DIASTEREOSELECTIVE ADDITION OF α-METALATED SULFOXIDES TO IMINES REVISITED: MECHANISM, COMPUTATIONAL STUDIES, AND THE EFFECT OF EXTERNAL CHIRAL LIGANDS

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Dedicated to the memory of Professor Otakar Červinka.

Some new results on asymmetric synthesis *via* the addition of α-metalated methyl tolyl sulfoxides to imines are presented. Good diastereoselectivity (up to >98% d.e. for product **3g**) can be obtained under conditions of kinetic control (short reaction time, low temperature). The transition state (a six-membered "flat chair") was probed by quantum mechanical calculations, which underpinned the idea of using external chiral ligands to enhance the diastereoselectivity of otherwise moderately selective reactions. In this way, the diastereomeric ratio of the product **3a** could be raised from (84:16) to (>99:1) by use of a readily available C_2-symmetric bis(sulfonamide) ligand.

Keywords: Diastereoselectivity; Chiral sulfoxides; Imines; N ligands; Quantum mechanical calculations; Asymmetric additions; Carbanions; Organolithium reagents.

Chiral nucleophilic species generated by α-metalation of sulfoxides are attractive reagents for asymmetric carbon–carbon bond formation, with most examples of synthetically useful reactions involving either 1,2-addition to carbonyl groups or Michael addition[1]. Diastereoselective 1,2-addition to imines has recently been of increasing interest[2,3] (Scheme 1).

This type of reaction dates back to 1973, when Tsuchihashi and coworkers[4] reported the completely diastereoselective addition of the lithium derivative of enantiomerically pure methyl *p*-tolyl sulfoxide to *N*-(benzylidene)aniline. However, this result was later challenged by the group of Kagan[5] who demonstrated that the actual diastereomeric ratio under the Tsuchihashi conditions was only 75:25 and that the diastereoselectivity was markedly affected by variations in the temperatures used for generation of the anion and for the addition reaction, respectively. Under optimized con-

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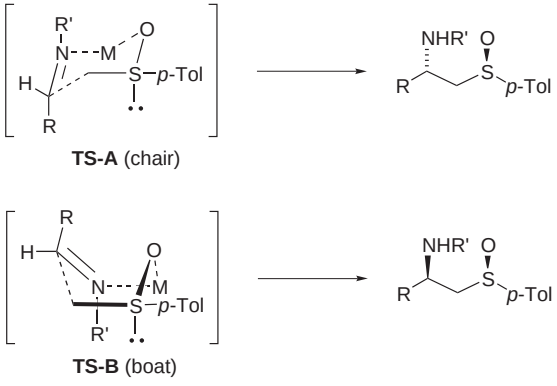
1a–1g **3a–3g**

1 or **3**	R	R'
a	Ph	Ph
b	Ph	2-MeO-C_6H_4
c	Ph	4-CF_3-C_6H_4
d	4-MeO-C_6H_4	Ph
e	4-MeO-C_6H_4	Ph
f	Ph	Ts
g	*t*-Bu	2-MeO-C_6H_4

SCHEME 1
Diastereoselective addition of α-metalated sulfoxides to imines

ditions, a near-quantitative yield of the adduct was obtained after only a few minutes at –78 °C, the diastereomeric ratio being 92:8. Pyne[6] then showed that the reaction is reversible, and can be subject to either kinetic or thermodynamic control; it was also noted that, in general, diastereoselectivity was substantially lower under conditions of thermodynamic control. Two possible chelated transition states for the reaction (Fig. 1) were proposed with the chair-like assembly (**TS-A**) being favoured for steric reasons.



R = Ph, 4-MeOC_6H_4, 4-$CF_3C_6H_4$, *t*-Bu, R' = Ph, 2-MeOC_6H_4, 4-$CF_3C_6H_4$, Ts

FIG. 1
Transition states proposed for addition to imines **1** (see refs[2a,6])

More recently, Zanda and coworkers[2a] have made an extensive study of the addition of lithium (*R*)-methyl *p*-tolyl sulfoxide to *N*-(arylmethylidene)-*p*-anisidines (*N*-PMP imines) and confirmed that good diastereoselectivity can be obtained under kinetic control. They also obtained some interesting results by varying the electronic nature of the benzylidene group, and suggested that in certain cases the boat-like transition state (**TS-B** in Fig. 1) could be stabilized by attractive π-p interactions between an electron-deficient benzylidene moiety and the sulfoxide oxygen. This would allow **TS-B** to better compete with **TS-A**, thus explaining the lower diastereoselectivity observed in the reactions of imines carrying electron-withdrawing substituents on the benzylidene group.

As part of a research project involving the use of chiral sulfoxides in asymmetric synthesis[7] we have recently had occasion to study the addition of α-metalated sulfoxides to imines. In the present paper we present (i) results which complement those reported earlier by others[2,5,6], (ii) the first computational studies of the reaction mechanism, and (iii) the first use of external chiral ligands to enhance the diastereoselectivity of the reaction.

RESULTS AND DISCUSSION

We began by examining the reaction of lithium (*R*)-methyl *p*-tolyl sulfoxide with a number of imine substrates, including two studied previously[2,5,6], under conditions of kinetic control. In our experiments, the sulfoxide anion was generated at –78 °C using LDA in THF, and a precooled (–78 °C) solution of the imine in THF was added, followed by stirring for 10 min before the reaction was quenched. The results are gathered in Table I; the degree of conversion and the d.e. values were measured by HPLC of the crude reaction products. Before discussing the results, we would like to point out that we had considerable difficulty in obtaining high isolated yields of the products by conventional flash chromatography; in our hands, commercial silica gel (from two different sources) was not suitable, and only by using demetalated silica gel[8] could acceptable isolated yields (>50%) be obtained. We surmise that the β-amino sulfoxides are good ligands for any metals present in the silica gel, and it is surprising that this problem has not been mentioned so far.

For the "standard" substrate (Table I, entry 1), we observed 68% d.e. which is very similar to that obtained[6a] by Pyne (72%) by mixing the reactants at –78 °C followed by reaction at 0 °C for 5 min. For this substrate, Kagan[5] obtained 84% d.e. by generation of the anion at 0 °C, followed by reaction with the imine at –78 °C for 10 min. The *o*-MeO-substituted imine

in entry 2 gave 62% d.e. and this can be compared with Zanda's results[2a] with the corresponding *N*-PMP imine which gave a markedly higher d.e. (84%) under conditions similar to ours (generation of the anion and reaction at –70 °C). In entry 3, an electron-withdrawing substituent in the *para* position of the *N*-aryl moiety (which could be expected to accelerate the reaction by stabilization of the presumed *N*-anion intermediate) gave only 60% d.e. An improvement to 84% d.e. was observed for an electron-donating *para* substituent on the benzylidene group (entry 4), while an electron-withdrawing group in this position eroded the diastereoselectivity (54%, entry 5). The former result can be compared with the 72% d.e. obtained under the optimized Kagan conditions[5], while the latter is in line with Zanda's observations[2a] that substrates with electron-deficient benzylidene groups generally give lower diastereoselectivity. Detailed mechanistic interpretation is difficult since the variations in d.e. values shown in entries 1–5 are generally quite modest. However, two extremes were observed for entries 6 and 7: the *N*-tosyl group in the former totally obliterated the diastereoselectivity, while the latter combination of a *tert*-butyl and an *o*-methoxyphenyl group provided a single diastereomer of the product. This material could be obtained as X-ray-quality crystals, which allowed unambiguous assignment of the relative and absolute stereochemistry (Fig. 2).

The configuration at the newly-formed stereogenic center is thus in line with that expected from the chair-like transition state (**TS-A** in Fig. 1) pro-

TABLE I
Diastereoselectivity for the reaction of (*R*)-methyl *p*-tolyl sulfoxide (**2**) with imines **1**

Entry	Compound	R	R′	Conversion %[a]	d.r.[b]
1	**3a**	Ph	Ph	87	84:16
2	**3b**	Ph	2-$MeOC_6H_4$	82	81:19
3	**3c**	Ph	4-$CF_3C_6H_4$	98	80:20
4	**3d**	4-$MeOC_6H_4$	Ph	92	92:8
5	**3e**	4-$CF_3C_6H_4$	Ph	93	77:23
6	**3f**	Ph	Ts	75	50:50
7	**3g**	*t*-Bu	2-$MeOC_6H_4$	92	>99:1

[a] Measured by chiral HPLC; [b] d.r. means diastereomeric ratio, major product has ($2S,R_S$) configuration.

posed by Pyne[6a] and the (2*S*,R_S) configuration of the major diastereomers of the other new compounds in Table I (entries 2, 3, and 5) is assigned by analogy with compound **3g**. The (2*S*,R_S) configuration has earlier been assigned[5,6a] to the major products shown in entries 1 and 4, and our assignments are also in agreement with those of Zanda[2a]. We suggest that the *tert*-butyl substituent in substrate **1g** enhances the diastereoselectivity by purely steric effects, while the *N*-tosyl group in **1f** may stabilize the intermediate *N*-anion to the extent that the reaction becomes reversible, thus eroding the selectivity.

If chelated transition states such as **TS-A** are indeed important, then the diastereoselectivity of the reaction would be expected to be dependent on the nature of the metal cation. We have investigated this in the simple set of experiments summarized in Table II.

The (*N*-benzylidene)aniline substrate **1a** was reacted with the chiral sulfoxide **2** which had been deprotonated by the bases shown in Table II. It was noted (entries 1 and 2) that the use of LiHMDS gave a slower reaction, but slightly improved d.e., compared with LDA. For the hexamethyldisilazane bases (entries 2–4), diastereoselectivity decreased as the metal cation varied from Li to Na to K, as expected on the basis of a chelated transition state.

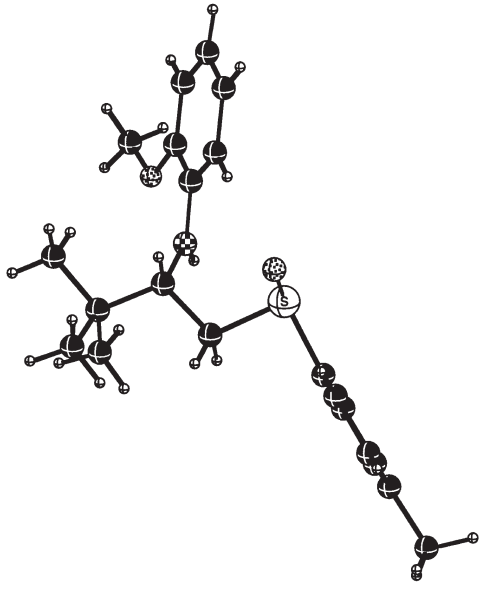


FIG. 2
X-ray structure of **3g**

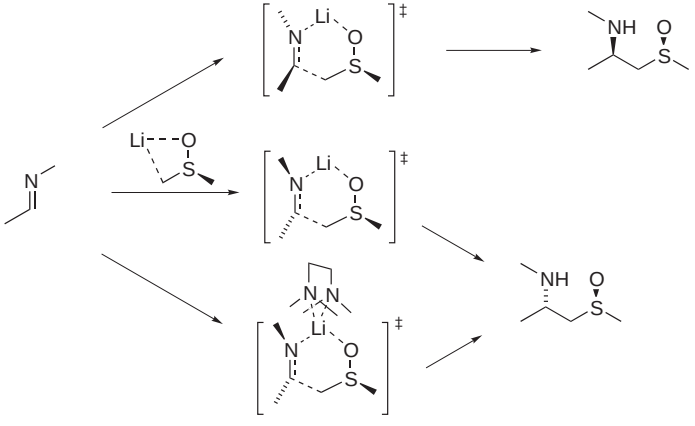
To further investigate possible transition state geometries, we performed DFT calculations on the small model system shown in Scheme 2, where all aryl substituents have been replaced by methyl groups. The model sulfoxide, DMSO, is of course not chiral, but the corresponding α-metalated species is, thus allowing the location of diastereomeric transition states. Hence, it is possible to estimate the diastereoselectivity in the reaction from the model systems used here.

All calculations were performed at the B3LYP/6-31+G* level of theory using[9] Jaguar version 4.0. For the simplest model system, the calculated activation energy was in fact negative. This is a well-known phenomenon in bimolecular reactions, resulting from the formation of a strong pre-reaction

TABLE II
Reaction between imine **1a** and sulfoxide **2** under kinetic control. Dependence of conversion and diastereoselectivity on base and metal counterion

Base	Conversion, %	d.r.[a]
LDA	90	84:16
LiHMDS	50	87:13
NaHMDS	60	81:19
KHMDS	77	69:31

[a] d.r. means diastereomeric ratio.



SCHEME 2
Model systems investigated by DFT calculations

complex in the gas phase. A more correct representation can be obtained either by calculating the pre-complex, or by estimating the influence of the solvent on the reaction. Here, we have chosen the latter alternative, calculating the final energies using the PB-SCRF method[9] in Jaguar at the geometries determined in gas phase, with parameters appropriate for THF (ε = 7.43, probe radius = 2.52372). From previous experience with anionic reactions[10], we expect that this combination procedure will provide relative energies of sufficient accuracy for the comparisons of interest. Employing gas phase geometries also allowed us to verify the stationary points by normal mode analysis, and to add the thermodynamic contributions to arrive at final, composite Gibbs free energies of activation (Eq. (*1*)).

$$\Delta G^{\ddagger} = \Delta E(\text{B3LYP/6-31+G*}) + \Delta\Delta G_{\text{THF}} + \Delta ZPE + \Delta\Delta G_{\text{therm}} \qquad (1)$$

In the reactant, the Li cation coordinates to both O and C of the sulfoxide anion. This is most probably an artefact in the simplified model system (monomeric gas-phase structure with solvation only included as single-point calculation). The real complex is solvated, and is expected to be present as a dimer or higher oligomer, with a Gibbs free energy lower than that of the monomeric complex. Thus, activation barriers will most probably be underestimated by an unknown but constant factor. However, as we are only interested in relative activation barriers, no attempt was made to determine the constant error. In the TS, the distance between Li and C has increased to allow formation of a normal six-membered cyclic transition state. The diastereomeric transition states for the smallest model system (no ligand) are shown in Fig. 3. For the most favored TS, the six atoms in the cyclic array form a flattened chair, with the two substituents on the imine necessarily occupying axial positions, and the sulfur substituent occupying an equatorial position. The diastereomeric TS is similar, but the conformation is now more boat-like in order to keep the sulfur substituent in an equatorial position, away from the axial imine substituent. Since O and Li do not bear substituents, the twisted boat conformation does not result in any compressed gauche interactions, and is therefore only slightly higher in energy than the flat chair, *ca* 8 kJ/mol.

The experimental result obtained for the reaction of the chiral sulfoxide and *N*-benzylideneaniline shown in Table I, entry 1 (diastereomeric ratio 84:16) corresponds to an energy difference of *ca* 4 kJ/mol between the diastereomeric paths. Thus, keeping in mind the simplicity of the model

system used for the calculations, there is good agreement between theory and experiment, and this encouraged us to use our computational methods as a predictive tool in further refinement of the stereoselectivity, as described below.

A possible way of enhancing the diasteroselectivity of these reactions would be to use an external chiral ligand[11], thus providing the opportunity of a "match" and "mismatch" between the ligand and the chiral sulfoxide. We began by investigating the effect of a simple achiral external ligand (TMEDA) on the calculated transition states, as shown in the lower part of Scheme 2.

The lowest activation energy in the absence of ligand is 95 kJ/mol, whereas the presence of TMEDA raises the barrier to 117 kJ/mol, reflecting the higher crowding around Li in the transition state compared with the ground state. Thus, for any ligand that binds Li by less than 20 kJ/mol (corresponding to an equilibrium constant around 1000), the reaction is expected to go exclusively *via* free metal ion in equilibrium with the bound metal. From this, we conclude that in order to influence the reaction with a chiral ligand, it is important that metal "leakage" is prohibited. In view of the theoretical prediction that coordination of the metal cation slows down the reaction, metals that are stronger Lewis acids than Li^+ should also be of interest. To test these ideas, we screened a variety of metal–ligand combinations as depicted in Schemes 3 and 4.

We chose the C_2-symmetric bidentate ligands (**4**, **5**, **6** and **7**, Schemes 3 and 4) in order to reduce the number of possible competing transition states, and combinations of these ligands and different cations (Li^+, Zn^{+2},

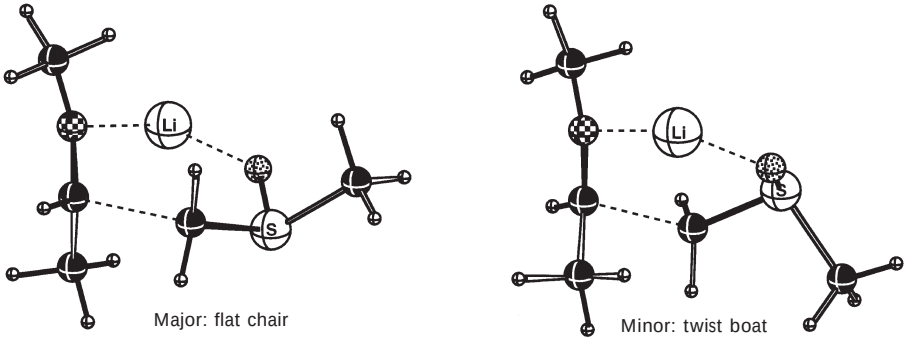
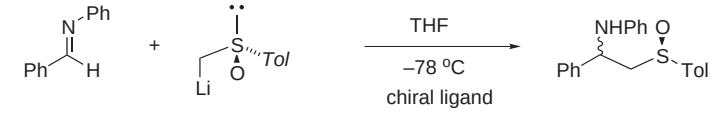
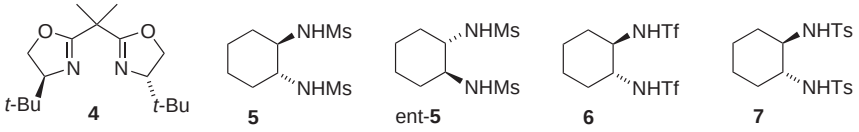


FIG. 3
Calculated diasteromeric transition states for a small model system



Chiral ligands

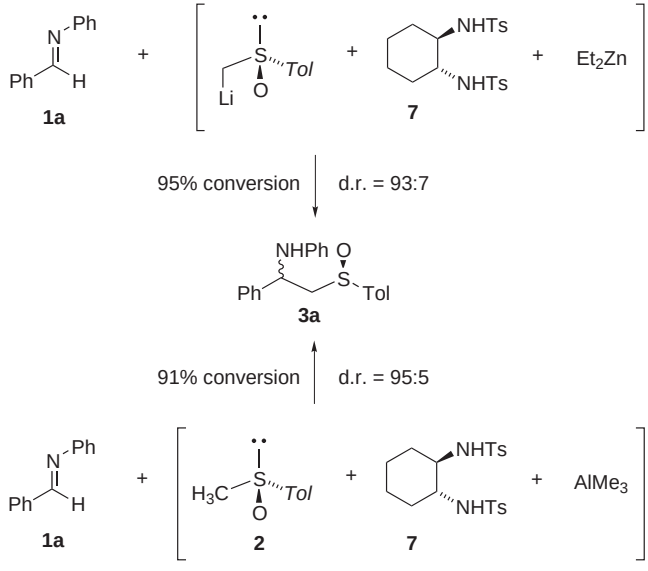


(**5**, ent-**5**, **6**, and **7** used as *N,N*-dianions)

Ligand	Conversion%	d.r.
none	87	84:16
4	43	85:15
5	98	91:9
6	80	99:1
7	90	88:12

SCHEME 3

Effect of external chiral ligands on diastereoselectivity (Li cation)

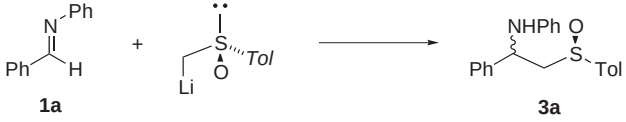


SCHEME 4

Effect of external chiral ligands (Zn and Al cations)

Al^{+3}) were used. For the experiments with lithium (Scheme 3), a total of three equivalents of BuLi were used to deprotonate both the sulfoxide and ligand **5** or **6**; for the case of zinc (Scheme 4), the lithiated sulfoxide (metalated with BuLi) was added to the complex generated by reaction of ligand **7** with one equivalent of diethylzinc; for aluminium (Scheme 4), one equivalent of $AlMe_3$ was used to deprotonate both the sulfoxide and ligand **7**.

As shown in Scheme 3, the neutral species **4** had little or no effect on the diastereoselectivity, and this ligand was tested only with lithium. The dianions of ligands **5** and **6**, however, enhanced the diastereoselectivity, with **6** giving essentially a single diastereomer of the product. To the best of our knowledge, this is the highest diastereomeric ratio yet recorded for this reaction. Ligand **7** proved to be the best for both zinc and aluminium (Scheme 4) the diastereomeric ratios being 93:7 and 95:5, respectively. Both these values are better than that for the "standard" reaction (84:16, Table I, entry 1). We are currently investigating the transition states for these reactions computationally, and results will be reported elsewhere. Finally, the concept of "match and mismatch" was demonstrated as shown in Scheme 5, using the enantiomers of ligand **5** together with lithium (*R*)-methyl *p*-tolyl sulfoxide.



No ligand: d.r. = 84:16
In the presence of ligand **5**: d.r. = 91:9 (91% conversion)
In the presence of ligand ent-**5**: d.r. = 73:27 (72% conversion)

SCHEME 5
Match and mismatch between chiral sulfoxide and chiral ligand

In conclusion, we have demonstrated that external chiral ligands can be used to enhance the diastereoselectivity of the addition of α-metalated sulfoxides to imines, a concept which was the direct result of detailed computational studies of the reaction mechanism.

EXPERIMENTAL

Melting points are uncorrected. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded for $CDCl_3$ solutions on a Varian Mercury 300 spectrometer, with residual solvent peaks as reference. Chemical shifts are given in the δ-scale (ppm), coupling constants *J* in Hz. Specific

rotations were measured at 20 °C on a Perkin Elmer 241 polarimeter and are given in 10^{-1} deg cm^2 g^{-1}. Chiral HPLC analyses were performed using a Varian 9012 solvent delivery system and a Varian 9065 polychrom photodiode array detector, with OD-H or OJ chiral columns from Diacel and eluting with mixtures of hexane and 2-propanol. High-resolution mass spectra (HRMS) were provided by the University of Copenhagen. The imines were prepared by standard procedures from commercially available aldehydes and primary amines. Imines **1a**–**1f** are known compounds[12] and spectral and physical data for data for **1g** are given below. Ligands **5**–**7** were prepared by standard methods from the commercially available (1*R*,2*R*)-cyclohexane-1,2-diamine. (*R*)-Methyl *p*-tolyl sulfoxide and its enantiomer were purchased from Aldrich. Tetrahydrofuran (THF) was distilled under nitrogen from Na-benzophenone immediately before use. Diisopropylamine was dried over calcium hydride and distilled under nitrogen. All reactions were carried out under nitrogen.

N-(2-Methoxyphenyl)pivalimine (**1g**)

Pivaldehyde (1.4 ml, 14.9 mmol), *o*-anisidine (1.5 ml, 13.5 mmol) and a catalytic amount of *p*-toluenesulfonic acid were dissolved in benzene (50 ml) and heated to reflux overnight, using a Dean–Stark apparatus. The mixture was concentrated by rotary evaporation and the crude product distilled at reduced pressure to yield the product as a colorless oil (b.p. 70–75 °C at 3.5 mm Hg) which was pure according to TLC and HPLC. Yield 2.1 g (81%); R_F 0.77 (EtOAc/hexane 1:1). HRMS, *m/z* for $C_{12}H_{17}NO$ calculated: [M^+] 191.2693; found: 191.2690. ^{1}H NMR: 1.20 s, 9 H; 3.81 s, 3 H; 6.82 m, 1 H; 6.90 m, 2 H; 7.11 m, 1 H; 7.65 s, 1 H. ^{13}C NMR: 26.9, 37.2, 56.1, 111.9, 120.7, 121.1, 125.8, 142.5, 152.0, 174.3.

General Procedure for the Addition of α-Lithiated Sulfoxides to Imines

Diisopropylamine (41 μl, 0.36 mmol) was dissolved in THF (0.5 ml) and cooled with stirring to –78 °C. A solution of butyllithium (1.6 M in hexane, 0.225 ml, 0.36 mmol) was added and the resulting solution was stirred at –78 °C for 30 min. A solution of (*R*)-methyl *p*-tolyl sulfoxide (**2**; 46 mg, 0.3 mmol) in THF (0.5 ml) was added and the mixture was stirred –78 °C for 30 min. A precooled (–78 °C) solution of an imine **1** (0.3 mmol) in THF (0.5 ml) was added *via* cannula and the reaction mixture was stirred at –78 °C for 10 min before addition of aqueous Na_2EDTA buffer solution (0.5 M, 1 ml). The reaction mixture was allowed to warm to room temperature and was extracted with dichloromethane (3 × 2 ml). The combined organic phases were dried over anhydrous magnesium sulfate and concentrated to afford the crude product **3** which was analysed by chiral HPLC. Pure samples of single diastereomers (one spot on TLC) were obtained by flash chromatography on demetalated silica gel, eluting with mixtures of ethyl acetate and hexane. Only the data for the major isomers are given below. The diastereomers of compound **3f** (pale yellow oil, 1:1 mixture of isomers) could not be separated by flash chromatography and the NMR spectra were complex, due to overlapping signals. These data are not included here.

Data for Compounds Isolated as Single Diastereomers

2-(Anilino)-2-phenylethyl p-tolyl sulfoxide (**3a**). According to the general procedure, reaction of imine **1a** (54.4 mg) and sulfoxide **2** (46.3 mg) gave compound **3a** (70.3 mg, 70%). Spectral and physical data were in agreement with literature[5] values.

2-(2-Methoxyanilino)-2-phenylethyl p-tolyl sulfoxide (**3b**). According to the general procedure, reaction of imine **1b** (63.4 mg) and sulfoxide **2** (46.3 mg) gave compound **3b** (63.5 mg, 58%); m.p. 112–114 °C; $[\alpha]_D$ +157 (*c* 0.17, $CHCl_3$); R_F 0.50 (EtOAc/hexane 1:1). HRMS, *m/z* for $C_{22}H_{23}NO_2S$ calculated: $[M^+]$ 365.1450; found: 365.1447. ^{1}H NMR: 2.40 s, 3 H; 3.00 dd, 1 H, *J* = 13.4, 9.8; 3.20 dd, 1 H, *J* = 13.4, 3.4; 3.80 s, 3 H; 4.9 m, 1 H; 5.70 br s, 1 H; 6.51 m, 2 H; 6.73 m, 2 H; 6.80 m, 2 H; 7.33 m, 5 H; 7.61 d, 2 H, *J* = 8. ^{13}C NMR: 21.6, 53.8, 55.9, 65.8, 109.8, 112.5, 117.7, 121.3, 124.2, 126.5, 127.8, 129.1, 130.2, 135.8, 140.8, 141.3, 141.8, 145.5.

2-Phenyl-2-[4-(trifluoromethyl)anilino]ethyl p-tolyl sulfoxide (**3c**). According to the general procedure, reaction of imine **1c** (63.4 mg) and sulfoxide **2** (46.3 mg) gave compound **3c** (72.5 mg, 60%); m.p. 191–193 °C; $[\alpha]_D$ +181 (*c* 0.45, $CHCl_3$); R_F 0.69 (EtOAc). HRMS, *m/z* for $C_{22}H_{20}F_3NOS$ calculated: $[M^+]$ 403.4007; found: 403.4009. ^{1}H NMR: 2.40 s, 3 H; 3.20 m, 2 H; 4.80 m, 1 H; 5.91 br s, 1 H; 6.52 d, 2 H, *J* = 8; 7.32 m, 9 H; 7.50 d, 2 H, *J* = 8. ^{13}C NMR: 21.6, 55.2, 63.1, 112.9, 113.5, 121.1, 123.9, 124.1, 124.2, 126.2, 128.2, 129.1, 130.1, 132.1, 140.5.

2-Anilino-2-[4-(methoxyphenyl)]ethyl p-tolyl sulfoxide (**3d**). According to the general procedure, reaction of imine **1d** (72.4 mg) and sulfoxide **2** (46.3 mg) gave compound **3d** (56.9 mg, 52%). Spectral and physical data were in agreement with literature[5] values.

2-Anilino-2-[4-(trifluoromethyl)phenyl]ethyl p-tolyl sulfoxide (**3e**). According to the general procedure, reaction of imine **1e** (63.4 mg) and sulfoxide **2** (46.3 mg) gave compound **3e** (65.2 mg, 54%); m.p. 188-190 °C; $[\alpha]_D$ +142 (*c* 0.30, $CHCl_3$); R_F 0.64 (EtOAc). HRMS, *m/z* for $C_{22}H_{20}F_3NOS$ calculated: $[M^+]$ 403.4007; found: 403.4005. ^{1}H NMR: 2.40 s, 3 H; 3.10 m, 2 H; 4.80 m, 1 H; 5.41 br s, 1 H; 6.50 d, 2 H, *J* = 8; 6.70 m, 1 H; 7.00 m, 2 H; 7.32 d, 2 H, *J* = 8; 7.51 m, 4 H; 7.60 d, 2 H, *J* = 8. ^{13}C NMR: 21.6, 54.5, 63.8, 114.1, 114.2, 118.5, 121.1, 123.7, 124.2, 125.91, 125.96, 126.7, 129.1, 129.4, 135.8, 144.5.

2-tert-Butyl-2-(2-methoxyanilino)ethyl p-tolyl sulfoxide (**3g**). According to the general procedure, reaction of imine **1g** (63.4 mg) and sulfoxide **2** (46.3 mg) gave compound **3g** (62.1 mg, 60%); m.p. 131–132 °C; $[\alpha]_D$ +130 (*c* 0.15, $CHCl_3$); R_F 0.54 (EtOAc/hexane 1:1). HRMS, *m/z* for $C_{20}H_{27}NO_2S$ calculated: $[M^+]$ 345.1763; found: 345.1758. ^{1}H NMR: 0.90 s, 9 H; 2.40 s, 3 H; 2.55 dd, 1 H, *J* = 12, 11; 2.95 dd, 1 H, *J* = 12, 1; 3.42 m, 1 H; 3.80 s, 3 H; 5.42 br s, 1 H; 6.55 m, 1 H; 6.65 m 1 H; 6.75 m, 1 H; 6.95 m, 1 H; 7.22 d, 2 H, *J* = 8; 7.43 d, 2 H, *J* = 8. ^{13}C NMR: 21.3, 26.8, 36.4, 55.5, 57.5, 64.0, 109.9, 112.0, 114.1, 116.7, 121.9, 124.2, 130.1, 138.97, 142.3, 146.9.

X-Ray Crystallography

Pale yellow crystals of the compound **3g** were cooled to 120 K using a Cryostream nitrogen gas cooler system. The data were collected on a Siemens SMART platform diffractometer with a CCD area-sensitive detector. Crystal data: $C_{20}H_{27}NO_2S$, *M* = 345.49, orthorhombic, space group $P2_12_12_1$, *a* = 6.4435(6) Å, *b* = 7.3607(7) Å, *c* = 38.800(3) Å, *V* = 1840.2(3) Å^3, *Z* = 4. The structures were solved by direct methods and refined by full-matrix least-squares against F^2 of all data. The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were at calculated positions using a riding model with C–H = 0.95–0.99 Å and fixed thermal parameters [*U*(H) = 1.2*U* for attached atom]. The Flack *x* parameter[13] is –0.13(15), indicating that this is the correct absolute configuration. Programs used for data collection, data reduction and absorption were SMART, SAINT, and SADABS [14,15]. The SHELXTL version 5.03 [16] program was used to solve the structures and for molecular graphics. PLATON [17] was

used for molecular geometry calculations. The final residuals were *R*1(obs) = 0.0697, *wR*2(all) = 0.1525 and GOF = 1.048.

Addition of α-Metalated Sulfoxides in the Presence of Chiral Ligands: Li^+ as Cation

A solution of (*R*)-methyl *p*-tolyl sulfoxide (**2**; 46 mg, 0.3 mmol) in THF (0.5 ml) was cooled with stirring to –78 °C, a solution of butyllithium (1.6 M in hexane, 225 μl, 0.36 mmol) was added and the resulting solution was stirred at –78 °C for 30 min. In another flask, a solution of the ligand **5**, ent-**5** or **6** (0.3 mmol) in THF (0.5 ml) was cooled to –78 °C before addition of solution of butyllithium (1.6 M in hexane, 388 μl, 0.62 mmol) and the resulting solution was stirred at –78 °C for 30 min. The contents of the two flasks were mixed *via* cannula, before addition of a precooled (–78 °C) solution of the imine **1a** (0.3 mmol) in THF (0.5 ml). The solution was stirred at –78 °C for 30 min before being quenched and worked up as described earlier. The crude mixture was analyzed by chiral HPLC as previously described. Isolation after chromatography afforded 52 mg (52%, d.r. 91:9), 49.2 mg (49%, d.r. 73:27) and 50.2 mg (50%, d.r. 99:1) of compound **3a**, respectively, which showed spectral and physical data in agreement with an authentic sample, prepared as described earlier.

Addition of α-Metalated Sulfoxides in the Presence of Chiral Ligands: Zn^{2+} as Cation

(*R*)-Methyl *p*-tolyl sulfoxide (**2**; 46 mg, 0.3 mmol) was lithiated with butyllithium as described above. In another flask, a solution of ligand **7** (0.3 mmol) in THF (0.5 ml) was cooled to –78 °C before addition of a solution of diethylzinc (1.0 M in hexane, 310 μl, 0.31 mmol) and the resulting solution was stirred at –78 °C for 30 min. The contents of the two flasks were mixed, before addition of a precooled (–78 °C) solution of the imine **1a** (0.3 mmol) in THF (0.5 ml). The solution was stirred at –78 °C for 30 min before being quenched, worked up, and analyzed as described earlier to afford 72.3 mg (72%, d.r. 93:7) of compound **3a**.

Addition of α-Metalated Sulfoxides in the Presence of Chiral Ligands: Al^{3+} as Cation

A solution of (*R*)-methyl *p*-tolyl sulfoxide (**2**; 46 mg, 0.3 mmol) and ligand **7** (127 mg, 0.3 mmol) in THF (0.5 ml) was cooled with stirring to –78 °C before addition of trimethylaluminum (2 M in hexane, 150 μl, 0.3 mmol). The solution was stirred at –78 °C for 30 min before addition of a precooled (–78 °C) solution of the imine **1a** (0.3 mmol) in THF (0.5 ml). The resultant solution was then stirred at –78 °C for 30 min before being quenched, worked up, and analyzed as described earlier to afford 70.2 mg (70%, d.r. 95:5) of compound **3a**.

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