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Ligand-mediated addition of organometallic reagents to azomethine functions

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Despite the enormous progress made in the asymmetric addition of nucleophiles to prochiral carbonyl compounds for the preparation of chiral alcohols, the corresponding study of enantioselective conversion of prochiral azomethine functions to chiral amines remains a relatively undeveloped area of research. This account reviews the current state of this new field of investigation.

Introduction

The development of new and practical methods of stereoselective synthesis is currently among the major objectives in organic chemistry laboratories throughout the world.[1,2] The invention of new asymmetric reactions *via* the use of both chiral auxiliaries and chiral catalysts has become a major concern of chemists in academic and industrial settings. The availability of enantiomerically pure compounds is of critical importance to pharmaceutical and agricultural chemistry, where biologically important molecules often show effective activity as one enantiomer; the other is at best ineffective or at worst detrimental.[3]

The routes to enantiomerically pure compounds (resolution notwithstanding) represent two modes of asymmetric synthesis: (1) chiral-auxiliary-based asymmetric synthesis (asymmetric diastereoselective synthesis), and (2) external chiral-ligand-controlled asymmetric synthesis (asymmetric enantioselective synthesis). Our interest in this area focused on the asymmetric synthesis of amines and amine derivatives.[4,5] Optically active amines[6] are indeed important compounds utilized extensively in organic synthesis as resolving agents,[7] raw materials or intermediates in the production of biologically active substances[8] and chiral auxiliaries for asymmetric synthesis.[9]

We first became intrigued by the unique reactivity of organocerium reagents with chiral hydrazones, leading to the development of a general method for the synthesis of enantiomerically enriched α-branched amines and amine derivatives.[10] The chiral-auxiliary-based addition of organometallic reagents to the hydrazone functionality was shown to be a valuable method of diastereoselective synthesis. We then turned our attention to the asymmetric addition of carbon nucleophiles to the azomethine function in the presence of external chiral ligands,[11] and we have recently reported our preliminary results.[12] The objective of this Feature Article is to review the current state of the art of stoichiometric and catalytic addition for the asymmetric synthesis of chiral amines.

Enantioselective addition to azomethine *vs.* carbonyl groups

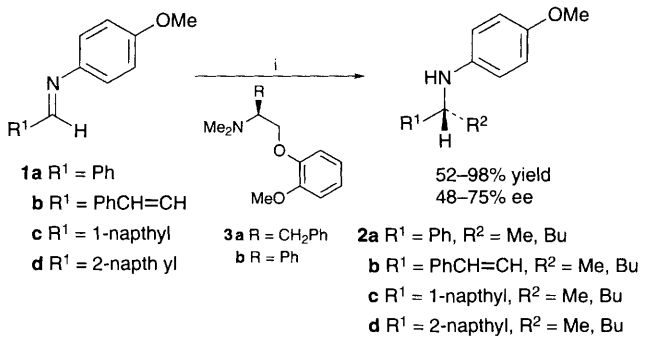
The asymmetric addition of organometallic reagents to the azomethine group in the presence of chiral ligands is quite underdeveloped in comparison to the effort on record in the area of stoichiometric enantioselective addition to carbonyl compounds.[13] This situation is primarily due to the poor electrophilicity of the C=N function and also the tendency of enolizable azomethines to undergo deprotonation rather than addition.

The ultimate goal of using an external, chiral ligand in a chemical reaction is the potential for a catalytic, asymmetric synthetic transformation.[14] Thus, the catalytic enantioselective addition of organozinc reagents to aldehydes represents a major accomplishment,[15] whereas a similar catalytic process for azomethine derivatives has yet to be achieved.

Enantioselective addition to imines using RLi

The first report of external chiral-ligand-mediated addition of organometallic reagents to an azomethine function appeared in 1990. Tomioka and co-workers reported the addition of organolithium compounds to *N*-aryl imines in the presence of a stoichiometric amount of a chiral β-amino ether as the asymmetric controller.[16a,17a] Tomioka *et al.* studied the addition of methyllithium (MeLi) and butyllithium (BuLi) to unsaturated *N*-(4-methoxyphenyl) imines derived from benzaldehyde (**1a**), cinnamaldehyde (**1b**), and 1-/2-naphthalenecarboxaldehydes (**1c,d**). The 1,2-addition reactions were performed in the presence of an excess (2.6 equiv. per equiv. of **1**) of the chiral β-amino ether **3a** as the external chiral ligand, Scheme 1.[16e,18] The optimization of ligand structure was carried out using the methyllithium addition to imine **1a**. The ligands **3a,b** were selected because they exhibited the same high level of enantioselectivity (70% ee).

The reactions were run in toluene, at −78 or −100 °C. Using a twofold excess of the alkyllithium, the secondary amines **2a–d** were isolated in good yields: up to 98%, and with moderate to good enantiomeric purities: 48–75% ee. The formation of the 1,4-addition product was not observed. It is important to note that the chiral ligands **3a,b** were recovered quantitatively for reuse, without any loss of enantiomeric purity. The highest enantioselectivities were observed with the imines derived from benzaldehyde and naphthalenecarboxaldehydes: 65–75% ee. The additions of MeLi consistently provided the highest enantioselectivities for every substrate examined, compared to the use of BuLi. The authors have mentioned that toluene and diethyl ether were the solvents of choice, whereas THF and



Scheme 1 *Reagents and conditions*: i, R^2Li (2 equiv.), PhMe, −78 or −100 °C, 20 min to 2 h, **3a** (26 equiv.)

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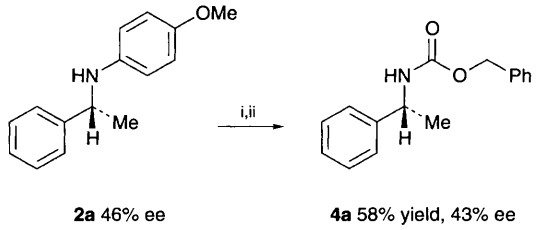
DME afforded the amines **2a–d** in nearly racemic form. They also noted that the enantioselectivity of the reaction of imine **1a** with lithium bromide-complexed MeLi at −42 °C was not significantly affected.[16e] However, a recent study by Tomioka and co-workers on the effects provided by the change of the *N*-phenyl ring substitution in the starting imines has shown that higher enantioselectivities (up to 90% ee) could be obtained, particularly in the case of the addition to imines derived from 2-methylanisidine, in the presence of **3a**.[16c]

The synthetic utility of the enantioselective addition to an azomethine function relies on a practical method for the dearylation of the resulting chiral amines. A two-step procedure was illustrated for amine **2a** (R^2 = Me), which begins with a protection step (BuLi/$ClCO_2CH_2Ph$) followed by oxidative cleavage of the aryl moiety (ceric ammonium nitrate: CAN). The *N*-protected amine **4a** was isolated in only 58% overall yield without significant loss of enantiomeric purity, Scheme 2.

Shortly after this report, Tomioka and co-workers disclosed a catalytic process for the enantioselective addition reaction described just above, by the use of a substoichiometric amount of the chiral tridentate ligand **3a**.[16b] To compare the data obtained from both stoichiometric and catalytic processes, MeLi and BuLi were used as the carbon nucleophiles in additions to the imines **1a–d**. Substoichiometric amounts of **3a** (0.05–0.5 equiv.) were used in these addition reactions. Most of the reactions were run in toluene, at −42 or −78 °C depending on the nucleophile. In a similar manner to the previous study, 2 equiv. of the organolithium compound was employed, and uniformly high yields of the secondary amines **2a–d** were obtained: 81–99%. A significant catalytic asymmetric induction was observed in the addition of MeLi and BuLi to the naphthalenecarboxaldehyde-derived imines **1c,d**: 50–59% ee with 0.3 equiv. of **3a**. At comparative loadings of the ligand **3a**, the additions of MeLi again provided the highest enantioselectivities compared to the additions of BuLi. The results of the experiments conducted with MeLi and the imine **1a** were particularly interesting with regard to the catalytic activity of the ligand **3a**. Indeed, while practically no reaction occurred with 0.05 equiv. of **3a** at −78 °C, when the reaction was carried out at −42 °C, the resulting amine **2a** (R^2 = Me) was isolated in 96% yield and 40% ee. It is noteworthy that the reaction proceeded as well at −42 °C in the absence of **3a** to afford 91% yield of racemic **2a** (R^2 = Me). In the case of BuLi additions, the choice of the solvent was critical for asymmetric catalysis. Indeed, the reaction with **1a** and 0.3 equiv. of **3a** in toluene, at −78 °C, afforded the corresponding amine **2a** (R^2 = Bu) in only 25% ee whereas the use of Et_2O or Pr^i_2O as solvent afforded the chiral amine in 45 and 60% ee, respectively. The use of LiBr-complexed MeLi for the catalytic enantioselective methylation of imine **1a** at −42 °C significantly decreased the enantioselectivity of the reaction,[16e] but the catalytic enantioselective addition to imines derived from 2-methylanisidine resulted again in higher enantioselectivities.[16d]

Although the level of enantioselectivity reported in this study remained moderate, the chiral ligand **3a** still exhibited a remarkable catalytic effect on asymmetric induction to produce the enantiomerically enriched secondary amines **2a–d**.[19]



2a 46% ee **4a** 58% yield, 43% ee

Scheme 2 *Reagents*: i, BuLi, THF then $ClCO_2CH_2Ph$; ii, CAN, aq. MeCN

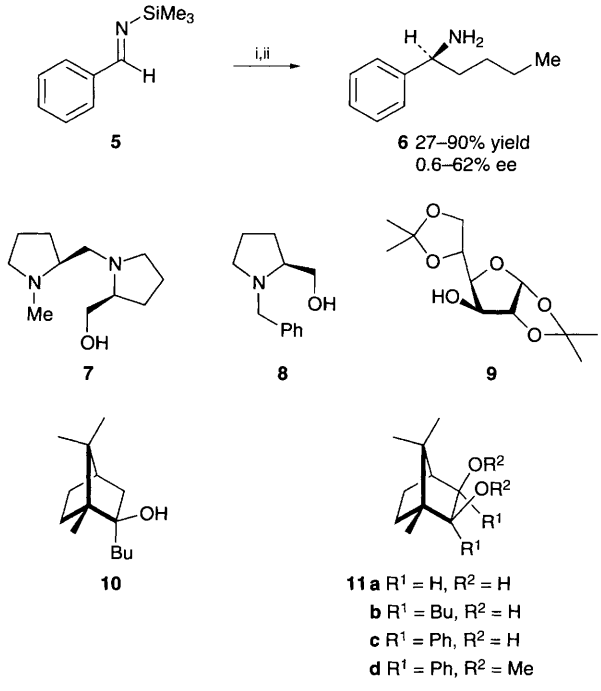
The second report of enantioselective organolithium additions to the imine group came in 1991 from the laboratories of Itsuno and co-workers.[20a] These researchers studied the addition of BuLi to benzaldehyde *N*-(trimethylsilyl) imine **5** in the presence of chiral modifiers such as chiral alcohols, diols and amino alcohols. The enantiomerically enriched primary amine **6** was obtained in 27–90% yield depending on the nature of the chiral ligand and the reaction solvent, Scheme 3.

Since the formation of a chiral lithium alkoxide is likely to be involved in the asymmetric addition process, various ratios of the components (chiral ligand : BuLi : **5**) were examined. The results of this study revealed a remarkable solvent effect on both efficiency and selectivity for BuLi additions, and also a dependence of the absolute configuration of the amine **6** on the solvent employed. The amino alcohols such as **7** and **8** gave only poor enantioselectivities in the asymmetric butyl addition to **5**, but the chiral alcohols **9–11** proved to be superior ligands in all respects. Whereas the chiral ligands **9,10** and **11a,b** afforded the amine **6** in 3–25% ee, the use of the chiral diol **11c** in Et_2O (**11c** : BuLi : **5** = 2 : 5 : 0.5) gave the best result: 62% ee favouring the *S*-enantiomer. It should be noted that the use of the chiral bis-ether **11d** afforded a racemic compound. The authors proposed that a chiral lithium alkoxide could act as a chiral modifier of BuLi during the addition step.

The same group has recently reported new findings on the reaction of BuLi with *N*-(metallo) imines.[20b] They examined the addition of BuLi to an *N*-alumino imine, *N*-boryl imine and *N*-silyl imine in the presence of chiral nitrogen ligands including (−)-sparteine and proline-derived amino alcohols, Scheme 4.

The reaction of the preformed (−)-sparteine·BuLi complex (1 equiv.) with benzaldehyde *N*-(diisobutylalumino) imine (1 equiv.) at −78 °C in pentane gave the best result: 70% yield and 74% ee favouring the *R*-enantiomer. On the other hand, a preformed (−)-sparteine·benzaldehyde *N*-boryl imine complex (1 equiv.) was treated with BuLi (1 equiv.) at −78 °C in Et_2O to give the corresponding primary amine in 68% yield and 50% ee, favouring also the *R*-enantiomer.[21]

Our own contributions to this field were disclosed in 1994.[12a] At the outset we established the following boundary conditions to develop a practical method of enantioselective addition to imines:[22] (1) at most, a stoichiometric amount of chiral promoter should be used (ideally, catalytic quantities); (2) the

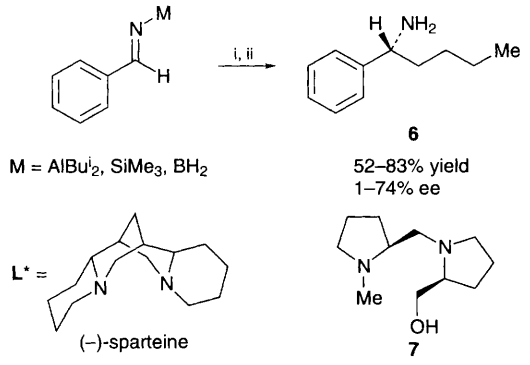


Scheme 3 *Reagents and conditions*: i, BuLi, **7–11**, solvent −78 °C, 5 h; ii, H_2O, HCl

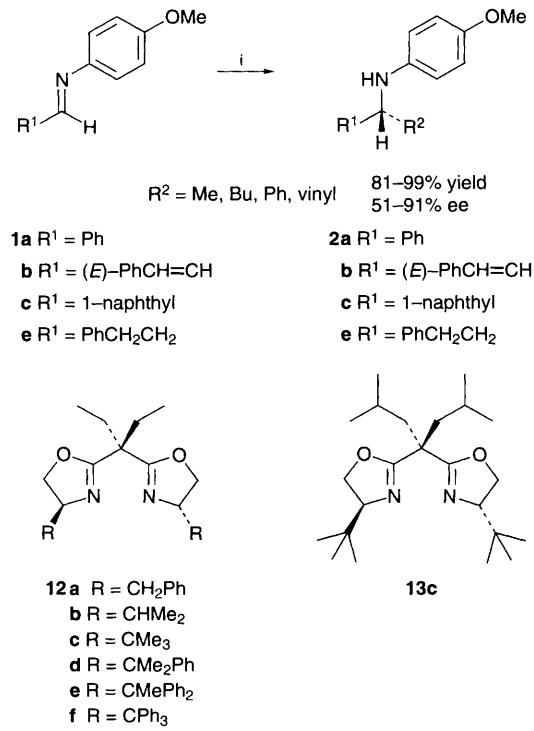
method should be general for nucleophile and imine structure; (3) the ligand should be easily prepared and recoverable; and (4) simple organolithium compounds should serve as the nucleophiles.

For the ligands, we selected the readily available chiral 2,2′-bis(oxazolino)methanes **12** and **13**, Scheme 5. This class of compounds has been extensively employed as ligands in a wide variety of transition metal-catalysed asymmetric reactions.[23] The chiral C_2-symmetric bis(oxazoline) ligands **12a–f** and **13c** used in our work are easily synthesized from naturally-derived or synthetic amino alcohols and malonyl dichloride derivatives.[12b]

The first study focused on the optimization of ligand structure using the addition of MeLi (2 equiv. in toluene at −63 or −78 °C) to imine **1a** in the presence of a stoichiometric amount of the ligand (1 equiv. based on **1a**). The secondary amine **2a** (R^2 = Me) was isolated in good yields: up to 99% with **12e**, and with good enantiomeric purities: up to 85% ee with **13c**.‡ Since



Scheme 4 *Reagents and conditions*: i, BuLi, **L***, solvent, −78 °C; ii, H_3O^+



Scheme 5 *Reagents and conditions*: i, R^2Li (2 equiv.), PhMe, temp., time, **12a–f** or **13c** (0.1–1 equiv.)

‡ The absolute configurations of the products were established by degradation to the amines by the following sequence: (1) BuLi/$ClCO_2Me$, (2) $Ce(NH_4)_2(NO_3)_6$, (3) Me_3SiI and comparison of $[\alpha]_D$ with authentic samples.

the *tert*-butyl series is more readily available, **12c** and **13c** were selected for the survey of substrate and nucleophile generality. In all stoichiometric additions using **12c** and **13c**, the ligand was recovered in enantiomerically pure form in 91–100% yield. The highest enantioselectivities in the MeLi addition to other imines were observed with aliphatic imines **1e** compared to aromatic **1a,c** and conjugated imines **1b**: 91% *vs.* 85% ee. To assay the generality of this procedure for the addition of other organolithium nucleophiles, we selected the aliphatic imine **1e**. It was found that MeLi consistently provided the highest enantioselectivities (91% ee) compared to the use of BuLi (51% ee), PhLi (30% ee) and vinyllithium (89% ee). The effect of solvent was evaluated using the BuLi addition to imine **1e** in the presence of the ligand **12c**.[24] The use of Pr^i_2O as solvent afforded amine **2e** (R^2 = Bu) in 86% yield and 69% ee, whereas toluene, Et_2O, and *tert*-butyl methyl ether (TBME) gave the same compound in 82–90% yield and 48–57% ee.

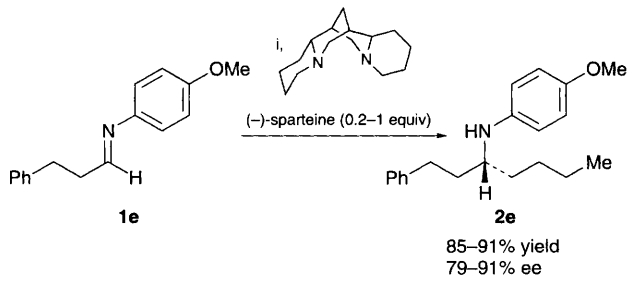
Similar to the results reported by Tomioka and co-workers,[16d] we observed that the reaction of MeLi with **1a** in the absence of an added ligand hardly proceeded in toluene at −78 °C, affording **2a** (R^2 = Me) in only 6% yield after 4 h; the potential for catalysis was therefore obvious. Indeed, the addition of MeLi to imines **1a–c,e** with substoichiometric amounts of **12c** (0.1–0.2 equiv.), in toluene at −41 or −63 °C, proceeded in excellent yield (81–98%), albeit with somewhat reduced enantioselectivity (60–82% ee). The catalytic addition of vinyllithium to **1e** using **12c** (0.2 equiv.) afforded the corresponding amine with a comparable level of enantioselectivity (82% ee). The lesser selectivities observed in the stoichiometric and catalytic addition of BuLi to **1e** suggested that a stronger chelating ligand was necessary. The bidentate tertiary amine (−)-sparteine was found to serve effectively as the external ligand, Scheme 6.[25]

The use of (−)-sparteine had a dramatic effect on the rate of reaction, in both stoichiometric and catalytic quantitites, allowing complete conversion of **1e** with BuLi between −78 and −94 °C. The enantioselectivity of the butylation of **1e** was significantly improved, affording **2e** (R^2 = Bu) in 90% yield and 91% ee (in Et_2O). The presence of (−)-sparteine (1 equiv.) also effected the enantioselective addition of PhLi to **1e**, affording **2e** (R^2 = Ph) in 82% ee compared to 30% ee using **12c** (1 equiv.).

Enantioselective addition to imines using R_2Zn

The tremendous success in the catalytic enantioselective addition of organozinc reagents to aldehydes spurred Itsuno and co-workers to examine the reactivity of diethylzinc with silyl imines in the presence of chiral amino alcohols and diols. Unfortunately, this type of azomethine failed to react.[20a] The use of activated *N*-acyl and *N*-phosphinoyl imines turned out to be crucial as evidenced by two reports on the enantioselective addition to the azomethine function using dialkylzinc reagents in the presence of a stoichiometric and/or catalytic amount of a chiral amino alcohol.

In 1992, Katritzky and Harris reported the use of diethylzinc for the chiral amino alcohol-mediated enantioselective addition

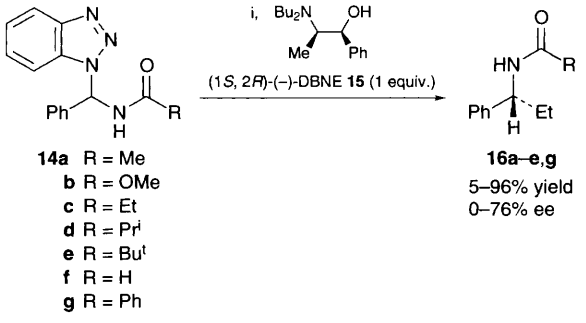


Scheme 6 *Reagents and conditions*: i, BuLi (2 equiv.), solvent, −78 or −94 °C, 1 h

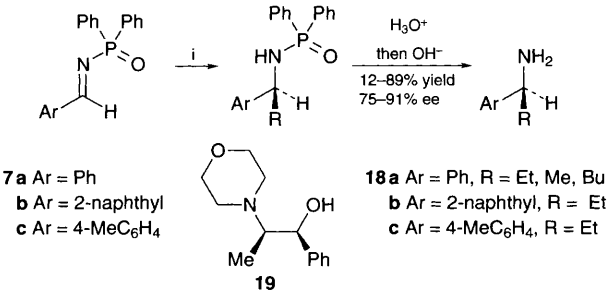
to the C=N bond in *N*-(amidobenzyl)benzotriazoles, Scheme 7.[26,27] These substrates act as masked activated *N*-acyl imines. Of the large variety of ligands available for the catalytic asymmetric reactions of dialkylzinc reagents, (−)-*N*,*N*-dibutylnorephedrine **15** was selected for this study. Some preliminary experiments conducted with the use of *N*-(aminobenzyl)benzotriazoles gave the ethylated product, but with no enantioselectivity. Diethylzinc (Et_2Zn) was found to react even in the absence of a chiral promoter. The behaviour of the less reactive *N*-(amidobenzyl)benzotriazoles **14a–g** was then investigated. These various substrates differed in the nature of the amide function (R substituent).

Orienting experiments were carried out with the benzotriazole derivative **14a**. Initially, the use of a catalytic amount (0.2 equiv.) of **15** in toluene afforded the *N*-(1-phenylpropyl)amide **16a** in only 13% ee. In the presence of an equimolar mixture of **14a** and **15**, the amide **16a** was isolated in 14% yield and 55% ee. It is important to note that no ethyl addition occurred at −78 °C. With 3 equiv. of Et_2Zn, and 1 equiv. of **15**, the amide **16a** was isolated in 46% yield and 76% ee. With these optimal conditions the reactivity of the other substrates **14b–g** was examined. In these cases the excess of Et_2Zn was found to have no additional effect and 2 equiv. of Et_2Zn was employed. With the exception of the formamide derivative **14f**, all the other substrates afforded the corresponding amides **16b–e,g**, with however a wide range of chemical yields: 5–96% yield, and with moderate enantioselectivities: 0–42% ee. Although the level of enantioselectivity observed in this study was modest, this contribution has documented for the first time the use of a dialkylzinc reagent for the stereoselective addition of a carbon nucleophile to the imine function.

The second publication also appeared in 1992 from Soai and co-workers on the asymmetric synthesis of optically active amines by the reaction of organozinc reagents with *N*-diphenylphosphinoyl imines.[28] The diphenylphosphinoyl moiety provided the necessary activation of the C=N bond to observe dialkylzinc additions. The reactivity of a series of three *N*-diphenylphospinoyl imines **17a–c** was examined in the presence of Et_2Zn and a catalytic or a stoichiometric amount of the chiral β-amino alcohols **15** or **19**, Scheme 8.



Scheme 7 *Reagents and conditions*: i, Et_2Zn (2.2 equiv.), PhMe, −78 °C → room temp.



Scheme 8 *Reagents and conditions*: i, R_2Zn (3 equiv.), PhMe, 0 °C → room temp., **15** or **19**

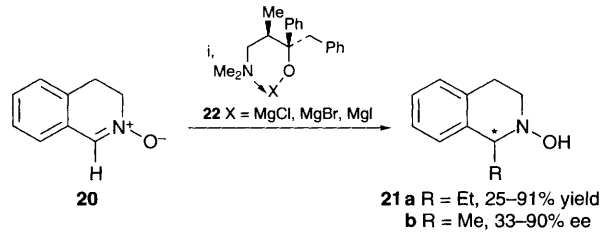
When the chiral ligand **19** was used stoichiometrically (**17** : R_2Zn : **19** = 1 : 3 : 1), the reaction of imine **17a** with Et_2Zn afforded the corresponding (*S*)-phosphinamide **18a** (R = Et) in 89% yield and 90% ee. In the presence of **15**, (*S*)-**18a** (R = Et) was obtained in 61% yield and 84% ee. The highest enantioselectivity was recorded with the use of imine **17b**, affording the phosphinamide **18b** in 84% yield and 91% ee. In the presence of a substoichiometric amount of the chiral ligand **19**, *i.e.* 0.5 equiv., the phosphinamides **18a–c** (R = Et) were obtained in 85–87% ee. However, a significant drop of the chemical yield was observed: 57–69%. With a catalytic amount of **15** (0.1 equiv.), only 12% yield of **18a** (R = Et) was obtained, but a good level of enantioselectivity was preserved: 75% ee. Finally, the methyl and butyl addition to the imine **17a** using 1 equiv. of **19** gave the phosphinamides **18a** (R = Me) and **18a** (R = Bu) in 46% yield and 85% ee, and 56% yield and 87% ee, respectively. The acidic hydrolysis of the phosphinamides liberated the corresponding aromatic primary amines with no loss of enantiomeric purity.

Enantioselective addition to nitrones using RMgX and R_2Zn

One of the most recent publications in the field of enantioselective addition to an azomethine function has documented the use of a nitrone as the acceptor.[29] Ukaji, Inomata and co-workers were anticipating that the oxygen atom of the nitrone would strongly coordinate a metal incorporated in a chiral environment to activate the nucleophilic addition of an organometallic reagent. Using the *in situ* generated metal alkoxide of (2*S*,3*R*)-4-dimethylamino-1,2-diphenyl-3-methylbutan-2-ol (Chirald®) (**22**, X = H) as the external chiral ligand, the authors studied the reaction of alkylmetals such as EtMgX (X = Cl, Br, I), MeMgBr, Et_2Zn and Me_2Zn with nitrone **20** as the substrate, Scheme 9.

The addition reactions using Grignard reagents were performed as follows: RMgCl (2.2 equiv.) was treated with (Chirald®) (1.1 equiv.) to generate magnesium alkoxide **22** (X = MgCl) (1.1 equiv.), and then the nitrone **20** (1.0 equiv.) was added to the solution at −78 °C. Of the three ethyl Grignard reagents suveyed, the reaction using EtMgBr in Et_2O in the presence of magnesium alkoxide **22** (X = MgBr) afforded the alkylated product (*S*)-**21a** in 54% yield and with the best enantioselectivity (75% ee). The enantioselectivity of the reaction was further improved, by the use of $MgBr_2$ (1.1 equiv.) as an additive. In dimethoxyethane (DME), the addition of EtMgBr to **20** afforded (*S*)-**21a** in 90% ee. In contrast, the addition reactions using dialkylzinc reagents gave rise to a reversal of the enantioselectivity. The use of Et_2Zn (2.2 equiv.) in THF at 25 °C in the presence of magnesium alkoxide **22** (X = MgBr) afforded the alkylated product (*R*)-**21a** in 74% yield and 57% ee. The same trends as above were observed when the addition reactions were performed with MeMgBr [(*S*)-**21b** in 80% ee] and Me_2Zn [(*R*)-**21b** in 66% ee].

The work of these researchers is quite innovative. Although the reaction mechanism is yet unknown, the reversal of the enantioselectivity obtained by the simple change of the organometallic species is of great interest.



Scheme 9 *Reagents and conditions*: i, RM (1.1 or 2.2 equiv.), solvent, −78 °C → room temp.

Conclusion

The results disclosed in various recent communications and reported in this account have contributed to the emergence of an interesting new area of research. The stereoselective synthesis of amines starting from an achiral substrate and using an organometallic compound in the presence of an external chiral auxiliary has become a viable process. While several types of carbon nucleophiles have been already examined, new methods of enantioselective addition might originate from the choice of different azomethine functions and/or different chiral sources. The search for a new and practical enantioselective addition to azomethine functions will remain a challenge in synthetic chemistry for some time to come.[30]

Scott E. Denmark was born in New York in 1953. He obtained an S. B. degree from MIT in 1975 and carried out research with Daniel Kemp and Richard Holm. His graduate studies at the ETH-Zürich with Albert Eschenmoser culminated with the DSc. Tech. degree in 1980. That same year he joined the faculty of the University of Illinois at Urbana-Champaign and was promoted to full professor in 1987. In 1991 he was named the Reynold C. Fuson Professor of Chemistry. His research interests are primarily in the invention of new synthetic reactions, structure and reactivity of organometallic reagents, and the origin of stereocontrol fundamental carbon–carbon bond forming reactions.

Olivier Jean-Charles Nicaise was born in Reims, France in 1960. He completed his Maîtrise de Chimie in June 1985 (with Honours) at the Université Pierre et Marie Curie. Olivier began his doctoral studies in chemistry with Professor Henri B. Kagan at the Université de Paris-Sud. He completed his first year of the French Ph.D. degree in June 1987, receiving the degree of D.E.A. de Chimie Organique with High Honours. In 1987, he moved to the US and joined the research group of Professor Scott E. Denmark at the University of Illinois. His thesis (completed in September 1993) involved the chemistry of the lanthanides which led to a new synthetic method for the chiral auxiliary-based asymmetric synthesis of amines and amine derivatives. This work then evolved to stoichiometric and catalytic enantioselective addition of organolithium reagents to imines. Olivier is currently a Postdoctoral Research Associate with Professor Léon Ghosez at the Université Catholique de Louvain, Laboratoire de Chimie Organique de Synthèse, in Louvain-la-Neuve, Belgium.

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