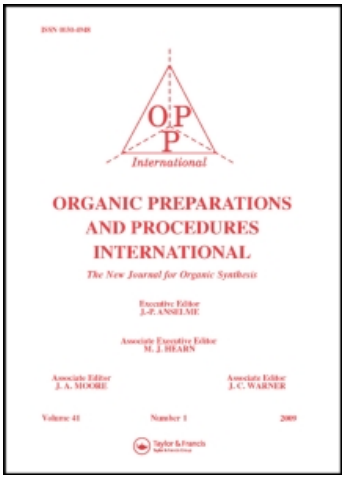

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CHIRAL ENOLATE EQUIVALENTS. A REVIEW

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CHIRAL ENOLATE EQUIVALENTS. A REVIEW

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INTRODUCTION

Although enolate chemistry is a very mature subject, it was long after the enolate was recognized as a pivotal functionality for carbon-carbon bond forming processes that stereochemical control in this reaction was finally achieved. Following more than three decades of research and development, chiral enolates may now be used to create a wide variety of carbon-carbon and carbon-heteroatom bonds with a remarkable level of stereocontrol.[1,2] Yet, the level of stereochemical control is not the only reason why chiral enolate reactions are included as key elements in so many natural product syntheses.[3] The carbonyl function that is left after the

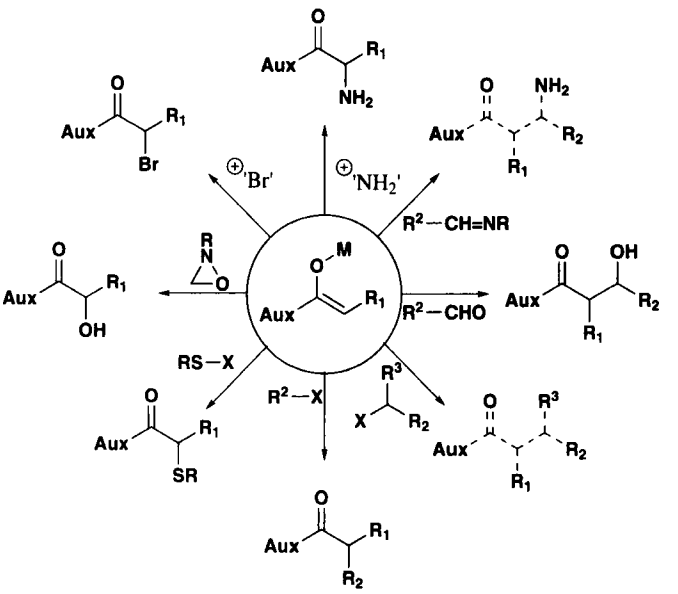


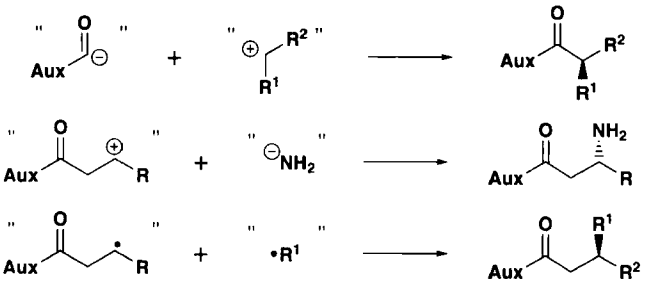
Fig. 1

Structural Motifs Associated with Acyclic Enolate Chemistry
(structures in dotted lines are not easily constructed from enolate chemistry)

reaction provides an extraordinarily versatile chemical handle to complete the targeted structures. Enolate reactions can, in principle, create two new chiral centers α and β to the carbonyl function. The formation of new C-C and also of C-N, C-O, C-S, and C-X bonds fall within the sphere of enolate reactions. Typical enolate products are depicted in *Fig. 1* and those structures for which enolate chemistry has not yet proved to be a satisfactory means of preparation are indicated in dotted lines.

Despite this impressive track record, the weak reactivity of enolates in general confines the range of usable electrophiles to aldehydes, some primary or activated alkyl halides, unsaturated carbonyls, electrophilic halogens, oxaziridines, aza compounds, and a handful of other reactive electrophiles.[3] Intramolecular reactions may tolerate slightly less reactive electrophiles. With few exceptions, secondary, tertiary, or branched primary alkyl halides, as well as aryl or vinyl halides, imines, unactivated alkenes or alkynes, and many other less reactive functional groups are not able to react directly with enolates. In addition, reactions of enolates seldom tolerate more than one substituent on the nucleophilic carbon of the enolate, cyclic enolates being an exception.[4]

The need to access compounds having one of the general structures shown in *Fig. 1* is immense. Many products, such as amino acid and polyacetate metabolites, possessing or encompassing such structures, play key roles in the pharmaceutical and agrochemical industries among others. Compounds like these may also be intermediates in the synthesis of more complex products. Furthermore, the impetus to obtain these compounds in a state of high stereochemical purity has paralleled the need for the compound itself, especially so in industries dealing with human health. As a consequence of this need, the number of stereoselective synthetic methods leading to one or more of these structural motifs has increased significantly in the last two decades. Several general strategies to make non-racemic enolate-type compounds from nearly all conceivable bond disconnections (see examples in *Scheme 1*) can be found in the literature. Many of these strategies employed either a stoichiometric chiral auxiliary or a chiral catalyst to achieve asymmetric bond formation. The objective of this review is to inform the reader of all possible means of constructing non-racemic enolate-type products without having recourse to enolate chemistry.



Scheme 1

Surprisingly, no review of chiral enolate equivalents has appeared in the literature thus far, although many of the strategies described below have been reviewed separately. Too many strategies could be identified as alternatives to chiral enolate chemistry if defined as approaches or methods that produce a compound possessing a carbonyl function with an α- or β-chiral carbon. For that reason, the contents of this review article are restricted to processes that yield chiral products similar to the ones produced by the reactions of electrophiles onto an *acyclic chiral enolate*. Processes that create a functional group easily converted into a carbonyl (*e. g.* primary alcohols, terminal alkenes and so on) are also included so long as they are inscribed in a general strategy for making such compounds. Strategies in which the starting substrate is already chiral are discussed only if appropriate. An overview of each strategy is given with an emphasis on the more efficient, the more recent, or the lesser known methodologies. In view of the apparent disparate nature of the different strategies uncovered, they were regrouped according to: (a) the position of the newly created bond with respect to the carbonyl (or latent carbonyl) function (b) the electronic "role" (electrophilic, nucleophilic or neutral) of the carbon closest to the carbonyl in that newly formed bond (*Fig. 2*).

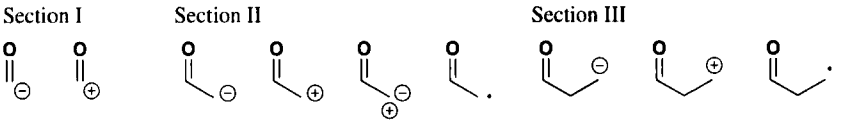
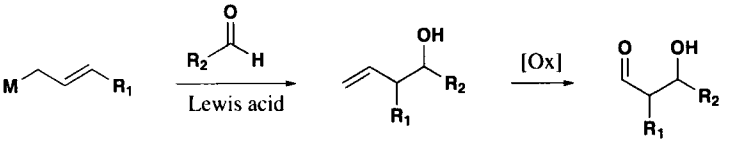


Fig. 2

Classification of Sections According to the Position and Polarity of the New Bond

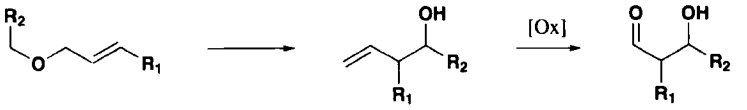
Because of this rather inclusive approach and because not all strategies were presented by their authors as chiral enolate equivalents, some worthy contributions may have been inadvertantly omitted. Readers should bring any omission to the attention of the author so that future discussions may include such work. Strategies involving chiral enolates themselves were purposefully omitted, with the exception of those that involve transformation of the enolate to another species prior to its stereoselective reaction.

Chiral enolate equivalents have existed for a long time although they were not necessarily regarded as such. The term 'equivalent' was mostly reserved for closely related reactions such as those involving chiral metallated enamines or hydrazones.[5] For example, while the addition of allylic metals to aldehydes (*Eq. 1*) was immediately recognized as a close relative of the aldol reaction,[6] the Wittig rearrangement (*Eq. 2*)[7] was not presented in those terms,



(1)

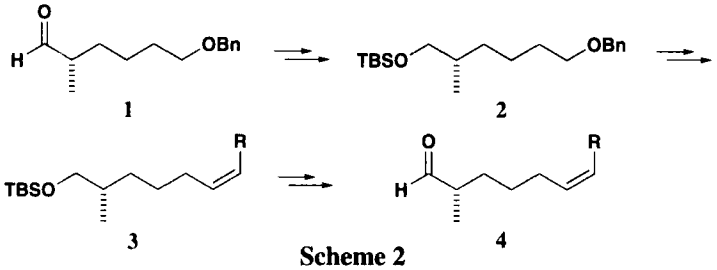
even though their products share very similar features. Other reactions, like the intermolecular insertion of α-oxo carbenes into C-H or X-H bonds or the intermolecular alkylation of α-oxo



(2)

radicals, are slow to emerge as true chiral enolate equivalents because of serious stereochemical challenges still unresolved.

Several methods for generating chiral carbonyl compounds start with molecules that do not contain a carbonyl or a closely related function such as an imine. There are several reasons for this: a) many functional groups, for instance alcohols, alkenes, acetals, and their analogs, can be transformed in one step into a carbonyl functionality. Hence, a strategy generating chiral molecules that contain one of these latent carbonyl functions may constitute a synthetic equivalent to reactions of chiral enolates; b) the reactivity of the surrogate function may be higher and/or different from that of an enolate, potentially allowing the use of structurally different or complementary substrates with which they may react; c) the alternative method may provide a better access to a type of carbonyl in the final product (an aldehyde vs an ester for example); d) the unmasking of the carbonyl function may take place at a synthetically opportune time. The carbonyl is thus protected without recourse to additional steps as is often required in the case of a product arising from chiral enolate chemistry. A quick literature survey indicates that this latter concept may not have received all the attention it deserves. For example, in order to survive a long synthetic sequence, a carbonyl function may need to be reduced to a primary alcohol which is then protected, subsequently deprotected, and later re-oxidized to the carbonyl function, adding four unwanted steps to the synthesis (*Scheme* 2).[8] However, this oversight could also be a consequence of the wide applicability and ease of use of enolate chemistry, a status certainly not yet shared by many equivalent strategies.



Scheme 2

As will be seen, the methodologies described below nicely complement the diversity of carbonyl products currently attainable by classical enolate chemistry. Lastly, it should be pointed out that many of the strategies described herein are much wider in scope than just being chiral enolate equivalents. The reader should be aware that a false impression of their limitations may possibly arise from the fact that their survey was limited to the generation of acyclic carbonyl compounds. Also, the yields of reaction are not systematically reported. They are reported only if they add substantially to the discussion or if they are particularly low (or high in the case of a difficult reaction).

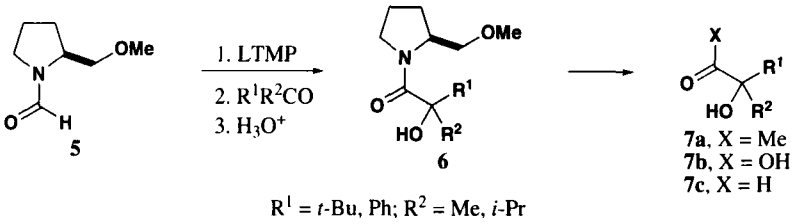
I. STEREOSELECTIVE INTRODUCTION OF THE CARBONYL

This section surveys the strategies which mimic enolate chemistry by introducing the carbonyl carbon in the stereoselective step. The carbonyl can be in the form of an electrophilic reagent or a nucleophilic substitute (as in cyanide ion).

1. Nucleophilic Surrogate Carbonyls

a) Chiral Acyl Anions and Equivalents

Introducing a carbonyl function in the form of an acyl anion equivalent can be done in several ways. Among others, cyanide and lithiated dithianes have occupied a place of choice. One of the rare chiral acyl anions reported makes use of formamide **5** derived from (*S*)-2-methoxymethylpyrrolidine (SMP) which is susceptible to deprotonation by lithium tetramethylpiperidide (LTMP) at low temperature (-100°C). The resulting anion adds to aldehydes and ketones to give, after the appropriate transformation and hydrolysis, a plethora of chiral α-hydroxycarbonyl compounds (*Scheme 3*).[9] The addition step was actually poorly

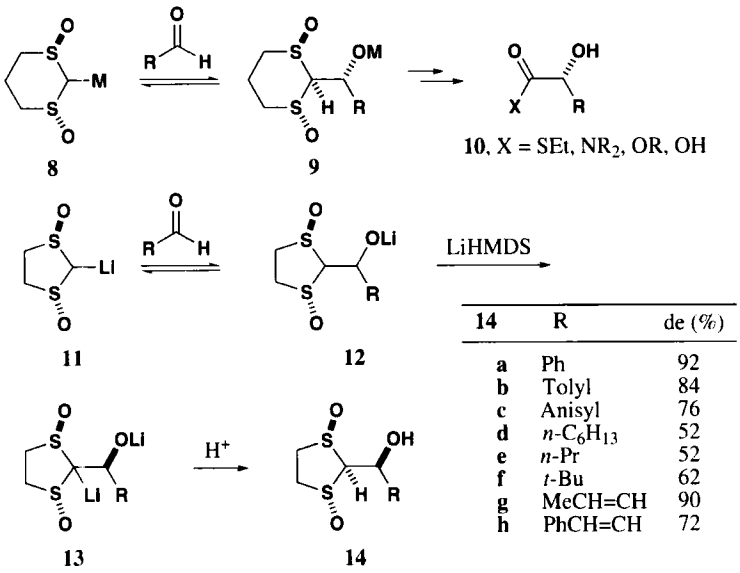


R^1 = *t*-Bu, Ph; R^2 = Me, *i*-Pr

Scheme 3

selective (5-20% de) and a separation and a recrystallization was needed to bring the final product to >90% ee. This was, nonetheless, among the first methods which permitted the preparation of enantiomerically pure α-hydroxy acids by the acyl anion strategy. The thioformamide analog of **5** (C=S instead of C=O) gave similar results.

Aggarwal and co-workers prepared the anion of dithiane-1,3-dioxide, **8** (M = Na), which added with high stereoselectivity, under equilibrium conditions, to aromatic aldehydes to give **9** (*Scheme 4*).[10] The lithium analog of **8** (M = Li) gave **9** with the opposite stereochemistry under kinetic control while equilibrating conditions caused the partial elimination of the hydroxyl group. Optically active **8** (M = H) was prepared from a Sharpless-type chiral oxidation of the carbethoxy derivative (**8**, M = CO_2Et) followed by decarboxylation.[11] The auxiliary in **9** could be transformed to thioesters, and subsequently to acids, esters, amides, and aldehydes.[12] Aliphatic aldehydes remain problematic, giving low diastereoselectivity of addition; better results were obtained using the lithiated dithiolane-1,3-dioxide **11** at –78°C.[13] Interestingly, when intermediate **12** was deprotonated with a second equivalent of lithium hexamethyldisilazide (LiHMDS) and the resulting dianion **13** quenched with acid, alcohol **14** was isolated with better overall selectivity than when it was obtained directly from **12**.



14	R	de (%)
a	Ph	92
b	Tolyl	84
c	Anisyl	76
d	n-C_6H_{13}	52
e	n-Pr	52
f	t-Bu	62
g	MeCH=CH	90
h	PhCH=CH	72

Scheme 4

Other chiral acyl anion equivalents are presented in *Fig. 3*.[14-19] Their reactions with aliphatic and aromatic aldehydes proceeded with modest to good diastereoselectivities, respectively. One advantage shared by these reagents is the ease of removal of the chiral auxiliary after the reaction under mild reaction conditions. However, the reported preparation of enantiopure auxiliaries **15-18** either required a resolution step or was rather lenghty. The use of achiral acyl anion equivalent with sparteine as a chiral inducer shortened the overall procedure but the observed diastereoselectivities were somewhat lower (cf. **19** and **20** in *Fig. 3*).[18,19]

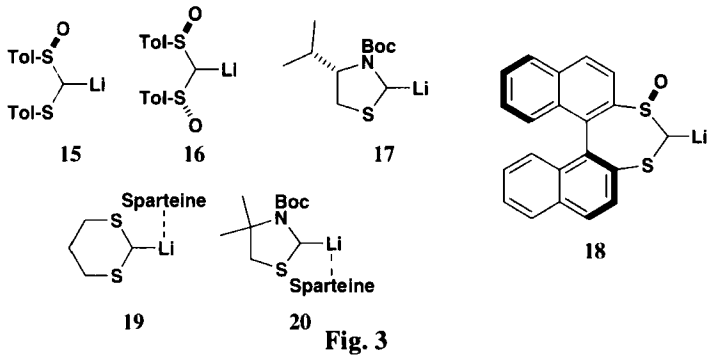
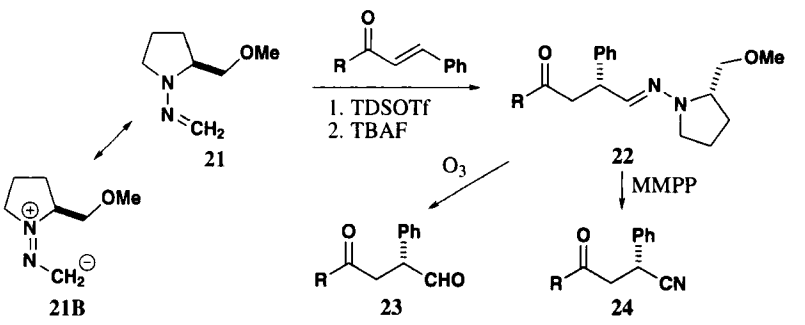


Fig. 3

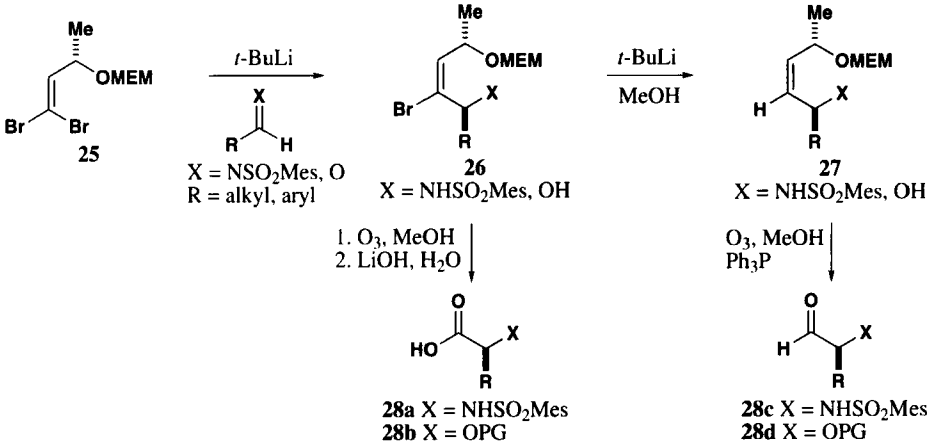
Chiral Dithianes or Analogous Auxiliary as Chiral Acyl Anion Equivalents

Lassaletta and Enders used (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) hydrazone **21** as a mild nucleophilic chiral formyl anion equivalent.[20] Only reactive electrophiles such as nitroalkenes,[21] activated enones,[22] or trifluoroketones[23] participated in this reaction. α-Chiral nitriles or aldehydes were produced depending on the final treatment of the product (*Scheme 5*).



Scheme 5

Braun and co-workers used a carbenoid generated from the metal-halogen exchange reaction of chiral dibromide **25** as a formyl anion equivalent (*Scheme 6*).[24] The more accessible bromine atom *trans* to the chiral appendage is lithiated first under kinetic conditions, but the *E*-lithio derivative can be obtained under equilibrium conditions for both steric reasons and accrued stability of the anion caused by internal coordination of the lithium to the methoxymethyl (MEM) group.

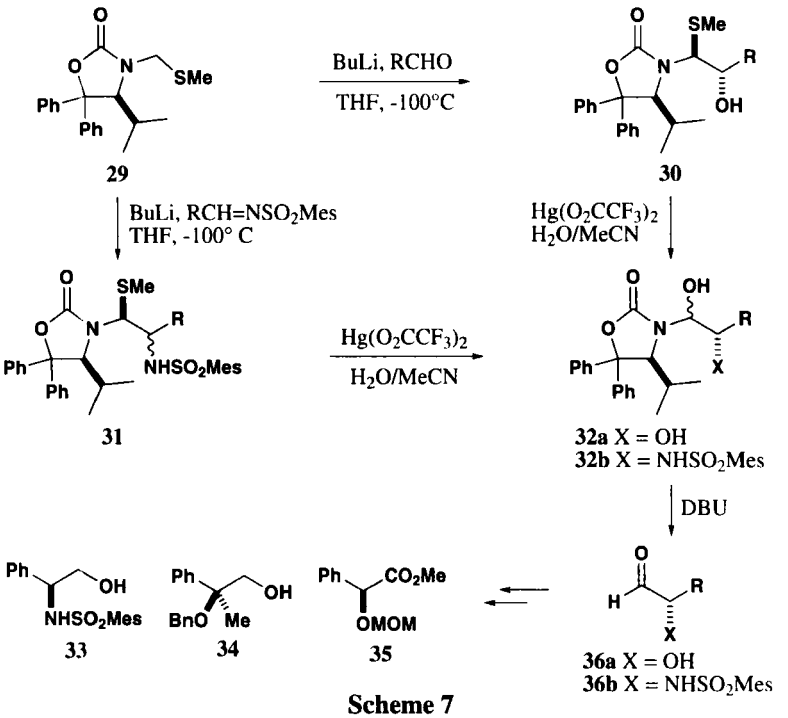


Scheme 6

Highly diastereoselective addition to aldehydes and imines gave rise to products **26**. After protection of the alcohol, oxidative cleavage of the alkene gave optically active *N*-protected α-amino acids **28a** or *O*-protected (OPG) α-hydroxy acids **28b**. When, on the other hand, the bromine atom was first replaced by a hydrogen atom, oxidative cleavage of the resulting alkene **27** led to the corresponding aldehyde products **28c** and **d**.

Oxazolidinones, such as **29**, with *N*-CH_2R groups do not normally undergo heteroatom-directed deprotonation at the CH_2 group because of the intrinsic reactivity of the carbamate carbonyl towards strongly nucleophilic bases such as alkyllithiums. However, Seebach and co-workers were able to effect lithiation of **29** with BuLi, thanks to its congested unreactive

carbonyl, and used it as a formyl anion equivalent.[25] Diastereoselective addition of lithiated **29** to aldehydes and imines gave products **30** and **31** respectively. Hg-assisted hydrolysis of the *S,N*-acetals led to the corresponding aminals **32a** or **b** which were subsequently decomposed to α-hydroxy or protected α-amino aldehydes (**36a** or **b**) with DBU (*Scheme 7*). The aldehydes were then transformed into a host of carbonyl-derived products, including amino alcohol (**33**), diol (**34**), and α-hydroxy ester (**35**).

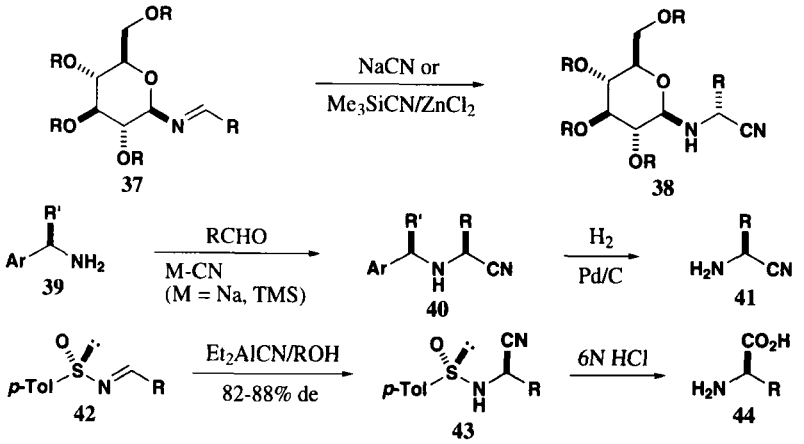


Scheme 7

b) Asymmetric Cyanation of Aldehydes and Imines

Cyanide has served as a formyl anion equivalent for many years. Its reaction with aldehydes and imines (or oxonium and iminium ions), catalyzed by Brønsted or Lewis acids or bases, lead to α-amino or α-hydroxy nitriles, which can be hydrolyzed to the corresponding carboxylic acid. Included in this category is the Strecker synthesis of α-amino acids, which dates back more than 150 years.[26] Its asymmetric version (the two component version starting from the imine) is still under intense investigation as it is one of the most direct methods for fabrication of non-natural amino acids.[27,28] Initial success came when *N*-glycosylimines **37** were subjected to the action of a Lewis acid and NaCN or Me_3SiCN to give good yields of product **38** (*Scheme 8*, top).[29] Chiral *N*-(alkylbenzyl)imines, made from the condensation of alkylbenzylamine **39** with aldehydes, were also apt to undergo a stereoselective addition of cyanide ion to give **40** (*Scheme 8*, middle). In both methods, stereoselectivities were in general modest and varied wildly with the nature of the aryl and alkyl groups on the aldehyde, the solvent, and the cyanide source.[30] Removal of the chiral appendage in **38** or **40**, while simple, causes the destruction of the initial

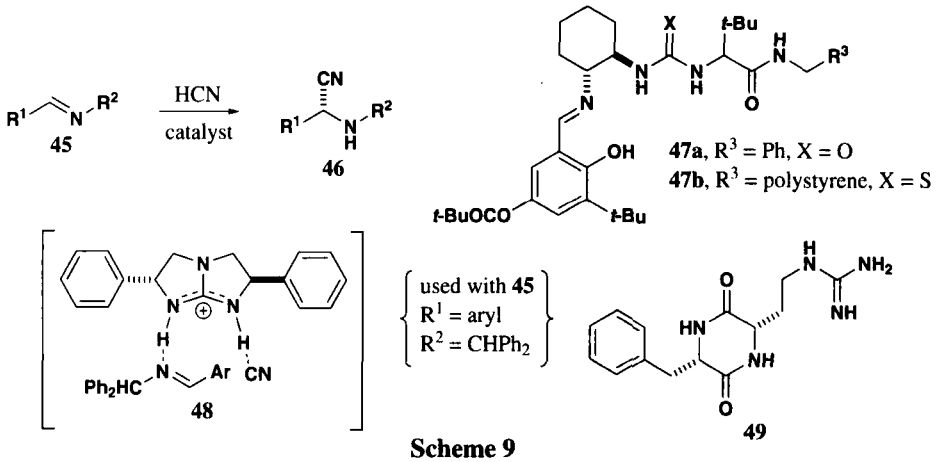
auxiliary. Davies' sulfimines **42** gave respectable results and allowed for an isomerization-free hydrolysis of the chiral appendage in **43** to free the amine **44** (*Scheme 8*, bottom).[31]



Scheme 8

Several cyanide sources were tested in all of these methods but a polymer-supported heme cyanide-Fe complex gave especially high diastereoselectivity upon addition to imines derived from alkylbenzyl- or alkylnaphthylamines.[32] Diastereoselectivities were lower in the absence of the hemin copolymer. In any case, as catalytic methods became more successful (*vide infra*), investigation into chiral auxiliary-based cyanation faded away.

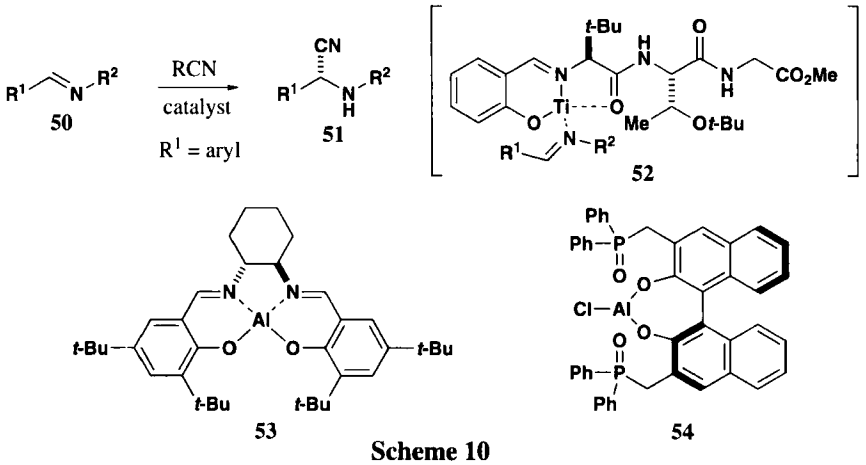
Several catalysts have been developed over the last few years that provide excellent enantioselectivities for the addition of cyanide on pre-formed aldimines. Chiral guanidinium salts, as in **48**, provide chiral induction by bringing together the imine and cyanide through hydrogen bonds. Corey and Grogan obtained good enantioselectivies with a chiral cyclic guanidine which held the reacting molecules in proximity owing to two different hydrogen bonds (**48** in *Scheme 9*).[33] Jacobsen[34] and Lipton[35] used the more complex derivatives **47a** and



Scheme 9

49 respectively, and observed excellent ee's with aromatic aldimines. Catalyst **47a**, in particular, proved applicable to both aromatic and aliphatic aldimines. Polymer-bound catalyst **47b** proved effective and was used to prepare libraries of α-amino nitriles. Catalyst **47a** added to imines derived from methyl ketones to produce α,α-disubstituted-α-amino acids.[36] With aryl methyl ketimines, enantioselectivities above 90% were achieved, with the exception of the *o*-bromophenyl derivative. Additions on imines derived from aliphatic methyl ketones were not reported except for *t*-butylmethyl-*N*-benzylimine that gave the corresponding Strecker product in 70% ee.

The enantioselective metal-catalyzed addition of cyanide to aldimines is very recent.[37] Several metal salen complexes like **53** were screened and Al was identified as giving the best results (*Scheme 10*).[37] Also, polypeptide complexing to Ti (**52**) was used to catalyze

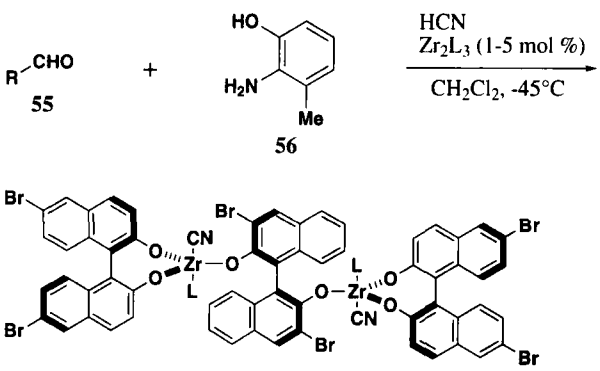


Scheme 10

the addition of Me_3SiCN to aryl aldimines (R^2 = Bn).[38] Shibasaki and co-workers developed a bifunctional Lewis acid/Lewis base Al complex **54** that catalyzed the reaction of aryl *N*-fluorenylimines with Me_3SiCN-PhOH or HCN.[39] They were recently able to fasten this catalyst to different resins and gels for solid-phase catalysis.[40]

The sources of cyanide ion used with all these catalysts are varied ranging from straight HCN to Me_3SiCN or R_3SnCN. Aromatic aldimines consistently gave products with high ee's, often in excess of 90%. However, aliphatic aldimines remain problematic giving unsatisfactory stereoselectivities in many cases.

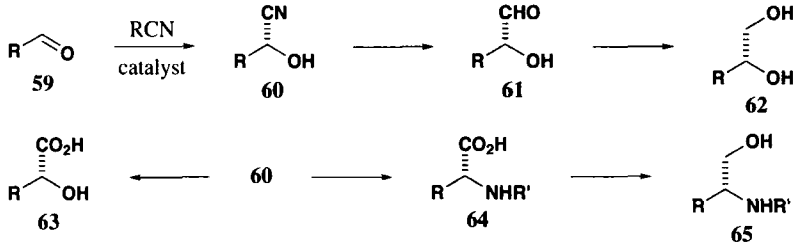
A three component asymmetric reaction, *i.e.* a true asymmetric Strecker-type synthesis, was recently and successfully devised by Kobayashi's group.[41] Their catalyst **58**, a BINOL-Zr bimetallic trimer complex, was able to promote the cyanation of pre-formed aryl aldimines with Bu_3SnCN. However, when an aldehyde, amino phenol **56**, and HCN were mixed in the presence of the catalyst, a good yield of the α-amino nitrile was isolated. The enantioselectivity both for aromatic and aliphatic aldehydes was remarkably high, making this methodology one of the most efficient available today (*Scheme 11*). Selected amino nitriles were converted to amino esters without loss of optical purity.



R	ee (%)
$Ph(CH_2)_2$	94
n-C_9H_{19}	90
c-C_6H_{11}	94
i-Bu	94
t-Bu	88
Ph	86
1-Naphthyl	85

Scheme 11

Aldehydes are also good substrates for the catalytic enantioselective cyanation reaction, giving cyanohydrins which are easily transformed into a multitude of useful chiral synthons including α-hydroxy acids (**63**), α-hydroxy aldehydes (**61**), α-hydroxy ketones, and α-amino acids (**64**) (*Scheme 12*).



Scheme 12

Me_3SiCN is a common source of cyanide for this reaction. An astonishing variety of metal complexes have been used as catalysts to effect this transformation, some of which are represented in *Fig. 4*.[42,43] It is not necessary to discuss the particulars of every catalytic system and only a few selected examples will do for the purpose of this review article. Like aliphatic aldimines, aliphatic aldehydes tend to give products with lower enantioselectivities than aromatic aldehydes with all of the metal catalysts. Very recently the concept of bifunctional catalysis was applied by Shibasaki to the cyanation of aldehydes using Al-complex **52** discussed above (cf. *Scheme 10*).[44] The ee's recorded were high and the catalyst was effective on a broad range of aromatic and aliphatic substrates.

$Zr(Ot\text{-}Bu)_4$ was effective in catalyzing the transfer of cyanide from acetone cyanohydrin to aldehydes, and did so enantioselectively in the presence of chiral ligands. The best ligand in that respect was TADDOL (**74**) (*Scheme 13*).[45] This catalyst system is among the most general for this reaction giving respectable enantioselectivities for aliphatic as well as aromatic aldehydes.

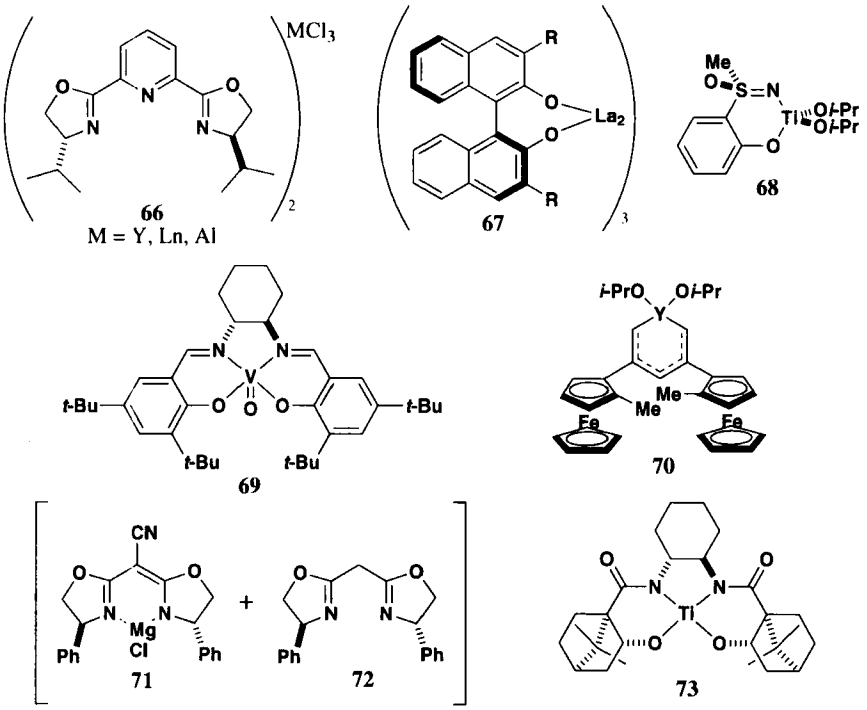
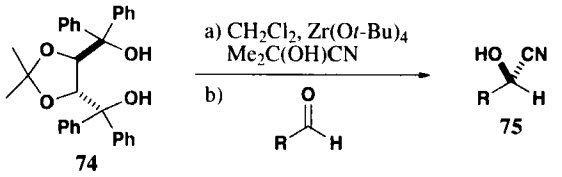


Fig. 4

Catalysts Able to Effect the Asymmetric Cyanation of Aldehydes



R	ee (%)
$Ph(CH_2)_2$	80
n-C_9H_{19}	84
c-C_6H_{11}	79
t-Bu	72
$PhCH_2$	59
Ph	63
Furyl	61
Thiophenyl	54
(*E*)-Cinnamyl	29

Scheme 13

Using Ti complexes (*Fig. 5*), Shibasaki[46] and North[47] and their co-workers were able

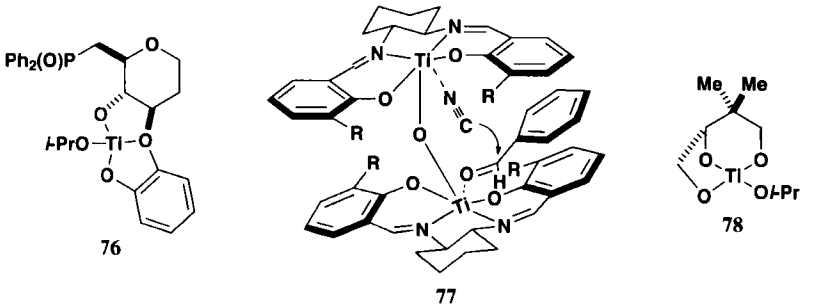
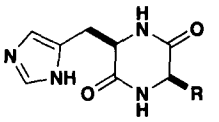


Fig. 5

Metal Catalysts Effecting the Asymmetric Cyanation of Ketones and Aldehydes

to effect the catalytic asymmetric cyanation of aldehydes and ketones, the latter formally leading to α,α-disubstituted-α-hydroxy acids. Transition state **77** was proposed to account for the sense of asymmetry in the case of this unusual bridged dimeric Ti oxide catalyst.[47] Choi used high pressure and catalyst **78** to effect a modest level of asymmetric induction in the addition of cyanide to acetophenone.[48]

D-Oxynitrilase enzymes found in almonds and other natural sources catalyze the addition of HCN to aldehydes. The purified enzymes are capable of converting a large spectrum of aromatic and aliphatic aldehydes into cyanohydrins with high enantiomeric purities using HCN.[47] Crushed, defatted almonds can be used in conjunction with acetone cyanohydrin *in lieu* of HCN without loss of yield or selectivity making this procedure extremely user-friendly.[49] Electron-withdrawing or donating substituents on the aromatic aldehyde are tolerated as are functional groups or branching in aliphatic aldehydes. Moreover, methyl ketones are excellent substrates for this enzymatic reaction giving high yields of disubstituted cyanohydrins with excellent enantioselectivities. Diketopiperazines **79** (*Fig. 6*) were effective in cata-



79

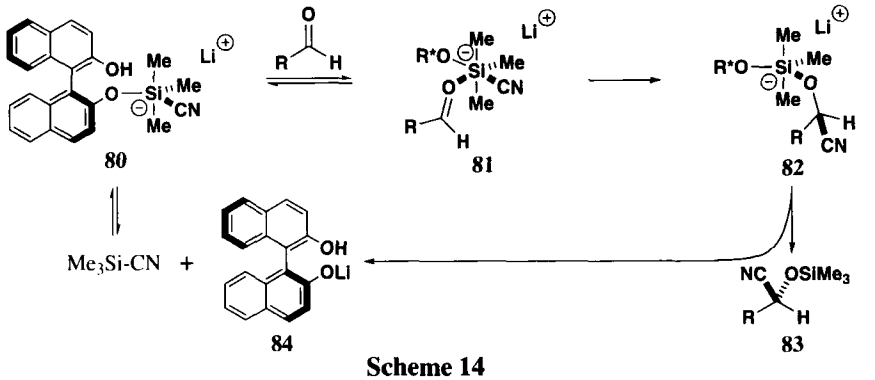
R = CH_2Ph, CH_2CHMe_2, CH_2Ph-OMe

Fig. 6

Diketopiperazines Capable of Enantioselective Cyanation of Aldehydes

lyzing the addition of HCN to a large number of aldehydes.[47] The mode of catalysis of **79** was the subject of several investigations and Lipton demonstrated that under the conditions where **79** catalyzes the reaction, auto-induction of asymmetry was a general phenomenon.[50]

Kagan and Holmes reported the only Lewis base-catalyzed cyanation of aldehydes (*Scheme 14*). The monolithio derivative of BINOL adds to Me_3SiCN to form a pentavalent Si

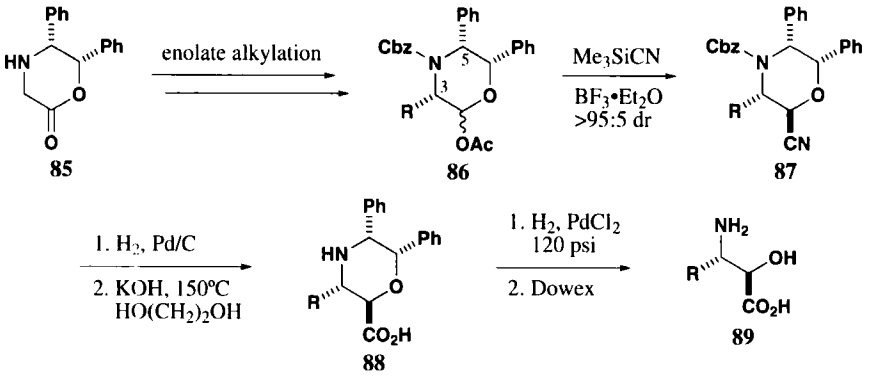


Scheme 14

species **80** as the active catalyst. The hexavalent Si species **81** is then able to transfer cyanide to the activated aldehyde with moderate selectivity. The limited success thus far reflects the many

side-reactions which may impede chirality transfer: a) ejection of free cyanide from **80** and its participation in racemic cyanation of the aldehyde; b) trimethylsilylation of **84** killing the catalyst (which occurs when intermediate **82** casts out the lithiated cyanohydrin instead of **84**).[51]

Williams and co-workers employed glycine template **85** for cyanation reactions using Me_3SiCN.[52] This versatile template leads to α-hydroxy-β-amino acids **89** *via* enolate alkylation chemistry (**85** → **86**) followed by cyanation of an oxonium ion generated by treatment of acetate **86** with $BF_3{\bullet}Et_2O$ (*Scheme 15*). Although the complete process to the final α-hydroxy-β-amino acid involves several steps, the method allows the introduction of a variety of alkyl

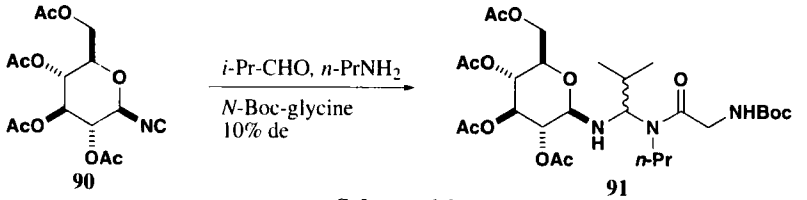


Scheme 15

groups (R). In addition, the C-3 epimer of compound **86** was also accessible from **85**, leading to the enantiomer of **89** *via* the same sequence of reaction. Therefore, both enantiomers of **89** can be obtained from intermediate **85**.

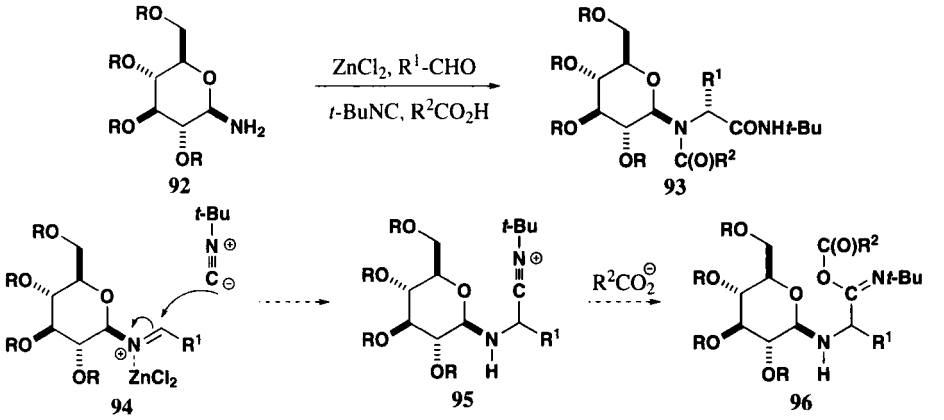
c) Asymmetric Ugi Condensation

The Ugi condensation is a useful variant of the Strecker α-amino acid synthesis involving an amine, an aldehyde, an isocyanide and a carboxylic acid.[53] In general, the isocyanide moiety and the carboxylic acid fragment have little bearing on the stereochemical outcome of the reaction. For example, Ziegler and co-workers have performed the four component condensation (4CC) with glucosyl isonitrile **90** and obtained low diastereoselectivity and a moderate yield of the condensed product **91** (*Scheme 16*).[54]



Scheme 16

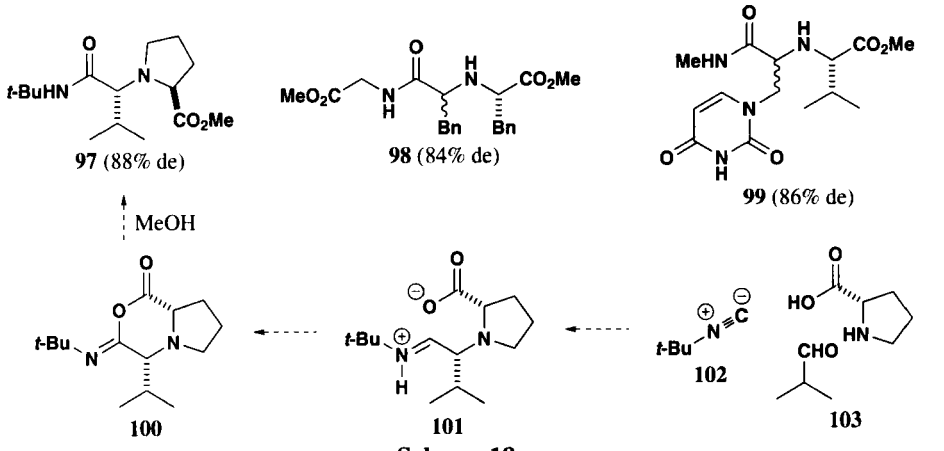
In contrast, chiral amines were shown to induce asymmetry quite efficiently in the Ugi condensation. Kunz and Ugi have developed a sugar-based chiral template for the synthesis of α-amino acids using this technique (*Scheme 17*).[55,56] The stereoselective step in this



Scheme 17

4CC probably occurs upon addition of the *t*-butylisocyanide to the imine **94** derived from chiral amine **92** (R = Piv) and the aldehyde. Conceivably, the addition of the carboxylic acid could be concerted with the addition of the isocyanide without the intermediacy of **95**. Releasing the free amino acid from **93** was performed in three steps, namely cleavage of the $R^2C(O)$- group, deglycosylation, and *t*-butylamide hydrolysis.[55] Selectivities were higher when tetra-*O*-isoamyl-1-aminoglucose was used (**92**, R = i-C_5H_{11}). This auxiliary also permitted the synthesis of dipeptides because of milder cleavage conditions.[56] Kunz recently adapted this methodology to solid phase synthesis.[57]

Non-racemic amino acids underwent the Ugi 4CC in a highly diastereoselective manner, effectively setting up the chirality α to the newly formed carbonyl in products **97-99** (*Scheme 18*). This is a variant of the Ugi 4CC where the amino acid plays the dual role of the



Scheme 18

amine and the carboxylic acid. The reaction proceeds *via* a cyclic *O*-acyl amide like **100** and opening by methanol gives the corresponding ester **97**.[58] The relative stereochemistry of **98** and **99** was not determined. This methodology is highly suitable for the production of chemical libraries and may also serve for polypeptide synthesis.

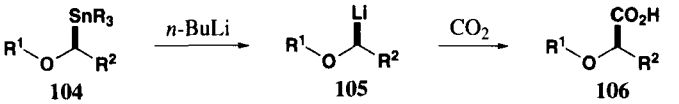
One limitation of the Ugi protocol is the scarcity of commercial isocyanides which are often difficult to prepare and cannot be stored for long periods of time. This factor narrows the possibilities for varying the nature of the resulting secondary amide. Subsequent modification of that amide in Ugi adducts for synthetic purposes is not necessarily trivial except in small molecules. Thus, Armstrong introduced the concept of a 'universal isocyanide' from which the resulting amide can be easily converted to other functionalities.[59] For that purpose, 1-isocyanocyclohexene proved highly versatile and the resulting Ugi condensation product was converted to a wide spectrum of useful derivatives such as esters, thioesters, acids, or other amides

In 1921, Passerini described the three-component condensation of a carboxylic acid, an aldehyde, and an isocyanide, of which the Ugi condensation is a close relative. This technique allows the preparation of chiral α-hydroxy acids instead of amino acids. There are very few reports of chiral versions of this reaction and in all cases little or no diastereoselectivity is obtained.[53,54,60,61]

2. Electrophilic Carbonyls or Surrogate Carbonyls

a) Chiral Deprotonation/Carbonylation

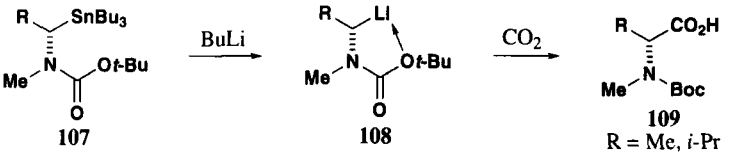
The metallation of suitably substituted chiral amines or ethers and the subsequent reaction of the metallated species with CO_2 leads to non-racemic α-amino or α-hydroxy acids respectively. Chiral α-alkoxystannanes are known to undergo transmetallation to give α-alkoxylithio species that retain their original stereochemistry even after reaction with an electrophile (*Eq. 3*). When the electrophile is a chloromethyl ester or CO_2, optically active α-hydroxy esters or acids, respectively, are formed in high yield and stereoselectivity. There



104 105 106 (3)

were a number of contributions in the mid- to late 1980's which demonstrated this strategy,[62] including methods to generate chiral α-alkoxystannanes.[63]

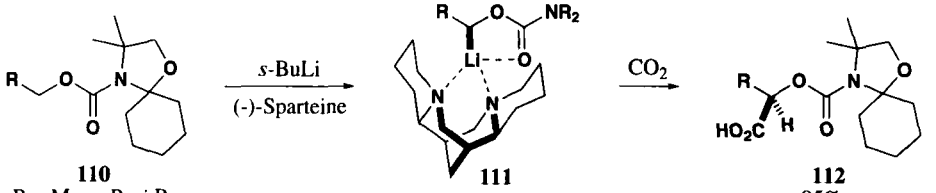
Chong and his group were the first to report this reaction using α-(aminoalkyl)stannanes like **107** (*Scheme 19*).[64] As it turns out, the corresponding lithio species **108** was not as configurationally stable as their α-alkoxy counterparts but could nevertheless be generated and trapped with electrophiles at low temperature to afford products with complete retention of configuration.[65]



107 108 109
R = Me, *i*-Pr

Scheme 19

The enantioselective deprotonation of a benzylic or allylic ether or amine is a more convenient method to achieve this transformation. This can be done using an alkyllithium in the presence of (-)-sparteine.[66] Often, a complexing group attached to the oxygen or nitrogen helps in stabilizing the organolithium formed. Carbamates **110** were deprotonated in this fashion, using *s*-BuLi and (-)-sparteine, and the resulting organolithiums **111** were quenched with CO_2 to give the corresponding α-alkoxy acids in high yield and >95% ee (*Scheme 20*).[67] When

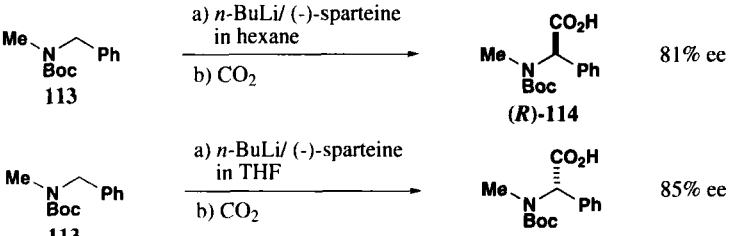


110 111 112
R = Me, *n*-Pr, *i*-Pr
>95% ee

Scheme 20

CO_2 was replaced by Me_3SnCl, the resulting chiral stannane was obtained and could be used as a stable, storable precursor of the organolithium since it could be transmetallated back to **111** with *n*-BuLi in the presence of tetramethylethylenediamine.

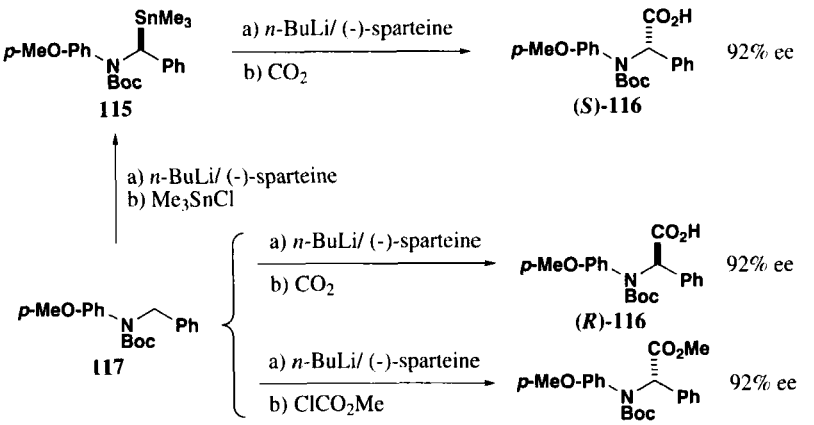
N-Boc methylbenzylamine **113** was enantioselectively deprotonated by *s*-BuLi/(-)-sparteine. Addition of CO_2 had to follow quickly because the diastereomeric organolithium/ (-)-sparteine complex slowly equilibrated at low temperature in hexane or tetrahydrofuran. However, reaction of **113** in hexane gave (*R*)-**114** while its reaction in tetrahydrofuran gave the enantiomer (*S*)-**114** (*Scheme 21*).[68]



113 (*R*)-114 (*S*)-114

Scheme 21

Beak and co-workers could effect the enantioselective deprotonation of *N*-protected aryl benzylamines **117** with the couple *n*-BuLi/(-)-sparteine. The resulting configurationally stable organolithium was alkylated with a variety of carbon electrophiles. When CO_2 was added as the electrophile, amino acid (*R*)-**116** was isolated in good yield (*Scheme 22*). Amines

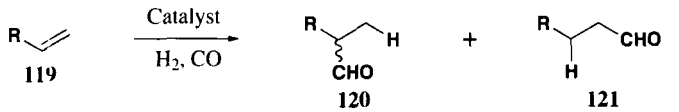


Scheme 22

117 substituted with aryl groups other than phenyl gave identical results. The amino acid (*S*)-**116** of opposite absolute configuration was obtained by initially adding Me_3SnCl as the electrophile and subsequently transmetallating **115** to Li in the presence of (-)-sparteine before reaction with CO_2. It appears the alkylation with Me_3SnCl proceeds with the same sense of asymmetric induction as CO_2 and that it is in the subsequent transmetallation step that inversion occurs. Surprisingly, the electrophile methyl chloroformate gave product having the opposite stereochemistry as that obtained with CO_2 or Me_3SnCl.[69] The reason for this difference is subtle and not clearly understood but the phenomenon has been observed and discussed elsewhere.[70]

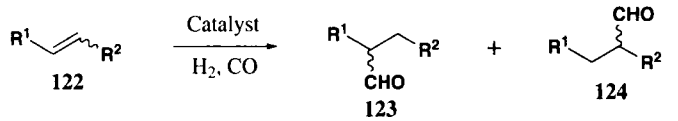
b) Enantioselective Hydrocarbonylation

Catalytic hydroformylation is a very important industrial process by which carbonyl compounds are made. Asymmetric induction in this reaction reached a useful level in the mid-1990's[71] following a large collection of promising results obtained in the preceeding decade. Terminal and 1,2-disubstituted alkenes (**119** and **122** respectively) pose different complications to catalytic enantioselective hydroformylation, the problem of regioselectivity being perhaps the most trying of them. Indeed, the undesired, achiral, structural isomer **121** is often formed as the major product in the case of terminal olefins (*Eq. 4*) while unsymmetrical 1,2-disubstituted alkenes lead to unpredictable mixtures of regioisomers **123** and **124** (*Eq. 5*).



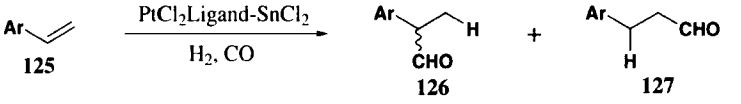
(4)

Other problems include *in situ* racemization of the product aldehyde and competitive hydrogenation of the alkene.



(5)

Pt, Rh, and Co complexes have catalyzed the enantioselective carbonylation of olefins with more success than other transition metals. In early studies, styrene (**125**, Ar = Ph) was hydroformylated in 70-80% ee using $PtCl_2/SnCl_2$ and a chiral ligand (*Scheme 23*).[72]



Scheme 23

Several chiral ligands are shown in *Fig. 7*. The Sn salt inserts into a Pt-Cl bond to form an activated species.[73] In all of these cases, the regioisomeric ratio **126/127** was low. The asymmetric hydroformylation of styrene derivatives is important for the production of nonsteroidal

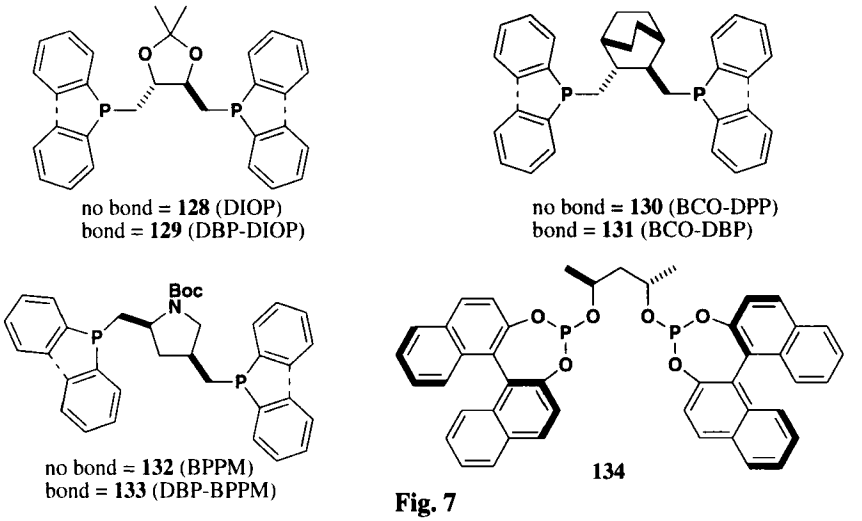


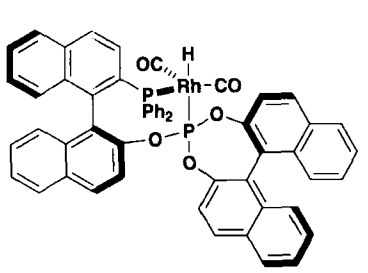
Fig. 7

Ligands Used with Pt-$SnCl_2$ For the Asymmetric Hydroformylation of Styrenes

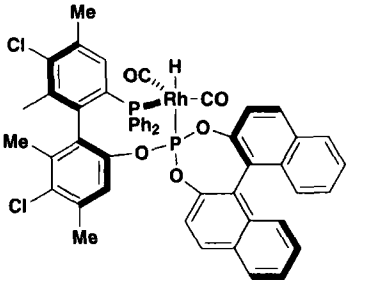
anti-inflammatory 2-arylalkanoic acids like ibuprofen (**126**, CO_2H instead of CHO, Ar = *s*-Bu-Ph) and naproxen (**126**, CO_2H instead of CHO, Ar = 2-[6-MeO-2-naphthyl]).

The problem of racemization under the reaction conditions was circumvented by making the diethyl acetal of the aldehyde *in situ* using triethyl orthorformate. With such reaction conditions and using BPPM-Pt complex (**132**), the chiral regioisomer **126** was obtained in >96% ee.[74] More recent work using Pt complexes include the discovery of a pressure dependence on enantioselectivity.[75] Other research groups have tried to improve on the current accomplishments with Pt catalysts made with chiral ligands, several of which are shown in *Fig. 7*.[76]

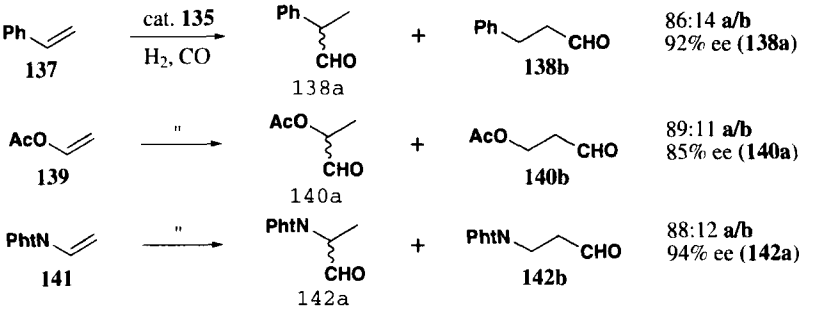
Although Rh-catalyzed hydroformylation met with little success in early studies,[71] a major improvement came about with the advent of the BINAPHOS-Rh complex **135** (*Scheme 24*).[77] With this catalyst, several types of substrate olefins were successfully hydroformylated



135 (BINAPHOS-Rh)



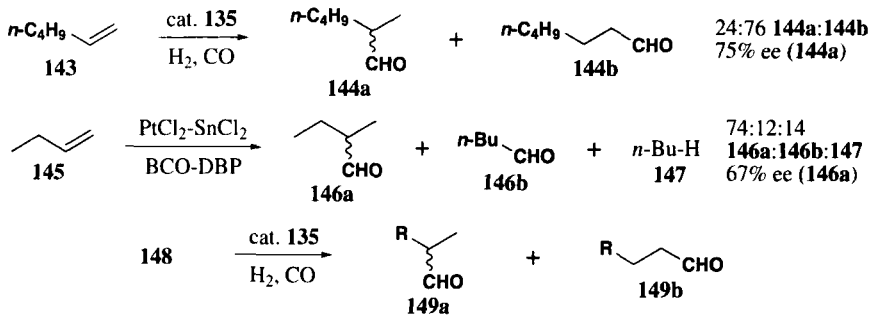
136 (BIPHEMPHOS-Rh)



Scheme 24

into carbonyl products with high ee's. In particular, vinyl acetate **139** led to α-hydroxy aldehyde **140a** and *N*-vinylphthalimide **141** gave aldehyde **142a**, which was oxidized to the corresponding α-amino acid.[78] A polymer-bound version of this catalyst also exists.[79] The catalyst BIPHEMPHOS-Rh **136** gave similar results.[80] New phosphonite-phosphite,[81] aminophosphonite-phosphite,[82] gluco-furanose diphosphite,[83] diphosphine,[84] polyether-phosphite,[85] and chiral thiourea[86] ligands were recently reported to effect the enantioselective hydroformylation of styrene when complexed to Rh. Leitner has used supercritical CO_2 to effect the enantioselective hydroformylation of styrene with the BINAPHOS-Rh catalyst **135**.[87] The low solubility of complex **135** led him to develop a perfluorinated analog which gave similar ee's but with increased regioselectivity in favor of the desired chiral aldehyde.[88] The question of environmentally friendly solvents to effect organic reactions is drawing more interest from synthetic chemists.

Aliphatic terminal alkenes do not hydroformylate with as much success as their aromatic analogs, as exemplified in *Scheme 25*. One of the better results was obtained with the $PtCl_2/SnCl_2$ system on 1-butene (**145**) (67% ee, 74% of the correct regioisomer).[72a] It is noteworthy that no racemization occurred under these conditions despite the absence of triethylorthoformate. Conjugated dienes **148** underwent hydroformylation in reasonable regio- and enantioselectivities with the BINAPHOS-Rh catalytic system. However, the selectivities were quite dependent on the substitution pattern (*Scheme 25*).

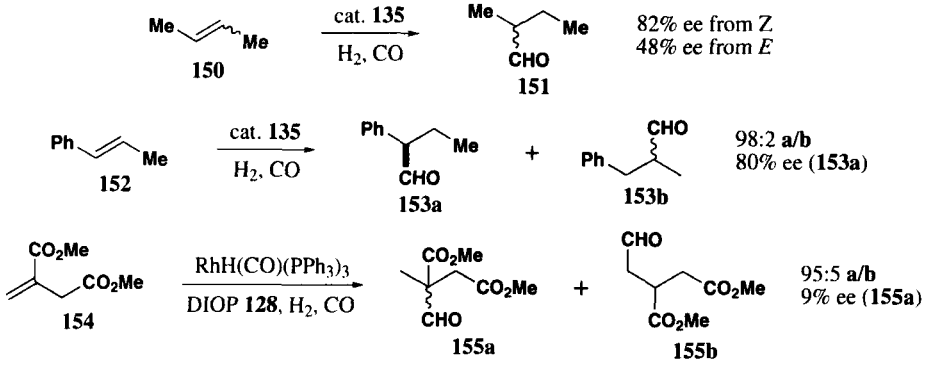


148	149a ee (%)	149a:149b
	---	0:100[a]
	22	78:22
	72	78:22
	96	87:13
Ph	81	95:5

a: mixture of β,γ- and γ,δ-pentenal

Scheme 25

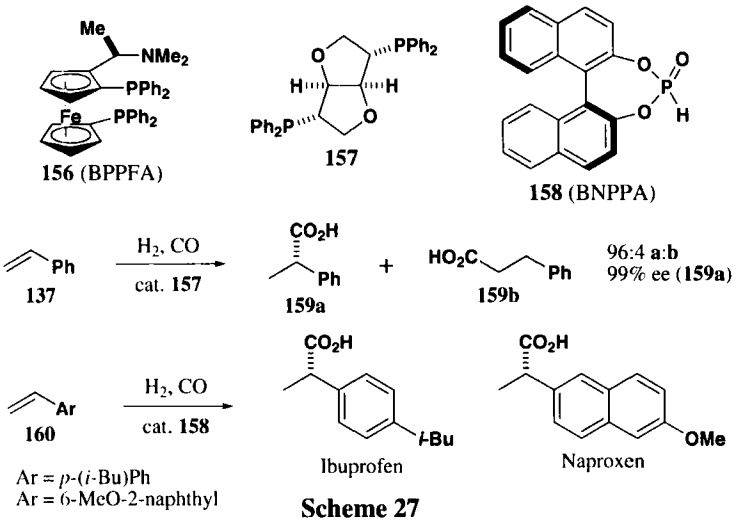
Symmetrically 1,2-disubstituted alkenes do not pose a problem of regioselectivity to the hydroformylation reaction and quite high enantioselectivities were achieved with the BINAPHOS-Rh catalyst **135** (*Scheme 26*).[71c] There is a marked difference in reactivity and



Scheme 26

enantioselectivity between the *Z*- and *E*-isomers of **150**, the former being more reactive and giving α-chiral aldehydes with higher enantiomeric purity. The use of 1,1-disubstituted alkenes would lead to quaternary carbon centers, but apart from itaconate derivatives **154**, there are no examples of successful hydroformylation with such systems. Even then, the enantioselectivities obtained with **154** were low. Tri- and tetrasubstituted alkenes would give rise to two adjacent chiral centers upon hydroformylation but they are generally unreactive.

Enantioselective hydrocarboxylation is still a relatively ignored subject.[89] Until recently, a high pressure of CO was required with Pd catalysts to get the reaction to work and the chiral acids obtained were of low optical purity. In 1997, Inoue reported the hydrocarboxylation of styrene in 86% ee using the ligand BPPFA **156** with $Pd(OAc)_2$ and tosic acid as the catalysts.[90] The same year, Zhou *et al.* reported the same reaction in 99% ee using diphosphine **157**.[91] Alper and his group prepared ibuprofen and naproxen in 84 and 91% ee respectively[92] by direct hydrocarboxylation using their $PdCl_2$-$CuCl_2$ couple and BNPPA **158** as chiral ligand (*Scheme 27*).[93]



Scheme 27

II. REACTIONS α- TO A CARBONYL OR SURROGATE CARBONYL

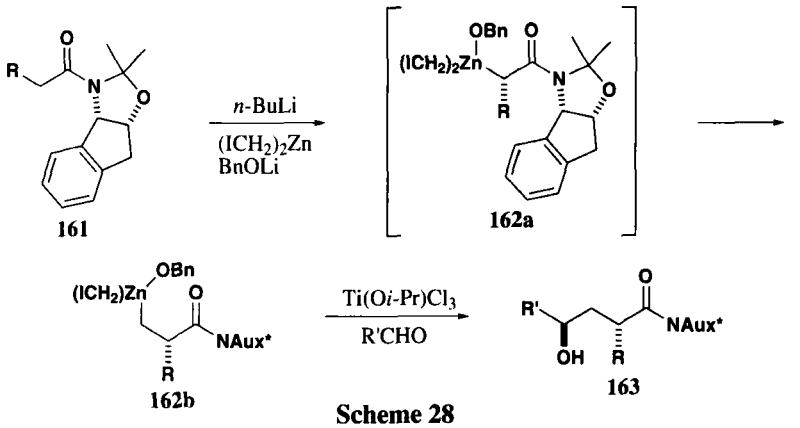
Many of the following alternatives to asymmetric enolate chemistry share the one basic advantage of the latter: (a) generation of the desired carbonyl compound in the enantioselective step; (b) creation of up to two chiral centers in the same operation; (c) wide scope and generality. Advantage (b) implies the creation of a chiral carbon β to the carbonyl and in fact many of the methods described below are suitable for the generation of α,β-chiral as well as α-chiral carbonyl compounds. The reader should also consult the appropriate sub-sections of section III that deal with reactions β to a carbonyl or surrogate carbonyl.

1. Nucleophilic α-Carbon

Conceptually close to the classical chiral enolate chemistry, the following strategies were aimed at solving some of the problems encountered in enolate chemistry without abandoning its basic advantages. Replacement of enolates by azaenolates (metallated enamines), for example, has reduced the problems of self-condensation, polyalkylation, and to some extent, control of regiochemistry.

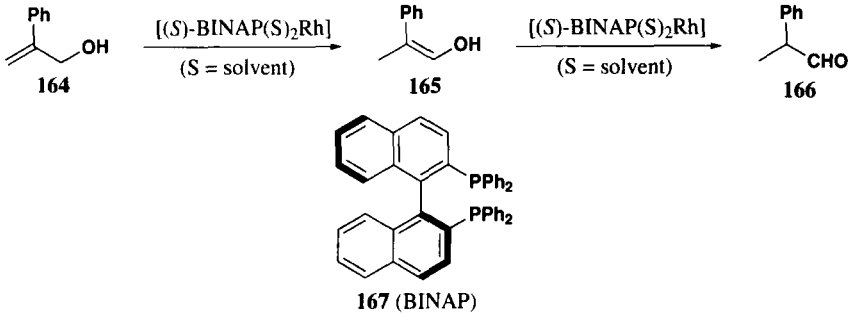
a) Enols and Enolates

As mentioned in the introduction, the reaction of enolates are not covered in this review.[1,94] There are, however, a few reactions involving enols or metal enolates that possess distinct features or mechanisms and they will be discussed briefly in this section. The conversion of chiral Zn enolates **162a** into Zn homoenolates **162b** was described in 1996. A α-chiral center is produced in the process, and the resulting homoenolate **162b** was transmetallated with Ti(IV) prior to adding aldehydes, which afforded δ-hydroxy-α-alkyl amides (*Scheme 28*).[95]



Scheme 28

Trisubstituted allylic alcohol **164** was converted to α-chiral aldehyde **166** in 18% ee using the catalyst $[(BINAP)Rh]^+$ (*Scheme 29*). Although this reaction involves the isomerization of an allylic alcohol (see section III.2.c), the stereodefining step occurs in the tautomerization of the enol which justifies its inclusion in this section.[96] The mechanism of the enantioselective tautomerization is not understood but it presumably involves a chelation between the enol **165** and the Rh complex.



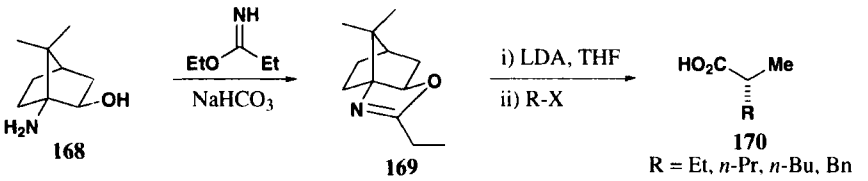
Scheme 29

b) Metallated Oxazolines, Imines and Hydrazones

Chiral oxazolines, introduced by Meyers and co-workers in 1974, are now well entrenched as chiral enolate equivalents. The subject has been reviewed periodically[5d,97] so this

review will only cover the very latest developments. Like its enolate counterpart, the metallated oxazoline reacts only with activated electrophiles and control of the azaenolate geometry is limited to trisubstituted ones.

A new chiral oxazoline **169** derived from camphor was deprotonated with lithium diisopropylamide (LDA) and alkylated with primary alkyl halides (*Scheme 30*).[98] The yield and de's of the alkylation step were superior to the original oxazoline system of Meyers. The subsequent hydrolysis to the acid gave modest yields but little or no racemization.

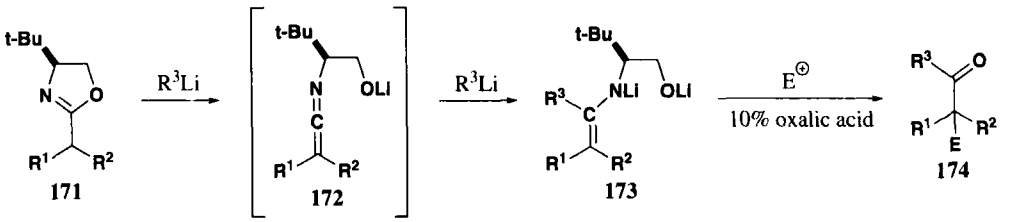


168 **169** **170**

R = Et, *n*-Pr, *n*-Bu, Bn

Scheme 30

Metallated imines, and perhaps more successfully, metallated hydrazones, have been used for years as chiral enolate equivalents. Enders in particular has contributed to this field a great deal, and several reviews are available.[5] Recently, Meyers reported an asymmetric oxazoline-ketenimine rearrangement (**171** → **172**) leading to chiral α-trisubstituted ketones **174** (*Scheme 31*).[99] Two equivalents of base (R^3Li) are needed, the second equivalent adds to



171 **172** **173** **174**

R^1 = Me, Et, *n*- Bu, *i*-Pr
R^2 = Me, Ph; R^3 = *n*- Bu, Ph
E^+ = BnBr, $H_2C{=}CHCH_2Br$
yields: 50-72%, ee's: 35-87%

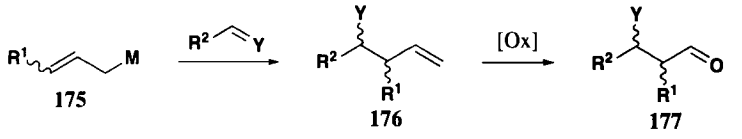
Scheme 31

ketenimine **172** to create the metallated enamine **173**. Although the enantioselectivities achieved in the alkylation step are modest, there are only a few other examples of the construction of chiral quaternary carbon centers in acyclic chiral enolate chemistry.[100]

c) Allylmetal Addition to Carbonyls or Analogs

Perhaps the best known alternative to aldol methodology is allylic metal addition to aldehydes (*Eq. 6*).[101,102] The similarity between the two is evident, the only difference being a carbon replacing the enolate oxygen in the allylic metal species. Many reported carbohydrate and polyketide syntheses made use of both carbons of the adduct's double bond (**176**), but oxidative cleavage to a carbonyl (**177**) or alcohol function is straightforward and thus this sequence consti-

tutes a useful alternative to asymmetric aldol chemistry. Allyl- and crotylboron, -silicon, and -tin compounds still dominate this area of research although allyl- and crotyltitanium, -zirconium, -chromium, and -magnesium species have been put to good use in asymmetric syntheses.[101,102]



(6)

a) R^1 = H, Y = OH (acetate adduct)
b) R^1 = Me, Y = OH (propionate adduct)

The more useful allylmetal additions proceed by transposition of the double bond (A_E2') to generate two chiral centers in the final product. This area of research has been reviewed periodically so the present review will survey the different strategies and recount recent developments. This section covers only examples where the final alkene in the product served, or could serve, as a masked carbonyl function. Cases where the double bond was not actually converted to a carbonyl were included if oxidative cleavage of the double bond appeared feasible and practical. The discussion will center mainly around two types of final carbonyl adducts **177a** and **177b**, the acetate and propionate adducts, which are defined in *Eq. 6*.

There are three types of allylmetal additions to aldehydes (*Fig. 8*). Additions of type I follow the 'Zimmerman-Traxler' cyclic transition state model. Boron is the more common metal for this type of addition. Additions of type II require an external Lewis acid and usually

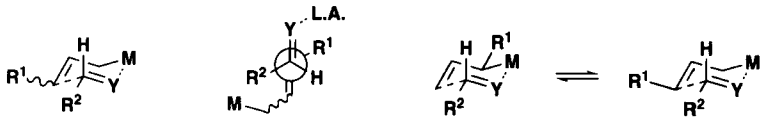


Fig. 8

The Three Types of Allylmetal Addition to Aldehydes

involve Sn and Si as the metal. The reactions proceed *via* an 'open-chain' transition state. They are on average less diastereoselective than type I reactions but the asymmetry may be brought in catalytically through the use of chiral Lewis acids (*vide infra*). Type III additions are much like type I but involve an equilibrium between the α- and γ-forms of the allylic metal. This equilibrium also permits the interconversion between the *E* and *Z*-configuration of the double bond.

Chirality in the product is induced either by a chiral allyl fragment (with chiral ligands on the metal or with a chiral allyl unit) or by chiral Lewis acids coordinated to the aldehyde. The following sections will briefly discuss each of these.

i. Chirality on the Metal

Typical examples of allylmetals bearing chiral ligands on the metal are shown in *Fig. 9*.[101,102] Allylboronates **178-180**, **184-186**, and allylzinc **182** react with aldehydes through a type I

mechanism while allyltin **181** proceeds *via* a type II pathway and allyltitanium **183** *via* a type III pathway (see *Fig. 8*, p. 27).

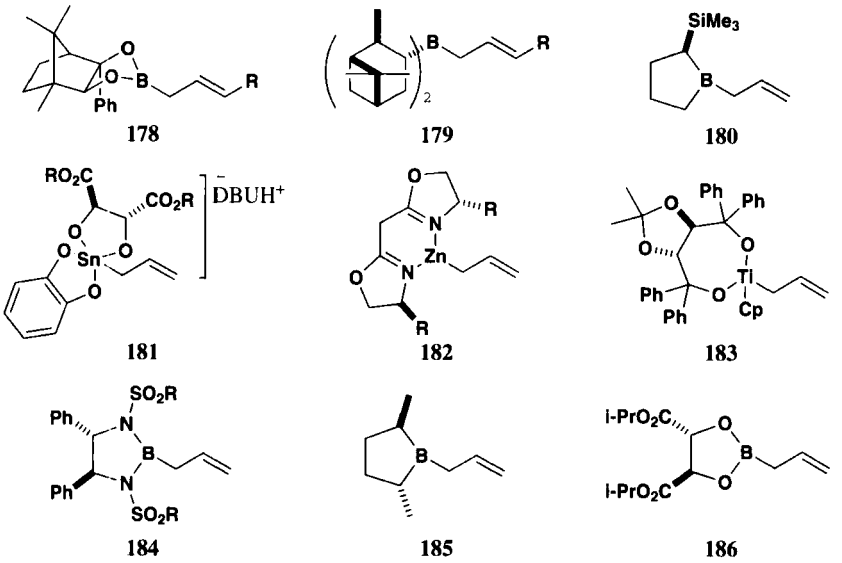
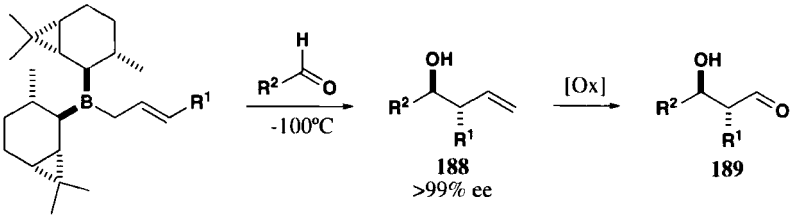


Fig. 9

Chiral Allyl Units Bearing Chirality on the Metal

Near perfect enantioselectivities in the addition of both allyl- (R^1 = H) and crotylbis(2-isocaranyl)borane **187** (R^1 = Me) at –100°C under Mg salt free conditions (*Scheme 32*).[103] The



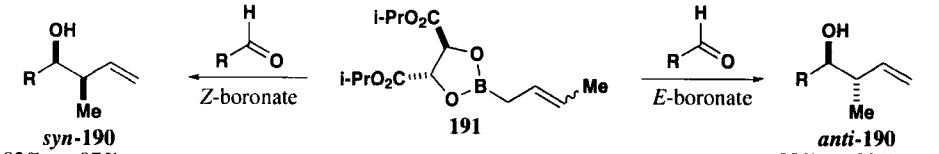
Scheme 32

same is true for the diisopinocampheyl analog **179** (*Fig. 9*). However, these reagents are not easily prepared and handled. Several other auxiliaries have found widespread use and are discussed in other review articles.[102]

Many features of the reaction and the resulting products make the allylation of aldehydes a distinctively useful alternative to aldol chemistry: a) the metal auxiliary is severed during the reaction, alleviating the need for a cleaving step; b) the adduct **188** (*Scheme 32*) is not prone to epimerization or retroaldol reaction and will thus withstand harsher basic or acidic conditions, permitting the protection of the alcohol as almost any desired functional group (this is not the case with normal aldol adducts); c) the oxidative cleavage of the double bond allows access to acids, aldehydes, or alcohols directly; d) in contrast to aldol chemistry,[1,2] so-called 'acetate

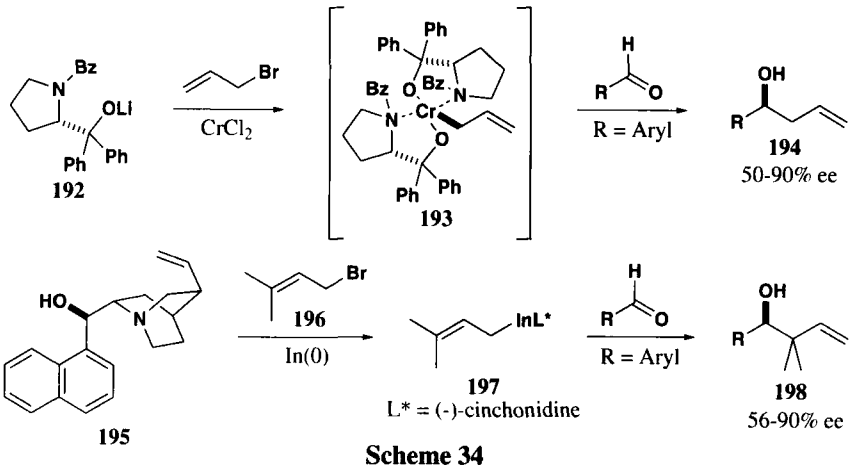
adducts' such as **189** (R^1 = H) can be obtained in high % ee. As is the case with aldol condensations, the stereochemistry of the adducts is often controlled by the chiral ligands on the allylmetal (reagent controlled). This allows a high level of stereocontrol even when α-chiral aldehydes are utilized. In only a few cases must the chirality of the reagents and the aldehyde be matched in order to obtain high stereochemical inductions.

Most of the stoichiometric reagents depicted in *Fig. 9* also work well with the crotyl fragment (**187**, R^1 = Me, *Scheme 32*) that leads to the formation of so-called propionate-like units (**188**, R^1 = Me, *Scheme 32*). The *E*-crotylboronate *E*-**191** gave *anti*-**190** in high diastereoselectivity while *Z*-**191** afforded *syn*-**190** in slightly lower enantiomeric and de (*Scheme 33*).[104] This reaction proceed *via* a type I mechanism (see *Fig. 8*, p. 27).



Scheme 33

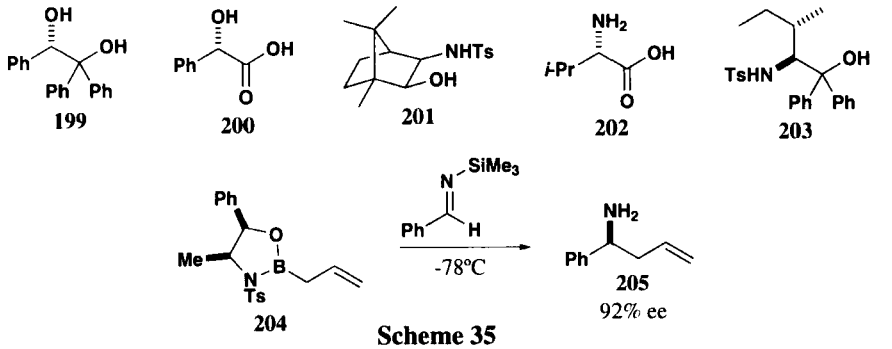
Recent work in the area of allylmetal addition to aldehydes includes that of Kibayashi. Chiral allylchromium **193** underwent a stereoselective Nozaki-Hiyama reaction with a variety of aldehydes (*Scheme 34*, top).[105] A type III mechanism is likely in this case and is common with organochromiums. Loh and co-workers recently developed an In complex of (-)-cinchonidine **195** to promote the addition reaction of prenyl bromide **196** to aldehydes in water (*Scheme 34*, bottom).[106] Enantioselectivities were in the 60-80% range and somewhat lower with allyl bromide, which gave better results in dichloromethane.[107]



Scheme 34

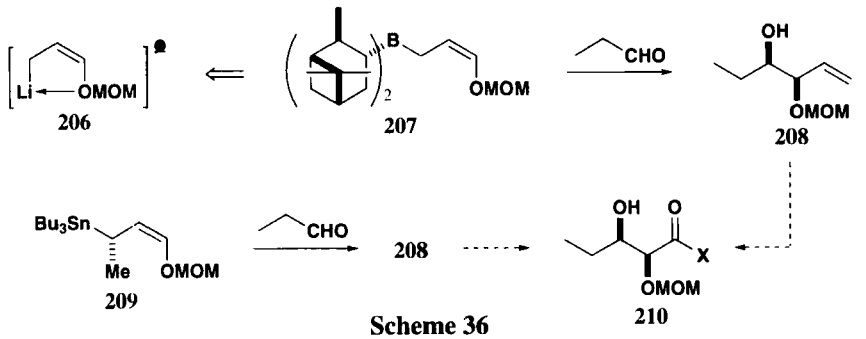
Addition of chiral allylmetals to imines provide a good route to homoallyl amines and therefore to β-amino acids after oxidative cleavage. Itsuno and co-workers described the first

enantioselective addition of chiral allylborane to the trimethylsilylimine of benzaldehyde.[108] They used Roush's allylboronate **186** or Brown's allylborane **179** (R^1 = H, cf. *Fig. 9*) but the stereoselectivity was low to moderate (23-73% ee). Several other allylboron reagents made from chiral ligands **199-203** were later tested and their best results were obtained with *B*-allyloxazaborolidine **204** (*Scheme 35*).[109] A polymer-supported chiral allylboron reagent derived from **201** was constructed to induce asymmetry in the allylation reaction of the trimethylsilylimine of benzaldehyde.[110] Other imines gave reduced chemical yields.



Scheme 35

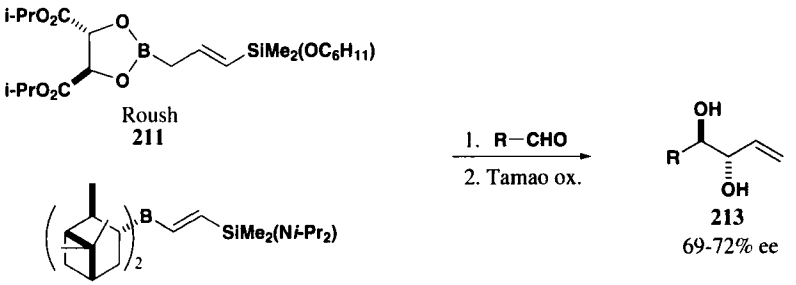
Syn 1,2-diols like **208**, and more recently, *anti* 1,2-diols were built from the addition of allylboranes or boronates to aldehydes (*Scheme 36*). Such products can be transformed to α,β-dihydroxy carbonyls by oxidative cleavage of the double bond. *Syn* 1,2-diols **208** was made from



Scheme 36

(*Z*)-alkoxyallylborane[111] **207** or -stannane[37,112,113] **209** and propionaldehyde. The *Z*-geometry of the alkene in **207** was obtained by metallation of the methoxymethyl enol ether of propionaldehyde, which generated a chelated species **206**. Subsequent transmetallation from Li to boron gave *Z*-allylborane **207**. The analog (*E*)-**207** was not readily accessible and thus indirect methods to make diols with the *anti* relative configuration were sought.

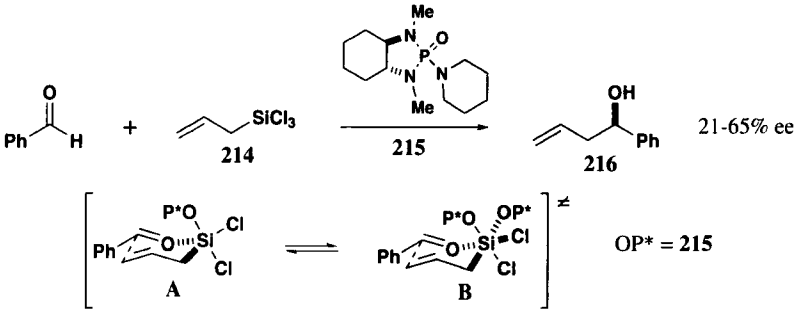
E-Silylallylboranes **211** and **212** provided a useful, albeit indirect, solution to this problem (*Scheme 37*). Roush[114] and Barrett[115] have adapted a clever strategy developed by Ito and Tamao[116] which utilizes a alkoxydimethylsilyl or (diisopropylamino)dimethylsilyl group as a



Scheme 37

disguised hydroxyl unit. Upon oxidation of the addition product, the silyl group is replaced by an alcohol with retention of the original stereochemistry. Brown and Nara have devised a similar approach with a (borinanyl)allylborane.[117]

Allyl- or crotylsilanes or -stannanes with chiral ligands on Si or Sn were described,[118] but the observed enantioselectivities in their addition reactions to aldehydes were modest on average. This may be due to the need for activation of the aldehyde by a Lewis acid in these additions, forcing a less selective type II mechanism (cf. *Fig. 8*). On the other hand, hypervalent Si complexes were used for allylation reactions under basic conditions.[119,120] Contrary to tetravalent Si, hypervalent Si species are sufficiently reactive to add to unactivated aldehydes *via* a type I mechanism. The first asymmetric allylation of aldehydes using allylsilyl trichloride **214** and chiral phosphoramide **215** led to modest enantioselectivities (*Scheme 38*).[121] The low enantioselectivity was rationalized on the basis of an unfavorable equilibrium between monophosphoramide **A** and diphosphoramide **B**, the former leading to lower chiral induction than the

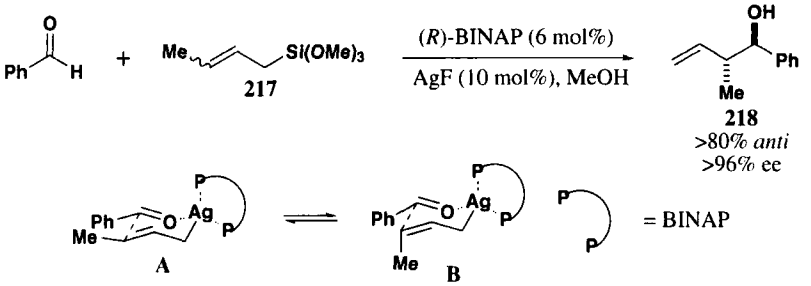


Scheme 38

latter. This hypothesis led to the development of tethered bisphosphoramide ligands with greater chiral inductive powers.[122] Other research groups obtained acceptable enantioselectivities using different chiral phosphoramides,[123] diamines,[124] formamides,[125] or *N,N'*-dioxides as Lewis bases.[126]

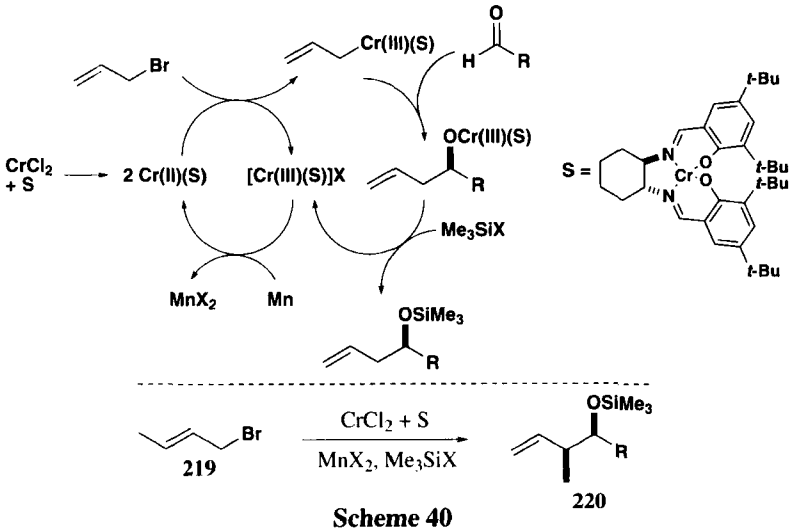
A high enantioselectivity was obtained in the allylation of benzaldehyde with crotyltrimethoxysilane **217** using a BINAP•AgF complex as catalyst (*Scheme 39*).[127] Interest-

ingly, a mixture of *E* and *Z*-**217** (83:17) gave a 92:8 ratio of the two diastereomers of product **218**. The major diastereomer had the methyl and hydroxy groups in an *anti* stereochemical relationship and was isolated in 96% ee. This result, along with some NMR evidence, supports the idea that crotylsilver molecules undergo the allylation reaction rather than the corresponding pentacoordinate Si species. Presumably, the *E*- and *Z*-crotylsilver react *via* a type III mechanism (cf. *Fig. 8*) in which transition states **A** and **B** are in equilibrium, which would explain the apparent isomerization of the starting crotylsilane **217**. Simple allylation of aromatic aldehydes with the allyl analog of **217** using (*R*)-*p*-Tol-BINAP•AgF complex gave products in >90% ee in most cases.[127]



Scheme 39

Recently, significant advances were made toward the desirable goal of using a catalytic quantity of a chiral metal complex to catalyze the allylation of aldehydes by allyl halides. Umani-Ronchi and co-workers used a Cr salen complex to catalyze the enantioselective allylation of several aldehydes with allyl bromide (*Scheme 40*).[128] A chiral allylchromium(III) species was generated by insertion of a Cr(II) species into the carbon-bromine bond of allyl bromide.

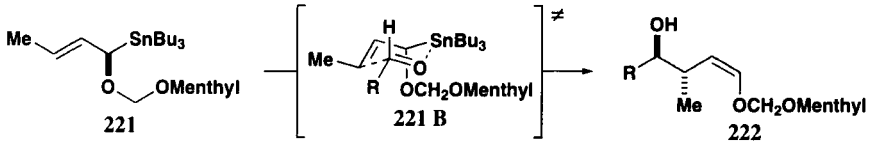


Scheme 40

After the addition on the aldehyde, the Cr(III) complex was put back into the catalytic cycle by displacement with trimethylsilyl halide and reduction to Cr(II) with Mn. The enantioselectivities obtained in the allylation reaction with such a system were modest to good (42-89% ee). Better enantioselectivities were obtained with crotyl bromide **219** (mostly >80% ee), though the *syn/anti* diastereoselectivity was only 4:1.[128b] It was found that the diastereoselectivity of the reaction depended on the ratio of chiral ligand to Cr salt. Moreover, the *syn* diastereomer **220** was favored while normally, allylchromiums lead to *anti* adducts *via* a type III transition state (cf. *Fig. 8*). This could imply a type II mechanism where the Mn or Cr salt act as a Lewis acid. The role of aggregates and of the weak Lewis acid generated during the reaction (MnX_2) was later investigated and led to improved diastereoselection for this process.[129]

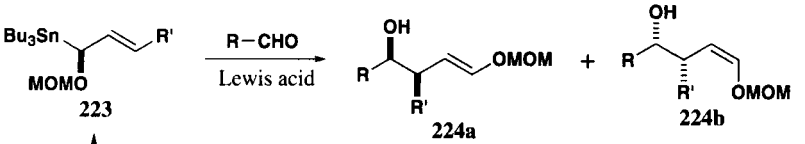
ii. Chirality on the Allyl Unit

The bulk of the research conducted on the allylation of aldehydes using allyltin and allylsilicon reagents involved chirality at the allyl fragment, either α or γ to the metal. In particular, Thomas and his collaborators have shown interesting remote asymmetric induction in alkoxy- and aminoallylstannanes (*vide infra*). In the first example of this type of reaction, allylstannane **221**, resolved as its menthyl acetal (Men), added thermally to aldehydes *via* a cyclic transition state with near complete stereoselectivity in some cases (*Scheme 41*).[130]



Scheme 41

Optically active α-alkoxystannanes **223** are now conveniently made from the enantioselective reduction of the corresponding acylstannane **225** (*Scheme 42*).[131] Their Lewis acid catalyzed reactions with aldehydes led preferentially to *syn* adducts as a mixture of *cis* and *trans* double bond isomers **224a** and **b** (type II mechanism).[132] This is of no consequence if the alkene



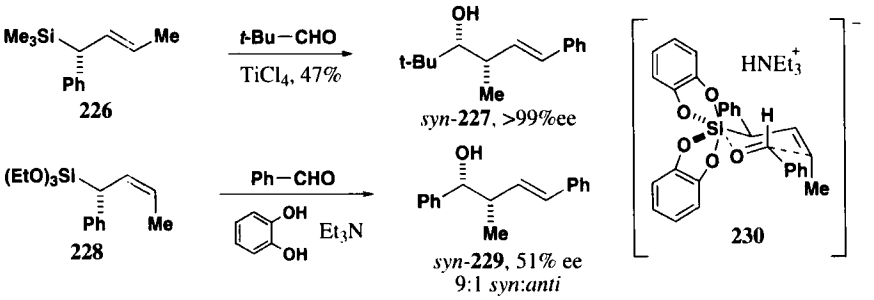
R	de (%)	224a/b	de (%)
n-C_6H_{13}	98	70:30	80
E-BuCH=CH	98	81:19	80
Bu—≡	76	58:42	20

Scheme 42

is to be oxidatively cleaved to a carbonyl function. Note that the resulting enol ether can also be hydrolyzed to a β-chiral aldehyde (cf. section III.1.1). As can be seen, the transfer of chirality is

not perfect and this kind of reagent has been better utilized in double asymmetric reactions (*i.e.* with α-chiral aldehydes). Although allylstannanes are capable of undergoing addition to aldehydes thermally or under high pressure by a type I mechanism, relatively few examples of asymmetric induction under those conditions were reported.[102a]

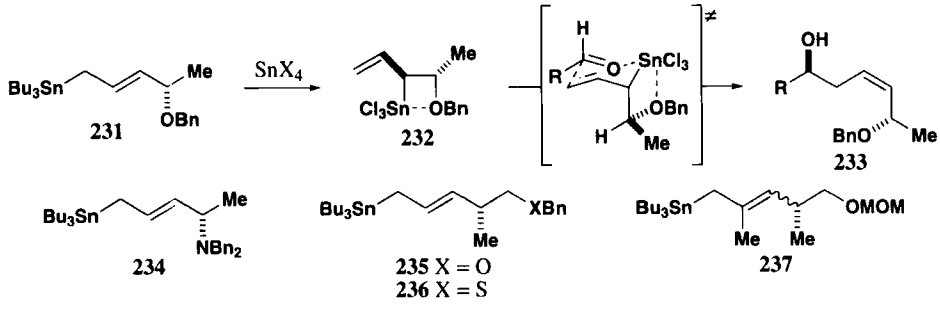
Building chiral crotylsilanes has been challenging until more recently.[133] The details of the synthesis of chiral crotylsilanes will not be discussed here, but their reactions with aldehydes proceeds with high levels of chiral induction under a range of reaction conditions. Two typical cases are illustrated in *Scheme 43*. In the first, a typical Lewis acid is used to promote the reaction *via* a type II mechanism. The fact that the *E* and *Z* isomers of **226** both give the *syn* product



Scheme 43

227 (with opposite absolute stereochemistry) provide evidence for this mechanism.[134a] In the second case, a hexavalent Si species **230** is obtained by addition of catechol and a base to allylsilane **228**. A 9:1 ratio of *syn:anti* adducts **229** is obtained *via* a type I mechanism.[134b] Note the same absolute stereochemistry between adducts **227** and **229** supporting the hypothesis that *Z*-**228** is adding to benzaldehyde *via* a type I mechanism. More examples can be found in the literature.[102] Allylboranes or boronates with C-1 or C-4 chirality on the allyl fragment have also been reported and react *via* a type I mechanism.[102b]

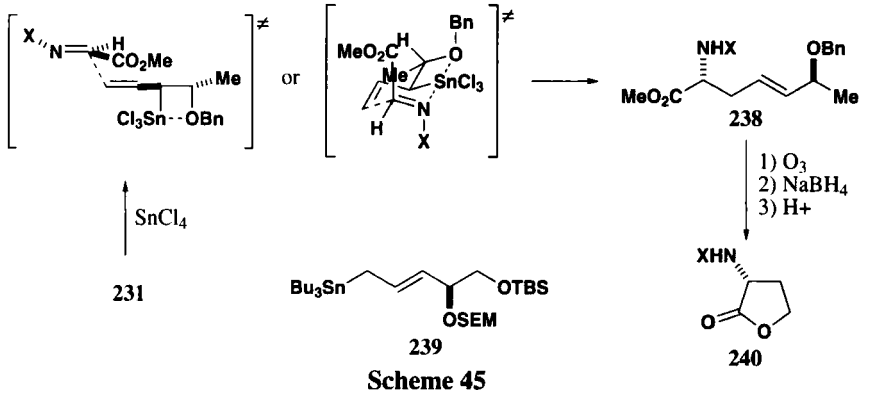
Useful 1,5-asymmetric induction in the allylation of aldehydes with chiral allylstannane **231** was achieved by prior transmetallation with $SnCl_4$ (*Scheme 44*).[135] The presence of the heteroatom (N, S, or O) in **231** is essential for the regiochemical control of the reaction, although



Scheme 44

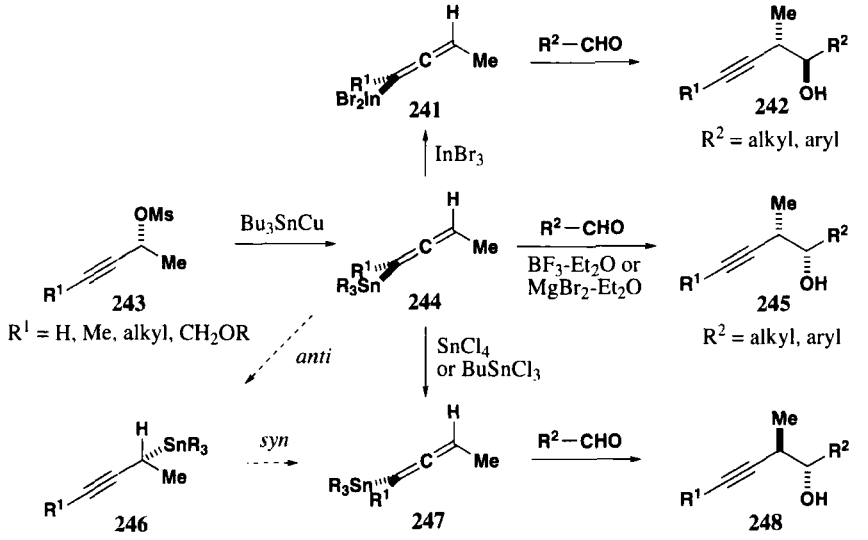
its position may vary (compare **231**, **234-236**).[134b,d-f] The regio- and stereochemistry of intermediate **232** is controlled by the heteroatom since both the *E* and the *Z* geometries of the starting allylstannane give the same adduct. Recently, evidence for this transmetallation mechanism was reported.[136] The nature of the heteroatom protecting group and of the Lewis acid changed the level of selectivity, and in some cases could reverse the sense of asymmetric induction.[137] Oxidative cleavage to carbonyl products was not systematically done in these studies but doing so would produce a carbonyl compound as well as regenerate the chiral fragment which served to make the stannane.[134c] Therefore, this strategy constitutes a useful route to aldol adducts of the 'acetate-type' (cf. *Eq. 6*). Similarly, good 1,6- and 1,7-asymmetric induction was observed with the appropriately substituted chiral allylstannanes.[138] Interestingly, the allylsilane analog of **231** led to significantly reduced selectivities, purportedly because of a slower rate of exchange with $SnCl_4$.[139] Methyl ketones could, in principle, be obtained from the oxidative cleavage of the addition products of trisubstituted allylstannane **237** with aldehydes.[140]

Glyoximines reacted with **231** and other allylstannanes to give good yields of homoallylic amines **238** (*Scheme 45*).[141] The *E* geometry of the adduct implies that the mode of addition is different than with aldehydes. An acyclic rather than cyclic transition state appears more likely in view of the previous results with aldehydes. The product **238** was converted to homoserine lactone **240** by ozonolysis of the chiral auxiliary, reduction of the resulting aldehyde, and lactonization.



Scheme 45

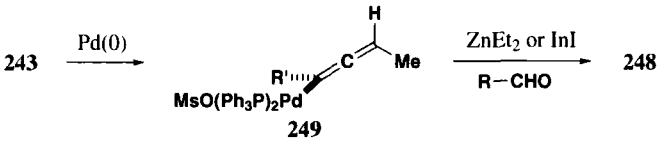
Chiral allenyl metal addition to aldehydes constitutes a powerful alternative to aldol chemistry.[142] Allenylstannanes, -zinc, and more recently allenylindium reagents have been used successfully to create chiral homopropargyl alcohols.[143] The triple bond may be oxidized to a carboxylic acid[144] or it may serve as a useful lever for further synthetic elaboration of the adduct. Allenylstannane **244**, made from an S_N2' displacement of the mesylate in **243** by a stannyl cuprate, reacted with aldehydes in the presence of $BF_3 \cdot Et_2O$ or $MgBr_2 \cdot Et_2O$ to give mostly (often >99:1) *syn* adducts **245** *via* an open chain transition state (*Scheme 46*).[143,132] Prior transmetallation of **244** with $SnCl_4$ (or $BuSnCl_3$) or with InX_3 afforded 1,2-*anti* propionate-like adducts **248**



Scheme 46

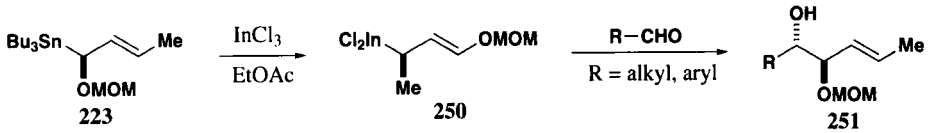
or **242** respectively. $InBr_3$ must transmetallate with retention of configuration at the allenyl carbon (**244** → **241**) since alkynols **242** having the same absolute stereochemistry at the propargyl carbon as adducts **245** were obtained.[145] The transmetallation process with the tin chloride species is quite interesting and may proceed by way of two transpositions *via* **246** as shown at the bottom of *Scheme 46*.[142a] *Ent-anti* adducts **248** (with respect to In adducts **242**) are obtained through an alleged six-center transition state.

Alternatively, *anti*-adducts **248** were obtained when propargyl mesylate **243** was directly treated with Pd(0) followed by transmetallation with Zn[146] or In (*Scheme 47*).[147] Disposal of toxic Sn residues are thus avoided and products **248** were obtained in high *syn-anti* ratios (>80:20) and ee's (>90%).



Scheme 47

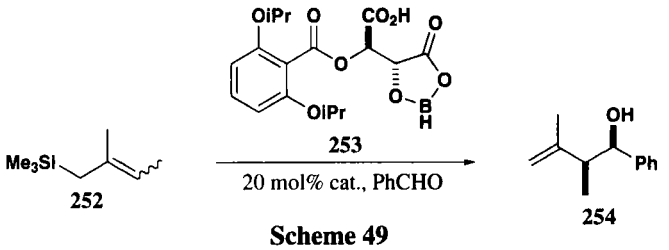
In 1995, Marshall and Hinkle reported the S_E2' transmetallation of α-alkoxystannane **223** to the hypothetical allylindium species **250** (*Scheme 48*).[148] The latter added stereoselectively to aldehydes to give high yields of homoallylic alcohols **251** with excellent diastereoselectivity and transfer of chirality. For the first time, *anti* 1,2-diols of this type were accessible directly, although the preparation of alkoxystannane **223** required 3 steps from crotonaldehyde.[37]



Scheme 48

iii. Chirality on the Aldehyde or Imine

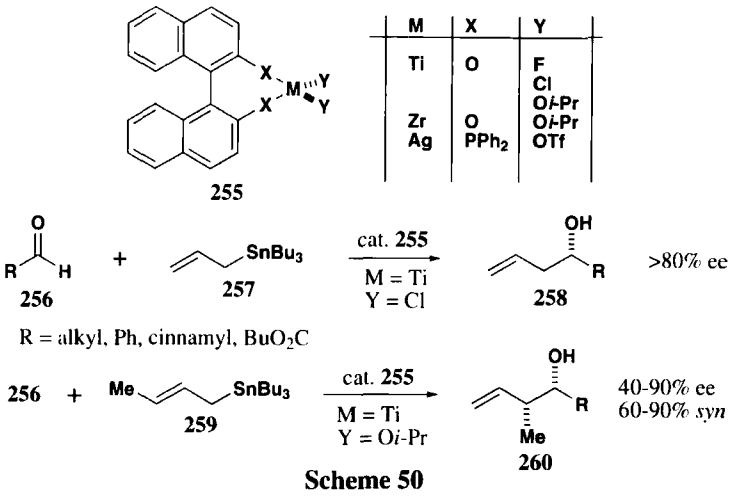
There are a number of chiral Lewis acids that promote the enantioselective allylation of aldehydes using a catalytic amount of chiral molecules.[149] Yamamoto reported the first asymmetric catalysis of an allylation reaction using chiral acyloxyborane **253** (*Scheme 49*).[150] Trisubstituted allylsilane **252** gave *syn*-**254** (*syn/anti* 96/4) in 92% ee under these conditions. Allylsilanes lacking the methyl at C-2 (internal olefinic carbon) gave poor enantioselectivities (55% ee). Marshall applied this methodology using allylstannanes and later improved on the reaction conditions to obtain good diastereo- and enantioselectivities for crotylstannanes with several aldehydes (syn/anti ratios ≥80:20, and 70-92% ee).[151]



Scheme 49

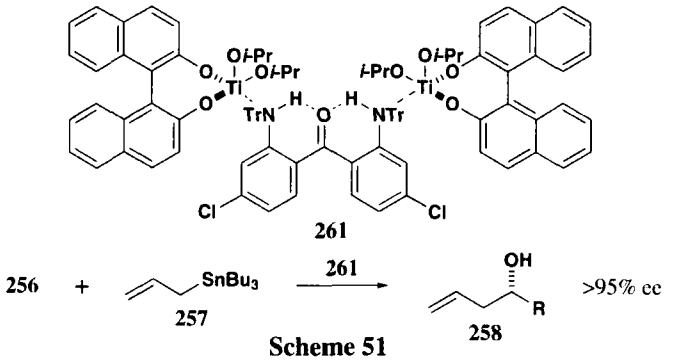
The BINOL (**255**, X = O) and BINAP (**255**, X = PPh_2) ligands, now famous for being part of so many catalysts, have been exploited for the allylation of aldehydes.[149] Ti,[152] Zr,[153] and even Ag[154,155] complexes of BINOL and BINAP were utilized for the allylation of aldehydes with several allylstannanes. Ti catalysts proved superior with **257** and **259**, affording products **258** or **260**, respectively, in 88-93% ee. Product **260** was obtained mostly as the *syn* isomer (60-84% *syn*). The allylation of aldehydes by allyltributylstannane using Zn or In catalysts, made with bisoxazoline and phosphino-oxazoline ligands respectively, gave selectivities in the 25-46% ee range (*Scheme 50*).[156,149]

More current accomplishments include the highly enantioselective allylation of aldehydes by allyltributylstannane using the bidentate Ti complex **261** of Maruoka (*Scheme 51*).[157] Enantioselectivities in this reaction with a range of aldehydes were very high indeed (≥97%). The Hf or Zr analog of **261** gave similar results. Also, Brenna improved on the BINOL-Ti strategy, described above, by preparing a ligand analog of BINOL that has one naphthyl replaced by a benzoate derivative.[158] Not only were higher selectivities achieved for the reaction between aldehydes **256** and **257**, but the ester function offers a potential site for attachment to a polymer



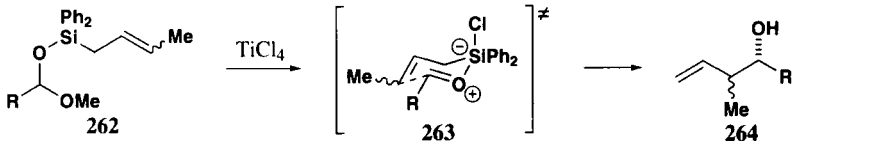
Scheme 50

resin. Other recent results include the enantioselective allylation of aldehydes by allyltributylstannane catalyzed by an air and water stable Rh bisoxazoline complex,[159] and by Rh and Ru salts with bidentate pyrrolidine ligands.[160] Aryl methyl ketones were allylated using tetraallyltin and a BINOL-Ti catalyst with modest enantioselectivities.[161]



Scheme 51

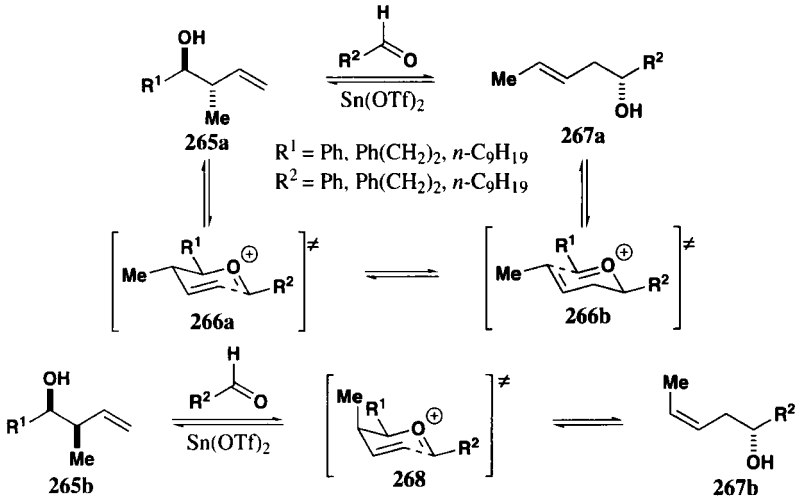
Simple diastereocontrol (*syn/anti* ratios) in the allylation of aldehydes is a continuing challenge when crotylstannanes are used in conjunction with the above-mentioned catalysts. *Syn* adducts are usually preferentially formed regardless of the crotylmetal geometry. This is consistent with an open chain transition state (cf. *Fig. 8*). Oshima *et al.* developed a clever approach to solve this problem. An oxocarbenium ion was generated from methoxy-crotylsilyloxy mixed acetal **262** and then underwent an intramolecular allylation reaction *via* cyclic transition state **263** (*Scheme 52*).[162] Fluoride treatment afforded the *anti* or *syn* homoallyl alcohol **264** depending on the geometry of the starting crotyl **262**. Since the hydroxydiphenylsilyl ether of **264** was the major product in the crude mixture (before fluoride treatment) we can conclude that the allylation was presumably promoted by chloride ion through a pentavalent Si. Although no asymmetric version of this strategy has been demonstrated yet, its implementation could be imagined in many ways.



E-crotylsiloxane: 9:91 *syn:anti*
Z-crotylsiloxane: 93:7 *syn:anti*

Scheme 52

An interesting stratagem was employed by Nokami and his group to convert propionate-like allylation product **265**, so-called γ-adduct, into the corresponding acetate-like allylation product **267**, or α-adduct (cf. *Eq. 6*).[163] An equilibrium mixture is produced by combining $Sn(OTf)_2$, the γ-homoallyl alcohol **265**, and an aldehyde (*Scheme 53*). If $R^1 \neq R^2$, the α-adduct **267** predominates because of steric reasons and an increased stability of the oxonium ion **266b**

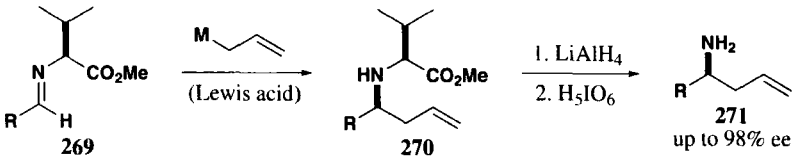


Scheme 53

with respect to **266a**. The stabilities of the oxonium ions **266a** and **266b** will be affected by the nature of the R^1 and R^2 groups on the starting adduct **265a** and aldehyde respectively. If $R^1 = R^2$, the final adduct **267a** predominates because of steric reasons and an increased stability of the double bond. The transfer of chirality was complete as revealed by the conversion of optically pure *anti*-adduct **265a** into α-adduct **267a**, obtained with greater than 98% ee. The same was true for the corresponding *syn*-adduct **265b** which produced the alcohol **267b** with the same absolute stereochemistry but having a *Z*-olefin. Therefore, in a context where the double bond in the product would be oxidatively cleaved to a carbonyl compound, an optically pure mixture of *syn*- and *anti*-γ-adducts **265a** and **265b** would lead to an optically pure β-hydroxy carbonyl compound.

The diastereoselective addition of allylmetals to imines bearing a nitrogen-bound chiral appendage were surveyed.[102a,164] Early on, Yamamoto and co-workers conducted a study of allyl-

metal addition to aldimines derived from phenethylamine.[165] In this reaction, allylborane and allyltin reagents gave reasonable 1,3-asymmetric induction (>84% ee) and allylmagnesium reagents gave products with lower ee's (36-68%). (*S*)-Valinate-derived imine **269** proved to be another good chiral imine system for the allylation reaction. Both aromatic and aliphatic aldimines gave good to excellent diastereoselectivities in the Barbier-type addition of allylzinc, -lead, -copper, -bismuth, -cerium, -aluminum, -indium, and -tin reagents (*Scheme 54*).[166]

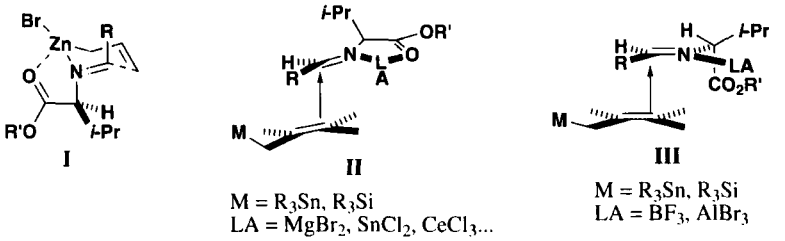


269 **270** **271**

R = aryl, alkyl up to 98% ee

Scheme 54

Several transition state models were put forth to explain the fact that virtually all the different allylmetals, whether coordinating or not and whether Lewis acids were used or not, gave the same sense of diastereoselection in their addition to all imines studied. Allymetals possessing a metal capable of chelation would bring the imine and allyl unit together into a chair-like disposition (**I**) and coordination with the ester of the valine fragment would insure rigidity and thus good face differentiation (*Fig. 10*). Bis-coordinating Lewis acids capable of chelating



I **II** **III**

M = R_3Sn, R_3Si
LA = $MgBr_2$, $SnCl_2$, $CeCl_3$...

M = R_3Sn, R_3Si
LA = BF_3, $AlBr_3$

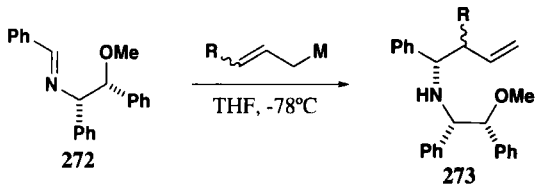
Fig. 10

Three Proposed Transition Sates for the Allylation of Valine-Derived Aldimines

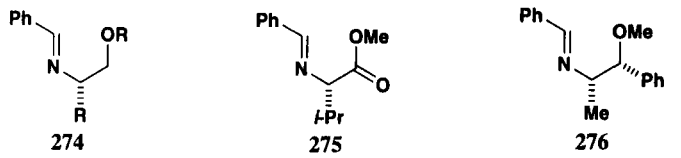
the imine nitrogen and the ester oxygen would direct the attack of a non-chelating allylmetal away from the bulky isopropyl group on the planar 5-membered ring arrangement (**II**). Results from the catalyzed allylation of imines **269** using Lewis acids with one coordination site are more difficult to explain. An interesting argument was proposed to the effect that conformer **III** of the imine would be favored due to allylic strain and *syn* addition (with respect to the ester group) of a non-chelating allylmetal would afford the observed product.

Hashimoto and Saigo and their co-workers have studied the addition reaction of several crotylmetals (Si, Sn, Mg, Li, Cr) on chiral non-racemic aldimine **272** derived from *erythro*-2-amino-1,2-diphenylethanol. 1,3-Asymmetric induction was complete in some cases but the simple diastereoselection (*syn*/*anti* ratio) was low to modest (*Scheme 55*, top).[167] Recently, Yanada *et al.* reported the Barbier-type allylation of a series of imines derived from amino alco-

hols, amino ethers, and amino esters **274-276** with allyl bromide in the presence of Sm metal and a catalytic amount of iodine.[158] A transition state like **II** (*Fig. 10*, M = Sm^{III}) was invoked to explain the selectivities.



R	M	de (%)	*syn/anti*
H	Li	98	---
Me	Li	>99	84:16
	MgCl	>99	64:36
	$SnBu_3$	0	42:58



Scheme 55

iv. Chirality at the Metal

Allylation with allylmetals where the chirality resides on the metal is known.[169] Two examples are given in *Fig. 11*. However, the scope of this technology is at present limited and it has not seen much use in synthesis so far.

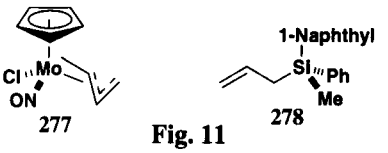
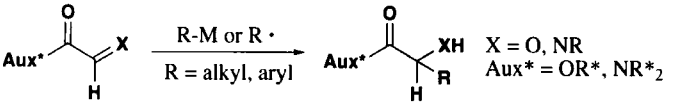


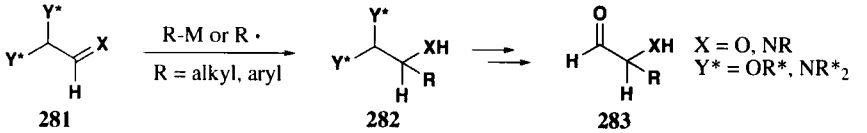
Fig. 11

Two Allylmetals Bearing Chirality at the Metal Center

2. Electrophilic α Carbon

Adding a nucleophile or radical species to a glyoxylic unsaturation like the one shown in structure **279** produces an α-hetero-substituted carbonyl **280** directly (*Scheme 56*). Given that





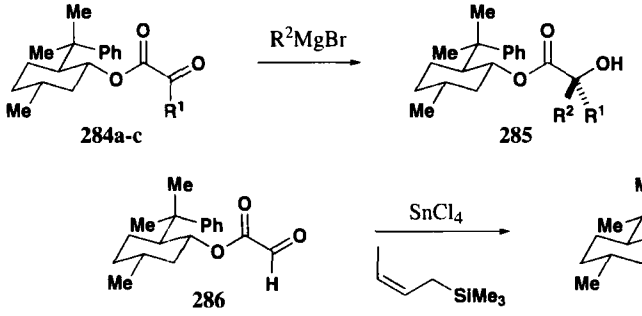
Scheme 56

the carbon being attacked in **279** is in the same relative position as the nucleophilic carbon of the corresponding chiral enolate, one can expect that attaching the same chiral auxiliaries as those

used for enolates to **279** should provide a similar level of stereoselectivity. Carbon-carbon double bonds (-C(O)-HC=CH-Y), if polarized in the correct direction, could in principle be used in the same manner, though regioselectivity becomes an issue due to the competing electrophilic characters of the α- and β-carbons. The spectator carbonyl function in **279** can also be masked as an acetal, aminal or other functionality which could also serve as the carrier of chirality (c.f. **281**). Cleaving the auxiliary in **282** would furnish aldehydes **283**, complementary to the carboxylic derivatives **280** (Aux* contains an oxygen or nitrogen).

a) Glyoxylates, Glyoximines, and Derivatives

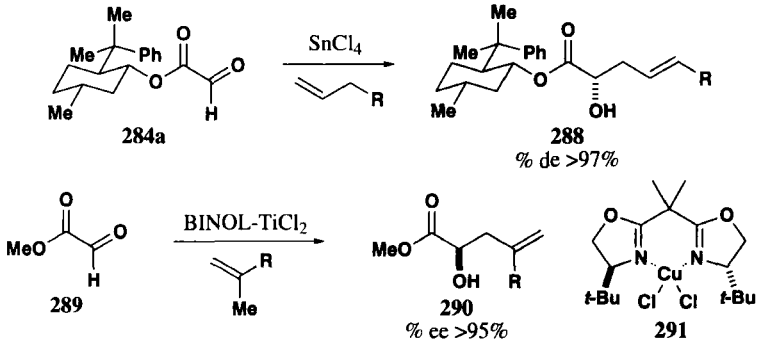
Whitesell has reviewed the use of menthol-derived glyoxylate **284** (R^1 = H) and related cyclohexyl systems.[170] This system provides a practical and highly stereoselective way to prepare α-hydroxy acids. *Scheme 57* gives typical examples but more can be found in Whitesell's review and references therein.



285	R^1	R^2	de (%)
a	H	Me	>98
a	H	n-C_6H_{13}	>98
a	H	c-C_6H_{11}	>98
a	H	Ph	>98
b	Me	Ph	>95
c	Ph	Me	>95

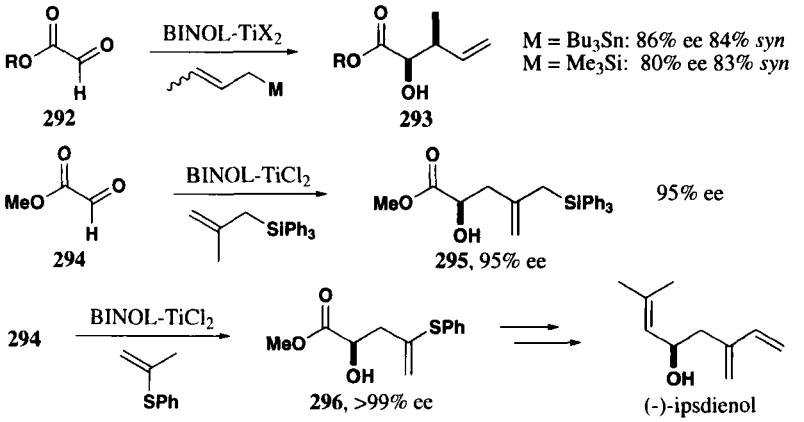
Scheme 57

The *ene* reaction is an allylation reaction akin to the addition of allylic metals to aldehydes (cf. section II.1.3).[171] Ene reactions have the desirable feature of not requiring activation of the allylic carbon on the ene fragment. However, electron-poor enophiles, usually glyoxylates or activated imines, and a strong Lewis acid are essential for the reaction to take place. Whitesell pioneered the area with the diastereoselective ene reaction of alkenes to chiral glyoxylate ester **284a** (*Scheme 58*, top).[172,173] Yamamoto then reported the first catalytic enantioselective carbonyl-ene reaction, though the scope of the reaction was limited.[174] Mikami *et al.* reported the enantioselective ene reaction of 1,1-disubstituted alkenes with methyl glyoxylate catalyzed with various BINOL-derived Ti complexes (*Scheme 58*, bottom).[175,176] Later, a BINAP complex of a Pd salt was used to extend the scope of this reaction to trisubstituted alkenes.[177] Evans and coworkers have utilized chiral bis(oxazoline)-Cu complex **291** which functioned with a wider range of substituted alkenes (typical ee >80%).[178] Lanthanide complexes of BINOL derivatives gave low to moderate enantioselectivities in the glyoxylate ene reaction between alkenes and **289** (12-38% optical purity).[179]



Scheme 58

Crotylstannanes and -silanes added to glyoxylates in the presence of catalytic quantities of BINOL-Ti complex to give the Sakurai-Hosomi reaction product **293** (*Scheme 59*).[180] High diastereo- and enantioselectivity was achieved in this reaction except with unsubstituted allylmetals. It seems, however, that an ene reaction may take precedent over allylmetal addition in some cases as shown by the formation of **295** (*Scheme 59*, middle). The ratio of ene / Sakurai-Hosomi product varied depending on the solvent used and on the substitution of the allylsilane. For example, allyltrimethylsilane afforded the normal Sakurai-Hosomi product.[181]

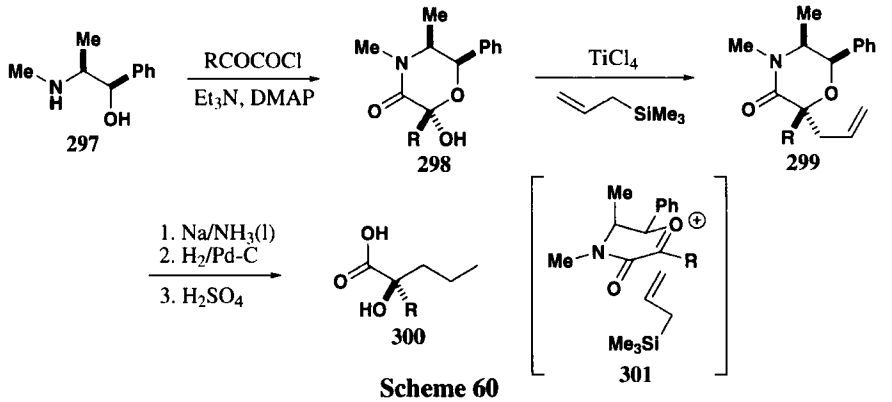


Scheme 59

Interestingly, mono- and 1,2-disubstituted olefins were not reactive enough to undergo the ene reaction under normal conditions of catalysis. Vinylsulfides and selenides were exploited to confer a more pronounced nucleophilic character to the alkene and thereby surmount this problem. With vinylsulfides, the reaction rate was superior to normal alkenes and enantioselectivities were high (>99%). Sulfur can be reduced or put to better use as demonstrated by the conversion of **296** into the bark beetle's aggregation pheromone *R*-(-)-ipsdienol.[182]

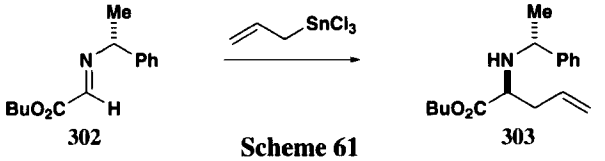
A cyclic ephedrine-derived template **298** underwent highly diastereoselective allylation with allyltrimethylsilane in the presence of $TiCl_4$ providing access to α,α-disubstituted α-

hydroxy acids **300** (*Scheme 60*).[183] The reaction is thought to proceed *via* an oxonium ion **301** and the diastereoselectivity arises from addition to the least hindered face of this rather planar structure as shown.



Scheme 60

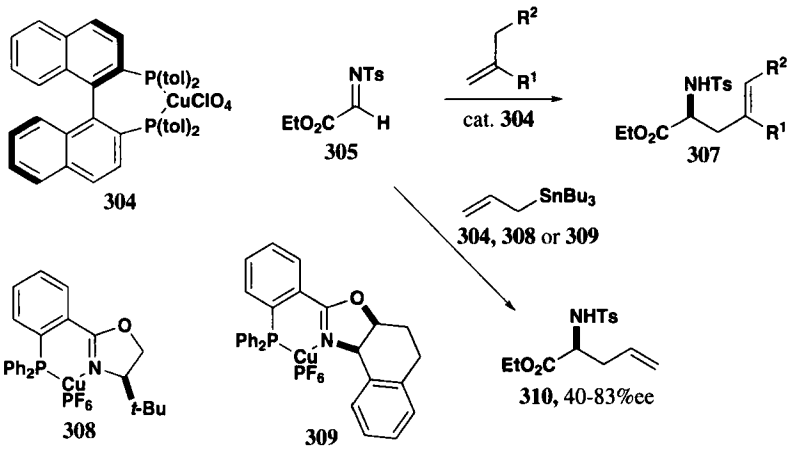
Glyoximines undergo a related allylation reaction, which provides access to optically active α-amino acids. Imine and oxime derivatives of Whitesell's auxiliary **284** (cf. *Scheme 58*) underwent stereoselective addition of Grignard reagents[184] or allylzinc bromide[185] to give useful amino acid-like products. Similarly, chiral α-imino ester **302** reacted with allyltin trichloride in a highly stereoselective manner to give **303** (*Scheme 61*).[186] This strategy was used with allylboranes before[187] but gave the opposite stereochemistry in the adduct **303**, which is an interesting



Scheme 61

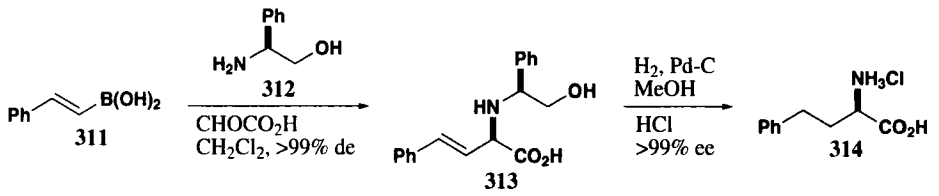
fact. When chiral allylstannanes **231** or **234** (see *Scheme 44*) were reacted with **302**, double asymmetric induction could effectively raise the stereoselectivity for matched pairs. Similar additions involving alkyl radicals is described in section II.3.4.

The catalytic enantioselective *ene* reaction of allymetals to achiral α-imino esters was published simultaneously by Lectka and Jørgensen. The Cu complex **304** was used to achieve high enantioselectivity in the ene reaction of acyclic and exocyclic alkenes to *N*-tosyl imine **305** (*Scheme 62*).[188,189] Other metals in place of Cu gave unsatisfactory results. One problem associated with this catalyst was that monosubstituted alkenes were not reactive enough to take part in this ene reaction. Thus Jørgensen used allylstannanes and -silanes in conjunction with Cu complex **304** and $CuPF_6$ complexes **308** and **309** to obtain the simple homoallyl amine **310** in moderate to good ee's depending on the reaction conditions and catalyst used.[190] *E*-Crotylstannane underwent the allylation reaction with **305** under the influence of catalysts **304**, **308**, or **309** to give the corresponding homoallylamine with similar levels of enantioselectivity and 6-10:1 ratios of *syn:anti* diastereomers (not shown).



Scheme 62

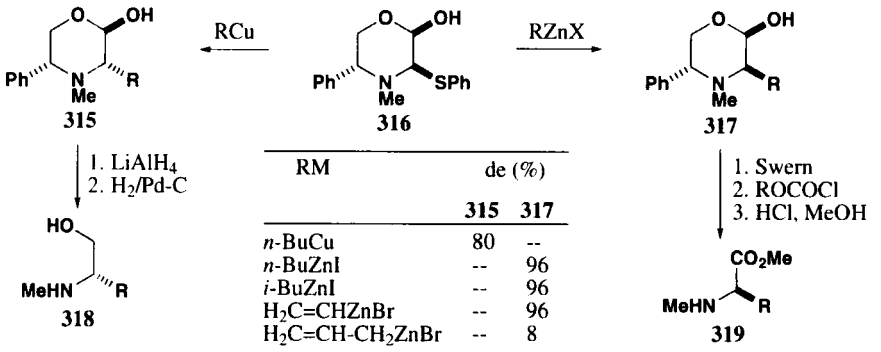
An impressive one-pot, three-component procedure was recently reported by Petasis and Zavialov. Homophenylalanine **314** in >99% ee was prepared in a synthesis involving phenylglycinol **312**, glyoxylic acid, and vinylboronic acid **311** (*Scheme 63*). Presumably, vinylboronic acid **311** underwent a highly stereoselective addition to the chiral imine derived from **312** and glyoxylic acid. Phenethylamine was not as efficient as phenylglycinol **312** at inducing chirality.[191]



Scheme 63

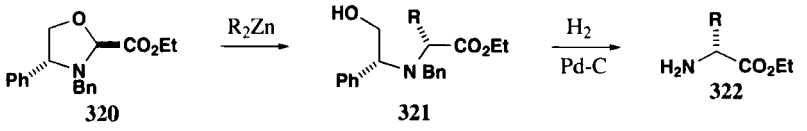
Several glycine cation equivalents have been designed over the last decade or so for the synthesis of chiral α-amino acids.[184,192] Morpholine **316**, made from *N*-methyl phenylglycinol and phenylthio acetaldehyde, added monoalkylzinc or cuprate reagents stereoselectively to give, after proper treatment, alcohols **318** or amino esters **319** (*Scheme 64*).[193] The reaction likely proceed *via* an iminium ion in the case of dialkylzinc additions but seems to involve a direct nucleophilic displacement of phenylthiolate in the case of alkylcopper reagents, as judged from the stereochemical outcome for each reaction (**317** and **315**, respectively).

The reaction dialkylzincs with cyclic aminal **320**, derived from ethyl glyoxylate, proceeded with good diastereoselectivity (>85:15) to give the acyclic amino alcohol **321** (*Scheme 65*).[194] The stereoselectivity was explained in terms of an iminium ion intermediate in a tight chelate ion pair with the Mg salt formed in the preparation of the dialkylzinc from Grignard reagents and $ZnCl_2$. The availability of the dialkylzinc currently imposes a limitation to this method.



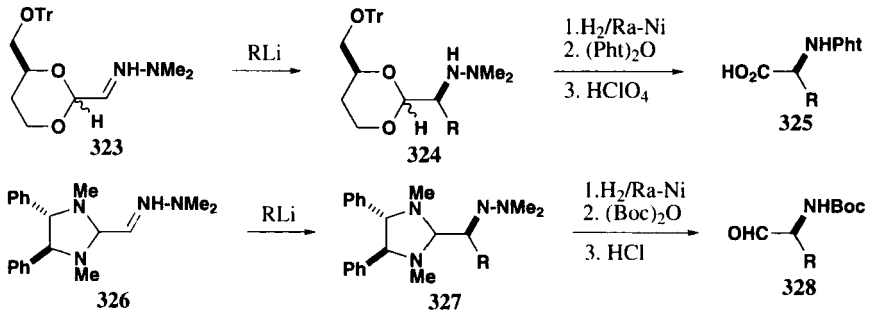
RM	de (%)	
	315	317
n-BuCu	80	--
n-BuZnI	--	96
i-BuZnI	--	96
H_2C=CHZnBr	--	96
H_2C=CH-CH_2ZnBr	--	8

Scheme 64



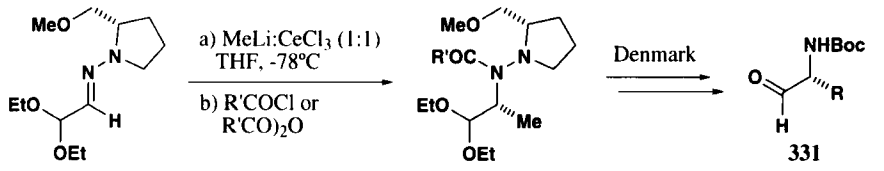
Scheme 65

Chiral α-hydrazono acetals **323** gave good diastereoselectivities upon addition of alkyl Grignards (*Scheme 66*).[195] The product **324** was obtained as a mixture of four diastereomers because of the acetal stereocenter. Reduction of the hydrazine product **324**, protection of the resulting amine, and deprotection/oxidation of the aldehyde furnished *N*-protected amino acid **325**. The interesting C_2-symmetric aminal **326** has no stereochemistry at C1 thus creating only two diastereomers of **327** upon addition of alkyllithium reagents.[196] Similar treatment of the adduct **327** afforded sensitive α-amino aldehyde **328**.



Scheme 66

Enders[197] and Denmark[198] simultaneously published an approach to chiral α-amino acids based on the SAMP hydrazone to access the sensitive α-amino aldehydes **331** (*Scheme 67*). Both used organocerium reagents to effect good diastereocontrol over their addition reactions to **329**. Interestingly, Enders reported higher % de's for identical products under reaction conditions seemingly indentical to those reported by Denmark. The only palpable difference between the



Scheme 67

two procedures was the precaution taken by the Enders group to stir dry $CeCl_3$ in THF for a longer period of time using ultrasound. We, and others, have observed this phenomenon where dry $CeCl_3$ that had been vigorously stirred for 48 h or sonicated for several hours in THF prior to the addition of organolithium reagents gave a markedly higher stereoselectivity (compared to non-stirred $CeCl_3$) upon addition to chiral aldehydes.[199]

α,β-Unsaturated esters and amides **332A** are able to participate in nucleophilic additions or cyclization reactions at the carbon α to the carbonyl. Although counter-intuitive because the carbonyl normally confers an electrophilic character to the β-carbon (cf **332B**), this umpoled regioselectivity can be better explained when considering that the type of cyclization referred to here is promoted by an electrophilic activation of the double bond *via* a halonium or mercuronium bridge **333**. In this case, the α-carbon becomes indeed more electrophilic than the β-carbon thanks to the electron withdrawing ability of the carbonyl (*Fig. 12*).

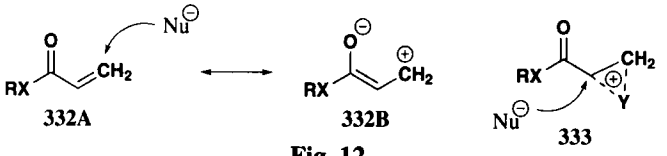
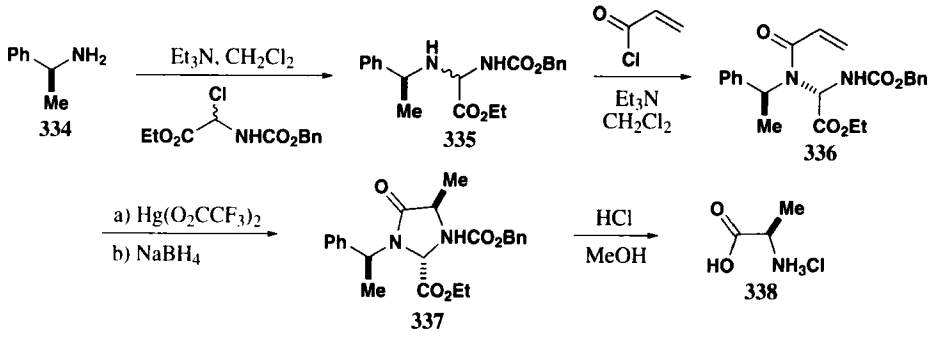


Fig. 12

Explanation of the Umpolung Reactivity of 332A vs 333

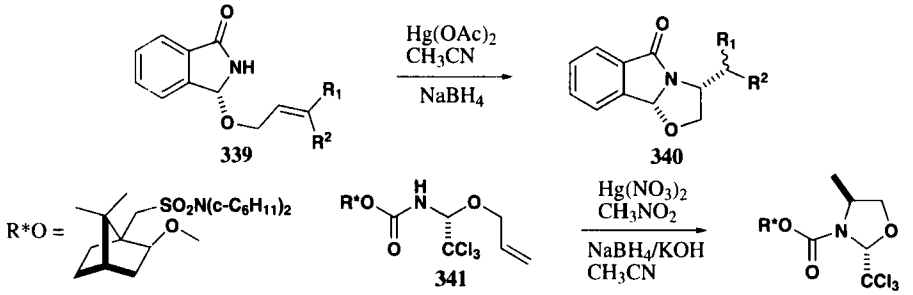
This and the kinetic preference for the formation of 5-membered over 6-membered rings, enabled aminal **336** to cyclize to the five-membered heterocycle **337** under the influence of a Hg(II) salt. Complete control of the stereochemistry was achieved in this step (*Scheme 68*).[200]



Scheme 68

Cleavage of the cyclic structure **337** to amino acid **338** occurred with hydrochloric acid in methanol. The auxiliary phenethylamine was recovered after hydrolysis. One drawback of this method is that a 1:1 mixture of aminal **335** was obtained in the first reaction of the sequence and the two diastereomers had to be separated by chromatography.

An analogous amido mercuration performed on allylic *N*-acylaminals **339** was published by Takacs, Helle, and Yang leading to protected amino alcohols **340** (*Scheme 69*, top).[201] Less than 1% of the epimer of **340** was observed in these cyclizations. Disubstituted



Scheme 69

alkenes (R^1 or $R^2 \neq H$) require a higher temperature to react. Harding disclosed an analogous cyclization of **341** where a CCl_3 group was able to relay the stereochemical induction brought about by the sultam chiral auxiliary in the formation of **341** (*Scheme 69*, bottom). Carbamate **341** was formed as an 86:14 mixture of diastereomers which had to be separated before cyclization. However, only one diastereomer of **342** was formed in the cyclization. The absence of the chloride atoms led to a loss of stereoselectivity (presumably due to a steric factor). The epimer of **341** gave a diastereomer of **342** having both stereocenters in the oxazoline ring inverted.[202]

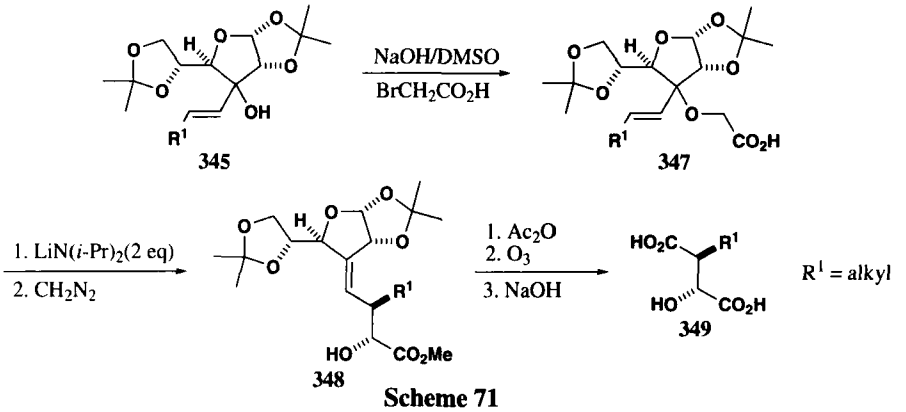
b) Sigmatropic Rearrangements

Sigmatropic rearrangements have been known to proceed with transfer of chirality for quite some time. The recognition by Kakinuma in the early 1980's that the final double bond created in this reaction is a latent carbonyl function has led to the development of a number of elegant chiral enolate equivalents. In the examples below, the carbon ending α to the carbonyl takes on an electrophilic character, hence their inclusion in this section.

Kakinuma and co-workers have designed a glucose-based template which allowed the stereoselective construction of chiral allylic alcohols **345**-**346** (*Scheme 70*).[203] Alkynyllithium reagents added stereoselectively to **343** to give propargyl alcohols **344**. Reduction to the *E*-alkene **345** or *Z*-alkene **346** was possible using aluminum hydrides or hydrogenation respectively. Allylic alcohols are quite versatile intermediates and may undergo many rearrangements or displacement reactions with varying degrees of chirality transfer.

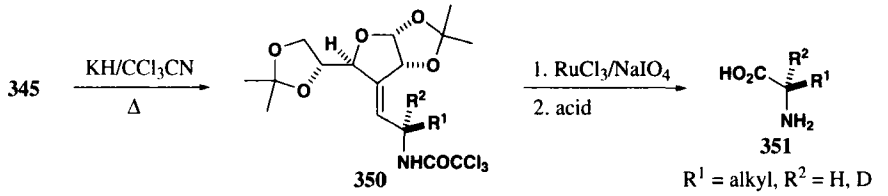
Scheme 70

The [2,3]-Wittig rearrangement of **347** derived from *E*-**345** was reported first and proceeded with excellent transfer of chirality when R_1 was ethyl or isopropyl (*Scheme 71*).[203] The geometrical *Z*-isomer **346** afforded the complementary stereochemistry in even higher stereoselectivity. After the rearrangement, oxidative cleavage of the double bond generated chiral 3-alkylmalic acid derivatives while regenerating the starting glucosulose **343**. Midland and co-workers used camphor, menthone or fenchone as chiral auxiliaries for this rearrangement.[203b] However, with the first two ketones, the rearrangement gave approximately 2:1 mixtures of isomers. The rearrangement with fenchone was highly selective. Oxidative cleavage of the double bond was not possible, presumably because of steric impediment around the alkene.



Scheme 71

More importantly, the transfer of chirality was equally good in the 3,3-sigmatropic rearrangement of trichloroimidates derived from **345** so that chiral α-amino acids **351** could be isolated by oxidative cleavage of the rearrangement products **350** (*Scheme 72*).[204] Amino acids of



Scheme 72

the other enantiomeric series could be prepared in the same manner but starting from *Z*-**346**. In addition, deuterium atoms could also be introduced in **345** by reduction of **344** with deuterated reagents, allowing the synthesis of deuterium-labeled glycine by the sequence described in *Scheme 72*.

The transfer of chirality was explained in terms of a double steric repulsion, later referred to as 'intrinsic antiparallel double repulsion'. This is shown for the Wittig rearrangement (*Fig. 13*). In fact, the transition state for the Overman rearrangement of trichloroimidates was modeled by computer and the stereochemistry of the major isomer was accurately predicted by these calculations.[205]

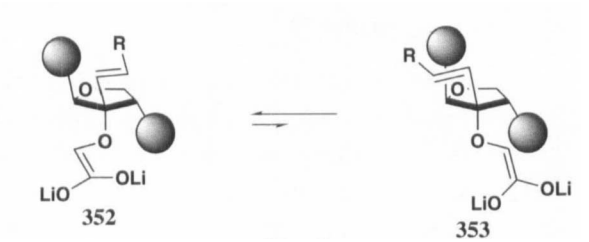
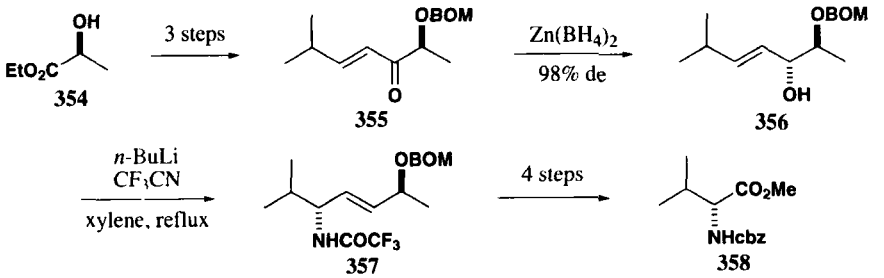


Fig. 13

Double Steric Repulsion Model for the Wittig and Overman Rearrangements

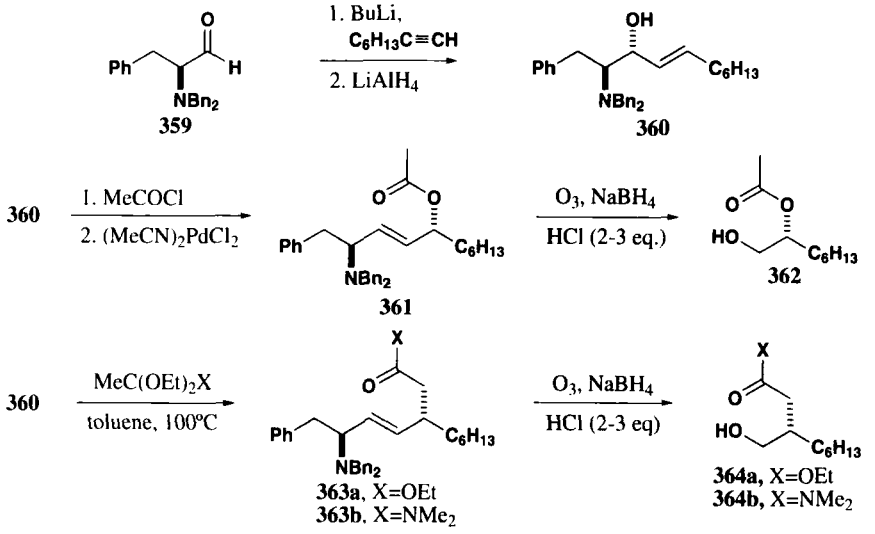
While the impetus for the development of Kakinuma's methodology was to access isotope-labeled compounds for biological studies, the method could in principle be used for the synthesis of α,α-dialkylated amino acids. One reason why it has not been used for this purpose yet may be the sensitivity of the rearrangements to steric effects. In addition, relatively few reactions, other than rearrangments, were investigated with the allylic alcohol intermediate **345**. Displacement reactions and metal-catalyzed coupling reactions, for example, were not reported on this system.

Thomas and co-workers used ethyl lactate to prepare chiral alcohol **356** in four steps. The trifluoroacetamidate derived from **356** underwent a 3,3-sigmatropic shift to give **357** with good transfer of chirality. Oxidative cleavage of the double bond and further manipulations gave α-amino ester **358** (*Scheme 73*).[206] Recycling of the chiral auxiliary was also possible in this case. The chiral auxiliary **354** is cheap and available in both enantiomeric forms. The methodology was applied to the synthesis of polyoxamic acid and thymine polyoxin C, two complex amino acids.[207] However, the pivotal secondary chiral alcohol **356** must be prepared by a diastereoselective reduction of the precursor α-alkoxy ketone **355** which makes the entire sequence rather long compared to Kakinuma's glucose template methodology. There was no mention of the direct addition of vinylmetals to lactaldehyde, which may have shortened the sequence.



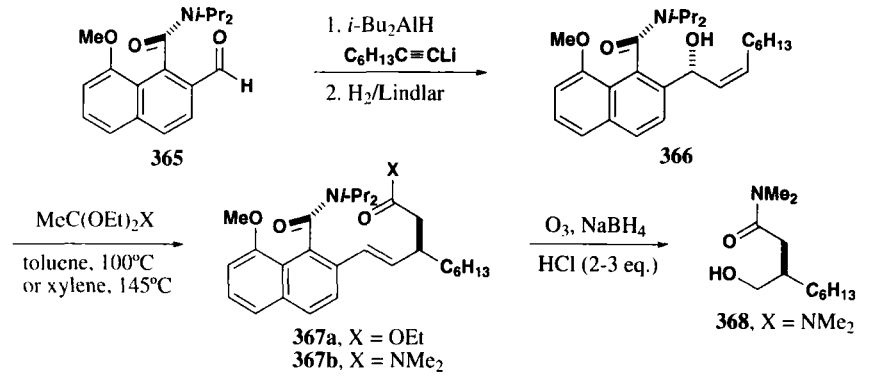
Scheme 73

Clayden and co-workers made use of (*S*)-2-dibenzylamino-3-phenylpropanal **359** to access the critical secondary alcohol **360** in 92% de (*Scheme 74*). The Pd(II)-catalyzed allylic ester rearrangement and the Johnson or Eschenmoser variants of the Claisen rearrangement were chosen for investigation. While the first yielded an equilibrium mixture of starting material and rearranged acetate **361**, the other rearrangements proceeded with good levels of chirality transfer to give products **363a-b**. Unfortunately, problems in the ozonolysis of the rearranged products currently impede full application of the method. These include partial oxidation of the dibenzylamine and lactonization of the hydroxyester **362**.[208]



Scheme 74

Recently, the same strategy was applied with an atropisomerically pure 2-formyl naphthamide auxiliary **365** (*Scheme 75*).[209] The nucleophilic addition of 1-octynyllithium to **365**

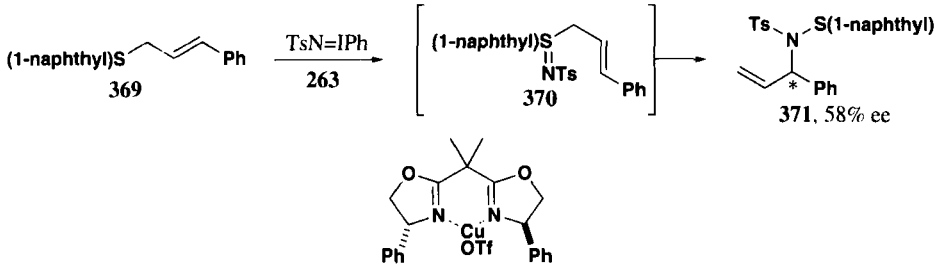


Scheme 75

catalyzed by diisobutylaluminum hydride provided an interesting and surprisingly high ratio (99:1) of adducts in favor of **366**. The rest of the reaction sequence proceeded as per the previ-

ously reported auxiliary **359**. However, chiral aldehyde **365** must be resolved beforehand with a diamine made in four steps from proline making **365** less available than **359**. In addition, auxiliary **365** could not be recovered after the reaction sequence as it was destroyed by ozone during the oxidative cleavage step.

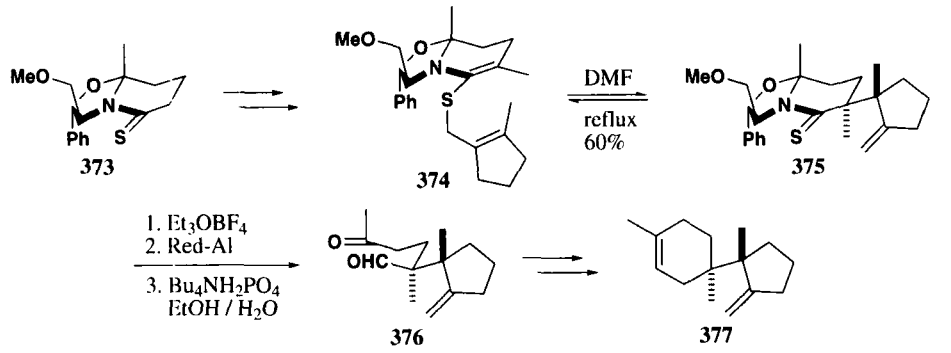
Sulfide **369** underwent a Cu-catalyzed asymmetric oxidation using complex **372** followed by a 3,3-sigmatropic rearrangement of the resulting sulfoximine **370** to give optically active allyl amine **371** in 58% ee (*Scheme 76*).[210] It can be assumed that the ee of the product **371**



Scheme 76

represents the ee of the sulfoximine **370** which implies a complete transfer of chirality in the rearrangement step. Other chiral sulfimides or selenimides have been made to undergo a diastereoselective sigmatropic rearrangement to allylic amines which are precursors to amino acids.[211]

Meyers used the thio analog **373** of his now famous bicyclic lactam system to create two adjacent chiral quaternary carbon centers *via* a thio-Claisen rearrangement (*Scheme 77*).[212] Removal of the auxiliary in **375** by partial reduction gives the keto-aldehyde **376** which was



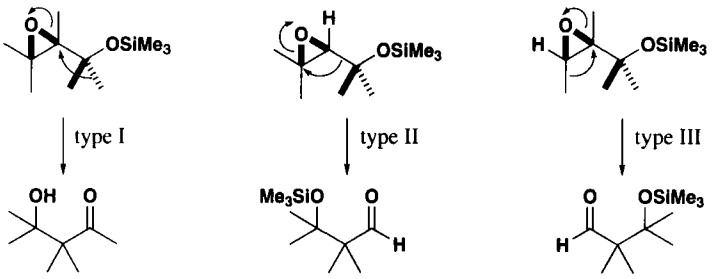
Scheme 77

converted to (-)-trichodiene **377** in three steps.[212a] This thio-Claisen was reversible under the reaction conditions and the authors found that the solvent played a crucial role in the position of the equilibrium.

c) Rearrangements of Epoxides

Epoxides were known for a long time to rearrange to a host of different products in acidic media.[213] More specifically, 1,2-hydrogen or carbon shifts may occur upon acid-catalyzed epoxide opening. Although the incoming hydrogen or carbon was shown to displace the epoxide C-O bond in an *anti* fashion, it was only after chiral non-racemic epoxides became widely available (*e. g.* by the Sharpless-Katsuki asymmetric epoxidation protocol) that the acid-catalyzed epoxide rearrangement started being applied on a larger scale to make useful chiral carbonyl compounds.

Among recent strategies, epoxy silyl ethers were reported to undergo a facile rearrangement when exposed to Lewis acids.[214] Three pathways are available for the reaction, depending on the substitution pattern of the epoxide, leading to various β-hydroxy ketones or aldehydes (*Eq. 7*). Each pathway (type I, II, and III) involves a stereospecific 1,2-sigmatropic shift and one



(7)

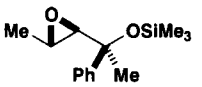
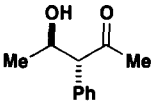
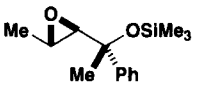
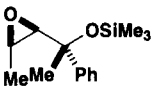
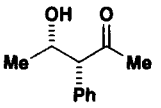
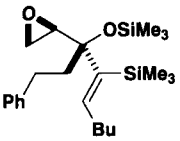
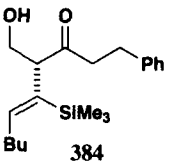
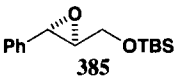
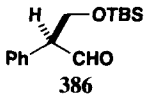
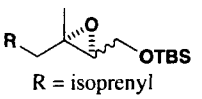
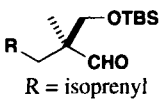
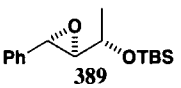
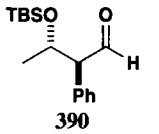
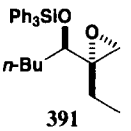
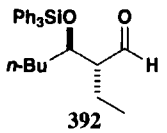
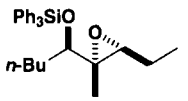
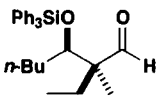
of them can be forced to take place by controlling the stability of the developing carbocation. It has, therefore, become an attractive alternative to asymmetric aldol condensation.

A type I pathway was operative with $TiCl_4$ or BF_3•Et_2O as the Lewis acid. The reaction under those conditions proved highly stereospecific with respect to the stereochemistry of the leaving group (Table 1),[214] as shown by the rearrangement of both *trans*-epoxides **378** and **380** to the same threo aldol adduct **379** while the *cis*-epoxide **381** gave adduct **382** (entries 1-3).

When the carbon β to the silyloxy group was made more electrophilic by substitution, a type II migration occurred in the presence of methylaluminum bis(4-bromo-2,6-di-*t*-butylphenoxide (MABR) as the promoter.[215] This gave rise to aldehydes bearing an α-chiral tertiary or quaternary carbon (entries 5-7).[216] Preparing aldol adducts bearing a quaternary carbon is not a feat easily accomplished using aldol chemistry.

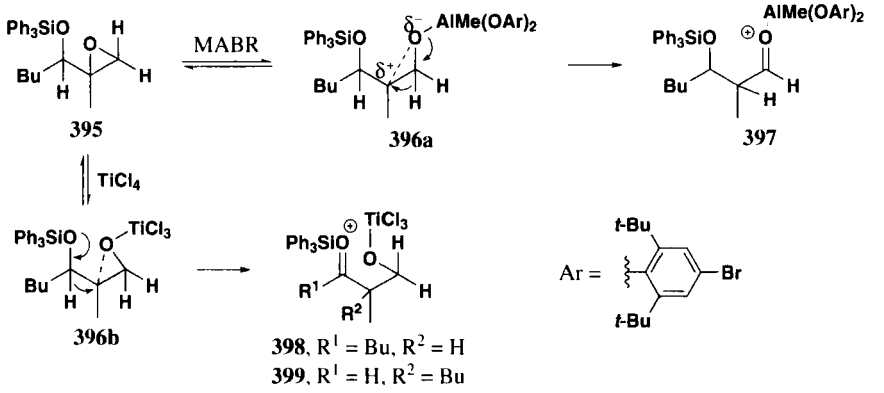
In rearrangements of type I and II, migrating unsymmetrical alkenyls retain their geometry (entry 4) and a chiral migrating alkyl keeps its stereochemistry intact during migration (entry 7). Type III rearrangements were effected with the MABR promoter on chiral β-triphenylsilyloxy epoxides. Useful aldehyde products flanked by tertiary or quaternary carbons were obtained (entries 8 and 9).[217] The starting epoxides **391** and **393** were obtained by kinetic resolution of the racemic allylic alcohol using the Katsuki-Sharpless asymmetric epoxidation. Erythro/threo ratios of the products **392** and **394** ranged from 4:1 to > 200:1, depending on the amount of MABR used and the nature of the solvent.

Table 1. Lewis Acid Catalyzed Rearrangements of Chiral Epoxides.

Entry	Type	Epoxide	Migrating group	Catalyst	Product
1	I	 378	Ph	$TiCl_4$	 379
2	I	 380	Ph	$TiCl_4$	379
3	I	 381	Ph	$TiCl_4$	 382
4	I	 383	vinyl	$BF_3 \cdot Et_2O$	 384
5	II	 385	CH_2OR	MABR	 386
6	II	 R = isoprenyl 387	CH_2OR	MABR	 R = isoprenyl 388
7	II	 389	CH(Me)OR	MABR	 390
8	III	 391	H	MABR	 392
9	III	 393	Me	MABR	 394

It is interesting to note that type I and type III rearrangements are in effect always in competition and the factors governing their relative preponderance is not all that clear at the moment. In fact, the regioselectivity of these migrations deserves some comment. As alluded to earlier, one can control the regioselectivity of epoxide opening by appropriately substituting one of the epoxide carbons. Epoxide opening occurs at the carbon best able to stabilize the developing carbocation. In all cases studied, the migration was then controlled by the migrating ability

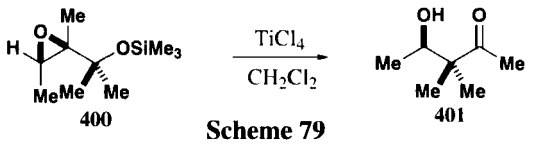
of the different groups (vinyl~phenyl > alkyl ≥ hydride) and also by the presence of a donor oxygen atom on the carbon bearing the migrating group. Perhaps the most telling example is that of triphenylsilyloxy epoxide **395** which rearranged to aldehyde **397** upon treatment with MABR but to a mixture of **398** and **399** when $TiCl_4$ was used (*Scheme 78*). Presumably, the epoxide C-O bond is "loosened" quite a bit when complexed with the strong Lewis acid MABR conferring a



Scheme 78

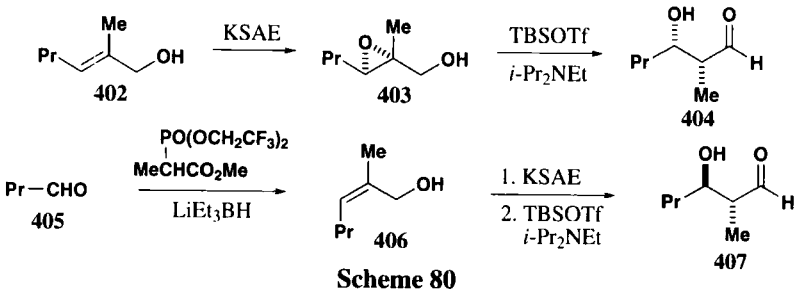
strong partial negative charge to the oxygen bound to Al in **396a**, which becomes sufficiently donating to accelerate the migration of one of the hydrogens on the adjacent carbon to give **397**. $TiCl_4$, on the other hand, may not weaken the epoxide C-O bond to the same extent (**396b**), which effectively prevents the epoxide oxygen from becoming a strong donor. Thus, the more electron-rich O-SiR_3 group controls the outcome of the migration resulting in a mixture of products of alkyl and hydride migration (ratio of **398/399** not reported, alkyls are usually better migrating groups than hydride as seen in entry 9 of Table 1).

This competition between type I and type III rearrangements is also clearly demonstrated in the example below. The two epoxide carbons are secondary and equally able to stabilize a positive charge. Of the three possible migrating methyl groups in **400**, only one from the carbon bearing the trimethylsilyloxy group migrates (*Scheme 79*). This shows that the donating ability of the ether oxygen accelerates the migration.



Scheme 79

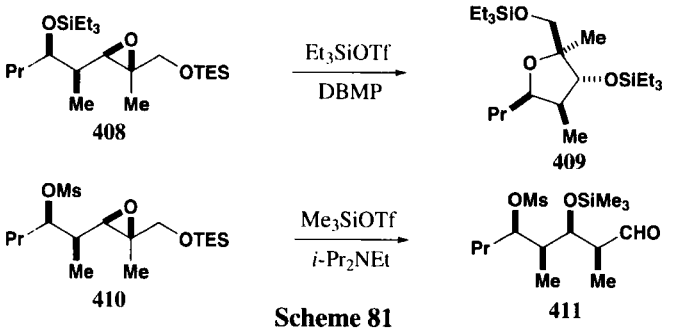
Serendipitously, Yamamoto, Tsuchihashi, and their co-workers did not report a hydride migration of type I. In 1993, Jung and D'Amico described the preparation of all four isomers of 3-alkoxy-2-methylalkanals **404** using a trialkylsilyl triflate and Hunig's base on the appropriately substituted epoxy alcohol (*Scheme 80*).[218] In line with the discussion above, the mild Lewis



Scheme 80

acidity of the triflate coupled with the increased electron-releasing capacity of an alcohol (hydrogen-bonded to a base) ensured a hydrogen migration from the side of the alcohol, even if it is not *a priori* the group with the best ability to migrate. All four pre-requisite chiral epoxides were made from the Katsuki-Sharpless asymmetric epoxidation (KSAE) on the allylic alcohol of appropriate geometry. The overall sequence from an allylic alcohol, since dubbed "non-aldol aldol chemistry", provides a good substitute for the asymmetric aldol condensation.[218]

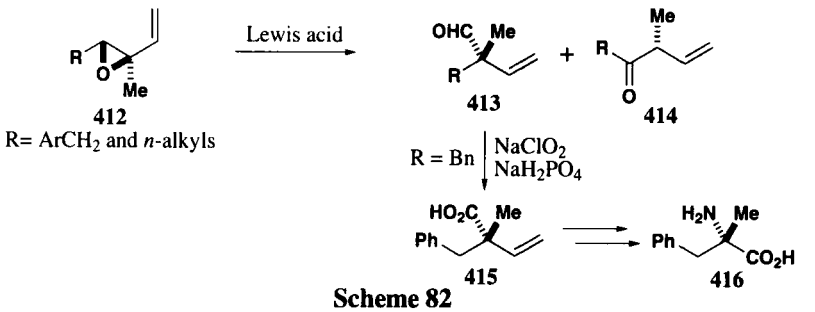
Utilization of this strategy in an iterative way for polypropionate synthesis seemed doomed for failure at first because of competing cyclization to tetrahydrofurans like **409** or tetrahydropyrans (*Scheme 81*, top).[219] It was found later that using a mesylate as protecting group



Scheme 81

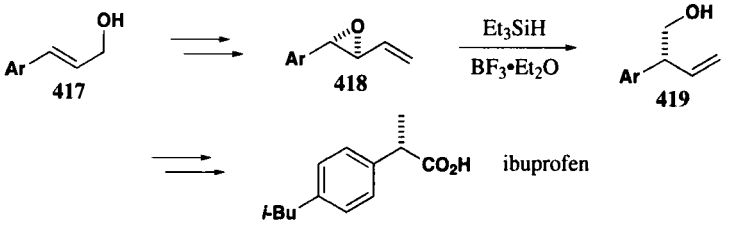
on **410** rendered the pendant oxygen less nucleophilic allowing the desired migration to take place (*Scheme 81*, bottom).[220] Me_3SiOTf instead of the triethyl analogue was also necessary for the reaction. At the same time, the mesylate served to fabricate amino derivatives by displacement with azide and reduction.[221] An approach to the synthesis of the tedanolides using this chemistry has been disclosed.[222]

The KSAE protocol was used to build a series of chiral tertiary allylic epoxides **412** which were rearranged to aldehydes **413** bearing an α-chiral quaternary carbon (*Scheme 82*).[223] This reaction involved a preferential migration of the alkyl group (R). In certain cases, hydride migration competed effectively with the desired alkyl migration giving rise to a chiral non-racemic β,γ-unsaturated ketone **414**. A synthesis of (*S*)-(-)-methylphenylalanine **416** has been described using this strategy.[223]



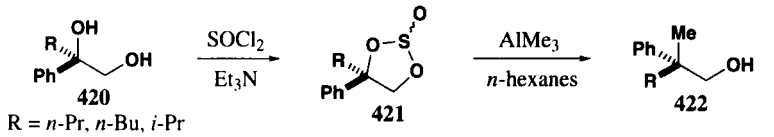
Scheme 82

α-Tertiary aldehydes and acids are also accessible by this method.[224] In this case, the vinyl moiety in **418** can be made to migrate selectively to give **419** if the opposite carbon is substituted with a phenyl group (which ensures regioselective opening of the epoxide). The resulting aldehyde is reduced *in situ* by triethylsilane. The synthetic utility of the method was demonstrated by the synthesis of ibuprofen (*Scheme 83*).



Scheme 83

Chiral 1,2-diols such as **420** can be converted to chiral carboxylic acids bearing a quaternary α stereogenic carbon *via* cyclic sulfite intermediate **421** (*Scheme 84*).[225] Both *endo* and *exo* sulfites afforded the same primary alcohols **422** in ee's ranging from 35-79%. The



Scheme 84

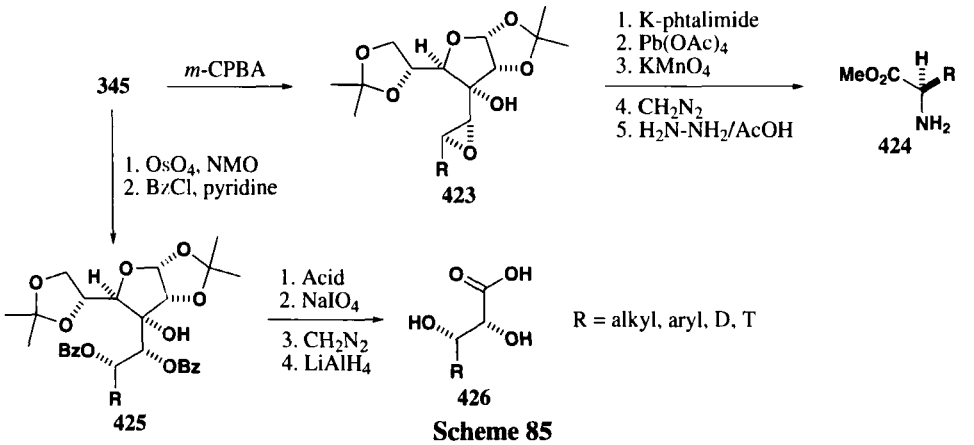
method is limited by the availability of trialkylaluminum reagents but, on the other hand, chiral diols such as **420** are not particularly difficult to obtain. The reaction presumably proceeds by an S_N2 displacement, as indicated by the major product having suffered inversion at C-2. The modest selectivity may come from a competing S_N1 process. The latter hypothesis is supported by the enhanced selectivities observed in non-polar solvents.

d) *Displacement Reactions*

i. S_N2 Displacements

As an alternative method to amino acid synthesis, Kakinuma's allylic alcohol **345** (cf. *Scheme 70*) could be epoxidized with *m*-CPBA to **423** or dihydroxylated with OsO_4 to the diol

corresponding to **425** with modest stereoselectivity (ratios of 3-5:1, *Scheme 85*).[226] After separation of the isomeric epoxide **423**, epoxide opening at the least hindered carbon on **423** with nucleophiles such as phthalimide or deuterides (or tritides) proceeded with complete inversion of

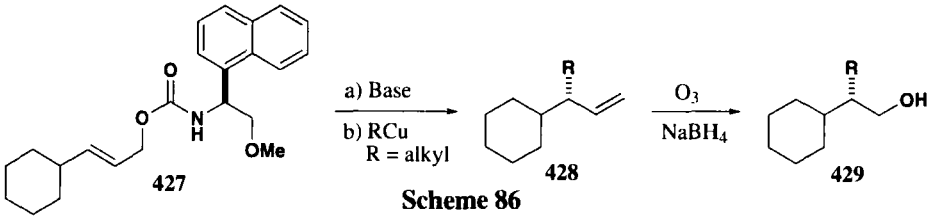


Scheme 85

stereochemistry (S_N2). Treating the resulting diol with periodate did not release the carbonyl product because the stereochemistry of the resulting diol conferred a high energy conformation to the rotamer bearing the two alcohols in a *syn* relationship. However, $Pb(OAc)_4$ was efficacious and gave the amino acids **424** (or labeled acetic acids depending on the nucleophile) and the glucosulose auxiliary was recovered. In the case of the protected dihydroxylation products **425**, cleavage of both acetonides on the auxiliaries resulted in a polyol intermediate which was exhaustively oxidized with periodate to give the corresponding carboxylic acid **426**. Unfortunately, the auxiliary was sacrificed in this procedure. However, valuable isotope-labeled chiral glycerols were obtained in this way.

ii. Nucleophilic Addition to Allylic Substrates

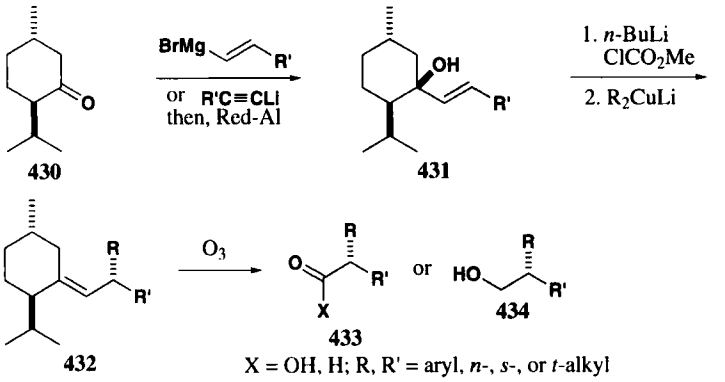
Denmark and Marble have reported a displacement reaction of cuprate reagents onto chiral carbamates **427** derived from the corresponding achiral alcohol (*Scheme 86*).[227] The asymmetric induction was remarkable as it was effective across 7 atoms. It produced terminal alkenes



Scheme 86

428 with good ee's and regenerated the chiral amine in the process. Ozonolysis of alkene **428** was performed to give alcohol **429**. Formaldehyde is lost as a by-product. Only 3-cyclohexyl-2-propen-1-ol was surveyed so it is not known if other substrates function as well.

Kakinuma's carbohydrate scaffold **345** was engineered for the stereoselective rearrangement of the allylic alcohol moiety (see section II.2.2). The possibility of displacement reactions with nucleophiles was mentioned but no examples were ever reported. Presumably, the large groups on each side of the carbinol carbon prevent the perpendicular alignment of the alkene and leaving group which is necessary for any displacement reaction. Our own strategy started with the stereoselective addition of alkenyl- or alkynylmetals to menthone **430** to give allylic alcohols **431** (*Scheme 87*).[228] Alkynylmetals are easier to produce than vinylmetals and their addition to carbonyls gives higher yields. However, being smaller nucleophiles, 10 to 15%



Scheme 87

of the equatorial alcohol often accompanied the desired product. Chromatographic separation of the two propargylic alcohols was never a problem, however, and subsequent reduction with Red-Al afforded an overall better yield of the allylic axial alcohol than the direct and completely selective addition of alkenyllithium or -magnesium to **430**. Alkenyllithiums possess a strong basic character and may enolize the relatively encumbered ketone in **430** resulting in lower yields. Use of $CeCl_3$ somewhat improved yields of alkenyllithium addition.

Derivatization of the alcohol **431** into its carbonate and '*anti*' displacement with several types of cuprate reagents bearing aryls, primary, secondary, or tertiary alkyls yielded adducts **432** with essentially complete transfer of chirality. Gilman's type cuprate gave slightly higher yields but monocyanocuprates and other monoalkylcuprates bearing dummy ligands were effective in avoiding the unnecessary wasting of one equivalent of alkyl. Ozonolysis led directly to a wide variety of α-chiral acids, aldehydes, or primary alcohols in high enantiomeric purities (*Fig. 14*). Advantages over the classical alkylation of chiral enolates include a better tolerance to sterically demanding 'alkylating' agents, participation of aryl groups on either of the reacting partners (allylic carbonate or cuprate reagent), control of the final oxidation state of the carbonyl carbon directly from the cleavage step, and higher ee's in the final products. One of the main limitations of enolate alkylation reactions is the need for reactive alkylating agents because their reactivity diminishes rapidly with increasing size. Cuprates show a comparatively modest reduction of reactivity as the size of the nucleophile increases. Limitations of the present method consist of a

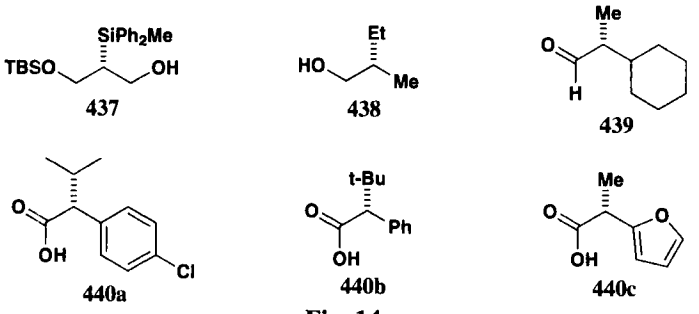
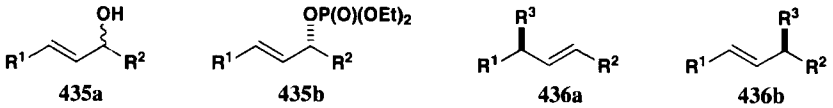


Fig. 14

Examples of Acids, Aldehydes, and Primary Alcohols Obtained from 320

lower tolerance for base-sensitive spectator functional groups on either the electrophile or nucleophile, a dependence of the stereoselectivity on the nature of the aryl group attached to the allylic carbonate (in some cases), and the necessity of using ozone in the cleavage step. Applications of the method so far include the synthesis of ibuprofen (cf. *Scheme 83*) and other arylalkanoic acids.[229]

Chong and Belelie reported a similar strategy using chiral allylic alcohols **435a** (*Fig. 15*).[230] The racemic allylic alcohols **435a** were kinetically resolved by epoxidizing one enantiomer selectively using the Katsuki-Sharpless procedure. The resulting alcohols (84-94% ee)



R^1 = Me, *n*-Bu; R^2 = *n*-Bu, *i*-Pr, *c*-C_6H_{11}, 3-C_5H_{11}; R^3 = Me, *n*-Bu, Bn, *t*-Bu

Fig. 15

Substrates and Products in the Strategy used by Chong and Belelie.

were then converted to the corresponding diethyl phosphonate **435b**. Addition of higher order cuprates [$(R^3)_2CuCNLi_2$] to **435b** gave a mixture of the desired alkene **436a** and alkene **436b**. The observed ratios of regioisomers **436a** and **436b** increased from 67:33 to 98:2 with increasing the size of R^2. The ee's of **436a** ranged from 40% (R^1 = Me, R^2 = R^3 = *n*-Bu) to 84% (R^1 = Me, R^2 = *n*-C_6H_{11}, R^3 = *n*-Bu). However, *t*-$Bu_2CuCNLi_2$ gave almost no stereoselectivity. The alkenes **436a** were successfully converted to the corresponding acids or aldehydes by ozonolysis.

Chiral quaternary carbon centers are not easily constructed from chiral enolates due to their low reactivity and difficulties in controlling the enolate geometry. Meyers' bicyclic lactam system is an exception but the necessity of a cyclic enolate somewhat limits its scope (*vide supra*). The S_N2' displacement technology just described lends itself to the construction of quaternary chiral centers with high enantiomeric purity. However, menthone or any chiral ketone cannot serve as an auxiliary for this purpose because the only two reactive conformers **441a** and **441c** (having the double bond perpendicular to the leaving group) are too high in energy when $R^2 \neq H$ (*Fig. 16*).

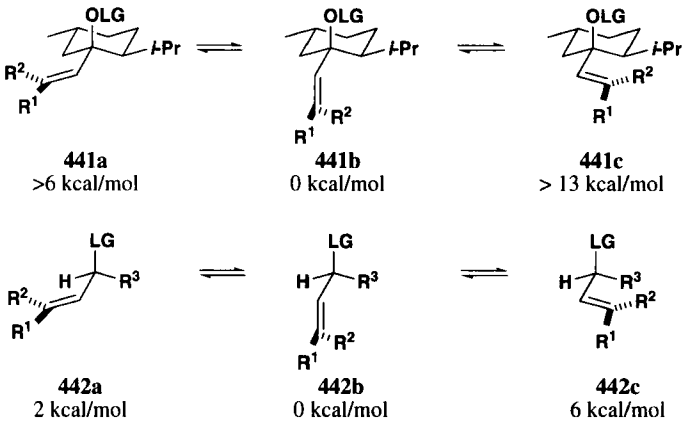
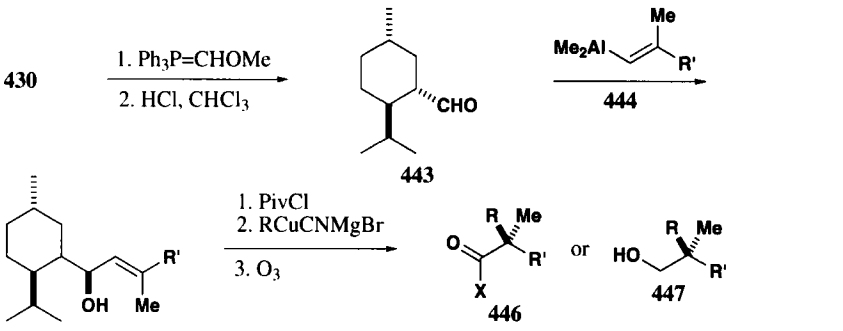


Fig. 16

Calculated Energies for the Different Conformations of Quaternary and Tertiary Allylic Carbonates (R^2 H)

The problem could be solved if an alkenylmetal could be made to add stereoselectively to a chiral aldehyde providing a chiral tertiary allylic alcohol **442** (*Fig. 16*, LG = OH). In this case, one of the reactive conformers of the derived carbonate (**442a**, LG = OCO_2Me) becomes sufficiently low in energy to allow the cuprate addition reaction to take place (*Fig. 16*, $R^2 \neq H$). Unfortunately, most α-chiral aldehydes do not provide a satisfactory level of selectivity upon addition of a wide spectrum of nucleophiles.[231] Moreover, the question of regioselectivity in the subsequent cuprate displacement reaction on **442** becomes central to the success of the method. A bulky chiral auxiliary would help ensure an S_N2' displacement of the leaving group by the cuprate reagent.

Menthyl aldehyde **443**, made in two easy steps from menthone **430**, adds alkenyllithium or -magnesium species unselectively (*Scheme 88*). However, we have found that vinylalanes **444**, made from the Zr-catalyzed carboalumination of alkynes, add with high stereoselectivity to

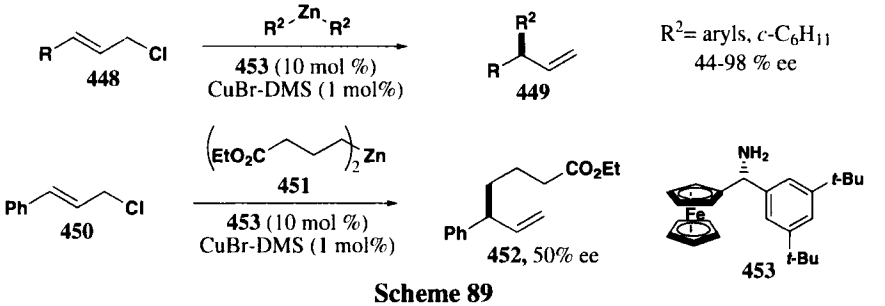


Scheme 88

this aldehyde.[232] The two diastereomers obtained typically in 15-20:1 ratios were always easily separable by chromatography. After derivatizing the major alcohol **445** into the corresponding

pivalate, the addition of monocyanocuprates, made from alkylmagnesiums, proceeded with complete regio- and stereoselectivity giving rise to adducts possessing a chiral quaternary carbon in 60-75% yield and >98% ee. Contrary to the analogous tertiary carbon construction (*vide supra*), *t*-butyl and phenylcyanocuprates have so far proved unreactive. Aldehyde **443** requires vinylalanes for stereoselectivity in the first addition step, which currently limits the method to quaternary carbons bearing a methyl group.

Dübner and Knochel reported a highly enantioselective addition of diorganozincs to allylic chlorides **448** catalyzed by CuBr and chiral ferrocenyl **453** (*Scheme 89*).[233] The ratio of S_N2'/S_N2 products was astonishingly high (>98:2) considering the allylic chlorides were all

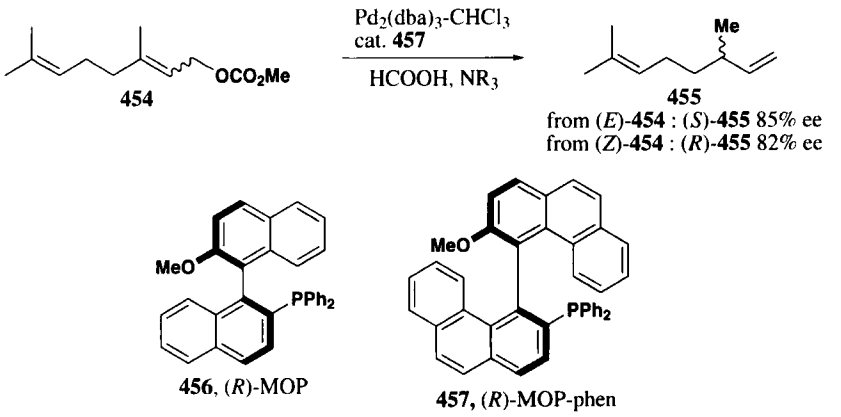


Scheme 89

primary. Oxidative cleavage of the adducts was not performed but could be used to afford carbonyl compounds. Although only hindered dialkylzincs gave satisfactory results, dialkylzincs bearing sensitive functionalities such as the esters in **451** underwent the reaction, albeit with lower selectivities. Some drawbacks are that one equivalent of the alkyl portion on Zn is wasted and the oxidative cleavage would produce formaldehyde as a by-product. Similar catalytic enantioselective carbocupration using Grignard type organometallics instead of organozincs was less successful in terms of the ee's of the products obtained. The regioselectivity of the displacement was nevertheless complete.[234]

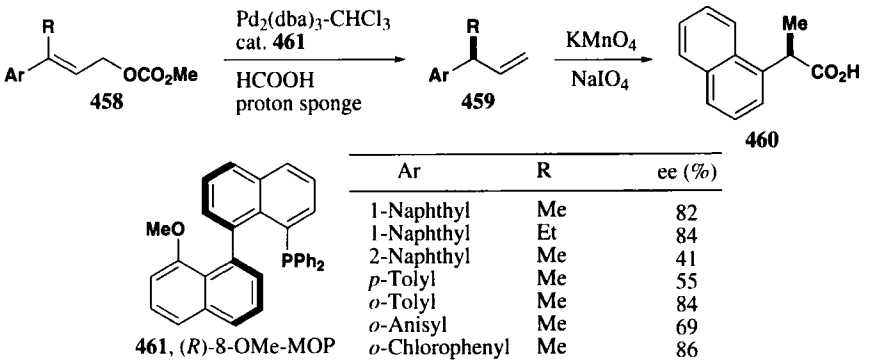
The Pd-catalyzed allylic substitution is much wider in scope than the cuprate displacement reaction as far as the substrate is concerned. The huge amount of research into the area Pd-catalyzed allylic substitution is apparent from the list of chiral ligands that can be found in a recent review on the subject.[235] However, the reaction involves nearly always soft anions such as β-dicarbonyls and related species and those are not reviewed here because they are in effect enolates.

Of the few reported cases of enantioselective allylic substitution involving unstabilized nucleophiles, the reduction by hydrido-Pd complexes stands out as a useful means of preparing monosubstituted alkenes.[236] Hayashi and co-workers reported the first enantioselective example.[237] Geranyl and neryl carbonates, *E*- and *Z*-**454** respectively, were treated with Pd, formic acid, and chiral ligands **456** or **457** to give high yields of terminal alkenes (*S*)-**455** and (*R*)-**455** respectively in good ee's (*Scheme 90*). Other examples were reported with similar success.



Scheme 90

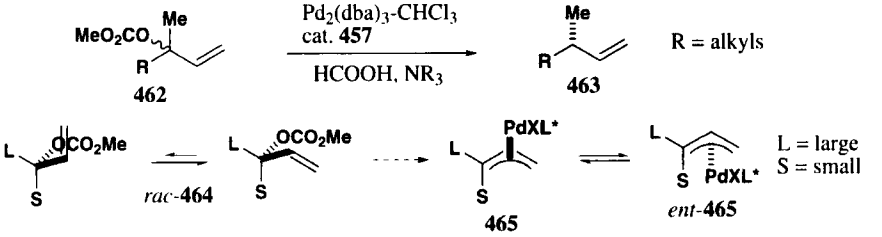
Ligand **461** was equally successful when tested on several substrate carbonates **458** (*Scheme 91*). In one example, the terminal alkene was actually converted to acid **460** substantiating the method as a route to α-chiral carbonyl compounds.[238] Arylalkanoic acids form an important family of compounds, particularly as non-steroidal anti-inflammatory agents.



Ar	R	ee (%)
1-Naphthyl	Me	82
1-Naphthyl	Et	84
2-Naphthyl	Me	41
p-Tolyl	Me	55
o-Tolyl	Me	84
o-Anisyl	Me	69
o-Chlorophenyl	Me	86

Scheme 91

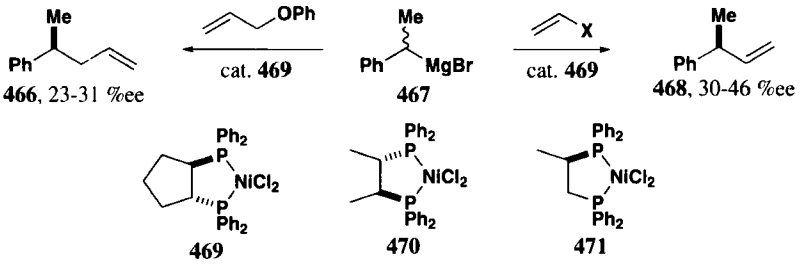
As an alternative, racemic carbonates **462** can be converted into non-racemic **463** under similar reaction conditions (*Scheme 92*). Racemic carbonates **462** are easily prepared from the corresponding ketone. Good enantioselectivities were achieved when the two groups on the



Scheme 92

carbinol carbon in **462** were sterically very different. The mechanism likely involves a preferential formation of the *syn*-π-complexes **465** and *ent*-**465**, which equilibrate to the more stable *ent*-**465** before addition. This method is presently limited by the requirement that the two alkyl groups in the starting carbonate be sterically dissimilar.[239]

Consiglio and Indolese have shown that racemic Grignard reagent **467** can displace achiral allylic ethers or can cross-couple to vinyl halides under the action of Ni complexes (**469**-**471**) to give **466** or **468** respectively (*Scheme 93*). This methodology led to products in low ee's,

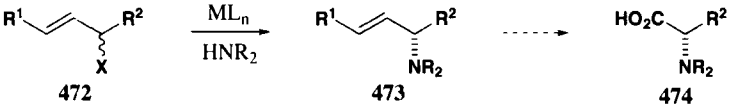


Scheme 93

but its concept of dynamic kinetic asymmetric transformation is interesting and further research may lead to an improved procedure. Both α- and β-chiral carbonyl compounds would become available using this methodology, which would benefit from the wide availability of racemic Grignard reagents.[240]

iii. Allylic Aminations

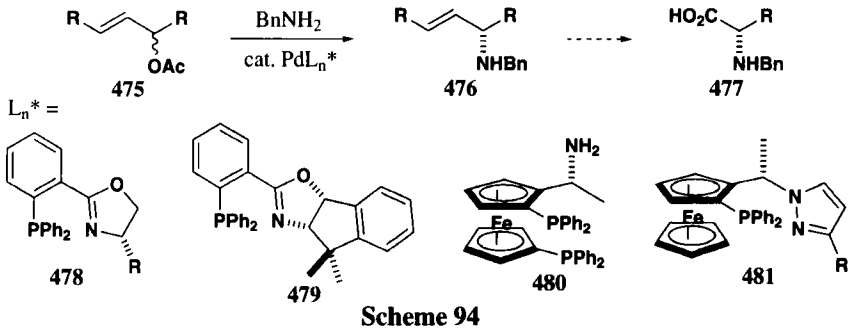
The transition metal-catalyzed enantioselective allylic substitution by amine nucleophiles on appropriate allylic acetates **472** (or other suitable allylic leaving groups X) leads to α-amino acids **474** after oxidative cleavage (*Eq. 8*). This reaction is a useful alternative to chiral



(8)

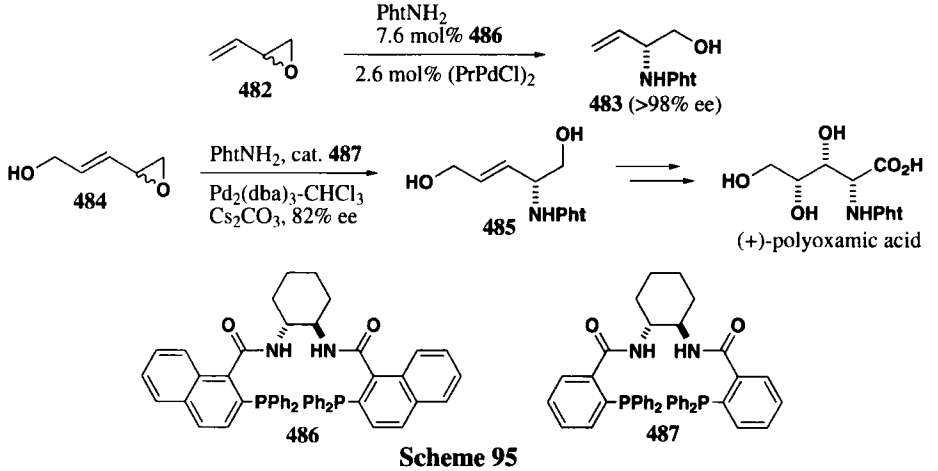
enolate reactions. Pd is the prime metal being used, especially in enantioselective reactions.[241,235b] The question of regioselectivity is crucial in this context. Generally, the reaction proceeds *via* a Pd π-complex intermediate and the nucleophilic attack takes place at the least hindered site, although mixtures are often obtained.

Several chiral ligands have been designed for this purpose. Ligands **478** and **479** led to product **476** in 30-73% ee. Ligands **480** and **481** have proven particularly efficient in this reaction giving ee's ranging from 80-99% (*Scheme 94*). So far, only a limited range of allylic substrates **475** (R = Me, Ph) have yielded useful enantioselectivities with these ligands.[242]



Scheme 94

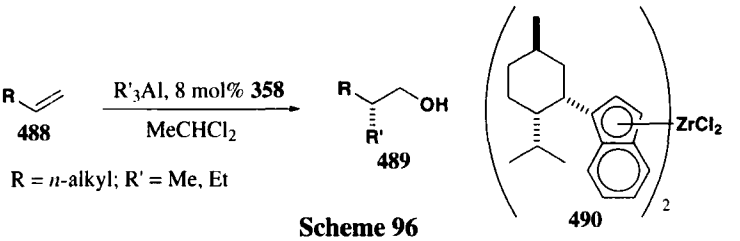
Trost *et al.* had more success with chiral ligands **486** and **487** in substitution reactions with allylic acetates and epoxides (*Scheme 95*).[243] This ligand was part of a family of ligands which gave good results on acyclic as well as cyclic allylic substrates.[235b,244] A short synthesis of (+)-polyoxamic acid was achieved using ligand **487** starting from racemic epoxide **484**.[245]



Scheme 95

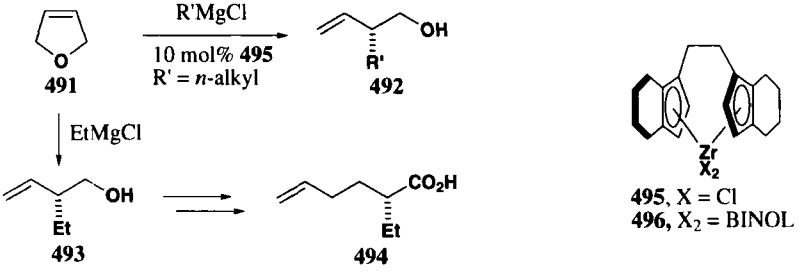
e) Asymmetric Carbometalation of Alkenes

Negishi and Kondakov have reported a useful method for the asymmetric carboalumination of alkenes catalyzed by Zr complex **490**. After oxidation of the vinylalane intermediate, chiral primary alcohols **489** are obtained.[246] In this umpoled alternative to chiral enolate alkylation, the alkyl being added does indeed have a nucleophilic character. The solvent strongly affects the outcome of the reaction. Initially, methylalumination was carried out in hexanes but under these conditions, higher trialkylaluminums proceeded instead to yield diols in low % ee *via* a cyclic intermediate. A switch to more polar dichloromethane resulted in much better results and eventually it was found that 1,1-dichloroethane led to high yields of alcohol **489** in ee's generally above 90% (*Scheme 96*). Alcohol and amine functionalities elsewhere in the starting alkene were tolerated but only primary substituents were viable, either on the alkene (R) or in the trialkylaluminum reagent (R').



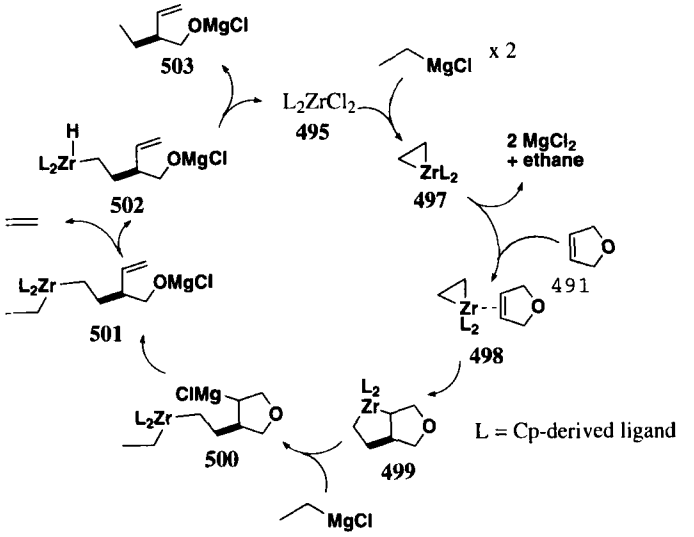
Scheme 96

2,5-Dihydrofuran **491** is a substrate for the enantioselective carbomagnesiation reaction catalyzed by Zr complex **495** (*Scheme 97*).[247] The reaction creates a primary homoallylic alcohol **492** which can be oxidized to a carbonyl compound as was **493** in the synthesis of **494**, a fragment of macrolactam Sch 38516.[248]



Scheme 97

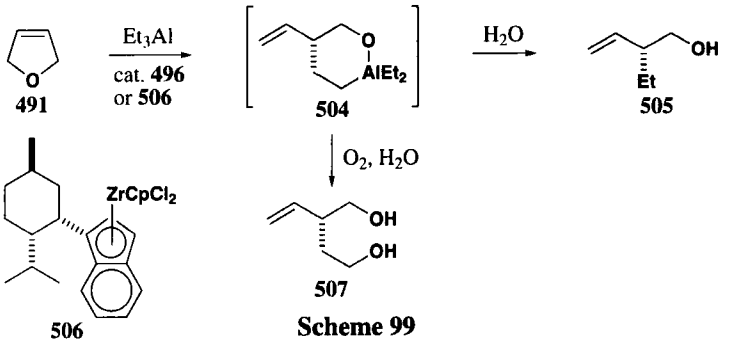
This reaction possibly proceeds first by reaction between the Grignard reagent and the catalyst with formation of a zirconacyclopropane **497** (*Scheme 98*). This species carbozirconates the dihydrofuran with concomitant expansion to a zirconacyclopentane **499**. Then, the addition



Scheme 98

of a second molecule of the Grignard reagent is followed by an elimination with concomitant opening of the tetrahydrofuran ring to give **501**. Finally, β-elimination of ethylene and reductive coupling completes the catalytic cycle. The transfer of chirality probably occurs in the ring expansion step (**498** → **499**).

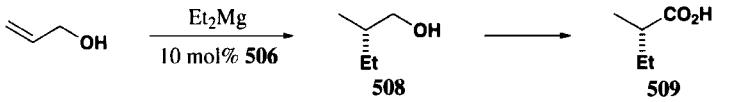
A similar process with triethylaluminum and catalyst **496** or **506** was recently developed.[249] 2,5-Dihydrofuran was converted to alcohol **505** or diol **507** depending on the work-up conditions utilized (*Scheme 99*). The enantioselectivities achieved in this reaction were close to perfect using catalyst **496**. The mechanism is evidently different from that shown above for alkylmagnesiation. Substituted furans were also investigated as substrates but a mixture of two regioisomers was invariably obtained.



491 504 505 506 507

Scheme 99

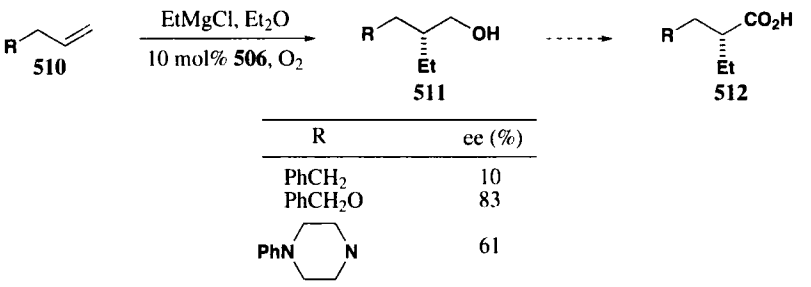
Allyl alcohol was ethylated by diethylmagnesium to give the primary alcohol **508**, although the enantioselectivity was modest (20-56% ee) and the scope of the reaction is still unknown (*Scheme 100*).[250] Alcohol **508** can be converted to different carbonyl products, for example **509**, by simple oxidation. Hoveyda had previously studied the ethylmagnesiation of chiral racemic allylic alcohols and ethers. High diastereoselectivities (up to 99:1) were obtained depending on the nature of the ether group and the substitution pattern of the substrate.[251]



508 509

Scheme 100

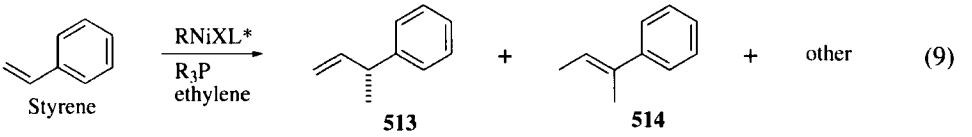
Simple terminal alkenes underwent Zr-catalyzed ethylmagnesiation in low to modest enantioselectivity (*Scheme 101*).[250b] The intermediate alkylmagnesium could be trapped with different electrophiles. When a proton was used, a simple alkane resulted but when oxygen was used, a primary alcohol **511** was formed. It appears that the presence of a coordinating nitrogen or oxygen on the alkene (R) is essential to obtain good levels of enantioselection. The product **511** can be made equivalent to chiral enolate alkylation products by simple oxidation to **512**. Whitby's ethylalumination procedure (cf. *Scheme 99*) can also be applied to terminal alkenes but the ee's were low to modest (30-64% ee).[249]



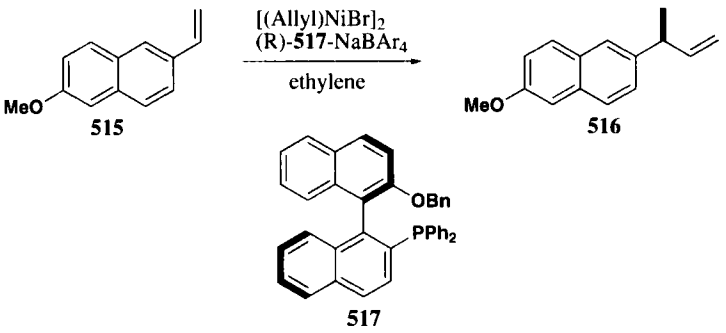
R	ee (%)
$PhCH_2$	10
$PhCH_2O$	83
PhN, N	61

Scheme 101

The asymmetric vinylmetalation of styrene-like molecules was first reported by Wilke and then by several other groups using mostly Ni catalysts (*Eq. 9*).[252] In these systems, the formation of several isomers and oligomers in addition to the reaction product was problematic, although the enantiomeric purity of the desired product **513** was good in many cases.



Some problems were traced back to a nickel hydride transitory species which could isomerize the final product. Also, the use of a Lewis acid, necessary to create a reactive 16-electron Ni species, was detrimental to the optical purity of the final product. In addition, the Lewis acid prevented reactions with substrates containing basic heteroatoms. By fine-tuning the electronics of the phosphine ligands and by choosing a non-coordinating counterion Ar_4B^- (to alleviate the need for a Lewis acid), high yields of the desired product were achieved. Use of the MOP ligand **517** in the Ni-catalyzed hydrovinylation of **515** furnished **516**, a precursor to naproxen, in 97% yield and 80% ee (*Scheme 102*).[253]



Scheme 102

Salzer used Pd complexes to effect the asymmetric hydrovinylation of styrene with ethylene. The catalysts were made *in situ* from $[(\eta^3\text{-}C_4H_7)Pd(COD)]BF_4$ and ligands **518-520**,

the later being particularly effective (*Fig. 17*). At 70% conversion, the amount of isomer **514** (cf. *Eq. 9*) was negligible and the ee of **513** was nearly 79%. At higher conversion, the ee of **513** increased dramatically to 92% due to the selective conversion of *ent*-**513** into the isomer **514**. Unfortunately this improvement in % ee was accompanied by a loss in chemical yield.[254]

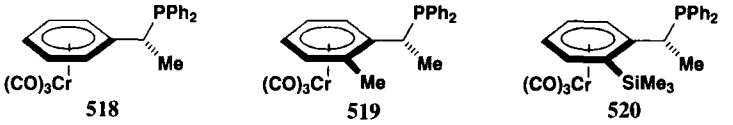
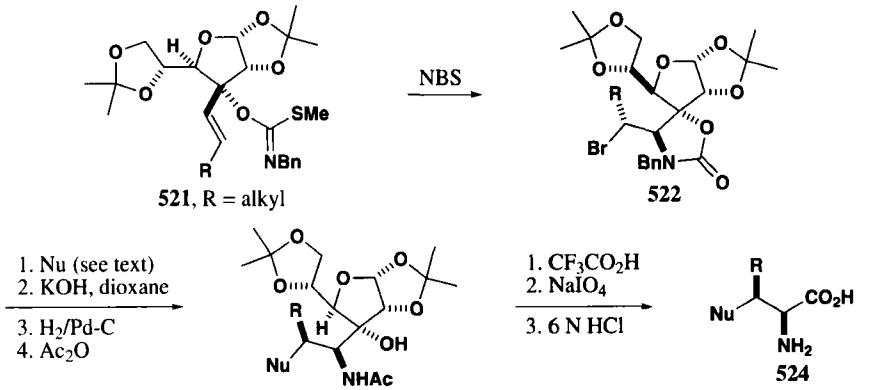


Fig. 17

Ligands Used in the Pd-Catalyzed Hydrovinylation of Styrene

f) Electrophilic Cyclizations

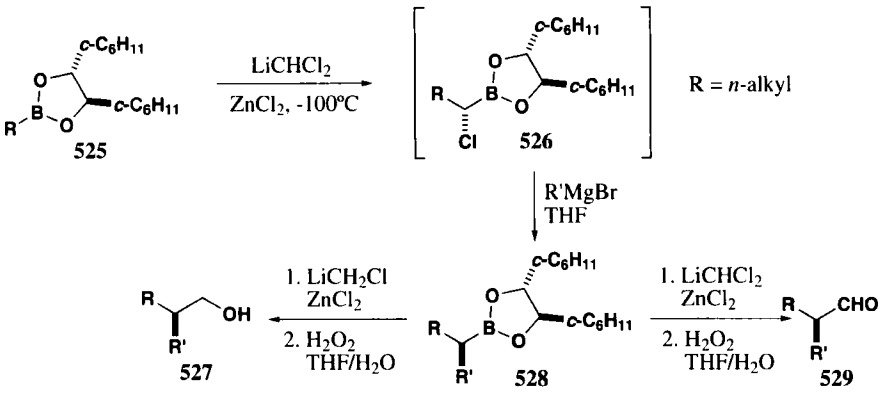
Intramolecular electrophilic cyclization of the *N*-benzylmethylthioformamide **521**, derived from **345** (cf. *Scheme 70*) and *N*-bromo or *N*-iodosuccinimide, led to the stereoselective formation of oxazolidinones **522**.[255] Only trace amounts of the diastereomers were detected and none of the six-membered ring product was observed. Deuterated L-serine was prepared by displacement of the pending bromide in **522** with acetate ion. Malonate, cyanide, and thioacetate also displaced the bromide effectively and the resulting adducts served for the synthesis of labeled glutamic acid, aspartic acid, and cysteine respectively. Unfortunately, the chiral auxiliary was destroyed in the process (*Scheme 103*). Other cyclizations of this type to make a bond β to a carbonyl can be found in section III.2.2.



Scheme 103

g) Rearrangement of α-Chloromethylboronates

An ingeneous method developed by Matteson and his co-workers converts chiral α-chloromethylboronates to chiral alkylboronates and leads to the creation of a carbon chain with adjacent chiral centers reminescent of enolate alkylation or aldol products.[256-258] It may be associated to an umpoled equivalent of chiral enolate reactions since the newly created chiral center is formed from the nucleophilic displacement of the chlorine by an alkyl Grignard (*Scheme 104*).

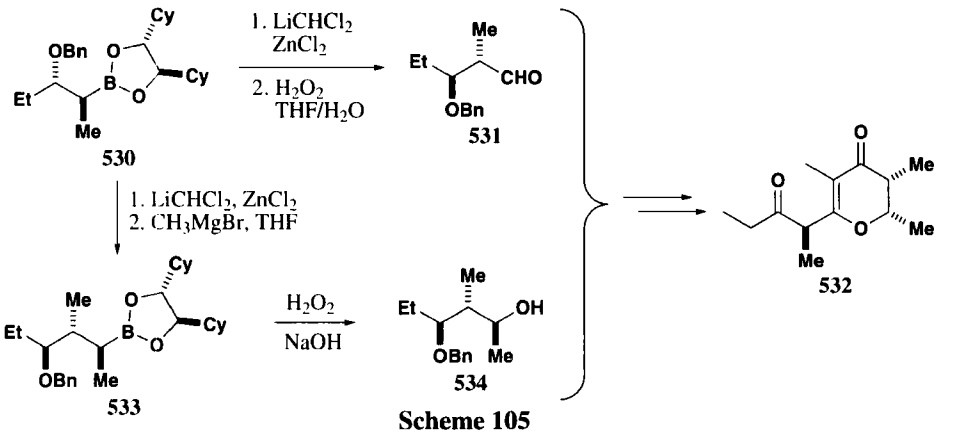


Scheme 104

The α-chloromethylboronate was prepared by the stereoselective addition of $LiCHCl_2$ to chiral alkylboronate **525** to give α-chloromethylboronate **526**. Addition of Grignard reagents to this intermediate led to a new alkylboronate **528**. The stereocontrol achieved in the two key steps was essentially complete. Alcohol **527**, either primary or secondary, was easily obtained by peroxide oxidation of the final boronate. Alternatively, the chloromethylboronate furnished aldehyde **529** upon oxidation.

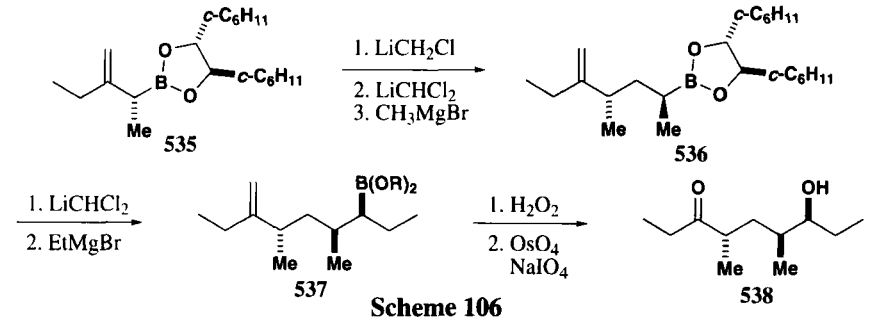
It was possible to exchange the chiral diol ligand for its enantiomer during the course of the synthetic sequence (for example in **528**), thereby allowing for the construction of adjacent chiral centers with alternate stereochemistries.[259]

Matteson has used this strategy for the total synthesis of stegobinone **532**.[260] Here, the demonstration of the iterative capability of the method to make adjacent chiral centers was impressive as each iteration requires only 2 steps (*Scheme 105*). A single intermediate **530** served as a common substrate to make two fragments **531** and **534** which were connected to make the natural product.



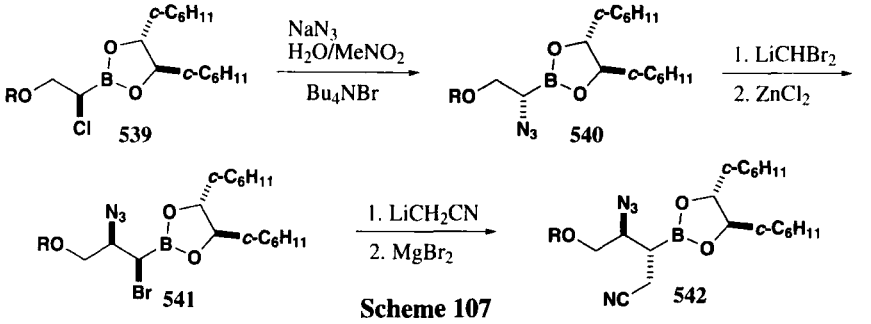
Scheme 105

In a synthesis of serricornin **538**, stereocenters in a 1,3-relationship were also built by an iterative method (*Scheme 106*).[261] A methylene unit was introduced between the chiral centers using $LiCH_2Cl$ (**535** → **536**). Another iterative step, this one to introduce the next chiral center, was performed giving **537** before oxidative treatment gave serricornin. One may suppose that more than one such methylene unit could be introduced in this way enabling the synthesis of branched alkyl chains with chiral centers in 1,4- and higher relationships.



Scheme 106

More recently, new conditions to introduce the azido group were reported.[262] This functional group had been used to produce amino acids[263] but the earlier phase-transfer conditions in water/dichloromethane were somewhat hazardous with the potential production of diazidomethane. With the new conditions (water/nitromethane and an ammonium salt), good yields of azido boronic esters **540** were obtained from **539**. The later underwent the chain extension described above to give **541** (*Scheme 107*). Here, the anion of acetonitrile was used to displace the bromide in **541**. Extension beyond **542** was not satisfactory.

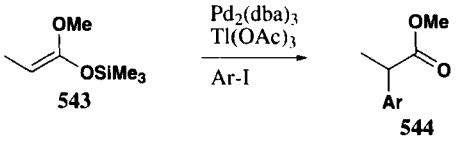


Scheme 107

3. Neutral α-Carbon

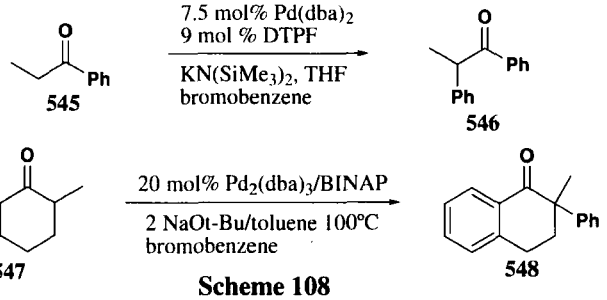
a) Pd-Catalyzed Arylation Reactions

In 1992, the asymmetric Pd-catalyzed arylation of silyl ketene acetal **533** using a stoichiometric amount of Tl(III) acetate was shown to yield α-tertiary chiral ester **544** in 40-50% ee (*Eq. 10*).[264] Arylations of enol ethers have a different mechanism than alkylations of enolates and it can be said that the aryl group being added is not electrophilic since the carbon-carbon bond probably forms from a $X_2Pd(Ar)(CH{=}C(O)R)$ species.[265]



(10)

Direct arylation of enolates is not trivial. In 1997, several groups demonstrated the racemic arylation of ketone[265,266] and amide[267] enolates catalyzed by Pd (*Scheme 108*, top). The use of non-racemic BINAP as ligand was reported soon after, although it involved only examples of cyclic ketone to form quaternary carbon centers and the absolute stereochemistry of the products was not determined (*Scheme 108*, bottom).[268] Although this methodology is only at its beginning, it would be desirable from a synthetic point of view to see it evolve into a more general and stereoselective process.



Scheme 108

b) Intermolecular Radical Reactions

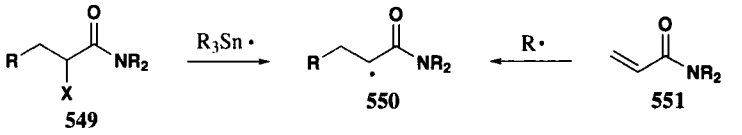
Synthetically useful radical reactions were scarce before the 1970's.[269] Moreover, until the late 1980's/early 1990's, nearly all instances of stereochemical control in radical reactions involved cyclic radicals.[270] Acyclic stereocontrol using radical chemistry is therefore young and although the rate of discoveries and developments in this area is exceptional, many challenges remain to be solved (*vide infra*).[271,272] Comparable radical and anionic chemistries often display complementary features in the nature of the reactants and in their tolerance for spectator functional groups. For example, many alkenes, unreactive to enolates, will participate in radical reactions with ease. By contrast, carbonyls and alkyl halides, the main reacting partners with enolates, are often poor radical acceptors. Alkoxy groups β to an anion can undergo elimination, but not when they are β to a free radical. The reverse is true for sulfide groups.

On the other hand, controlling the stereochemical outcome of an intermolecular α-oxo radical reaction requires managing many of the same structural features of the chiral auxiliary as for an intermolecular chiral enolate reaction. Such features include the geometry of the radical enolate, the proximity of the inducing chiral centers to the radical, and the conformation and/or rotational freedom of the chiral group. Radical reactions tend to have a rather early transition state where steric effects do not exert their full influence resulting, on average, in somewhat

lower selectivities than their anionic counterpart.[269-272] In addition, intermolecular radical reactions are so far limited to hydrogen abstractions, halide or selenide transfer reactions, and allylation reactions.

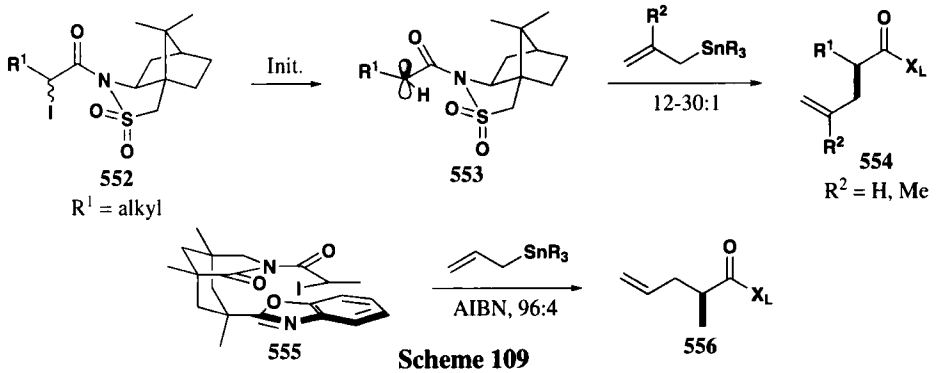
c) α-Oxo Radicals

Carbon radicals generated next to a carbonyl function readily add to unsaturated bonds to give alkylated carbonyl compounds with the potential creation of a new chiral center. A radical α to the carbonyl can be generated in one of two ways. It can be formed by C-X bond cleavage, X being an halogen or selenide, or it can result from the intermolecular addition of a radical to an unsaturated ester or amide **551** (*Eq. 11*).



(11)

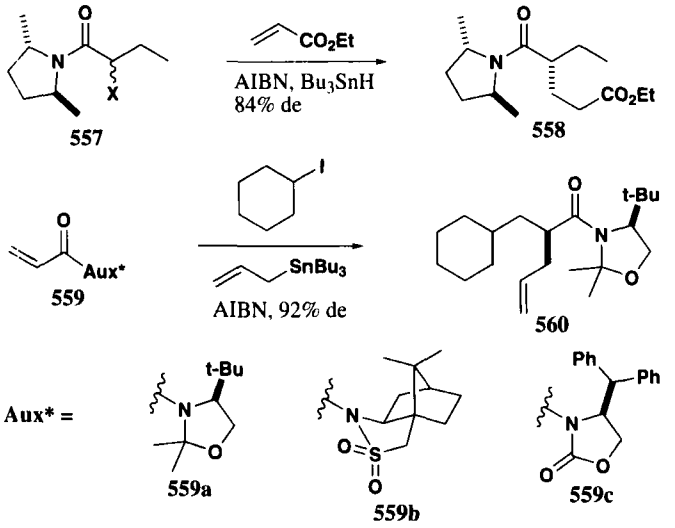
The groups of Guindon,[273] Hart,[274] and Giese,[270] among others, studied diastereocontrol in hydrogen abstractions and allylations of acyclic radicals α to an ester. They have extensively contributed to the generation of aldol-type adducts *via* the diastereoselective reduction and allylation of β-alkoxyesters. These are examples of 1,2-asymmetric induction brought about by a chiral center already on the substrate. Several research teams were successful in getting a highly stereoselective allylation of radicals α to chiral amide auxiliaries. Strategies of conformational control resembled those used in the alkylation of the analogous enolate, including *dipole-dipole* and steric interactions. Curran used the Oppolzer chiral sultam auxiliary to effect good to excellent diastereoselection in allylation of radical **553** depending on the method of initiation (*Scheme 109*, top).[275,276] Later, a collaboration between two research groups led to the utilization of



Scheme 109

Rebek's auxiliary to prepare iodoamide **555**. Its allylation reaction under free radical conditions led to amide **556** as a 96:4 mixture of diastereomers (*Scheme 109*, bottom).[277]

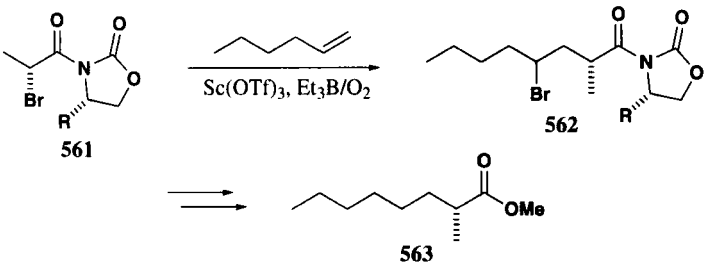
Porter used the C2-symmetric amide **557** and obtained good diastereoselection on the addition reaction of its radical to ethyl acrylate (*Scheme 110*).[278a] The same group reported the allylation of the radical generated by the addition of cyclohexyl radical to oxazolidine-derived



Scheme 110

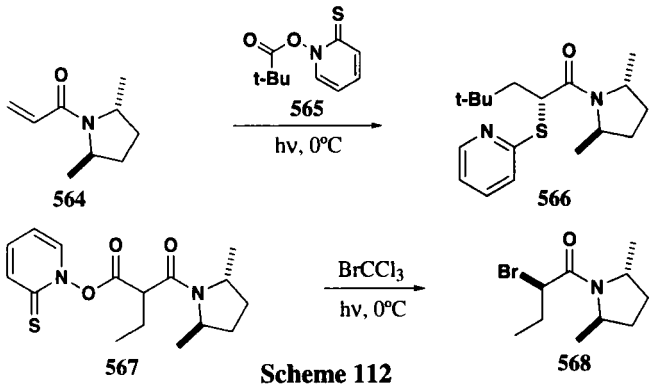
acrylamide **559a**. A ratio of 25:1 was measured for the product **560**, which was formed along with some accompanying bis-allylation product. The same reaction was also conducted on the sultam analog **559b**.[277] Sibi and co-workers used acrylamide **559c** derived from his diphenylalaninol oxazolidinone auxiliary in combination with a Lewis acid ($MgBr_2$-Et_2O or lanthanide triflates) to effect excellent diastereoselection in radical allylation reactions (>100:1).[279] They used Et_3B as the initiator and ethyl iodide instead of cyclohexyl iodide.

To effect a good conversion in the intermolecular addition of an α-oxo radical to a double bond, a hydride-free reaction mixture is desirable due to competing hydrogen abstraction by the α-oxo radical. The atom-transfer addition, also termed the Kharasch reaction, provides such conditions in addition to maintaining a potentially useful functional group in the final product. However, high temperatures, long reaction times and large excesses of the halogenated substrate are often needed in the Kharasch reaction. Guindon,[273d] and Porter[280] have improved on the protocol by using Lewis acids to render the C-X bond weaker and thus increase the rate of propagation relative to the rate of hydrogen abstraction.[281] Porter and co-workers established a diastereoselective protocol that takes advantage of this strategy (*Scheme 111*). Oxazolidinone **561** was treated with a lanthanide Lewis acid to keep its conformation rigid and predictable during its radical addition to 1-hexene. Diastereoselectivities ranging from 82:18 to 96:4 were observed depending on the nature of R and the solvent.[280]



Scheme 111

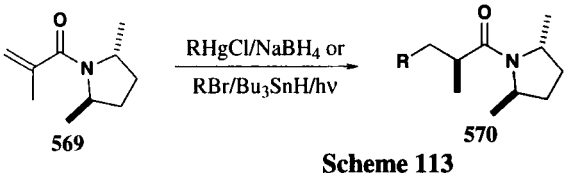
Giese and co-workers used the C_2-symmetrical dimethylpyrrolidine acrylamide **564** to which they added *tert*-butyl radical followed by a stereoselective atom transfer step of the thiopyridyl group to give **566** as a 14:1 mixture of diastereomers (*Scheme 112*, top). Conversely,



Scheme 112

the radical α to the amide can be generated directly from the decomposition of **567** and quenched with bromotrichloromethane to give bromide **568** and its diastereomer in a 17:1 ratio (*Scheme 112*, bottom).[282]

The same group observed a dependence of the diastereoselectivity on the nature of the alkyl radical being added to methyl acrylamide **569** (*Scheme 113*).[283] Larger alkyls afforded higher diastereoselectivities upon reduction with a hydrogen donor. By contrast, acrylamide **564**

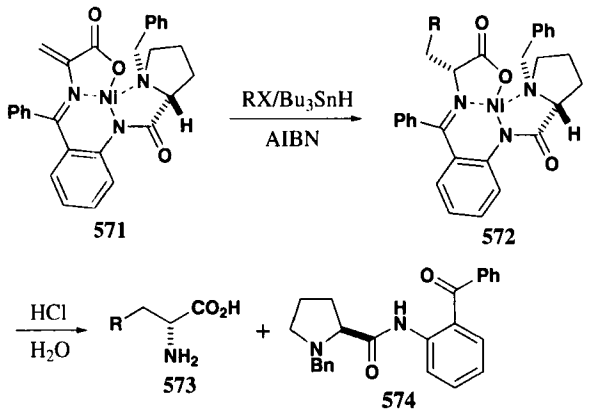


R	de (%)
t-Bu	80
c-C_6H_{11}	60
Me	34

Scheme 113

did not display the same dependence with respect to its reaction with pyridinethione **565**. Note also that the initial attack of the alkyl radical on **569** is much slower than the corresponding reaction with **564** due in large part to the methyl substituent which twists the amide bond out of conjugation.

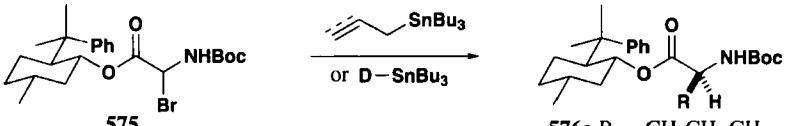
Belokon's team developed a rather intricate enoate complex of Ni built from dehydroalanine, which suffered addition of alkyl radicals followed by diastereoselective hydrogen abstraction (*Scheme 114*). Alkyl halides were reacted with **571** under standard radical chain reaction conditions to give **572** with moderate to high stereoselectivity depending on the nature of the adding alkyl radical. Hydrolysis to amino acid **573** occurred in mildly acidic medium, which permitted the recovery of the chiral auxiliary **574**.[284] Note that nucleophiles also added to **571** to give, after protonation of the enolate, intermediate **572**.[285]



571 572 573 574

Scheme 114

Esters have been used as chiral auxiliaries for intermolecular radical reactions with much less success. A notable exception is the radical reactions of protected glycine derivative **575**, which reacted with allyl- and propargylstannanes[286] or tributyltindeuteride[287] to give **576** in up to 90% de (*Scheme 115*). However, doubts have been cast on the free radical mechanism for this reaction based on the fact that (a) AIBN is not a necessary additive, (b) 10% hydroquinone does not stop the reaction and (c) propargylstannanes proceed by S_N2 rather than S_N2' substitution.[288,272]

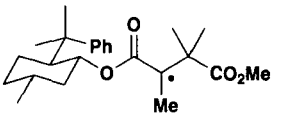


575

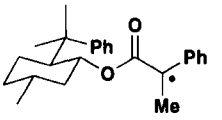
576a R = -$CH_2CH{=}CH_2$
576b R = -$CH_2C{\equiv}CH$
576c R = -D

Scheme 115

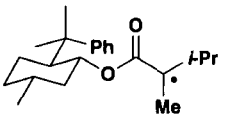
Naturally, stereoselectivity in addition reactions of trisubstituted α-oxo radicals to olefins are much less selective than the corresponding reaction of disubstituted α-oxo radicals. This is due in part to the small energy difference between the *E*- and *Z*-configuration of the radical. The high stereoselectivities obtained by Chen *et al.*[289] using phenylmenthol-derived tertiary radicals **577-579** stand in constrast to this assertion (*Scheme 116*). Reduction of these radicals proceeded with moderate selectivities for **578** but good selectivities for **577** and **579**. Surprisingly, selectivities of greater than 99:1 could be achieved in the allylation of **578** at –80°C.



577



578



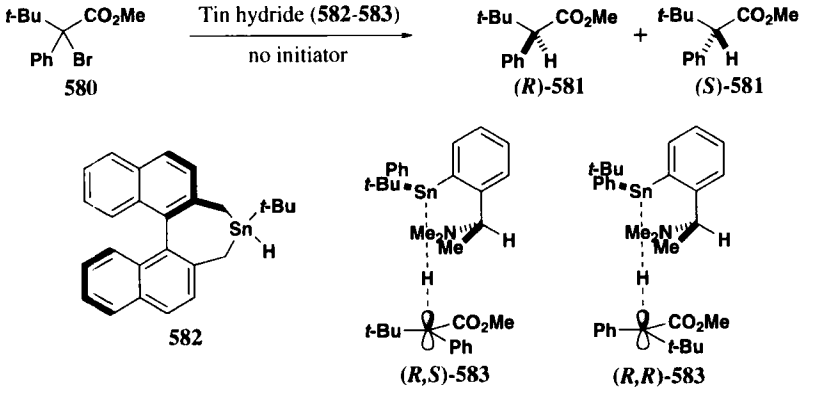
579

Scheme 116

The approach described so far to produce α-chiral carbonyl compounds by an addition reaction or by reduction of chiral α-oxo radicals provides useful information on acyclic radical behavior. However, it is only a modest complement to chiral enolate chemistry because of the severe limitation on the type of radical acceptors that can be used (the equivalent of the electrophile in the classical chiral enolate approach). Also, allylstannanes are toxic materials while acrylate acceptors often lead to the concomitant formation of oligomers. In addition, it is an indirect approach to enolate chemistry because of the extra synthetic steps needed to build a suitable radical precursor (*e. g.* installing a bromine atom on the chiral amide or ester fragment). On the other hand, this alternative to enolate chemistry tolerates a wide variety of spectator functional groups present on the starting material.

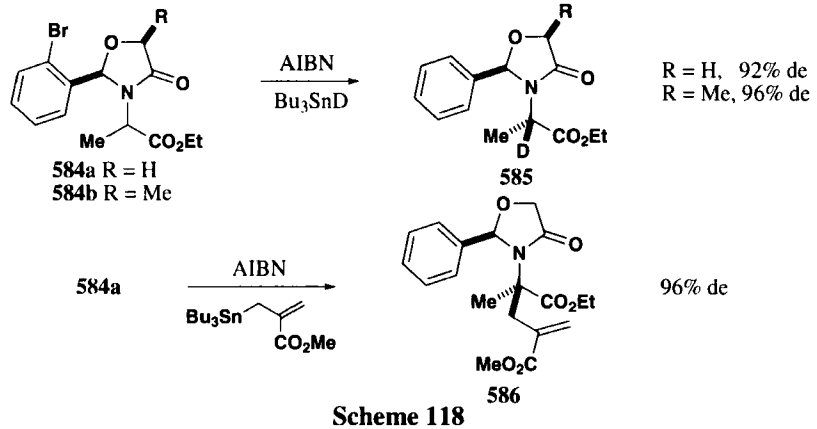
More recently, several authors have pursued the goal of achieving high asymmetric induction in the reduction of α-keto radicals with a chiral tin hydride. The corresponding approach of reducing an α,α-disubstituted enolate with a hydrogen attached to a chiral atom has met with only moderate success.[290] The asymmetric induction in the radical reduction by a chiral tin hydride is dependent on the steric differentiation of the two alkyl groups attached to the carbon bearing the radical, just like the protonation of α,α-disubstituted enolates is. This may prove as difficult as controlling the geometry of α,α-disubstituted enolates. Compounding the problem is the fact that radical reactions proceed by an early transition state making it less susceptible to steric constraints. Indeed, stereoselectivities in the tin hydride reduction of chiral racemic α-bromo esters or amides bearing a covalently bound chiral auxiliary (*vide supra*) are generally lower than that observed in the conventional alkylation of chiral enolates. Tin hydride reagents bearing chiral ligands, or chiral at the Sn atom[191] have not yet yielded notable levels of selectivity despite Metzger's efforts toward this goal.[192] Metzger and co-workers reported that a mixture of diastereomeric tin hydrides **583** effected the reduction of bromo ester **580** to give a mixture of enantiomeric esters **581** in a ratio of 55:45 (*Scheme 117*). They proposed, in fact, that (*R,S*)-**583** may have effected near perfect asymmetric induction if one assumed no asymmetric induction on the part of (*R,R*)-**583**. This assumption was based on the model shown in *Scheme 117*. Alternatively, chiral tin hydride **582** based on the BINOL construct reduced bromoester **580** to the ester (*R*)-**581** in 53% ee.

Renaud and Giraud devised an ingeneous strategy to make α-amino acids by reduction of α-oxazolidinoester radicals. The oxazolidinoester precursors **584a** and **b** were both obtained as inconsequential diasteromeric mixtures. The radical α to the ester was generated by radical



Scheme 117

translocation (*Scheme 118*). The observed diastereoselectivities were high in the reduction experiments. Allylation of **584a** gave even better results.[293] The method can thus be used to prepare α-alkylated and dialkylated amino acids



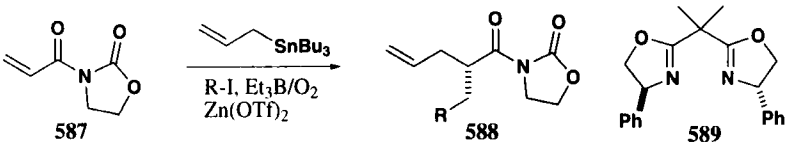
Scheme 118

A dipole-dipole repulsion argument was used to rationalize the selectivities reported in Scheme 118 (*Fig. 18*). This repulsion leads to a higher concentration of the conformation on the right and the phenyl and R groups on the oxazolidinone ring direct the allyl or hydride reagent to the opposite face of the molecule.

Fig. 18

The Two Competing Conformations of the Radical Generated from 584

Catalytic enantioselective radical addition/allylation on acrylate-type molecules can be achieved through the use of chiral Lewis acids. The first example of this type of reaction involving acyclic radicals was published by Porter in 1995. Achiral acrylamide **587** underwent radical addition of cyclohexyl or *tert*-butyl radical promoted by $Zn(OTf)_2$ complexed to ligand **589**. The resulting radical underwent enantioselective allylation with allyltributylstannane (*Scheme 119*).[294] The Lewis acid not only supplies the chiral environment but also accelerates the

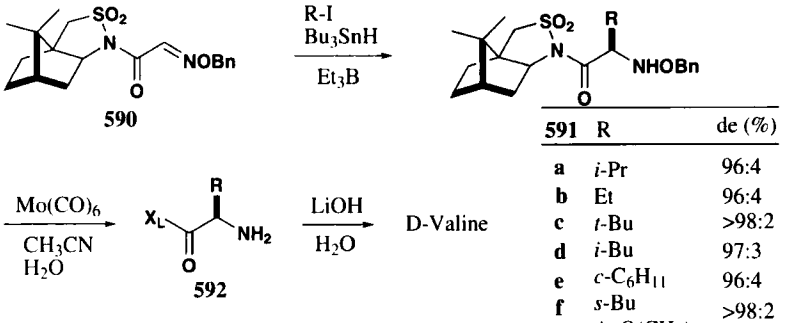


Scheme 119

addition step, something which is actually essential to prevent the racemic allylation of non-chelated acrylamide. In this and other examples, the enantioselectivity reached up to 95:5 and was strongly dependent on the chiral ligand, the solvent, the Lewis acid, and the radical undergoing the addition step. Disappointingly, ligand **589** was somewhat ineffective at inducing chirality in the addition of the radical derived from **561** (R = H) on 1-hexene (cf. *Scheme 111*).

d) Radical Addition to Glyoximines

Much like its anionic counterpart (cf. section II.2.1), the intermolecular addition of alkyl radicals to glyoxylic oxime ethers gives rapid access to α-amino acids. In contrast to the corresponding nucleophilic addition, which sometimes gives addition on nitrogen, the radical method seems to escape this problem of regioselectivity. Naito and co-workers added alkyl radicals to the camphorsultam derivative of glyoxylic benzyloxime, **590**, and achieved good diastereocontrol (*Scheme 120*).[195a] Lewis acids marginally improved the selectivity but the absence of



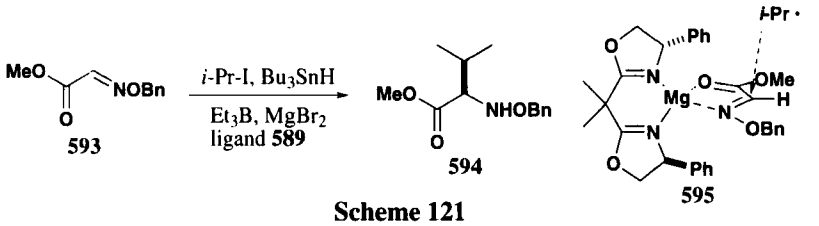
591	R	de (%)
a	*i*-Pr	96:4
b	Et	96:4
c	*t*-Bu	>98:2
d	*i*-Bu	97:3
e	*c*-C_6H_{11}	96:4
f	*s*-Bu	>98:2
g	$AcO(CH_2)_4$	>98:2
h	$Cl(CH_2)_3$	>98:2

Scheme 120

tri-*n*-butyltin hydride led to a slight decrease in selectivity and a larger proportion of the ethylated adduct **591b** (R = Et). The latter is formed by addition of ethyl radical produced by the

triethylborane initiator. The benzyloxy group was removed by reductive cleavage of the N-O bond and conversion of the amine product **592** to D-valine was done with LiOH in water. Other chiral glyoximines, including cyclic ones, gave lower selectivity of alkyl radical additions.[295b]

Achiral glyoxylic oxime **593** reacted with low to moderate enantioselectivity (2-52% ee) when treated under the same reaction conditions as per **590** but in the presence of a 1:1 mixture of a Mg salt and chiral ligand **589** (*Scheme 121*).[295a] The nature of the Lewis acid was

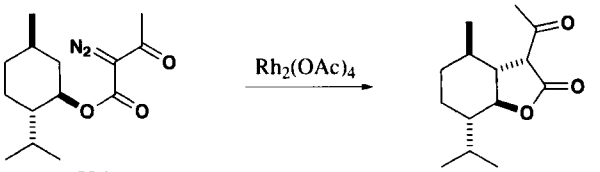


Scheme 121

crucial, $MgBr_2$ leading to higher enantioselectivity. Model **595** explains the formation of the major product. Jørgensen and co-workers used a BINAP-Cu complex to effect addition on imine **593** and obtained low enantioselectivity (33% ee).[295c]

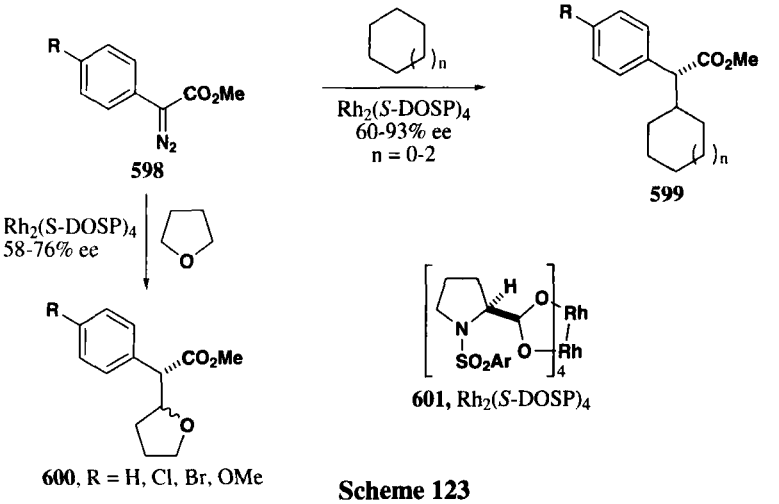
e) *α-Diazo Carbonyls*

Carbenes generated from α-diazo carbonyl compounds undergo insertion reactions into C-H, Si-H, and heteroatom-H bonds rather efficiently. The insertion reaction may create a chiral center next to the carbonyl function making it a close relative of the electrophilic reaction of enolates. Because insertion occurs on C-H bonds, with no prior activation being necessary, this is a highly desirable alternative to enolate chemistry. Unfortunately, until recently, only intramolecular insertions were deemed useful because of the lack of control over the chemo-, regio-, and stereoselectivity of the intermolecular version of the reaction.[296] In addition, intramolecular reactions often compete with the desired intermolecular process and so a large excess of the substrate that undergoes insertion has to be used. This may be the reason why attaching a temporary chiral auxiliary to the carbonyl, a strategy that has proven so successful with enolate chemistry, is not considered viable with carbene insertion reactions. Menthol derivative **596** is an example (*Scheme 122*). Treatment of **596** with dirhodium diacetate led to intramolecular attack on the methylene of the menthol backbone giving bicyclic product **597**.[297] Intermolecular processes could not compete with this cyclization.



Scheme 122

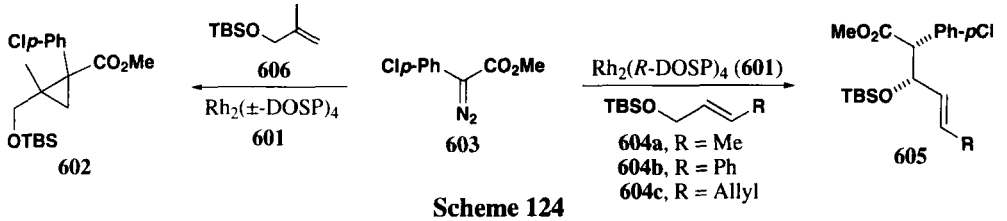
Once Noels[298] and Callott[299] had shown that the intermolecular insertion of ethyl diazoacetate proceeded efficiently with cycloalkanes as solvents, Davies was able to effect enantioselectivity in their reaction using a chiral catalyst **601** (*Scheme 123*).[300] Aryldiazo esters such as **598** do not undergo intramolecular insertion because the only available hydrogens are the



Scheme 123

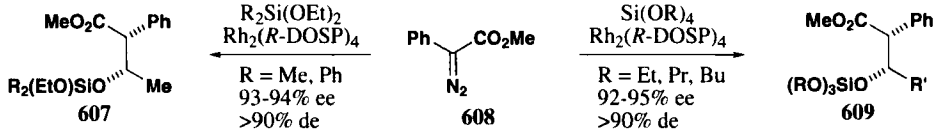
ortho hydrogens on the aryl ring and those would lead to the formation of a four-membered ring. Therefore, its insertion reaction with cyclohexane proceeded to give **599** in good to excellent ee. The ee of the product diminished with increasing electron-donation from the aryl *para* substituent (R) and with increasing temperature. The issue of chemoselectivity was addressed using tetrahydrofuran as the substrate. Only insertion into the etheral C-H bond took place to give **600** but with lower enantioselectivity than with cycloalkanes. Also, a mixture of diastereomers was produced.

The excellent control of chemoselectivity obtained with tetrahydrofuran led Davies and co-workers to perform the insertion reaction between *p*-chlorophenyl diazoester **603** and allylic ethers.[301] The result was *syn* adduct **605** for *E*-disubstituted allyl ethers **604a-c**. Diastereoselectivities were >96% and enantioselectivities ranged from 74-90% ee (*Scheme 124*). Compounds *Z*-**604**, having the *cis* double bond, gave lower diastereoselectivity while 1,1-disubstituted allyl ether **606** gave exclusively the cyclopropanation adduct **602**.



Scheme 124

Shortly after this work, tetraalkoxysilanes were shown to react readily with phenyldiazoacetate in a highly diastereo- and enantioselective manner (*Scheme 125*).[302] It was shown that insertion occurred preferentially at methylene carbons as shown in the transformation of **608** to



Scheme 125

609 using triethoxy, tri-*n*-propoxy, or tri-*n*-butoxysilane. In fact tetramethoxysilane did not give an insertion product while tetra-*i*-propoxysilane gave a low yield of adduct. It was therefore possible to perform the reaction with $Me_2Si(OR)_2$ or $Ph_2Si(OR)_2$ giving rise to aldol-like products **607** that bear a more stable alcohol protecting group.

The *syn* stereochemistry of the adduct **609** arises from a concerted, non-synchronous transition state in which the larger $OSi(OR)_3$ group is pointing away (180°C) from the bulky metal ligands and the medium group R' is pointing toward the smaller ester (*Fig. 19*).[300b,301,303] The whole system is actually sandwiched between the ligands on Rh (pictured by the lines in bold), which explains why the R' group is pointing inward toward the ester.

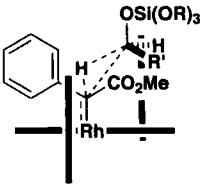
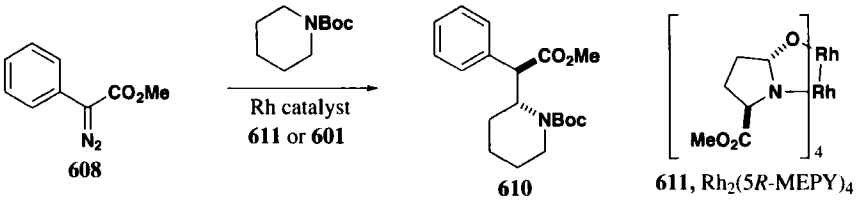


Fig. 19

Proposed Transition State for the Stereoselective C-H Insertion of **608** into Alkoxysilanes

The promise of highly efficient asymmetric syntheses of natural products using this method was demonstrated shortly thereafter by Davies[304] and Winkler[305] who targeted the economic mastodont methyl phenidate (ritalin) as shown in *Scheme 126*. Insertion of methyl



$Rh_2(5R\text{-MEPY})_4$, gave 94% de, 60% ee (yield not reported)
$Rh_2(S\text{-DOSP})_4$, gave 43% de, 80% ee in 73% yield

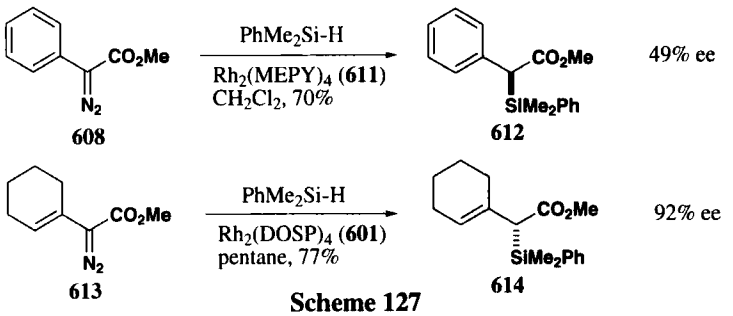
Scheme 126

phenyldiazoacetate **608** took place chemoselectively on protected piperidine to give the desired product **610** with a respectable level of diastereo- and enantiomeric purity. Cyclohexadienes

were also good substrates for the asymmetric C-H insertion reaction and this led to a formal synthesis of the *gem*-diarylalkyl (+)-sertaline.[306]

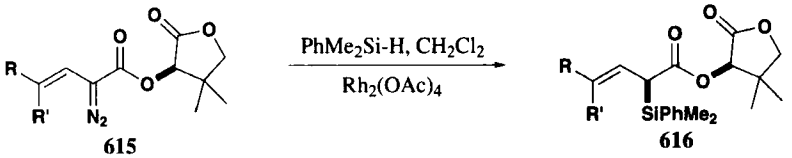
The true power of carbene insertion reactions is that it allows plain C-H bonds to react, avoiding unnecessary synthetic steps to make an activated form of the substrate (alkyl halides for example). However, there are two main obstacles that prevent the intermolecular C-H insertion reaction from being a full-fledged chiral enolate equivalent. First, the substrate must have no C-H bond in a 1,4- or 1,5-relationship capable of intramolecular insertion with the carbene center. This restriction seriously limits the list of usable diazo carbonyl substrates. Second, the low chemoselectivity of Rh carbenes for normal alkanes curtails the use of simple acyclic or unsymmetrical alkyls as 'electrophile equivalents.' Several examples of asymmetric insertions into branched alkanes were reported but only a few were synthetically viable.[300b]

Such is not the case for the Si-H bond, which inserts efficiently into metal carbenes. The asymmetric version of that reaction was successfully demonstrated by Doyle and Moody[307]and Davies[308] and their co-workers on phenyl and vinyldiazoacetates respectively. Levels of ee ranged from close to 50% for phenyldiazoacetate **608** to higher than 90% for vinyldiazoacetate **613** (*Scheme 127*). The method provides a very efficient entry into chiral α-silyl esters which cannot be easily attained by classical chiral enolate chemistry because of the preponderance of *O*-silylation.



Scheme 127

Landais utilized chiral non-racemic pentalactone-derived α-diazo esters **615** to control the diastereoselectivity of Rh carbene insertion into Si-H bonds.[309] The de of the product **616** ranged from 30 to 70% (*Scheme 128*).



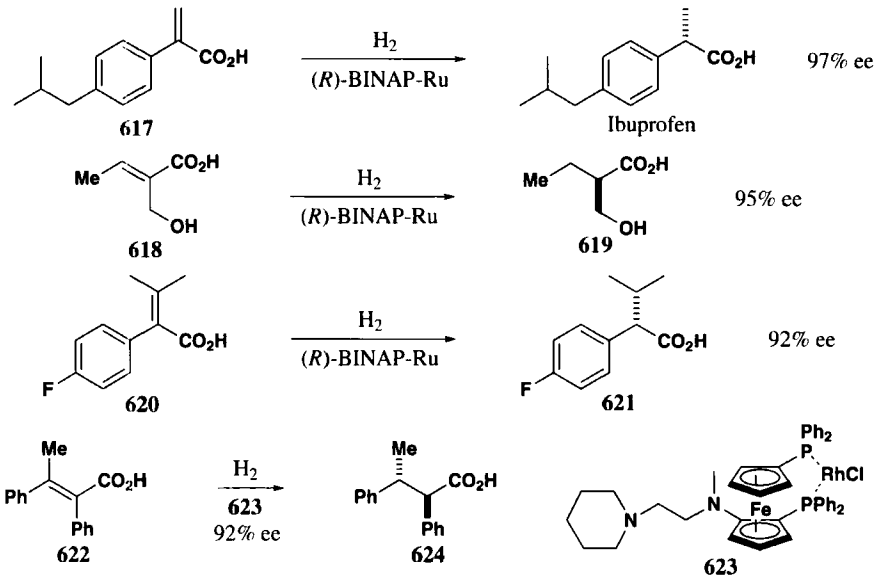
Scheme 128

f) Asymmetric Hydrogenation of α,β-Unsaturated Carbonyls

The asymmetric hydrogenation of alkenes is among the most effective methods for the synthesis of optically active compounds, both industrially and on a laboratory scale. Application of this technology on prochiral α,β-unsaturated carbonyls leads to useful molecules which include α-hydroxy and α-amino acids. The topic of asymmetric hydrogenation has been amply reviewed and only selected examples will be included here to give a general idea of what can be achieved in the context of chiral enolate equivalents.[310] By far, the most common catalysts for the hydrogenation are chiral phosphine complexes of Rh, Ru, and Ir.[311]

i. Acrylic Acids

In this reaction, Ru catalysts, and in particular BINAP-Ru complexes, have provided a good level of asymmetric induction.[312] *Scheme 129* provides selected examples of the enantioselective catalytic hydrogenation of acrylic acid derivatives leading to alkylated carbonyl products.

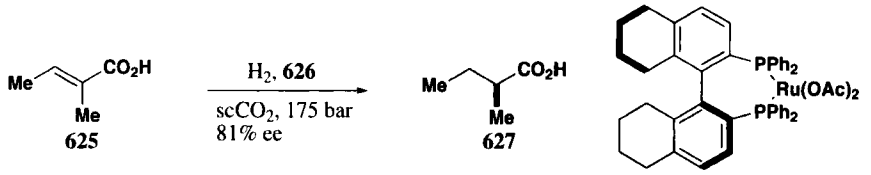


Scheme 129

Many 2-substituted propenoic acids such as **617** were successfully hydrogenated to lead to useful commercial products such as ibuprofen and naproxen. Propenoic acids substituted at C-3 (**618** and **620**) are also hydrogenated efficiently, more forcing conditions being required for trisubstituted cases such as the one leading to the mibefradil fragment **621**.[313] The catalytic asymmetric hydrogenation of unsymmetrically trisubstituted propenoic acid **622** gave rise to product **624** having two new chiral centers. Compound **624** was obtained with good enantioselectivity using Rh complex **623** under 50 atm of hydrogen.[314]

Other recent achievements include a heterogeneous version of a BINAP-Ru complex held in a film of ethylene glycol on a porous support. It was used to hydrogenate various acrylic acids with high enantioselectivity (96% ee).[315] Another BINAP-Ru catalyst dissolved in a molten

imidazolium salt gave asymmetric induction reaching or surpassing that obtained in homogeneous solution. After extraction of the final product, the recovered ionic liquid can be re-used indefinitely.[316] Noyori used the Ru complex **626** in supercritical CO_2 to hydrogenate (*E*)-2-methyl-2-butenoic acid **625** to chiral acid **627** in 81% ee, a result which parallels that obtained in methanolic solution (*Scheme 130*). The tetrahydronaphthalene ligand in **626** (as opposed to the fully aromatic bis-naphthalene ligand) was necessary for a higher solubility in the supercritical fluid.



Scheme 130

Itaconic acid derivatives such as **628** are both α,β-unsaturated and β,γ-unsaturated acids (or esters) and are precursors to chiral succinic acids **629** used as building blocks in peptidomimetics. Their asymmetric hydrogenation has been extensively studied.[309] Recently, Burk and co-workers were able to achieve the enantioselective hydrogenation of β-aryl or alkyl-itaconates using Et-DUPHOS-Rh (>97% ee, cf. **384** in *Fig. 20*).[317] They also hydrogenated itaconate **628** with the Rh cationic complex of ligand **630** in 91% ee (*Scheme 131*).

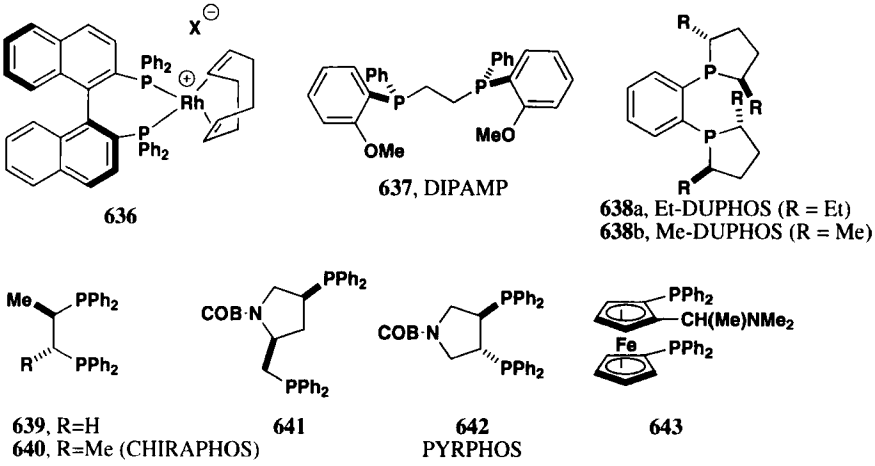
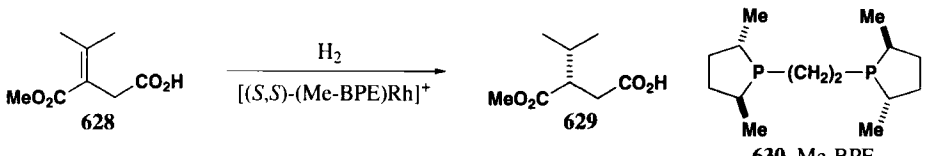


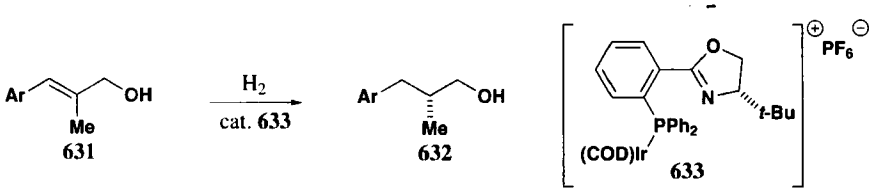
Fig. 20

Several Ligands for the Asymmetric Catalytic Hydrogenation of Dehydroamino acid



Scheme 131

In addition to unsaturated acids, 2-substituted and 2,3-disubstituted allylic alcohols **631** are efficiently hydrogenated to α-chiral primary alcohols **632** by several catalyst systems, including Ir complex **633** (*Scheme 132*).[318,319] In contrast, α,β-unsaturated esters, amides, aldehydes, or ketones are hydrogenated to products of lower enantiomeric purity using these catalysts. Thus the range of substrates which undergo this process in a highly stereoselective fashion

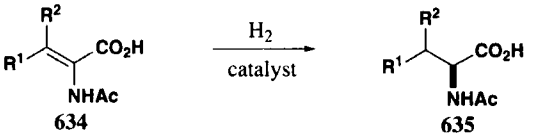


Scheme 132

is limited. Coordination of the metal by the acid or hydroxyl group may explain the higher enantioselectivities obtained in the catalytic asymmetric hydrogenation of these two families of alkenes.

ii. α-Carboxy Enamides

Optically active amino acids **635** are produced on an industrial scale using asymmetric catalytic hydrogenation of dehydro-amino acids **634**, attesting to the importance of this method.[320] Additionally, methods of preparation of α,β-dehydro-α-amino acids **634** abound.[28,321] Amino acids of very high enantiomeric purity are obtained from carboxy enamides like **634** for a variety of substitution patterns (*Eq. 12*).

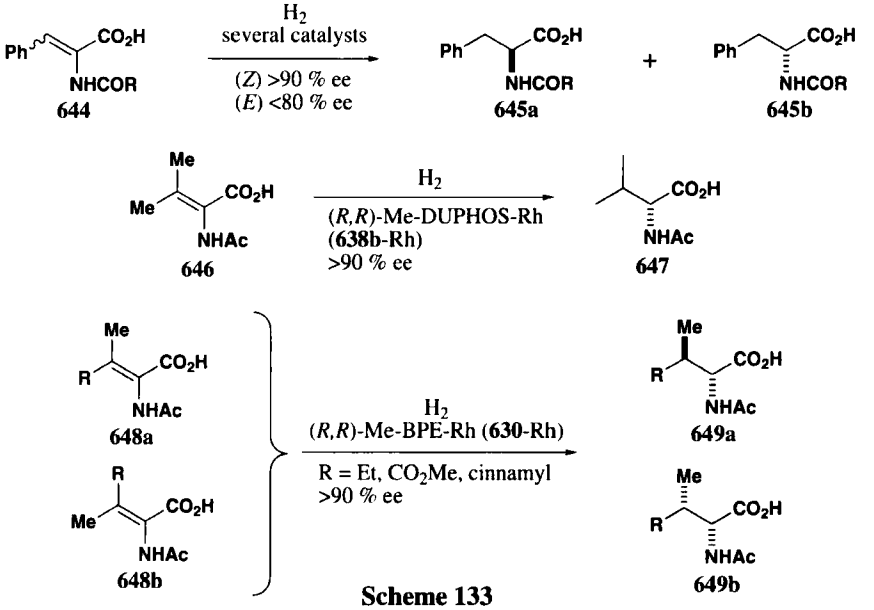


(12)

Several exhaustive lists of suitable substrates and catalysts are described in several reviews and it is not necessary to include them here.[28,309] Among the frequently used ligands are DIPAMP **637**, (*R,R*)-Et-DUPHOS **638a**, and its methyl analog **638b** as complexes of Rh (*Fig. 20*). The choice of ligand depends on the starting dehydroamino acid **634**. DEGUPHOS **642** displays excellent catalytic turnover (>10 000) for this reaction.

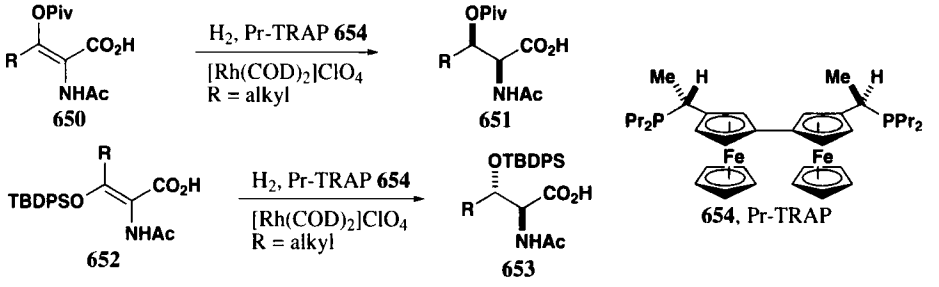
The following schemes illustrate selected examples covering substrates with different substitution patterns. *Z*-Enamide **644** gave higher stereoselectivities than the corresponding *E*-enamide with several catalyst systems including BINAP-Rh (*Scheme 133*).[309] The difficulty with the *E*-enamide probably stemmed from double bond isomerization prior to hydrogenation. The (*R,R*)-Me-DUPHOS-Rh complex solved this problem and was able to effect a highly enantioselective hydrogenation on a wide array of substrates, even particularly difficult ones.[322] This catalyst was also effective for the hydrogenation of β,β-disubstituted enamides[323] as were other, less

hindered, Rh complexes.[324] Unsymmetrical *E*- or *Z*-β,β-disubstituted enamides **648a** and **648b** led to *anti* or *syn* β-branched-α-amino acids **649a** or **649b** respectively, with equal enantioselectivities.[322,325] Novel thiourea ligands complexed with Rh and Ru gave mixed results in the hydrogenation of enamides in recent studies.[326]



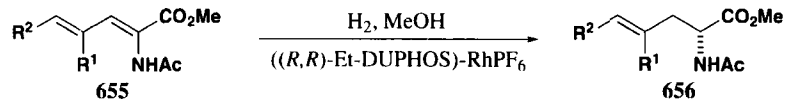
Scheme 133

β-Hydroxy-α-amino acids[327] **651** and **653** were prepared *via* the asymmetric hydrogenation of the corresponding unsaturated compounds **650** and **652** respectively (*Scheme 134*). A Rh complex of ligand **654** was used in this instance. α,β-Diamino acids were also accessible by this method from the appropriate precursors.[328]



Scheme 134

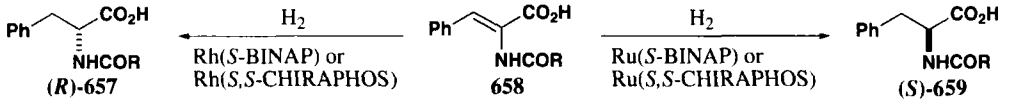
Allyl glycines **656** are important targets because they are not only found in nature but they serve as intermediates for the synthesis of non-natural amino acids (*Scheme 135*). Burk and co-workers have found that Et-DUPHOS-Rh cationic complex **638** reduced the enamide double bond in **655** in >200:1 chemoselectivity leading to γ,δ-unsaturated-α-amino acids **656** with high enantiomeric purity.[329]



R^1 and R^2 = alkyls, aryls,

Scheme 135

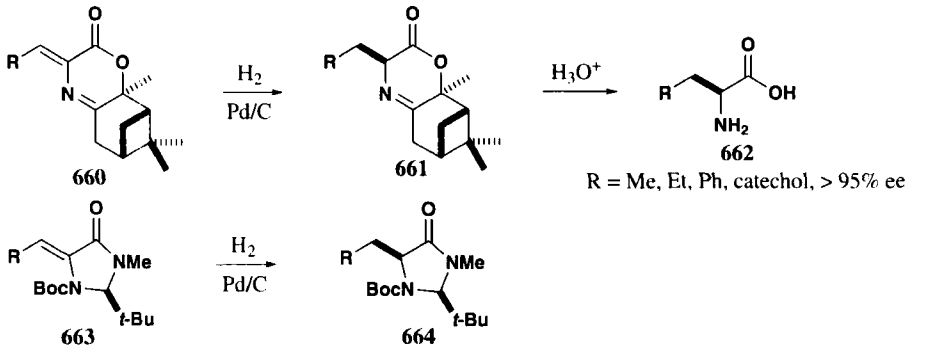
Interestingly, the Ru-based[330] catalytic asymmetric hydrogenation of α-carboxyenamide **658** gave the opposite sense of asymmetric induction when compared to its Rh counterpart (*Scheme 136*).[331] This difference originates in distinct mechanisms involving a Ru-monohydride intermediate for the former[332] and a Rh-dihydride species for the latter.[309]



Scheme 136

Supercritical CO_2 was used as solvent to effect the Rh-based catalytic enantioselective hydrogenation of prochiral α-enamide esters. DUPHOS ligands and Rh(I) cation with a bis(trifluoromethyl)phenyl borate counterion proved effective in giving high enantioselectivities (>97% ee).[333] Valine of 85% ee was also accessible *via* this methodology, which is higher than that obtained from any solution hydrogenation. Catalysts fixed on solid supports have existed for several years[334] but a more recent development includes the synthesis of a PYRPHOS-Rh complex (**642**-Rh) bound to a polyethylene oxide-grafted styrene resin that produced acetylphenylalanine in 97% ee.[335]

Chiral auxiliaries have also been used to effect asymmetric induction in heterogeneous catalytic hydrogenation. An effective strategy is to lock the chirality in a ring using the amino and carboxyl groups. The chemoselective hydrogenation of **660** gave **661** in high yield and diastereomeric purity. Hydrolysis of the product gave α-amino acid **662** in >95% ee (*Scheme 137*).[336] Seebach *et al.* hydrogenated chiral enamide **663** over Pd with similar effectiveness to give **664**.[337]

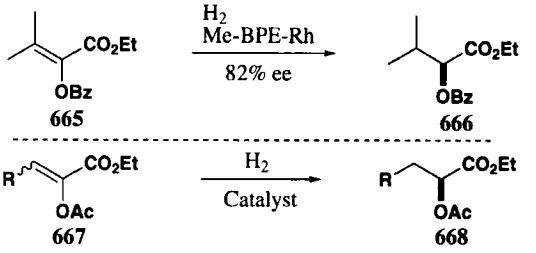


Scheme 137

iii. α-Carboxy Enol Esters

α-Carboxyenols are hydrogenated just as easily as their enamide counterparts using the same Rh and Ru catalyst systems. Table 2 displays some examples. The sense of asymmetric induction is also in line with those of the enamides, although one unique advantage of α-carboxyenol esters is that β-monosubstituted substrates can be hydrogenated as pure geometrical isomers or as mixtures of *E-Z* isomers since both give the same final product (entries 4-9). Deuteration experiments have shown no isomerization of the double bond prior to hydrogenation.[338]

Table 2. Selected Examples of Hydrogenation of α-Carboxy Enols.



Entry	R	**667** *E:Z*	Cat.	**668** ee (%)
1	H	---	DIPAMP-Rh (**637**-Rh)	89
2	H	---	PROPHOS-Rh	81
3	H	---	Et-DUPHOS-Rh (**638a**-Rh)	>99
4	*n*-Pent	78:22	Et-DUPHOS-Rh (**638a**-Rh)	>99
5	*n*-Bu	75:25	DIPAMP-Rh (**637**-Rh)	92
6	*i*-Pr	86:14	Et-DUPHOS-Rh (**638a**-Rh)	97
7	*i*-Pr	70:30	DIPAMP-Rh (**637**-Rh)	92
8	*i*-Pr	70:30	BINAP-Ru (**167**-Ru)	98
9	Ph	0:100	DIPAMP-Rh (**637**-Rh)	95

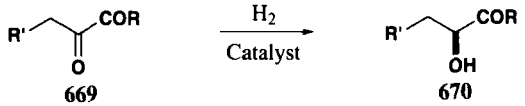
iv. α-Keto and α-Imino Carbonyls

Ketones flanked with a carbonyl are activated toward metal-catalyzed homogeneous hydrogenation. A heteroatom-metal coordination also helps in controlling the stereochemical outcome of the reaction. α-Keto esters are the most studied type of substrates leading to chiral α-hydroxy esters (see section III.3.3 for β-hydroxy esters by the same method). Table 3 provides typical examples (the catalyst ligands are defined in the glossary).[311i,339]

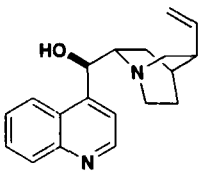
Heterogeneous catalysis using Pt metal on alumina with a chiral modifier has gained considerable attention since first introduced by Orito in 1979.[340] The simplicity of this technology offers considerable advantage. Traces of modifier are sufficient to reach high levels of enantioselectivity in the reduction of methyl or ethyl pyruvate.[341] Cinchonidine **671** and 10,11-dehydrocinchonidine gave enantioselectivities above that provided by other alkaloids or synthetic chiral modifiers **672-676** (*Fig. 21*).[342] The factors affecting the enantioselection have been reviewed.[343] The key structural features of the chiral modifier were the quinuclidine

nitrogen and having two sites of absorption for the Pt surface (i.e naphthalene ring or functionalized phenyl ring). A model for the enantioselective hydrogenation of methyl pyruvate was recently proposed.[344]

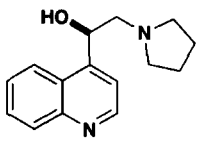
Table 3. Selected Examples of Hydrogenation of α-Ketoesters.



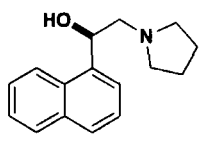
669 R	R'	Cat.	670 ee (%)
OMe	Me	MCCPM-Rh	87
OMe	Me	tetraMe-BITIANP-Ru	88
OEt	Me	Cy,Cy-OxoPRONOP-Rh	95
OMe	Ph	MeO-BIPHEP-Ru	86
OMe	Ph	BICHEP-Ru	99
OMe	Tol	BINAP-Ru	93
OEt	Cinn	NORPHOS-Rh	96
NHBz	Ph	Ph,Cp-*i*-ALANOP-Rh	88
NHBz	Ph	Cy,Cy-OxoPRONOP-Rh	95
NHBz	Ph	Cp,Cp-INDONOP-Rh	91
NHBz	Ph	BICHEP-Ru	96
NHBz	Ph	$Cr(CO)_3$-Cp,Cp-IndoNop-Rh	97



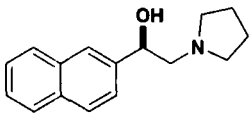
671, Cinchonidine, >90% ee (1 bar)



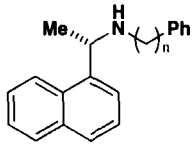
672, 66% ee (75 bar)



673, 68% ee (1 bar)



674, 42% ee (1 bar)



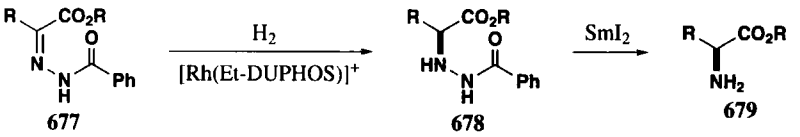
675, n = 1, 67% ee
676, n = 3, 66% ee

Fig. 21

Chiral Alkaloids and Amines as Modifiers in Hydrogenation Reactions

The catalytic enantioselective hydrogenation of α-ketoesters in supercritical fluids was investigated by Minder and co-workers.[345] The system Pt/Al_2O_3 with cinchonidine alkaloid provided faster reaction rates in supercritical ethane with levels of enantioselection similar to that obtained in toluene solution. Supercritical CO_2 was detrimental to the reaction.

Although the catalytic asymmetric hydrogenation of imines has some precedent,[71c] few examples have been carried out on α-carboxyimines. Burk and co-workers described the hydrogenation of *N*-acylhydrazone **677** to give α-hydrazino esters **678** (*Scheme 138*). The latter could be reduced to α-amino acids **679** without epimerization.[346]

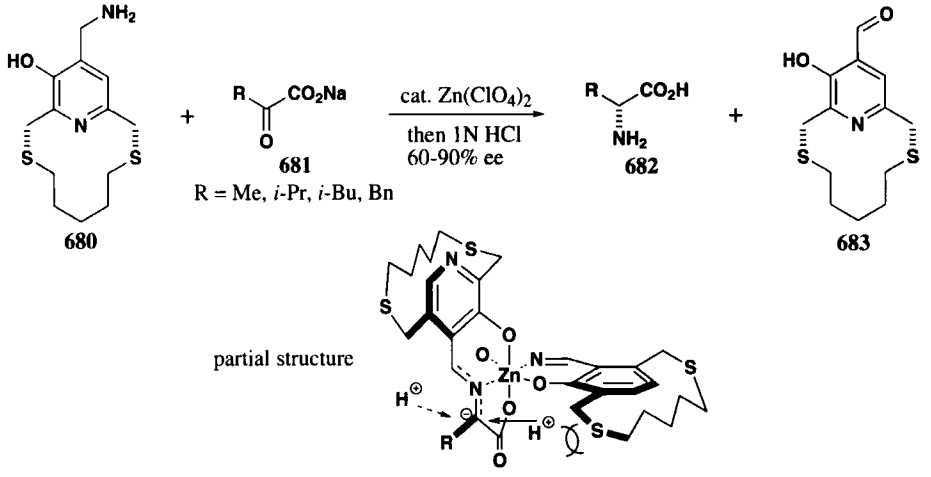


Scheme 138

g) Reductive Amination of α-Keto Carbonyls

α-Ketoacids may be reductively aminated using isolated enzymes.[28,347] Reductive amination is a natural process happening in many biosynthetic steps where pyridoxamine serves as the main carrier of nitrogen. In the laboratory, several sources of nitrogen have been used from ammonium salts to amino acids. In the case of amino acids as nitrogen donors, the unwanted α-keto acid resulting from the transfer reaction is removed by enzymatic reduction or decarboxylation.[347] Chemical methods to remove the keto acid are also available.[347] This strategy suffers from the fact that chirality is not created but simply transferred from one chiral molecule to another.

Pyridoxamine analog **680** with planar chirality induced the reductive amination of α-keto acids, sodium salt, **681** in the presence of a Zn(II) salt (*Scheme 139*).[348] The stereoselective step was proposed to occur *via* an octahedral Zn chelate involving two molecules of the ketimine



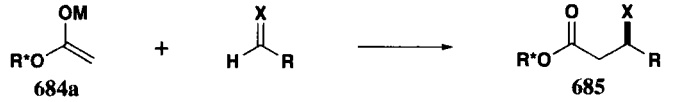
Scheme 139

formed between **680** and **681**. The complexed ketimine would undergo a deprotonation followed by a stereoselective reprotonation as shown. The level of enantioselectivity achieved in this biomimetic approach is impressive. Another method consists of hydrogenating chiral imines derived *in situ* from phenylglycinol **312** (cf. *Scheme 63*) and α-keto acids to give the corresponding amino acids. This catalytic method affords low to good ee's.[349]

A protein-bound chiral pyridoxamine was shown to promote the reductive amination of several α-keto acids with good to excellent enantioselectivity.[350] A catalytic version, employing an additional amino acid was also devised although the rate of reaction and turnover remain problematic in both systems.[351]

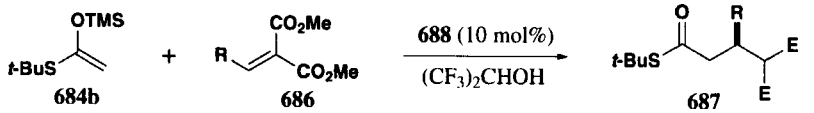
III. REACTIONS β TO A CARBONYL OR SURROGATE CARBONYL.

Unsubstituted chiral enolates **684** produced β-hydroxy and β-amino carbonyls **685** when they reacted with aldehydes or imines or their equivalents (*Eq. 13*). Such systems are actually the Achilles' heel of chiral enolate chemistry as the stereoselectivity achieved has never

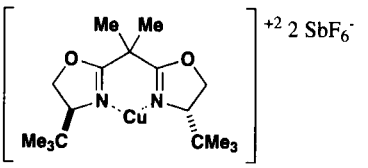


684a **685** (13)

reached the levels we are used to with chiral enolates. Enolates and enol ethers like **686** are also capable of adding to activated alkenes like **686**, an example of which is shown in *Eq. 14*,[352] creating a chiral center β to the final carbonyl. Although these approaches have not been widely



684b **686** **687** (14)



688, [Cu((*S,S*)-*t*-Bu-BOX)](SbF$_6$)$_2$

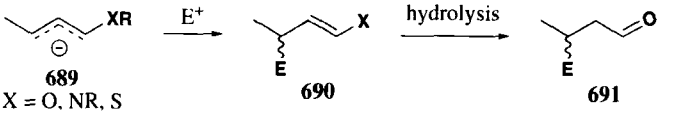
successful, a number of methods can produce these structural motifs with better efficiency and generality. They will be discussed in the following sections.

1. Nucleophilic β Carbons

a) Homoenolate Equivalents

Ahlbrecht and Beyer recently reviewed the topic of chiral homoenolate equivalents in which the carbon β to the carbonyl is nucleophilic. Generally, they are in the form of an enamine anion **689** (X = N), although true homoenolate **689** (X = O) and the sulfur analog are known (*Eq. 15*).[353] Only selected examples have been included in this section to give the reader a general idea of the scope of this strategy.

Allyl anions **692**, and **694** derived from the corresponding chiral enamines or allylamines (made from *S*-O-methyl prolinol) reacted with alkyl or allyl halides to give, after hydrolysis of the enamine product, β-branched aldehydes **693** or ketones **695** respectively (*Scheme 140*).[354] Regioselectivity is rarely a problem in this reaction and stereoselectivity is generally



689
X = O, NR, S

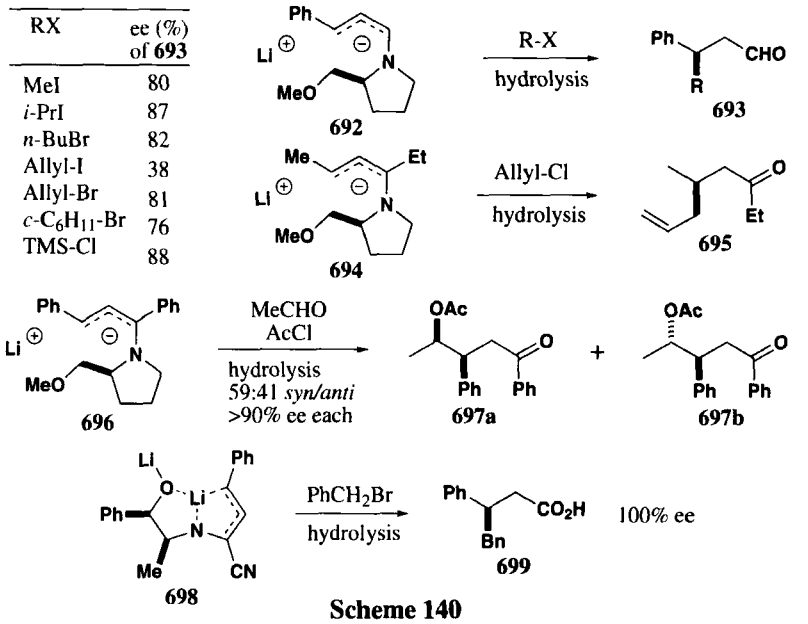
690

691

(15)

high making it widely applicable as a chiral homoenolate equivalent. Chelation of the Li counterion by the methoxy group produced a conformationally rigid allyl nucleophile. Attack then took place from the least hindered face of the anion. Aldehydes were suitable electrophiles giving rise to 'homo-aldol' adducts **697** in high ee but as mixtures of *syn* and *anti* diastereomers.[355] α-Cyano allylamines **698** gave β-chiral carboxylic acids **699** directly after hydrolytic work-up.[356]Aliphatic enamines or allyl amines were best converted to the corresponding anion by metal-metal exchange from a tributyltin species since simple deprotonation led to mixtures of products.[357] Enamines and allylamines derived from chiral amines other than prolinol were also investigated and found to lead to useful levels of diastereoselection.[353]

RX	ee (%) of **693**
MeI	80
i-PrI	87
n-BuBr	82
Allyl-I	38
Allyl-Br	81
c-C_6H_{11}-Br	76
TMS-Cl	88



692

693

694

695

696

697a

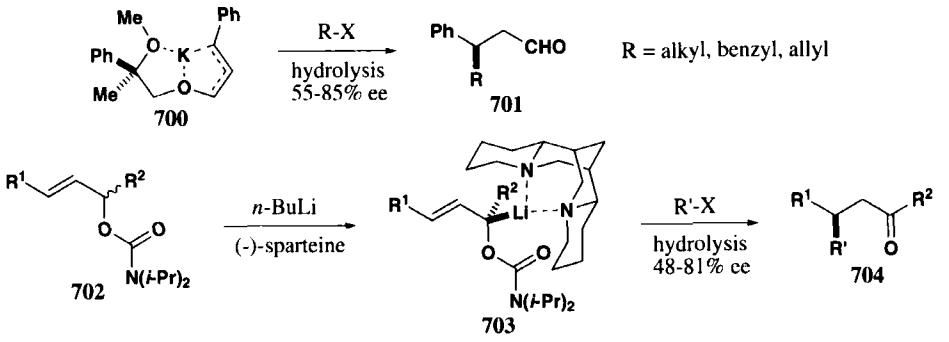
697b

698

699

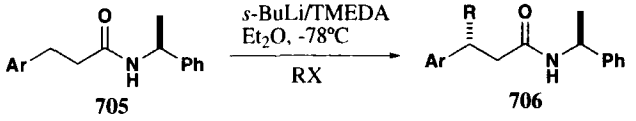
Scheme 140

Chiral allylic ethers can be deprotonated with strong base to yield an oxyallyl anion which can be alkylated in much the same way as its nitrogen analog to afford, after hydrolysis, β-chiral carbonyl compounds.[358] For example, the allylpotassium anion **700**, made from the corresponding allyl ether gave product **701** with moderate to high ee depending on the electrophile (*Scheme 141*). A convenient way to achieve the same result is to deprotonate achiral allyl carbamate **702** in the presence of (-)-sparteine.[359] Direct alkylation gave **704** while transmetallation of **703** with Ti proceeded with inversion of stereochemistry. The resulting oxyallyltitanium enabled the stereoselective reaction with aldehydes and ketones.[360]



Scheme 141

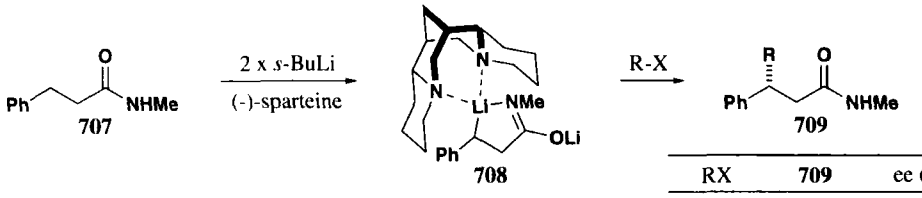
True lithium homoenolates are not easily generated since the formation of the enolate is normally strongly favored. Substituting the β-position with another electron-withdrawing group, such as a sulfone, is one way to circumvent this problem.[361] However, this extraneous group must then be removed with retention of the stereochemical integrity of the product, a difficult task. Instead, Beak and co-wokers described the deprotonation of chiral phenylpropionamide **705** to its lithium homoenolate (*Scheme 142*).[362] Alkylation with various electrophiles gave moderate yields and de's of β,β-disubstituted amides **706**.



Ar	RX	de (%)
Ph	MeI	82
Ph	*n*-BuBr	80
Ph	$PhCH_2Br$	88
Ph	TMS-Cl	76
o-MeO-Ph	*n*-BuBr	86

Scheme 142

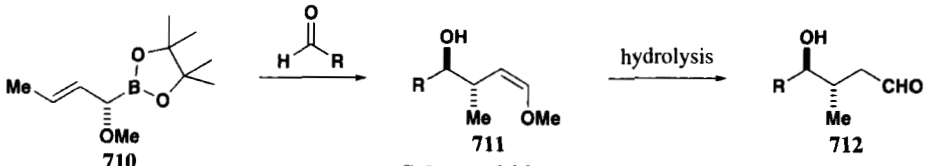
Sparteine efficiently induced asymmetry in the alkylation of achiral lithium homoenolate **708** (*Scheme 143*).[363] It was demonstrated that sparteine could be added after the deprotonation step and that the sparteine-Li homoenolate complex **708** was configurationally stable at −100°C. When the product amide **709e** (R = Bu_3Sn) was transmetallated with Li at low temperature, the resulting Li homoenolate **708** was alkylated with complete retention of stereochemistry.[364] Unfortunately, the starting material **709e** was obtained in only 60% ee.



RX	709	ee (%)
MeI	**a**	78
n-BuBr	**b**	88
$PhCH_2Br$	**c**	80
TMS-Cl	**d**	94
Bu_3Sn-Cl	**e**	60

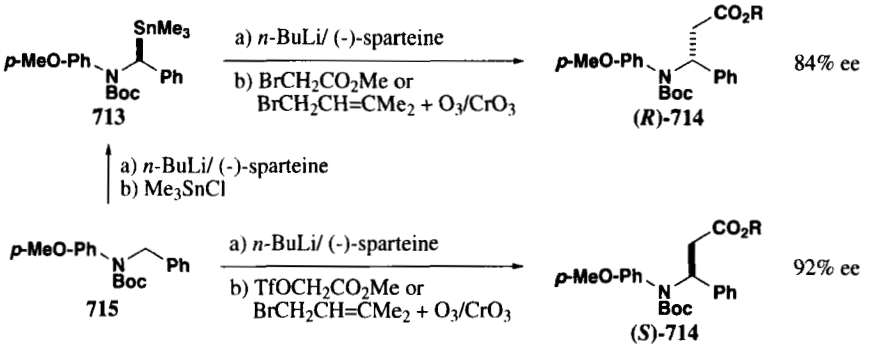
Scheme 143

Allylboron and -tin compounds such as **710**, which possess an ether functionality, were described in section II.1.c.ii. Compound **710** reacted with aldehydes to give β-hydroxy aldehyde **712**, after hydrolysis of the initial enol ether **711** (*Scheme 144*).



Scheme 144

β-Amino ester (R = alkyl) or acid (R = H) (*S*)-**714** were prepared by chiral deprotonation of *N*-protected arylbenzylamine **715** and alkylation with methyl α-bromo or α-trifluoroacetate (*Scheme 145*). In this case, the carbonyl fragment is electrophilic. Respectable ee's were

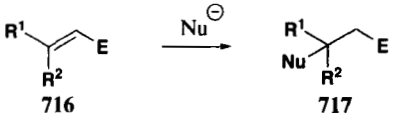


Scheme 145

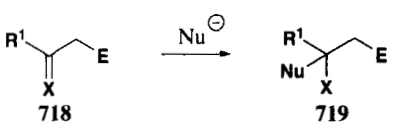
obtained. The two enantiomeric series of **714** can be reached by choosing the proper sequence of events. If Me_3SnCl is added to the anion of **715**, compounds **713** is obtained. Transmetallation of **713** with *n*-BuLi in the presence of sparteine and quenching with α-bromoacetate gave (*R*)-**714**.

2. Electrophilic β-Carbons

Strategies that fall in this category invariably involve the addition of a nucleophile to an activated substituted double bond of the type **716** or one containing a carbon-heteroatom double bond as in **718** (*Eq. 16* and *17*). This creates a new chiral center at the β-position of the final



(16)



(17)

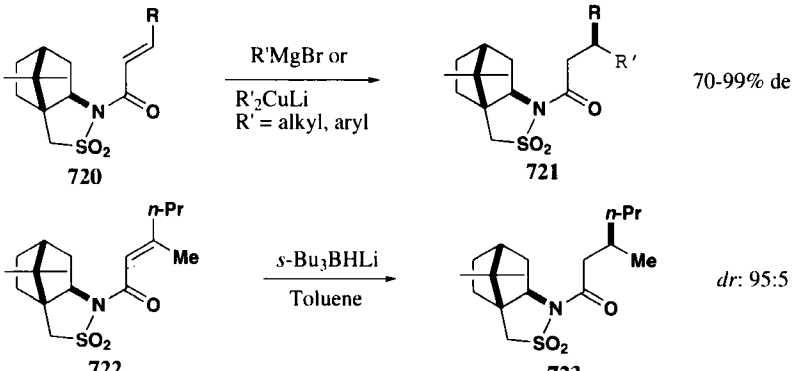
carbonyl moiety in the products **717** or **719**. In some cases, these methodologies, inherently or by extension, also create an α-chiral center *via* an intermediate enolate. It is the first addition step that will be the focus of this section. The intermediate created from the addition of a nucleophile to **716** is an enolate and its stereoselective chemistry will not be discussed unless appropriate or necessary. Also, the conjugate addition of enolates (Nu = enolate) is not considered here as it represents genuine enolate chemistry.

a) Asymmetric Michael Additions to α,β-Unsaturated Carbonyls

Conjugate addition is a vast field in organic chemistry. Activated alkenes are susceptible to nucleophilic attack at the β olefinic carbon by soft nucleophiles. If the alkene possesses at least one substituent at that same carbon, a chiral center is created β to the activating group. This review will be concerned, of course, with carbonyl activating groups on acyclic alkenes only. It is safe to say that stereocontrol in the conjugate addition of acyclic systems has been more challenging than cyclic ones for reasons of conformational freedom.[365] The asymmetric version of this type of reaction has not escaped this predicament and if the number of reported methods of addition on acyclic systems is modest, a vast number of highly enantioselective conjugate additions to cyclic α,β-unsaturated carbonyls have been reported.[366]

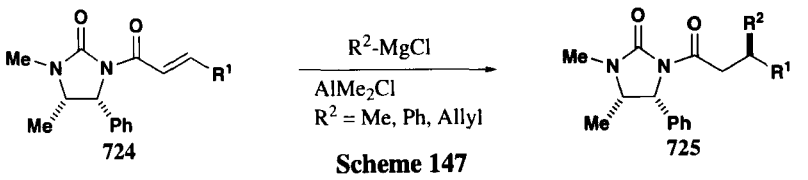
i. Addition of Organometallics and Metal Hydrides

Chiral α,β-unsaturated amides are known to add alkyl nucleophiles stereoselectively. For example, Oppolzer's sultam auxiliary was acylated with a vast number of α,β-unsaturated acyl chlorides to give disubstituted α,β-unsaturated amides like **720** or trisubstituted ones like **722**. In turn, these unsaturated amides reacted with various organometallics of various nature to give **721** or hydrides to yield products **723** (*Scheme 146*).[367]



Scheme 146

Various other chiral auxiliaries were recently developed or improved upon for asymmetric conjugate addition.[368] For example, the conjugate addition of Grignard reagents to **724** promoted by Me_2AlCl gave **725** (*Scheme 147*). Selectivities varied from poor (45:55) to very

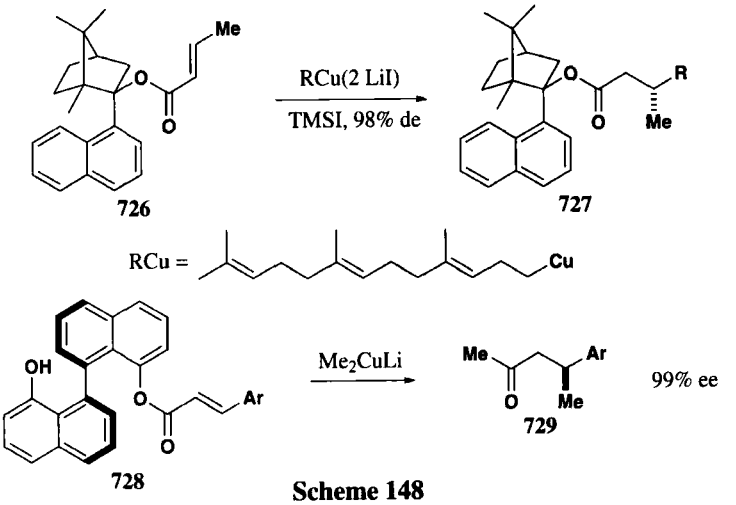


724 725

Scheme 147

good (93:7) depending on the Lewis acid used and the nature of R^1 and R^2. In the case of a cuprate reagent derived from allylmagnesium chloride (R^2 = allyl), the addition product **725** was isolated in greater than 98% de. Allylboronate was also highly selective in its addition to **724**.[369]

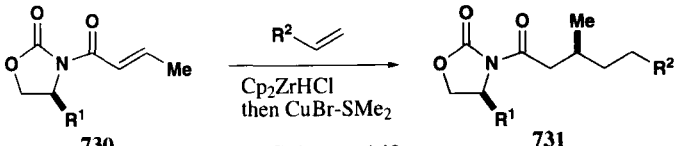
Cuprate additions to **726**[370] and **728** afforded β-chiral ester **727** and **729**, respectively, in high de (*Scheme 148*). In the case of **728**, the excess cuprate reagent added in a 1,2-fashion to extrude the BINOL auxiliary and gave ketone **729** all in one pot (70-100% ee).[371]



726 727 728 729

Scheme 148

Cu-catalyzed addition of organozirconocenes to **730** was published by Wipf and Takahashi (*Scheme 149*).[372] Diastereoselectivities ranged from 51-94% depending on R^1 (R^1 = Ph > *i*-Pr > Bn). The organozirconocenes are readily available from the hydrozirconation of alkenes using Schwartz's reagent. These reaction conditions were compatible with sensitive functional groups on the chain R^2, including a silyl ester.

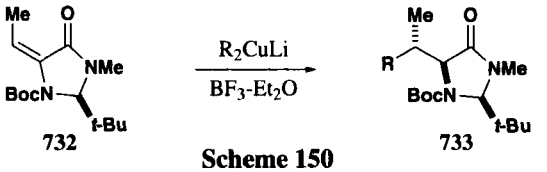


730 731

Scheme 149

The addition of dialkylcuprates to *E*-**732** promoted by $BF_3 \cdot Et_2O$ gave heterocycle **733** while its epimer was obtained starting from *Z*-**732** (*Scheme 150*). Compound **733** is a precursor to β-alkyl-α-amino acids. Similar precursors were synthesized by the same research group by

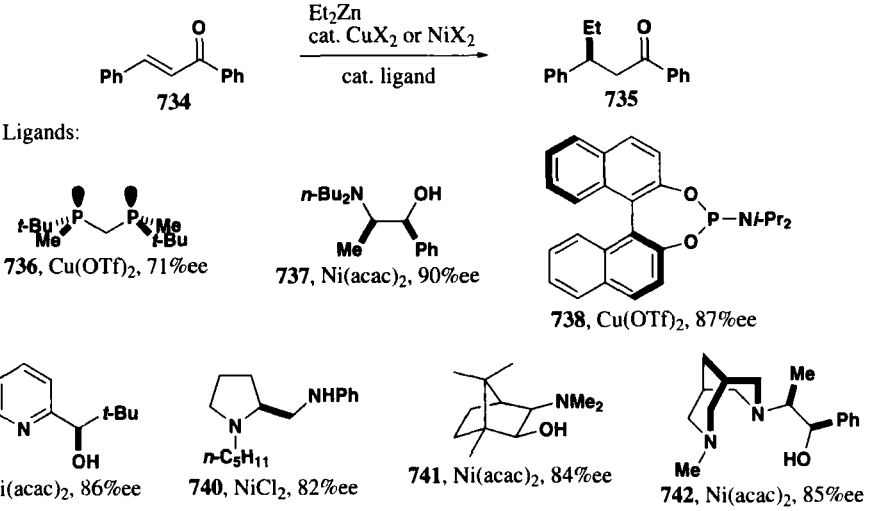
addition of phenyl cuprate to various chiral α-acetamido acrylates, albeit in lower diastereomeric purities than **733**.[373]



732 **733**

Scheme 150

Many enantioselective catalytic Michael reactions have been developed over the last decade or so.[374] Cu, Ni and Rh are often used as the catalytic species, which promote the addition of organolithium, -magnesium, or -zinc reagents to enones. The number of selective additions on cyclic Michael acceptors far outweigh the successful cases with acyclic ones. One of the first convincing results on an acyclic enone (chalcone **734**) was realized with diethylzinc and a complex made between $Cu(OTf)_2$ and ligand **736** (*Scheme 151*). Enantiomeric excesses approaching 90% were achieved with this system but some 1,2-addition product accompanied



734 **735**

736, $Cu(OTf)_2$, 71%ee

737, $Ni(acac)_2$, 90%ee

738, $Cu(OTf)_2$, 87%ee

739, $Ni(acac)_2$, 86%ee

740, $NiCl_2$, 82%ee

741, $Ni(acac)_2$, 84%ee

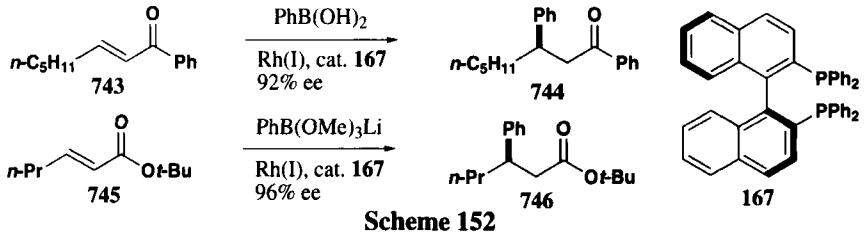
742, $Ni(acac)_2$, 85%ee

Scheme 151

the desired β-chiral ketone **735**.[375] The same product **735**, and closely related ones, were obtained in 80-90% ee using other BINOL-related ligands complexed to Cu[376] or various other ligands with Ni[377] or Co.[378] Trimethylaluminum and Grignard reagents have also been added to enones with moderate selectivity using a BINOL-Cu complex.[379] *Scheme 151* depicts several of the chiral ligands used in Michael additions to chalcone **734**. The metal to which the ligand is complexed and the ee of the product **735** are indicated.

In contrast to Cu- or Ni-catalyzed 1,4-addition, Rh-catalyzed conjugate addition to enones or enoates proved more general (for acyclic enones and enoates) and offered similar levels of enantioselectivity. In particular, the Rh-catalyzed additions of aryl- and alkenylboronic acids developed by Hayashi and Miyaura were particularly well suited for addition to acyclic

α,β-unsaturated ketones and esters like **743** and **745**.[380] BINAP **167**, in conjunction with these reaction conditions, gave adducts with high enantiomeric purity (*Scheme 152*).



Scheme 152

Enantioselective additions of organometallics to enoates without recourse to catalysis by a metal complex have been reported. Enantioselectivities of up to 93:7 were realized with organolithium additions to achiral crotonates in the presence of (-)-sparteine.[381]

ii. Heteroatom Additions

The conjugate addition of heteroatom nucleophiles to α,β-unsaturated carbonyls provides a very efficient synthetic route to β-hydroxy, β-amino, and β-thio carbonyl compounds.[374] Hydroxy or alkoxy anions are hard nucleophiles and their conjugate additions to unsaturated carbonyls are limited. By contrast, amines and thiols add readily to chiral enoates (chiral auxiliary) or achiral enoates (chiral catalyst). The classical approach of an unsaturated ester or amide bearing a chiral auxiliary was used in this context but all successful examples are fairly recent. D'Angelo and co-workers utilized 8-naphthylmenthyl ester **747** and a host of other chiral cyclohexanol-based esters, including esters **748** and **749**, to achieve high diastereoselectivity in the addition of benzylamine under high pressure (*Fig. 22*).[382] The sense of asymmetric induction was in line with an attack on the less hindered face of the crotonate when it was in the *s-trans* conformation, as shown. Ester **748** displayed an even better selectivity in the addition of benzylamine, a result which was attributed to an increase in stability of π-stacked conformations in the starting crotonate.[383]

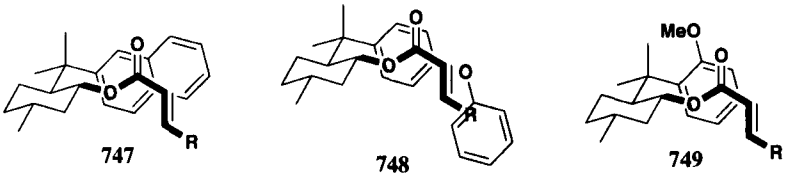
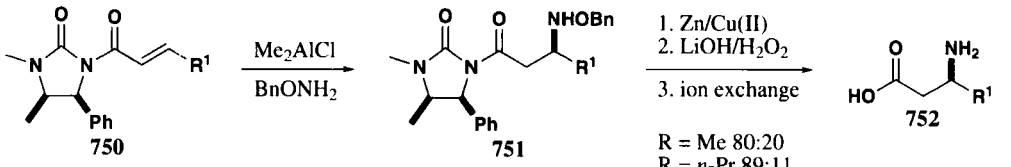


Fig. 22

Cyclohexanol-Based Auxiliaries for the Conjugate Addition of Amines and Thiols

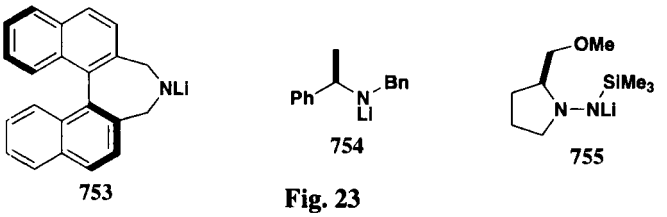
Amide **750** was utilized in conjunction with *O*-benzylhydroxylamine as the nucleophile and a Lewis acid to obtain high yields of β-amino amide **751** with moderate diastereomeric purity (*Scheme 153*).[384] Phthalimide was less effective as a nucleophile but allowed α-bromation in the same pot.[385] Reductive cleavage of the weak N-O bond and hydrolysis gave chiral β-amino acids **752**.



750 751 752

Scheme 153

Advantageously, amines bearing chiral groups can be used to induce asymmetry in their Michael reaction to achiral crotonate esters as demonstrated by the recent work of several groups.[386a-388a] *t*-Butyl crotonate was used in most cases and the chiral 'ammonia' equivalents **753-755** shown in *Fig. 23* gave consistently good diastereomeric ratios for many alkyl-substituted crotonates. Aryl-substituted crotonates usually gave reduced selectivities. In all cases, reductive conditions liberated the free amino acid in good yield.

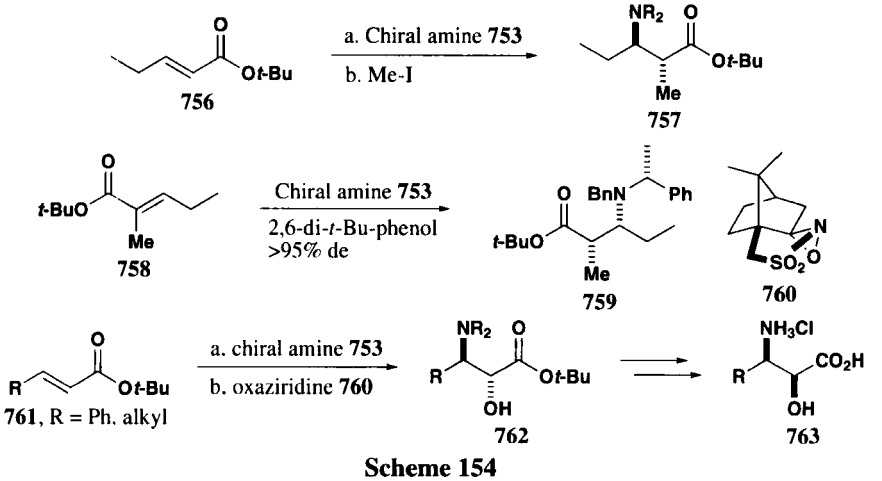


753 754 755

Fig. 23

Chiral Amines that Add Stereoselectively to t-Butyl Crotonate and Other Unsaturated Esters

The transient enolate created after the addition of lithium amides **753-755** to crotonate **756** was further alkylated to give *trans* α-alkylated-β-amino ester **757**.[386b,387b-d,388] When tigliate **758** was used and the resulting enolate was quenched with a proton source, the *syn* diastereomer **759** was obtained (*Scheme 154*).[387b-d] Addition of chiral amine **753** on α,β-unsaturated ester **761** and quench of the enolate with oxaziridine **760** afforded α-hydroxy-β-amino esters **762** in high

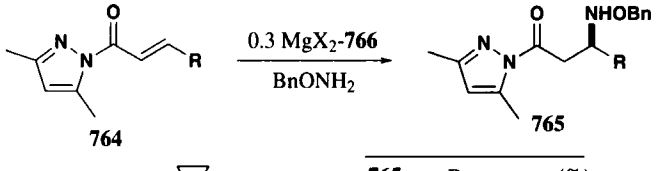


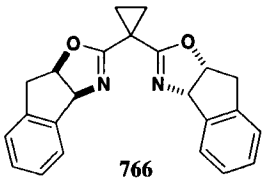
756 757 758 759 760 761, R = Ph, alkyl 762 763

Scheme 154

diastereomeric purity. Both amino esters **759** and **762** are precursors to important natural amino acids present in the angiotensin-converting enzyme inhibitor microginin and anti-cancer taxol, respectively.[389]

Efficient catalysts for the conjugate addition of heteroatoms to enoates have also been developed. Ligand **766** was coordinated to Mg to create an effective chiral Lewis acid which catalyzed the addition of *O*-benzylhydroxylamine to α,β-unsaturated amide **764**. The results were excellent for a wide range of substitution (*Scheme 155*).[390]

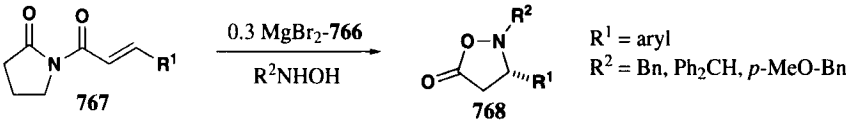




765	R	ee (%)
a	Me	92
b	Et	92
c	n-C_7H_{15}	90
d	Bn	95
e	i-Pr	87
f	Ph	83

Scheme 155

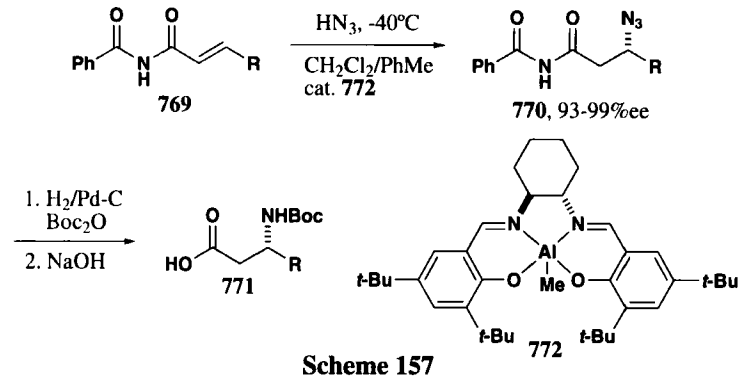
Aryl substituted enamides (**764** R = aryl) are much less active toward addition of nitrogen nucleophiles. However, more nucleophilic alkyl hydroxylamines (R^2NHOH, *Scheme 156*) were able to add stereoselectively to **767** in the presence of catalyst **766** (*Scheme 156*). Cyclization occurred after the initial conjugate addition to produce **768** in high ee (60-96% ee). The product is precursor to β-amino acids.[391]



Scheme 156

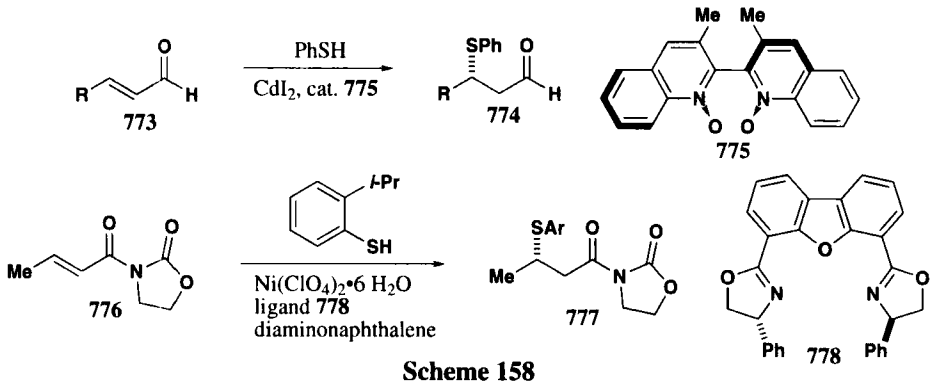
The enantioselective conjugate addition of hydrazoic acid to imide **769** catalyzed by Al salen complex **772** was reported in 1999 (*Scheme 157*).[392] A high ee was obtained when R was alkyl but not when R was phenyl.

Solid phase catalysis for the addition of benzylamine to cinnamate was also reported. The catalyst is an aminodiol-Al complex which was fixed on a polystyrene resin. Adducts were obtained in >80% ee. Thiols were also suitable nucleophiles for this system, providing β-thiocarbonyls in 33-76% ee.[393]



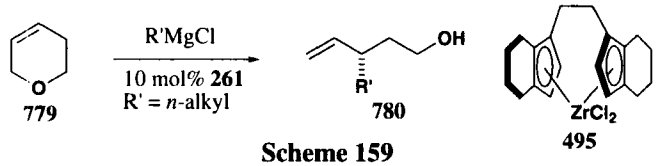
Scheme 157

β-Thiocarbonyls were also accessible by means of a catalytic asymmetric reaction. Nakajima and co-workers recently published results on the addition of benzenethiol to enals **773** catalyzed by a chiral Cd complex made from *N,N'*-dioxide ligand **775**.[394] Enantioselectivities were in the 60-70% range for a good number of alkyl-substituted enals. Kanemasa *et al.* designed ligand **778** which, when complexed to Ni, induced asymmetry in the addition of *o*-isopropylbenzenethiol to enamide **776** (*Scheme 158*).[395]



Scheme 158

Lastly, dihydropyrans **779** behaved like their dihydrofuran counterparts in the Zr-catalyzed carbomagnesiation reaction (complex **495**, cf. section II.2.e) to give γ-chiral alcohols **780** (and thus β-chiral carbonyl compounds if the hydroxyl is oxidized, *Scheme 159*).[247,248]

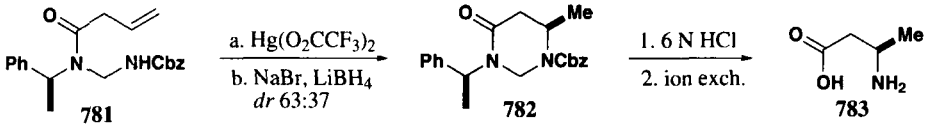


Scheme 159

b) Electrophilic Cyclizations

As an extension to what was discussed in section II.2.f, β,γ-unsaturated amides, like their α,β-counterparts, are subject to Hg-promoted electrophilic cyclization by an internal amine

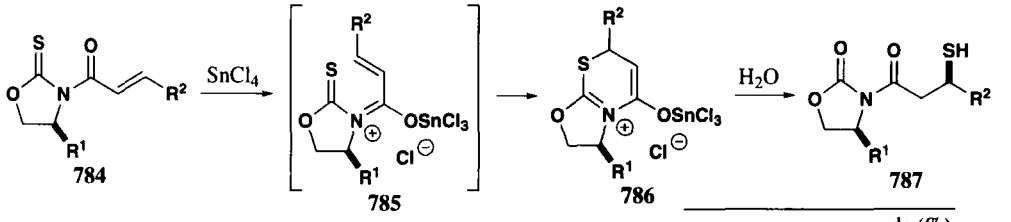
nucleophile. Using α-phenethylamine as a chiral auxiliary, Cardillo and co-workers prepared several β-amino acids by this method. For example, amide **781** cyclized to give perhydropyrimidinone **782**. Its subsequent hydrolysis gave the desired β-amino acid **783** (*Scheme 160*).[396] The



Scheme 160

diastereomeric ratios of **782** and several analogs were modest but an advantage of the method is that each diastereomer of **782** can be purified and futher alkylated *via* its lithium enolate to give α-alkyl-β-amino acids (not shown).[397]

Very recently, Palomo *et al.* reported an interesting electrocyclic ring closure of a charged enoyl imide **785** giving β-thioamide **787** with a high degree of stereocontrol (*Scheme 161*). The rearrangement of intermediate **785** took place with virtually complete diastereoselectivity except when (R^2) was an aromatic group. Then, a higher reaction temperature was essential



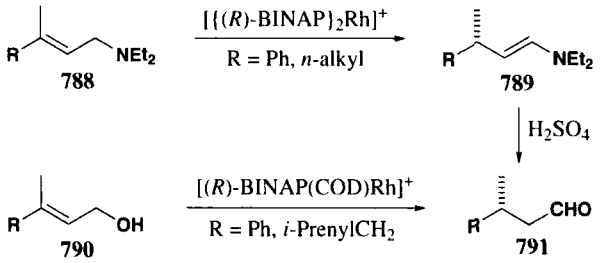
R^1	R^2	de (%) of **787**
i-Pr	Me	>96
	Et	>96
	i-Pr	>96
	Ph	74
	4-Cl-Ph	50
Bn	Me	>96
Ph	Me	>96

Scheme 161

for good conversion. This methodology has advantages over the classical or even catalytic Michael addition of arylthiols to α,β-unsaturated carbonyls (cf. preceeding section) in that the reaction leads directly to the thiol group in an unprotected form. Therefore, no dearylation of sulfur in the final product is necessary. After cleavage of the oxazolidinone auxiliary in **787**, the oxazolidine-2-thione, required to prepare **784**, can be regenerated with Lawesson's reagent.[398]

c) Isomerization of Allylic Alcohols and Amines

Cationic Rh complexes are effective in converting 1,2,2-trisubstituted prochiral allylic amines **788** or alcohols **790** to β-chiral aldehydes *via* the enamine or enol forms respectively (*Scheme 162*). Allylic amines[399] **788** are more effective substrates and give enamines **789** in higher ee than the aldehydes **791** (enols) obtained from the rearrangement of the corresponding

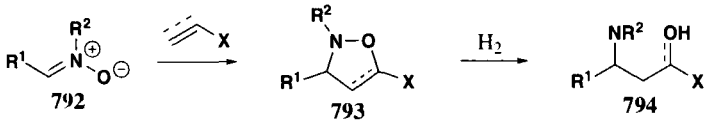


Scheme 162

allylic alcohols **790**.[400] Although limited in scope, this methodology is important industrially. Among the various terpenoids produced industrially by this process are (+)-citronellal, (-)-menthol, and (*S*)-7-methoxy-citronellal (insect growth regulator).[401] Inoue suggested a mechanism where an oxidation of the allyl amine to the α,β-unsaturated iminium ion occurs with concomitant formation of a Rh-hydride bond. Then, migration of the hydride from Rh to the γ-position of the unsaturated iminium occurs with asymmetric induction. This step may be reversible with the equilibrium lying on the side of the enamine. Finally, the enamine **789** is hydrolyzed to the aldehyde **791** in a subsequent step.[402]

d) *Asymmetric Dipolar Cycloadditions*

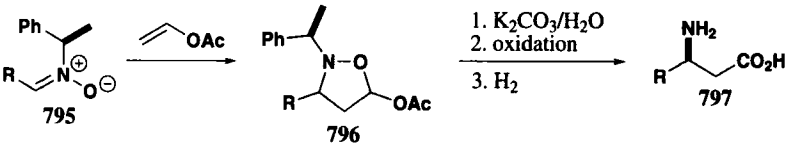
Nitrones **792** are excellent dipoles and take part in asymmetric 1,3-dipolar cycloadditions[403] with alkenes or alkynes to give, after hydrogenolysis of the nitrogen-oxygen bond in the cycloadduct **793**, β-amino alcohols or carbonyls **794** (*Eq. 18*). Chiral dipoles, dipolarophiles, and



(18)

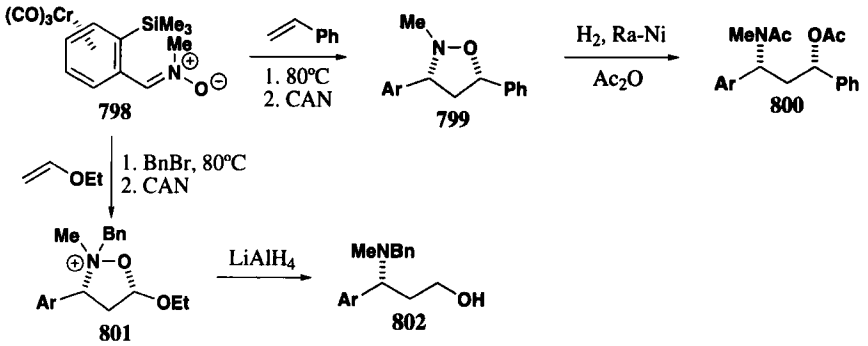
chiral Lewis acids have all been used to impart asymmetry in this reaction. Nitrones add preferentially to electron-rich olefins and although this is formally a cycloaddition, the imine bond imparts a partial positive charge to the carbon which will occupy the β-position in the final carbonyl compound, hence its classification in this section.

The phenethyl group attached to the nitrogen atom in nitrone **795** was used by several research groups to induce chirality in isoxazoline **796** *via* a 1,3-dipolar cycloaddition with electron-rich alkenes.[403] Unfortunately, this strategy led to poor control of diastereo- and enantioselectivity. For example, Overton described an approach to chiral β-amino acids using this strategy and they obtained ee's around 40% (*Scheme 163*).[404] The chiral auxiliary was conveniently removed in the reduction step that cleaved the N-O bond. Alternatively, *N*-glycosides were used several years ago by Vasella and his team to provide isoxazolines with higher asymmetric induction (70-90% ee).[403]



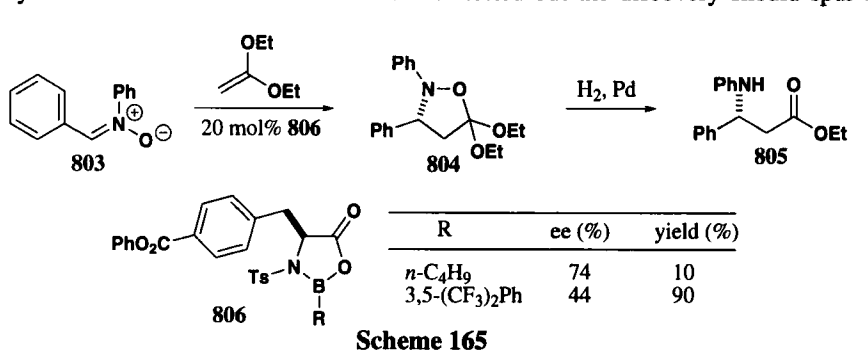
Scheme 163

The $Cr(CO)_3$ complex **798** of Hanaoka proved to be an effective chiral auxiliary, even though an initial resolution of racemates was needed to obtain **798** optically active. Nitrones **798** were generated from a chiral *o*-trimethylsilylbenzaldehyde-$Cr(CO)_3$ complex and reacted by heating with various electron-rich olefins to give cycloadduct **799** with complete diastereoselectivity (*Scheme 164*).[405] Cr was removed by oxidation with ceric ammonium nitrate.



Scheme 164

Chiral Lewis acids can promote the enantioselective 1,3-cycloaddition of nitrones to vinyl ethers or ketene acetals. In this case, there is evidence that the reaction is actually stepwise. In 1994, Scheeren and co-workers reported the first chiral Lewis-acid catalyzed nitrone dipolar cycloaddition.[406] Ketene acetals were used to access β-amino esters **805** by 1,3-dipolar cycloaddition with nitrone **803** catalyzed by oxazoborolidinone **647** (*Scheme 165*). The enantioselectivities and yields were variable for the two nitrones tested but the discovery should spur further



R	ee (%)	yield (%)
n-C_4H_9	74	10
3,5-$(CF_3)_2$Ph	44	90

Scheme 165

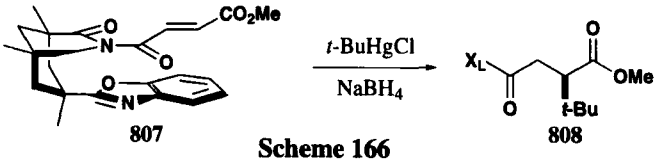
research efforts to improve on catalyst **806**. When the diethylketene acetal of propionaldehyde was reacted with nitrones in the presence of catalyst **806**, low to moderate enantioselectivities of α-alkyl-β-amino acids were obtained.

Lastly, allylic alcohols were transformed enantioselectively to isoxazolines using Et_2Zn-DIPT and nitrones.[407]

3. Neutral β-Carbons

a) Asymmetric Radical 1,4-Additions to α,β-Unsaturated Carbonyls

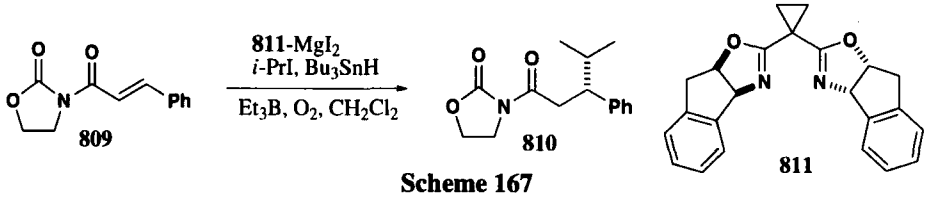
Conjugate additions of radicals to unsaturated esters or amides provide chiral β-alkyl carbonyl compounds. Controlling the addition of alkyl radicals to alkenes bearing a chiral auxiliary represents a formidable challenge due to the large distance between the β-carbon and the auxiliary. The 'Rebek' imide **807**, derived from fumaric acid, is apparently not subject to this limitation and gave a 97:3 mixture of diastereomers favoring **808** (*Scheme 166*). The regioselectivity of addition was dictated by the polar effect of the more electron-withdrawing imide. Although no other auxiliary can match this performance, the lengthy synthesis of **807** somewhat hampers its use.[277]



807 808

Scheme 166

Chiral Lewis acids chelated to the carbonyls of *N*-acyl oxazolidinone run a better chance of 'reaching' the β-carbon. Sibi and Porter reported the Lewis-acid catalyzed enantioselective radical conjugate addition to oxazolidinone **809** (*Scheme 167*).[408] Several chiral bisoxazolines like **811** complexed to Mg were tested with loadings of 5 mol%. They catalyzed the reaction between alkyl radicals and imide **809** and gave product **810** with high enantioselectivity (mostly >90% ee).[409] Radical reactions are usually more tolerant of spectator functional groups so this discovery is significant for the synthesis of β-chiral carbonyl compounds.

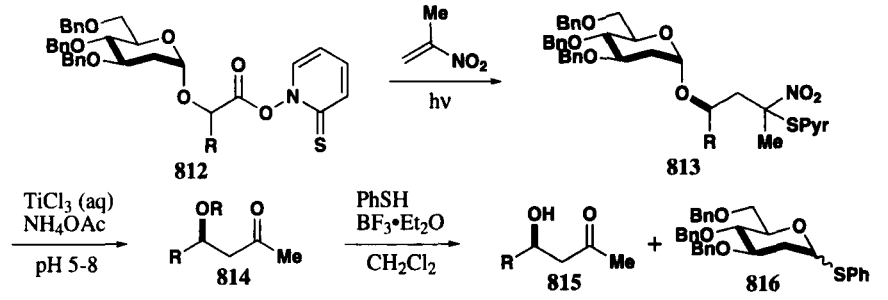


809 810 811

Scheme 167

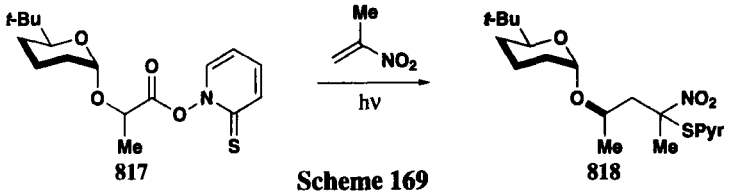
Garner and his group developed a successful alternative to the acetate aldol reaction with the addition of alkoxymethyl radicals to 2-nitropropene.[410] The method uses racemic α-hydroxy acids which are first derived into their α-glycosidyl acids and then converted to their PTOC esters **812** (*Scheme 168*). Irradiation under a sunlamp in the presence of 2-nitropropene leads to β-hydroxy ketones **815**, after hydrolysis and deprotection, with selectivities ranging from 5-8:1. Initially, acid hydrolysis of the glycoside-bound aldol adduct **814** presented difficulties due to side reactions. However, the glycoside was conveniently cleaved using benzenethiol

and BF_3•Et_2O giving the desired adduct **815** along with the thioglycoside **816**. The latter could be recycled to a reusable form in two steps.



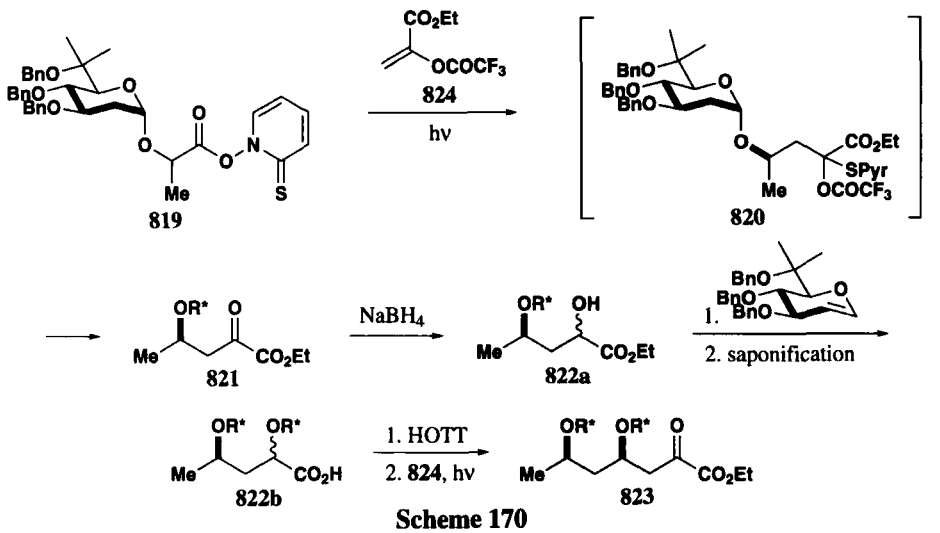
Scheme 168

A year later, an improved auxiliary was reported by the same group. Compound **817** bears a structurally simplified glycoside in which the larger *t*-butyl group provides added steric hindrance to the attack of the radical (*Scheme 169*). This time selectivities were up to 35:1 in favor of **818** and acrylates were also usable substrates leading to γ-chiral esters (not shown). Although simpler in structure, the preparation of precursor **817** required nine steps from a chiral epoxide.[411]



Scheme 169

The method was astutely extended to include an iterative construction of polyols having a 1,3-relationship (*Scheme 170*). Trifluoroacetoxyacrylate **824** was reacted with PTOC ester **819**

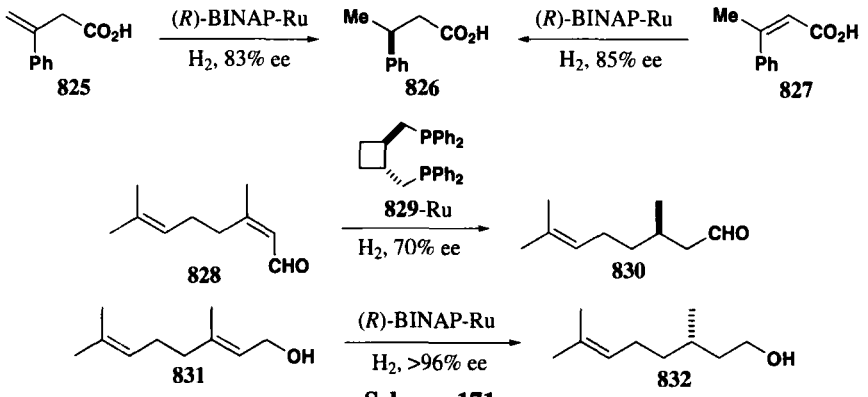


Scheme 170

under the standard irradiation conditions. Hydrolysis of the intermediate **820** presumably occurred *in situ* giving rise to the first adduct **821** in >9:1 ratio. Reduction of the ketone gave an inconsequential mixture of alcohols **822a** which were derivatized to the glycosylate **822b** in two steps. This precursor was transesterified with (*S*-1-oxido-2-pyridinyl) 1,1,3,3-tetramethylthiouronium hexafluorophosphate (HOTT) and irradiated as before in the presence of **824** to allow the construction of the *syn* 1,3-diol **823**. The corresponding *anti* 1,3-diol was also constructed using a pseudo-antipodal glycoside.[412]

b) Asymmetric Hydrogenation of α,β-Unsaturated Carbonyls and Related Molecules

Chiral acid **826** was obtained from the asymmetric hydrogenation of β,γ-unsaturated acid **825** or from α,β-unsaturated acid **827** (*Scheme 171*). The ee of the final product **126** was

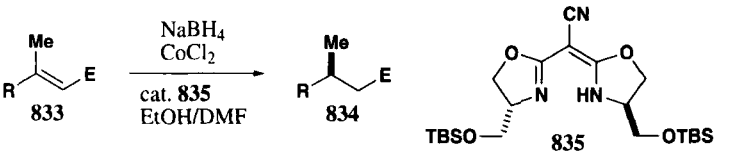


Scheme 171

good and comparable in either case. In line with what was mentioned in section II.3.f.i, unsaturated aldehyde **828** was hydrogenated with lower enantioselectivity.[413] On the other hand, primary allylic alcohol **831** was efficiently reduced by BINAP-Ru complex and other catalysts (*Scheme 171*). Note that with the BINAP-Ru catalyst, only the allylic alcohol was hydrogenated.[414,415]

The sodium borohydride reduction of α,β-unsaturated carbonyls or nitrile **833** in the presence of Co(II) and semicorrin ligand **835** can be viewed as an enantioselective Michael addition or an asymmetric hydrogenation depending on the reaction mechanism. Unsaturated esters, amides, and nitriles **833** were hydrogenated in high yields and enantioselectivities (*Scheme 172*). Amides gave better results than esters or nitriles but it is noteworthy that Rh- and Ru-catalyzed hydrogenations normally require a carboxylic acid or hydroxy functional group present on the substrate. The *Z*-isomers of all examples in *Scheme 172* gave the product with opposite absolute configuration to **834** but in similar enantiomeric purity.[416]

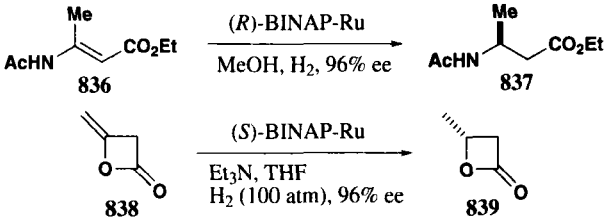
β-Amino ester **837** was prepared by catalytic hydrogenation of β-acylamino ester **836** (*Scheme 173*).[417] Little success was reported for acyclic β-hydroxy acids although the four-membered lactone **838**, with an exocyclic methylene, was reduced to the β-lactone **839** in 96%



E	R	ee (%)
CO_2Et	$Me_2C{=}CH(CH_2)_2$	94
CO_2Et	$Ph(CH_2)_2$	94
CO_2Et	*i*-Pr	96
CO_2Et	Ph	81
CO_2NHR	$Ph(CH_2)_2$	99
CO_2NHR	Cyhex	99
CO_2NHR	Ph	92
CN	$Ph(CH_2)_2$	69

Scheme 172

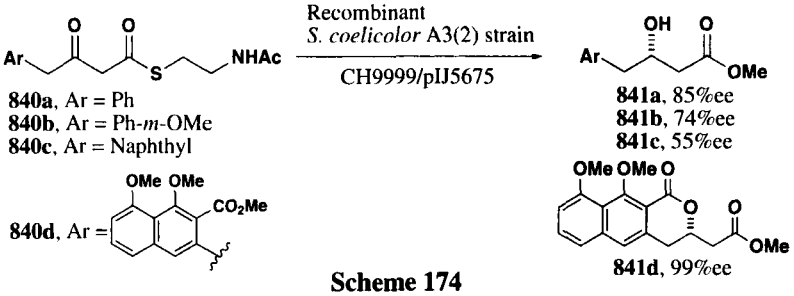
ee.[418] The optical yield in each case is high, but this route to β-amino and β-hydroxy acids has not proved as successful as the closely related synthesis of α-amino and α-hydroxy acids.



Scheme 173

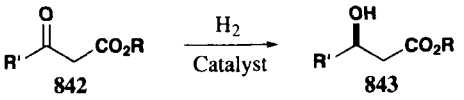
c) Asymmetric Hydrogenation of β-Dicarbonyls

If was found early in the century that whole cell enzymes, such as Baker's yeast, were able to reduce β-ketoesters and β-diketones chemo- and stereoselectively. Advances in molecular biology have enabled the precise manipulation of genes in order to produce enzymes with desirable substrate-recognition ability as well as sense and level of asymmetric induction in reduction reactions.[419] A very recent example is shown in *Scheme 174* where a recombinant plasmid was constructed specifically to allow reduction of unnatural β-keto thioester substrates **840a-d**.[420]



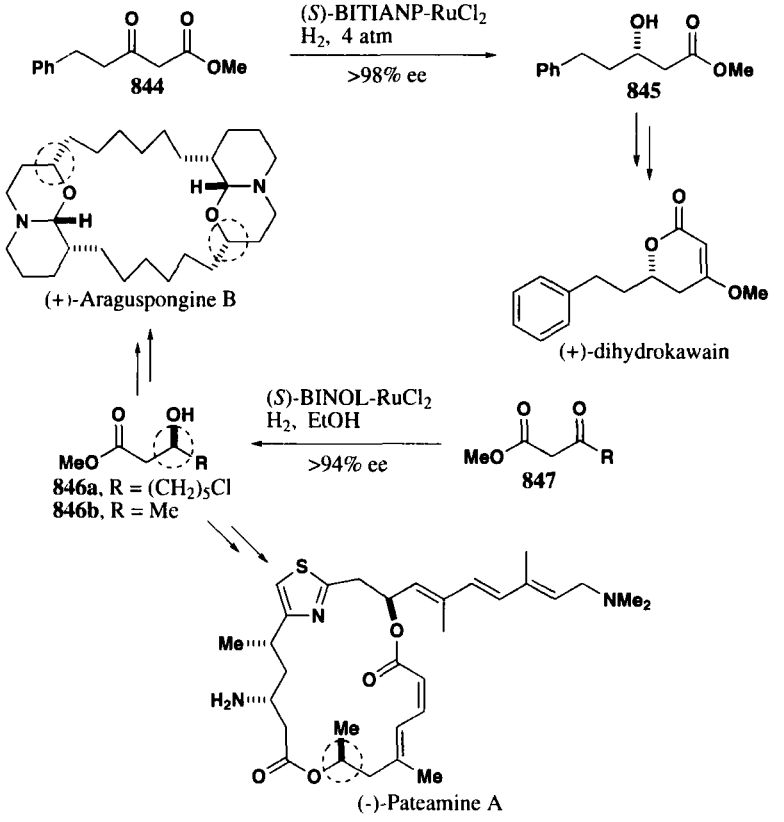
Scheme 174

The metal-catalyzed asymmetric hydrogenation of β-dicarbonyls proved more general and provided very high asymmetric induction. The Ru-catalyzed hydrogenation of β-ketoesters has reached an especially high level of sophistication in the last decade with an impressive number of active catalysts now able to produce optically pure β-hydroxy esters from a wide range of starting materials (*Eq. 19*).[310,421] An exhaustive list of examples with different Ru and Rh catalysts has been published.[310] Section II.3.f.iv on α-ketoesters should also be consulted.



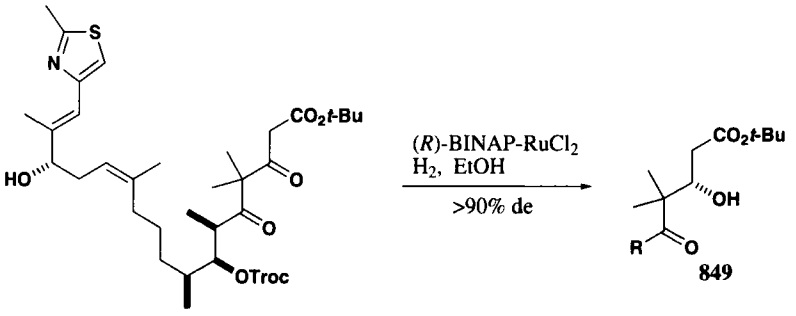
(19)

The metal-catalyzed asymmetric hydrogenation of β-dicarbonyls is so reliable that it has surpassed the enzymatic reduction of β-ketoesters (*vide supra*) in the synthesis of natural products. *Schemes 175* and *176* depict key steps in recent syntheses of several natural products that made use of the catalytic enantioselective hydrogenation of β-ketoesters. The syntheses of (+)-dihydrokawain,[422] (+)-araguspongine B[423] and (-)-pateamine A[424] used fairly simple β-ketoester substrates as building blocks for larger structures (*Scheme 175*).



Scheme 175

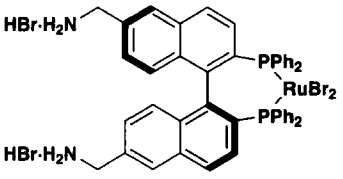
The reduction of the complex β-ketoester **848**, however, underscores the generality of this method (*Scheme 176*). The product **849** was used in a recent synthesis of epothilone B.[425]



848 **849**

Scheme 176

More recently, a water-soluble DIAM-BINAP-Ru catalyst **850** (*Fig. 24*) was developed to hydrogenate ethyl acetoacetate enantioselectively (94% ee). The product was extracted with organic solvents and the catalyst solution could be reused, though the enantioselectivity dropped slightly after the third recycling.[426]



850

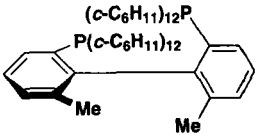
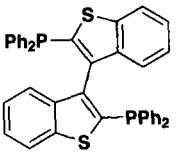
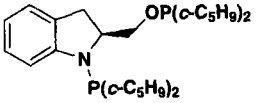
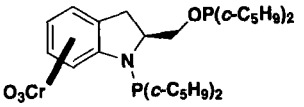
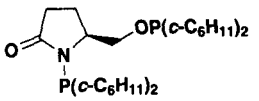
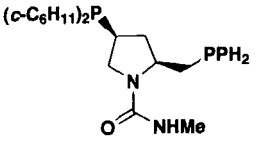
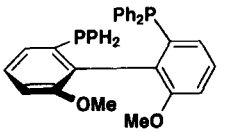
Fig. 24

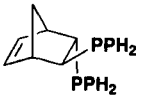
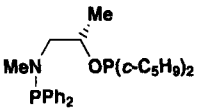
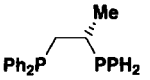
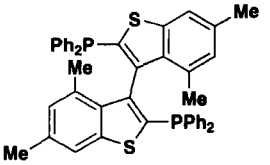
Water-Soluble Catalyst Used to Hydrogenate Ethyl Acetoacetate

IV. CONCLUSIONS

The sheer number of methods described in this review in addition to all the methods based on enolate chemistry underscore the importance of the structural motifs depicted in *Fig. 1* to organic and bioorganic chemistry. Even so, most synthetic methods which were herein labeled as alternatives to chiral enolate chemistry can accomplish much more. This may explain why few of them were actually compared to enolate chemistry by their creators. Moreover, many of the methodologies described here possess a catalytic version and it is perhaps ironic, in fact, that enolate alkylation and aldol reactions are only now beginning to enter the realm of asymmetric catalysis. Alternatives to enolate chemistry will continue to be desirable for a long time to come. Although we can expect some of the current limitations in aldol chemistry to be surmounted, some limitations will always remain such as the intrinsic reactivities of enolates and the sensitivity of the final adducts to retro-aldol and epimerization.

V. GLOSSARY

Symbol	Name or Structure
AIBN	2,2'-Azobisisobutyronitrile
BICHEP	
BINAL-H	1,1'-Bi-2-naphthoxyaluminum hydride
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-Bi-2-naphtol
BITIANP	
Boc	t-Butyloxycarbonyl
BOM	Benzyloxymethyl
COD	1,5-Cyclooctadienyl
Cp,Cp-IndoNop	
Cr(CO)3-Cp,Cp-IndoNop	
Cy,Cy-OxoProNOP	
dba	Dibenzylideneacetone
DBMP	2,6-di-tert-butyl-4-methylpyridine
DPPF	Bis(diphenylphosphino)ferrocene
DTPF	1,1'-Bis(di-*o*-tolylphosphino)ferrocene
LiHMDS	Lithium hexamethyldisilazane
LTMP	Lithium tetramethylpiperidine
MABR	Bis(4-bromo-2,6-di-*t*-butylphenoxide
MCCPM	
MeO-BIPHEP	

Mes	2,4,6-Trimethylphenyl
MMPP	Magnesium monoperoxyphtalate
MOM	Methoxymethyl
NBS	N-Bromosuccinimide
NORPHOS	
Ph,Cp-iAlaNop	
Pht	Phthalyl
PROPHOS	
PTOC	2-pyridinethione 1-oxycarbonyl
SAMP	(S)-1-amino-2-methoxymethylpyrrolidine
SEM	Trimethylsilylethoxymethyl
SMP	(S)-2-methoxymethylpyrrolidine
TBS	*t*-Butyldimethylsilyl
TDSOTf	Dimethylthexylsilyl triflate
TetraMe-BITIANP	
Ts	Tosyl (*p*-toluenesulfonyl)

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