Chiral Tertiary Diamines in Asymmetric Synthesis

Jean-Claude Kizirian

Chem. Rev., **2008**, 108 (1), 140-205 • DOI: 10.1021/cr040107v

Chiral Tertiary Diamines in Asymmetric Synthesis

Jean-Claude Kizirian*

Laboratoire SPOT, EA 3857, Université François Rabelais, UFR Sciences et Techniques, Batiment J, Parc de Grandmont, 37200, Tours, France

Received March 3, 2006

Contents

1. Introduction

In the development of new systems for asymmetric synthesis it has always been a big challenge to obtain optically active compounds with good yields and selectivities. For this purpose, diamines have shown, since their first use, much success in many important and useful transformations. They have become widely studied by many groups as chiral auxiliaries, chiral reagents, or chiral external ligands. Some aspects of the use of these compounds have already been discussed.[1−5] This review will focus more specifically on the use of bis-tertiary diamines (this term refers to the diamines for which both nitrogen atoms are tertiary) as chiral external ligands. As bis-secondary diamines and secondary-tertiary diamines are often used in the same reactions, they will be both mentioned and compared to tertiary diamines when necessary. We will consider any structures containing two tertiary nitrogen atoms regardless of the structure of the spacer. Diamines containing nitrogen atoms substituted with

* To whom correspondence should be addressed. Phone: 0033 247367041. Fax: 0033 247367073. E-mail: jean-claude.kizirian@voila.fr.

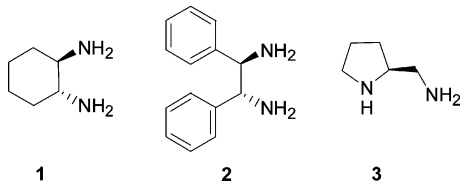
10.1021/cr040107v CCC: $71.00
Published on Web 12/15/2007

Jean-Claude Kizirian was born in Paris, France, in 1974. He obtained his DEA in Chemistry from the University of Pierre et Marie Curie of Paris in 1998 under the guidance of Pr. Claude Agami and his Ph.D. degree in 2003 from the University of Geneva, Switzerland, working with Pr. Alexandre Alexakis on the development of new C_2-symmetric tertiary diamines. He then spent two years as a research associate in the laboratory of Dr. David J. Procter at the Universities of Glasgow and Manchester. He worked on supported chiral auxiliaries derived from pseudoephedrine to synthesize various enantioenriched compounds. In 2005, he joined the research & development department of Zambon S.A. in Barcelona as a process chemist and in 2006 obtained an "ATER" position in the group of Pr. Hamid Dhimane. Since 2007, he has held the position of "Maître de conférences" at the University of Tours in the laboratory of Pr. Alain Duchêne. His research interests focus on tin chemistry, asymmetric synthesis, and synthesis of biologically active products.

heteroatoms such as phosphorus and boron (etc.) as well as the corresponding ammonium salt of bis-tertiary diamines will not be covered. In the diamines we are discussing the element of chirality can be located in three places: between the nitrogen atoms (internal chirality), on the nitrogen substituents (external chirality), or on the nitrogen atom itself. Thus, the element of chirality is located with regard to the diamino functionality. It is common practice to compare emerging diamine ligands with the established, efficacious (−)-sparteine ligand; whenever this is possible comparisons have been made. Nevertheless, (−)-sparteine is a ligand apart for which the use in asymmetric synthesis has already been covered in several reviews, and we will overlap with them as little as possible.[6−8] On the contrary, the C_2-symmetric diastereoisomers, α- and β-isosparteine, have not aroused much interest as they are usually less efficient. Recently, many efforts have been made to understand the real reason for the efficiency of (−)-sparteine, and few analogues possessing a simpler structure have been synthesized and tested in several transformations. Furthermore, one major drawback is that only one enantiomer of sparteine is available. Considering its efficiency and the synthetic difficulties to access (+)-sparteine, sparteine surrogates available in both enantiomerically pure forms have been developed.

In contrast with bis-imine ligands which possess a π orbital available for electronic retrodonation from the metal, diamine ligands do not have any orbital for such interactions. Nevertheless, they have shown their ability to coordinate alkali or transition metals efficiently, making them particularly useful in organometallic chemistry. Indeed, they have been associated with most of the common metals used in organic synthesis. All of these combinations will be discussed later in the text. NMR studies of some of these complexes, mainly with lithium, have been thoroughly investigated, leading to a better understanding of their structures. In some

Scheme 1



cases, X-ray structure determination has been possible, leading to very accurate data about complexes closely related to the reactive intermediates. Organometallic species exist in solution in different aggregated states, often several in equilibrium, which depend on the reagent itself, the solvent, and other additives. These aggregation states are responsible for the particular reactivity of organometallic compounds, and these factors can be important for the outcome of the reaction. Tertiary diamines are used to dissociate aggregated organometallics to monomers or dimers, which are much more reactive. The main interest is that when chiral diamines are used the organometallic becomes a chiral reagent, which ensures access to asymmetric synthesis. As the new reagent is often more reactive than the parent one, catalysis is theoretically possible and has been in some cases very nicely and efficiently applied. Concerning diamines containing a secondary amine, the corresponding amide could be used as a chiral base or a ligand of organometallic species. In the latter case, mixed aggregates are responsible for the reactivities and selectivities observed.

Synthesis of these diamines will not be discussed here as it has already been partially covered by the previous existing reviews. Since the first use of this type of diamine with (−)-sparteine in 1966, a large number of other derivatives have been described that are enantiomerically pure. Although many of them have been used for asymmetric catalysis, a large number still need to be explored. *trans*-1,2-Diaminocyclohexane, **1**, 1,2-diphenyldiaminoethane, **2**, and (2-aminomethyl)-pyrrolidine derivatives, **3**, are well-known core structures of diamines (Scheme 1) and among the most-often used. However, new ones have been discovered, and this has led to improvements in several asymmetric transformations. This growing field is of prime importance because of the big potential of these ligands in many different processes and also because of their large-scale availability and low cost.

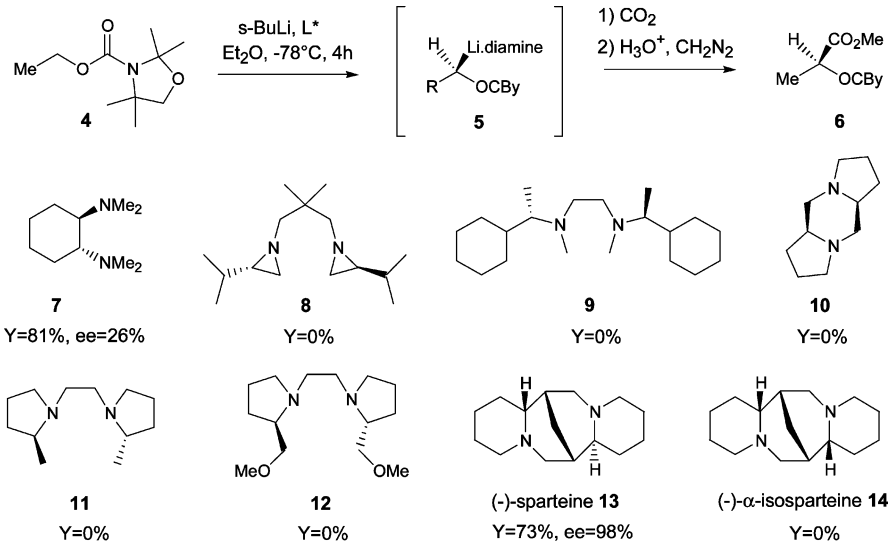
This review will be organized on the basis of reaction type. Spectroscopic data concerning organometallic complexes with a diamine ligand will also be discussed because it is one of the keys of further breakthroughs. Indeed, several recent studies have been developed based on these new understandings.

2. Deprotonation Reactions

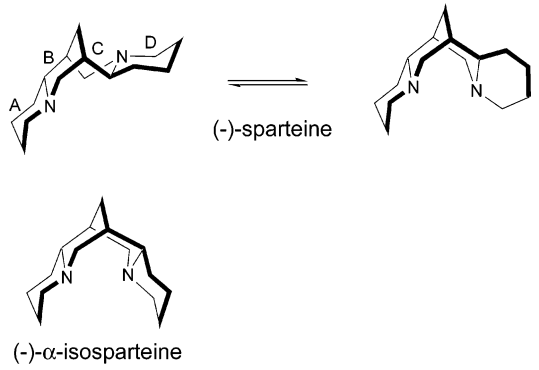
2.1. Deprotonation on a sp^3 Carbon

D. Hoppe was the first to obtain a high level of enantioselectivity for deprotonation of a very weak acid proton.[9] The deprotonating system, introduced by Nozaki et al. in 1971,[10] is formed by an alkyllithium base complexed to (−)-sparteine, and this was first applied to alkylcarbamates such as **4** (Scheme 2). This chiral base is able to efficiently differentiate between two protons of a methylene group, which leads to a configurationally stable lithiated intermediate **5**. It can be subsequently trapped by an electrophile with complete stereoretention,[11] but stereoinversion has been

Scheme 2



Scheme 3



observed for benzylic derivatives depending on the electrophile.[12] Some comparisons were made with several C_2-symmetric tertiary diamines including (−)-α-isosparteine, but apart from **7**, none of them induce this reaction.[13,14] Calculations showed that a combination of steric hindrance in the substrate, the base, and the ligand is responsible for the selectivity. No obvious differences between the two transition states have been detected, and the sum of several small deviations in different parts of the complexes has been pointed out. Semiempirical PM3 calculations were able to reproduce the selectivity obtained with diamine **7**,[13] and quantum chemical DFT calculations at the B3LYP/6-31G(d) level gave better insight into its origin.[15]

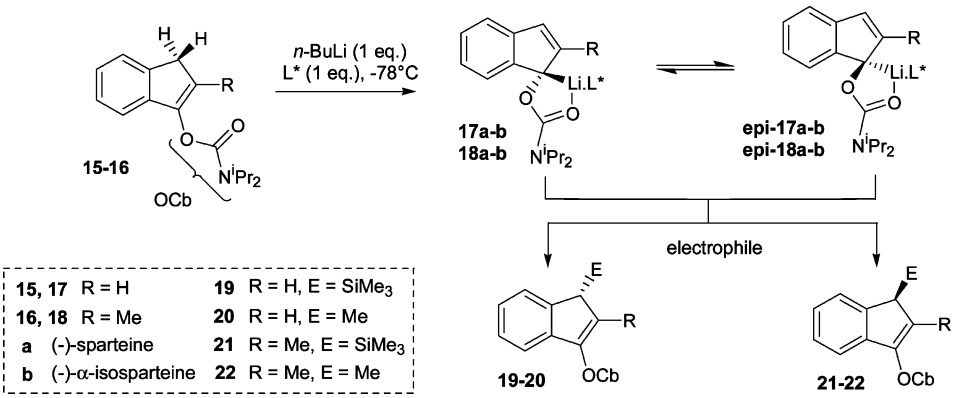
(−)-Sparteine and (−)-α-isosparteine are diastereomers and differ by the stereochemistry of one carbon at one of the ring junctions. Their C rings prefer boat and chair conformations, respectively (Scheme 3). However, the monoperchlorate of sparteine adopts the chair−chair conformation.[16] The steric hindrance existing between the two nitrogen atoms is quite different. In the case of (−)-isosparteine, both cycles A and D point in the same direction, which is reverse for the syn conformation of (−)-sparteine. The higher bulkiness of (−)-isosparteine can have a big influence on the reactivity and totally suppressed the reaction as shown in Scheme 2. The conformations of all the diastereoisomers were studied, in particular (−)-sparteine and (−)-α-isosparteine. Both structures must be considered to be flexible compounds as the energy differences for the two lowest energy conformers are, respectively, 3.4 and 5.8 kcal/mol. Several other conformers of higher energy have been determined by MM2*-assisted conformational searches, but there is no difference in the conformational flexibility of these stereoisomers.[17]

Hoppe also carried out a study on lithio-indenyl carbamates **17** and **18** complexed with (−)-sparteine and (−)-α-isosparteine (Scheme 4).[18] The enol carbamates **15** and **16** were first deprotonated at −78 °C in the presence of the diamine. The carbanionic intermediates were then trapped with trimethylsilyl chloride or methyl iodide. In all cases, changing (−)-sparteine to (−)-α-isosparteine led to opposite enantiomers and a significant increase in selectivity, though modest.

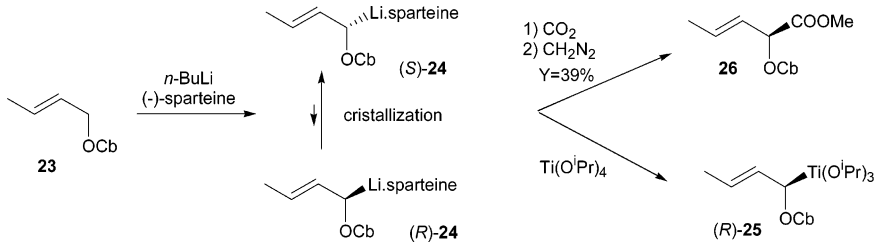
The interconversion barriers of the lithiated intermediates **17** and **18** were recorded by ^{1}H NMR. The data indicates that the complex shows better stability when the organolithium is associated with (−)-sparteine. Complexes **17a** and **18a** equilibrate very slowly because the temperature at which two sets of signals appear is 285 K and greater than 363 K, respectively. On the contrary, complexes **17b** and **18b** need much lower temperatures for equilibration, particularly **17b**, which shows only one set of signals at 200 K. The complex formed with (−)-α-isosparteine has a very high rate of epimerization and is much less configurationally stable than the complex formed with (−)-sparteine. This difference may result from a longer carbon−lithium bond length caused by the greater steric bulk of (−)-α-isosparteine.

Acyclic primary *O*-2-alkenyl carbamates **23** were deprotonated with *n*-butyllithium in the presence of (−)-sparteine or (−)-α-isosparteine (Scheme 5).[19] The complexed organolithium **24** obtained is not configurationally stable and interconverts at −70 °C, although the secondary allyl[20] or alkyl[9] carbamate are stable. Nevertheless, and contrary to what was first thought,[21] the major diastereoisomer of complex **24** has the 3-(*S*) configuration and crystallized preferentially in a second-order asymmetric process. An X-ray structure was obtained for a vinylsilane derivative,[22] and a chemical correlation proved the absolute configuration to be (*S*)-**24**. A certain amount of cyclohexane is required for crystallization and to obtain reproducible results.[23] Transmetalation to the allyltitanate with $Ti(O^iPr)_4$ occurs with stereoinversion to give (*R*)-**25**, which does not racemize below −30 °C. When (*S*)-**24** was reacted with dry carbon dioxide below −70 °C, the adduct **26** was obtained in 39% yield and the *R* configuration. The carboxylation also proceeds with stereoinversion. This methodology has been

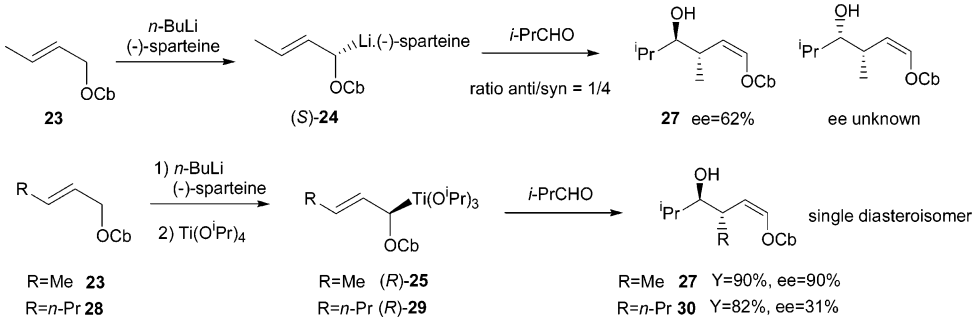
Scheme 4



Scheme 5



Scheme 6

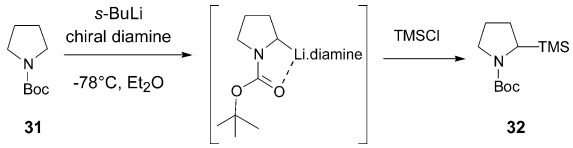


extended to geranyl and meryl *N*,*N*-diisopropylcarbamate[24] and also to aromatic substrates (1,3-diphenyl-1-propenyl *N*,*N*′-diisopropylcarbamate), which lead to an organolithium intermediate with high mesomeric stabilization and configurational stability.[25]

On the other hand, when (*S*)-**24** was reacted with 2-methylpropanal, adducts were obtained as a 1:4 ratio of anti and syn diastereoisomers (Scheme 6). Interestingly, (*S*)-**24** and (*R*)-**25** formed the same major enantiomer **27**. The absolute configuration of the organotitanium compound **25** was determined after a chemical sequence which involved its reaction with a homochiral aldehyde. The result showed that (*R*)-**25** was produced from (*S*)-**24** in 80% ee. Nevertheless, several adducts such as **27** could be formed with slightly higher selectivities. The explanation given for the stereochemical outcome was that the allylithium species **24** reacts via an unusual anti-$S_{E'}$ process (giving a mixture of syn and anti stereoisomers), while **25** reacts via the classical Zimmerman−Traxler transition state (giving one single stereoisomer). When (−)-α-isosparteine was used in the deprotonation step with **28** and following transmetalation and reaction with 2-methylpropanal, compound **30** was obtained in only 16% enantiomeric excess against 31% for (−)-sparteine.

Beak showed that the above deprotonation−alkylation sequence can be successfully adapted to a variety of substrates.[26] He found that compounds containing a nitrogen

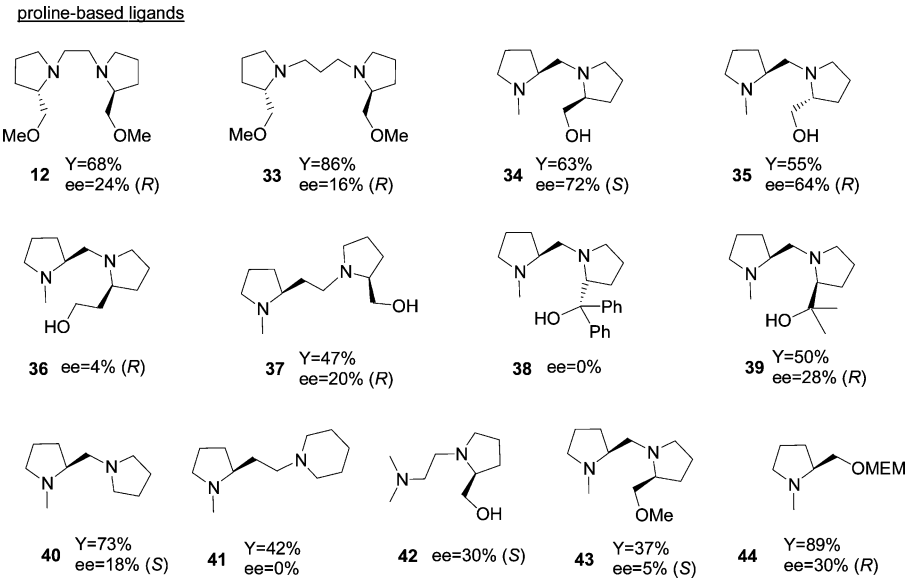
Scheme 7



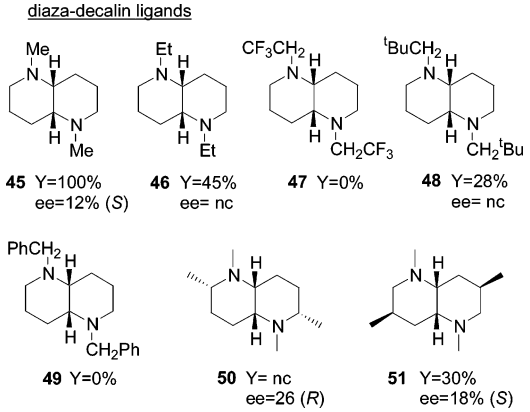
atom substituted by a Boc protecting group could undergo an efficient α-deprotonation, leading in some cases to a configurationally stable organolithium species.[27] Depending on the substrate, the origin of the enantioselectivity was recognized to be an asymmetric deprotonation, a dynamic kinetic resolution, or a dynamic thermodynamic resolution.[28−30] Beak et al. demonstrated that *N*-Boc-pyrrolidine **31** undergoes an enantioselective deprotonation leading to a configurationally stable organolithium intermediate. **31** was used as a test substrate to evaluate the efficiency of numbers of diamines in asymmetric deprotonation (Scheme 7). It was found that (−)-sparteine is usually the most efficient chiral inductor compared to (−)-α-isosparteine (Scheme 12), *N*,*N*,*N*′,*N*′-tetramethyl-*trans*-1,2-cyclohexanediamine **7** (Scheme 14), *N*,*N*,*N*′,*N*′-tetramethyl-binaphtyl-2,2′-diamine **71** (Scheme 14), proline-based ligands (Scheme 8), bispidines derivatives (Scheme 12),[31] and diaza-*cis*-decaline (Scheme 9).[32]

(+)-Sparteine was reported to be a natural product but is not available on a large scale.[33] Resolution of racemic

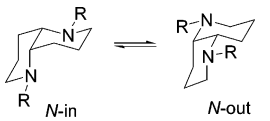
Scheme 8



Scheme 9



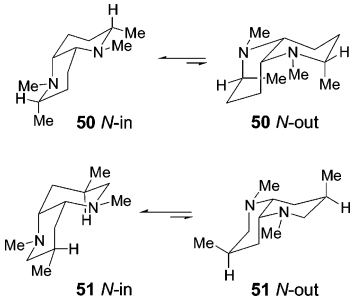
Scheme 10



diamine	R	*N*-in / *N*-out
53	H	> 90/10
45	Me	60/40
46	Et	< 90/10
52	*n*-Bu	< 90/10
47	CH_2CF_3	< 90/10

lupanine and sparteine which can lead to (+)-sparteine was described.[34,35] As a consequence, a few strategies have been developed to produce both enantiomers of the same compound using (−)-sparteine.[11,23,28,36] Nevertheless, none of these methods are a general solution to replace (+)-sparteine. Many efforts have been made to find a ligand as efficient as (−)-sparteine which could be available in both enantiomerically pure forms. The (−)-sparteine-mediated methodology has been extremely useful as it allows access to (*R*)-proline derivatives, while the (*S*)-proline series is the natural product. Both enantiomers of the proline-based ligand can be readily prepared. A few of them were tested in the asymmetric deprotonation of *N*-Boc-pyrrolidine (Scheme 7). The best selectivities were obtained with diamines **34** and **35**, which are diastereoisomers. Interestingly, the result showed that each of these ligands led to a different enantiomer of the

Scheme 11



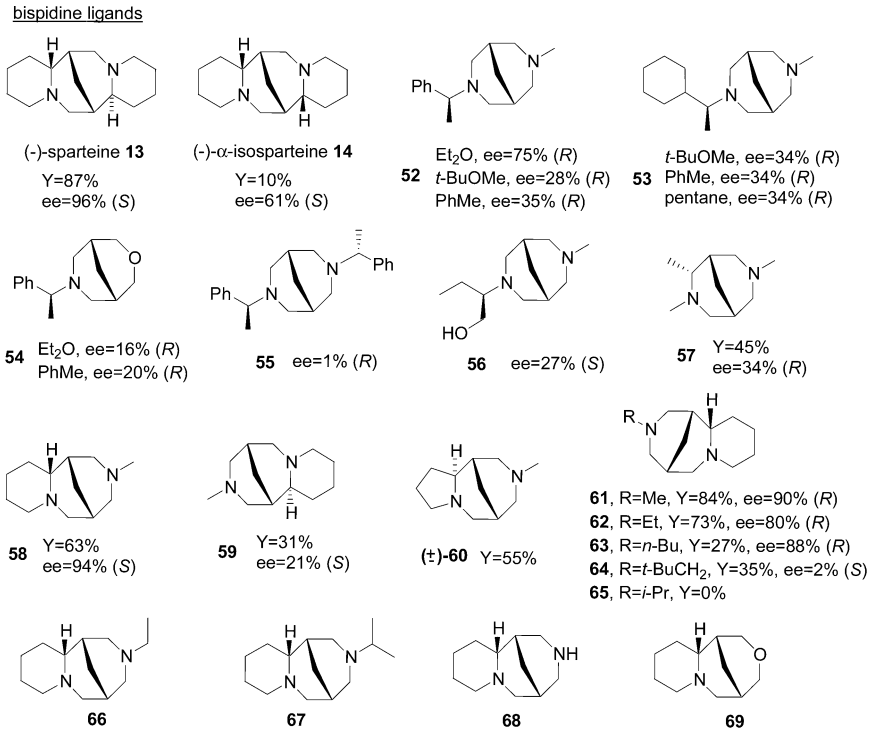
product. Diamine **34** produced (*S*)-**32** in 72% ee, while diamine **35** produced (*R*)-**32** in 64% ee. Several modifications around the structure of the ligand did not improve these selectivities (Scheme 8).[31]

In 2000, Kozlowski et al. developed a new kind of diamine with a 1,5-diaza-*cis*-decalin core that is based on computer-aided identification of novel ligands scaffold. Unfortunately, in the case of substrate **31**, low selectivity was obtained. Some other derivatives were prepared with different alkyl substituents on the nitrogen atom. The results showed that the smaller the R substituent is, the better the selectivities are (Scheme 9, Ligands **47**−**49**).[32] The reason for these poor results was attributed to the conformational equilibrium of the diamine. Compounds **50** and **51** were prepared to increase the *N*-in conformation (Scheme 10) of the ligand and improve the chiral discrimination around the lithium.[37,38] Both slightly improved the selectivity but gave rise to the opposite enantiomers, indicating that the stereochemical outcome is not related to the configuration of the diamine core but to its substitution.

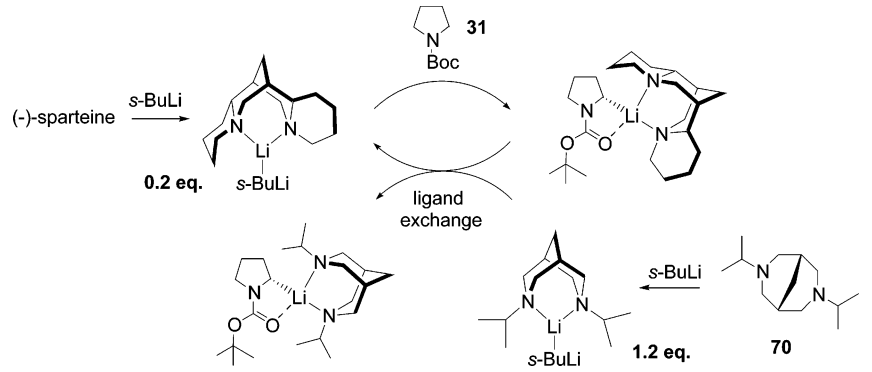
Conformational studies of these 1,5-diaza-*cis*-decalin were carried out using molecular mechanics (amber*) and ab initio analysis (HF/6-31G*, B3LYP/6-31+G*). These results were compared to experimental data obtained from ^{1}H and ^{13}C NMR studies.[39] These diamines exist in predominantly two conformations *N*-in and *N*-out. It turned out that the *N*-in conformer is preferred for small R substituents (H and Me), while *N*-out is the major conformer for all the other compounds (Scheme 10).

Conformational analysis of diamines **50** and **51** was made by NMR and showed that both methyl substituents are in

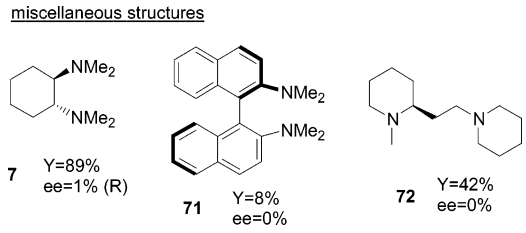
Scheme 12



Scheme 13



Scheme 14



equatorial positions in the *N*-in conformation. This additional stability helps to overcome the torsional effect of the *N*,*N*′-dimethyl substitution and shift the conformational equilibrium in favor of the *N*-in conformers. The difference of energy between the two conformations of **50** and **51** was calculated to be 1.1 and 1.9 kcal/mol, respectively, which indicates that *N*-out conformer may be present (Scheme 11).[37]

Bispidine represents the core structure of (−)-sparteine and (−)-α-isosparteine. Simple chiral derivatives **52**−**56** were studied by Beak et al. using a chiral lateral chain (Scheme 12).[31] In the case of diamine **52**, a strong solvent effect could be observed. Nevertheless, in Et_2O, 75% ee could be achieved. None of the other derivatives were able to provide similar enantiomeric excesses.

Attempts to find a surrogate of (+)-sparteine led researchers to focus on the structure itself and simplify it. It was thought by O'Brien et al., from calculation made with sparteine derivatives complexing a lithium atom, that the D ring was not a key element in the enantiodiscrimination process.[40,41] Indeed, they showed that partially resolved diamine **58** (55% ee), having the same stereochemistry as (−)-sparteine, led to (*S*)-**32** in 53% ee.[42] This was the first experimental evidence that the ABC ring system of (−)-sparteine is sufficient to obtain high enantiomeric excess for the asymmetric deprotonation of **31**. Afterward, Lesma and Silvani reported an enantioselective synthesis of tricyclic diamines **58** and **59**, which represent the ABC and BCD ring system of (−)-sparteine, respectively.[43] They pointed out the dramatic difference between these two diamines and were able to confirm the result obtained by O'Brien. The latter found that **61**, i.e., the ABC ring system of (+)-sparteine, can be readily accessible in three steps from (−)-cytisin,[44−46] which is isolated from *Laburnum anagyroids* seeds.[47] This diamine led to (*R*)-**32** in high enantiomeric excess. When other derivatives **62**−**65** with various *N*-alkyl substituents were used, lower enantioselectivities were obtained even with the *N*-ethyl derivative **62** (Scheme 12).[48] The molecular

orbital calculations were able to reproduce the experimental observations of **61** and **66** and pointed out, as postulated previously by Beak, that high enantioselectivity involves steric interaction in the prelithiated complex RLi/diamine/**31**. While similar activation energies were calculated for **67**, no product was isolated. The explanation given by the authors was that steric crowding inhibits formation of the prelithiation complex. Diamine **60** was prepared in a racemic manner because it could not be resolved and produced **32** in 55% yield. The enantiomeric excesses calculated for diamine **60**, **68**, and **69** predict significantly lower ee's than for **61**. Diamine **57** prepared by Kozlowski et al. gave a very curious result as (*R*)-**32** was formed, although the ligand is structurally analogous to (−)-sparteine. Furthermore, the selectivity was very low, which indicates that the entire A ring of sparteine is essential for high asymmetric induction.

In 2005 O'Brien addressed the problem of catalysis in the enantioselective deprotonation of **31**.[49] This had already been studied by Beak but proved unsuccessful.[31b] Indeed, when **31** was deprotonated in the presence of 0.25 or 0.5 equiv of (−)-sparteine, products were isolated in only 64% or 78% ee, respectively. Furthermore, a racemic product was obtained when the reaction was carried out with 0.1 equiv of (−)-sparteine and 0.9 equiv of TMEDA, which means that *s*-BuLi/TMEDA deprotonates faster than *s*-BuLi/(−)-sparteine. O'Brien et al. found that **70** was very sluggish to catalyze the reaction. In another study of competition experiments, this diamine was found to be the least reactive compared to TMEDA, **7**, (−)-sparteine, and several (+)-sparteine surrogates.[50] It then follows that **70** allows ligand exchange from the intermediate lithiated species and liberates (−)-sparteine, which can be engaged in another deprotonation step (Scheme 13). Applying these reaction conditions to (−)-sparteine and **61**, (*S*)- and (*R*)-**32** were isolated in 80% and 88% ee, respectively. In all cases, catalysis was more efficient with **61** than (−)-sparteine, while this was the reverse in stoichiometric reactions.

Having developed a very efficacious ligand equivalent to (+)-sparteine, diamine **61** was naturally used in the well-established (−)-sparteine chemistry to validate his status of (+)-sparteine surrogate. Deprotonation of *O*-alkyl carbamate developed by Hoppe was repeated with various (+)-sparteine surrogates, among which **61** was found to be the best.[51]

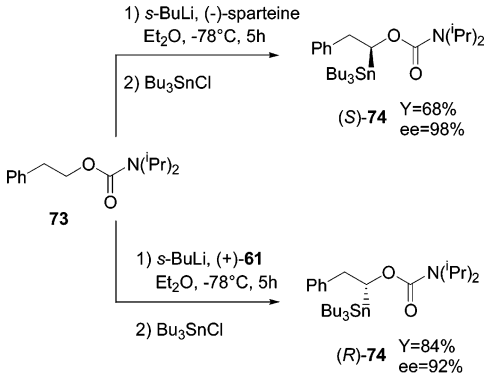
Diamines **7** and **71** studied by Beak and **72** by O'Brien gave essentially racemic product **32**. Theoretical studies performed with **7** have explained the inefficiency of this diamine compared to (−)-sparteine.[41,52,53]

The (+)-sparteine surrogate **61** was tested with alkyl carbamate developed by Hoppe.[44] Asymmetric lithiation of **73** α to the oxygen followed by stannylation gave **74** in high enantiomeric excess in both cases, although **61** is slightly less efficient (Scheme 15).

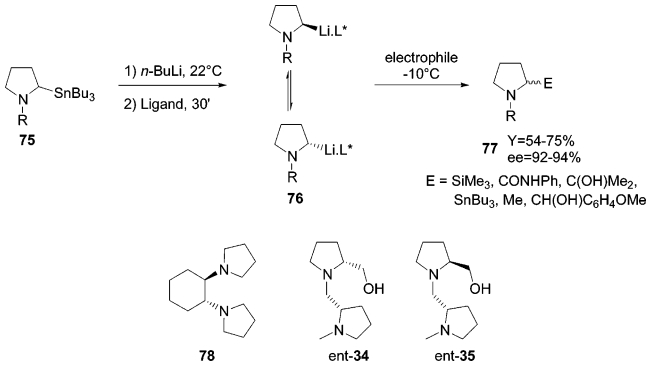
Applications in the synthesis of **61** have rapidly been made. Fukuyama et al. were able to accomplish the synthesis of (−)-Kainic acid using *s*-BuLi/**61** as the deprotonating system for the regio- and stereoselective introduction of a carboxylic group at the C2 position.[54]

Coldham studied the dynamic resolution of *N*-Boc- and *N*-alkyl-2-lithiopyrrolidine **76**, the latter being formed by tin−lithium exchange from racemic stannane **75** (Scheme 16).[55] Although **31** has always been the test substrate, the dynamic resolution of its corresponding organolithium derivatives was only achieved in 2005.[55d] In the case of *N*-alkylpyrrolidine, the α-amino-organolithium species were

Scheme 15

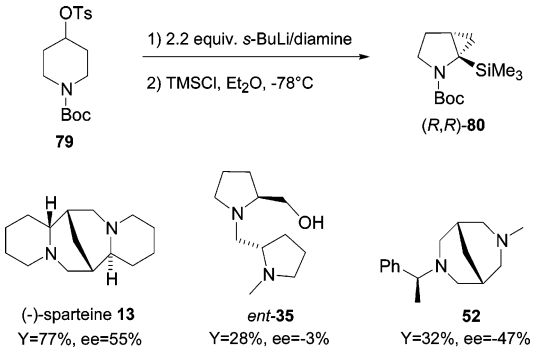


Scheme 16



generated at room temperature and a chiral ligand was then added. Two diastereoisomeric complexes **76** can be formed, and they react at different rates. Indeed, when the organolithium species was cooled to −78 °C before addition of the ligand, the reaction with the electrophile led to a racemic product. On the contrary, when the reaction occurred at −10 °C with formation of the complex at room temperature, very high enantioselectivity was obtained, but this did not occur when the ligand was (−)-sparteine or **78**. The best ligand was the commercially available prolinol derivative *ent*-**35**. Very good results, with ee's up to 94%, were obtained with all the electrophiles used. The diastereoisomeric ligand *ent*-**34** led to the opposite enantiomer of **77** with the same level of enantioselectivity. These results showed that both diastereoisomeric complexes interconvert slowly compared to the rate of the reaction. Interestingly, when (−)-sparteine was used as ligand, lower ee and an opposite absolute configuration were obtained from that formed by asymmetric deprotonation. An experiment was performed with a shortage of electrophile to determine which of the diastereoisomers reacts faster. Complex **76** obtained as a 1:1 mixture of diastereoisomers from (±)-**75**, in the presence of ligand *ent*-**35**, reacts with 0.3 mol equiv of TMSCl and produces **77** in a ratio 61:39 (*R*:*S*). At the beginning of the reaction, the product was formed with the opposite absolute configuration to the one it had at the end. The stereochemical pathway occurs via a dynamic thermodynamic resolution with the minor diastereoisomeric complex reacting faster. By choosing either *ent*-**34** or its diastereoisomer *ent*-**35**, it was therefore possible to produce both enantiomers of 2-substituted pyrrolidine **77** with high enantiopurity.[55a] In the case of *N*-Boc-pyrrolidine, identical reaction conditions led to a very low asymmetric induction. It turned out that an overall 10 equiv of *n*-butyllithium was needed to reach similar level of enantioselectivity. Here again, best results were obtained with

Scheme 17



ligands *ent*-**34** and *ent*-**35**, which led to **32** in 82% (*R*) and 90% ee (*S*), respectively.[55d]

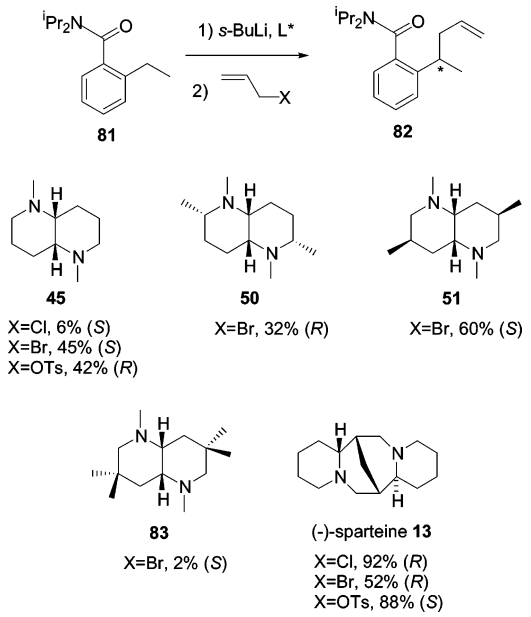
Beak also described the asymmetric deprotonation of *N*-Boc-piperidines. Compared to *N*-Boc-pyrrolidine an important difference in behavior was observed. Indeed, the silylated product was obtained in low yield and only 74% ee (in favor of the *S* enantiomer).[56] The study showed that the least acidic equatorial α-hydrogen of the carbamate is removed. Calculation of the activation parameters accounted accurately with the experimental results. Metallinos and Dudding showed that (−)-sparteine is more efficient than **7** or **61** for this substrate.[57] Furthermore, they reported that deprotonation of *N*-protected octahydrophenanthroline lead to 72% ee, also for the *S* enantiomer. Piperazine derivatives were also used as substrate but only in a racemic manner.[58] Beak reported derivatives of *N*-Boc piperidines functionalized in C4 (Scheme 17).[56,59] The organolithium intermediate cyclized to the 2-azabicyclo-[3.1.0]-hexane, which underwent further deprotonation leading to **80**. The enantiomeric excesses were highly dependent on the nature of the leaving group. The best result was obtained with (−)-sparteine and a tosylate leaving group. The bispidine ligand **52** and the proline derivative *ent*-**35** led to 47% and 3% ee, respectively.

Benzamide **81** is a substrate which, upon deprotonation, leads to a nonstable organolithium intermediate. The two diastereoisomeric complexes are in a rapid equilibrium. One of these complexes reacts faster than the other to form the enantioenriched product **82**. This is a case of dynamic kinetic resolution, which can be described by the Curtin−Hammett principle.[28]

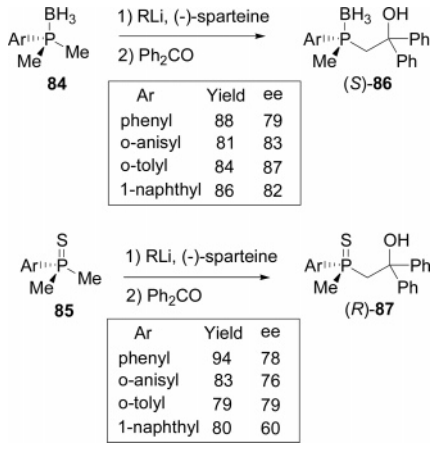
Kozlowski et al. used diamines **45** and **49** with a methyl and benzyl substituent on the nitrogen, respectively.[32] With acetone or different allyl electrophiles, only low to moderate selectivities were obtained. (−)-Sparteine was much more efficient in the case of allyl electrophiles. It is notable that both enantiomers could be obtained by changing the leaving group from a halide to a tosylate (Scheme 18). Modified 1,5-diaza-decalins **50**, **51**, and **83** were also tested.[37] Diamine **83** exists predominantly in an *N*-out conformation, but if the reaction occurs through the *N*-in chelated form, dramatic effects were expected. However, the low selectivity of the reaction indicates that this *N*-in chelated form was not involved. On the contrary, diamines **50** and **51** exist more in the *N*-in form, which should be a positive factor for the reaction. Although **50** did not increase the selectivity, **51** showed a significant improvement. In this case, opposite enantiomers were also obtained.

Desymmetrization of prochiral aryldimethylphosphine boranes **84** or aryldimethylphosphine sulfides **85** have become a very straightforward way to access P-chirogenic ligands

Scheme 18



Scheme 19



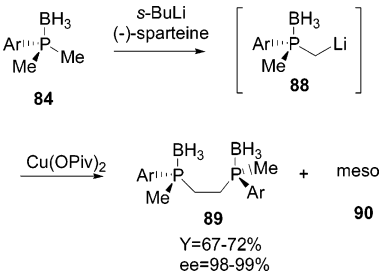
since the first efficient examples given by Evans et al.[60] The (−)-sparteine-alkyllithium system has been successfully used to enantioselectively deprotonate these substrates. Dimethylphosphine oxide has previously been reported to proceed with low enantioselectivity (∼12%) (Scheme 19).[61]

As chiral diphosphines are extremely powerful ligands and due to the difficulties associated with the synthesis of enantiomerically enriched phosphorus stereocenters,[62] asymmetric deprotonation has been used to address these issues. The organolithium compound **88** could be dimerized through oxidative coupling with the THF-soluble copper(II) pivalate [$Cu(OPiv)_2$]. The diphosphine was obtained with high enantiomeric excess because the meso diastereoisomer was also produced (Scheme 20). In the absence of double stereodifferentiation for the oxidative coupling, the anticipated products enantiomeric excess should be the square of the one of the metalated precursor. In all cases, diphosphines were isolated in an enantiomerically pure form after a single recrystallization.

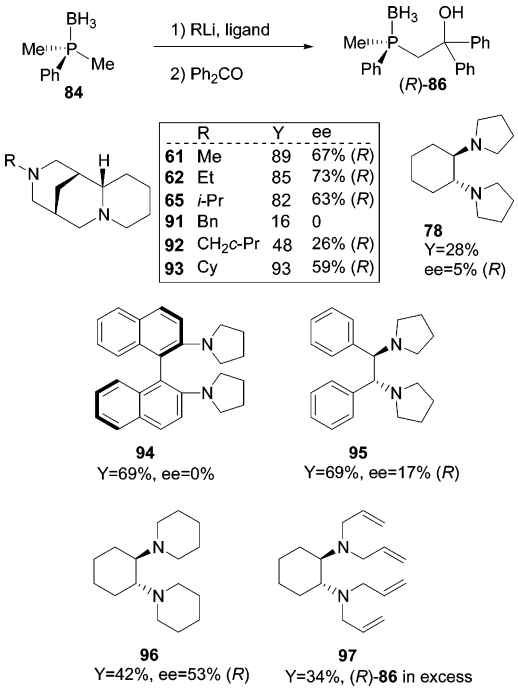
Imamoto extended the methodology for the synthesis of chiral C_2-symmetric bis(trialkylphosphine) linked with an ethylene or a methylene bridge.[63,64] Phospholane derivatives were also successfully employed with (−)-sparteine.[65,66]

Several ligands were tested in the asymmetric deprotonation of **84** but with very limited efficiency.[67,68] Ligands **78**

Scheme 20



Scheme 21



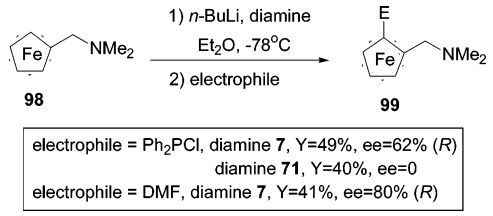
and **96** gave very different results despite their similar structure. Bispidine ligands related to the configuration of (+)-sparteine gave better ee depending on the nitrogen substituent (Scheme 21).

2.2. Deprotonation of Aromatic Systems

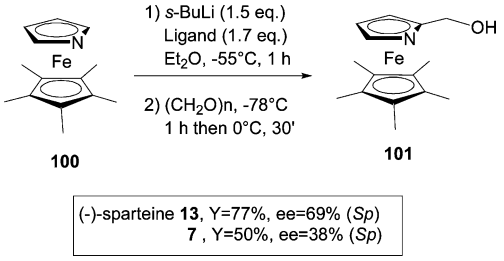
All cases listed involve organometallic compounds where the metal atom is borne by an sp^3 carbon. As described in the previous section, the configurational stability of this kind of species is key to understanding the outcome of the processes where they are involved. By contrast, an organometallic borne by an sp^2 carbon is configurationally stable, such as in the aromatic series in which the processes involved will be mainly asymmetric deprotonations. Arene−metal compounds have been widely studied as substrates for deprotonation as the aromatic protons are much more acidic and easier to remove.

Although the asymmetric lithiation of ferrocene derivatives has been studied for many years,[69] the first enantioselective ortholithiation was made by Snieckus in 1996.[70] High levels of enantioselectivities were achieved with the *n*-butyllithium−sparteine base system. This reaction is very important because it leads to a very useful ligand with planar chirality. Almost at the same time, Uemura et al. investigated two other diamine ligands for the asymmetric ortholithiation of some other ferrocene derivatives.[71] In the case of substrate **98**, (−)-sparteine afforded the product in only trace amounts, while with diamine **7**, deprotonation occurred efficiently and

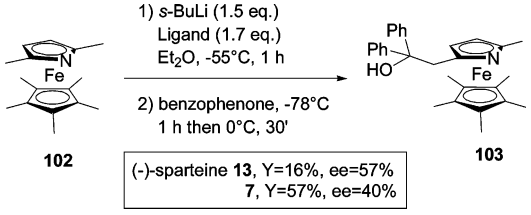
Scheme 22



Scheme 23



Scheme 24

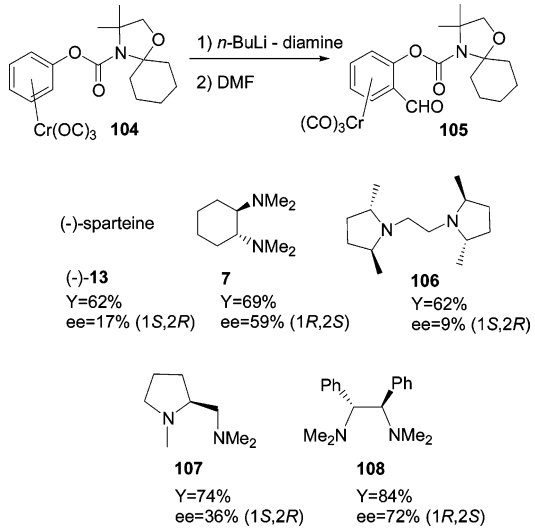


the organolithium intermediate was trapped with chlorodiphenylphosphine to give the product in 49% yield and 62% ee. On the other hand, diamine **71** led to the racemic mixture. When the electrophile was DMF, the ee increased up to 80% but the yield was reduced to 41% (Scheme 22).

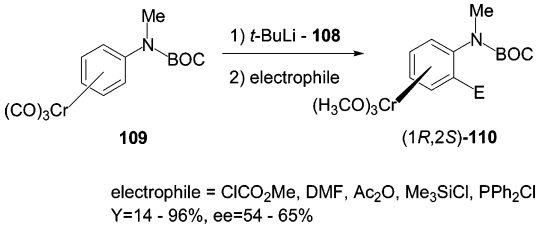
Iwao et al. prepared enantiomerically enriched azaferrocene derivatives by asymmetric lithiation (Schemes 23 and 24).[72] A preliminary study was made to compare the selectivities obtained with (−)-sparteine, diamine **7**, and a bis(oxazoline) derived from *S*-valine. Substrate **100** was ortholithiated using *s*-BuLi associated with the chiral ligand. (−)-Sparteine was much more efficient than the two other ligands. Substrate **102** underwent a lateral lithiation using the same deprotonating system. In this instance, (−)-sparteine was still more efficient than diamine **7**, but the best result was obtained with the bis(oxazoline) ligand, which gave the product with very high enantioselectivity.

(Arene)chromium complexes were also studied because they represent the activated form of aromatic derivatives. Uemura studied the ortholithiation of masked phenol and aniline−chromium complexes (Scheme 25).[73] Previous results showed that in the presence of diamine **7** ortholithiation of tricarbonylchromium complexes of phenyl methoxymethylether and phenyl methoxyethoxymethyl ether resulted in low enantioselectivities, while the corresponding tricarbonyl(phenyl-*N*,*N*-diethylcarbamate)chromium produced (l*R*,2*S*)-(2-formyphenyl carbamate)chromium complex in 43% ee. The coordination of the lithium on the carbonyl oxygen of the carbamate was essential for asymmetric ortholithiation. Complex **104** was deprotonated with *n*-butyllithium in the presence of several diamines and reacted with an electrophile to give enantioenriched complex **105**. The best selectivity was observed with diamine **108** in toluene; this was due to formation of a reactive dimer intermediate. In ether, the competition between the solvent

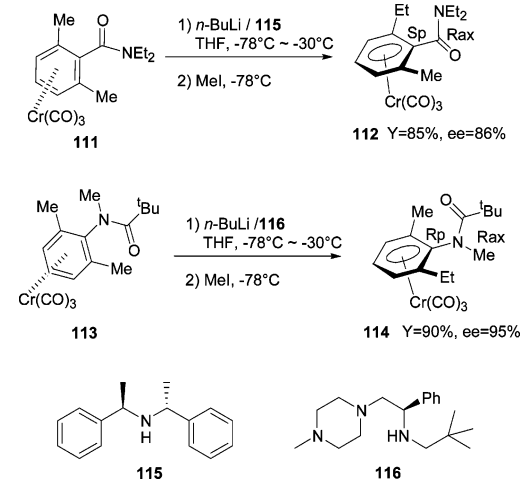
Scheme 25



Scheme 26



Scheme 27

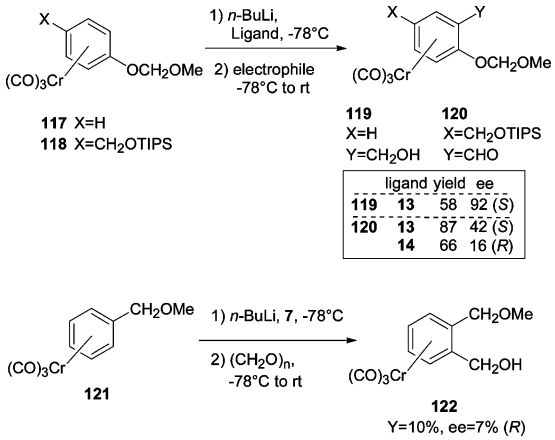


and the diamine to coordinate the *n*-butyllithium led to a less selective process.

Deprotonation of aniline chromium complex **109** in the presence of diamine **108** led to an ortholithiated intermediate, which was reacted with several electrophiles to give the enantioenriched product **110**. In that case, deprotonation with *tert*-butyllithium was more selective (Scheme 26).

Benzylic lithiation of prochiral (arene)chromium complexes of benzamides **111** and anilides **113** were also studied by Uemura (Scheme 27).[74] Ligands such as (−)-sparteine, **7**, or **108** were not efficient at all for this transformation. The best results were obtained with ligands **115** and **116**, respectively. Axial and planar chirality were determined by either X-ray analysis or comparison with the optical rotation of an authentic sample. The conformation of the amide in compound **112** has the dimethylamino part oriented in an

Scheme 28



anti-conformation to the tricarbonylchromium moiety, and the amide carbonyl oxygen is in a *syn*-orientation. The dihedral angle between the plane of the amide and the aryl ring is approximately perpendicular. Concerning compound **114**, the pivaloyl group is exo to the tricarbonylchromium fragment, and the amide oxygen is trans to the *N*-methyl group. Interestingly, with the same chiral base compounds **111** and **113** were not lithiated on the same side leading to opposite planar chirality. Although the conformation of the substrate is crucial for the stereochemical outcome of the lithiation, the precise mechanism is not clear. After oxidative demetalation, benzamides and anilides were isolated with very high enantiopurity. Although the conformational stability depends on the bulkiness of the substituent, most of them kept their enantiopurity after 24 h at room temperature.

Widdowson et al. reported several examples of asymmetric lithiation of (arene)tricarbonylchromium complexes **117**, **118**, and **121** with (−)-sparteine, (−)-α-isosparteine, and **7** as ligands.[75] The best result was obtained using **118**, with (−)-sparteine as ligand and paraformaldehyde as electrophile. When (−)-α-isosparteine and **7** were used, products were isolated with very low enantiopurity (Scheme 28).

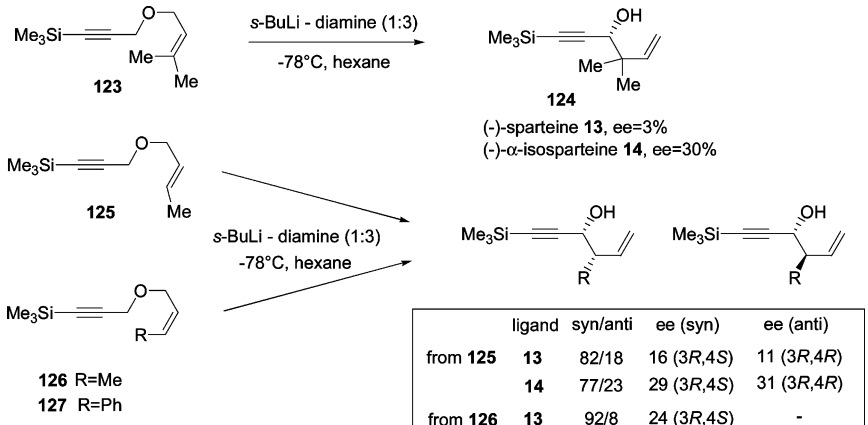
2.3. Wittig Rearrangement

The 2,3-Wittig rearrangement is a very useful transformation that is initiated by deprotonation of an unsaturated ether. The organolithium intermediate undergoes further rearrangement due to the presence of a double bond, which can interact via a five-membered ring cyclic transition state.

Allyl propargyl ethers are known to have nonclassical behavior as both (*E*) and (*Z*) starting olefins led predominantly to the syn compound.[76] Kang et al. reported the reaction in the presence of (−)-sparteine and (−)-α-isosparteine (Scheme 29).[77] It was found that the best ratio of substrate:diamine:*s*-BuLi was 1:6:2. While good diastereoselectivities were obtained, the enantioselectivity was always moderate. In all cases, (−)-α-isosparteine was superior in terms of enantioselectivity and 71% ee could be achieved with substrate **127**. In that case, (−)-sparteine was a very poor inductor but led, surprisingly, to the opposite diastereoselectivity. In this reaction both diamines had two very different behaviors. A short discussion of some mechanistic aspects of the reaction was given by the authors to explain these results. They attributed the stereochemical outcome essentially to the hydrogen abstraction and conformation of the allylic ether moiety.

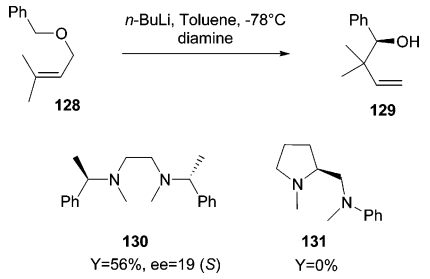
Ligands **130** and **131**, which were derived from (*R*)-(+)-α-methylbenzylamine and (*S*)-proline, respectively, were

Scheme 29

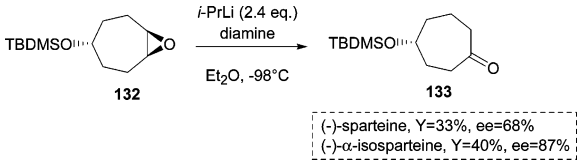


	ligand	syn/anti	ee (syn)	ee (anti)
from **125**	**13**	82/18	16 (3*R*,4*S*)	11 (3*R*,4*R*)
	14	77/23	29 (3*R*,4*S*)	31 (3*R*,4*R*)
from **126**	**13**	92/8	24 (3*R*,4*S*)	-
	14	100/0	42 (3*R*,4*S*)	-
from **127**	**13**	38/62	12 (3*R*,4*R*)	2 (3*S*,4*R*)
	14	74/26	71 (3*R*,4*R*)	46 (3*R*,4*S*)

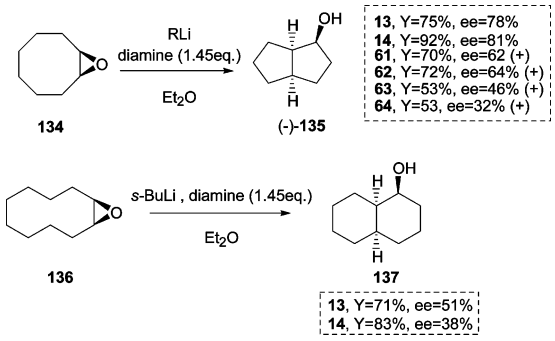
Scheme 30



Scheme 31



Scheme 32



studied by Breeden et al. for the [2,3]-Wittig rearrangement of benzyl prenyl ether **128**.[78] Diamine **131** did not give the rearranged product, while **130** led to **129** with 78% yield but only moderate enantioselectivity (Scheme 30). Use of *n*-BuLi in toluene was found to be the best conditions. Use of THF as solvent or some additives such as HMPA, TMEDA, or lithium chloride was detrimental in most cases. *s*-BuLi as a base was slightly less efficient as well. Among the other ligands tested, several bis(oxazolines) were much more selective leading for the best result to **129** in 66% ee.

2.4. Deprotonation of Epoxides

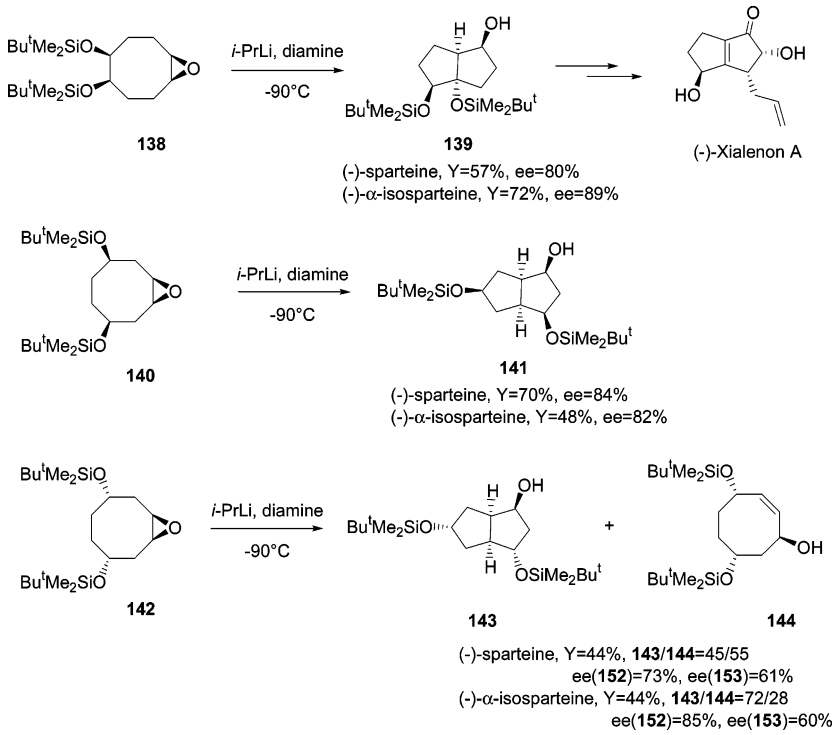
The opening of epoxides has been widely studied and can occur through several pathways. The three possibilities are the direct addition of an organometallic reagent and α or *β* deprotonation. The mechanism of the reaction depends on the structure of the substrate and the base used. After deprotonation, epoxides derived from medium size cycloalkenes undergo an intramolecular rearrangement. Cycloheptene oxide was reported to rearrange predominantly to cycloheptanone using *n*-BuLi in Et_2O−hexane. Deprotonation of epoxide **132** in the presence of (−)-sparteine or (−)-α-isosparteine gave ketone **133** with moderate yield but good enantioselectivity. In this case, (−)-α-isosparteine was the most selective diamine (Scheme 31).[79]

cis-Cyclooctene oxide **134** is a substrate with a very different behavior from **132** since the product is bicyclic alcohol **135** (Scheme 32). This transformation results from the particular shape of medium-sized cycloalkene oxide. It favors an intramolecular hydrogen migration in the oxiranyl anion intermediate leading after transannular cyclization to the bicyclic alcohol **135**. The enantioselectivity obtained for this alcohol was better with (−)-α-isosparteine than with (−)-sparteine (Scheme 32).[80] In contrast, *cis*-cyclodecene oxide **136** gave better selectivity with (−)-sparteine. The organolithium base has to be a secondary organolithium to obtain a good level of enantioselectivity. When the amount of ligand was reduced to 20%, the selectivities obtained were in the same order. With a 1% level of ligand, although the decrease of the enantiomeric excess was significant, (−)-α-isosparteine was still efficient.[81,82]

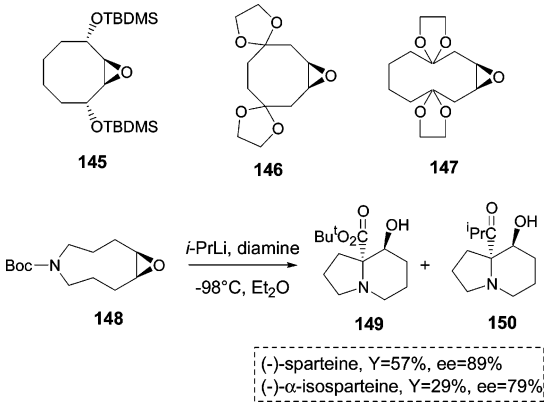
Bispidine derivatives **61**−**64** with various steric hindrance were evaluated by O'Brien et al.[44,83] In this series, the best ee was obtained with the less hindered diamines **61** and **62** which gave comparable selectivities to that obtained with (−)-sparteine. With bulkier nitrogen substituents such as in **63** and **64**, a strong decrease of the selectivities was observed. These results contrast with those obtained with (−)-α-isosparteine, which gave better selectivities than (−)-sparteine although it is a more hindered ligand.

In order to obtain functionalized bicyclic alcohol, the desymmetrization reaction was examined on *cis*-cyclooctene oxide derivatives possessing a protected hydroxyl substituent on the ring.[84] Epoxides **138**, **140**, and **142** are still meso and gave access to interesting polyhydroxylated bicyclic compounds (Scheme 33). The same reaction conditions set up

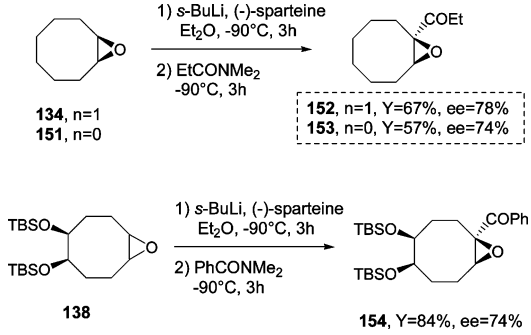
Scheme 33



Scheme 34



Scheme 35



for the *cis*-cyclooctene oxide were applied, and (−)-α-isosparteine was clearly more efficient than (−)-sparteine. This strategy was employed for the first total synthesis of (−)-Xialenon A.[85] The epoxide **142** showed a different reactivity as the bicyclic product **143** was obtained along with the allylic alcohol **144**, which was normally obtained for smaller cyclic epoxide such as cyclohexene oxide. The shape of the cyclooctene ring was sufficiently affected by the presence of the substituent in this position to undergo a different type of rearrangement. In addition, when TMEDA was used as ligand instead of (−)-sparteine or (−)-α-isosparteine, the only product formed was allylic alcohol **144**.

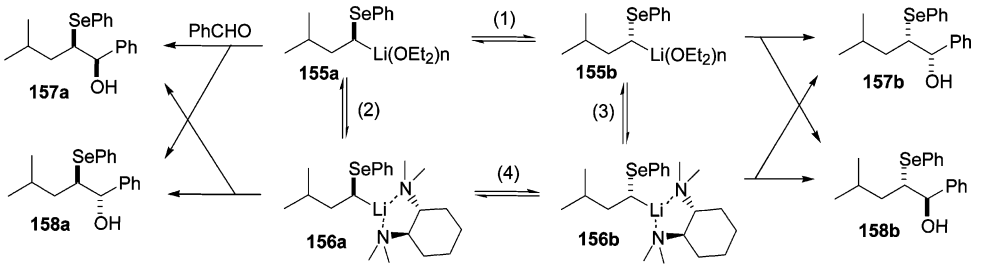
Some other substrates were tried, such as **145** when the protected alcohols are β to the epoxide or **146** and **147** with a ketal function in the ring (Scheme 34).[86] None of the three substrates led to the product; only decomposition occurred. On the other hand, azacyclic epoxide **148** reacted well to give **149** as the major product with 89% and 79% enantioselectivity with (−)-sparteine and (−)-α-isosparteine, respectively. On the other hand, when a catalytic amount of diamine was used, 10 mol % with respect to *i*-PrLi, good levels of induction were obtained and there was only a slight decrease of selectivity. Furthermore, it was observed with this substrate that a partial amount of the organolithium base was incorporated in the product to give compound **150** as the minor product.

As we can see, the chemistry performed on medium-sized cycloalkene oxide does not consider the oxiranyl anion itself as it rearranges very rapidly. Nevertheless, Hodgson et al. were able to set up experimental conditions which ensured its use without losing the epoxide function (Scheme 35).[87,88] After deprotonation at cold temperature, the lithiated species underwent rearrangement as the temperature increased to room temperature overnight. On the other hand, the oxiranyl anion was trapped when an electrophile was added at −90 °C shortly after deprotonation. Substrates derived from cyclooctene oxide **134** were used successfully with a wide range of electrophiles, leading to the corresponding trisubstituted enantioenriched epoxide in good isolated yield. While simple cyclopentene oxide **151** gave good results, a few of its derivatives did not work successfully.

3. Configurational Stability of Organolithium Compounds

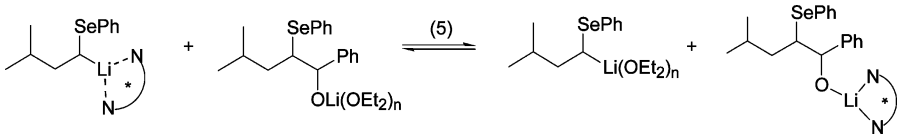
Deprotonation reactions can lead to chiral lithiated species, and it is necessary to know about their configurational

Scheme 36[a]



[a] Reproduced from ref 96a by permission of the Royal Society of Chemistry.

Scheme 37[a]



[a] Reproduced from ref 96a by permission of the Royal Society of Chemistry.

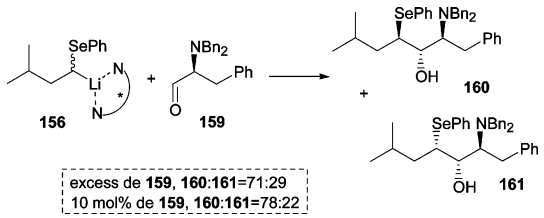
stability. Several types of organolithium species are known to racemize, even at low temperature, such as allyl,[89] benzyl,[90] α-seleno,[91,92] and α-thio.[93] Nevertheless, there are examples of their use in asymmetric synthesis in combination with (−)-sparteine as shown by the pioneering example of Noyori with α-methylbenzyllithium.[94]

It is clear that complexation of an organolithium species by a diamine can influence its configurational stability and behavior in an asymmetric process. Hoffmann used a test he developed[95] to study the case of α-phenylselenoalkyllithium complexed by tertiary diamines (Scheme 36).[96] Equilibria 2 and 3 show the competition for complexation of the organolithium between *N*,*N*,*N*′,*N*′-tetramethyl-*trans*-1,2-cyclohexanediamine **7** and the solvent (Et_2O). Equilibria 1 and 4 show the possibility of inversion of the configuration of the organolithium. When the complex RLi/diamine reacts with benzaldehyde, two sets of diastereoisomers **157** and **158** can be obtained.

The reaction between the free organolithium and benzaldehyde gave a selectivity for **157**/**158** of 55/45, whereas in the presence of **7** the ratio was 78/28. In the case of a shortage of diamine, the selectivity stayed the same as at the beginning of the reaction. However, as the amount of benzaldehyde was increased, the ratio became closer to that characteristic of the noncomplexed organolithium **155**. This result showed that complex RLi/**7** reacts faster than the free organolithium and that equilibrium 5 exists (Scheme 37).

To determine if the complex is configurationally stable, Hoffmann's test was used. It is based on the observation of the stereochemical outcome of the reaction with α-aminoaldehyde **159**. In the present case, the complexed organolithium **156** was reacted either with an excess of electrophile or with 10% (Scheme 38). The differences between the two ratios showed the kinetic resolution existing between the two complexes, one reacting 1.5 times faster than the other. Furthermore, the ratio obtained (**160**/**161**) with an excess of aldehyde was close to that obtained by ^{77}Se NMR for **156** (ratio of 70/30). We can therefore conclude that the addition reaction was faster than the isomerization. A competition experiment showed that benzaldehyde reacts 2.2 times faster than **159**; the conclusion was then also true for benzaldehyde. The situation cannot be described by the Curtin−Hammett principle but represents a case of dynamic thermodynamic resolution.

Scheme 38[a]



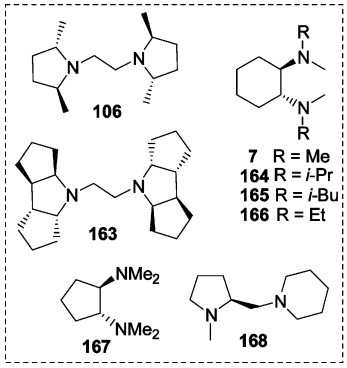
[a] Reproduced from ref 96a by permission of the Royal Society of Chemistry.

The measure of enantiomeric excess of **157** and **158** shows that both diastereoisomers are formed with similar selectivity, respectively, 40% and 44%. Both complexes react with approximately equal selectivity as long as the addition reaction is faster than the equilibrium regardless of the electrophile. This was also verified in the case of fluorodimethoxyborane and isopropylisocyanate.

Few other organolithium−diamine complexes were studied.[97] We collected in Scheme 39 the diastereoisomeric ratios measured by ^{77}Se NMR of α-phenylselanylalkyllithium **155** or **162** complexed by several C_2-symmetric tertiary diamines. Indeed, diamine **167** led to a very good diastereoselectivity of complexation (9/1). Addition of **155** complexed by 2 equiv of diamine **167** to benzaldehyde resulted in a ratio of diastereoisomers of 68/32 in 74% and 86% enantiomeric excess, respectively. On the other hand, in a shortage of ligand (0.5 equiv of ligand and 0.15 equiv of benzaldehyde), a ratio of 62/38 was obtained in 44% and 46% enantiomeric excess, respectively. The difference in these diastereoisomeric ratios proves that free and complexed organolithium species **155** and **156** react with similar rates. It means that diamine **167** does not increase the rate of addition.

According to the ^{77}Se NMR experiment, diamine **165** afforded two complexes in a 3/1 ratio, close that obtained with diamine **7**. On the other hand, with 1.4 equiv of diamine, the diastereoselectivity of the addition on benzaldehyde was 56/44 and enantiomeric excesses were low (16% and −12%). Indeed, the adduct came from the reaction of the free organolithium. In this case, the diamine slows down the rate of the reaction. Because of the low concentration of the free organolithium due to the complexation equilibrium, addition on the benzaldehyde was also decreased. It follows that isomerization became faster than addition and the Curtin−Hammett principle applies. These examples showed that

Scheme 39



diastereomeric ratio measured by ^{77}Se NMR

155	**7** - 72/28 **164** - 55/45 **165** - 75/25 **166** - 50/50 **167** - 90/10
162	**13** - 60/40 **106** - 62/38 **163** - 59/41 **168** - 68/32

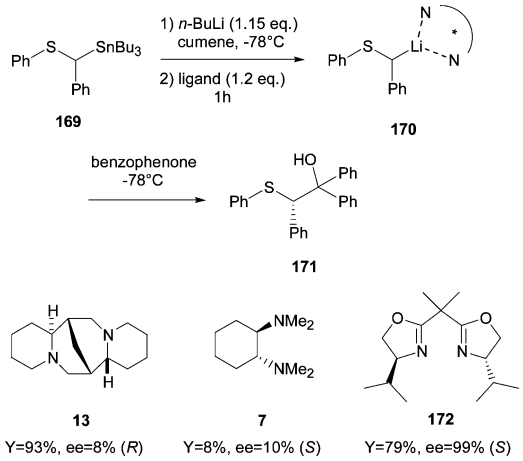
reaction of **155** and benzaldehyde

diamine	de complexation (%)	de reaction (%)	ee(**157**)/ee(**158**)
-	-	10	-
7 (1.8 eq.)	40	44	40 / 44
167 (2 eq.)	80	36	74 / 86
165 (1.4 eq.)	50	12	16 / -12

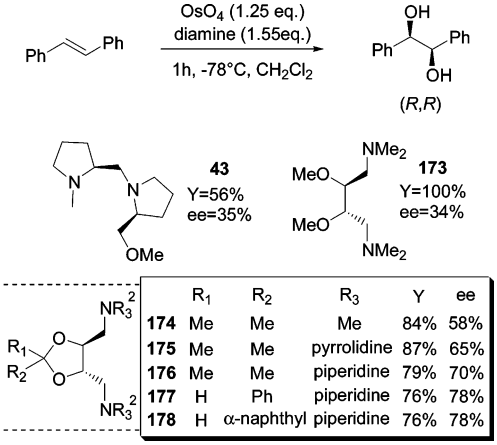
diamines with very similar structures can have a very different influence on the organolithium species with which they are complexed. Scheme 39 sums up the results obtained with diamines **7**, **165**, and **167** and gives a comparison of their behavior as a ligand in the reaction of organolithium **155** with benzaldehyde.

Toru et al. used the configurationally unstable behavior of α-thiobenzyllithium **170** to perform a dynamic resolution by association with diamines and bisoxazolines.[98] In the case of this kind of organolithium compounds, it was found that (−)-sparteine and **7** gave very low selectivity. However, bisoxazoline **172** showed excellent chiral induction. It was confirmed by Hoffmann's test in the same study that **170** was not configurationally stable. Some other α-lithio aryl benzyl sulfides were studied, but lower selectivities were obtained. The reason suggested was that bulkier substituents on sulfur increase the configurational stability of **170**. A strong influence of the aryl substituent was observed as when it was 2-pyridyl; the reaction proceeded through a dynamic thermodynamic resolution with inversion of configuration of the carbanionic center.

Scheme 40



Scheme 41



	R_1	R_2	R_3	Y	ee
174	Me	Me	Me	84%	58%
175	Me	Me	pyrrolidine	87%	65%
176	Me	Me	piperidine	79%	70%
177	H	Ph	piperidine	76%	78%
178	H	α-naphthyl	piperidine	76%	78%

4. Oxidation Reactions

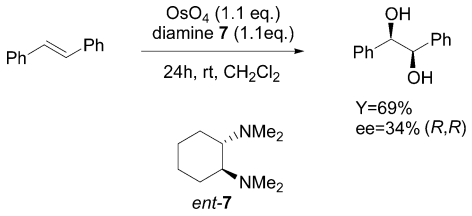
4.1. Olefin Dihydroxylation

Since the discovery of the acceleration of the rate of alkene dihydroxylation with osmium tetroxide in the presence of nitrogen ligand,[99] many catalytic or stoichiometric asymmetric systems have been developed. Intensive work has been carried out to improve the reactivity of the oxidative complex and the selectivity of the diols obtained.[100] Tertiary diamines have been used for their binding properties with metal and for the stability of the intermediate complex. Although very high selectivities have been achieved with bidentate diamines, the osmium glycolate diamine complex formed during the reaction is too stable and prevents any possibility of in situ recycling the osmium and the ligand. Nevertheless, numerous diamines have been tested with various structures, and they will be presented in this section.

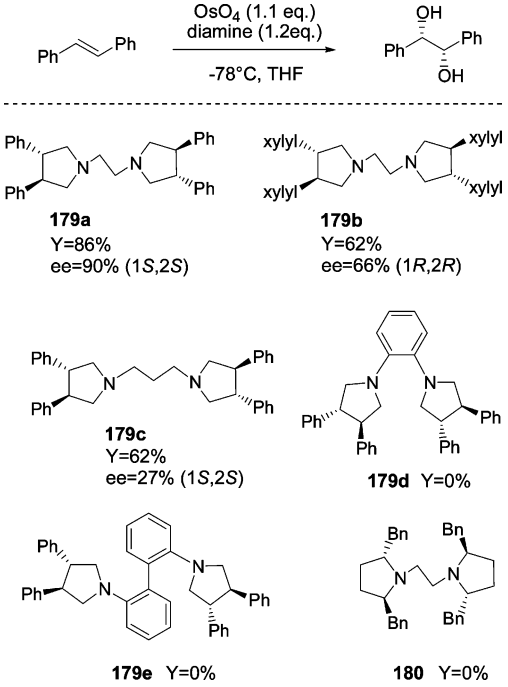
In 1986, Yamada was the first to use tertiary diamines in this reaction.[101] All of the ligands were prepared from readily available L-tartaric acid. The nitrogen substituent and nature of the acetal both had a strong influence on the enantioselectivity. The best result was obtained when the nitrogen bears a piperidino group (Scheme 41). The variation on the acetal showed that the most bulky substituent led to high enantiomeric excess in the case of *trans*-stilbene. When the reaction was carried out at −100 °C, up to 90% ee was obtained with diamine **178**. The selectivity was poorer with other substrates. Indeed, it seems that the olefin needs to be substituted with an aromatic group to undergo selective oxidation. Several silylketene acetals were tested leading to very useful α-hydroxyesters, and enantiomeric excesses up to 66% were achieved. These are the only examples of α-ester hydroxylation; all other diamines were used with classical olefins.

Snider used (*S*,*S*)-*N*,*N*,*N*′,*N*′-tetramethyl-*trans*-1,2-cyclohexanediamine *ent*-**7**, and interesting differences compared to Yamada's experimental conditions can be noticed (Scheme 42).[102] All reactions were run in dichloromethane using 1.1 equiv of osmium tetroxide and *ent*-**7** at room temperature. The reactivity was much lower than in Yamada's system with the reaction taking several hours at room temperature. The best selectivity was obtained with 1-heptene, leading to

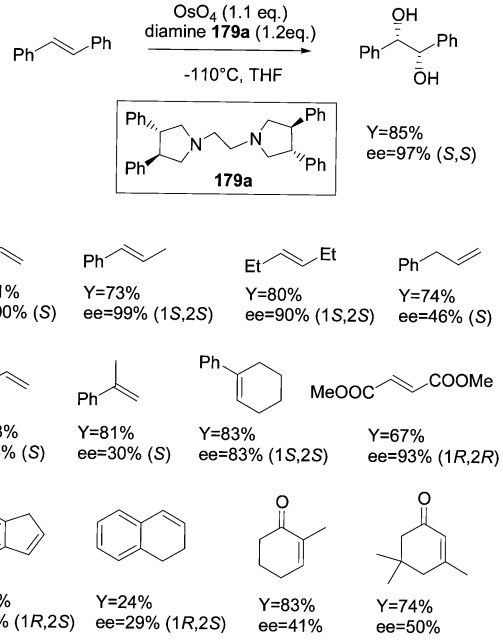
Scheme 42



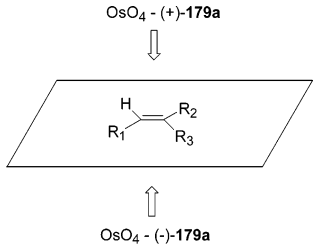
Scheme 43



Scheme 44



Scheme 45



the diol in 86% ee, but when the temperature was lowered to −35 °C, a decrease in selectivity was observed. While dimethylfumarate reacts well despite a moderate enantioselectivity, chalcone was totally inert to the oxidative conditions.

In 1987, Tomioka et al. described diamines **179** which consist of two *trans*-3,4-diphenylpyrrolidine units linked by a spacer.[103] In this case, reactions were run in THF as solvent with 1.1 equiv of OsO_4 and 1.2 equiv of diamine at −78 °C (Scheme 43). The results obtained showed that the ethylene spacer was more efficient than the trimethylene, 1,2-phenylene, or 2,2′-biphenylene. When the pyrrolidine moiety was substituted in the 2,2′,5,5′ position, such as for **180**, no oxidation product was formed. A very surprising result was obtained with diamine **179b** as the product of the oxidation of *trans*-stilbene was obtained with good enantioselectivity but with the opposite absolute configuration of that obtained with **179a**. This inversion of facial selectivity was also observed with styrene, while the other substrate gave low selectivity but the same enantiomer as **179a**. These very particular results were related to the mechanism of the oxidation process and will be discussed later.

Diamine **179a** was selected to carry on the study in the same reaction conditions but at lower temperature (Scheme 44). Diols obtained from styrene and *trans*-di- and trisubstituted olefins were isolated in high enantiomeric excesses. On the other hand, few other substrates, among which *cis* and *gem* disubstituted olefins, did not give good selectivities.

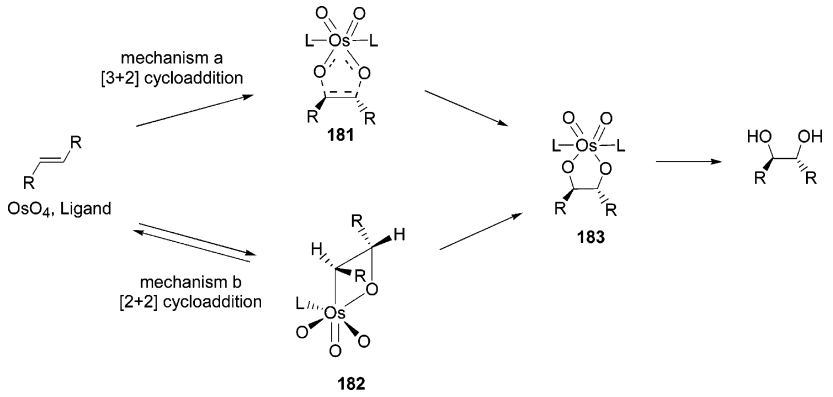
The face selected by the OsO_4−diamine complex is shown in Scheme 45. Solvent effects were studied with *trans*-stilbene at −78 °C. Significant variations of reactivity and selectivity were observed when the solvent was changed from THF to diethyl ether, toluene, dichloromethane, or dimethoxy ether.

Two mechanisms were proposed for the dihydroxylation of alkene with osmium tetroxide (Scheme 46). The first, initially suggested by Böeseken and supported by Corey, is a direct [3 + 2] cycloaddition between the alkene double bond and the osmium tetroxide with a concerted five-membered cyclic transition state **181**.[104,105] The second, supported by Sharpless et al., involves a fast, reversible [2 + 2] cycloaddition of the alkene and the Os−O double bond leading to a metallocyclic intermediate **182**.[106] It subsequently undergoes a rate-determining rearrangement to form the osmate ester **183**.

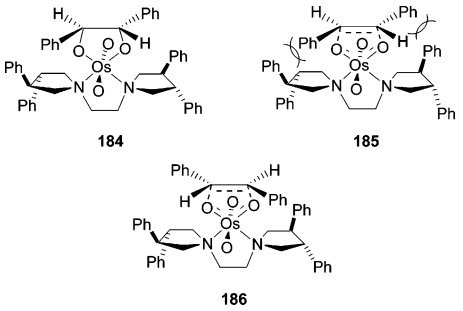
On the basis of their experimental data, Tomioka et al. proposed a stepwise mechanism involving intermediate **182**. The osmate ester (VI) diamine complex obtained during the oxidation reaction was isolated and characterized. The structure determined by X-ray crystallography was **184**.[103b,e] The two transition states of the [3 + 2] cycloaddition were **185** and **186.** However, the prediction obtained with this model led to the wrong enantiomer as **186** would have been the favored transition state.

Considering the mechanism involving the [2 + 2] cycloaddition, they were able to explain the stereochemical outcome of the reaction (Scheme 48. The case of diamine **179a**, formation of **187** which was favored over the three other metallocycles, can explain the formation of the enantiomer obtained (the disfavored interactions are indicated

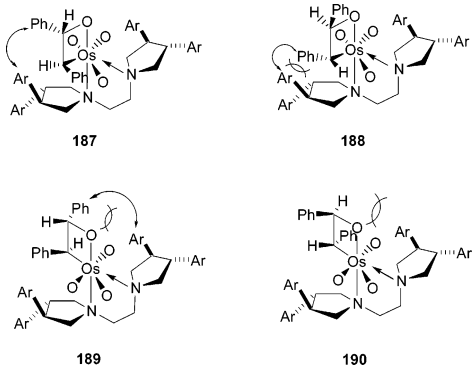
Scheme 46



Scheme 47



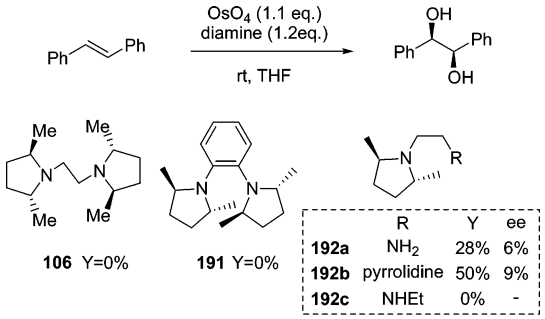
Scheme 48



with the cross). On the contrary, when diamine **179b** was used, the steric interactions increase in **187** (double arrow) and the reaction may occur to some extent through **190**. Nevertheless, these mechanistic considerations were seriously criticized by Corey and Houk. Calculations showed that the qualitative prediction discussed in Scheme 47 was wrong and that transition structure **185** was more stable than **186** by 1.5 kcal/mol.[107] Contrary to what was thought, the result of the calculations pointed out that the steric interactions in the transition structure are quite different from those in the osmate product. At the time of the study the mechanism of the reaction was still unclear and the [2 + 2] and [3 + 2] pathways were under debate. However, it is now recognized that the reaction goes via the [3 + 2] pathway.[108]

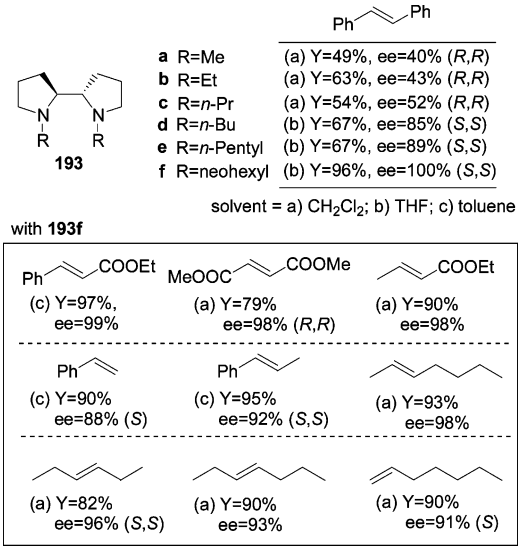
Robinson et al. reported the use of hindered diamines **191** and **106** which are nitrogen analogues of Me-DuPHOS and Me-BPE (Scheme 49).[109] In their study, diamines **192a**−**c** were also evaluated. They found that all these ligands led to the diol with low yield and selectivity. ^{1}H NMR studies showed that diamine **106** is not able to displace pyridine in the bis(pyridine) osmium glycolate complex obtained with *trans*-stilbene. Molecular modeling of the osmate ester of

Scheme 49



	R	Y	ee
192a	NH_2	28%	6%
192b	pyrrolidine	50%	9%
192c	NHEt	0%	-

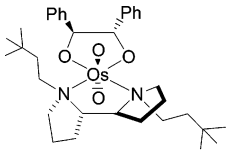
Scheme 50



106 indicated that the methyl group impedes the access to the axial oxygen atoms but allowed free access to the equatorial oxygens. On the basis of the mechanism proposed by Corey in which one axial and one equatorial oxygen are involved in formation of a five-membered transition state with the alkene, it was assumed that the lack of accessibility might be responsible for the lack of reactivity.

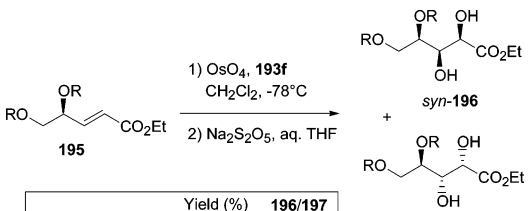
In 1989, Hirama introduced the *N*,*N*′-dialkyl-2,2′-bipyrrolidine **193** as a very efficient ligand for asymmetric dihydroxylation (Scheme 50).[110] Several derivatives were studied, and solvent effects were also evaluated. The reactions were run with 1.1 equiv of osmium tetroxide and 1.2 equiv of diamine at −78 °C. While the reaction in dichloromethane with **193a**−**c** led to the (*R*,*R*)-diol, the opposite selectivity was observed in toluene with **193d**−**f**. Furthermore, (*S*,*S*) selectivity increased in toluene as the length of

Scheme 51



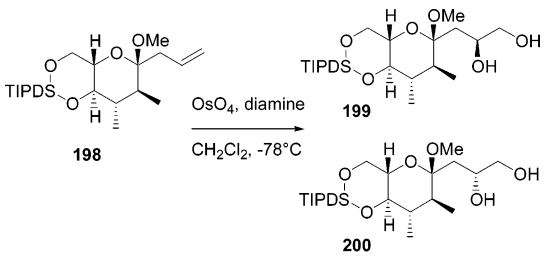
194

Scheme 52



		Yield (%)	196/197
R=Ac	no diamine	79	1/4.1
	193f	93	17/1
	ent-**193f**	97	1/23
R=Me	no diamine	64	1/7.4
	193f	72	15/1
	ent-**193f**	73	1/>50

Scheme 53



no diamine, Y=76%, **199**/**200** = 1/1
diamine **193f**, Y=60%, **199**/**200** > 10/1
diamine *ent*-**193f**, Y=77%, **199**/**200** < 1/10

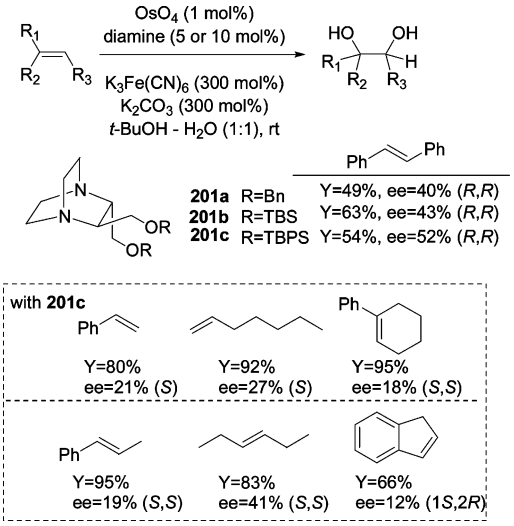
the alkyl group increased. Diamine **193f**, which had a neohexyl substituent on the nitrogen, gave the best result with complete control of selectivity. The solvent effects were not explained, but weak complexes between OsO_4 and aromatic compounds are well known and might be taken into account for the mechanistic discussion. The other substrates were dihydroxylated in the presence of diamine **193f**, and very high enantiomeric excesses were obtained in most cases. Olefins conjugated with a phenyl group gave a better result in toluene, while nonaromatic olefins did so in nonaromatic solvent.

The osmium(VI) glycolate ester−diamine complex **194** was prepared from OsO_4, diamine **193f**, and stilbene in toluene. The complex is octahedral and free of toluene. Both phenyl groups are facing the bulky neohexyl substituent as is the case with Tomioka's diamine (Scheme 51).

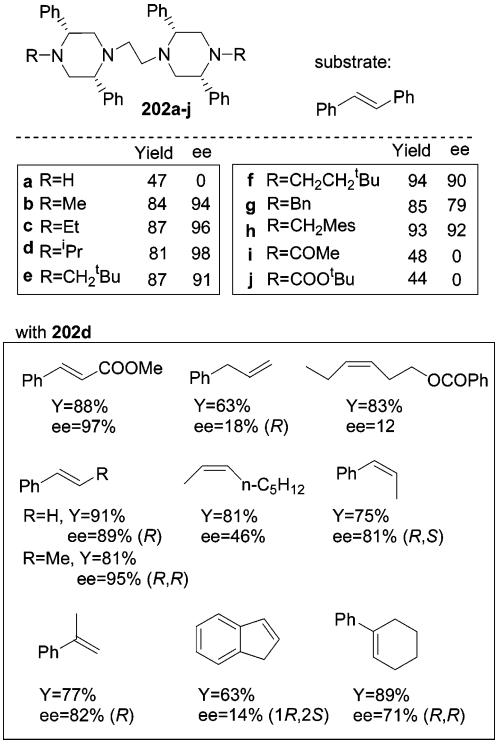
The asymmetric dihydroxylation of chiral substrates such as **195** using **193f** increased the diastereoselectivity in favor of either the syn or the anti product (Scheme 52). Diamine *ent*-**193f** favored hydroxylation on the less hindered side of the olefin and formed a matched pair with **195**. Very high diastereoselectivities were obtained in this case. Although diamine **193f** formed the mismatched pair, selectivities were still very good. This reagent control of diastereomers was used for the synthesis of the LM ring moiety of ciguatoxin.

Hirama et al. reported in 1992 the use of a chiral derivative of DABCO (Scheme 54).[111] As bidentate diamines are usually used in a stoichiometric amount and at cold temperature, the monodentate C_2-symmetric tertiary diamines **201** have a behavior closer to that of the cinchona alkaloids used by Sharpless. The osmium tetroxide was used in catalytic amounts and recycled with potassium hexacyanoferrate(III) [$K_3Fe(CN)_6$] as the stoichiometric cooxidant. Diamine **201c** was the best of the three ligands tested. Although the selectivities were low, the need for only a catalytic amount of OsO_4 and diamine make this system very advantageous.

Scheme 54



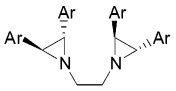
Scheme 55



		Yield	ee
a	R=H	47	0
b	R=Me	84	94
c	R=Et	87	96
d	R=^{i}Pr	81	98
e	R=$CH_2{}^t$Bu	87	91
f	R=$CH_2CH_2{}^t$Bu	94	90
g	R=Bn	85	79
h	R=CH_2Mes	93	92
i	R=COMe	48	0
j	R=COO^{t}Bu	44	0

In 1992, Fuji et al. reported the use of bis-piperazine in order to improve the results obtained previously with monocyclic piperazine derivatives.[112] The reactions were carried out in toluene at −78 °C with 1.1 equiv of osmium tetroxide and 1.2 equiv of diamine. Scheme 55 summarizes the results obtained for oxidation of *trans*-stilbene. Decreasing the temperature to −100 °C did not improve the ee. While several diamines gave ee better than 90%, the best

Scheme 56



203a	R=Ph	Y=90%, ee=95% (*S*,*S*)
203b	R=*p*-FC_6H_4	Y=75%, ee=83% (*S*,*S*)
203c	R=Bn	Y=78%, ee=33% (*S*,*S*)
203d	R=CH_2OBn	Y=61%, ee=6% (*S*,*S*)

ligand was **202d** in which the nitrogens are substituted with isopropyl groups. As shown in Scheme 55, the selectivities were significantly influenced by the R substituent. When this substituent was a hydrogen atom or a carbonyl group, the diols were obtained without any selectivity. As usual, a strong solvent effect was observed, no reaction occurred in THF, and lower results were obtained in CH_2Cl_2. When the spacer between the two piperazine rings was three or four methylene units, the reaction was completely suppressed. The five-membered coordination in the osmate ester complex was an essential factor for the reaction. Other olefins were oxidized with **202d** in toluene at −78 °C. High levels of selectivity were obtained with *trans*-disubstituted olefins as well as mono- and disubstituted terminal olefins, especially those bearing aromatic substituents. On the contrary, *cis*-olefins proved to be less good substrates.

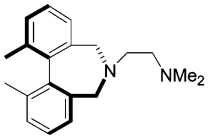
C_2-symmetric bis(aziridines) **203** were developed by Tanner et al. in 1994.[113] This study was based on the known hyperconjugative stabilization in 2,3-disubstituted aziridines which also occurred for diamines **203**.[114] The orbital interactions between the phenyl moiety and the bent bonds of the three-membered ring are maximized when the planes of the aryl group are arranged nearly perpendicular to the plane of the heterocyclic ring. Another effect which can be taken into account is the possible hyperconjugative interaction between the nitrogen lone pair and the π system of the aromatic ring. The lower inversion barrier for **203a** compared to **203c** (60 and 84 kJ·mol^{-1}, respectively) can be explained by these interactions as they tend to flatten the nitrogen and bring it closer to the planar situation it has in the transition state of the inversion.

The reactions were carried out on *trans*-stilbene in toluene at −78 °C (Scheme 56). The most hindered diamine **203a** was the most efficient. As a general trend, the further the phenyl ring was, the lower the selectivity.

Haubenstock et al. studied the efficiency of atropoisomeric diamine ligand **204**[115] which was initially introduced by Suda et al. for asymmetric polymerization.[116] Dihydroxylation of *trans*-stilbene was carried out in THF at −80 °C, and the corresponding diol was obtained in 96% ee. When the reaction was carried out at room temperature, the diol was obtained in 76% ee. The authors added that (*R*)- or (*S*)-2,2′-bis(dimethylamino)-6,6′-dimethylbiphenyl is an ineffective catalyst for the dihydroxylation of stilbene and 1-heptene.

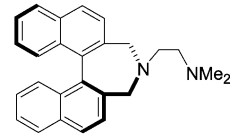
On the basis of these results, Salvadori studied atropoisomeric diamine **205** which was previously developed by Cram and Mazaleyrat.[117,118] The reactions were carried out in THF at −78 °C with a molar ratio of olefin/OsO_4/(*S*)-**205** = 1/1/1. The same characteristics of the asymmetric dihydroxylation, previously noticed with the other diamines, were observed. There was a strong temperature effect on the ee, and *trans*-disubstituted and terminal conjugated olefins were the most suitable substrates. In the specific case of *trans*-stilbene, up to 98% ee was achieved. Only moderate ee's were obtained with nonconjugated and cis olefins. Another

Scheme 57



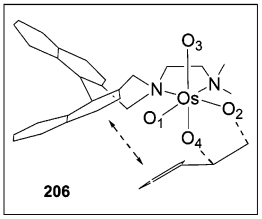
204

at -80°C, Y=94%, ee=96%
at +25°C, Y=70%, ee=76%



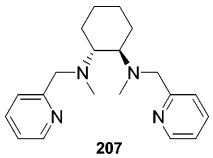
205

at -78°C, Y=47%, ee=98% (*R*,*R*)



206

Scheme 58



207

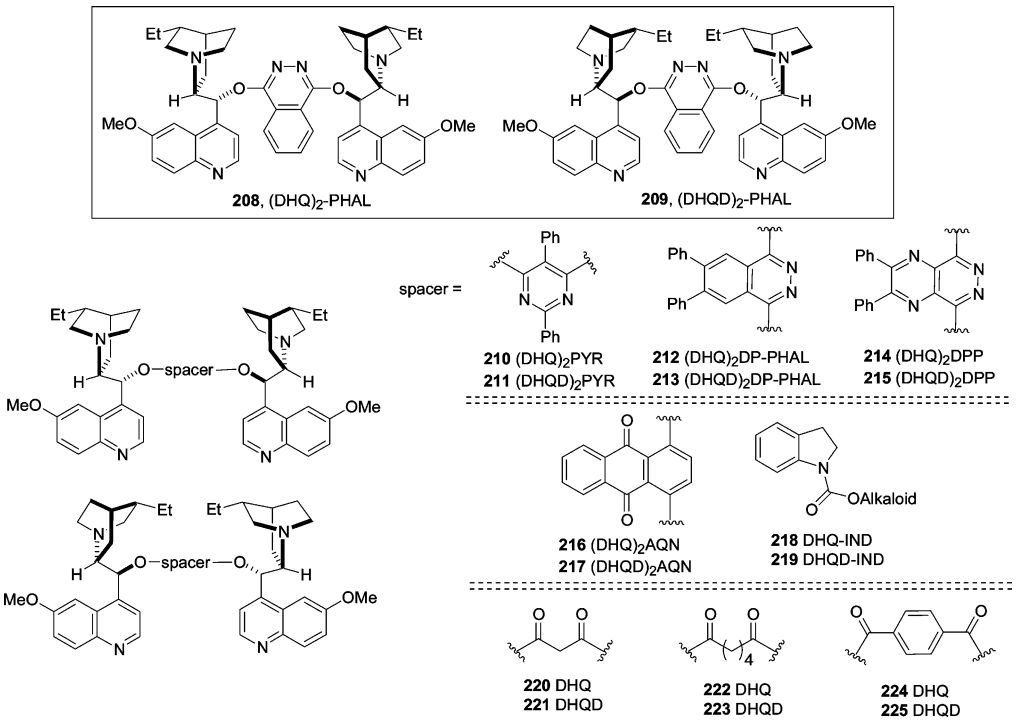
interesting point is that nonlinear effects were absent in this reaction.

The model **206** was suggested to explain the stereochemical outcome of the reaction. Due to the steric hindrance caused by the CH_2 groups around O_1 and O_3 it is only possible for the olefin to coordinate to O_2 and O_4. The proposed pathway for the oxidation is the [3 + 2] mechanism described by Corey. The aromatic substituent is placed near the binaphthyl moiety, exposing the reactive site to the *si* face of the olefin. A $\pi-\pi$ interaction between the two aromatic moieties stabilizes this transition state (Scheme 57). The other approach would have been to place the aromatic substituent near the dimethylamino group and induce a significant steric repulsion. For the substrates without conjugated aromatic substituents, there is no stabilizing $\pi-\pi$ interaction to favor the *si* approach of the olefin. The other possible pathway, namely, addition on the *re* face, becomes nearer in energy and lower ee's were obtained for these substrates. In the case of indene, it was shown that steric repulsion between the CH_2 group of indene and one naphthyl ring prevents a full $\pi-\pi$ interaction.

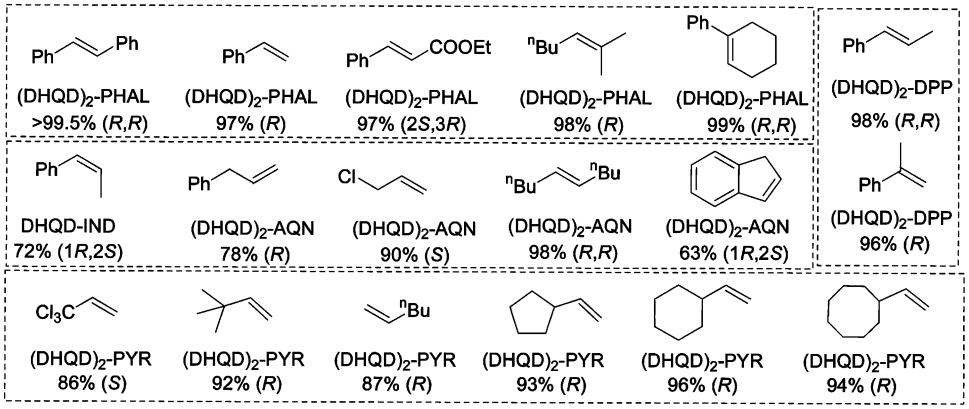
In 2001, as an alternative to the osmium-based oxidation, Que et al. reported the first iron-catalyzed asymmetric dihydroxylation.[119] Despite the fact that the reaction led to a mixture of diol and epoxide, they set up conditions to perform the reaction and produce dihydroxylated product in ee's up to 88%. The best ligand was found to be **207**. It can be noted that this ligand was also used in other oxidation processes.[120]

Dihydroquinine DHQ and dihydroquinuclidine DHQD have become very famous ligands for asymmetric olefin dihydroxylation. The dimer derivatives developed by Sharpless et al.,[121a] abbreviated $(DHQ)_2$-PHAL **208** and $(DHQD)_2$-PHAL **209** and used in AD-mix-α and AD-mix-β, respectively, are the most efficient. Since the discovery of the effectiveness of these ligands, the design of others to improve upon the moderate selectivity obtained in reactions involving terminal and cis olefin has become an interesting challenge. The Sharpless ligands **208**−**219** outlined in Scheme 59 are the most efficient C_2-symmetric ligands. The three classes

Scheme 59



Scheme 60



of ligands PHAL, PYR, and IND are complementary, and with suitable choice of ligand, almost any olefin can be dihydroxylated efficiently.[100] More recently, the AQN class of ligand turned out to be even more efficient than PHAL and PYR, while IND is still needed in the specific case of cis olefin.[121c] Ligands **220**−**225** were studied by Lohray for mechanistic considerations.[122] Sharpless' asymmetric dihydroxylation has already been discussed in a more detailed review.[100] Nevertheless, in order to give some comparison with the results obtained with diamines, some examples are shown in Scheme 60.

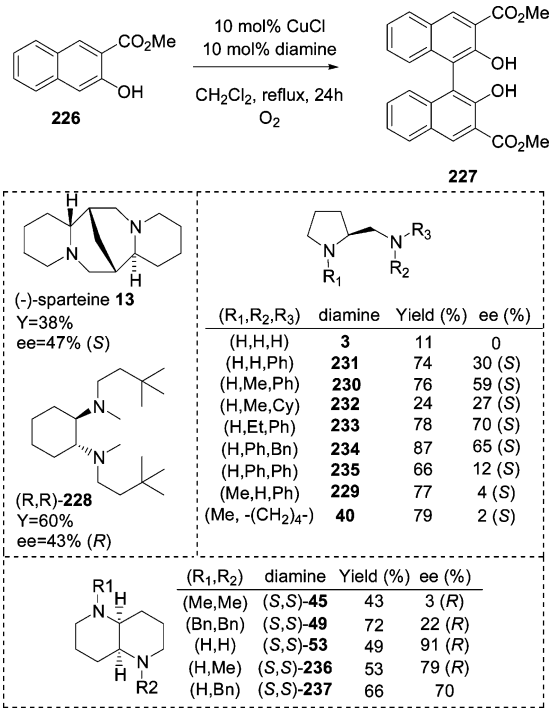
4.2. Olefin Aminohydroxylation

Sharpless and co-workers first reported the aminohydroxylation of olefin in 1975, but the one-step catalytic enantioselective method appeared in 1996.[123] Several methods which differed only in the nature of the nitrogen source have been developed. The first source used was the chloramine salt of tosylsulfonamide, but it was not of general efficiency. The other procedures developed using alternative sources of nitrogen have extended the efficiency of the reaction to a large number of olefins.[124] The regioselectivity is highly dependent on the reaction conditions and substrates. Reversal of regioselectivity can be observed by changing the ligand, solvent system, substituents on the substrate, and N-protecting group introduced.[124] For cyclic allylic carbamates, the nitrogen is delivered intramolecularly and ensures the regioselectivity of the aminohydroxylation.[125]

4.3. Oxidative Coupling

Homochiral 1,1′-binaphthalene derivatives have become very common chiral inducers in a broad area of asymmetric synthesis.[126] Their preparation in an enantiopure manner has also become extensively studied, and many different kinds of methods have been reported.[126] Among these, the enantioselective oxidative coupling of 2-naphthol derivatives, which was first attempted by Wynberg et al.,[127] has recently received more attention in a catalytic version. The first enantioselective oxidative coupling using a chiral copper−amine complex as catalyst was introduced by Nakajima et al. in 1995.[128] The ligands used were diamines derived from L-proline because of their availability and sterically rigid conformation in chelation. Tertiary diamines **40** and **13** were tested along with primary-secondary diamine **3** and second-

Scheme 61



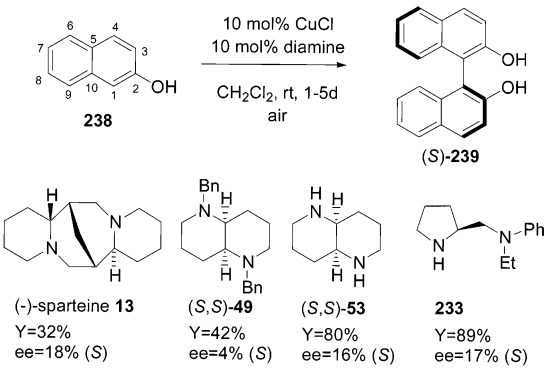
ary-tertiary diamines **229**−**235**. On the basis of that study, Kozlowski et al. reported in 2001 the use of 1,5-diaza-*cis*-decalin derivatives containing bis-tertiary, bis-secondary, or secondary-tertiary nitrogen atoms (Scheme 61).[129] In both works, the conditions of the reaction were set up by studying solvent and salt effects. The reactions were best carried out with copper(I) salt in refluxing dichloromethane, dichloroethane, or acetonitrile under oxygen atmosphere. Almost all the copper(I) sources provided the product with the same level of enantioselectivity, but the counterion effects were relevant to turnover. The copper(II) sources led in some case to good yield but always with lower selectivities except for $Cu(BF_4)_2$.

Among bis-tertiary diamines, sparteine led to (*S*)-**227** with 47% of enantiomeric excess, which is the best result for this type of diamine. Alexakis et al. used diamine **228** derived from (1*R*,2*R*)-*trans*-cyclohexanediamine, which gave the coupling product in 43% ee in favor of the *R* enantiomer.[130] Among proline-based ligands developed by Nakajima, the best ligands were those which bear a lateral tertiary nitrogen atom and a nonsubstituted cyclic nitrogen. Particularly, diamine **233** led to the best selectivity leading to (*S*)-**227** in 70% ee. The presence of a secondary nitrogen was also found to be crucial for Kozlowski's ligand. Nevertheless, in this case, the bis-secondary diamine (*S*,*S*)-**53** was far better leading to (*R*)-**227** in 91% ee.

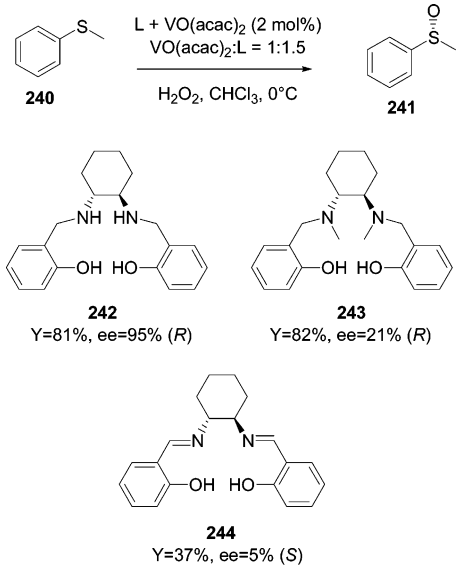
For the oxidation of 2-naphthol, overoxidation occurred under an oxygen atmosphere and the reaction had to be done under air, which reduced formation of byproduct. Diamines (*S*)-**233** and (*S*,*S*)-**53** gave (*S*)-**239** in 17% and 16% ee, respectively. In contrast to substrate **226**, which was oxidized to (*R*)-**227** with (*S*,*S*)-**53**, 2-naphthol **238** led to (*S*)-Binol **239** (Scheme 62).

A number of other substrates were investigated by Kozlowski, and the influence of the C3 substituent was particularly examined. As the best ligand for the reaction was **53** in the preliminary study, all of the following investigations were carried out using it. Interestingly, when the C3 substituent was $P(O)Ph_2$, 96% ee was obtained for the dimerized product.[131] This reaction was applied for the synthesis of perylenequinones and Nigerone, which are natural products containing axial chirality.[132]

Scheme 62



Scheme 63



From a mechanistic point of view, the reaction proceeded through a radical coupling of a tetrahedral copper(I) intermediate. The product was tested by treating racemic **239** under normal reaction conditions. No deracemization of **239** was observed, excluding the possibility of a second-order asymmetric transformation. Furthermore, the Hammett analysis and stereochemical models supported the mechanism, which implies an enantioselective coupling through the radical intermediate.[131]

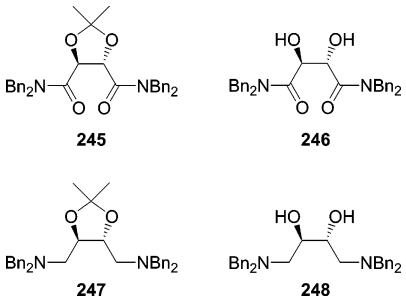
4.4. Sulfide Oxidation

The synthesis of chiral sulfoxide compounds via a direct asymmetric oxidation of sulfide was initially studied by Kagan with a modified Sharpless reagent.[133] Zhu et al. used vanadium complexes and tested the C_2-symmetric tertiary diamines **243** along with salan ligand **242** and salen ligand **244**.[134] The selectivities obtained with **242** were excellent, but when the nitrogens were methylated, the ee decreased to 21% and 37% in $CHCl_3$ and CH_2Cl_2, respectively (Scheme 63).

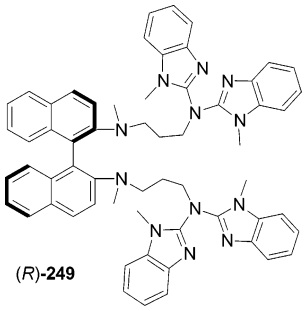
4.5. Baeyer–Villiger Oxidation

Several oxidative systems were developed for the asymmetric Baeyer−Villiger oxidation of ketones.[135] Nevertheless,

Scheme 64



Scheme 65



C_2-symmetric diamine ligands were only used by Lopp et al. (Scheme 64).[136] They tested several derivatives of tartaric acid in catalytic amount with two different reaction conditions consisting of a Lewis acid ($Ti(OiPr)_4$ or $Cu(OTf)_2$), the ligand, and an oxidant (*t*-BuOOH or O_2). The results obtained were low, in terms of both yields and enantioselectivities (up to 37% ee), for all the ligands regardless to the oxidative system used.

4.6. Oxidation with Biomimetic Copper Complexes

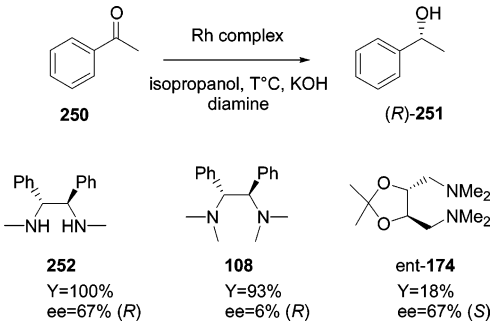
The dinuclear and trinuclear copper(II) complexes $[Cu_2(\mathbf{249})]^{4+}$ and $[Cu_3(\mathbf{249})]^{6+}$ derived from both (*R*)- and (*S*)-**249** were evaluated in the biomimetic oxidation of catechol derivatives L- and D-Dopa and their methyl esters (Scheme 65).[137] The unstable *o*-quinone products were trapped by formation of adducts with 3-methyl-2-benzothiazolinone hydrazone (MBTH). The kinetics parameters of the oxidation were recorded. The enantioselectivity in catalytic reactions can be described by the ratio $R = [(k_{cat}/K_M)_L - (k_{cat}/K_M)_D]/[(k_{cat}/K_M)_L + (k_{cat}/K_M)_D]$. This corresponds to a selectivity for the oxidation of L/D-Dopa and L/D-DopaOMe by $[Cu_2(R\text{-}\mathbf{249})]^{4+}$ of 35% and 31%, respectively. The complex $[Cu_3(R\text{-}\mathbf{249})]^{6+}$ was not selective for L/D-Dopa but showed 24% of selectivity for both L/D-DopaOMe. In oxidations using (*R*)-**249**, the preferred substrate had the L configuration. A dramatic increase of selectivities was observed with (*S*)-**249**. Complex $[Cu_2(S\text{-}\mathbf{249})]^{4+}$ led to 74% ee for the oxidation of L/D-DopaOMe, which is the highest reported so far for catalytic oxidation of Dopa derivatives by biomimetic Cu complexes. The selectivity dropped to 20% for L/D-Dopa. Complex $[Cu_3(S\text{-}\mathbf{249})]^{6+}$ was even less selective.

5. Reduction Reactions

5.1. Hydrogen Transfer

The most common reductive process which uses tertiary diamines is the asymmetric hydrogen transfer. Many ligands have been used in this reaction,[138] but it was only in 1993 that Lemaire et al. introduced C_2-symmetric diamines as ligands for asymmetric hydrogen transfer catalyzed by rhodium complexes.[139] Indeed, nitrogen ligands present many advantages over their phosphorus analogues (accessibility, ease of recovery, stability to oxidation, etc.). Among the diamines tested, **252** gave the best yield of reductive product in 67% ee. The tertiary diamine **108** afforded the product in good yield but very low enantiomeric excess (Scheme 66).[140]

Scheme 66



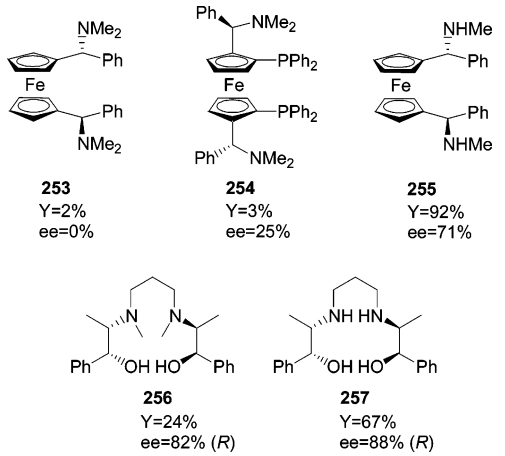
Cationic complexes of rhodium were used by Pertici[141] and Shainyan.[142] In the case of 2,2′-bis(dimethylamino)-1,1′-binaphthyl **71**, used by Pertici et al., the cationic complex could not be synthesized; it was necessary to have the corresponding secondary or primary amines, namely, 2,2′-diamino-1,1′-binaphthyl- and 2,2′-bis(methylamino)-1,1′-binaphthyl diamine. In these ligands, the NH_2 and NHMe fragments are coplanar with the aromatic ring and the naphthalene planes form a dihedral angle of about 90°. On the other hand, concerning **71**, the dihedral angle is 75° and the NMe_2 fragments are not coplanar with the naphthalene planes but twisted by about 30° due to steric repulsion between one of the methyl substituents with the other naphthalene ring. The nitrogen lone pair is only partially conjugated with the aromatic ring, and the compromise between these steric and electronic factors gives rise to a stable conformation which makes the diamine **71** a rigid molecule.

The complex Rh(ent-$\mathbf{174}^2$)$_2^+CF_3SO_3^-$ was used by Shainyan et al. It was formed in situ by mixing diamine *ent*-**174** and $[(1,5\text{-COD})_2Rh]^+CF_3SO_3^-$. This complex was able to catalyze the reduction, but the yields were quite low. Use of two extra equivalents of diamine led to a much better result (Scheme 66).

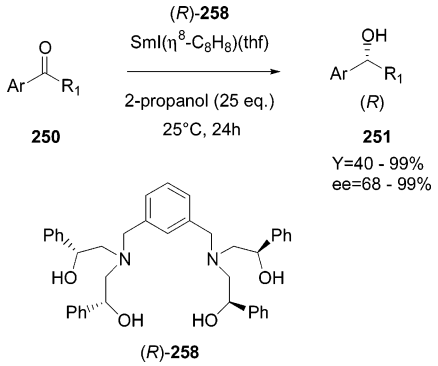
Ruthenium-catalyzed hydrogen transfer was investigated by Knochel[143] and Van Leeuwen[144] with diamines **253**−**255** and **256**−**257**, respectively (Scheme 67). For these ligands, the reaction studied was the asymmetric reduction of benzophenone **250** in the presence of 0.5 mol % of a ruthenium complex and 2 or 1 mol % of ligand. Both ferrocenyl diamines **253** and **254** gave an only very moderately active system. By contrast, the corresponding C_2-symmetric secondary diamine **255** was much more efficient in terms of both reactivity and selectivity. The same trend was observed with **256** and **257**. It was suggested by Noyori that a NH moiety in the ligand may promote a cyclic transition state through hydrogen bonding to the ketone substrate.[138b] It has to be noted that *N*-benzyl-1*R*,2*S*-norephedrine, which is a bidentate ligand, was the best catalyst found for this transformation, and selectivities up to 97% were obtained.

Mashima reported the use of multidentate ligand **258** for the samarium-catalyzed asymmetric reduction of aryl ketone

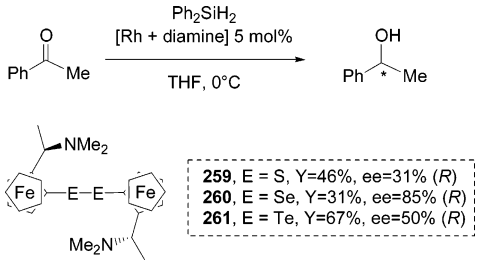
Scheme 67



Scheme 68



Scheme 69

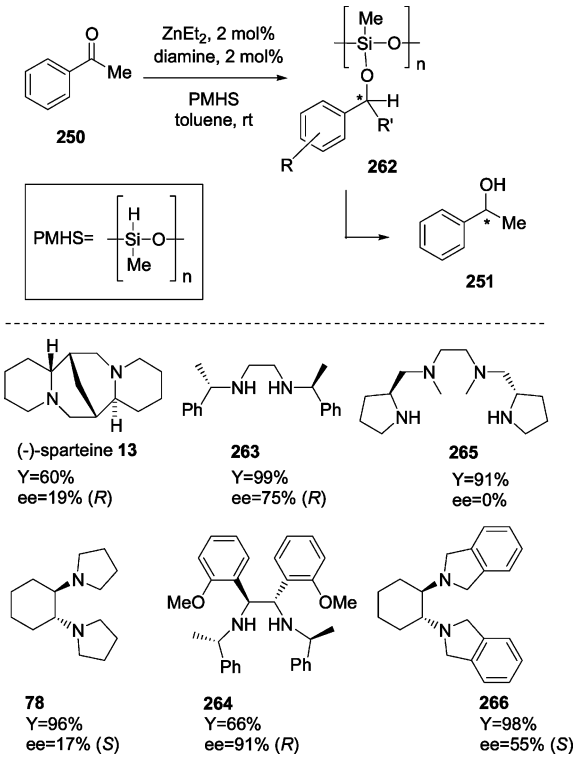


(Scheme 68).[145] The dinuclear samarium−diamine complex $[(\mathbf{258})_2Sm_2]_2$ was formed in situ upon mixing 2 equiv of SmI-(η^8-cyclooctatetraene)(thf) with 1 equiv of diamine. While in most cases the reduction products were obtained in high ee's, up to 99% for several substrates, cyclic ketones led to the alcohols in low yields and moderate selectivities.

5.2. Hydrosilylation

The asymmetric hydrosilylation of aryl ketones with diphenylsilane catalyzed by rhodium complexes in the presence of diferrocenyl dichalcogenides **259**−**261** was developed by Uemura et al. in 1994 (Scheme 69).[146] They showed that good yields and ee's up to 88% were achieved. Bulky ortho substituents tend to decrease the yield, and electron-donating substituents such as *p*-Me or *p*-OMe inhibit it. Reasonably high ee values were obtained in many cases. The exact mechanism of the reaction is not certain. The authors postulated that ligand exchange occurs in the first step between the cyclooctadiene and the diamine followed by oxidative addition of diphenylsilane on Rh and subsequent coordination of the carbonyl oxygen to Rh.

Scheme 70



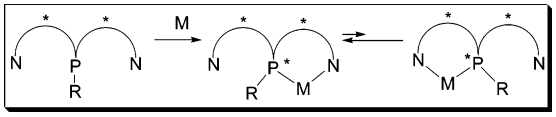
Several C_2-symmetric tertiary diamines were used in the zinc-catalyzed hydrosilylation of ketones with polymethylhydrosiloxane (PMHS) (Scheme 70). $ZnEt_2$ alone has no catalytic activity, but activation by the diamine transforms the linear C−Zn−C arrangement into a monomeric tetrahedral $ZnEt_2$(diamine) complex which is an active catalyst for the reduction. Mimoun et al. studied several types of diamines and found that the best ligand was the secondary diamine (*S*,*S*)-*N*,*N*′-dibenzyl-1,2-diphenyl-1,2-ethanediamine. A mechanistic study made by the authors suggested several possibilities for the mechanism. Among the tertiary diamines used by Mimoun, **78**, **266**, and (−)-sparteine **13** were much less efficient.[147] Diamine **263** and **265** were used by Carpentier along with few other secondary diamines.[148] Enantiomer excesses up to 91% were achieved with ligand **264**, while **265** did not give any selectivity.

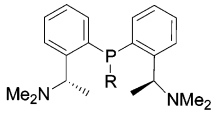
5.3. Hydrogenation

Although many ligands have been developed in the asymmetric hydrogenation, only few tertiary diamine ligands have been used. Yamagishi et al. described phosphinediamines **267** and **268** which can chelate the metal with the PN unit; the other free amine serves in a secondary interaction with the substrate.[149] Rhodium−PN_2 complexes were formed from diamine **267** and the neutral rhodium complex $[RhCl(nbd)]_2$ (nbd = bicyclo[2.2.1]hepta-2,5-diene), and the structures were examined in solution by CD and NMR spectroscopy. Two diastereoisomeric complexes were formed in a 97:3 ratio, indicating that selective ligation of the amino group occurs. With diamine **268** this ratio was only 75:25. In such complexes the former central phosphorus atom becomes a stereogenic center. NOE experiments showed that complex **267A** was the major form (Scheme 71).

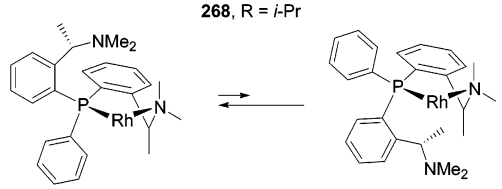
The results obtained from **268** for hydrogenation of acrylic acid derivatives were good, and ee's up to 92% were

Scheme 71



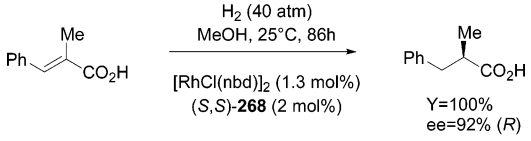


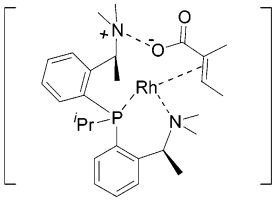
267, R = Ph
268, R = *i*-Pr



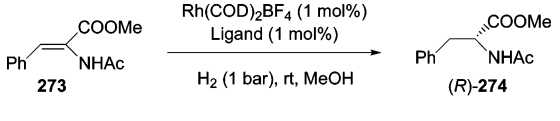
267A **267B**

Scheme 72

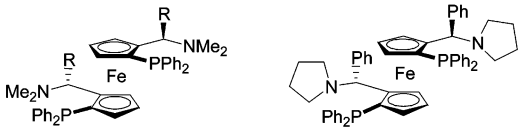




Scheme 73

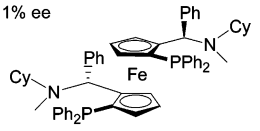


273 (*R*)-**274**



254, R=Ph, 98% ee
269, R=Me, 97.6% ee
270, R=Et, 95.1% ee

271, 97.7% ee

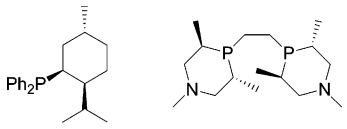


272, 97.8% ee

achieved. In the case of esters, the reaction was much slower and the enantioselectivities were low. This difference may be due to the electrostatic interaction between the free amine and the carboxylic acid, which formed an ammonium salt and incorporated the substrate into the complex (Scheme 72). On the contrary, phosphinodiamine **267** did not catalyze the reaction.

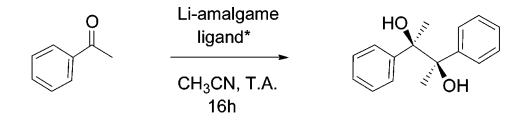
In 1999, Knochel et al. reported the use of C_2-symmetric diamino FERRIPHOS for the rhodium-catalyzed enantioselective reduction of methyl-α-acetamidoacrylates (Scheme 73).[150] The reaction proceeded under very mild conditions (1 bar of H_2 and room temperature) in the presence of 1% of catalyst prepared in situ. High ee's were constantly obtained with various substituted substrates and ligands. The

Scheme 74



275 **276**

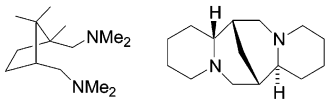
Scheme 75



130
Y=93%
ee=0%
dl/meso = 64/36

ent-**173**
Y=74%
ee=10% (*R*,*R*)
dl/meso = 55/45

108
Y=73%
ee=7.9% (*S*,*S*)
dl/meso = 76/24



277
Y=88%
ee=6.2% (*S*,*S*)
dl/meso = 62/38

(-)-sparteine **13**
Y=60%
ee=0%
dl/meso=59/41

amount of ligand was lowered for one experiment to 0.2 mol %, and the product obtained was isolated with the same enantiomeric purity. The reaction was not affected by the substrate concentration either. Hydrogenation attempted on (*Z*)-α-acetamidocinnamic acid gave the product in 73% ee, while 89% ee was obtained by addition of 2% of CF_3COOH.

Shainyan reported the use of diamine **174** for the asymmetric hydrogenation of itaconic acid and α-acetamidocinnamic acid, which gave (*S*)-(−)-methylsuccinic acid and (*R*)-(−)-*N*-acetylphenylalanine in only 25% and 2% ee, respectively.[151] Reactions were conducted in a 2:1 solvent mixture of methanol:benzene at 25 °C under 35 atm of hydrogen pressure. However, when hydrogenation was performed in the presence of Rh(I) complexes and phosphine **275** (Scheme 74), a strong matched effect was observed. In the case of itaconic acid, the hydrogenated product was isolated in 74% ee.[152]

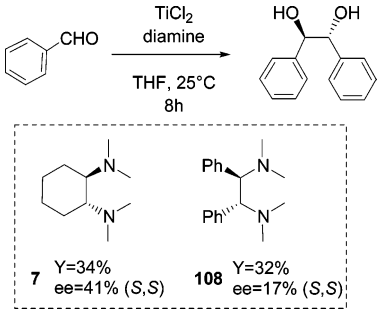
Zhang et al. reported in 2006 a six-membered bis-(azaphosphorinane) ligand **276** synthesized in three steps and 36% overall yield (Scheme 74).[153] In the presence of 1 mol % of $[Rh(nbd)_2]SbF_6$ and under 15 psi of H_2 atmosphere, *β*-alkyl-*β*-(acylamino)acrylates and α-arylenamides were hydrogenated in ee's almost constantly as high as 99%. Even when a mixture of *E*/*Z* α-arylenamide was used, the same selectivities were obtained.

5.4. Pinacol Coupling

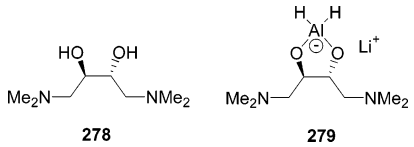
A metallic amalgam was used for the asymmetric reduction of prochiral ketones in the presence of diamine ligands.[154] The reaction led to a mixture of carbinol and pinacol coupling products. The best selectivity for the pinacol product was obtained using acetonitrile as solvent. Moderate *dl-meso* selectivities and low ee's were obtained (Scheme 75).

Matsubara showed that diamines can be used with low-valent titanium, $TiCl_2$, to perform asymmetric pinacol couplings.[155] The amine is thought to facilitate the electron

Scheme 76



Scheme 77



transfer and reduction coupling. The best selectivity was obtained with **7**, which gave 41% ee.

5.5. Reduction with Hydride Reagents

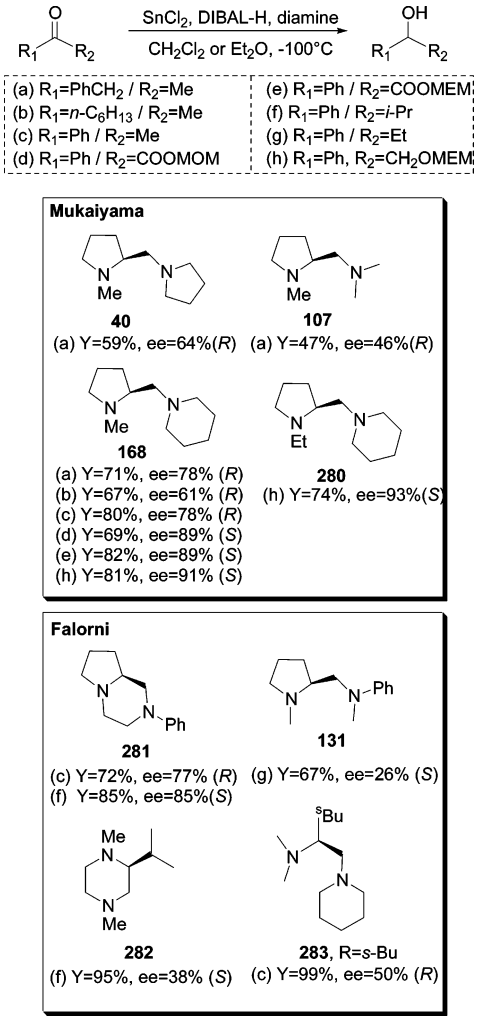
The enantioselective reduction of carbonyl derivatives using chirally modified aluminohydride and borohydride reagents is an extremely powerful tool to produce enantioenriched secondary alcohols.[156] However, the combination of chiral diamines and hydride reagents did not arouse much interest despite its very large potential. In 1974, Seebach and Daum used ligand **278**, deriving from tartaric acid, to decompose LAH into complex **279**, which was able to reduce ketones in ee's up to 75%.[157]

In 1984, Mukaiyama showed that prochiral ketones are reduced enantioselectively using a reducing agent formed by treating a mixture of stannous chloride and a chiral diamine with DIBAH in a ratio of $SnCl_2$:diamine:DIBAH = 1:1:0.5 (Scheme 78).[158] They used chiral diamines derived from (*S*)-proline as ligand. The best selectivity was obtained with diamine **168**, which reduced 1-phenyl-2-propanone in 78% ee, while diamines **40** and **107** led to the product in 64% and 46% ee, respectively. When keto-esters were used, ee's up to 89% were achieved with diamine **168**.[159] Other functionalized substrates such and α- and *β*- OMEM-ketone gave ee's up to 93% and 87% ee using diamine **280**.[160]

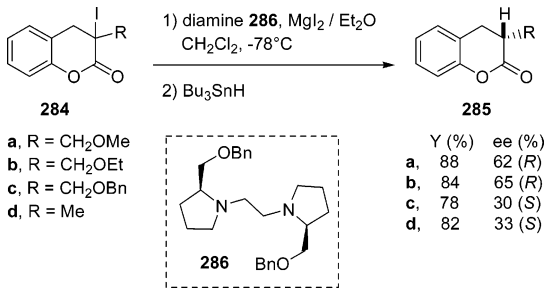
Falorni et al. also studied the reaction with chiral piperazine (Scheme 78).[161,162] They found that better selectivities were obtained in diethyl ether. Ligand **281** was the most efficient, leading to the reduction of isopropyl phenyl ketone in 85% ee in favor of the *S* enantiomer. Interestingly, acetophenone was reduced to the corresponding alcohol with the *R* absolute configuration. Although ligands **282** and **283** gave modest ee's with arylketones, ee's up to 82% were achieved for α-acetylenic ketone with **283**.

Radical-mediated reductions of α-alkyl-α-iododihydrocoumarins **284** were studied by Murakata and Hoshino (Scheme 79).[163] A diamine and magnesium salt were used to form a chiral Lewis acid in situ. The selectivities depended on the concentration of the substrate. The best results were obtained by reaction at a 36 mM concentration of **284**. The substrate **284d**, which does not contain an oxygen atom in the side chain, reacts with the same sense of induction but lower ee. Comparison showed that Bu_3SnH is more efficient than Ph_3SnH or TMS_3SiH.

Scheme 78



Scheme 79

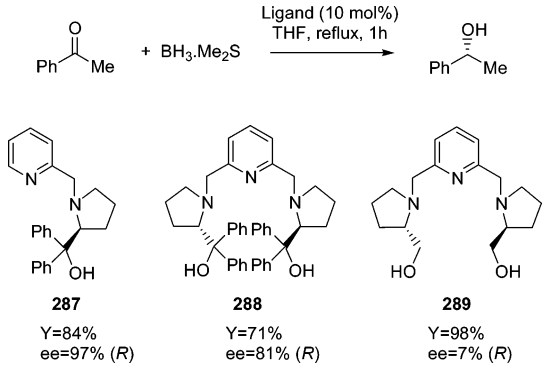


In 2004, Du et al. reported the use of pyridinylmethyl pyrrolidinemethanols in the enantioselective reduction of ketones by boranes (Scheme 80).[164] In the presence of 10 mol % of ligand **287**, a high level of enantioselectivity was achieved for aromatic ketones. On the other hand, ligand **288**, having C_2 symmetry and possessing two diphenylpyrrolidinol unit, led to a good level of enantioselectivity, while with aliphatic ketones it was inefficient. Ligand **289**, which also contains a C_2 symmetry axis, gave a very low level of induction.

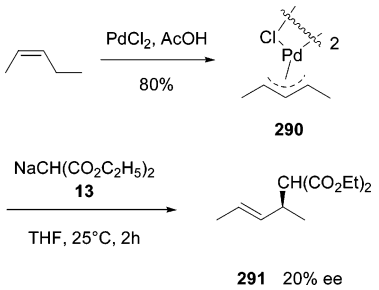
6. Allylic Substitution

The asymmetric allylic alkylation is a very powerful reaction which allows a Pd-catalyzed substitution of an allylic leaving group by a soft nucleophile.[165] Before the develop-

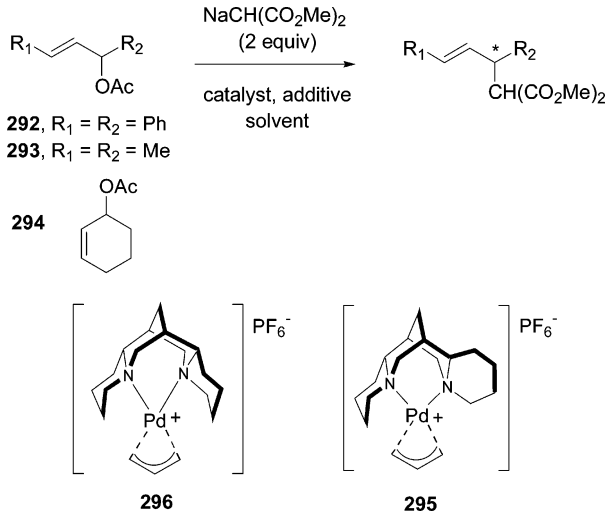
Scheme 80



Scheme 81



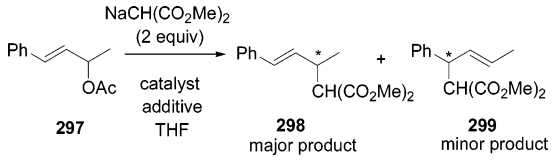
Scheme 82



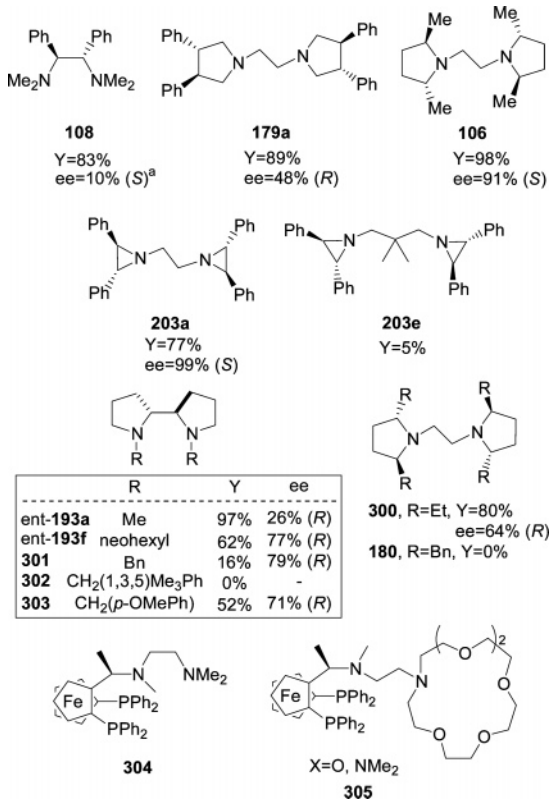
ment of this catalytic method,[166] (−)-sparteine **13** was used in stoichiometric amounts by Trost for the alkylation of π-allylpalladium intermediate **290** leading to compound **291** in 20% ee (Scheme 81).[167]

(−)-Sparteine **13** was re-examined by Togni[168] in 1991 and Kang[169] in 1994 along with (−)-α-isosparteine **14** as a ligand in the catalytic reaction (Scheme 82). Contrary to Togni, who performed the reactions at room temperature, Kang found that a better yield and ee were obtained when the reactions were carried out at reflux. Solvents such as DMF and THF were found to be the most suitable for the reaction. High ee's, up to 95%, were only obtained for substrate **292**, which bears two phenyl substituents. In that particular case (−)-sparteine was slightly better than (−)-α-isosparteine, but for the other substrates, (−)-α-isosparteine was found to be more efficient. Substrates **293** and **294** were transformed in the presence of **296** in up to 69% and 62% ee, respectively.

Scheme 83



Scheme 84[b]



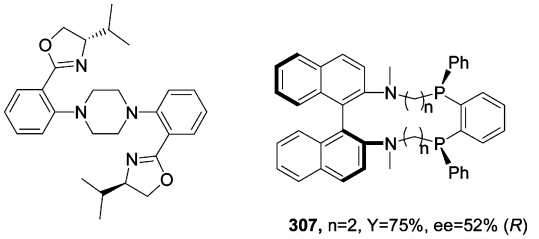
	R	Y	ee
ent-**193a**	Me	97%	26% (*R*)
ent-**193f**	neohexyl	62%	77% (*R*)
301	Bn	16%	79% (*R*)
302	CH_2(1,3,5)Me_3Ph	0%	-
303	CH_2(*p*-OMePh)	52%	71% (*R*)

[a] With **294**. [b] Yields and ee's are given for the reaction of **292** with dimethylmalonate.

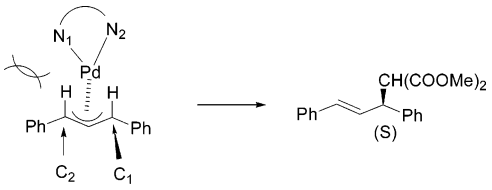
In the case of an unsymmetrical acetate **297**, two products were obtained (Scheme 83). As previously reported for this reaction, the major product came from addition at the less hindered site of the allyl fragment. It must be noted that very different results were obtained by Togni and Kang for the case of (−)-sparteine at room temperature. Indeed, Togni reported that the product formed in 62% yield and 21% ee, while Kang et al. obtained only trace amounts of product. By changing the reaction conditions, that is the concentration, solvent, or temperature, the product was isolated in good yield and moderate ee.

Since then, a wide range of diamine structures has been studied as asymmetric inductors. Lemaire studied the diamine derived from diphenylethylenediamine and found that the best results were obtained with the *N*,*N*′-dimethyl-1,2-*trans*-diphenylethane diamine, while **108** led to low selectivities.[170] Studies carried out by Koga et al. and Alexakis et al. showed that increasing the steric hindrance in the ligand dramatically decreased the reactivities and selectivities (Scheme 84).[171,172] In the bis-pyrrolidine series, the most electron-rich diamine **303** gave higher yields by comparison to **301** and **302**, while the effect on the enantioselectivity was low. Bis-pyrrolidine diamines **106** and **301** led to 91% and 79% ee, respectively. Tanner et al. developed bis-aziridine **203a**, which gave 99% ee.[173] Other derivatives such as **203e** with a longer spacer between the two aziridines units gave a very low result.

Scheme 85



Scheme 86

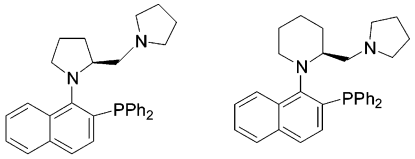


Ferrocenyl ligands were evaluated by Ito et al.[174] The ligand **305** bearing an aza crown ether moiety was much more efficient than **304**, and ee's up to 80% were obtained. The reaction conditions involve the use of 2 equiv of RbF as a base with 1 equiv of $RbClO_4$ as additive. However, the exact role of this cation is not yet fully understood. The piperazine derivative **306** which proved to be inefficient was studied along with mono-oxazoline, which showed better selectivities.[175] Wildhalm et al. developed several very efficient aminophospine ligand[176,177] and evaluated macrocyclic diaminodiphosphine ligands **307** and **308** which contain a local C_s symmetry of the diphosphine subunit (Scheme 85). X-ray structures of complexes **308**·$NiCl_2$ did not reveal any coordination of nitrogen atoms. Diphosphine **308** exhibits significantly higher selectivities than **307**. One can notice that in the study the concentration of reactant influences the rate of the reaction without affecting the ee. While reaction conditions are sometimes fairly different from each other, there is a general trend which conventionally uses a metal to ligand ratio of 1:2, the palladium source being the complex $[Pd(\eta^3(C_3H_5)\mu\text{-}Cl)]_2$ which is used in a catalytic amount varying from 1 to 5 mol % depending on the ligand. The best solvent can be dichloromethane, diethyl ether, THF, or more polar ones such as acetonitrile or DMF.

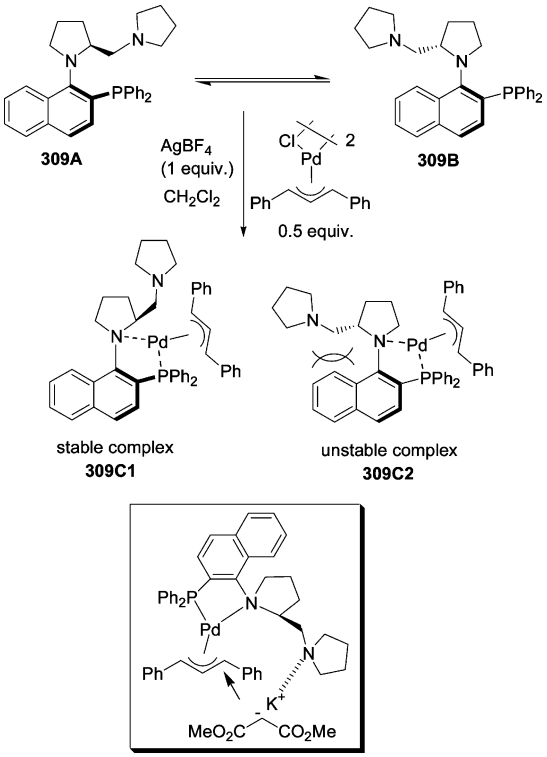
Koga obtained a crystal of the (1,3-diphenylallyl)palladium diamine (**106**) complex and determined the structure by X-ray diffraction studies (Scheme 86). The complex has a distorted square-planar geometry with different bond lengths between the palladium and the two allylic termini ($d(C_1-Pd) = 2.18$ Å, $d(C_2-Pd) = 2.22$ Å, $d(N_1-Pd) = 2.17$ Å, $d(N_2-Pd) = 2.19$ Å). The ^{13}C NMR chemical shift of C1 and C2 are 13 ppm different, which suggests that C1 has a more cationic character than C2. Andersson also studied the complex formed with diamine **203a** and found a difference of 18.4 ppm. The optimized structure obtained by MM2 calculation accurately accounts for the enantiomer obtained. The nucleophilic attack occurs anti to the palladium, and both electronic and steric effects lead to nucleophilic attack at C_1.

Kondo and Murakami reported in 2002 a new type of chiral ligand mimicking N−Ar axial chirality (Scheme 87).[178] The rotation barrier of 13 kcal/mol at 0 °C was calculated for diamine **309**, and NMR study of the conformation was carried out.[179] As described in Scheme 88, these diamines, which have two conformers in equilibrium, led to only one diastereoisomer of the π-allyl−palladium complex. Complex

Scheme 87



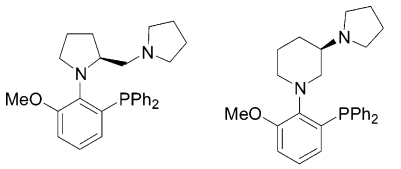
Scheme 88



309C1 was characterized by NMR spectroscopy. The allylic substitution reaction was carried out on the standard test system, that is, (*E*)-1,3-diphenyl-2-propenyl acetate **292** as substrate and dimethylmalonate as nucleophile in DMF at −10 °C employing 2.5 mol % of $[Pd(\eta^3(C_3H_5)\mu\text{-}Cl)]_2$ and 5 mol % of diamine in the presence BSA and KOAc. High levels of enantioselectivities were obtained with all the ligands tested, but among them, **310** showed the best selectivities leading to the product in 98% ee in toluene and 99% in trifluorotoluene. In all cases, the product was obtained with the *S* absolute configuration, which can be explained by the reactive intermediate shown in Scheme 88. Due to the trans effect arising from the fact that the pyrrolidinyl group acts as a donor while the phosphinyl group acts as a π acceptor, the alkylation occurs from the back side of the palladium catalyst, opposite to the phosphorus atom. In addition, lower selectivities were obtained with ligands that lacked the lateral amino function, suggesting coordination between the lateral amino function and the nucleophile.

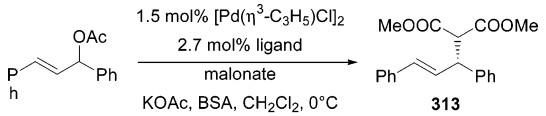
In 2005, Mino et al. described diaminophosphine **311** (Scheme 89).[180] In the standard reaction conditions ($[Pd(\eta^3(C_3H_5)\mu\text{-}Cl)]_2$ (2 mol %), diamine (4 mol %), BSA, KOAc, −10 °C, Et_2O) with **292** as substrate, better reactivity was observed when toluene and ether were used as solvent. Most of the ligands gave good yields and enantioselectivities, and some of them led to the product in ee's up to 95%. By contrast, diamine **312**, which contains a six-membered ring, gave very low results. In addition, the product was isolated

Scheme 89

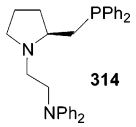


311 Y=99%, ee=95% (*S*) **312** Y=65%, ee=15% (*R*)

Scheme 90



313 ee=87% (*R*)



314

Scheme 91

315 **316**

with the *R* absolute configuration. By changing the malonate, the selectivity was improved in up to 98% ee.

Hii et al. reported terdentate diaminophosphine ligands **314** (Scheme 90).[181] Moderate selectivities were obtained using the classic experimental conditions. The best ratio Pd/ligand was better than 1 (Pd/L = 1/0.9), which means that the ligand has to be slightly less than 1 equiv with regard to the metal. On the basis of the ^{31}P NMR study made on the ligand bearing a *N*-diethyl moiety, it was suggested that the intermediate palladium complexes **315** and **316** are in equilibrium, and the pyrrolidinyl nitrogen atom acts as the hemilabile site (Scheme 91). A slow addition of BSA (over 8 h) at −20 °C improved the ee's by 10%, leading to the product in up to 94% ee. Introduction of an additional stereogenic center on the ligand, α to the NPh_2 position of **314**, led to a significant match−mismatch effect. However, better selectivities were obtained without this additional stereogenic center.

7. Nucleophilic Additions

7.1. 1,2-Addition of Organolithium onto Carbonyl Compounds

Direct asymmetric nucleophilic addition of organolithium reagents onto carbonyl compounds has been extensively studied in the presence of a wide range of ligands. Despite their high reactivity, their use in asymmetric synthesis is still widely studied because these species are very easily prepared and cheaper than other organometallics. Diamines have often been used with organolithium reagents because they produce species of lower aggregated states which are more reactive. In return, reactions run in the presence of such additives are cleaner, leading to the product usually in higher yields with lower amounts of byproducts.

The first attempt was made by Nozaki et al. using (−)-sparteine **13** and *n*-butyllithium in a 1:1 ratio to perform asymmetric addition to carbonyl compounds.[182] Addition onto benzaldehyde gave the corresponding *R* alcohol in 6% ee.

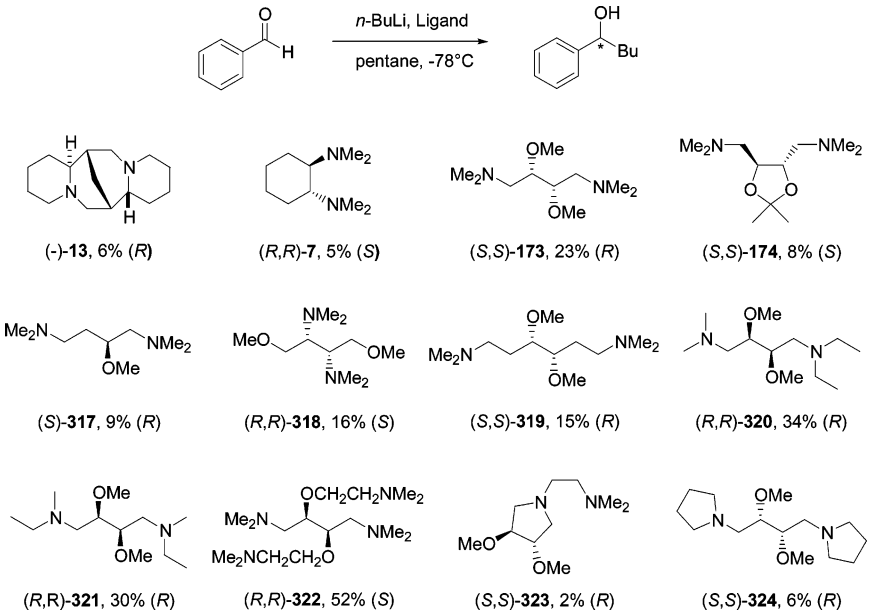
It was 9 years later that another study was reported by Seebach et al. with ligands derived from tartaric acid (Scheme 92). He also reexamined (−)-sparteine and obtained the same result as Nozaki. Diamine **7** also led to a very low selectivity. A screening of ligand using addition of *n*-butyllithium to benzaldehyde led to the selection of **173** as the most efficient of the family producing the *R* alcohol in 29% ee.[183] The best result was obtained with *o*-tolualdehyde, which led to the alcohol in 45% ee, while aliphatic aldehydes were transformed in a less selective manner. Other organolithium reagents were tested on various electrophiles such as valeraldehyde, benzaldehyde, and benzophenone, but only moderate selectivities were obtained.[184]

Shortly thereafter, ligands **320**−**322** were designed as derivatives of promising ligand **173**. The aim was to check the effect on selectivities by removing the C_2 symmetry, introducing a chiral nitrogen atom in the reactive complex, or stabilizing it with a multidentate ligand. All three ligands improved the selectivities compared to **173**, but **322** turned out to be much more efficient leading to the *S* alcohol in 52% ee. Addition of PhLi to valeraldehyde in the same conditions gave only 15% ee. Although better selectivities were also obtained with other aldehydes, even aliphatics, the best result was 56% ee on *o*-tolualdehyde.[185]

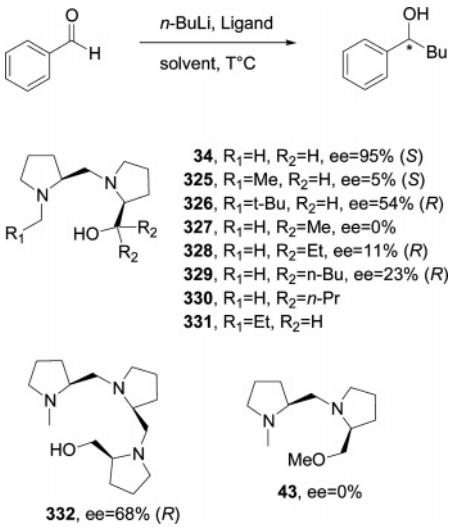
Kang et al. studied the addition of 2-lithio-1,3-dithiane on aldehydes in the presence of (−)-sparteine and (−)-α-isosparteine. While (−)-sparteine led to the product in only 3% ee, the C_2-symmetric diastereoisomer (−)-α-isosparteine produced it in a remarkable 70% ee.[186]

Proline-based ligands were studied by Mukaiyama and Scolastico. In 1978, Mukaiyama et al. introduced ligand **34** and reported ee's up to 72% ee for addition of *n*-butyllithium on benzaldehyde in diethyl ether at −123 °C. Addition of phenyllithium to valeraldehyde led, in the same conditions, to 11% ee only, and methyllithium was added to benzaldehyde at −78 °C in 21% ee.[187] In the latter case, improvements were obtained with ligand **330** used at −123 °C which increased the ee to 86%.[188] One can notice that the presence of the free hydroxyl group is critical for selective reactions. Indeed, O-methylated derivative **43** was not efficient at all.[187] Strong solvent effects were also observed and used to improve the enantioselectivity up to 95% in the particular solvent system dimethoxymethane−dimethyl ether (DMM/Me_2O = 1/1).[188,189] However, with all the other ligands **325**−**329** reactions were run only in Et_2O at −123 °C. On the basis of a different maximum value of $[\alpha]_D^{20}$ considered for the alcohol, the ee value was corrected to 83% by Cram et al.[190] The size of substituents R_1 and R_2 in these ligands had a dramatic effect on the asymmetric induction (ligands **34** and **325**−**329**, Scheme 93). Generally, **34** was more efficientthan any other ligand; however, among the more hindered series **325**−**329**, better induction was obtained using more hindered ligands. Interestingly, they did not all lead to the same enantiomer of the alcohol. Ligand **332** containing three pyrrolidine units led to 68% ee, which was close to the selectivity obtained with **34** under the same reaction conditions. Furthermore, while a very good selectivity was obtained using methyllithium prepared from methyl iodide and Li, almost no selectivity was recorded when it was prepared from methyl bromide and Li.[188] The methodology was extended to the functionalized organolithium reagent.

Scheme 92



Scheme 93



Among them, alkynyllithium led to a high level of asymmetric induction, up to 92%, using **34** as the ligand.[191,192]

In 1982, Scolastico developed C_2-symmetric ligands **12** and **333**. Optimized reaction conditions led to moderate selectivities, up to 36% ee using **333**, for addition of *n*-butyllithium to benzaldehyde. The low selectivity obtained with **12** (15% ee) showed that the lithium alkoxide played an important role in the mechanism of the reaction.[193] Ligand **334** was easily prepared by Sato et al. from camphoric acid and used with various organometallic species. Acting as a bidentate ligand, the chelate intermediate has a conformationally rigid structure, which is usually an important factor for good selectivities. However, *n*-butyllithium associated with **334** added to benzaldehyde with only 4% ee.[194]

Diamine ligands containing axial chirality where introduced by Cram et al. in 1981. They used the binaphthyl derivatives **205** and **337** for addition of various organolithium reagents to benzaldehyde. Diamine **205** led to moderate selectivities, up to 58% in the case of *n*-butyllithium, while **337**, containing two binaphthyl units, produced the *R* alcohol in 95% ee at −150 °C (based on optical rotation, while 89% ee was measured based on ^{1}H NMR of Moscher's ester). Interestingly, addition of phenyllithium to valeraldehyde led to the alcohol with opposite configuration in 43% ee.[190,195] Diamine (*S*)-**338** also contains a binaphthyl unit, but both nitrogen atoms are connected by an ethylene chain which make the diamine nonchelating. Indeed, the conformational hindrance prevents formation of the complex *n*-BuLi−diamine, and the product was obtained in good yield but as the racemic mixture.[196]

On the basis of this work, Suda et al. tested the biaryl derivatives **204** and **336**. As described above, the ligand containing two biaryl units was much more effective. In the classic case of the addition of *n*-butyllithium to benzaldehyde, (*R*,*R*)-**336** at −120 °C produced the *R* alcohol in 99% ee. Again, addition of phenyllithium to valeraldehyde was much less efficient leading to the alcohol in only 18% ee.[197]

Although many 3-aminopyrrolidines lithium amides were used for this reaction, only one example of a tertiary diamine was reported. Diamine **335** was used for the addition of benzaldehyde to *o*-tolualdehyde leading to the racemic alcohol in quantitative yield, whereas analogues having a secondary-tertiary diamine structure led to the product in 80% ee.[198,199]

7.2. 1,2-Addition of Organolithium onto Imines

Synthesis of enantiomerically enriched amines is still a challenging task. Although many different strategies have been developed using chiral imines and nucleophiles, enantioselective reactions provide the most attractive method. Several efficient methods have appeared since 2000, which are based on addition of organozinc or organotin to activated imines catalyzed by copper salts or rhodium complexes.[200] However, because of the low reactivity of nonactivated imines toward the nucleophilic addition, most of the studies have been limited to use of organolithium reagents complexed to an external chiral ligand. Small numbers of different structural of ligands have been used; these are mainly aminoalcohols, bis-oxazoline, and few diamines.

Although it was an isolated example, the first enantioselective addition was reported by Seebach et al. in 1979 using 2-lithio-2-methyl-1,3-dithiane as the nucleophile and *N*-benzylidenaniline **339** as the electrophile in the presence

of 10 equiv of **173**. The product **340** was isolated with 70% yield, but the ee was not determined.[184]

In 1989, Tomioka et al. reported the first complete study in this area as well as a high level of selectivities. However, as this study is concerned with the conjugate addition onto unsaturated imines, this study will be briefly developed in section 7.3. Furthermore, it was found in this study that diethers are more effective than diamines. The latter has therefore not been studied for 1,2 addition reactions.

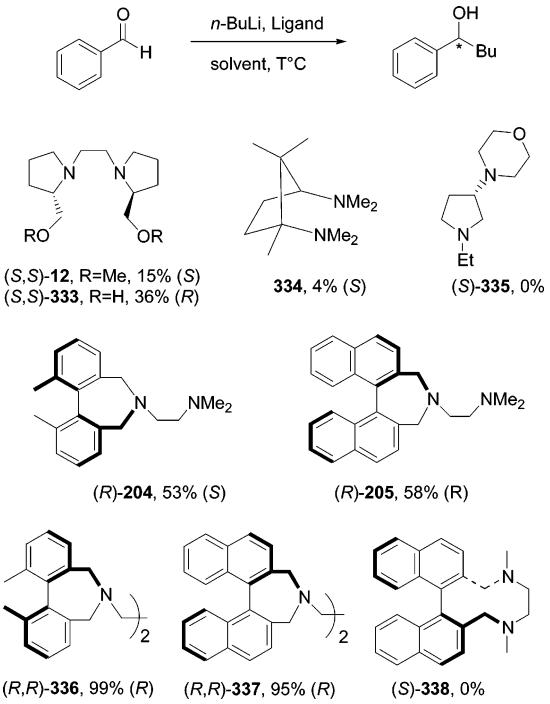
In 1991, Itsuno et al. studied addition of *n*-butyllithium to *N*-trimethylsilyl imines and extended it afterward to other *N*-metalloimines such as *N*-aluminum imine and *N*-boryl imines.[201,202] *N*-Trimethylsilyl imines gave very low levels of selectivity, while *N*-boryl imines were transformed in much better yields although it remained moderate. In order to recover the ligand more easily, a polymer-supported version was tested and gave similar selectivities. Eventually, *N*-aluminum imines gave the best selectivities, up to 74%, but only (−)-sparteine was evaluated with this substrate.

Denmark,[203] North,[204] Lete,[205] and Senanayake[206] used (−)-sparteine as ligand. In almost all cases, *N*-PMP imines (PMP = paramethoxyphenyl) were used because the PMP substituent is an amine protecting group that is usually easily removed with an oxidizing agent such as CAN. Denmark et al. found that (−)-sparteine is a better ligand than bis-oxazolidine for enolizable imines **344**. MeLi and PhLi gave fairly good selectivities, 72% and 82%, respectively, whereas *n*-BuLi reached 91% ee with a stoichiometric amount of ligand at −94 °C. However, with 20% of (−)-sparteine at −78 °C, the ee dropped to 79% showing the problem related to catalysis. In 1997, North et al. considered unsaturated imines **348** which underwent very regioselective 1,2 addition. Addition of MeLi and *n*-BuLi led to the corresponding product in 76% and 88% ee, respectively. However, the problems encountered when removing the PMP protecting group prompted North et al. to investigate other nitrogen substituents which would be easier to deprotect. *N*-Triphenylmethyl imine **349** and *N*-trimethylsilyl imine **350** were selected, but they did not undergo very selective additions. Lete et al. explored addition of various organolithium reagents to aromatic imines **353** in the presence of (−)-sparteine. This substrate was studied previously by Denmark using bis-oxazoline. Solvent effects and substituent effects on the nitrogen were evaluated and ultimately led to the best result of 34% ee for MeLi and 29% for *n*-BuLi. An isolated example reported by Senanayake et al. indicates that PhLi adds to imine **356** to give the corresponding imine **357** in 50% ee. The authors described formation of the (*S*)-enantiomer.

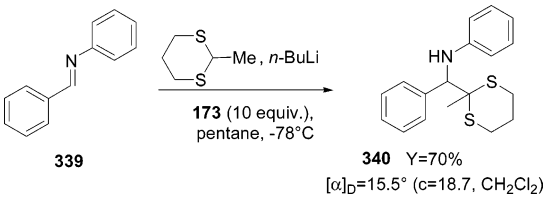
Tanner[207] and Alexakis[208] developed their own ligand in order to address the subject. Tanner set up C_2-symmetric bis-aziridine ligands in which the aziridine moiety is separated with various spacers and bearing various substituents (Scheme 98). Reasonable selectivities could be achieved with alkyllithium and vinyllithium reagents, but almost no selectivity or reactivity was observed with aryllithium. Ligand **203a** was the most effective in the addition of methyllithium and *n*-butyllithium onto imine **353**, leading to **354** and **355** in 67% and 68% ee, respectively. Addition of vinyllithium could also be performed to produce the corresponding amine in 89% ee.

Alexakis et al. prepared C_2-symmetric diamines, derived from *trans*-cyclohexane-1,2-diamine, in which both nitrogens

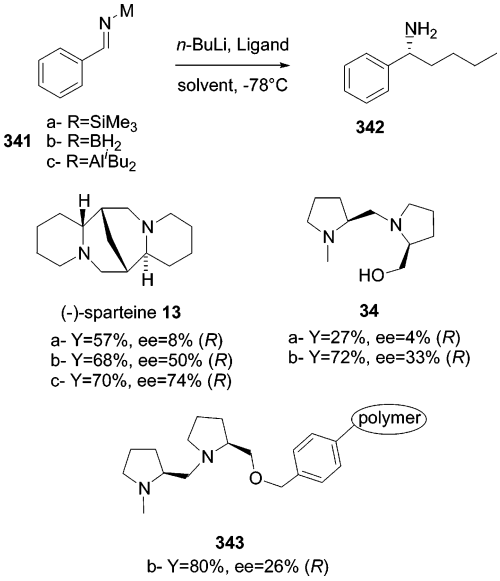
Scheme 94



Scheme 95

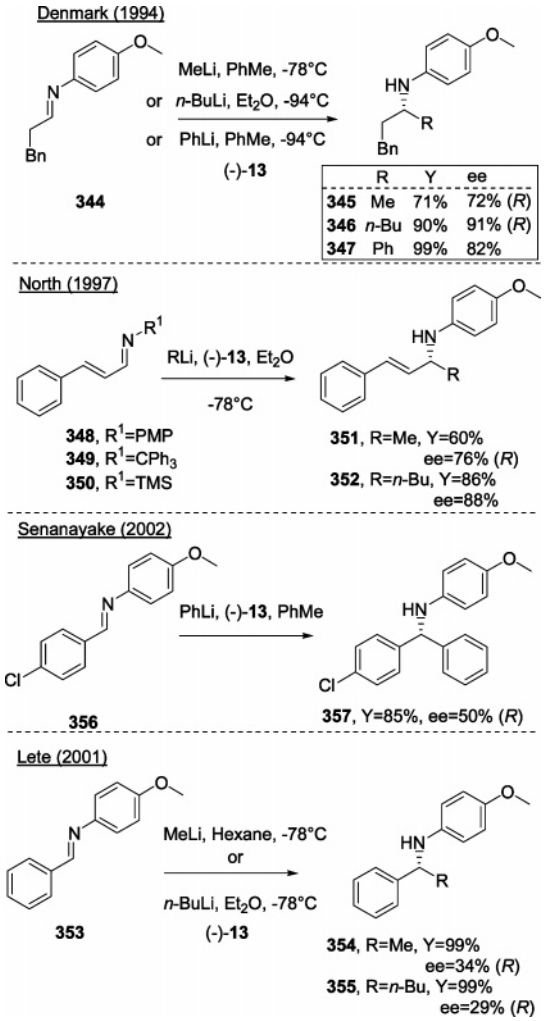


Scheme 96

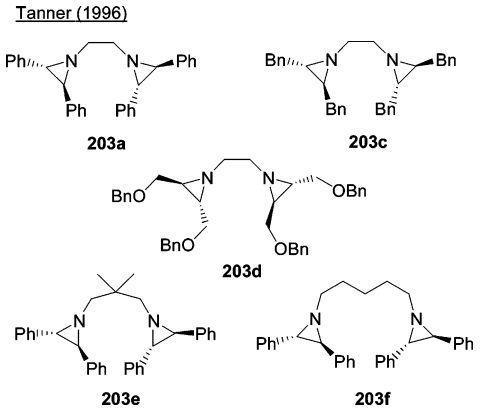


bear two different substituents. In the cyclic complex **359** formed with an organolithium reagent, the nitrogen atom becomes stereogenic and brings the chirality closer to the reactive site (Scheme 99). This concept proved successful for the nucleophilic addition of alkyllithium reagents onto aromatic imines, and dramatic increases in selectivity were observed when changing the ligand from **7** to **228** or **358**. Numerous derivatives were tested, but the latter two gave

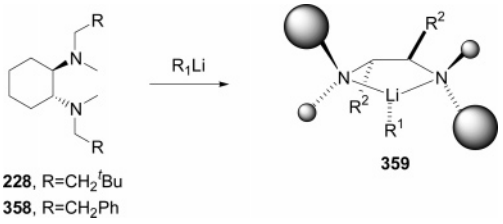
Scheme 97



Scheme 98

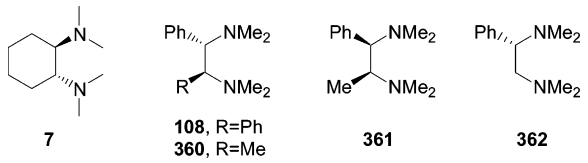


Scheme 99

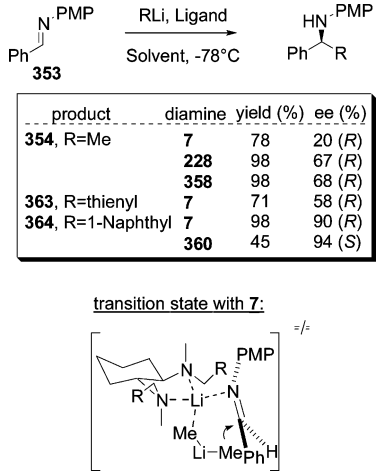


the best results and were found to be equivalent in efficiency. Furthermore, reactions were done with 20% of diamine with respect to imine (namely 7% with respect to MeLi) without any loss of enantioselectivity. However, an important condition to ensure this selectivity was the presence of bulky substituents two methylene units away from the nitrogen.[208] The reaction is thought to proceed through an open dimer transition state in which imines react with the *re* face (Scheme 101).[209]

Scheme 100



Scheme 101



Interestingly, aryllithium reagents also gave good selectivities but only when using the less hindered diamine **7** (Scheme 100).[210] Among the other nonhindered diamines, **360**, which derived from pseudoephedrine, gave very good ee's with several imines. Diamines **361** and **362**, which derived from ephedrine and phenylglycinol, respectively, both gave much lower ee's, pointing out the importance of both stereogenic center in a trans relationship. In the particular case of 1-naphthyllithium, **360** used in a stoichiometric amount provided the corresponding *R* amine in 94% ee, while in the presence of only 20% of **360**, a high induction of 80% was observed.[211] The stereochemistry of the stereogenic center was determined by X-ray analysis. Using (*R*,*R*)-**7** as chiral inducer, addition of aryllithium reagent onto nonactivated aromatic imine occurs from the *si* face leading to the aminodiarylmethane product. An intermediate of cetirizine, a nonsedating histamine H1-receptor antagonist used for the treatment of allergies, was also obtained in 69% ee.

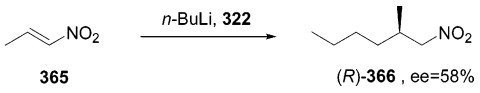
7.3. 1,4-Addition of Organolithium onto Unsaturated Nitro, Esters, and Imines

Organolithium reagents are hard nucleophiles as described by the HSAB theory[212] and usually react at the hard electrophilic site, which for an unsaturated system corresponds to a 1,2 addition. However, in some cases, the structure of the substrate can force the reaction to occur in a conjugated manner.

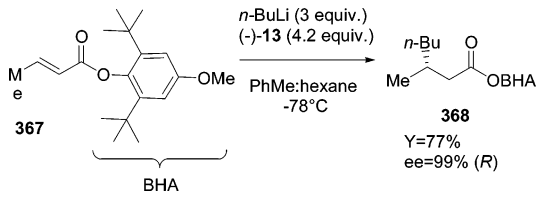
In 1979, Seebach et al. showed that nitro-olefin **365** undergoes conjugate addition with the nucleophilic system *n*-BuLi/**322**. Product **366** was obtained in 58% ee.[185]

The reaction of esters with organolithium reagents usually occurs at the carbonyl site leading to tertiary alcohol or

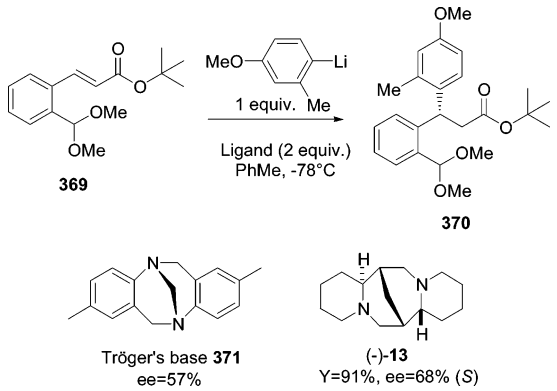
Scheme 102



Scheme 103



Scheme 104

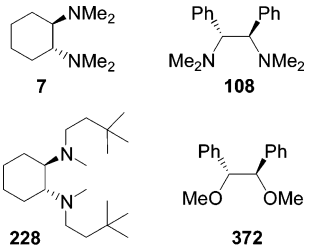


ketone depending upon the substrate. However, hindered esters such as BHA-ester (BHA = 2,6-di-*tert*-butyl-4-methoxyphenyl) or *tert*-butyl ester give exclusively the 1,4 adduct. Tomioka described the use of (−)-sparteine with alkyl-, vinyl-, and aryllithium reagents for the conjugate addition to BHA-esters (Scheme 103). High levels of enantioselectivity were obtained in many cases; however, vinyllithium was added with moderate selectivity. Use of substoichiometric amounts of ligand led to a significant decrease of ee, giving in most cases moderate selectivities, but ee's up to 85% were achieved.[213,214] Thanks to this method, the first asymmetric synthesis of dihydrexine, a benzophenanthridine dopamine D1 agonist, was achieved in 16% overall yield.[215]

Xu et al. explored conjugate addition of *tert*-butyl esters in the presence of chiral additives such as diethers, amino-ethers, or diamines.[216] In this reaction, the 1,4 adduct was produced in 68% and 57% ee with (−)-sparteine and Tröger's base, respectively (Scheme 104).

Conjugate addition onto imines was studied by Tomioka et al.[217,218] This was the first complete and successful study concerning the enantioselective addition of organolithium reagent to imines using an external chiral ligand. The imines used, which derived from 1-naphthaldehyde or unsaturated aldehyde and cyclohexylamine, selectively underwent conjugate addition. The regioselectivity was opposite to that obtained with substrate which bears a *N*-PMP substituent and led to the 1,2 addition product. Several chiral inducers were evaluated such as diether **372** and diamine **108**. Alexakis et al. evaluated diamines **7** and **228** in the reaction with the difference that the intermediate was quenched with methyl iodide (Scheme 106).[130] The product of the reaction **375** has a quaternary benzylic center and cannot rearomatize. It was obtained in significantly higher ee using **228** as the ligand instead of **7**. In Tomioka's study, the product was directly hydrolyzed leading to an aldehyde quite sensitive

Scheme 105



to rearomatization, which was therefore reduced quickly to the stable corresponding alcohol. When using diamine **108**, the alcohol **374** was obtained in only 11% ee, while diether **372** was much more efficient (Scheme 106).

7.4. Addition of Organometallic Reagents onto Quinoline and Isoquinoline

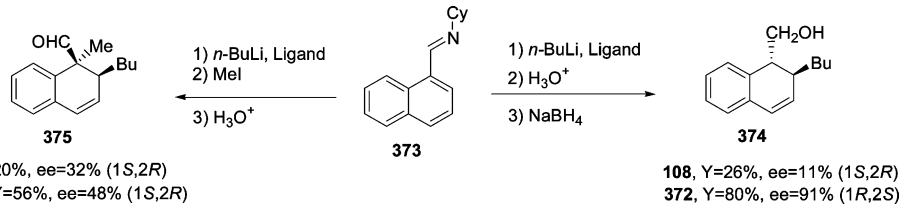
In 2002, Alexakis et al. reported the first direct enantioselective addition of an organometallic reagent onto an aza-aromatic system, such as isoquinoline[219] and quinoline,[220] using (−)-sparteine **13**, Tomioka's diether **372**, and bisoxazoline. These studies were later extended using derivatives of *trans*-cyclohexane-1,2-diamine.[221] Isoquinoline was alkylated at the benzylic position, and subsequent trapping of the resulting ene-amide occurred at either the N or the C position. Addition of methyl-, butyl-, and phenyllithium occurred in moderate to good yield leading to the adducts in up to 57% ee. On the other hand, quinoline underwent regioselective addition of organolithium reagent leading to the 1,2 adduct as a single product. Methyllithium was found to be very difficult to add selectively, and indeed, none of the ligands tested were able to induce significant selectivities. (−)-Sparteine led to low selectivities with alkyllithium but showed much higher selectivities with aryllithium, up to 78% with 2-naphthyllithium. In the case of *n*-butyllithium, diamine **228** was much more efficient than (−)-sparteine or **7**, and the product was formed in 63% ee. It has to be noted that in all cases decreasing the amount of ligand reduces the ee's, sometimes dramatically, which makes catalysis a not yet efficient process for these systems.

7.5. 1,2-Addition of Organomagnesium onto Carbonyl Compounds

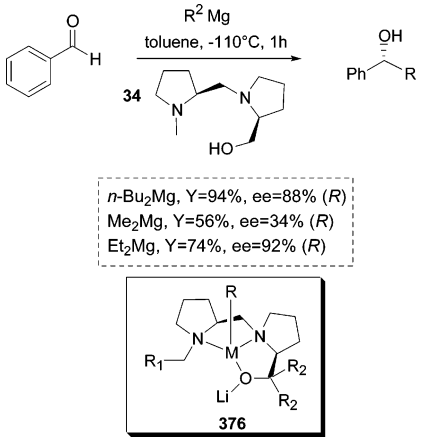
Association of an organometallic reagent with a chiral ligand was first described by Nozaki in 1968 for addition of organolithium and Grignard reagents to aldehydes and ketones.[182] Ethylmagnesium bromide was combined with (−)-sparteine, and the resulting chiral nucleophile was added to benzaldehyde leading to the adduct in 22% ee with the *R* configuration. Addition of ethylbenzoylformate gave the *S* product in 18% ee, and acetophenone was transformed to the corresponding racemic tertiary alcohol. In 1979, Seebach et al. described the addition of butylmagnesium iodide and dibutylmagnesium to benzaldehyde in the presence of **173**. Alcohols with the *S* absolute configuration were obtained in 6% and 8% ee, respectively.[184]

Mukaiyama reported the first good result in this area in 1978 using the proline-based ligand **34**.[188,222] Both Grignard and dialkylmagnesium reagents were tested, but the latter led to better selectivities. Furthermore, better results were obtained in noncoordinating solvents such as toluene at low temperature. Enantiomeric excesses up to 92% were recorded; however, the induction efficiency was highly de-

Scheme 106



Scheme 107



pendent on the substrate and nucleophile. All alcohols were obtained with the *R* configuration unlike alkyllithium, where the stereochemistry of the product is dependent on the size of the reagent. Dimethylmagnesium, which gave significant lower selectivity, was tested with more hindered ligands such as **327** and **330**. While **327** slightly increases the ee to 43%, **330** reduced it to 21%. This behavior was opposite to that observed with methyllithium. The authors suggested that a rigid complex **376** is formed, namely, a mixed aggregate,[223] which was responsible for the selectivities observed. However, no spectroscopic data was given to support formation of this rigid intermediate complex.

In 1987, Tomioka et al. reported the use of diamines **179a** and **179b** in the asymmetric addition of Grignard reagent to aldehydes.[224] They found that when these diamines were used alone, the selectivity of the addition of alkylmagnesium bromide was rather low, while in the presence of aryloxymagnesium bromide or aryloxyaluminum dichloride, much better results were obtained and ee's up to 70% were achieved. On the other hand, arylmagnesium bromide led to reasonable ee's without any other assistance. Enantiomeric excesses up to 75% were recorded in the most favorable case of the hindered 1-naphthylmagnesium bromide (Scheme 108).[225,226] Organolithium reagents did not give any selectivities with these ligands, and diorganomagnesium reagents gave lower selectivities than Grignards. The stereochemical outcome of the reaction is explained with the model depicted in Scheme 108. The explanation for the improvement observed with alkylmagnesium reagent using Lewis acid **377** or **378** was based on control of the geometry of coordination. The metal halide is supposed to coordinate the aldehyde syn to the aldehyde hydrogen which allows the magnesium to coordinate the only other position anti to the aldehyde hydrogen. The additional steric hindrance introduced in the reactive intermediate led to better induction.

Diamine **334**, developed by Sato et al., was tested with butylmagnesium bromide; however, for the addition reaction on benzaldehyde, only 8% ee was recorded.[194]

In 1994, Markó reported the observation of unusual behavior with diamine **379** (Scheme 109).[227] Despite the rather moderate selectivities obtained, up to 42% ee, it was noticed that an inverse correlation between ee and temperature existed. Usually lowering the temperature results in an increase of the ee, though a few cases exist showing the opposite behavior.[228] In the case of the addition of isopropylmagnesium chloride to cyclohexylcarboxaldehyde, 9% ee was recorded at −40 °C, while selectivity increased to 42% at 35 °C. An inversion point on the graph *T*/ee was discussed on a mechanistic level. However, little is known about the real mechanism of the reaction, and no explanation was given to rationalize this behavior.

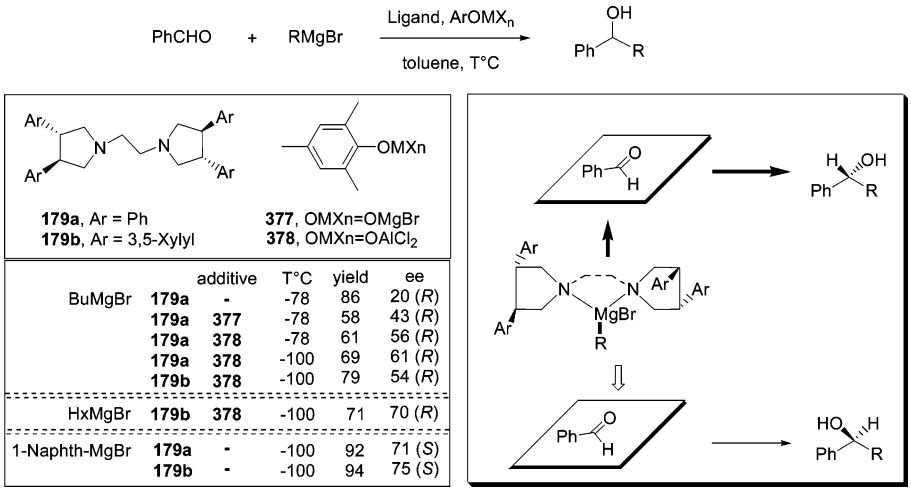
In 1994, Breitmaier reported an elegant and simple way to form opposite enantiomeric products from the same chiral inducer.[229] Diamine **10** was used stoichiometrically with Grignard and dialkylmagnesium reagents, and the resulting complex was added to aldehydes and ketones. A wide range of alkyl groups was added in high ee, often above 90% and up to 98%. In the presence of 1 equiv of triethylamine, a reversal of selectivity was obtained. Furthermore, the same level of induction was kept (Scheme 110).

7.6. 1,4-Addition of Organomagnesium onto Carbonyl Compounds

Conjugate addition is an extremely popular method for carbon−carbon bond formation which has underwent considerable development since its discovery.[230] Kretchmer was the first to report the enantioselective conjugate addition of an organometallic reagent modified by an external chiral ligand, which was (−)-sparteine.[231] Grignard reagents modified with an equimolar equivalent of (−)-**13** have a reactivity considerably reduced. Low yields were obtained at room temperature or even in refluxing solvent, and products were obtained with almost no selectivity. In the presence of copper salt (CuCl or CuI) yields were improved but selectivities were still very low.

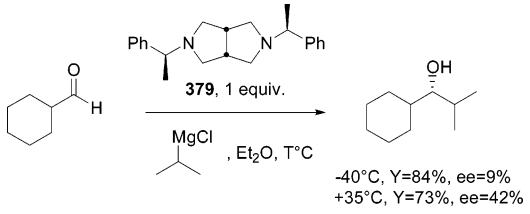
On the basis of various works describing the use of triorganozincate or Grignard reagents in the presence of TMEDA and $ZnCl_2$, Feringa et al. reported in 1988 the enantioselective conjugate addition of Grignard reagents catalyzed by zinc complexes.[232] During a preliminary study the best conditions were those using 1 equiv of potassium *tert*-butoxide as a nontransferable ligand which allowed the use of 2 equiv of Grignard reagent instead of 3. Under these conditions, isopropylmagnesium chloride was added to cyclohexenone in the presence of ligand **130** in 17% ee. Several diamines, among the ligands screened, gave the highest selectivities reported by this study. Using only 1 mol % of catalyst, diamines **34** and **380** reached 22% and 26% ee, respectively, while by increasing the amount of catalyst to 5%, ee increased to 29% and 33% ee, respectively. Several factors having significant effects on the selectivities can be emphasized. The rather low level of induction may be due partly to the noncatalyzed conjugate addition which is very

Scheme 108

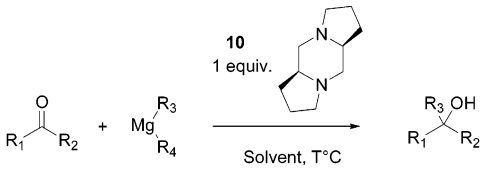


		additive	T°C	yield	ee
BuMgBr	**179a**	-	-78	86	20 (*R*)
	179a	**377**	-78	58	43 (*R*)
	179a	**378**	-78	61	56 (*R*)
	179a	**378**	-100	69	61 (*R*)
	179b	**378**	-100	79	54 (*R*)
HxMgBr	**179b**	**378**	-100	71	70 (*R*)
1-Naphth-MgBr	**179a**	-	-100	92	71 (*S*)
	179b	-	-100	94	75 (*S*)

Scheme 109



Scheme 110



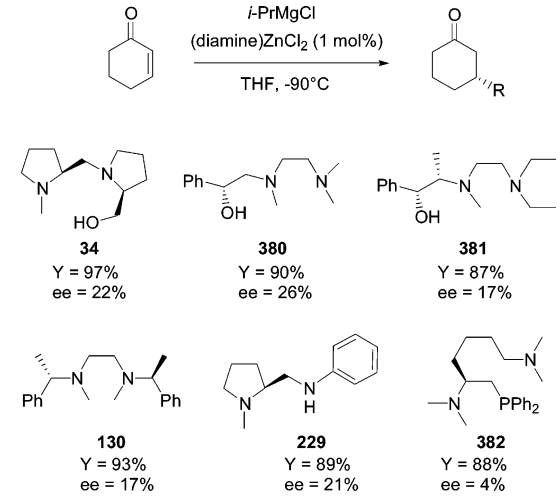
	R_3R_4Mg	solvent	T°C	additive	yield	ee
Ph, H	*i*-Pr_2Mg	Et_2O/pentane	-90	-	70	89 (*R*)
	i-Pr_2Mg	Et_2O/pentane	-90	Et_3N	70	82 (*S*)
	EtMgBr	THF/toluene	-100	-	68	93 (*R*)
	EtMgBr	THF/toluene	-100	Et_3N	60	89 (*S*)
Ph, Me	Et/Br	THF/toluene	-100	-	65	98 (R)
	Et/Br	THF/toluene	-100	Et_3N	58	97 (S)
	Pr/Br	THF/toluene	-100	-	68	97 (R)
	Pr/Br	THF/toluene	-100	Et_3N	62	95 (S)

fast even at low temperatures. The halide of the Grignard reagent had a strong effect, but the nature of its influence is unknown. Significant improvements were observed by introducing a lithium cation with the lithium salts of aminoalcohols or upon addition of lithium alkoxides. Although the catalytic cycle is not known, the model described in Scheme 112 was considered to rationalize the results obtained. It was suggested that the reactive complex **384** is formed from the tetracoordinated (sp^3) Zn(II) monoalkyl complex **385** on which coordination of the Grignard reagent lead to binuclear species. The enone is then activated through coordination to Zn, which becomes pentacoordinated. Transfer of the Mg-bonded alkyl group occurs leading to the *R* product.

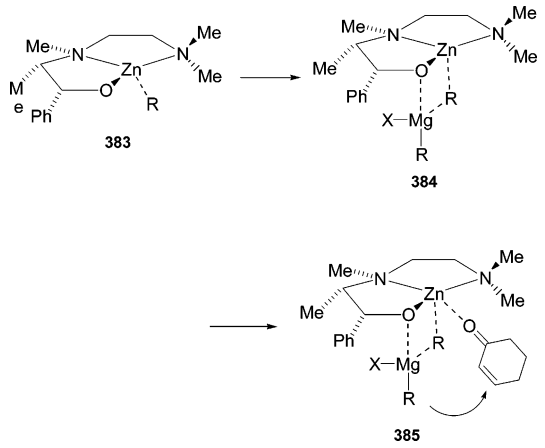
7.7. Addition of Organocopper Reagents

Organocopper reagents are soft nucleophiles well known to react selectively with unsaturated systems to perform conjugate additions. Indeed, they have been modified with

Scheme 111



Scheme 112



tertiary diamines and used in direct 1,2 addition on aldehydes, but to this present day, no highly selective reaction has been reported. Mukaiyama,[188] Seebach,[184] and Sato[194] studied organocopper and dialkylcuprate reagents, but only moderate selectivities could be obtained. *n*-Butylcopper was added to benzaldehyde in the presence of **34** without any selectivity, while with 1.2 equiv of **334**, the product was obtained in 17% ee. On the other hand, lithium di-*n*-butylcuprate was added to benzaldehyde in 10% ee with **108**, 15% ee with **173**, and 35% ee with **334**. Concerning the conjugate

addition, only three examples were found which associate (noncovalently) alkylcopper and phenylcopper with either (−)-sparteine **13**[231] or **7**[233] and diorganocuprate with **13**.[234] Addition of *n*-butylcopper onto cyclohexenone gives 6% ee with **13** and the racemate with **7**. In the case of dimethylcuprate associated with **13**, no selectivity was recorded upon its addition to cyclohexenone, while *n*-dibutylcuprate led to the product with an optical activity ($[\alpha]_D = +0.12°$).

Corey and Rossiter succeeded to set up efficient diamine ligands which form mixed aggregate intermediates and react in a very selective manner to give highly enantiomerically enriched adducts. This approach was used before by many groups with considerable success using other chiral sources such as alkoxides, dialkylamides, or arenethiolates.[235] In this approach, cuprates are formed with a covalently bonded and nontransferable chiral ligand and one unique transferable ligand.

In 1986, Corey et al. described diamine **386**, which is very easily prepared from (+)-ephedrine, as a chiral ligand for organocuprate species.[236] In the first procedure, organolithium of high purity was required to get high ee. However, a convenient modification could be found using methyl iodide as an alkoxide scavenger. The sequential stoichiometric protocol uses 1.0 equiv of aminoalcohol **386**, 0.89 equiv of RLi, 0.18 equiv of MeI, 0.67 equiv of CuI, 0.45 equiv of RLi, 0.09 equiv of MeI, and finally 0.3 equiv of enone. Additions of the chiral nucleophile derived from ethyllithium, *n*-butyllithium, and (*tert*-butoxymethyl)lithium to cyclohexenone led to products in 92%, 89%, and 85% ee, respectively. Lower ee's were obtained with cyclopentenone, 77%, 72%, and 81% ee, respectively. Ligand **387** was prepared in four steps from mandelic acid and used to produce a mixed methyl cuprate, which reacted at −78 °C with cyclohexenone to give the product in 90% ee.

In 1990 Rossiter et al. introduced diamine **388**, which they refer to as "MAPP", which could be used for conjugate addition achieving ee's up to 97%. However, such a level of induction was only obtained with cyclohexenone and cycloheptenone. Intense screening of diamines and tetraamines did not improve these results.[237]

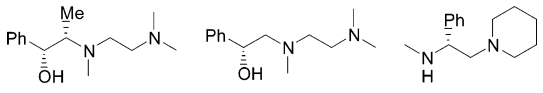
Davies and Wollowitz used mixed organocopper reagents for the asymmetric opening of cyclohexene oxide. Using various reaction conditions and chiral inducers, including **34**, low yield and enantioselectivities were recorded. It is to be noted that no product was formed with diamine **34**.[238]

7.8. Addition of Organozinc Reagents onto Carbonyl Compounds

7.8.1. 1,2-Addition

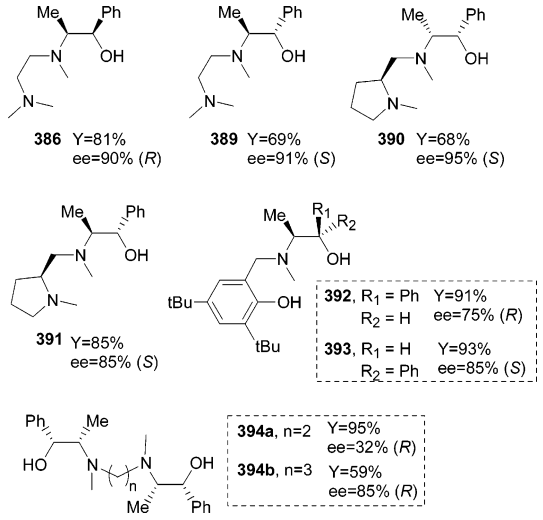
Diethylzinc was the first organometallic discovered and isolated by Frankland in 1849.[239] However, these reagents were introduced very late as nucleophilic reagents due to their poor reactivity and side reactions such as reductions, which usually occurred. These reagents were first used in processes such as Simmon−Smith reactions, Reformatsky reactions, and polymerization of oxiranes. It became extremely popular after the discovery that a catalytic process was able to enhance their reactivity. Soai and Niwa reviewed this topic in 1992 including all details about the mechanism.[240] Mukaiyama showed in 1978 that addition of diethylzinc to benzaldehyde in the presence of **34** gave a clean reaction but without any induction.[188] Seebach used trialkylzincate with **173** and got 15% ee on addition to

Scheme 113

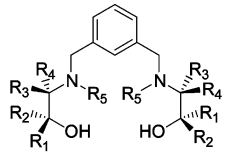


386 **387** **388**

Scheme 114

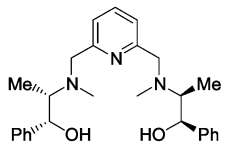


Scheme 115



	R1	R2	R3	R4	R5	Y (%)	ee(%)
395	Ph	H	Me	H	Me	95	78 (*S*)
396	Ph	H	Me	H	Et	82	95 (*S*)
397	Ph	H	Me	H	Bn	80	78 (*S*)
398	H	Ph	H	Me	Bn	82	78 (*R*)
399	Ph	H	Ph	H	Me	85	75 (*S*)
400	Me	Me	Ph	H	Me	75	75 (*S*)
401	Me	Me	Ph	H	Et	84	79 (*S*)
402	Me	Me	H	i-Bu	Me	81	98 (*R*)
403	Me	Me	H	i-Bu	Et	87	91 (*R*)
404	Ph	Ph	H	i-Bu	Me	82	87 (*R*)
405 [b]	H	Ph	H	Me	Me	72	76 (*R*)

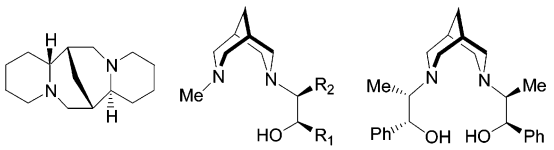
reaction on *p*-chlorobenzaldehyde
b- reaction of benzaldehyde



406 [b]
Y=82%, ee=90% (*S*)

benzaldehyde.[184] However, the first enantioselective addition of diorganozinc was reported by Oguni et al. in 1984 using (*S*)-leucinol with ee's of up to 49% being obtained.[241] This major breakthrough led to tremendous interest in the reaction, opening new opportunities and challenges in asymmetric catalysis. Since then, numerous ligands have been developed. We will focus only on those which contain a tertiary diamino functionality. We classified the ligands on the basis of their structures that are derived from ephedrine and pseudoephedrine (Schemes 114 and 115), bispidine (Scheme 116), binaphthyldiamine (Scheme 117), cyclohexanediamine (Scheme 118), piperazines, D-mannitol, diselenide, ketopinic acid, and

Scheme 116

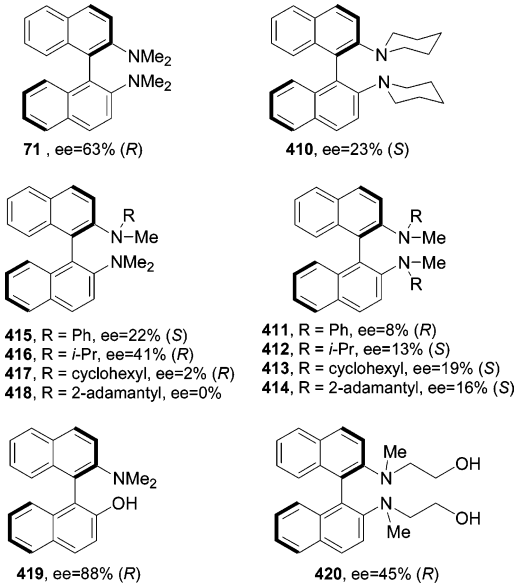


(-)-sparteine **13**

407, R_1 = Ph, R_2 = Me
408, R_1 = *i*-Pr, R_2 = H

409

Scheme 117



71 , ee=63% (*R*)

410, ee=23% (*S*)

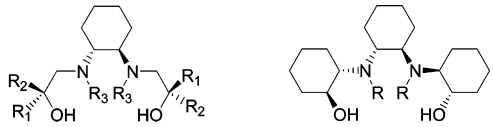
415, R = Ph, ee=22% (*S*)
416, R = *i*-Pr, ee=41% (*R*)
417, R = cyclohexyl, ee=2% (*R*)
418, R = 2-adamantyl, ee=0%

411, R = Ph, ee=8% (*R*)
412, R = *i*-Pr, ee=13% (*S*)
413, R = cyclohexyl, ee=19% (*S*)
414, R = 2-adamantyl, ee=16% (*S*)

419, ee=88% (*R*)

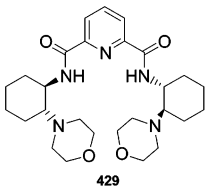
420, ee=45% (*R*)

Scheme 118



	R_1	R_2	R_3	Y (%)	ee (%)
421	H	H	H	30	8
422	H	H	Me	0	-
423	H	Ph	H	40	23 (*R*)
424	H	Ph	Me	55	54 (*S*)
425	Ph	H	H	42	45 (*S*)
426	Ph	H	Me	51	16 (*R*)

427, R = H Y=50% ee=80% (*R*)
428, R = Me Y=25% ee=92% (*S*)



429
Y=95%, ee=75% (*S*)

camphoric acid (Scheme 119). The most popular reaction used as a reference is the addition of diethylzinc to benzaldehyde, and unless otherwise stated, any discussion will refer to this reaction.

Corey et al. used diamine **386** along with derivatives q **389**−**393** (Scheme 114). High enantioselectivities were usually obtained for the addition of diethylzinc to benzaldehyde, the best being with **390**. However, when changing to dibutylzinc or other aldehydes, selectivities dropped significantly.[242] Soai et al. studied ligands containing two ephedrine units linked with two or three methylene groups. Ligands **394a** and **394b** were used as the lithium salts and led to very different results. Three methylene units were necessary to obtain good selectivity as well as the lithiated ligand. Interestingly and by contrast to Corey's system, the non-lithiated ligand led to much lower inductions.[243]

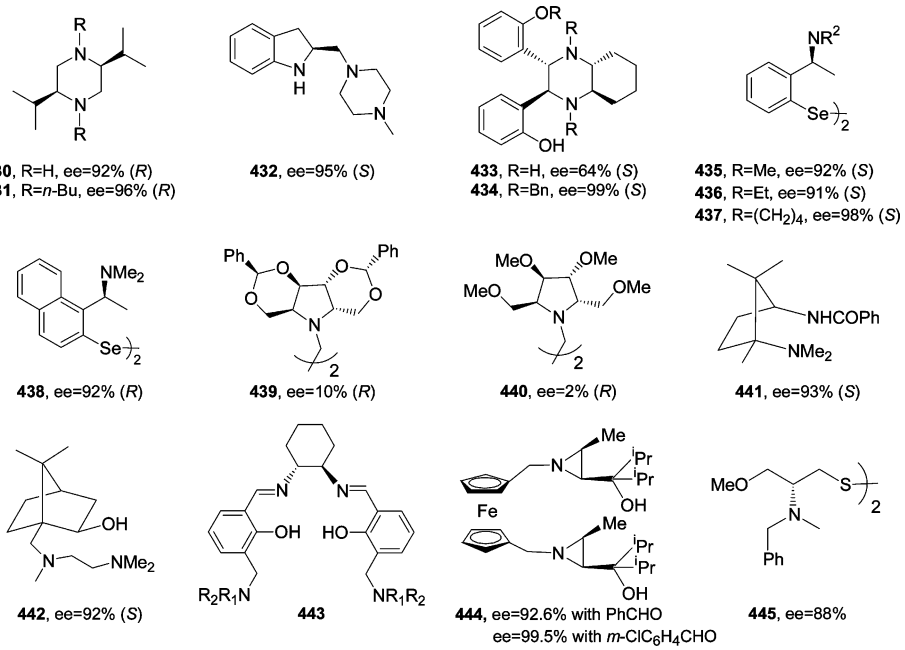
Bis-diamino ligands linked by a *m*-xylylene unit were first studied by Pedrosa et al. in 1994 (Scheme 115).[244] The best conditions were set up using **396**, and diethylzinc was added to *p*-chlorobenzaldehyde in 78% ee and 2-naphthaldehyde in 87% ee. Better induction was obtained when the nitrogen substituent was changed from methyl to ethyl as for **396**, while the *N*-benzyl ligand **397** did not improve the ee's. Ligands **402**−**404** derived from (*S*)-leucine and possessing a hindered tertiary alcohol moiety also led to the product in very high enantiomeric excesses up to 98% ee at room temperature. Williams et al. used ligands **405** (which is the enantiomer of **395**) and **406** and found a dramatic increase in reactivity when the link is pyridine.[245] Reactions occur with **406** at −70 °C instead of 0 °C for **405** leading to the product in 90% and 76%, respectively. Interestingly, opposite enantiomers were constantly obtained simply by exchanging the ligand.

O'Brien and Wyatt used the complex formed between (−)-sparteine and dimethylzinc for the asymmetric addition on benzaldehyde. After refluxing for 17 h in THF, they obtained the product in 39% yield and 15% ee in favor of the *R* enantiomer.[246] Waldman et al. used bispidine derivatives **407**−**409** bearing a chiral aminoalcohol moiety on one or both nitrogens (Scheme 116).[247] Those ligands efficiently catalyzed the addition of diethylzinc to benzaldehyde with very high induction. Ligands **407** and **408** led to the product in 98 and 96% ee, respectively, while on *n*-heptaldehyde products were obtained in 85% and 77% ee, respectively. Tetradentate ligand **409** was found to be consistently less efficient. Harmata et al. prepared Tröger's base derivatives by regioselective alkylation.[248] In the best case, the adduct was produced in 86% ee.

Salvadori et al. first explored atropoisomeric ligands for the enantioselective addition of diethylzinc onto benzaldehyde.[249] *N*,*N*′-Tetramethyl binaphtyldiamine **71** was used for the first time in such an asymmetric reaction. The addition occurred in 94% yield and 63% ee (*S*); similar results were obtained with 2-naphthaldehyde, but it appeared to be much lower with other substrates. Vyskočil and Kočovský explored other derivatives of binaphthyldiamine as well as NOBIN derivatives (Scheme 118).[250] All diamines tested, regardless of the nitrogen substitution, gave lower selectivities than **71**. C_2-symmetric ligands with both nitrogens bearing the same substituents such as **410**−**414** or with two different groups such as **415**−**418** led to ee's in up to 41% ee. By contrast, NOBIN derivatives were far superior, although the best ee obtained was 88% on benzaldehyde with the lithium salt of **419**. Derivatives of the same family such as **420** studied by Shi also led to moderate selectivities.[251]

N,*N*′-Bistosylated *trans*-cyclohexane-1,2-diamines were successfully used in this reaction.[2] Using the same diamine framework, Marson et al. developed tetradentate ligands containing two vicinal β-amino alcohol subunits.[252] For each amino alcohol, a ligand with both a secondary and a tertiary amine was studied (ligands **421**−**428**, Scheme 118). Diamines **421** and **422** bearing a lateral aminoethanol moiety without chirality gave very low results. However, by introducing a new stereogenic center in this lateral chain, a large increase in the reactivity and selectivity was observed and a match−mismatch effect for diastereoisomers **423**/**425** and **424**/**426**. The best results with those ligands were

Scheme 119



obtained with tertiary diamine **428** which led to the product in 92% ee but only 25% yield. Gotor and Rebolledo used ligand **429**, which catalyzed the reaction and led to the adduct in up to 75%.[253] Reaction conditions optimization showed that the best selectivity is obtained using 6 mol % of ligand at 20 °C.

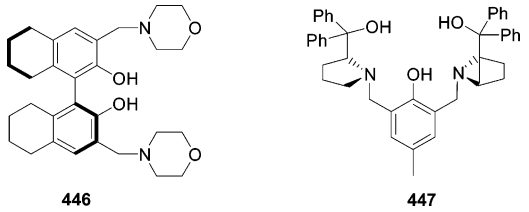
Piperazine ligands such as **430** were first used by Soai in 1987 as the bis-lithium salt leading to ee's up to 92% (98% ee onto *p*-chlorobenzaldehyde). Other derivatives with alkyl substituents also gave a high level of selectivity; up to 94% in the case of **431**.[254] Shono et al. efficiently prepared chiral piperazine from (*R*,*R*)-*trans*-cyclohexane-1,2-diamine using an electroreductive method, and ee's up to 99% ee were achieved with **434** for aromatic aldehydes, while **433** gave much lower selectivity. In a study based on the use of (*N*,*N*-disubstituted aminomethyl)indoline, Asami et al. designed **432** as the best derivatives of this study which led to ee's between 59% and 95%.[255]

Chiral diaminodiselenides **435**−**438** were used successfully by Wirth in 1995.[256] He showed that very high ee's could be achieved, up to 98% on benzaldehyde with **437**, with only 1 mol % of ligand. However, by changing the aldehyde or the organozinc reagent, much lower efficiency was observed. β-Aminodisulfide derived from (*S*)-phenylglycine used by Gibson et al. led to the adducts in up to 80% ee.[257]

Diamines derived from D-mannitol were used by Masaki et al.[258] He showed that tertiary diamines **439** and **440** gave very low selectivities, 10% and 2% ee, respectively. The best result, 82% ee, was obtained with a derivative of **440** which contains a β-amino alcohol moiety. Ligands **441** and **442**, derived from camphoric acid and ketopinic acid, respectively, were studied by Sato and Oppolzer, respectively.[194,259] Ligand **441** catalyzed the addition of diethylzinc to aromatic aldehydes with very good selectivity. On the other hand, Oppolzer studied the addition of dialkylzinc and divinylzinc to aromatic and aliphatic aldehydes with **442** and obtained selectivities in a range from 82% to >96% ee.

In 2005, Kozlowski et al. reported the use of salen ligand which contained a basic moiety leading to bifunctional catalyst (Scheme 120).[260] They tested ligands such as **443** with various nitrogen substituents in the addition of diethylzinc to aldehydes and α-ketoesters leading to the corresponding product in up to 87% ee. Wang and Braga designed ligands **444** and **445**, respectively.[261,262] Braga obtained high level of selectivities up to 99.5% ee.

Scheme 120



H_8BINOL-based ligand **446** was used by Pu et al. to perform enantioselective addition of diphenylzinc onto aldehydes (Scheme 120).[263] Best reaction conditions use THF as solvent with 10 mol % of ligand at room temperature. Addition onto aliphatic and para-substituted aromatic aldehydes was almost constantly superior to 90% ee, while ortho-substituted and unsaturated aldehydes led to much lower selectivity. It was also possible to perform asymmetric alkynylation in the presence of $Ti(OiPr)_4$ (100 mol %), Et_2Zn (4 equiv), phenylacetylene (4 equiv), and the ligand. Addition onto aromatic aldehydes occurred in ee up to 98%.

In 2006, Trost reported the enantioselective alkynylation of aldehyde using **447** as bimetallic catalyst.[264] They added phenyl- and trimethylsilyl acetylene in good yields and selectivities, up to 99% ee, onto aromatic and unsaturated aldehyde. The catalytic cycle suggested involves an alkynylzinc reagent that coordinates with the aldehyde onto the ligand to perform the addition.

7.8.2. 1,4-Addition

Organozinc reagents have become very efficient reagents to perform conjugate additions following the discovery that they can be used in the presence of catalytic amounts of copper salt and phosphorus-based chiral ligands.[265] However, very little work has been devoted to the use of diamine

ligands. Gibson first used ligand **448** for the conjugate addition of diethylzinc to chalcone and obtained ee's up to 50%.[266] The reaction was performed in the presence of 7 mol % of $Ni(acac)_2$ and 17% of ligand in acetonitrile at −30 °C. Feringa et al. described the cobalt-catalyzed addition of diethylzinc to chalcone with several aminoalcohol, among them **34** and **449**, which led to 28% and 83% ee, respectively.[267] Tetradentate ligands **450** and **451** were studied for the nickel-catalyzed addition and led to 21% and 69% ee, respectively, which is much less than **449** for which 84% was reached.[268,269] Addition of diethylzinc onto cyclohexenone catalyzed by **450** and **451** gave only racemic products. One possible explanation involves the *s-cis* and *s-trans* conformation of the substrate which may or may not favor enantioselective addition.

7.9. Reaction of Organotin Reagents

Organotin reagents have become extremely useful as soft organometallic partners. Nowadays, allyltin derivatives are one of the most popular reagents to perform asymmetric allylation of aldehydes.[270] Many external chiral ligands have been used to control the chirality of the product. However, very limited interest has been devoted to the use of tertiary diamines. Allylation through Lewis base catalysis was first introduced by Sakurai in 1989.[271] On the basis of their studies concerning the asymmetric reduction of ketones, Mukaiyama et al. adapted this methodology for the asymmetric allylation by replacing DIBAL-H by allyldialkylaluminium.[272] In the presence of 1.8 equiv of stannous trifluoromethanesulfonate (stannous triflate $Sn(OTf)_2$), 1.8 equiv of diamine **168**, and 1.4 equiv of allyldiisobutylaluminium, the allylated product was isolated in good yield and with a good level of asymmetric induction, up to 82% ee.

Kobayashi et al. pointed out that diallyltin dibromide reacts with aldehydes at −78 °C in the presence of tertiary diamines such as TMEDA, while other allylating agents such as tetraallyltin and allyltributyltin do not.[273] Chiral diamines derived from (*S*)-proline were used to introduce asymmetric induction into the homoallylic alcohol obtained. In all cases, alcohols with the *R* configuration were isolated. The best results were obtained with diamine **453**, which contains a *n*-butyl nitrogen substituent and a lateral piperidine ring. Reactions were performed with stoichiometric amounts of ligand; however, it was shown with **455** that 0.5 equiv of ligand could be used without significant loss of selectivity.

7.10. Reaction of Organogallium Reagents

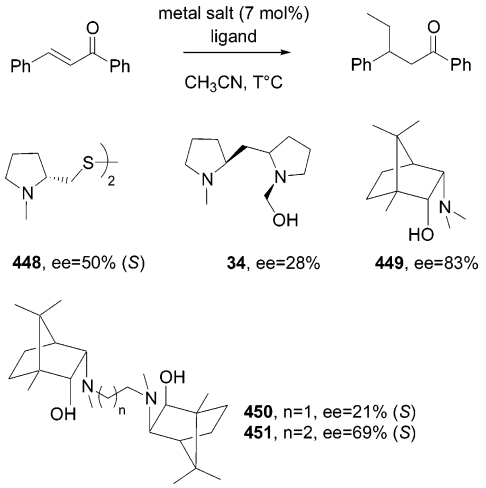
Although organogallium reagents were first synthesized in 1932, they were used very scarcely in organic synthesis because of their low reactivity. In 2005, Zhu and Pan reported the first asymmetric addition of organogallium onto aldehydes.[274] Reactivity was achieved with a strong Lewis acid such as titanium tetrachloride, while selectivity was introduced with diamine **456**. Addition of trimethyl- and triethylgallium occurred at −60 °C leading to the secondary alcohols in ee's up to 84%.

7.11. Cyanation Reaction

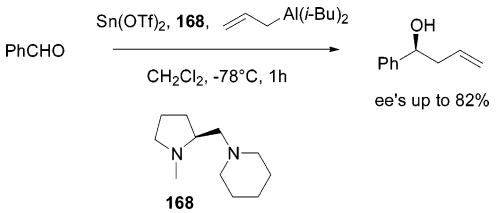
Asymmetric cyanation of aldehydes and ketones has proven to be a very powerful reaction to prepare cyanohydrins which are important intermediates as chiral building blocks.[275] On the basis of Poirier's work,[276] Deng reported in 2001 that chiral tertiary amines, derived from cinchona alkaloids, could be used for asymmetric cyanation of ketones.[277] Among the chiral amines used, $(DHQD)_2AQN$ gave the best result in the preliminary study performed on 2-heptanone. Cyclic ketones were particularly good substrates, and ee's up to 97% were achieved. Acyclic ketones bearing a tertiary or quaternary carbon in the α position also gave very good results.

Nájera and Saá introduced in 2002 a new bifunctional ligand referred to as "BINOLAM" which is derived from binol.[278] They showed that ligand (*S*)-**457** is a precursor of the catalyst for efficient cyanation of aldehydes using a very convenient procedure. In several examples, ee's up to 99% were achieved using trimethylsilyl cyanide in the presence of 10 mol % of ligand and dimethylaluminium chloride. Two additives, triphenylphosphine oxide and 4 Å molecular sieves, were found to be crucial to increase both the yield and selectivities. However, ketones did not react under these conditions. Indeed, thermogravimetric analysis of the 4 Å MS dried 4 h at 120 °C used in the reaction reveal the presence of 7.5% of water content. By contrast, ultradry 4 Å MS (6 h at 200 °C under high vacuum) led to very low results as well when 1 equiv of water was used without molecular sieves. These results suggest that 4 Å MS act as a carrier of a limited amount of water.[279] In the presence of this small amount of water, TMSCN is hydrolyzed to HCN. The reaction is thus a hydrocyanation followed by *O*-silylation. The hydrogen cyanide is trapped by the dimethylamino group and becomes more nucleophilic. The aldehyde is activated by the Lewis acid part of the ligand with the interaction taking place between the oxygen atom of the aldehyde and the aluminum atom. A second weaker interaction occurs between the hydrogen atom of the aldehyde and the chlorine atom as described in Scheme 127. The importance of this effect has been observed by changing the dimethylaluminium chloride to dimethylaluminium cyanide. Contrary to (*S*)-**458**, catalyst (*S*)-**459** led to good yields but almost no selectivities.[280] Pu et al. reported the use of **460**

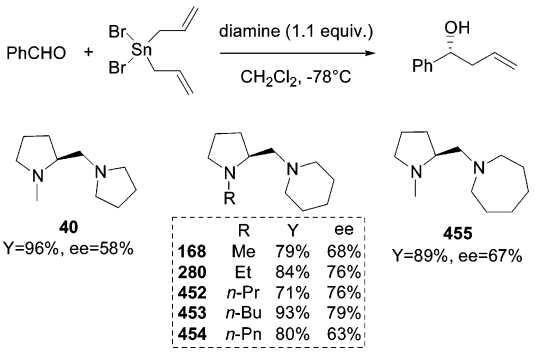
Scheme 121



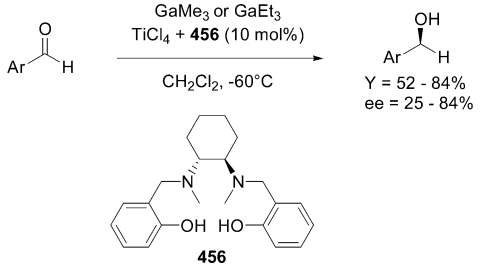
Scheme 122



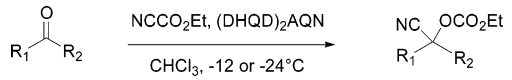
Scheme 123



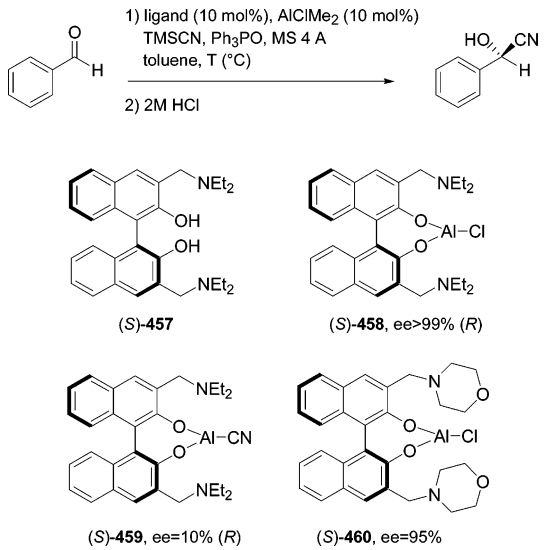
Scheme 124



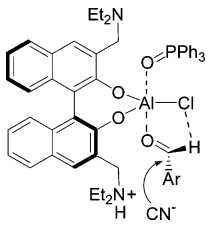
Scheme 125



Scheme 126

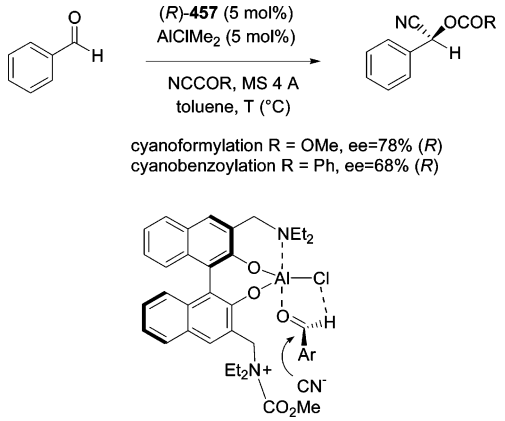


Scheme 127



in similar reaction conditions except that Ph_3PO was replaced by HMPA, which was found to accelerate the reaction.[281] They reached a high level of enantioselectivities with both aromatic and aliphatic aldehydes. Later, they noticed that diethyl ether is indeed more suitable for aliphatic aldehydes,

Scheme 128



and using the same reaction conditions in this solvent, these substrates react in selectivities up to 99% ee and almost constantly above 95%.[263]

BINOLAM (*R*)-**457** was also used in the cyanoformylation[282] and cyanobenzoylation[283] of carbonyl compounds. In the presence of dimethylaluminium chloride and 4 Å MS at 25 °C, methyl cyanoformate was added to aldehydes to give *O*-methoxycarbonylcyanohydrins in high yields and enantiomeric ratios up to 82%. In these reaction conditions, ketones did not react as in the hydrocyanation. Furthermore, monofunctional ligand BINOL-AlCl was not able to catalyze the reaction. As for the hydrocyanation, the mechanistic discussion given by the authors favored the double action of the catalyst which acts as a Lewis acid and a Lewis base. It led to the reactive complex shown in Scheme 127 and explained the stereochemical outcome of the reaction. Cyanobenzoylation was performed using benzoyl cyanide and [(*S*)-**457**-Ti(O*i*-Pr)$_2$] complex as catalyst. *O*-Benzoylated cyanohydrins were obtained in high yields and ee's up to 68%.

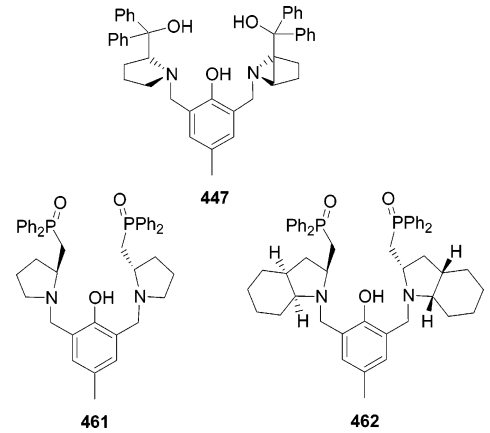
Trost showed that cyanosilylation of aldehyde occurs in the presence of 11 mol % of **447**, 10 mol % of $AlMe_3$, and TMSCN.[284] The reaction conditions were carefully studied, and the adduct was obtained in up to 86% ee. Shortly after, Kim et al. reported the use of **461** and **462**.[285] In contrast to Trost's conditions, they obtained the best result with Ti(O*i*-Pr)$_4$ as the Lewis acid. Ligand **462** (10 mol %) led to the best ee's, up to 95%, at −20 °C using CH_2Cl_2 as the solvent and in the presence of 2 equiv of O═PPh$_3$ and TMSCN.

Feng et al. reported the enantioselective Strecker reaction of ketoimines using a C_2-symmetric diamine (Scheme 129).[286] The procedure involves the in situ oxidation with *m*-CPBA that produces the effective ligand, that is to say the corresponding *N*,*N*′-dioxide. Addition of TMSCN led to the α-amino nitrile in high yield and up to 92% ee.

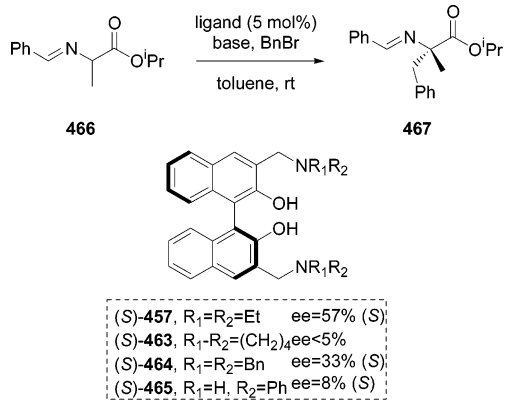
7.12. Phase-Transfer Catalysis

Phase-transfer catalysis has become a very useful and powerful method, particularly for alkylation of glycine derivatives (Scheme 130).[287] Many ammonium salts were found to be very efficient in terms of reactivity and selectivity. However, free tertiary diamines did not arouse much interest in this reaction. Nájera and Saá used BINOLAM derivatives as phase-transfer catalysts for *C*-alkylation of alanine-derived isopropyl iminoester **466**.[288] When sodium hydride was used, the alkylated product **467** was obtained in 40% ee, while using sodium hydroxide it was obtained in

Scheme 129



Scheme 130

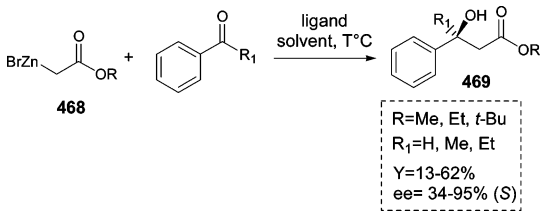


57% ee. Use of other bases such as potassium hydroxide, cesium hydroxide, and lithium *tert*-butoxide gave poorer results. By changing the nitrogen substituents on the ligand, selectivities dropped significantly. Indeed, best selectivities were obtained with **457**.

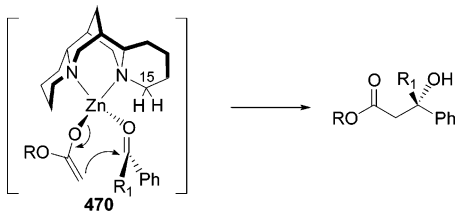
7.13. Reformatsky Reaction

Enantioselective Reformatsky reactions were first studied by Guetté et al. in 1971 using (−)-sparteine as a ligand.[289,290] Reaction conditions were carefully set up to avoid several problems of compatibility with the reagents: (a) they used an apolar solvent to ensure the efficient complexation of the ligand to the metal and (b) as (−)-sparteine is easily alkylated by the halide, it is necessary to avoid direct mixing of these species. Two different procedures were used. In the first one, both (−)-sparteine and bromoesters are introduced slowly and simultaneously in refluxing benzene containing zinc powder (method A). The second procedure occurs in two steps. First, the Reformatsky reagent is prepared, and then (−)-sparteine is added to complex the metal (method B). Low yields and ee's were obtained in most cases, except for addition of the ethyl ester to benzaldehyde, which gave the *β*-hydroxyester in 95% ee (Scheme 131). When methylal was used as a solvent, 98% ee was achieved. Both *O*- and *C*-metalated reagents **468** were observed either by NMR or IR spectroscopy. However, no data was given for the (−)-sparteine complexed reagent because of its insolubility. It may exist in both forms and react preferentially through one only. Indeed, the results obtained in the study tend to support reactivity through the enolate. Furthermore, by considering the reaction of the C-metalated reagent, modelization of the transition state leads to the wrong enantiomer.

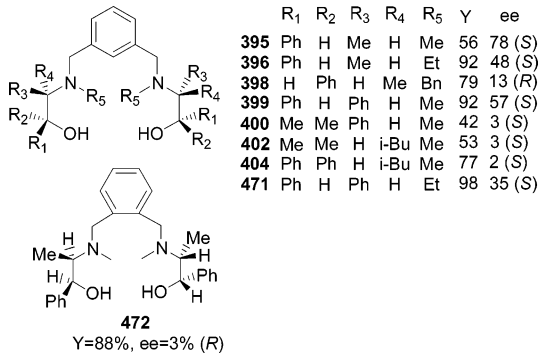
Scheme 131



Scheme 132



Scheme 133



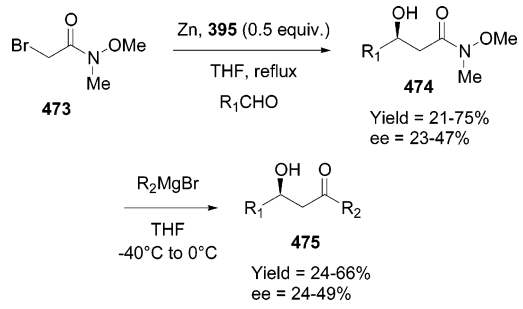
	R1	R2	R3	R4	R5	Y	ee
395	Ph	H	Me	H	Me	56	78 (*S*)
396	Ph	H	Me	H	Et	92	48 (*S*)
398	H	Ph	H	Me	Bn	79	13 (*R*)
399	Ph	H	Ph	H	Me	92	57 (*S*)
400	Me	Me	Ph	H	Me	42	3 (*S*)
402	Me	Me	H	i-Bu	Me	53	3 (*S*)
404	Ph	Ph	H	i-Bu	Me	77	2 (*S*)
471	Ph	H	Ph	H	Et	98	35 (*S*)

A model was established considering the zinc enolate−(−)-sparteine complex reacting to a carbonyl in a cyclic six-membered transition state. The phenyl substituent of the carbonyl is positioned on the back face to minimize unfavored interactions with hydrogens borne by C15 of (−)-sparteine (Scheme 132). This can explain the drop in selectivity when the bulkiness of R_1 is increased. Indeed, interactions with hydrogens H15 increase as well, which leads to less efficient differentiation between both enantioselective processes. Strong influences were also observed for the ester moiety R of the Reformatsky reagent. The authors suggested that electronic effects may have more influence than steric effects as the ester moiety is in a clear space. Considering that the inductive effect is minimum for an ethyl substituent and that it is transmitted to the other part of the ester function, it was suggested that it could influence the equilibrium between *C*- and *O*-metalated forms of the reagent.[291] As a consequence, ethyl esters are more likely to be in the *O*-metalated form than methyl or *tert*-butyl esters and therefore lead to better selectivities.

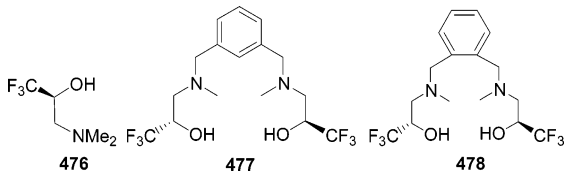
Seebach et al. used ethyl and *tert*-butyl esters of Reformatsky reagents with ligand **173** for the addition onto benzaldehyde. Adducts were obtained with 88% and 95% yield in 22% and 24% ee, respectively.[184]

Pedrosa et al. explored the ligands outlined in Scheme 133 with Reformatsky reagents prepared from *tert*-butyl-bromoacetate.[292] Several aldehydes and acetophenone were tested as substrates. Diamine **395** was the most efficient, leading to the product in ee's up to 78% with benzaldehyde. Aromatic aldehydes gave better results than the aliphatics, while acetophenone was transformed in 68%ee.

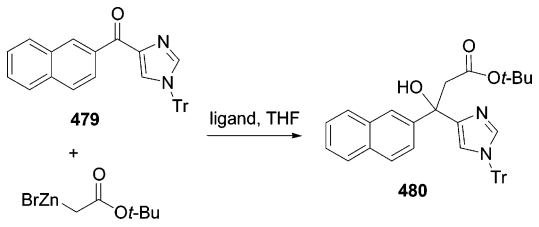
Scheme 134



Scheme 135



Scheme 136

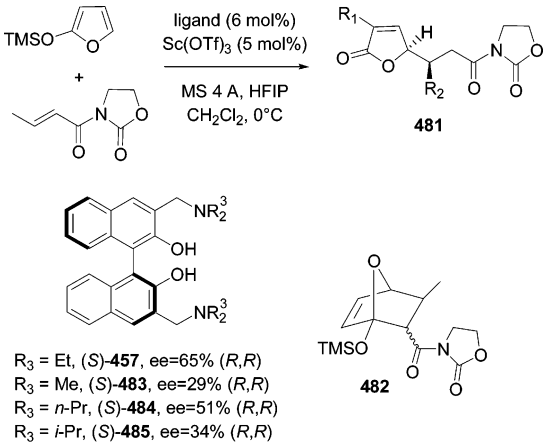


Afterward, they extended their methodology using α-bromo-*N*-methoxy-*N*-methylacetamide **473** (Weinreb amide) (Scheme 134).[293] The resulting product was subsequently easily transformed to the chiral nonracemic aldol product. Only the one-step procedure was used as the Reformatsky reagent derived from **473** could not be prepared. Diamines **395** and **399** were used along with (1*S*,2*R*)-*N*-methylephedrine. Again, in this case, diamine **395** gave the best selectivities leading to *β*-hydroxyamide **474** in ee's up to 47%. The corresponding ketones were obtained in moderate yields by addition of the Grignard reagents without affecting the enantiomeric excesses.

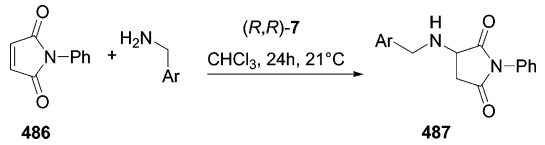
Uneyama et al. evaluated similar ligands containing a trifluoromethylated aminoalcohol moiety (Scheme 135).[294] Reactions were performed on the classic system using ethyl bromoacetate and benzaldehyde. Indeed, the best result was obtained with aminoalcohol **476** with up to 89% ee, while tetradentate ligands **477** and **478** gave lower results. However, these ligands showed a very different behavior in a way consistent to Pedrosa's original report.[292] Ligands containing an aminoalcohol moiety in the ortho position to each other such as in **478** or **472** led to racemic products. On the contrary, when both aminoalcohols were in the meta position to each other such as in **395** or **477**, much better results were obtained with up to 78% and 68% ee, respectively.

Yamano et al. studied the Reformatsky reaction on ketones containing a heteroatom capable of participating in the formation of a geometrically defined complex intermediate (Scheme 136).[295] Most of the substrates bear a heteroaromatic moiety with a nitrogen atom. Among the ligands used, two contained the tertiary diamine functionality, (−)-sparteine **13** and (DHQ)2-PHAL **208**. Other cinchona alkaloids were used, such as cinchonine, cinchonidine, quinidine, and quinine. In the presence of cinchonine, **480** was obtained in

Scheme 137



Scheme 138



68% ee while **13** and **208** gave 19% and 0% ee, respectively. Reaction conditions were improved using 2 equiv of pyridine at −40 °C, and **480** was obtained with 1.5 equiv of cinchonine in 97% ee. Several other examples containing sp^2-nitrogen atoms adjacent to the carbonyl were transformed in high enantiomeric excesses.

7.14. Conjugate Addition of 2-(Trimethylsilyloxy)-furans

2-(Trimethylsiloxy)furans have been often used as nucleophiles for the synthesis of butenolides. Katsuki et al. reported in 1997 the first enantioselective conjugate addition of this nucleophile to oxazolidinone enolates (Scheme 137).[296,297] In the presence of *N*,*N*,*N*′,*N*′-tetraalkyl-BINOL-3,3′-aminomethyl and $Sc(OTf)_3$, they obtained butenolides **481** with excellent diastereoselectivity and 73% enantioselectivity. A Diels−Alder-type adduct **482** was the major byproduct of the reaction and could be avoided by adding 1 equiv of isopropyl alcohol. However, these modified conditions improved the yield of butenolide but were detrimental to the enantioselectivity. Almost all the selectivities were recovered using hexafluoroisopropyl alcohol (HFIP), which is more acidic and has poor coordinating ability.

7.15. Aza-Michael Addition

Benzylic amines were added onto maleimide **486** in the presence of diamine **7** and produced **487** in low ee's, up to 16% (Scheme 138).[298]

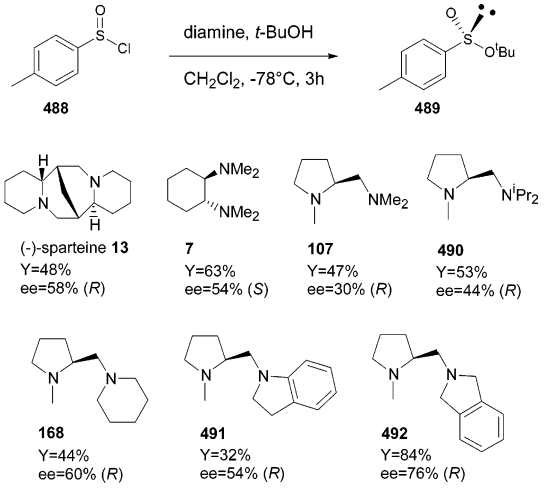
7.16. Addition to Sulfinyl Chloride

Chiral sulfinate are used as precursors of chiral sulfoxide by addition of an organometallic reagent (Andersen's method).[299] In 2005, Toru et al. reported the addition of *tert*-butyl alcohol onto *p*-toluenesulfinyl chloride **488** in the presence of a stoichiometric amount of chiral diamines (Scheme 139).[300] The best result was obtained with 2 equiv of diamine **492**, which produced the corresponding sulfinate **489** in 76% ee.

8. Cross Coupling

Transition-metal-mediated reactions involving an organometallic reagent and an electrophile, usually referred to as

Scheme 139



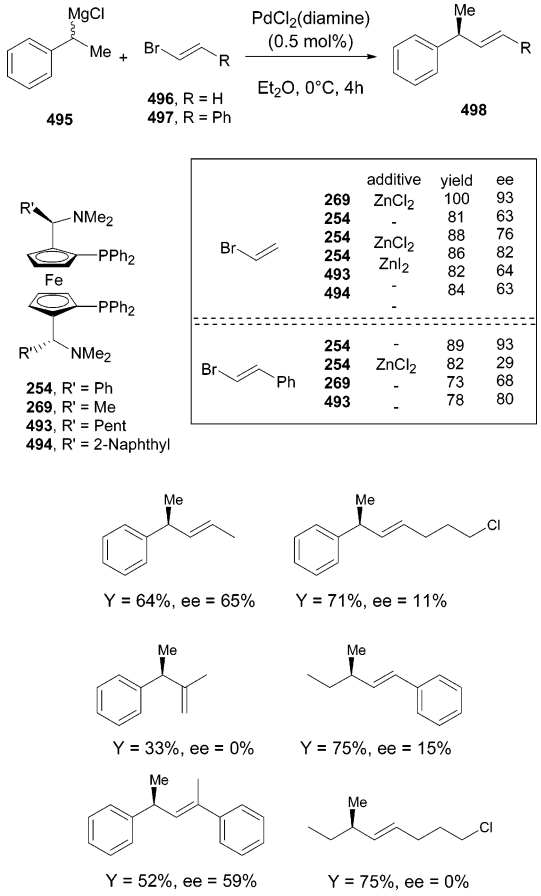
cross-coupling reactions, are of prime importance in total synthesis and also for ligand preparation. It has become one of the most important classes of reactions among which are Heck, Suzuki, Stille, Sonogashira, Kumada−Corriu, Negishi reactions, etc. The effectiveness and scope of cross-coupling reactions, associated with asymmetric synthesis, have led to enantioselective processes which are now extremely powerful in synthesis.[301] We will focus in this section on systems that involve chiral tertiary diamines.

Ligand **269** was first prepared by Hayashi et al. in 1989 for the enantioselective coupling of **495** with **496** in the presence of zinc chloride.[302] Only one example was reported, and the product was obtained in 93% ee. Almost 10 years later, Knochel evaluated other ferrocenyl ligand derivatives for enantioselective palladium-catalyzed cross-coupling between Grignard reagent **495** and vinyl bromide **496** or **497**.[303] Complexes were formed by mixing palladium salt and the diaminodiphosphine, and the crude isolated complexes were used without further purifications. In the case of vinyl bromide **496**, all diamines gave very similar results. However, selectivities were improved by adding zinc salt. On the contrary, vinyl bromide **497** was sensitive to the ligand, and best selectivities were obtained with **254**. Addition of zinc chloride made the ee drop drastically. A few of the examples reported are outlined in Scheme 140. It can be noticed that when cross coupling was attempted with *s*-BuLi, very low selectivities were obtained.

In 1996, Wildham et al. reported a study concerning the influence of distance between the asymmetric moiety and the transition-metal center.[177] Nickel-catalyzed cross coupling between Grignard reagent **495** and vinyl bromide **496** is one reaction that has been adopted as a test reaction. Previous studies made by Kumada et al. pointed out the importance of an amino substituent capable of *N*-Mg interaction for high selectivity.[304,305] Here again, ligand **308**, with three methylene units between the nitrogen and phosphorus atom, gave better selectivities compared to **307**. However, **498** was obtained with only 1% and 16% ee using **307** and **308**, respectively.

Kondo and Aoyama developed a *P*-*N* axially chiral ligand specifically for asymmetric cross coupling of *β*-bromostyrene for which selective transformations have been found to be particularly difficult.[306,307] The main feature of these ligands is to form two diastereoisomeric complexes by coordination to a metal (Scheme 88). One of these complexes is more stable and possesses a stable chiral axis. A ligand possessing a pyrrolidine central core slows down the reaction because

Scheme 140

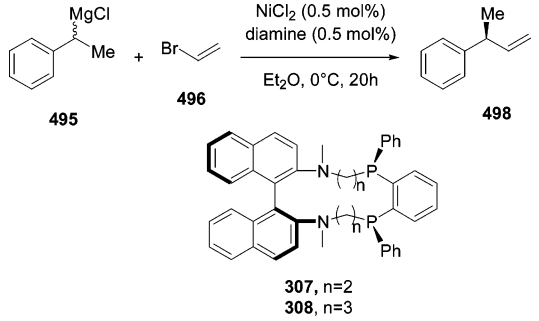


of a strong coordination to the metal. Reaction time was typically 24 h and led to 20−43% yield in up to 65% ee with **499**. However, the aromatic substituents present on the phosphorus atom had little influence on the reaction, and similar selectivities were obtained with **309**. On the other hand, piperidine base ligands were much more reactive. Indeed, they led to less favored bidentate coordination to the metal because of torsional effects. Better yields were obtained but with a similar level of selectivities. Other bromostyrene were examined, and *p*-isopropyl-bromostyrene led to the coupling product in 49% yield and 80% ee.

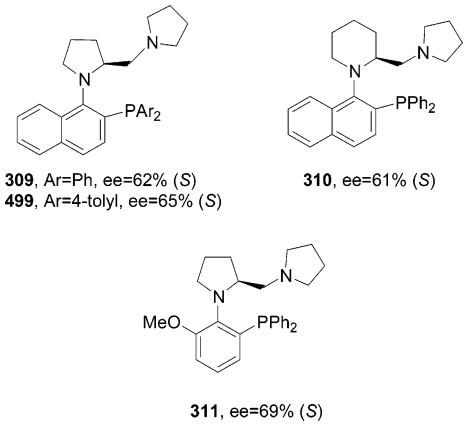
The first highly asymmetric coupling between phenols and arylleads was reported in 1999 by Yamamoto et al.[308] Among the few aminated ligands tested, diamine **168** led to only a 3% yield of racemic product. Best selectivities were obtained with brucine. Lithium phenoxide had to be used to obtain good yields as well as 4 Å molecular sieves. Using 2 equiv of brucine, axially chiral biaryls with up to 93% ee were obtained.

Since 2002 Malinakova et al. developed a synthetic methodology to access heterocycles via palladacycle intermediates **500** with a metal-bonded stereogenic carbon.[309] They succeeded in the insertion of alkyne and obtained benzopyrans in up to 88% and 56% ee in the presence of diphosphine and diamine ligands, respectively.[310,311] The latter was also reacted with azapalladacycle to prepare dihydroquinoline in up to 91% ee. Among all diamines used (**7**, **71**, **108**, **166**, **174**, and (1*R*,2*R*)-*N*,*N*,*N*′,*N*′-tetraethyl-1,2-diaminocyclohexane), the best results were achieved with ligand **7**. This was also applied for the synthesis of 3,4-dihydro-2*H*-1-benzopyran via insertion of allenes (Scheme 143).[312] The products obtained depend on the allene substitu-

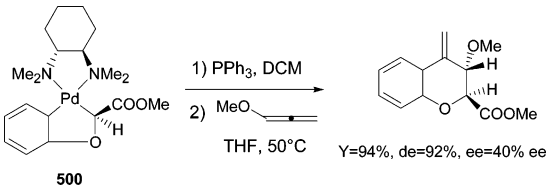
Scheme 141



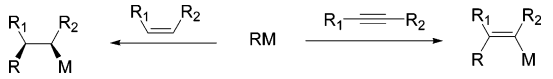
Scheme 142



Scheme 143



Scheme 144



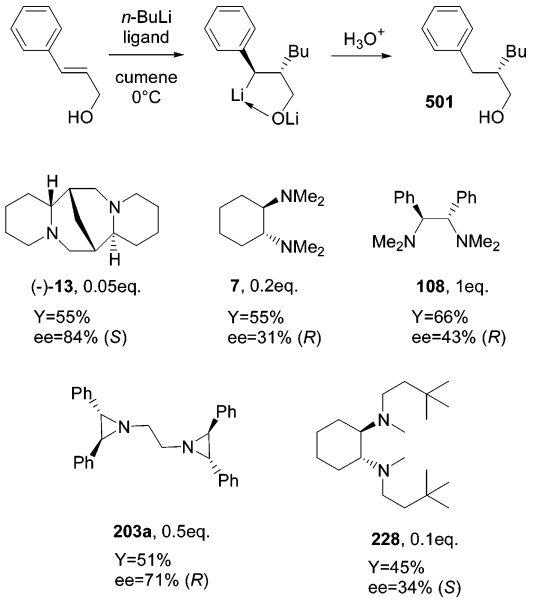
tion that influences the regiochemistry of the cyclization. Enantiomerically enriched palladacycle was obtained and furnished benzopyrans in ee up to 47%.

Since 2001, Oshima et al. developed the cobalt-catalyzed coupling reaction.[313] This metal has been less used than others but shows very interesting possibilities like the coupling between two sp^3 carbon atoms.[314] In 2006, they found that $CoCl_2-$**7** is an efficient catalyst that allows arylating primary and secondary alkyl halides. However, in very few cases, low enantioselectivities were observed.[315]

9. Carbometalation

Carbometalation is the addition of an organometallic reagent onto unsaturated systems such as alkene or alkyne. The product of the reaction is either an alkylmetal or a vinylmetal (Scheme 144). Two main problems have been pointed out which are allylic or propargylic deprotonations and polymerization if the newly formed organometallic reagent reacts on the starting material. The tricks usually used to avoid these problems are to increase the reactivity of either the unsaturation or the organometallic, to stabilize

Scheme 145

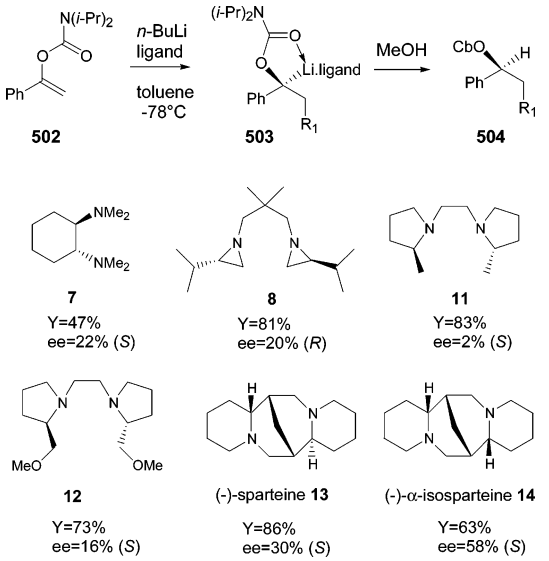


the product with an intramolecular coordination, or to perform an intramolecular reaction. Regioselectivity is highly dependent on the substrate, but generally selectivity of the addition is syn.

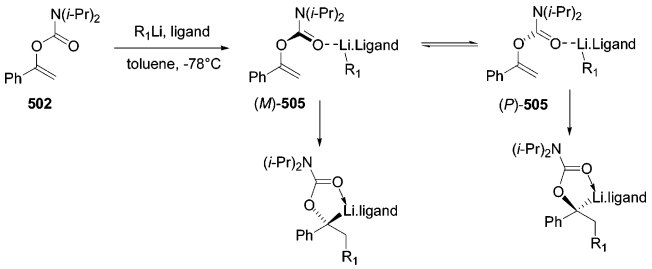
Most of the asymmetric carbometalations have been studied with (−)-sparteine as a ligand. However, few other tertiary diamines were evaluated. Normant et al. reported in 1995 excellent levels of induction for the carbometalation of cinnamic alcohol and some of its derivatives in the presence of (−)-sparteine.[316,317] In the particular case of (*E*)-cinnamic alcohol, addition of *n*-butyllithium with a stoichiometric amount of (−)-sparteine led to alcohol **501** in 82% yield and 82% ee. With only 5% of ligand, the product was obtained with 84% ee and only 55% yield because of the formation of 32% of dimer. Addition onto (*Z*)-cinnamic alcohol led to a lower ee of 70%. In both cases, the intermediate was trapped with a wide range of electrophile. When other diamines were used, lower selectivities were obtained. Bis-aziridine **203a** was able to induce a good level of selectivity, while ligands derived from *trans*-1,2-diphenylethylenediamine and *trans*-1,2-cyclohexanediamine led to moderate selectivity only.[130,318]

Hoppe et al. developed a very efficient method to synthesize highly enantioenriched molecules using the association of an organolithium reagent and (−)-sparteine in the case of asymmetric deprotonation. Carbamates undergo deprotonation in the α position to the oxygen atom leading to organolithiated intermediates which were trapped by a variety of electrophiles very selectively. They used alkenyl carbamates such as **502** which underwent carbometalation and led to similar lithiated intermediates.[319] With substituted olefins, very good diastereoselectivities were obtained. Protonation occurred with retention of configuration, while other electrophiles such as methyl iodide reacted with stereoinversion. Some examples of intramolecular carbometalation have also been reported. When asymmetric reactions were performed, best selectivities were recorded with (−)-α-isosparteine, while all the other diamines, including (−)-sparteine, gave moderate ee. Substituted carbamates gave even lower selectivities.[319,320] The authors suggested that the induction is established in the intermediate complexes (*M*)-**505** and (*P*)-**505** (Scheme 147). Both complexes are in slow equi-

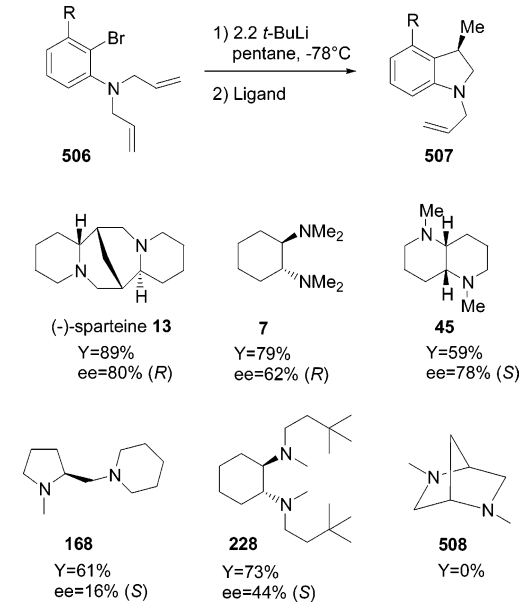
Scheme 146



Scheme 147



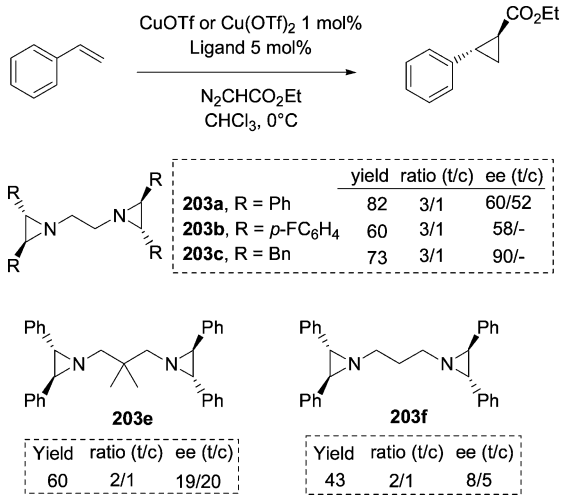
Scheme 148



librium and react with similar activation energies.

Bailey et al. investigated the efficiency of several diamines as ligands for the cyclization of 2-(*N*,*N*-diallylamino)phenyllithium **506** (Scheme 148).[321] (−)-Sparteine and Kozlowski's diamine **45** gave a similar level of induction but for opposite enantiomers. Interestingly, diamine **228** led to lower selectivities than the less hindered analogue **7**. This latter result is in agreement with those previously obtained by Alexakis et al. concerning addition of aryllithium reagent to imines.[210]

Scheme 149



10. Aziridination and Cyclopropanation

10.1. Cyclopropanation

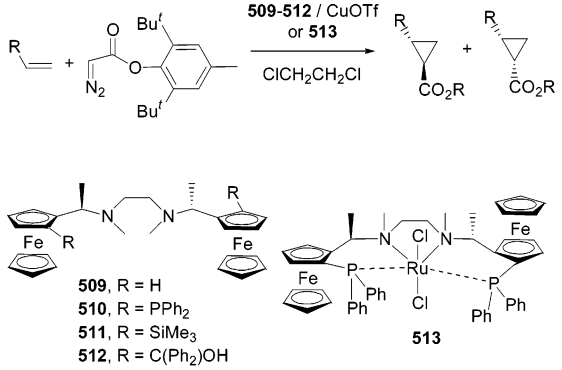
Asymmetric synthesis of cyclopropane has been extensively studied for many natural products containing this ring. Furthermore, it is also a very interesting intermediate because of its high reactivity.[322] Among all the ligands used for its synthesis, very few studies have been made using tertiary diamines. The first report concerning the enantioselective synthesis of cyclopropane using tertiary diamine came from Nozaki et al. in 1966 using (−)-sparteine.[323] They prepared cyclopropane derivatives in good yields but very low enantioselectivities. In 1994 Tanner and Andersson reported the use of bis(aziridine) ligands for several enantioselective reactions.[113] In the copper-catalyzed cyclopropanation of styrene, best results were obtained with bis(aziridine) **203c**, which induced 90% ee for the *trans*-cyclopropane (Scheme 149). With 1,1-diphenylethene as substrate, the product was obtained in 74% yield and 63% ee.

Kim et al. reported the cyclopropanation with the ruthenium complex **513** obtained from **510** and *trans*-Ru(DMSO)$_4$Cl$_2$ (Scheme 150).[324] The complex was purified by silica gel chromatography and recrystallized in CHCl$_3$/isooctane (1/3) as the solvent mixture. When 2,6-di-*tert*-butyl-4-methylphenyl diazoacetate was used, a very high level of diastereoselectivity was observed, up to 96%, and also a very high level of enantioselectivity, up to 95% for indene (Scheme 150). Few derivatives were used such as **509**−**512** with copper salt. Very high enantioselections were achieved with **511** in up to 96% for indene. The study done with ethyl diazoacetate showed that the more hindered the ligand is, the better enantioselectivities are.[325] It can be increased when the reacting partner is a bulkier diazoacetate such as 2,6-di-*tert*-butyl-4-methylphenyl diazoacetate.

O'Hagan et al. studied ligands containing a perfluoroalkyl chain to facilitate separation of the ligand after the reaction (Scheme 151).[326] With secondary diamines and diimine ligands, no detrimental influence of the perfluoroalkyl chain was observed neither on the reactivity nor on the selectivity compared to the corresponding classical non-fluorinated ligands. However, with **514** and **515**, cyclopropanation of styrene using ethyl diazoacetate led to the product in 67% and 57% yield and 16% and 11% ee, respectively. The trans/cis ratio of the reaction was in both cases 58/42.

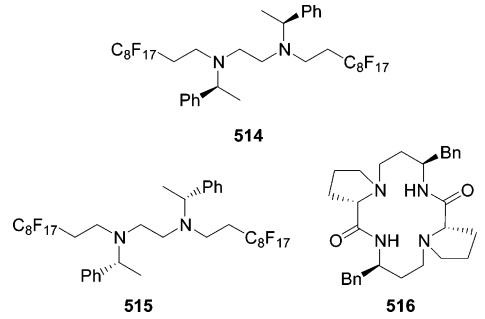
Achmatowicz et al. studied macrocyclic ligands **516** because of their molecular recognition properties.[327] It was

Scheme 150



		trans/cis	yield(%)	ee(%) trans/cis
Bu	**509**	92/8	78	83/84
	511	94/6	59	86/88
	509	98/2	83	89/55
Ph	**511**	97/3	58	92/66
	513	93/7	66	87/84
Ph	**513**	98/2	51	82/55
	509	93/7	71	97/80
	511	98/2	65	96/93
	513	98/2	50	95/82

Scheme 151



tested as the copper complex Cu·**516** for the cyclopropanation of methylstyrene with ethyl acetate. Although no yields or a cis/trans ratio were given, the authors reported that the trans isomer was obtained in 30% ee and the cis isomer was obtained as the racemic mixture.

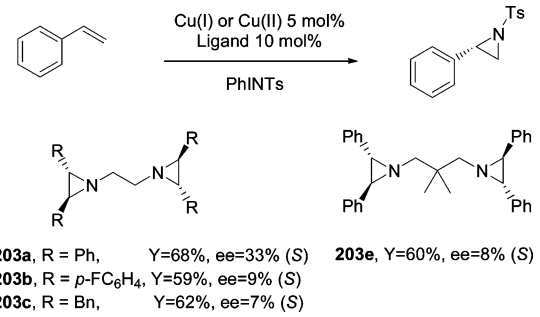
10.2. Aziridination

Aziridines are extremely important molecules as chiral building blocks for asymmetric synthesis and because they appear in biologically active molecules. Their synthesis and reactivity have been extensively studied, and numerous methods have appeared in the literature.[328] However, considering the whole range of chiral ligands available to produce enantioenriched aziridines, to the best of our knowledge, only one study has been found using bis-tertiary diamine. Tanner and Andersson used their bis(aziridine) ligand for the copper-catalyzed aziridination of styrene with PhINTs.[113] In contrast with the results obtained for cyclopropanation, low selectivities were recorded despite the similar mechanistic pathway which was suggested (Scheme 152).[329]

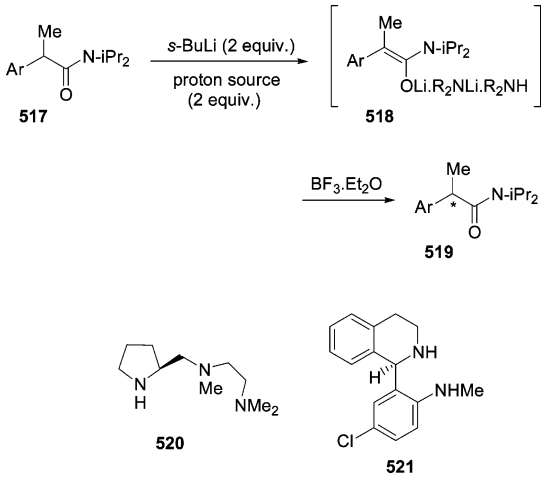
11. Asymmetric Protonation

Preparation of enantioenriched molecule using asymmetric protonation is conceptually a very simple and straightforward

Scheme 152



Scheme 153

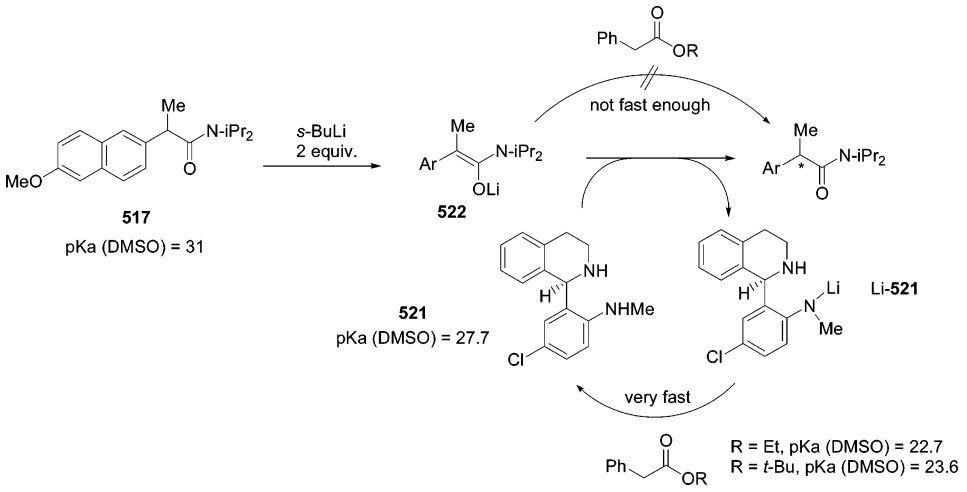


method. This reaction needs a species such as enamine or enolate to be protonated and a chiral proton source which has to be weakly acidic to favor better facial selectivity. The main features of this process have been thoroughly discussed in a previous review published in 1996;[330] we will focus our attention on systems with diamines. Although the first example of asymmetric protonation was recognized in 1974 by Miwa with a very low induction (3% ee),[331] the main development came from Duhamel et al.[332]

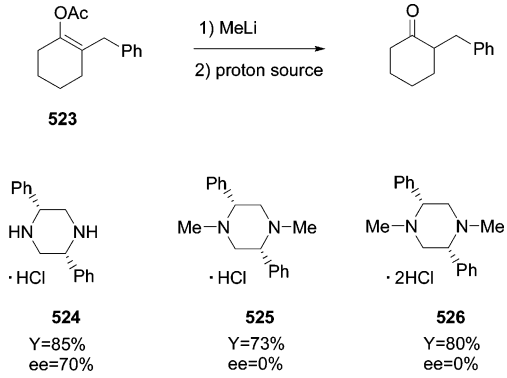
In 1991, Vedejs et al. developed an efficient method using the internal proton return process (IPR).[333] The principle relies on activation (with a Lewis acid) of the amine function present in the 1:1:1 enolate:amide:amine complex **518** in order to increase its acidity and take advantage of intramolecular protonation. A screening of Lewis acid showed that $BF_3 \cdot Et_2O$ was most efficient, allowing **520** to protonate the enolate, through intermediate **518**, in high selectivities. However, when **521** was used as a proton source, no Lewis acid was needed and the protonation occurred directly from **521** to give the enantiomerically enriched starting material. Amides such as **517** were deracemized in ee's up to 97% (Scheme 153). However, apart from one carboxamide that derived from pipecolic acid and studied by Duhamel et al.,[334] only these types of amides were deracemized in high ee's with **521**.[335]

A catalytic version was developed using the same system, which allowed use of 10 mol % of **521** (Scheme 154).[336] Protonation occurs directly from the proton source without any activation. A second protonating agent, which is achiral, is used to react selectively with **521** rather than with the enolate and ensure an efficient catalytic cycle. To achieve this selectivity, a screening of various proton sources was investigated. Best results were obtained with ethyl and *tert*-butyl phenylacetate, which led to the deracemized product

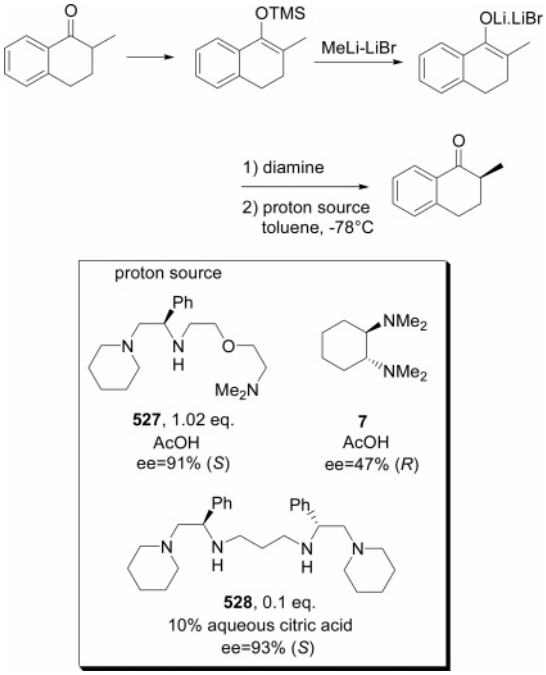
Scheme 154



Scheme 155



Scheme 156



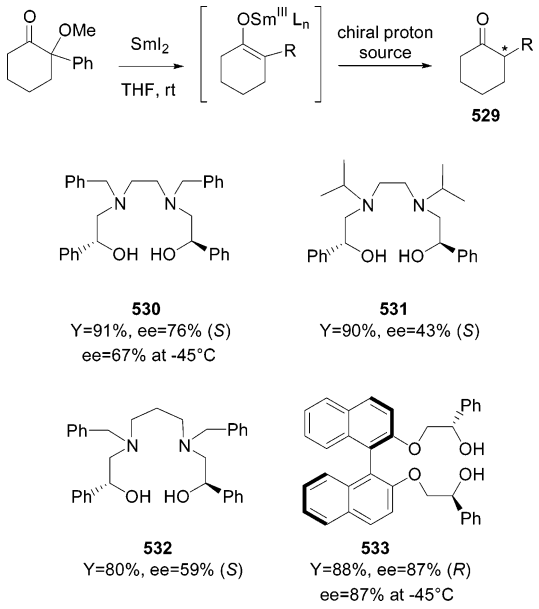
in 92% and 94% ee, respectively. Very weak acid protons have to be used to ensure that the carbon acid (secondary acid) can discriminate between the enolate **522** and the heteroatom base **521**. This corresponds to the general behavior that proton transfer between a heteroatom base and a carbon acid is much faster than transfer involving a carbon acid and carbon base.[337]

Fuji et al. reported in 1993 the direct protonation of cyclic ketones lithium enolate using the hydrochloride salt of chiral piperazine.[338] Acetoxy-alkene **523** were first transformed into the lithium enolate, which was subsequently submitted to the enantioselective protonation (Scheme 155). Among the various proton sources tested, it was the mono-hydrochloride salt **524** that gave the best selectivities. Proton sources **525** and **526** that have the bis tertiary diamine moiety led to the corresponding ketone in 73% and 80% yield, respectively, but as the racemic mixture. Better induction was usually observed when at least one NH function is present in the proton source and using the monosalt derivatives. Solubility factors were pointed out by the authors to explain the small differences observed between the various proton sources as the hydrochloride salts of piperazines were not very soluble in organic solvent at low temperature.

In 1993, Koga et al. also reported the use of multidentate ligand **527** as chiral inducer, which forms a complex with the lithium enolate without protonating it (Scheme 156). By adding a proton source (acetic acid, water, succinimide, etc.) this ternary complex enolate−amine−LiBr was protonated to give the corresponding ketone in ee's up to 91%.[339] Several variations were made during this study about the intermediate complex and the proton source. Indeed, the exact mode of protonation is not clear and has not been fully studied. In the presence of a stoichiometric amount of **527**, best results were obtained in toluene, with lithium enolate aggregated with LiBr, and with acetic acid as the proton source. Under these conditions, the ketone was isolated in 91% ee. However, slightly different experimental conditions were needed for the catalytic version. Indeed, using 0.1 equiv of **527** and acetic acid, only 28% ee was obtained. However, by changing the proton source to succinimide, which has a very low solubility in toluene, much better induction was observed. Using 0.2 equiv of **527** and 10 equiv of succinimide, the ketone was isolated in 83% ee.[340] The tetraamine **528** was as efficient as **527**, leading to the ketone in 93% ee with aqueous workup. The same level of enantioselectivities was reached with only 10 mol % of **528** and 2 equiv of *N*,*N*,*N*′,*N*′-tetramethyl-1,4-butanediamine. Under these new conditions, use of 5 mol % and 2.5 mol % of **528** led to the ketone in 91% and 88% ee, respectively.[341]

Eames et al. evaluated diamine **7** as chiral additive for protonation of lithium enolate of tetralone derivatives (Scheme 156).[342] Best results were obtained when the

Scheme 157



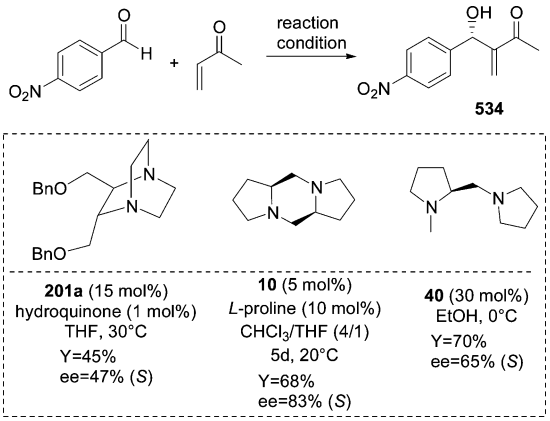
enolate·LiBr·**7** complex was protonated with acetic acid. Other proton sources gave very low selectivities as well when the enolate was free from LiBr. However, when diamine **7** monoprotonated with acetic acid was used, an almost racemic mixture of the product was isolated. In addition, when the tetrabutylammonium enolate was used as substrate in the presence of **7** and quenched with acetic acid, a racemic product was obtained. In that case, the mechanism of protonation is more likely to be a direct *C*-protonation of the lithium enolate.

Mikami et al. studied the enantioselective protonation of samarium enolate.[343] The reductive cleavage of α-heterosubstituted carbonyl substrate with SmI_2 is a common way to produce samarium enolate.[344] In their study, they tested α-alkyl cyclohexanone bearing various α-heterosubstituents such as methoxy, acetoxy, bromo, and chloro. Many proton sources were evaluated, few of them having a C_2-symmetric tertiary diamine core (Scheme 157). Indeed, best selectivities were obtained with **533**, which gave **529** in 87% ee. Proton sources with a diamine core gave lower results, although 76% ee was reached with **530**. Further study showed that other α-substituents than a methoxy can be used without affecting the selectivities very much. However, among the substrates tested, only cyclohexanone derivatives gave such results, while acyclic aliphatic or aromatic ketone, lactone, and tetralone derivatives were protonated in much lower selectivities.

12. Baylis–Hillman Reaction

The Baylis−Hillman reaction was first reported in a German patent in 1972 and has been reviewed several times since then.[345,346] It has rapidly drawn the attention of synthetic chemists thanks to the simplicity of the process and also to the high selectivities obtained. However, introducing chirality in the Baylis−Hillman adduct has turned out to be a very challenging task. Besides several successful diastereoselective reactions using various chiral auxiliaries, efficient asymmetric catalysis was achieved much later.[346] The Baylis−Hillman reaction requires catalysts with a very nucleophilic tertiary nitrogen atom, for instance, the bridgehead nitrogen atom contained in quinuclidine systems.

Scheme 158



DABCO has been the most popular catalyst for this reaction, and chiral catalysts based on its structure were developed by Hirama et al. in 1995 (Scheme 158).[347] When reactions were performed under atmospheric pressure, products were obtained in moderate yields and low enantioselectivities after 3 weeks. However, under high pressure, both yields and selectivities were improved. The best result was obtained, under 5 Kbar of pressure, with **201a**, which led to the product with a *S* configuration in 47% ee. With one specific catalyst bearing TBPS substituent instead of Bn, the sense of induction was dependent on the pressure applied. Under atmospheric pressure, (*R*)-**534** was obtained in 15% ee, while under 5 Kbar, (*S*)-**534** was formed in 34% ee. When the reaction was tested with less reactive substrates such as benzaldehyde and methylacrylate in the presence of **201a**, no reaction occurred at 5 Kbar while at 10 Kbar a 14% yield of product was isolated in 10% ee. However, using methanol as a cosolvent, a dramatic increase in the reactivity was observed and the product was isolated with the same selectivity and in 72% yield.

Hayashi et al. showed that a pyrrolidine-based diamine can be used in a substoichiometric amount to obtain **534** in up to 75% ee (65% ee with *p*-nitrobenzaldehyde) (Scheme 158).[348] In this study, various aldehydes were used with methyl vinyl ketone using **40** as catalyst. Contrary to other systems, the catalyst did not contain an acidic moiety, which was able to stabilize the oxyanion intermediate.

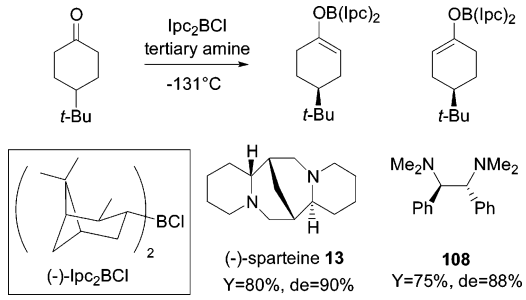
Zhou and Zhao used diamine **10** as well as benzodiazepine and aminoalcohol ligand.[349] They observed that **10** did not catalyze the reaction alone. However, in the presence of L-proline as cocatalyst, the adduct was obtained in 66% ee. The benzodiazepine ligand was more efficient, leading to the adduct in up to 83% ee.

13. Enolborination

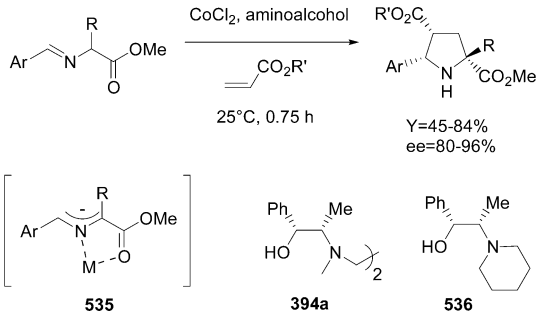
Desymmetrization of cyclic ketone substrates was studied by Ward et al.[350] Preliminary results, using Ipc_2BCl in the presence of triethylamine, showed very low selectivities, which correspond to the first report made by Paterson et al.[351] However, using the double-differentiation strategy,[352] improvements were made. In the presence of chiral diamines such as (−)-sparteine **13** or **108**, boron enolates of symmetric cyclohexanones were obtained in very high diastereoselectivities at −131 °C (Scheme 159). Usually (−)-sparteine was always slightly more selective than **108**.

With chiral racemic starting materials such as 2- and 3-methylcyclohexanone, kinetic resolution was performed

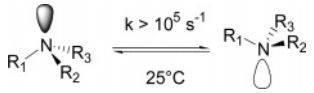
Scheme 159



Scheme 160



Scheme 161



with very high selectivities. This was found to be very useful for the latter as the kinetic resolution by enantioselective deprotonation is not very efficient.[353]

14. Cycloadditions

In 1991, Grigg et al. reported a 1,3-dipolar cycloaddition reaction of azomethine ylides, derived from arylidene imines of glycine, and acrylic esters in the presence of a stoichiometric amount of anhydrous $CoCl_2$ and 2 equiv of aminoalcohol as ligands (Scheme 160).[354] The diamine **394a**, which consists of two ephedrine units separated by two methylene groups, failed to give any pyrrolidine products. However, very good results were obtained with the aminoalcohol **536**, which led to the product in high yields and ee's up to 96% in several cases.

In 2004, Gagné et al. described the synthesis of chiral complexes in which nitrogen atoms are the only source of chirality.[355] Amines are known to be conformationally labile with a very fast rate of inversion (Scheme 161).[356] Therefore, stable chirality centered on nitrogen atoms is only found on polycyclic molecules or induced by another stereogenic center which already exists nearby.[357] However, Gagné et al. managed to fix the stereochemistry of nitrogen atoms by complexation to a metal. Diamines **537**−**539** were resolved with (*R*)-Me_2BINOL, which was removed afterward to give the enantiomerically pure complexes **540** and **541** (Scheme 162). The Me_2BINOL/Cl^- exchange for **545a** gave a mixture of *dl* and *meso* complexes, which indicates that epimerization occurs during the reaction. The complexes they obtained were purified by crystallization or chromatography and showed configurational stability at the nitrogen atom, which is the only stereogenic center of the molecule.

Good reactivities were observed with all catalysts in the Diels−Alder reaction of olefin **546** with furan, and the adduct **547** was isolated with high endo:exo selectivities. However, enantioselectivities were low. The best selectivity was obtained using the ditriflate complex containing amine **539** (prepared from **545a** and TfOH) leading to **547** in 25% ee. The ditriflate complex formed with **537** gave 21% ee, while the silver salt led to **547** in 18% ee.

15. Aza- and Oxabicyclic Ring Opening

Lautens et al. studied the enantioselective opening of oxabicyclic substrate **548** in the presence of (−)-sparteine and **108** (Scheme 165).[358] At −78 °C with a (−)-sparteine:RLi:substrate ratio of 25:5:1, **549** was isolated in 52% ee. At −40 °C, 5 equiv of the equimolar mixture of (−)-sparteine/RLi still gave a selectivity of 40%. The variation in the amount of ligand at this temperature showed that a slightly better level of selectivity (52% ee) was obtained with only 15 mol % of (−)-sparteine compared to the substrate. When **108** was used, the product was obtained in only 4% ee.

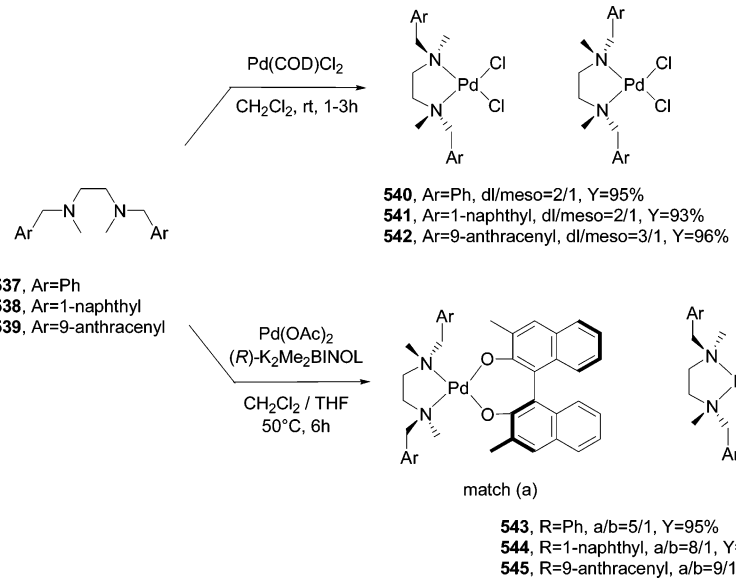
Since 2000, Lautens et al. also developed a very successful methodology to open oxabenzonorbornadiene ring systems. First, palladium catalysis was performed in association with phosphine ligands and dialkylzinc nucleophiles.[359] Rhodium catalysis was used for nucleophiles such as alcohols,[360] phenol derivatives,[361] and amines despite the latter adding much less selectivity.[360,361] In addition, carboxylate nucleophiles were added in ee's up to 92% in the presence of PPF−P^{t}Bu.[362] During this study, C_2-Ferriphos **269** showed similar reactivity and selectivity to PPF−P^{t}Bu. Eventually, after optimization of the reaction conditions[363] and in the presence of C_2-Ferriphos **269**, various amines were added onto *N*-Boc-azabenzonorbornadiene in selectivities up to 99% ee (Scheme 166).[364]

16. Alcohol Acylation

Although the first examples of kinetic resolution were observed by Pasteur by using enzymes,[365] the first example of nonenzymatic kinetic resolution was reported in 1899 by Marckwald and McKenzie for the enantioselective esterification of racemic mandelic acid by (−)-menthol.[366] With the increasing importance of synthesizing enantiopure compounds, numerous methodologies based on this concept have appeared. Nowadays, it has become an extremely powerful tool in asymmetric synthesis.[367] As chiral diamines also turned out to be very efficient chirality inducers, few kinetic resolution methodologies have been reported based on their use. However, use of diamines in this domain has not been studied very much.

In 1983, Mukaiyama et al. reported the kinetic resolution of glycerol derivatives using tin(II) alkoxides formed in situ from the alcohol and 1,1′-dimethylstannocene or (methylcyclopentadienyl) tin(II) chloride (Scheme 167).[368] Then, the dialkoxide diamine tin complex **551** was formed in the

Scheme 162

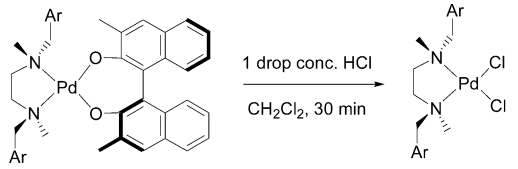


537, Ar=Ph
538, Ar=1-naphthyl
539, Ar=9-anthracenyl

540, Ar=Ph, dl/meso=2/1, Y=95%
541, Ar=1-naphthyl, dl/meso=2/1, Y=93%
542, Ar=9-anthracenyl, dl/meso=3/1, Y=96%

543, R=Ph, a/b=5/1, Y=95%
544, R=1-naphthyl, a/b=8/1, Y=60%
545, R=9-anthracenyl, a/b=9/1, Y=61%

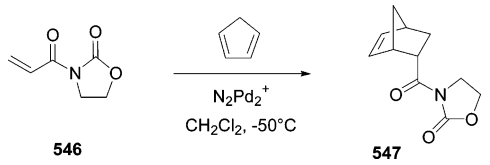
Scheme 163



543a, R=Ph
544a, R=1-naphthyl
545a, R=9-anthracenyl

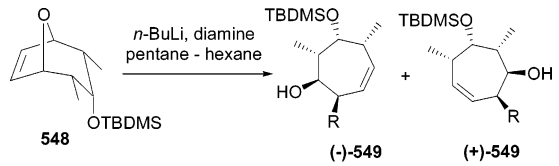
540, Ar=Ph
541, Ar=1-naphthyl
542, Ar=9-anthracenyl

Scheme 164

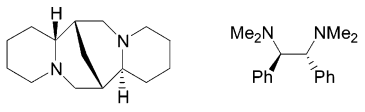


546 **547**

Scheme 165



548 **(-)-549** **(+)-549**

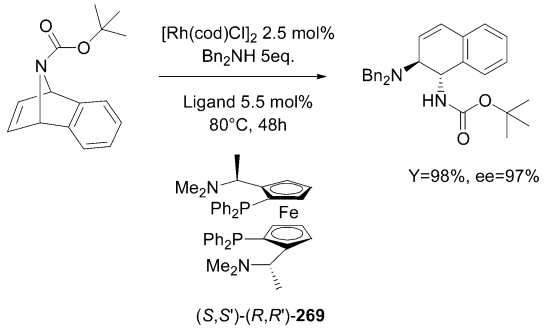


(-)-sparteine **13**

108

presence of a stoichiometric amount of diamine **550**. A selective acylation occurred with benzoyl chloride (used in excess compared to the substrate) leading to the monobenzoylated product **553** in 20% yield and 84% ee. The bis-acylated product **554** was also formed in 57% yield. Much better selectivities were obtained when an excess of acylating reagent was used because of the possibility of a second kinetic resolution, which occurs on the monoacylated glycerol derivatives. The bis-acylated product **554** would be formed preferentially from the minor enantiomer **552**, resulting in the enrichment of major enantiomer **553**.

Scheme 166

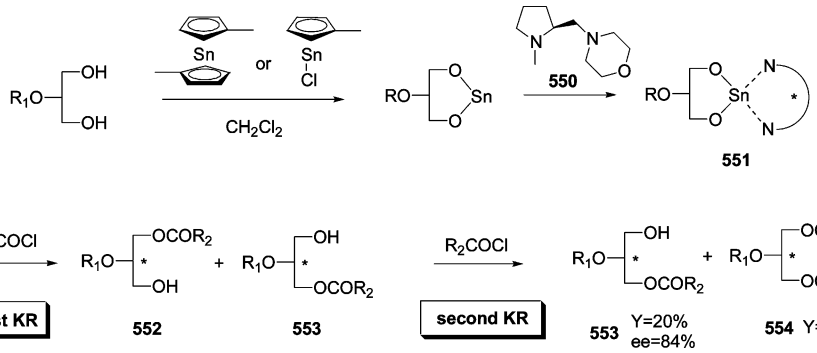


(*S*,*S*')-(*R*,*R*')-**269**

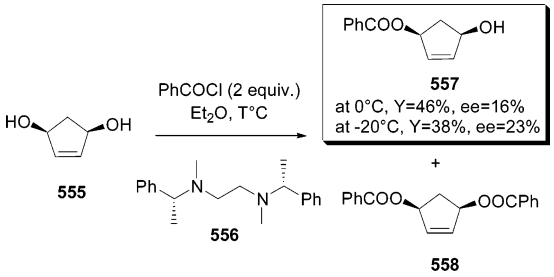
Duhamel et al. described the kinetic resolution of the diol **555** in the presence of several amines (Scheme 168). When diamine **556** was used, the monobenzoylated product was isolated in good yield but low selectivities. No improvement was observed when an excess of acylating reagent was used.[369]

In 1996, Oriyama et al. reported an efficient diamine catalyst for the kinetic resolution of chiral racemic alcohol.[370] *trans*-2-Phenyl-1-cyclohexanol was used to set up the reaction conditions which were best with acyl bromide in the presence of 0.3 mol % of $SnBr_2$−diamine **492** complex (Scheme 169). It appeared that 4 Å MS was crucial to obtain better selectivities. At 44% conversion, the ester was isolated in 97% ee and the alcohol in 84% ee. Under the same reaction conditions, several similar cyclic alcohols were resolved in high enantioselectivities. However, with meso diols, the best reaction conditions were slightly different as benzoyl chloride was used in the presence of stoichiometric amount of diamines catalyst and without tin bromide. Several other meso diols were resolved in high enantiomeric excesses.[371] Important improvements were achieved using a combination of chiral diamine **559** with an achiral amine. Indeed, with 0.5 mol % of **559** and a stoichiometric amount of triethylamine, the monobenzoylated diol was isolated in high yield and ee's up to 97%.[372] These new reaction conditions were used successfully with several cycloalkanols, improving the yields and selectivities previously obtained. A comparison between diamines **492** and **559** showed that **492** was superior in terms of reactivity and selectivity.[373] *meso*-1,3-Propane diol was a more challenging substrate as

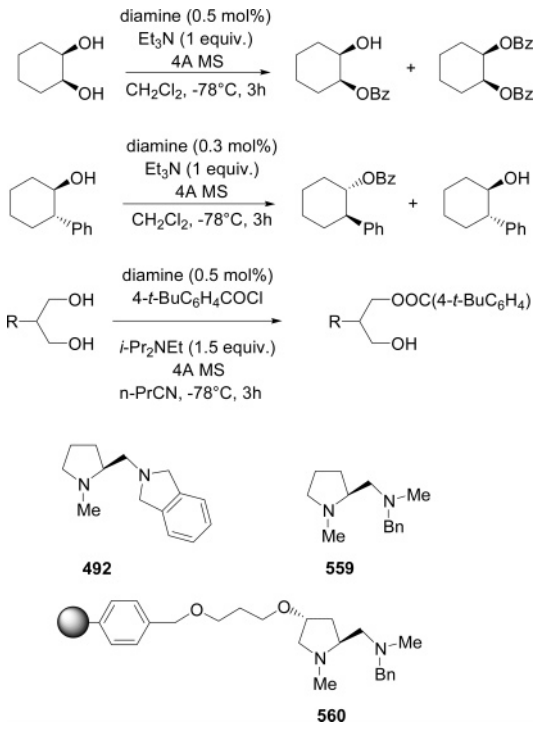
Scheme 167



Scheme 168



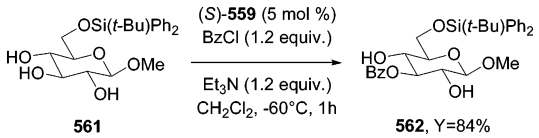
Scheme 169



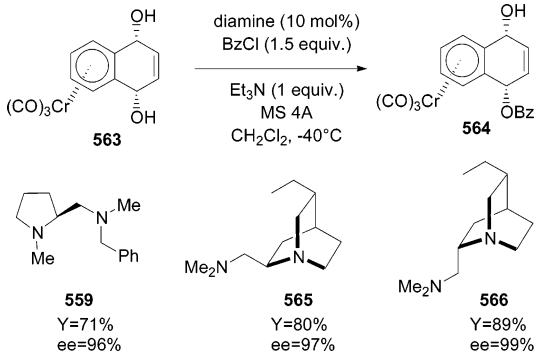
it contains two primary alcohols which are more difficult to differentiate than secondary alcohols. Indeed, it was acylated with 4-*tert*-butylbenzoylchloride in *n*-butyronitrile, leading to the product in ee's up to 98% but with low yields, in a range of 22−33%.[374] Other primary alcohols deriving from glycerol or bearing a heterocyclic ring such as epoxide, aziridine, tetrahydrofuran, or tetrahydropyran were evaluated, but they led to much less selective transformations.[375]

Janda et al. developed a polymer-supported version of diamine **559** (Scheme 169).[376] Although slightly lower conversion rates were observed, similar levels of selectivities were obtained compared to the solution-phase catalyst. Furthermore, ee's up to 95% were retained after five recycling runs of the polymeric-supported catalyst. In 2003, Trost et al. applied the dinuclear zinc catalyst **447** they developed for desymmetrization of meso 1,3- and 1,4-diols.[377] Reactions run at −15 °C in toluene led to monobenzoylated products in moderate to good selectivities and ee's up to 93%.

Scheme 170



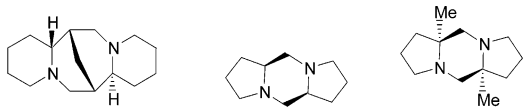
Scheme 171



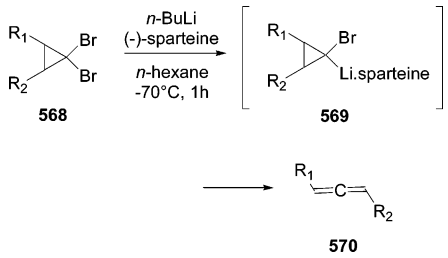
In order to address the regioselective *O*-acylation of carbohydrates, Vasella et al. evaluated Oriyama's methodology (Scheme 170).[378] Methyl 6-*O*-(*tert*-butyldiphenylsilyl)-*β*-D-glucopyranoside **561** was benzoylated preferentially in position 3 in the presence or absence of the catalyst. Although (*R*)-**559** did not improve the yield of **562** compared to benzoyl chloride alone, with the diamine (*S*)-**559**, 84% yield was obtained. In this report, the selective acylation of numerous other carbohydrate isomers partially protected was studied. The influence of the molecule structure and also the neighborhood of the hydroxyl group were clearly highlighted.

In 2004, Kundig et al. reported the desymmetrization of a diol which derived from a chromecarbonyl complex (Scheme 171).[379] Although **559** led to very good results, the fact that its enantiomer is less available prompted the search for new diamines available in both enantiomerically pure forms. Pseudo-enantiomeric quincorine and quincoridine were evaluated with diamines **565** and **566**, which were derived from their structures. They led to better results in terms of both reactivity and enantioselectivity. Interestingly, no dibenzylated product was observed; the reaction stopped after the first acyl transfer.

Scheme 172



Scheme 173



In 2006, Shirai et al. designed new diamine **567** derived from a piperazine structure (Scheme 172).[380] On the basis of the procedure described by Breitmeier et al., they developed a new synthesis to introduce the angular methyl substituent. However, Breitmeier's procedure, which was not found to be reproducible, was reinvestigated and improved. Several meso alcohols were reacted with 3 mol % of the copper complexes of diamines. The best enantioselectivities were obtained with (−)-sparteine, up to 97%, while **567** also gave very high ee, constantly higher than **10**. Furthermore, compared to (−)-sparteine, (*S*,*S*)-**567** led to the opposite enantiomer of the acylated product.

17. Allene Synthesis

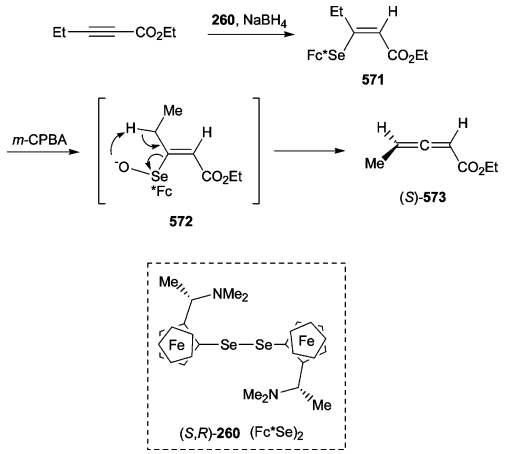
In 1968, Nozaki et al. described an asymmetric version of the Skattebøl−Moore allene synthesis.[381] This reaction is the dehalogenation of *gem*-dihalocyclopropane such as **568** with alkyllithium.[382] Optical rotations were recorded, but optical yields of the product were not known at that time (Scheme 173).

Uemura et al. used an enantiomerically pure diselenide reagent **260** to prepare vinylselenide **571**.[383] After oxidation to selenoxide **572**, an enantioselective elimination occurred leading to the enantiomerically enriched allene **573**. The best result was obtained at −78 °C in dichloromethane and in the presence of molecular sieves 4 Å (powder). Allene **573** was isolated in 43% yield and 89% ee. This highly selective process was the result of two very diastereoselective steps, namely, oxidation of selenide **571** and elimination of selenoxide **572** (Scheme 174).

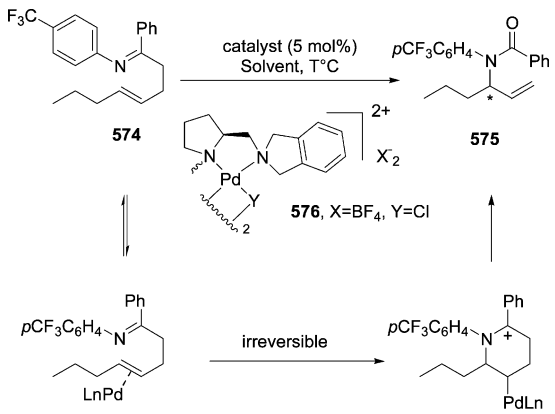
18. Rearrangements

In 1974, Overman reported the rearrangement of allylic trichloroacetamidate which gave allylic amines from allylic alcohols.[384] The rearrangement can be thermally induced or catalyzed by a metallic salt. It appears that palladium complexes are very efficient and can tolerate a wide range of functionality. In 1997, Overman et al. used tertiary diamine ligands on palladium to perform an enantioselective version of this reaction.[385] On the basis of the assumption that the alkene complexation would probably be the enantiodifferentiating step, *N*-phenylbenzimidate was studied since the cyclization is the first irreversible step for this substrate (Scheme 175). To ensure a sufficient activation of the alkene, strongly electron-donating ligands such as phosphine were

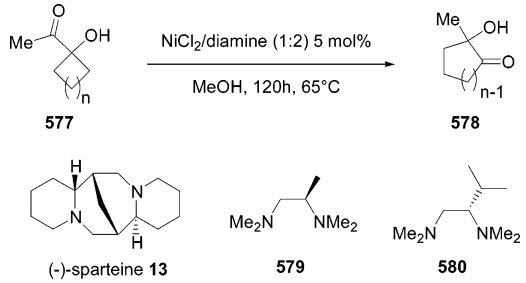
Scheme 174



Scheme 175



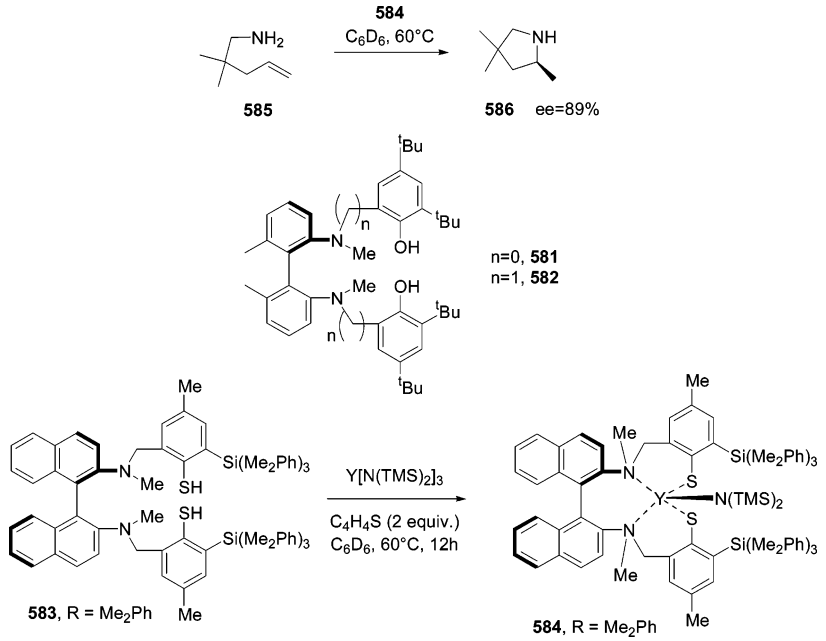
Scheme 176



not suitable. It was found that these ligands either suppressed the reaction or favored the elimination pathway. On the other hand, less electron-rich ligands such as diamines led efficiently to the rearranged product. However, dicationic dimeric complexes and nonbasic substrates such as *p*-trifluorophenylbenzimidate **574** had to be used to obtain reasonable yields. In the best case, the rearranged product was isolated in 60% ee when complex **576** was prepared from a diastereomerically pure sample of the starting monomeric $PdCl_2$diamine complex. Otherwise, some contamination with the other diastereoisomeric complex led to a less selective catalyst with which **575** was isolated in 55% ee.

In 2003, Brunner et al. reported the enantioselective version of the α-ketol rearrangement (Scheme 176).[386] The reaction consists of migration of an R substituent from the hydroxy carbon atom to the carbonyl carbon atom.[387] The process is reversible, and in order to avoid any equilibration in the system, the starting material with strained ring systems was used. Diamines **13**, **579**, and **580** led to the rearranged products in enantioselectivities lower than 5%. The best

Scheme 177



results were obtained with chiral (oxazoline)pyridine derivatives, which produced **578** in ee's up to 47%.

19. Hydroamination

Peter Scott was the first to use C_2-symmetric tertiary diamines as a ligand for this reaction. He reported in 2003 that the complex formed between (*S*)-**581** and [M{N(SiMe$_2$H)$_2$}(THF)$_2$], M being Y, La, or Sm, catalyzed the transformation to produce the cyclic amine essentially as a racemic mixture. However, by changing **581** ($n = 0$) to **582** ($n = 1$), **586** was obtained in ee's up to 61%.[388] On the other hand, use of a cationic zirconium complex obtained from [Zr(CH$_2$Ph)$_4$] and **582**, secondary amines cyclized in ee's up to 82% while primary amine was found to be an unreactive substrate (Scheme 177).[389]

Livinghouse et al. reported the use of yttrium(III) complexes **584** formed in situ by mixing the diamine ligand **583** and Y[N(TMS)$_2$]$_3$ in the presence of 2 equiv of thiophene.[390] Several primary and secondary aminoalkenes were treated with 5 mol % of this catalyst and afforded pyrrolidine and piperidine rings at 60 °C in 3−36 h. Under these reaction conditions, good levels of enantioselectivities were obtained, from 60 to 87%. When performed at 30 °C, cyclization of **585** with **584** gave 95% of conversion after 23 days in 89% ee.

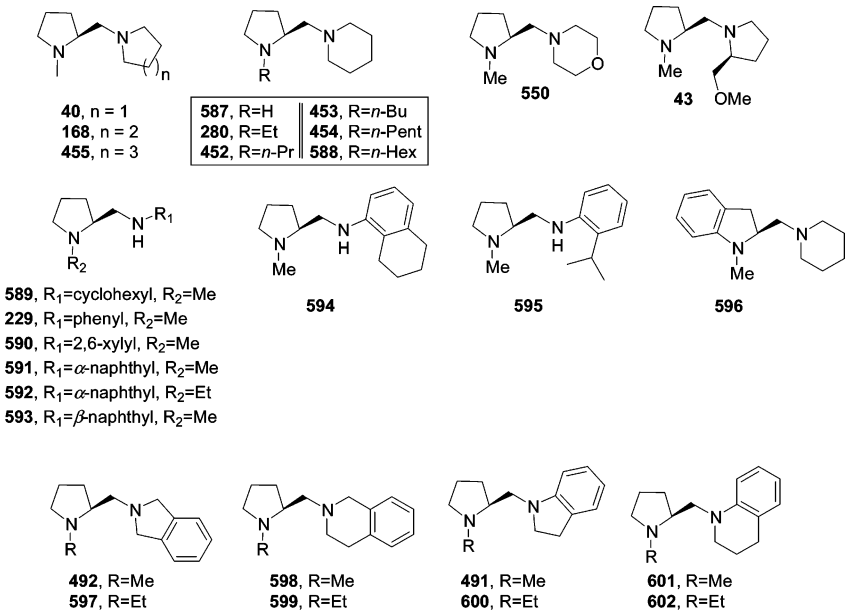
20. Aldolization

The aldol reaction groups together the condensation of a nucleophilic enolate species with an electrophilic carbonyl moiety. The product of the reaction, the aldol product, is extremely important as it is contained in macrolides or polyether antibiotics. Furthermore, this reaction is one of the basic biosynthetic transformations, which makes it even more important. It has therefore been widely studied with many metals and many combinations of substrates and reagents in order to synthesize very selectively syn or anti aldol products with a high level of enantioselectivity.[391]

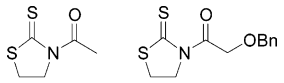
In 1982, Mukaiyama et al. reported that stannous trifluoromethanesulfonate (triflate) Sn(OTf)$_2$ can generate divalent tin enolate from the corresponding ester in the presence of *N*-ethylpiperidine.[392] It can react with aldehyde or ketone to give the aldol product in good yield.[393] Furthermore, in the case of aldehydes, high syn (also called erythro) selectivity was observed. Since this discovery, tin enolate has been the subject of thorough studies in order to use it as a new tool for asymmetric synthesis and more interestingly for enantioselective catalysis. Indeed, the element tin is very interesting as tin(II) derivatives have vacant d orbitals in low energy levels and can accept up to five ligands. Furthermore, it forms tight complexes with diamines. Particularly, when chiral diamines were employed, very high levels of enantioselectivities were achieved. This represents a very attractive method as it uses a noncovalently bound ligand, which can therefore be used in a catalytic amount. We will develop the evolution of this methodology based on tin and silicon chemistry being careful that several systems were developed which were efficient for different substrates. Furthermore, large numbers of diamine ligands which derived from L-proline were evaluated during these studies (Scheme 178).

In 1982, Mukaiyama et al. reported the first enantioselective aldol reaction.[394] Stannous triflate was treated with an aromatic ketone in the presence of a base, and then a chiral diamine was used in a stoichiometric amount to form a chiral tin enolate which was enabled to react onto aldehydes at −95 °C to form enantiomerically enriched *syn*-aldol product in ee's up to 90%. The best result was obtained with diamine **168**. When aliphatic ketones were used, *syn*-aldol products were isolated in lower enantioselectivities. Use of diamine **43** was necessary to reach 80% with these substrates.[395] When 3-acetylthiazolidine-2-thione **603** was employed as a substrate (Scheme 179) very good enantioselectivities were obtained, up to 90% ee using diamine **168**, upon reaction with aromatic or aliphatic aldehydes.[395,396] However, using the same reaction conditions, addition onto α-ketoesters gave very low ee's. Evaluation of several diamines showed that **591** was much more efficient and able to produce the malate derivatives in ee's superior to 95% with a wide range of α-ketoesters.[397] A similar substrate, the 3-(2-benzyloxyacetyl)thiazolidine-2-thione **604**, was found

Scheme 178



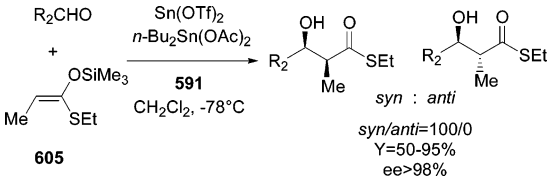
Scheme 179



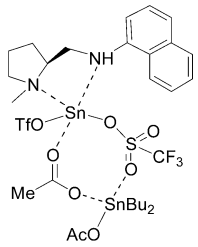
to be very interesting as the *syn*-aldol (isomer erythro) adduct is preferentially formed in the absence of TMEDA while the *anti*-aldol (isomer threo) adduct is formed in its presence. This reversal of selectivity is more likely due to the influence of the diamine on the transition state because no $E-Z$ equilibration was observed under these reaction conditions. Indeed, the same configuration of the enolate was obtained when trapped by an acyl chloride either in the presence or in the absence of TMEDA. By replacing TMEDA with diamine **168**, *anti*-aldol products were isolated in good diastereoselectivities and ee's up to 94%.[398]

With the emerging new challenge introduced by asymmetric synthesis, new powerful methodologies have been developed. The efficiency found in asymmetric aldol-type reactions with Mukaiyama's system, associated with the importance of the reaction, led to major breakthroughs using ketene silyl acetals derived from thioesters. Stoichiometric and catalytic systems were developed in parallel, although the latter was derived from the stoichiometric process. For more clarity we will first detail the stoichiometric systems, which is the first step to understanding the evolution toward the catalytic enantioselective aldol reaction. In 1989, following the development of their tin-based enantioselective aldol methodology, Mukaiyama et al. reported a very efficient system using silyl enol ether of thioesters for addition to various aromatic, aliphatic, and α,β-unsaturated aldehydes.[399] While tin(II) triflate associated with a chiral diamine was sufficient to give excellent results with enolate derived from ketones, with silyl enol ether this system gave the aldol product in good yield but as a racemic mixture. However, in the presence of tributyltin fluoride *n*-Bu_3SnF or dibutyltindiacetate *n*-$Bu_2Sn(OAc)_2$, high ee's were obtained (Scheme 180). The nature of the additive was crucial. Other fluorinated salts such as AlF_3 or MgF_2 led to the racemic mixture,[400] and other tin alkoxide or tin carboxylate did not give optimum results.[401] Among all the diamines

Scheme 180



Scheme 181

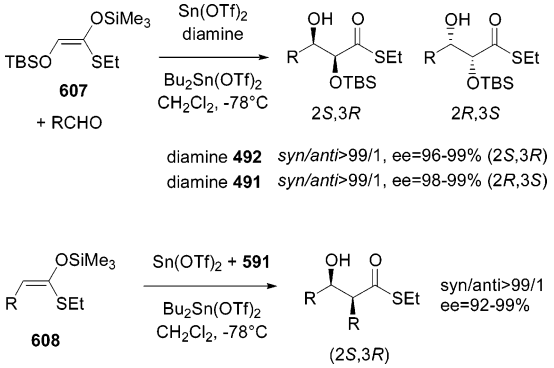


evaluated, many led to the aldol product in very high enantioselectivities; however, diamine **591** consistantly gave the highest asymmetric induction. Indeed, silyl enol ether derived from propionic acid thioester react with aldehydes in the presence of a stoichiometric amount of tin(II) triflate, diamine **591**, and tributyltin fluoride or dibutyltindiacetate to give the aldol product with a total control of both the diastereo- and the enantioselectivities. With silyl enol ether derived from acetic acid thioester, a very good level of induction was also observed, in up to 92% ee.[399,402,403]

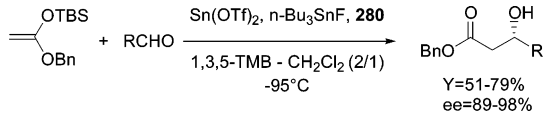
From a mechanistic point of view, the reaction proceeded through an active complex **606**, which activated both the aldehyde and the silyl enol ether (double activation) (Scheme 181). No metal exchange from silicon to tin was observed by NMR spectroscopy, which supported the fact that the reaction proceeded through the silicon enolate rather than the tin enolate. Furthermore, when the reaction was conducted with the tin enolate formed from the thioester and tin(II) triflate, the aldol adduct was isolated in lower yield, diastereoselectivity, and enantioselectivity.[403]

Kobayashi et al. later used this methodology with (*Z*)-1-(ethylthio)-1-(trimethylsiloxy)-2-(*tert*-butyldimethylsiloxy)-

Scheme 182



Scheme 183

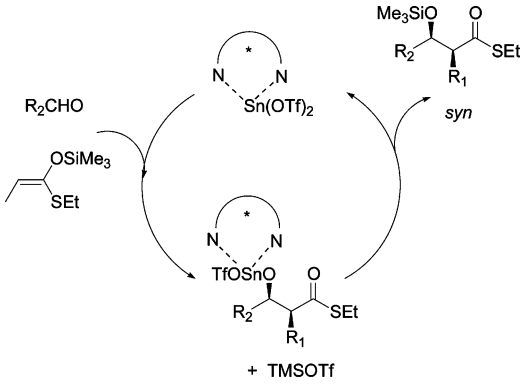


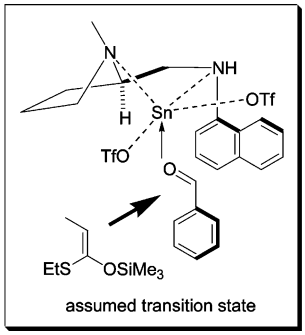
ethene **607** for aldol reactions with aldehydes (Scheme 182).[404] The same reaction conditions were used, namely, a stoichiometric combination of tin(II) triflate, dibutyltindiacetate, and chiral diamine. A very interesting behavior was observed with two different series of ligands, **597**−**599** which have a benzylic nitrogen atom and **600**−**602** which have a conjugated nitrogen atom. Indeed, all the diamines led to the aldol product in high diastereoselectivities and enantiomeric excesses, greater than 90% and up to 98% ee; in addition, both series of ligands led to opposite enantiomers of the aldol adduct. Diamines **491** and **492** were used with a wide range of aldehydes as they both produce the aldol product with complete control of both diastereo- and enantioselectivity. The origin of the selectivities was attributed to the difference of conformation of the bicyclic tin−diamine complexes. Other silylenol ether derivatives **608**, bearing various R substituents, led to very good syn selectivities and high enantioselectivities only with diamine **591**, while much lower ee's were obtained with all the other diamines tested. However, when R is *t*-BuS, the *anti*-aldol product was obtained as the major product (syn/anti = 24/76) in 93% ee.[405]

Most of the studies detailed so far have concerned the silyl enol ether of thioester. However, ketene silyl acetals of acetic acid ester were also explored as nucleophiles for the aldol reaction onto aldehydes.[406] The reaction conditions used were slightly different, as the best results were obtained in a mixed solvent mesitylene:dichloromethane (2/1) and best selectivities with diamine **280**, while **591** gave the aldol product in good yield but only 5% enantiomeric excess. Optimization of the ester moiety showed that the best result was obtained when the substrate bears a benzyl substituent. Therefore, when all these conditions were put together, aldol products were isolated in good yields and high enantiomeric excesses (Scheme 183).

As described above, the stoichiometric enantioselective aldol reactions have been very successful. However, development of catalytic systems allowing the use of only a catalytic amount of both the metal and the catalyst is indeed very attractive and has been also successfully developed. First attempts using 10 mol % of tin enolate of the corresponding carbonyl derivatives and chiral diamine **168** for addition onto benzaldehyde gave a very low yield and selectivities, which is far from the result obtained with the stoichiometric system.

Scheme 184

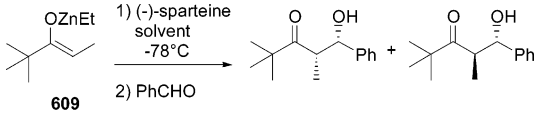




However, more promising results were obtained with trimethylsilyl enethiolate and α,β-unsaturated ketone as electrophile since an identical level of enantioselectivities was obtained in both the stoichiometric and catalytic methods.[407] A mixture of α,β-unsaturated ketone and 10 mol % of the tin−diamine complex was treated with the silyl enolate, which has to be added very slowly, over several hours. The driving force of the process relies on the affinity of tin to sulfur and the weakness of the silicon−sulfur bond. The mechanism of the reaction was described starting with a silicon−tin metal exchange and then conjugate addition, which releases the tin−diamine complex and affords the silylated aldol product. The assumption that the tin enolate pathway was supported by experimental results obtained when the reaction conditions were set up.[407b]

Considering the reaction of silyl enol ether of thioesters with aldehydes, the catalytic aldol reaction became, indeed, as efficient as the stoichiometric system as long as the silyl enol ether was added very slowly.[408] The system used was almost exactly the same than the stoichiometric one, except that neither the tributyltin fluoride nor the dibutyltindiacetate was used. Slow addition keeps TMSOTf in low concentration which otherwise promotes the achiral aldol reaction and therefore lowers the selectivities. According to the catalytic cycle described in Scheme 184, TMSOTf serves for the tin−silicon exchange which produces the silyl ether of the aldol product and releases the tin−diamine complex. The catalytic cycle relies on the rate of tin−silicon exchange because if this step is too slow the nonselective process can occur more easily. In more polar solvents, such as propionitrile, faster rates for this exchange were observed, while in THF or DME no reaction occurred.[409] The best conditions for the catalytic aldol reaction were using 20 mol % of tin triflate and chiral diamine in propionitrile, to which was added over a period of 3 h a mixture of the aldehyde and the silyl enol ether of *S*-ethyl ethanethioate or *S*-ethyl propanethioate.[410] In the presence of diamine **591**, *syn*-aldol products were isolated in high yield and enantioselectivities from 89% to 98%. The

Scheme 185



609

solvent	yield	*syn/anti*	ee (*syn*)
THF	66%	17/83	20% (*S*,*S*)
ether	74%	16/84	26% (*R*,*R*)
toluene	86%	23/77	23% (*R*,*R*)

tin−diamine complex activates the aldehyde, which is oriented in the complex with the *re* face blocked by the naphthyl substituent of the ligand. Addition of the silyl enolate occurred on the *si* face via an acyclic transition state.

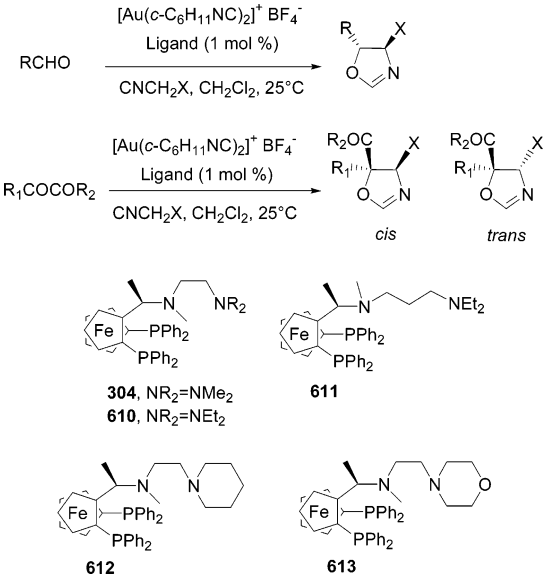
Interestingly, the association tin triflate/diamine **168** did not catalyze the aldol reaction on its own (an additive such as *n*-Bu_3SnF is needed), while the association tin triflate/diamine **591** led to the aldol product in good yield and selectivities.[399,409] Indeed, the structure of the diamine is responsible for the dramatic difference of reactivity between these two systems. All catalytic reactions were performed with diamines containing a conjugated nitrogen, cf. **591**, which was the most selective over other similar diamines tested (diamines **229**, **592**, **594**, and **595**).[410b]

Mukaiyama et al. described another catalyst based on the use of tin oxide associated with trimethylsilyl triflate used as an activator.[411] It results in a cationic tin complex which was coordinated by a chiral diamine ligand and produced a suitable catalyst for the aldol reaction. The best result was obtained with a stoichiometric amount of tin oxide, 0.65 equiv of TMSOTf and 0.5 equiv of chiral diamine **591**. With this system *syn*-aldol products were obtained in high ee's but slightly lower than the other systems. On the basis of this idea, Kobayashi et al. reported in 1994 a similar system which involved tin oxide as scavenger for TMSOTf as it decreases its Lewis acidity. Indeed, it was postulated that in the catalytic system lower ee's were due to the nonselective process catalyzed by TMSOTf. Using the catalytic system, namely, 20 mol % of tin triflate and chiral diamine, along with 40 mol % of tin oxide in propionitrile, for the reaction of silyl enol ether **605** with aldehyde, increased yield and enantioselectivities were obtained.[412]

In 1987, Heathcock et al. studied the structure and reactivity of zinc enolate (Scheme 185). The aldol reaction between benzaldehyde and **609** associated with (−)-sparteine gave the *anti*-aldol product as the major isomer, but ee's were only measured on the syn isomer, which was obtained in 26% ee when the solvent used was ether (20% in THF, 23% in toluene).[413]

In 1986, Hayashi et al. reported the use of a ferrocenylphosphinegold(I) complex bearing a diamine moiety for the catalytic asymmetric aldol reaction between isocyanoacetate (X = CO_2Me),[414] (isocyanomethyl)phosphonate (X = $PO(OR^2)_2$),[415] or *N*,*N*-dimethyl-α-isocyanoacetamide (X = $CONMe_2$)[416] and aldehyde or α-ketoesters (Scheme 186). The two former reagents were used with aldehydes in the presence of ligands **304**, **610**, **611**, and **612**, respectively, leading in both cases to the *trans*-oxazoline in high enantiomeric excesses (up to 97% and 96% ee, respectively). On the contrary, reaction of isocyanoacetate and *N*,*N*-dimethyl-α-isocyanoacetamide with α-ketoesters in the presence of **613** led to a mixture of *cis*- and *trans*-oxazoline in good enantioselectivities (up to 90% ee for the syn isomer and

Scheme 186



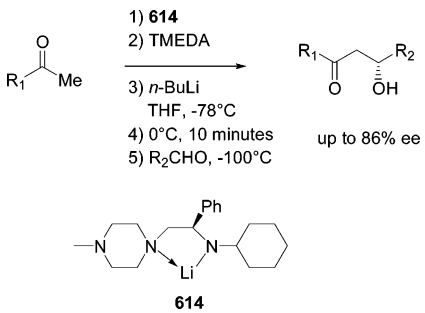
304, NR_2=NMe_2
610, NR_2=NEt_2

611

612

613

Scheme 187



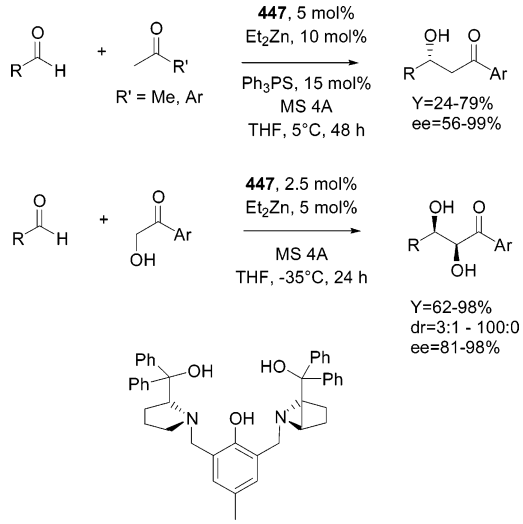
614

84% ee for the trans isomer) (Scheme 186). Mechanistic considerations were discussed in 1990 by Togni and Pastor.[417]

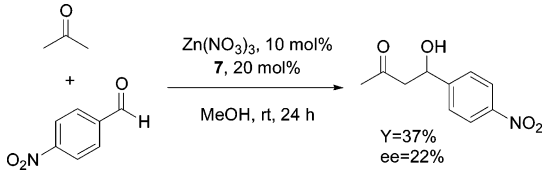
In 1988, Koga used chiral lithium amides to form mixed aggregates with enolate derived from aromatic or aliphatic methyl ketones.[418] This intermediate was reacted with various aldehydes at very low temperature, leading to the adduct in good yields and ee's up to 86% (Scheme 187).

Despite the efficiency of the catalytic asymmetric aldol reaction described above, all systems displayed a major drawback because of the need to use a stoichiometric amount of base or adjunct reagents. The direct catalytic enantioselective aldol reaction (DCEAR) has been a major breakthrough as it is a real atom economic process as the original aldol reaction was.[419] It is important to briefly note here that diamines containing a secondary nitrogen atom have been used with great success as organocatalyst for the DCEAR.[420] In 2000, Trost et al. designed semi-crown **447** for their molecular recognition properties to perform the DCEAR. The turnover was increased to a practical level by adding a weak coordinating agent for zinc that helps to displace the product. Good yields and a high level of induction were recorded with various aryl methyl ketones,[421,422] methyl ynones,[423] methyl vinyl ketone,[424] and acetone[425] upon reaction with various aldehydes. Several important differences were noticed when α-hydroxyketones were used as substrates. The absolute configuration of the stereocenter, which derived from the aldehyde, was opposite to that obtained using acetophenone. Furthermore, turnovers efficient enough were obtained without the help of any additive, which allowed performing the reaction at lower temperature in 24 h (Scheme

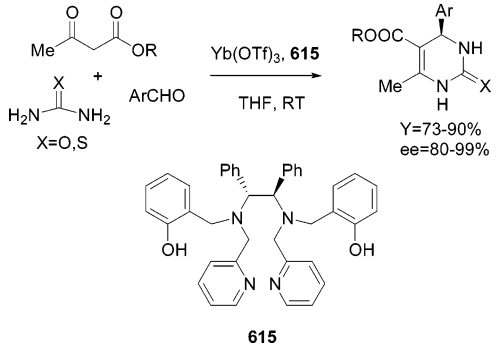
Scheme 188



Scheme 189



Scheme 190



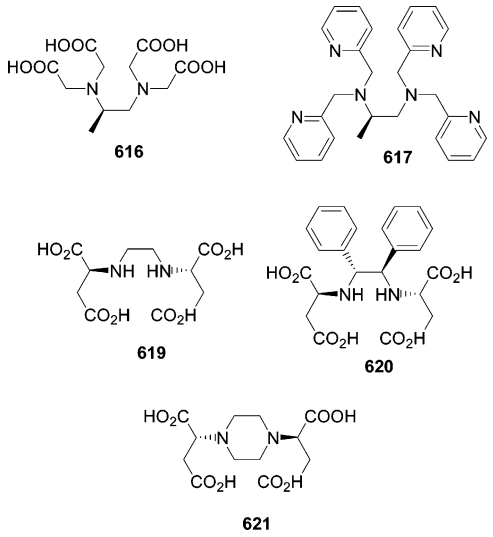
188). The Henry, Mannich, and Michael reactions, which are closely related to the aldol condensation reaction, were studied using this methodology.[426] Maheswaran et al. performed a Henry reaction (nitroaldol) using copper(II) complexes of (−)-sparteine.[427] They showed that high enantioselectivities are obtained under double catalytic activation conditions. Using methanol as solvent and in the presence of 3 mol % of triethylamine and 20 mol % of $CuCl_2$[(−)-sparteine)-*N*,*N*'], ee's up to 97% were achieved.

Calter et al. reported the use of diamine **7**, which gave the best result among all the chiral amines he tested (Scheme 189).[428] The aldol product was isolated in moderate yield and selectivity.

21. Biginelli Reaction

The Biginelli reaction is a multicomponent reaction that makes an aldehyde, 1,3-ketoester, and urea react together (Scheme 190).[429] Zhu et al. reported in 2005 an asymmetric version of this transformation.[430] The reaction conditions were first set up showing that best results were obtained in THF with ytterbium triflate and 10 mol % of chiral diamine

Scheme 191



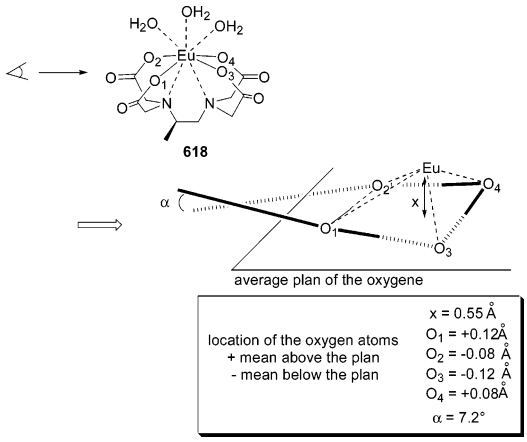
ligand. Variations were made with the three partners of the reaction, leading to a small library of dihydropyrimidines, which were obtained in good yield and ee's up to 99%.

22. Enantiomeric Excess Determination by NMR Spectroscopy

With the growing importance of synthesizing chiral molecules, mainly because of pharmaceutical companies, development of new methodologies to produce nonracemic chiral compounds has become one of the main challenges in organic synthesis. Inevitably, the very closely related task of determining the enantiopurity of these molecules has received considerable attention. Several techniques have been developed; they involve either the enantiomeric mixture itself or a derivatized form into a pair of diastereoisomers. Although the latter is still currently the more widely used method and has great success,[431−433] the former technique is by far the most attractive in terms of simplicity.[431,434] Indeed, measuring the optical rotation was the only way to determine the enantiomeric excess of chiral nonracemic molecules until the mid-1960's. However, several important drawbacks accompany this technique as the optical purity is not necessarily equivalent to the enantiomeric excess,[435] the relatively low sensitivity of the method, the high sensitivity to optically active byproduct contamination, and ultimately the high number of incorrect optical rotations reported in the literature.[431] The two NMR techniques which allow direct determination of enantiomeric excesses, meaning without derivatization, imply chiral lanthanides shift reagents and chiral solvating agents. It is interesting to note that the latter method is efficient to measure the enantiomeric purity of primary, secondary, or tertiary diamines.[436]

Secondary diamines have been very efficiently used as chiral derivatizing agents;[437] however, very little has been reported with tertiary diamines. Kabuto and Sasaki reported an extremely efficient chiral shift reagent formed by mixing europium oxide Eu_2O_3 and chiral EDTA derivatives **616** and **617** (Scheme 191). The europium complexes **618** (Scheme 192) were used efficiently with α-aminoacids,[438] α-hydroxyacids,[438a,439] and simple carboxylic acids. It was found that the hydrogen α to the acid function, Hα, was resolved in a range of 0.03− 0.6 ppm ($\Delta\Delta\delta$) depending on the substrate. In addition, there was a consistent correlation

Scheme 192



between the absolute configuration and the shift of the α proton signals. Therefore, it was possible to not only measure the enantiomeric excess of the substrate but also determine the absolute configuration of the stereogenic center. For all substrates described and when (*R*)-**616** was used, the α proton of the *S* enantiomer appeared in a higher field than for the *R* enantiomer. In all cases studied, there was a wide tolerance with the presence of functional groups, which was demonstrated by the effectiveness of the method even with aldonic acids (carboxylic acid related to aldose).[440] All of the above-mentioned studies were made on a 90 MHz ^{1}H NMR instrument, and spectra were recorded using **618** under basic conditions. When using **617** in the complex, neutral conditions were used and the method could also be extended to *N*-acyl amino acids substrates.[441] The structure of the racemic complex of **618** was determined by X-ray analysis showing several unusual features.[442] It consists in an asymmetric unit cell formed by six complex molecules. In each cell the hexamer contains a ligand of identical chirality and each hexameric unit is linked to four neighboring hexamer units forming a two-dimensional zigzag network. In the complex the four coordinating oxygen atoms deviate significantly from the average plane and both axes formed by (O_1O_3) and (O_2O_4) have an angle of 7.2°. The direction of this deviation, which is induced by the chirality of the propylene moiety, is an important factor for the ability to differentiate enantiomers.

By changing from a 90 to a 400 MHz NMR instrument, serious line broadening appeared with the europium complex **618**. This problem was overcome using the samarium anion, which has the smallest magnetic moment of all the paramagnetic lanthanides.[443] This allowed enhancing the range of substrate to be resolved in both ^{1}H and ^{13}C NMR spectroscopy and in keeping with the same consistency between the absolute configuration and the shift of Hα. An interesting application of this methodology was reported for determination of the absolute configuration of metabolites in body fluids, which is important for diagnosis of some inborn errors of metabolism. Direct analysis of the urine sample of a patient was made, showing that in the case of 2-hydroxyglutaric acid and 5-oxoproline enantiomers of D and L absolute configuration, respectively, were eliminated, which was in agreement with the known clinical and biochemical data.[444]

In 1994, Feringa et al., based on the work of Kido which previously described the diamine **619**,[445] reported diamine **620** and **621** which upon association to europium salt form effective chiral shift reagent.[446] When used with racemic amino acids, complexes Eu−**620** and Eu−**621** showed very good separation of proton signals in the α or β position in a range of 0.31−1.31 and 0.14−0.51 ppm, respectively. These results were significantly better than those obtained with complex Eu−**619**, which induced a separation in a range of 0.08−0.41 ppm.

Another application of NMR spectroscopy techniques was reported in 1981 by Meinwald et al. for determination of glycols stereochemistry.[447] They used the osmate ester of glycols chelating with *N*,*N*,*N*′,*N*′-tetramethyl-1,2-*trans*-cyclohexanediamine **7** and observed both of the enantiomers by resolution of the *N*-methyl signals of the diamine. In this way, they attributed the absolute configuration of a pyrrolizidine alkaloid obtained from *M. scorpioides* L.

23. Molecular Recognition

Molecular recognition of chiral molecules is very important for asymmetric synthesis and chromatographic resolution of enantiomers. The basic principle relies on formation of a stable complex between the chiral macromolecule and the host. The rigidity of the macromolecule and multiple binding sites ensure a better efficiency for the molecular recognition. Large numbers of reviews have already fully covered this area,[448] and the purpose of this section is to point out that a few aza macrocycles have been described.[449]

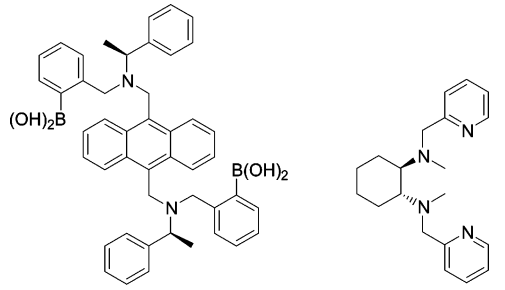
In 2004, the enantioselective fluorescent sensor **622** for sugar acids was designed by James et al.[450] The sensor contains two boronic acid functions as a binding site and an anthracene moiety as a fluorophore.[451] Using (*S*,*S*)-sensor a large enhancement of fluorescence was observed in the presence of L-tartaric acid, whereas in the presence of D-tartaric acid only a small enhancement was observed. In this case best selectivities were obtained at pH 7. Fluorescence intensity changes were linear with the ee of tartaric acid, which allowed using this as a method for ee determination with an accuracy of only 1%.

The Zn(II) complex of cyclohexanediamine derivative **623** was able to stereoselectively recognize vicinal diamine.[452] For all diamines tested the same sense of stereoselectivity was observed, i.e., rac-**623** in the presence of $Zn(OTf)_2$ and the racemic guest diamine led to two major homochiral complexes [(*R*,*R*)-**623**-Zn(II)-(*R*,*R*)-diamine] and [(*S*,*S*)-**623**-Zn(II)-(*S*,*S*)-diamine].

24. Polymerization

Polymerization of alkene is one of the most important industrial processes. Nonracemic chiral polymers have raised great interest and found many applications in asymmetric synthesis, chiral separation, ferroelectric, and nonlinear optical application. They have interesting chiral recognition abilities and can effectively resolve many racemates as a chiral stationary phase for high-performance liquid chromatography. Indeed, most biomacromolecules such as proteins, nucleic acids, polysaccharides, or ribonucleic acids are chiral and possess these molecular recognition abilities and catalytic activities. Synthetic enantioenriched polymers can be obtained in three ways: (1) asymmetric synthesis polymerization, where the monomer bears a chiral auxiliary which controls the selectivity of the polymerization process; (2) helix sense-selective polymerization which produces aright- or left-handed helix; (3) enantiomer-selective polymerization

Scheme 193



622 **623**

where one enantiomer of a racemic monomer is selectively polymerized in a kinetic resolution process.

Vinyl polymer obtained from achiral monomer cannot be optically active even if it is highly isotactic. Indeed, apart from the carbon located near the ends of the polymer chain, each asymmetric carbon which is formed in the polymerization process becomes pseudo asymmetric. However, many macromolecules are known to take a helical conformation in the solid state which confers to the polymer an element of chirality. Even though most isostatic vinyl polymers such as polystyrene and polypropylene without chiral pendant groups cannot be optically active in solution because the dynamics of the polymer chain is extremely fast at room temperature, the polymer cannot maintain a helical conformation. However, when large groups are present on the backbone such as in poly(triarylmethyl methacrylate), the helical conformation becomes stable even in solution and the polymer is chiral. On the other hand, poly(methyl methacrylate) and poly(benzyl methacrylate) do not maintain their helical conformation in solution as such ester groups are not bulky enough.

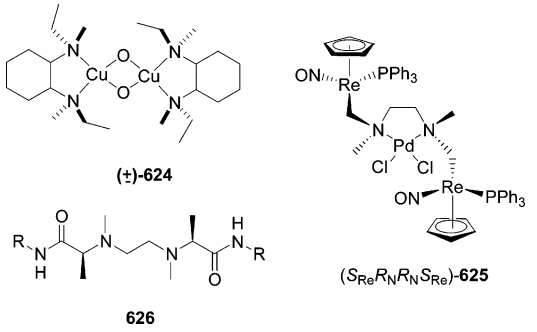
The polymerization domain is extremely vast, and many different aspects of this topic have been reviewed.[453] We are limited in the present review to diamine ligands for which most aspects of their use in polymerization have already been thoroughly reviewed, and few diamine structures have been reported since then.[454,455]

25. Diamine–Metal Complexes

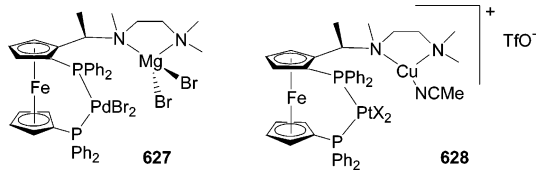
Diamines are very good ligands for most metals, and a large number of complexes have been reported. It is indeed the case for most of the diamines described so far in this review. Other crystal structures of diamine−metal complexes were reported with a large number of metals such as cobalt,[456] copper,[457] manganese,[458] palladium,[459] platinium,[459c] nickel,[460] titanium,[461] and lanthanides.[462]

Complexes **624** and **625**, which imply copper and palladium metals, respectively, are depicted in Scheme 194.[457c,459b] In both cases, the parent diamines have a tertiary nitrogen atom in such a substitution that it becomes a stereogenic center upon complexation. The X-ray crystallographic data showed that the large substituents of the nitrogen atoms are trans to each other. Miyake et al. reported the interesting behavior of Co(II) complexes of diamine **626**. It was found that the diamine is a tetradentate N_2O_2 ligand complexing the metal to form a Λ *cis*-α configuration around the Co(II) center. However, in the presence of NO_3^- anion, complete inversion of helicity from Λ to Δ was induced.[463] Other ligands such as **623** or **289** were also used to bring chirality at the metal centers.[464]

Scheme 194



Scheme 195



Kumada's ferrocene ligand **304** was used in 2003 by Bell and Tilley as a framework for the synthesis of heterobimetallic complexes.[459c] First, monometallic complexes were studied with Pd(II), Pt(II), and Mg(II) ions which led preferentially to (*P*,*N*), (*P*,*P*), and (*N*,*N*) chelation, respectively. The two bimetallic complexes Pd−Mg **627** and Pt−Cu **628** were isolated in good yield and studied using NMR spectroscopy (Scheme 195).

Other kinds of complex have been widely studied, although much more difficult from a practical point of view. Indeed, organolithium−diamine complexes are extremely important reagents, and it is important to know more about their structure.[465] This is closely related to the aggregation state problems which are strongly influenced by solvent and structural effects of both the diamines and the organolithium reagent. In the presence of a Lewis base, such as diamines, a competition situation arises between the Lewis base and the anion for coordination of the lithium cation. If the Lewis base is strong enough, this solvation will result in deaggregation of the complex into smaller aggregates.[466] For example, phenyllithium, one of the best understood of all organolithium reagents, is a tetramer in diethyl ether,[467] a dimer in the presence of TMEDA,[468] and an monomer−dimer equilibrium in THF solution.[469] On the other hand, Lewis base free phenyllithium consists of Ph_2Li_2 units which interact with an adjacent identical unit forming a polymeric structure.[470] Several other organolithium reagents have been studied upon complexation with a Lewis base.[471] Many techniques have been developed to characterize the structure of organolithium reagents. Their aggregation state can be determined from their colligative properties (cryoscopy, ebullioscopy, density measurement) by X-ray crystallography or studies in solution (UV−vis, IR, NMR). In 1984, Okamoto et al. reported the circular dichroism of arylmethyllithium carbanions induced by diamines such as **13** and **173**.[472] They observed that in the presence of these diamines an induced CD was recorded which suggests that a tight complex was formed between the organolithium reagent and the diamine. Furthermore, UV and CD spectral patterns and their relative intensity were not varied by the presence of an excess of diamine, which indicates that a 1:1 complex was formed. The most popular method is certainly NMR spectroscopy of the ^{13}C nucleus because of its large range of chemical shift which reduces the problem of overlapping signals.

Indeed, both ^{6,7}Li nuclei have been used in NMR, although it suffers from several drawbacks. The chemical shift range is relatively small, from −2 to +2 ppm; furthermore, it is very sensitive to several parameters such as viscosity, temperature, concentrations, solvation, and the nature of the standard used (which are usually $LiClO_4$, LiBr, or LiCl used in concentrations ranging from 0.1 to 1.0 M in water or THF). Pioneering work of Fraenkel introduced ^{6}Li isotopic labeling to take advantage of the spectroscopic properties given by the spin number of this nuclei ($I = 1$), and the ^{6}Li labeling technique is now a common routine.[473] Detection of the ^{13}C−^{6}Li *J* coupling is, indeed, the most direct information concerning the aggregation state of an organolithium complex.[474] It was found, from theoretical studies, that the nature of the carbon−lithium bond of methyllithium is 88% ionic and 12% covalent,[475] which may be important for the scalar coupling between the two nuclei. However, it was also shown by Streitweiser that *J* coupling can be visible even though the interaction is strictly electrostatic.[476] Problems with overlapping signals can often be circumvented using 2D techniques based on spin−spin couplings. All the common 2D experiments using the homonuclear and heteronuclear coupling are indeed applicable to ^{6}Li NMR.

A few studies were carried out using chiral diamine as ligands despite the importance of such systems in asymmetric synthesis. (−)-Sparteine has been undoubtedly the most widely studied ligand for which many crystal structures have been reported upon complexation with *t*-BuLi, *n*-BuLi, *i*-PrLi, MeLi, PhLi, and lithiosilane.[477] In the solid state, a mixed aggregate [PhLi•PhOLi•2(−)-sparteine] was isolated. It was shown that the structure contains a single C−Li−O−Li four-membered ring.[478] The great interest devoted to find a (+)-sparteine equivalent having eventually been successful, the crystal structure of (+)-sparteine surrogate with MeLi and PhLi has been reported.[479] Furthermore, Collum et al. carried out NMR studies with complexes containing (−)-sparteine or **7** as ligand that showed that a dimeric complex was present in solution.[480] However, attempts to clarify a simple structure−reactivity relationship failed, mainly because van der Waals interactions are dominant and specific to each combination of the solvent, organolithium, and substrate. Kinetics of reaction between RLi/diamine complexes and imines were studied.[480,481] Reactions occurred through a monomer- or dimer-based transition structure depending on the substrate and concentration of the reagents. It was proposed from these studies that either a four-membered transition state or an open dimer occurs as a mechanistic pathway. The complexation kinetics of organomagnesium reagents with (−)-sparteine were also studied by NMR spectroscopy. While the rate of exchange of dialkylmagnesium compounds between the dietherate and the TMEDA was too fast to be measured on the NMR time scale, the rate of exchange for (−)-sparteine was much slower for steric reasons.[482] Due to the importance of lithium amide bases, many studies have been reported on the structure of LiHMDS in the presence of diamines such as (−)-sparteine or **7**, showing that, in this case, the complex is monomeric.[483]

26. Conclusions and Outlook

Diamines have become a large and important topic in organic synthesis. The particular case of tertiary diamines has never been the central topic in a review. Our review covers their use in asymmetric synthesis in the most exhaustive manner (articles were collected until January 2007). Considering the importance of diamine-based ligands, it appeared to us to be necessary, after so many developments, to set the record straight about the subject. Although some diamines have demonstrated broader capacity than others, this review shows that none of them is broad enough to cover the whole range of applications. However, they are flexible enough to introduce various types of diversity through the framework or nitrogen substitution, which has allowed chemists to access almost any reaction. The diamine function is able to support both of the basic requirements needed for an effective ligand, which are the capacity to catalyze a reaction and induce selectivity. Despite this, improvements are still needed in the area already covered and also to enlarge their application field. For these challenges, new structures of diamines have been synthesized and new concepts have been developed.

The reader will note, even with a rough reading of this review, the very large number of diamines used. Other new structures appeared over the years either from computing assistance or the intuition of chemists. New breakthroughs may come from some of these new diamines or improvements of some of the already existing and studied structures. Indeed, diamines having a bridgehead structure,[484−488] based on aziridine,[489] azetidine,[490] pyrrolidine,[491−495] or piperidine core,[496,497] derived from cyclobutane,[498] cyclopentane,[494,499] or cyclohexane diamines,[500−504] derived from metallocene[505−507] or other structures,[508−513] have already been reported in the literature, but they have not yet been used as tertiary diamines. Considering the restriction we made describing only those having tertiary nitrogen atoms, one can easily obtain a glimpse of the huge potential of diamines in the broad sense of the term when added to all other substitution possibilities. Indeed, if one considers secondary and primary diamines, a much broader range of reactions can be reached, extending the real possibilities of the diamine family. This topic, although already widely studied, is still under continuing evolution and brings regularly new possibilities in synthesis.

27. Acknowledgments

I would like to thank everyone who has helped me in the correction of this review. Namely, Dr. Iain Rudkin, Dr. Lisa Sloan, Dr. Andrea McGhee, and Claire Morawiec for their time and kindness for having transformed the original version into a more readable document. I owe my greatest thanks to Pr. Claude Agami, Pr. Alexandre Alexakis, and Dr. David Procter for having transmitted to me so much in chemistry, the discussions we had, and their advice. I also thank Dr. Mariona Canto for her help and support all along the writing of this manuscript. This review is dedicated to Pr. Claude Agami for his carrier achievement.

28. Note Added in Proof

Since the submission of the accepted version of the manuscript, several publications have appeared on various aspects of diamines.[514]

29. References

(1) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580.
(2) Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161.
(3) Fache, F.; Schulz, E.; Tommasino, L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159.

(4) Anaya de Parrodi, C.; Juaristi, E. *Synlett* **2006**, 2699.
(5) Douthwaite, R. E. *Coord. Chem. Rev.* **2007**, *251*, 702.
(6) Hoppe, D.; Hintze, F.; Tebben, P.; Paetow, M.; Ahrens, H.; Schwerdtfeger, J.; Sommerfeld, P.; Haller, J.; Guarnieri, W.; Kolczewski, S.; Hense, T.; Hoppe, I. *Pure Appl. Chem.* **1994**, *66*, 1479.
(7) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 2283.
(8) Schütz, T. *Synlett* **2003**, 901.
(9) (a) Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1422. For recent reviews on asymmetric deprotonations, see: (b) Organolithium in enantioselective synthesis. *Topics in organometallic synthesis*; Hodgson, D. M., Ed.; Springer: Oxford, 2003. (c) Patai suie in *The chemistry of organolithium compounds.* Rappaport, Z., Marek, I., Eds.; *The chemistry of functional groups*; Wiley: New York, 2004.
(10) Nozaki, H.; Aratani, T.; Toraya, T.; Noyori, R. *Tetrahedron* **1971**, *27*, 905.
(11) Hoppe, D.; Paetow, M.; Hintze, F. *Angew. Chem., Int. Ed. Engl.* **1993**, *29*, 394.
(12) Hoppe, D.; Carsten, A.; Krämer, T. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1424.
(13) Würthwein, E.-U.; Behrens, K.; Hoppe, D. *Chem. Eur. J.* **1999**, 3459.
(14) Peters, J. G.; Seppi, M; Fröhlich, R.; Wibbeling, B.; Hoppe, D. *Synthesis* **2002**, 381.
(15) Würthwein, E.-U.; Hoppe, D. *J. Org. Chem.* **2005**, *70*, 4443.
(16) (a) Galasso, V.; Asaro, F.; Berti, F.; Kovač, B.; Habŭs, I.; Sacchetti, A. *Chem. Phys.* **2003**, *294*, 155. (b) Borowiak, T.; Wolska, I. *J. Mol. Struct.* **1996**, *374*, 97. (c) Jeyaraman, R.; Avila, S. *Chem. Rev.* **1981**, *81*, 149. (d) Skolik, J.; Wiewiorowski, M.; Krueger, P. J. *J. Mol. Struct.* **1970** *5*. 461. (c) Leonard, N. J.; Thomas, P. D.; Gash, V. M. *J. Am. Chem. Soc.* **1955**, *77*, 1552. (e) Wiewiorowski, M.; Edwards, O. E.; Bratek-Wiewiorowska, M. D. *Can. J. Chem.* **1967**, *45*, 1447. (f) Sadykov, A. S.; Kamayev, F. G.; Korenevsky, V. A.; Leont'ev, V. B.; Ustynyuk, Yu. A. *Org. Magn. Reson.* **1972**, *4*, 837. (g) Bohlmann, F.; Schumann, D.; Arndt, C. *Tetrahedron Lett.* **1965**, 2705. (h) Borowiak, T. E.; Kokii, N. G.; Struchkov, Y. T. *Zh. Strukt. Khim.* **1973**, *14*, 387; *Chem. Abstr.* **1973**, *79*, 24503y. (i) Bohlmann, F. *Chem. Ber.* **1958**, *91*, 2157.
(17) (a) Belostotskii, A. M.; Markevich, E. *J. Org. Chem.* **2003**, *68*, 3055. (b) Wiberg, K. B.; Bailey, W. F. *J. Mol. Struct.* **2000**, *556*, 239.
(18) Heinl, T.; Retzow, S.; Hoppe, D.; Fraenkel, G.; Chow, A. *Chem. Eur. J.* **1999**, *5*, 3464.
(19) Zschage, O.; Hoppe, D. *Tetrahedron* **1992**, *48*, 5657.
(20) Zschage, O.; Schwark, J.-R.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 296.
(21) (a) Hoppe, D.; Zschage, O. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 69. (b) Hoppe, D.; Hanko, R.; Brönneke, A.; Lichtenberg, F. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 1024.
(22) Marsch, M.; Harms, K.; Zschage, O.; Hoppe, D.; Boche, G. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 321.
(23) Paulsen, H.; Graeve, C.; Hoppe, D. *Synthesis* **1996**, 141.
(24) Zeng, W.; Fröhlich, R.; Hoppe, D. *Tetrahedron* **2005**, *61*, 3281.
(25) Reuber, J.; Fröhlich, R.; Hoppe, D. *Eur. J. Org. Chem.* **2005**, 3017.
(26) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552.
(27) Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708.
(28) Basu, A.; Thayumanavan, S. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 716.
(29) Beak, P.; Anderson, D. R.; Curtis, M. D.; Laumer, J. M.; Pippel, D. J.; Weisenburger, G. A. *Acc. Chem. Res.* **2000**, *33*, 715.
(30) Caddick, S.; Jenkins, K. *Chem. Soc. Rev.* **1996**, 448.
(31) (a) Gallagher, D. J.; Wu, S.; Nikolic, N. A.; Beak, P. *J. Org. Chem.* **1995**, *60*, 8148. (b) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231.
(32) Li, X.; Schenkel, L. B.; Kozlowski, M. *Org. Lett.* **2000**, *2*, 875.
(33) Orechoff, A.; Rabinowitch, M.; Kolowanowa, R. *Ber. Dtsch. Chem. Ges.* **1933**, *66*, 621.
(34) Ebner, T.; Eichelbaum, M.; Fischer, P.; Meese, C. O. *Arch. Pharm. (Weinheim)* **1989**, *322*, 399.
(35) Leonard, N. J.; Beyler, R. E. *J. Am. Chem. Soc.* **1950**, *72*, 1316.
(36) (a) Paetow, M.; Kotthaus, M.; Grehl, M.; Fröhlich, R.; Hoppe, D. *Synlett* **1994**, 1034. (b) Schlosser, M.; Limat, D. *J. Am. Chem. Soc.* **1995**, *117*, 12342. (c) Park, Y. S.; Beak, P. *J. Org. Chem.* **1997**, *62*, 1574. (d) Wilhelm, R.; Sebhat, I. K.; White, A. J. P.; Williams, D. J.; Widdowson, D. A. *Tetrahedron: Asymmetry* **2000**, *11*, 5003. (e) Tan, Y.-L.;White, A. J. P.; Widdowson, D. A.; Wilhelm, R.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3269. (f) Kimachi, T.; Takemoto, Y. *J. Org. Chem.* **2001**, *66*, 2700.
(37) Xu, Z.; Kozlowski, M. C. *J. Org. Chem.* **2002**, *67*, 3072.
(38) Kozlowski, M. C.; Xu, Z.; Santos, A. G. *Tetrahedron* **2001**, *57*, 4537.
(39) Ganguly, B.; Freed, D. A.; Kozlowski, M. C. *J. Org. Chem.* **2001**, *66*, 1103.
(40) Wiberg, K. B.; Bailey, W. F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2127.
(41) Wiberg, K. B.; Bailey, W. F. *J. Am. Chem. Soc.* **2001**, *123*, 8231.
(42) Harrison, J. R.; O'Brien, P.; Porter, D. W.; Smith, N. M. *Chem. Commun.* **2001**, 1202.
(43) Danieli, B.; Lesma, G.; Passarella, D.; Piacenti, P.; Sacchetti, A.; Silvani, A.; Virdis, A. *Tetrahedron Lett.* **2002**, *43*, 7155.
(44) Dearden, M. J.; Firkin, C. R.; Hermet, J.-P. R.; O'Brien, P. *J. Am. Chem. Soc.* **2002**, *124*, 11870.
(45) Hermet, J.-P. R.; Porter, D. W.; Dearden, M. J.; Harrison, J. R.; Koplin, T.; O'Brien, P.; Parmene, J.; Tyurin, V.; Whitwood, A. C.; Gilday, J.; Smith, N. M. *Org. Biomol. Chem.* **2003**, *1*, 3977.
(46) Stead, D.; O'Brien, P. *Tetrahedron* **2007**, *63*, 1885.
(47) Marrière, E.; Rouden, J.; Tadino, V.; Lasne, M.-C. *Org. Lett.* **2000**, *2*, 1121.
(48) O'Brien, P.; Wiberg, K. B.; Bailey, W. F.; Hermet, J.-P. R.; McGrath, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 15480.
(49) (a) McGrath, M. J.; O'Brien, P. *J. Am. Chem. Soc.* **2005**, *127*, 16378. (b) McGrath, M. J.; O'Brien, P. *Synthesis* **2006**, 2233.
(50) McGrath, M. J.; Bilke, J. L.; O'Brien, P. *Chem. Commun.* **2006**, 2607.
(51) Genet, C.; McGrath, M. J.; O'Brien, P. *Org. Biomol. Chem.* **2006**, *4*, 1376.
(52) Wiberg, K. B.; Bailey, W. F. *Tetrahedron Lett.* **2000**, *41*, 9365.
(53) Phuan, P.-W.; Ianni, J. C.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 15473.
(54) Morita, Y.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2006**, *7*, 4337.
(55) (a) Coldham, I.; Dufour, S.; Haxell, T. F. N.; Howard, S.; Vennall, G. P. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 3887. (b) Ashweek, N. J.; Brandt, P.; Coldham, I.; Dufour, S.; Gawley, R. E.; Hæffner, F.; Klein, R.; Sanchez-Jimenez, G. *J. Am. Chem. Soc.* **2005**, *127*, 449. (c) Coldham, I.; Dufour, S.; Haxell, T. F. N.; Vennall, G. P. *Tetrahedron* **2005**, *61*, 3205. (d) Coldham, I.; Patel, J. J.; Sanchez-Jimenez, G. *Chem. Commun.* **2005**, 3083.
(56) Bailey, W. F.; Beak, P.; Kerrick, S. T.; Ma, S.; Wiberg, K. B. *J. Am. Chem. Soc.* **2002**, *124*, 1889.
(57) Metallinos, C.; Dudding, T.; Zaifman, J.; Chaytor, J. L.; Taylor, N. J. *J. Org. Chem.* **2007**, *72*, 957.
(58) Berkheij, M.; van der Sluis, L.; Sewing, C.; De Boer, D. J.; Terpstra, J. W.; Hiemstra, H.; Iwema Bakker, W. I.; Van den Hoogenband, A.; Van Maarseveen, J. H. *Tetrahedron Lett.* **2005**, *46*, 2369.
(59) Park, Y. S.; Beak, P. *Tetrahedron* **1996**, *52*, 12333.
(60) Muci, A. R.; Campos, K. R.; Evans, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 9075.
(61) Byrne, L. T.; Engelhardt, L. M.; Jacobsen, G. E.; Leung, W.-P.; Papasergio, R. I.; Raston, C. L.; Skelton, B. W.; Twiss, P.; White, A. H. *J. Chem. Soc., Dalton Trans.* **1989**, 105.
(62) Pietrusiewicz, K. M.; Zablocka, M. *Chem. Rev* **1994**, *94*, 1375.
(63) Imamoto, T.; Watanabe, J.; Wada, Y.; Masuda, H.; Yamada, H.; Tsuruta, H.; Matsukawa, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **1998**, *120*, 1635.
(64) Yamanoi, Y.; Imamoto, T. *J. Org. Chem.* **1999**, *64*, 2988.
(65) Kobayashi, S.; Shiraishi, N.; Lam, W. W.-L.; Manabe, K. *Tetrahedron Lett.* **2001**, *42*, 7303.
(66) (a) Tang, W.; Zhang, X. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1612. (b) Tang, W.; Wang, W.; Zhang, X. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 943.
(67) Johansson, M. J.; Schwartz, L.; Amedjkouh, M.; Kann, N. *Eur. J. Org. Chem.* **2004**, 1894.
(68) Johansson, M. J.; Schwartz, L.; Amedjkouh, M.; Kann, N. *Tetrahedron: Asymmetry* **2004**, *15*, 3531.
(69) (a) Aratani, T.; Gonda, T.; Nozaki, H. *Tetrahedron Lett.* **1969**, *27*, 2265. (b) Aratani, T.; Gonda, T.; Nozaki, H. *Tetrahedron* **1970**, *26*, 5453. (c) Marquading, D.; Klusacek, H.; Gokel, G. W.; Hoffmann, P.; Ugi, I. K. *J. Am. Chem. Soc.* **1970**, *92*, 5389.
(70) Tsukazaki, M.; Tinkl, M.; Roglans, A.; Chapell, B. J.; Taylor, N. J.; Snieckus, V. *J. Am. Chem. Soc.* **1996**, *118*, 685.
(71) Nishibayashi, Y.; Arikawa, Y.; Ohe, K.; Uemera, S. *J. Org. Chem.* **1996**, *61*, 1172.
(72) Fukuda, T.; Imazato, K.; Iwao, M. *Tetrahedron Lett.* **2003**, *44*, 7503.
(73) Uemura, M.; Hayashi, Y.; Hayashi, Y. *Tetrahedron: Asymmetry* **1994**, *5*, 1427.
(74) (a) Hata, T.; Koide, H.; Taniguchi, N.; Uemura, M. *Org. Lett.* **2000**, *13*, 1907. (b) Koide, H.; Hata, T.; Uemura, M. *J. Org. Chem.* **2002**, *67*, 1929. (c) Koide, H.; Hata, T.; Yoshihara, K.; Kamikawa, K.; Uemura, M. *Tetrahedron* **2004**, *60*, 4527.
(75) Wilhelm, R.; Sebhat, I. K.; White, A. J. P.; Williams, D. J.; Widdowsona, D. A. *Tetrahedron: Asymmetry* **2000**, *11*, 5003.
(76) Mikami, K.; Azuma, K.; Nakai, T. *Tetrahedron* **1984**, *40*, 2303.
(77) Kang, J.; Cho, W. O.; Cho, H. G.; Oh, H. J. *Bull. Korean Chem. Soc.* **1994**, *15*, 732.
(78) Barrett, I. M.; Breeden, S. W. *Tetrahedron: Asymmetry* **2004**, *15*, 3015.
(79) Hodgson, D. M.; Robinson, L. A.; Jones, M. L. *Tetrahedron Lett.* **1999**, *40*, 8637.
(80) Hodgson, D. M.; Lee, G. P. *Chem. Commun.* **1996**, 1015.
(81) Hodgson, D. M.; Lee, G. P. *Tetrahedron: Asymmetry* **1997**, *8*, 2303.

(82) Hodgson, D. M.; Lee, G. P.; Marriott, R. E.; Thompson, A. J.; Wisedale, R.; Witherington, J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2151.
(83) Dearden, M. J.; McGrath, M. J.; O'Brien, P. *J. Org. Chem.* **2004**, *69*, 5789.
(84) Hodgson, M. D.; Cameron, I. D. *Org. Lett.* **2001**, *3*, 441.
(85) Hodgson, D. M.; Galano, J.-M.; Christlieb, M. *Tetrahedron* **2003**, *59*, 9719.
(86) Hodgson, D. M.; Cameron, I. D.; Christlieb, M.; Green, R.; Lee, G. P.; Robinson, L. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2161.
(87) Hodgson, D. M.; Norsikian, S. L. M. *Org. Lett.* **2001**, *3*, 461.
(88) Hodgson, D. M.; Buxton, T. J.; Cameron, I. D.; Gras, E.; Kirton, E. H. M. *Org. Biomol. Chem.* **2003**, *1*, 4293.
(89) (a) Fraenkel, G.; Chow, A.; Winchester, W. R. *J. Am. Chem. Soc.* **1990**, *112*, 2582. (b) Fraenkel, G.; Cabral, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 1551.
(90) (a) Peoples, P. R.; Grutzner, J. B. *J. Am. Chem. Soc*. **1980**, *102*, 4709. (b) Paquette, L. A.; Ra, C. S. *J. Org. Chem*. **1988**, *53*, 4978. (c) Keys, B. A.; Eliel, E. L.; Juaristi, E. *Isr. J. Chem*. **1989**, *29*, 171. (d) Kato, T.; Marumoto, S.; Sato, T.; Kuwajima, I. *Synlett* **1990**, 671. (e) Krief, A.; Hobe, M.; Dumont, W.; Badaoui, E.; Guittet, E.; Evrard, G. *Tetrahedron Lett.* **1992**, *33*, 3381. (f) Krief, A.; Hobe, M. *Tetrahedron Lett.* **1992**, *33*, 6529. (g) Hoffmann, R. W.; Rühl, T.; Chemla, F.; Zahneisen, T. *Liebigs Ann. Chem*. **1992**, 719. (h) Hoffmann, R. W.; Rühl, T.; Harbach, J. *Liebigs Ann. Chem*. **1992**, 725. (i) Marumoto, S.; Kuwajima, I. *J. Am. Chem. Soc*. **1993**, *115*, 9021. (j) Zhang, P.; Gawley, R. E. *J. Org. Chem*. **1993**, *58*, 3223. (k) Ahlbrecht, H.; Harbach, J.; Hoffmann, R. W.; Ruhland, T. *Liebigs Ann. Chem*. **1995**, 211. (l) Klein, S.; Marek, I.; Poisson, J.-F.; Normant, J.-F. *J. Am. Chem. Soc*. **1995**, *117*, 8853.
(91) (a) Krief, A.; Evrard, G.; Badaoui, E.; De Beys, V.; Dieden, R. *Tetrahedron Lett.* **1989**, *30*, 5635. (b) Hoffmann, R. W.; Julius, M.; Oltmann, K. *Tetrahedron Lett.* **1990**, *31*, 7419. (c) Krief, A.; Badaoui, E.; Dumont, W. *Tetrahedron Lett.* **1993**, *34*, 8517.
(92) (a) Reich, H. J.; Bowe, M. D. *J. Am. Chem. Soc*. **1990**, *112*, 8994. (b) Hoffmann, R. W.; Dress, R. K.; Ruhland, T.; Wenzel, A. *Chem. Ber*. **1995**, *128*, 861.
(93) (a) McDougal, P. G.; Condon, B. D.; Laffosse, M. D.; Lauro, A. M.; VanDerveer, D. *Tetrahedron Lett.* **1988**, *29*, 2547. (b) Lutz, G. P.; Wallin, A. P.; Kerrick, S. T.; Beak, P. *J. Org. Chem*. **1991**, *56*, 4938. (c) Brickmann, K.; Hamblock, F.; Spolaore, E.; Brückner, R. *Chem. Ber*. **1994**, *127*, 1949. (d) Kaiser, B.; Hoppe, D. *Angew. Chem*. **1995**, *107*, 344. (e) Kaiser, B.; Hoppe, D. *Angew. Chem., Int. Ed.* Engl. **1995**, *34*, 323. (f) Wang, F.; Tang, J.; Labaudinière, L.; Marek, I.; Normant, J.-F. *Synlett* **1995**, 723.
(94) Nozaki, H.; Aratani, T.; Toraya, T.; Noyori, R. *Tetrahedron* **1971**, *27*, 905.
(95) Hirsch, R.; Hoffmann, R. W. *Chem. Ber.* **1992**, *125*, 975.
(96) (a) Klute, W.; Dress, R.; Hoffmann, R. W. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1409. (b) Hoffmann, R. W.; Klute, W.; Dress, R. K.; Wenzel, A. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1721. (c) Hoffmann, R. W.; Klute, W. *Chem. Eur. J*. **1996**, 694.
(97) Klute, W. Dissertation, univ. Marburg, 1994.
(98) (a) Nakamura, S.; Nakagawa, R.; Watanabe, Y.; Toru, T. *Angew. Chem., Int. Ed. Engl*. **2000**, *39*, 353. (b) Nakamura, S.; Nakagawa, R.; Watanabe, Y.; Toru, T. *J. Am. Chem. Soc.* **2000**, *122*, 11340.
(99) Criegee, R.; Marchand, B.; Wannowius, H. *Justus Liebigs Ann. Chem.* **1942**, *550*, 99.
(100) (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, B. *Chem. Rev.* **1994**, *94*, 2483. (b) Zaitsev, A. B.; Adolfsson, H. *synthesis* **2006**, 1725. (c) Kolb, H. C.; Sharpless, B. K. In *Transition metals for organic synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weiheim, 2004; Vol. 2, p 275. Secondary diamines were found to be very efficient as well, see: Hannessian, S.; Meffre, P.; Girard, M.; Beaudoin, S.; Sancéau, J.-Y.; Bennami, Y. *J. Org. Chem.* **1993**, *58*, 1991.
(101) Yamada, T.; Narasaka, K. *Chem. Lett.* **1986**, 131.
(102) Tokles, M.; Snyder, J. K. *Tetrahedron Lett.* **1986**, *27*, 3951.
(103) (a) Tomioka, K.; Nakajima, M.; Koga, K. *J. Am. Chem. Soc.* **1987**, *109*, 6213. (b) Tomioka, K.; Nakajima, M.; Iitaka, Y.; Koga, K. *Tetrahedron Lett.* **1988**, *29*, 573. (c) Tomioka, K.; Nakajima, M.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1921. (d) Tomioka, K.; Nakajima, M.; Koga, K. *Tetrahedron Lett.* **1990**, *31*, 1741. (e) Nakajima, M.; Tomioka, K.; Iitaka, Y.; Koga, K. *Tetrahedron* **1993**, *49*, 10793.
(104) Böeseken, J. *Rec. Trav. Chim. Pays-Bas* **1922**, *41*, 199.
(105) (a) Corey, E. J.; Da Silva Jardine, P.; Virgil, S.; Yuen, P.-W.; Connell, R. D. *J. Am. Chem. Soc.* **1989**, *111*, 9243. (b) Corey, E. J.; Noe, M. C.; Sarshar, S. *J. Am. Chem. Soc.* **1993**, *115*, 3828. (c) Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1993**, *115*, 12579. (d) Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *J. Am. Chem. Soc.* **1994**, *116*, 12109. (e) Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *J. Am. Chem. Soc.* **1995**, *117*, 10805. (f) Corey, E. J.; Noe, M. C.; Guzman-Perez, A. *J. Am. Chem. Soc.* **1995**, *117*, 10817. (g) Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 319. (h) Corey, E. J.; Sarshar, S.; Azimioara, M. D.; Newbold, R. C.; Noe, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 7851.
(106) (a) Sharpless, K. B.; Teranishi, A. Y.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1977**, *99*, 3120. (b) Nelson, D. W.; Gypser, A.; Ho, P. T.; Kolb, H. C.; Kondo, T.; Kwong, H.-L.; McGrath, D. V.; Rubin, A. E.; Norrby, P.-O.; Gable, K. P.; Sharpless, K. B. *J. Am. Chem. Soc.* **1997**, *119*, 1840.
(107) Wu, Y.-D.; Wang, Y.; Houk, K. N. *J. Org. Chem.* **1992**, *57*, 1362.
(108) (a) Pidun, U.; Boehme, C.; Frenking, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2817. (b) Dapprich, S.; Ujaque, G.; Maseras, F.; Lledós, A.; Musaev, D. G.; Morokuma, K. *J. Am. Chem. Soc.* **1996**, *118*, 11660. (c) Corey, E. J.; Noe, M. C.; Grogan, M. J. *Tetrahedron Lett.* **1996**, *37*, 4899. (d) Torrent, M.; Deng, L.; Duran, M.; Sola, M.; Ziegler, T. *Organometallics* **1997**, *16*, 13. (e) Del Monte, A. J.; Haller, J.; Houk, K. N.; Sharpless, K. B.; Singleton, D. A.; Strassner, T.; Thomas, A. *J. Am. Chem. Soc.* **1997**, *119*, 9907.
(109) Illesinghe, J.; Ebeling, R.; Ferguson, B.; Patel, J.; Campi, E. M.; Jackson, W. R.; Robinson, A. J. *Aust. J. Chem.* **2004**, *57*, 167.
(110) (a) Oishi, T.; Hirama, M. *J. Org. Chem.* **1989**, *54*, 5834. (b) Hirama, M.; Oishi, T.; Itô, S. *J. Chem. Soc., Chem. Commun*. **1989**, 665. (c) Oishi, T.; Iida, K.-I.; Hirama, M. *Tetrahedron Lett.* **1993**, *34*, 3573.
(111) Oishi, T.; Hirama, M. *Tetrahedron Lett.* **1992**, *33*, 639.
(112) Fuji, K.; Tanaka, K.; Miyamoto, H. *Tetrahedron Lett.* **1992**, *33*, 4021.
(113) (a) Tanner, D.; Andersson, P. G.; Harden, A.; Somfai, P. *Tetrahedron Lett.* **1994**, *35*, 4631. (b) Tanner, D.; Harden, A.; Johansson, F.; Wyatt, P.; Andersson, P. G. *Acta Chem. Scand*. **1996**, *50*, 361. (c) Tanner, D.; Johansson, F.; Harden, A.; Andersson, P. G. *Tetrahedron* **1998**, *54*, 15731.
(114) (a) Cromwell, N. H.; Graff, M. A. *J. Org. Chem.* **1952**, *17*, 414. (b) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: Chichester, 1976; pp 80−85.
(115) Haubenstock, H.; Subasinghe, K. *Chirality* **1992**, *4*, 300.
(116) Kanoh, S.; Suda, H.; Kawaguchi, N.; Motoi, M. *Makromol. Chem.* **1986**, *187*, 53.
(117) Rosini, C.; Tanturli, R.; Pertici, P.; Salvadori, P. *Tetrahedron: Asymmetry* **1996**, *7*, 2971.
(118) Mazaleyrat, J.-P.; Cram, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 4585.
(119) Costas, M.; Tipton, A. K.; Chen, K.; Jo, D.-H.; Que, L., Jr. *J. Am. Chem. Soc.* **2001**, *123*, 6722.
(120) (a) Murphy, A.; Pace, A.; Stack, D. P. *Org. Lett.* **2004**, *6*, 3119. (b) Murphy, A.; Dubois, G.; Stack, D. P. *J. Am. Chem. Soc.* **2003**, *125*, 5250. (c) Costas, M.; Que, L., Jr. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 2179.
(121) (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768. (b) Crispino, G. A.; Jeong, K. S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785. (c) Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 448.
(122) Lohray, B. B.; Bhushan, V. *Tetrahedron Lett.* **1992**, *33*, 5113.
(123) (a) Sharpless, K. B.; Patrick, D. W.; Truesdale, L. K.; Biller, S. A. *J. Am. Chem. Soc.* **1975**, *97*, 2305. (b) Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 451.
(124) O'Brien, P. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 326.
(125) (a) Donohoe, T. J.; Chughtai, M. J.; Klauber, D. J.; Griffin, D.; Campbell, A. D. *J. Am. Chem. Soc.* **2006**, *128*, 2514. (b) Donohoe, T. J.; Johnson, P. D.; Cowley, A.; Keenan, M. *J. Am. Chem. Soc.* **2002**, *124*, 12934. (c) Donohoe, T. J.; Johnson, P. D.; Pye, R. J.; Keenan, M. *Org. Lett.* **2004**, *6*, 2583. (d) Donohoe, T. J.; Johnson, P. D.; Pye, R. J. *Org. Biomol. Chem*. **2003**, *1*, 2025. (e) Donohoe, T. J.; Jonhson, P. D.; Helliwell, M.; Keenan, M. *Chem. Commun*. **2001**, 2078.
(126) (a) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155. (b) Kočovsky, P.; Viskočil, S.; Smrčina, M. *Chem. Rev.* **2003**, *103*, 3213.
(127) Feringa, B.; Wynberg, H. *Tetrahedron Lett.* **1977**, *18*, 4447.
(128) (a) Nakajima, M.; Kanayama, K.; Miyoshi, I.; Hashimoto, S.-I. *Tetrahedron Lett.* **1995**, *36*, 9519. (b) Nakajima, M.; Miyoshi, I.; Kanayama, K.; Hashimoto, S.-I. *J. Org. Chem.* **1999**, *64*, 2264.
(129) Li, X.; Yang, J.; Kozlowski, M. C. *Org. Lett.* **2001**, *3*, 1137.
(130) Kizirian, J.-C. Ph.D. Dissertation, University of Geneva, No. 3467, 2003.
(131) Li, X.; Hewgley, B.; Mulrooney, C. A.; Yang, J.; Kozlowski, M. C. *J. Org. Chem.* **2003**, *68*, 5500.
(132) (a) Mulrooney, C. A.; Li, X.; DiVirgilio, E. S.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2003**, *125*, 6856. (b) DiVirgilio, E. S.; Dugan, E. C.; Mulrooney, C. A.; Kozlowski, M. C. *Org. Lett.* **2007**, *9*, 385.
(133) Kagan, H. B.; Dunach, E.; Nemecek, C.; Pitchen, P.; Samuel, O.; Zhao, S. H. *Pure Appl. Chem.* **1985**, *57*, 1911.
(134) Sun, J.; Zhu, C.; Dai, Z.; Yang, M.; Pan, Y.; Hu, H. *J. Org. Chem.* **2004**, *69*, 8500.

(135) ten Brink, G.-J.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Rev.* **2004**, *104*, 4105.
(136) (a) Ilmarinen, K.; Kriis, K.; Paju, A.; Pehk, T.; Lopp, M. *Proc. Estonian Acad. Sci. Chem.* **2001**, *50*, 147. (b) Lopp, M.; Paju, A.; Kanger, T.; Kriis, K.; Ilmarinen, K.; Pehk, T. *Proc. Estonian Acad. Sci. Chem.* **2001**, *50*, 124.
(137) (a) Mimmi, M. C.; Gullotti, M.; Santagostini, L.; Saladino, A.; Casella, L.; Monzani, E.; Pagliarin, R. *J. Mol. Catal., Part A: Chem.* **2003**, *204*−*205*, 381. (b) Mimmi, M. C.; Gullotti, M.; Santagostini, L.; Battaini, G.; Monzani, E.; Pagliarin, R.; Zoppellaro, G.; Casella, L. *Dalton Trans.* **2004**, 2192.
(138) (a) Zassinovitch, G.; Mestroni, G. *Chem. Rev.* **1992**, *92*, 1051. (b) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97.
(139) Gamez, P.; Fache, F.; Mangeney, P.; Lemaire, M. *Tetrahedron Lett.* **1993**, *85*, 131.
(140) (a) Gamez, P.; Fache, F.; Lemaire, M. *Tetrahedron: Asymmetry* **1995**, *6*, 705. (b) Gamez, P.; Fache, F.; Lemaire, M. *Tetrahedron: Asymmetry* **2005**, *16*, 747.
(141) Pertici, P.; D'Arata, F.; Rosini, C. *J. Organomet. Chem.* **1996**, *515*, 163.
(142) Nindakova, L. O.; Shainyan, B. A.; Belonogova, L. N. *Russ. J. Org. Chem.* **2003**, *39*, 1484.
(143) Schwink, L.; Ireland, T.; Püntener, K.; Knochel, P. *Tetrahedron: Asymmetry* **1998**, *9*, 1143.
(144) Petra, D. G. I.; Kamer, P. C. J.; Van Leeuwen, P. W. N. M.; Goubitz, K.; Van Loon, A. M.; De Vries, J. G.; Schoemaker, H. E. *Eur. J. Inorg. Chem.* **1999**, 2335.
(145) Ohno, K.; Kataoka, Y.; Mashima, K. *Org. Lett.* **2004**, *6*, 4695.
(146) Nishibayashi, Y.; Singh, J. D.; Segawa, K.; Fukuzawa, S.-I.; Uemura, S. *J. Chem. Soc., Chem. Commun.* **1994**, 1375.
(147) Mimoun, H.; De Saint Laumer, J.-Y.; Giannini, L.; Scopelliti, R.; Floriani, C. *J. Am. Chem. Soc.* **1999**, *121*, 6158.
(148) Bette, V.; Mortreux, A.; Savoia, D.; Carpentier, J.-F. *Tetrahedron* **2004**, *60*, 2837.
(149) (a) Yamada, I.; Yamaguchi, M.; Yamagishi, T. *Tetrahedron: Asymmetry* **1996**, *7*, 3339. (b) Yamada, I.; Ohkouchi, M.; Yamaguchi, M.; Yamagishi, T. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1869.
(150) Perea, J. J. A.; Lotz, M.; Knochel, P. *Tetrahedron: Asymmetry* **1999**, *10*, 375.
(151) Shainyan, B. A.; Ustinov, M. V.; Bel'skii, V. K.; Nindakova, L. O. *Russ. J. Org. Chem.* **2002**, *38*, 104.
(152) Nindakova, L. O.; Shainyan, B. A.; Albanov, A. I.; Shmidt, F. K. *Russ. J. Org. Chem.* **2003**, *39*, 926.
(153) Zhang, X.; Yan, Y. *Tetrahedron Lett.* **2006**, *47*, 1567.
(154) Horner, L.; Dickerhof, K. *Liebigs Ann. Chem.* **1984**, 1240.
(155) Matsubara, S.; Hashimoto, Y.; Okano, T.; Utimoto, K. *Synlett* **1999**, 1411.
(156) (a) Daverio, P.; Zanda, M. *Tetrahedron: Asymmetry* **2001**, *12*, 2225. (b) Apsimon, J. W.; LeeCollier, T. *Tetrahedron* **1986**, *42*, 5157. (c) Apsimon, J. W.; Seguin, R. P. *Tetrahedron* **1979**, *35*, 2797.
(157) Seebach, D.; Daum, H. *Chem. Ber.* **1974**, *107*, 1748.
(158) Oriyama, T.; Mukaiyama, T. *Chem. Lett.* **1984**, 2071.
(159) Mukaiyama, T.; Tomimori, K.; Oriyama, T. *Chem. Lett.* **1985**, 813.
(160) Mukaiyama, T.; Tomimori, Oriyama, T. *Chem. Lett.* **1985**, 1359.
(161) Falorni, M.; Lardicci, L.; Giacomelli, G.; Marchetti, M. *Tetrahedron Lett.* **1989**, *30*, 3551.
(162) Falorni, M.; Giacomelli, G.; Marchetti, M.; Culeddu, N.; Lardicci, L. *Tetrahedron: Asymmetry* **1991**, *2*, 287.
(163) (a) Murakata, M.; Tsutsui, H.; Hoshino, O. *J. Chem. Soc., Chem. Commun.* **1995**, 481. (b) Murakata, M.; Tsutsui, H.; Takeuchi, N.; Hoshina, O. *Tetrahedron* **1999**, *55*, 10295.
(164) Zhang, Y.-X.; Du, D.-M.; Chen, X.; Lü, S.-F.; Hua, W.-T. *Tetrahedron: Asymmetry* **2004**, *15*, 177.
(165) Trost, B.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395.
(166) Trost, B. M.; Strege, P. E. *J. Am. Chem. Soc.* **1977**, *99*, 1650.
(167) Trost, B. M.; Dietsche, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 8200.
(168) Togni, A. *Tetrahedron: Asymmetry* **1991**, *2*, 683.
(169) Kang, J.; Cho, W. O.; Cho, H. G. *Tetrahedron: Asymmetry* **1994**, *5*, 1347.
(170) Gamez, P.; Dunjic, B.; Fache, F.; Lemaire, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1109.
(171) Kubota, H.; Nakajima, M.; Koga, K. *Tetrahedron Lett.* **1993**, *34*, 8135.
(172) Andrey, O. Ph.D. Dissertation, University of Geneva, N*o*. 3531, 2003.
(173) Andersson, P.; Harden, A.; Tanner, D.; Norrby, P.-O. *Chem. Eur. J.* **1995**, *1*, 12.
(174) (a) Sawamura, M.; Nagata, H.; Sakamoto, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 2586. (b) Sawamura, M.; Nakayama, Y.; Tang, W.-M.; Ito, Y. *J. Org. Chem.* **1996**, *61*, 9090.
(175) Canal, J. M.; Gómez, M.; Jiménez, F.; Rocamora, M.; Muller, G.; Duñach, E.; Franco, D.; Jiménez, A.; Cano, F. H. *Organometallics* **2000**, *19*, 966.
(176) (a) Bourghida, M.; Widhalm, M. *Tetrahedron: Asymmetry* **1998**, *9*, 1073. (b) Wimmer, P.; Widhalm, M. *Tetrahedron: Asymmetry* **1995**, *6*, 657.
(177) Widhalm, M.; Wimmer, P.; Klintschar, G. *J. Organomet. Chem.* **1996**, *523*, 167.
(178) Kondo, K.; Kazuta, K.; Fujita, H.; Sakamoto, Y.; Murakami, Y. *Tetrahedron* **2002**, *58*, 5209.
(179) Sakamoto, Y.; Kondo, K.; Tokunaga, M.; Kazuta, K.; Fujita, H.; Murakami, Y.; Aoyama, T. *Heterocycles* **2004**, *63*, 1345.
(180) Mino, T.; Saito, A.; Tanaka, Y.; Hasegawa, S.; Sato, Y.; Sakamoto, M.; Fujita, T. *J. Org. Chem.* **2005**, *70*, 1937.
(181) (a) Lam, H.; Cheng, X.; Steed, J. W.; Aldous, D. J.; Hii, K. K. *Tetrahedron Lett.* **2002**, *43*, 5875. (b) Cheng, X.; Hii, K. K. *Tetrahedron: Asymmetry* **2003**, *14*, 2045.
(182) Nozaki, H.; Aratani, T.; Toraya, T. *Tetrahedron Lett.* **1968**, *38*, 4097.
(183) Seebach, D.; Kalinowski, H.-O.; Bastani, B.; Crass, G.; Daum, H.; Dörr, H.; DuPreez, N. P.; Ehrig, V.; Langer, W.; Nüssler, C.; Oei, H.-A.; Schmidt, M. *Helv. Chim. Acta* **1977**, *60*, 301.
(184) Seebach, D.; Langer, W. *Helv. Chim. Acta* **1979**, *62*, 1701.
(185) Seebach, D.; Crass, G.; Wilka, E.-M.; Hilvert, D.; Brunner, E. *Helv. Chim. Acta* **1979**, *62*, 2695.
(186) Kang, J.; Kim, J. I.; Lee, J. H. *Bull. Korean Chem. Soc.* **1994**, *15*, 865.
(187) Mukaiyama, T.; Soai, K.; Kobayashi, S. *Chem. Lett.* **1978**, 219.
(188) Mukaiyama, T.; Soai, K.; Sato, T.; Shimizu, H.; Suzuki, K. *J. Am. Chem. Soc.* **1979**, *101*, 1455.
(189) Soai, K.; Mukaiyama, T. *Chem. Lett.* **1978**, 491.
(190) Mazaleyrat, J.-P.; Cram, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 4585.
(191) Soai, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3371.
(192) Mukaiyama, T. *Tetrahedron* **1981**, *23*, 4111.
(193) Colombo, L.; Gennari, C.; Poli, G.; Scolastico, C. *Tetrahedron* **1982**, *17*, 2725.
(194) Urabe, H.; Yamakawa, T.; Sato, F. *Tetrahedron: Asymmetry* **1992**, *3*, 5.
(195) Mazaleyrat, J.-P. *Tetrahedron: Asymmetry* **1997**, *8*, 2709.
(196) Maigrot, N.; Mazaleyrat, J.-P. *J. Chem. Soc., Chem. Commun.* **1985**, 508.
(197) Kanoh, S.; Muramoto, H.; Maeda, K.; Kawaguchi, N.; Motoi, M.; Suda, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2244.
(198) Corruble, A.; Valnot, J.-Y.; Maddaluno, J.; Duhamel, P. *J. Org. Chem.* **1998**, *63*, 8266.
(199) Corruble, A.; Davoust, D.; Desjardins, S.; Fressigné, C.; Giessner-Prettre, C.; Harrisson-Marchand, A.; Houte, H.; Lasne, M.-C.; Maddaluno, J.; Oulyadi, H.; Valnot, J.-Y. *J. Am. Chem. Soc.* **2002**, *124*, 15267.
(200) (a) Zhang, X.-M.; Zhang, H.-L.; Lin, W.-Q.; Gong, L.-Z.; Mi, A.-Q.; Cui, X.; Jiang, Y.-Z.; Yu, K.-B. *J. Org. Chem.* **2003**, *68*, 4322. (b) Zhang, H.-L.; Zhang, X.-M.; Gong, L.-Z.; Mi, A.-Q.; Cui, X.; Jiang, Y.-Z.; Choi, M. C. K.; Chan, A. S. C. *Org. Lett.* **2002**, *4*, 1399. (c) Hermanns, N.; Dahmen, S.; Bolm, C.; Bräse, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3692. (d) Dahmen, S.; Bräse, S. *J. Am. Chem. Soc.* **2002**, *124*, 5940. (e) Zhang, X.; Lin, W.; Gong, L.; Mi, A.; Cui, X.; Jiang, Y.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron Lett.* **2002**, *43*, 1535. (f) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 984. (g) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 10409. (h) Fujihara, H.; Nagai, K.; Tomioka, K. *J. Am. Chem. Soc.* **2000**, *122*, 12055. (i) Hayashi, T.; Ishigedani, M. *J. Am. Chem. Soc.* **2000**, *122*, 976. (j) Jimeno, C.; Reddy, S. K.; Solà, L.; Moyano, A.; Pericàs, M. A.; Riera, A. *Org. Lett.* **2000**, *2*, 3157. (k) Brandt, P.; Hedberg, C.; Lawonn, K.; Pinho, P.; Andersson, P. G. *Chem. Eur. J.* **1999**, *5*, 1692. (l) Guijarro, D.; Pinho, P.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 2530. (m) Andersson, P. G.; Guijarro, D.; Tanner, D. *J. Org. Chem.* **1997**, *62*, 7364. (n) Andersson, P. G.; Guijarro, D.; Tanner, D. *Synlett* **1996**, 727.
(201) Itsuno, S.; Yanaka, H.; Hachisuka, C.; Ito, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1341.
(202) Itsuno, S.; Sasaki, M.; Kuroda, S.; Ito, K. *Tetrahedron: Asymmetry* **1995**, *6*, 1507.
(203) Denmark, S. E.; Nakajima, N.; Nicaise, O. J.-C. *J. Am. Chem. Soc.* **1994**, *116*, 8797.
(204) Gittins, C. A.; North, M. *Tetrahedron: Asymmetry* **1997**, *8*, 3789.
(205) Arrasate, S.; Lete, E.; Sotomayor, N. *Tetrahedron: Asymmetry* **2001**, *12*, 2077.
(206) Pflum, D. A.; Krishnamurthy, D.; Han, Z.; Wald, S. A.; Senanayake, C. H. *Tetrahedron Lett.* **2002**, *43*, 923.
(207) (a) Tanner, D.; Harden, A.; Johansson, F.; Wyatt, P.; Andersson, P. G. *Acta Chem. Scand.* **1996**, *50*, 361. (b) Andersson, P. G.; Johansson, F.; Tanner, D. *Tetrahedron* **1998**, *54*, 11549.
(208) (a) Kizirian, J.-C.; Caille, J.-C.; Alexakis, A. *Tetrahedron Lett.* **2003**, *44*, 8893. (b) Kizirian, J.-C.; Cabello, N.; Alexakis, A. *Tetrahedron* **2005**, *61*, 8939. (c) Gille, S.; Cabello, N.; Kizirian, J.-C.; Alexakis, A. *Tetrahedron: Asymmetry* **2006**, *17*, 1045.

(209) (a) Fukuda, T.; Takehara, A.; Hamiu, N.; Iwao, M. *Tetrahedron: Asymmetry* **2000**, *11*, 4083. (b) Yamada, H.; Kawate, T.; Nishida, A.; Nakagawa, M. *J. Org. Chem.* **1999**, *64*, 8821.
(210) Cabello, N.; Kizirian, J.-C.; Alexakis, A. *Tetrahedron Lett.* **2004**, *45*, 4639.
(211) Cabello, N.; Kizirian, J.-C.; Gille, S.; Alexakis, A.; Bernardinelli, G.; Pinchard, L.; Caille, J.-C. *Eur. J. Org. Chem.* **2005**, 4835.
(212) (a) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533. (b) Pearson, R. G. *J. Chem. Educ.* **1987**, *64*, 561. (c) Woodward, S. *Tetrahedron* **2002**, *58*, 1017.
(213) Asano, Y.; Iida, A.; Tomioka, K. *Tetrahedron Lett.* **1997**, *38*, 8973.
(214) Asano, Y.; Iida, A.; Tomioka, K. *Chem. Pharm. Bull.* **1998**, *46*, 184.
(215) Asano, Y.; Yamashita, M.; Nagai, K.; Kuriyama, M.; Yamada, K.-I.; Tomioka, K. *Tetrahedron Lett.* **2001**, *42*, 8493.
(216) Xu, F.; Tillyer, R. D.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron: Asymmetry* **1998**, *9*, 1651.
(217) Tomioka, K.; Shindo, M.; Koga, K. *J. Am. Chem. Soc.* **1989**, *111*, 8266.
(218) Shindo, M.; Koga, K.; Tomioka, K. *J. Org. Chem.* **1998**, *63*, 9353.
(219) Alexakis, A.; Amiot, F. *Tetrahedron: Asymmetry* **2002**, *13*, 2117.
(220) Amiot, F.; Cointeaux, L.; Jan Silve, E.; Alexakis, A. *Tetrahedron* **2004**, *60*, 8221.
(221) Cointeaux, L.; Alexakis, A. *Tetrahedron: Asymmetry* **2005**, *16*, 925.
(222) Sato, T.; Soai, K.; Suzuki, K.; Mukaiyama, T. *Chem. Lett.* **1978**, 601.
(223) Pratt, L. M. *Mini-Rev. Org. Chem.* **2004**, *1*, 209.
(224) Tomioka, K.; Nakajima, M.; Koga, K. *Tetrahedron Lett.* **1987**, *28*, 1291.
(225) Tomioka, K.; Nakajima, M.; Koga, K. *Chem. Lett.* **1987**, 65.
(226) Nakajima, M.; Tomioka, K.; Koga, K. *Tetrahedron* **1993**, *43*, 9751.
(227) Markó, I. E.; Chesney, A.; Hollinshead, D. M. *Tetrahedron: Asymmetry* **1994**, *5*, 569.
(228) Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem., Int. Ed. Engl.*, **1991**, *30*, 477.
(229) Zadel, G.; Breitmaier, E. *Chem. Ber.* **1994**, *127*, 1323.
(230) Karash, M. S.; Tawney, P. O. *J. Am. Chem. Soc.* **1941**, *63*, 2308.
(231) Kretchmer, R. A. *J. Org. Chem.* **1972**, *37*, 2744.
(232) (a) Jansen, J. F. G. A.; Feringa, B. L. *Tetrahedron Lett.* **1988**, *29*, 3593. (b) Jansen, J. F. G. A.; Feringa, B. L. *J. Chem. Soc., Chem. Commun.* **1989**, 741. (c) Jansen, J. F. G. A.; Feringa, B. L. *J. Org. Chem.* **1990**, *55*, 4168.
(233) Jonhson, C. R.; Marren, T. J. *Tetrahedron Lett.* **1987**, *28*, 27.
(234) Zweig, J. S.; Luche, J. L.; Barreiro, E.; Crabbé, P. *Tetrahedron Lett.* **1975**, *28*, 2355.
(235) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771.
(236) Corey, E. J.; Naef, R.; Hannon, F. J. *J. Am. Chem. Soc.* **1986**, *108*, 7114.
(237) (a) Rossiter, B. E.; Eguchi, M. *Tetrahedron Lett.* **1990**, *31*, 965. (b) Rossiter, B. E.; Eguchi, M.; Hernández, A. E.; Vickers, D. *Tetrahedron Lett.* **1991**, *32*, 3973. (c) Rossiter, B. E.; Miao, G.; Swingle, N. M.; Eguchi, M.; Hernández, A. E.; Patterson, R. G. *Tetrahedron: Asymmetry* **1992**, *3*, 231. (d) Rossiter, B. E.; Eguchi, M.; Miao, G.; Swingle, N. M.; Hernández, A. E.; Vickers, D.; Fluckiger, E.; Patterson, R. G.; Reddy, K. V. *Tetrahedron* **1993**, *49*, 965. (e) Swingle, N. M.; Reddy, K. V.; Rossiter, B. E. *Tetrahedron* **1994**, *50*, 4455. (f) Miao, G.; Rossiter, B. E. *J. Org. Chem.* **1995**, *60*, 8424.
(238) Davies, S. G.; Wollowitz, S. *Tetrahedron Lett.* **1980**, *21*, 4175.
(239) Frankland, E. *Justus Liebigs Ann. Chem.* **1849**, *71*, 171.
(240) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833.
(241) Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984** ,*25*, 2823.
(242) (a) Corey, E. J.; Hannon, F. J. *Tetrahedron Lett.* **1987**, *28*, 5233. (b) Corey, E. J.; Hannon, F. J. *Tetrahedron Lett.* **1987**, *28*, 5237.
(243) Soai, K.; Nishi, M.; Ito, Y. *Chem. Lett.* **1987**, 2405.
(244) Andrés, J. M.; Martinez, M. A.; Pedrosa, R.; Pérez-Encabo, A. *Tetrahedron: Asymmetry* **1994**, *5*, 67.
(245) Williams, D. R.; Fromhold, M. G. *Synlett* **1997**, 523.
(246) Motevalli, M.; O'Brien, P.; Robinson, A. J.; Walsh, J. R.; Wyatt, P. B. *J. Organomet. Chem.* **1993**, *461*, 5.
(247) Spieler, J.; Huttenloch, O.; Waldmann, H. *Eur. J. Org. Chem.* **2000**, 391.
(248) (a) Harmata, M.; Rayanil, K.-O.; Barnes, C. L. *Supramol. Chem.* **2006**, *18*, 581. (b) Harmata, M.; Kahraman, M. *Tetrahedron: Asymmetry* **2000**, *11*, 2875.
(249) Rosini, C.; Franzini, L.; Iuliano, A.; Pini, D.; Salvadori, P. *Tetrahedron: Asymmetry* **1991**, *2*, 363.
(250) Vyskočil, S.; Jaracz, S.; Smrčina, M.; Štícha, M.; Hanuš, V.; Polášek, M.; Kočovský, P. *J. Org. Chem.* **1998**, *63*, 7727.
(251) Shi, M.; Wang, C.-J. *Tetrahedron: Asymmetry* **2002**, *13*, 2161.
(252) Cobb, A. J. A.; Marson, C. M. *Tetrahedron: Asymmetry* **2001**, *12*, 1547.
(253) González-Sabín, J.; Gotor, V.; Rebolledo, F. *Tetrahedron: Asymmetry* **2006**, *17*, 449.
(254) (a) Soai, K.; Niwa, S.; Yamada, Y.; Inoue, H. *Tetrahedron Lett.* **1987**, *28*, 4841. (b) Niwa, S.; Soai, K. *J. Chem. Soc., Perkin Trans 1* **1991**, 2717.
(255) Asami, M.; Watanabe, H.; Honda, K.; Inoue, S. *Tetrahedron: Asymmetry* **1998**, *9*, 4165.
(256) Wirth, T. *Tetrahedron Lett.* **1995**, *36*, 7849.
(257) Gibson, C. L.; Fulton, D. A. *Tetrahedron Lett.* **1997**, *38*, 2019.
(258) Masaki, Y.; Oda, H.; Kazuta, K.; Usui, A.; Itoh, A.; Xu, F. *Tetrahedron Lett.* **1992**, *35*, 5089.
(259) Oppolzer, W.; Radinov, R. N. *Tetrahedron Lett.* **1988**, *29*, 5645.
(260) Fennie, M. W.; DiMauro, E. F.; O'Brien, E. M.; Annamalai, V.; Kozlowski, M. C. *Tetrahedron* **2005**, *61*, 6249.
(261) Wang, M. C.; Hou, X.-H.; Xu, C.-L.; Liu, L. T.; Li, G.-L.; Wang, D.-K. *Synthesis* **2005**, 3620.
(262) (a) Braga, A. L.; Alves, E. F.; Silveira, C. C.; Zeni, G.; Appelt, H. R.; Wessjohann, L. A. *Synthesis* **2005**, 588 (b) Gibson, C. L. *Chem. Commun.* **1996**, 645.
(263) Qin, Y.-C.; Liu, L.; Sabat, M.; Pu, L. *Tetrahedron* **2006**, *62*, 9335.
(264) Trost, B. M.; Weiss, A. H.; von Wangelin, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 8.
(265) (a) Alexakis, A.; Mutti, S.; Normant, J.-F. *J. Am. Chem. Soc.* **1991**, *113*, 6332. (b) Alexakis, A.; Frutos, J.-C.; Mangeney, P. *Tetrahedron: Asymmetry* **1993**, *4*, 2427.
(266) Gibson, C. L. *Tetrahedron: Asymmetry* **1996**, *12*, 3357.
(267) de Vries, A. H. M.; Feringa, B. L. *Tetrahedron: Asymmetry* **1997**, *13*, 1377.
(268) de Vries, A. H. M.; Jansen, J. F. G. A.; Feringa, B. L. *Tetrahedron* **1994**, *50*, 4479.
(269) de Vries, A. H. M.; Imbos, R.; Feringa, B. L. *Tetrahedron: Asymmetry* **1997**, *13*, 1467.
(270) Denmark, S. E.; Fuji, J. *Chem. Rev.* **2003**, *103*, 2763.
(271) Sakurai, H. *Synlett* **1989**, 1.
(272) Mukaiyama, T.; Minowa, N.; Oriyama, T.; Narasaka, K. *Chem. Lett.* **1986**, 97.
(273) Kobayashi, S.; Nishio, K. *Tetrahedron Lett.* **1995**, *36*, 6729.
(274) Dai, Z.; Zhu, C.; Yang, M.; Zheng, Y.; Pan, Y. *Tetrahedron: Asymmetry* **2005**, *16*, 605.
(275) (a) North, M. *Tetrahedron: Asymmetry* **2003**, *14*, 147. (b) Gregory, R. J. H. *Chem. Rev.* **1999**, *99*, 3649. (c) Effenberger, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1555. (d) North, M. *Synlett* **1993**, 807.
(276) (a) Berthiaume, D.; Poirier, D. *Tetrahedron* **2000**, *56*, 5995. (b) Poirier, D.; Berthiaume, D.; Boivin, R. P. *Synlett* **1999**, 1423.
(277) Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 6195.
(278) Casa, J.; Nájera, C.; Sansano, J. M.; Saá, J. M. *Org. Lett.* **2002**, *4*, 2589.
(279) (a) Shimizu, M.; Ogawa, T.; Nishi, T. *Tetrahedron Lett.* **2001**, *42*, 5463. (b) Terada, M.; Matsumoto, Y.; Nakamura, Y.; Mikami, K. *Chem. Commun.* **1997**, 281.
(280) Casa, J.; Nájera, C.; Sansano, J. M.; Saá, J. M. *Tetrahedron* **2004**, *60*, 10487.
(281) Qin, Y.-C.; Liu, L.; Pu, L. *Org. Lett.* **2005**, *7*, 2381.
(282) Casa, J.; Baeza, A.; Sansano, J. M.; Nájera, C.; Saá, J. M. *Tetrahedron: Asymmetry* **2003**, *14*, 197.
(283) Baeza, A.; Nájera, C.; Sansano, J. M.; Saá, J. M. *Tetrahedron: Asymmetry* **2005**, *16*, 2385.
(284) Trost, B.; Martínez-Sánchez, S. *Synlett* **2005**, 627.
(285) Kim, Y. B.; Kim, M. K.; Kang, S. H.; Kim, Y. H. *Synlett* **2005**, 1995.
(286) Huang, J.; Liu, X.; Wen, Y.; Qin, B.; Feng, X. *J. Org. Chem.* **2007**, *72*, 204.
(287) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013.
(288) Casa, J.; Nájera, C.; Sansano, J. M.; González, J.; Saá, J. M.; Vega, M. *Tetrahedron: Asymmetry* **2001**, *12*, 699.
(289) Guetté, M.; Guetté, J.-P.; Capillon, J. *Tetrahedron Lett.* **1971**, *30*, 2863.
(290) Guetté, M.; Capillon, J.; Guetté, J.-P. *Tetrahedron* **1973**, *29*, 3659.
(291) Clarke, H. T. *J. Chem. Soc.* **1910**, 416.
(292) Andrés, J. M.; Martín, Y.; Pedrosa, R.; Pérez-Encabo, A. *Tetrahedron* **1997**, *53*, 3787.
(293) Andrés, J. M.; Pedrosa, R.; Pérez-Encabo, A. *Tetrahedron* **2000**, *56*, 1217.
(294) Fujiwara, Y.; Katagiri, T.; Uneyama, K. *Tetrahedron Lett.* **2003**, *44*, 6161.
(295) Ojida, A.; Yamano, T.; Taya, N.; Tasaka, A. *Org. Lett.* **2002**, *4*, 3051.
(296) Kitajima, H.; Katsuki, T. *Synlett* **1997**, 568.
(297) Kitajima, H.; Ito, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 17015.
(298) Bi, Y.; Bailly, L.; Marsais, F.; Levacher, V.; Papamicaël, C.; Dupas, G. *Tetrahedron: Asymmetry* **2004**, *15*, 3703.
(299) (a) Andersen, K. K. *Tetrahedron Lett.* **1962**, *3*, 93. (b) Andersen, K. K.; Gaffield, W.; Papanikolaou, N. E.; Foley, J. W.; Perkins, R. I. *J. Am. Chem. Soc.* **1964**, *86*, 5637. (c) Andersen, K. K. *J. Org. Chem.* **1964**, *29*, 1953.

(300) Nakamura, S.; Tateyama, M.; Sugimoto, H.; Nakagawa, M.; Watanabe, Y.; Shibata, N.; Toru, T. *Chirality* **2005**, *17*, 85.

(301) (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed. Engl.* **2005**, *44*, 4442. (b) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945. (c) Cardeñas, D. J. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 384. (d) Cardeñas, D. J. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3018. (e) Luh, T.-Y.; Leung, M.-K.; Wong, K.-T. *Chem. Rev.* **2000**, *100*, 3187. (f) Shibasaki, M.; Vogl, E. M. *J. Organomet. Chem.* **1999**, *576*, 1. (g) Loiseleur, O.; Hayashi, M.; Keenan, M.; Schmees, N.; Pfaltz, A. *J. Organomet. Chem.* **1999**, *576*, 16. (h) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (i) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(302) Hayashi, T.; Yamamoto, A.; Hojo, M.; Ito, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 495.

(303) Schwink, L.; Knochel, P. *Chem. Eur. J.* **1998**, *4*, 950.

(304) Hayashi, T.; Konishi, M.; Fukushima, M.; Mise, T.; Kagotani, M.; Tajika, M.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 180.

(305) Brown, J. M.; Cooley, N. A. *Chem. Rev.* **1988**, *88*, 1031.

(306) Horibe, H.; Kazuta, K.; Kotoku, M.; Kondo, K.; Okuno, H.; Murakami, Y.; Aoyama, T. *Synlett* **2003**, 2047.

(307) Horibe, H.; Fukuda, H.; Kondo, K.; Okuno, H.; Murakami, Y.; Aoyama, T. *Tetrahedron* **2004**, *60*, 10701.

(308) Saito, S.; Kano, T.; Muto, H.; Nakadai, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 8943.

(309) Portscheller, J. L.; Malinakova, H. C. *Org. Lett.* **2002**, *4*, 3679.

(310) Portscheller, J. L.; Lilley, S. E.; Malinakova, H. C. *Organometallics* **2003**, *22*, 2961.

(311) Lu, G.; Malinakova, H. C. *J. Org. Chem.* **2004**, *69*, 4701.

(312) Lu, G.; Malinakova, H. C. *J. Org. Chem.* **2004**, *69*, 8266.

(313) (a) Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 5374. (b) Tsuji, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 4137. (c) Ohmiya, H.; Tsuji, T.; Yorimitsu, H.; Oshima, K. *Chem. Eur. J.* **2004**, *10*, 5640.

(314) (a) Kharasch, M. S.; Fields, E. K. *J. Am. Chem. Soc.* **1941**, *63*, 2316. (b) Cotton, F. A. *Chem. Rev.* **1955**, *55*, 551. (c) Elsom, L. F.; Hunt, J. D.; McKillop, A. *Organomet. Chem. Rev. A* **1972**, *8*, 135. (d) Cahiez, G.; Avedissian, H. *Tetrahedron Lett.* **1998**, *39*, 6159. (e) Avedissian, H.; Bérillon, L.; Cahiez, G.; Knochel, P. *Tetrahedron Lett.* **1998**, *39*, 6163.

(315) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2006**, *128*, 1886.

(316) Klein, S.; Marek, I.; Poisson, J.-F.; Normant, J.-F. *J. Am. Chem. Soc.* **1995**, *117*, 8853.

(317) Norsikian, S.; Marek, I.; Klein, S.; Poisson, J.-F.; Normant, J.-F. *Chem. Eur. J.* **1999**, *5*, 2055.

(318) Norsikian, S. Ph.D. Dissertation, University of Pierre et Marie Curie, 1999.

(319) Peters, J. G.; Seppi, M.; Fröhlich, R.; Wibbeling, B.; Hoppe, D. *Synthesis* **2002**, 381.

(320) Behrens, K. Dissertation, University of Münster, Germany, 1997.

(321) Mealy, M. J.; Luderer, M. R.; Bailey, W. F.; Sommer, M. B. *J. Org. Chem.* **2004**, *69*, 6042. Carbolithiation using (−)-sparteine as ligand: (a) Bailey, W. F.; Mealy, M. J. *J. Am. Chem. Soc.* **2000**, *122*, 6787. (b) Gil, G. S.; Groth, U. M. *J. Am. Chem. Soc.* **2000**, *122*, 6789.

(322) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977.

(323) Nozaki, H.; Moriuti, S.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1966**, *10*, 5239.

(324) Song, J.-H.; Cho, D.-J.; Jeon, S.-J.; Kim, Y.-H.; Kim, T.-J. *Inorg. Chem.* **1999**, *38*, 893.

(325) Cho, D.-J.; Jeon, S.-J.; Kim, H.-S.; Cho, C.-S.; Shim, S.-C.; Kim, T.-J. *Tetrahedron: Asymmetry* **1999**, *10*, 3833.

(326) Shepperson, I.; Quici, S.; Pozzi, G.; Nicoletti, M.; O'Hagan, D. *Eur. J. Org. Chem.* **2004**, 4545.

(327) Achmatowicz, M.; Szumna, A.; Zieliński, T.; Jurczak, J. *Tetrahedron* **2005**, *61*, 9031.

(328) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905.

(329) Li, Z.; Quan, R. W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5889.

(330) Fehr, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2566.

(331) Kinoshita, T.; Miwa, T. *J. Chem. Soc., Chem. Commun.* **1974**, 181.

(332) (a) Duhamel, L. *C. R. Acad. Sci.* **1976**, *282C*, 125. (b) Duhamel, L.; Plaquevant, J.-C. *Tetrahedron Lett.* **1977**, *26*, 2285. (c) Duhamel, L.; Plaquevant, J.-C. *J. Am. Chem. Soc.* **1978**, *100*, 7415. (d) Duhamel, L.; Plaquevant, J.-C. *Tetrahedron Lett.* **1980**, *29*, 2521.

(333) Vedejs, E.; Lee, N. *J. Am. Chem. Soc.* **1991**, *113*, 5483.

(334) Martin, J.; Lasne, M.-C.; Plaquevant, J.-C.; Duhamel, L. *Tetrahedron Lett.* **1997**, *41*, 7181.

(335) (a) Vedejs, E.; Lee, N.; Sakata, S. T. *J. Am. Chem. Soc.* **1994**, *116*, 2175. (b) Vedejs, E.; Lee, N. *J. Am. Chem. Soc.* **1995**, *117*, 891. (c) Vedejs, E.; Kruger, A. W.; Suna, E. *J. Org. Chem.* **1999**, *64*, 7863. (d) Vedejs, E.; Kruger, A. W.; Lee, N.; Sakata, S. T.; Stec, M.; Suna, E. *J. Am. Chem. Soc.* **2000**, *122*, 4602.

(336) Vedejs, E.; Kruger, A. W. *J. Org. Chem.* **1998**, *63*, 2792.

(337) (a) Bernasconi, C. F.; Ni, J. X. *J. Am. Chem. Soc.* **1993**, *115*, 5060. (b) Bernasconi, C. F.; Ni, J. X. *J. Org. Chem.* **1994**, *59*, 4910.

(338) Fuji, K.; Tanaka, K.; Miyamoto, H. *Tetrahedron: Asymmetry* **1993**, *4*, 247.

(339) Koga, K.; Yasukata, T. *Tetrahedron: Asymmetry* **1993**, *4*, 35.

(340) Koga, K.; Riviere, P. *Tetrahedron Lett.* **1997**, *38*, 7589.

(341) Yamashita, Y.; Emura, Y.; Odashima, K.; Koga, K. *Tetrahedron Lett.* **2000**, *41*, 209.

(342) Eames, J.; Weerasooriya, N. *Tetrahedron Lett.* **2000**, *41*, 521.

(343) Mikami, K.; Yamaoka, M.; Yoshida, A. *Synlett* **1998**, 607.

(344) (a) Namy, J. L.; Girard, P.; Kagan, H. B. *Nouv. J. Chim.* **1977**, *1*, 5. (b) Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693. (c) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135. (d) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307. (e) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371.

(345) Baylis, A. B.; Hillman, M. E. D. German Patent 2155113, 1972; *Chem. Abstr.* **1972**, *77*, 34174q.

(346) For review of the Baylis−Hillman reaction: (a) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653. (b) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001. (c) Langer, P. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3049. (d) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811.

(347) Oishi, T.; Oguri, H.; Hirama, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1241.

(348) Hayashi, Y.; Tamura, T.; Shoji, M. *Adv. Synth. Catal.* **2004**, *346*, 1106.

(349) Tang, H.; Zhao, G.; Zhou, Z.; Zhou, Q.; Tang, C. *Tetrahedron Lett.* **2006**, *47*, 5717.

(350) Ward, D. E.; Lu, W.-L. *J. Am. Chem. Soc.* **1998**, *120*, 1098.

(351) Paterson, I.; McClure, C. K.; Schumann, R. C. *Tetrahedron Lett.* **1989**, *30*, 1293.

(352) Masamune, S.; Choy, W.; Pedersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

(353) Bambridge, K.; Clark, B. P.; Simpkins, N. S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2535.

(354) Allway, P.; Grigg, R. *Tetrahedron Lett.* **1991**, *32*, 5817.

(355) Pelz, K. A.; White, P. S.; Gagné, M. R. *Organometallics* **2004**, *23*, 3210.

(356) Saunders, M.; Yamada, F. *J. Am. Chem. Soc.* **1963**, *85*, 1882.

(357) Alexakis, A.; Mangeney, P.; Lensen, N.; Tranchier, J.-P.; Gosmini, R.; Raussou, S. *Pure Appl. Chem.* **1996**, *68*, 531.

(358) Lautens, M.; Gajda, C.; Chiu, P. *J. Chem. Soc., Chem. Commun.* **1993**, 1193.

(359) Lautens, M.; Renaud, J.-L.; Hiebert, S. *J. Am. Chem. Soc.* **2000**, *122*, 1804.

(360) Lautens, M.; Fagnou, K.; Rovis, T. *J. Am. Chem. Soc.* **2000**, *122*, 5650.

(361) Lautens, M.; Fagnou, K. *J. Am. Chem. Soc.* **2001**, *123*, 7170.

(362) Lautens, M.; Fagnou, K. *Tetrahedron* **2001**, *57*, 5067.

(363) Lautens, M.; Fagnou, K.; Zunic, V. *Org. Lett.* **2002**, *4*, 3465.

(364) (a) Cho, Y.-H.; Zunic, V.; Senboku, H.; Olsen, M.; Lautens, M. *J. Am. Chem. Soc.* **2006**, *128*, 6837. (b) Cho, Y.-H.; Fayol, A.; Lautens, M. *Tetrahedron: Asymmetry* **2006**, *17*, 416.

(365) Pasteur, M. L. *C. R. Hebd. Seances Acad. Sci.* **1858**, *46*, 615.

(366) Marckwald, W.; McKenzie, A. *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 2130.

(367) For previous general reviews on kinetic resolution using nonenzymatic catalysts, see: (a) Vedejs, E.; Jure, M.; *Angew. Chem., Int. Ed. Engl.* **2005**, *44*, 3974. (b) Robinson, D. E. J. E.; Bull, S. D. *Tetrahedron: Asymmetry* **2003**, *14*, 1407. (c) Keith, M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5. (d) Cook, G. R. *Curr. Org. Chem.* **2000**, *4*, 869. (e) Hoveyda, A. H.; Didiuk, M. T. *Curr. Org. Chem.* **1998**, *2*, 489. (f) Drueckhammer, D. G.; Hennen, W. J.; Pederson, R. L.; Barbas, C. F., III; Gautheron, C. M.; Krach, T.; Wong, C.-H. *Synthesis* **1991**, 499. (g) Klibanov, A. M. *Acc. Chem. Res.* **1990**, *23*, 114. (h) Chen, C.-S.; Sih, C. J. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 695. (i) Whitesides, G. M.; Wong, C.-H. *Angew. Chem., Int. Ed.* Engl. **1985**, *24*, 617. For an introduction into the principles of kinetic resolution for asymmetric synthesis, see: (a) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249. (b) Kagan, H. B. *Tetrahedron* **2001**, *57*, 2449. (c) Faber, K. *Chem. Eur. J.* **2001**, *7*, 5005. For a treatise on the principles and application of dynamic kinetic resolution for stereoselective synthesis, see: (a) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36. (b) Ward, R. S. *Tetrahedron: Asymmetry* **1995**, *6*, 1475.

(368) (a) Mukaiyama, T.; Ichikawa, J.; Asami, M. *Chem. Lett.* **1983**, 293. (b) Ichikawa, J.; Asami, M.; Mukaiyama, T. *Chem. Lett.* **1984**, 949.

(369) Duhamel, L.; Herman, T. *Tetrahedron Lett.* **1985**, *26*, 3099.

(370) Oriyama, T.; Hori, Y.; Imai, K.; Sasaki, R. *Tetrahedron Lett.* **1996**, *37*, 8543.
(371) Oriyama, T.; Imai, K.; Hosoya, T.; Sano, T. *Tetrahedron Lett.* **1998**, *39*, 397.
(372) Oriyama, T.; Imai, K.; Sano, T.; Hosoya, T. *Tetrahedron Lett.* **1998**, *39*, 3529.
(373) Sano, T.; Imai, K.; Ohashi, K.; Oriyama, T. *Chem. Lett.* **1999**, 265.
(374) (a) Sano, T.; Miyata, H.; Oriyama, T. *Enantiomers* **2000**, *5*, 119. (b) Oriyama, T.; Taguchi, H.; Terakado, D.; Sano, T. *Chem. Lett.* **2002**, 26.
(375) Terakado, D.; Koutaka, H.; Oriyama, T. *Tetrahedron: Asymmetry* **2005**, *16*, 1157.
(376) Clapham, B.; Cho, C.-W.; Janda, K. D. *J. Org. Chem.* **2001**, *66*, 868.
(377) Trost, B. M.; Mino, T. *J. Am. Chem. Soc.* **2003**, *125*, 2410.
(378) Hu, G.; Vasella, A. *Helv. Chim. Acta* **2003**, *86*, 4369.
(379) Kündig, P.; Lombergert, T.; Bragg, R.; Poulard, C.; Bernardinelli, G. *Chem. Commun.* **2004**, 1548.
(380) Nakamura, D.; Kakiuchi, K.; Koga, K.; Shirai, R. *Org. Lett.* **2006**, *8*, 6139.
(381) Nozaki, H.; Aratani, T.; Noyori, R. *Tetrahedron Lett.* **1968**, *17*, 2087.
(382) (a) Skattebøl, L. *Acta Chem. Scand.* **1963**, *17*, 1683. (b) Moore, W. R.; Ward, H. R. *J. Org. Chem.* **1962**, *27*, 4179.
(383) Nishibayashi, Y.; Singh, J. D.; Uemura, S. *Tetrahedron Lett.* **1994**, *35*, 3115.
(384) Overman, L. E. *J. Am. Chem. Soc.* **1974**, *96*, 597.
(385) Calter, M.; Hollis, T. K.; Overman, L. E.; Ziller, J.; Zipp, G. G. *J. Org. Chem.* **1997**, *62*, 1449.
(386) Brunner, H.; Kagan, H. B.; Kreutzer, G. *Tetrahedron: Asymmetry* **2003**, *14*, 2177.
(387) Honzl, J.; Lövy, J. *Tetrahedron* **1984**, *40*, 1885.
(388) O'Shaughnessy, P. N.; Knight, P. D.; Morton, C.; Gillepsie, K. M.; Scott, P. *Chem. Commun.* **2003**, 1770.
(389) Knight, P.; Munslow, I.; O'Shaughnessy, P. N.; Scott, P. *Chem. Commun.* **2004**, 894.
(390) Kim, J. Y.; Livinghouse, T. *Org. Lett.* **2005**, *7*, 1737.
(391) For reviews on aldolization reactions: (a) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095. (b) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357. (c) Csáky, A. G.; Plumet, J. *Chem. Soc. Rev.* **2001**, *30*, 313. (d) Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Eur. J.* **2002**, *8*, 37.
(392) Batchelor, R. J.; Ruddick, J. N. R.; Sams, J. R.; Aubke, F. *Inorg. Chem.* **1977**, *16*, 1414.
(393) Mukaiyama, T.; Stevens, R. W.; Iwasawa, N. *Chem. Lett.* **1982**, 353.
(394) Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1982**, 1441.
(395) Mukaiyama, T.; Iwasawa, N.; Stevens, R. W.; Haga, T. *Tetrahedron* **1984**, *40*, 1381.
(396) Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1983**, 297.
(397) Stevens, R. W.; Mukaiyama, T. *Chem. Lett.* **1983**, 1799.
(398) Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1984**, 753.
(399) Kobayashi, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 297.
(400) Mukaiyama, T.; Kobayashi, S. *J. Organomet. Chem.* **1990**, *382*, 39.
(401) Mukaiyama, T.; Uchiro, H.; Kobayashi, S. *Chem. Lett.* **1989**, 1757.
(402) Mukaiyama, T.; Uchiro, H.; Kobayashi, S. *Chem. Lett.* **1989**, 1001.
(403) Kobayashi, S.; Uchiro, H.; Fujishita, Y.; Shiina, I.; Mukaiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 4247.
(404) Kobayashi, S.; Horibe, M. *J. Am. Chem. Soc.* **1994**, *116*, 9805.
(405) Kobayashi, S.; Horibe, M. *Tetrahedron: Asymmetry* **1995**, *6*, 2565.
(406) (a) Kobayashi, S.; Sano, T.; Mukaiyama, T. *Chem. Lett.* **1989**, 1319. (b) Mukaiyama, T.; Kobayashi, S.; Sano, T. *Tetrahedron* **1990**, *46*, 4653.
(407) (a) Yura, T.; Iwasawa, N.; Narasaka, K.; Mukaiyama, T. *Chem. Lett.* **1988**, 1025. (b) Iwasawa, N.; Yura, T.; Mukaiyama, T. *Tetrahedron* **1989**, *45*, 1197.
(408) Mukaiyama, T.; Kobayashi, S.; Uchiro, H.; Shiina, I. *Chem. Lett.* **1990**, 129.
(409) Kobayashi, S.; Fujishita, Y.; Mukaiyama, T. *Chem. Lett.* **1990**, 1455.
(410) (a) Kobayashi, S.; Furuya, M.; Ohtsubo, A.; Mukaiyama, T. *Tetrahedron: Asymmetry* **1991**, *2*, 635. (b) Kobayashi, S.; Uchiro, H.; Shiina, I.; Mukaiyama, T. *Tetrahedron* **1993**, *49*, 1761.
(411) Mukaiyama, T.; Uchiro, H.; Kobayashi, S. *Chem. Lett.* **1990**, 1147.
(412) Kobayashi, S.; Kawasuji, T.; Mori, N. *Chem. Lett.* **1994**, 217.
(413) Hansen, M. M.; Bartlett, P. A.; Heathcock, C. H. *Organometallics* **1987**, *6*, 2069.
(414) (a) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405. (b) Ito, Y.; Sawamura, M.; Hayashi, T. *Tetrahedron Lett.* **1987**, *28*, 6215.
(415) Sawamura, M.; Ito, Y.; Hayashi, T. *Tetrahedron Lett.* **1989**, *30*, 2247.
(416) Ito, Y.; Sawamura, M.; Hamashima, H.; Emura, T.; Hayashi, T. *Tetrahedron Lett.* **1989**, *30*, 4681.
(417) Togni, A.; Pastor, S. D. *J. Org. Chem.* **1990**, *55*, 1649.
(418) Muraoka, M.; Kawasaki, H.; Koga, K. *Tetrahedron Lett.* **1988**, *29*, 337.
(419) (a) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1871. (b) Yamada, Y. M. A.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 5561. (c) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168. (d) Shibasaki, M.; Sasai, H. *Top. Stereochem.* **1999**, *22*, 201. (e) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395. (f) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (g) Agami, C.; Platzer, N.; Sevestre, H. *Bull. Soc. Chim. Fr.* **1987**, 358.
(420) (a) Nakadai, M.; Saito, S.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8167. (b) Alexakis, A.; Andrey, O. *Org. Lett.* **2002**, *4*, 3611. (c) Andrey, O.; Alexakis, A.; Bernardinelli, G. *Org. Lett.* **2003**, *5*, 2559.
(421) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003.
(422) Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367.
(423) Trost, B. M.; Fettes, A.; Shireman, B. T. *J. Am. Chem. Soc.* **2004**, *126*, 2660.
(424) Trost, B. M.; Shin, S.; Sclafani, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 8602.
(425) Trost, B. M.; Silcoff, E. R.; Ito, H. *Org. Lett.* **2001**, *3*, 2497.
(426) (a) Trost, B. M.; Yeh, V. S. C. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 861. (b) Trost, B. M.; Yeh, V. S. C.; Ito, H.; Bremeyer, N. *Org. Lett.* **2002**, *4*, 2621. (c) Trost, B. M.; Terrell, L. R. *J. Am. Chem. Soc.* **2003**, *125*, 338. (d) Trost, B. M.; Hisaindee, S. *Org. Lett.* **2006**, *8*, 6003.
(427) Maheswaran, H.; Prasanth, K. L.; Krishna, G. G.; Ravikumar, K.; Sridhar, B.; Kantam, M. L. *Chem. Commun.* **2006**, 4066.
(428) Calter, M. A.; Orr, R. K. *Tetrahedron Lett.* **2003**, *44*, 5699.
(429) Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360.
(430) Huang, Y.; Yang, F.; Zhu, C. *J. Am. Chem. Soc.* **2005**, *127*, 16386.
(431) (a) Parker, D. *Chem. Rev.* **1991**, *91*, 1441. (b) Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17.
(432) Seco, J. M.; Quiñoá, E.; Riguera, R. *Tetrahedron: Asymmetry* **2001**, *12*, 2915.
(433) Hulst, R.; Kellogg, R. M.; Feringa, B. L. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 115.
(434) Finn, M. G. *Chirality* **2002**, *14*, 534.
(435) (a) Horeau, A. *Tetrahedron Lett.* **1969**, *9*, 3121. (b) Horeau, A.; Guette, J.-P. *Tetrahedron* **1974**, *30*, 1923.
(436) Benson, S. C.; Cai, P.; Colon, M.; Haiza, M. A.; Tokles, M.; Snyder, J. K. *J. Org. Chem.* **1988**, *53*, 5335.
(437) (a) Alexakis, A.; Frutos, J. C.; Mutti, S.; Mangeney, P. *J. Org. Chem.* **1994**, *59*, 3326. (b) Alexakis, A.; Mutti, S.; Mangeney, P.; Normant, J. F. *Tetrahedron: Asymmetry* **1990**, *1*, 437. (c) Alexakis, A.; Mutti, S.; Mangeney, P. *J. Org. Chem.* **1992**, *57*, 1224. (d) Cuvinot, D.; Mangeney, P.; Alexakis, A.; Normant, J. F.; Lellouche, J.-P. *J. Org. Chem.* **1989**, *54*, 2420. (e) Alexakis, A.; Frutos, J. C.; Mangeney, P. *Tetrahedron Lett.* **1994**, *35*, 5125. (f) Alexakis, A.; Chauvin, A.-S.; Stouvenel, R.; Vrancken, E.; Mutti, S.; Mangeney, P. *Tetrahedron: Asymmetry* **2001**, *12*, 1171. (g) Chauvin, A.-S.; Bernardinelli, G.; Alexakis, A. *Tetrahedron: Asymmetry* **2004**, *15*, 1857. (h) Anaya de Parrodi, C.; Moreno, G. E.; Quintero, L.; Juaristi, E. *Tetrahedron: Asymmetry* **1998**, *9*, 2093.
(438) (a) Kabotu, K.; Sasaki, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 316. (b) Kabotu, K.; Sasaki, Y. *J. Chem. Soc., Chem. Commun.* **1987**, 670. (c) Kabotu, K.; Sasaki, Y. *Tetrahedron Lett.* **1990**, *31*, 1031.
(439) Kabotu, K.; Sasaki, Y. *Chem. Lett.* **1989**, 385.
(440) Kabuto, K.; Sasaki, K.; Sasaki, Y. *Tetrahedron: Asymmetry* **1992**, *3*, 1357.
(441) Hazama, R.; Umakoshi, K.; Kabuto, C.; Kabuto, K.; Sasaki, Y. *Chem. Commun.* **1996**, 15.
(442) Kabuto, C.; Kabuto, K.; Sasaki, Y.; Nishiyama, T.; Umakoshi, K. *J. Chem. Soc., Chem. Commun.* **1993**, 381.
(443) Inamoto, A.; Ogasawara, K.; Omata, K.; Kabuto, K.; Sasaki, Y. *Org. Lett.* **2000**, *2*, 3543.
(444) Bal, D.; Gradowska, W.; Gryff-Keller, A. *J. Pharm. Biomed. Anal.* **2002**, *28*, 1061.
(445) Kido, J.; Okamoto, Y.; Brittain, H. G. *J. Org. Chem.* **1991**, *56*, 1412.
(446) Hulst, R.; de Vries, N. K.; Feringa, B. L. *J. Org. Chem.* **1994**, *59*, 7453.
(447) Resch, J. F.; Meinwald, J. *Tetrahedron Lett.* **1981**, *22*, 3159.
(448) Zhang, X. X.; Bradshaw, J. S.; Izatt, R. M. *Chem. Rev.* **1997**, *97*, 3313 and references cited herein.
(449) (a) Demirel, N.; Bulut, Y. *Tetrahedron: Asymmetry* **2003**, *14*, 2633. (b) Miyahara, Y.; Izumi, K.; Ibrahim, A. A.; Inazu, T. *Tetrahedron Lett.* **1999**, *40*, 1705. (c) Schultz, A. G.; Pinto, D. J. P.; Welch, M. *J. Org. Chem.* **1988**, *53*, 1372. (d) Cowart, M. D.; Sucholeiki, I.; Bukownik, R. R.; Wilcox, C. S. *J. Am. Chem. Soc.* **1988**, *110*, 6204.
(450) Zhao, J.; Davidson, M. G.; Mahon, M. F.; Kociok-Köhn, G.; James, T. D. *J. Am. Chem. Soc.* **2004**, *126*, 16179.
(451) Pu, L. *Chem. Rev.* **2004**, *104*, 1687.
(452) Kim, W.; So, S. M.; Chagal, L.; Lough, A. L.; Kim, B. M.; Chin, J. *J. Org. Chem.* **2006**, *71*, 8966.

(453) (a) Farina, M.; Peraldo, M.; Natta, G. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 107. (b) Wulff, G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 21. (c) Nolte, R. J. M. *Chem. Soc. Rev.* **1994**, 11. (d) McGrath, M. P.; Sal, E. D.; Tremont, S. J. *Chem. Rev.* **1995**, *95*, 381. (e) Britovsek, G. J. P.; Gibson, V. C.; Wass, D. F. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 428. (f) Coates, G. W.; Hustad, P. D.; Reinartz, S. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 2236. (g) Gibson, V. C.; Spitzmesser, S. K. *Chem. Rev.* **2003**, *103*, 283.

(454) Okamoto, Y.; Nakano, T. *Chem. Rev.* **1994**, *94*, 349.

(455) (a) Johnson, R. M.; Ng, C.; Samson, C. C. M.; Fraser, C. L. *Macromolecules* **2000**, *33*, 8618. (b) Carpentier, J.-F.; Martin, A.; Swenson, D. C.; Jordan, R. F. *Organometallics* **2003**, *22*, 4999. (c) Ng, C.; Sabat, M.; Fraser, C. L. *Inorg. Chem.* **1999**, *38*, 5545.

(456) (a) Fenton, R. R.; Stephens, F. S.; Vagg, R. S.; Williams, P. A. *Inorg. Chim. Acta* **1995**, *236*, 109. (b) Bernauer, K.; Stoeckli-Evans, H.; Hugi-Cleary, D.; Hilgers, H. J.; Abd-el-Khalek, H.; Porret, J.; Sauvain, J.-J. *Helv. Chim. Acta* **1992**, *75*, 2327.

(457) (a) Kim, B.-J.; Lee, Y.-M.; Kim, E. H.; Kang, S. K.; Choi, S.-N. *Acta Crystallogr.* **2002**, *C58*, m361. (b) Bernauer, K.; Chuard, T.; Stoeckli-Evans, H. *Helv. Chim. Acta* **1993**, *76*, 2263. (c) Stack, T. D. P. *Dalton Trans.* **2003**, 1881. (d) Mahadevan, V.; Hou, Z.; Cole, A. P.; Root, D. E.; Lal, T. K.; Solomon, E. I.; Stack, T. D. P. *J. Am. Chem. Soc.* **1997**, *119*, 11996.

(458) Park, W.; Shin, M. H.; Chung, J. H.; Park, J.; Lah, M. S.; Lim, D. *Tetrahedron Lett.* **2006**, *47*, 8841.

(459) Chooi, S. Y. M.; Leung, P.-H.; Lim, C. C.; Mok, K. F.; Quek, G. H.; Sim, K. Y.; Tan, M. K. *Tetrahedron: Asymmetry* **1992**, *3*, 529. (b) Alvey, L. J.; Delacroix, O.; Wallner, C.; Meyer, O.; Hampel, F.; Szafert, S.; Lis, T.; Gladysz, J. A. *Organometallics* **2001**, *20*, 3087. (c) Karshtedt, D.; Bell, A. T.; Tilley, T. D. *Organometallics* **2003**, *22*, 2855.

(460) Van de Kuil, L. A.; Veldhuizen, Y. S. J.; Grove, D. M.; Zwikker, J. W.; Jenneskens, L. W.; Drenth, W.; Smeets, W. J. J.; Spek, A. L.; Van Koten, G. *J. Organomet. Chem.* **1995**, *488*, 191.

(461) Balsells, J.; Carroll, P. J.; Walsh, P. J. *Inorg. Chem.* **2001**, *40*, 5568.

(462) (a) Pittet, P.-A.; Früh, D.; Tissières, V.; Bünzli, J.-C. G. *J. Chem. Soc., Dalton Trans.* **1997**, 895. (b) Chin, K. O. A.; Morrow, J. R.; Lake, C. H.; Churchill, M. R. *Inorg. Chem.* **1994**, *33*, 656. (c) Williams, M. A.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 1151. (d) Forsberg, J. H.; Delaney, R. M.; Zhao, Q.; Harakas, G.; Chandran, R. *Inorg. Chem.* **1995**, *34*, 3705. (e) Di Bari, L.; Pintacuda, G.; Salvadori, P. *Eur. J. Inorg. Chem.* **2000**, 75. (f) Di Bari, L.; Pintacuda, G.; Salvadori, P. *J. Am. Chem. Soc.* **2000**, *122*, 5557. (g) Loussouarn, A.; Duflos, M.; Benoist, E.; Chatal, J.-F.; Le Baut, G.; Gestin, J.-F. *J. Chem. Soc., Perkin Trans. 1* **1998**, 237.

(463) Miyake, H.; Yoshida, K.; Sugimoto, H.; Tsukube, H. *J. Am. Chem. Soc.* **2004**, *126*, 6524.

(464) Knof, U.; von Zelewsky, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 303.

(465) Schleyer, P. v. R. *Pure Appl. Chem.* **1984**, *56*, 151.

(466) Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448.

(467) Hope, H.; Power, P. P. *J. Am. Chem. Soc.* **1983**, *105*, 5321.

(468) (a) Thoennes, D.; Weiss, E. *Chem. Ber.* **1978**, *111*, 3157. (b) Jackman, L. M.; Scarmoutzos, L. M. *J. Am. Chem. Soc.* **1984**, *106*, 4627. (c) Reich, H. J.; Green, D. P.; Medina, M. A.; Goldenberg, W. S.; Gudumndsson, B. Ö.; Dykstra, R. R.; Phillips, N. H. *J. Am. Chem. Soc.* **1998**, *120*, 7201.

(469) Bauer, W.; Winchester, W. R.; Schleyer, P. v. R. *Organometallics* **1987**, *6*, 2371.

(470) Dinnebier, R. E.; Behrens, U.; Olbrich, F. *J. Am. Chem. Soc.* **1998**, *120*, 1430.

(471) (a) Lewis, H. L.; Brown, T. L. *J. Am. Chem. Soc.* **1970**, *92*, 4664. (b) Nichols, M. A.; Willard, P. G. *J. Am. Chem. Soc.* **1993**, *115*, 1568. (c) Waldmüller, D.; Kotsatos, B. J.; Nichols, M. A.; Willard, P. G. *J. Am. Chem. Soc.* **1997**, *119*, 5479.

(472) Okamoto, Y.; Takeda, T.; Hatada, K. *Chem. Lett.* **1984**, 757.

(473) (a) Fraenkel, G.; Fraenkel, A. M.; Geckle, M. J.; Schloss, F. *J. Am. Chem. Soc.* **1979**, *101*, 4745. (b) Fraenkel, G.; Henrichs, M.; Hewitt, J. M.; Su, B. M.; Geckle, M. J. *J. Am. Chem. Soc.* **1980**, *102*, 3345.

(474) Bauer, W. *J. Am. Chem. Soc.* **1996**, *118*, 5450.

(475) Kaufmann, E.; Raghavachari, K.; Reed, K.; Schleyer, P. v. R. *Organometallics* **1988**, *7*, 1597.

(476) Streitwieser, A.; Williams, J. E.; Alexandratos, S.; McKelvey, J. M. *J. Am. Chem. Soc.* **1976**, *98*, 4778.

(477) (a) Strohmann, C.; Seibel, T.; Strohfeldt, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 4531. (b) Strohmann, C.; Strohfeldt, K.; Schildbach, D. *J. Am. Chem. Soc.* **2003**, *125*, 13672. (c) Vestergren, M.; Eriksson, J.; Hilmersson, G.; Hakansson, M. *J. Organomet. Chem.* **2003**, *682*, 172. (d) Strohmann, C.; Däschlein, C.; Auer, D. *J. Am. Chem. Soc.* **2006**, *128*, 704.

(478) Strohmann, C.; Dilsky, S.; Strohfeldt, K. *Organometallics* **2006**, *25*, 41.

(479) Strohmann, C.; Strohfeldt, K.; Schildbach, D.; McGrath, M. J.; O'Brien, P. *Organometallics* **2004**, *23*, 5389.

(480) Rutherford, J. L.; Hoffmann, D.; Collum, D. B. *J. Am. Chem. Soc.* **2002**, *124*, 264.

(481) Qu, B.; Collum, D. B. *J. Am. Chem. Soc.* **2006**, *128*, 9355.

(482) Fraenkel, G.; Appleman, B.; Ray, J. G. *J. Am. Chem. Soc.* **1974**, *96*, 5113.

(483) (a) Lucht, B. L.; Collum, D. B. *Acc. Chem. Res.* **1999**, *32*, 1035. (b) Lucht, B. L.; Bernstein, M. P.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1996**, *118*, 10707.

(484) Martínez, A. G.; Vilar, E. T.; Fraile, A. G.; Martínez-Ruiza, P. *Tetrahedron: Asymmetry* **2001**, *12*, 2153.

(485) Caselli, A.; Giovenzana, G. B.; Palmisano, G.; Sisti, M.; Pilati, T. *Tetrahedron: Asymmetry* **2003**, *14*, 1451.

(486) (a) Berkessel, A.; Schröder, M.; Sklorz, C. A.; Tabanella, S.; Vogl, N.; Lex, J.; Neudörfl, J. *J. Org. Chem.* **2004**, *69*, 3050. (b) Berkessel, A.; Menche, D.; Sklorz, C. A.; Schröder, M.; Paterson, I. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 1032.

(487) Tanyeli, C.; Özçubukçu, S. *Tetrahedron: Asymmetry* **2003**, *14*, 1167.

(488) Busacca, C. A.; Campbell, S.; Dong, Y.; Grossbach, D.; Ridges, M.; Smith, L.; Spinelli, E. *J. Org. Chem.* **2000**, *65*, 4753.

(489) Morán-Ramallal, R.; Liz, R.; Gotor, V. *Org. Lett.* **2007**, *9*, 521.

(490) (a) Shi, M.; Jiang, J.-K.; Shen, Y.-M.; Feng, Y.-S. *J. Chem. Res.* **2001**, *9*, 375. (b) Marinetti, A.; Hubert, P.; Genêt, J.-P. *Eur. J. Org. Chem.* **2000**, 1815. (c) Couty, F.; Evano, G.; Prim, D.; Marrot, J. *Eur. J. Org. Chem.* **2004**, 3893. (d) Mlostoń, G.; Celeda, M. *Helv. Chim. Acta* **2005**, *88*, 1658. (e) Couty, F.; Evano, G.; Prim, D. *Mini-Rev. Org. Chem.* **2004**, *1*, 133.

(491) Bailey, D. J.; O'Hagan, D.; Tavasli, M. *Tetrahedron: Asymmetry* **1997**, *8*, 149.

(492) Pettersen, D.; Ahlberg, P. *Tetrahedron: Asymmetry* **2005**, *16*, 2075.

(493) Eilers, J.; Wilken, J.; Martens, J. *Tetrahedron: Asymmetry* **1996**, *7*, 2343.

(494) Marson, C. M.; Melling, R. C. *Synthesis* **2006**, 247.

(495) Greco, J. F.; McNevin, M. J.; Hagadorn, J. R. *Organometallics* **2005**, *24*, 5167.

(496) Elliott, M. C.; Williams, E.; Howard, S. T. *J. Chem. Soc., Perkin Trans. 2* **2002**, 201.

(497) Baskakov, D.; Herrmann, W. A.; Herdtweck, E.; Hoffmann, S. D. *Organometallics* **2007**, *26*, 626.

(498) (a) Daly, A. M.; Gilheany, D. G. *Tetrahedron: Asymmetry* **2003**, *14*, 127. (b) Zhao, D.; Wang, Z.; Ding, K. *Synlett* **2005**, 2067.

(499) Bit, C.; Mitrochkine, A. A.; Gil, G.; Pierrot, M.; Réglier, M. *Tetrahedron: Asymmetry* **1998**, *9*, 3263.

(500) (a) Padmaja, M.; Periasamy, M. *Tetrahedron: Asymmetry* **2004**, *15*, 2437. (b) Arjan, H.; Boyd, E.; Coumbarides, G. S.; Eames, J.; Jones, R. V. H.; Stenson, R. A.; Suggate, M. J. *Tetrahedron Lett.* **2005**, *46*, 1921. (c) Boyd, E.; Coumbarides, G. S.; Eames, J.; Jones, R. V. H.; Motevalli, M.; Stenson, R. A.; Suggate, M. J. *Tetrahedron Lett.* **2005**, *46*, 3473.

(501) (a) Boga, C.; Fiorelli, C.; Savoia, D. *Synthesis* **2006**, 285. (b) Alvaro, G.; Grilli, S.; Martelli, G.; Savoia, D. *Eur. J. Org. Chem.* **1999**, 1523. (c) Donohoe, T. J.; Mitchell, L.; Waring, M. J.; Helliwell, M.; Bell, A.; Newcombe, N. J. *Org. Biomol. Chem.* **2003**, *1*, 2173.

(502) Orsini, F.; Sello, G.; Bestetti, G. *Tetrahedron: Asymmetry* **2001**, *12*, 2961.

(503) Annunziata, R.; Benaglia, M.; Caporale, M.; Raimondi, L. *Tetrahedron: Asymmetry* **2002**, *13*, 2727.

(504) Groaz, E.; Banti, D.; North, M. *Tetrahedron Lett.* **2007**, *48*, 1927.

(505) (a) Marr, G.; Moore, R. E.; Rockett, B. W. *Tetrahedron* **1969**, *25*, 3477. (b) Anderson, J. C.; Blake, A. J.; Arnall-Culliford, J. C. *Org. Biomol. Chem.* **2003**, *1*, 3586. (c) Spescha, M.; Duffy, N. W.; Robinson, B. H.; Simpson, J. *Organometallics* **1994**, *13*, 4895.

(506) (a) Molander, G. A.; Schumann, H.; Rosenthal, E. C. E.; Demtschuk, J. *Organometallics* **1996**, *15*, 3817. (b) Schumann, H.; Rosenthal, E. C. E.; Demtschuk, J.; Molander, G. A. *Organometallics* **1998**, *17*, 5324.

(507) Blank, N. F.; Glueck, D. S.; Zakharov, L. N.; Rheingold, A. L.; Saybolt, M. D.; Ghent, B. L.; Nataro, C. *Organometallics* **2005**, *24*, 5184.

(508) (a) Dieter, R. K.; Lagu, B.; Dieter, J. W.; Deo, N.; Pennington, W. T. *Synlett* **1990**, 109. (b) Dieter, R. K.; Deo, N.; Lagu, B.; Dieter, J. W. *J. Org. Chem.* **1992**, *57*, 1663.

(509) (a) O'Brien, P.; Poumellec, P. *Tetrahedron Lett.* **1996**, *37*, 5619. (b) de Sousa, S. E.; O'Brien, P. *Tetrahedron Lett.* **1997**, *38*, 4885. (c) O'Brien, P.; Osborne, S. A.; Parker, D. D. *Tetrahedron Lett.* **1998**, *39*, 4099.

(510) (a) Saravanan, P.; Bisai, A.; Baktharaman, S.; Chandrasekhar, M.; Singh, V. K. *Tetrahedron* **2002**, *58*, 4693. (b) Saravanan, P.; Singh, V. K. *Tetrahedron Lett.* **1998**, *39*, 167.

(511) Seebach, D.; Hayakawa, M.; Sakaki, J.; Schweizer, W. B. *Tetrahedron* **1993**, *49*, 1711.

(512) (a) Stará, I. G.; Starý, I.; Závada, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1365. (b) Stará, I. G.; Starý, I.; Závada, J. *J. Org. Chem.* **1992**,

57, 6966. (c) Stará, I. G.; Starý, I.; Tichý, M.; Závada, J.; Fiedler, P. *J. Org. Chem.* **1994**, *59*, 1326.
(513) Vachon, J.; Rentsch, S.; Martinez, A.; Marsol, C.; Lacour, J. *Org. Biomol. Chem.* **2007**, *5*, 501.
(514) (a) Cyano-ethoxycarbonylation: Gou, S.; Liu, X.; Zhou, X.; Feng, X. *Tetrahedron* **2007**, *63*, 7935. (b) Cyanosilylation: Qin, B.; Liu, X.; Shi, J.; Zheng, K.; Zhao, H.; Feng, X. *J. Org. Chem.* **2007**, *72*, 2374. (c) Henry reaction: Arai, T.; Watanabe, M.; Fujiwara, A.; Yokoyama, N.; Yanagisawa, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 5978. (d) Arai, T.; Watanabe, M.; Yanagisawa, A. *Org. Lett.* **2007**, *9*, 3595. (e) Cyclopropanation: Lesma, G.; Cattenati, C.; Pilati, T.; Sacchetti, A.; Silvani, A. *Tetrahedron: Asymmetry* **2007**, *18*, 659. (f) Phenylation of aldehydes: Bastero, A.; Font, D.; Pericàs, M. A. *J. Org. Chem.* **2007**, *72*, 2460. (g) Enolization using LiHMDS/diamine: Godenschwager, P. F.; Collum, D. B. *J. Am. Chem. Soc.* **2007**, *129*, 12023. (h) Crystal structure of RLi/(*R*,*R*)-**7** complexes: Strohmann, C.; Gessner, V. H. *J. Am. Chem. Soc.* **2007**, *129*, 8952. (i) Alkane oxidation: England, J.; Britovsek, G. J. P.; Rabadia, N.; White, A. J. P. *Inorg. Chem.* **2007**, *46*, 3752. (j) Brönsted basicity of diamine: Rõõm, E.-I.; Kütt, A.; Kaljurand, I.; Koppel, I.; Leito, I.; Koppel, I. A.; Mishima, M.; Goto, K.; Miyahara, Y. *Chem. Eur. J.* **2007**, *13*, 7631. (k) Ketone hydrogenation: Shen, W.-Y.; Zhang, H.; Zhang, H.-L.; Gao, J.-X. *Tetrahedron: Asymmetry* **2007**, *18*, 729. (l) Ru- and Fe-based diamine complexes: Soundiressane, T.; Selvakumar, S.; Ménage, S.; Hamelin, O.; Fontecave, M.; Singh, A. P. *J. Mol. Catal. A: Chem.* **2007**, *270*, 132. (m) Hydroamination: Heck, R.; Schulz, E.; Collin, J.; Carpentier, J.-F. *J. Mol. Catal. A: Chem.* **2007**, *268*, 163. (n) Chiral shift reagent: Peña, C.; González-Sabín, J.; Alfonso, I.; Rebolledoa, F.; Gotora, V. *Tetrahedron: Asymmetry* **2007**, *18*, 1735.

CR040107V