α-Hydroxyallylation Reaction of Carbonyl Compounds

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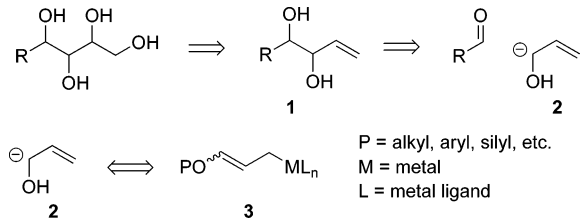
1. Introduction

The stereoselective synthesis of carbohydrates and related bioactive compounds containing a polyhydroxylated chain embedded in their structural framework remains a topic of great current interest.[1] Thanks to the strength of numerous asymmetric transformations of the carbon−carbon double bond developed in the last decades,[2] alk-1-en-3,4-diols **1** have inspired many elegant solutions for the synthesis of structural domains containing sequences of contiguous oxygen-bearing stereocenters.

This review deals with the straightforward and versatile approach to the alk-1-en-3,4-diol motif **1**, represented by the formal α-hydroxyallylation of carbonyl compounds by means of synthetic equivalents of the 1-hydroxyallyl anion (**2**) (Scheme 1). Among the efficient synthetic protocols developed in the last two decades, attention is focused on properly designed 3-oxyallyl organometallic compounds **3** capable of providing stereocontrolled routes to **1**.

Scheme 1



Oxyallyl organometallic compounds **3**, where M is a metal center, L is a charged or neutral ligand, including a donor solvent molecule, and P is a protective group, will be discussed first. Then, the chemistry of 3-silylated or 3-borylated allyl organometallic complexes will be included, since both emerge as potential precursors of **1** after the eventual oxidation of the carbon−silicon and the carbon−boron bonds to a carbon−oxygen bond.

Of course, when allylic organometallics are involved, the fluxional equilibrium between σ-bonded or monohapto (η^1) and π-bonded or trihapto (η^3) structures of metal complexes **3** must be carefully investigated.

The overall picture of the potential equilibrium between η^1 and η^3 structures of metal complexes **3** is shown in Scheme 2. The values of the energy barriers determine the configurational stability of 3-oxyallyl organometallics **3**.

Kubota and co-workers investigated the structure of model 3-hydroxyallyl lithium and zinc species (P = H) through B3LYP/631A calculations. For M = lithium, two η^3 structures were located, the η^3 *anti*-**3** complex, stabilized by intramolecular Li−O coordination, being 12.9 kcal/mol more stable than the η^3 *syn*-**3** isomer. Moving from M = lithium to M = zinc, three η^1 structures were located; the most stable structure was the η^1 γ-*Z*-**3**, where coordination of the oxygen atom to zinc prevents hyperconjugation between the C−Zn σ-orbital and the C=C π* orbital. Such a conjugation occurs

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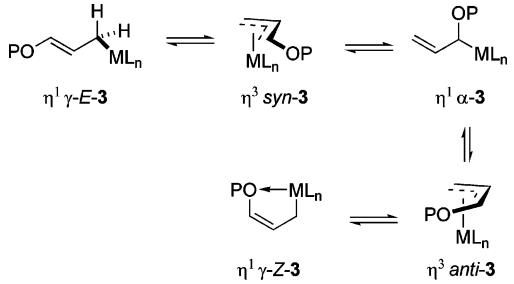
Marco Lombardo was born in Bologna (Italy) in 1969. He received his Laurea Cum Laude in Chemistry in 1994 and his Ph.D. Degree in 1999 from the University of Bologna under the supervision of Prof. Claudio Trombini, working in the field of organomercury and organoboron chemistry. In 1998 he got a Master Degree in Analytical Chemistry from the University of Bologna. He was appointed Research Associate in 1999 at the Department of Chemistry "G. Ciamician" of the University of Bologna. His current research interests are focused on the development of new synthetically useful organometallic methodologies. They include the stereoselective addition of organometallic compounds to the nitrone functionality, the design of new functionalized allylic organometallic compounds, the use of Co(I) catalysis in classic carbon–carbon bond forming reactions (Reformatsky reaction, Reppe reaction, homoaldol condensation), as well as the total synthesis of natural products.

Claudio Trombini is professor of organic chemistry and green chemistry at the University of Bologna. He was born in Ravenna (1949) and received his Laurea Cum Laude (1973) from the University of Bologna, working with Prof. A. G. Giumanini. After an Euratom fellowship (1974–1976) at the Joint Research Centre of Ispra under the supervision of Prof. S. Facchetti, he joined the Prof. Umani-Ronchi group as an Italian C.N.R. fellow at the University of Bologna, where he was appointed Lecturer in 1979 and Associate Professor in 1985 at the Faculty of Mathematical, Physical and Natural Sciences. In 1990 he moved to the Ravenna Campus of the University of Bologna, teaching at the Faculty of Environmental Sciences, where he was appointed Full Professor in 1994. He served as managing director of the Ravenna Campus (1995–1999). In 2003 he moved back to the University of Bologna, where he now oversees a research group (one Research Associate, one Postdoctoral fellow, one Ph.D. student, and four graduate students) at the Department of Chemistry "G. Ciamician". Throughout his career he has been interested in organometallic chemistry, with a particular focus on the development of new metal-based stereoselective synthetic methodologies. His work has appeared in nearly 140 publications, reviews, book chapters, and patents. Prof. Trombini's current research areas include the development of novel hydroxyallylation protocols of carbonyl compounds and azomethine derivatives in aqueous solutions, the use of ionic liquids and the development of new catalytic protocols in these innovative media, and organocatalysis and transition-metal-catalyzed asymmetric processes.

Scheme 2



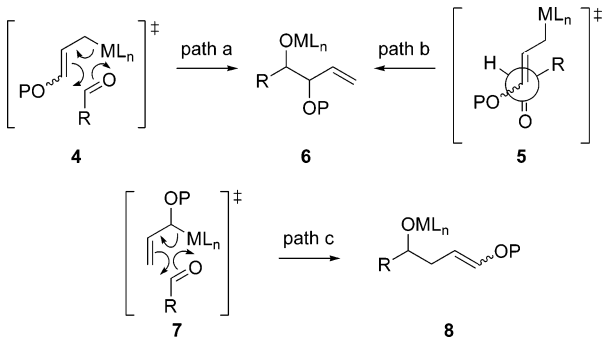
in the less stable η^1 γ-*E*-**3**, while η^1 α-**3** is the least stable σ-complex.[3]

1.1. Regiochemistry of the Addition Reaction to Aldehydes

Several features govern the regio- and stereochemistry of the addition of η^1-complexes **3** to aldehydes: (i) the shape of the energy profile for the metallotropic rearrangement (Scheme 2), (ii) the structures of the transition states (TSs) in the reaction with an aldehyde, and (iii) the reversibility (thermodynamic control)[4] or the irreversibility (kinetic control) of the addition step.[5]

Since, in general, the addition reactions to aldehydes follow a S_E' mechanism, η^1 γ-**3** complexes afford enediol precursors **6**, while η^1 α-**3** leads to adducts **8**. Either cyclic TSs (**4** and **7**) or open-chain TSs, such as the anticlinal TS **5**, are adopted, mainly depending on the metal used (Scheme 3).

Scheme 3



According to this general mechanistic frame, **6** or **8** is regioselectively formed if one of these two conditions is met. In the first case, the fluxional rearrangement is slow compared to the addition to the aldehyde at the selected reaction temperature. Such a condition ensures, indeed, constitutional stability to the allylic complex **3**, as happens in the cases of 3-methoxyallyl tributylstannanes[6] and of 3-alkoxyallyl cyclic boronates,[7] which are constitutionally stable at room temperature. Alternatively, the energy barriers for the metallotropic rearrangement must be low, and one among the equilibrating complexes **3** must be markedly favored on thermodynamic grounds or more reactive on kinetics grounds. This second hypothesis is encountered in the case of 3-alkoxyallyl chromium(III) complexes.[8] In all other borderline cases, mixtures of **6** and **8** are to be expected. In addition, lack of regiochemistry could result from the concurrency of S_E mechanisms or from the involvement of η^3-**3** species in the addition step.

The reaction of η^1 α-**3** with aldehydes, a version of the homoaldol reaction, will not be considered here, since excellent review articles are available.[9] However, it is interesting to notice how thermodynamic stabilization of η^1

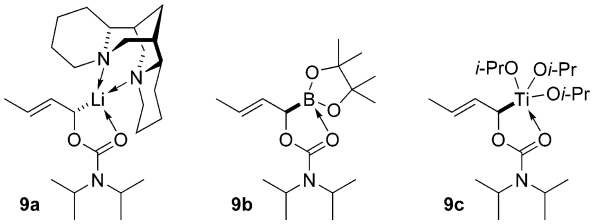


Figure 1. Carbamates stabilized α-oxyallyl metal complexes as synthetic equivalents of homoenolate ions.

α-**3** complexes can be achieved by forcing the metal to stick on the oxygen-bound carbon terminus through intramolecular chelation by a properly tailored P substituent. Examples derived from Hoppe's group are given in Figure 1, where different metals such as lithium (**9a**),[10] boron (**9b**),[11] and titanium (**9c**),[12] are efficiently coordinated by the strong donor carbonyl oxygen of a carbamate functionality. In these examples, the stereogenic oxymetalated carbon is configurationally stable and perfectly stereocontrolled homoaldol products are obtained.

1.2. Stereochemistry of the Addition Reaction to Prochiral Aldehydes

With a configurationally defined η^1 γ-**3** complex in our hands, the question is now how to achieve good diastereocontrol in the nucleophilic addition to a prochiral aldehyde. In the most favorable cases, we can distinguish among three types of oxyallyl metal complexes, henceforth defined as types A−C organometallics.

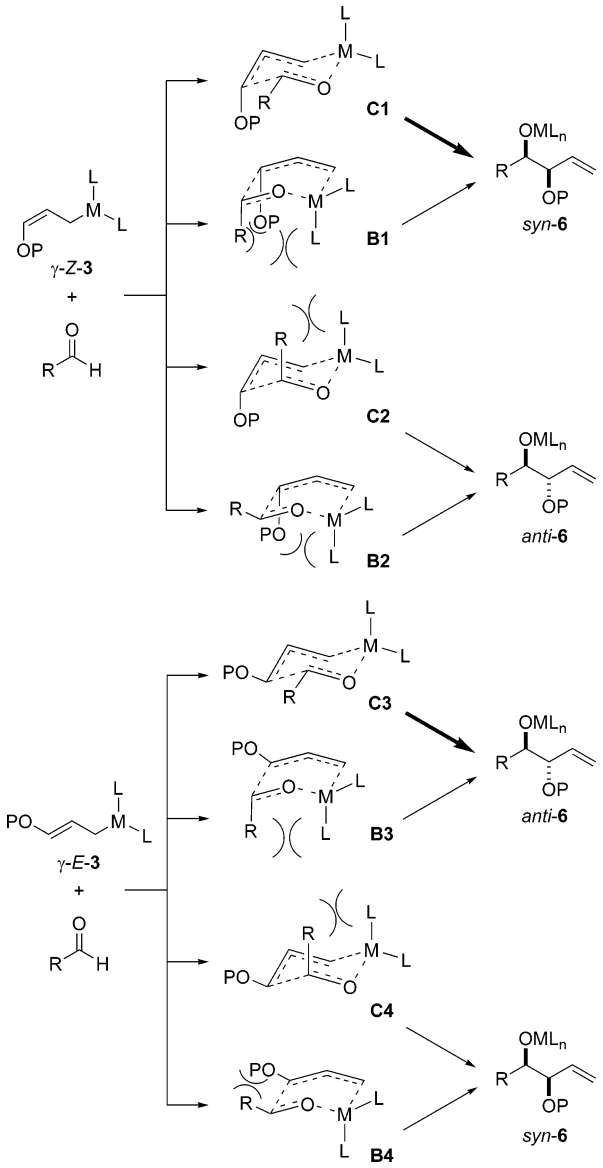
With type A species, diastereoselectivity depends both on the metal and on the C═C bond configuration, while, with type B or C complexes, diastereoselectivity depends on the metal only, with the stereochemical outcome being independent of the configuration of the C═C double bond.

Type A reactivity is rationalized in terms of cyclic TSs (chairlike **C1**−**C4** and boat-like **B1**−**B4** TSs), and the diastereochemical outcome of the nucleophilic addition can be easily anticipated on the basis of a simple conformational analysis (Scheme 4).[13] With regard to boatlike structures, we consider only **B1**−**B4**, having the carbonyl oxygen and the allylic CH group in the bow and stern positions, thus avoiding repulsive bowsprit−flagpole interactions; **B1** and **B4** are highly destabilized by the R/OP eclipsing interactions. In any case, when compared to chairlike TSs, structures **B2** and **B3** are inherently disfavored as a result of eclipsing interactions, which can be only partially but not substantially relieved by the adoption of a twist-boat conformation.

Chairlike TSs **C1** and **C3**, at a first glance, look like the most stable ones, since repulsive steric interactions are minimized, if we suppose that the 1,3-diaxial interactions in **C2** and **C4** are larger than the gauche interactions between R and OP in **C1** and **C3**. A frequently observed trend, indeed, is that diastereogenic C−C bond formation occurs with nonequilibrating η^1 γ-**3** complexes, with the *Z* complex favoring the *syn*-adduct **6**, and the *E* complex favoring *anti*-**6**.

However, exceptions to this rule exist, depending on the nature of P and L, and, particularly, on the presence of supplementary substituents on the oxyallyl structure, as the result of subtle balances between repulsive and attractive interactions which may favor a different TS, including a boatlike TS. An analogous uncertainty affects the oxyallylation reaction of ketones, where TS stabilization depends on the difference between the steric requirements of the ketone substituents.

Scheme 4



Type B oxyallyl organometallics react in a stereoconvergent *anti*-fashion due to a rapid haptotropic rearrangement which accumulates the more reactive isomer γ-*E*-**3**, which, then, adds to the aldehyde, adopting a cyclic TS (e.g., allylic chromium complexes which stereoconverge to *anti*-**6** adducts).[8]

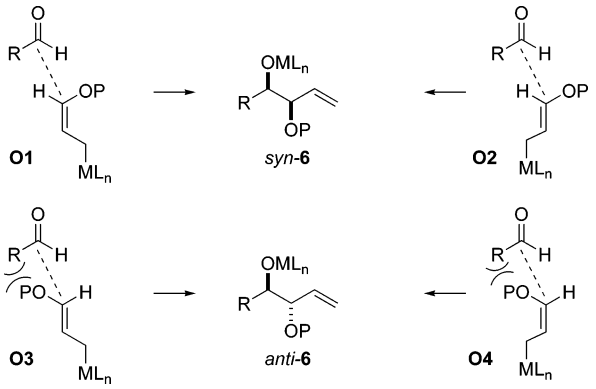
Type C oxyallyl organometallics, on the other hand, react in a stereoconvergent *syn*-fashion; in this last case, open-chain TS structures **O1**−**O4** are involved (Scheme 5). Trajectories **O1** and **O2** identify the less sterically hindered approaches between γ-*Z*-**3** and γ-*E*-**3**, respectively, and the carbonyl compound, with both paths converging into adduct *syn*-**6**. This is the case of constitutionally stable complexes such as 3-oxyallylic stannanes.[6]

2. 3-Alkoxyallyl Lithium, Zinc, Aluminum, and Titanium Complexes

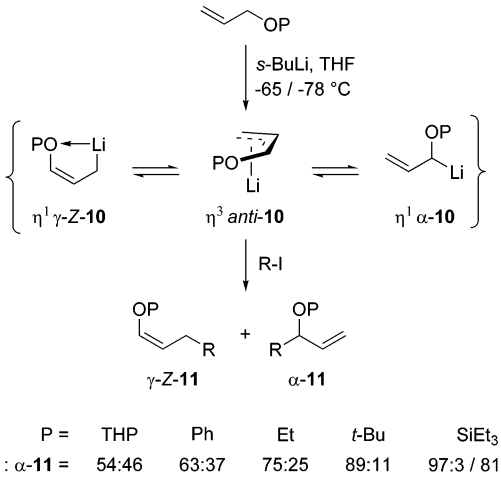
2.1. Lithium Complexes

In the world of real chemistry, organolithium compounds **10** are the closest analogue of the 1-hydroxyallyl anion (**2**); they are prepared by metalation of allyl ethers by means of alkyl lithium bases at low temperature, in order to avoid the

Scheme 5



Scheme 6



P =	THP	Ph	Et	*t*-Bu	$SiEt_3$
γ-**11** : α-**11** =	54:46	63:37	75:25	89:11	97:3 / 81:19

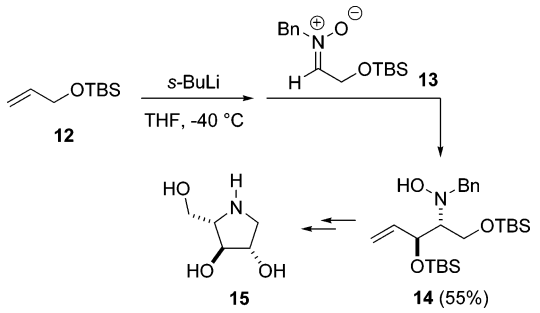
Wittig or the Brook (P = SiR_3) 1,2-migration. In 1974, in two consecutive papers, Evans and co-workers[14] and Still and Macdonald[15] reported the metalation of allyl ethers with *s*-BuLi in THF at low temperature and the reaction of the resulting intermediates, bidentate umpolung synthons possessing donor properties at C1 and C3, with electrophiles. Chemical evidence, such as the regio- (γ-adducts **11** prevail) and stereochemistry (*Z*-**11** only) of the alkylation reaction of **10** with alkyl halides (Scheme 6), supported the hypothesis that the most likely structures of **10** had to be η^3 *anti*-**10**, as proposed by Evans[14] and in agreement with calculations by Kubota's group,[3] or a fluxional equilibrium of η^1 γ-*Z*-**10** and η^1 α-**10** structures, as originally suggested by Still.[15]

Moving from alkyl halides to carbonyl compounds, the regiochemical course of the reaction with **10** is reversed when P = *t*-Bu in favor of the α-adduct **6** (M = Li), while a slight preference for **8** is preserved when P = Me (see Scheme 3).

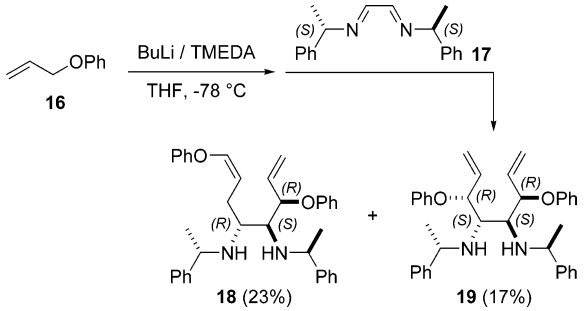
Reactions of oxyallyllithium reagents with azomethine derivatives have also been reported. Thus, a stereoselective synthesis of 2-hydroxymethyl-3,4-pyrrolidinediol (**15**) started with the reaction of nitrone **13** with silylallyl ether **12**, previously metalated with *s*-BuLi (Scheme 7). *Anti* adduct **14** was diastereoselectively obtained, accompanied by trace amounts (0.5%) of the γ-adduct.[16]

Allyl phenyl ether **16**, after metalation with BuLi/TMEDA, reacted with the chiral nonracemic glyoxal diimine **17** to give the double adducts **18** and **19**. Product **18** was the result of α and γ attack to the diimine, while product **19** was due to a double α-hydroxyallylation reaction.[17] The complete simple *anti* diastereoselectivity paired with an outstanding asymmetric induction exerted by the α-phenylethylamino auxiliary, which selectively directed the nucleophilic attack to the diimine *si* face (Scheme 8).

Scheme 7

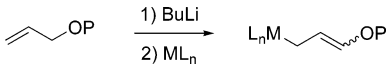


Scheme 8



Even though very few studies on the direct addition of lithiated allyl ethers to carbonyl compounds are available in the literature, they find an exceptionally useful application as precursors for a number of oxyallyl metal complexes via transmetalation with suitable metal salts ML_n (Scheme 9). Most of the species discussed in this review are prepared from lithiated allyl ethers using the transmetalation protocol.

Scheme 9

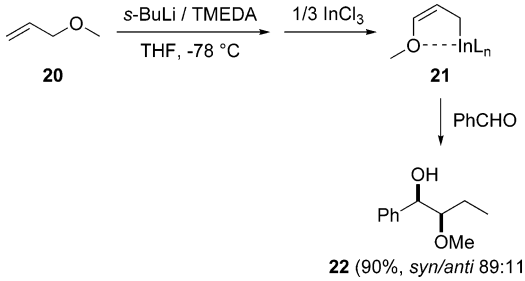


2.2. Indium and Zinc Complexes

The structure of oxyallyl complexes of zinc and indium prepared via transmetalation protocols was not spectroscopically determined, but it was deduced on the basis of the regio- and stereochemical outcome of the addition to carbonyl compounds.

For instance, the configuration of **21**, prepared from allyl methyl ether **20** with $InCl_3$, was assumed to be *Z* on the basis of the *syn* stereochemistry of adducts **22**, as anticipated by Type A reactivity (section 1.2) (Scheme 10).[18]

Scheme 10



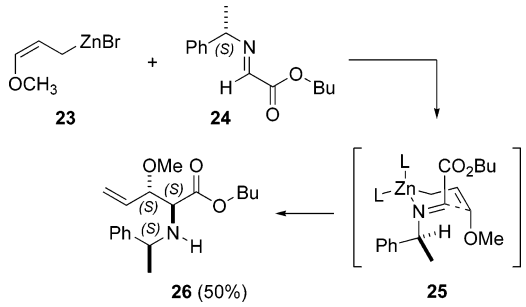
Evans observed that, moving from an oxyallyl lithium derivative to the corresponding oxyallyl zinc complex, the

formation of γ-adducts in the reaction with carbonyl compounds was suppressed.[14] The same observation was recorded by Savoia et al. in the reaction of the oxyallyl zinc complex derived from **16** with diimine **17**, which afforded **19** (46%) accompanied by its all *S* isomer (11%).[17] The foregoing results were in perfect agreement, in terms of simple *anti* selectivity and of diastereofacial preference, with the reaction of allylic zinc complex **23** with imine **24**, where again the nucleophilic attack was directed to the imine *si* face to deliver **26**. The *anti* selectivity exhibited by *Z*-**23** was explained by the six-membered transition state **25**, where the sterically crowded α-methylphenylamino group finds its energetically more favored location in the axial orientation (Scheme 11).[19]

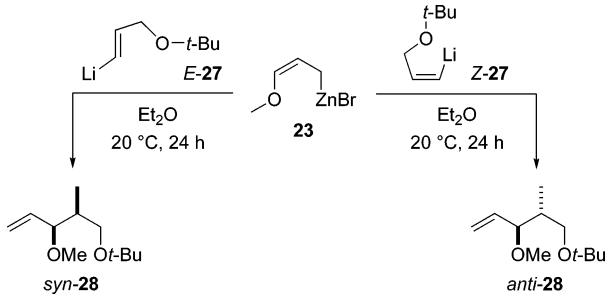
In analogy to simple allyl zinc complexes, 3-alkoxyallyl zinc species (e.g., **23**) add to vinyl lithium or magnesium derivatives (e.g., **27**) in a regio- and diastereoselective fashion, opening a route to *syn* or *anti* 1,3-dialkoxy derivatives **28**.[20] In the example shown in Scheme 12, the *syn*/*anti* relationship in **28** was controlled by the *E* or *Z* configuration of the starting vinylmetal **27**.[21]

The carbometalation reaction, or zinca-ene reaction, of lithium derivative **29** with **30** produced a *gem*-bismetallic intermediate **31** which spontaneously underwent cyclopropanation, leading to the enantiomerically enriched derivative **32** (Scheme 13).[22]

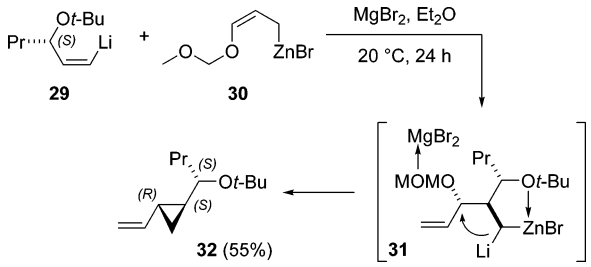
Scheme 11



Scheme 12



Scheme 13



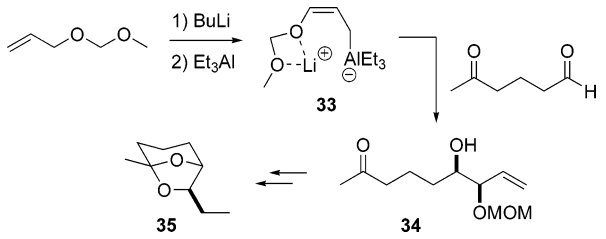
2.3. Aluminum and Boron Ate Complexes

Trialkylalanes and trialkylboranes were also proposed as modifiers for the addition of lithiated allyl alkyl ethers to aldehydes.[23] γ-*Z*-Oxyallyl borate or aluminate ions, e.g., **33**, appeared to be excellent candidates for the promotion of a *syn* addition to aldehydes, according to Type A reactivity (section 1.2). An example is presented in Scheme 14, where the chemo-, regio-, and stereoselective addition of allyl MOM ether aluminate complex **33** to 5-oxohexanal afforded **34**, a straightforward precursor of *exo*-brevicomin **35**.[24]

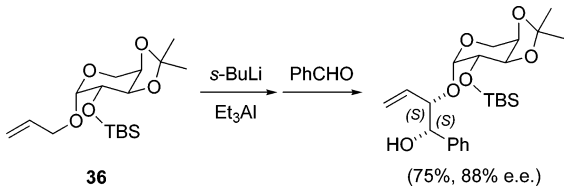
The protective group P offers the opportunity to insert a chiral auxiliary on the allyl ether backbone. Thus, allyl arabinopyranoside **36**, subjected to the usual lithiation/transmetalation protocol, was reacted with prochiral aldehydes. In terms both of simple and of facial diastereoselectivity, trialkylalanes were found to warrant the best results (Scheme 15).[25]

Less effective, on the other hand, was the reaction of γ-alkoxyallyl aluminate **37** with the chiral aldehyde **38**. A perfect control of simple *syn* stereochemistry was achieved, but no diastereoface discriminating ability was observed (Scheme 16).[26]

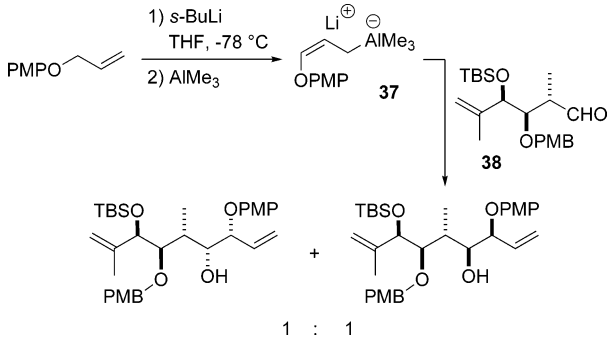
Scheme 14



Scheme 15



Scheme 16



2.4. Titanium Complexes

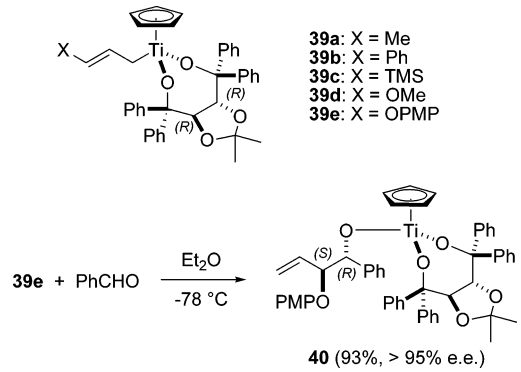
In 1992, as a development of allyl titanium chemistry carrying sugar-derived alkoxy ligands on the metal,[27] Hafner, Duthaler, and co-workers proposed a series of substituted chiral allyl titanium complexes of general structure **39**, which included the oxyallyl species **39d** and **39e**.[28] They were synthesized by transmetalation of the corresponding lithium, potassium, or magnesium allyl complex with TADDOLCpTiCl at 0 °C. Two crucial features characterized **39**: (i) a fast fluxionality, proved by NMR analysis of the crotyl reagent, favoring the γ-*E* isomer, precursor of *anti* adducts with aldehydes (Type B mechanism), and (ii) an astonishing

enantioface discriminating ability toward prochiral aldehydes. Impressive was the chemical and stereochemical efficiency of the reaction of **39e** with benzaldehyde to give **40** (Scheme 17).

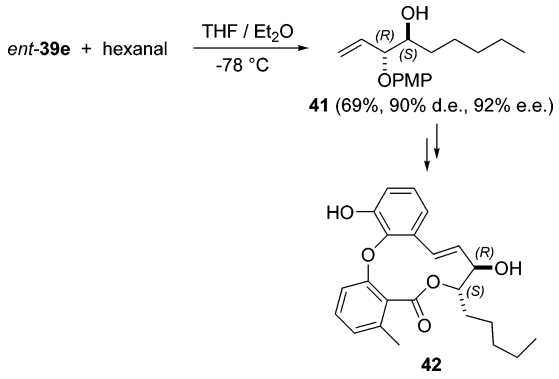
A few applications of **39e** to the synthesis of natural products have been reported. For instance, the reaction of *ent*-**39e** with hexanal gave the adduct **41** (Scheme 18), an intermediate in an asymmetric synthesis of the fungal metabolite aspercyclide C (**42**).[29]

The chiral aldehyde **43** afforded the *anti* adduct **44** upon reaction with **39e**, a key intermediate in a total synthesis of the neurotoxic fungal metabolite slaframine (**45**) (Scheme 19).[30]

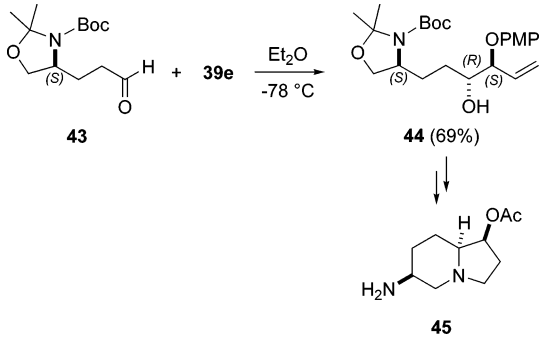
Scheme 17



Scheme 18

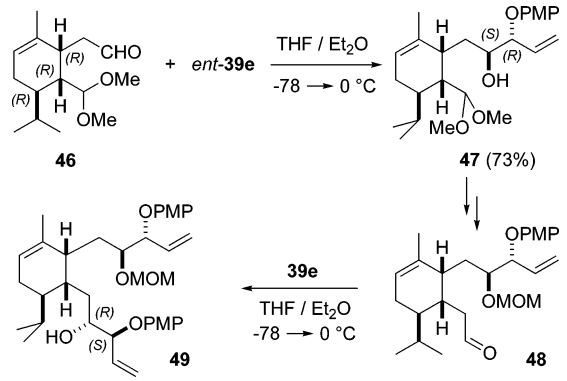


Scheme 19



Gennari and co-workers exploited both enantiomers **39e** and *ent*-**39e** in two different steps of a synthesis of the diterpene glycoside eleutherobin, a coral metabolite with cytotoxic activity.[31] The two key steps are outlined in Scheme 20. Aldehyde **46** was first reacted with *ent*-**39e** to give the *anti* adduct **47** upon attack to the aldehyde *si* face. The intermediate **47** was then elaborated into aldehyde **48**, which in turn was treated with **39e** to give *anti*-**49**, via nucleophilic

Scheme 20



attack to the aldehyde *re* face. With both chiral aldehydes **46** and **48**, the diastereofacial preference of the oxyallyl titanium complex dominated the stereochemical outcome of the process (reagent-control).

3. 3-Alkoxyallyl Boronates and Boranes

3.1. 3-Alkoxy-substituted Allyl Boronates

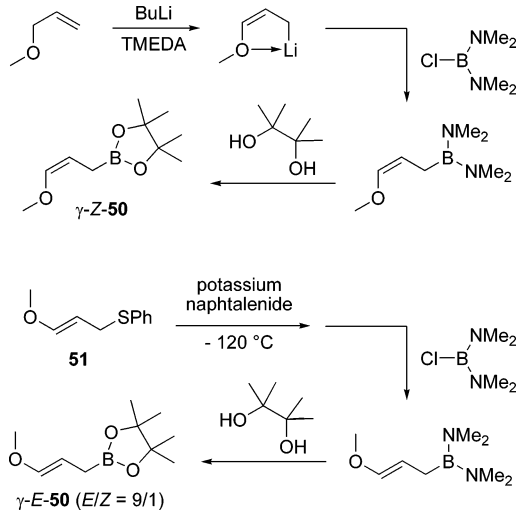
Thanks to the pioneering studies by Hoffmann[32] and Wuts[33] in the early 1980s, both γ-*E*- and γ-*Z*-alkoxy-substituted allyl boronates became available and their diastereoselective addition to aldehydes provided one of the first efficient routes to *syn* and *anti* enediols **1**.

The preparation of γ-*E*- and γ-*Z*-alkoxy-substituted allyl boronates required rather different synthetic approaches, as outlined in Scheme 21. Direct lithiation of allyl methyl ether only affords γ-*Z*-methoxyallyllithium, so subsequent borylation leads to γ-*Z*-**50**. On the other hand, for the preparation of γ-*E*-**50**, Hoffmann proposed a two step protocol involving metalation of the *E* configurated allyl sulfide **51**, followed by transmetalation with bis(dimethylamino)chloroborane, at very low temperature, in order to preserve the configurational integrity of the intermediate η^3-*anti*-methoxyallyl potassium.[34]

Instead of the methoxy protective group in **50**, silyloxy, phenyloxy, tetrahydropyranyloxy, and methoxymethyloxy groups can also be used.

Haptotropic rearrangement in substituted allyl boronates is known to be slow on a macroscopic time scale, conferring constitutional stability to γ-*E*- and γ-*Z*-alkoxy-susbstituted allyl boronates.[35]

Scheme 21

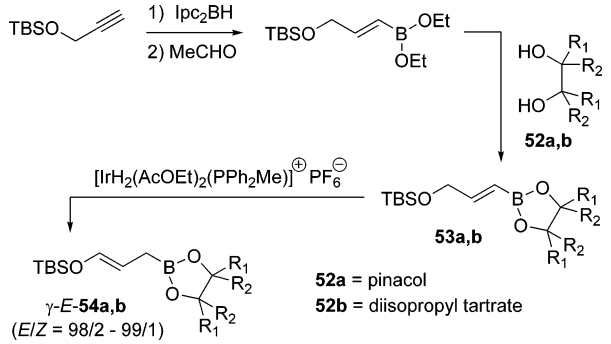


Type A reactivity rationalizes the excellent *syn* diastereoselectivity displayed by γ-*Z*-**50** in the addition to aldehydes through chairlike TS **C1** (Scheme 4), as well as the good *anti* diastereoselectivity exhibited by γ-*E*-**50** through chairlike TS **C3**.

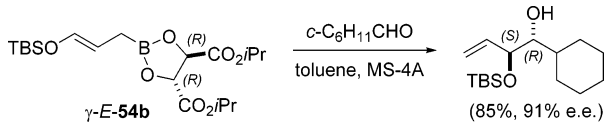
A more practical route to *E*-configurated γ-alkoxy-substituted allyl boronates **54a**,**b** was devised by Miyaura, who exploited the iridium-catalyzed isomerization of the double bond of vinylboronate **53a**,**b**, which was easily accessible via hydroboration of a propargyl ether (Scheme 22).[36] An asymmetric *anti* α-hydroxyallylation of cyclohexanecarboxaldehyde could be carried out with **54b**, where optically active diisopropyl tartrate was used as diol component (Scheme 23).

A further approach to γ-*E*-**56** was proposed by Hoffmann[37] and involved the direct zirconium-catalyzed hydroboration of ynolether **55** with pinacolborane, followed by a Matteson-type homologation with $LiCH_2Cl$ (Scheme 24).

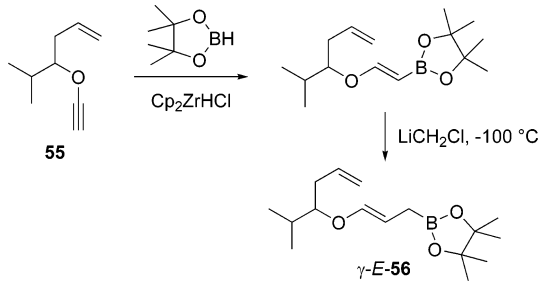
Scheme 22



Scheme 23



Scheme 24

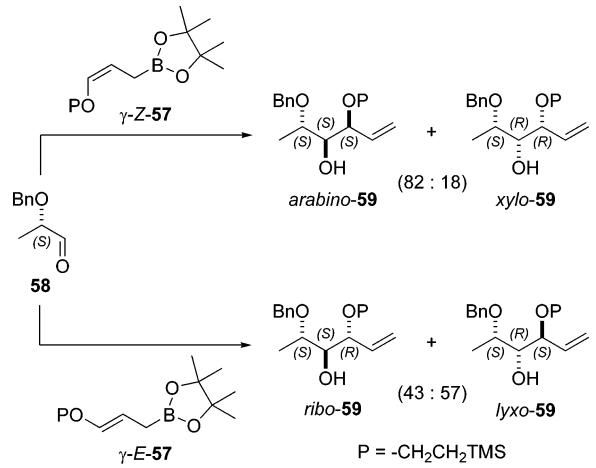


The α-hydroxyallylation of aldehydes containing an oxygen-bearing stereocenter on the α-position offers an attractive route to carbohydrates from acyclic precursors. Critical in this approach is the control of diastereofacial selectivity.

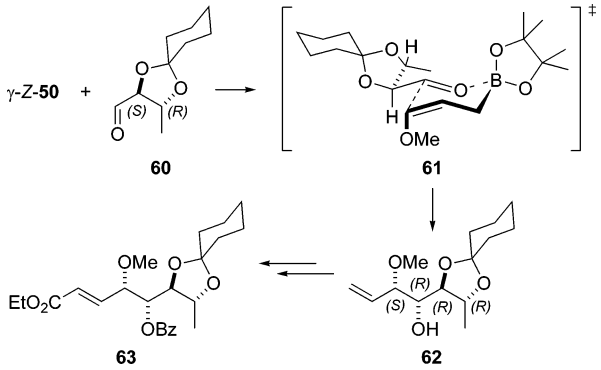
In the reaction with protected lactaldehyde **58**, γ-*Z*-**57** discriminated much better than γ-*E*-**57** between the two diastereotopic faces of the aldehyde. Four triads of contiguous stereocenters were generated in products **59** (Scheme 25), which could be converted into 2,6-dideoxy-L-hexoses with *arabino*, *xylo*, *ribo*, and *lyxo* configurations.[38]

In a synthesis of olivomycin A, a member of the aureoleic acid family of antitumor antibiotics, the construction of the D-fucose intermediate **63** commenced with a highly stereoselective addition of γ-*Z*-**50** to aldehyde **60**, available from

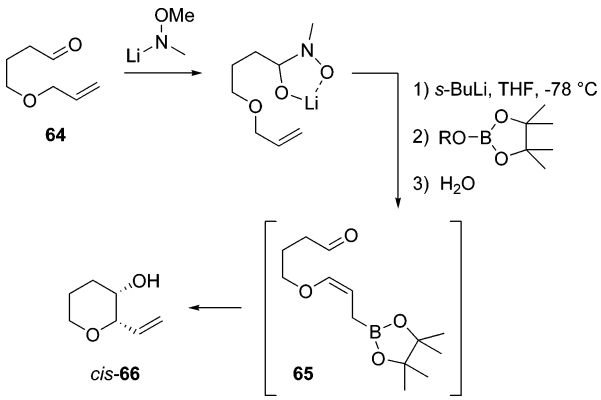
Scheme 25



Scheme 26



Scheme 27

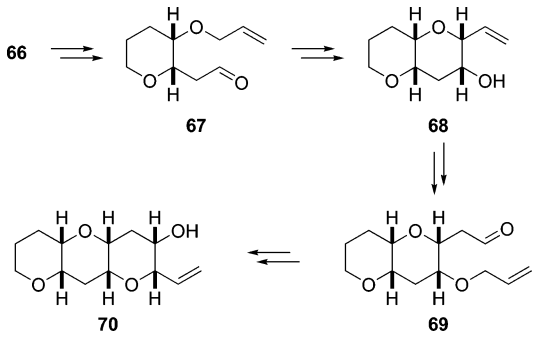


L-threonine. The reaction was supposed to proceed by way of the Cornforth transition state **61** (Scheme 26).[39]

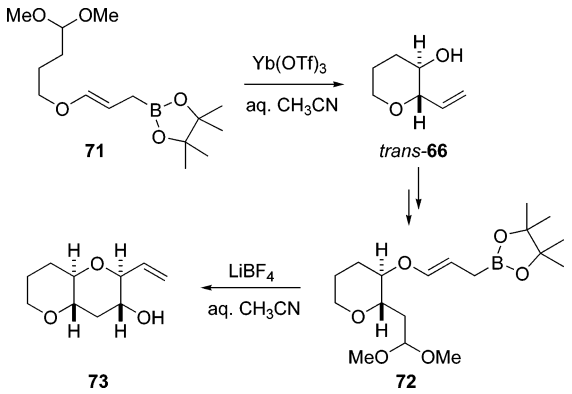
The intramolecular version of the α-alkoxyallylboration of aldehydes was also investigated. Hoffmann recognized that *cis*-fused tetrahydropyran rings could be fashioned from **64**, through a synthetic sequence involving multiple intramolecular α-alkoxyallylboration reactions.[40] After protection of the carbonyl group of **64** with the Weinreb lithium amide, lithiation/borylation, and aqueous hydrolysis at pH 7, formation of *Z*-boronate **65** was immediately followed by the spontaneous diastereoselective cyclization to *cis*-tetrahydropyran **66** (Scheme 27). The last intermediate could be easily converted into **67**, which, upon reiteration of the same reaction sequence, gave **68**, in turn a precursor of **69** and, hence, of the tri-tetrahydropyran **70**, having a pure *cis*-*syn*-*cis*-*syn*-*cis*-configuration (Scheme 28).

A solution was then devised to approach *trans*-fused tetrahydropyrans. The ytterbium triflate-catalyzed intramolecular alkoxyallylboration of *E*-**71** afforded *trans*-**66**. Following the strategy shown in Scheme 28, *trans*-**66** was transformed into *E*-boronate **72**, having the correct double bond configuration to induce the formation of the desired *trans-syn-trans* bis-tetrahydropyran **73** (Scheme 29).[37]

Scheme 28



Scheme 29

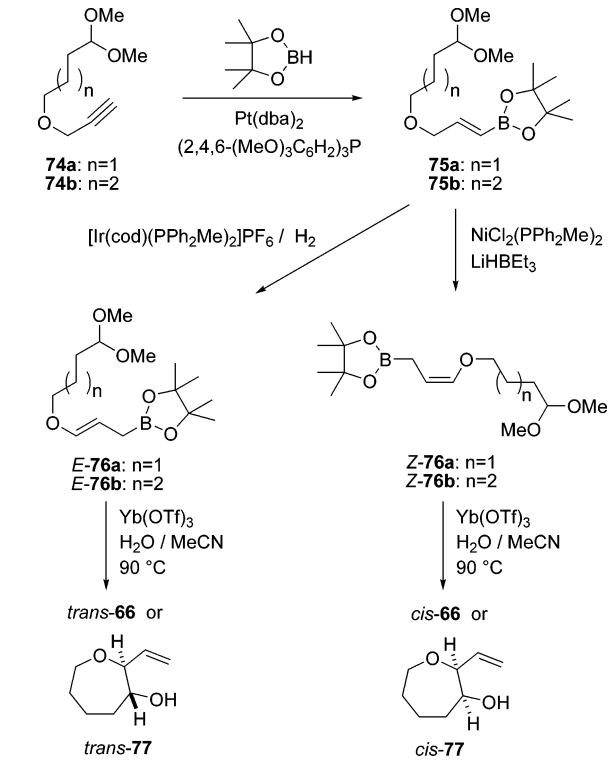


Miyaura improved the Hoffmann approach to *trans*- or *cis*-**66** by exploiting his route to allyl boronates via isomerization of vinyl boronates (see Scheme 22).[41] Platinum-promoted hydroboration of the triple bond of **74** with pinacolborane afforded **75**, which could be stereodivergently isomerized to both *Z*- and *E*-**76** by using iridium or nickel catalysts, respectively. With the synthesis of *Z*- and *E*-**76** accomplished, good cyclization routes were sought next. Best results were obtained using the ytterbium triflate-promoted cyclization of **76** in water/acetonitrile at 90 °C, which directly afforded *trans*- and *cis*-**66**, as well as the corresponding *cis*- or *trans*-2-vinyl-oxepan-3-ols **77** (Scheme 30).

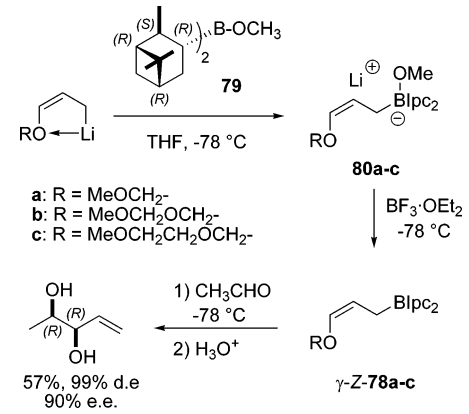
3.2. 3-Alkoxy-substituted Allyl Boranes

In the frame of his studies on diisopinocampheylallyl and crotyl boranes, Brown reported in 1988 the synthesis of γ-*Z*-methoxyallyl boranes **78a**, γ-*Z*-(methoxy)methoxyallyl boranes **78b**, and γ-*Z*-(2-methoxyethoxy)methoxyallyl boranes **78c**, as well as the preliminary results in the reactions with a few model prochiral aldehydes, demonstrating a striking *syn*-diastereoselectivity (≥99%) and an excellent enantiocontrol (≥90% ee).[42] To achieve such a level of diastereocontrol, it was necessary to conduct the reaction at −78 °C, since allyl boranes undergo a much faster metallotropic rearrangement than their boronate counterparts,[35] due to the greater Lewis acidity of the boron center in boranes. Both enantiomers of pinene, directly available from the chiral pool at a low price, confirmed superior advantages as chiral

Scheme 30



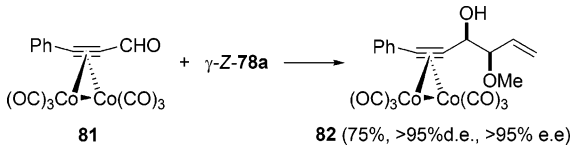
Scheme 31



boron ligands in terms of aldehyde enantioface discriminating ability. The preparation of **78b** is shown in Scheme 31. Lithiated allyl MOM ether is borylated with Ipc_2BOMe (**79**) to give allyl ate complex **80b**, which, upon treatment with BF_3 undergoes dequaternization to γ-*Z*-**78b**. All these steps, including the reaction of γ-*Z*-**78** with aldehydes, were conducted at −78 °C.

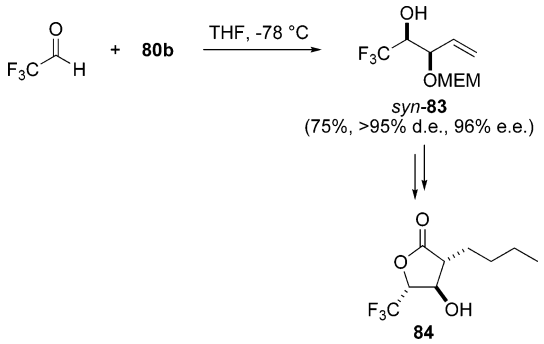
Among conjugated aldehydes, while α,β-enals react with γ-*Z*-**78c** in good yields with complete *syn* diastereocontrol and high enantiocontrol (93−94% ee),[43] conjugated ynals such as phenylpropynal, when exposed to **78a**, underwent extensive decomposition and the expected adduct was isolated in less than 5−10% yield. Since the carbon−carbon triple bond was the likely culprit for the very poor results, Ganesh and Nicholas devised an attractive solution by converting the α,β-ynal into the corresponding dicobalt hexacarbonyl complexed aldehyde **81**. The expected addition product, *syn*-**82**, was eventually obtained in good chemical yield with excellent stereocontrol (≥95% de, ≥95% ee) (Scheme 32).[44] Once **82** was decomplexed with CAN, the authors also found conditions for the chemoselective dihy-

Scheme 32



81 **82** (75%, >95%d.e., >95% e.e)

Scheme 33



syn-**83** (75%, >95% d.e., 96% e.e.)

84

droxylation (NMO, OsO_4) and epoxidation of the carbon−carbon double bond (TBHP, $VO(acac)_2$) in the presence of the carbon−carbon triple bond.

Boronate γ-*E*-**78** was also accessible by exploiting the protocol shown in Scheme 21; the addition of γ-*E*-**78** to a few cobalt-complexed ynals afforded, as expected, *anti*-**82** in good chemical yields and in ≥95% de and ee.[44]

Fluoral was another example of an aldehyde that, exposed to γ-*Z*-**78b**, undergoes extensive polymerization. In this case, the addition product *syn*-**83** was formed uneventfully from the direct reaction of fluoral with quaternary borate complex **80b** at −78 °C, as shown in Scheme 33. The completion of a total synthesis of fluoroblastmycinolactol (**84**) required the inversion of the configuration of the hydroxylated stereocenter in *syn* adduct **83** via an oxidation (Dess−Martin periodinane)/reduction with $Zn(BH_4)_2$ sequence.[45]

The α-hydroxyallylation of aldehydes by means of γ-*Z*-alkoxyallyl boranes **78** found valuable applications in a number of total syntheses of natural products. A group of 1-en-3,4-diol derivatives **85** is presented in Figure 2 along with the first manipulation(s) that the enediol intermediate has been subjected to, the structure of the target molecules, and ee's.[46−55]

When azomethine compounds are used as electrophiles, 1-en-3-alkoxy-4-amino derivatives become accessible. Ramachandran reported the use of *N*-silylimines **86** as electrophiles. Since **86** is not compatible with $BF_3{\cdot}Et_2O$, required to generate **78** from the ate complex **80** (Scheme 31), *N*-silylimines were directly reacted with **80c**, allowing authors to gain an easy entry to *syn* aminol **87** in very high de and ee (Scheme 34).[56]

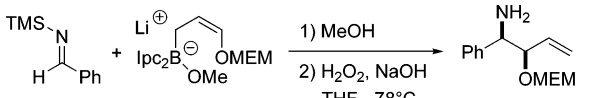
Analogous results were obtained with *N*-aluminoimines **88**, prepared *in situ* via reduction of nitriles with DIBAL-H. Reaction of **88** with the ate complex **80c** in THF at −78 °C afforded virtually pure protected *syn* aminol **89** in high ee (Scheme 35).[56] Ozonolysis of the double bond followed by aldehyde oxidation ($NaClO_2$) completed a useful approach to enantiopure α-hydroxy-β-amino acids, a class of compounds of utmost importance in medicinal and biochemical research.

The nitrogen-substituted γ-*E*-allylborane **91** was produced by borylation of **90** with Ipc_2BCl (Scheme 36).[57] The perfect control of the *E* configuration in **91** was governed by the *trans*-W-shaped conformation of **90**.[58] The *in situ* reaction of **91** with prochiral aldehydes was characterized by a perfect control of the relative *anti* stereochemistry (>90% de) as well as by an excellent control of the absolute stereochemistry (>90% ee). The *anti* aminol **93** (constitutional isomer of **87**) was freed by simple acidic hydrolysis of the intermediates imines **92**.

In the attempt to convert the iminoalcohol **92a** into an aziridine upon activation of the hydroxyl group with triflic anhydride, Barrett and co-workers observed an unexpected rearrangement.[57] Through the likely involvement of the iminium ion **94** followed by nucleophilic attack of the triflate ion to the more reactive allylic carbon of the aziridium ion, the intermediate **95**, precursor of the *anti* aminoalcohol **96**, was regioselectively formed (Scheme 37).

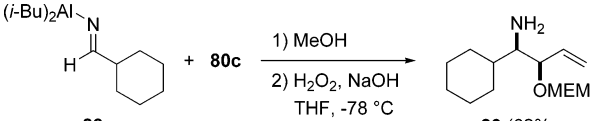
In conclusion, starting from γ-*E*-allylborane **91**, both alk-1-en-3-amino-4-ol (e.g., **93**) and its structural isomer alk-1-en-4-amino-3-ol (e.g., **96**) are accessible.

Scheme 34



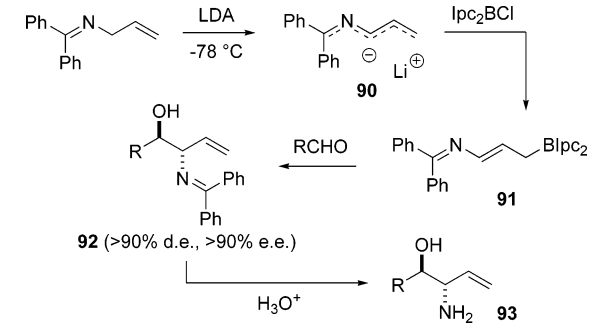
86 **80c** **87** (65%, 98% d.e., 95% e.e.)

Scheme 35



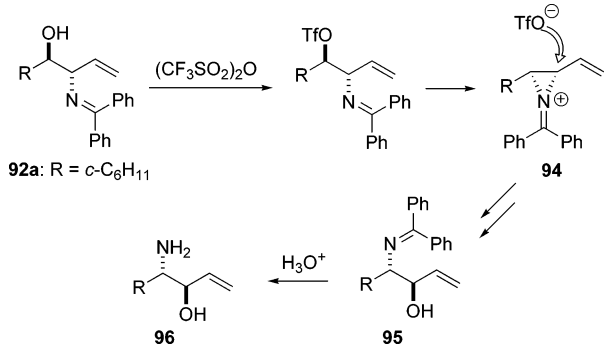
88 **89** (62%, > 98% d.e., 89% e.e.)

Scheme 36



90 **91** **92** (>90% d.e., >90% e.e.) **93**

Scheme 37



92a: R = *c*-C_6H_{11} **94** **95** **96**

4. 3-Alkoxyallyl Stannanes

4.1. Prochiral and Chiral 3-Alkoxyallyl Stannanes

In 1987, Keck and co-workers[59] and Koreeda and Tanaka,[60] independently, published the preparation of γ-alkoxy-

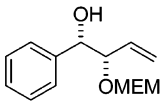
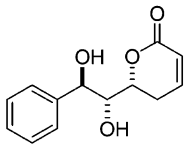
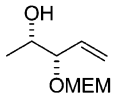
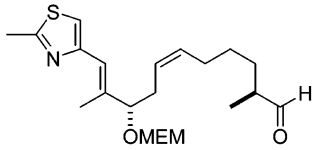
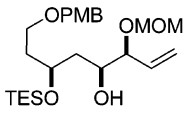
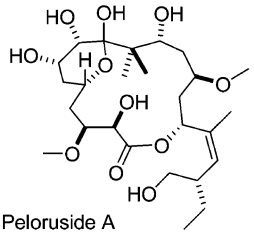
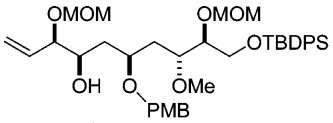
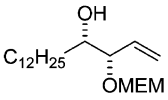
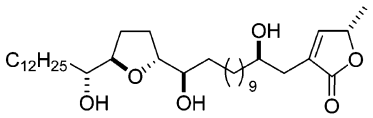
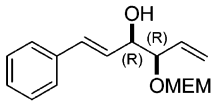
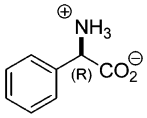
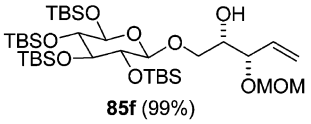
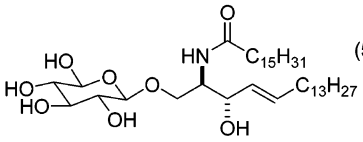
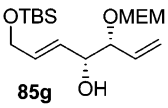
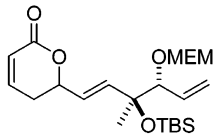
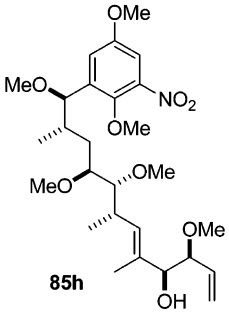
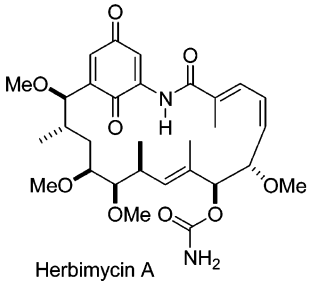
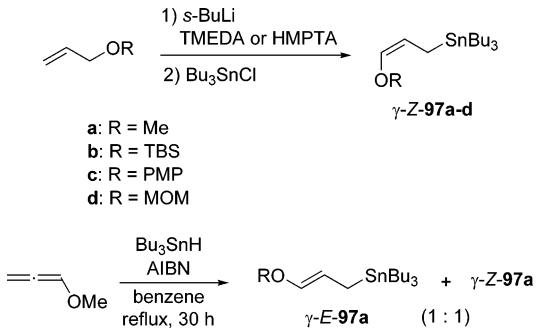
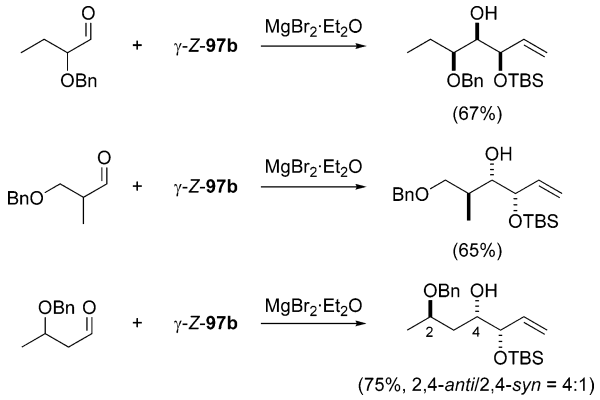
1-En-3,4-diol	Key Synthetic Elaborations	Target molecule	Ref.
 **85a** (98% e.e.)	Mitsunobu inversion at the alcoholic stereocenter and oxidative cleavage of the C=C bond (OsO_4, $NaIO_4$)	 Goniodiol	(46)
 **85b** (95% e.e.)	Oxidative hydroboration followed by Dess-Martin periodinane oxidation and Wittig reaction	 C7-C21 Segment of epothilone A	(47)
 **85c** (>90% d.e.)	In a later stage of the total synthesis, the C=C bond is oxidatively cleaved and oxidized to the ester functionality (OsO_4, $Pb(OAc)_4$, $NaClO_2$, CH_2N_2)	 Peloruside A	(48)
 **85i**		Peloruside A	(49)
 **85d** (95% e.e.)	Oxidative hydroboration followed by CH_2OH to CH_2I transformation and Negishi coupling with a vinyl zinc derivative	 Murisolin	(50)
 **85e** (94% e.e.)	Conversion of the alcohol into trichloro acetoimidate followed by the Overman [3,3]-rearrangement which occurs with complete chirality transfer		(51)
 **85f** (99%)	*O*-Silylation with a dimethyl chlorovinyl silane followed by ring closing metathesis and O-Si bond cleavage. The neat result of this procedure is an *E* stereo-selective cross-metathesis at the terminal C=C bond of **85f** (ref. 52)	 D,L-Glucosylceramide	(52,53)
 **85g**	Alcohol oxidation to carbonyl group (Dess-Martin periodinane) followed by diastereoselective Grignard addition to give a monoprotected *anti*-diol	 C1-C11 Subunit of C_8-*epi*-fostriecin	(54)
 **85h**	Double bond oxidative cleavage (OsO4, NMO) followed by a sequence of Horner-Wittig and Wittig olefinations and final macrocyclization.	 Herbimycin A	(55)

Figure 2. Synthetic applications of the α-alkoxyallylation of aldehydes by means of γ-*Z*-**78**.

Scheme 38



Scheme 39



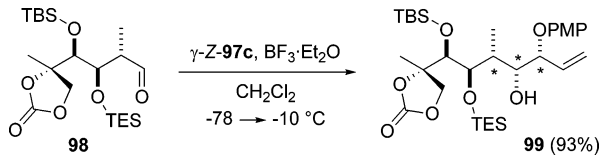
allyl stannanes and the first data on the Lewis-acid-catalyzed reaction with aldehydes. Since then, γ-alkoxyallyl stannanes have been the most widely used synthetic equivalents of the 1-hydroxyallyl anion (**2**). Their good fortune is also due to their easy purification and storability. Metalation of an allyl ether with *s*-BuLi in the presence of TMEDA or in a THF/HMPTA solvent mixture followed by transmetalation with R_3SnCl furnishes γ-*Z*-alkoxyallyl stannanes **97**. Less efficient was the route to γ-*E*-alkoxyallyl stannanes **97** proposed by Koreeda and Tanaka,[60] consisting of the AIBN-catalyzed hydrostannation of methoxyallene. This route gave a 1:1 mixture of γ-*Z*- and of γ-*E*-**97** (Scheme 38).

In the presence of $BF_3{\cdot}Et_2O$, both γ-*Z* and γ-*E*-**97** stereoconvergently afforded *syn*-adducts when reacted with prochiral aldehydes.[60] Type C reactivity discussed in section 1.2 is generally considered for the mechanism of the Lewis-acid-catalyzed addition of allylic stannanes with aldehydes. Good facial selectivity was also observed with racemic chiral aldehydes, using $MgBr_2{\cdot}Et_2O$ as Lewis acid, as shown in Scheme 39.[59] It is worth of note that the facial selectivity is inverted when the stereocenter on the α-position of the aldehyde bears a benzyloxy group (*syn*−*syn* stereotriad, first example of Scheme 39) or a methyl group (*syn*−*anti* stereotriad, second example of Scheme 39).

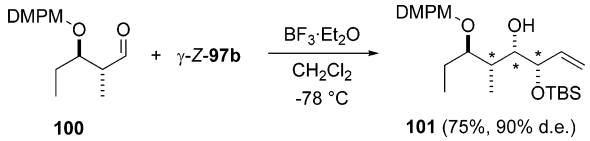
The facial diastereopreference may be reversed by using different Lewis acids, for example working under chelation control (e.g., $MgBr_2$) or under nonchelation control (e.g., BF_3), as in the case shown in Scheme 40. The *syn*−*syn* starred stereotriad in **99** was formed when nonracemic chiral aldehyde **98**, bearing a silyloxy group on the α-position, reacted with **97c** in the presence of $BF_3{\cdot}Et_2O$ (Scheme 40).[26]

The inversion of facial selectivity was confirmed by the reaction of γ-*Z*-**97b** with the chiral aldehyde **100** in a partial synthesis of tedanolide, a potent cytotoxic macrolide isolated from a sponge. Using $BF_3{\cdot}Et_2O$, the *syn*−*syn* starred ste-

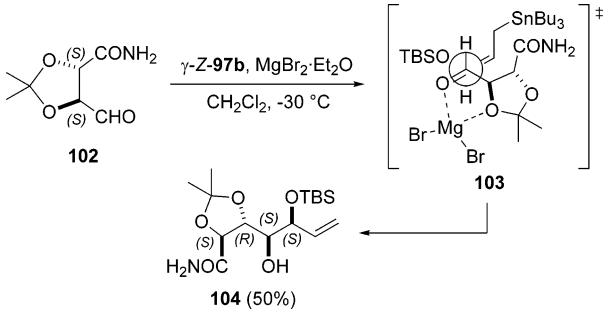
Scheme 40



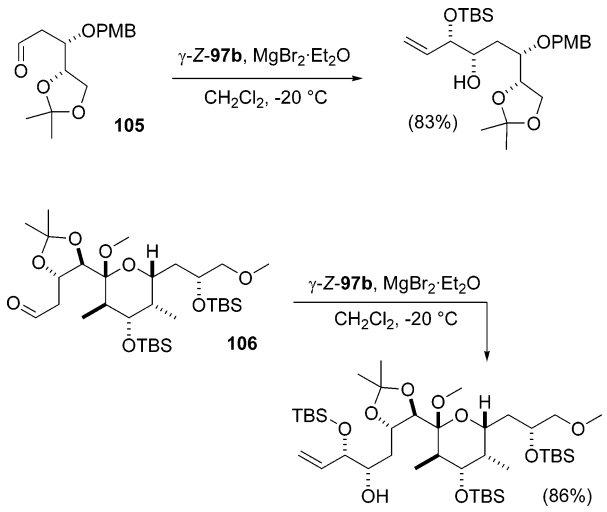
Scheme 41



Scheme 42



Scheme 43



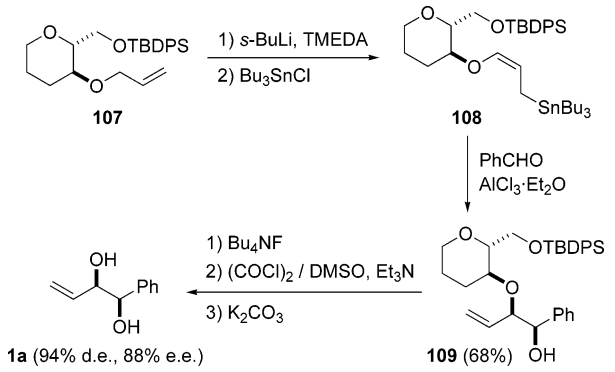
reorelationship of **101** was achieved (Scheme 41), as opposed to that obtained in the second reaction of Scheme 39.[61]

Aldehyde **102**, derived from D-tartaric acid, was coupled with γ-*Z*-**97b** in a synthesis of a phosphonate analogue of moenomycin A_{12}. In the presence of $MgBr_2{\cdot}Et_2O$, a single stereoisomer, L-*galacto*-**104** was obtained, presumably via the α-chelated TS **103** (Scheme 42).[62]

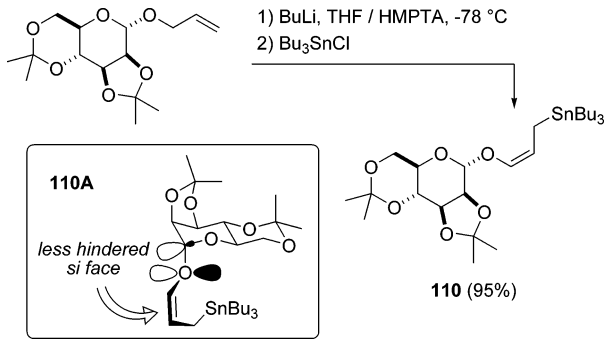
Stannane γ-*Z*-**97b** also found two interesting applications in the construction of two fragments of apoptolidin, a novel drug which selectively induces apoptosis of cancer cells. In both examples, two chiral aldehydes with an oxygen-bearing stereocenter on the β position, **105**[63] and **106**,[64] reacted in the presence of $MgBr_2{\cdot}Et_2O$ with high stereoselectivity, consistent with a β-chelation model (Scheme 43).

Allyl stannanes incorporating a chiral auxiliary group R* were reported for the enantioselective synthesis of *syn*-**1**. Thus, lithiation/transmetalation of the D-glucal-derived allyl ether **107** according to the standard protocol (*s*-BuLi/

Scheme 44



Scheme 45



TMEDA then Bu_3SnCl) afforded chiral γ-*Z*-stannane **108**, which reacted with aldehydes to give adducts **109**. The best results were obtained with aromatic aldehydes using $AlCl_3 \cdot Et_2O$ as Lewis acid (Scheme 44). The chiral auxiliary is then destructively removed to free the enantiomerically enriched *syn*-diol **1a** (R = Ph).[65]

Anticipating a diastereofacial bias exerted by the mannosyl auxiliary (exo anomeric effect in the conformation **110A**), the γ-*Z*-mannopyranosiloxyallyl stannane **110** was prepared by the usual lithiation/stannylation procedure (Scheme 45), and the stereochemical course of the reaction with chiral aldehydes was carefully monitored.[66]

A selection of the results reported by Roush and Van-Nieuwenhze using **110** is summarized in Figure 3,[66] where a perfect simple *syn* diastereoselectivity was accompanied by variable levels of facial selectivity (de's refer to Felkin/anti-Felkin isomers).

In the $BF_3 \cdot Et_2O$-promoted reaction of **110** with both enantiomers of **111** and **112**, the diastereofacial bias of γ-*Z*-mannopyranosiloxyallyl stannane **110** invariably dominated. The role of the Lewis acid in promoting the adoption of chelated or nonchelated TS structures found a beautiful application in the case of **112**, where opposite pairs of diastereotopic faces were involved in the reaction with **110**, using $MgBr_2 \cdot Et_2O$ or $BF_3 \cdot Et_2O$. These results also proved that, using $MgBr_2$ with the mismatched pair **110**/(*S*)-**112**, the aldehyde diastereofacial preference controlled the stereochemical outcome. With both enantiomers of **113**, the same stereochemical outcome recorded for (*R*)- and (*S*)-**112**, using either $BF_3 \cdot Et_2O$ or $MgBr_2 \cdot Et_2O$, was observed.

4.2. 3-Alkoxyallyl Stannanes Carrying a Supplementary Substituent

A substituted allyl ether, subjected to the classic lithiation/stannylation protocol, produces a substituted γ-alkoxyallyl stannane. An example is offered by stannane **115**, which

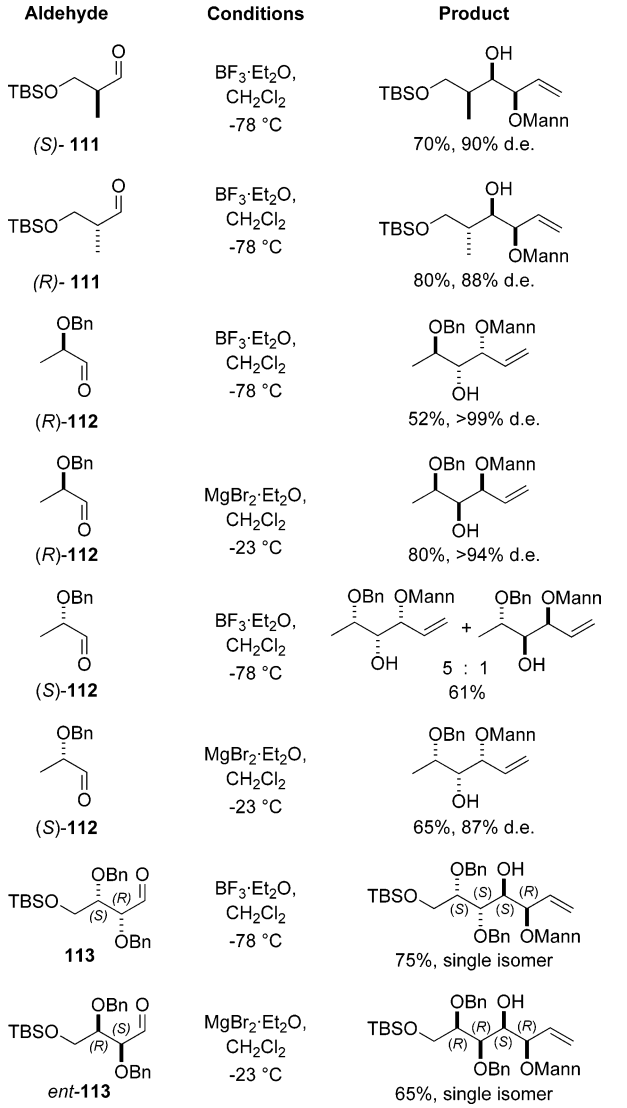
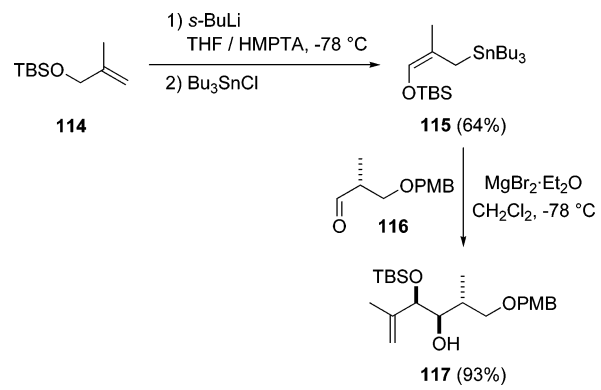


Figure 3. Reactions of γ-*Z*-(mannopyranosyloxy)allyl stannane **110** with chiral aldehydes.

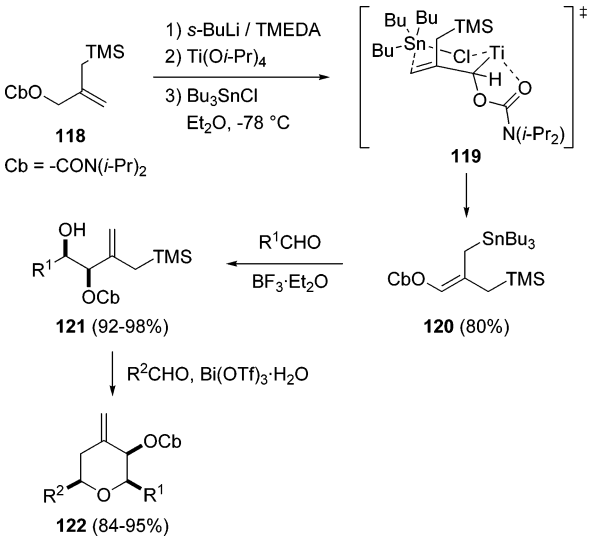
Scheme 46



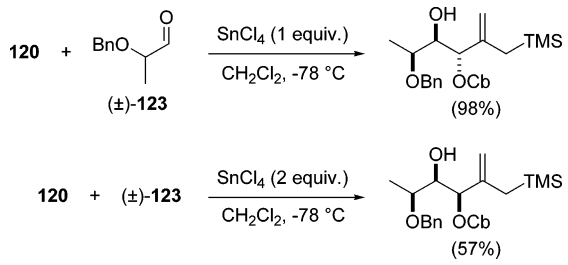
stereoselectively reacted with the enantiopure aldehyde **116** to give the *syn*−*anti* adduct **117** (Scheme 46).[67]

2-Silylmethyl-substituted allyl carbamate **118**, after a three-step lithiation/titanation/stannylation sequence, produced the stereodefined *Z*-allyl stannane **120**. The Ti/Sn exchange presumably occurs via the chelated chairlike TS **119** with the carbamate substituent in a pseudoaxial orientation (titanium ligands are omitted for clarity). The addition to prochiral aldehydes was mediated by $BF_3 \cdot Et_2O$ and afforded

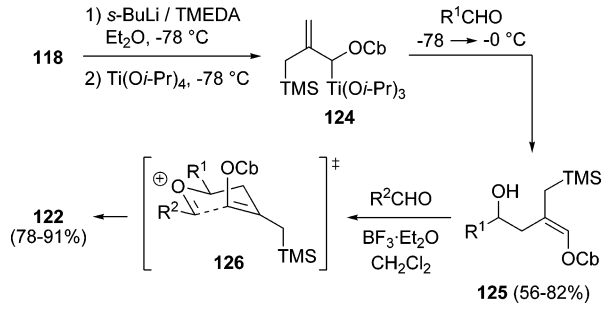
Scheme 47



Scheme 48



Scheme 49

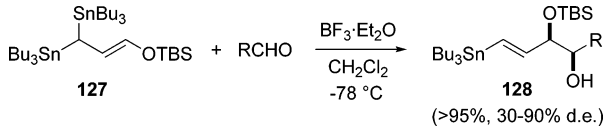


the *syn*-adduct **121**. The allyl silane functionality in **121** can then be exploited in the Sakurai reaction with a second aldehyde. The last step of this multicomponent sequential condensation strategy was catalyzed by $Bi(OTf)_3$ and led to the stereodefined polysubstituted tetrahydropyran **122** (Scheme 47).[68]

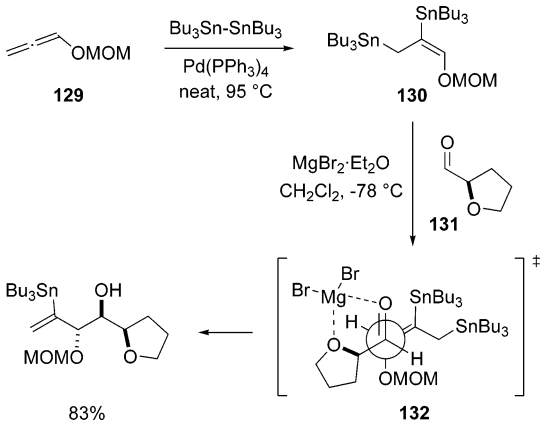
However, the reaction of **120** with α-alkoxy aldehydes failed, unless $SnCl_4$ was used as Lewis acid instead of $BF_3{\cdot}Et_2O$. Moreover, simple *anti* diastereoselectivity could be reversed to *syn* by simply doubling the amount of $SnCl_4$, as shown in Scheme 48 with racemic aldehyde **123**.

An analogous stereodefined route to polysubstituted tetrahydropyrans **122** was based on a multicomponent condensation strategy. The α-carbamoyloxy allyl titanium complex **124** reacted with an aldehyde to give the enol carbamate **125**, which then was forced to react with a second aldehyde under Lewis acid conditions to give **122** (Scheme 49).[69] Sakurai reactions **125** → **122** and **121** → **122** (Scheme 47) were suggested to occur intramolecularly via a transient oxonium ion **126** derived from the aldehyde and the hydroxyl functionality of **125**.

Scheme 50



Scheme 51



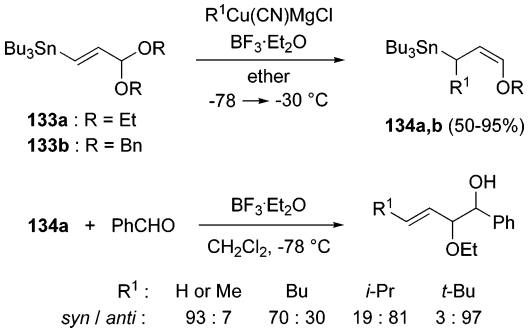
In the search for bisorganometallic species to be applied in multistep multicomponent processes, two bistannylated propenyl ethers were designed and their reactivities were properly checked. Double addition of the higher order cuprate $[Bu_3Sn(Bu)Cu(CN)Li_2]$ to propynal diethyl acetal, to propynoic acid methyl ester, or to malonic aldehyde sodium salt, followed by *O*-silylation, afforded the *gem*-bistannylated propenyl ether **127** in variable yields.[70] In the presence of $BF_3{\cdot}Et_2O$, **127** added to aldehydes, including conjugated enals and ynals, to give *syn* adducts **128** in moderate to excellent diastereomeric ratios (Scheme 50). The vinyl−tin bond in **128** looks very flexible from a synthetic point of view; it allowed, indeed, tin/halogen exchange reactions as well as palladium-catalyzed cross coupling (Stille or Sonogashira) reactions.[71]

The second bisorganometallic species is the *vic*-bistannylated propenyl ether **130**, prepared from palladium-catalyzed bis-stannylation of 1-alkoxyallene **129** (Scheme 51). Reactions of **130** with prochiral aldehydes were better promoted by $BF_3{\cdot}Et_2O$, while the bidentate $MgBr_2{\cdot}Et_2O$ was the Lewis acid of choice when chiral α-oxygenated aldehydes (e.g., **131**) were involved; with the latter promoter, the reaction likely proceeded via the chelated TS **132**, responsible for the *anti* diastereoselectivity observed (Scheme 51).[72]

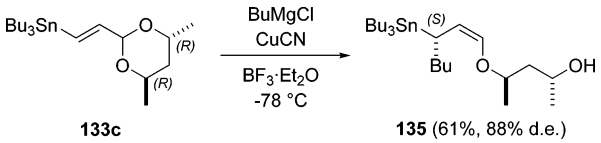
A general route to α-substituted γ-alkoxyallyl stannanes *Z*-**134** was demonstrated by Quintard and co-workers;[73] it was based on the S_N2' reaction of a lower order magnesium cyanocuprate combined with $BF_3{\cdot}Et_2O$, with the readily available vinyl stannanes *E*-**133**.[74] As usual, condensation with aldehydes was promoted by $BF_3{\cdot}Et_2O$, but simple diastereoselectivity was heavily affected by the steric demand of the R^1 substituent. While the double bond *E* configuration was always maintained, simple diastereoselectivity progressively shifted from *syn* when R^1 = H or Me to *anti* when R^1 = *t*-Bu (Scheme 52).[73,75] The same authors reported the addition of **134b** to *R*- or *S*-cyclohexylidene glyceraldehyde followed by ozonolysis of the carbon−carbon double bond, thus opening a route to aldopentoses.[76]

When cyanocuprates were added to chiral **133c**, enantiomerically enriched stannanes (e.g. **135)** were obtained (Scheme 53).[73.]

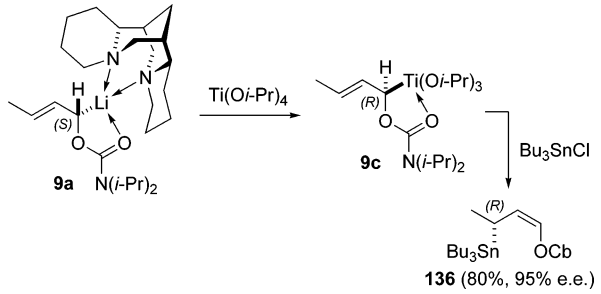
Scheme 52



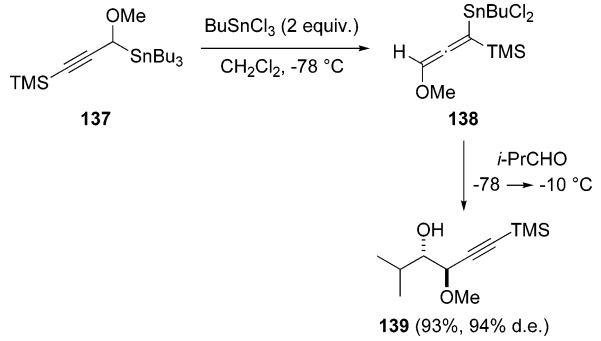
Scheme 53



Scheme 54



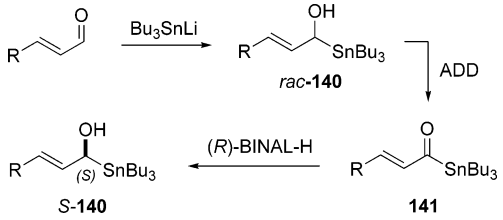
Scheme 55



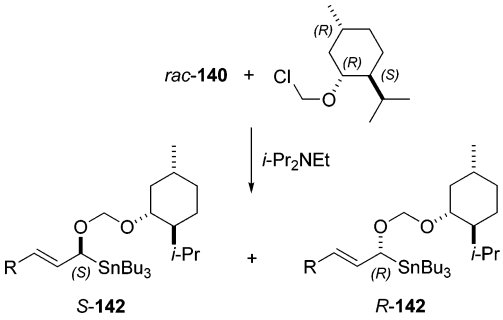
An alternative route to enantiomerically enriched α-substituted γ-alkoxyallyl stannanes **136** was based on Hoppe chemistry and exploited a sequence analogous to the conversion of **118** into **120** (Scheme 47). The chiral lithiated crotyl carbamate **9a** (Figure 1), generated by preferential crystallization from an interconverting mixture of diastereomeric sparteine complexes, was first transmetalated with $Ti(Oi\text{-}Pr)_4$ to give **9c** with inversion at the metal-substituted stereocenter; then it was stannylated with Bu_3SnCl. Titanium/tin exchange took place according to an *anti*-S_E' mechanism to give *Z*-configured **136** with clean 1,3-chirality transfer (Scheme 54).

Tin/tin exchange reactions following a S_E' mechanism are common processes in crotyl stannane chemistry.[77] An example reported by Roush showed the isomerization of the α-alkoxypropargyl stannane **137** into allenyl stannane **138** and the subsequent addition to aldehydes to give *anti*-propargylic diol derivative **139** (Scheme 55).[78] In this case, the more acidic $SnBuCl_2$ group favors the adoption of a cyclic TS, which accounts for the *anti* diastereoselectivity observed.

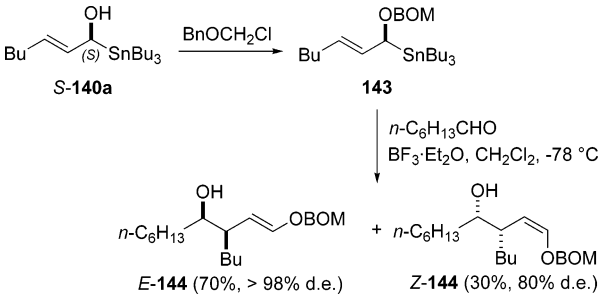
Scheme 56



Scheme 57



Scheme 58



A relevant contribution to the chemistry of α-substituted γ-alkoxyallyl stannanes came from the Marshall group with the preparation of enantiopure tin complexes: literature prior to 1996 was reviewed by the author, and readers are directed to this article.[79]

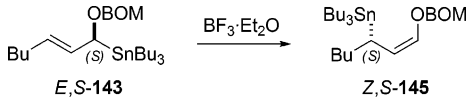
The Marshall route to chiral nonracemic α-substituted γ-alkoxyallyl stannanes exploited as starting materials *rac*-α-hydroxyallyl stannanes **140**, generated by 1,2-nucleophilic addition of Bu_3SnLi to α,β-unsaturated aldehydes. ADD (azodicarbonyldipiperidine) oxidation of **140** to acyl stannane **141** followed by enantioselective carbonyl reduction led to enantiomerically enriched **140**; for instance, 95% ee was obtained with Noyori's BINAL-H (Scheme 56).[80]

Alternatively, *rac*-**140** were chromatographically resolved after derivatization into diastereomeric acetals, for example **142**, as shown in Scheme 57.

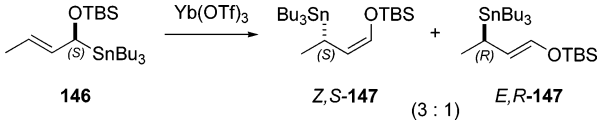
Lewis-acid-promoted condensation of protected **143** with aldehydes afforded enantioenriched enol ether derivatives **144** via the usual allylic inversion (S_E2' reaction). An example is shown in Scheme 58.[79]

In the absence of an electrophile, on the other hand, the interaction of $BF_3{\cdot}Et_2O$ or other mild Lewis acids (TBSOTf, Bu_3SnOTf, $LiClO_4$) with enantioenriched *E*,*S*-**143** brought about the stereospecific isomerization to α-substituted γ-alkoxyallyl stannanes *Z*,*S*-**145**. The process was irreversible and proceeded with allylic and configurational inversion (Scheme 59). Stronger Lewis acids lead to the decomposition of starting stannanes.[80a]

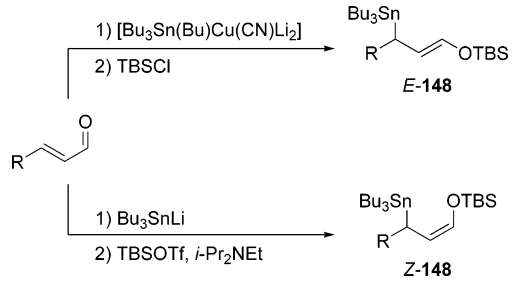
Scheme 59



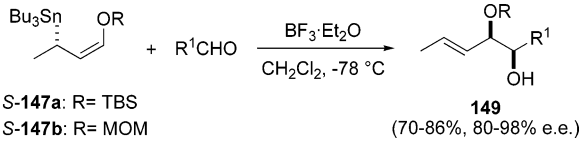
Scheme 60



Scheme 61



Scheme 62



Interestingly, when the same isomerization was catalyzed by lanthanide triflates, particularly $Yb(OTf)_3$, thermodynamic control led to a mixture of *E* and *Z* stannanes. The last reaction has been applied to the isomerization of *E*,*S*-**146** into a thermodynamically equilibrated mixture of *Z*,*S*-**147** and *E*,*R*-**147** in a 3:1 ratio (Scheme 60).[81]

α,β-Unsaturated aldehydes are useful precursors of both *E*- and *Z*-3-siloxyallyl stannanes **148**, as shown in Scheme 61.

Thus, α-substituted allyl stannanes *E*-**148** were generated in racemic form from 1,4-addition of the higher order cuprate $[Bu_3Sn(Bu)Cu(CN)Li_2]$ to the α,β-enal, followed by trapping of the intermediate enolate with TBSCl.[82] Conversely, 1,2-addition of Bu_3SnLi to the same enal, followed by tandem silylation/1,3-rearrangement upon treatment with TBSOTf (see Schemes 59), led to *rac*-*Z*-**148**.

γ-Alkoxyallyl stannanes *R*- or *S*-**147** displayed good to excellent *syn* selectivity when reacted with prochiral aldehydes in the presence of Lewis acids, for example $BF_3 \cdot Et_2O$.[82,83]

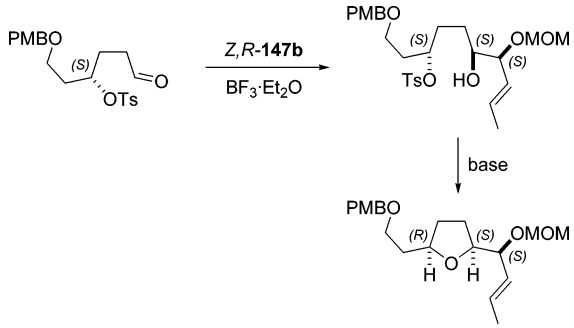
An example is offered by *Z*,*S*-**147** in Scheme 62, where adducts *E*-**149** were obtained in high ee's.

Marshall's review collected a number of examples where the foregoing γ-alkoxyallyl stannanes, and particularly **147**, were reacted with enantiopure α-alkoxy and α-amino aldehydes, opening useful synthetic routes to carbohydrates and related structures.[79]

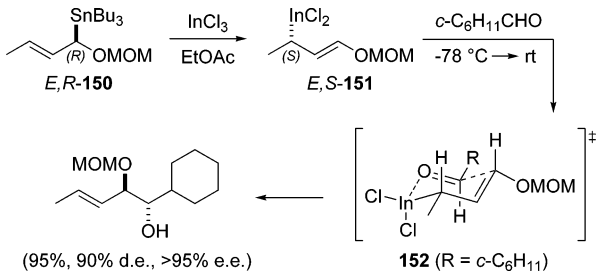
A recent application of *Z*,*R*-**147b** is presented in a synthesis of the C6−C21 segment of Amphidinolide E, isolated from marine dinoflagellates. The diastereo- and enantioselective hydroxyallylation step is shown in Scheme 63, as well as the formation of an enantioenriched 2,5-disubstituted tetrahydrofuran.[84]

The same authors devised a simple solution for the synthesis of *anti*-diols starting from α-alkoxyallyl stannanes.

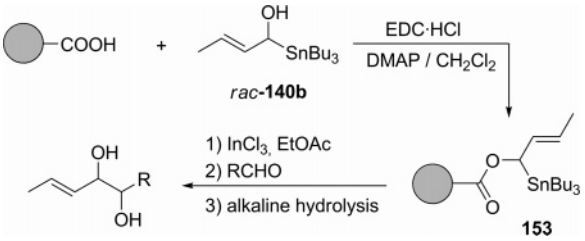
Scheme 63



Scheme 64



Scheme 65

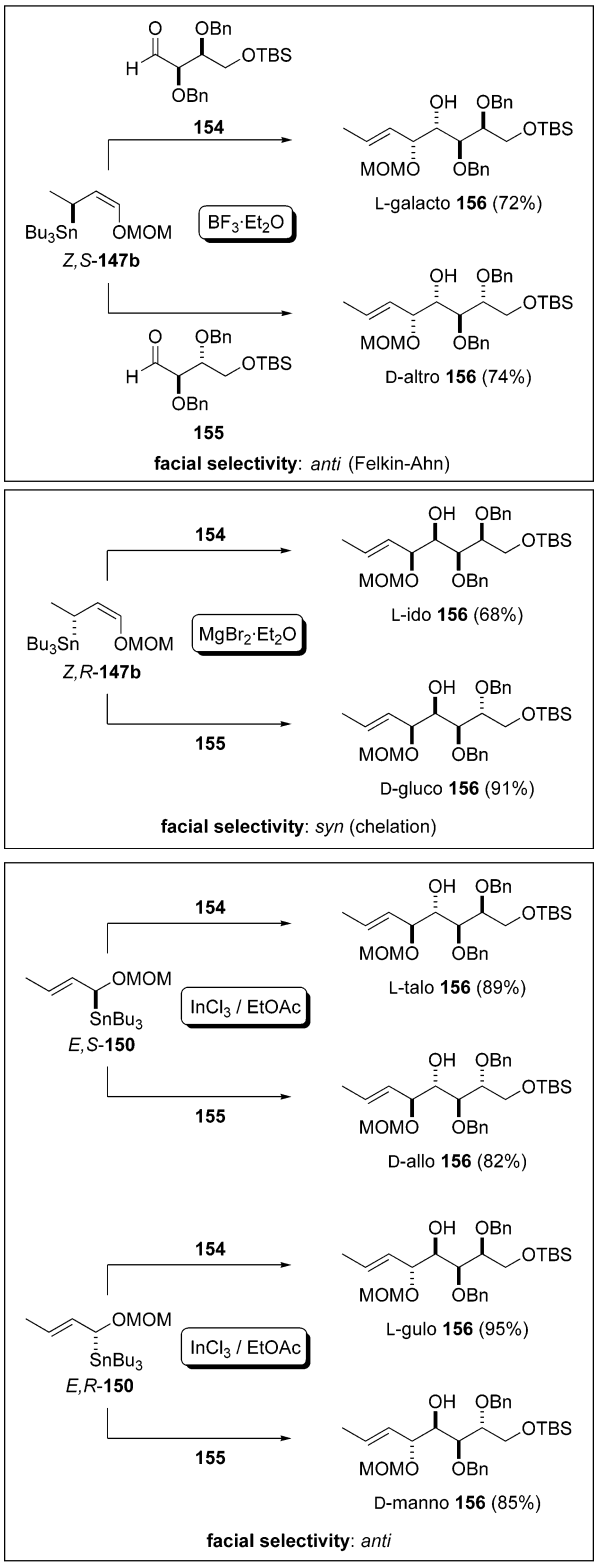


When *E*,*R*-**150** was treated with an aldehyde in the presence of $InCl_3$, an apparent transmetalation took place (*anti*-S_E' reaction) to give **151**, which then added to the aldehyde to give the *anti*-adduct according to the cyclic TS **152**.[85] Polar solvents (acetone, MeCN, DMF, aq EtOH) showed a benign effect on both reaction rates and stereoselectivity, but the best results were obtained with ethyl acetate (Scheme 64).[86]

The foregoing process, in racemic form, was also adapted for a solid-phase synthesis of 1-ene-3,4-diols **1**. *rac*-α-Hydroxyallyl stannane **140b** (R = Me, Scheme 56) was linked to a carboxylic polystyrene resin using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl) and DMAP in CH_2Cl_2; then the resulting polymer-bound stannane **153** was subjected to the same protocol depicted in Scheme 64, involving a sequential transmetalation reaction with $InCl_3$ followed by treatment with an aldehyde (Scheme 65). Good to excellent yields were obtained, but a new observation, independently confirmed by us, was made about diastereoselectivity: that is, almost pure *anti*-adducts were obtained with saturated aldehydes, while stereoselectivity dropped to almost zero with aromatic and conjugated aldehydes.[87] The mechanistic aspects of these results will be discussed in section 7.1.

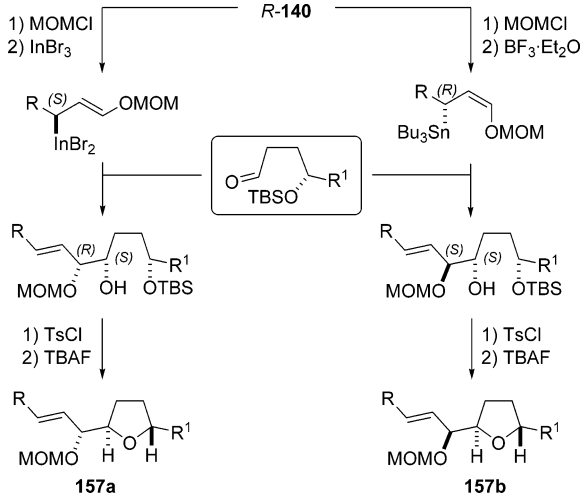
The synthetic potentiality associated with *Z*,*R*- and *Z*,*S*-**147b** or *E*,*R*- and *E*,*S*-**150** is fully exhibited in the synthesis of differentially protected precursors of aldohexoses **156** (Scheme 66). Enantiopure stannanes **147** were reacted with protected threose **154** and erythrose **155** in the presence of $BF_3 \cdot Et_2O$ (Felkin−Ahn model) or $MgBr_2 \cdot Et_2O$ (chelation

Scheme 66



control, see examples collected in Figure 3), while **150** were reacted in the presence of $InCl_3$.[86] Even in the cases of mismatched pairs, the diastereofacial preference of the chiral stannane prevailed and dictated the stereochemical course of the hydroxyallylation reaction. Thus, chiral stannanes **147** represent an example of the reagent-control strategy to stereocontrol, since by a proper choice of the chiral stannane/Lewis acid pair the diastereofacial preference of the chiral aldehyde can be overridden.

Scheme 67



An elegant regio- and stereoselective conversion of optically pure α-hydroxyallyl stannanes **140** (see Schemes 57 and 58) into either chiral γ-alkoxyallyl indium compounds ($InBr_3$) or chiral γ-alkoxyallyl stannanes (BF_3•Et_2O) was also exploited in two stereoselective syntheses of nonracemic 2,5-disubstituted tetrahydrofurans **157**, as shown in Scheme 67.[88]

Striving for a convergent synthesis of Annonaceous acetogenins, in particular of Asiminocin (**158**), Marshall disconnected the target molecule in four fragments **A**−**D**, shown in Figure 4. Each fragment was translated into a

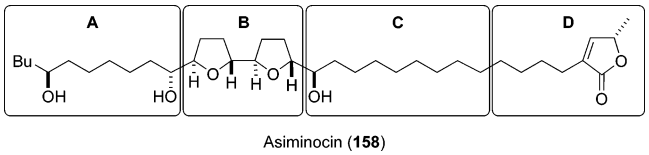
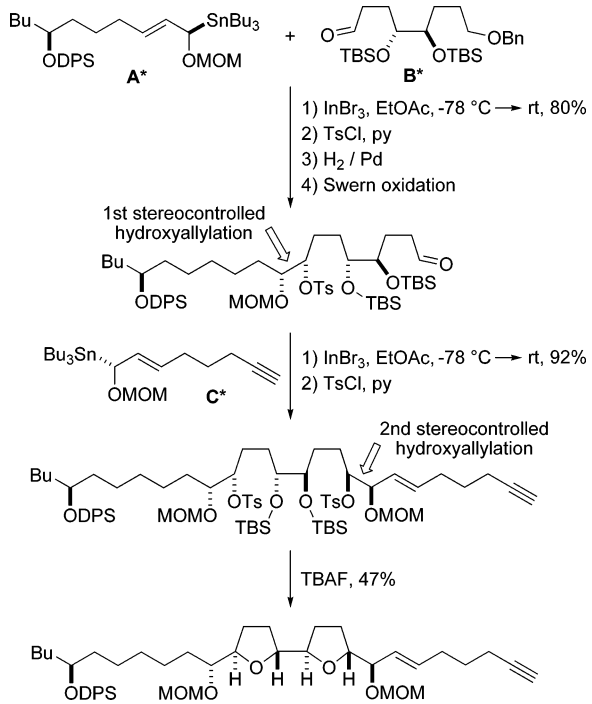
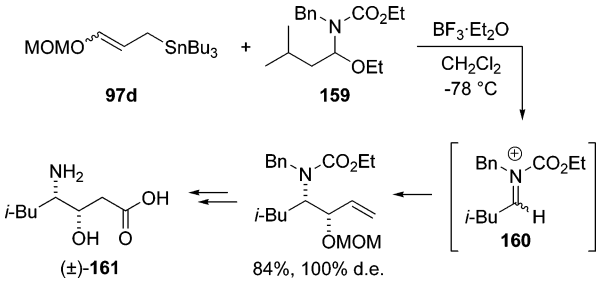


Figure 4. Asiminocin disassembling in Marshall convergent synthesis.

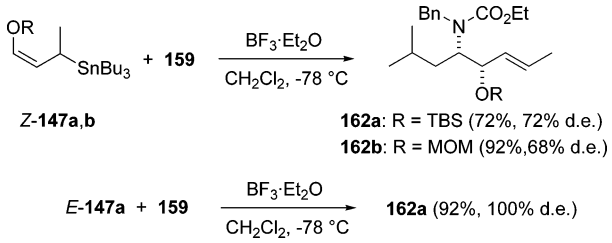
Scheme 68



Scheme 69



Scheme 70



properly designed synthetic equivalent **A***−**D***. The coupling of **B*** with **A*** and **C*** is reported in Scheme 68.[89]

Synthon **B***, which will supply the carbon atoms to be incorporated in the bistetrahydrofuran core structure **B** in Figure 4, was connected to **A*** and **C*** by two separate steps by exploiting the foregoing hydroxyallylation methodology. At last, the terminal alkyne functionality in synthon **C*** ensured an efficient completion of the synthesis of the target acetogenin skeleton through a Sonogashira coupling with a vinyl iodide incorporating the butenolide terminus of **158**.

4.3. α-Alkoxyallyl Stannylation of Azomethine Derivatives

The Lewis-acid-promoted addition of an *E*/*Z* mixture of MOM-protected **97d** (see Scheme 38) to α-ethoxy carbamates **159**, *in situ* precursors of *N*-acyliminium ions **160**, has been reported by Yamamoto to produce *syn*-aminoalcohols with good to quantitative de's. An application to the synthesis of the precursor for the synthesis of (±)-statine **161** is shown in Scheme 69.[90]

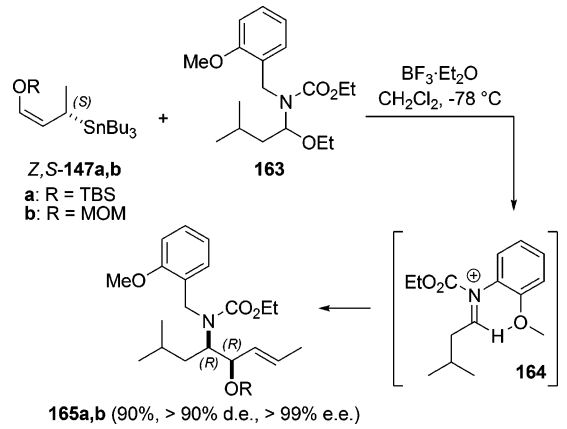
The reaction of α-ethoxy carbamate **159** with *E*- and *Z*-**147a**,**b** in the presence of BF_3·Et_2O was also reported.[91] Results collected in Scheme 70 confirmed that (i) two isomeric stannanes stereoconverged to the *syn* adducts **162** and (ii) a remarkably higher diastereoselectivity was demonstrated by γ-*E*-silyloxy allylic stannane compared to the *Z* isomer.[81]

When both *Z*,*S*-**147a** and *Z*,*S*-**147b** were reacted with *N*-*ortho*-methoxybenzyl **163**, enantiopure *syn*-**165** was obtained in very high yield (Scheme 71).[91b] The chelated structure of the intermediate electrophile **164** (CH−O bond) ensured the high level of stereocontrol.

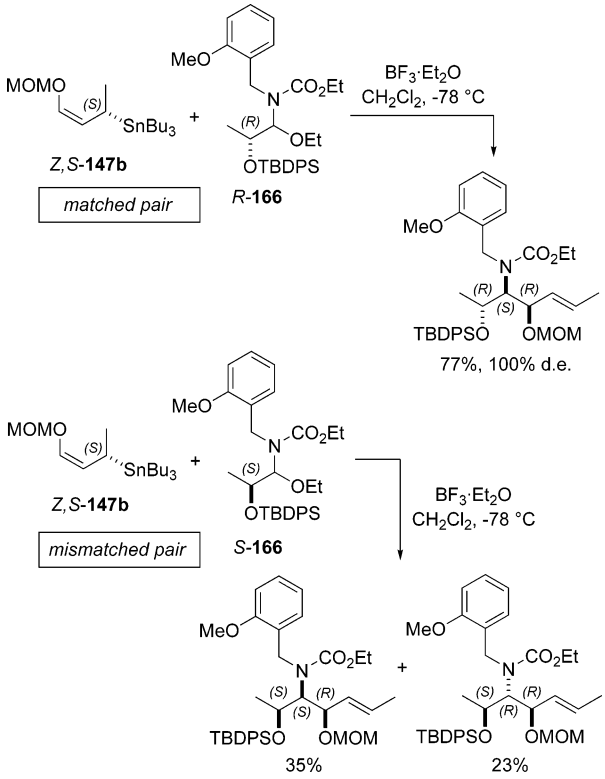
The utility of nonracemic γ-alkoxyallyl stannanes (e.g., *Z*,*S*-**147a**) was confirmed by the reaction with enantiopure α-ethoxy carbamate **166** derived from *R*- and *S*-lactaldehyde (Scheme 72).[91]

The α-alkoxyallylation of azomethine derivatives by means of γ-alkoxyallyl stannanes has also been investigated in the intramolecular version. Thus, hydrazones **167**, when treated with Lewis acids, were stereoselectively cyclized to *trans*-tetrahydropyrans **169** via acyclic synclinal TS **168** (Scheme 73). Among a series of Lewis acids and Brönsted

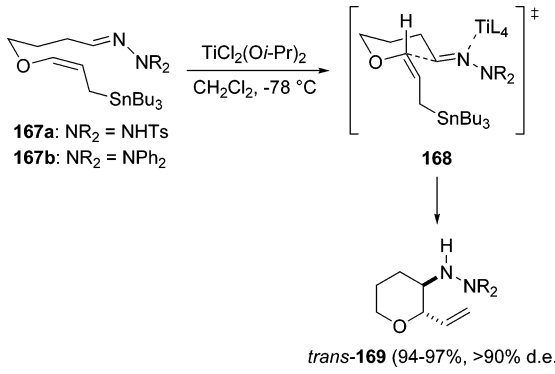
Scheme 71



Scheme 72



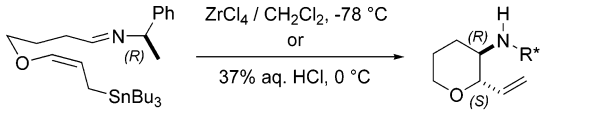
Scheme 73



acids tested, $TiCl_2$(*i*-PrO)$_2$ furnished **169** in virtually quantitative yield within 5 min at −78 °C.[92]

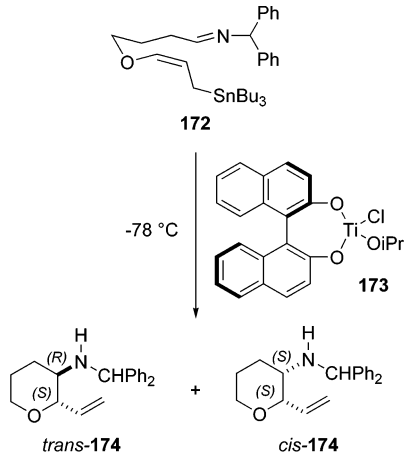
Exploiting the chiral auxiliary approach, chiral imine **170**, derived from (*R*)-1-phenylethylamine, was treated with Lewis acids or protic acids. The two cyclization promoters showed

Scheme 74



170 *trans*-**171** (95%, 92% d.e.)

Scheme 75



172 **173** *trans*-**174** *cis*-**174**

173 (equiv) :	2	0.5	1	1
Solvent :	CH_2Cl_2	CH_2Cl_2	toluene	THF
trans-**174** (Y, e.e.) :	20%, 53%	27%, 41%	17%, 62%	8%, 15%
cis-**174** (Y, e.e.) :	61%, 82%	60%, 64%	53%, 62%	65%, 44%

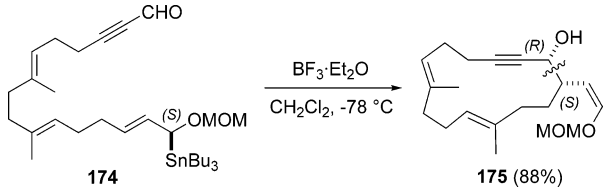
in Scheme 74 afforded a virtually quantitative yield of *trans*-**171**.[92a,93]

Finally, cyclization of the achiral imine **172** by means of the Tagliavini chiral titanium−BINOL catalyst **173**[94] has been investigated. Tetrahydropyrans **174** were obtained in different de's and ee's, depending on the solvent and catalyst loading (Scheme 75).[92a]

4.4. Intramolecular α-Alkoxyallyl Stannylation Reactions

In the late 1980s the intramolecular version of the alkoxyallyl stannylation reaction was proposed by Marshall as a promising macrocyclization technique. He used the BF_3·Et_2O-promoted cyclization of α-alkoxyallylstannylated ynal **174** to construct the 14-membered ring of the cembranoid precursor **175**. The valuable features of the Marshall procedure were that (i) regioselectivity was perfectly ensured by the S_E' mechanism, affording in this case a homoaldolization reaction, and (ii) complete chirality transfer from the stannylated stereocenter of **174** to the newly formed stereocenters in *cis*-**175** was ensured (Scheme 76).[95]

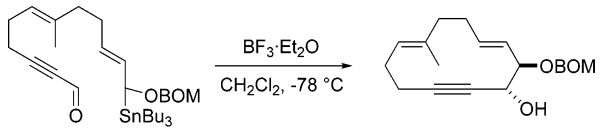
Scheme 76



174 **175** (88%)

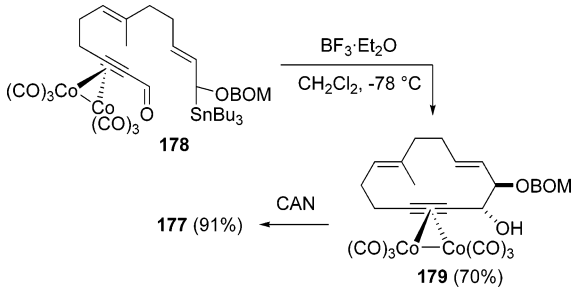
Of course, regio- and stereochemistry are controlled by the conformational biases of the starting open-chain ω-oxostannane. Thus, **176**, subjected to BF_3·Et_2O-promoted cyclization, exhibited opposite regio- (α-alkoxy allylation) and

Scheme 77



176 **177** (25%)

Scheme 78



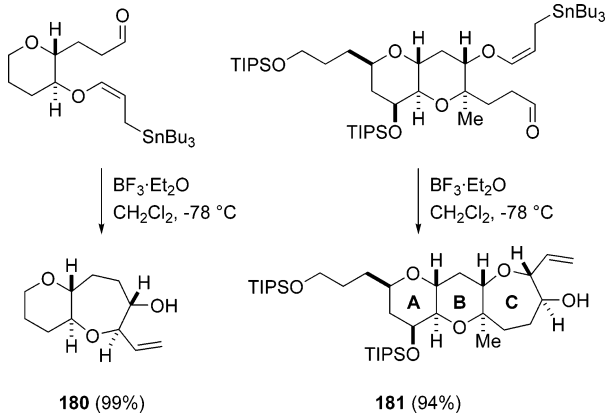
178 **177** (91%) **179** (70%)

diastereochemistry, affording *trans*-**177** in low yield (Scheme 77). Complexation of the triple bond with $Co_2(CO)_8$ was again the solution (see Scheme 32). Dicobalt hexacarbonyl derivative **178** afforded, indeed, **179** in the presence of BF_3·Et_2O in good yield. Having served its purpose of reactivity-controlling device, the dicobalt hexacarbonyl group was oxidatively removed (CAN), delivering **177** in 63% overall yield (Scheme 78).[96]

In the early 1990s, Yamamoto started his adventure in the world of marine toxins possessing an iterated *trans*-fused polycyclic ether frame, for which he developed several synthetic approaches. Here, his strategy based on the intramolecular α-oxyallylation reaction is analyzed.[97]

The first attempts consisted of stereocontrolled cyclizations to *trans*-fused tetrahydrofuro-oxepane systems **180**[98] and **181**,[99] currently found in the skeleton of marine products such as brevetoxin, ciguatoxin, gambierol, and yessotoxin (Scheme 79).

Scheme 79



180 (99%) **181** (94%)

The vinyl substituent on the oxepane **C** ring of **181** was subjected to routine transformations in order to install the 3-pivaloxypropyl side chain of **182**, while the reaction protocol shown in Scheme 44 (conversion of **107** into **108**) was applied to the substrate having a free OH on ring **C** in order to install a γ-alkoxyallyl stannane group. To achieve the latter transformation, the OH was allylated, then lithiated, and finally stannylated with Bu_3SnCl. However, lithiation of the bulky allyl ether was exceedingly slow, and most of the starting material decomposed. After several attempts, a

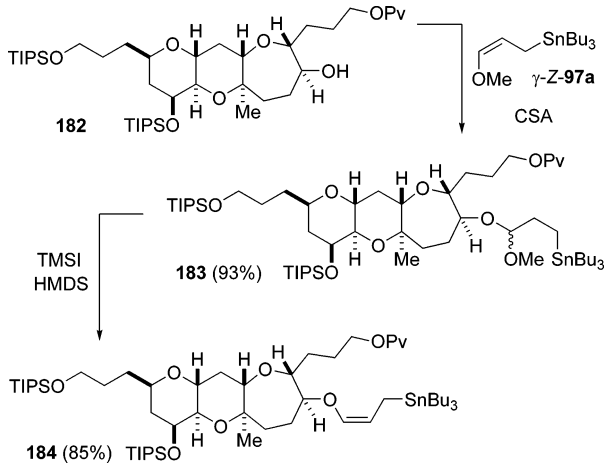
brilliant technique allowing incorporation of the CH═CH−CH_2−$SnBu_3$ unit on a hydroxyl group, was developed (Scheme 80).[99]

Alcohol **182** was treated with γ-*Z*-**97a** (see Scheme 38) in the presence of camphorsulfonic acid (CSA) to give a mixture of diastereomeric acetals **183**, which were successively converted into **184** using TMSI/HMDS, with an overall 85% yield. Oxidation of the pivalate-protected terminus of **184** to a carbonyl group allowed authors to reiterate the standard cyclization and to accomplish the total synthesis of hemibrevetoxin B through a linear approach based on a sequential use of intramolecular α-oxystannylation reactions.[99]

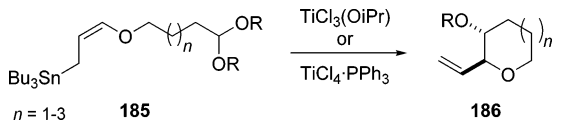
Tetrahydropyrans, analogous to the ones synthesized in Schemes 27−29 with the aid of γ-alkoxyallyl boron derivatives, were also obtained through the intramolecular reaction of γ-alkoxyallyl stannanes **185**, carrying an ω-acetal functional group (Scheme 81). In the presence of titanium salts, cyclic ethers **186** were accessible in good yield and in moderate to good *trans*-stereoselectivity, depending on the ring size and on the acetal structure (open chain or cyclic).[100]

As an example, the reaction of **187**, derived from (*R*,*R*)-2,4-pentadiol, furnished *trans*-substituted tetrahydrofuran **188** in appreciable enantiopurity (Scheme 82).[101]

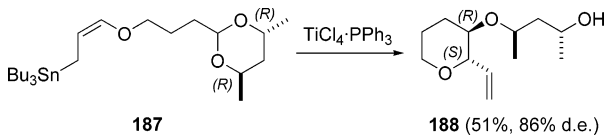
Scheme 80



Scheme 81

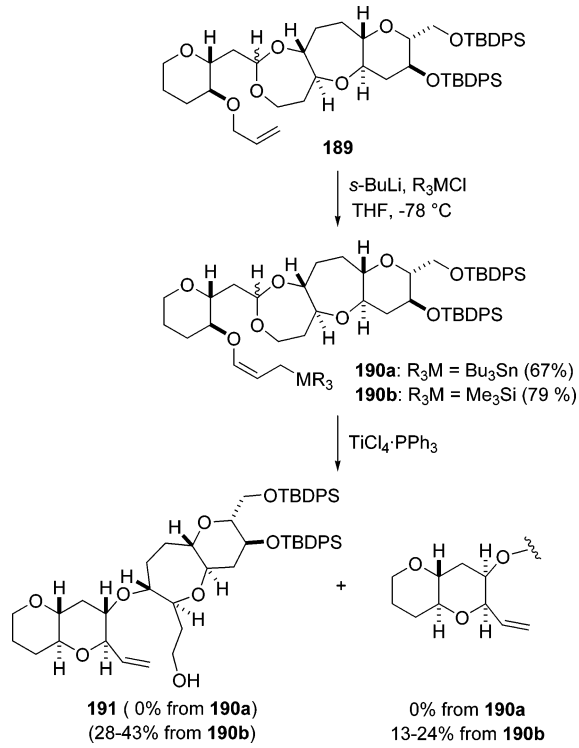


Scheme 82



On the basis of these results, Sasaki and Tachibana planned a convergent synthesis of ciguatoxin where the key step involved the cyclization of **190** to **191**. However, this synthetic plan encountered two critical steps: (i) the lithiation/transmetalation procedure to convert **189** into **190**, and (ii) the cyclization step itself. Since the latter step, indeed, did not work at all with stannane **190a**, authors shifted their attention to allyl silane **190b**, which afforded the desired

Scheme 83



product in moderate yield and modest diastereoselectivity (Scheme 83).[102]

The problems encountered in the cyclization of molecules containing a cyclic acetal functionality inspired Yamamoto to test an alternative convergent approach to polyether marine toxins. Besides the outstanding contributions recently reviewed by Yamamoto,[97] a partial synthesis of yessotoxin[103] and a total synthesis of brevetoxin B[104] (structure **192** and **193**, respectively, in Figure 5) are here discussed..

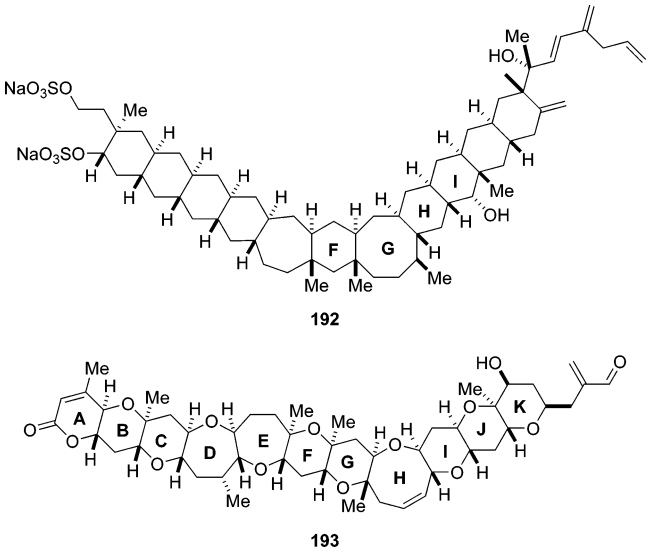
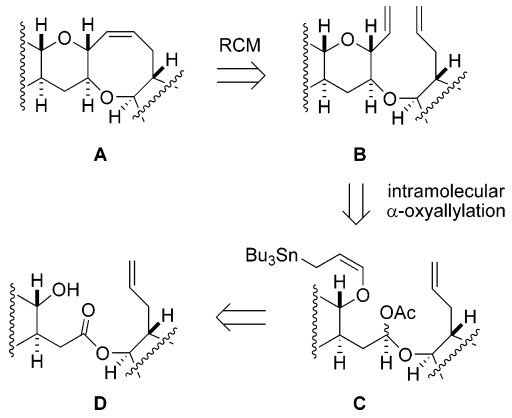


Figure 5. Structure of yessotoxin (**192**) and brevetoxin B (**193**).

The strategy for the synthesis of fused oxepane or oxocane ring systems (for example, see the GH domain of brevetoxin B) is outlined retrosynthetically in Scheme 84.

An important initial design clue for a reliable avenue toward framework **A** was provided by RCM, which ensured in the synthetic direction an efficient construction of the 8-membered ring. In assessing a promising retrosyn-

Scheme 84



thetic transformation to apply to **B**, authors focused their attention on the intramolecular oxyallylation methodology. This goal was admirably met by **C** as substrate for the $MgBr_2$-promoted cyclization step. In **C** the intramolecular oxyallylation step was made more efficient by using an α-acetoxy ether as the electrophilic terminus, which was much more reactive than the cyclic acetal terminus shown in Scheme 83.

Once **C** was identified as a valuable intermediate, the next hurdles were (i) how to affix the $OCH{=}CH{-}CH_2{-}SnBu_3$ group and (ii) how to generate the desired α-acetoxy ether functionality.

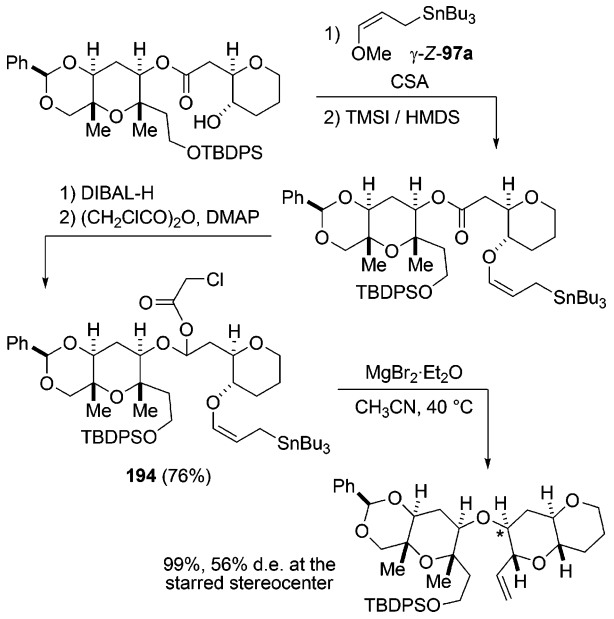
A route was developed to affix the allyl stannane moiety to a free hydroxyl group, via a CSA-catalyzed *trans* enol etherification reaction of **D** with *γ*-*Z*-**97a**. A mixed acetal was formed which, upon treatment with TMSI/HMDS, underwent elimination of methanol to give the corresponding *Z*-3-alkoxy-substituted allyl stannane moiety.[97] To achieve the second goal, namely the introduction of the α-acetoxy ether, an ester group was forecasted to be an effective precursor. In the synthetic direction, indeed, DIBAL-H reduction in CH_2Cl_2 at −90 °C followed by acetylation (Ac_2O, py, DMAP) at the same temperature, according to Dahanukar and Rychnovsky,[105] allowed the authors to accomplish the synthesis of intermediate **C** starting from **D**. The best applications of the above-mentioned strategy described up to 2004 are reviewed in ref 97.

The intramolecular oxyallylation in **194** took place quantitatively using $MgBr_2$ under new reaction conditions developed for the partial synthesis of yessotoxin, using acetonitrile at 40 °C (Scheme 85).[103]

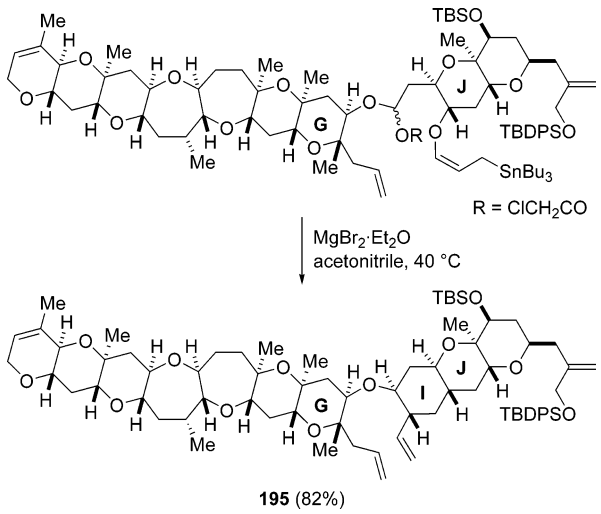
In the synthesis of brevetoxin B, although the architectural skeleton of the intermediate subjected to internal oxyallylation is quite daunting, the cyclization reaction was carried out under the same experimental conditions quoted in Scheme 85, and adduct **195** was obtained in high yield as a single stereoisomer (Scheme 86).[104] With **195** in hand, the only remaining task was the construction of the oxocane ring system. For this purpose, it was anticipated that RCM would be an effective choice, and indeed RCM enabled the arrival at the target toxin.

In this same study, a modification of the electrophilic acetal terminus was proposed, if an intermediate reluctant to internal oxyallylation was encountered. An *O*,*S*-acetal provided the solution. Cyclization of **196** to **197** was, indeed, effectively promoted by silver triflate. The reaction protocol followed to construct the *O*,*S*-acetal in **196** is shown in Scheme 87.[104]

Scheme 85



Scheme 86



5. Allyl Complexes Carrying a 3-Silyl or Boryl Substituent as a Hydroxyl Surrogate

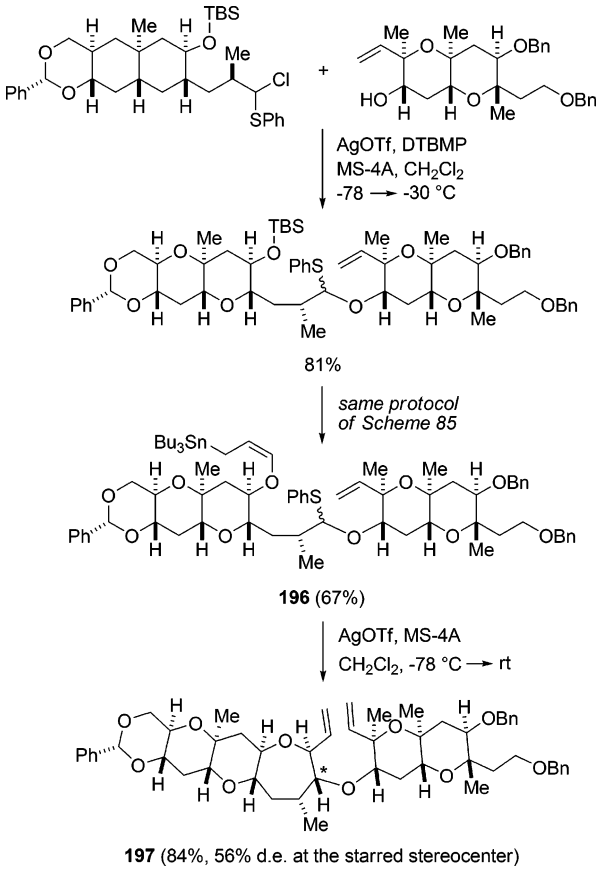
Allyltrimethylsilane underwent metalation by *s*-BuLi/TMEDA to give an allyllithium complex for which the η^3 *syn* structure **198** was assigned on the basis of NMR studies in solution[106] and the *E* configuration of products was derived from trapping experiments with electrophiles (Scheme 88).[107]

For example, using oxazolidines[108] or carbonyl compounds[109] as electrophiles, *γ*-addition products **199** and **200** were regio- and stereoselectively formed (Scheme 89).

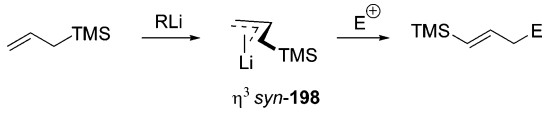
On the other hand, it was demonstrated in the early 1980s that *anti* α-adducts **202** were obtained when treating **198** with Et_3Al,[110] $B(OMe)_3$,[111] and Cp_2TiCl,[112] prior to the reaction with aldehydes (Scheme 90). The reactions proceeded via formation of *γ*-*E*-(trimethylsilyl)allyl aluminum, boron, or titanium complexes **201a**−**c**, which then added to the carbonyl compound through a cyclic TS (type A reactivity, section 1.2).

The interest in adducts **202**, precursors of dienes via Peterson elimination, greatly increased when the easy oxida-

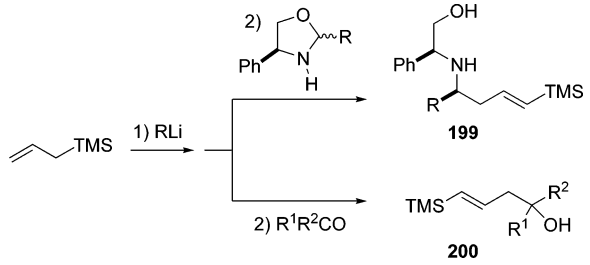
Scheme 87



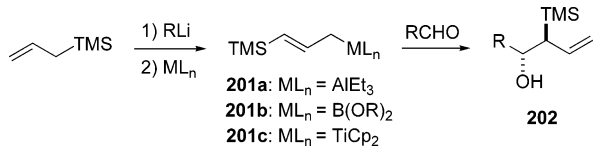
Scheme 88



Scheme 89

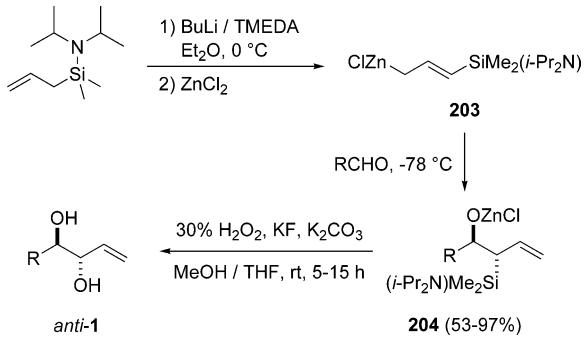


Scheme 90



tion of the C−Si bond of silanes containing a hydride, halogen, amino, or alkoxy group on silicon by means of H_2O_2 in the presence of fluoride ions was reported by Tamao.[113] An analogous oxidation of silanes containing an allyl or aryl group on silicon by means of a peracid or H_2O_2 was also developed by Fleming; with these substrates an acidic protodesilylation (removal of the allyl or aryl group) was followed by oxidative cleavage.[114] In all the oxidative desilylation protocols proposed by Tamao and Fleming, replacement of silicon with OH occurred with retention of

Scheme 91



configuration at the silylated carbon. Thus, allyl organometallic species carrying a suitable allyl substituent were targeted as promising reagents for the stereoselective synthesis of *anti*-enediols **1**.

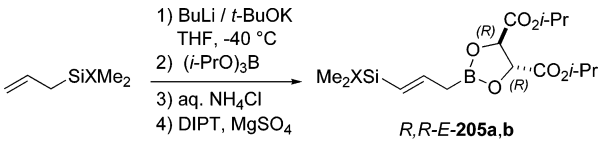
Tamao and co-workers proposed the 3-silylallyl zinc complex **203** for the diastereocontrolled synthesis of *anti* enediols **1**. The overall process is presented in Scheme 91. The presence of the bulky N(*i*-Pr)$_2$ group, besides ensuring the stereoretentive oxidation of the C−Si bond to C−OH, prevented the occurrence of Peterson olefination in the intermediate β-alkoxysilane **204**.[115]

5.1. 3-Silylallyl Boronates and Boranes

In this section, the most widely used systems, namely allyl boranes and boronates carrying a silylated group on the γ-position, are examined.

The higher stability of η^3 *syn*-silylallyl lithium complexes **198** compared to their η^3 *anti*-isomers, joined to their tendency to undergo transmetalation at the less hindered terminus of the allylic moiety, inspired Roush to develop an enantioselective *anti* α-hydroxyallylation protocol of aldehydes based on chiral γ-*E*-silylallyl boronates **205** (Scheme 92). The source of chirality in **205** was an easily available ester of (*R*,*R*)-tartaric acid.[116] As silicon ligands X suitable for the later oxidative desilylation, the cyclohexyloxy (**205a**) and the phenyl groups (**205b**) were envisaged.

Scheme 92

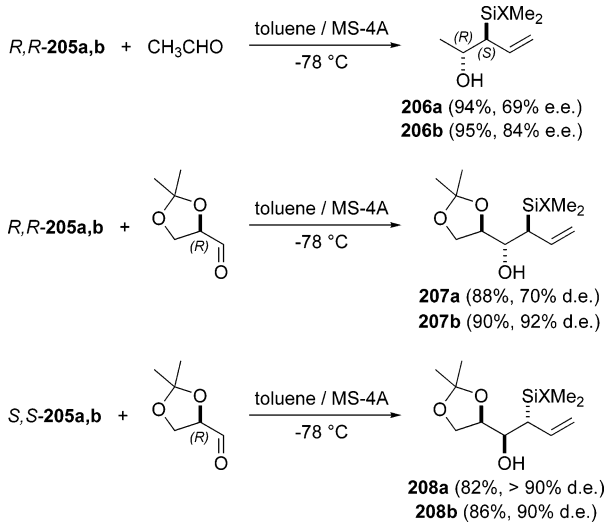


a: X = *c*-C$_6$H$_{11}$O-
b: X = Ph

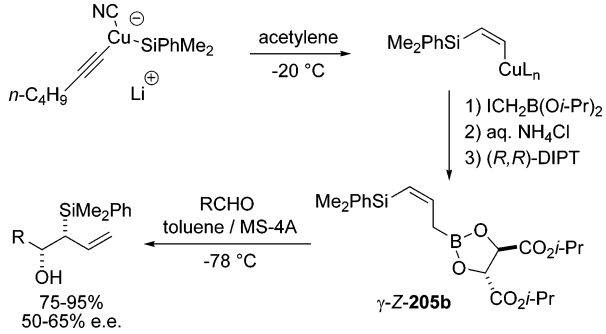
The addition of **205a** and **205b** to simple aliphatic aldehydes or protected glyceraldehyde gave **206**, **207**, or **208** with perfect *anti*-selectivity and acceptable ee's (Scheme 93). The phenyldimethylsilyl group in **205** ensured a higher stereocontrol compared to the cyclohexyloxydimethylsilyl group.

The isomeric γ-*Z*-silylallyl boronate **205b** is also available, exploiting the protocol depicted in Scheme 94. Silylcupration of acetylene was followed by the addition of the intermediate vinylic cuprate to diisopropoxyiodomethyl boronate. Hydrolysis of boronate and esterification with (*R*,*R*)-diisopropyl tartrate (DIPT) provided γ-*Z*-**205b** in good yield. Unfortunately, lower enantiocontrol resulted in the *syn*-addition of γ-*Z*-**205b** to aldehydes (Scheme 94).[117]

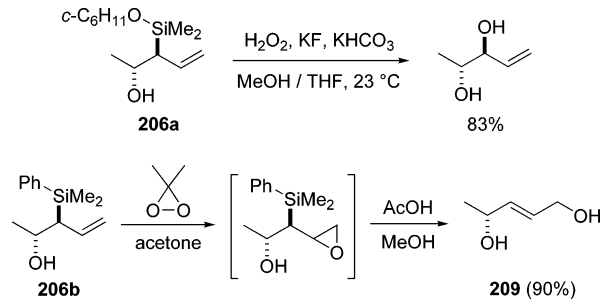
Scheme 93



Scheme 94



Scheme 95

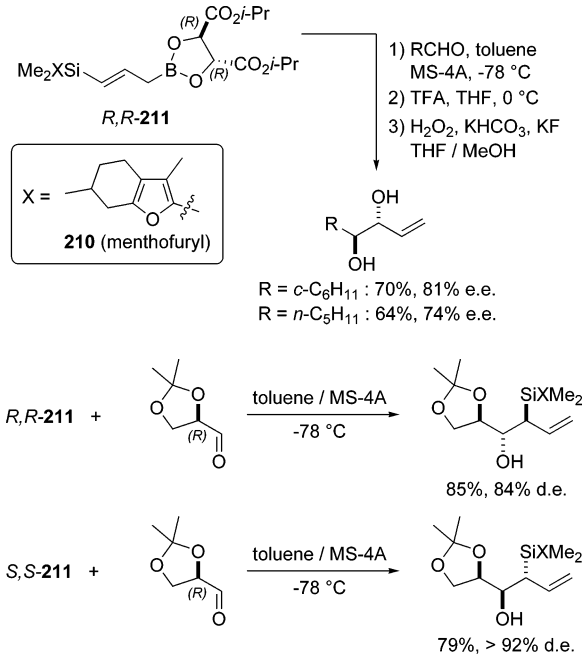


However, while **206**-**208a** could be oxidized under Tamao conditions, the Fleming procedure could not be applied to the phenyldimethylsilyl-substituted substrates **206**−**208b**, since the preliminary acidic protodesilylation is not compatible with its allylic structure (a desilylated homoallylic alcohol was obtained from **206b**).

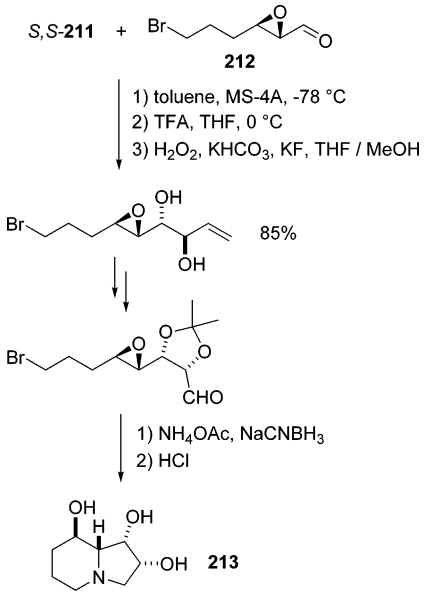
However, while seeking for alternative oxidation conditions, the authors found that treatment of **206b** with dimethyl dioxirane followed by acidic treatment cleanly led to the rearranged 1,4-diols **209** in about 90% yield (Scheme 95).[116]

Thus, efforts were directed by Roush to targeting an aryl substituent for silicon which would be much more reactive than the allylic moiety in **206** toward electrophilic protodesilylation. After screening several aryl groups, attention was directed to a furane derivative, a highly reactive heteroaromatic ring in electrophilic aromatic substitution reactions. Eventually, furyl ligand **210** (the menthofuryl ligand) was identified as one of the best solutions, since it underwent a fast protodesilylation under mild acidic conditions (CF_3COOH in THF at 0 °C, Scheme 96).[118]

Scheme 96



Scheme 97

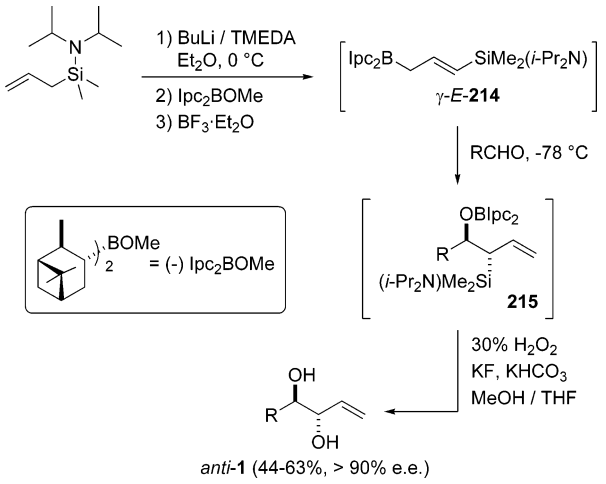


The mildness of the whole α-hydroxyallylation procedure developed with **211** made the use of the very sensitive epoxyaldehyde **212** possible, in a total synthesis of (−)-swainsonine **213** (Scheme 97).[118]

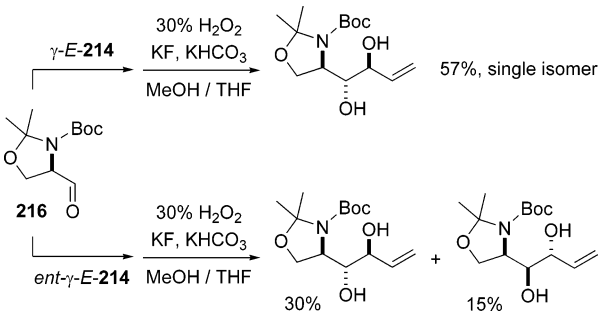
Boranes are the obvious alternatives to boronates. Barrett and Malecha proposed in the early 1990s optically active 3-silylallyl boranes **214** as fully *anti* diastereoselective and highly enantioselective α-hydroxyallylating agents for carbonyl compounds.[119]

The preparation of **214** is an extension of the Brown methodology used for chiral allyl, crotyl, and 3-alkoxy-substituted allyl boranes, which involves lithiation of an allylsilane followed by quenching with Ipc_2BOMe (Scheme 98). The allyl boron complex *γ-E*-**214** was not isolated and was directly reacted with an aldehyde to give *anti*-**215**. Subsequent oxidative quenching under Tamao conditions left

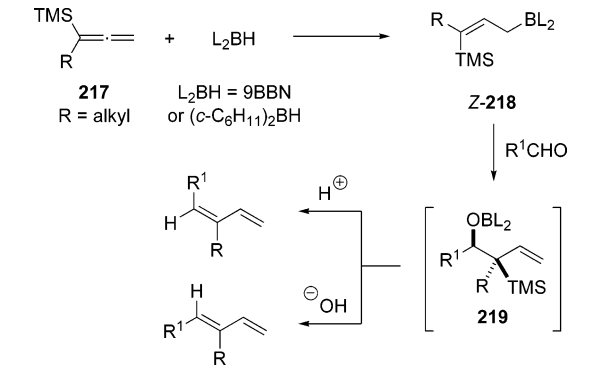
Scheme 98



Scheme 99



Scheme 100

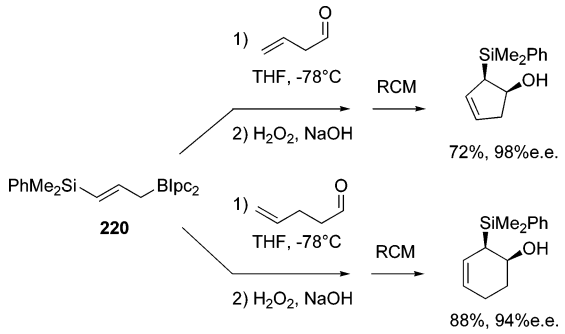


the desired *anti* diol **1** in acceptable overall yields. Thus, γ-*E*-**214** played the role of the *anti* selective reaction that complements the *syn* selective reaction with γ-*Z*-**78** (Scheme 31). The results obtained from the matched and mismatched pairs in the reaction of (*R*)-Garner aldehyde[120] **216** with the two antipodes **214** derived from (−) and (+)-pinene show that substrate control is here in action (Scheme 99).

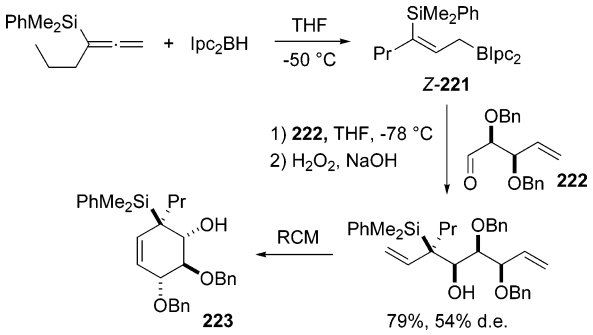
Z-3-Alkyl-3-silylallyl boranes **218** were prepared by Gu and Wang by an alternative procedure, consisting of the hydroboration of the allenylsilane **217** with a secondary borane (Scheme 100).[121] Adduct **219**, formed in good to high diastereoselectivity (up to 98% ee), was used as a precursor of *Z*- or *E*-dienes via acidic (H_2SO_4, *anti* elimination) or alkaline (NaOH, *syn* elimination) treatment. NMR evidence on the fluxional behavior of **218** was also obtained, which accounted for the dependence of diastereoselectivity on reaction time and temperature.

A comparative study of the performances of γ-*E*-(dimethylphenylsilyl)allyl $BIpc_2$ **220** and its analogous γ-*E*-(dimethylphenylsilyl)allyl boronate **205b** (see Scheme 92) allowed Roush to verify the superior performance of the diisopinocampheylboranyl group[122] compared to the tartrate derived 1,3-dioxa-2-borolanyl group in terms of enantioface-discriminating ability.[123]

Scheme 101



Scheme 102

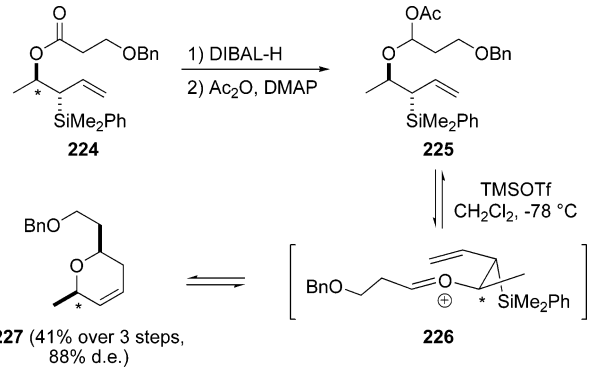


In a further study from the same group, the enantioenriched adducts coming from the addition of *E*-**220** to both β,γ- and γ,δ-unsaturated aldehydes were subjected to RCM, leading to a diastereo- and enantioselective synthesis of 5- and 6-membered cyclic β-hydroxyallyl silanes (Scheme 101).[124]

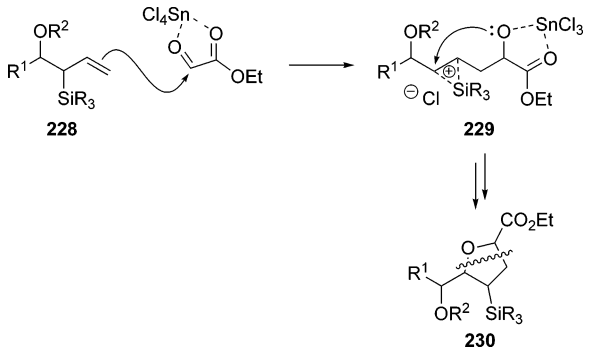
The same allylation/RCM sequence was applied to *Z*-**221** (obtained by hydroboration of an allenyl silane with Ipc_2BH according to the procedure previously shown in Scheme 100) and the chiral aldehyde **222**, leading to the formation of the cyclitol precursor **223** (Scheme 102).[124]

Up to now, chiral β-hydroxyallyl silanes have been discussed as precursors of enediols **1**, but their synthetic potentialities exceed this application. It is well-known, indeed, that allylic silanes may participate in Lewis-acid-promoted reactions with electrophiles, for example in the Sakurai additions to carbonyl compounds.[125] Roush sought to develop an intramolecular version of the Sakurai reaction by preassociating the carbonyl compound to the β-hydroxyallyl silane via an acetal linkage. The α-acetoxy ether functionality was forecasted as an effective version of the acetal functionality. Thus, **225** was readily assessed in just a few operations from a β-hydroxyallyl silane by acylation with the proper acyl chloride, reduction of the ester group of the intermediate **224** with DIBAL-H, and acetylation of the resulting hemiacetal *in situ* with acetic anhydride/DMAP according to the procedure developed by Rychnovsky (Scheme 103).[126] Treatment of **225** with TMSOTf resulted in a key domino sequence involving formation of the oxonium intermediate **226** followed by the [3,3]-oxonia-Cope rearrangement, which led to the *cis* 2,6-disubstituted dihydropyrans **227**, presumably via a boatlike transition state (Scheme 103).[127] The configurational integrity of the starred stereocenter was preserved in the whole process.

Scheme 103



Scheme 104

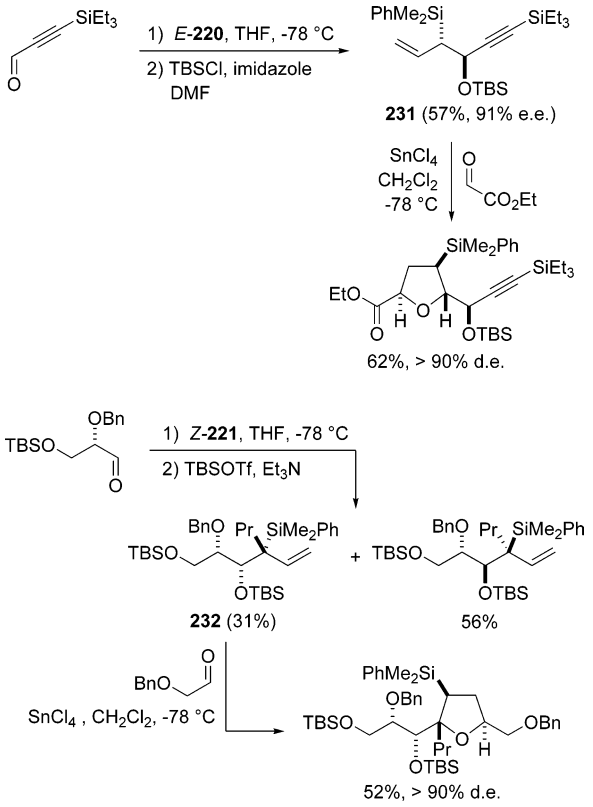


When an *O*-protected *β*-hydroxyallyl silane **228** was reacted with glyoxylate ester (or glycolate ester) in the presence of a chelating Lewis acid, the allylation step was followed by a spontaneous *5-endo-tet* heterocyclization on the nonclassical silylium ion **229** (Scheme 104). The result of the formal [3+2] annulation process was cycloadduct **230**.[125]

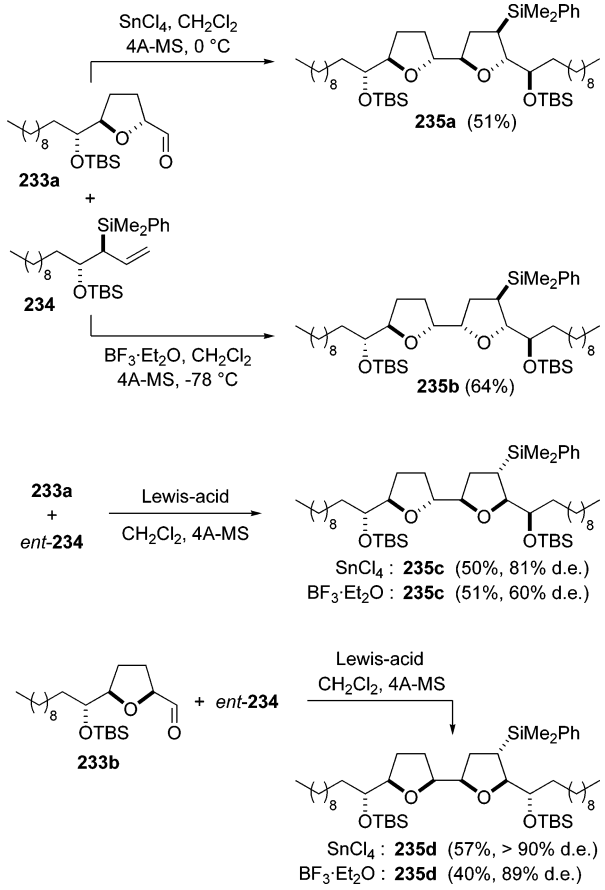
When an optically active adduct such as **231** was used, excellent levels of diastereocontrol were achieved according to a chelation-controlled model of asymmetric induction. Scheme 105 shows two successful applications of analogous [3+2] annulations applied to **231** and **232**, as key steps in two formal syntheses of amphidinolide F[128] and of angelmicin B,[129] respectively.

The versatility of the previous [3+2] annulation protocol was demonstrated in a stereocontrolled synthesis of bis-tetrahydrofuran structures **235a**−**d**, the core subunits of members of the Annonaceous acetogenins family. The double asymmetric reaction between chiral 2-tetrahydrofuranyl carboxaldehydes **233a,b** and chiral allyl silane **234** led to bis-tetrahydrofurans with a stereochemistry governed not only by the two chiral reaction partners but also by the choice of the Lewis acid. For example, the reaction of **233a** with **234** provided 2,5-*trans*-substituted tetrahydrofuran **235a** using $SnCl_4$, via a chelation-controlled model of asymmetric induction. On the other hand, in the presence of $BF_3{\cdot}Et_2O$, 2,5-*cis*-**235b** was generated via a nonchelated TS (Scheme 106).[130] Conversely, the reaction of **233a** with *ent*-**234**, as well as the reaction of **233b** with *ent*-**234**, converged to the same isomers **235c** and **235d**, irrespective of whether $SnCl_4$ or $BF_3{\cdot}Et_2O$ was used.

Scheme 105



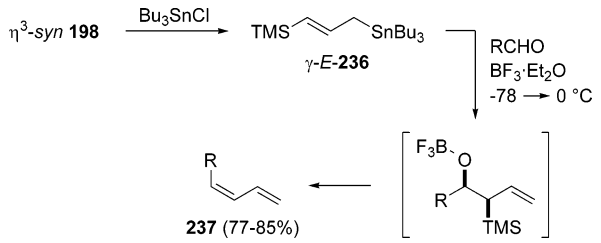
Scheme 106



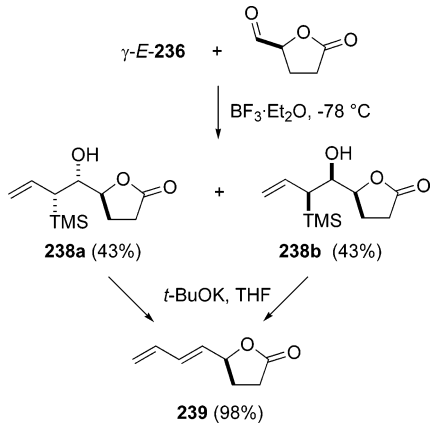
5.2. 3-Silylallyl Stannanes

Despite the fact that 3-trimethylsilylallyl tributylstannane *γ*-*E*-**236** was first reported in 1985, it did not receive the same attention compared to its 3-alkoxylated analogue *γ*-*Z*-**97** (Scheme 38). Even though the $BF_3{\cdot}Et_2O$-promoted addition of *γ*-*E*-**236** to benzaldehyde and *n*-decanal afforded

Scheme 107



Scheme 108



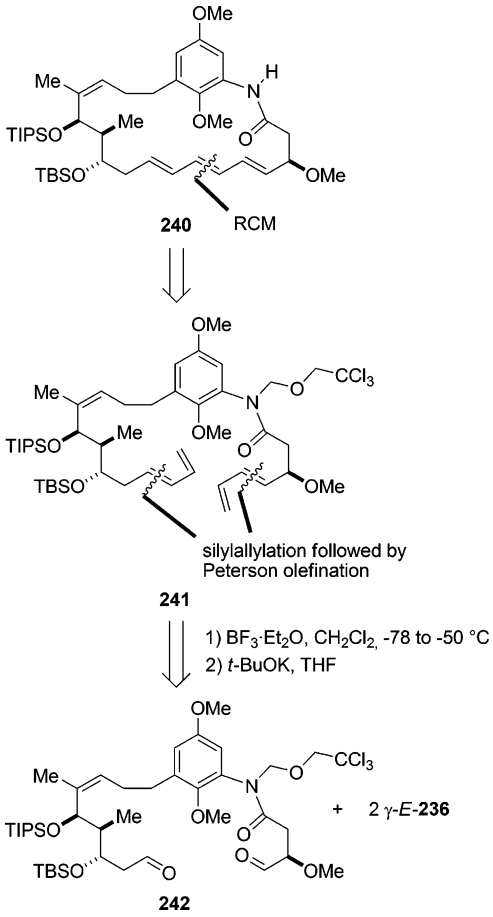
syn-adducts, as anticipated by the Type C reactivity model (section 1.2), the difficult isolation of *syn*-adducts, which in the presence of $BF_3 \cdot Et_2O$ easily undergo acid-catalyzed *anti*-elimination to monosubstituted *Z*-dienes **237**, hampered more extensive studies (Scheme 107).[131]

Later on, Keck and Romer[132] demonstrated, and Roush and co-workers confirmed,[117] that it was sufficient to quench the preceding reaction with $NaHCO_3$ at −78 °C, in order to isolate *syn* adducts in good yields. For example, **238a** and **238b** were isolated as a 1:1 mixture and then converted into *E*-diene **239** upon treatment with *t*-BuOK (*syn* Peterson elimination). The *E*-diene **239** was an intermediate in a synthesis of indolizidine alkaloids (Scheme 108).[132]

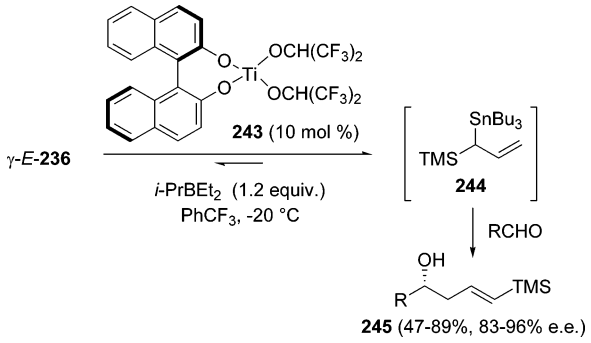
The synthetic efficiency of the preceding olefination reaction leading to monosubstituted *E*-dienes was recently exploited by Panek and co-workers. From a retrosynthetic standpoint, the triene group of the macrocyclic core of cytotrienins **240** was disassembled into bis *E*-diene **241**, since in the forward direction it was anticipated that the construction of the central C═C bond of the conjugated triene moiety of **240** could be achieved through a reliable RCM reaction. The challenging structure of bis *E*-diene **241** suggested the use of a double α-silyloxyallylation reaction on dialdehyde **242**. The anticipated bidirectional bis silyloxyallylation/elimination sequence afforded **241** in 61% yield, after treatment of **242** with 2 equiv of γ-*E*-**236**, followed by *t*-BuOK-induced *syn*-elimination (Scheme 109).[133]

The regioselectivity of the reaction of γ-*E*-**236** with prochiral aldehydes was reversed, as reported by Yu and co-workers, when the BINOL−Ti(IV) complex **243** was used as Lewis acid in combination with *i*-$PrBEt_2$, a crucial coactivator whose precise role was not determined. To unravel the unexpected formation of **245** in high ee's, the authors claimed that it derived from a fluxional conversion of γ-*E*-**236** into the isomeric α-trimethylsilylallyl tributylstannane **244**, which then added to the aldehyde according to the usual S_E' mechanism (Scheme 110).[134]

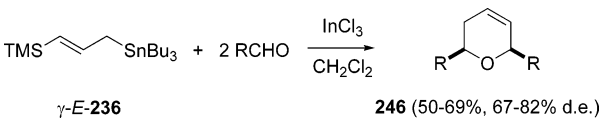
Scheme 109



Scheme 110



Scheme 111

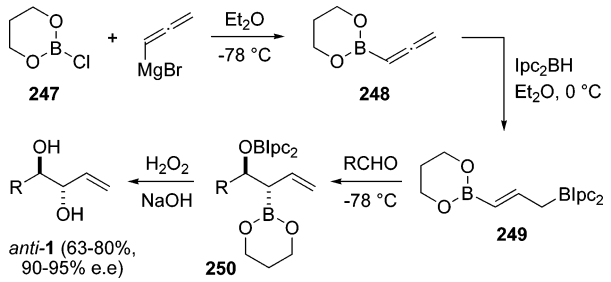


The bifunctional nature of γ-*E*-**236** as allylating agent was exploited by Li and co-workers in a synthesis of 2,6-disubstituted *cis*-dihydropyrans **246.** The reaction was carried out by simply treating 2 equiv of an aliphatic aldehyde and γ-*E*-**236** with a catalytic amount of $InCl_3$. The reaction did not work with aromatic aldehydes (Scheme 111).[135] For a comparison, see Scheme 103.

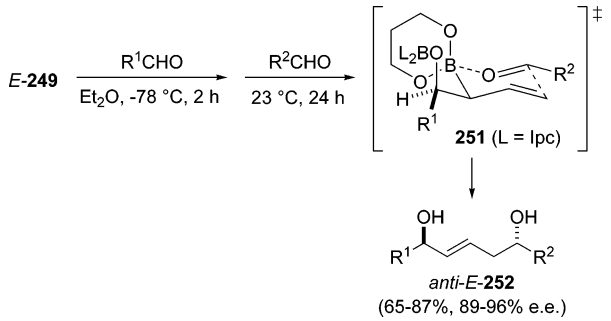
5.3. 3-Borylallyl Boranes

An obvious surrogate of the hydroxyl group is represented by the boron atom. The exceptional reliability of boron

Scheme 112

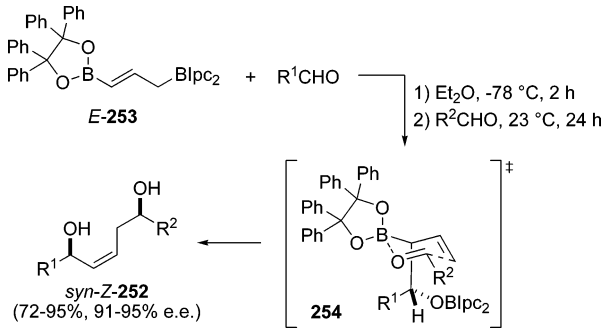


Scheme 113



chemistry was exploited by Brown and Narla in the preparation of the bifunctional diboron derivative *E*-**249**. Nucleophilic attack to **247** by allenyl magnesium bromide followed by a regio- and stereoselective hydroboration of allenylboronate **248** with Ipc_2BH provided *E*-**249**. The latter bifunctional boron derivative added to aliphatic and aromatic aldehydes with an exceptionally high *anti*-diastereocontrol and with excellent enantiomeric excesses. The resulting intermediates **250** were oxidized by alkaline H_2O_2 with

Scheme 114



retention of configuration at the stereogenic borylated carbon (Scheme 112). From the hydroboration of **247** to the oxidation of **250**, all the reactions were carried out in a one-pot fashion, by successively adding the appropriate reagent to the reaction mixture.[136]

The potentiality of *E*-**249** as a difunctional allylating agent was envisaged by Roush, who developed two efficient three-component condensation protocols leading either to *E* or *Z* bis-adducts **252**. In the opening event, *E*-**249** was reacted with the first aldehyde at −78 °C for 2 h; then the second aldehyde was added and the mixture was warmed to room temperature and stirred for 24 h. The different reaction conditions of the two addition steps reflect the different reactivities of allyl boranes compared to allyl boronates. A plausible TS model for the last reaction is represented by the chairlike structure **251**, which would ensure an efficient 1,3-chirality transfer and a perfect control of the *anti* 1,5-stereorelationship in diol **252** (Scheme 113).[137]

Guided by the inspection of the TS architecture, Roush envisioned that the CHR^1BOIpc_2 substituent in TS **251** could

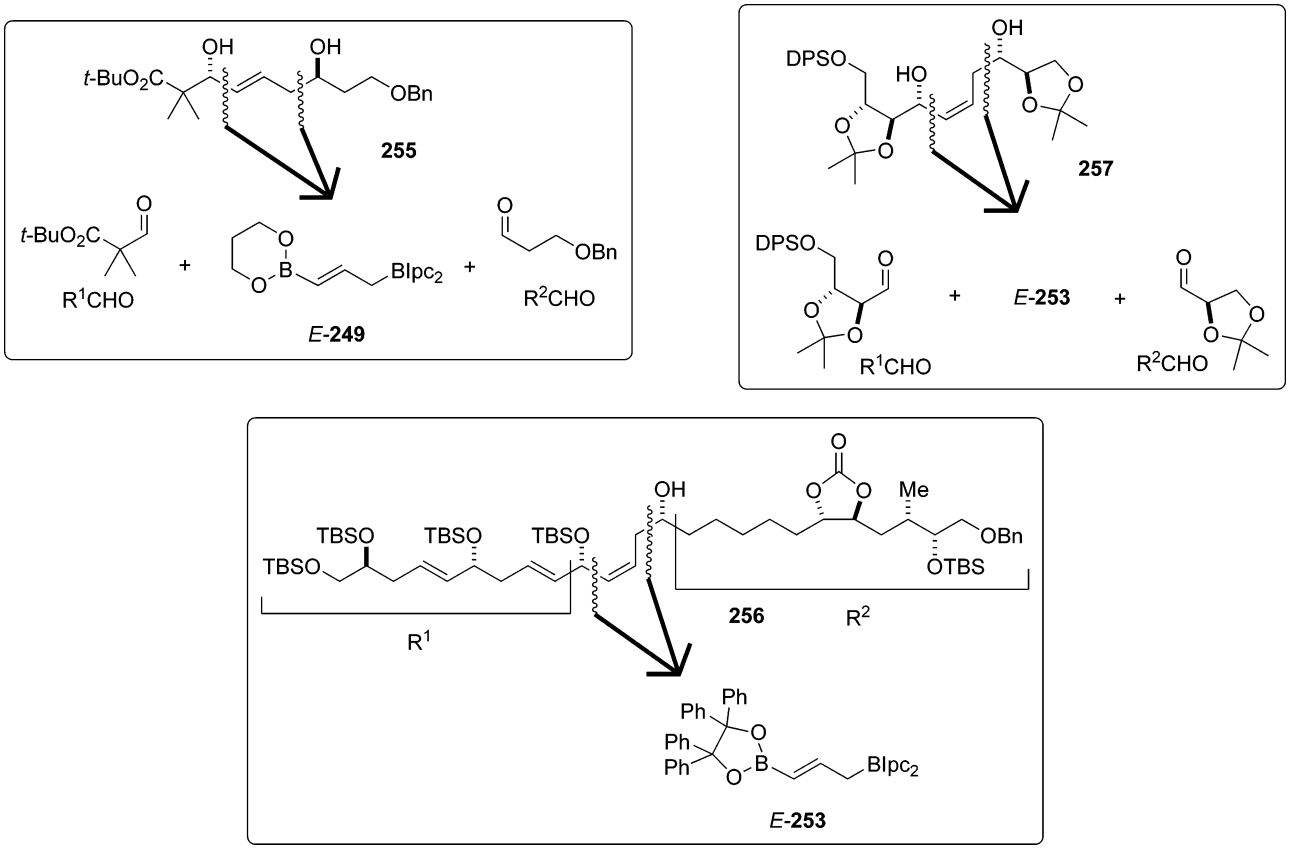


Figure 6. Roush retrosynthetic disassembling of *anti*-*E*- and *syn*-*Z*-2-en-1,5-diols.

be forced to adopt an axial orientation if a more sterically congested boronate moiety was used. Replacement of *E*-**249** with *E*-**253** led to the formation of *syn*-*Z*-diol **252** in excellent chemical and stereochemical yields (Scheme 114). As correctly anticipated, the stereochemical outcome could be rationalized in terms of TS **254**.[137]

That Schemes 113 and 114 represent two robust protocols for the synthesis of *anti*-*E*-**252** and *syn*-*Z*-**252**, respectively, was recently demonstrated by Roush and co-workers, who applied them in crucial steps of formal syntheses of peloruside A[138] and of amphidinol 3.[139,140] Figure 6 shows how three key synthetic intermediates, namely **255**, **256**, and **257**, were retrosynthetically disassembled, with the central three-carbon allylic unit being provided by either 3-borylallyl boranes *E*-**249** or *E*-**253**.

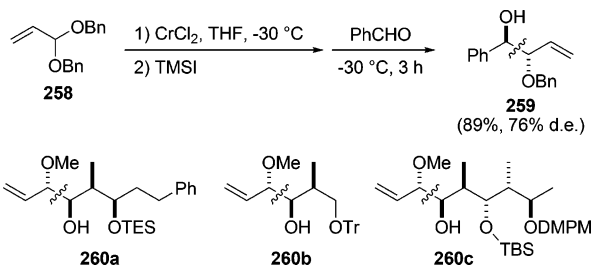
6. 3-Alkoxyallyl Chromium and Zirconium Complexes

Most of the allylic complexes bearing a heterosubstituent on the γ position examined so far share a common protocol for their preparation, based on the lithiation of a suitable allyl derivative (ether, silane, etc) followed by transmetalation with a proper metal salt. The chromium and zirconium complexes described in this section, conversely, require an oxidative addition process for the construction of the required C−Cr or C−Zr bond. The new preparative protocol entails the identification of proper precursors of the 3-alkoxyallyl ligand, in order to promote a facile insertion of the low valent metal species into a suitable carbon−leaving group bond.

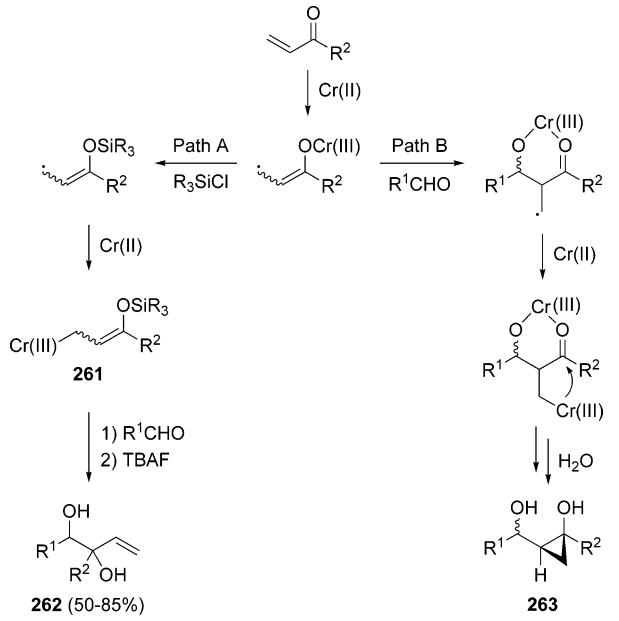
6.1. 3-Alkoxyallyl Chromium Complexes

Reduction of alkyl halides with 2 equiv of a one-electron reductant chromium(II) species generates organochromium(III) compounds, which add to aldehydes to give the corresponding alcohols. The reaction, known as the Nozaki−Hiyama−Kishi (NHK) reaction, has proven to be a powerful C−C bond-forming methodology by virtue of its high chemo- and stereoselectivity and mild reaction conditions.[141] Takai and Utimoto applied Cr(II) chemistry to acrolein acetals, e.g., dibenzylacetal **258**, in the presence of TMSI.[142a] Addition of an aldehyde to the reaction mixture at −30 °C resulted in the formation of *anti*-diol derivatives **259** in excellent yield and good de's, as shown in Scheme 115. The accelerating effect of TMSI was ascribed to the *in situ* formation of an α-iodo ether, which was much more prone than **258** to undergo the insertion of Cr(II). The authors accounted for the observed *anti* stereochemistry by suggesting the formation of a γ-*Z*-alkoxyallylchromium species and the adoption of a boatlike TS geometry.[141] The *anti*-selectivity, in our opinion, could also be ascribed to a rapid fluxional equilibrium between α- and γ-alkoxyallylchromium complexes which favors the formation of the γ-*E*-complex.

Scheme 115



Scheme 116



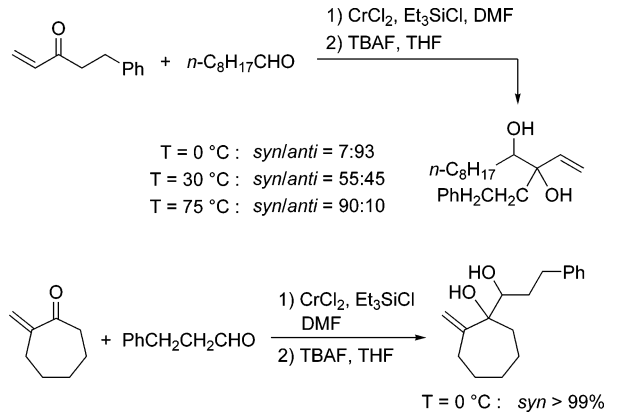
The subsequent addition of the γ-*E*-complex to the aldehyde should occur according to Type B reactivity (section 1.2). The Takai-Utimoto reaction was applied in three syntheses of polyketides where acrolein dimethylacetal was coupled to chiral aldehydes: structure **260a** was an intermediate in a synthesis of bafilomycin V_1,[142b] **260b**[142c] and **260c**[142d] were intermediates in two syntheses of bafilomycin A_1 (Scheme 115).

α,β-Unsaturated ketones can be directly reduced by Cr(II) salts in the presence of R_3SiCl to give γ-silyloxyallylchromium complexes **261**, which add to aldehydes to give *syn*/*anti* mixtures of diols **262**, according to reaction path A (Scheme 116). On the other hand, the same reduction carried out in the absence of R_3SiCl furnishes cyclopropyl carbinols **263** via path B.[143] From a mechanistic point of view, path A corresponds to a pinacol cross-coupling between an α,β-unsaturated ketone and an aliphatic aldehyde. The weak point of this procedure is given by the use of 8 equiv of $CrCl_2$ and 6 equiv of R_3SiCl with respect to the aldehyde.

The *syn*/*anti* ratio of adducts **262** was dramatically influenced by temperature (first equation in Scheme 117). When the *E*-configuration of **261** was blocked as in the case of the cyclic enone shown in the second equation of Scheme 117, the *syn* adduct was the sole product.[143]

With ever-increasing pressure from green chemistry issues, the use of stoichiometric (or more than stoichiometric)

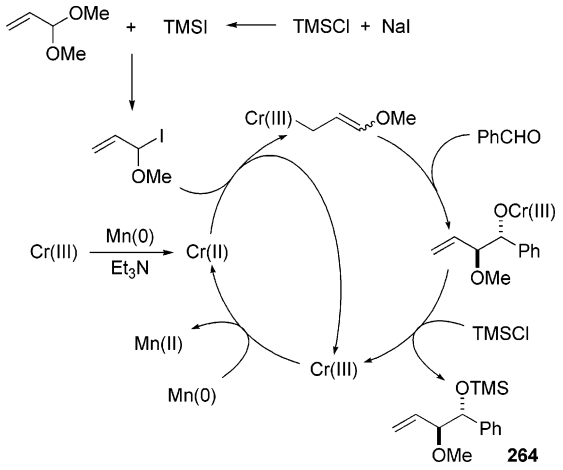
Scheme 117



amounts of chromium, a transition metal classified by the US EPA as one of the priority pollutants,[144] is no longer considered acceptable in large scale production. That is why the original protocols of the NHK reaction and of the Takai−Utimoto hydroxyallylation reaction do not fulfill sustainability criteria. However, an outstanding improvement granted the NHK reaction a new dawn, namely the development of the Fürstner catalytic version of the NHK reaction, where Cr(II) is regenerated by manganese powder in the presence of a silylating agent.[145] A key role in the Fürstner modified catalytic protocol is played by trimethylsilyl chloride. Silylation of the initially formed chromium alkoxide indeed released a Cr(III) halide derivative which was very efficiently reduced to Cr(II) by Mn(0) powder, the stoichiometric nontoxic and cheap reducing agent.

The Fürstner new catalytic version of the NHK reaction was then successfully extended by Boeckman[146] to the Takai−Utimoto reaction. To a stirred mixture of $CrCl_2$ (0.07 equiv), Mn(0) powder (2.5 equiv), and NaI (0.2 equiv) were sequentially added, at −30 °C, 1,1-dimethoxy-2-propene (2.3 equiv), benzaldehyde (1 equiv), and TMSCl (3.2 equiv). After 20 h at −30 °C, acceptable yields (46−93%) of the *anti*-diol derivative **264** were obtained from a set of prochiral and chiral aldehydes, with de's ranging from 60 to 83%. The overall catalytic cycle is depicted in Scheme 118. The

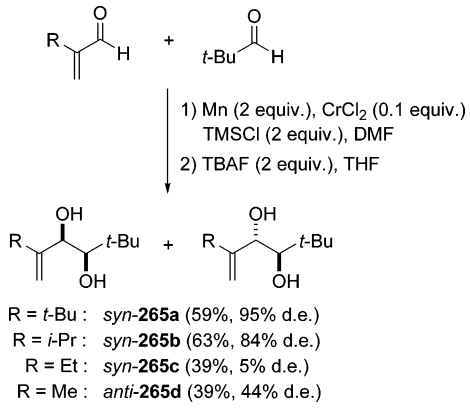
Scheme 118



key to success in this specific application is the addition of catalytic amounts of NaI to the reaction mixture, which likely converts TMSCl into TMSI, thus allowing the transformation of acrolein acetal into an α-iodo ether.

Analogous studies have been presented by Groth and Jung. Addition of an aldehyde (the addition rate must be slow to achieve good results) to a mixture containing an α,β-unsaturated ketone, 10 mol % of $CrCl_2$, an excess of manganese, and TMSCl in DMF delivered adducts **262** in 50−80% yields and good diastereomeric excesses (see Scheme 116).[147] When α-substituted acroleins were used, the diastereoselection depended on the α-substituent structure.[148] Branched α-substituents favored the formation of *syn*-diols **265**, while the opposite diastereopreference was observed with linear α-substituents, as shown in Scheme 119.

Scheme 119

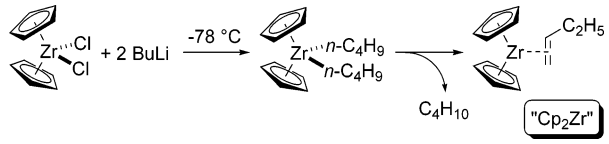


6.2. 3-Alkoxyallyl Zirconium Complexes

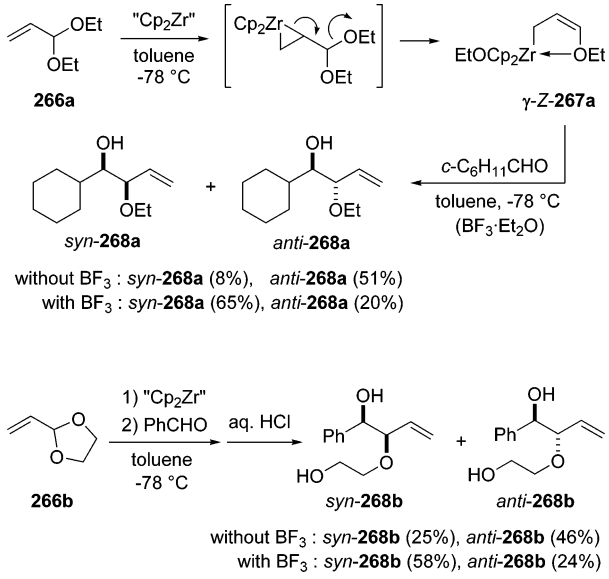
For the last 10 years, Taguchi and co-workers have been investigating the coupling of acrolein acetals or acrylic acid ortho esters with aldehydes, mediated by a low valent zirconium species, hereinafter abbreviated as "Cp_2Zr".[149] This species is prepared by reacting Cp_2ZrCl_2 with 2 equiv of BuLi, as originally reported by Negishi (Scheme 120).[150]

The oxophilic nature of the zirconium atom, joined to its low oxidation state, renders "Cp_2Zr" extremely reactive toward allylic and propargylic ethers as well as toward acetals of conjugated aldehydes. The insertion of "Cp_2Zr" into the carbon−oxygen bond of **266** gave the γ-*Z*-alkoxyallyl zirconium complex **267**, as shown in Scheme 121. ^1H, ^{13}C NMR spectra and NOE experiments were consistent with the assigned *Z* configuration of **267**. Addition of **267** to an aldehyde resulted in the formation of the adduct **268**, although with modest diastereoselectivity.[151] Diastereoselectivity, however, could be reversed by running the reaction in the presence of $BF_3{\cdot}Et_2O$, as shown in the two reactions reported in Scheme 121.

Scheme 120

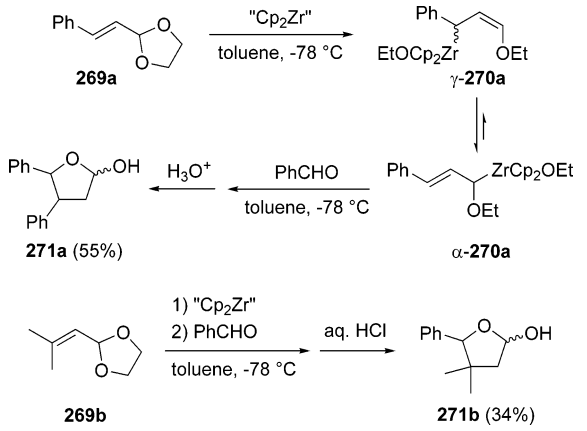


Scheme 121

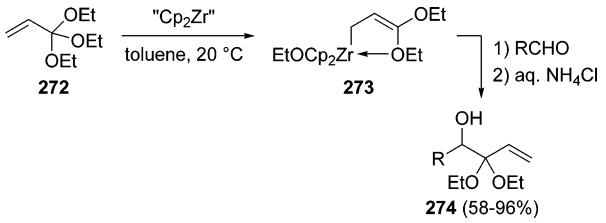


Moving from acrolein acetals **266** to acetals of cinnamaldehyde **269a** or prenal **269b**, the regiochemical course of the reaction was reversed in favor of homoaldol products

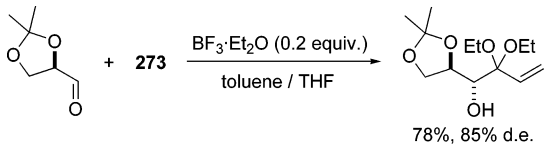
Scheme 122



Scheme 123



Scheme 124



271, since, in this case, metallotropic equilibrium favored the formation of the thermodynamically more stable conjugated α-alkoxyallyl zirconium complex **270** (Scheme 122).[151]

Triethyl orthoacrylate **272**, also, reacted with "Cp_2Zr" at room temperature to generate the γ,γ-diethoxyallyl zirconium complex **273**, a synthetic equivalent of the formal acryloyl anion. The addition of **273** to an aromatic or an α,β-unsaturated aldehyde afforded adducts **274** in good to excellent yields (Scheme 123).[152]

To force aliphatic aldehydes to react cleanly with **273**, 0.2−0.3 equiv of BF_3·Et_2O were necessary; moreover, THF had to be used as cosolvent.[153] Under these conditions, a satisfactory coupling of glyceraldehyde acetonide with **273** was recorded (Scheme 124).

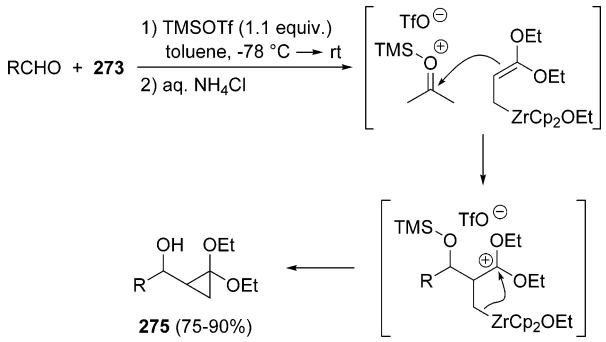
However, when a Lewis acid, for example TMSOTf, was used in a stoichiometric amount in toluene as solvent while raising temperature from −78 °C to room temperature, the reaction of **273** with conjugated or unconjugated aldehydes, as well as with saturated ketones, followed a different reaction channel, affording, after neutral workup, cyclopropanone ketals **275**. An aldol type addition of the ketene acetal moiety existing in **273** to the carbonyl compound promoted by the Lewis acid was followed by spontaneous cyclization as shown in Scheme 125.[154] The relative stereochemistry in **275** was not determined.

In an analogous way, **273** added to conjugated ketones, under the preceding reaction conditions, in a conjugate fashion, affording cyclopropanone ketals **276** (Scheme 126).[154]

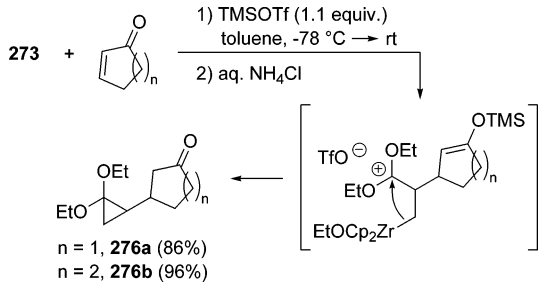
γ,γ-Diethoxyallyl zirconium complex **273** did not react with Schiff bases. When Lewis acids such as TMSOTf, $TiCl_4$, or BF_3·Et_2O were added, the reaction resulted in the formation of a complex mixture. However, the addition of CuCN (1 equiv) to an equimolar mixture of **273** and an imine in toluene/THF (1:1 v/v) led to adducts **277** in good to excellent yield. The process likely involves an intermediate Zr/Cu transmetalation process. The reaction temperature is critical, and it must lie in the 0−25 °C interval. Below 0 °C, the reaction was extremely slow, while, at higher temperature, black precipitates appeared, indicating decomposition of copper intermediates (Scheme 127).[155]

At last, we wish to mention the allylation reaction of **273** by means of allylic and propargylic phosphates. Again, the presence of CuCN was essential. The reaction involved a S_N2' mechanism, very often observed using cuprates, affording 5-alkenoates and 4,5-alkadienoates, as shown in Scheme 128.[156]

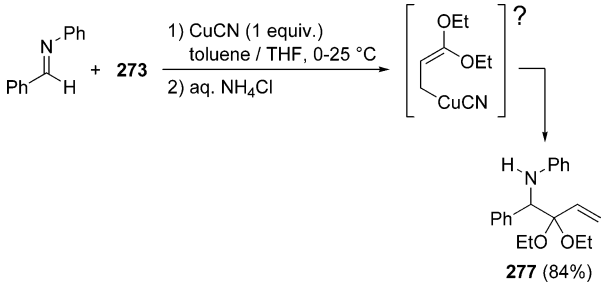
Scheme 125



Scheme 126



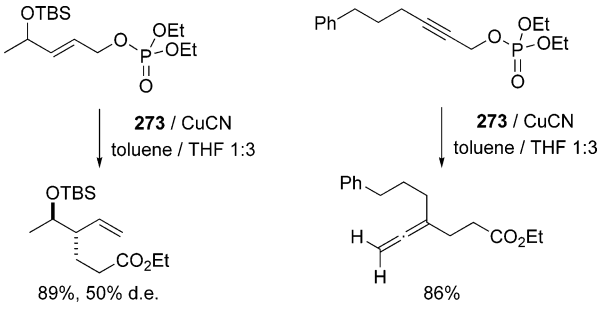
Scheme 127



7. 3-Acyloxyallyl and 3-Alkoxycarbonyloxyallyl Metal Complexes

With the aim to develop a general, simple, economically and environmentally friendly solution for the hydroxyallylation route to enediols **1**, we pursued this challenge by relying on oxidative addition techniques for the preparation of 3-oxyallyl metal complexes, rather than on the much more demanding lithiation/transmetalation procedure (use of alkyl lithium bases, anhydrous solvents, low temperature, etc.). Thus, we sought to identify flexible and versatile oxy-

Scheme 128

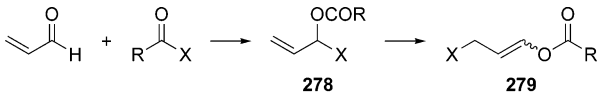


substituted allyl halides to be tested in oxidative addition processes with low valent metals. Searching through the old literature, we found that Kirrmann had reported in 1938 the preparation of 3-bromopropenyl acetate **279a**.[157] Thus, it was envisioned that allyl halides **279**, carrying an acyloxy substituent in position 3,[158] could be suitable substrates for our purposes. The original preparation of **279** involved the addition of acetyl chloride to acrolein. The kinetic product was the 1,2-addition product **278**, which slowly equilibrated into the thermodynamically more stable 1,4-adduct **279**, upon standing for a few days. Later on, Neuenschwander demonstrated that conversion of **278** into **279** could be completed in a few hours by simply stirring the reagents at 0 °C in the presence of 5−10% anhydrous $ZnCl_2$.[159]

Using acetyl bromide, the formation of 3-bromopropenyl acetate **279a** was even more rapid, taking place at −20 °C in the presence of $ZnCl_2$ (Scheme 129).

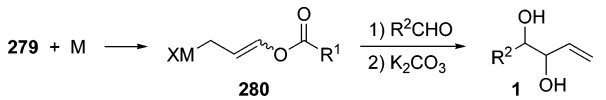
Concerning the carbon−carbon double bond configuration, an *E*/*Z* mixture was generally obtained and the ratio depended on the reaction and the purification conditions, as well as on the nature of the acyl halide. With the key 3-halopropenyl esters secured as starting materials, attention was turned to their reactivity with low valent metal species which are known to insert into the carbon−halogen bond of organic halides, affording 3-acyloxyallyl metal complexes **280** capable of reacting with carbonyl compounds (Scheme 130).

Scheme 129



279a : X = Br, R = CH_3 **279c** : X = Cl, R = CH_3
279b : X = Br, R = Ph **279d** : X = Cl, R = *t*-Bu

Scheme 130

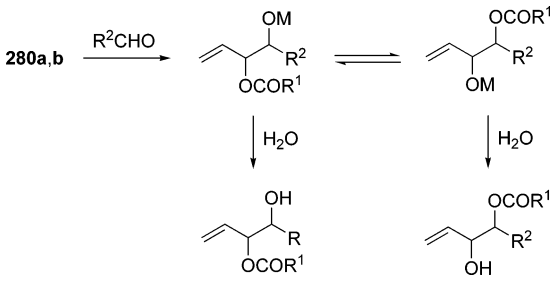


280a : M = Zn(II), R^1 = Me
280b : M = In(I) and/or In(III), R^1 = Me
280c : M = Cr(III), R^1 = Me
280d : M = Cr(III), R^1 = *t*-Bu

7.1. 3-Acyloxyallyl and 3-Alkoxycarbonyloxyallyl Zinc and Indium Complexes

For the development of practical, economic, and green organometallic procedures directed to the construction of carbon−carbon bonds, great attention has been devoted by the chemical community over the last 20 years to allylation reactions in water as solvent.[160] After the work by Luche in 1985,[161] who first carried out the classical Barbier reaction

Scheme 131



using an aldehyde, allyl bromide, and zinc metal in aqueous ammonium chloride, efforts in allylation reactions were focused on the use of indium in water.[162] The reason why indium attracted the attention of synthetic chemists can be found in its physicochemical properties. First, indium possesses a relatively low reduction potential (−0.338 V) compared to zinc (−0.763 V), which makes it a more selective reducing agent. Furthermore, indium powder is not affected by boiling water or alkali and it is relatively stable to air. Lack of surface passivation means that there is no need for specific activation of indium, such as heat, sonication, or acid catalysis, as is necessary for other elements, such as magnesium, zinc, etc.

Having targeted 3-halopropenyl esters **279a** as a promising reagent for the hydroxyallylation of carbonyl compounds, both zinc in aqueous ammonium chloride and indium in water were tested under one-pot Barbier conditions. The metal of choice was found to be zinc, which allowed us to synthesize in saturated ammonium chloride solutions the corresponding adducts in very good yields.[163] Indium in water, on the other hand, gives its best results at pH 2−3, a value which is not compatible with the acid-labile enol ester functionality present in **279**. Owing to the occurrence of intramolecular transesterification processes (Scheme 131), the extracted crude product mixture was directly hydrolyzed with methanolic potassium carbonate to deliver unprotected *syn*/*anti* diols **1** (Scheme 130).[164]

Ketones also reacted, but 20% THF was added to the saturated ammonium chloride solution in order to enhance the substrate solubility.[165] Typical results are shown in Figure 7, protocol B, where yields and diastereomeric compositions of adducts obtained with a few reference aldehydes and ketones are reported.

The oxidative addition of 3-halopropenyl esters to zinc and indium also occurred in aprotic solvents, such as THF, acetonitrile, DMF, DMSO, etc. In aprotic solvents, two alternative reaction protocols can be applied, either a one-pot Barbier protocol, where the metal is added to a solution of the 3-halopropenyl ester and the carbonyl compound, or a classical two-step Grignard protocol, where the organometallic species is formed first and then treated with a carbonyl compound. The latter procedure must be adopted when pinacolization reaction of the carbonyl compound competes with the formation of the organometallic species.[164,166] Typically, enediol adducts **1** were formed in slightly higher yields and diastereomeric excesses with respect to reactions in water (Figure 7, protocol A). Since both inter- and intramolecular transesterification reactions occurred, an alkaline workup was again necessary to directly deliver **1** from the crude reaction mixture.

Combining the hydroxyallylation step to the ozonolysis of the terminal C=C bond of **1**, a simple two-carbon homologation of carbohydrates was developed. Thus, **279a**

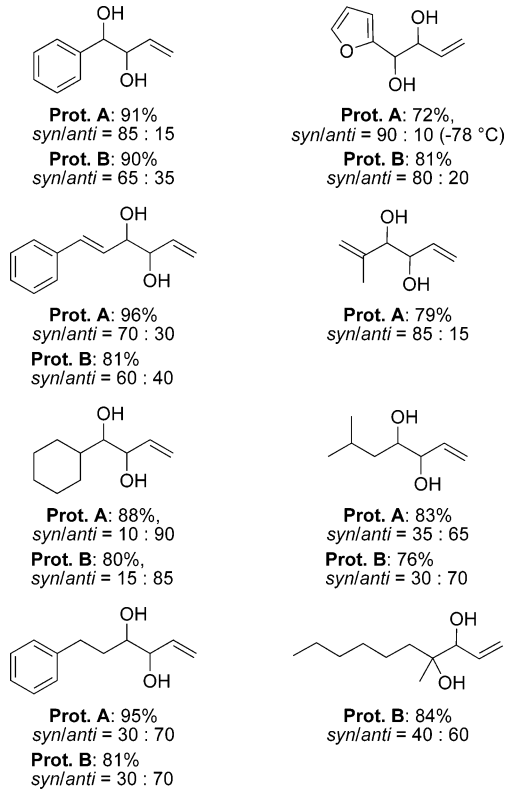
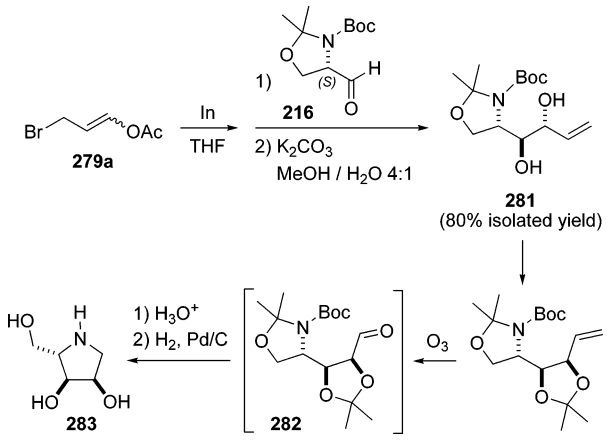


Figure 7. The reaction of **280a** and **280b** with carbonyl compounds. Prot. A = Grignard procedure using In(0) in THF. Prot. B = Barbier procedure using Zn(0) in aq NH_4Cl.

Scheme 132

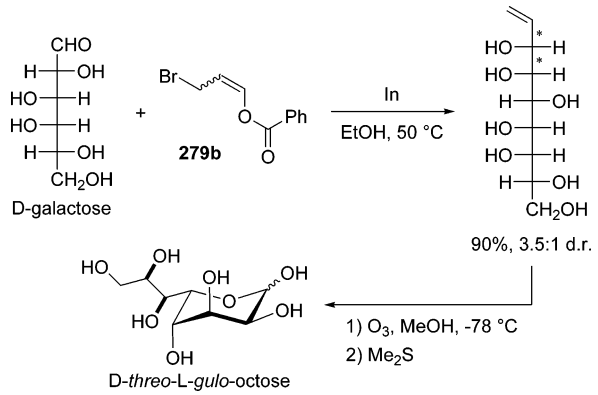


reacted with the Garner aldehyde **216** (Grignard protocol, THF, In(0)), giving rise to adduct **281** in excellent yield and diastereocontrol. Protection of the diol as an acetonide followed by ozonolysis of the carbon−carbon double bond afforded the protected aldehyde **282**, which was directly treated with aqueous TFA followed by reductive cyclization (H_2, Pd/C), delivering 1,4-dideoxy-1,4-L-iminoribitol (**283**), as shown in Scheme 132.[167]

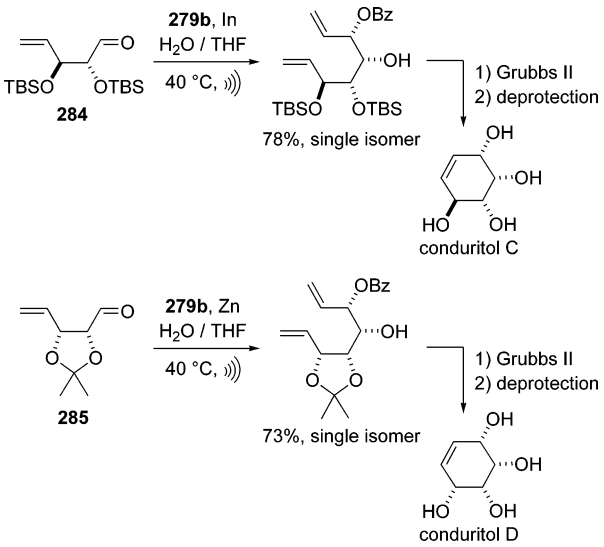
Following an analogous approach, Madsen developed an efficient two-carbon homologation of aldopentoses and hexoses into higher sugars using **279b** under Barbier conditions in ethanol at 50 °C (Scheme 133).[168]

If an unsaturated aldehyde is used, the corresponding hydroxyallylation adduct may be transformed into a carbocyclic compound via RCM. Madsen exploited γ,δ-unsaturated aldehydes **284** and **285** to address a synthesis of conduritols C and D via the elegant sequence shown in

Scheme 133



Scheme 134



Scheme 134.[169] The hydroxyallylation step was sped up using ultrasound irradiation in aqueous THF at 40 °C, and under these experimental conditions, both the ester migration and the formation of *syn* adducts were not observed.

In all the hydroxyallylation experiments carried out with **279**, simple diastereoselectivity was characterized by the same unprecedented trend: *anti*-adducts being formed when saturated aldehydes were used, and *syn*-enriched adducts being formed when conjugated or aromatic aldehydes were used.

Since starting material **279** was not configurationally pure, we modeled all transition states in the addition of *E* and *Z* zinc complexes **280a** both to benzaldehyde and to 2-methylpropanal in dimethyl ether as solvent. Figure 8 shows that, at the DFT-B3LYP/DZVP level, the formation of the *anti*-adduct over the *syn*-adduct is favored in all cases, while only the reaction of *E*-**280a** with benzaldehyde shows two almost degenerate diastereomeric TSs (the 0.2 kcal/mol energy difference is not significant). While **A** and **B** correspond to the more stable chairlike TSs on the basis of the Zimmerman−Traxler rationale, **C** and **D**, presenting the aldehyde R group in the pseudoaxial orientation, are not anticipated as the more stable ones by the same reactivity model. The reason is that the presence of a bromine atom on zinc in the axial orientation produces a 1,3-diaxial Br/R interaction that is less destabilizing than the R/OAc gauche interaction present in the diastereomeric TSs, where the R group is in the pseudoequatorial orientation.

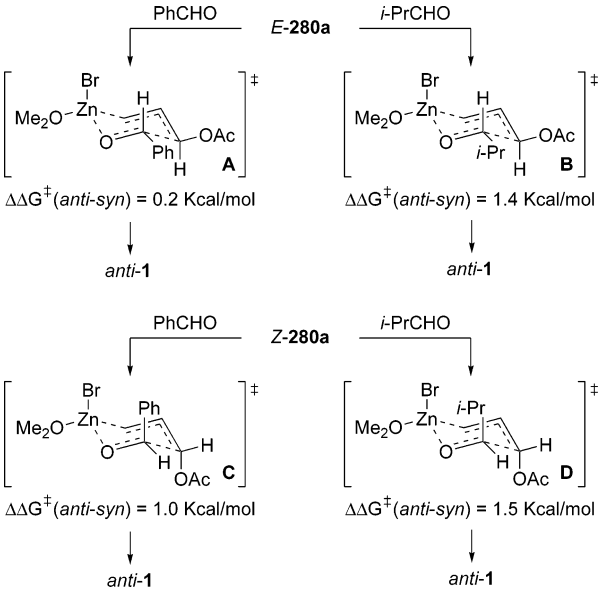
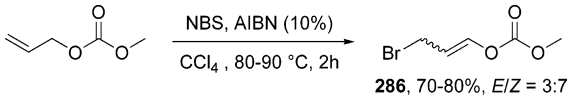
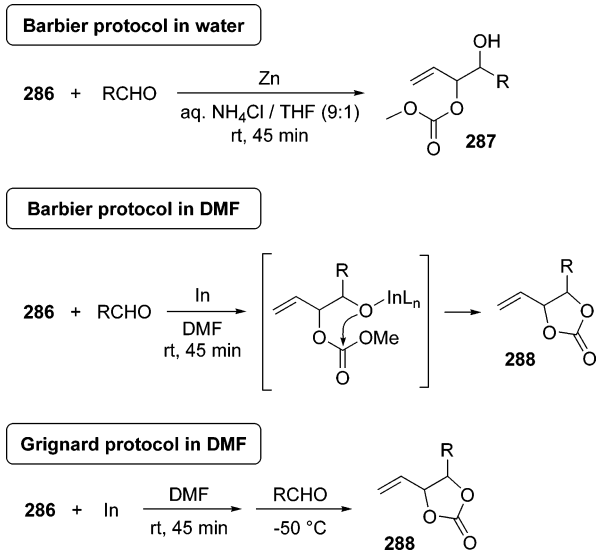


Figure 8. TS modeling for the addition of *E*- and *Z*-**280a** to benzaldehyde and to 2-methylpropanal: A−D correspond to the lowest energy transition state (TS). In each case, $\Delta\Delta G^{\ddagger}$ refers to the activation energy difference between the most stable TSs leading to the *anti* and *syn* adducts, respectively.

Scheme 135



Scheme 136



The structure of compounds **279** suggests that their performances as hydroxyallylating agents can be modified by changing the ester group. It was assumed on this basis that replacement of the ester group with a carbonate functionality could positively affect the reaction course, for example by solving the problem of the ester migration shown in Scheme 131. The preparation of 3-bromopropenyl methyl carbonate **286** was simply achieved in multigram scale via the free-radical bromination of allyl methyl carbonate (Scheme 135).

Most gratifyingly, 3-halopropenyl methyl carbonate **286** worked beautifully with simple model aldehydes, acting as an exceptionally robust and reliable substrate for zinc- and indium-promoted hydroxyallylation reactions (Scheme 136). Four main reasons made **286** more attractive than **279** for hydroxyallylation processes: (i) the starting material, allyl methyl carbonate, is less toxic than the acrolein required for the preparation of esters **279**; (ii) contrary to **279**, **286** is stable and storable for months without appreciable decomposition; (iii) under all the reaction protocols used, **286** performed better than 3-halopropenyl esters **279** in terms of yield, but with a similar stereochemical outcome (Figure 9); (iv) no scrambling of the carbonate functionality in the adducts was observed in aqueous reaction media, thus allowing isolation of a regioselectively monoprotected *vic*-diol **287**,[170] while cyclic carbonates **288** were obtained in aprotic solvents.[171]

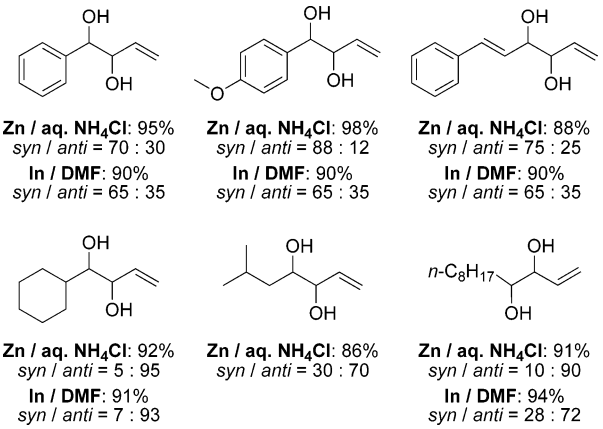


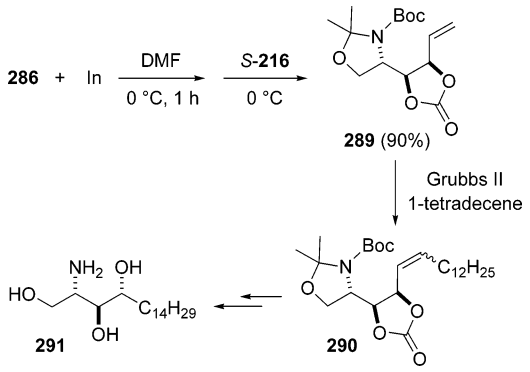
Figure 9. Barbier coupling of **286** with aldehydes using Zn(0) in aq NH_4Cl or In(0) in DMF.

The indium-promoted coupling of Garner aldehyde **216** with **286** under Grignard conditions at 0 °C in DMF took place with high diastereocontrol, and the adduct **289** was isolated in 90% yield. A very efficient microwave-promoted cross-metathesis reaction with 1-tetradecene allowed installation of the correct chain on **289**, necessary to convert **290** into D-ribophytosphingosine **291** (Scheme 137).[172] The target molecule **291** was obtained in overall 75% yield from Garner aldehyde **216**.

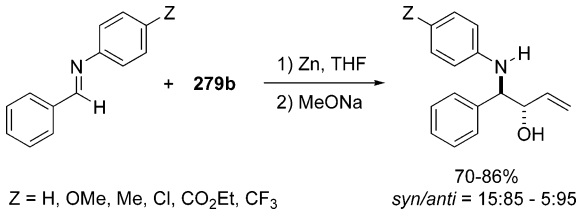
Imines[173] (Scheme 138) or imines produced *in situ*[174,175] from α-amidoalkyl phenylsulphones[176] (Schemes 139 and 140) underwent a clean hydroxyallylation reaction by means of **279a**, **279b**, and **286** in aprotic solvents. Reactions produced *anti*-adducts, regardless of the nature of the azomethine compound. The hydroxyallylation of imines followed by eventual cleavage of the protective groups freed *anti* 1-en-4-amino-3-ols in good yields (Schemes 138−140).

Nitrones were also examined as electrophiles.[177] However, using **279a**, all the hydroxyallylation protocols analyzed so far did not work with nitrones. To force nitrones to react, precomplexation with TMSOTf was necessary. The reactions were run using zinc in DMF at room temperature (Scheme 141). Under Lewis acid activation, a *syn* diastereopreference was observed as the result of the adoption of open-chain antiperiplanar transition states. The resulting *syn*-homoallylic hydroxylamines **292** underwent clean iodocyclization by means of *N*-iodosuccinimide (NIS), affording the sterically congested *all-cis* trisubstituted isoxazolidines **293**. Following an analogous pathway, the minor *anti*-homoallylic hydroxylamines when subjected to iodocyclization conditions (NIS) gave isomeric 3,4-*trans*-4,5-*cis*-**293**.[177]

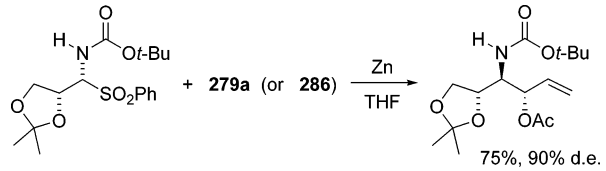
Scheme 137



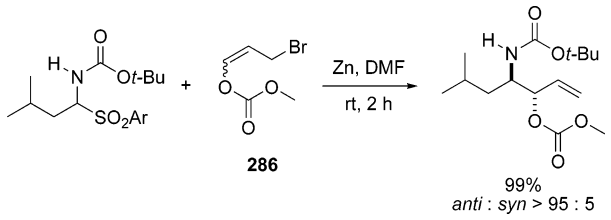
Scheme 138



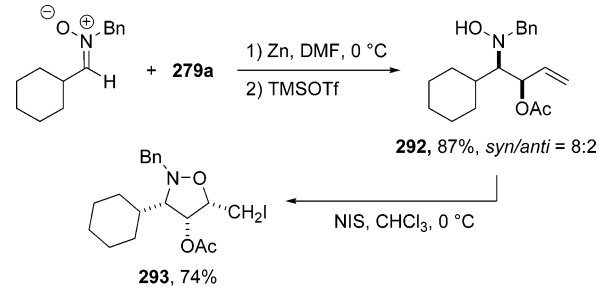
Scheme 139



Scheme 140



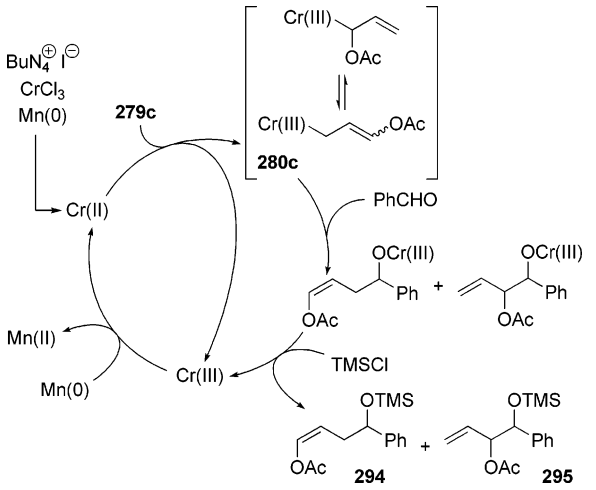
Scheme 141



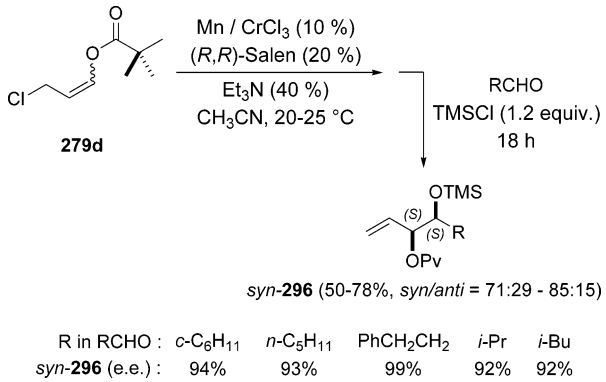
7.2. 3-Acyloxyallyl Chromium Complexes

In section 6.1, the scope and limitations of the chemistry of 3-alkoxyallyl chromium complexes prepared via insertion of Cr(II) to the carbon−oxygen bond of acrolein acetals have been examined. Analogous 3-acyloxyallyl chromium complexes were available by the interaction of Cr(II) salts with 3-chloropropenyl acetate or pivalate (**279c**,**d**). In particular, catalytic protocols were developed following the Fürstner strategy.[145] Regiochemistry was determined by the nature of the ester group in **279** and by the presence of a supplementary Lewis base. In the first reaction protocol shown in Scheme

Scheme 142



Scheme 143



R in RCHO :	*c*-C_6H_{11}	*n*-C_5H_{11}	$PhCH_2CH_2$	*i*-Pr	*i*-Bu
syn-**296** (e.e.) :	94%	93%	99%	92%	92%

142, an aldehyde, 3-chloropropenyl acetate **279c**, TMSCl, and Bu_4NI (0.2 molar %, the Lewis base additive) were successively added to a premixed suspension of Mn powder (3 equiv) and $CrCl_3$ (0.1 equiv) in acetonitrile, and the reaction mixture was stirred at room temperature or at 65 °C. Under these conditions, the protected homoaldol derivative **294** was the major product, particularly when the reaction was run at 65 °C.[178] The addition of a source of iodide ions was necessary to achieve acceptable conversions. In the authors' opinion, the iodide ion, rather than promoting the formation of a more reactive 3-iodopropenyl ester, acted as a Lewis base, activating the chromium center. The conceptual framework of the enhancement of the local Lewis acidity of a metal center by means of a Lewis base has recently been rationalized by Denmark.[179] Thus, the Cr(III) atom in the intermediate oxyallyl chromium complex **280c**, upon coordination with a supplementary iodide ion, could give rise to a hypervalent chromium species with an enhanced Lewis acidity on the metal center, resulting in a faster nucleophilic addition to the aldehyde.

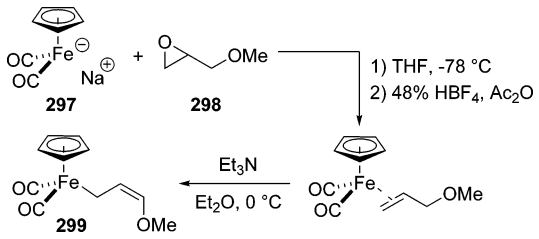
If the Lewis base is enantiomerically pure, enantioface discrimination may be observed in the hydroxyallylation step. Seeking for chiral organic Lewis bases, Jacobsen salen, previously used by Umani−Ronchi in an asymmetric catalytic version of the NHK reaction,[180] was found to be a superb solution. Thus, a new catalytic protocol was developed (Scheme 143), where salen (20 mol %) and Et_3N (40 mol %) provided the chiral basic activator for Cr(III) in the oxyallyl chromium intermediate **280d** (see Scheme 130). The new process displayed a number of unexpected features: (i) the regiochemistry was completely reversed. Homoaldol

derivatives **294** were absent, and hydroxyallylation adducts **296** were the only products. (ii) Simple diastereoselectivity was *syn*, contrary to the known behavior of other oxyallyl chromium (see Scheme 115) or crotyl chromium reagents.[181] (iii) Both *syn* and *anti* adducts were formed in enantiomerically enriched forms, and in the case of *syn*-adducts from aliphatic aldehydes, ee's were constantly higher than 90%.[182] The process outlined in Scheme 143 is the first example of catalytic asymmetric addition of an oxyallylic organometallic reagent to an aldehyde, while a number of catalytic asymmetric strategies for the synthesis of homoallylic alcohols via allyl and crotyl organometallic reagents are available in the literature.[181]

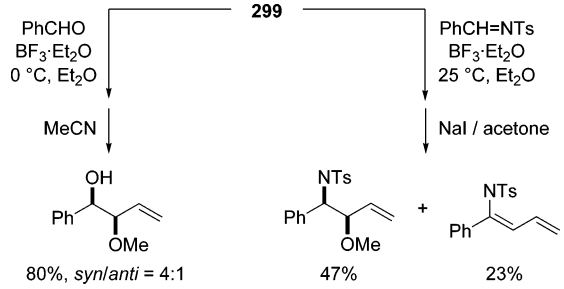
8. Miscellaneous Routes to Oxyallyl Organometallic Reagents

A few examples of alternative preparations of α-alkoxyallyl metal complexes are examined in this section. The nucleophilic addition of sodium [(cyclopentadienyl)iron(II) dicarbonyl] **297** to glycidyl methyl ether **298** opened a route to the *Z*-3-alkoxyallyl iron reagent **299** (Scheme 144).[183] Turos and co-workers found that **299** could be forced to react with carbonyl compounds, imines, and acetals under mild conditions in the presence of $BF_3 \cdot Et_2O$. Iron−olefin π-adducts were obtained, from which the target organic adduct could be freed by simple treatment with acetonitrile or NaI in acetone (Scheme 145).[184]

Scheme 144



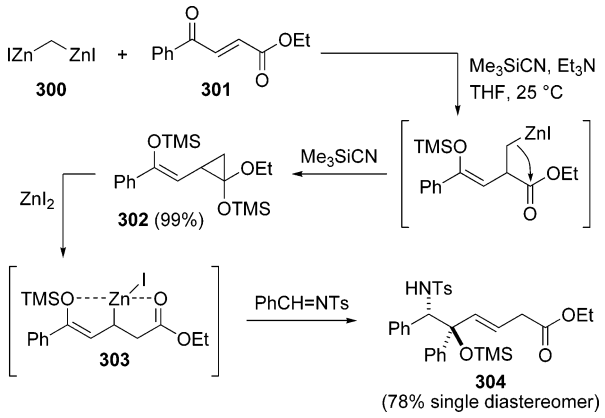
Scheme 145



Further examples of α-alkoxyallyl metal complexes carrying specific substituents on the allylic framework were targeted to achieve the synthesis of peculiar target molecules. Matsubara and co-workers developed an original and stereoselective route to γ-*Z*-silyloxyallyl zinc reagents.[185] Addition of *gem*-dizinc reagent **300** to the β-acylenoate **301** in the presence of a silylating agent and Et_3N afforded **302** in high yield (Scheme 146). When the reaction was carried out at 80 °C in the presence of ZnI_2 and *N*-tosylimine, cyclopropyl ketal **302** first underwent Lewis-acid-mediated ring opening to **303**. The latter intermediate **303** contained a *Z* configurated γ-silyloxyallyl zinc moiety and was capable of reacting with *N*-tosylimine to deliver the *anti*-adduct **304**.

The last example examined was based on an alternative assembly of chiral cyclic allylboronate **307** by an asymmetric

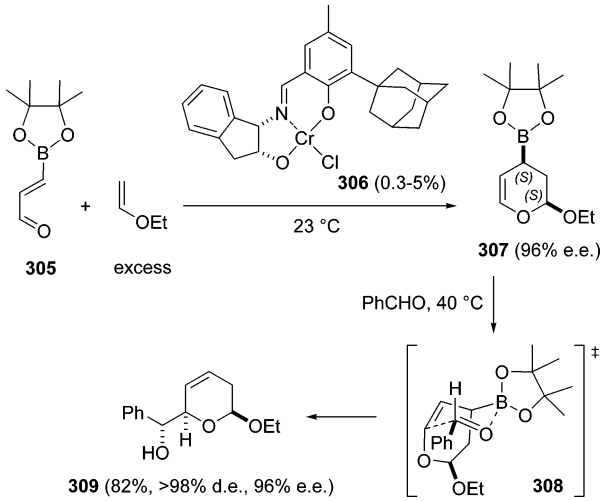
Scheme 146



hetero-Diels−Alder reaction between boronate **305** and ethyl vinyl ether.[186] The cycloaddition was catalyzed by Jacobsen's tridentate chromium complex **306**.[187] Complete conversion to adduct **307** with 96% ee was realized with 0.3−0.5 mol % catalyst loading, in the presence of 4 Å molecular sieves or of BaO, and using an excess of ethyl vinyl ether as solvent.

Noticeably, boronate **307** could be isolated by distillation or flash chromatography on silica gel without loss of stereochemical integrity. When **307** was reacted with carbonyl compounds, the polysubstituted α-hydroxyalkylpyran **309**, a structural motif found in a number of natural products with antibiotic and anticancer activity, was obtained (Scheme 147). The authors succeeded in integrating the Diels−Alder reaction and the allylboronation step into a three-component one-pot consecutive protocol, by simply adding the aldehyde after completion of the cycloaddition step, in ethyl vinyl ether as solvent. The stereochemical outcome is consistent with the Zimmerman−Traxler TS structure **308**, and the scope of the reaction was extended to substituted vinyl ethers.

Scheme 147



9. Concluding Remarks

The scope of organic synthesis at both the academic and industrial levels has been profoundly impacted and expanded by developments in asymmetric synthesis, acyclic stereoselection, asymmetric catalysis, etc. The allylation reaction of carbonyl compounds by means of allylic organometallic compounds is considered a variant of the aldol reaction. From a mechanistic point of view, transition state modeling of allylation reactions parallels that of aldol reactions (Zim-

merman−Traxler model, etc). From a synthetic point of view, homoallylic alcohols can be easily converted into aldols, furnishing outstanding improvements in terms of acyclic stereoselection compared to the corresponding aldol reactions.

This review surveys the state of the art of the chemistry of 3-oxyallyl organometallic compounds, which are important members of the broader family of allylic complexes. Many of them are discrete and isolable chemical entities which afford alk-1-en-3,4-diols **1** with predictable and efficient diastereocontrol. Moreover, environmentally friendly conditions for the development of protocols for the *in situ* generation and use of allylic organometallic species have been recently proposed, capable of producing alk-1-en-3,4-diols **1** with good diastereo- and/or enantiocontrol.

The versatility and usefulness of alk-1-en-3,4-diols **1** as precursors of densely functionalized carbon chains have been documented by encompassing a number of target molecules, whose total synthesis relied on a key hydroxyallylation step.

However, while over the past decade excellent progresses have been made in the development of catalytic enantioselective versions of the simple allylation reaction, similar achievements have not been recorded with 3-oxyallyl organometallic compounds. Thus, the challenge in the hydroxyallylation reaction is to focus efforts into the development of asymmetric catalytic protocols, simultaneously addressing economy and sustainability issues, as required by the modern perspective of a green organic synthesis.

10. Acknowledgments

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