Additions of Organometallic Reagents to C═N Bonds: Reactivity and Selectivity

Robert Bloch

Institut de Chimie Moléculaire d'Orsay, Bât. 420, Université de Paris XI, 91405 Orsay Cedex, France

Received June 25, 1997 (Revised Manuscript Received April 1, 1998)

Contents

Robert Bloch received a chemical engineering degree in 1961 from the Ecole Nationale Supérieure de Chimie de Paris and his Ph.D. degree in 1965 from Paris University. He then spent four years as a CNRS researcher in the group of Jean-Marie Conia at Caen University and moved to Canada where he spent $1^1/_2$ years as a postdoctoral fellow with Paul de Mayo at the University of Western Ontario. He subsequently joined the University of Paris XI in Orsay, becoming a CNRS research director in 1974. His research interests center around the development of new stereoselective methods in organic synthesis including the addition of organometallic reagents to carbonyl compounds and imines and thermal reactions such as retro-Diels–Alder reactions.

I. Introduction

As is the case for the addition reaction of carbanions to the carbonyl group of aldehydes and ketones, the addition of organometallic reagents to the C═N bonds of imines or imine derivatives (hydrazones, oximes) is an old and well-known reaction. However, the development of these additions has been severely limited both by the poor electrophilicity of the azomethine carbon and by the tendency of enolizable imines and imine derivatives to undergo deprotonation rather than addition.

To circumvent these two problems, a variety of methods have been developed and have greatly improved the scope of organometallic additions to imines or imine derivatives. The electrophilicity of the carbon atom of the C═N bond can be increased by *N*-alkylation, *N*-oxidation, *N*-acylation, or *N*-sulfonylation to give reactive iminium salts, reactive nitrones, acylimines, and sulfonimines, but this method requires the removal of the activating groups to generate free amines, which is not always easy. For this reason another strategy has involved activation of the C═N bond of imines or imine derivatives by coordination of a Lewis acid with the nitrogen lone pair or by addition of external promoters. The use of resonance-stabilized allyl organometallics which are more reactive compared to ordinary organometallic reagents in imine addition reactions has also supplied a partial solution to these problems. Finally in order to minimize the secondary reactions due to proton abstraction, less basic reagents such as allylboranes, allylboronates, allylstannanes, alkylcoppers or alkyl cuprates, and organocerium reagents have been used.

S0009-2665(94)00474-7 CCC: $30.00
Published on Web 06/03/1998

Diastereoselective addition of organometallic reagents to the C=N bond of chiral imines and their derivatives and addition to nonchiral imines in the presence of a chiral catalyst have been the subject of considerable interest because they might provide synthetically useful methodology for preparing enantiopure amines. Optically active amines are used to generate pharmaceutically important compounds which are also utilized in organic syntheses as resolving agents, as chiral auxiliaries for asymmetric synthesis, or as useful intermediates. For all these reasons, addition of carbanions to imines and imine derivatives has attracted the attention of organic chemists and is still a very active field of investigation. As testimony to this interest several excellent reviews covering various aspects of this chemistry have appeared.[1] The present review will survey some recent advances in the addition of various organometallic reagents including allyl organometallics to the free C=N bond of imines, hydrazones, oximes, and nitrones. The review will not attempt to provide exhaustive coverage of the literature but is intended to focus on the most recent developments and will cover published material through June 1997. However, sometimes older data will be used to provide a good understanding of the scope of these additions.

II. Reactivity

The nucleophilic 1,2-addition of organometallic reagents to C=N double bonds is a valuable method for the synthesis of primary and secondary amines. As a result a great variety of imines or imine derivatives and of organometallic reagents as well as numerous activating additives have been tested in these reactions in order to improve the electrophilicity and the reactivity of the C=N bonds. An overview of the influence of such factors on the reactivity of these C=N bonds is reported in this section.

A. Influence of the Substrate

1. Imines

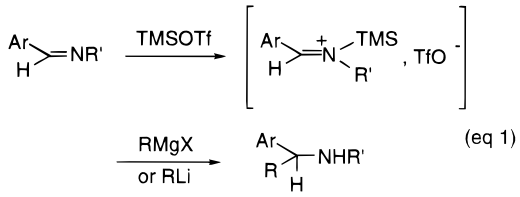
Due to the poor electrophilicity of the azomethine carbon, addition of organometallics to imines is often plagued by competititive enolization, reduction, or coupling reactions.

Alkyl Grignard reagents add with difficulty to imines derived from enolizable aldehydes or ketones and can induce their total enolization in refluxing THF.[2] In contrast, alkyl- and aryllithiums add to enolizable aldimines[3] and cyclic imines[4] in fair to moderate yields, but the reaction is not general: lithium alkynides or (perfluoroalkyl)lithium does not react under these conditions. To increase the scope of organometallic addition to imines, several methods have been explored: (i) activation of the C=N bond either by *N*-substitution with an electron-withdrawing group or by *N*-coordination to a Lewis acid, (ii) use of less basic organometallic reagents, and (iii) use of external ligands complexing the organometallic reagent.

2. Activated Imines

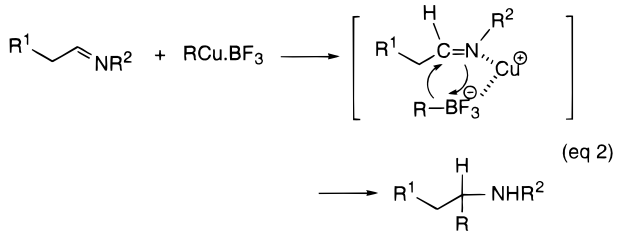
Thomas[5] has shown that the addition of 2 equiv of magnesium bromide to dialkylcadmium or dialkylzinc promotes the addition of these reagents to Schiff bases and can also improve the yield of addition of organomagnesium reagents: 92% yield for Et_2Cd, $2MgBr_2$; 89% yield for EtMgBr, $2MgBr_2$. However, only imines derived from aromatic aldehydes (non enolizable) have been investigated. The use of trimethylsilyl triflate (TMSOTf) gave similar results and was reported to facilitate the addition of Grignard reagents to several arylaldimines.[6]

The mechanism proposed involved the formation of an iminium salt (eq 1).



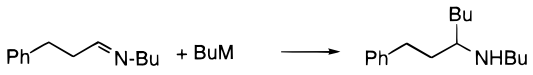
(eq 1)

An important breakthrough has been made by Akiba and collaborators[7] who recommended the use of $RCu{\cdot}BF_3$, a reagent with low basicity, which can activate imines by coordination and makes simultaneous addition possible (eq 2).



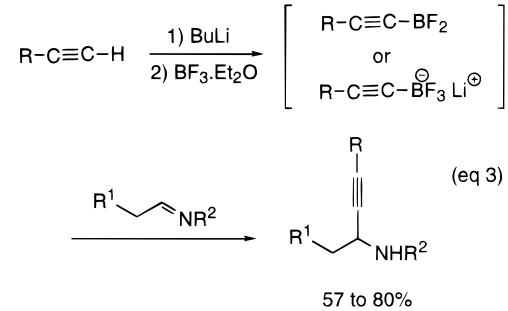
(eq 2)

Complexation of the cuprous reagent with BF_3 is essential as shown below:



BuMgX	0%
BuCu	0%
BuLi	54%
$BuCu.BF_3$ (2 eq.)	78%

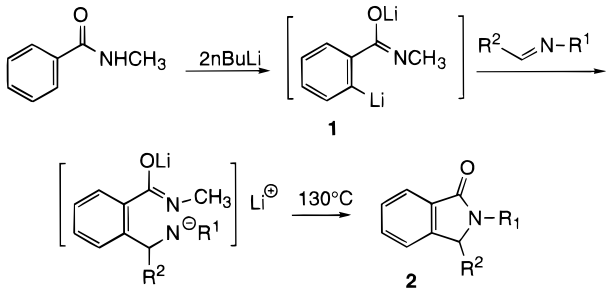
Cuprates R_2CuLi in the presence of BF_3 also gave excellent results as well as organolithium reagents complexed with BF_3. Lithium acetylides alone do not add to enolizable aldimines but give good yields of adducts in the presence of $BF_3{\cdot}Et_2O$ [8] (eq 3).



(eq 3)

57 to 80%

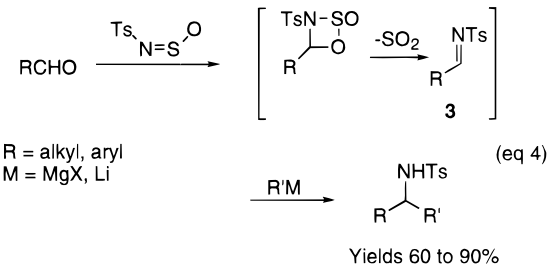
Similar improvements have been observed for (polyfluoroalkyl)lithiums[9] or recently for aryllithium **1** during the synthesis of isoindolones **2**.[10]



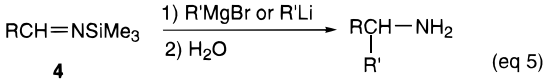
without $BF_3.Et_2O$ 0°C R^2 = Ph, R^1 = Et Yield 79%
R^2 = Pr, R^1 = Bu Yield 12%
with $BF_3.Et_2O$ -78°C R^2 = Pr, R^1 = Bu Yield 48%

Lewis acid additions are also required for the addition of poorly reactive allylic organometallic reagents such as allylsilanes or allylstannanes to imines or imine derivatives. This topic will be more developed in the part dealing with allylmetal reactivity.

Activation by *N*-substitution was thoroughly reviewed several years ago,[1a] and only recent examples will be reported here. Several other examples will be found in the section devoted to stereoselectivity. The addition of Grignard and organolithium reagents to *N*-sulfonyl aldimines **3** generated in situ from aldehydes and *N*-sulfinyl sulfonamides proved to be quite general[11] (eq 4).

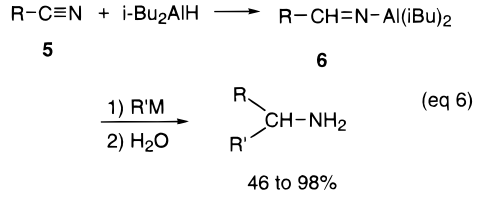


N-Tosyl aldimines **3** are highly electrophilic and react with all types (alkyl, aryl, allylic, acetylenic) of Grignard and organolithium reagents. This reaction has however limited synthetic utility for primary amine synthesis due to the harsh conditions required for the removal of the N-protecting group. As a result the use of *N*-metallo imines has been recently explored. The *N*-trimethylsilyl aldimines **4** of nonenolizable aldehydes treated with Grignard reagents or alkyllithiums followed by an aqueous workup gave primary amines in moderate to excellent yields[12,13] (eq 5).



R' = alkyl, aryl, allyl Yields = 30 to 97%

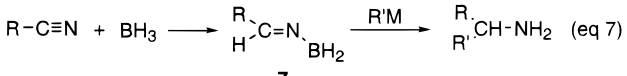
Since the use of *N*-trimethylsilyl imines is generally restricted to nonenolizable aldimines, the reaction of other *N*-metallo imines has been tested. It has been found that enolizable as well as nonenolizable *N*-diisobutylalumino imines **6**, obtained from nitriles **5** and diisobutylaluminum hydride,[14] act as masked imine derivatives of ammonia and react with allylic Grignard reagents or alkyllithiums to afford a variety of primary amines (eq 6).



46 to 98%

R = alkyl or aryl
R'M = alkyl Li, benzyl or allyl MgCl

Very similar results have been observed with *N*-boryl imines:[15] *N*-boryl imines **7** obtained from partial reduction of nitriles with borane−tetrahydrofuran have been alkylated with organolithium reagents to give, after hydrolysis, primary amines in modest to excellent yields (eq 7).

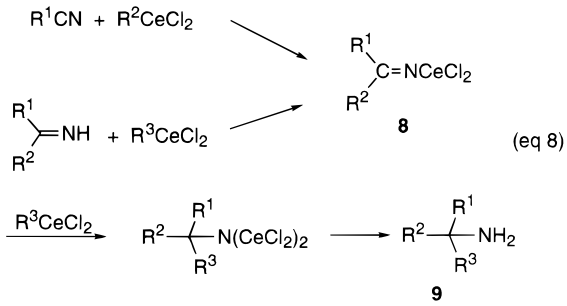


34 to 95%

R = alkyl or aryl
R'M = alkyllithium or alkylmagnesium bromide

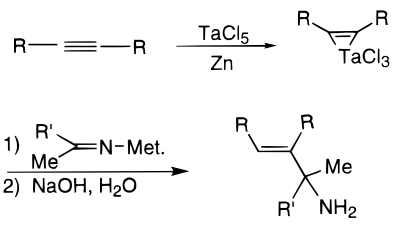
Even alkylmagnesium bromides add to these *N*-boryl imines, however with modest yields (34−38%).

Organocerium reagents react with nitrile or with *N*-unsubstituted ketimines to give the *N*-metallo imine **8**[16] (eq 8).



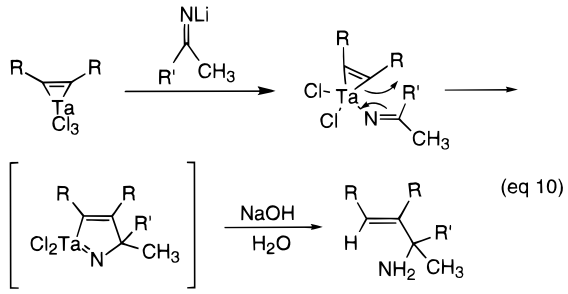
Another molecule of organocerium adds to the salt **8** to afford after hydrolysis the tertiary carbinamine **9**. (Organometallic reagents such as RLi or RMgX do not add normally to N-unsubstituted ketimines.)

Finally it has been recently reported,[17] that treatment of tantalum−alkyne complexes with *N*-lithio, *N*-magnesio, or *N*-alumino imines affords primary (*E*)-allylic amines (eq 9).

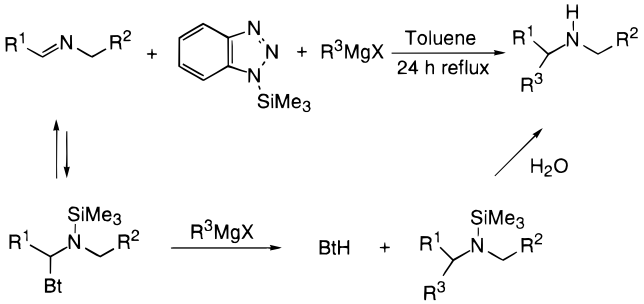


Met = Li, MgI or $AlMe_2$ 65 to 75%

The reaction may be rationalized by the mechanism shown in eq 10.

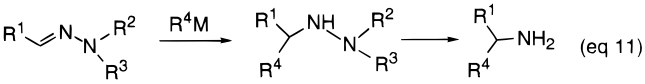


Activation of the C=N moiety of aldimines by coordination of a Lewis acid with the nitrogen lone pair can be complicated by the presence of other Lewis basic centers in the imine structure. Activation of the C=N bond by addition of 1-(trimethylsilyl)-benzotriazole ($BtSiMe_3$), which is neither appreciably acidic nor appreciably basic, minimizes the potential problem associated with Lewis acids[18] as illustrated by the additions of Grignard reagents to imines derived from furan, thiophene, ... The role of $BtSiMe_3$ is vital, and the reaction mechanism is believed to involve initial reversible addition of 1-(trimethylsilyl)-benzotriazole to the imine followed by displacement of the benzotriazolyl group by Grignard reagents.



3. Hydrazones

Organometallic reagents add to *N*,*N*-dialkylhydrazones derived from aldehydes to give hydrazines[19] which after hydrogenolytic N−N cleavage, lead to branched primary amines (eq 11).

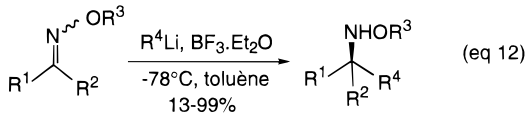


Hydrazones can therefore be regarded as stable equivalents of imines derived from ammonia. Although their reactivity was not found to be better than that of simple imines, they have often been used for the enantioselective synthesis of primary amines, and several interesting synthetic applications have been described and will be reported later.

4. Oxime Ethers

Oximes and oxime ethers are in general less electrophilic than the corresponding imines and are also more easily α-deprotonated. Thus, the addition of organometallics to oximes and oxime ethers is sometimes problematic and can give rise to a variety of products in addition to the desired hydroxy(or alkoxy)amines.[1a] However, oximes and oxime ethers seem to be attractive starting materials for the synthesis of amino compounds since the N−O bond of alkoxyamines is much easier to cleave[20] than the amine C−N bond or the hydrazine N−N bond which require harsh conditions not compatible with a wide range of functional groups.

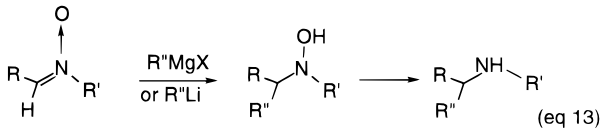
Addition of nonstabilized organolithium reagents to *O*-benzylaldoximes activated by the presence of 1 equiv of boron trifluoride etherate affords *O*-benzylhydroxyamines in acceptable yields. In tetrahydrofuran, addition of aryllithium, acetylenic lithium, and vinyllithium reagents was successful while alkyllithiums failed to produce the desired compound.[21] Furthermore, the *Z* isomer of the oxime ether reacts preferentially, and no addition products could be detected with the *E* isomer. The scope of this reaction is considerably increased when the reaction is carried out in toluene.[22] In these conditions, alkyllithiums add with fair yields and *E* isomers of the oxime ethers, although less reactive than the *Z* isomers, react to give the expected alkoxyamines (eq 12).



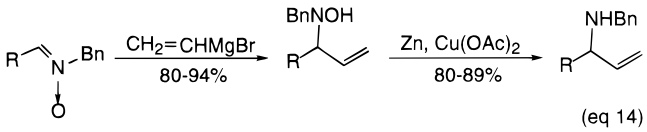
5. Nitrones

Nitrones offer interesting advantages with respect to imines, hydrazones, and other nitrogen derivatives of carbonyl compounds in reactions with nucleophiles. They possess the most highly polarized C=N bond, which is responsible for their good electrophilic reactivity, and a reactive oxygen atom, which can give easily rigid chelates useful to control the stereoselectivity of addition reactions.

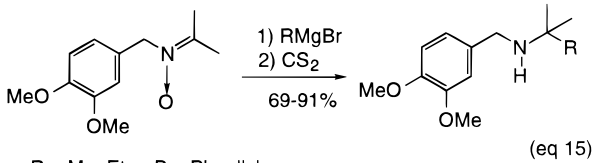
Addition of organomagnesium or organolithium reagents to aldonitrones provides N,N-disubstituted hydroxyamines which can be reduced to secondary amines (eq 13).[1a]



Recently an efficient synthesis of secondary allylamines has been reported via addition of vinyl organomagnesium bromide to a variety of alkyl or aryl nitrones (eq 14).[23]



Organometallic additions to ketonitrones are in general limited to cyclic nitrones[24] and occur with modest yields. However, it has been found that Grignard reagents in benzene add to acyclic ketonitrones with good to excellent yields (eq 15).[25]



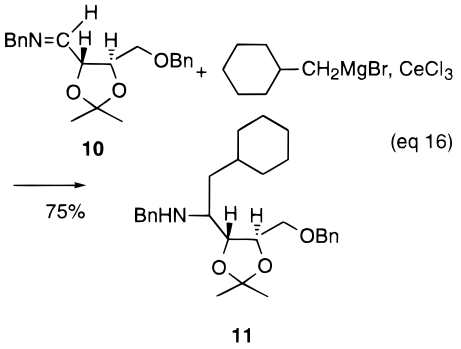
R = Me, Et, n-Bu, Ph, allyl

B. Influence of the Organometallic Reagents

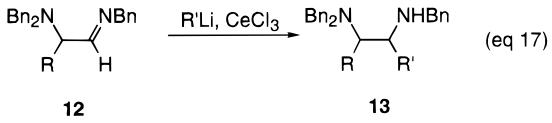
It has already been reported above that, although the reactivity was not improved, organocopper reagents ($RCu\cdot BF_3$ or $R_2CuM\cdot BF_3$), less basic than organolithium or organomagnesium reagents, are more efficient for addition to imines derived from aliphatic aldehydes. Interesting results have also been obtained by the use of organocerium reagents and, for the synthesis of homoallylic amines, by the use of a variety of allylic organometallic reagents.

1. Use of Organocerium Reagents

In 1984, Imamoto and collaborators[26] discovered that organocerium reagents, prepared in situ from cerium(III) chloride and organomagnesium or organolithium reagents, smoothly add to carbonyl compounds. In particular, these new reagents, less basic than Grignard compounds, react in good yields with carbonyl compounds prone to side reactions such as enolization. These reagents have rapidly been used with great success for addition to hydrazones,[27] but it was only six years later that the additions of these useful reagents to simple imines were tested independently by two groups. Terashima and collaborators[28] reported that cyclohexylmethylmagnesium bromide did not add at all with the imine **10** prepared from tartaric acid, but when this reagent was first treated with $CeCl_3$, the addition proceeded efficiently to give the amine **11** in 75% yield (eq 16).



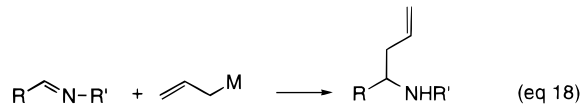
At the same time, Reetz and collaborators[29] found that organocerium reagents prepared in situ from RLi and $CeCl_3$ add with high yields to α-amino aldimines **12** to give the diamines **13** (eq 17).



Since then the addition of organocerium reagents to a variety of imines has been reported to occur generally in high yields, and the stereoselectivity of these reactions will be discussed later.

2. Use of Allylic Organometallic Reagents

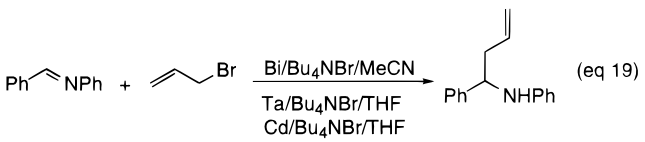
a. Introduction. Reaction of allylic organometallic compounds with imines provides a potentially valuable route to homoallylic amines which are of particular interest owing to the various possible transformations of the C=C double bond of the allyl moiety. Accordingly this reaction has attracted the attention of a wide range of organic chemists, and the literature before 1992 has been covered in recent review articles.[1b,c] A very brief summary of the ancient works will be given in this introduction followed by the report of the most recent developments of these allylation reactions (eq 18).



Allylic organometallic reagents are in general more reactive than nonstabilized organometallic compounds for imine addition reactions. A greater ionization of the carbon−metal bond, due to the resonance stabilization of the allyl anion, has been suggested to explain this increase of reactivity. However, owing to α-deprotonation, reactions involving basic lithium, magnesium, and zinc allylic reagents are limited to imines derived from nonenolizable or α-alkyl-substituted aliphatic aldehydes. A variety of metals including Mg, Li, Zn, B, Sn, Pb, Ti, Al, and Cu were tried in such allylation reactions. Less reactive allylsilanes as well as allylstannanes require the use of Lewis acid additives to enhance the electrophilicity of the imines, but in general allylsilanes are not of great synthetic utility. The good reactivity of allylboranes was attributed to the Lewis acidity of boron, which improves imine electrophilicity by coordinating to the nitrogen lone pair. Furthermore, among the allylmetal reagents investigated, allylboronates or allylboranes such as allyl-9-borabicyclo[3.3.1]nonane (allyl-9-BBN), due to their low basicity, were found to be the reagent of choice for allylation of imines derived from enolizable aldehydes.

To improve the yields and the selectivity of the addition of allyl organometallic reagents to imine, new reagents, new Lewis acid additives, and new methods have been investigated during these past few years and are outlined below.

b. Barbier-Type Allylation. The Barbier procedure for imine allylation, involving the formation of the allylmetal reagent in situ, has been the subject of significant advances in recent years. Thus, cadmium,[30] bismuth[31] and tantalium [31] mediated allylation of aldimines takes place with good (Ta) to excellent (Cd, Bi) yields in very mild conditions (eq 19). The effect of Bu_4NBr, not well understood, was found to be remarkable since no allylation occurred when it was replaced by other salts such as NaBr, KBr, or $MgBr_2$.

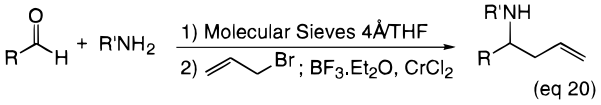


Yields = 95% (Bi), 60% (Ta) or 90% (Cd)

Arylaldimines have also been allylated by the use of a mixture of allyl bromide and indium powder[32] in fair to good yields (25−91%). Some stereocontrol

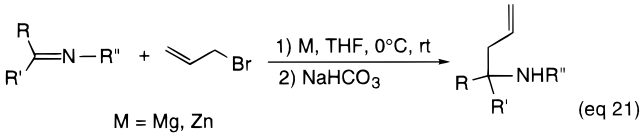
(ca. 4:1) was observed when a chiral imine derived from (*S*)-1-phenylethylamine was used, but the selectivity decreased when the phenyl group was replaced by the 1-naphthyl group (2:1).

Allylic bromides add to aryl- or alkylaldimines activated with BF_3-Et_2O in the presence of chromium(II) chloride to give the corresponding homoallylamines [33] in good yields (45−75%). The reaction can be performed in one pot starting from the aldehyde and amine in the presence of molecular sieves (eq 20). A very good diastereoselectivity (de = 86%) was obtained for the allylation of the imine derived from benzaldehyde and (*S*)-valine.



(eq 20)

The samarium/allyl bromide system[34] has also been recently used for the allylation of arylimines in fair to good yields (52−80%). More interesting was the report of very high yield allylation of both aldimines and ketimines under Barbier-type conditions using allyl bromide and simple magnesium foil or zinc dust in tetrahydrofuran (eq 21).[35] However, when chiral imines derived from (*S*)- or (*R*)-1-phenylethylamine were used, the diastereoselectivity was not higher (1:1 to 2.5:1) than that obtained with preformed allylmagnesium or -zinc.

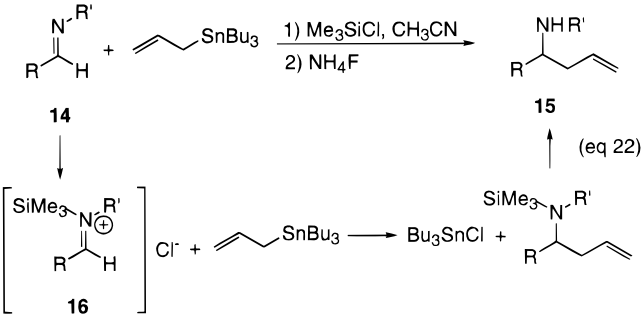


M = Mg, Zn

(eq 21)

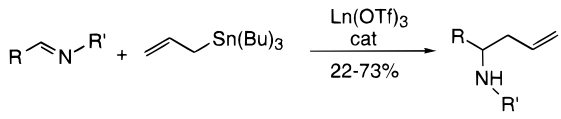
Yields = 77 to 99%

c. New Promoters. The Lewis acid promoted reaction of allyltrialkylstannanes to aldehydes is now a well-established procedure and an important synthetic tool. In contrast addition reactions of allylstannanes to imines are scarcely developed, but several important improvements have been very recently described. Allyltributylstannane reacts with aldimines **14**, promoted by chlorotrimethyl(or phenyl)silane [36] to give the corresponding homoallylamines **15** in smooth condition and with excellent yields (eq 22). No allylation occurred in the absence of chlorotrimethylsilane which activated the imines through the probable formation of iminium salts **16**. This reaction proved very efficient, but poor selectivity was obtained for the addition to chiral aldimines.



(eq 22)

Allylation of imines with allylstannanes can also take place using a promoter in catalytic amount. Lanthanide triflates are effective catalysts for this reaction[37] and gave homoallylic amines with fair to good yields (22−73% with 0.15−0.20 equiv of Ln(OTf)$_3$) (eq 23).



(eq 23)

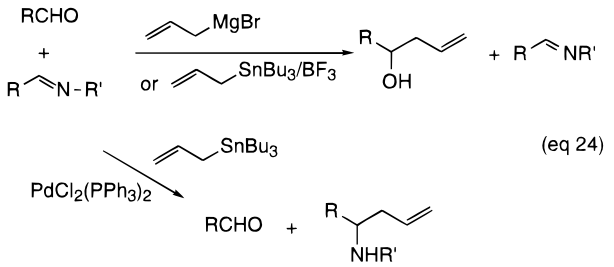
R = C_6H_5, $C_6H_5CH{=}CH$, C_6H_{11}, CO_2Et, furyl

R' = C_6H_5, 4-$CH_3OC_6H_4$, $(C_6H_5)_2CH$, $C_6H_5CH_2$

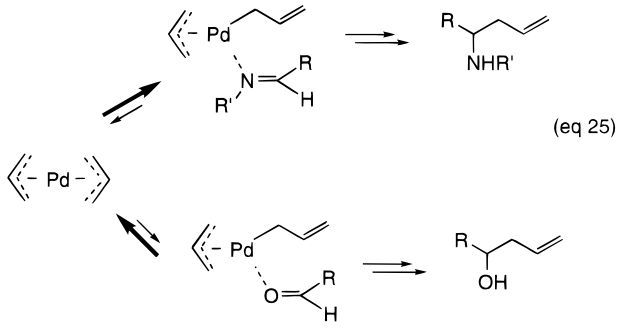
Ln = Yb, Sc, La

Very interesting results have been reported by Yamamoto and co-workers[38] related to the allylation of imines with allylstannanes catalyzed by Pd(II) or Pt(II) complexes. The additions of allyl-, crotyl-, and methallyltributylstannanes to various aldimines proceed smoothly to give the corresponding homoallylamines in good to excellent yields (72−98%).

Furthermore, a surprising and unprecedented chemoselective allylation of imines in the presence of aldehydes has been found (eq 24). The best chemoselectivity was obtained using π-allylpalladium chloride dimer with imines derived from methyl *p*-aminobenzoate. This selectivity can be explained by the difference of the coordination ability between N and O atoms to the transition metal (eq 25). This reversal of chemoselectivity observed by changing the allylation promoter can be synthetically very useful.



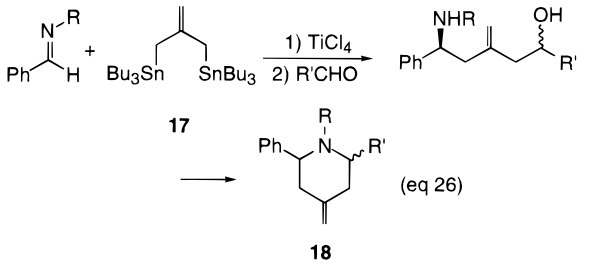
(eq 24)



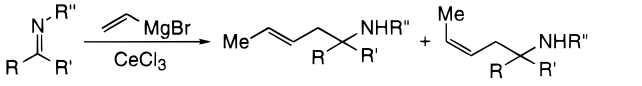
(eq 25)

d. New Reagents. A new method for the construction of 2,6-disubstituted piperidines **18** has been established, starting from the $TiCl_4$-promoted addition of the bis-stannane **17** to imines[39] followed by a Mitsunobu cyclization, but this method suffers from a lack of stereoselectivity (eq 26).

When γ-substituted allylic metals are added to imines, a mixture of linear (α-adduct) and branched

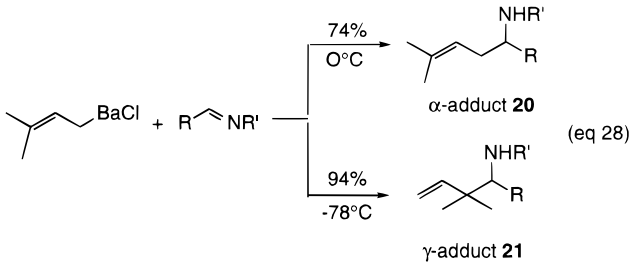


(γ-adduct) products is usually formed with predominance of the branched product. It has been found that the addition of an excess of vinylcerium dichloride to imines leads surprisingly to the linear homoallylic amines **19**[40] with fair yields (eq 27). Two different mechanistic pathways were proposed to explain the formation of the homoallylic amines **19**.



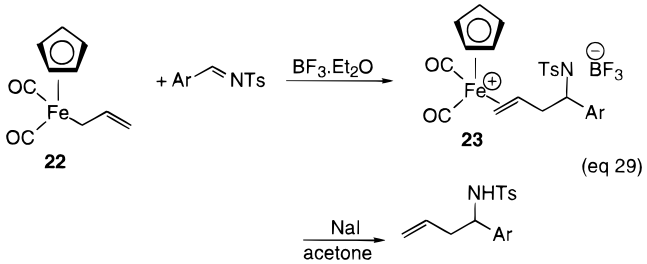
38 to 57% yield Z/E = 71/29 to 87/13

A very interesting regioselective allylation of aldimines by allylic barium reagents allows the obtention of either the linear or the branched products by a simple change of the reaction temperature[41] (eq 28).

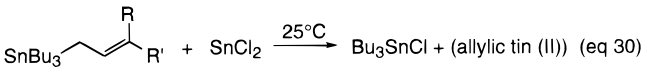


The regioselectivity is in general very high (>80%), and the allylic barium reagents are reactive enough to add to aliphatic aldimines. The surprising change of regiochemistry was attributed to the reversibility of the reaction of allylic barium reagents with aldimines: the γ-adduct **21** kinetically formed isomerized to the thermodynamically stable α-adduct **20** when the temperature increased.

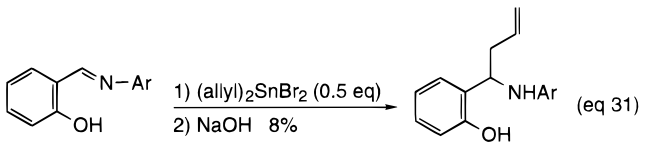
The reaction of allyl(cyclopentadienyl)iron dicarbonyl **22** with aromatic aldimines has been investigated.[42] The addition was promoted by the presence of a Lewis acid such as $BF_3{\cdot}Et_2O$ and took place only when a strong electron-withdrawing group was bound to the imine nitrogen (eq 29). Demetalation of **23** afforded homoallylic amines with fair to good yields (20−88%).



When allyltributylstannanes are treated with tin(II) chloride, Sn(IV)−Sn(II) transmetalation takes place (eq 30), generating allylic tin(II) reagents as novel reacting species for the allylation of arylaldimines in excellent yields.[43]

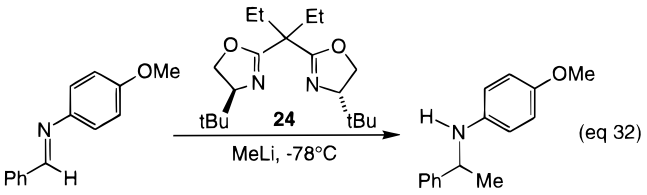


It has been found that diallyltin dibromide, $(allyl)_2SnBr_2$, is a very efficient allylation reagent[44] which reacts with (hydroxy)arylimines without any Lewis acid catalyst and without interference of the OH group (eq 31).



3. Use of Activated Organometallics

The addition reaction of organolithium compounds to imines can also be considerably accelerated by the use of chiral ligands which modify the nature of the organometallic reagent by complexation. For example, the influence of bis-oxazoline **24** was evaluated in the reaction of addition of MeLi to the imine **25** (eq 32). In the absence of ligand the reaction hardly proceeded at −78 °C, affording the amine **26** in only 6% yield after 4 h. In the presence of a stoichiometric amount of **24**, the addition was accelerated to afford **26** in 95% yield after 1 h.[45]



25 26 (95% yield)

III. Stereoselectivity

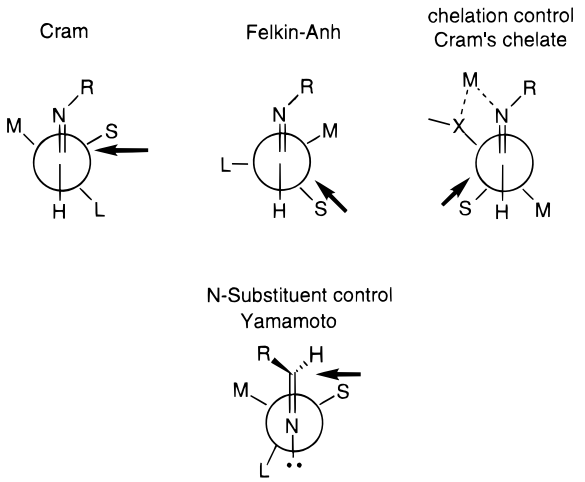
A. Addition To Chiral Imines

1. Generality

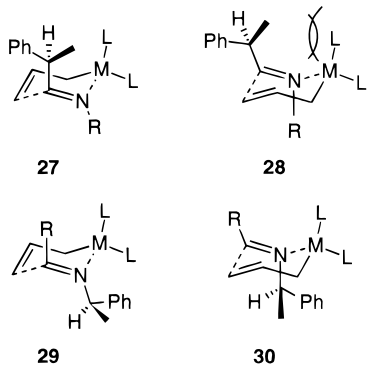
Although organometallic additions to the carbonyl of aldehydes and ketones possessing an α- or β-chiral center have been extensively studied, the additions to analogous chiral imines have only recently begun to attract the attention of organic chemists. Chiral imines used in these investigations have been arising from (i) chiral aldehydes and achiral amines, (ii) achiral aldehydes and chiral amines, and (iii) chiral aldehydes and chiral amines; additions to achiral imines in the presence of chiral catalysators have also been a strategy developed during the past few years.

Models that have been utilized to explain or predict the diastereofacial selectivity of organometallic imine reactions are based on the models used for the addition of organometallic reagents to carbonyl compounds: Cram's or Felkin-Ahn's model for non-chelation-controlled reaction and Cram's chelate model

for chelation controlled addition.[46] However, in imines, the nitrogen substituent constitutes a new factor which can influence the stereoselectivity of the reaction. A model described by Yamamoto accounts for the facial selectivity brought about by the chiral nitrogen auxiliary.[47]



The stereoselectivity of the addition of allylmetal reagents to imines could be rationalized by the general models described above. However, the very high level of selectivity observed for the allyl-9-BBN addition to imines containing either an α-chiral center (Cram:anti-Cram > 95:5) or a chiral center attached to the nitrogen atom (de > 99%) has been explained by the cyclic chair transition states **27** and **28** or **29** and **30**. The additional steric demands created by the nonbonded 1,3-diaxial interactions between the ligands L and the different substituents might be responsible for the energy difference between **27** and **28** on one hand and **29** and **30** on the other hand.[1c]

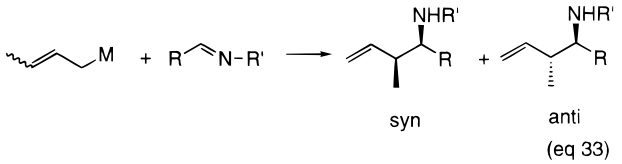


27 **28**

29 **30**

In the case of α-alkoxy-substituted aldimines, the chelation product was preponderant for reactions with allylmagnesium (chelation:nonchelation = 80:20) when allyl-9-BBN provided excellent Cram diastereocontrol (nonchelation:chelation > 99:1). For the addition of allylmagnesium as well as allyl-9-BBN to imines containing two chiral centers, the influence of the nitrogen chiral auxiliary is negligible in the case of α-alkoxy aldimines but is found to be preponderant for *β*-alkoxy aldimines.

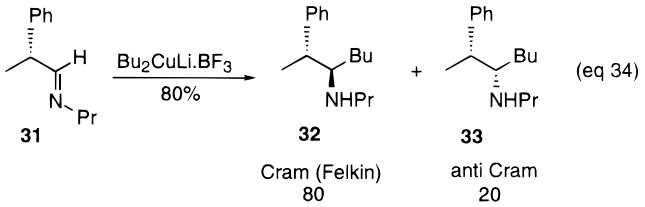
The regioselectivity of addition of crotyl organometallic reagents has been investigated, and usually the branched homoallylamines were the major products formed. The diastereoselectivity of these reactions (eq 33) is very dependent both on the nature of



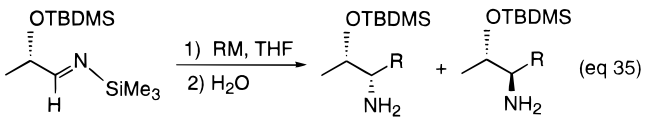
the metal and on the structure of the imine. Crotylmagnesium, -lithium, or -zinc adds with very low selectivity to arylaldimines. In contrast the addition of crotyl-9-BBN to α-arylimines gave the anti product whereas syn selectivity was obtained with α-alkylimines. Boat and chair cyclic transition states have been postulated to account for these divergent results.[1c]

2. Addition to Chiral Imines Derived from Chiral Aldehydes

Very few reports concerning stereoselective addition of nonstabilized organometallic reagents under non-chelation-controlled conditions have been reported up to now. Yamamoto[48] was the first to show that the addition of dibutyl lithiocuprate complexed with BF_3 to the chiral imine **31** (eq 34) gave with good selectivity the anti product **32** in agreement with the Cram (or Felkin) model.



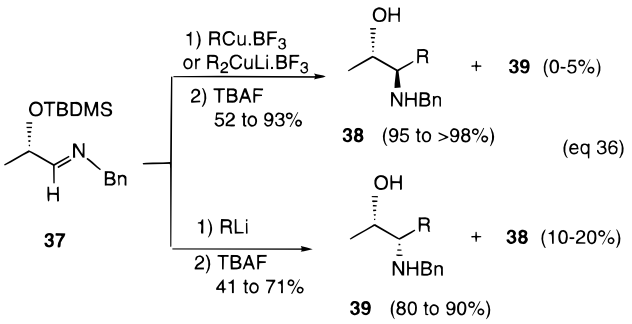
Since then it has been confirmed that organocuprate or organocopper compounds complexed with BF_3 are excellent reagents for the obtention of anti products under nonchelation control even if the imines contain a chelating α-alkoxy group. Thus, if organolithiums add to *N*-trimethylsilyl imines **34** derived from (*S*)-lactaldehyde to give *syn*-1,2 aminols **35** with excellent selectivity,[49] a remarkable reversal of diastereoselectivity in favor of the *anti*-1,2-aminols **36** is observed with organocopper compounds prepared from Grignard reagents[50] (eq 35).



RM =		
BuLi	46% yield	*syn/anti* = 98/2
BuMgBr	0%	
BuMgBr, CuI, BF_3	54% yield	*syn/anti* = 1/99
BuLi, CuI, BF_3	28% yield	*syn/anti* = 43/57

Several experimental results have not been well explained such as the anti selectivity observed for the addition of allylmagnesium chloride (anti:syn = 96:4), the great variation of selectivity with the temper-

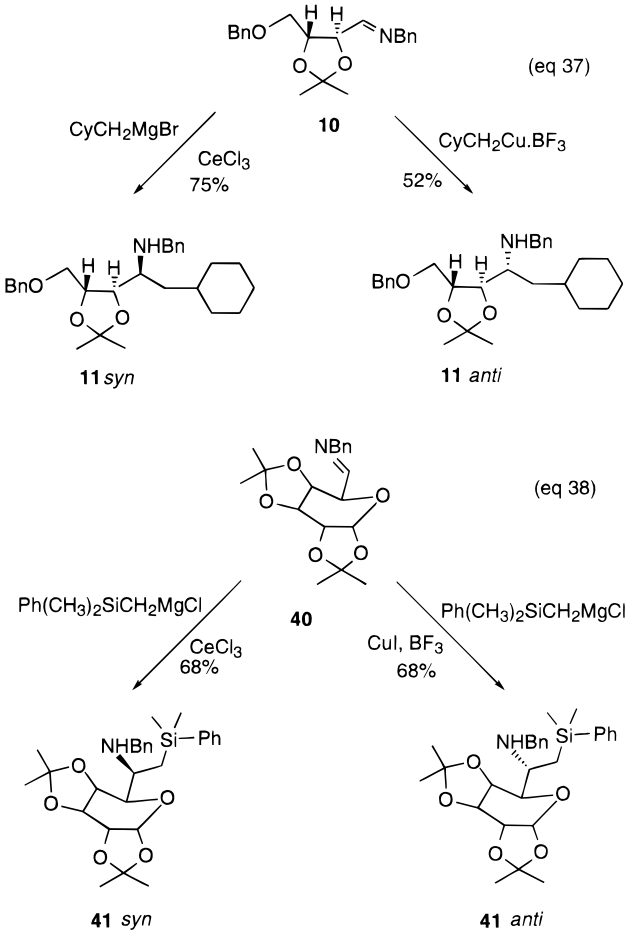
ature or the change of solvent,[51] and the poor selectivity obtained when the copper species is coming from organolithium reagents. This last observation is not consistent with the excellent selectivity found for the addition of the same reagents to the *N*-benzyl imine **37** derived from (*S*)-lactaldehyde.[52] Effectively, the reactions with RLi, CuI, BF_3, or $R_2CuLi{\cdot}BF_3$ lead to the anti isomers almost exclusively, the syn isomer being formed by using the simple RLi reagents (eq 36).



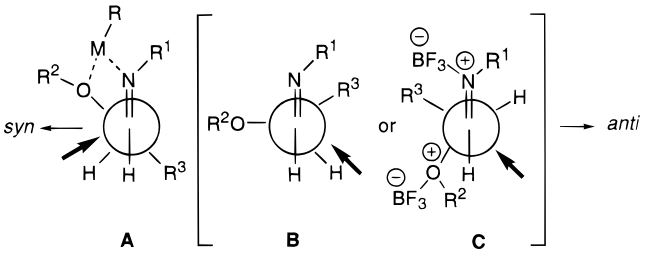
(eq 36)

R = nBu, nOct, Me, $PhCH_2CH_2$, Ph

Very similar results were observed for imine derived from sugar such as threose[28] or galactose.[53] In these two cases, a total reversal of selectivity was obtained, changing the reagent from organocerium to $RCu{\cdot}BF_3$, unique stereoisomers always being formed (eqs 37 and 38).

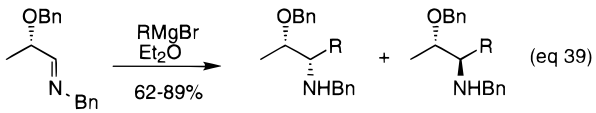


In all cases, the diastereofacial selectivity of the addition of RLi or $RCeCl_2$ can be well explained assuming a chelation control with the formation of the cyclic intermediate **A**. The stereoselectivity of the addition of $RCu{\cdot}BF_3$ or $R_2CuLi{\cdot}BF_3$ can be rationalized either by a Cram (Felkin) model **B** or better by formation, after double BF_3 complexation, of the open transition state **C** with rigid antiperiplanar conformation due to electrostatic repulsion.



Several other reports related to the chelation-controlled addition of organometallics to α-alkoxy or α-amino aldimines have been recently published. The reaction conditions as well as the nature of the substrate seem to be very important since a few conflicting results have been obtained.

A very interesting study has been carried out by Jäger and collaborators[54] with the imine **42** derived from benzylamine and lactaldehyde protected as its benzyl ether. Although this aldimine possesses an H α to the imine groups, the addition of nonstabilized Grignard reagents in ether led to high yields of products with an excellent diastereoselectivity (eq 39).

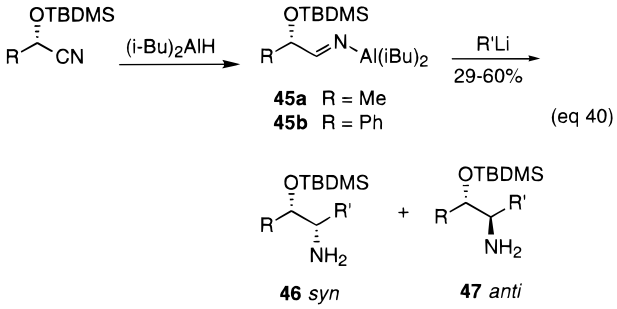


(eq 39)

syn/anti = 81/19 to 95/5

R = Me, nBu, iPr, iBu, $CyCH_2$, Ph, Bn, allyl

The successful outcome of all these reactions has been attributed to prior formation of a five-membered chelate with the 2-benzyloxy group due both to the inductive effect and the coordinative ability of OBn[55] and to the Lewis basicity of the imine nitrogen atom. If the protections of the hydroxyl and of the imino groups are different, the syn selectivity is preserved but the reactivity is changed. Alkylmagnesium compounds do not add any more to the *N*-metallo imines **45**, but alkyllithium compounds add to give α-alkoxy primary amines[56] with high syn selectivity (eq 40). The addition of Lewis acids such as $ZnBr_2$

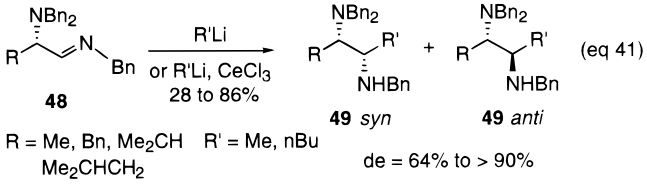


(eq 40)

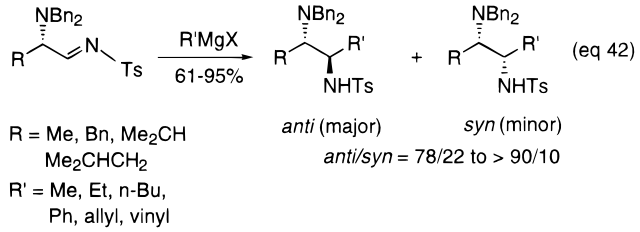
R' = Allyl, Me, n-Bu, s-Bu, n-Pent, n-Hex *syn/anti* = 67/33 to 91/9

or BF_3 does not show any effect on the reaction yield but normally lowers the syn stereoselectivity of the addition.

Replacement of the benzyloxy group of **42** by a dibenzylamino group decreased considerably the reactivity of the imines since addition of Grignard reagents in several solvents, R_2CuLi in the presence of BF_3 or of alkyllithium compounds in THF, to **48** was totally ineffective.[57] On the other hand, alkyllithium compounds in ether in the presence or not of $CeCl_3$ add with high diastereoselectivity with predominant formation of the chelation-controlled syn adducts **49** (eq 41).

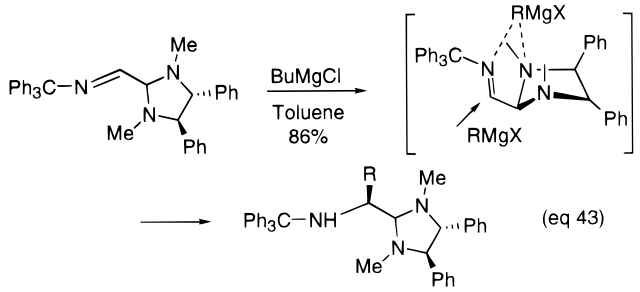


These results contrast with the addition of RLi or RLi/$CeCl_3$ to the corresponding α-dibenzylamino aldehydes which undergo 90% nonchelation-controlled reactions[58] but are in good agreement with the chelation controlled addition of diethylzinc to the same aldehydes.[59] To reverse the diastereoselectivity, the benzyl group attached to the aldimine nitrogen was replaced by an electron-withdrawing tosyl group which decreased the Lewis basicity of the aldimine nitrogen and favored the formation of the non-chelation-controlled adducts (eq 42).

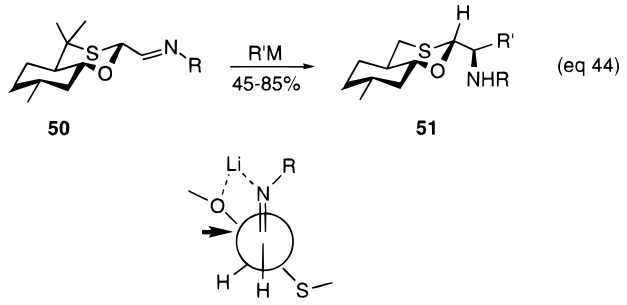


It must be noted that the tosyl group increased the electrophilicity of the C=N bonds and allowed excellent yields for the addition of Grignard reagents.[57]

If the adjacent amino group is part of a chiral aminal,[60] an excellent chelation-controlled addition[61] of Grignard reagents has been observed, leading to a single diastereomer (eq 43).

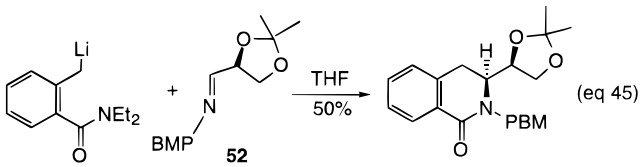


When there is a competition for the chelation between an oxygen or a sulfur, the oxygen is much more preferred as shown by additions of various organometallic reagents to the C=N double bond of imines **50** bearing a 1,3-oxathiane auxiliary (eq 44).

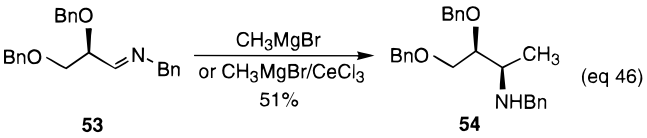


In all cases, the syn C–O/C–N diastereomers **51** were obtained with a diastereomeric ratio higher than 99:1.[62]

With α,*β*-dialkoxy imines two different chelated models can be considered involving either a five-membered or a six-membered chelate. Usually the stereochemistry of the products formed can be rationalized by the predominant formation of a five-membered chelate as shown by the various investigations described below. One of the first examples of such additions reports the addition of an organolithium compound to the *p*-methoxybenzyl (PMB) imines of (*R*)- or (*S*)-glyceraldehyde acetonide **52** to give a single adduct[63] (eq 45).

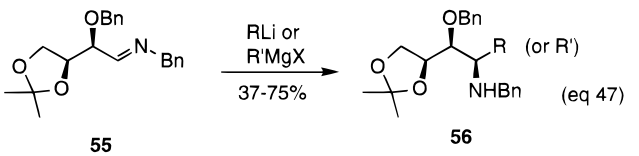


Methylmagnesium bromide in the presence or not of $CeCl_3$ as well as phenylmagnesium bromide adds to the *N*-benzyl imine **53** derived from (2*R*)-2,3-di-*O*-benzylglyceraldehyde to give also a single syn diastereomer **54** corresponding to the formation of a five-membered chelate[64] (eq 46).



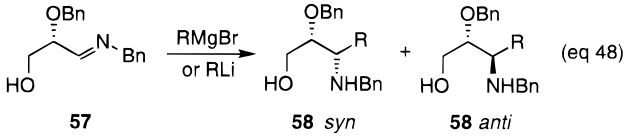
Other organometallic reagents such as CH_3Li or $CH_3Cu{\cdot}BF_3$ were used, but no reaction occurred.

In contrast addition of simple organolithium compounds at −78 °C or Grignard reagents at 0 °C to the *N*-benzyl imine **55** derived from commercially available 2-*O*-benzyl-L-threitol[65] afforded the threo adducts **56** with very high selectivity (eq 47).



Addition of the organometallic reagents on the less hindered face of a five-membered chelate can also account here for the stereoselectivity observed.

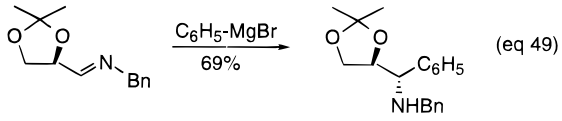
If only the hydroxy group adjacent to the imino function of *N*-benzylglyceraldehydimine is protected, the alkoxide obtained by the addition of 1 equiv of an organometallic reagent is prone to form a six-membered chelate which could compete with the formation of the usual five-membered one.[54] Effectively the addition of Grignard reagents as well as organolithium compounds to *N*,*O*-dibenzylglyceraldimine **57** gave rise to two diastereomers with various selectivities (eq 48).



57 **58** *syn* **58** *anti*

RLi gave practically no selectivity as well as Grignard reagents with R = methyl, ^{t}Bu, allyl, and Bn. Only Grignard reagents with R = ^{i}Pr, ^{i}Bu, 3-MeBu, $CyCH_2$, and vinyl gave good selectivities in favor of the syn adduct (60−90%). Remarkably organocerium reagents $RMgX/CeCl_3$ lead to a reversal of selectivity, giving predominantly the anti adduct (anti:syn = 95:5). This behavior was attributed to the efficient formation of a cerium alkoxide coordinating to the N-atom, giving rise to a six-membered chelate with an $O^{-}\cdots Ce^{3+}\cdots N$ arrangement.[54]

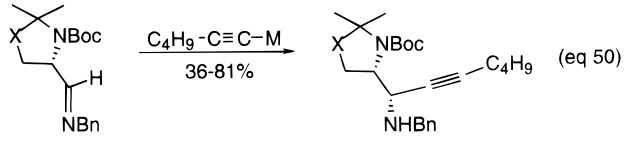
Very recently, a six-membered chelate was also suggested[64b] for the addition of phenylmagnesium bromide to the *N*-benzyl imine of (2*R*)-2,3-*O*-isopropylidene glyceraldehyde **59** which affords the unique anti compound **60** (eq 49). This result is totally



59 **60**

opposite that of the syn addition of the same reagent to the "open chain" α,*β*-dibenzyloxy imine **53** (eq 46). It must be noted that a similar effect had already been reported for the addition of organometallic reagents to the corresponding aldehydes[66] and had been attributed to the lack of chelate formation, maybe as a consequence of the ring strain which would develop in the chelated structures.

Surprising results have also been reported for the additions of acetylides to the chiral imines **61a** and **61b** derived from L-serine or L-cysteine.[67] In all cases, the addition afforded only the syn product, regardless of the acetylide metal, under both chelation (M = Li, ZnBr) and nonchelation (M = Cu·BF_3) conditions (eq 50).

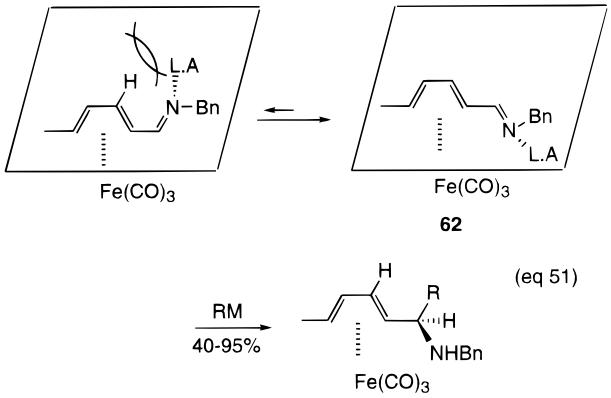


61a X = O
61b X = S

syn/anti > 99/1

The sense of stereoselectivity for M = Li or ZnBr which could be due to chelation of the metal by the imine and the carbamate nitrogens[68] is very difficult to explain for M = Cu·BF_3.

The addition of organometallic reagents to imines derived from chiral transition metal complexes of dienyl aldehydes has also been investigated.[69] In the presence of Lewis acids such as boron tribromide or cerium(III) chloride, very high diastereoselectivity has been observed for the addition of organometallics to 1-imino-(*E*,*E*)-butadiene−iron tricarbonyl complexes. This selectivity could be explained by attack of the reagent from the less hindered face of the more stable conformer **62** (eq 51).



62

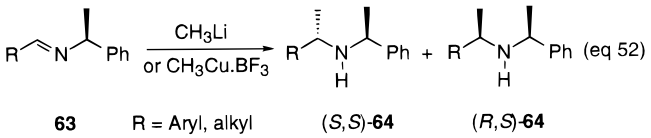
RM = nBuLi, BBr_3 ; Allyl MgBr ; R'MgBr, $CeCl_3$; R'$CeCl_2$

In conclusion the stereoselectivity of the addition of organometallic reagents to aldimines derived from chiral aldehydes and achiral amines is characterized with very few exceptions by some general trends. The stereochemistry of the amino adducts can be controlled easily by changing the nature of the reagents; RMgX, RLi, and $RCeCl_2$ give syn adducts arising from a chelation control whereas RCu·BF_3 or R_2CuLi·BF_3 afford the opposite anti adducts. Furthermore, due to the greater Lewis basicity of the nitrogen of the imines compared to the oxygen of carbonyl compounds, much better selectivities are usually obtained for organometallic additions to chiral imines compared to similar additions to aldehydes or ketones.

3. Addition to Chiral Imines Derived from Chiral Amines

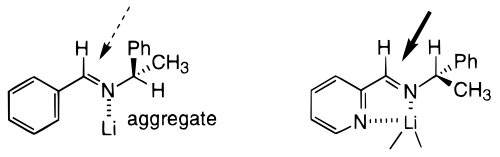
a. Imines Derived from α-Arylethylamines. The addition of organometallic reagents to aldimines derived from chiral amines provides another option, unique to imines, for controlling reaction diastereofacial selectivity. The reactions of methylmetal reagents with imines **63** derived from (*S*)-1-phenylethylamine have been thoroughly studied by varying several factors.[70] CH_3MgCl as well as copper reagents in the absence of BF_3 is unreactive, and the organocerium reagent CH_3Li·$CeCl_3$ works unsatisfactorily. In contrast CH_3Li, CH_3Cu·BF_3, and $(CH_3)_2$-CuLi(MgBr)·BF_3 add in fair to good yields (38−97%) to **63** with good to excellent diastereoselectivity in favor of (*S*,*S*)-**64** (eq 52).

The ratio *S*,*S*:*R*,*S*, which is around 70:30 for the addition of MeLi, can reach 95:5 for the addition of organocopper·BF_3 reagents. When the imine **63** is able to form chelate complexes with lithium, such as



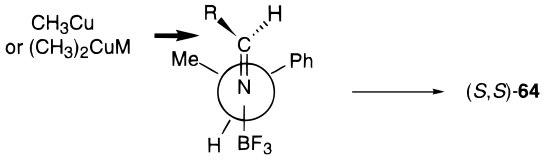
63 R = Aryl, alkyl (*S,S*)-**64** (*R,S*)-**64**

bidentate **63** (R = 2-pyridyl or 2-furyl), the sense of asymmetric induction with MeLi is reversed. A rationalization of these results has been proposed, assuming the preliminary formation of a complex between the imine and methyllithium. Depending on the nature of R and the MLn groups, the complexes could take different preferred conformations such as **65** or **66** by rotation of the R−C and N−C* bonds. This view is supported by NOE experiments performed on several imine−Lewis acid complexes in which different orientations of the auxiliary were observed depending on the nature of the Lewis acid.



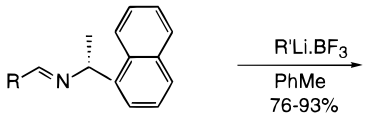
65 **66**

The reactions of methylcopper·BF_3 or dimethylcuprate·BF_3 reagents take place through the preliminary coordination of BF_3 to the imine nitrogen and the reagent attack from the less hindered side of the preferred conformation **67** where the C*−H bond is almost eclipsed with BF_3.



67

Very similar results were obtained by addition of RLi·BF_3 to imines **68** derived from (*R*)-α-naphthylethylamine[71] (eq 53).



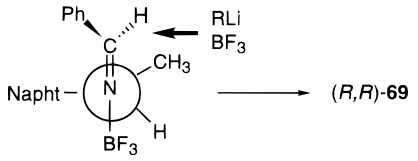
68

R = Ph, t-Bu R' = nBu, Me (eq 53)

(*R,R*)-**69** (*S,R*)-**69**

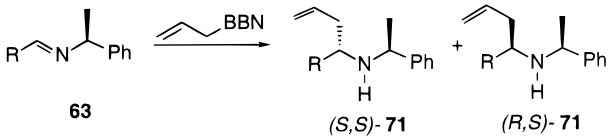
RR/SR = 85/15 to > 99/1

The lowest energy conformation **70** of the BF_3 complex was proposed according to semiempirical molecular orbital calculation (MOPAC, AM1). In this conformation the naphthyl group (Napht) is almost perpendicular to the π-plane which consisted of the C=N double bond and the phenyl (or *tert*-butyl) group.



70

A systematic study of the addition of various allyl organometallic compounds to chiral imines **63** derived from (*S*)-1-phenylethylamine has shown that the sense and the degree of stereoselectivity is dependent on the nature of both the imine and the metal.[72] In contrast with the addition of alkyl organometallic reagents to the same imines (see above), a reversal of selectivity was observed in the addition of aliphatic versus aromatic aldimines. Confirming earlier reports,[47] the best selectivities were obtained with allyl-9-BBN, and some representative results are given in eq 54. The opposite sense

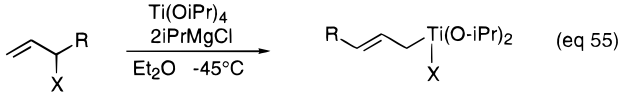


63 (*S,S*)- **71** (*R,S*)- **71**

R = iPr *S,S/R,S* = 93/7
R = Ph, 4-pyridil, 2-MeOC$_6$H$_4$ *S,S* / *R,S* = 3/97 (eq 54)

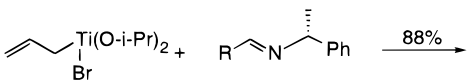
of asymmetric induction was attributed to the isomerization of *E*- to *Z*-aromatic imines prior to C−C bond formation. The diastereoselectivities observed were rationalized in terms of nine different cyclic transition states, boat or chairs, depending on the nature of the imine and of the allylating reagents.[72]

New allylic titanium compounds **72** prepared by addition of 2 equiv of isopropylmagnesium chloride to a mixture of tetraisopropoxytitanium and allylic halides or alcohol derivatives (eq 55) have been reported



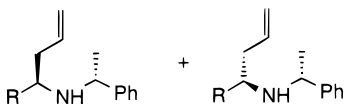
72

to be excellent allylation reagents adding to chiral imines with high stereoselectivity.[73] The reaction of allyltitanium reagent **72a** with the alkylimines **73** derived from (*R*)-1-phenylethylamine proceeds with very high 1,3-asymmetric induction to give predominantly the amines **74**. The diastereoselectivities are at least equal to that observed by using allyl-9-BBN (eq 56). Furthermore, the crotyltitanium reagent **72b**



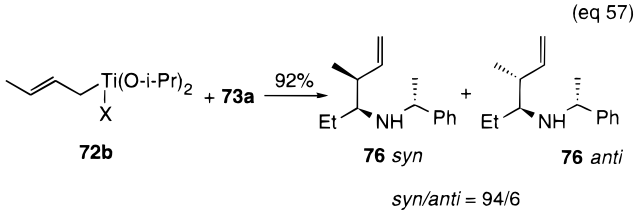
72a **73a** R = Et
73b R = i-Pr

(eq 56)



74 **75**

adds to **73a** with total 1,3-asymmetric induction and a very high 1,2-syn diastereoselectivity (eq 57). This

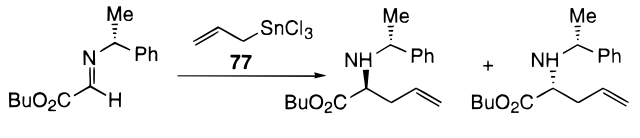


72b **76** *syn* **76** *anti*

syn/anti = 94/6 (eq 57)

is the best selectivity obtained for the moment since crotyl-9-BBN gave the ratio syn:anti = 75:25. These excellent diastereoselectivities have been explained considering the six-membered chairlike transition state **27** proposed by Yamamoto for the allylic boron reagents.[1c]

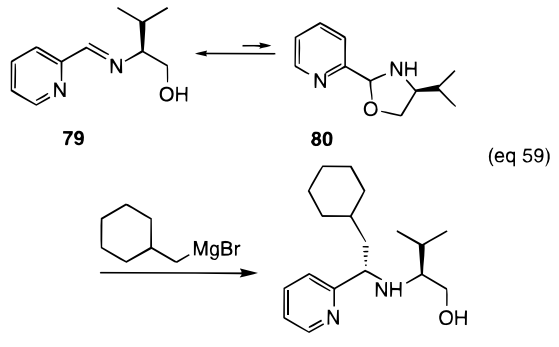
Several interesting features have been drawn from addition of the allylic trichlorostannane **77** generated from allyltributylstannane and $SnCl_4$ to the imine **78** derived from butyl glyoxylate and (*R*)-1-phenylethylamine.[74] The high stereoselectivity (93:7) of the addition of **77** to the imine **78** is opposite the selectivity already observed for the reaction of allyl-9-BBN with the same imine[75] (eq 58).



78 93 / 7 (eq 58)

For the moment, no justification of this experimental result has been suggested.

b. Imines Derived from β-Hydroxy Amines. Introduction of a heteroatom, which could coordinate to a metal, into the chiral group bound to the imine nitrogen might give rise, depending on the kind of metal used, to different transition states and then to different stereoselectivities. Imines derived from valinol have been the first imines of that sort to be reacted either with organolithium or organomagnesium reagents with good to excellent selectivities.[1a] A recent example of addition of a Grignard reagent to the imine **79** arising from (*S*)-valinol is described in eq 59. Cyclohexylmethylmagnesium bromide was

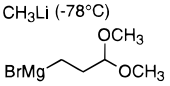
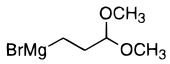
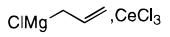
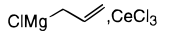
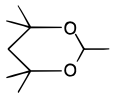
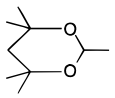


79 **80** (eq 59)

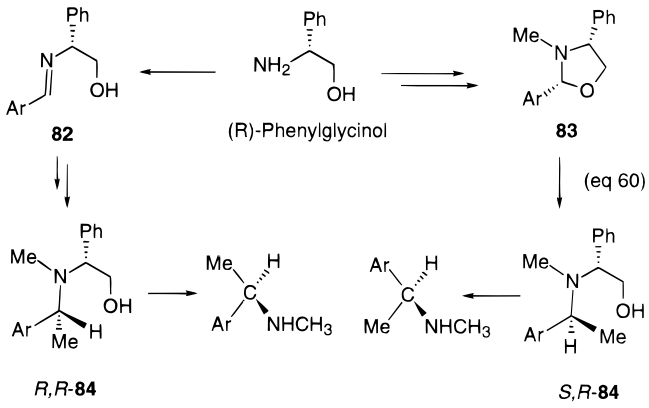
R,R-**81**

added to an equilibrium mixture of the imine **79** and the corresponding oxazolidine **80** (in THF the ratio **79**:**80** is 95:5) to give the (*R,R*)-amine **81** as the major product (*RR:SR* = 87:13).[76]

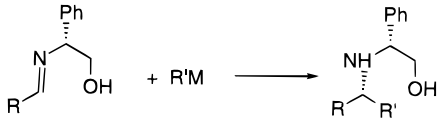
Table 1. Diastereoselective Addition of Organometallics to Imines 85

Entry	*R*	*R'M*	*Yield*	*de*	*lit.*
1	Ph	CH_3Li (-55°C → r.t.)	82	94	77
2	4-MeOPh	CH_3Li	73	94	77
3	2-furyl	CH_3Li	62	90	77
4	Ph	CH_3Li (-78°C)	48	90	79
5	Ph		63	>99	78
6	4-MeOPh		64	>99	78
7	Ph		78	84	80
8	Ph		94	86	81
9	4-BrPh		98	88	81
10	Ph	ClMgEt	62	96	79
11	Ph	$ClMgEt.CeCl_3$	85	>98	79
12	Ph	$C_6H_5CH_2MgCl$	87	92	79
13	Ph	$C_6H_5CH_2MgCl.CeCl_3$	78	96	79
14	4-MeOPh	CH_3MgCl	45	94	79
15		CH_3MgCl	92	98	82
16		PhMgCl	92	>98	82
17	Ferrocenyl	CH_3Li	28	84	83
18	Ferrocenyl	PhLi	66	96	83

The addition of organometallic reagents to imines derived from (*R*)- or (*S*)-phenylglycinol gives in general a better stereoselectivity and has been the last few years the object of numerous investigations. Takahashi and collaborators have developed a method for the stereoselective synthesis of both amine enantiomers starting from a single enantiomeric source, using the diastereoselective addition of organolithium[77] or Grignard[78] reagents to the chiral arylimines **82** and the corresponding 1,3-oxazolidines **83** derived from (*R*)-phenylglycinol (eq 60).



Good yields and very high stereoselectivities (de > 80%) have been observed for the addition of RLi, RMgBr, and $RCeCl_2$ to the imines **85**, and some selected examples are reported in Table 1.

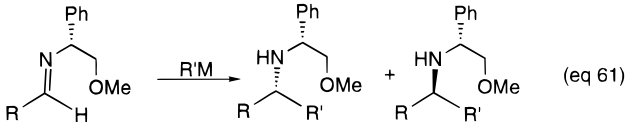


85 86

Tetrahydrofuran was found to be the best solvent for the additions to imines arising from arylaldehydes (entries 1−14). In the last two cases (entries 15 and 16) toluene seems to give slightly better results. It must be noted that we could not find any detailed example involving an enolizable imine derived from aliphatic aldehydes. The success of such a reaction has just been, however, pointed out in a footnote of ref 79.

The high degree of stereocontrol of these reactions has been attributed to a highly ordered transition state arising from chelation of the imine nitrogen to the metal bound to the oxygen and delivery of the organometallic reagent from the less hindered side of the carbon−nitrogen double bond. The synthetic potential of this strategy has been illustrated by the asymmetric synthesis of piperidine alkaloids,[84] indolizidine alkaloids,[85] C_2-diethanolamines,[80] bis(1-arylethyl)amines,[86] a protease inhibitor,[87] and a mimic of an extended dipeptide.[88]

c. Imines Derived from β-Alkoxy Amines. Another very interesting approach for the synthesis of both amine enantiomers from (*R*)-methoxyphenylglycinol as a single starting material has been reported.[89] This method is based on the reversal of diastereofacial selectivity in the addition reactions of organometallic reagents to chiral imines **87** derived from (*R*)-methoxyphenylglycinol: organolithium and organocerium reagents added from the *re*-face of the C=N bond of the imines while organocopper reagents in the presence of BF_3 approached from the *si*-face (eq 61).

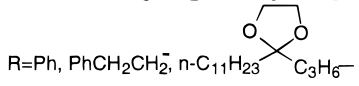


(eq 61)

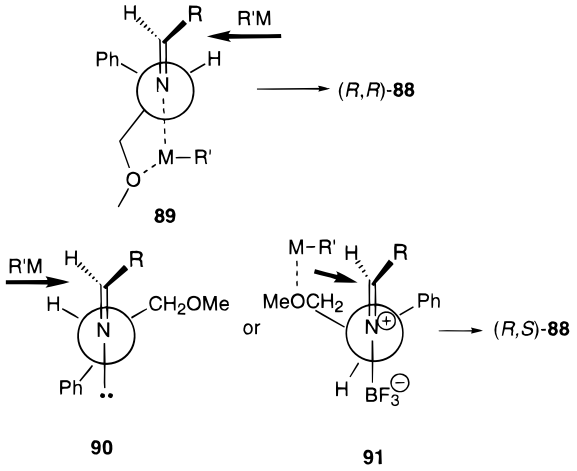
87 *R,R*-88 *R,S*-88

R'M = MeLi, n-BuLi, MeLi/$CeCl_3$, n-BuLi/$CeCl_3$ *R,R*/*R,S* > 95/5

R'M = MeCu.BF_3, $Me_2CuLi.BF_3$, n-$Bu_2CuLi.BF_3$ *R,R*/*R,S* = 2/98 to 14/86

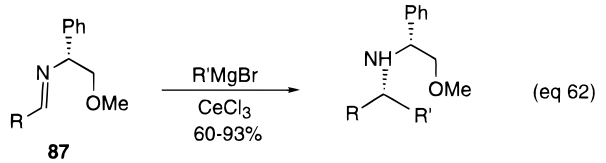


The stereoselection can be rationalized in terms of either a chelation-controlled or an open-chain model. For lithium or cerium reagents, one molecule would be coordinated by the nitrogen and oxygen atoms of the imine and the attack of a second molecule might occur from the less hindered side of the chelate **89** to give the *R,R* isomer. On the other hand, in the reaction with copper reagents, the simultaneous chelation of two heteroatoms to the metal would not occur and the reaction might proceed either through the open-chain transition state **90**[47] or, after coordination of BF_3 to the nitrogen atom, via an internal alkoxy-mediated delivery of the organometallic reagent to the open-chain transition state **91** to afford the *R,S* isomer.



89 90 91

The high stereoselectivity of such additions has been confirmed by extension of the reaction to organocerium reagents prepared from Grignard reagents with imines **87** derived from aliphatic aldehydes and (*R*)-methoxyphenylglycinol[90] (eq 62).

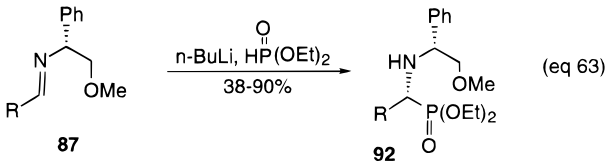


(eq 62)

87 (*R,R*)-88 de 88 to ≥ 99%

R = CH_3, C_2H_5, i-C_3H_7 R' = C_6H_5, CH_3, C_2H_5

Furthermore, a very efficient synthesis of highly enantioenriched α-amino phosphonate diesters has been described[91] by addition of lithium diethyl phosphite to a variety of chiral imines **87** (eq 63).

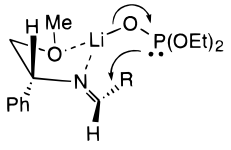


(eq 63)

87 92 de = 76 to ≥ 98%

R = cyclohexyl, methyl, i-Pr, i-Bu, n-Hexyl, phenyl, metyhylthioethyl, benzyloxymethyl, cyclohexylmethyl

To account for the diastereofacial selectivity, formation of the chelated intermediate **93** was proposed, followed by an internal delivery of the nucleophile from the less hindered side of the chelate.

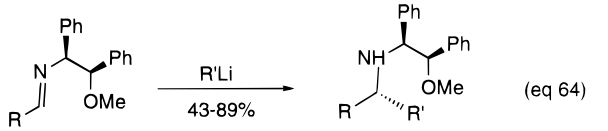


93

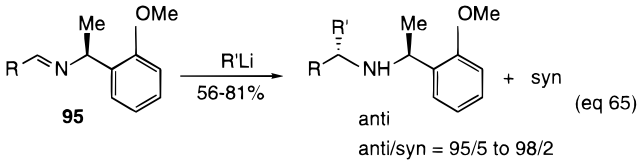
Hydrogenolysis of the chiral directing group in **92** with catalytic palladium hydroxide on carbon in absolute ethanol afforded the amino esters in 83−100% yields without any racemization.

Excellent levels of 1,3-asymmetric induction have also been observed during the addition of organometallic reagents to chiral imines derived from artificial chiral auxiliaries possessing a β- or γ-alkoxy sub-

stituent. Thus, alkyllithium adds stereoselectively to imines **94** derived from *erythro*-2-amino-1,2-diphenylethanol[92] or to imines **95** derived from 1-(2-methoxyphenyl)ethylamine[93] (eqs 64 and 65).

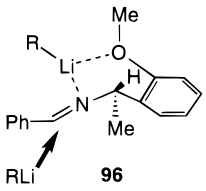


R = Ph, p-ClC$_6$H$_4$, p-MeO-C$_6$H$_4$ R' = Me, n-Bu, Ph
PhCH=CH, i-Pr

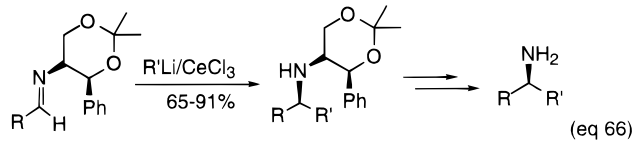


R = Ph, 4-ClPh, 1-naphtyl, Ph-CH=CH
R' = Me, nBu, allyl

The diastereoselection observed was explained by formation of the usual five-membered chelate by coordination of **94** to the metal and of the less common six-membered ring **96** by chelation of the *O*-methoxy group and the imino group of **95** to the lithium cation. The nucleophilic attack occurring from the less hindered side of this chelate leads predominantly to the anti adduct.



1,2-Addition of organocerium reagents to the chiral α,β-unsaturated aldehyde imines **97** derived from (*S,S*)-2,2-dimethyl-4-phenyl-1,3-dioxan-5-amine afford allyl- and propargylamines in high enantiomeric purity[94] (eq 66) but the method suffered from the poor yields of amine regeneration.



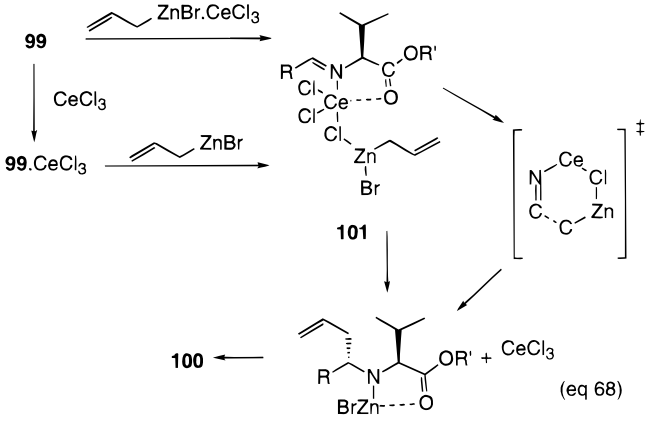
(S,S)-**97** *(S,S,S)*-**98** de 86 to ≥ 98%

R = (E)-PhCH=CH, PhC≡C, t-BuC≡C
R' = Me, Et, Bu, CH$_2$=CHCH$_2$, t-BuMe$_2$SiO(CH$_2$)$_3$

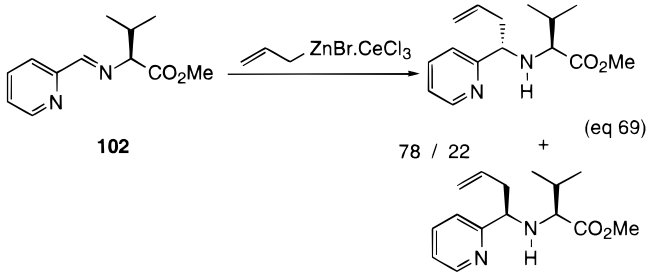
d. Imines Derived from α-Amino Esters. The addition of allylic metal compounds to chiral imines derived from methyl (*S*)-valinate had been investigated in a few cases by several research groups.[31,33,37,95] Then a systematic and well-documented survey of the enantioselective synthesis of homoallylic amines by addition of allylmetal reagents to imines derived from (*S*)-valine esters appeared recently in the literature.[96] A great variety of reagents have been prepared and tested: (a) preformed allylmetal species (allyl)$_m$MX$_n$ with M = Pb, Bi, Cu, Al, Zn; (b) allylmetal reagents formed in situ using either the usual Barbier procedure (M = Zn, Al, In) or a modified procedure in which the active metal M (M = Pb, Ti, Bi, In, Sn) is formed in situ by reduction of its salt MX$_n$ with aluminum. Most of these reagents proved to give good to excellent yields with high stereoselectivity (eq 67). In all cases the major stereoisomers **100** come

R' = Me, R = Ph, 4MeOPh, 3-pyridyl, nC$_5$H$_{11}$, iPr (eq 67)
R' = t-Bu, R = Ph

from an attack of the *si*-face of the imine **99**, and this selectivity has been rationalized by different stereochemical models.[96] The zinc-mediated, CeCl$_3$·7H$_2$O-catalyzed Barbier reaction of the imines **99** with allyl bromide in THF was particularly convenient, efficient, and selective, providing the homoallylamines **100** in quantitative yields with excellent to perfect diastereoselectivity (diastereomeric ratios 98:2 to 100:0). A plausible mechanism for this reaction is depicted in eq 68. The addition of the allylzinc bromide·CeCl$_3$



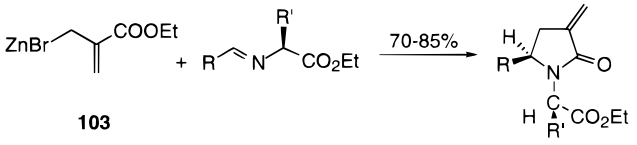
complex to **99** or the addition of allylzinc bromide to the complex **99**·CeCl$_3$ would give the threecomponent complex **101** which will deliver the allyl group on the less hindered side of a cyclic six-membered transition state.[96b] When the same reagent was added to the imine **102** derived from 2-pyridinecarboxaldehyde and methyl (*S*)-valinate, the stereoselectivity was decreased,[97] due to the possibility of formation of bidentate or tridentate chelates (eq 69).



In agreement with the addition of allyl $SnCl_3$ to the imine **78** derived from methyl glyoxylate,[74] the opposite sense of asymmetric induction was observed for the reaction of imine **102** with allyltin trihalides (allyl $SnCl_3$, allyl $SnICl_2$). The lack of coordination between the oxygen of the ester group and the metal might be responsible for this inversion of selectivity.[97]

Very recently it has been reported that excellent diastereoselectivities (de > 98%) are obtained by reaction of alkyl- or arylimines **99** with allylindium prepared separately from indium and allyl bromide in dimethylformamide.[98]

Functionalized allylzinc reagent **103** derived from 2-(bromomethyl)acrylate adds with perfect diastereoselectivity (only one diastereomer formed) to chiral imines derived from alanine or phenylglycine.[99a] Interestingly after cyclization, α-methylene γ-lactams **104** are obtained in high yields (eq 70). Furthermore

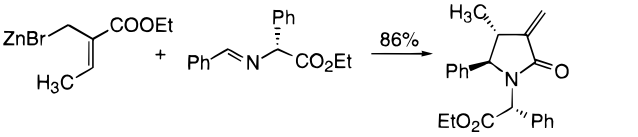


103 **104**

R = C_6H_5, t-Bu
R' = CH_3, C_6H_5

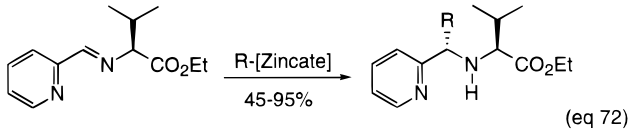
(eq 70)

when the crotyl reagent **105** is reacted with chiral imines derived from (*R*)- or (*S*)-phenylglycine, a remarkable and complete stereocontrol is observed,[99b] giving the unique trans diastereomer **106** (eq 71).



105 **106** (eq 71)

The selectivity and the versatility of these allylation reactions demonstrate the usefulness of the valine esters as chiral auxiliaries in the addition of allylmetal reagents to chiral imines. Therefore, it should be of interest to develop efficient procedures for the addition of other organometallic species (alkyl, vinyl, aryl, ...) to the same imines. The problem is here to conciliate reactivity and chemoselectivity. If methylcopper and dimethyl cuprate in the presence of BF_3 are unreactive, it has been reported very recently that triorganozincates react with the valine-derived imine **107** in the absence of BF_3 to afford the amines **108** with good to excellent diastereoselectivity[100] (eq 72).

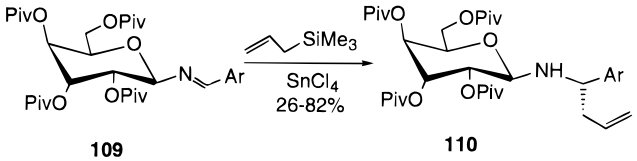


107 **108** de = 50-99% (eq 72)

R-[Zincate] = $Me_3ZnMgCl$, Me_3ZnLi, $Et_2MeZnMgCl$, $Et_2BuZnMgCl$, Me_2t-BuZnMgCl, Me_2t-BuZnLi, $Me_2BnZnMgCl$, Me_2allylZnMgBr, Me_2vinylZnMgBr

However, this reaction is not general and must be improved in order to offer a large synthetic utility.

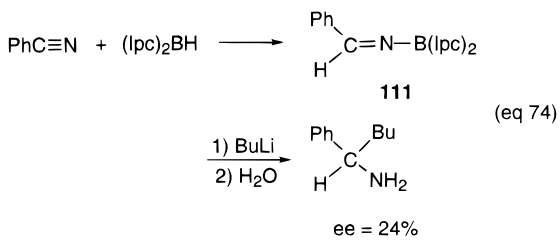
e. Imines Derived from Miscelleanous Chiral Amines. Addition of allyltrimethylsilane in the presence of $SnCl_4$ to imines **109**, arising from aromatic aldehydes and 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine, takes place with high diastereoselectivity and without any anomerization (eq 73).[101]



109 **110** (eq 73)

Allylation of imines derived from the same amine and aliphatic aldehydes is more problematic and needs the use of allyltributylstannane instead of the silane. In these conditions a mixture of α- and β-anomers is formed.

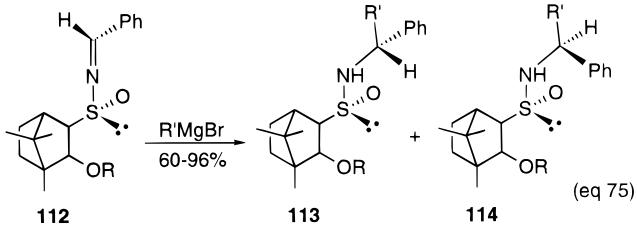
An interesting development of the additions of organometallics to chiral imines would be the attachment on the imine nitrogen of an easily removable chiral auxiliary which could both activate the C=N double bond and control the stereofacial selectivity of the alkylation. Following these considerations different approaches have been reported in the literature. Limited success due to poor stereoselectivity has been obtained for the addition of alkyllithiums to the chiral boryl imine **111**[102] prepared in situ by reduction of benzonitrile with diisopinocampheylborane, $(Ipc)_2BH$ (eq 74).



111 (eq 74)

ee = 24%

The use of recyclable mercapto chiral auxiliaries derived from camphor[103] proved to be more attractive as shown in eq 75.

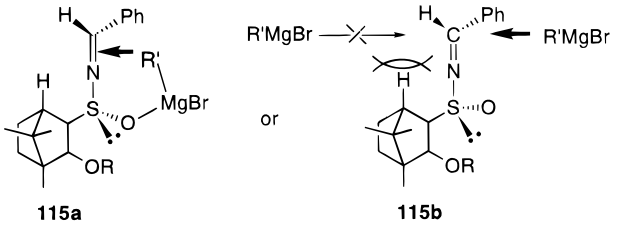


112 **113** **114** (eq 75)

R = neopentyl, benzyl
R' = Me, Et, n-Bu, i-Pr, t-Bu

113/**114** = 85/15 to > 99/1

The diastereoselectivity in favor of amines **113** has been rationalized assuming that the imines adopt the preferred conformation **115**. The *si*-face of this conformation is more prone to attack by the organometallic reagent, due either to chelation between the sulfinyl oxygen and the metal or to the shielding of the *re*-face by the camphor skeleton.



115a 115b

It has also been reported that chiral imines **116** derived from a simple chiral, nonracemic, *p*-toluenesulfinamide and aromatic ketones or aldehydes react with allylmagnesium bromide[104] or benzylmagnesium chloride[105] to afford stereoselectively the sulfinamides **117** (eq 76). Unfortunately addition reactions with other organometallic reagents (MeMgBr, vinyl-MgBr, *n*-BuLi) were unsuccessful.

116 **117** (eq 76)

Ar = Ph, R = Me	R'M = allylMgBr (98%)	de > 99%
Ar = Ph, R = nBu	R'M = allylMgBr (92%)	de = 82%
Ar = Ph, 4-OMePh, 4-ClPh		
4-$(CH_3)_2$NPh, 1-naphtyl R = H	R'M = BnMgCl (53-80%)	de = 60-74%

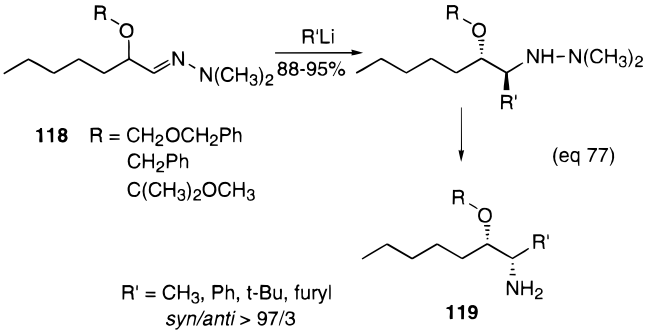
f. Conclusion. The additions of organometallic reagents to chiral imines derived from 1-arylethylamines are often highly stereoselective. However, the sense of selection, directly related to the structure of both the imine and the reagent, is sometimes difficult to predict. Imines arising from amino acids or derivatives give in general excellent results regarding yields and diastereoselectivities. Valinol and phenylglycinol are very effective auxiliaries for the addition of various organometallics (RMgX, RLi, $RCeCl_2$) to aromatic aldimines. Methoxyphenylglycinol leads to excellent yields for aliphatic aldimines and allows the sense of induction to be chosen by changing the reagent (organocerium or organocopper reagent). Finally valine methyl ester is a choice auxiliary for the synthesis of homoallylamines via the addition of a variety of allylmetals to either aliphatic or aromatic aldimines.

B. Addition To Chiral Imine Derivatives

1. Hydrazones

Organometallic reagents add to *N*,*N*-dialkylhydrazones derived from aldehydes to give hydrazines[19] which, after hydrogenolytic N−N cleavage, lead to substituted amines. This methodology has been applied to the stereo- and enantioselective syntheses of amines, starting from chiral hydrazones derived either from chiral aldehydes or from chiral hydrazines and, in a few cases, from both chiral aldehydes and chiral hydrazines. Several interesting synthetic applications have been described and will be reported in this section.

a. Addition to Chiral Hydrazones Derived from Chiral Aldehydes. A highly diastereoselective addition of organolithium reagents to α-alkoxy *N*,*N*-dimethylhydrazones **118**, reported by Claremon and collaborators 10 years ago[106] provides an attractive route to *syn*-2-amino alcohols **119** (eq 77).

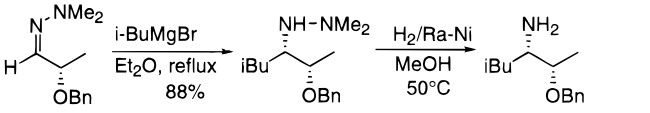


118 R = CH_2OCH_2Ph, CH_2Ph, $C(CH_3)_2OCH_3$ (eq 77)

119

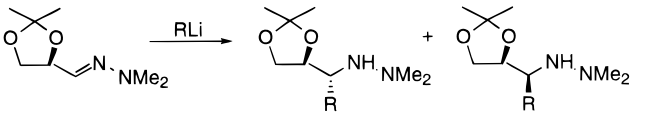
The syn selectivity is well explained assuming a Cram chelation model: effectively if the chelating effect of the oxygen atom is decreased by the presence of a bulky group (R = trityl), the anti diastereomer formed through a Felkin-Anh model is predominant (*anti*:*syn* = 10:1).

Grignard reagents are sluggish in this reaction but can give however useful results:[107] the addition of isobutylmagnesium bromide with the *N*,*N*-dimethylhydrazone **120** derived from (*S*)-ethyl lactate gave rise after hydrogenolysis to the *syn*-amino alcohol **121** without epimerization (eq 78).



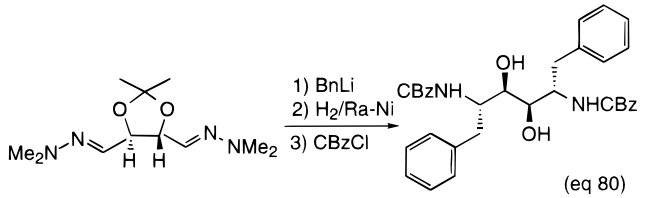
120 **121** (de > 96%) (eq 78)

The stereoselectivity of the addition of organolithium reagents depends on the nature of the reagents as shown by the results obtained with the dimethylhydrazone of (*R*)-glyceraldehyde acetonide (eq 79).



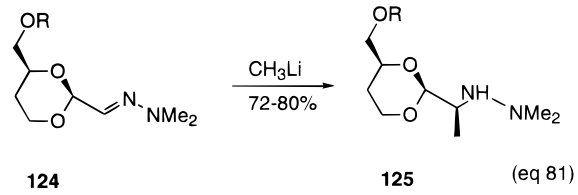
	syn	anti	
R = CH_3	*syn/anti* = 3/1	Ref. 106	(eq 79)
CH_2	= 3/1	Ref. 108	
$PhCH_2$	> 98/2	Ref. 109	

Extension of this organolithium addition method to bis-hydrazones gave excellent results.[108] Treatment of the bis-hydrazone **122** with benzyllithium give a single bis-hydrazine stereomer which was transformed to the diol **123** corresponding to a double chelation-controlled addition (eq 80).



122 **123** (eq 80)

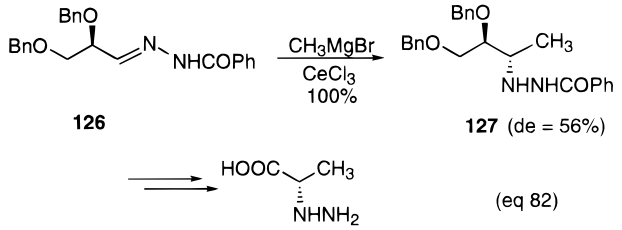
The diastereoselective addition of organolithium compounds to hydrazones **124** vicinal to chiral cyclic acetals derived from glyoxal shows that the chelating oxygen can be part of an acetal (eq 81). The best stereoselectivities were reported when R was sterically demanding.[110] This observation accounts for a chelation-controlled intermediate in which only the acetalic oxygen far from the bulky CH_2OR substituent is involved.



124 **125** (eq 81)

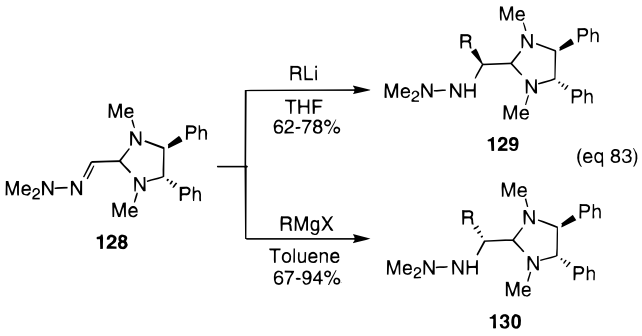
R = Me, de = 60% ; R = $PhCH_2$, de = 80% ; R = Ph_3C, de > 98%

It has been observed that an electron-attracting group bound to the sp^3 nitrogen can modify the chelation process and reverse the stereoselectivity:[111] the hydrazone **126** undergoes addition with CH_3MgBr without any selectivity and with $CH_3MgBr \cdot CeCl_3$ to give preferentially the anti stereomer **127** which has been transformed into (*S*)-hydrazinopropanoic acid (eq 82).



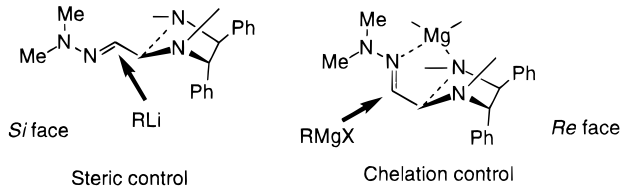
126 **127** (de = 56%) (eq 82)

Very interesting results were reported for the addition of organometallics to chiral hydrazones **128** derived from glyoxal where the acetal group has been replaced by an aminal protection (eq 83).[61,112]



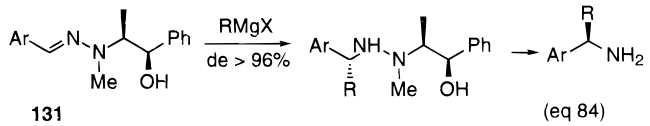
128 **129** **130** (eq 83)

Primary, secondary, and tertiary alkyl- as well as phenyl- and alkenyllithium reagents in THF give the single diastereomers **129** (de > 99%). In contrast, alkyl and phenyl Grignard reagents in toluene afford the opposite diastereomers **130** but still with an excellent diastereoselectivity (de > 99%). The observed selectivities have been assigned either to a steric control (RLi) or to a chelation control (RMgX). In the case of organolithium reagents in a strongly coordinating solvent such as THF, an approach of the nucleophile from the *re*-face (for an (*S,S*)-diamine) will be prevented by the sterically demanding pseudoequatorial NCH_3 substituent. In the case of Grignard reagents in a noncoordinating solvent such as toluene, a chelate could be formed involving one nitrogen of the imidazoline ring and one nitrogen of the hydrazine group. Due to this chelation the hydrazone group will adopt a different conformation and the pseudoequatorial NCH_3 substituent will mask in this case the *si*-face of the hydrazone moiety, giving rise to the opposite diasteromer.

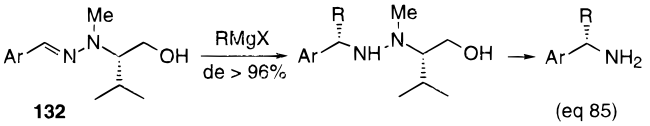


The hydrolysis of aminals occurs under very mild acidic conditions, preventing epimerization, so that this method is an excellent one for the synthesis of enantiomerically pure α-amino aldehydes.

b. Addition to Chiral Hydrazones Derived from Chiral Hydrazines. The first examples of addition of organometallic reagents to chiral hydrazones derived from chiral amines have been studied by Takahashi and collaborators.[113] The addition of alkyl Grignard reagents to hydrazones **131** and **132** derived respectively from arylaldehydes and either *N*-aminoephedrine or (*S*)-valinol proved to be highly stereoselective, leading after hydrogenolysis to (*R*)- or (*S*)-α-arylalkylamines (eqs 84 and 85).



131 (eq 84)

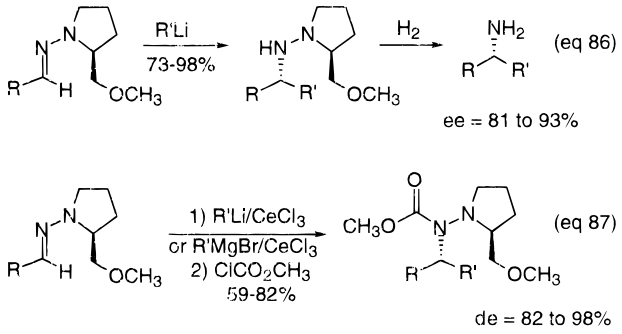


132 (eq 85)

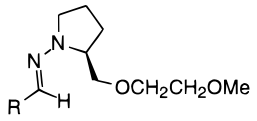
These reactions were assumed to proceed via chelated six-membered ring intermediates, but the sense of stereoselectivity was not well understood. Furthermore, this method was limited to aryl aldehydes and gave good selectivities only with alkyl Grignard reagents.

More general and efficient routes to enantiomerically pure amines have been described by nucleophilic addition of organolithium[114] or organocerium[115] reagents to SAM or RAMP hydrazones ((*S*)- or (*R*)-1-amino-2-(methoxymethyl)pyrrolidine hydrazones) (eqs 86 and 87).

As for the addition to imines, the less basic organocerium reagents gave excellent results even with enolizable hydrazones. The mechanistic details of these additions are still unknown, but the absolute stereochemistry of the products suggests that the RLi or "$RCeCl_2$" reagents are coordinated to the methoxymethyl group and deliver R to the *re*-face of the C=N bond.



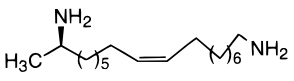
To improve the selectivity, several other proline-derived hydrazines have been prepared, and the reaction of their corresponding hydrazones with organocerium reagents have been tested.[116] The (*S*)-1-amino-2-((2-(methoxyethoxy)methyl)pyrrolidine (SAMEMP) hydrazones **133** gave the highest selectivities but only slightly higher than the selectivities observed with the SAMP hydrazones.



133 (SAMEMP Hydrazones)

A study related to the effects of reagent stoichiometry on the efficiency and the selectivity of organocerium additions to SAMEMP hydrazones shows that at least 2 equiv of the reagent is required to obtain acceptable yields.[117] This suggests that the chelating side chain coordinates to the first equivalent of organometallic reagent and makes it unavailable for nucleophilic addition. Furthermore, the results of this study show that a 1:1 $RLi/CeCl_3$ reagent stoichiometry affords the best yields and stereoselectivies. Combined with new efficient N−N bond cleavage protocols,[118] the addition of organocerium reagents to SAMP (RAMP) hydrazones provides an efficient method for the obtention of enantiomerically enriched amino compounds, and some applications of this reaction are reported below.

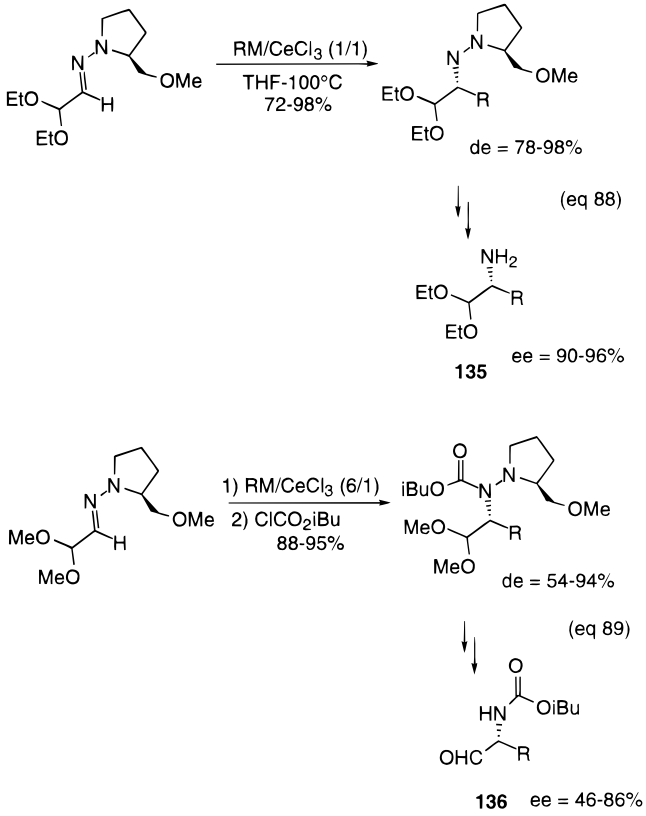
The synthesis of simple α-branched amines has been illustrated by the highly enantioselective (ee > 97%) synthesis of the ladybug defense alkaloid **134** termed harmonine.[119]



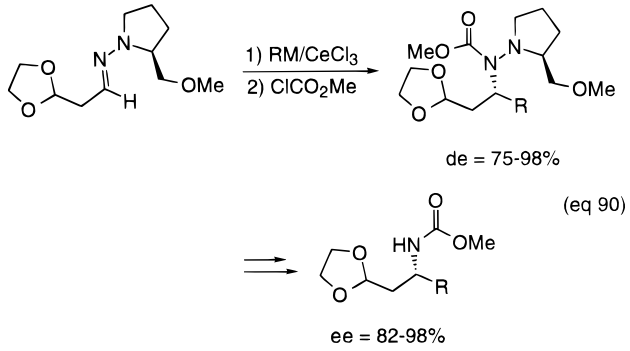
134

Additions of organocerium reagents to chiral α,α-dialkoxy acetaldehyde SAMP hydrazones proceed with high enantioselectivity and lead after further transformations to enantiomerically enriched α-amino acetals **135**[120] (eq 88) or *N*-protected α-amino aldehydes **136**[121] (eq 89).

A novel synthesis of *N*-protected *β*-amino acetals (easily transformed into *β*-amino acids) have been established via the addition of organocerium reagents



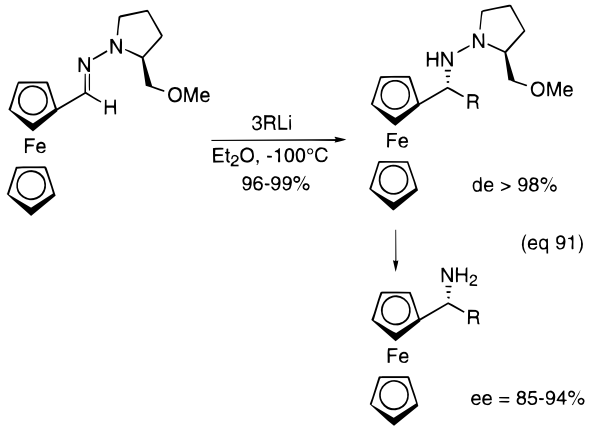
to 3,3-(ethylenedioxy)propanal SAMP hydrazone [122a] (eq 90).



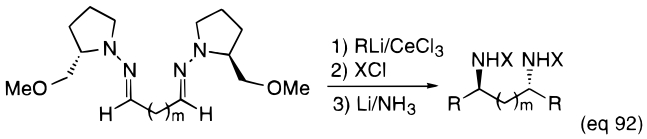
In some cases, replacement of cerium by ytterbium leads to better yields and higher selectivities, and the 1,2-addition of organoytterbium reagents $RLi/YbCl_3$ (3:1) to aldehyde SAMP hydrazones was the key step of new enantioselective syntheses of both enantiomers of coniine.[122b]

Simple organolithium reagents add to ferrocenecarboxaldehyde SAMP hydrazone to give the corresponding hydrazines in almost quantitative yields and with virtually complete asymmetric induction.[123] Subsequent hydrogenolysis (H_2, Ra−Ni) affords 1-ferrocenylalkylamines with however partial racemization (eq 91).

On the basis of the same method, a double addition of alkylithium reagents to the C=N bonds of ferrocene-1,1′-dicarbaldehyde bis-SAMP hydrazone followed by reductive N−N bond cleavage leads to the corresponding 1,1′-bis(1-aminoalkyl)ferrocenes with high enantiomeric excesses (ee = 90−98%) and *dl*:meso ratios up to 95:5.[124] Similar results are ob-



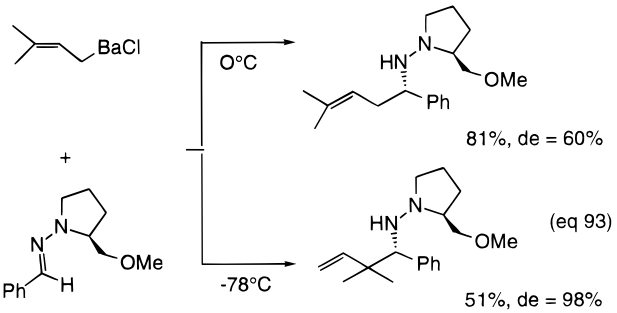
tained[125] by two successive 1,2-additions of organocerium reagents to bis-SAMP hydrazones **137** derived from 1,*n*-dialdehydes (eq 92). Allylcerium reagents



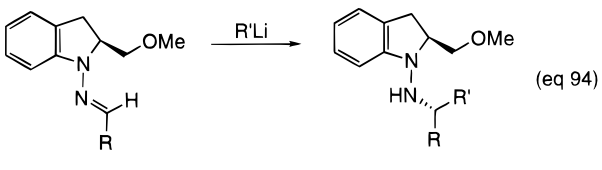
137 m = 0, 2, 3

ee ≥ 98%
de = 69-98%

in THF as well as allylic Grignard reagents in toluene add stereoselectively to aldehyde SAMP/RAMP hydrazones to give protected homoallylamines in good yields and high enantiomeric excesses (ee = 90−98%).[126] Prenyl baryum reagent adds also with good stereoselectivity to the SAMP hydrazone of benzaldehyde but with different regioselectivity depending on the reaction temperature (eq 93) as was already observed for the addition of the same reagent to imines.[41]



Removal of the chiral auxiliary by cleavage of the N−N bond is sometimes difficult and leads to partial racemization. It has been recently reported that additions of organolithium reagents to (*S*)-1-amino-2-(methoxymethyl)indoline (SAMI) hydrazones afford the corresponding chiral hydrazines with excellent stereoselectivity[127] and that the N−N bond cleavage required only mild conditions (H_2, $Pd(OH)_2$, rt) (eq 94).

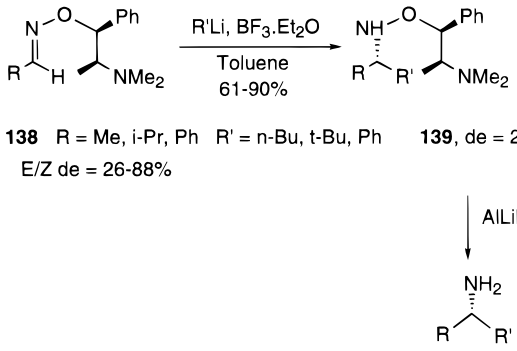


de = 94 to > 98%

2. Oxime Ethers

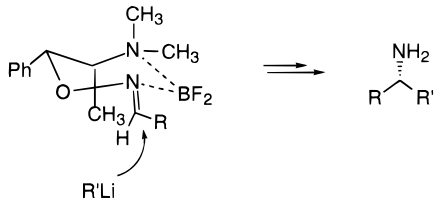
It has been reported in the first section of this review that organolithium compounds in the presence of BF_3·Et_2O add with fair to excellent yields to (*E*)- and (*Z*)-oxime ethers provided that toluene is used as the solvent.

This reaction has been applied to the enantioselective synthesis of amines by addition of organolithium reagents to chiral oxime ethers derived from chiral amines. A first report[128] describes the addition of alkyllithium reagents to the chiral oxime ethers **138** derived from ephedrine (eq 95).



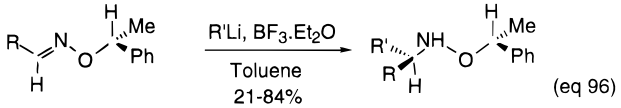
138 R = Me, i-Pr, Ph R' = n-Bu, t-Bu, Ph **139**, de = 20-88%
E/Z de = 26-88%

It appears that the addition reaction of organolithium reagents with these chiral oxime ethers is highly stereospecific, with the diastereoselectivity reflecting the ratio of *E* to *Z* isomers undergoing the reaction. The configuration of the stereogenic center created in the reaction has been explained by the formation of a complex such as **140** in which the axial methyl substituent of the *N*,*N*-dimethyl group controls the facial selectivity.



140

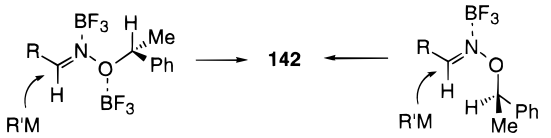
The addition of organolithium reagents as well as allyl Grignard to *O*-(1-phenylethyl)aldoximes **141** gave similar results,[129] the alkoxyamines **142** being formed in reasonable yields with diastereoselectivities controlled in part by the *E*:*Z* ratios of **141** (eq 96).



141 **142**

R = Ph, t-Bu, i-Pr R' = n-Bu, t-Bu, Ph de = 38-95%
E/Z, de = 52-100%

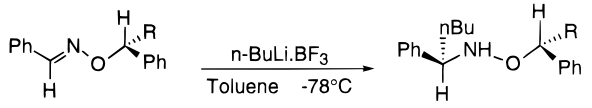
The two models **143** and **144** have been proposed for the BF_3-complexed oxime ethers, and the configuration of the newly formed sp^3-center is explained by an approach of the organometallic on the less hindered *re*-face of the C=N bond.



143 144

To improve the level of diastereoselectivity of this reaction, a series of oxime ethers containing different chiral auxiliaries were tested.[130] On the basis of models **143** and **144**, it was thought that increasing the size of the aryl or alkyl group would increase the stereoselectivity. When the phenyl is replaced by the bulkier naphthyl group, the diastereoselectivity of the addition is in fact decreased (55% de compared to 71% de). In contrast, increasing the size of the alkyl group improves significantly the selectivity as shown in Table 2.

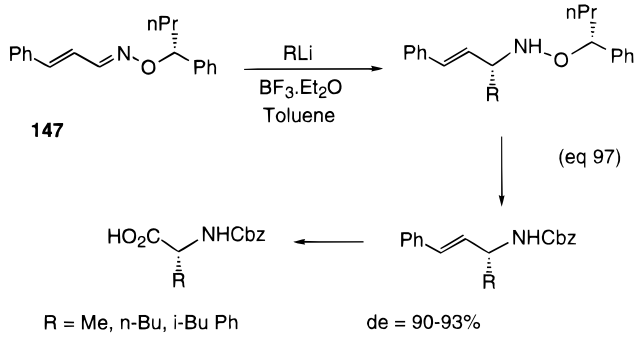
Table 2. Diastereoselective Addition of *n*-BuLi to (*E*)-Oxime Ethers 145



145 146

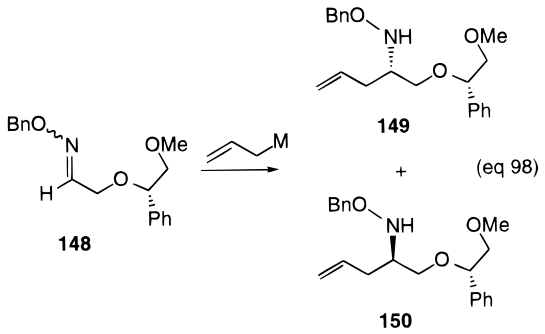
R	(*E*)-oxime ether	product	yield (%)	de (%)
Me	**145a**	**146a**	64	71
Et	**145b**	**146b**	91	93
^{n}Pr	**145c**	**146c**	87	90
^{i}Pr	**145d**	**146d**	74	>95
^{n}Bu	**145e**	**146e**	80	90

Since 1-phenylbutanol required for the formation of oxime ether **145c** is easily available in both enantiomeric forms, the auxiliaries derived from this alcohol, (*S*)- or (*R*)-*O*−(1-phenylbutyl)hydroxyamines (SOPhy or ROPhy), were selected for further applications. This method has been successfully applied to the synthesis of (−)-coniine starting from the SOPhy oxime of butyraldehyde[131] and to the obtention of α-amino acids[132] starting from the ROPhy oxime of cinnamaldehyde **147** (eq 97).

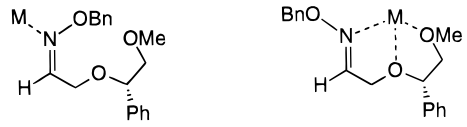


Intriguing results have been reported[133] for the addition of allyl reagents to the chiral alkoxymethyl *O*-benzyloximes **148** (eq 98).

No selectivity was observed starting from the (*Z*)-oxime ether **148**, but good to excellent stereoselectivity was found for the addition to the (*E*)-oxime



ether **148**. Furthermore, the selectivity depends on the nature of the metal: de(**149**:**150**) = 42:58 for M = MgBr, 86:14 for M = MgBr·$CeCl_3$, and 9:92 for M = Li or Li·$CeCl_3$. The authors assumed that the simultaneous coordination to metal of the three heteroatoms (only possible with the *E* isomer of **148**) is necessary for diastereofacial discrimination.

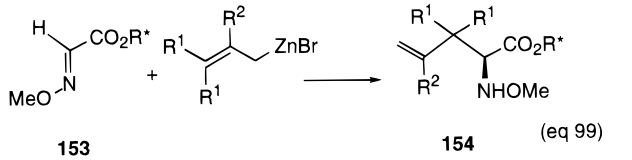


The sense of the stereochemical course of the addition is related to the coordination ability of the metal used.

The diastereoselective addition of organometallics to glyoxylic acid oxime ether derivatives could provide another convenient and efficient route to α-amino acids. The reaction of alkyllithium reagents with the chiral oxime ethers **151** and **152** of either glyoxylic acid or glyoxylic acid amide takes place with modest stereoselection (de = 30−40%) and is not really useful.[134]

151 152

Allylic zinc reagents gave much better selectivities. The addition of such reagents to the 8-(−)-phenylmenthyl ester of *O*-methyl glyoxylic acid oxime **153** gave the methoxyamino esters **154** with good to excellent diastereoselectivity (eq 99).[75]

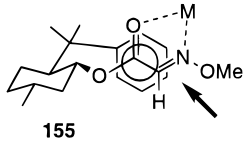


153 154

$R^1 = R^2 = H$ de = 74%

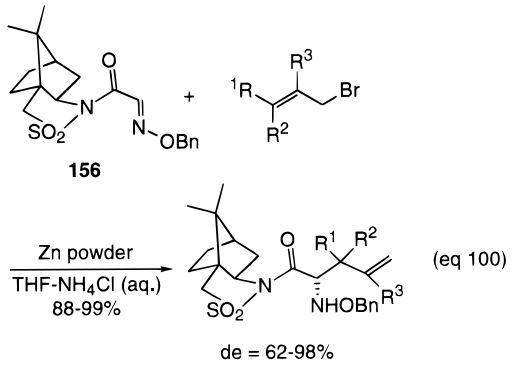
$R^1 = R^2 = CH_3$ de > 98%

This selectivity is rationalized by metal chelation of the syn form of **153** followed by an attack of the less-hindered *si*-face of the complex **155** formed.



155

Enantiomerically enriched allylglycine and analogues have been synthesized through the reaction of Oppolzer's camphor sultam derivative of *O*-benzyl glyoxylic acid oxime **156** with allylic bromides in the presence of powdered zinc in aqueous ammonium chloride (eq 100).[135]

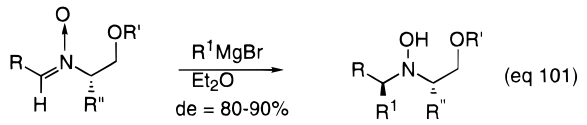


156 (eq 100)

It must be noted that a very high degree of stereocontrol (de = 92% to >95%) has very recently been achieved for the addition of aliphatic radicals to the same sultam derivative **156**, allowing the synthesis of enantiomerically pure alkyl α-amino acids.[136]

3. Nitrones

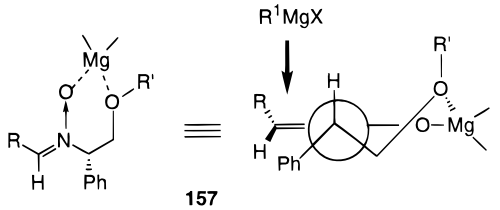
a. Addition to Nitrones Bearing Stereogenic N-Substituents. The diastereoselective additions of Grignard reagents to nitrones bearing α-stereogenic center have been published by Coates and collaborators.[137] Practically no selectivity is observed with nitrones bearing stereogenic α-arylethyl groups on nitrogen. However, high diastereoselectivity is obtained in the addition of Grignard reagent to nitrones bearing on nitrogen potentially chelating stereogenic groups such as alkoxy groups derived from phenylglycinol or valinol (eq 101).



(eq 101)

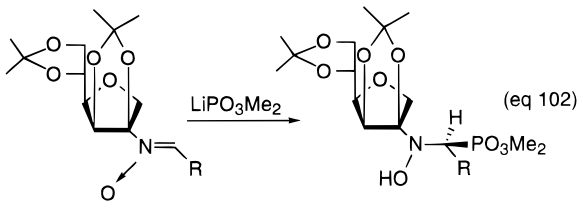
R = Ph,Me, Et R' = Me, Bn R" = Ph, i-Pr R^1 = Me, Ph, Et

The major stereomers formed can be rationalized in terms of the chelated transition state model **157**. An approach of the Grignard reagent from the less hindered side (anti to the phenyl or the isopropyl group) of the six-membered magnesium chelate **157** accounts for the stereochemistry of the major isomer obtained.



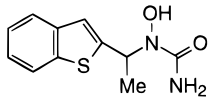
157

The *N*-chiral substituent can also be a carbohydrate derivative, and a series of papers describing the addition of lithium dialkyl phosphites to *N*-glycosyl nitrones (eq 102) have been published.[138]



(eq 102)

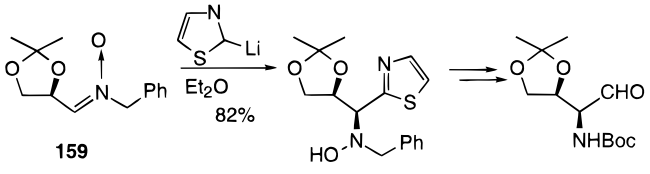
The diastereoselectivity observed has been explained on the basis of a stereoelectronic effect controlling the conformation of the starting nitrone followed by a steric effect responsible of the direction of nucleophilic attack. This reaction has been applied to the synthesis of either enantiomer of zileuton **158**, an inhibitor of mammalian 5-lipoxygenase constituting a new class of therapeutic agents in asthma.



(±) **158**

The key steps of the described synthesis rely on the diastereoselective additions of Grignard reagents to mannose-derived *N*-glycosyl nitrones.[139,140]

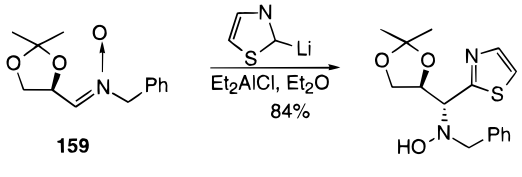
b. Addition to Nitrones Derived from Chiral Aldehydes. Dondoni and collaborators have devised a very interesting method for the homologation of aldehydes to enantiomerically enriched α-amino aldehydes (aminohomologation) via the diastereoselective addition of 2-lithiothiazole to *N*-benzyl nitrones derived from chiral nonracemic aldehydes. Treatment of the readily available nitrone **159** derived from D-glyceraldehyde acetonide with 2-lithiothiazole affords with high stereoselectivity (de = 84%) the syn diastereomer **160** (eq 103), which after deoxygenation, debenzylation, and thiazole to formyl transformation gives the *N*-Boc protected amino aldehyde **161**.[141]



159 **160** **161**

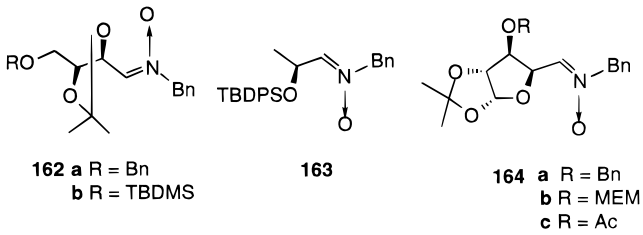
(eq 103)

When the nitrone is precomplexed with the Lewis acid Et_2AlCl, a remarkable reversal of diastereoselectivity in favor of the anti diastereomer is achieved (eq 104).[141,142]



159 (eq 104)

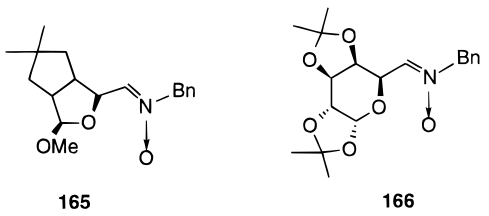
The same trend of facial stereodifferentiation without any additive or in the presence of the Lewis acid Et_2AlCl has been observed for the addition of lithiothiazole to the various nitrones **162**−**166**.[143]



162 a R = Bn
b R = TBDMS

163

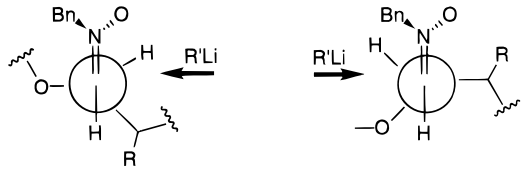
164 a R = Bn
b R = MEM
c R = Ac



165 **166**

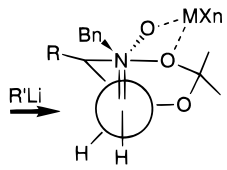
The level of stereoselectivity is dependent on the structure of the nitrones used: the best results (de(syn) = 80%; de(anti) = 80−90%) are obtained with the nitrones **164a**−**c** whereas no selectivity is observed with nitrone **163** in the same conditions.

In the absence of complexing agents, the observed syn selectivity has been best rationalized by the transition state model **167** similar to the model developed by Houk[144] for nucleophilic additions to alkenes. However, when R is sterically demanding, the proposed transition state **168** accounts for the lower syn selectivity.



167 ⟶ *syn* **168** ⟶ *anti*

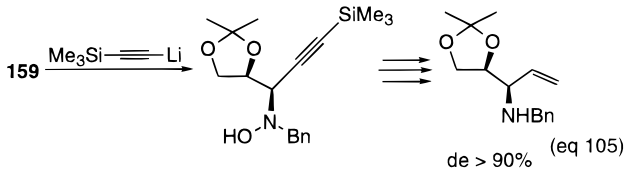
The anti selectivity observed after precomplexation of the nitrones with Et_2AlCl can be explained by the formation of the six-membered chelate **169** followed by an approach of the reagent from the less hindered side of this chelate.



169 ⟶ *anti*

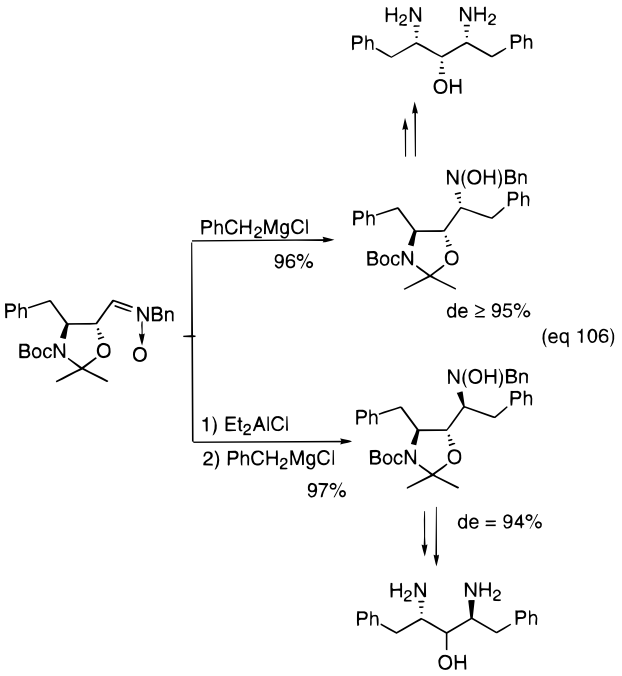
These diastereoselective additions are not limited to 2-lithiothiazole: 2-lithiofuran adds to α-alkoxy nitrones with similar selectivities so that after oxidation of the furan ring, either diastereomer of α-amino acids can be formed.[145] An application of this latter reaction to the elegant and efficient synthesis of (+)-polyoxin J, one component of a class of nucleoside antibiotics, has been recently reported.[146]

The addition of vinyl and ethynyl organometallic reagents to the nitrone **159** derived from D-glyceraldehyde gives with good to excellent selectivies *syn*- or *anti*-allyl- and -propargylhydroxyamines which are easily converted into the corresponding allylamines.[147] One illustration of these reactions is given in eq 105.



de > 90% (eq 105)

Benzylmagnesium chloride adds with high stereoselectivity[148] to β-amino, α-hydroxy nitrones to afford dibenzyl-1,3-diamino-2-propanols, the key core units of potent and selective inhibitors of HIV-1 protease (eq 106).

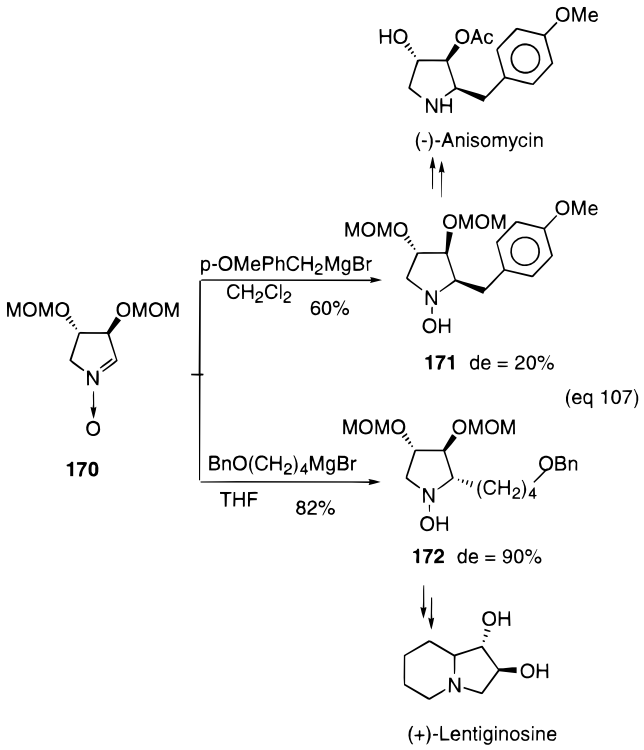


(eq 106)

The scope of this methodology has been extended to the stereoselective nucleophilic addition of a variety of Grignard reagents to α,β-dialkoxy nitrones,[149] to α-amino nitrones,[150] and to protected nitrones derived from L-serine,[151] allowing the synthesis of enantiomerically enriched 3-amino-1,2-diols, 1,2-diamines, and 2,3-diaminobutanoic acids, respectively.

c. Addition to Chiral Cyclic Nitrones. The stereoselective additions of Grignard reagents to the cyclic nitrones **170**, derived from L-tartaric acid, constitute the key steps of the synthesis of the antibiotic (−)-anisomycin[152] or of the glycosidase inhibitor (+)-lentiginosine.[153] Thus, the addition of (4-methoxybenzyl)magnesium chloride or of (4-(benzyloxy)butyl)magnesium bromide in THF to the nitrone **170** affords, respectively, with poor (de = 20%) or high (de = 90%) selectivity a mixture of stereomers in which the 2,3-trans isomers predominate (eq 107).

A reversal of selectivity in favor of the 2,3-cis isomer **171** is observed when the nitrone **170** is precomplexed with $MgBr_2$. These different levels of selectivity are not well understood. Standard trans-

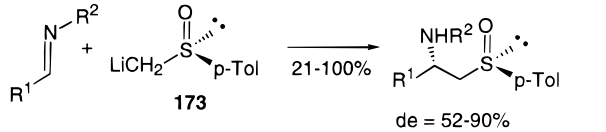


formations allow the synthesis of (−)-anisomycin from **171** and (+)-lentiginosine from **172**.

C. Addition of Chiral Organometallic Reagents to Imines and Imine Derivatives

The addition of chiral, nonracemic, organometallic reagents to prochiral imines or imine derivatives constitutes a methodology for the synthesis of enantiomerically enriched amines, which has received only limited attention.

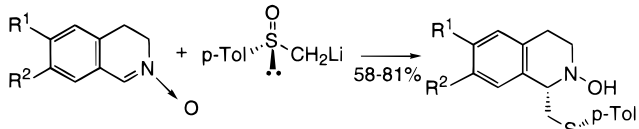
Tsuchihashi and collaborators[154] were the first to report that the addition of (*R*)-(+)-methyl *p*-tolyl sulfoxide **173** to *N*-benzylideneaniline was a highly diastereoselective reaction. The generality of this addition has been shown for imines derived either from aromatic[155] or from aliphatic[156] aldehydes (eq 108).



R^1 = Ph, 4-OMePh, Me, Et, iPr, iBu

R^2 = Ph, 4-OMePh, Me, nPr, iPr, cyclopropyl, n-pentyl

The addition of racemic lithiated methyl phenyl sulfoxide to various nitrones[157] appears to be fairly stereoselective (de = 0−72%), the highest product diastereoselection being observed with the cyclic isoquinoline nitrone **174b**. However, the addition of (*R*)-methyl *p*-tolyl sulfoxide anion to the same compound without additive gives a quite low diastereomeric ratio (de = 28% only).[158] Addition of 1 equiv of the lithium salt of quinidine improves the diastereomeric ratio dramatically: de = 76−88% for the various 3,4-dihydroisoquinoline *N*-oxides **174a**−**e** (eq 109). The high diastereoselectivity may be explained



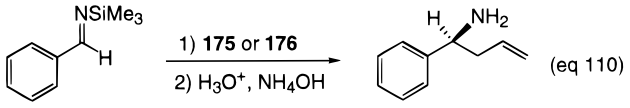
174 a) $R^1 = R^2 = OMe$
b) $R^1 = R^2 = H$
c) $R^1 = R^2 = OCH_2O$
d) $R^1 = MeO$, $R^2 = PhCH_2O$
e) $R^1 = PhCH_2O$, $R^2 = MeO$

by formation of a "facial discriminating reagent derived from quinidine and α-sulfinyl carbanion and its enantioselective addition to nitrones".

Although a number of chiral allylic boron reagents have been developed for enantioselective addition to aldehydes, they have scarcely been used for addition to the carbon−nitrogen double bond. The first report of this kind of reaction[159] described the additions of dialkyl-2-allyl-1,3,2-dioxaborolane-4,5-dicarboxylates **175** and of B-allyldiisopinocampheylborane **176**

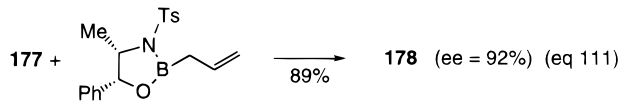
175 **176**

to the *N*-(trimethylsilyl) imine **177** derived from benzaldehyde. After hydrolysis the homoallyl primary amine was obtained in good yields (54−90%) with enantioselectivities up to 73% (eq 110).



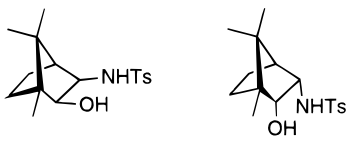
177 **178**

Arylaldimines, sulfeneimines, and oxime ethers were also asymmetrically allylated with **176,** but their reactivity was found to be much lower. *N*-(Trimethylsilyl) imines were then chosen for further investigations of enantioselective allylation with chiral allylboron reagents prepared from triallylborane and an appropriate chiral modifier. A variety of chiral modifiers were tested[160] including chiral diols, hydroxy acids, *N*-sulfonylated amino acids, and *N*-sulfonyl amino alcohols. The best results were obtained with B-allyloxazaborolidine **179** derived from (−)-norephedrine (eq 111).



179

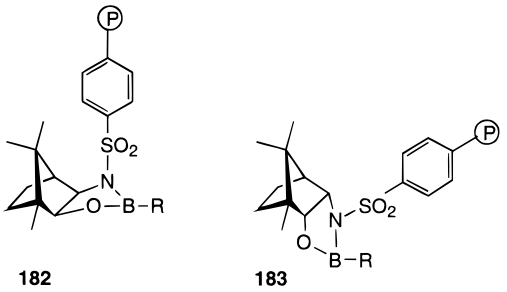
The chiral *N*-tosyl amino alcohols **180** and **181** were also found to be very efficient ligands for boron,



180 **181**

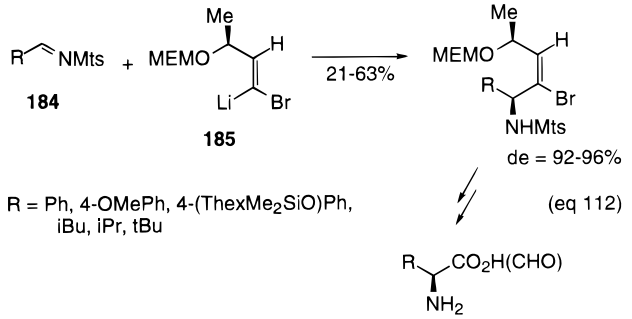
leading, respectively, to homoallylamines of *S* or *R* absolute configuration.

Still more interesting was the recent report[161] on the use of polymer-supported chiral allylating reagents **182** and **183** derived from **180** and **181**.



N-(Trimethylsilyl)benzaldehyde imine **177** reacts with the polymeric chiral reagents to afford the corresponding primary homoallylamines in high yields (89−94%) and very good enantioselectivities (ee = 75−90%). Furthermore, under the same reaction conditions, enantioselectivities obtained from polymer-supported reagents are superior to those obtained from nonpolymerized reagents in solution. This methodology seems quite interesting and deserves further investigation.

A synthesis of α-amino acids or α-amino aldehydes which involves the stereoselective addition of the chiral vinyllithium reagent **185** to prochiral mesitylsulfonyl imines **184** has been newly disclosed.[162] This reaction works with excellent stereoselectivities in all the cases examined but gives only poor yields for imines derived from aliphatic aldehydes (eq 112).



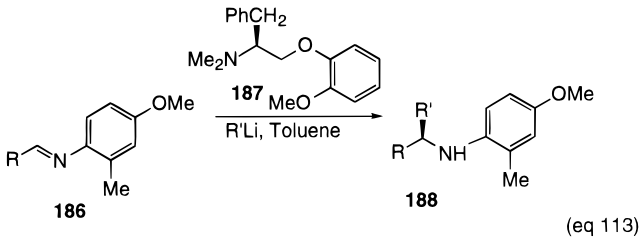
Chiral, nonracemic organometallic reagents can also be generated "in situ" by the addition of a homochiral ligand to an achiral reagent, and this methodology will be described in the next paragraph.

D. Addition in the Presence of an External Homochiral Auxiliary

The asymmetric addition of organometallic reagents to the C=N bonds of imines or imine derivatives in the presence of a stoichiometric or catalytic amount of a chiral ligand has been neglected for a long time but is now an active field of investigation. An excellent feature article reviewing the state of art of this reaction has been very recently published,[1e] and we will concentrate on the reports concerning the last developments of this new method of stereoselective synthesis of amino compounds.

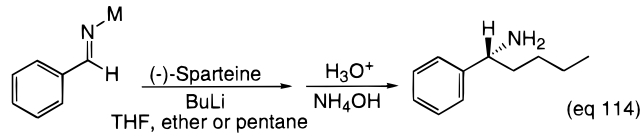
1. Organolithium Reagents

Tomioka and co-workers[163] were the first to report the addition of organolithium reagents to *N*-aryl imines in the presence of homochiral catalysts. A systematic survey of the reaction conditions showed that the chiral amino ether **187** was an excellent asymmetric controller[164] which can be used in substoichiometric amounts.[165] Some representative results[166] concerning imines **186** derived from arylaldehydes and 2-methylanisidine are given in eq 113. If excellent results have been obtained for the stoichiometric reaction, the level of enantioselectivity reported for the catalytic reaction remained moderate.

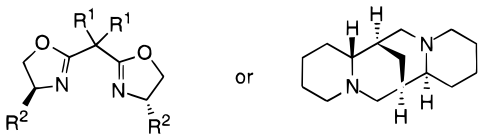


1°) Imine / R'Li/**187** = 1 / 2 / 2.6 -100°C Yields = 90-98% ee = 70-90%
2°) Imine / R'Li/**187** = 1 / 2 / 0.3 -42°C Yields = 75-88% ee = 47-66%

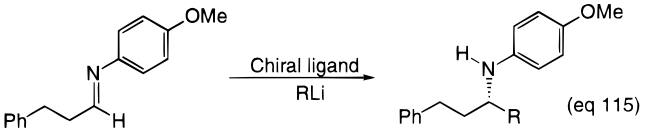
The enantioselective addition of organolithium compounds to *N*-silyl imines, *N*-alumino imines, and *N*-boryl imines in the presence of different chiral promoters such as alcohols, diols, amino alcohol, and diamines was reported by Itsuno and co-workers.[167,168] All the reactions are described in the presence of stoichiometric amounts of the chiral ligand, and the best results were obtained by addition of the preformed (−)-sparteine−BuLi complex to benzaldehyde *N*-diisobutylalumino imine in pentane at −78 °C (80% yield, 74% ee) (eq 114). The use of polymer-supported promoters allows the asymmetric alkylation of an *N*-boryl imine to give the primary amine with 44% ee.



(−)-Sparteine had been used with success for the first time in such reactions by Denmark and coworkers.[45] Excellent results have been obtained for addition of organolithium compounds RLi (R = Me, *n*Bu, Ph, vinyl) to imines derived from aryl- as well as alkylaldehydes in the presence of (−)-sparteine or chiral bis-oxazolines **189**. The chiral ligand was used



R1 = Et, i-Bu
R2 = CH_2Ph, iPr, t-Bu, CMe_2Ph, $CMePh$, CPh_3

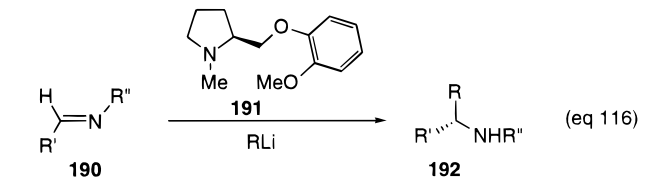


R = Me, nBu, vinyl substrate / RLi / **189** (R^1 = Et, R^2 = tBu) = 1 / 1 / 0.2
Yields = 81-92% ee = 51-82%

R = Me, nBu, Ph substrate / RLi /(-)-sparteine = 1 / 2 / 1
Yields = 71-91% ee = 72-91%

in stoichiometric or catalytic amounts. Some representative results are given in eq 115. High enantioselectivities were observed even when the chiral promoter (**189** or (−)-sparteine) was used in catalytic amounts.

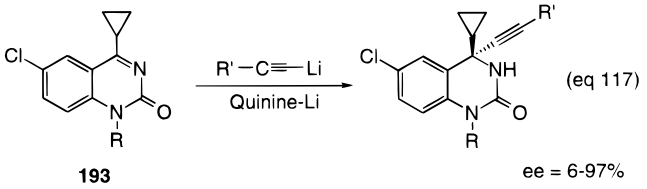
The (*S*)-proline-derived chiral ligand **191**, similar to the amino ether **187** used by Tomioka, catalyzes the asymmetric addition of organolithium compounds to arylimines **190** with relatively low enantioselectivity (1.5−21% ee) but produced the (*S*)-enantiomer **192** of the resulting chiral amine (eq 116). The reason for the opposite sense of asymmetric induction exerted by catalysts **187** and **191** is not yet clear.[169]



190 **192**

R' = Ph, PhCH=CH R" = Ph, 4-OMePh Yields = 37-96%
R = Me, nBu, Ph ee = 1.5-21%

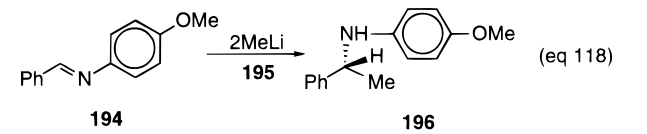
During the search of new catalysts for the additions of alkyllithium to imines, it has been reported[170] that lithium alkoxide of quinine can be used as a stoichiometric chiral ligand to carry out highly asymmetric addition of lithium acetylide to cyclic *N*-acyl imines **193** (eq 117).



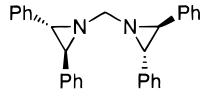
193 ee = 6-97%

R = methyl, benzyl, 9-anthrylmethyl, 4-chlorobenzyl, 4-methoxybenzyl
R' = 2-pyridyl, 3-pyridyl, 4-pyridyl, phenyl, butyl, trimethylsilyl, 4-methoxyphenyl, 4-chlorophenyl

Finally a preliminary account of the use of chiral aziridines such as **195** has been recently published by Tanner[171] for the addition of MeLi to the imine **194** (eq 118).



194 **196**

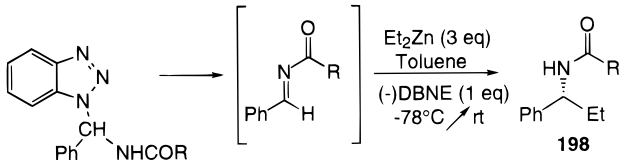


195 (1 eq) Yield = 47% ee = 67%
195 (0.1 eq) Yield = 70% ee = 14%

195

2. Organozinc Reagents

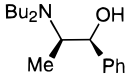
Although the catalytic enantioselective addition of organozinc reagents to carbonyl compounds has proved very efficient, these reagents failed to react with nonactivated *N*-silyl,[167] *N*-phenyl, or *N*-benzyl[172] imines even in the presence of chiral diols or amino alcohols. The use of activated *N*-acyl or *N*-phosphinoyl imines has been necessary to observe enantioselective alkylation promoted by chiral amino alcohols of carbon−nitrogen double bonds with dialkylzinc compounds. A recent report of Katritzky and coworkers[173] described the enantioselective addition of diethylzinc to *N*-(amidobenzyl)benzotriazoles **197** acting as masked *N*-acyl imines. This reaction catalyzed by 1 equiv of the chiral amino alcohol *N*,*N*-dibutylnorephedrine (DBNE) afforded chiral *N*-(1-phenylpropyl)amides **198** with up to 76% enantiomeric excess (eq 119).



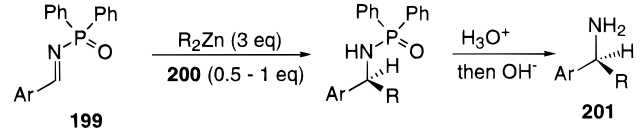
197 **198**

R = Me, OMe, Et, iPr, Ph Yields = 5-82%
ee = 21-76%

(-)DBNE =



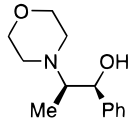
The first publication of Soai and collaborators reporting the use of *N*-diphenylphosphinoyl imines appeared at the same time.[172] In this paper the reactivity of three *N*-diphenylphosphinoyl imines **199a**−**c** was examined in the presence of dialkylzincs and a stoichiometric or catalytic amount of chiral ligand **200** (eq 120).



199 **201**

R = Et, Me, nBu

a Ar = Ph
b Ar = 2-Naphtyl
c Ar =4-MeC_6H_4

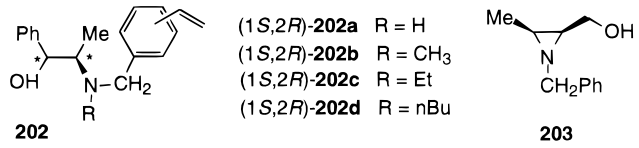


200 (1*S*,2*R*)

With a stoichiometric amount of **200**, the reaction of imines **199** with Et_2Zn gave the corresponding (*S*)-phosphinamide with excellent yields (75−84%) and enantioselectivity (90−91%). Equivalent results were obtained by methylation or *n*-butylation of **199a** with dimethyl- or dibutylzinc (85−87% ee). When only 0.5 equiv of the chiral amino alcohol **200** was used, good levels of enantioselectivity were preserved (85−87% ee), but a drop in the chemical yields was observed (57−69%) for the addition of Et_2Zn to **199a**−**c**. Enantiomerically enriched primary amines **201** were

easily obtained without racemization by acid hydrolysis of the phosphinamides.

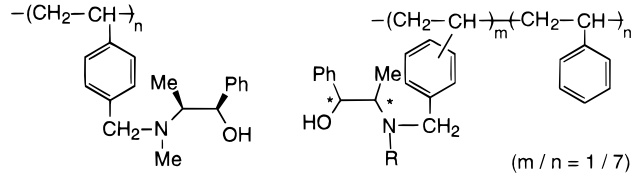
Better enantioselectivities were recently observed in the presence of the chiral ligands **202**[174a] or **203**.[174b]



202 **203**

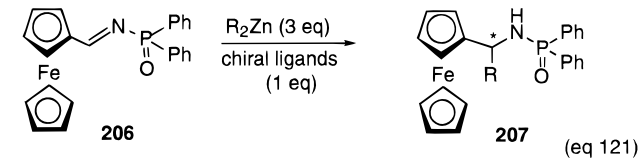
For example, when the *N*-methyl-*N*-vinylbenzylnorephedrine (1*R*,2*S*)-**202b** was used stoichiometrically, the reaction of imine **199a** with Et_2Zn afforded the corresponding (*R*)-phosphinamide in 81% yield and 95% ee. The same (R)-phosphinamide was obtained in 63% yield and 94% ee in the presence of a stoichiometric amount of **203**.

Very interesting results have also been obtained using heterogeneous chiral ligands which can facilitate separation processes of the product from the chiral ligand. It has been shown that diethylzinc adds highly enantioselectively to the *N*-diphenylphosphinoyl imine **199a** in the presence either of (1*R*,2*S*)-ephedrine supported on polystyrene **204**[175] or of copolymers of *N*-alkyl-*N*-vinylbenzylnorephedrine with styrene and divinylbenzene **205**.[174a] When solvents possessing aliphatic and aromatic moieties in the same molecule such as alkylbenzenes (toluene, xylenes) were used, fair yields (30−56%) and high levels of enantioselectivity (64 to 88% ee) were observed.



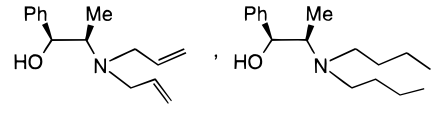
204 **205**

Ferrocenyl diphenylphophinyl imine **206** has also been found to be an excellent substrate for enantioselective alkylation with dialkylzincs[176] in the presence of chiral ligands (eq 121). When the reaction



206 **207** (eq 121)

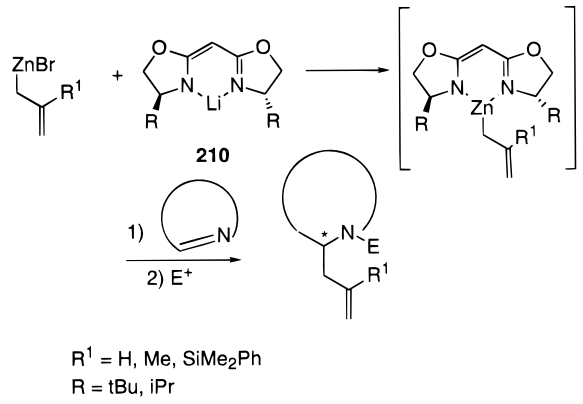
chiral ligands : **200**,



208 **209**

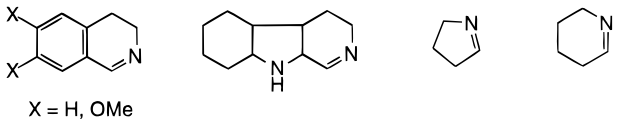
was performed at room temperature with Et_2Zn in the presence of **200**, the (+)-*N*-(diphenylphosphinyl)-ferrocenylamine **207** was obtained in 67% yield with 88% ee. When the ratio of **200** against the imine was decreased from 1 to 0.5, the yield was reduced (34%) but almost no decrease of the ee was observed (86% ee). This proves that only R_2Zn coordinated with the chiral ligand is effective in the reaction.

Nakamura[177] has also observed an enantioselective allylzincation of cyclic aldimines in the presence of lithiated bis-oxazoline ligands **210**.

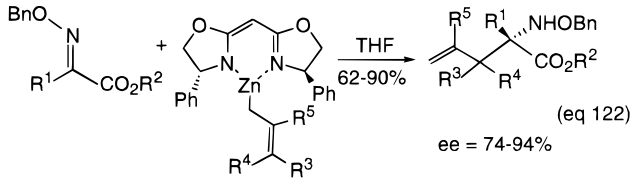


210

The best results were obtained with a ligand derived from (*S*)-valine (R = ^{i}Pr), and very high enantioselectivities (77−99% ee) were observed in the allylation of various cyclic imines:



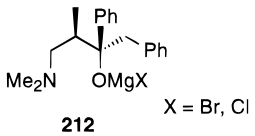
A similar bis-oxazoline ligand has been used for the asymmetric allylation of glyoxylate-derived oxime ethers with various allylic zinc reagents.[178] The best yields and selectivities were obtained with the reagent **211** possessing two phenyl substituents (eq 122).



211

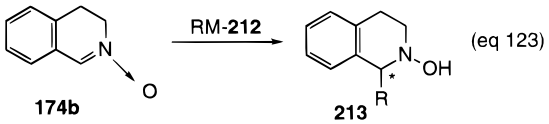
3. Organomagnesium Reagents

Nitrones possess an electronegative oxygen which could strongly coordinate to metals. If the metal is already coordinated to a chiral external auxiliary, tight aggregates (nitrone−metal−chiral auxiliary) could be formed and entail enantiofacial differentiation in the nucleophilic addition of organometallic reagents. On the basis of this concept, Ukaji and collaborators[179] have examined the addition of magnesium and zinc reagents to 3,4-dihydroisoquinoline *N*-oxide **174b** in the presence of stoichiometric amounts of the magnesium alkoxide derived from (2*S*,3*R*)-4-(dimethylamino)-1,2-diphenyl-3-methyl-2-butanol **212** (Chirald).



212

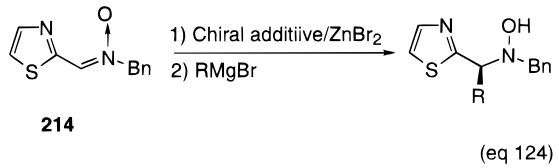
Grignard reagents (MeMgBr or EtMgBr) in the presence of 1 equiv of $MgBr_2$ as a second additive give rise to (*S*)-**213** in modest yields but with enantiomeric excess up to 90% (eq 123).



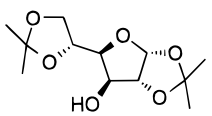
Dialkylzinc reagents lead to the opposite enantiomer (*R*)-**213** in better yields but with lower enantioselectivities (ee = 57−66%). The stereochemical course of the organomagnesium addition might be rationalized by the formation of rigid aggregates involving the Grignard reagents which forced the reagent to attack the *si*-face of the nitrone. In contrast, dialkylzinc could not participate in the formation of aggregates and approach the nitrone from the less hindered *re*-face.

If the chiral auxiliary **212** is used in catalytic amount (0.2 equiv) in the addition of dialkylzinc reagents to the nitrone **174b**, the enantiomeric excess is considerably lowered (33% ee compared to 65% ee with 1 equiv of **212**). However, further addition of 0.3 equiv of an achiral auxiliary such as bromomagnesium triphenylmethoxide restores the enantioselectivity.[180] This catalytic reaction has been extended with success to different cyclic nitrones.

On the basis of a similar approach, the addition of Grignard reagents to *N*-benzyl α-(2-thiazolyl) nitrone **214** in the presence of various chiral auxiliaries (alcohols, amines, diols, amino alcohols) has been recently reported[181] (eq 124). The highest selectivity



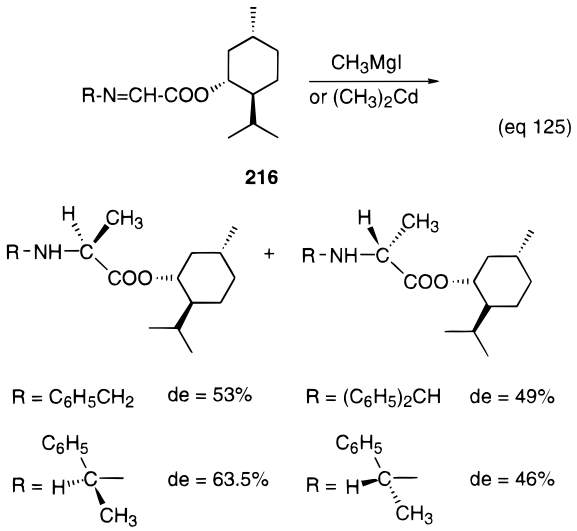
in the addition of phenylmagnesium bromide to the nitrone **214** was obtained with the use of 0.5 equiv of D-glucose diacetonide **215** and 0.5 equiv of $ZnBr_2$ (74% ee). In the same conditions methyl-, ethyl-, and



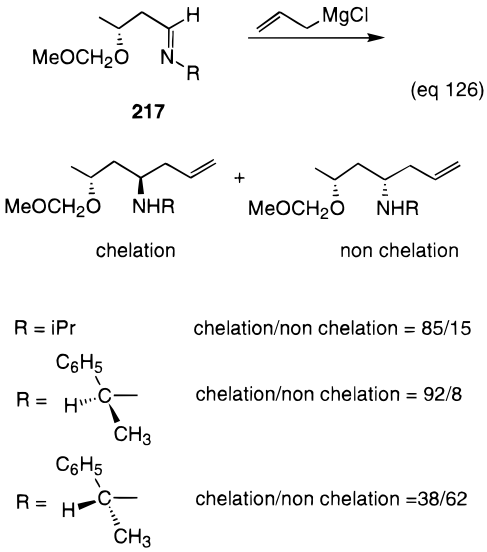
benzylmagnesium bromides add to the nitrone **214** to give the corresponding hydroxyamines in good yields (66−74%) but modest ee values (41−67%). The effect of $ZnBr_2$ can be rationalized by assuming its active participation in the formation of aggregates.

E. Double Induction

Not much attention had been paid till now to double induction, using imines (or imine derivatives) derived from both chiral amines and chiral aldehydes. The pioneering work of Kagan and Fiaud[182] showed that the diastereoselectivity of the addition of CH_3MgI or organocadmium compounds to imines **216** derived from (−)-menthyl glyoxylate and different amines is practically independent of the configuration of the amine used (eq 125).

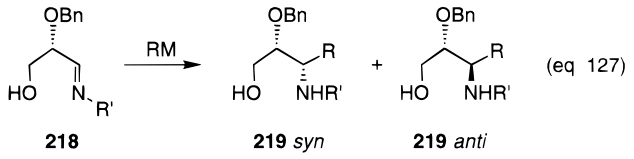


However, a few years later Yamamoto and collaborators[183] found that the concept of double stereodifferentiation could be applied to the reaction between achiral allylmagnesium chloride and imines derived from β-alkoxy aldehydes and α-methylbenzylamine (eq 126). The *R*,*S* combination was a matched pair for the chelation product.



In contrast, it has been shown in the same work that the chirality of the nitrogen substituent has no effect on the addition of allylmagnesium chloride to α-alkoxy imines. In agreement with this finding it has also been reported[184] that the stereoselectivity of the addition of Grignard compounds to imines of 2-*O*-benzyllactaldehyde is only slightly changed when (*R*)- or (*S*)-1-phenylethyl replaces the *N*-benzyl substituent of the imine. Thus, in these last two cases auxiliary control does not override substrate induction.

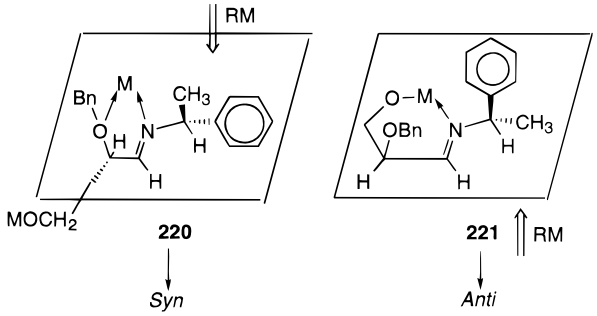
An interesting case of double stereodifferentiation has been very recently described by Jäeger et al.[185] for the addition of stabilized Grignard reagents to the imines **218** of 2-*O*-benzylglyceraldehyde (eq 127), and some representative results are given below.



218 **219** *syn* **219** *anti*

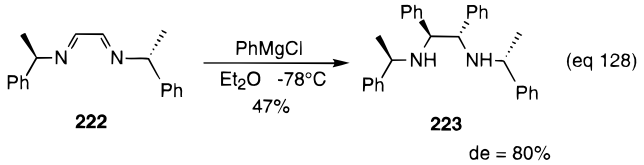
R'	RM	Yield	*Syn/Anti*
$CHPh_2$	BuMgBr	94	78 : 22
$CHPh_2$	BnMgBr	73	83 : 17
(*R*)-CHMePh	MeMgBr	67	92 : 8
	BuMgBr	86	98 : 1
(*R*)-CHMePh	BnMgBr		
(*S*)-CHMePh	MeM[illegible]	95	6 : 94
	BuMgBr	82	14 : 86
(*S*)-CHMePh	BnMgBr	96	67 : 33

To explain these results, two competing intermediate chelates have been proposed: a five-membered chelate **220** operating from (*R*)-(1-phenylethyl) imine and favoring the *syn*-amine, and a six-membered chelate **221** from (*S*)-(1-phenylethyl) imine and favoring the formation of the anti product.



The approach of the reagent to these chelates is controlled by the conformation of the 1-phenylethyl group depicted in the drawing as the one known to be preferred in related systems (minimization of allylic $A^{1,3}$ strain[186]).

Excellent diastereoselectivities have been observed for the addition of either allyl[187] or non stabilized[188] Grignard reagents to chiral bis-imines (eq 128). The

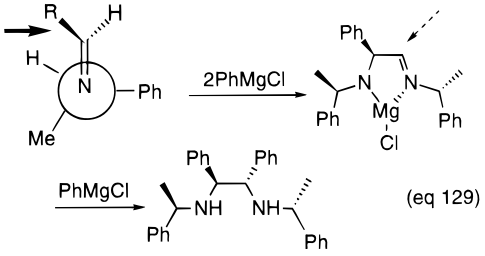


222 **223**

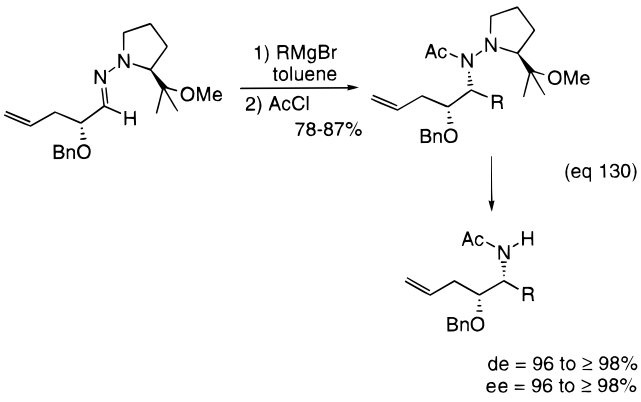
de = 80%

stereoselectivity of the first addition of the phenylmagnesium chloride can be rationalized through a control of the *N*-substituent: approach of the reagent from the least hindered face of the more stable conformer involved by Yamamoto[75] for such reactions.

In the second addition, the stereoselectivity was mainly controlled by chelation with the α-amino group created in the first reaction (eq 129). This selectivity could also be reinforced by a 1,3 effect of the chiral *N*-imine substituent. However, such a double stereodifferentiation has still not been proved.



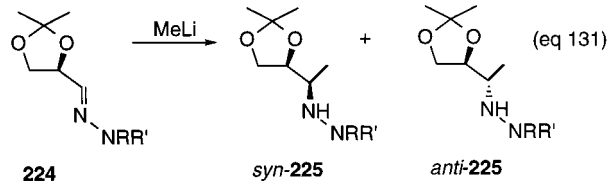
In the course of the diastereo- and enantioselective synthesis of *syn*-1,2-amino alcohols, it has been reported that Grignard reagents add to chiral hydrazones derived from both chiral aldehydes and hydrazines with a very high facial diastereoselectivity[189] (eq 130).



de = 96 to ≥ 98%
ee = 96 to ≥ 98%

The excellent stereoselectivity can be explained by a double stereodifferentiation: in addition to the directing effect of the chiral hydrazone function, the α-benzyloxy group should favor the same configuration according to the chelation model.

Such a double induction has been very recently confirmed by the addition of methyllithium to the SAMP and RAMP hydrazones of (*R*)-glyceraldehyde acetonide (eq 131). The addition to the SAMP

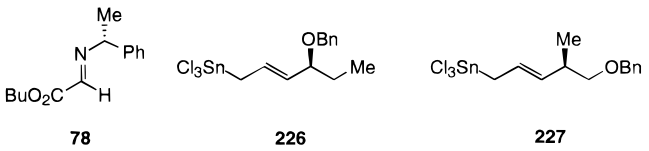


224 *syn*-**225** *anti*-**225**

Dimethyl hydrazone	*syn/anti* = 75/25	ref 106
SAMP hydrazone	*syn/anti* = 98/2	ref 114b
RAMP hydrazone	*syn/anti* = 10/90	ref 114b

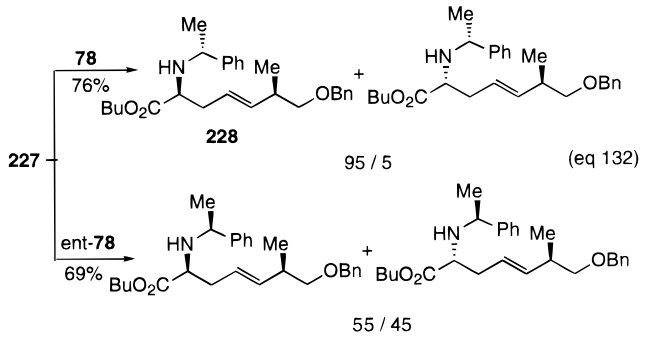
hydrazone corresponds to a matched process, and the addition to the RAMP hydrazone represents a "mismatched" one. Furthermore, the stereochemistry induced by the nitrogen chiral substituent overrides the substrate induction due to chelation.

To our knowledge, only one example of double stereodifferentiation involving a chiral substrate and a chiral reagent has been reported until now[74] and involves the addition of the tin reagents **226** and **227** to the imine **78**. The stereochemistry of reactions



78 **226** **227**

between the allyltin trichloride **226** and the imine **78** or its enantiomer *ent*-**78** was found to be entirely controlled by the stannane, giving predominantly the 1,5-anti stereomer. In contrast double stereodifferentiation was operating with the allyl reagent **227**, the observed stereoselectivities being due to the superimposition of the intrinsic facial selectivity of the imine and the 1,5-stereoselectivity of the stannane: the matched reaction between **227** and **78** gave highly stereoselectively the compound **228** since the mismatched reaction between **227** and *ent*-**78** was not selective at all (eq 132).



(eq 132)

IV. Concluding Remarks

The selectivity and the efficiency of nucleophilic additions of organometallic reagents to the C=N bonds of imines and imine derivatives have been considerably improved during the past few years. In particular the use of organocerium and organocopper reagents has greatly increased the scope and the interest of such reactions. Several methods of obtention of enantiomerically enriched amines and amino derivatives are now well defined by addition of organometallic reagents either to chiral nonracemic imines (or imine derivatives) or to achiral imines (or imine derivatives) in the presence of a stoichiometric amount of an external chiral auxiliary. The stereochemical course of such reactions is not always well understood. A better comprehension of the factors controlling the level and the sense of stereoselectivity of these additions would allow the adjustment of new reactions and in particular the use of external chiral auxiliaries in catalytic amounts. Furthermore, very few examples of addition of organometallic reagents to imines (or imine derivatives) derived from ketones have been reported. These reactions, which could give access to interesting amino derivatives bearing a quaternary asymmetric center, deserve more attention from organic chemists.

V. Acknowledgments

I thank Mrs. Henriette Mandville for all her help in preparing the manuscript and in particular for drawing all the structures.

VI. References

(1) For reviews see: (a) Volkmann, R. A. In *Comprehensive Organic Synthesis: Additions to C−X π-Bonds, Part 1*; Schreiber, S. L., Ed.; Pergamon: Oxford, 1991; Vol. 1, pp 355−396. (b) Kleinman, E. F.; Volkmann, R. A. In *Comprehensive Organic Synthesis: Additions to C−X π-Bonds, Part 2*; Heathcock, C. H., Ed.; Pergamon: Oxford 1991; Vol. 2, pp 975−1006. (c) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207−2293. (d) Johansson, A. *Contemp. Org. Synth.* **1995**, *2*, 393−407. (e) Denmark, S. E.; Nicaise, O. J. C. *J. Chem. Soc., Chem. Commun.* **1996**, 999−1004. (f) Risch, N.; Arend, M. In *Methods of organic chemistry: Stereoselective synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E.; Eds, George Thieme Verlag: Stuttgart, 1996; Vol. 3, pp 1883−1930. (g) After submission of this manuscript appeared a review article concerning a similar topic; see: Enders, D.; Reinhold: U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895−1946.

(2) Stork, G.; Dowd, S. R. *J. Am. Chem. Soc.* **1963**, *85*, 2178−2180.

(3) Huet, J. *Bull. Soc. Chim. Fr.* **1964**, 952−960 and 960−967.

(4) Scully, F. E. Jr. *J. Org. Chem.* **1980**, *45*, 1515−1517.

(5) Thomas, J. *Bull. Soc. Chim. Fr.* **1973**, 1300−1304.

(6) Brook, M. A.; Jahangir. *Synth. Commun.* **1988**, *18*, 893−898.

(7) Wada, M.; Sakurai, Y.; Akiba, K. *Tetrahedron Lett.* **1984**, *25*, 1079−1082.

(8) Wada, M.; Sakurai, Y.; Akiba, K. *Tetrahedron Lett.* **1984**, *25*, 1083−1084.

(9) Uno, M.; Shiraishi, Y.; Shimokawa, K.; Suzuki, H. *Chem. Lett.* **1988**, 729−732.

(10) Campbell, J. B.; Dedinas, R. F.; Trumbower-Walsh, S. A. *J. Org. Chem.* **1996**, *61*, 6205−6211.

(11) Sisko, J.; Weinreb, S. M. *J. Org. Chem.* **1990**, *55*, 393−395.

(12) Hirao, A.; Hattori, I.; Yamaguchi, K.; Nakahamas, S.; Yamazaki, N. *Synthesis* **1982**, 461−462.

(13) Hart, D. J.; Kanai, K.; Thomas, D. G.; Yang, T. K. *J. Org. Chem.* **1983**, *48*, 289−294.

(14) (a) Andreoli, P.; Billi, L.; Cainelli, G.; Panunzio, M.; Martelli, G.; Spunta, G. J. *Org. Chem.* **1990**, *55*, 4199−4200. (b) Cainelli, G.; Panunzio, M.; Andreoli, P.; Martelli, G.; Spunta, G.; Giacomini, D.; Bandini, E. *Pure Appl. Chem.* **1990**, *62*, 605−612.

(15) Itsuno, S.; Hachisuka, C.; Ito, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1767−1769.

(16) Ciganek, E. *J. Org. Chem.* **1992**, *57*, 4521−4527.

(17) Takai, K.; Odaka, H.; Kataoka, Y.; Utimoto, K. *Tetrahedron Lett.* **1994**, *35*, 1893−1896.

(18) (a) Katritzky, A. R.; Hong, Q.; Yang, Z. *J. Org. Chem.* **1994**, *59*, 7947−7948. (b) Katritzky, A. R.; Hong, Q.; Yang, Z. *J. Org. Chem.* **1995**, *60*, 3405−3408.

(19) Marxer, A.; Horvath, M. *Helv. Chim. Acta* **1964**, *47*, 1101−1113.

(20) Cicchi, S.; Goti, A.; Brandi, A.; Guarna, A.; De Sarlo, F. *Tetrahedron Lett.* **1990**, *31*, 3351−3354 and references cited therein.

(21) Rodriques, K. E.; Basha, A.; Summers, J. B.; Brooks, D. W. *Tetrahedron Lett.* **1988**, *29*, 3455−3458.

(22) Uno, H.; Terakawa, T.; Suzuki, H. *Synlett* **1991**, 559−560.

(23) Dondoni, A.; Merchan, F. L.; Merino, P.; Tejero, T. *Synth. Commun.* **1994**, *24*, 2551−2555.

(24) Murahashi, S.; Mitsui, H.; Shiota, T.; Tsuda, T.; Watanabe, S. *J. Org. Chem.* **1990**, *55*, 1736−1744.

(25) Schwartz, M. A.; Hu, X. *Tetrahedron Lett.* **1992**, *33*, 1689−1692.

(26) (a) Imamoto, T.; Kusumoto, T.; Tawarayama Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904−3912. (b) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Komiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392−4398.

(27) Denmark, S. E.; Weber, T.; Piotrowski, D. W. *J. Am. Chem. Soc.* **1987**, *109*, 2224−2225.

(28) (a) Matsumoto, T.; Kobayashi, Y.; Takemoto, Y.; Ito, Y.; Kamijo, T.; Harada, H.; Terashima, S. *Tetrahedron Lett.* **1990**, *31*, 4175−4176. (b) Kobayashi, Y.; Matsumoto, T.; Takemoto, Y.; Nakatani, K.; Ito, Y.; Kaimijo, T.; Harada, H.; Terashima, S. *Chem. Pharm. Bull.* **1991**, *39*, 2550−2555.

(29) Reetz, M. T.; Jaeger, R.; Drewlies, R.; Hübel, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 103−105.

(30) Sain, B.; Prajapati, D.; Sandhu, J. S. *Tetrahedron Lett.* **1992**, *33*, 4795−4798.

(31) Bhuyan, P. J.; Prajapati, D.; Sandhu, J. S. *Tetrahedron Lett.* **1992**, *33*, 7975−7976.

(32) Beuchet, P.; Le Marrec, N.; Mosset, P. *Tetrahedron Lett.* **1992**, *33*, 5959−5960.

(33) Giammaruco, M.; Taddei, M.; Ulivi, P. *Tetrahedron Lett.* **1993**, *34*, 3635−3638.
(34) Wang, J.; Zhang, Y.; Bao, N. *Synth. Commun.* **1996**, *26*, 2473−2477.
(35) Wang, D. K.; Dai, L. X.; Hou, X. L.; Zhang, Y. *Tetrahedron Lett.* **1996**, *37*, 4187−4188.
(36) Wang, D. K.; Dai, L. X.; Hou, X. L. *Tetrahedron Lett.* **1995**, *36*, 8649−8652.
(37) Belluci, C.; Cozzi, P. G.; Umani-Ronchi, A. *Tetrahedron Lett.* **1995**, *36*, 7289−7292.
(38) (a) Nakamura, H.; Iwama, H.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1996**, 1459−1460. (b) Nakamura, H.; Iwama, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6641−6647.
(39) Keck, G. E.; Palani, A. *Tetrahedron Lett.* **1993**, *34*, 3223−3224.
(40) Betz, J.; Heuschmann, M. *Tetrahedron Lett.* **1995**, *36*, 4043−4046.
(41) Yanagisawa, A.; Ogasawara, K.; Yasue, K.; Yamamoto, H. *J. Chem. Soc., Chem. Commun.* **1996**, 367−368.
(42) (a) Chen, T.; Jiang, S.; Turos, E. *Tetrahedron Lett.* **1994**, *35*, 8325−8328. (b) Jiang, S.; Agoston, G. E.; Chen, T.; Cabal, M. P.; Turos, E. *Organometallics* **1995**, *14*, 4697−4709.
(43) Yasuda, M.; Sugawa, Y.; Yamamoto, A.; Shibata, I.; Baba, A. *Tetrahedron Lett.* **1996**, *37*, 5951−5954.
(44) Kumaraswamy, S.; Nagabrahmanandachari, S.; Kumara-Swamy, K. C. *Synth. Commun.* **1996**, *26*, 729−744.
(45) Denmark, S. E.; Nakajima, N.; Nicaise, O. J. C. *J. Am. Chem. Soc.* **1994**, *116*, 8797−8798.
(46) See Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556−569.
(47) (a) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Am. Chem. Soc.* **1984**, *106*, 5031−5033. (b) Yamamoto, Y.; Nishii, S.; Maruyama, K.; Tomatsu, T.; Ito, W. *J. Am. Chem. Soc.* **1986**, *108*, 7778−7786.
(48) Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 947−948.
(49) Cainelli, G.; Giacomini, D.; Mezzina, E.; Panunzio, M.; Zarantonello, P. *Tetrahedron Lett.* **1991**, *32*, 2967−2970.
(50) Cainelli, G.; Giacomini, D.; Panunzio, M.; Zarantonello, P. *Tetrahedron Lett.* **1992**, *33*, 7783−7786.
(51) Cainelli, G.; Giacomini, D.; Walzl, M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2150−2152.
(52) Ishimaru, K.; Tsuru, K.; Yabuta, K.; Wada, M.; Yamamoto, Y.; Akiba, K. *Tetrahedron* **1996**, *52*, 13137−13144.
(53) Van Delft, F. L.; Dekort, M.; Van Der Marel, G. A.; Van Boom, J. H. *Tetrahedron: Asymmetry* **1994**, *5*, 2261−2264.
(54) Franz, T.; Hein, M.; Veith, U.; Jäger, V.; Peters, E. M.; Peters, K.; Von Schnering, H. G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1298−1301.
(55) Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778−1784.
(56) (a) Cainelli, G.; Mezzina, E.; Panunzio, M. *Tetrahedron Lett.* **1990**, *31*, 3481−3484. (b) Cainelli, G.; Panunzio, M.; Contento, M.; Giacomini, D.; Mezzina, E.; Giovagnoli, D. *Tetrahedron* **1993**, *49*, 3809−3826.
(57) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531−1546.
(58) Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141.
(59) Andres, J. M.; Barrio, R.; Martinez, M. A.; Pedrosa, R.; Perez-Encabo, A. *J. Org. Chem.* **1996**, *61*, 4210−4213.
(60) Alexakis, A.; Tranchier, J. P.; Lensen, N.; Mangeney, P. *J. Am. Chem. Soc.* **1995**, *117*, 10767−10768.
(61) Alexakis, A.; Lensen, N.; Tranchier, J. P.; Mangeney, P. *J. Org. Chem.* **1992**, *57*, 4563−4565.
(62) Matsubara, S.; Ukita, H.; Kodama, T.; Utimoto, K. *Chem. Lett.* **1994**, 831−834.
(63) Clark, R. D.; Jahangir; Souchet, M.; Kern, J. R. *J. Chem. Soc., Chem. Commun.* **1989**, 930−931.
(64) (a) Cativiela, C.; Diaz De Villegas, M. D.; Galvez, J. A. *Tetrahedron: Asymmetry* **1996**, *7*, 529−536. (b) Badorrey, R.; Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A. *Tetrahedron* **1997**, *53*, 1411−1416.
(65) Veith, U.; Schwardt, O.; Jäger, V. *Synlett* **1996**, 1181−1183.
(66) Mead, K.; Macdonald, T. L. *J. Org. Chem.* **1985**, *50*, 422−424.
(67) Fujisawa, T.; Nagai, M.; Koike, Y.; Shimizu, M. *J. Org. Chem.* **1994**, *59*, 5865−5867.
(68) A similar chelation-controlled addition of alkylcopper and -manganese reagents to *N*-Bocprotected α-amino aldehydes has been reported: Reetz, M. T.; Rölfing, K.; Griebenon, N. *Tetrahedron Lett.* **1994**, *35*, 1969−1972.
(69) (a) Takemoto, Y.; Takeuchi, J.; Iwata, C. *Tetrahedron Lett.* **1993**, *34*, 6069−6072. (b) Iwata, C.; Takemoto, Y. *J. Chem. Soc., Chem. Commun.* **1996**, 2497−2504.
(70) Alvaro, G.; Savoia, D.; Valentinetti, M. R. *Tetrahedron* **1996**, *52*, 12571−12586.
(71) Kawate, T.; Yamada, H.; Yamaguchi, K.; Nishida, A.; Nagakawa, M. *Chem. Pharm. Bull.* **1996**, *44*, 1776−1778.
(72) Alvaro, G.; Boga, C.; Savoia, D.; Umani-Ronchi, A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 875−882.
(73) Gao, Y.; Sato, F. *J. Org. Chem.* **1995**, *60*, 8136−8137.
(74) Hallet, D. J.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1995**, 657−658.
(75) Yamamoto, Y.; Ito, W. *Tetrahedron* **1988**, *44*, 5415−5423.
(76) Miao, C. K.; Sorcek, R.; Jones, P. J. *Tetrahedron Lett.* **1993**, *34*, 2259−2264.
(77) Higashiyama, K.; Inoue, H.; Takahashi, H. *Tetrahedron Lett.* **1992**, *33*, 235−238.
(78) Higashiyama, K.; Inoue, H.; Takahashi, H. *Tetrahedron* **1994**, *50*, 1083−1092.
(79) Wu, M. J.; Pridgen, L. N. *J. Org. Chem.* **1991**, *56*, 1340−1344. See also Carillo, L.; Badia, D.; Dominguez, E.; Vicario, J. L.; Tellitu, I. *J. Org. Chem.* **1997**, *62*, 6716−6721.
(80) Scialdone, M. A.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 7533−7536.
(81) Wu, M. J.; Pridgen, L. N. *Synlett* **1990**, 636−637.
(82) Muralidharan, K. R.; Mokhallalati, M. K.; Pridgen, L. N. *Tetrahedron Lett.* **1994**, *35*, 7489−7492.
(83) Glorian, G.; Maciejewski, L.; Brocard, J.; Agbosson, F. *Tetrahedron: Asymmetry* **1997**, *8*, 355−358.
(84) Higashiyama, K.; Nakahata, K.; Takahashi, H. *Heterocycles* **1992**, *33*, 17.
(85) Higashiyama, K.; Nakahata, K.; Takahashi, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 351.
(86) Higashiyama, K.; Inoue, H.; Yamauchi, T.; Takahashi, H. *J. Chem. Soc., Perkin Trans. 1* **1995**, 111−115.
(87) Pridgen, L. N.; Mokhallalati, M. K.; McGuire, M. A. *Tetrahedron Lett.* **1997**, *38*, 1275−1278.
(88) Chen, L.; Trilles, R. V.; Tilley, J. W. *Tetrahedron Lett.* **1995**, *36*, 8715−8718.
(89) Ukaji, Y.; Watai, T.; Sumi, T.; Fujisawa, T. *Chem. Lett.* **1991**, 1555−1558.
(90) Higashiyama, K.; Fujikura, H.; Takahashi, H. *Chem. Pharm. Bull.* **1995**, *43*, 722−728.
(91) Smith, A. B., III; Yager, K. M.; Taylor, C. M. *J. Am. Chem. Soc.* **1995**, *117*, 10879−10888.
(92) Hashimoto, Y.; Takaoki, K.; Sudo, A.; Ogasawara, T.; Saigo, K. *Chem. Lett.* **1995**, 235−236.
(93) Hashimoto, Y.; Kobayashi, N.; Kai, A.; Saigo, K. *Synlett* **1995**, 961−962.
(94) (a) Enders, D.; Schankat, J. *Helv. Chim. Acta* **1993**, *76*, 402−406. (b) Enders, D.; Schankat, J. *Helv. Chim. Acta* **1995**, *78*, 970−992.
(95) Tanaka, M.; Inoue, K.; Pokorski, U.; Taniguchi, M.; Torii, S. *Tetrahedron Lett.* **1990**, *31*, 3023−3026.
(96) (a) Bocoum, A.; Savoia, D.; Umani-Ronchi, A. *J. Chem. Soc., Chem. Commun.* **1993**, 1542−1544. (b) Basile, T.; Bocoum, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem.* **1994**, *59*, 7766−7773.
(97) Alvaro, G.; Savoia, D. *Tetrahedron: Asymmetry* **1996**, *7*, 2083−2092.
(98) Loh, T. P.; Ho, D. S. C.; Xu, K. C.; Sim, K. Y. *Tetrahedron Lett.* **1997**, *38*, 865−868.
(99) (a) Dembele, Y. A.; Belaud, C.; Hitchcock, P.; Villieras, J. *Tetrahedron: Asymmetry* **1992**, *3*, 351−354. (b) Nyzam, V.; Belaud, C.; Zammatio, F.; Villieras, J. *Tetrahedron: Asymmetry* **1996**, *7*, 1835−1843.
(100) Alvaro, G.; Pacioni, P.; Savoia, D. *Chem. Eur. J.* **1997**, *3*, 726−731.
(101) Laschat, S.; Kunz, H. *J. Org. Chem.* **1991**, *56*, 5883−5889.
(102) Itsuno, S.; Hachisuka, C.; Kitano, K.; Ito, K. *Tetrahedron Lett.* **1992**, *33*, 627−630.
(103) (a) Yang, T. K.; Chen, R. Y.; Lee, D. S.; Peng, W. S.; Jiang, Y. Z.; Mi, A. Q.; Jong, T. T. *J. Org. Chem.* **1994**, *59*, 914−921. (b) Li, Y.; Yang, G.; Jiang, Y. Z.; Yang, T. K. *Synth. Commun.* **1995**, *25*, 1551−1556.
(104) Hua, D. H.; Miao, S. W.; Chen, J. S.; Iguchi, S. *J. Org. Chem.* **1991**, *56*, 4−6.
(105) Moreau, P.; Essiz, M.; Merour, J. Y.; Bouzard, D. *Tetrahedron: Asymmetry* **1997**, *8*, 591−598.
(106) Claremon, D. A.; Lumma, P. K.; Phillips, B. T. *J. Am. Chem. Soc.* **1986**, *108*, 8265−8266.
(107) Solladié-Cavallo, A.; Bonne, F. *Tetrahedron: Asymmetry* **1996**, *7*, 171−180.
(108) Baker, W. R.; Condon, S. L. *J. Org. Chem.* **1993**, *58*, 3277−3284.
(109) Remuzon, P.; Dussy, C.; Jacquet, J. P.; Roty, P.; Bouzard, D. *Tetrahedron: Asymmetry* **1996**, *7*, 1181−1188.
(110) (a) Thiam, M.; Chastrette, F. *Tetrahedron Lett.* **1990**, *31*, 1429−1432. (b) Thiam, M.; Chastrette, F. *Bull. Soc. Chim. Fr.* **1992**, 161−167.
(111) Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A. *Tetrahedron: Asymmetry* **1997**, *8*, 1605−1610.
(112) (a) Alexakis, A.; Lensen, N.; Mangeney, P. *Tetrahedron Lett.* **1991**, *32*, 1171−74. (b) Alexakis, A.; Lensen, N.; Tranchier, J. P.; Mangeney, P.; Feneau-Dupont, J.; Declercq, J. P. *Synthesis* **1995**, 1038−1050.
(113) (a) Takahashi, H.; Tomita, K.; Otomasu, H. *J. Chem. Soc., Chem. Commun.* **1979**, 668−669. (b) Takahashi, H.; Tomika, K.; Noguchi, H. *Chem. Pharm. Bull.* **1981**, *29*, 3387−3391. (c) Takahashi,

H.; Inagaki, H. *Chem. Pharm. Bull.* **1982**, *30*, 922−926. (d) Takahashi, H.; Suzuki, Y. *Chem. Pharm. Bull.* **1983**, *31*, 4295−4299.
(114) (a) Enders, D.; Schubert, H.; Nübling, C. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1109−1110. (b) Enders, D.; Nübling, C.; Schubert, H. *Liebigs Ann./Recueil* **1997**, 1089−1100.
(115) Denmark, S. E.; Weber, T.; Piotrowski, D. W. *J. Am. Chem. Soc.* **1987**, *109*, 2224−2225.
(116) Weber, T.; Edwards, J. P.; Denmark, S. E. *Synlett* **1989**, 20−22.
(117) Denmark, S. E.; Edwards, J. P.; Nicaise, O. *J. Org. Chem.* **1993**, *58*, 569−578.
(118) (a) Denmark, S. E.; Nicaise, O.; Edwards, J. P. *J. Org. Chem.* **1990**, *55*, 6219−6223. (b) Alexakis, A.; Lensen, N.; Mangeney, P. *Synlett* **1991**, 625−626.
(119) Enders, D.; Bartzen, D. *Liebigs Ann. Chem.* **1991**, 569−574.
(120) Enders, D.; Funk, R.; Klatt, M.; Raabe, G.; Hovestreydt, E. R. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 418−421.
(121) Denmark, S. E.; Nicaise, O. *Synlett* **1993**, 359−361.
(122) (a) Enders, D.; Klatt, M.; Funk, R. *Synlett* **1993**, 226−228. (b) Enders, D.; Tiebes, J. *Liebigs Ann. Chem.* **1993**, 173−177.
(123) Enders, D.; Lochtman, R.; Raabe, G. *Synlett* **1996**, 126−128.
(124) Enders, D.; Lochtman, R. *Synlett* **1997**, 355−356.
(125) Enders, D.; Meiers, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2261−2263.
(126) Enders, D.; Schankat, J.; Klatt, M. *Synlett* **1994**, 795−797.
(127) Kim, Y. H.; Choi, J. Y. *Tetrahedron Lett.* **1996**, *37*, 5543−5546.
(128) Dieter, R. K.; Datar, R. *Can. J. Chem.* **1993**, *71*, 814−823.
(129) (a) Gallagher, P. T.; Lightfoot, A. P.; Moody, C. J.; Slawin, A. M. Z. *Synlett* **1995**, 445−446. (b) Brown, D. S.; Gallagher, P. T.; Lightfoot, A. P.; Moody, C. J.; Slawin, A. M. Z.; Swann, E. *Tetrahedron* **1995**, *51*, 11473−11488.
(130) Gallagher, P. T.; Hunt, J. C. A.; Lightfoot, A. P.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2633−2637.
(131) Moody, C. J.; Lightfoot, A. P.; Gallagher, P. T. *J. Org. Chem.* **1997**, *62*, 746−748.
(132) Moody, C. J.; Lightfoot, A. P.; Gallagher, P. T. *Synlett* **1997**, 659−660.
(133) Ukaji, Y.; Kume, K.; Watai, T.; Fujisawa, T. *Chem. Lett.* **1991**, 173−176.
(134) Kolasa, T.; Sharma, S. K.; Miller, M. J. *Tetrahedron* **1988**, *44*, 5431−5440.
(135) Hanessian, S.; Yang, R. Y. *Tetrahedron Lett.* **1996**, *37*, 5273−5276.
(136) Miyabe, H.; Ushiro, C.; Naito, J. *J. Chem. Soc., Chem. Commun.* **1997**, 1789−1790.
(137) (a) Chang, Z. Y.; Coates, R. M. *J. Org. Chem.* **1990**, *55*, 3464−3474. (b) Chang, Z. Y.; Coates, R. M. *J. Org. Chem.* **1990**, *55*, 3475−3483.
(138) Huber, R.; Vasella, A. *Tetrahedron* **1990**, *46*, 33−58 and references therein.
(139) Rohloff, J. C.; Alfredson, T. V.; Schwartz, M. A. *Tetrahedron Lett.* **1994**, *35*, 1011−1014.
(140) Basha, A.; Henry, R.; McLaughlin, M. A.; Ratajczyk, J. D.; Wittenberger, S. J. *J. Org. Chem.* **1994**, *59*, 6103−6106.
(141) (a) Dondoni, A.; Junquera, F.; Merchan, F. L.; Merino, P.; Tejero, T. *Tetrahedron Lett.* **1992**, *33*, 4221−4224. (b) Dondoni, A.; Franco, S.; Merchan, F. L.; Merino, P.; Tejero, T. *Tetrahedron Lett.* **1993**, *34*, 5475−5478.
(142) Dondoni, A.; Franco, S.; Merchan, F. L.; Merino, P.; Tejero, T. *Synlett* **1993**, 78−80.
(143) Dondoni, A.; Franco, S.; Junquera, F.; Merchan, F. L.; Merino, P.; Tejero, T.; Bertolasi, V. *Chem. Eur. J.* **1995**, *1*, 505−520.
(144) Paddon-Row: M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162−7166.
(145) (a) Dondoni, A.; Franco, S.; Merchan, F. L.; Merino, P.; Tejero, T. *Tetrahedron Lett.* **1993**, *34*, 5479−5482. (b) Dondoni, A.; Junquera, F.; Merchan, F. L.; Merino, P.; Tejero, T. *Synthesis* **1994**, 1450−1456.
(146) Dondoni, A.; Junquera, F.; Merchan, F. L.; Merino, P.; Tejero, T. *J. Chem. Soc., Chem. Commun.* **1995**, 2127−2128.
(147) (a) Merino, P.; Andro, S.; Castillo, E.; Merchan, F.; Tejero, T. *Tetrahedron: Asymmetry* **1996**, *7*, 1887−1890. (b) Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1997**, *8*, 3489−3496.
(148) Dondoni, A.; Perrone, D. *Tetrahedron Lett.* **1997**, *38*, 499−502.
(149) Merino, P.; Castillo, E.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1997**, *8*, 1725−1729.
(150) Merino, P.; Lanaspa, A.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1997**, *8*, 2381−2401.
(151) Merino, P.; Lanaspa, A.; Merchan, F. L.; Tejero, T. *Tetrahedron Lett.* **1997**, *38*, 1813−1816.
(152) Ballini, R.; Marcantoni, E.; Petrini, M. *J. Org. Chem.* **1992**, *57*, 1316−1318.
(153) Giovannini, R.; Marcantoni, F.; Petrini, M. *J. Org. Chem.* **1995**, *60*, 5706−5707.
(154) Tsuchihashi, G.; Iriuchijima, S.; Maniwa, K. *Tetrahedron Lett.* **1973**, 3389−3392.
(155) Ronan, B.; Marchalin, S.; Samuel, O.; Kagan, H. B. *Tetrahedron Lett.* **1988**, *29*, 6101−6104.
(156) Pyne, S. G.; Diku, B. *J. Org. Chem.* **1990**, *55*, 1932−1936.
(157) Pyne, S. G.; Hajipour, A. R. *Tetrahedron* **1992**, *48*, 9385−9390.
(158) Murahashi, S. I.; Sun, J.; Tsuda, T. *Tetrahedron Lett.* **1993**, *34*, 2645−2648.
(159) Watanabe, K.; Ito, K.; Itsuno, S. *Tetrahedron: Asymmetry* **1995**, *6*, 1531−1534.
(160) Itsuno, S.; Watanabe, K.; Ito, K.; El-Shehawy, A. A.; Sarhan, A. A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 109−110.
(161) El-Shehawy, A. A.; Abdelaal, M. Y.; Watanabe, K.; Ito, K.; Itsuno, S. *Tetrahedron: Asymmetry* **1997**, *2*, 1731−1734.
(162) (a) Braun, M.; Opdenbusch, K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 578−580. (b) Braun, M.; Opdenbusch, K. *Liebigs Ann./Recueil* **1997**, 141−154.
(163) Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1990**, *31*, 6681−6684.
(164) Inoue, I.; Shindo, M.; Koga, K.; Kanai, M.; Tomioka, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2527−2533.
(165) Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1991**, *32*, 3095−3098.
(166) (a) Inoue, I.; Shindo, M.; Koga, K.; Tomioka, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1603−1606. (b) Inoue, I.; Shindo, M.; Koga, K.; Tomioka, K. *Tetrahedron* **1994**, *50*, 4429−4438.
(167) Itsuno, S.; Yanaka, H.; Hachisuka, C.; Ito, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1341−1342.
(168) Itsuno, S.; Sasaki, M.; Kuroda, S.; Ito, K.*Tetrahedron: Asymmetry* **1995**, *6*, 1507−1510.
(169) (a) Jones, C. A.; Jones, I. G.; North, M.; Pool, C. L. *Tetrahedron Lett.* **1995**, *36*, 7885−7888. (b) Jones, C. A.; Jones, I. G.; Mulla, M.; North, M.; Sartori L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2891−2896.
(170) Huffman, M. A.; Yasuda, D.; Decamp, A. E.; Grabowski, E. J. J. *J. Org. Chem.* **1995**, *60*, 1590−1594.
(171) (a) Tanner, D.; Harden, A.; Johansson, F.; Wyatt, P.; Andersson, P. G. *Acta Chem. Scand.* **1996**, *50*, 361−368. (b) Andersson, P. G.; Guijarro, D.; Tanner, D. *J. Org. Chem.* **1997**, *62*, 7364−7375.
(172) Soai, K.; Hatanaka, T.; Miyazawa, T. *J. Chem. Soc. Chem. Commun.* **1992**, 1097−1098.
(173) Katritzky, A. R.; Harris, P. A. *Tetrahedron: Asymmetry* **1992**, *3*, 437−442.
(174) (a) Suzuki, T.; Narisada, N.; Shibata, T.; Soai, K. *Tetrahedron: Asymmetry* **1996**, *7*, 2519−2522. (b) Andersson, P. G.; Guijarro, D.; Tanner, D. *Synlett* **1996**, 727−728.
(175) Soai, K.; Suzuki, T.; Shono, T. *J. Chem. Soc., Chem. Commun.* **1994**, 317−318.
(176) Hayase, T.; Inoue, Y.; Shibata, T.; Soai, K. *Tetrahedron: Asymmetry* **1996**, *7*, 2509−2510.
(177) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **1996**, *118*, 8489−8490.
(178) Hanessian, S.; Yang, R. Y. *Tetrahedron Lett.* **1996**, *37*, 8997−9000.
(179) Ukaji, Y.; Hatanaka, T.; Ahmed, A.; Inomata, K. *Chem. Lett.* **1993**, 1313−1316.
(180) Ukaji, Y.; Kenmoko, Y.; Inomata. *Tetrahedron: Asymmetry* **1996**, *7*, 53−56.
(181) K. Merchan, F. L.; Merino, P.; Rojo, I.; Tejero, T.; Dondoni, A. *Tetrahedron: Asymmetry* **1996**, *7*, 667−670.
(182) (a) Fiaud, J. C.; Kagan, H. B. *Tetrahedron Lett.* **1970**, 1813−1816. (b) Fiaud, J. C.; Kagan, H. B. *Tetrahedron Lett.* **1971**, 1019−1022.
(183) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1985**, 814−816.
(184) Jäger, V.; Hein, M.; Leurs, S. Unpublished results cited in ref 69a.
(185) (a) Veith, U.; Leurs, S.; Jäger, V. *J. Chem. Soc., Chem. Commun.* **1996**, 329−330. (b) Meunier, N.; Veith, U.; Jäger, V. *J. Chem. Soc., Chem. Commun.* **1996**, 331−332.
(186) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841−1860.
(187) Neumann, W. L.; Rogic, M. M.; Dunn, T. J. *Tetrahedron Lett.* **1991**, *32*, 5865−5868.
(188) Bambridge, K.; Begley, M. J.; Simpkins, N. S. *Tetrahedron Lett.* **1994**, *35*, 3391−3394.
(189) (a) Enders, D.; Reinhold: U. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1219−1222. (b) Enders, D.; Reinhold: U. *Liebigs Ann.* **1996**, 11−26.

CR940474E