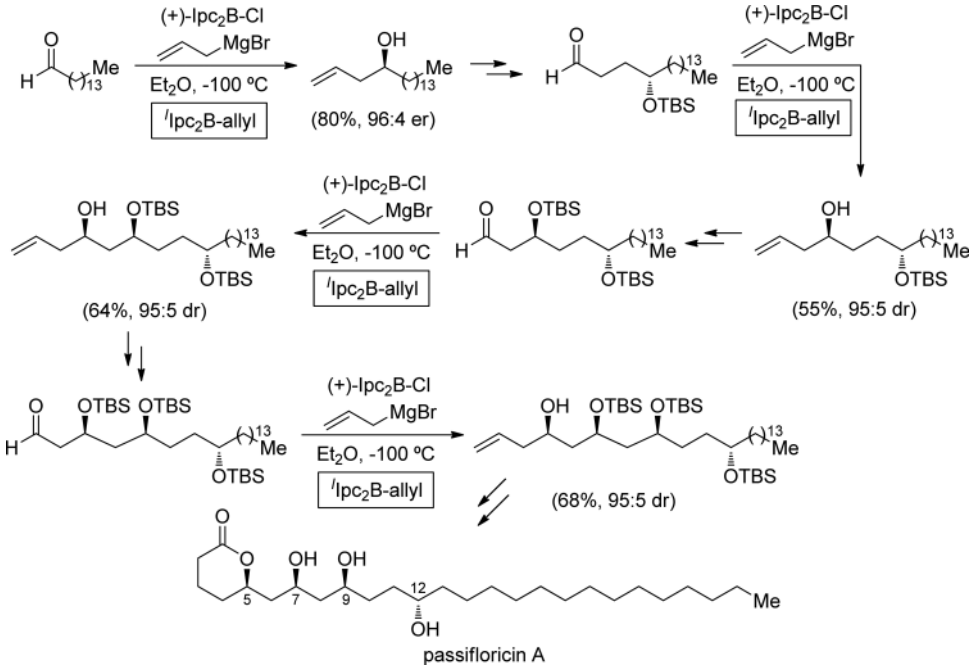
Scheme 102



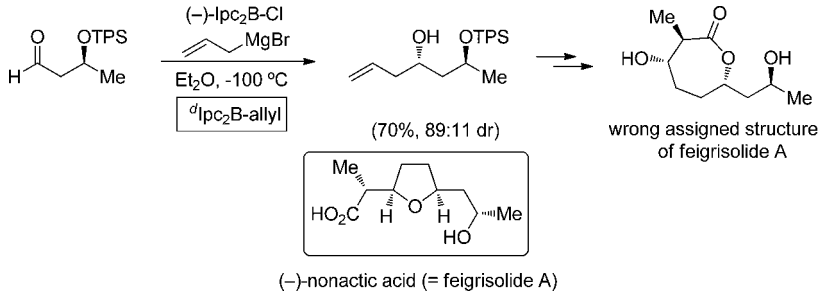
Thus, allylation of *O*-TBDPS-protected 5-hydroxypentan-2-one with allyltrimethyl silane in the presence of the trimethylsilyl ether of (*S*)-*N*-trifluoroacetyl-2-amino-1-phenylethanol and catalytic amounts of triflic acid, at temperatures ranging between −196 and −90 °C in dichloromethane, gave the corresponding tertiary homoallylic ether in 71% yield and excellent diastereoselectivity (Scheme 91).[218] Orizaterpenyl benzoate is a monoterpene with one stereogenic center that

dx.doi.org/10.1021/cr400008h | *Chem. Rev.* 2013, 113, 5595–5698

Scheme 103



Scheme 104



exhibits a minor cytotoxic effect against P388 murine leukemia cells and was isolated from the rice hulls of *Oryza sativa*.[219] A synthesis of the (*R*)-isomer of orizaterpenyl benzoate based on this multicomponent allylation was also reported by Tietze, using in this case the commercially available 6-methylheptano-2-one and the trimethylsilyl ether of (*R*)-1,2-diphenylethanol as chiral auxiliary. The allylation was performed at −78 °C leading to a 90:10 diastereomeric mixture of the expected tertiary homoallylic ether in 85% yield (Scheme 91).[220]

Robertson and co-workers developed an efficient synthetic route to taurospongin A in 15 steps in a 13.5% overall yield. This natural product was isolated from the sponge *Hippospongia sp.* and shows inhibitory activity against DNA polymerase and HIV reverse transcriptase.[221] In this synthesis, the C-3 stereogenic center in the carboxylic acid core of taurospongin A was set by Tietze asymmetric allylation. Grignard allylation of chiral diprotected 6,8-dihydroxynonan-2-one was completely nonstereoselective, but application of Tietze's procedure, which employs the trimethylsilyl ether of (*R*)-1,2-diphenylethanol as a chiral auxiliary, showed very high reagent control, yielding the expected product with the desired (*R*) configuration in 68% yield (Scheme 92).[222]

5.2. Reagent Control

5.2.1. Chiral Nucleophiles with Stereogenic Centers in the Transferred Hydrocarbon Backbone. *5.2.1.1. α-Substituted Allylboron Reagents.* The highly stereoselective catalytic asymmetric hetero-Diels–Alder/allylboration sequence methodology has been applied to the synthesis of the natural product (+)-gonodiol and an antibiotic thiomarinol by the groups of Carreaux and Hall, respectively. A family of cytotoxic compounds were found in the ethanolic extracts of stem bark of *Goniothalamus giganteus*,[223] among them (+)-gonodiol. This natural product contains a 5,6-dihydro-2*H*-pyran-2-one unit with three contiguous stereocenters. The dihydropyran unit possessing the right configuration was achieved by Carreaux and co-workers by performing first a stereoselective hetero-Diels–Alder reaction between a (*E*)-3-borylacrolein and ethyl vinyl ether in the presence of chiral Jacobsen's Cr(III) catalyst and then an allylboration reaction between the resulting chiral allylboronate and an the appropriate aldehyde. Importantly, the allylated product was obtained as the only stereoisomer (Scheme 93).[224] The same three-component coupling strategy was followed by Hall and Gao in the synthesis of the antibiotic thiomarinol isolated from the bacterium *Alteromonas rava* sp. nov. SANK 73390.[225] In this case, the same borylacrolein was used in the cycloaddition step with an *E*/*Z* mixture of the prenyl-substituted enol ether derivative. Fortunately, the *Z*-isomer was found to be more reactive than the *E*-isomer, leading after the allylation process

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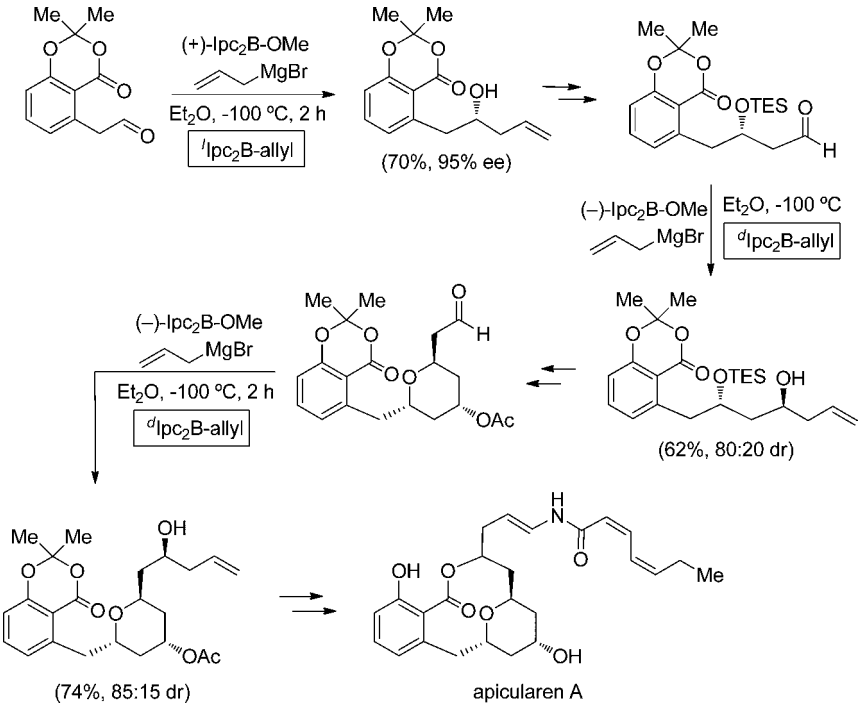
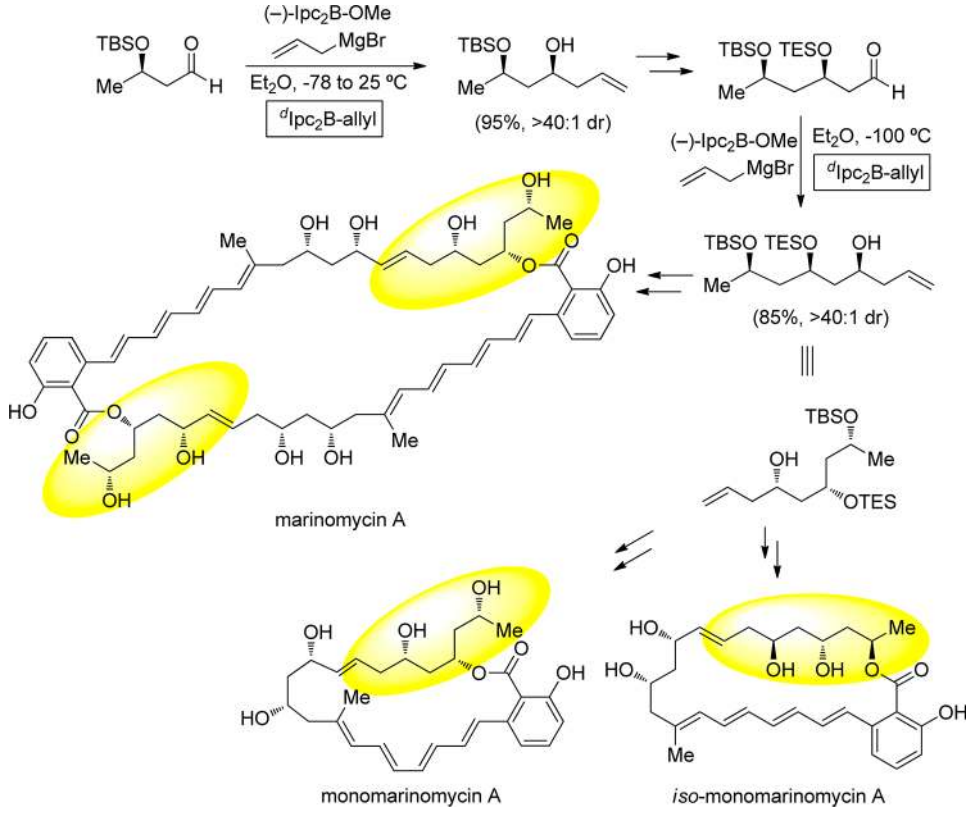
Scheme 105



Scheme 106

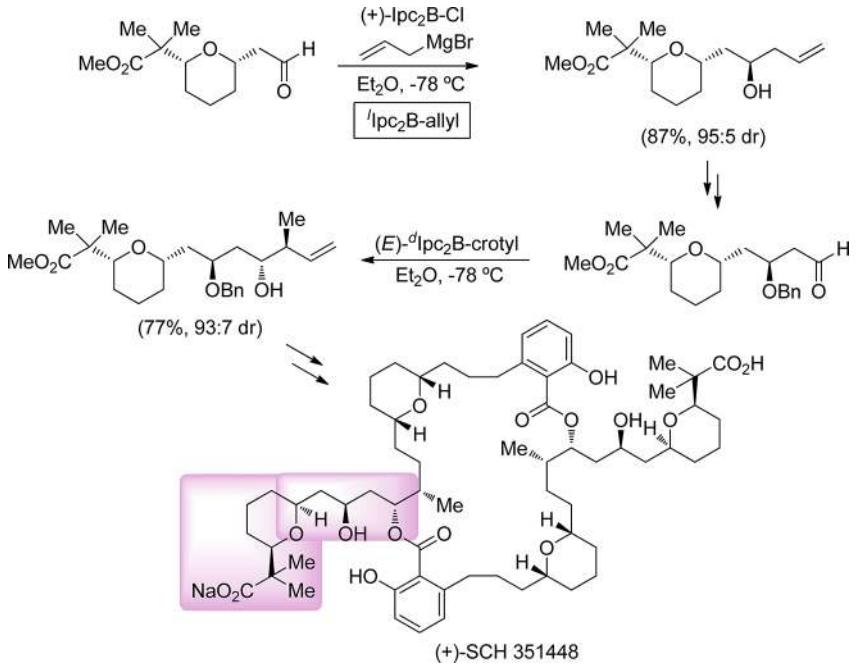


with a commercially available aldehyde to the desired pyran in 76% yield as a single diastereomer in >95% ee (Scheme 93).[226]

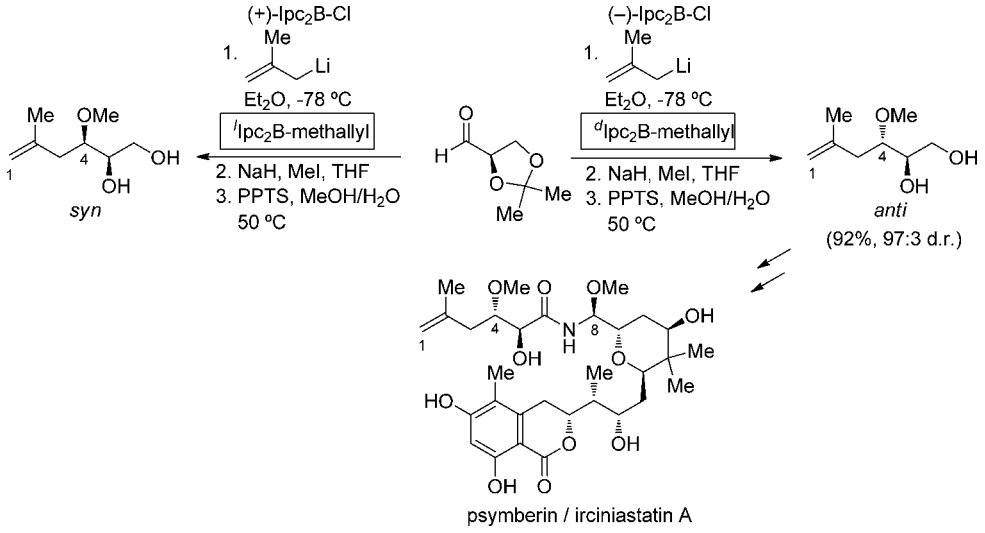
The method developed in the group of Aggarwal for the synthesis of chiral α-substituted allylboranes that add to aldehydes with almost complete stereoinduction, based on the reaction of chiral sulfur ylides with vinyl boranes, followed by stereospecific 1,2-migration of the vinyl group, was applied to the synthesis of iso-agatharesinol, a natural product with potent cytotoxic activity isolated from the roots of *Asparagus gobicus*.[227] In the synthesis depicted in Scheme 94, the resulting chiral allylborane was trapped with *O*-TBS-protected hydroxyacetaldehyde to produce the adduct in 72% yield and with

dx.doi.org/10.1021/cr400008h | *Chem. Rev.* 2013, 113, 5595–5698

Scheme 107



Scheme 108



greater than 99% ee (Scheme 94).[61] This synthesis allowed the relative and absolute stereochemistry of natural iso-agatharesinol to be established.

5.2.1.2. α-Substituted Allyltitanium Reagents. A convergent synthetic strategy was developed by Betzer, Ardisson, and co-workers for the synthesis of polyketide (+)-discodermolide. This natural product was isolated from extracts of the rare Caribbean marine sponge *Discodermia dissoluta*[228] and has been shown to inhibit the proliferation of cells. Key steps of the synthesis involved Hoppe crotyltitanation of chiral aldehydes using (*R*)-α-(*N*,*N*-diisopropylcarbamoyloxy) crotyltitanium [prepared *in situ* from crotyl diisopropylcarbamate, an equimolar mixture of *n*-BuLi/(−)-sparteine, and tetra(isopropoxy)titanium] in a mixture of pentane and cyclohexane at low temperature.[229] Independently of the configuration of the α-stereocenter in chiral aldehydes, *Si*-face addition always took place with (*R*)-crotyltitanium reagent, leading to the *anti*-adduct (considering the newly formed stereocenters). The configuration at C2−C4 and C10−C12 *syn,anti* methyl−hydroxy−methyl triads was totally controlled under these reaction conditions leading always to a single isomer (Scheme 95). On the other hand, a $BF_3{\cdot}OEt_2$-catalyzed allylation reaction using achiral (*Z*)-tri-*n*-butylcrotylstannane allowed the installation of the C16−C18 *syn,syn* stereotriad with a 95:5 dr under substrate control exclusively (Scheme 95).[230]

5.2.2. Chiral Nucleophiles with Stereogenic Centers in Nontransferred Ligands Bonded to the Metal Center. *5.2.2.1. Allylboron Reagents. 5.2.2.1.1. Allyl Boronates.* The first synthesis of the 18-membered macrocycle (+)-13-deoxytedanolide, isolated from the Japanese sea sponge *Mycale adhaerens*,[231] which exhibited antitumor activity, was reported by Smith and co-workers following a convergent strategy.[232] In this synthesis, the C15−C14 *anti* stereochemistry was stablished by performing a diastereoselective crotylation with

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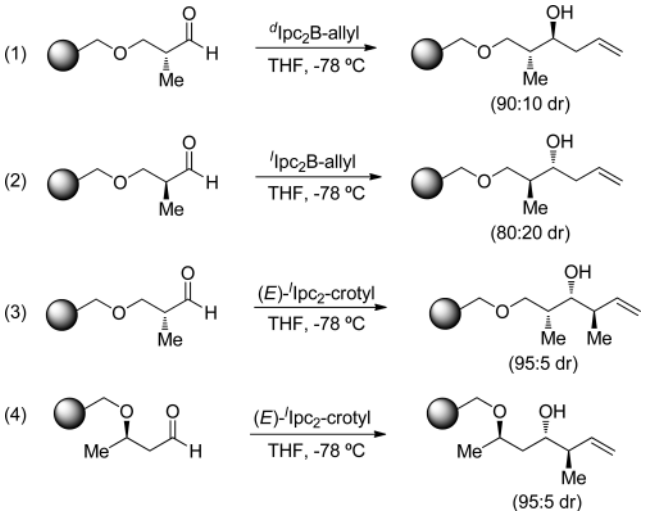
Scheme 109



Roush's (*E*)-crotylboronate (*S*,*S*)-diisopropyltartrate[111] of the aldehyde resulting from the oxidative cleavage of the terminal olefin shown in Scheme 96. The desired alcohol (*Re*-face addition) was exclusively formed in excellent yield (Scheme 96). Importantly, Brown crotylation[85] performed poorly in this case.

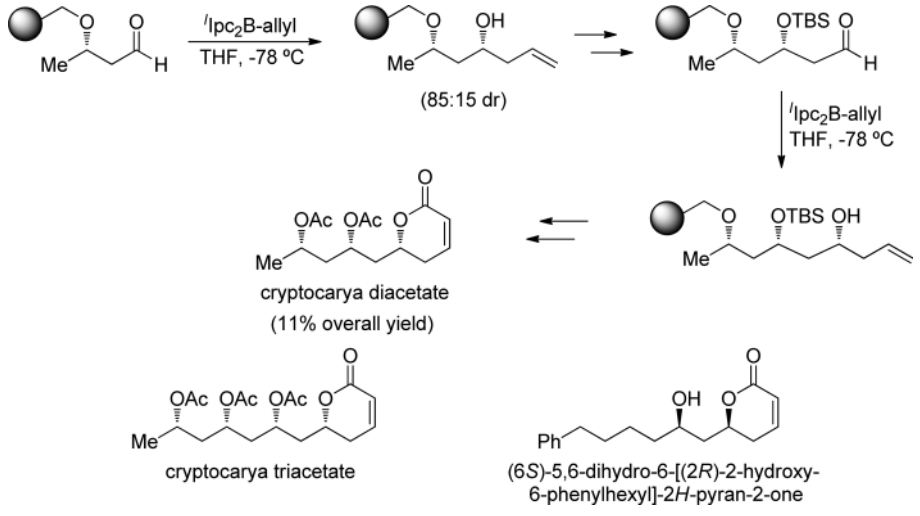
Lasonolide A is a 20-membered macrolide isolated from the Caribbean marine sponge *Forcepia sp.*[233] with promising anticancer activity. Kang and co-workers reported a total synthesis of this natural product following a convergent strategy. One of the subunits was synthesized stereoselectively performing two asymmetric allylations with Roush allylboronate diisopropyltartrate derivatives.[81] Thus, oxidation of the isopropylidene acetal derived from ethylidynetrimethanol followed by allylation with allylboronate (*R*,*R*)-diisopropyltartrate (DIPT) led to the corresponding homoallylalcohol in 86% yield and 76% ee (*Si*-face addition). A second diastereoselective allylation of a chiral aldehyde with the (*S*,*S*)-isomer of Roush allylboronate allowed access to the expected homoallylic alcohol with the right configuration at C23 in 77% yield and 91% ee (*Re*-face addition, Scheme 97).[234]

The Roush crotylation protocol was used in the synthesis of C13−C18 fragment of branimycin, an antibiotic isolated from a streptomyces stem that showed high activity against *Streptomyces viridochromogenes* combined with a low toxicity and a considerable oral availability. Mulzer and co-workers found that the reaction of D-glyceraldehyde isopropylidene acetal with (*Z*)-crotylboronate derived from (*R*,*R*)-DIPT produced the *anti*,*syn*-crotylation product in 96% yield and excellent diastereoselectivity. To achieve the desired *syn*,*syn* stereotriad, the configuration at C17 was inverted through an epoxide ring formation/ring-opening sequence (Scheme 98). A different strategy for the synthesis of the C13−C18 fragment consisted in the diastereoselective $TiCl_4$-catalyzed propargylation of the appropriate protected glyceraldehyde derivative with (*S*)-2-trimethylsilyl-2,3-pentadiene, a chiral allenylsilane. Under these conditions, a homopropargyl adduct was formed as a 20:1 diastereomeric mixture in 77% yield (Scheme 98).[235]

Williams and co-workers reported a formal synthesis of (+)-leucascandrolide A, a macrolactone isolated from *Leucascandra caveolata*, a calcareous sponge.[236] This bioactive natural product displayed strong *in vitro* anticancer properties. Diastereoselective allylation of a chiral aldehyde was a key step of this synthesis. The allylating reagent, generated *in situ* from (4*R*,5*R*)-2-bromo-4,5-diphenyl-1,3-ditosyl-1,3,2-diazoborolidine and an allyl stannane, reacted with the chiral aldehyde at low temperature to give the homoallylic alcohol in >98% yield and 91:9 dr. A six-membered chairlike model was proposed to rationalize the *Re*-face addition to the prostereogenic aldehyde due to the C_2-symmetric (*R*,*R*)-auxiliary interactions (Scheme 99).[237]

5.2.2.1.2. Allyl Boranes. Chiral pinane-derived allylating reagents developed by Brown[85] have been widely used in natural products syntheses. Importantly, they can be easily prepared from either (+)- or (−)-α-pinene, giving access to both enantiomers and, consequently, making it possible to differentiate the stereochemical pathways in the allylation of prochiral carbonyl compounds. In addition, the allyl reagents are stable under inert atmosphere in solution. However, the crotyl derivatives isomerize upon storage and must be prepared and used *in situ*. Regarding face selectivity in the allylation of aldehydes with allyl bisisopinocamphenylborane (Ipc_2B-allyl), the addition to the *Si*-face occurred predominantly with

Scheme 110



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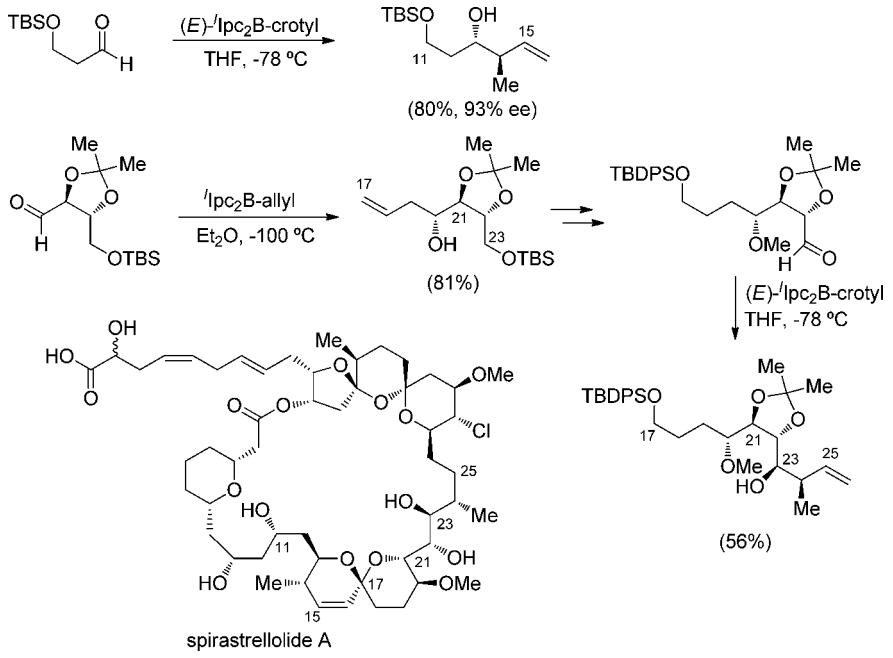
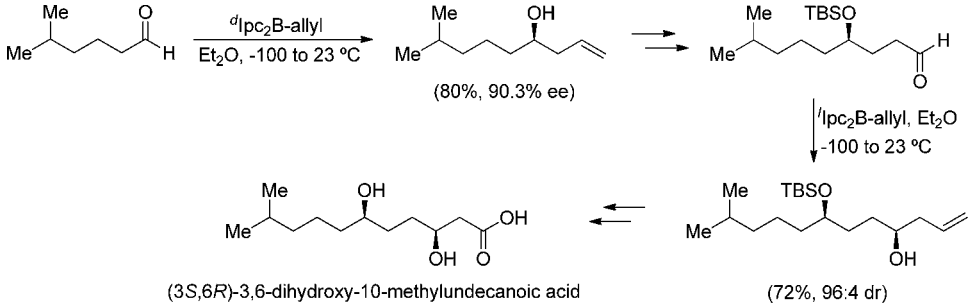
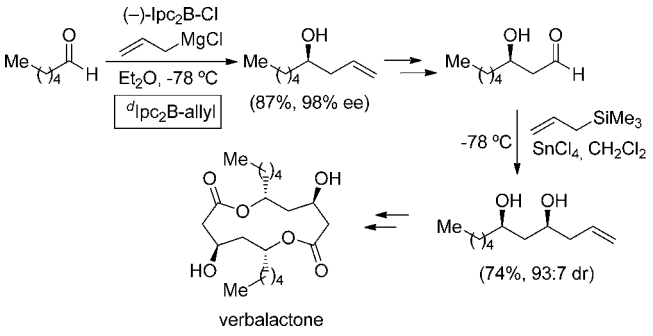
Scheme 111



Scheme 112



Scheme 113



(+)-enantiomer (from now on ^{d}Ipc$_2$B-allyl) through a favored Zimmerman–Traxler-type transition state (Figure 14).

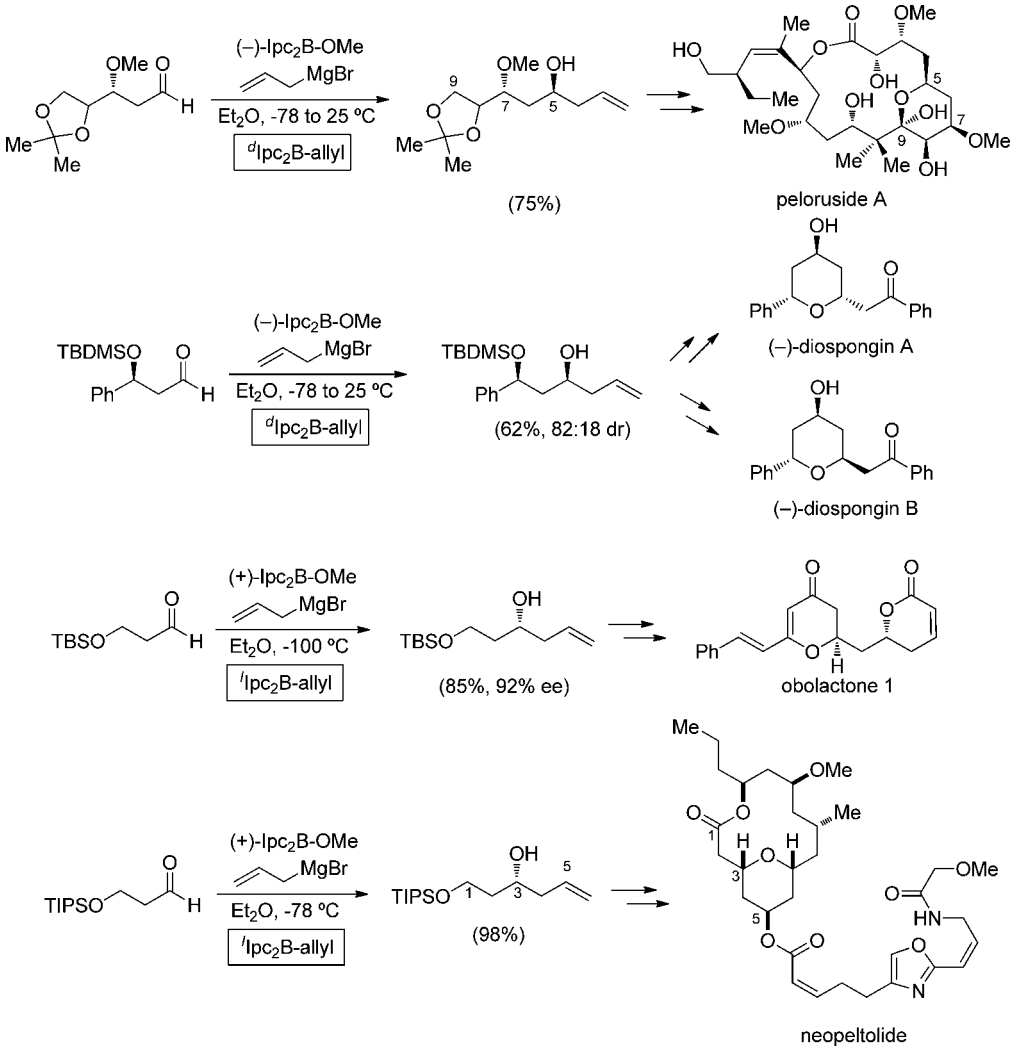
The stereoselective allylation of aldehydes with Ipc$_2$B-allyl has been a recurrent synthetic tool used for Carda, Marco, and co-workers in the synthesis of many natural products. They reported the first total synthesis of (+)-hyptolide, a naturally occurring lactone isolated from the leaves of *Hyptis pectinata* Poit.[238] The synthesis started with the asymmetric allylation with ^{l}Ipc$_2$B-allyl of a chiral aldehyde derived from (*S*)-ethyl lactate, to give the homoallylic alcohol (*Re*-face addition) in 82% yield and 98:2 dr (Scheme 100).[239] The allylating reagent was prepared *in situ* from (+)-diisopinocampheylchloroborane [(+)-Ipc$_2$B–Cl] and allylmagnesium bromide. A Carreira's asymmetric ethynylation and a ring closing metathesis were also key steps of this 15-step synthesis.

Asymmetric Brown allylation along with ring-closing metathesis were also key steps in the synthesis of naturally occurring α,β-unsaturated lactones (−)-spicigerolide and (+)-anamarine. These polyacetate/pyranone-containing natural products, isolated from leaves and flowers of *Hyptis* species,[240] display cytotoxicity againts tumor cells and antibacterial and antifungal activities. In the case of (−)-spicigerolide, the allylating reagent (^{l}Ipc$_2$B-allyl) was prepared from allylmagnesium bromide and (+)-Ipc$_2$B–Cl and reacted with an α,β-unsaturated aldehyde derived from commercially available L-rhamnose, leading to the expexted *cis*-allylic alcohol (*Re*-face addition), accompanied by its epimer at the newly formed stereogenic center in 85% yield and 88:12 dr (Scheme 101).[241] The same allylating reagent was used in the synthesis of (+)-anamarine. The reaction with the appropriate chiral α,β-unsaturated aldehyde produced the corresponding alcohol in 74% yield and 88:12 dr (Scheme 101).[242]

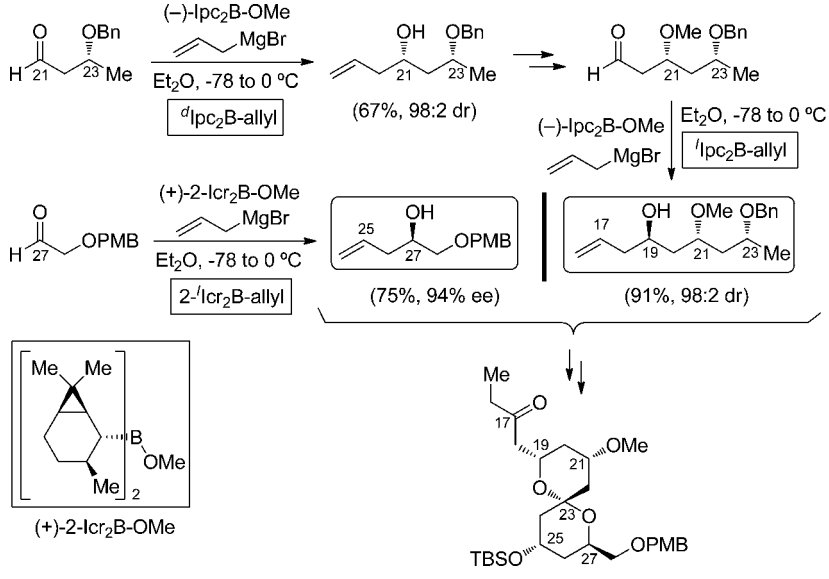
The same authors developed the stereoselective synthesis of the δ-lactone derived from (2*Z*,5*S*,7*R*,9*S*,11*S*)-tetrahydroxyhexacos-2-enoic acid, the structure reported for passifloricin A, a polyketide-type α-pyrone isolated from the resin of *Passiflora*

dx.doi.org/10.1021/cr400008h | *Chem. Rev.* 2013, 113, 5595–5698

Scheme 114



Scheme 115



foetida var. *hispida*, which structure was elucidated on the basis of purely spectroscopic findings.[243] In this synthesis, the creation of all stereogenic centers relied upon Brown's asymmetric allylation methodology, meanwhile the lactone ring was formed via ring-closing metathesis (Scheme 102).[244] Finally, they found that the NMR data of the synthetic product

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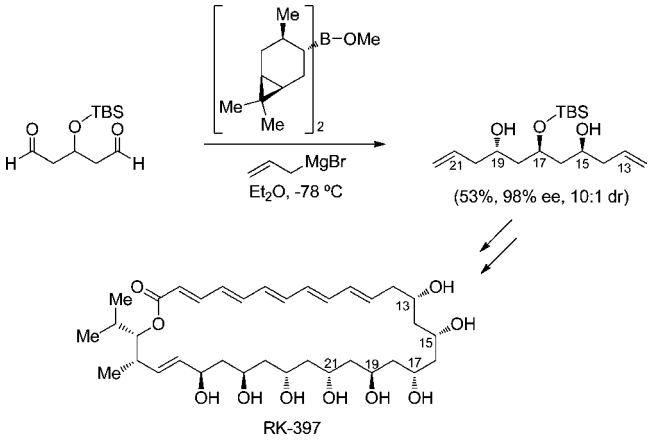
Scheme 116



were not coincident with those of the natural product. That meant that the published structure for passifloricin A was erroneous.

In order to assign the right structure for passifloricin A and making use of the same synthetic tools, Murga et al. synthesized eight isomers in enantiopure form. One interesting finding, based mostly on careful analysis of peak fragmentation in the mass spectra, was that C12 was a stereogenic center in the natural product instead of C11, as was initially proposed. The synthesis of passifloricin A is depicted in Scheme 103 starting from pentadecanal.[245] All the allylations took place with the same reagent ($^{l}Ipc_2B$-allyl) in a highly stereoselective fashion. Different structural analogues of the polyketide passifloricin lactone were synthesized taking advantage of this methodology. Some of them exhibit significant antiparasitic activity in addition to high cytotoxicity.[246]

Carda, Marco, and co-workers carried out also the synthesis of the proposed structure of feigrisolide A. The first step of the synthesis was a Brown's asymmetric allylation of (*S*)-*O*-TBS-protected 3-hydroxybutanal with $^{d}Ipc_2B$-allyl. A separable 89:11 diastereomeric mixture of the expected homoallylic alcohol was obtained (Scheme 104).[247] The major isomer in enantiopure form was further used to synthesize the structure published for natural feigrisolide A. However, the published structure does not correspond to that of the natural product. By comparison spectroscopic data, the authors suggested that feigrisolide A was identical to (−)-nonactic acid.

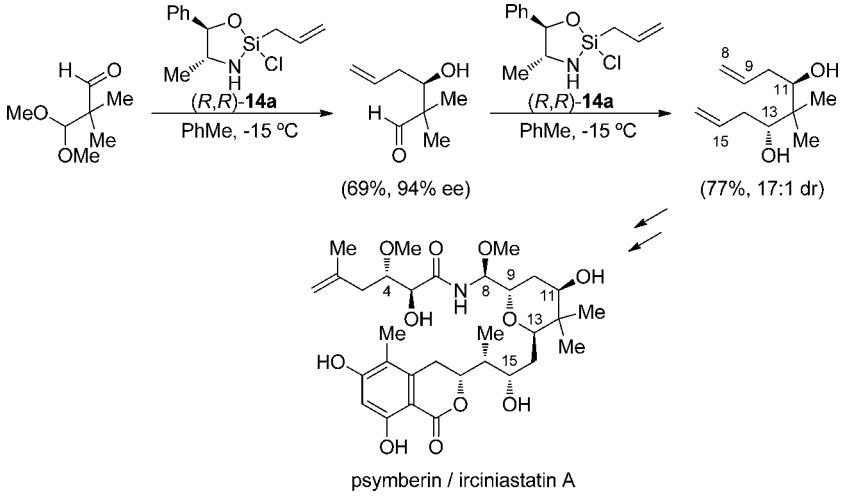
A total synthesis of apicularen A, a natural product isolated from a variety of strains of the myxobacterial genus *Chondromyces*[248] possessing highly cytotoxic properties, was reported by Nicolaou's group. In this synthesis, a reiterative two-step procedure featuring stereoselective allylation and ozonolytic cleavage was used. The three stereoselective allylations were performed with Brown's chiral allyl boranes Ipc_2B-allyl prepared *in situ* from the corresponding Ipc_2B-OMe and allylmagnesium bromide. All of the allylations proceeded in a stereoselective way (Scheme 105).[249]

Brown's stereoselective allylation and ozonolytic cleavage strategy was used in the syntheses of marinomycin A,[250] a potent natural antibiotic isolated from a novel marine actinomycete,[251] and its unnatural monomeric homologues, monomarinomycin A and *iso*-monomarinomycin A.[252] The synthesis started with the *O*-TBS-protected (*R*)-3-hydroxybutanal and $^{d}Ipc_2B$-allyl, to produce the corresponding homoallylic alcohol in high yield and diastereoselectivity. After appropriate functional group manipulation, including an ozonolytic cleavage, a second stereoselective allylation with the same chiral reagent proceeded in similar levels of chemical yield and diastereoselectivity. The resulting triol derivative was a common precursor of marinomycin A, monomarinomycin A and *iso*-monomarinomycin A (Scheme 106).

A 28-membered macrodiolide (SCH 351448) consisting of two identical hydroxy carboxylic acid units was isolated from the ethyl acetate extracts of the fermentation broths of *Micromonospora* sp.[253] This natural product was found to activate low-density lipoprotein receptor promoter involved in familial hypercholesterolemia disorders. Lee and co-workers reported the first total synthesis of this compound, using stereoselective Brown's allylation and crotylation as key steps. Allylation of the corresponding chiral aldehyde with $^{l}Ipc_2B$-allyl proceeded in high yield and diastereoselectivity (*Re*-face addition). On the other hand, crotylation with (*E*)-$^{d}Ipc_2B$-crotyl produced the expected *anti*-product (*Si*-face addition) in 77% yield and 93:7 dr (Scheme 107).[254]

Cytotoxins psymberin[255] and irciniastatin A[256] were isolated by two independent groups from marine sponges *Psammocinia* sp. and *Ircinia ramose*, respectively. The structures initially proposed for these compounds differed from the configuration

Scheme 117



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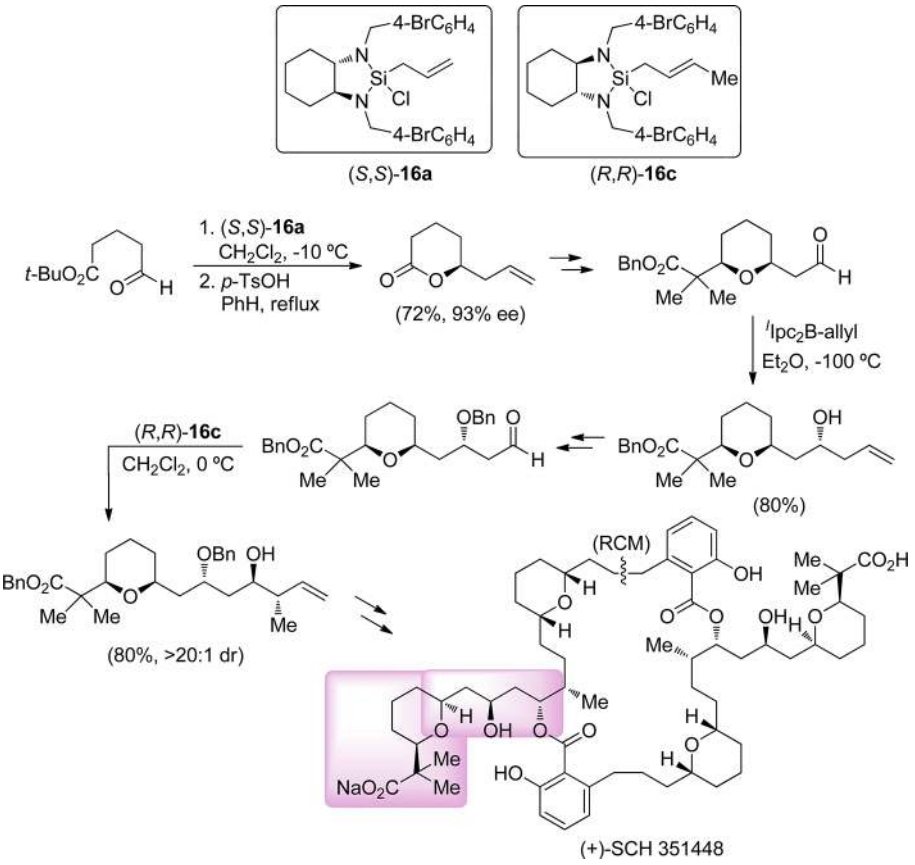
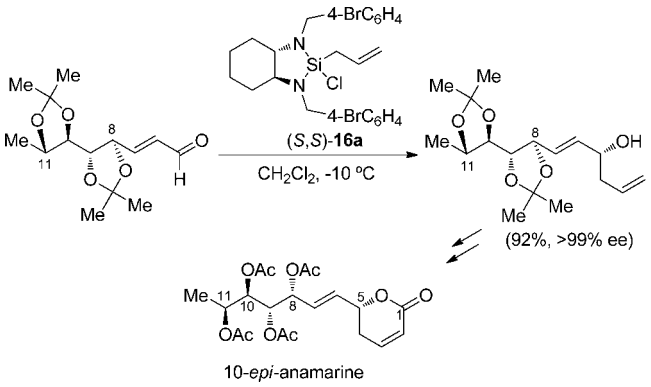
Scheme 118



Scheme 119



at C8, and in addition, the stereochemistry at C4 was not assigned at that time. In order to determine the configuration at C4, De Brabander and co-workers developed a convergent synthesis of both epimers of psymberin at C4, performing an asymmetric methallylation of D-glyceraldehyde isopropylidene acetal with both enantiomers of Ipc_2B-methallyl. They found that psymberin and irciniastatin A were identical compounds with (*S*)-configuration at C4 (Scheme 108).[257]

Waldmann and co-workers found that the stereoselective Brown's allylation and crotylation of polymer-bound aldehydes was an efficient solid-phase synthesis method for the stereocomplementary synthesis of collections of multiply functionalized carbon chains. Importantly, they found that for aldehydes bearing an α-stereocenter, the allylation−crotylation exhibited a remarkable match/mismatch effect. In addition to the expected reagent control, substrate control accounted to some extent for the stereochemical outcome. Thus, the *anti*-directed allylation gave rise to higher selectivity than the *syn*-directed transformation (compare eqs 1 and 2 in Scheme 109). As expected, the sequence worked equally well for the crotylated compound combination (Scheme 109).[258]

This methodology was applied to the synthesis of different natural products, such as cryptocarya diacetate and triacetate and (6*S*)-5,6-dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one (isolated from the tree *Ravensara crassifolia*). For instance, the synthesis of cryptocarya diacetate is depicted in Scheme 110. This synthesis commenced with the immobilization of (*S*)-3-hydroxybutyric acid ester on Wang resin and further conversion into polymer-bound aldehyde in two steps. Allylation with $^{l}Ipc_2B$-allyl yielded the expected homoallylic alcohol in a 85:15 *syn*/*anti* ratio. After protection of the hydroxyl group and careful ozonolysis of the double bond, the resulting aldehyde was subjected to a second allylation with $^{l}Ipc_2B$-allyl to form the *syn*,*syn* secondary alcohol, a precursor of target cryptocarya diacetate (Scheme 110). Based on this reaction sequence, all eight stereoisomeric configurations possible for the scaffold of the natural product were generated in a reaction sequence by employing the allylation reactions in a stereocomplementary fashion.[259]

Fürstner and co-workers reported a synthesis of spirastrellolide A, an antimitotic natural product isolated from the Caribbean sponge *Spirastrella coccinea*[260] that was shown to be a very potent and selective inhibitor of protein phosphatase PP2A. The synthesis relied upon stereoselective Brown's allylation and crotylation of aldehydes to establish the C11 to C25 fragment stereochemistry. Thus, stereoselective crotylation

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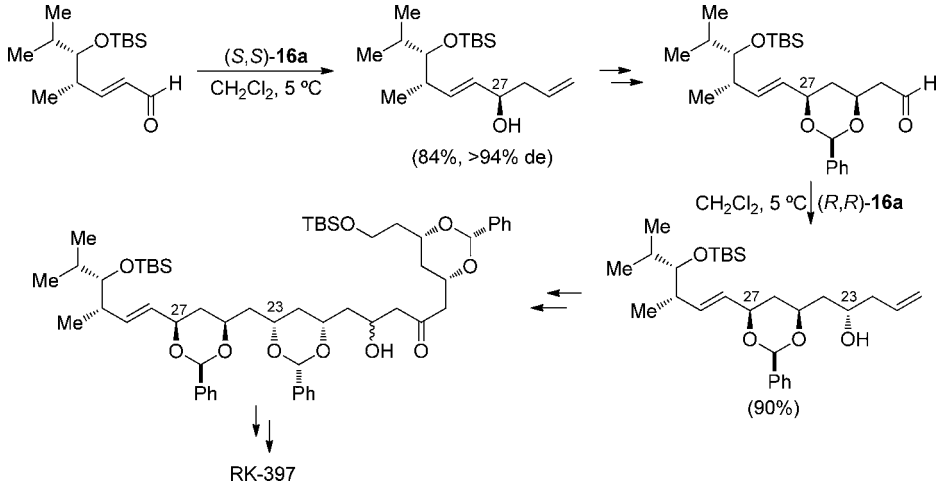
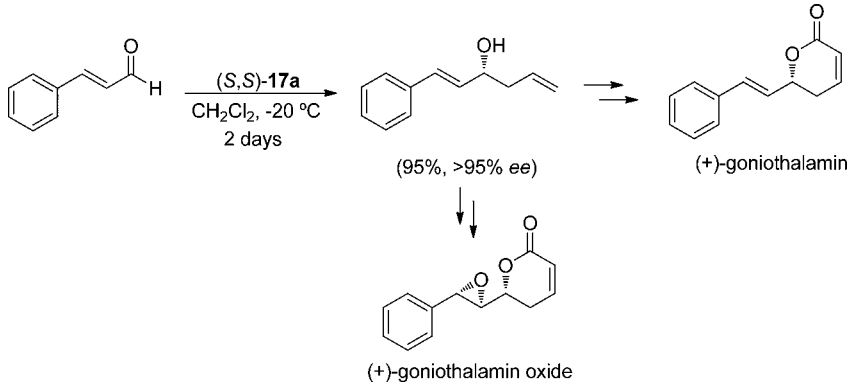
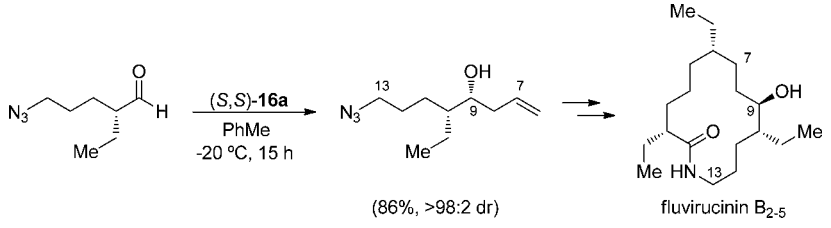
Scheme 120



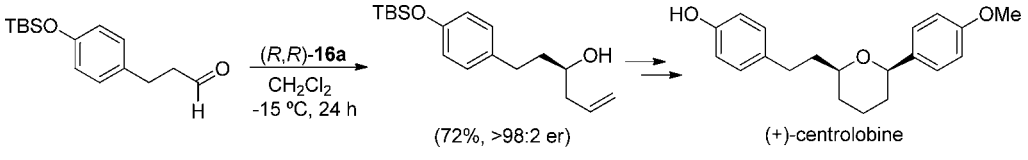
Scheme 121



Scheme 122



Scheme 123



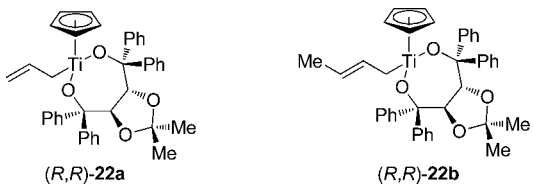


Figure 15. Structure of allyltitanium titanium complex (*R*,*R*)-**22a** and crotyltitanium complex (*R*,*R*)-**22b**.

of *O*-TBS-protected 3-hydroxybutanal produced the expected homoallyl alcohol in 80% yield and 93% ee, containing the C11−C15 fragment with the right stereochemistry. For the preparation of the C17−C25 segment, a tartrate-derived aldehyde served as a convenient starting material through a two-directional synthetic strategy. Brown's allylation of the aldehyde produced the secondary alcohol with (*R*)-configuration as a single diastereomer in 81% yield on a 20 g scale. This methodology was shown to be superior to many other procedures surveyed by the authors. The symmetry-related

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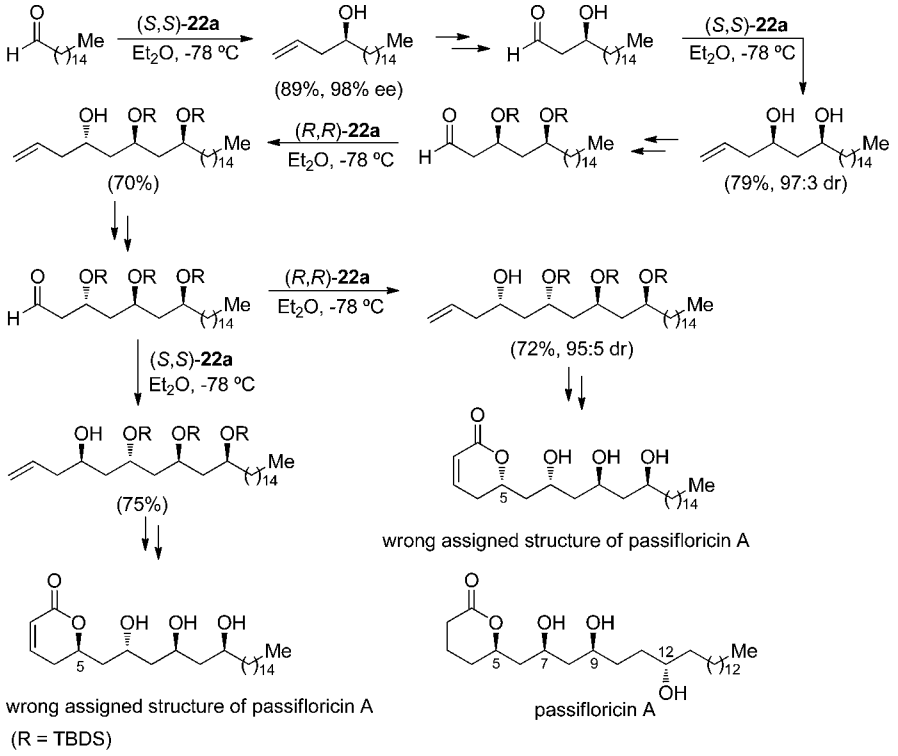
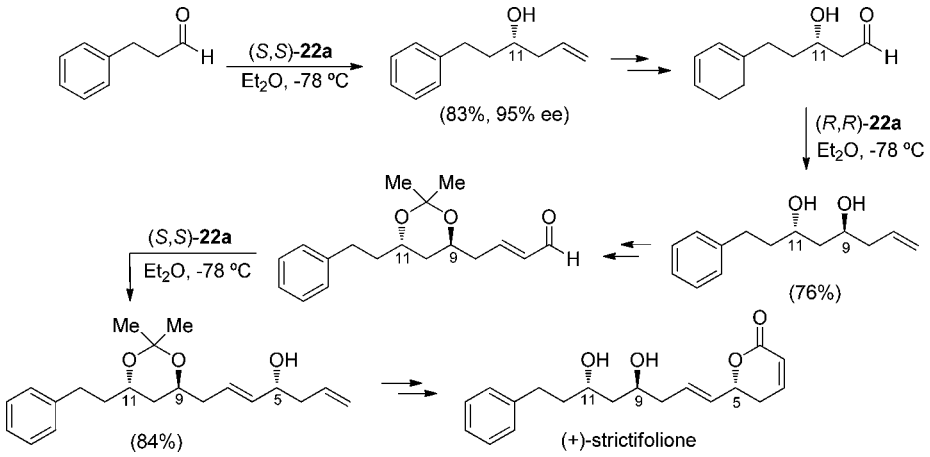
Scheme 124



Scheme 125



chain extension at the C23 terminus was analogously performed by Brown crotylation, which was also superior to alternative procedures in terms of scalability and stereoinduction (Scheme 111).[261]

The synthesis of (3*S*,6*R*)-3,6-dihydroxy-10-methylundecanoic acid was accomplished by Xie, Li, and co-workers in 11 steps and 25.8% overall yield from commercially available 1-bromo-3-methylbutane. This natural product was isolated from the chloroform extract of aerial parts of *Lafuentea rotundifolia Lag.*[262] Two Brown's allylations were key steps of the synthesis to establish the right configuration at the two stereocenters of the molecule. The reactions led to the expected homoallyl alcohol derivatives in high yields and stereoselectivities (Scheme 112).[263]

Verbalactone is a natural antibiotic isolated from the roots of *Verbascum undulatum* Lam.,[264] a biennial plant of the genus *Verbascum* that belongs to the family Scrophulariaceae. This natural product is a macrocyclic symmetrical dimer of lactone (3*R*,5*R*)-dihydroxy-5-decanolide. Cossy and co-workers reported a synthesis of this compound starting from hexanal. They performed a Brown's allylation using $^{d}Ipc_2B$-allyl (*Si*-face addition) to produce the homoallylic alcohol in 87% yield with a 98% ee. In a further step, the configuration of the other stereocenter of the monomer unit was established by a diastereoselective allylation of a γ-hydroxyaldehyde upon treatment with allyltrimethylsilane and $SnCl_4$ in CH_2Cl_2 at low temperature under substrate control conditions. The *syn*-diol was obtained as the major diastereomer in 74% yield and 93:7 dr (Scheme 113).[265]

Stereoselective Brown's allylations using either enantiomer of Ipc_2B-allyl were also key steps in the synthesis different natural products, such as peloruside A,[266] a polyoxygenated 16-membered macrolide isolated from the New Zealand marine sponge *Mycale sp.*,[267] (−)-diospongins A and B,[268] isolated

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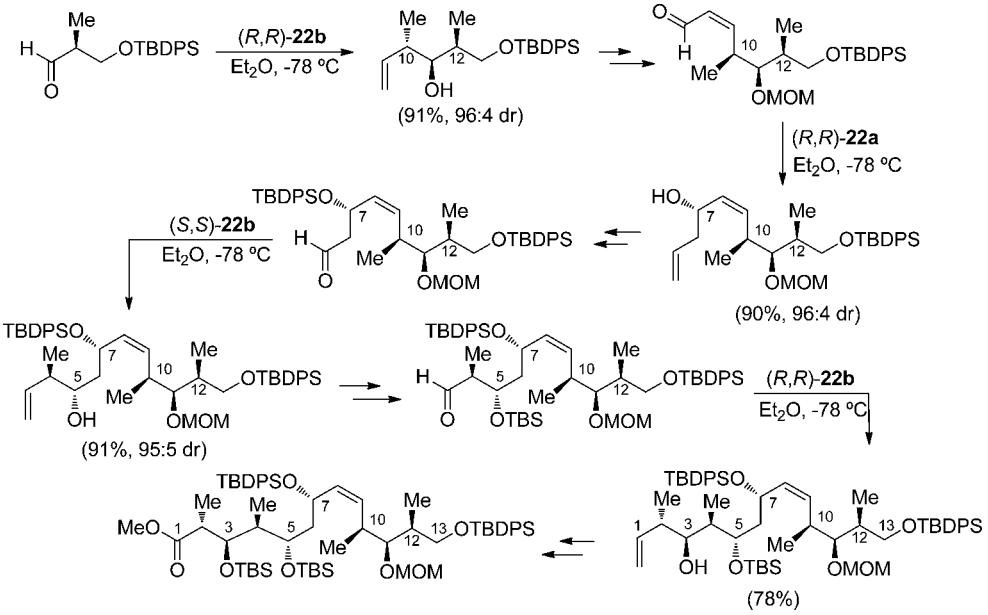
Scheme 126



from rhizomes of *Dioscorea spongiosa*,[269] obolactone 1,[270] isolated from *Cryptocarya obovata*,[271] a plant collected in northern Vietnam, and neopeltolide,[272] a marine macrolide that was isolated from a deep-sea sponge of the Neopeltidae family[273] (Scheme 114). Peroluside A, obolactone 1, and neopeltolide were found to be cytotoxic to different cancer cell lines, meanwhile (−)-diospongins A and B exhibited antiosteoporotic activity.

Paterson and co-workers reported the synthesis of the C16−C28 CD-spiroacetal subunit of spongistatin 1, a potent cytotoxic marine macrolide. Using Brown asymmetric allylation of appropriate aldehydes with both $^{l}Ipc_2B$-allyl (*Re*-face addition) and $^{d}Ipc_2B$-allyl (*Si*-face addition), they could reach the C17−C24 fragment with the right configuration at all stereocenters On the other hand, the synthesis of the C25−C28 fragment began with the asymmetric allylboration of *O*-PMB-protected hydroxyacetaldehyde with allylbis-(2-isocaranyl)borane (2-$^{l}Icr_2B$-allyl), instead of using a isopinocampheyl derivative, providing the corresponding homoallylic alcohol in 75% yield and 94% ee (Scheme 115).[274] Finally, both fragments C17−C24 and C25−C28 were connected through a stereoselective aldol reaction after convenient functional group manipulation.

Oxopolyene macrolide RK-397 is a natural product isolated from soil bacteria and was shown to possess antifungal, antitumor, and antibacterial activities.[275] Sammakia and co-workers reported a convergent synthesis of this complex molecule. For the preparation of the C12−C22 fragment, they performed a stereoselective bisallylation of a glutaraldehyde derivative using in this case the (+)-3-carene-derived allylboration reagent depicted in Scheme 116. The corresponding diol was obtained in this way in good yield and high selectivity.[276]

5.2.2.2. Allyl Silanes. The stereoselective allylation of aldehydes with five-membered silacycle allylsilanes derived from chiral 1,2-amino alcohols or 1,2-diamines developed by Leighton has also been used in the synthesis of natural products. Thus, De Brabander and co-workers carried out the stereoselective allylation of a monoprotected dimethylmalonaldehyde with Leighton's silane reagent (*R*,*R*)-**14a** in their synthesis of psymberin. The resulting hydroxyaldehyde (the carbonyl group was unmasked during the workup) was obtained in 69% yield and 94% ee (Scheme 117). A second allylation with the same reagent produced the C8−C15 central fragment of psymberin with the right configuration at C11 and C13 (*Re*-face addition).[257] In this convergent synthesis, a stereoselective Brown's methallylation was used to establish the stereochemistry at C4 (see Scheme 108).

Leighton and Bolshakov also achieved an efficient and stereocontrolled total synthesis of (+)-SCH 351448 (for another synthesis, see Scheme 107).[253] An asymmetric allylation with the silane reagent (*S*,*S*)-**16a** and a crotylation with reagent (*R*,*R*)-**16c** were key steps of this linear synthesis. Thus, the reaction of *tert*-butyl 5-oxopentanoate with (*S*,*S*)-**16a** followed by lactonization provided 6-allyl *δ*-lactone in 72% yield and 93% ee (*Re*-face addition). In the crotylation step using (*R*,*R*)-**16c**, the corresponding homoallyl alcohol was obtained in 80% yield as a single *anti*-isomer (*Si*-face addition). Finally, the synthesis of this dimeric polyketide was accomplished by performing a ring-closing metathesis (RCM), followed by hydrogenation of the alkene product (Scheme 118).[277]

Chiral allylation reagent (*S*,*S*)-**16a** was also used in the synthesis of 10-*epi*-anamarine, the epimer of natural product (+)-anamarine (see Scheme 101), developed by O'Doherty and Gao. The stereochemistry of C8−C11 was established by an enantio- and regioselective Sharpless dihydroxylation of either dienoates or trienoates. The reaction of a polyfunctionalized *α*,*β*-unsaturated aldehyde with (*S*,*S*)-**16a** gave the expected allylic alcohol in 92% yield with near complete stereocontrol (>99% ee, *Re*-face addition). The synthesis of the corresponding 5,10-*epi*,*epi*-anamarine isomer was also achieved when the allylation of the chiral aldehyde was carried out with (*R*,*R*)-**16a** (*Si*-face addition, Scheme 119).[278]

Leighton's reagents were also used in two steps of a formal total synthesis of macrolide antibiotic RK-397 (see Scheme 116). The synthesis reported by O'Doherty and co-workers proceeded in 19 steps from simple achiral conjugated dienoates.

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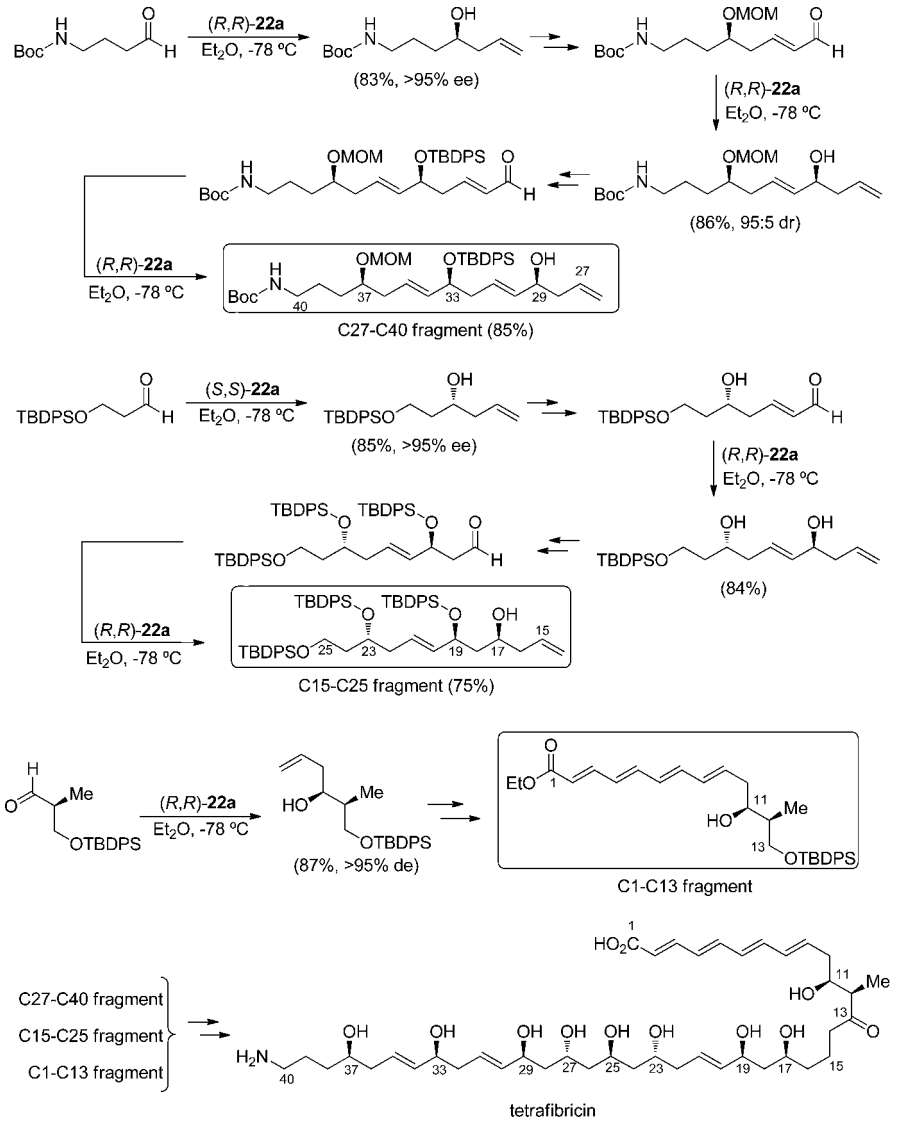
Scheme 127



The configuration at C27 was established by the asymmetric allylation of an enal with (*S*,*S*)-**16a**. The resulting homoallyl alcohol was obtained in good yield and selectivity (*Re*-face addition). A second allylation of the corresponding aldehyde with Leighton's reagent (*R*,*R*)-**16a** produced efficiently the corresponding alcohol with the right stereochemistry (*Si*-face addition) at C23 (Scheme 120).[279]

An expeditious synthesis of (+)-goniothalamin and (+)-goniothalamin oxide was developed by O'Doherty and Harsh starting from cinnamaldehyde.[280] Goniothalamin was isolated from the bark of *Cryptocarya caloneura* and possesses potent cytotoxicity toward a range of cancer cell lines.[281] The synthesis commenced with the allylation of *trans*-cinnamaldehyde with Leighton's reagent (*S*,*S*)-**16a** leading to a secondary alcohol (*Re*-face addition) in 95% yield with excellent stereoselectivity (>95% ee). The same alcohol was obtained in lower yield (68%) from cinnamyl alcohol using allyl acetate under Krische's conditions.[282] A stereoselective epoxidation followed by *O*-acryloylation and ring-closing metathesis provided (+)-goniothalamin oxide (Scheme 121).

Llàcer, Urpí, and Vilarrasa reported the first synthesis of fluvirucinin B_{2-5}, the common aglycon of antibiotics active against influenza A, fluvirucins B_2−B_5, isolated from diverse actinomycetes.[283] The stereochemistry at C9 was established by allylation of a chiral α-substituted aldehyde with Leighton's reagent (*S*,*S*)-**16a**. The resulting homoallylic alcohol was obtained in 86% yield as a single product (>98:2 dr) with relative *syn* configuration, a *Re*-face addition taking place (Scheme 122).[284] Ring-closing metathesis and ketone methylenation were also key steps of this synthesis.

All stereoisomers of the natural product centrolobine were selectively synthesized by Schmidt and Hölter, starting from 3-(4-hydroxyphenyl)propanal as a common precursor.[285] Interestingly, (−)-centrolobine was isolated from the heartwood of the tree *Centrolobium tomentosum*,[286] whereas its (+)-enantiomer occurs in the closely related species *Centrolobium robustum*.[287] For instance, allylation of *O*-TBS-protected 3-(4-hydroxyphenyl)propanal with (*R*,*R*)-**16a** produced the homoallylic alcohol in 72% yield as a single isomer (*Si*-face addition), a precursor of (+)-centrolobine (Scheme 123). Allylation with (*R*,*R*)-**16a** allowed the access to (−)-centrolobine.

5.2.2.3. Allyltitanium Reagents. Similarly to chiral pinane-derived allylating reagents (section 5.2.2.1.2.), cyclopentadienyldialkoxyallyltitanium reagents have also been used in the

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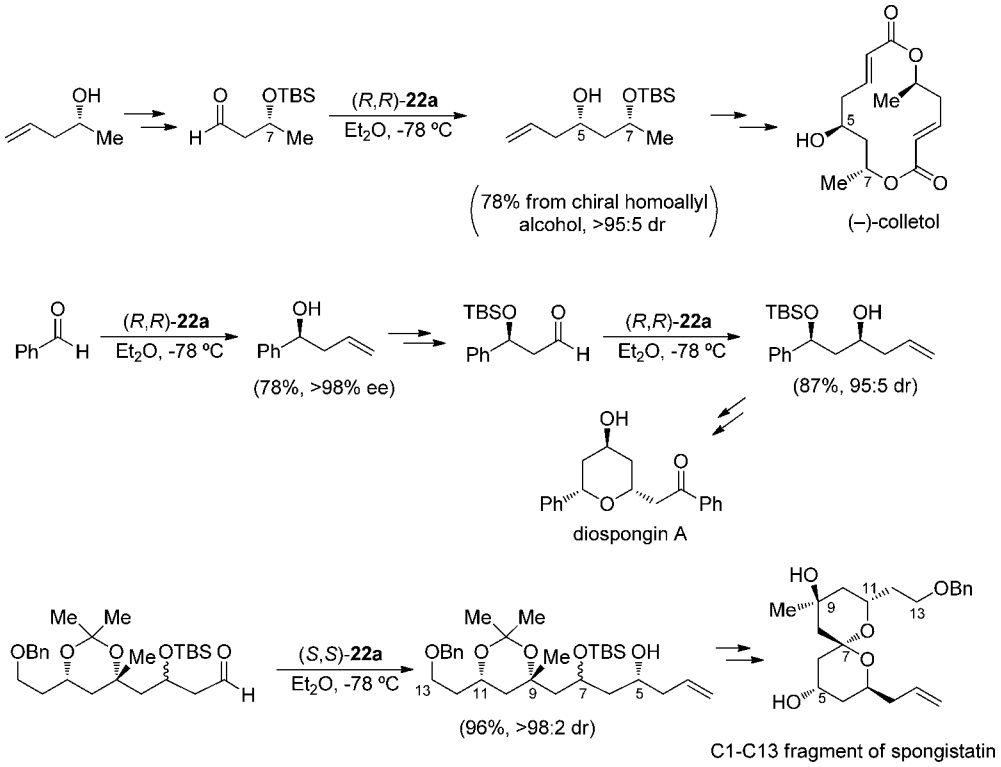
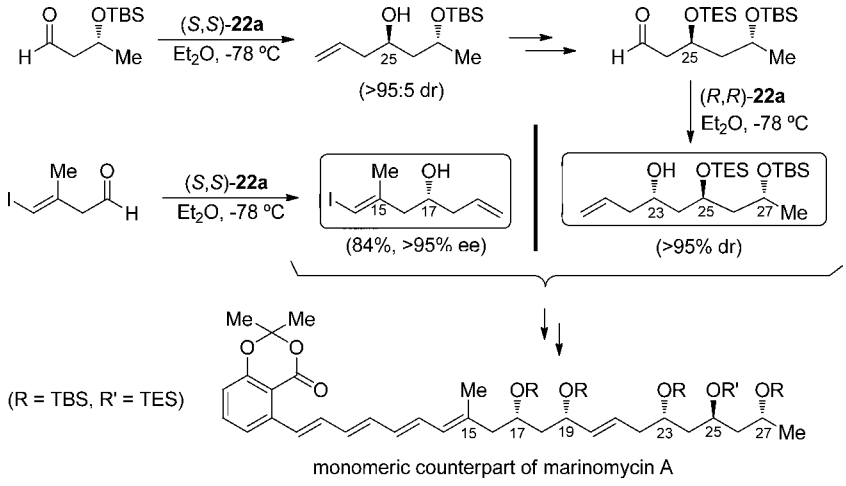
Scheme 128



Scheme 129



synthesis of natural products, especially by the group of Cossy. They are readily prepared from $CpTiCl_3$ and chiral 1,4-diols, leading to stable seven-membered titanacycles.[288] The chiral diols most commonly used are accessed upon reaction of tartrate ester acetals with Grignard reagents. Concerning face selectivity in the allylation reactions, *Si*-face addition takes place with allyltitanium and crotyltitanium complexes, (*R*,*R*)-**22a** and (*R*,*R*)-**22b** (the Duthaler–Hafner reagents), respectively (Figure 15). In addition, in the case of the crotyl derivative, two contiguous stereocenters with *anti* relative configuration are formed predominantly upon reaction with aldehydes.

Cossy and BouzBouz reported a stereoselective total synthesis of the C5-epimeric proposed structures for passifloricin A[243] in 12 steps from *n*-hexadecanal by using enantioselective allyltitanations and a ring-closing metathesis reaction as the key steps. They found that both proposed structures were different from passifloricin A. They used allyltitanium complexes (*S*,*S*)-**22a** and its enantiomer for the stereoselective allylations. Oxydative cleavage of the double bond of the allyl unit produced a *β*-hydroxyaldehyde ready for a subsequent stereoselective allylation. This iterative strategy was identical to that employed by the group of Carda and Marco (see Scheme 102)[244] and allowed the synthesis of the target 1,3,5,7-triol unit with total control of the stereochemistry by choosing the appropriate enantiomer of the allylating reagent. The main difference between these syntheses lay in the allylating reagent: pinene derivatives in the synthesis of Carda and Marco and allyltitanium complexes in this case. Concerning the yield, the synthesis of Cossy and BouzBouz proved to be

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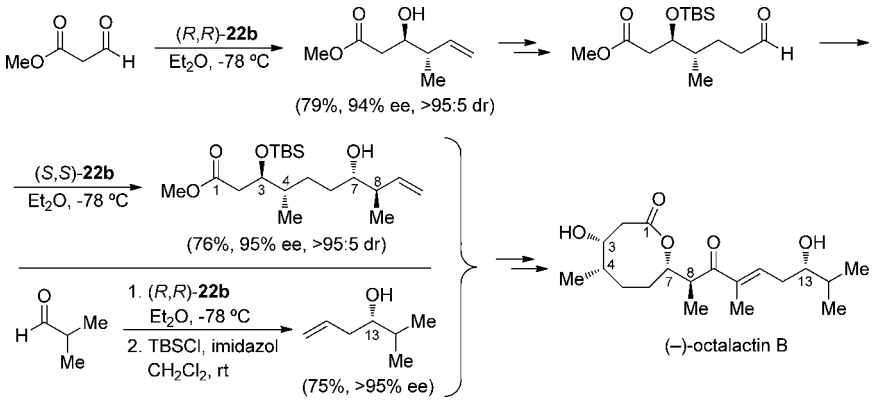
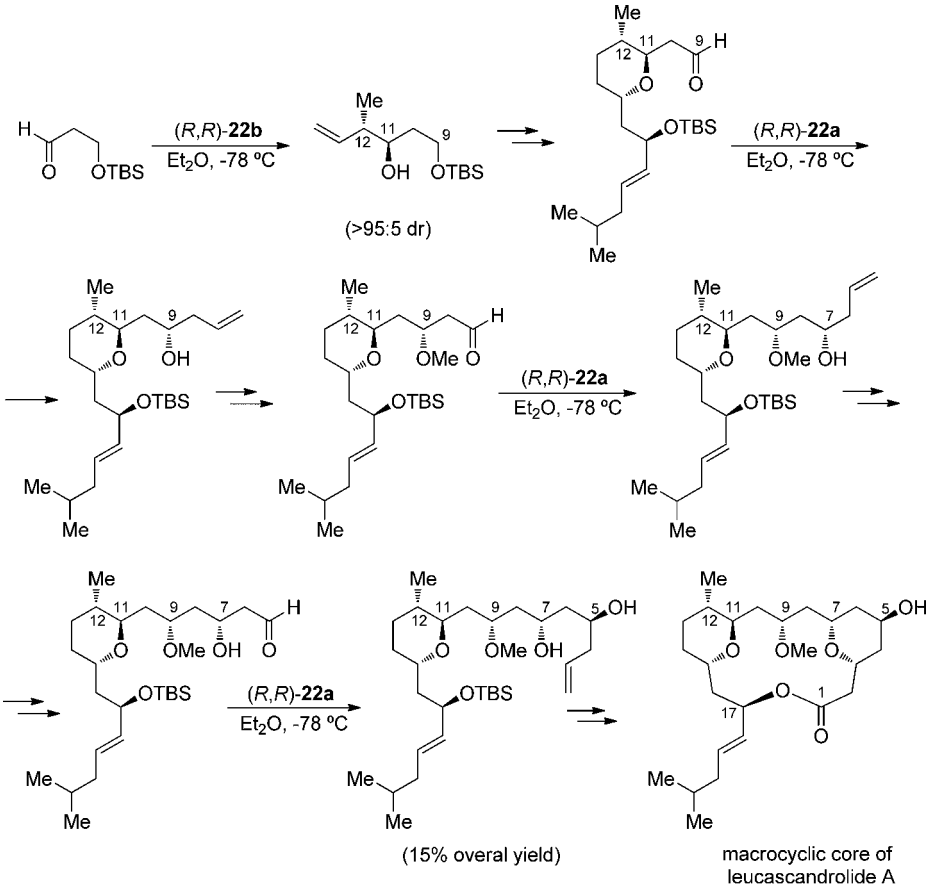
Scheme 130



Scheme 131



slightly superior although the stereoselectivities were similar (Scheme 124).[289]

Curran and co-workers reported the total synthesis of an eight-member stereoisomer library of passifloricins in which the stereocenters were introduced and tagged en route during the synthesis. The reaction path involved also three similar iterative cycles (oxidation of the homoallylic alcohol to aldehyde and stereoselective allylation with both enantiomers of the Duthaler–Hafner reagent). That library comprised the enantiomer of passifloricin A and all seven epimers at C5, C7, and C9. The synthesis contrasted with all prior mixture work, in which building blocks with coded stereocenters were premade and pretagged.[290]

The allylation–oxidation protocol was also used by Cossy and BouzBouz in the stereoselective synthesis of (+)-strictifolione, a natural product isolated from *Cryptocarya strictifolia*, which has been shown to display antifungal activity.[291] In this case, they performed three allyltitanations with both enantiomers of **22a** in high yields and stereoselectivities to establish the stereochemistry at C5, C9, and C11. The resulting triol was finally transformed into the target lactone by performing a selective O-acrylation followed by a ring-closing metathesis (Scheme 125).[292]

Discodermolide is a potent immunosuppressive and anticancer agent as well as an antifungal agent. This compound has a unique polyketide structure bearing 13 stereogenic centers and was isolated from the deep-water marine sponge

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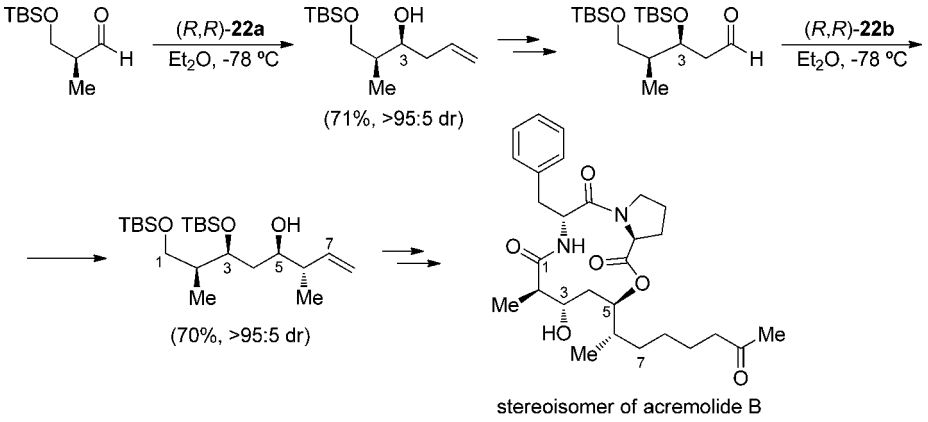
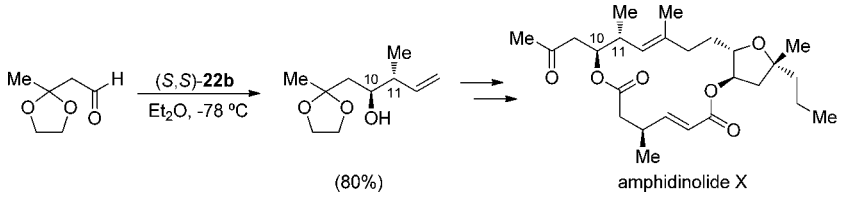
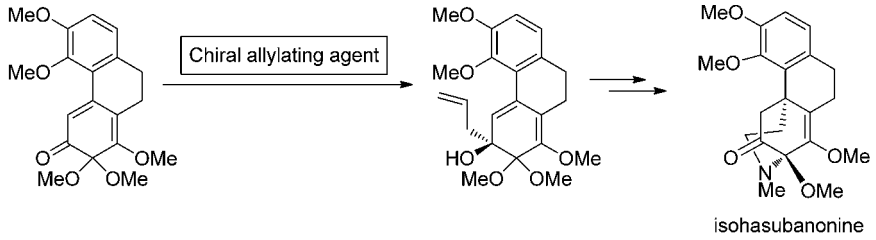
Scheme 132

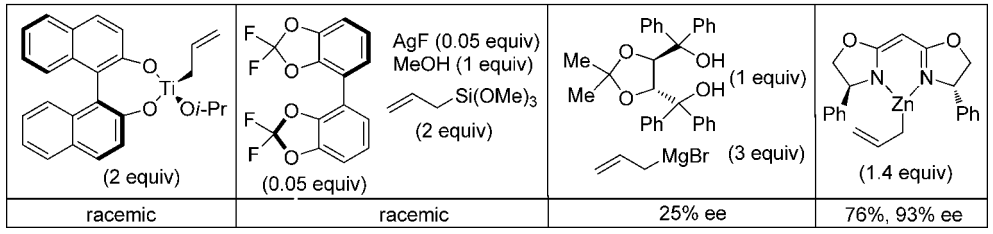


Scheme 133



Scheme 134





Discodermia dissoluta.[228] Cossy and BouzBouz reported also the synthesis of the C1−C13 fragment of (+)-discodermolide, controlling the configurations of the eight stereogenic centers of this fragment by enantioselective allyl- and crotyltitanations of aldehydes with (*R*,*R*)-**22a** and both enantiomers of **22b**, respectively. Thus, the synthesis began with the addition of the crotyltitanium complex (*R*,*R*)-**22b** to (*S*)-2-methyl-3-silyloxypropanal to produce two adducts. The major isomer was isolated in 91% yield and 96:4 dr. At this step, two stereogenic centers were introduced. The configuration at C7 was established by stereoselective allylation with (*R*,*R*)-**22a**, meanwhile the configurations at C4−C5 and C1−C2 were established by crotylation with (*R*,*R*)- and (*S*,*S*)-**22b**, respectively. All the stereoselective allylations occurred in high yields and with almost total *anti*-selectivity (Scheme 126).[293]

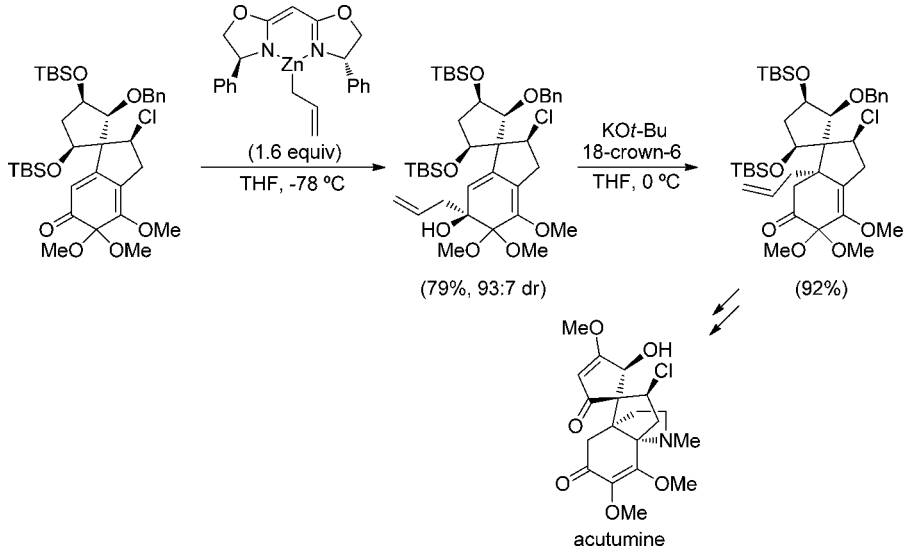
Tetrafibricin is a polyoxygenated polyene isolated from *Streptomyces neyagawaensis* NR0577,[294] which exhibits potent inhibition on platelet aggregation. The synthesis of C1−C13, C15−C26, and C27−C40 fragments of tetrafibricin was achieved by Cossy and BouzBouz using stereoselective allyltitanations of aldehydes (Scheme 127).[295] The stereochemical pathway of the allylation was totally controlled by the configuration of the allyltitanium complex used: (*R*,*R*)-**22a** led always to a *Si*-face addition and its (*S*,*S*)-**22a** enantiomer to a *Re*-face addition.

Stereoselective allyltitanations were also key steps in the synthesis of (−)-colletol,[296] a 14-membered bis-macrolactone isolated from the fermentation broth of *Collectotrichum capsici*,[297] (−)-diospongin A,[298] isolated from rhizomes of *Dioscorea spongiosa*,[269] and the AB spiroketal fragment C1−C13 of spongistatin[299] reported by the group of Cossy (Scheme 128).

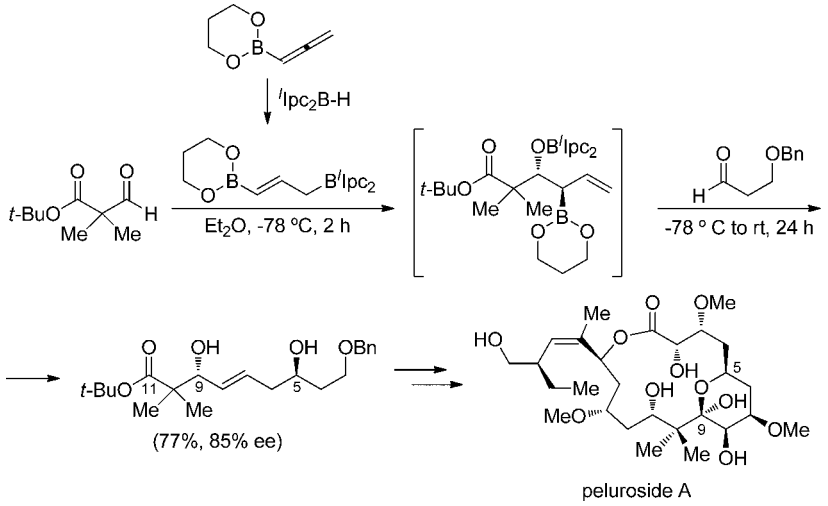
Marinomycin A is a 44-membered C_2-symmetrical dimeric macrodiolide constituted by a tetraene moiety conjugated with an aromatic unit derived from 2-hydroxybenzoic acid and

dx.doi.org/10.1021/cr400008h | *Chem. Rev.* 2013, 113, 5595−5698

Scheme 135



Scheme 136



connected to a pentahydroxylated polyketide chain. It has been isolated from the saline culture of a new group of marine actinomycetes, named *Marinispora* strain CNQ-140,[251] and exhibits antitumor and antibiotic activities. Cossy and co-workers carried out the synthesis of the monomeric counterpart of marinomycin A in 11 steps from the commercially available ethyl (*R*)-3-hydroxybutyrate. In this synthesis, the configurations of C17, C23, and C25 stereogenic centers were controlled by stereoselective allyltitanations of aldehydes. Other key steps were a regio- and stereoselective cross-metathesis to form the C20−C21 double bond and a stereocontrolled construction of the tetraene moiety based on an original Horner−Wadsworth−Emmons olefination followed by a Pd-catalyzed cross-coupling (Scheme 129).[300]

Stereoselective allyl- and crotyltitanations were also used by the group of Cossy in the synthesis of octalactin B, isolated from the marine bacterium *Streptomyces* sp. together with octalactin A.[301] Octalactin A exhibited potent cytotoxicity against different cancer cell lines, whereas octalactin B was completely inactive. However, octalactin B could be transformed into octalactin A by epoxidation. Isobutyraldehyde and methyl 3-butenoate (it was transformed into the corresponding aldehyde-ester by ozonolysis) were the starting materials in this synthesis. The stereochemistry at C3, C4, C7, and C8 was established by stereoselective crotylation with both enantiomers of **22b**, meanwhile an enantioselective allyltitanation of isobutyraldehyde was used to control the stereogenic center at C13 (Scheme 130).[302]

Leucascandrolide A was isolated from the calcareous sponge *Leucascandra caveolata* collected on east coast of New Caledonia.[236] Actually, this compound is not a metabolite of *Leucascandra* itself but rather that of an opportunistic bacteria that colonized the sponge.[303] This compound displayed a significant *in vitro* cytotoxicity, as well as significant antifungal properties. A chemoselective synthesis of the macrocyclic core of leucascandrolide A was also reported by Cossy. The synthesis started with the stereoselective crotyltitanation of *O*-TBS-protected 3-hydroxypropanal in order to control the stereogenic centers at C11 and C12. On the other hand, the stereochemistry at C9, C7, and C5 was established by stereoselective allyltitanation with (*R*,*R*)-**22a** (*Si*-face addition). An enantioselective Noyori reduction of a propargylic ketone and olefin metatheses were also key steps (Scheme 131).[304]

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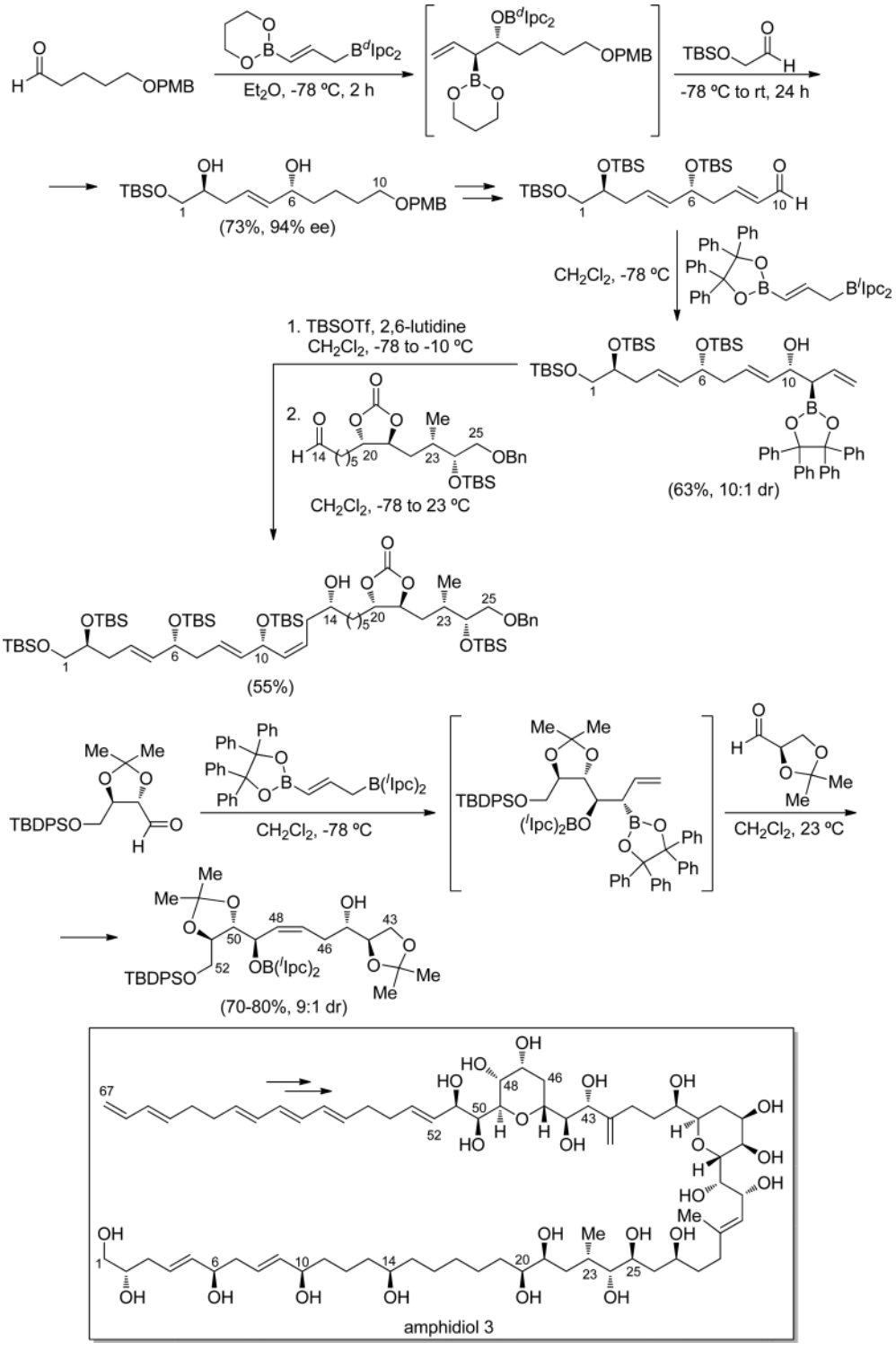
Scheme 137



Acremolide D is a lipodepsipeptide isolated from an Australian estuarine isolate of an *Acremonium sp.* (MST-MF588a).[305] The structure of this natural product along with the structures of other members of the same family, which were isolated from the same source, remained unknown. Cossy and co-workers reported a synthesis of one of the isomers of acremolide B in order to allow a straightforward access to these natural products and to various analogues. Again, two stereoselective allylation and crotylation were used to control all four stereogenic centers of the C1−C12 polypropionate segment. Other synthetic highlights included a cross-metathesis to couple the C1−C7 and the C8−C12 fragments, an esterification to introduce the dipeptide unit and a macrolactamization to build the macrolide core (Scheme 132).[306]

The stereocontrolled convergent synthesis of amphidinolide X, a cytotoxic macrolide isolated from *Amphidinium* dinoflagellates,[307] reported by Rodríguez-Escrich, Urpí, and Vilarrasa included a stereoselective crotylation of the

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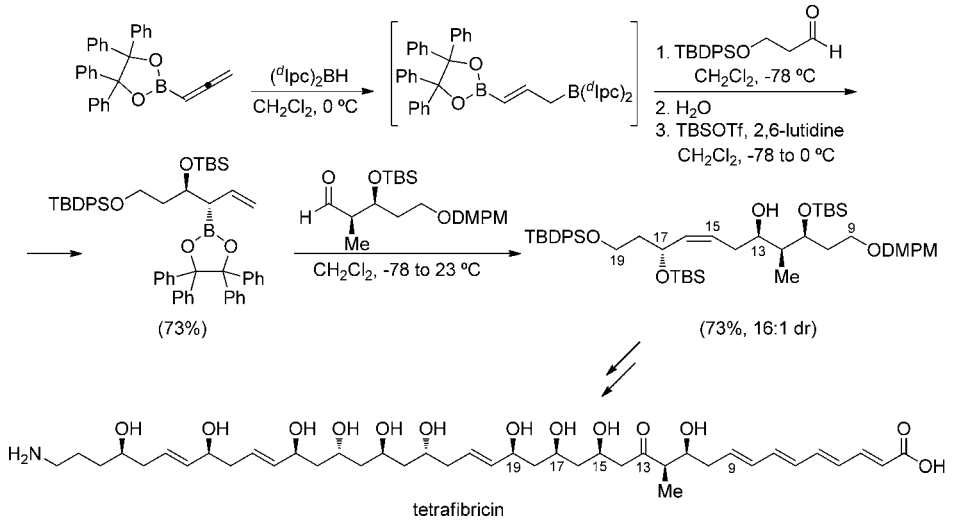
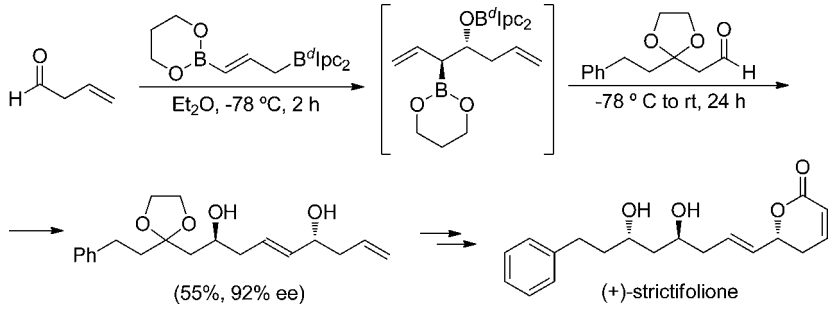
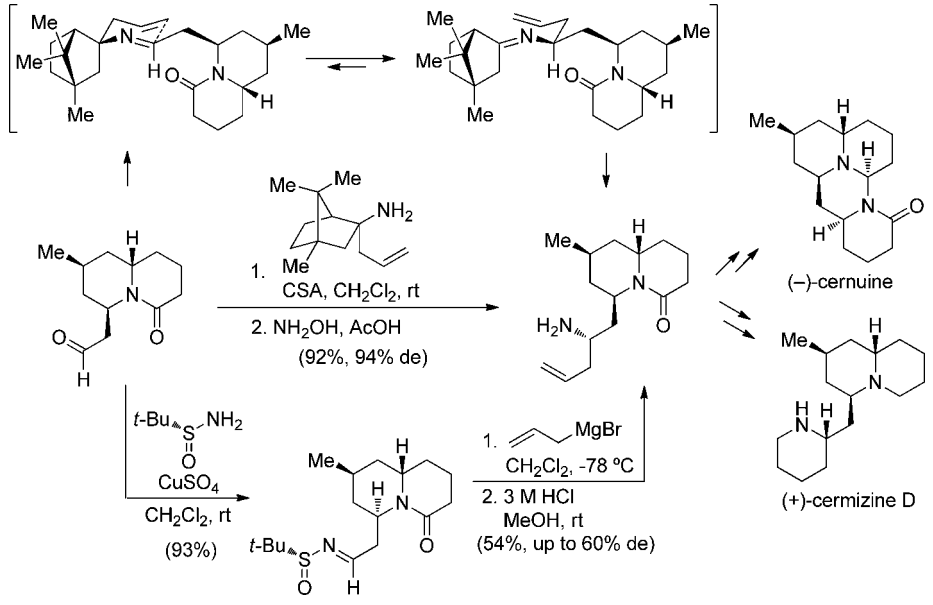
Scheme 138



Scheme 139



Scheme 140



monoketal-protected acetylacetaldehyde with the chiral crotyltitanium reagent (*S*,*S*)-**22b** to established the stereochemistry at C10 and C11. The *anti*-isomer was obtained in this way in 80% yield, taking place a *Re*-face addition taking place (Scheme 133).[308]

5.2.2.4. Allylzinc Reagents. Castle and co-workers attempted to synthesized the hasubanan alkaloids hasubanonine, runanine, and aknadinine via a unified route in which a phenanthrene ketone derivative was involved. However, at the final step of the synthesis, the unnatural isohasubanan alkaloid skeleton was produced through a pinacol-like rearrangement. One of the key steps of the synthesis was a stereoselective allylation of the achiral phenanthrene ketone derivative. The best result in the stereoselective allylation process was obtained

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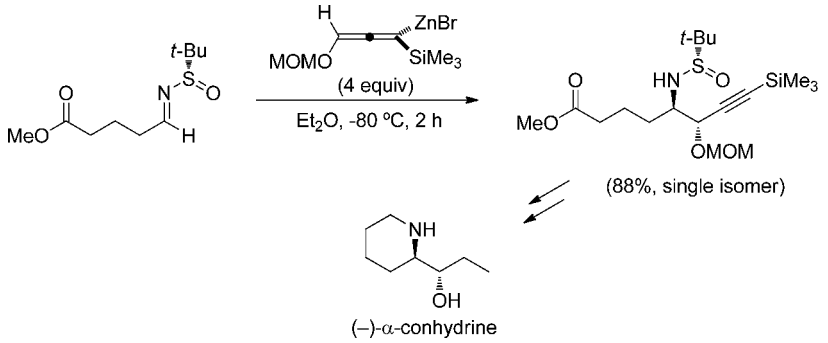
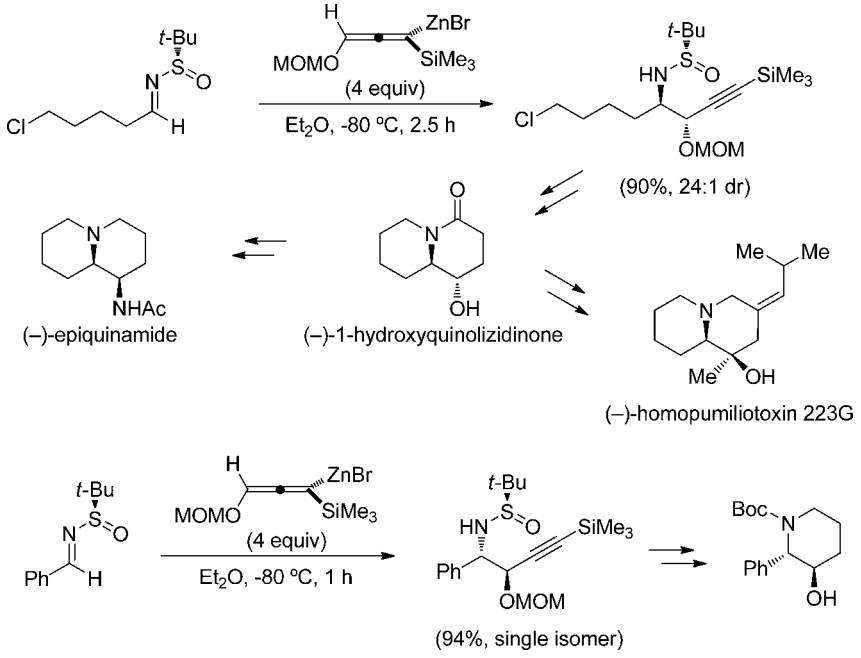
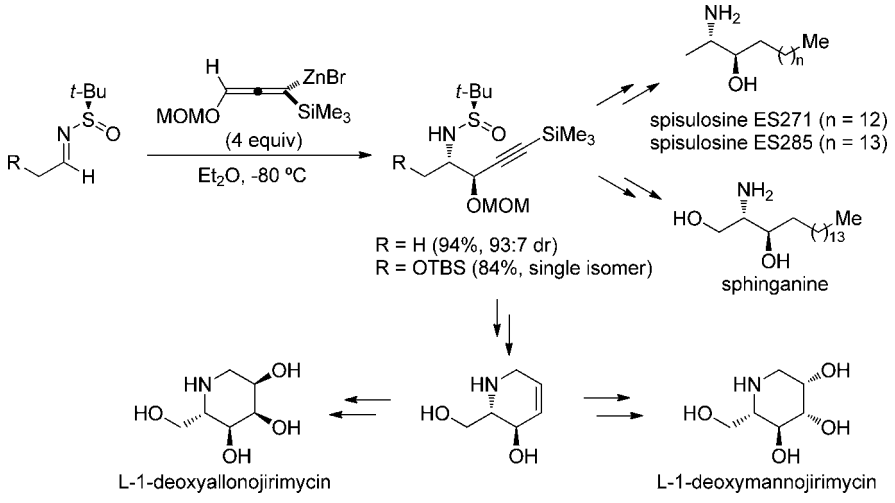
Scheme 141



Scheme 142



Scheme 143



when the Nakamura's chiral bisoxazoline-ligated allylzinc reagent[309] was used (76% yield and 93% ee). This reagent performed better than the Ti-BINOL complex with allylmagnesium chloride and allylmagnesium bromide in the presence of tetraphenyl TADDOL ligand. Even, the asymmetric Sakurai–Hosomi allylation reported by Wadamoto and Yamamoto[310] yielded also the corresponding racemic homoallylic alcohol (Scheme 134).[311]

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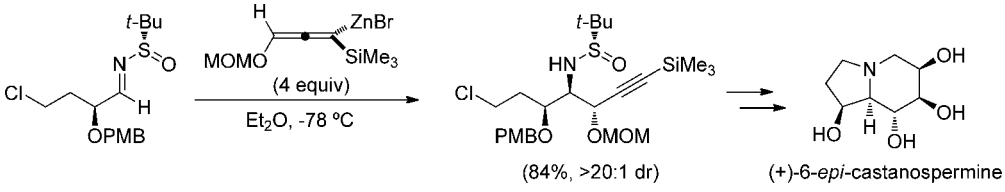
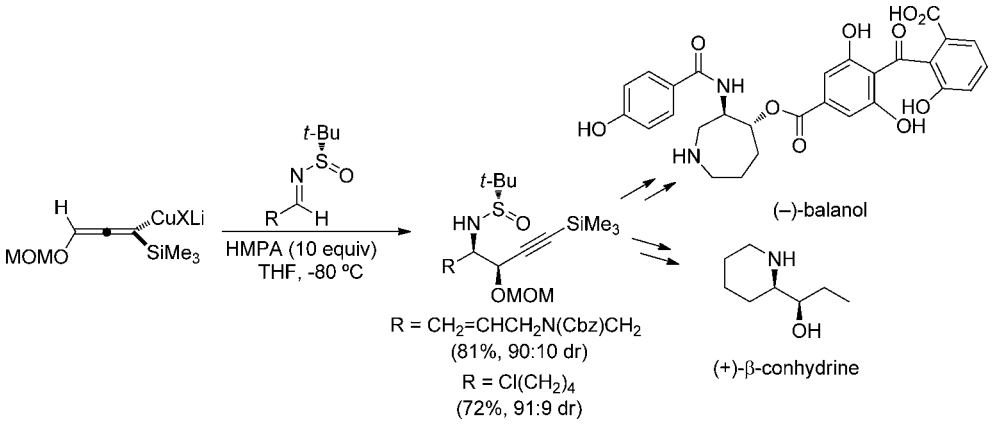
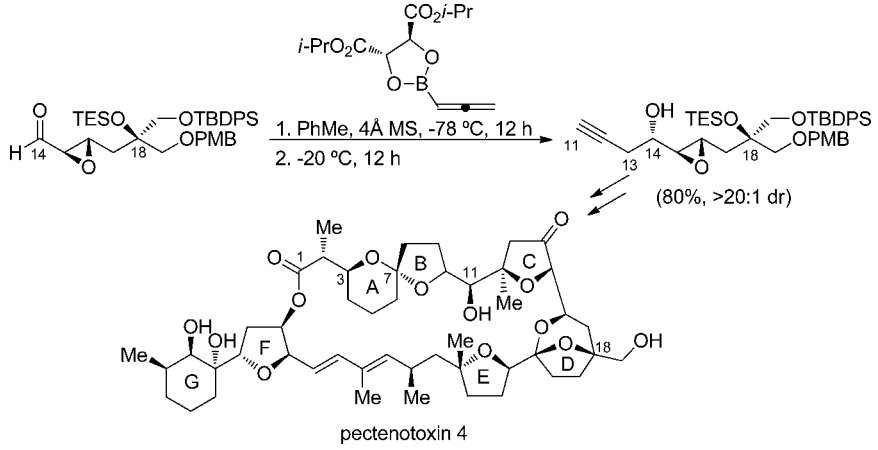
Scheme 144



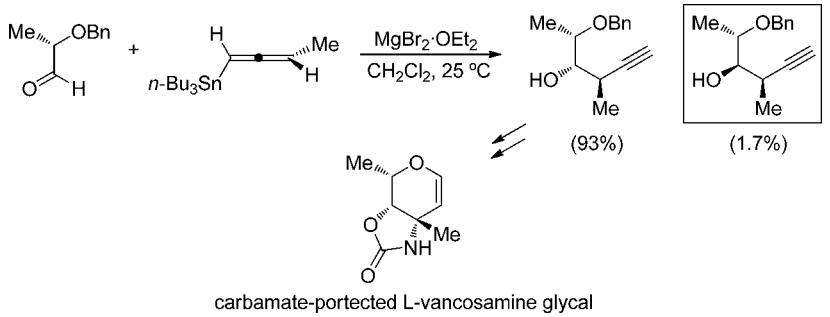
Scheme 145



Scheme 146



Scheme 147



Acutumine is a tetracyclic alkaloid isolated from the Asian vine *Menispermum dauricum*[312] and possesses selective cytotoxicity and antiamnesic properties. Castle and co-workers also performed the synthesis of this natural product. A stereoselective allylation of a chiral ketone was one key step of the synthesis. When they used allylmagnesium bromide (substrate control), a modest 70:30 dr was achieved (*Re*-face was slightly less hindered than the *Si*-face). Luckily, use of Nakamura's chiral allylzinc reagent led to the expected homoallylic alcohol in 79% yield and 93:7 dr. The configuration of the newly formed stereocenter was established by conversion of this alcohol into (−)-acutumine and is consistent with

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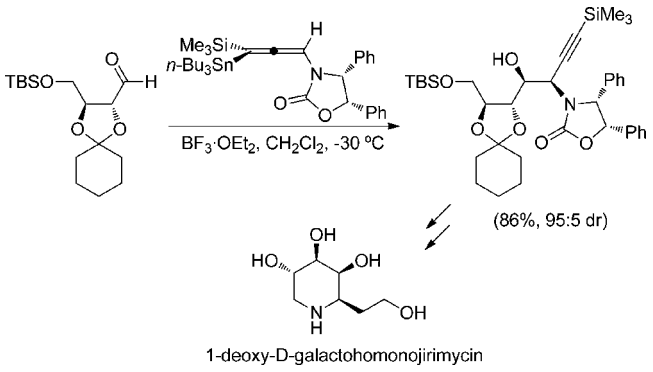
Scheme 148



Nakamura's proposed six-membered cyclic transition state where the bulky dimethyl ketal of the substrate occupies an equatorial position, thereby placing the less-hindered alkene carbon in an axial position, the facial selectivity of the allylation being controlled by the ability of the spirocycle to avoid steric interactions with the phenyl group of the bisoxazoline ligand (Scheme 135).[313]

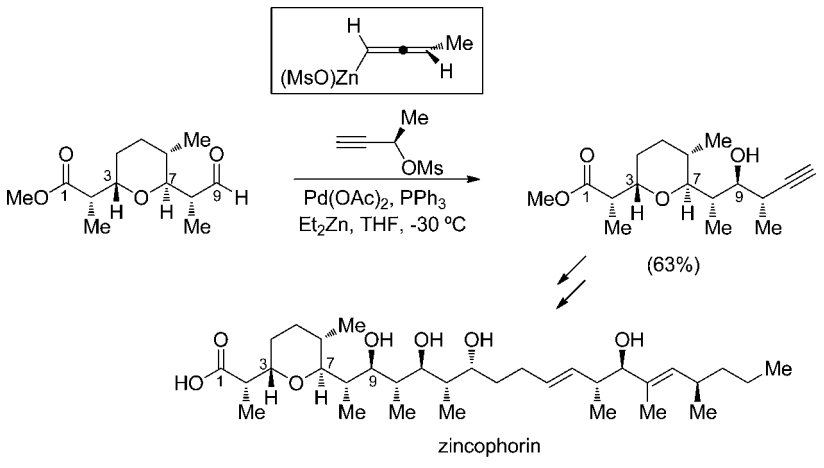
5.2.3. Double Allylation under Reagent Control. Roush and Owen reported the stereoselective synthesis of the C1−C11 fragment of peloruside A,[267] a microtubule-stabilizing agent and for that reason of potential interest for anticancer chemotherapy. A stereoselective double allylboration was the key step of the synthesis. This one-pot double allylboration methodology was developed in the group of Roush and proved to be highly efficient for the enantio- and diastereoselective synthesis of 1,5-diols.[314] Thus, the reaction of *tert*-butyl 2-formylisobutyrate with the ^{l}Ipc-derived γ-boryl-substituted allylborane (prepared *in situ* from the hydroboration of allenyl dioxaborinane with ^{l}Ipc$_2$B−H) followed by introduction of *O*-benzyl-protected 3-hydroxybutanal provided the desired 1,5-diol as a single diastereomer (double *Re*-face addition) in 77% yield and 85% ee (Scheme 136). The diastereoselectivity of the process was improved when the ^{l}Ipc$_2$B unit was replaced by 2-^{d}Icr$_2$B [derived from (+)-2-carene] in the double allylation reagent. Under the new reaction conditions, the expected diol was obtained in >95% ee, albeit in low yield (36%).[315]

Roush and Flamme described also the synthesis of the C1−C25 and C43−C67 fragments of amphidinol 3, a polyketide isolated from a toxic phytoplanktons within the waters surrounding the coasts of Japan,[316] possessing antifungal, hemolytic, cytotoxic, and ichthyotoxic activities. The C1−C14 fragment of amphidinol 3 contains three stereochemically and structurally distinct 1,5-diol units, and the synthesis featured two applications of double allylboration reaction methodology for the highly stereoselective synthesis of these 1,5-diol units as depicted in Scheme 137.[317] Roush and co-workers reported also the synthesis of the C43−C67 fragment of amphidinol 3, using a double allylboration reaction of a 2,3-*O*-isopropylidene-D-threose derivative and 2,3-*O*-isopropylidene-D-glyceraldehyde for the synthesis of a 1,5-diol, which serves as a precursor to the dihydropyran ring (Scheme 137).[318]

Taking advantage of this highly diastereoselective double allylboration reaction, Roush and Lira performed the synthesis of the C1−C19 fragment of tetrafibricin, a polyoxygenated fibrinogen receptor inhibitor that was isolated from the culture broth of *Streptomyces neyagawaensis* NR0577.[319] In this case, instead of a one-pot double allylation to produce the 1,5-diols, the step-by-step double allylboration sequence proved advantageous in order to differentiate the secondary C17 and C13 alcohols. Thus, the reaction of *O*-TBDPS-protected 3-hydroxypropanal with the *in situ* generated bifunctional (*E*)-allylborane led after hydrolysis to the corresponding hydroxyallylboronate, which was further protected upon treatment with TBSOTf and 2,6-lutidine to afford the corresponding allylboronate in 73% overall yield. The reaction of this allylboronate with the appropriate chiral aldehyde provided the homoallylic alcohol with the right configurations at C13 (Scheme 138).[320]

The one-pot double allylboration methodology was also used by She and co-workers in the synthesis of (+)-strictifolione.[291] This total synthesis proceeded in only five steps from readily available 3-butenal and is shorter than that previously reported by Cossy and BouzBouz (Scheme 125).[292] The synthesis commenced with the reaction of a ^{d}Ipc-derived γ-boryl-substituted allylborane (prepared *in situ* from allenyl dioxaborinane and ^{d}Ipc$_2$B−H) to give a β-alkoxyallylboronate intermediate (stereoselective *Si*-face addition), which subsequently reacted with the monoketal of β-keto-5-phenylpentanal to produce the expected 1,5-diol in 55% yield and 92% ee (*Si*-face addition). Further steps of the synthesis included double acryloylation, ring-closing metathesis, ketal and acryloyl hydrolysis, and finally diastereoselective ketone reduction (Scheme 139).[321]

Scheme 149



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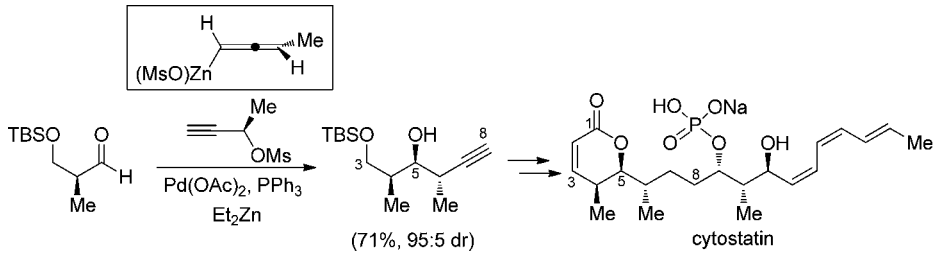
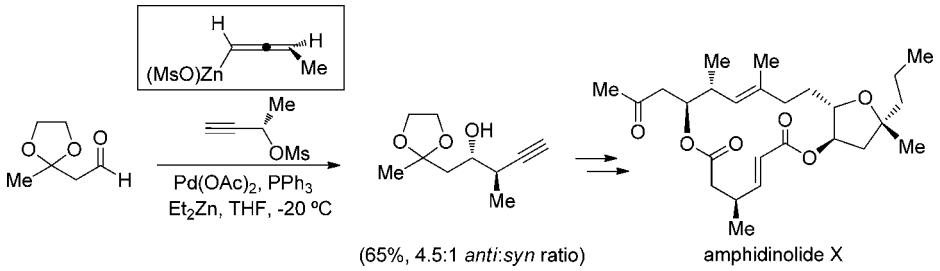
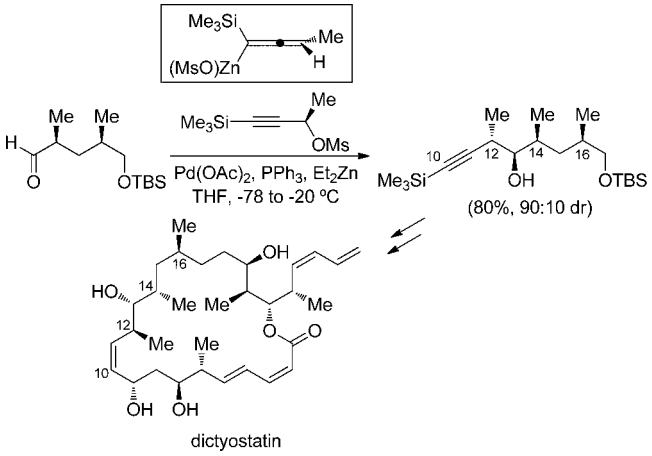
Scheme 150



Scheme 151



Scheme 152

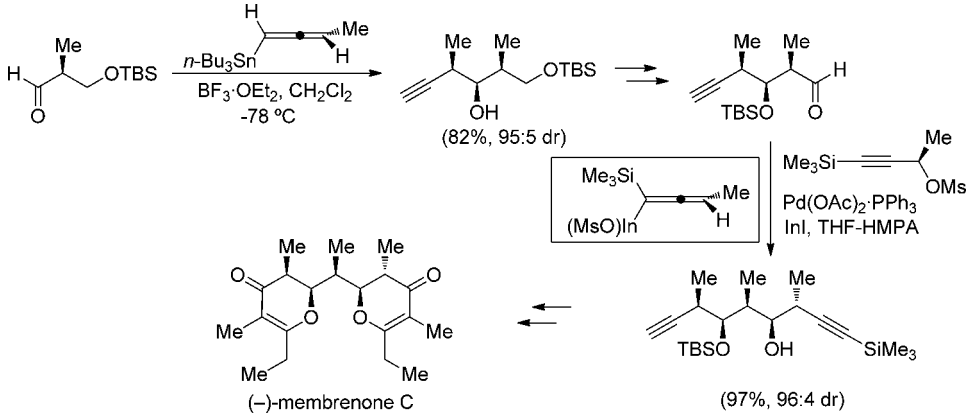


5.2.4. Allyl Transfer from a Chiral Homoallyl Amine. Takayama and co-workers reported the first total syntheses of two cernuane-type *Lycopodium* alkaloids, (−)-cernuine and (+)-cermizine D, using the asymmetric transfer α-aminoallylation developed by Kobayashi[134] as a key step. In the α-aminoallylation process, the chiral aldehyde substrate was prepared from (+)-citronellal and reacted with (1*R*)-camphor quinone homoallylamine derivative in the presence of camphorsulfonic acid to give the new homoallylamine in high yield and good selectivity (92%, 94% de) according to the mechanism depicted in Scheme 140.[322] On the other hand, the same homoallyl amine intermediate could be reached following the Ellman protocol.[213] Thus, condensation of the starting aldehyde and (*R*)-*tert*-butanesulfinamide, followed by reaction of the resulting imine with allylmagnesium bromide, and final removal of sulfinyl auxiliary under acidic conditions furnished the desired homoallylamine in good yield (54%, two steps) but with poor stereoselectivity (up to 60% de).[323] In this case, it seemed that the Kobayashi protocol proved to be superior to the diastereoselective allylation of the *t*-BS imine.

5.3. Propargylation and Allenylation Reactions

5.3.1. Propargylation Reactions. *5.3.1.1. Substrate Control (Chiral Sulfinyl Imines).* It has been previously mentioned that the reaction of 3-alkoxy allenylzinc compounds with *N*-*tert*-butanesulfinyl imines provided chiral acetylenic *anti*-1,2-amino alcohols via a kinetic resolution in a highly

Scheme 153



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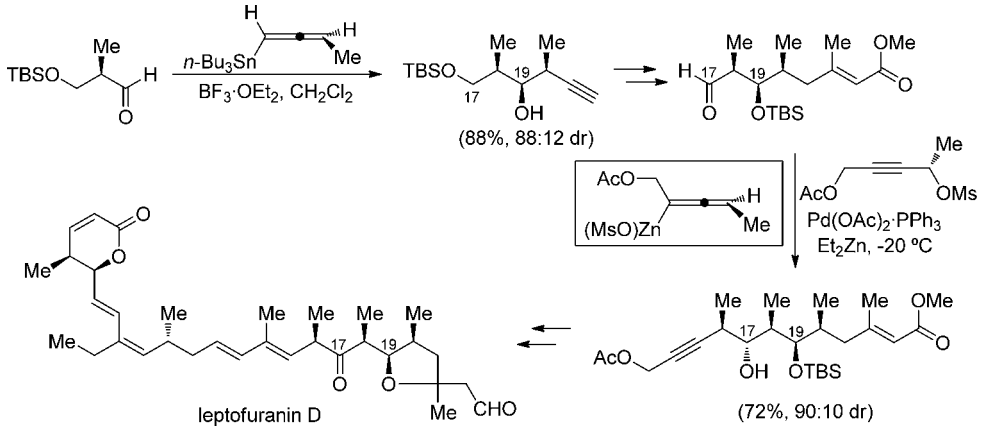
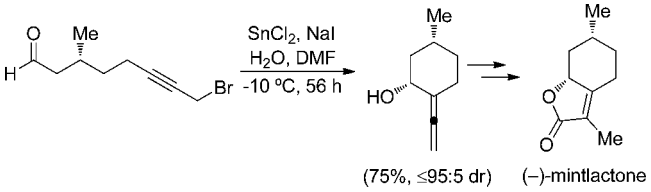
Scheme 154



Scheme 155



diastereoselective manner.[144] The configuration of the newly created stereogenic centers was determined by the configuration of the sulfur atom of the imine. This methodology developed by Ferreira and Chemla has been widely used in the synthesis of nitrogen-containing natural products and other biologically active compounds. The organometallic nucleophile was prepared *in situ* from the methoxymethyl ether of 3-trimethylsilylprop-2-yn-1-ol through a sequential deprotonation and reaction with $ZnBr_2$. Thus, a short and efficient synthesis of (−)-α-conhydrine, one of the alkaloids in hemlock, *Conium maculatum* L., isolated from the seeds and leaves of this poisonous plant, was accomplished with 41% overall yield in seven steps and high diastereo- and enantioselectivity. The reaction of the racemic allenylzinc compound with a *N-tert*-butanesulfinyl iminoester at low temperature in Et_2O provided the expected chiral acetylenic *anti*-1,2-amino alcohol in 88% with total diastereoselectivity (Scheme 141).[324]

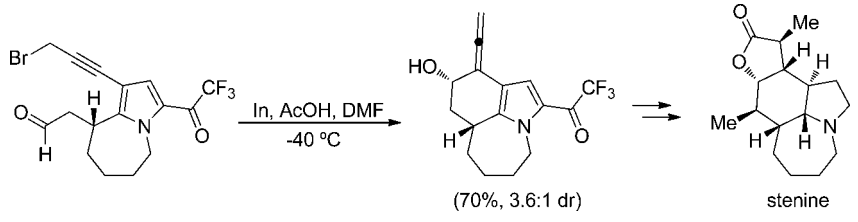
The reaction of the same 3-alkoxy allenylzinc compound with the (*S*)-*N-tert*-butanesulfinyl imine of 5-chloropentanal provided the *anti*-1,2-amino alcohol in high yield and also excellent diastereoselectivity. This compound was transformed after six additional steps into (−)-1-hydroxyquinolizidinone, a key intermediate in the formal syntheses of (−)-homopumiliotoxin 223G and (−)-epiquinamide, in 25% overall yield (Scheme 142).[325] On the other hand, a high-yielding synthesis of (2*S*,3*R*)-3-hydroxy-2-phenylpiperidine [an advanced key intermediate of some nonpeptide human NK-1 receptor antagonists such as (+)-CP-99,994, (+)-CP-122,721 and (+)-LP-733,060] was accomplished in seven steps starting from the (R_S)-*t*-BS imine of benzaldehyde. The stereoselective propargylation of the imine occurred with total diastereoselectivity, a ring-closing metathesis also being a key step (Scheme 142).[326]

This methodology was successfully applied to the syntheses of long-chain 1,2-amino alcohols that are found in a number of bioactive natural products, such as two spisulosines and sphinganine. For spisulosines ES271 and ES285, the imine derived from acetaldehyde was the starting material. In the case of sphinganine, the *O*-TBS-protected hydroxyacetaldehyde was the starting material (Scheme 143).[327] The last one was also the starting material of a common intermediate of azasugars, L-1-deoxyallonojirimycin and L-1-deoxymannojirimycin (Scheme 143).[328]

The polyhydroxylated alkaloid (+)-6-*epi*-castanospermine is a natural product extracted from the pod seeds of *Castanospermum australe* and is an inhibitor of α-glycosidases. Chemla and co-workers reported an asymmetric total synthesis of this natural product. The key step of this synthesis was the diastereoselective addition of the racemic allenylzinc reagent to an enantiopure α-alkoxy-*tert*-butylsulfinylimine, the reaction proceeding with high chemical efficiency and diastereoselectivity. Further transformations included the formation of a piperidine ring by ring-closing metathesis and subsequent *syn*-dihydroxylation of an alkene (Scheme 144).[329]

Ferreira, Chemla, and Pérez-Luna accomplished also the stereoselective synthesis of chiral acetylenic *syn*-1,2-amino alcohols from the racemic allenylcopper analogues, instead of the zinc derivatives, which were generated according the procedure reported in Table 60 (section 4.1.1.1). This methodology was applied to the synthetis of (−)-balanol (a metabolite isolated from the fungus *Verticillium balanoides*) and

Scheme 156



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(+)-β-conhydrine (one of the alkaloids in hemlock *Conium maculatum* isolated from the seeds and leaves of this poisonous plant) using the imines derived from (*S*)-*tert*-butanesulfinamide and *N*-allylaminoacetaldehyde and 5-chloropentanal as starting material, respectively. The propargylation occurred in a diastereoselective fashion in high yield (Scheme 145).[147]

5.3.1.2. Reagent Control. 5.3.1.2.1. Allenyl Boranes, Silanes, and Stannanes. Williams and co-workers reported the synthesis of a C1−C19 precursor to pectenotoxin 4, a highly functionalized 34-membered macrolide. A key step of the synthesis was the Yamamoto propargylation[330] of an epoxyaldehyde with a chiral allenyl boronate, which is prepared *in situ* from allenyl boronic acid and D-diisopropyl tartrate. The corresponding homopropargyl alcohol was obtained in good yield and stereoselectivity (Scheme 146).[331]

Vancosamine, a precursor for vancosamine derivatives, is a functionalized component of vancomycin, the glycopeptide used as antibiotic of last resort against resistant Gram-positive bacteria. Parker and Chang carried out a short and efficient synthesis of the carbamate-protected L-vancosamine glycal. A key step of the synthesis was the reaction of a (*S*)-allenylstannane with (*S*)-lactic aldehyde benzyl ether under Marshall homopropargylation conditions.[156] The desired alkynol was obtained as the major reaction product along with a small amount of a diastereomeric alkynol (Scheme 147).[332]

Polyhydroxylated piperidine alkaloids (azasugars) have been the subject of intensive investigation because of their ability to inhibit carbohydrate-processing enzymes. Achmatowicz and Hegedus performed a synthesis of the azasugar 1-deoxy-D-galactohomonojirimycin. They applied in this synthesis the highly diastereoselective Lewis acid promoted coupling of chiral α-oxazolidinonylallenylstannanes with aldehydes developed by them.[154] Thus, the reaction of an L-lactate-derived aldehyde with the optically active allenylstannane depicted in Scheme 34 in the presence of $BF_3{\cdot}OEt_2$ produced a protected aminotetraol, a direct precursor of the target azasugar, in 86% yield with greater than 95% *syn* selectivity (Scheme 148).[333]

5.3.1.2.2. Allenyl Zinc Reagents. Cossy, Meyer, and co-workers performed the synthesis of the methyl ester of zincophorin, a monocarboxylic acid ionophore antibiotic from strains of *Streptomyces griseus*. This compound exhibits good *in vitro* activity against Gram-positive bacteria,[334] and its methyl ester also possesses antiviral activity.[335] Diastereoselective titanium-mediated aldol coupling reactions and a Marshall homopropargylation reaction are key steps of the synthesis.[155] Thus, the reaction of the chiral allenylzinc (the real nucleophile), generated *in situ* from the mesylate of (*R*)-3-butyn-2-ol,[155] with the chiral aldehyde depicted in Scheme 149 occurred in the mismatched manifold, affording a diastereomeric mixture of three homopropargylic alcohols in a 80:12:8 ratio. Fortunately, the major diastereomer (*Si*-face addition), which possessed the requisite *anti*,*anti* relative configuration at C8−C10, was easily separated and isolated in 63% yield (Scheme 149).[336]

Marshall and Ellis carried out also the stereoselective synthesis of a C3−C13 precursor of polyketide cytostatin, a potent and selective inhibitor of protein phosphatase PP2A, was isolated from a strain of *Streptomyces*.[337] Key stereocenters were introduced by a chiral allenylzinc addition and a Noyori asymmetric transfer hydrogenation. The addition of the allenylzinc reagent, generated *in situ* from the mesylate of (*R*)-3-butyn-2-ol and Et_2Zn in the presence of a Pd(0) catalyst, to *O*-TBS-protected (*S*)-3-hydroxy-2-methylpropanal produced the homopropargylic alcohol in 71% yield with >95:5 *anti*/*syn* diastereoselectivity (Scheme 150).[338]

Amphidinolide X is a secondary metabolite produced by marine dinoflagellates of the genus *Amphidinium* living in symbiosis with the Okinawan flatworm *Amphiscolops sp.* and exhibits potent cytotoxicity against various cancer cell lines.[339] Interestingly, amphidinolide X is the only naturally occurring macrodiolide known to date that consists of a diacid and a diol unit rather than of two hydroxyacid entities.[307] Fürstner and co-workers performed a convergent stereoselective synthesis of this natural product, and one of the building blocks was accessed by addition of the allenylzinc reagent resulting from the mesylate of (*S*)-3-butyn-2-ol, upon palladium-catalyzed reaction with Et_2Zn, to the monoacetal of acetylacetaldehyde. The *anti* isomer was the major component of the reaction mixture (4.5:1 dr) in 65% yield, the nucleophilic addition of the allenylzinc to the *Re*-face of the carbonyl group taking place (Scheme 151).[340] Consistently, the opposite face selectivity was observed in Schemes 149 and 150 when the mesylate of (*R*)-3-butyn-2-ol was used.

Maier and co-workers developed a stereoselective synthesis of the C10−C23 fragment of dictyostatin combining enzymatic and classical diastereoselective synthetic methods. Dictyostatin is a 22-membered macrolide isolated from a marine sponge,[341] and it was found to act as an inducer of tubulin polymerization. In this synthesis, Marshall homopropargylation of a chiral aldehyde (accessed through enzymatic desymmetrization of the *meso*-diol) with (*R*)-4-trimethylsilyl-3-butyn-2-ol produced the *anti* isomer, considering C-12 and C-13 stereocenters with the right absolute configuration. The diastereoselectivity of the reaction was greater than 90:10, the attack of the allenylzinc intermediate taking place to the *Si*-face of the aldehyde under reagent control (Scheme 152).[342]

5.3.1.2.3. Combining Allenyl Metal Reagents. Membrenones A−C are chemical defense compounds isolated from the skin of the marine mollusc *Pleurobranchus membranaceus*.[343] Marshall and Ellis reported a synthesis of (−)-membrenone C and its (+)-enantiomer taking advantage of the stereocontrolled addition of chiral allenylmetal compounds to aldehydes. The first step of the synthesis included the $BF_3{\cdot}OEt_2$-promoted reaction of (*S*)-1-tri-*n*-butylstannyl-1,2-butadiene with *O*-TBS-protected (*S*)-3-hydroxy-2-methylpropanal, leading to the *syn*,*syn* adduct (*Si*-face addition) in >95:5 dr and in 82% yield (Scheme 153). The remaining two stereocenters were introduced in a subsequent stereoselective propargylation using the (*S*)-allenylindium reagent prepared from the mesylate of (*S*)-4-trimethylsilyl-3-butyn-2-ol. The propargylic adduct with *anti* relative configuration of the new stereocenters (*Re*-face addition) was obtained in 97% yield and 96:4 dr (Scheme 153).[344] The natural (+)-membrenone C isomer was accessible from the same reagents, but inverting the order of stereoselective propargylations: first reaction of the starting aldehyde with the allenylindium reagent to give the *anti*-isomer and then with the allenylstannane to produce the *syn*-adduct.

Leptofuranins A−D were isolated from the actinomycete strain *Streptomyces tanashiensis*[345] and display anticancer activity. A stereoselective synthesis of leptofuranin D was reported by Marshall and Schaff. The synthesis commenced with the Lewis acid promoted reaction of (*R*)-1-tri-*n*-butylstannyl-1,2-butadiene and *O*-TBS-protected (*R*)-3-hydroxy-2-methylpropanal. The expected *syn*,*syn* adduct (*Re*-face addition in this case) was obtained in 88:12 dr and in 88% yield

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(Scheme 154). For the introduction of the stereocenters at C-16 and C-17, addition of the allenylzinc reagent, generated *in situ* from a (*S*)-propargylic mesylate, gave the *anti* (*Re*-face addition) adduct as a 90:10 mixture of diastereomers in 72% yield (Scheme 154).[346]

5.3.2. Allenylation Reactions. Bates and Sridhar reported the synthesis of (−)-mintlactone using as a key step a highly diastereoselective intramolecular propargylic Barbier reaction. The propargylic aldehyde (*R*)-8-bromo-3-methyloct-6-ynal was subjected to propargylic Barbier cyclization by using a variety of reagents. Optimal results were obtained working with tin(II) chloride in a mixture of DMF−water in the presence of sodium iodide at −10 °C. The process took place under these reaction conditions with high diastereoselectivity to give the *cis*-cyclohexyl product in 75% yield (Scheme 155).[347] Further allenol cyclocarbonylation resulted in the formation of the expected (−)-mintlactone.

An intramolecular propargylic Barbier reaction was used by the same authors in the synthesis of the skeleton of stenine, a stemona alkaloid. Again, the cyclization was studied in the presence of a variety of reagents. No diastereoselectivity was observed using zinc and a slight improvement was found with stannous chloride at reduced temperature. The highest diastereoselectivity and yield were obtained using indium in an acetic acid/DMF mixture at −40 °C. However, replacing DMF with THF gave, under the same conditions, the same diastereoselectivity but a lower yield. The presence of acetic acid was essential to obtaining high reactivity at this low temperature. Under optimal reaction conditions the cyclization proceeded in 70% yield and in 3.6:1 dr, the major isomer being isolated in pure form in 52% yield after column chromatography (Scheme 156).[348]

6. CONCLUSIONS AND OUTLOOK

The unique synthetic value of enantioenriched homoallylic alcohols and amines as building blocks of complex molecules has greatly encouraged the development of stereoselective allylation protocols of carbonyl compounds and imines over the last decades. Despite the rapid evolution of catalytic methods in recent years, the use of stoichiometric reagents (including substrates and allylic organometallic partners) is still the favorite choice of organic chemists in the synthesis of key intermediates of natural products. Importantly, the existing working models allow anticipation of the major diastereoisomer in most of the cases where stoichiometric chiral reagents are used, which is of crucial importance in the synthetic applications of these methodologies. In addition to the use of diverse allylic organometallic reagents that react usually at γ-position, the allyl transfer reactions from chiral donors now make possible the formal α-allylation process through stereospecific sigmatropic rearrangements. Moreover, the recent advancements achieved in the regio- and stereoselective addition of propargyl or allenyl metal to carbonyl compounds and imines have significantly expanded the synthetic value of allenic and homopropargyl alcohols and amines as building blocks.

Important progress has been made in the development of protocols that make use of robust and nontoxic reagents with a chiral stereogenic unit that can be recovered. Given the rapid progress of this field, we believe that new reagents featuring these characteristics will emerge in the coming years. Furthermore, the development of efficient catalytic enantioselective allylation processes with high degree of predictability of the stereochemical result still remains as a very interesting challenge.

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Notes

The authors declare no competing financial interest.

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 2 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. Professor Yus has been visiting professor at different institutions and universities, among them ETH-Zentrum, Oxford, Harvard, Uppsala, Marseille, Tucson, Okayama, Paris, Strasbourg, Bolonia, Sassari, Tokyo, and Kyoto. He is coauthor of more than 500 papers (and four patents) and has supervised 53 Doctoral Theses and delivered more than 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), the Serratosa Lectureship (Barcelona 2010), the Conferencia Lourenço-Madinaveitia (Lisboa 2012), and the Medalla Felix Serratosa from the RSEQ (Madrid 2012), also being named recently Active Academician from the European Academy of Sciences and Arts (Salzburg 2012). Professor Yus has been on the Advisory Board of 20 international journals, among others, *Tetrahedron*, *Tetrahedron Letters*, *European Journal of Organic Chemistry*, *Chemistry Letters*, *The Chemical Record*, and *Current Organic 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.

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.

Francisco Foubelo was born in 1961. 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.

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ABBREVIATIONS

abs	absolute
Ac	acetyl
All	allyl
AM1	Austin model 1
aq	aqueous
ATP	adenosine triphosphate
BBD	borabicyclo[3.3.2]decane
BBN	borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bz	benzoyl
B3LYP	Becke, three-parameter, Lee−Yang−Parr
cat.	catalyst, catalytic amount
Cbz	carbobenzyloxy
config	configuration
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
Cy	cyclohexyl
dba	dibenzylideneacetone
DBBP	4,4′-di-(*tert*-butyl)-1,1′-biphenyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DCE	dichloroethane
de	diastereomeric excess
DFT	density functional theory
DIBAL-H	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DIPT	diisopropyl tartrate
DMF	dimethylformamide
DMP	Dess−Martin periodinane
DMSO	dimethyl sulfoxide
dppf	1,1′-bis(diphenylphosphino)ferrocene
DPS	diphenylsilyl
dr	diastereomeric ratio
ee	enantiomeric excess
equiv	equivalents
er	enantiomeric ratio
fod	6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedienoate
GC	gas chromatography
HMPA	hexamethylphosphoramide
HPLC	high-performance liquid chromatography
Icr	isocaranyl
Ipc	isopinocampheyl
L	ligand
LA	Lewis acid
M	metal
Mes	mesityl
METHOX	pinene-derived 2-(2,4,6-trimethoxiphenyl)-pyridine *N*-oxide
MOM	methoxymethyl
MS	molecular sieves
nd	not determined
NMR	nuclear magnetic resonance
NPED	norpseudoephedrine derivatives
PCM	polarizable continuum model
Pf	9-phenylfluoren-9-yl
pin	pinacolate
Piv	*tert*-butylcarbonyl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
PPTS	pyridinium *para*-toluene sulfonate
p-TSA	*para*-toluenesulfonic acid

QUINOX	1-(2-methoxynaphthalen-1-yl)isoquinoline *N*-oxide
quinoxP*	2,3-bis[*tert*-butyl(methyl)phosphino]-quinoxaline
R^L	largest substituent
R^S	smallest substituent
RCM	ring-closing metathesis
rt	room temperature
sat.	saturated
SET	single electron transfer
t	time
T	temperature
TADDOL	2,2-dimethyl-$\alpha,\alpha,\alpha',\alpha'$-tetraphenyldioxolane-4,5-dimethanol
TANIAPHOS	(S_P)-1-[(*S*)-α-(dimethylamino)-2-(diphenylphosphino)benzyl]-2-diphenylphosphinoferrocene
TBAF	tetrabutylamonium fluoride
TBDAS	*tert*-butyldiarylsilyl
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
t-BS	*N*-*tert*-butylsulfinyl
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	triflyl
TFA	trifluoroacetyl
TFAA	trifluoroacetic anhydride
TIPS	triisopropylsilyl
THF	tetrahydrofuran
TMEDA	tetrametylethylenediamine
TMS	trimethylsilyl
Tol	4-methylphenyl
Ts	*para*-tolylsulfonyl (tosyl)
TS	transition state
UAKS	united atom Kohn−Sham
X	halogen, OR, NR_2, ...
Xantphos	(9,9-dimethyl-9-*H*-xanthene-4,5-diyl)bis-(diphenylphosphine)
μW	microwaves

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