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Studies on the Bisoxazoline and (–)-Sparteine Mediated Enantioselective Addition of Organolithium Reagents to Imines

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Abstract

The enantioselective addition of organolithium reagents to *N*-anisyl aldimines promoted by chiral bisoxazolines and (–)-sparteine as external ligands is described. This reaction proceeds readily with a wide range of aldimine substrates (aliphatic, aromatic, olefinic) and organolithium nucleophiles (Me, *n*-Bu, Ph, vinyl) in excellent yields (81–99%) and with high enantioselectivities (up to 95.5:4.5 er). The external ligands can be used in substoichiometric amounts albeit with slightly attenuated enantioselectivities. A systematic evaluation of the structural features of the bisoxazolines revealed a primary contribution from the substituent at C(4) and a secondary influence from the bridging substituents. A computational analysis (PM3) provided a clear rationalization for the origin of enantioselectivity.

Keywords

organolithium; bisoxazoline; enantioselective addition; aldimines; catalysis

Introduction

Organic compounds containing nitrogen atoms on one or more stereogenic centers are ubiquitous in nature and are of unparalleled importance in pharmaceutical substances. From amino acids and amino sugars to alkaloids and penicillins, chiral nitrogen-containing compounds are of significant synthetic and biological interest. Because chiral amines were traditionally available from classical resolution, the development of general methods for the enantioselective construction of stereogenic carbons bearing nitrogen substituents lagged behind that for the synthesis of chiral alcohols. Indeed, the generation of chiral alcohols followed by displacement with a nitrogen nucleophile represented one of the earliest methods for the synthesis of chiral amines. However, the past two decades have witnessed an enormous increase in the development of new methods for the direct formation of chiral amines by asymmetric transformations of azomethine precursors.[1] The two most general approaches are: (1) the enantioselective reduction of azomethines bearing two non-hydrogen substituents (path a) and (2) the enantioselective addition of carbon nucleophiles (path b), Scheme 1. A third type of disconnection involves a conceptually distinct approach in which the C–N bond is formed in the stereodetermining step. The possibilities illustrated would require an enantioface discriminating reagent of either nucleophilic or electrophilic character (path c) or an enantiotopic group discriminating nitrenoid (path c'). Finally, hydroamination of alkenes should be mentioned as a fourth disconnection.

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^{*}This paper is dedicated to Professor Andreas Pfaltz on the festive occasion of his 60th birthday and in recognition of his pioneering and creative contributions to the field of asymmetric catalysis.”

The number of methods for the catalytic, enantioselective reduction of imines and imine derivatives is legion and beyond the scope of the current overview. Although excellent reviews are available,[2] seminal contributions from Mukaiyama (cobalt),[3] Burk (rhodium),[4] Buchwald (titanium),[5] Noyori (ruthenium),[6] Pfaltz (iridium),[7] Lipshutz (copper)[8] Toste (rhenium)[9] should be noted.

The earliest studies on (and still today some of the most effective methods for) the asymmetric addition of carbon nucleophiles to azomethines involved the use of chiral auxiliaries wherein the nitrogen carries a stereodirecting group.[10] However, the most notable advances in recent years involve the use of chiral additives and catalysts for the addition of a myriad of organometallic reagents based primarily on zinc, and copper. These reagents are versatile and have good functional group compatibility, but because of their lower reactivity, more activated azomethines are generally required. Accordingly, to facilitate the nucleophilic addition of these reagents, a host of nitrogen derivatives has been extensively examined. The collection of substrates shown in Chart 1 represents a vast spectrum of reactivity, from the weakly electrophilic imines that only react with strong organometallic reagents to the highly electrophilic acyliminium salts that react with alkenes and arenes.[11] Among these, the acylimines,[12] sulfonylimines,[13] and especially the phosphinoylimines[14] have found extensive use in catalytic, enantioselective additions of copper and zinc reagents and this field has been extensively reviewed.[15,16]

Although organolithium reagents were among the first to be studied they have received less attention in recent years, primarily because of their hyperreactivity and lesser functional group compatibility. For the purposes of this report, the background setting will focus on the state of the art in the addition of organolithium reagents to imines.[17]

Background

Enantioselective Organolithium Additions to Imines

The pioneering studies from the Koga/Tomioka laboratories beginning in 1990 laid the foundation for chiral–ligand–promoted addition of organolithium reagents to imines.[18] Chiral amino ether **1** promoted the addition of a number of lithium reagents to *N*-arylimines when used in superstoichiometric quantities (1.3 equiv/*RLi*), Scheme 2. The highest enantioselectivities were observed for the additions of MeLi to imines derived from aromatic aldehydes. Lowering the temperature (–95 to –100 °C) also markedly improved selectivities. [18g] Tomioka later described a catalytic (30 mol%) version of the process that afforded attenuated enantioselectivities. [18b,d,e] Increasing the steric bulk of the *N*-substituent (*Y*=Me, *i*-Pr) slightly improved selectivities.[18c] Modified versions of ligand **1** based on proline gave much poorer selectivities.[19]

Tomioka and coworkers also investigated the use of chiral ligand **2** (Scheme 2) and found that it generally gave poorer selectivities except in the addition of aryllithium reagents.[18d,e] This observation led to a *de-novo* synthesis of unnatural amino acids.[18h]

Itsuno[20] and coworkers have developed an enantioselective addition of organolithium reagents to *N*-metalloimines (Met = SiMe₃, Al(*i*-Bu)₂, BH₂) using a number of different modifiers derived from proline and camphor. For the addition to *N*-silylimines, the highest selectivity was obtained with ligand **3** (presumably as a dilithium salt), whereas with *N*-alumino or *N*-borylimines (obtained from *in situ* reduction of the corresponding nitrile), [20e] the highest selectivities were seen with (–)-sparteine (**4**) (up to 87:13 er), Scheme 3. Subsequent studies showed that chiral allylic boranes could also add to metalloimines with good selectivities.[20d]

In addition to the amino ethers and bisethers described above, chiral diamines have been employed as ligands for the enantioselective addition of organolithium reagents to imines. Andersson and coworkers investigated a family of bisaziridines of the general structure **5** for their ability to control the addition of organolithium reagents to anisylimines, Scheme 4.[21] These investigators studied the effect of ligand stoichiometry and temperature and obtained respectable results.

1,2-Diaminocyclohexane-based ligands have been thoroughly studied recently by Alexakis and coworkers.[22] After a broad survey of nitrogen substituents, the bis-1,2-(dimethylamino) cyclohexane (**6**) was found to give the best results with a wide range of aromatic and heteroaromatic *N*-anisylimines in combination with aryl- and heteroaryl lithium reagents, of which 1-naphthyllithium gave the best selectivities, Scheme 5.

In one of the few successful enantioselective additions of organomagnesium reagents, Ukaji has reported good enantiotopic face differentiation in the addition to a nitron.[23] Grignard reagents reacted readily with a cyclic nitron in the presence of the bromomagnesium salt of ligand **7** to afford the hydroxylamine product in 33% yield and 95:5 er (*S*). Interestingly, with the same ligand, zinc produced the enantiomer (74% yield and 78.5:21.5 er), Scheme 6.

Several other reports on the use of oxazolines,[24] bisoxazolines,[25] and (–)-sparteine[25, 26] that appeared after our initial findings will be included in the discussion section.

Chiral Ligands. Bisoxazolines

The emergence of bisoxazolines in the early 1990's as readily accessible, versatile and highly selective ligands for transition metal catalyzed transformations was a watershed event in the history of ligand design and development for asymmetric catalysis. The impact of this class of ligands has been amply chronicled in myriad reviews over the past 15 years that cover all aspects of their structural and chemical virtuosity.[27]

In continuation of our early studies on the stereoselective addition of organocerium reagents to chiral hydrazones,[28] we began to consider the use of ligands for enantioselective additions to imines. Remarkably, bisoxazolines had not been used as ligands for organolithium compounds. The conformationally rigid ligand framework and *C*₂-symmetric disposition of the stereogenic centers in close proximity to the coordination site were expected to have a strong influence on the reaction course. Moreover, the simple and modular methods of preparation of bisoxazolines in either enantiomeric form allow for high structural variability.

(–)-Sparteine (**4**)

(–)-Sparteine,[29] an optically active, naturally occurring and commercially available tertiary diamine has often been used as a chiral bidentate ligand for organometallic compounds.[30] Although first employed as a ligand in anionic olefin polymerization,[31] Nozaki and coworkers first introduced (–)-sparteine for enantioselective transformations (Skattebøl–Moore allene synthesis and additions of alkyllithium and Grignard reagents to prochiral carbonyl compounds).[32] More significant is the extensive work of Beak[33] and Hoppe [34] on the use of BuLi/sparteine complexes for the generation of chiral organolithium compounds by asymmetric deprotonation/complexation.

In preliminary reports we have disclosed the use of these two classes of ligands as promoters for the enantioselective addition of organolithium reagents to anisyl aldimines.[35] Herein, we describe in detail the optimization of the reaction protocol and the ligand structure. In particular, we were interested in establishing structure selectivity relationships by variation of the substituents at various positions on the bisoxazoline scaffold as well as any correlation with the bridging angle between the oxazoline rings. Several research groups have reported a

correlation between ligand geometry, specifically bite angle,[27c,36] and enantioselectivity. Trost has shown that in certain palladium catalyzed allylic alkylation reactions, the enantioselectivity can be correlated to ligand bite angle.[37] Of greater relevance is the study by Davies on the enantioselectivity of a copper(II) catalyzed Diels–Alder reaction that was significantly influenced by changing the bridging angle, Φ , of an indanol–based bisoxazoline.[38] By evaluating a series of spirocyclic bisoxazolines, Davies discovered that increasing Φ improved both the endo/exo selectivity and enantioselectivity (Scheme 7). Finally, we have carried out a computational analysis of possible complexes and transition structures in an attempt to rationalize the structural effects on selectivity.

Results

Substrate Preparation

The *N*-methoxyphenyl imines (*N*-anisyl imines) **8**,[39] **9**,[18a]**10**[40] were obtained standard methods (toluene, azeotropic removal of water) from the corresponding aldehydes with *p*-anisidine, Scheme 8. In the case of aliphatic imine **11**, the reaction was performed at room temperature with basic alumina as the dehydrating agent in THF. After removal of the basic alumina by filtration, the product was purified by recrystallization from THF/hexane and stored in freezer until ready to use because it was less stable than conjugated and aromatic imines **8**–**10**.

Preparation of Chiral Ligands

Detailed procedures for the preparation of the bisoxazoline ligands have been described.[41] Most commonly, an amino alcohol is condensed with a malonic acid derivative. The resulting bis(hydroxy amide) is cyclized to the bisoxazoline using one of a number of methods, such as treatment with SOCl₂ or activation of the terminal hydroxyl as a mesylate then treatment with base. By this method, enantiopure bisoxazolines **12ba–bf**, **12cc**, and **12ce** (designed to investigate the influence of the C(4) substituents) were prepared, Chart 2.

For further investigation of the role of the substituents on the bridging carbon and the bite angle of the bisoxazoline, enantiopure ligands **12ac–fc** and **12kc–nc** were designed, but given their common structural features, a different route was envisioned (Scheme 9). The unsubstituted bisoxazoline **12gc** is easily accessible from the condensation of *L*-*tert*-leucinol, **13**, and malonimide, **14**. All of the other substituted and spirocyclic bisoxazolines were prepared from this common intermediate. Treatment of **12gc** with LDA/TMEDA at –68 °C followed by sequential alkylation with the appropriate halide afforded the substituted bisoxazolines in serviceable yields. Likewise cycloalkylation of **12gc** with α,ω -diiodo- or dibromoalkanes afforded the desired spirocyclic bisoxazolines in acceptable yields (41–72%).

The dineopentyl substituted bisoxazoline **12fc** could not be prepared by direct alkylation of **12gc**, so an indirect route was attempted. Alkylation of **12gc** with methallyl chloride afforded the dialkylation product **12ic** which could be cyclopropanated by a modified Simmons–Smith reaction to afford **12jc** in good overall yield. Unfortunately, under no combination of pressure, heat, catalyst and solvent could the cyclopropane rings be hydrogenolyzed.[42] Thus, **12jc** was tested instead.

Asymmetric Addition to Imines. Background (Ligand-free) Reaction

The success of any asymmetric reaction between an achiral substrate and an achiral reagent promoted or catalyzed by a third chiral component requires a significant difference between the ratio of the promoted and unpromoted (background) reaction rates. Because of the high reactivity of organolithium reagents, we needed to identify reaction conditions under which the unpromoted process had a negligible rate. The test substrate, imine **8**, was combined with

MeLi to determine the influence of the reaction solvent and temperature on the addition rate. [43] The orienting reactions were performed as follows: a solution of imine (0.1 M) was added to a MeLi (2.0 equiv) solution (0.1 M) at -78°C and conversions were determined by GC analysis. The results of ligand-free addition of MeLi are collected in Table 1. No products other than expected amine **15** were detected. Toluene was examined first to maximize interaction of the ligand with the organolithium reagents (in subsequent experiments), entries 1–3. These reactions proceeded to only 6% conversion after 4 h at -78°C , but the conversion could be increased (up to 51% at -41°C). In ether (entry 4) the addition was quite fast (89% conversion, in 2 h), while in hexane/toluene no reaction was observed (entry 5).

On the basis of these preliminary data the initial survey of ligand structure would be carried out in toluene at -78°C . Although the reaction proceeded rapidly in Ether, its use is not necessarily precluded because it is the *relative* rates of promoted and unpromoted reaction that are relevant. A reexamination of polar solvents will be described subsequently.

Evaluation of Ligand Structure. Substituent on C(4)

An initial series of six bisoxazoline ligands, **12ba–bf**, was surveyed to examine the effect of steric bulk of the substituent at C(4) on the rate and selectivity of the addition. The results of this survey for aromatic imine **8** are presented in Table 2. The typical reaction procedure is as follows; a solution of imine **8** in toluene (0.1 M) was added to a mixture of bisoxazoline ligand (1.0 equiv) and MeLi (2.0 equiv in low halide ether solution) in toluene (0.1 M) at -63°C , this mixture was stirred at -63°C for 1 h then the reaction was quenched with methanol at -63°C . Workup and purification afforded **15** in 95% yield with 87.5:12.5 er. The ligand was recovered from the reaction mixture with no loss in enantiomeric composition.

The reaction promoted by benzyl substituted bisoxazoline **12ba**, afforded **15** in 91% yield with 67.0–33.0 er, favoring the *R* enantiomer (entry 1). Ligands bearing bulkier isopropyl and *tert*-butyl groups at R^4 provided 85.0:15.0 and 87.5:12.5 er, respectively (entries 2 and 4). Ligands bearing still bulkier groups at C(4) such as **12bd** decreased the reaction rate and enantioselectivity (75% yield; 82.0:18.0 er, entry 5). The reaction mediated by bisoxazoline **12be** ($\text{R}^4 = \text{CMePh}_2$) required higher reaction temperature. At -78°C , only 41% of **15** was obtained, whereas at -63°C , **8** was consumed and **15** was obtained in 99% yield with 90.5:9.5 er (entries 6 and 7). The ligand bearing the trityl substituent **12bf** afforded no product, most likely because imine could not be coordinated to the MeLi–ligand complex (entry 8). The ligand **12bc** with *tert*-Bu substituents at C(4) effectively controlled the steric course of the reaction and is easily prepared from *tert*-leucine.

Bridging Substituents. Non-cyclic

Although remote from the region of substrate binding, the bridging substituents can influence the conformation of the bisoxazoline and the bite angle, which in turn could affect the steric course of the reaction. Thus, a systematic evaluation of the bulk of the bridging substituents was first executed and the results are collected in Table 3.

In this series a clear trend is apparent such that enantioselectivity increases with increasing bulk of the substituents R^3 . Accordingly, the ligand with the smallest substituent (Me, **12ac**) led to the lowest selectivity (entry 1) whereas the ligand with the bulkiest substituent (*i*-Pr, **12ec**) led to the highest selectivity (entry 6). Interestingly, ligand **12dc** gave results that were intermediate between the dimethyl and diisopropyl substituted ligands (cf. entries 1, 6 and 7). Finally ligand **12ce** (not shown, see Chart 2) afforded no addition product most likely because of the enhanced steric hindrance at both C(3) and C(4) position.

A ligand survey was also performed on the addition of MeLi to aliphatic imine **11**, Table 4. As expected, this imine is less reactive and required higher reaction temperature compared to that for aromatic imine **8**. Here again, the *tert*-butyl substituted ligand **12bc** displayed the highest selectivity for the survey of C(4) substituents (entries 1–5), but no trend was observed for the C(3) substituents (entries 6–9). Interestingly, in this case the dimethyl substituted ligand **12ac** gave the highest selectivity of all (entry 6)

Finally, the ligand effect on the addition to a third class of imines, the conjugated (*E*)-cinnamyl imine **10** was carried out, Table 5. For this substrate, only those ligands bearing a *tert*-butyl group at C(4) were tested. As was the case for imine **11**, the ligand with a bridging geminal dimethyl group gave the highest selectivity in the formation of **17** by far (entry 1). For these last two substrates, a roughly inverse relationship was seen between bulk of the substituents R³ and enantioselectivity.

Bridging Substituents. Cyclic

The spiro-bisoxazolines were next evaluated in the addition of MeLi to imines **8**, **10**, and **11** promoted by **12kc-nc** and the results were compared to those from **12ac**. As before, the reactions were conducted with 2.0 equiv of MeLi, 1.0 equiv of the bisoxazoline ligand in toluene for 30 min at –75 °C, and the reaction was then quenched with methanol at that temperature.

Benzaldehyde imine **8** was the first substrate to be examined, Table 6. Bisoxazolines **12kc-nc** proved to be excellent promoters for the addition of MeLi to this imine. The product amine **15** was isolated in high yields (82–97%) from all of the reactions, however only modest enantioselectivities were seen (Table 6, entries 1–4). Four of the five ligands provided **15**, in approximately 85:15 er, and the cyclopropyl ligand **12kc** gave only a 75.5:25.5 er. If the geometric constraints of the spirocyclic bisoxazolines do produce geometrically unique complexes, the range of enantioselectivities seen suggests that the bite angle may have an effect on the course of the reaction, albeit a rather small one.

A similar trend in enantioselectivity was seen in the reactions with (*E*)-cinnamyl and hydrocinnamyl imines, **10** and **11**. Again the desired amines were isolated in high yield (75–94%) and varying levels of enantioenrichment (Table 6). As was seen in the reactions with **8**, cyclopropyl bisoxazoline afforded **17** and **16** with the lowest selectivities (entries 6 and 11). The other bisoxazolines all promoted the reaction with a high degree of selectivity, however none greater than the simplest ligand **12ac** bearing a bridging geminal dimethyl substituent (entries 10 and 15). The range of enantioselectivities suggests that a correlation between ligand geometry and selectivity may be possible. In each case only the cyclopropyl bisoxazoline produced a reaction that was significantly different from the others.

Studies on the Imines

A summary of the best results for the addition of MeLi to all of the imines **8–11** is compiled in Table 7. The 1-naphthylimine **9** was slightly less selective with ligand **12bc** than was **8**, but this selectivity improved to 91.5:8.5 by using branched ligand **12cc** (entries 2 and 3). These results were rather satisfying, but the use of only MeLi and the use of a stoichiometric amount of the ligand represented obvious limitations that are addressed below.

Expansion of Scope to Other Nucleophiles and Solvents

The first limitation addressed was the need to investigate the addition of other organolithium reagents, e.g., *n*-Bu, Ph and vinyl. For this investigation, the aliphatic imine **11** and **12bc**, were chosen for the survey of nucleophiles (Table 8). For the reaction with *n*-BuLi addition, the choice of solvent was very important. Combination of *n*-BuLi with imine **11** in toluene afforded

19 in 82% yield but only 78.5:21.5 er (entry 1). Under the same reaction conditions, reaction in diisopropyl ether and ether afforded **19** with 84.5:15.5 and 76.5:23.5 er, resp. (entries 3 and 4). From independent control experiments (Table 9), the rate of addition of *n*-BuLi under ligand-free conditions in toluene and ether were dramatically different (Table 9, entries 1 and 3), but the enantioselectivities were nearly the same (Table 8, entries 1 and 4). Interestingly, the reaction in toluene/ether, 8:1 increased the yield and afforded a higher enantioselectivity than toluene or Ether alone.

The addition of PhLi to imine **11** in the presence of ligand **12bc** gave the poorest selectivity. Commercially available PhLi (Aldrich, cyclohexane/ether, 7:3), to afford the corresponding amine **20** with only 65.0:35.0 er. Phenyllithium, prepared from bromobenzene and lithium metal in ether, gave the racemic product in 89% yield. Addition of vinylolithium to **11** proceeded selectively to give **21** in 94.5:5.5 er and 95% yield in toluene, in 92.0:8.0 er and 75% yield in *i*-Pr₂O (Table 8, entries 8 and 9). Vinylolithium was prepared by Sn/Li exchange from tetravinyltin and *n*-BuLi following the method of Seyferth and Soderquist.[44] Unsolvated vinylolithium was dissolved in ether and this solution was titrated prior to use.[45]

Catalytic Reactions

Although the ligands could be recovered in >90% yield in all cases, the use of a substoichiometric amount of the additive still has obvious practical advantages. To establish the identity and loading of the bisoxazoline additive, aromatic imine **8** was subjected to the standard conditions for addition of MeLi (Table 10). In contrast to the stoichiometric reaction which proceeded at -78 °C to provide **15** in nearly quantitative yield (entries 1, 5, 9), the catalytic reactions did not proceed readily at -78 °C. With 0.1 equiv of ligand for the addition of MeLi, the yields of **15** were only 27–46% (entries 4, 8, 12). Interestingly, the enantioselectivities decreased only slightly as the amount of ligand decreased. This trend indicates that the background reaction is not very competitive under these conditions, thus, higher selectivities with substoichiometric amounts of ligand should be obtainable with adjustment of reaction conditions.

For reaction of **8** in the presence of ligands **12bc** and **12be**, the transformation proceeded gradually with the increase of reaction temperature without any loss of enantioselectivity (Table 11, entries 3–5, 6–8). These results showed that regeneration of ligand–organolithium complex occurred at the requisite temperature. Taking into account the fact that the reaction in the absence of ligand afforded the racemic amine **15** in 51% yield after 30 min at -41 °C (Table 1, entry 3), these results clearly indicate that the rate of ligand-promoted reaction is much greater than that of the background reaction.

However, a decrease in enantioselectivity was observed for the reaction of imine **8** with ligand **12cc** (Table 11, entries 9 and 10) and of imines **9**, **10**, **11** with ligand **12bc** as the reaction temperature increases (Table 11, entries 11 vs. 12, 13 vs. 14, and 17–19). Apparently, in these cases the background reaction became significant at increasing reaction temperature.

With 0.10 equiv of ligand, the additions of other organolithium reagents (*n*-Bu and vinyl) to **11** did not proceed efficiently and a drop in the enantioselectivity was observed (Table 12, entries 4 and 8). However, using 0.20 equiv of ligand, improved enantioselectivity and yield were observed; compounds **16**, **19** and **21** were obtained in 97, 92 and 82% yield, respectively (entries 3, 7, 9).

Effect of Additives

To facilitate the turnover of the ligand, a silylating agent was added in an attempt to trap the initial lithium amide product and release the bisoxazoline. Thus, various silyl chlorides were

tested by combining the ligand, imine and silyl chloride in toluene at -78°C followed by the addition of 2 equiv of MeLi.[46] The results show that some of the silyl chloride reacted with MeLi at -78°C (yield up to 72%) and the yields of the product decreased. However neither the formation of *N*-silyl protected amine nor change in enantioselectivity was observed.

The effect of strongly coordinating additives was next investigated. To gauge the coordinating ability of the bisoxazoline, various Lewis bases were added to the reaction between **11** and *n*-BuLi containing 1.0 equiv of **12bc**. Although only 2 equiv of ether or THF did not influence the enantioselectivity, 5–25 equiv of ether marginally increased the enantioselectivity from 78.5:21.5 er to 83.0:17.0 er. In the presence of 2 equiv of TMEDA or HMPA, the reaction proceeded smoothly to afford racemic **19** in good yield. Clearly, these more Lewis basic additives preferentially coordinate to MeLi and therefore do not promote an asymmetric addition reaction. The weak chelating ability of the bisoxazoline ligands was problematic for additions of *n*-BuLi and PhLi and led to the search for stronger chiral ligands.

(–)-Sparteine-promoted Reaction

To address the poor coordinating ability of bisoxazolines and in an attempt to improve the enantioselectivity, the more basic, bidentate tertiary diamine, (–)-sparteine, **4** was tested. Under the standard reaction conditions, (–)-sparteine did promote the addition of MeLi to imine **11**, but afforded only 86.0:14.0 er (Table 13, cf. entries 1 and 2). Unfortunately, *C*₂-symmetric (–)-isosparteine,[47] **4a** gave also disappointing results (entry 3). However, the addition of *n*-BuLi promoted by **4** gave improved enantioselectivity compared to the bisoxazoline ligands. For example with 1.0 equiv of **4**, the reaction in toluene proceeded at -94°C to afford **19** with a 89.5:10.5 er in 86% yield (cf. entries 4 and 7), whereas in polar solvents, such as diisopropyl ether and ether, the selectivities increased even more significantly (cf. entries 5 and 6 vs. 8 and 9). With 0.20 equiv of **4**, the reaction in ether afforded **19** with an improved selectivity compared to that with **12bc** (cf. entries 10 and 11). (–)-Sparteine (1.0 equiv) also showed great improvement in the addition of PhLi to **11**, with a selectivity up to 91.0:9.0 er in toluene at -94°C (cf. entries 12 and 13). Unfortunately, poorer selectivities were observed in other solvents or with lower loadings of **4** (entries 14–17).

The aromatic imine **8** also underwent chiral ligand-promoted addition of *n*-BuLi. In the presence of an excess of bisoxazoline **12bc**, the product **22** was formed in quantitative yield but only in 66.0:34.0 er (Table 14, entry 1). With (–)-sparteine as the ligand, the enantioselectivity improved only slightly (entries 5 and 6). The best, albeit still modest, selectivity was obtained from the reaction of **8** in ether at -94°C to afford **22** in 95% yield (entry 7). Here again, (–)-isosparteine was not effective (entry 9).

Determination of Absolute Configuration

The 4-methoxyphenyl group of the amines **15–22**, was easily removed by a two-step sequence. [48] Treatment of the amine with *n*-BuLi followed by trapping of the amide with methyl chloroformate provided the methoxycarbonyl protected amine (Scheme 10). Subsequent oxidative removal of 4-methoxyphenyl group was carried out with ceric ammonium nitrate (CAN)[49] in aqueous acetonitrile to afford methoxycarbamates **23–27**. The absolute configurations of **23**, **24**, and **25** were determined after deprotection with trimethylsilyl iodide [50] (yields: **28** 54%; **29** 50%; **30** 59%), followed by comparison of the optical rotations of the amines to literature values (**28**,[51] **29**,[52] **30**[53]). The absolute configurations of **26** and **27** were determined by comparison of the elution order of the 3,5-dinitrobenzamides **31** and **32** by CSP-HPLC.[54] All products possessed the *R* configuration.

Discussion

General Substrate Features

The addition of organolithium reagents to *N*-anisyl imines shows a wide range of rates and selectivities. The most significant observation is the dramatic difference in rate of addition for the common organolithium compounds, namely, Me < vinyl < *n*-Bu < Ph. Thus, whereas selective ligand-promoted reactions could be found for all of these nucleophiles, as the loading of the ligand decreased, selectivities eroded in the same order because of the competitive background reaction.

The structure of the imine also affected the success of the addition reactions. For example, whereas good yields and selectivities could be found for the addition of MeLi to all four substrates (**8–11**), the addition of *n*-BuLi was not uniformly selective. For example, the addition of *n*-BuLi to **11** was fairly selective (95.5:4.5 er), but the addition to **8** was no better than 72.0:28.0 er.

Ligands

Bisoxazolines served as a viable platform for developing ligands for the enantioselective additions of organolithium reagents to imines. A number of general trends were noted. First, the size of the group on the C(4) position was critical for high conversions and selectivities. Smaller groups (Bn or *i*-Pr) led to rapid reactions but modest selectivities. Larger groups (*t*-Bu, CMe₂Ph, CMePh₂) led to slower reactions, but generally higher selectivity (for MeLi, where background is negligible). The high selectivity and general accessibility of the *t*-Bu substituted bisoxazoline made it the ligand of choice.

The bridging group played a secondary, but nonetheless important role. The nature of these substituents had different influence depending upon the imine studied. A correlation was found between the size of the bridging group and the enantioselectivity of the reactions. Interestingly, this trend is not the same for each substrate (Table 15). For reactions with benzaldehyde imine **8**, high selectivity is obtained with bisoxazolines possessing large bridging groups as evidenced by the consistent improvement in er in the following order: dimethyl (**12ac**) < (**12bc**) < diisobutyl (**12cc**) < diisopropyl (**12ec**). The opposite trend holds for the olefinic (**10**) and aliphatic (**11**) imines where selectivity increases as the bridging groups decrease in bulk from isopropyl to methyl.

Given the shape of the bisoxazoline methyllithium complex, as predicted by semi-empirical calculations (see Figure 1, below) it is not surprising that a correlation between bridge group size and selectivity can be made. The boat-like shape of the molecule places the bridging carbon and lithium atoms below the rest of the molecule. This orientation then forces one of the bridge substituents into the general area of the lithium atom, causing it to play a greater role in the environment near the reaction centers and hence affecting the enantioselectivity of the addition. However, the difference between the selectivity profiles for **8** and **10/11** is not immediately clear.

The second set of ligands bearing bridging substituents, the spiro-fused bisoxazolines also provided an interesting trend (Table 17). The most obvious correlation between selectivity and ligand geometry is that in all cases the cyclopropyl-based ligand **12kc** gave the lowest enantioselectivity (Table 16, column 2). The low selectivity of the cyclopropyl bisoxazoline may be due to an interruption in the complexation of MeLi. To evaluate the influence of ring size and substituents on the “bite angle” of the bisoxazolines, the ground state geometries were calculated both as free ligands as well as with MeLi complexed.

Initially, molecular mechanics geometry optimizations of the free spiro bisoxazoline ligands were performed, analogous to the calculations performed by Davies.[38] The conformational searches produced a large number of energy minima for each ligand. As a first approximation, it was expected that as ring size increased the bridge angle would decrease. The lowest energy minima did not follow this trend (Table 17, column 2). Furthermore, none of the conformations placed the carbon-nitrogen double bonds of the molecule in a coplanar or nearly coplanar orientation as predicted by Davies calculations.[38] Examining the numerous low energy conformations that did contain coplanar arrangements of the C=N bonds also provided a series of angles that did not conform to the expected trend (Table 17, column 3).

A similar set of calculations was performed at a higher level of theory. The free ligands were geometry-optimized using the semi-empirical method PM3.[55] Unlike the molecular mechanics calculations, the low energy structures produced by this level of theory had the carbon-nitrogen bonds nearly coplanar for each of the ligands. But as before the bridge angles did not conform to the expected pattern (Table 17, column 4).

Finally, bisoxazolines with MeLi complexed between the two nitrogen atoms were geometry optimized using the PM3 method.[55b] The general shape of the ligand-MeLi complex is that of a boat, with the bridging ring and lithium rising above the plane formed by the two C=N bonds and the oxazoline rings sloping below (Figure 1). The depth of the boat varies from ligand to ligand. As was seen in the calculations for the free ligand, the expected trend of bridge angles was not seen. The optimization of the dimethyl bisoxazoline produced an angle that did not conform to the expected relative order (Table 17, column 5 entry 5).

Co-planarity of the nitrogens should facilitate the complexation of Li by both lone pairs, increasing the rigidity of the system and perhaps the selectivity of the ligand as well. From the selectivity data it would appear that the optimal angle around the bridging carbon is between 109° and 111° (Table 16, columns 3–5). Apparently, if the bridge angle is too large or small the enantioselectivity decreases, although the effect is more pronounced at larger angles. No correlation is found between enantioselectivity and any ligand geometry predicted by these calculations. Indeed it seems that the enantioselectivity of the reaction is very ligand and substrate dependent.

As for all calculations, the accuracy of the geometries that are generated must be questioned. Furthermore, it must be kept in mind that the calculations are in the gas phase and therefore, energies and conformations may not truly depict solution state structures. Another possible method for determining the desired angles would be to obtain X-ray crystal structures for both uncomplexed and complexed ligands. The lithium species may not need even to be methyl-lithium. Lithium chloride may act as a suitable substitute that could alleviate any air sensitivity issues that a methyllithium complex would present. However, solid state geometries also may not accurately describe solution state structures.

Transition Structure Calculations

Given the uniformity of the stereochemical pathway, it is reasonable to consider possible transition state structures for bisoxazoline-catalyzed organolithium additions to imines, with the aid of computational analysis. The C_2 -symmetric “pocket” (or “cleft”) of appropriately substituted bisoxazolines has been widely used to differentiate the enantiotopic faces in a substrate for many different reactions.[27] Bisoxazoline•copper complex-catalyzed ene reactions,[56] Diels-Alder cycloadditions[57] and cyclopropanations,[58] bisoxazoline•borane complex-catalyzed reductions,[59] as well as bisoxazoline•titanium-[60] and rhenium-catalyzed[61] hydrosilylation reactions have been investigated computationally at correlated level ab initio theory to provide insights into reaction mechanisms and enantioselectivities. For the bisoxazoline-induced enantioselective

allylzincation of cyclopropenes, the four diastereomeric transition structures could be optimized in MNDO.[62] Accordingly, the addition pathway of an organolithium•bisoxazoline complex to an imine (Figure 2) has been computationally investigated below.

MNDO[63] and PM3[55a] methods have been successfully employed for a large number of lithium-mediated addition and substitution reactions.[64] Because of its high selectivity and structural simplicity, bisoxazoline **12ac** was chosen as the model auxiliary and aromatic imine **8** as the substrate.

The generally accepted pathway for the lithium-mediated addition of a nucleophile to a C=O double bond[65] can be translated to the imine addition as outlined in Figure 2. In the weakly coordinating solvent toluene, bidentate complexation of MeLi by the nitrogen lone pairs of the bisoxazoline auxiliary is assumed, (**12ac**•MeLi). This conjecture is corroborated by the X-ray structures of the copper,[66] zinc,[67] and palladium complexes[27a] with very similar bisoxazolines and the fact that the doubly oxygen-coordinated structure is computationally far less stable (MNDO: 5.3; PM3: 12.2 kcal/mol). The bisoxazoline system is strongly distorted in MNDO forming a cavity similar to the experimental zinc structure[67] and less so in PM3 thus resembling the planar copper[66] and palladium geometries.[27a] The second and more significant difference between both semi-empirical geometries is the longer Li-N bond in MNDO (2.27 Å) than with PM3 (2.06 Å). Although the Li-N distance in LiNH₂ is computed equally accurately by either method, multicoordinated lithium exhibits considerably longer bonds (0.09 – 0.13 Å) to sp²-hybridized nitrogen atoms in MNDO than in PM3.[68] As a consequence, the imine substrate could readily be attached to **12ac**•MeLi in PM3 whereas in MNDO, the approach of the imine ultimately leads to the opening of the bidentate coordination mode of the bisoxazoline.[69] This complication precluded further use of MNDO and all of the following arguments are made on the basis of PM3-optimized structures.

Coordination of the imine nitrogen in **8** to the lithium in **12ac**•MeLi leads to three stable complexes (**A**–**C**). In the two lowest energy complexes, the imine moiety is aligned below the plane of the bisoxazoline such that either the phenyl group (complex **A**) or the anisyl group (complex **B**) is located directly beneath the bisoxazoline system (Figure 2). In complexes **A** and **B**, both aryl rings are strongly twisted (27 – 56°) in contrast to the perfectly planar conformation of the isolated imine. The bisoxazoline system is distorted to form a cavity (cf. dihedral angles in Table 18) which finds analogy in the deformation of the planar palladium bisoxazoline complex upon addition of an allyl moiety.[27]

The reaction coordinate for the methyl addition in the energetically favored complex **A**, leads to a pronounced rise in energy accompanied by a strong elongation of the Li-N bond (> 3.0 Å). The position of the imine in complex **A** is not well suited for approach of the nucleophile. On the other hand, in the less favorable complex **B** (1.1 kcal/mol higher in energy than complex **A**), the imine carbon is in a more proximal position to the anionic methyl group, leading to the transition structure **TS-1**. *Si*-face addition in this structure eventually yields the experimentally observed minor product.

In the least stable complex **C** (2.9 kcal/mol higher in energy than complex **A**), the imine is perpendicular to its position in the other two complexes, and the N=C bond is now aligned parallel with the Li-C bond. Delivery of the methyl group from complex **C** leads to the *Re*-face attack in **TS-2** giving rise to the major enantiomer of the amine. Although **TS-2** is only 1.1 kcal/mol more favorable than **TS-1**, their structural dissimilarity is striking.

In **TS-2**, the Z-shaped imine fits comfortably into the “pocket” formed by the two *tert*-butyl groups of the C₂-symmetric auxiliary (cf. Figure 2, second orientation of **TS-2**). The C=N group of the imine and MeLi form a distorted, nearly planar (13.7°) four-membered ring, resembling the ab initio transition structures for the MeLi addition to carbonyl groups.[65,

70] Moreover, the bisoxazoline moiety is distorted in such a way as to enlarge the “pocket” for the imine. This distortion folds the six-membered ring made from the lithium, two C=N moieties, and the bridging carbon into a boat-like conformation leaving the anionic methyl group in the flagpole position.

The approach of the imine in **TS-1** occurs in a parallel fashion with respect to the bisoxazoline, far away from the defined “pocket” (Figure 2). The bisoxazoline system is bent into the opposite boat conformation to that in **TS-2** leaving the anionic Me in the bowsprit position. Although the characteristic bond lengths are fairly similar in both structures (Table 18), the sum of the dihedral angles for the out-of-plane bending of the bisoxazoline is considerably larger for **TS-2** (89°) than for **TS-1** (67°). This fact and the different positions of the imines in both transition structures can be used as the basis for the modification of this chiral auxiliary.

Formation of the C-C bond yielding a bisoxazoline-complexed lithio amide is strongly exothermic (45 kcal/mol). The *R*-isomer of the lithio amide is slightly favored (0.8 kcal/mol). From the change in the imine C-N bond length, both transition structures are early on the reaction coordinate in accord with the Hammond postulate[71] for exothermic reactions and with the ab initio results for MeLi addition to carbonyl groups.[65]

The insights acquired from this computational analysis about the arrangement of the nucleophile and the imine in both transition structures can now be used to design a steric environment that increases the enantiofacial selectivity in the addition reaction. The experimental results have demonstrated that simply increasing the bulk of the oxazoline substituents eventually impedes the addition completely (e.g., with CPh₃). The chiral ligand obviously has to maintain a certain accessibility of the nucleophile to accommodate the imine. The larger dihedral angles in the bisoxazoline system in **TS-2** (Table 18) suggests that a more flexible connection between the oxazoline rings (e.g., via a heteroatom) might lower the energy of **TS-2** more effectively than that of **TS-1**. This may well be the reason that **12ac** and **12lc** are more selective than **12kc**. Another strategy might focus on reducing the interactions between the flagpole positions in **TS-2** e.g., by replacing the methyl groups at the tertiary, bridging carbon by fluorines.

Conclusions

Chiral bisoxazolines are capable of activating and controlling the addition of organolithium reagents to anisyl aldimines. The best selectivities were obtained for the addition of methyllithium and vinylolithium, primarily because of their low background reactions. Aromatic, olefinic and aliphatic imines underwent addition with yields and high selectivities with a full equivalent of the bisoxazoline and slightly attenuated selectivities with substoichiometric amounts. For the addition of other organolithium reagents (*n*-BuLi and PhLi) (–)-sparteine was a superior ligand, but only in stoichiometric quantities.

A systematic evaluation of the structural features of the bisoxazoline substituent revealed a strong dependence on the group at C(4) and a secondary dependence on the bridging group. Spiro bisoxazolines with varying ring sizes did influence the selectivity of addition of MeLi, but none more selectively than those bearing a simple geminal-dimethyl substituent. Computational modeling at the PM3 level provided important insights into the origin of enantioselectivity for the intramolecular delivery of methyl via a ternary complex of bisoxazoline, MeLi and imine. Although further studies are needed to improve the enantioselectivity of addition, especially for the reactive organolithium reagents such as *n*-Bu and PhLi, the results presented herein lay the foundation for the development of catalytic enantioselective additions to imines.

Experimental Section

General Remarks

See Supporting Information for general experimental details as well as procedures for the preparation and characterization of all precursors and products.

Asymmetric Addition to Imines. 1. (*R*)-*N*-(4-Methoxyphenyl)- α -methylbenzenemethanamine (15). Stoichiometric (Table 3, entry 4)

To a solution of **12cc** (760 mg, 2.0 mmol) in toluene (20 mL) in a flame-dried, 250-mL, 3-necked, round-bottom flask equipped with a stir bar, a thermometer, a septum and a nitrogen inlet was added MeLi (2.06 mL, 1.94 M in Et₂O 4.0 mmol) at –63 °C. The resulting mixture was stirred for 30 min, and a toluene solution (10 mL) of imine **8** (425 mg, 2.0 mmol) was added over a period of 5 min. The remaining imine was washed in 10 mL of toluene. This yellow solution was stirred for 1 h at –63 °C and quenched with MeOH (3 mL) at that temperature. The reaction mixture was warmed to rt, and diluted with TBME (20 mL) and water (20 mL). The mixture was extracted with TBME (3 × 50 mL). The combined organic layers were washed with brine (200 mL) and then dried over Na₂SO₄. Concentration followed by SiO₂ column chromatography (hexane/EtOAc, 10:1) afforded recovered **12cc** (757 mg, 100%). The desired amine **15** (434 mg, 95%) was obtained by continued elution (hexane/EtOAc, 3:1). An analytical sample was obtained after Kugelrohr distillation:

$[\alpha]_D^{24} = +2.74$ ($c = 1.02$, CHCl₃); bp 140–150 °C (0.006 mmHg); mp 61.0–62.0 °C; ¹H NMR 7.20–7.38 (m, 5 H, HC(Ar)), 6.66–6.72 (m, 2 H, HC(3'), HC(5')), 6.44–6.50 (m, 2 H, HC(2'), HC(6')), 4.41 (q, $J = 6.7$, 1 H, HC(2)), 3.80 (br s, 1 H, NH), 3.70 (s, 3 H, OMe), 1.50 (d, $J = 6.7$, 3 H, Me(1)); ¹³C NMR 151.90 (C(4')), 145.57 (C(1')), 141.63 (C(3)), 128.68 (C(5), C(7)), 126.88 (C(6)), 125.95 (C(4), C(8)), 144.79 (C(3'), C(5')), 114.58 (C(2'), C(6')), 55.76 (OMe), 54.28 (C(2)), 25.23 (C(1)); IR (KBr) 3420 (br m), 3061 (m), 3029 (s), 2961 (s), 2832 (s), 1619 (m), 1512 (s), 1464 (s), 1406 (m), 1372 (m), 1350 (m), 1291 (s), 1239 (s), 1206 (m), 1181 (s), 1140 (m), 1107 (m), 1086 (m), 1044 (s), 820 (s); MS (70 eV) 229 (9), 228 (51), 227 (M⁺, 100), 212 (M⁺–15, 26), 168 (2), 123 (8), 108 (5), 105 (16), 77 (3); Chiral HPLC t_R (*R*)-**15**, 17.45 (92.5%); t_R (*S*)-**15**, 19.79 (7.5%) (column A; hexane/EtOH, 99.2/0.8, 0.5 mL/min). Anal. Calcd for C₁₅H₁₇NO (227.31): C, 79.26; H, 7.54; N, 6.16. Found: C, 79.22; H, 7.60; N, 6.15.

(*R*)-*N*-(4-Methoxyphenyl)- α -methyl-1-naphthalenemethanamine (16). Stoichiometric with **12cc**. (Table 7, entry 3)

To a solution of **12cc** (763 mg, 2.02 mmol) in toluene (20 mL) in a flame-dried, 250-mL, 3-necked, round-bottom flask equipped with a stir bar, a thermometer, a septum and a nitrogen inlet was added MeLi (2.70 mL, 1.50 M in Et₂O, 4.0 mmol) at –41 °C. The resulting mixture was stirred for 30 min, and a toluene solution (10 mL) of imine **9** (526 mg, 2.01 mmol) was added over a period of 5 min. The remaining imine was washed in 5 mL of toluene, twice. This yellow solution was stirred for 1 h at –41 °C and quenched with MeOH (2 mL) at that temperature. The reaction mixture was warmed to rt, and diluted with TBME (20 mL) and water (20 mL). The mixture was extracted with TBME (3 × 50 mL). The combined organic layers were washed with brine (200 mL) and then dried over Na₂SO₄. Concentration followed by SiO₂ column chromatography (hexane/EtOAc, 10:1) afforded recovered **12cc** (746 mg, 98%). The desired amine **18** (531 mg, 95%) was obtained by continued elution (hexane/EtOAc, 3:1). An analytical sample of **18** was obtained after Kugelrohr distillation: bp 190–195 °C (0.4 mmHg); $[\alpha]_D^{23} = -158.4$ ($c = 0.87$, CHCl₃); ¹H NMR 8.17 (d, $J = 8.3$, 1 H, C₁₀H₇), 7.91 (d, $J = 8.9$, 1 H, C₁₀H₇), 7.75 (d, $J = 8.1$, 1 H, C₁₀H₇), 7.67 (d, $J = 7.0$, 1 H, C₁₀H₇), 7.49–7.60 (m, 2 H, HC(8), HC(9)), 7.42 (t, $J = 7.7$, HC(5)), 6.64–6.69 (m, 2 H, HC(3'), HC(5')), 6.43–6.69 (m, 2 H, HC(2'), HC(6')), 5.23 (q, $J = 6.6$, 1 H, HC(2)), 3.68 (s, 3 H, OMe), 1.65 (d, $J = 6.6$, 3 H, Me); ¹³C NMR 151.69, 141.27, 140.12, 133.98, 130.65, 129.02, 127.22, 125.91, 125.79,

125.29, 122.51, 122.20, 114.66, 114.18, 55.52, 49.91, 23.60; IR (KBr) 3400 (s), 3051 (s), 2900 (s), 2831 (s), 1766 (s), 1761 (s), 1754 (s), 1746 (s), 1743 (s), 1738 (s), 1733 (s), 1729 (s), 1717 (s), 1510 (s), 1463 (s), 1440 (s), 1291 (s), 1248 (s), 1204 (s), 1174 (s), 1038 (s), 818 (s), 800 (s); MS (70 eV) 278 ($M^+ + 1$, 5), 363 (M^+ , 26), 262 ($M^+ - 15$, 9), 155 ($C_{10}H_7CHMe^+$, 100), 123 (35), 108 (10), 84 (9), 77 (6); Anal. Calcd for $C_{19}H_{19}NO$ (277.37): C, 82.28; H, 6.90; N, 5.05. Found: C, 82.31; H, 6.89; N, 5.04. Chiral HPLC t_R (*R*)-**18**, 23.58 (92%); t_R (*S*)-**18**, 24.72 (8%) (column A; hexane/EtOH, 99.5/0.5, 0.5 mL/min).

(*R*)-*N*-(4-methoxyphenyl)- α -methylbenzenepropenamine (17**). Stoichiometric with **12bc**. (Table 5, entry 2)**

To a solution of **12bc** (649 mg, 2.01 mmol) in toluene (20 mL) in a flame-dried, 250-mL, 3-necked, round-bottom flask equipped with a stir bar, a thermometer, a septum and a nitrogen inlet was added MeLi (2.70 mL, 1.50 M in Et₂O, 4.0 mmol) at -63°C . The resulting mixture was stirred for 30 min, and a toluene solution (10 mL) of imine **10** (526 mg, 2.01 mmol) was added over a period of 5 min. The remaining imine was washed in 5 mL of toluene, twice. This yellow solution was stirred for 1 h at -63°C and quenched with MeOH (2 mL) at that temperature. The reaction mixture was warmed to rt, and diluted with TBME (20 mL) and water (10 mL). The mixture was extracted with TBME (3 $\times$ 50 mL). The combined organic layers were washed with brine (200 mL) and then dried over Na₂SO₄. Concentration followed by SiO₂ column chromatography (hexane/EtOAc, 20:1) afforded the amine **17** (394 mg, 79%) as a yellow oil and **12bc** (602 mg, 91%) was recovered by continued elution (hexane/EtOAc, 3:1). An analytical sample of **17** was obtained after Kugelrohr distillation: bp 210–220 $^\circ\text{C}$ (0.4 mmHg); $[\alpha]_D^{24} = +110.1$ (c 1.05, CHCl₃); ¹H NMR 7.19–7.37 (m, 5 H, HC(Ar)), 6.74–6.78 (m, 2 H, HC(3'), HC(5')), 6.61–6.65 (m, 2 H, HC(2'), HC(6')), 6.57 (d, $J = 16.0$, 1 H, HC(4)), 6.22 (dd, $J = 6.0, 16.0$, 1 H, HC(3)), 4.07 (dq, $J = 6.0, 6.6$, 1 H, HC(4)), 3.74 (s, 3 H, OMe), 1.39 (d, $J = 6.6$, 3 H, Me); ¹³C NMR 152.0 (C(4')), 141.49 (C(1')), 136.94 (C(5)), 133.47 (C(4)), 129.14 (C(3)), 128.41 (C(7), C(9)), 127.21 (C(8)), 126.21 (C(6), C(10)), 114.48 (C(3'), C(5')), 114.26 (C(2'), C(6')), 55.63 (OMe), 51.73 (C(2)), 22.00 (C(1)); IR (KBr) 3397 (s), 3079 (m), 3057 (s), 3025 (s), 2966 (s), 2831 (s), 1627 (m), 1577 (s), 1494 (s), 1463 (s), 1447 (s), 1406 (m), 1370 (s), 1310 (s), 1291 (s), 1233 (s), 1177 (s), 1159 (s), 1038 (s), 967 (s), 818 (s); MS (70 eV) 254 ($M^+ + 1$, 7.5), 253 (M^+ , 41), 238 ($M^+ - 15$, 8), 206 (0.6), 160 (1), 146 (5), 131 (100), 108 (19), 91 (30), 77 (11), 62 (7); Anal. Calcd for $C_{17}H_{19}NO$ (227.31): C, 80.60; H, 7.56; N, 5.53. Found: C, 80.56; H, 7.58; N, 5.50. Chiral HPLC t_R (*S*)-**17**, 27.07 (7.5%); t_R (*R*)-**17**, 31.68 (92.5%) (column A; hexane/EtOH, 99.2/0.8, 0.5 mL/min).

(*R*)-*N*-(4-Methoxyphenyl)- α -butylbenzenepropanamine (19**). Stoichiometric with **4**. (Table 13, entry 9)**

To a solution of **4** (470 mg, 2.01 mmol) in Et₂O (20 mL) in a flame-dried, 250-mL, 3-necked, round-bottom flask equipped with a stir bar, a thermometer, a septum and a nitrogen inlet was added *n*-BuLi (1.65 mL, 2.43 M in Et₂O, 4.01 mmol) at -94°C . The resulting mixture was stirred for 30 min, and a Et₂O solution (14 mL) of imine **11** (481 mg, 2.01 mmol) was added over a period of 5 min. The remaining imine was washed in 3 mL of Et₂O, twice. Resulting yellow solution was stirred for 1 h at -94°C and quenched with MeOH (0.9 mL) at that temperature. The reaction mixture was warmed to rt, and diluted with TBME (20 mL) and water (15 mL). The mixture was extracted with TBME (3 $\times$ 50 mL). The combined organic layers were washed with brine (200 mL) and then dried over Na₂SO₄. Concentration followed by SiO₂ column chromatography (hexane/EtOAc, 15:1) afforded the amine **19** (539 mg, 90%) as a pale-yellow oil. An analytical sample of **19** was obtained after Kugelrohr distillation: bp 185–190 $^\circ\text{C}$ (0.15 mmHg); $[\alpha]_D^{24} = +1.4$ (c=2.15, CHCl₃); ¹H NMR 7.15–7.30 (m, 5 H, HC(Ar)), 6.48–6.77 (m, 2 H, HC(3'), HC(5')), 6.48–6.51 (m, 2 H, HC(2'), HC(6')), 3.15 (s, 3 H, OMe), 3.27 (quint, $J = 5.7$, 1 H, HC(5)), 3.15 (br s, 1 H, NH), 2.62–2.78 (m, 2 H, H₂C(7)), 1.73–1.86

(m, 2 H, H₂C(6)), 1.48–1.55 (m, 2 H, H₂C(4)), 1.29–1.37 (m, 4 H, H₂C(3), CH₂C(2)), 0.88 (t, *J* = 6.9, 3 H, H₃C(1)); ¹³C NMR 151.63 (C(4')), 142.34 (C(1')), 142.34 (C(8)), 128.48 (C(10), C(12)), 128.39 (C(9)), C(13)), 125.81 (C(11)), 114.98 (C(3'), C(5')), 114.39 (C(2'), C(6')), 55.86 (OMe), 53.34 (C(5)), 36.69 (C(7)), 34.69 (C(6)), 32.37 (C(4)), 28.14 (C(3)), 22.92 (C(2)), 14.19 (C(1)); IR (CCl₄) 3420 (br, w), 3027 (m), 2932 (s), 2852 (m), 2832 (m), 1603 (w), 1512 (s), 1464 (m), 1455 (m), 1441 (m), 1406 (m), 1379 (w), 1242 (s), 1181 (m), 1046 (s), 818 (s); MS (70 eV); 299 (4), 298 (27), 297 (M⁺, 76), 240 (M⁺-C₄H₉, 92), 192 (M⁺-C₆H₅CH₂CH₂, 100), 162 (3), 149 (35), 136 (13), 134 (18), 122(10), 117(6), 108 (8), 105 (6), 91 (42), 79 (5), 65 (8); Chiral HPLC *t*_R (S)-**19**, 20.36 (4.5%); *t*_R (R)-**19**, 23.33 (95.5%) (column B; hexane/EtOH, 99.5/0.5, 0.5 mL/min). Anal. Calcd for C₂₀H₂₇NO (297.44): C, 80.76; H, 9.15; N, 4.71. Found: C, 80.89; H, 9.10; N, 4.71.

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Figure 1.
Idealized projections of **12ac•MeLi** complex (PM3).

Figure 2. Calculated (PM3) complexes, transition structure and products for the addition of MeLi to **8** promoted by **12ac**.

Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.

Scheme 5.

Scheme 6.

Scheme 7.

Scheme 8.

Scheme 9.

Scheme 10.

Chart 1.

12ba: $R^3 = \text{Et}$, $R^4 = \text{CH}_2\text{Ph}$

12bb: $R^3 = \text{Et}$, $R^4 = \text{CHMe}_2$

12bc: $R^3 = \text{Et}$, $R^4 = \text{CMe}_3$

12bd: $R^3 = \text{Et}$, $R^4 = \text{CMe}_2\text{Ph}$

12be: $R^3 = \text{Et}$, $R^4 = \text{CMePh}_2$

12bf: $R^3 = \text{Et}$, $R^4 = \text{CPh}_3$

12cc: $R^3 = \text{CH}_2i\text{-Pr}$, $R^4 = \text{CMe}_3$

12ce: $R^3 = \text{CH}_2i\text{-Pr}$, $R^4 = \text{CMePh}_2$

12ac: $R^3 = R^{3'} = \text{Me}$

12dc: $R^3 = \text{Me}$, $R^{3'} = \text{CHMe}_2$

12ec: $R^3 = R^{3'} = \text{CHMe}_2$

12fc: $R^3 = R^{3'} = \text{CH}_2\text{CMe}_3$

12gc: $R^3 = R^{3'} = \text{H}$

12kc: $n = 3$

12lc: $n = 4$

12mc: $n = 5$

12nc: $n = 6$

Chart 2.

Table 1Ligand-Free addition of MeLi to imine **8**

entry	solvent	temp, °C	time, h	conv., % ^a
1	toluene	-78	4	6
2	toluene	-63	2	17
3	toluene	-41	0.5	51
4	Et ₂ O	-63	2	89
5	hexane-toluene (9/1)	-78	4	0

^a Determined by GC analysis of the crude reaction product.

Table 2
Evaluation of ligand structure in additions of MeLi to imine **8**

entry	R ⁴	ligand	temp, °C	yield, % ^a	cr ^b
1	CH ₂ Ph	12ba	-78	91	67.0:33.0
2	CHMe ₂	12bb	-78	90	85.0:15.0
3	CMe ₃	12bc	-94	32	84.0:16.0
4	CMe ₃	12bc	-78	95	87.5:12.5
5	CMe ₂ Ph	12bd	-78	75	82.0:18.0
6	CMePh ₂	12be	-78	41	89.0:11.0
7	CMePh ₂	12be	-63	99	90.5:9.5
8	CPh ₃	12bf	-63	0	—

^aYield of chromatographically homogeneous material.

^bAll compounds have *R* configuration. Determined by CSP-HPLC analysis.

Table 3
Evaluation of ligand structure in additions of MeLi to imine **8**

entry	R ³	ligand	temp, °C	yield, % ^a	er ^b
1	Me	12ac	-75 ^c	90	83.5:16.5
2	Et	12bc	-78	95	87.5:12.5
3	CH ₂ CHMe ₂	12cc	-78	65	92.0:8.0
4	CH ₂ CHMe ₂	12cc	-63	95	92.5:7.5
5	CH ₂ (Me) <i>c</i> -Pr	12jc	-75 ^c	85	92.6:7.4
6	CHMe ₂	12ec	-75 ^c	87	94.5:5.5
7	Me, CHMe ₂	12dc	-75 ^c	97	87.0:13.0

^aYield of chromatographically homogeneous material.

^bAll compounds have *R* configuration. Determined by CSP-HPLC analysis.

^cInternal temperature.

Table 4
Evaluation of ligand structure in additions of MeLi to imine **11**

entry	R ³	R ⁴	ligand	temp, °C	yield, % ^a	er ^b
1	Et	CHMe ₂	12bb	-63	86	86.5:13.5
2	Et	CMe ₃	12bc	-63	96	95.5:4.5
3	Et	CMe ₃	12bc	-78	83	94.5:5.5
4	Et	CMePh ₂	12be	-63	21	82.0:18.0
5	Et	CMePh ₂	12be	-41	90	84.5:15.5
6	Me	CMe ₃	12ac	-75 ^c	81	96.5:3.5
7	CH ₂ CHMe ₂	CMe ₃	12cc	-75 ^c	97	93.5:6.5
8	CH ₂ (Me) <i>c</i> -Pr	CMe ₃	12jc	-75 ^c	92	88.5:11.5
9	CHMe ₂	CMe ₃	12ec	-75 ^c	77	93.5:6.5

^aYield of chromatographically homogeneous material.

^bAll compounds have *R* configuration. Determined by CSP-HPLC analysis.

^cInternal temperature.

Table 5
Evaluation of ligand structure in additions of MeLi to imine **10**

entry	R ³	ligand	temp, °C	yield, % ^a	er ^b
1	Me	12ac	-75 ^c	73	97.0:3.0
2	Et	12bc	-78	65	91.5:8.5
3	Et	12bc	-63	79	92.5:7.5
4	Et	12bc	-41	90	89.5:10.5
5	CH ₂ CHMe ₂	12cc	-41	90	86.5:13.5
6	CH ₂ (Me) <i>c</i> -Pr	12jc	-75 ^c	87	89.0:11.0
7	CHMe ₂	12ec	-75 ^c	77	90.5:9.5

^aYield of analytically pure material.

^bAll compounds have *R* configuration. Determined by CSP-HPLC analysis.

^cInternal temperature.

Table 6
Evaluation of ligand structure in additions of MeLi to imines **8**, **10** and **11**

entry	R (no.)	ligand	n	product	yield, % ^a	er ^b
1	Ph (8)	12kc	3	15	82	75.5:24.5
2	Ph (8)	12lc	4	15	97	86.5:13.5
3	Ph (8)	12mc	5	15	94	85.5:14.5
4	Ph (8)	12nc	6	15	87	85.0:15.0
5	Ph (8)	12ac	Me, Me	15	90	83.5:16.5
6	PhCH=CH (10)	12kc	3	17	93	51.0:49.0
7	PhCH=CH (10)	12lc	4	17	85	92.0:8.0
8	PhCH=CH (10)	12mc	5	17	81	95.0:5.0
9	PhCH=CH (10)	12nc	6	17	70	95.5:4.5
10	PhCH=CH (10)	12ac	Me, Me	17	73	97.0:3.0
11	PhCH ₂ CH ₂ (11)	12kc	3	16	72	72.0:28.0
12	PhCH ₂ CH ₂ (11)	12lc	4	16	80	95.0:5.0
13	PhCH ₂ CH ₂ (11)	12mc	5	16	87	95.5:4.5
14	PhCH ₂ CH ₂ (11)	12nc	6	16	83	87.5:12.5
15	PhCH ₂ CH ₂ (11)	12ac	Me, Me	16	81	96.5:3.5

^aYield of chromatographically homogeneous material.

^bAll compounds have *R* configuration. Determined by CSP-HPLC analysis.

Table 7

Summary of MeLi addition to imines **8**, **9**, **10** and **11**

entry	R ¹ (no.)	ligand	temp, °C	product	yield, % ^a	er ^b
1	Ph (8)	12ec	-75 ^c	15	87	94.5:5.5
2	1-naphthyl (9)	12bc	-78	18	91	85.5:14.5
3	1-naphthyl (9)	12cc	-41	18	95	92.0:8.0
4	PhCH=CH (10)	12ac	-75 ^c	17	73	97.0:3.0
5	PhCH ₂ CH ₂ (11)	12ac	-75 ^c	16	81	96.5:3.5

^aYield of analytically pure material.

^bAll compounds have *R* configuration. Determined by CSP-HPLC analysis.

^cInternal temperature.

Table 8
Addition of organolithium reagents to imine **11** promoted by **12bc**

		product	yield, % ^a	er ^b
entry	R ²	solvent				
1	<i>n</i> -Bu	toluene		19	82	78.5:21.5 ^c
2	<i>n</i> -Bu	toluene/Et ₂ O (8:1)		19	90	83.0:17.0 ^c
3	<i>n</i> -Bu	<i>i</i> -Pr ₂ O		19	86	84.5:15.5 ^c
4	<i>n</i> -Bu	Et ₂ O		19	90	76.5:23.5 ^c
5	<i>n</i> -Bu	TBME		19	86	74.0:26.0 ^c
6	Ph ^d	toluene		20	82	65.0:35.0 ^e
7	Ph ^f	toluene/Et ₂ O		20	89	50.0:50.0 ^e
8	CH ₂ =CH	toluene		21	95	94.5:5.5 ^e
9	CH ₂ =CH	<i>i</i> -Pr ₂ O		21	75	92.0:8.0 ^e

^aYield of chromatographically homogeneous material.

^bDetermined by CSP-HPLC analysis.

^c*R* absolute configuration.

^dReaction was performed using 2 equiv of PhLi (Aldrich).

^eAbsolute configuration not determined.

^fReaction was performed using 2 equiv of prepared PhLi.

Table 9Solvent effect on the ligand-free addition of *n*-BuLi to imine **11**.^a

entry	solvent	conv., % ^b
1	toluene	19
2	<i>i</i> -Pr ₂ O	91
3	Et ₂ O	95
4	TBME	100

^aReactions conducted for 1 h at – 78 °C.^bDetermined by GC analysis.

Table 10
Study of ligand stoichiometry in the addition of MeLi to imine **8**

entry	ligand	R ⁴	ligand, equiv	yield, % ^a	er ^b
1	12ba	CH ₂ Ph	1.00	91	67.0:33.0
2	12ba	CH ₂ Ph	0.50	71	71.0:29.0
3	12ba	CH ₂ Ph	0.25	47	71.0:29.0
4	12ba	CH ₂ Ph	0.10	27	68.5:31.5
5	12bb	CHMe ₂	1.00	90	85.0:15.0
6	12bb	CHMe ₂	0.50	68	83.0:17.0
7	12bb	CHMe ₂	0.25	57	81.0:19.0
8	12bb	CHMe ₂	0.10	30	81.5:18.5
9	12bc	CMe ₃	1.00	95	87.5:12.5
10	12bc	CMe ₃	0.50	88	86.5:13.5
11	12bc	CMe ₃	0.25	65	85.0:15.0
12	12bc	CMe ₃	0.10	46	83.0:17.0

^aYield of chromatographically homogeneous material.

^bAll compounds have *R* configuration. Determined by CSP-HPLC analysis.

Table 11
Catalytic ligand-mediated addition of MeLi to imines **8–11**

entry	R ¹	imine	ligand	temp, °C	product	yield, % ^a	er ^b
1	Ph	8	12ba	-78	15	27	68.5:31.5
2	Ph	8	12bb	-78	15	30	81.5:18.5
3	Ph	8	12bc	-78	15	46	83.0:17.0
4	Ph	8	12bc	-63	15	66	84.0:16.0
5	Ph	8	12bc	-41	15	97	84.5:15.5
6	Ph	8	12be	-78	15	12	77.5:22.5
7	Ph	8	12be	-63	15	51	81.0:19.0
8	Ph	8	12be	-41	15	99	81.5:18.5
9	Ph	8	12cc	-63	15	23	84.0:16.0
10	Ph	8	12cc	-41	15	83	77.0:23.0
11	1-naphthyl	9	12bc	-63	18	44	84.0:16.0
12	1-naphthyl	9	12bc	-41	18	97	80.0:20.0
13	PhCH=CH	10	12bc	-63	17	30	90.0:10.0
14	PhCH=CH	10	12bc	-41	17	92	84.0:16.0
15	PhCH=CH	10	12cc	-41	17	92	77.5:22.5
16	PhCH ₂ CH ₂	11	12bb	-63	16	45	70.5:29.5
17	PhCH ₂ CH ₂	11	12bc	-78	16	41	90.0:10.0
18	PhCH ₂ CH ₂	11	12bc	-63	16	52	89.5:10.5
19	PhCH ₂ CH ₂	11	12bc	-41	16	64	78.0:22.0

^aYield of chromatographically homogeneous material.

^bAll compounds have *R* configuration. Determined by CSP-HPLC analysis.

Table 12

Catalytic addition of organolithium reagents to imine **11**

entry	R ²	12bc, equiv	solvent	product	temp, °C	yield, % ^a	er ^b
1	Me	0.1	toluene	16	-78	41	90.0:10.0
2	Me	0.1	toluene	16	-63	52	89.5:10.5
3	Me	0.2	toluene	16	-63	97	91.5:8.5
4	<i>n</i> -Bu	0.1	toluene	19	-78	62	59.0:41.0
5	<i>n</i> -Bu	0.1	toluene/Et ₂ O, 8:1	19	-78	86	72.0:28.0
6	<i>n</i> -Bu	0.1	<i>i</i> -Pr ₂ O	19	-78	81	70.5:29.5
7	<i>n</i> -Bu	0.2	<i>i</i> -Pr ₂ O	19	-78	92	75.5:24.5
8	CH ₂ =CH	0.1	toluene	21	-78	49	83.0:17.0
9	CH ₂ =CH	0.2	toluene	21	-78	82	91.0:9.0

^aYield of chromatographically homogeneous material.

^bDetermined by CSP-HPLC analysis.

Table 13
(-)-Sparteine-promoted addition of organolithium reagents to imine **11**

entry	ligand	amount	R^2	solvent	temp, °C	product	yield, % ^a	er ^b
1	12bc	1.0	Me	toluene	-63	16	83	94.5:5.5
2	4	1.0	Me	toluene	-78	16	71	86.0:14.0
3	4a	1.0	Me	toluene	-78	16	79	70.0:30.0
4	12bc	1.0	<i>n</i> -Bu	toluene	-78	19	82	78.5:21.5
5	12bc	1.0	<i>n</i> -Bu	<i>i</i> -Pr ₂ O	-78	19	86	84.5:15.5
6	12bc	1.0	<i>n</i> -Bu	Et ₂ O	-78	19	90	76.5:23.5
7	4	1.0	<i>n</i> -Bu	toluene	-94	19	86	89.5:10.5
8	4	1.0	<i>n</i> -Bu	<i>i</i> -Pr ₂ O	-78	19	85	91.5:8.5
9	4	1.0	<i>n</i> -Bu	Et ₂ O	-94	19	90	95.5:4.5
10	12bc	0.2	<i>n</i> -Bu	<i>i</i> -Pr ₂ O	-78	19	92	75.5:24.5
11	4	0.2	<i>n</i> -Bu	Et ₂ O	-78	19	91	89.5:10.5
12	12bc	1.0	Ph	toluene	-78	20	82	65.0:35.0
13	4	1.0	Ph	toluene	-94	20	99	91.0:9.0
14	4	1.0	Ph	<i>i</i> -Pr ₂ O	-78	20	71	85.0:15.0
15	4	1.0	Ph	Et ₂ O	-78	20	85	81.0:19.0
16	4	0.1	Ph	Et ₂ O	-78	20	86	56.5:43.5
17	4	0.2	Ph	toluene	-78	20	97	69.5:30.5

^aYield of chromatographically homogeneous material.

^b Determined by CSP-HPLC analysis.

Table 14

(-)-Sparteine-promoted addition of *n*-BuLi to imine **4**

entry	ligand	equiv	solvent	temp, °C	yield, % ^a	cr ^b
1	12bc	2.6	toluene	-78	99	66.0:34.0
2	12bc	0.1	toluene	-78	39	56.5:43.5
3	12cc	1.0	<i>i</i> -Pr ₂ O	-94	94	67.0:33.0
4	4	1.0	toluene	-78	91	60.5:39.5
5	4	1.0	<i>i</i> -Pr ₂ O	-78	84	68.5:31.5
6	4	1.0	Et ₂ O	-78	99	68.0:32.0
7	4	1.0	Et ₂ O	-94	95	72.0:28.0
8	4	0.2	Et ₂ O	-78	89	63.5:26.5
9	4a	1.0	Et ₂ O	-78	91	57.0:43.0

^aYield of chromatographically homogeneous material.

^bAll compounds have *R* configuration. Determined by CSP- HPLC analysis.

Table 15
Correlation of bridging ligand substituent to the enantioselectivity of the addition

imine	ligand, er			
	12ac	12bc	12cc	12jc
8	83.5:16.5	87.5:12.5	92.0:8.0	94.5:5.5
10	97.0:3.0	91.5:8.5	86.5:13.5	90.5:9.5
11	96.5:3.5	94.5:5.5	93.5:6.5	93.5:6.5

8: R¹ = Ph
10: R¹ = PhCH₂CH₂
11: R¹ = PhCH₂CH₂
15: R¹ = Ph
17: R¹ = PhCH₂CH₂
16: R¹ = PhCH₂CH₂
12ac: R² = R³ = Me
12bc: R² = R³ = Et
12cc: R² = R³ = Me, R³ = CH₂CHMe₂
12dc: R² = R³ = Me, R³ = CHMe₂
12jc: R² = R³ = CH₂(Me)c-Pr
12ec: R² = R³ = CHMe₂

Table 16
Correlation of ligand geometry, bridge angle ($^{\circ}$) and enantioselectivity of addition

<p> 8: $R^1 = \text{Ph}$ 10: $R^1 = \text{PhCH=CH}$ 11: $R^1 = \text{PhCH}_2\text{CH}_2$ </p> <p> 12kc: $n = 3$ 12lc: $n = 4$ 12mc: $n = 5$ 12nc: $n = 6$ </p>	
imine/er	ligand, calculated bridge angle ($^{\circ}$)
12kc 112.7	12mc 111.8
8 75.5:24.5	12lc 110.0
10 51.0:49.0	12ac 109.7
11 72.0:28.0	12nc 106.8
	85.0:15.0
	95.5:4.5
	87.5:12.5

Table 17

Calculation of ligand geometries,

ligand (n)	bridging angle, °				N-Li-N, °
	MM2	MM2, coplanar N's	PM3 free ligand	PM3 Li•complex	PM3 Li•complex
12kc (3)	108.7	108.8	111.6	112.7	89.0
12lc (4)	113.0	116.0	108.3	110.0	89.8
12mc (5)	107.7	114.6	106.9	111.8	86.9
12nc (6)	104.5	104.5	108.2	106.8	90.7
12ac (Me ₂ C)	107.2	107.4	108.7	109.7	88.7

Table 18
Bond lengths (Å), dihedral angles (°) and energies (kcal/mol) in starting materials, complexes, transition structures and products

	imine	complexes				Transition States		Products	
		12ac•MeLi + 11	A	B	C	TS-1	TS-2	S	R
rel. energies		0.0	-12.3	-11.2	-9.4	8.5	7.4	-36.8	-37.6
Li-Me		2.048	2.070	2.059	2.069	2.129	2.123	2.9	3.2
imine C-N	1.296		1.303	1.302	1.304	1.358	1.357	1.482	1.482
C-C-C=N		-6.9	-29.8	+1.2	-5.3	-20.3	+58.1	-23.1	-36.5
N=C-C-C		+13.2	+61.0	+35.9	+33.2	+46.6	-28.2	+43.3	+52.6
Li-N _{imine}			2.189	2.156	2.137	2.089	2.050	1.951	1.944
Me-C _{imine}			4.6	4.2	4.4	2.302	2.320	1.538	1.530