Asymmetric Mannich-Type Reaction of a Chiral *N*-(*tert*-Butylsulfinyl) Ketimine with Imines: Application to the Synthesis of Chiral 1,3-Diamines

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Deprotonation of the chiral N-(tert-butylsulfinyl) ketimine 1 followed by trapping with imines 2 afforded the β -amino imines 3 as the Mannich-type products in high diastereoselectivities (99:1 dr). As versatile synthons chiral β -amino imines 3 could be transformed into enantiomeric β -amino ketone and chiral syn- or anti-1,3-diamines with high dia-

Introduction

The Mannich reaction is one of the most important reactions in organic synthesis because it is not only a classic method for carbon-carbon bond formation, but also able to afford versatile synthetic intermediates in organic synthesis. In general, the Mannich reaction involves the addition of carbon nucleophiles to imines.^[1] Most carbon nucleophiles used are enolates or enol ethers, and β-amino carbonyl compounds are obtained as the Mannich products. However, as the important equivalent of enolates, α -carbanions derived from imines used in the Mannich reaction are less noticed. Risch developed a synthetic method to 1,3diamines by means of the aminoalkylation of enamines or imines with tertiary iminium salts,^[2] followed by the reduction of the C=N double bond.^[3] Nevertheless, there were few efficient methods available to synthesize optically active β -amino imines^[3d,4] and 1,3-diamines^[3d] until very recently.

1,3-Diamines are important compounds or key structural units in natural products,^[5] pharmacologically active compounds,^[6] and chiral auxiliaries and ligands.^[7] They have been used in total synthesis, medicinal research, and asymmetric synthesis. Chiral 1,3-diamines can be prepared by regio- and stereoselective ring-opening of α-amino-substituted aziridines^[8] or epoxides^[9] with nucleophiles such as amines. Bonin and Micouin et al. reported the synthesis of

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stereomeric excess by hydrolysis or reduction, respectively. Moreover, the nucleophilic addition of organometallic reagents to chiral β -amino imines 3 could provide 1,1,3-trisubstituted 1,3-diamines with high diastereoselectivities. (© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2006)

polysubstituted chiral 1,3-diamines by a diastereoselective 1.3-dipolar cycloaddition of azomethine imine ylide and followed by electroreduction of the pyrazolidine intermediates.^[10] Chiral 1,3-diamines can also be obtained by functional-group transformation of optically active compounds such as 1,3-diols^[11] or β -amino nitriles^[12] and β -amino isocyanides.^[13] Recently, Kobayashi reported the Cu^{II}-catalyzed enantioselective addition of enamides to imino esters and the transformation of the β -amino imines into chiral 1,3-diamines with good diastereoselectivities.^[3d] Despite the availability of such methods, it remains indispensable to find new highly selective synthetic approaches to prepare structural diverse chiral 1.3-diamines in comparison with its analogues 1,2-diamines.

Chiral N-sulfinyl imines have attracted considerable interests in organic synthesis.^[14] The chiral N-sulfinyl group can serve not only as a good chiral auxiliary but also activate the C=N bond of imines. Therefore, chiral N-sulfinyl imines have been widely used in the nucleophilic addition reaction.^[15,16] Recently, Ellman reported the deprotonation of N-sulfinyl ketimines to provide metalloenamines, which were subsequently applied in a series of reactions with electrophiles, such as α -alkylation,^[17] Michael addition,^[18] and addition to aldehydes.^[19] as well as the self-condensation reactions of N-(tert-butylsulfinyl) aldimines.^[4] In most cases, high diastereoselectivities and good yields were achieved by using metal salts and other additives after deprotonation. Herein we would like to report an asymmetric Mannich-type reaction of metalloenamines derived from chiral N-(tert-butylsulfinyl) ketimine with imines.^[20] The βamino imines thus obtained are versatile synthons that can be transformed into chiral β-amino ketones or 1,3-diamines. The subsequent addition of organometallic regents to β-amino imines provided chiral 1,1,3-trisubstituted 1,3diamines.



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Results and Discussion

We initiated the study on the asymmetric Mannich-type reaction of metalloenamines derived from (R)-N-(tert-butylsulfinyl) ketimine (R)-1 with the N-tosyl imine 2a by screening solvents and bases (Scheme 1, Table 1). Compound (R)-1 was deprotonated with a base, followed by trapping with the imine 2a. The reaction proceeded smoothly in the presence of LDA in THF to provide the chiral β -amino imine **3a** in 89% yield and >99:1 dr (Entry 4). NaH could not deprotonate the N-sulfinyl imine 1 and the starting material was recovered (Entry 1). The use of nBuLi resulted in a complex mixture, and the product was obtained in only 45% yield. Although by the use of *n*BuLi or LHMDS as the base, the reaction gave only low to moderate yields, high diastereoselectivities of the product 3a were still observed (>99:1 dr) (Entries 2 and 3). THF was found to be the best solvent (Entry 4). Both the yield and the diastereoselectivity decreased when the reaction was carried out in Et₂O or toluene (Entries 5 and 6). Contrary to the aldol-type reaction of trapping metalloenamines derived from chiral N-sulfinyl ketimines by aldehydes,^[19] which requires an additional reagent (e.g. MgBr₂) to enable metal exchange which leads to better coordination to the carbonyl group and hence to achieve high diastereoselectivity [Figure 1(b)], the present Mannich-type reaction



Scheme 1.

Table 1. The Mannich-type reaction of N-(*tert*-butylsulfinyl) ketimine 1 with imine 2a.

Entry	Base	Solvent	Yield [%] ^[a]	dr ^[b]
1	NaH	THF	n.r.	
2	nBuLi	THF	45	>99:1
3	LHMDS	THF	75	>99:1
4	LDA	THF	89	>99:1
5	LDA	Et_2O	57	64:36
6	LDA	toluene	60	64:36

[a] Isolated yield. [b] Determined by ¹H NMR.



does not need any additives for high selectivity. This is probably because the coordination of the lithium ion of LDA with the nitrogen atom of the imine 2 is strong enough to make the transition state of the Mannich reaction more stable and reach a high diastereoselectivity [Figure 1(a)].

With the optimized reaction conditions in hand, we explored the scope of the substrates of the N-tosyl imines 2 (Table 2). As shown in Table 2, N-(p-substituted benzylidene)-p-toluenesulfonamides with either electron-withdrawing or -donating functional groups, such as -Cl (2b), $-NO_2$ (2c), -Me (2d), -MeO (2e) and N-(o-substituted) benzylidene)-p-toluenesulfonamides, such as -MeO (2f) and -Br (2g) could react smoothly with metalloenamines derived from N-(tert-butylsulfinyl) ketimine 1 to afford the corresponding β -amino imines **3b**-g in moderate to good yields and in high diastereoselectivities (>99:1 dr). For the furyl-substituted N-tosyl imine 2h, the reaction also generated the desired product in high yield and diastereoselectivity (Entry 8). It is worthy to mention that no 1,4-addition was observed for N-cinnamylidene-p-toluenesulfonamide (2i) (Entry 9). The electron-donating *p*-methoxyphenyl group (PMP; 2i) is not favorable to the addition reaction (Entry 10). Unfortunately, the N-tosyl imine 2k derived from an aliphatic aldehyde also could not give the product (Entry 11), perhaps due to the low electrophilicity of such a substrate. In all cases, the NMR signals of these products show that only one of the isomers was obtained (>99:1 dr). The absolute configuration of the formed β -amino imine was assigned to be (Rs,S) by X-ray crystallographic analysis of compound 3e (Figure 2). The observed stereochemistry for the addition reaction is consistent with a Zimmerman-Traxler-type six-membered-ring transition state [Figure 1(a)].^[19,21]

Hydrolysis of **3** in the presence of AcOH in MeOH/H₂O at 40 °C for 24 h provided important optically active β -amino ketones **4** (>80%yield). Excellent diastereoselectivities of the addition reaction were further confirmed by chiral HPLC analysis of the generated β -amino ketones **4**^[22] (98–99% *ee*; Table 3).

It is well known that the C=N double bond of β -amino imines can be easily reduced by NaBH₄, DIBALH, or NaCNBH₃ to provide racemic 1,3-diamines. In Kobayashi's work, chiral β -amino imines could be reduced by LiAl-H(O*t*Bu)₃ in the presence of LiI to generate the optically active 1,3-diamine in good diastereoselectivity (*synlanti* = 14:86).^[3d] On the other hand, Ellman^[19] reported the highly



Figure 1. (a) Addition of a metalloenamine to an imine; (b) addition of a metalloenamine to an aldehyde.

Table 2. Addition of metalloenamines derived from 1 to imines 2.



[a] Isolated yield. [b] The diastereoselectivity was determined by ¹H NMR.



Figure 2. ORTEP drawing of (Rs,S)-3e.

Table 3. Preparation of β -amino ketones 4 by hydrolysis of 3.

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diastereoselective reduction of β-hydroxy-sulfinyl imine with catecholborane or LiBHEt3, offering syn- and anti-1,3amino alcohols in >99:1 dr, respectively. Similarly β -aminosulfinyl imines 3 could be reduced with catecholborane to give syn-1,3-diamines (syn-5) in moderate yields and high diastereoselectivities (>99:1 dr; Table 4). Furthermore, when β -amino imines 3 were reduced with LiBHEt₃, chiral anti-1,3-diamines (anti-5) were obtained, also in good yields and high diastereoselectivities (>99:1 dr; Table 4). The syn and *anti* selectivities in the reduction of β -amino imines 3 under the conditions by using catecholborane and LiBHEt₃ as the reductants are the same as in the cases of β -hydroxy imines observed by Ellman.^[19] The chiral auxiliary could be easily removed by treating syn- and anti-5a with 4 M HCl in MeOH/dioxane, followed by neutralization to afford the chiral 1,3-diamines syn- and anti-6a, respectively (Scheme 2).

		Y S≈o				
	I	N NHTs	AcOH, M	MeOH/H ₂ O	0 NF	ITs
	Ph 🧹	Ar	40 ^o	°C, 24 h	Ph	`Ar
3				4		
Entry β-Amino imine		Product		Yield [%] ^[a]	ee [%] ^[b]	
1	3a		4a	Ph NHTs	90	>99
2	3b	CI	4b	Ph Cl	85	>99
3	3c	NO ₂	4c	Ph NHTs	88	n.d. ^[c]
4	3d	Me	4d	Ph Me	87	>99
5	3e	OMe	4e	Ph OM	80 e	>99
6	3f	MeO	4f	O NHTs Ph MeO	89	98
7	3g	Br	4g	Ph Br	91	>99
8	3h		4h	O NHTs Ph	84	>99
9	3i		4i	Ph NHTs	86	98

[a] Isolated yield. [b] Determined by chiral HPLC. [c] Not determined.

Table 4. Selective reduction of β -amino imines 3 with different reducing agents.



[[]a] Isolated yield. [b] Determined by ¹H NMR.

The absolute configuration of the produced *syn*-1,3-diamines was assigned as (*Rs*,1*R*,3*S*) by X-ray crystallographic analysis of compound *syn*-5i. In order to understand the origin of the stereochemistry of the reduction reaction, the reduction of chiral β -amino ketone 4a, which was obtained by the hydrolysis of β -amino imine 3a, was carried out with catecholborane. It was found that the generated 1,3-amino alcohol 7 was formed only in a low diastereoselectivity (60:40 *dr*). This result demonstrated that the stereoselectivity of the reduction of β -amino imines 3 was mainly controlled by the chiral *N*-sulfinyl group. $Ph \frac{2}{3} \frac{1}{1} Ph$

To further demonstrate the utility of the chiral β -amino imines **3** as versatile intermediates in organic synthesis, we investigated the nucleophilic addition reaction of organometallic reagents with β -amino imines **3**. It was found from screening several organometallic reagents that lithium enolates derived from ethyl acetate/LDA and benzylmagnesium

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bromide could react with β -amino imines **3**, respectively. The addition of lithium enolates to β -amino imines **3** provided the 1,1,3-trisubstituted 1,3-diamines **8** in good yields (Table 5). As shown in Table 5, the reactions of β -amino imines **3**, except 4-chlorophenyl- and furyl- β -amino imines (**3b** and **3h**) (Entries 2 and 7), with ethyl acetate/LDA exhibited high diastereoselectivities (99:1 *dr*) without using any additives such as CITi(O*i*Pr)₃.^[16]

The results of the nucleophilic addition of Grignard reagents to β -amino imines **3** are shown in Table 6. Benzylmagnesium bromide could react smoothly with aryl- β -amino imines **3a**, **3d**–**e**, as well as styryl- β -amino imine **3i** to afford the chiral 1,3-diamines **9** in very high diastereoselectivities. The absolute configuration of the newly formed stereocenter was assigned to be (*S*) based on the X-ray crystallography data of compound **9e**. The crystal structure of β -amino

Table 5. Addition of the enolate derived from ethyl acetate/LDA to 3.



[a] Determined by ¹H NMR. [b] Isolated yield.

Table 6. Addition of a Grignard reagent to β -amino imines 3.



[a] Isolated yield. [b] Determined by ¹H NMR.



Scheme 2.

imine **3e** showed that the distance between the nitrogen atom of the amino group and oxygen atom of the sulfinyl group is 2.876 Å, which indicates a hydrogen-bond interaction between the hydrogen atom of the sulfonamido group and the oxygen atom of sulfinyl group. The addition of benzylmagnesium bromide to the β -amino imine **3e** takes place through a transition state fixed by an intramolecular Mg complexation. The Grignard reagent attacks the sulfinimine group from the *Re* face which is consistent with the model of Yamamoto and results in the (*S*) configuration of the new chiral center. [Figure 3(b)]. The stereochemistry is consistent with the Cram rule. However, in contrary, it was documented that the addition of a Grignard reagent to simple sulfinyl aldimines without β -amino group occurred in an *anti*-Cram mode, because the stereochemistry of the reaction was consistent with a six-membered-ring transition state which resulted from the coordination of the Mg ion of the Grignard reagent to the oxygen atom of the sulfinyl group [Figure 3(a)].^[14b,15]



Figure 3. Transition state in the addition of Grignard reagents to sulfinyl imines.

Conclusions

We have developed a highly diastereoselective Mannich reaction of metalloenamines derived from enantiopure *N*-

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(*tert*-butylsulfinyl) ketimine **1** with imines **2**. Chiral β -amino imines **3** were obtained in 99:1 *dr*, which could be used as versatile synthons in organic synthesis: (1) hydrolysis of the resulting β -amino imines **3** provided enantiomeric β -amino ketones; (2) reduction of the β -amino imines **3** with different reducing agents gave selectively *syn-* or *anti-*1,3-diamines with high diastereoselectivities (99:1 *dr*); (3) nucleophilic addition of lithium enolate or benzylmagnesium bromide to β -amino imines **3** afforded 1,1,3-trisubstituted 1,3-diamines in good yields and with high diastereoselectivities.

Experimental Section

General Remarks: IR spectra were recorded with a Perkin–Elmer 782 IR spectrometer. ¹H NMR and ¹³C NMR spectra were obtained in CDCl₃ at room temperature with a Bruker DMX-300 (300 MHz) spectrometer. Chemical shifts are given in ppm relative to tetramethylsilane (TMS). Mass spectra were recorded with a Bruker APEX-2 spectrometer using the FAB technique. Elemental analyses were performed with a Carlo Erba 1102 Element Analysis instrument. Optical rotations were measured with a Perkin–Elmer 241 instrument (589 nm). HPLC analysis was performed with a Shimadzu CTO_10ASVP instrument equipped with the stated chiral columns. Melting points were measured with a Beijing-Taike X-4 apparatus and are uncorrected. Unless otherwise noted, all reagents were obtained from commercial suppliers and were used without further purification.

Typical Experimental Procedure for the Mannich-Type Reaction of *N*-(*tert*-Butylsulfinyl) Ketimine 1 with Imines 2: To a stirred solution of 1 (23 mg, 0.2 mmol) in THF (2 mL) at -78 °C was added LDA (0.11 mL, 2.0 M in THF/hexane) dropwise. After the reaction solution had been stirred at -78 °C for 1 h, a solution of the imine 2 (0.4 mmol) in THF (2 mL) was added in one portion, and the mixture was stirred at -78 °C for another 2 h. A saturated aqueous solution of NH₄Cl (5 mL) was then added to the mixture with stirring. The mixture was warmed to room temperature, followed by extraction with CH₂Cl₂. The combined organic phases were dried with Na₂SO₄ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the desired β-amino-sulfinyl imines **3**.

(Rs,S)-N-[3-(p-Methoxyphenyl)-1-phenyl-3-(tosylamino)propylidene]-2-methylpropanesulfinamide (3e): 96 mg, 94% yield. $[a]_{D}^{20} =$ +27.8 (c = 1.0, CHCl₃). M.p. 134–135 °C. ¹H NMR (CDCl₃/TMS, 300 MHz): $\delta = 1.45$ (s, 9 H, *t*Bu), 2.25 (s, 3 H, CH₃-Ts), 3.24 (dd, $J = 4.1, 13.4 \text{ Hz}, 1 \text{ H}, \text{H-CH}_2), 3.26-3.74 \text{ (m, 4 H, OCH}_3, \text{H-CH}_2),$ 4.56-4.63 (m, 1 H, CH-N), 6.64 (d, J = 8.3 Hz, 2 H, H_{arom}), 6.86 $(d, J = 7.9 \text{ Hz}, 2 \text{ H}, H_{arom.}), 7.10 (d, J = 8.3 \text{ Hz}, 2 \text{ H}, H_{arom.}), 7.24$ (d, J = 7.7 Hz, 2 H, H_{arom}), 7.44 (t, J = 7.3 Hz, 2 H, H_{arom}), 7.52– 7.61 (m, 2 H, NH, $H_{arom.}$), 7.78 (d, J = 7.7 Hz, 2 H, $H_{arom.}$) ppm. ¹³C NMR (CDCl₃/TMS, 100 MHz): δ = 21.3, 22.9, 41.3, 54.7, 55.3, 59.0, 113.8, 126.6, 127.5, 127.6, 128.7, 128.8, 132.1, 133.1, 136.5, 138.6, 141.7, 159.0, 175.4 ppm. IR: $\tilde{v} = 3121$, 1329, 1155 cm⁻¹. C₂₇H₃₂N₂O₄S₂ (512.18): calcd. C 63.25, H 6.29, N 5.46; found C 63.24, H 6.34, N 5.28. The crystal used for the X-ray study had the dimensions $0.57 \times 0.42 \times 0.18$ mm. Crystal data: C₂₇H₃₂N₂O₄S₂, M = 512.67, orthorhombic, space group $P2_12_12_1$, a = 10.4322(4), b =13.6353(6), c = 18.3325(7) Å, V = 2607.73(18) Å³, Z = 4, $D_{calcd.} =$ 1.308 g/cm³, $F_0 = 1092$, reflections collected: 3354, $\lambda = 0.71073$ Å.

Typical Experimental Procedure for the Hydrolysis of \beta-Amino Imines 3: To a 0.02 M solution of β -amino imines 3 (0.1 mmol) in

MeOH was added 4.0 N aqueous AcOH (8 mmol, 2 mL) and the mixture was stirred at 40 °C until the hydrolysis was determined to be complete by TLC. The mixture was reduced to half of its volume under reduced pressure and a saturated aqueous solution of NaCl was added. Then the mixture was extracted with CH₂Cl₂, dried with Na₂SO₄, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the β -amino ketones **4**.^[22]

(*S*)-1,3-Diphenyl-3-tosylamino-1-propanone (4a): 34 mg, 90%yield. [*a*]₂₀²⁰ -22.0 (*c* = 1.0, CHCl₃). M.p. 106–107 °C. ¹H NMR (CDCl₃/ TMS, 300 MHz): δ = 2.49 (s, 3 H, CH₃-Ts), 3.48 (dd, *J* = 6.1, 17.4 Hz, 1 H, H-CH₂), 3.62 (dd, *J* = 5.1, 17.4 Hz, 1 H, H-CH₂), 4.89–4.96 (m, 1 H, CH), 5.77 (d, *J* = 6.5 Hz, 1 H, NH), 6.98–7.24 (m, 7 H, H_{arom.}), 7.48 (t, *J* = 7.5 Hz, 2 H, H_{arom.}), 7.59 (t, *J* = 7.3 Hz, 1 H, H_{arom.}), 7.68 (d, *J* = 7.8 Hz, 2 H, H_{arom.}), 7.86 (d, *J* = 7.8 Hz, 2 H, H_{arom.}) ppm. ¹³C NMR(100 MHz): δ = 21.5, 44.7, 54.5, 126.7, 127.2, 127.7, 128.0, 128.6, 128.7, 129.5, 133.6, 136.4, 137.3, 139.3, 143.3, 197.8 ppm. IR: $\tilde{\nu}$ = 3280, 1681, 1327, 1158 cm⁻¹. C₂₂H₂₁NO₃S (379.12): calcd. C 69.63, H 5.58, N 3.69; found C 69.51, H 5.60, N 3.54. HPLC (Daicel Chiralcel OD, hexane/*i*PrOH, 9:1, flow rate 1.0 mL/min): *t*_R(minor) = 23.04 min, *t*_R(major) = 29.91 min.

Typical Experimental Procedure for the Reduction of β-Amino Imines 3 with Catecholborane: To a solution of a β-amino-sulfinyl imine **3** (0.1 mmol) in THF (2 mL) was added catecholborane (60 mg, 0.5 mmol) at -10 °C, and the mixture was stirred for 24 h. To this mixture was added MeOH (1.0 mL) and a saturated solution of sodium potassium tartrate (1 mL). The resulting mixture was stirred at room temperature for 1 h, then extracted with CH₂Cl₂. The combined organic phases were dried with Na₂SO₄, concentrated and purified by flash chromatography to provide the *syn*-1,3-diamines *syn*-**5**.

(Rs,1R,3S)-N-(tert-Butylsulfinyl)-1-phenyl-3-(2-phenylvinyl)-3-(tosylamino)propylamine (syn-5i): 36 mg, 71 % yield. $[a]_D^{20} = -37.3$ (c = 1.0, CHCl₃). M.p. 81–82 °C. ¹H NMR (CDCl₃/TMS, 300 MHz): δ = 1.21 (s, 9 H, tBu), 1.95–1.99 (m, 1 H, H-CH₂), 2.24 (s, 3 H, CH₃-Ts), 2.44–2.50 (m, 1 H, H-CH₂), 3.99–4.04 (m, 2 H, CH, NH), 4.60-4.61 (m, 1 H, CH), 5.62 (dd, J = 7.7, 15.9 Hz, 1 H, CH=), 5.89 (d, J = 8.6 Hz, 1 H, NH), 6.06 (d, J = 15.9 Hz, 1 H, CH=), 6.99–7.02 (m, 2 H, H_{arom}), 7.10 (d, J = 8.0 Hz, 2 H, H_{arom}), 7.18– 7.22 (m, 3 H, H_{arom.}), 7.28–7.34 (m, 5 H, H_{arom.}), 7.65 (d, J =8.3 Hz, 2 H, H_{arom}) ppm. ¹³C NMR (CDCl₃/TMS, 75 MHz): δ = 21.3, 22.8, 42.5, 54.3, 56.2, 126.3, 127.3, 127.5, 127.7, 128.1, 128.3, 128.5, 128.8, 129.4, 131.4, 136.1, 138.4, 141.5, 143.1 ppm. IR: v = 3258, 3062, 1326, 1157 cm⁻¹. HRMS (FAB): calcd. for C₂₈H₃₄N₂O₃S₂Na [M + Na] 533.1923; found 533.1899. The crystal used for the X-ray study had the dimensions $0.66 \times 0.53 \times 0.38$ mm. Crystal data: $C_{28}H_{34}N_2O_3S_2$, M = 510.69, monoclinic, space group C_2 , a = 24.3114(16), b = 11.7896(7), c = 10.3552(7) Å, $\beta =$ $105.9490(19)^{\circ}$, $V = 2853.8(3) \text{ Å}^3$, Z = 4, $D_{\text{calcd.}} = 1.189 \text{ g/cm}^3$, F_{o} = 1088, reflections collected: 3385, $\lambda = 0.71073$ Å.

Typical Experimental Procedure for the Reducion of β-Amino Imines 3 with LiBHEt₃: To a solution of β-amino-sulfinyl imines **3** (0.1 mmol) in THF (2 mL) at -78 °C was added LiBHEt₃ (0.25 mmol, 1.0 m in THF) and the solution was stirred at -78 °C for 3 h. A saturated aqueous solution of NH₄Cl was added to the solution. Then the solution was warmed to room temperature followed by extraction with CH₂Cl₂. The combined organic phases were dried with Na₂SO₄, concentrated, and purified by flash chromatography to provide *anti*-1,3-diamines *anti*-5.

(*Rs*,1*S*,3*S*)–*N*-(*tert*-Butylsulfinyl)-1,3-diphenyl-3-(tosylamino)propylamine (*anti*-5a): 39 mg, 81% yield. $[a]_D^{20} = -32.3$ (c = 1.0,

CHCl₃). M.p. 144–145 °C. ¹HNMR (CDCl₃/TMS, 400 MHz): δ = 1.20 (s, 9 H, *t*Bu), 2.30 (s, 3 H, CH₃-Ts), 2.35–2.42 (m, 1 H, H-CH₂), 2.50–2.57 (m, 1 H, H-CH₂), 4.17 (d, *J* = 6.0 Hz, 1 H, NH), 4.27–4.36 (m, 2 H, 2CH–N), 6.32 (d, *J* = 8.1 Hz, 1 H, NH), 6.94–6.96 (m, 2 H, H_{arom}), 7.00 (d, *J* = 8.3 Hz, 2 H, H_{arom}, H_{arom}), 7.11–7.20 (m, 5 H, H_{arom}), 7.28–7.40 (m, 5 H, H_{arom}) ppm. ¹³C NMR (CDCl₃/TMS, 100 MHz): δ = 21.4, 22.6, 45.1, 55.5, 56.1, 57.2, 126.6, 127.0, 127.1, 127.5, 127.7, 128.6, 128.7, 129.1, 137.3, 139.5, 141.2, 142.8 ppm. IR: \tilde{v} = 3267, 3064, 1324, 1156 cm⁻¹. HRMS (FAB): calcd. for C₂₆H₃₃N₂O₃S₂ [M + H⁺] 485.1927; found 485.1929.

Typical Experimental Procedure for the Cleavage of the Chiral Sulfinyl Auxiliary: Compound *syn*-**5a** (0.1 mmol) was treated with a 1:1 mixture (2 mL) of MeOH and 4.0 \times HCl in dioxane (2 mL) at room temperature for 1 h. To the mixture was added a saturated aqueous Na₂CO₃ solution and the mixture was extracted with CH₂Cl₂. The combined organic portions were dried with Na₂SO₄, concentrated under reduced pressure and recrystallized from CH₂Cl₂/hexane to give *syn*-**6a** as a white solid in 89% yield. According to the same procedure, compound *anti*-**5a** gave compound *anti*-**6a**.

(1*S*,3*R*)–1,3-Diphenyl-3-(tosylamino)propylamine (*syn*-6a): 34 mg, 89%yield. [a]_D²⁰ = -26.0 (c = 1.0, CHCl₃). M.p. 150–151 °C. ¹HNMR (CDCl₃/TMS, 300 MHz): δ = 1.88–2.01 (m, 2 H, CH₂), 2.36 (s, 3 H, CH₃-Ts), 3.75 (br., 1 H, CH), 4.42–4.47 (m, 1 H, CH), 7.10–7.32 (m, 12 H, H_{arom}), 7.54 (d, J = 8.1 Hz, 2 H, H_{arom}) ppm. ¹³C NMR (CDCl₃/TMS, 100 MHz): δ = 21.4, 44.9, 55.2, 58.6, 125.6, 126.5, 127.1, 127.4, 128.2, 128.5, 128.8, 129.0, 137.5, 141.4, 142.6, 145.5 ppm. IR: \tilde{v} = 3357, 3302, 3061, 3030 cm⁻¹. HRMS (FAB): calcd. for C₂₂H₂₅N₂O₂S [M + H⁺] 381.1631 found 381.1634.

(1*S*,3*S*)-1,3-Diphenyl-3-(tosylamino)propylamine (*anti*-6a): 35 mg, 92% yield. $[a]_D^{20} = -32.0$ (c = 1.0, CHCl₃). M.p. 129–130 °C. ¹HNMR (CDCl₃/TMS, 300 MHz): $\delta = 1.98-2.02$ (m, 2 H, CH₂), 2.36 (s, 3 H, CH₃-Ts), 3.87 (br., 1 H, CH), 4.52(t, J = 5.5, 1 H, CH), 7.07–7.11 (m, 5 H, H_{arom}), 7.16–7.19 (m, 4 H, H_{arom}), 7.21– 30 (m, 3 H, H_{arom}), 7.54 (d, J = 8.3 Hz, 2 H, H_{arom}) ppm. ¹³C NMR (CDCl₃/TMS, 100 MHz): $\delta = 21.4$, 44.6, 52.6, 56.0, 125.7, 126.4, 126.9, 127.1, 127.2, 128.3, 128.7, 129.2, 137.8, 140.6, 142.7, 145.5 ppm. IR: $\tilde{v} = 3278$, 3061, 3030 cm⁻¹. C₂₂H₂₄N₂O₂S (380.15): C 69.44, H 6.36, N 7.36; found C 69.05, H 6.30, N 7.36

Typical Experimental Procedure for Addition of the Enolate of Ethyl Acetate to β-Amino Imines 3: To a stirred solution of ethyl acetate (3.0 equiv., 0.3 mmol) in THF (2 mL) at -78 °C was added LDA (0.33 mmol, 0.16 mL, 2.0 M in THF/hexane) dropwise by a syringe. After the reaction solution was stirred for 30 min, a solution of β-amino imine 3 (0.1 mmol, 1.0 equiv.) in THF(2 mL) was added in one portion, and the reaction mixture was stirred at -78 °C for another 2 h. A saturated aqueous solution of NH₄Cl (5 mL) was then added to the mixture with stirring. The mixture was warmed up to room temperature, followed by extraction with CH₂Cl₂. The combined organic phases were dried with Na₂SO₄ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the desired products 8.

Ethyl 5-(4-Methylphenylsulfonylamino)-3-(2-methylpropylsulfinylamino)-3,5-diphenylpentanoate (8a): 45 mg, 80%yield. $[a]_D^{20}$ -56.7 (c = 1.0, CHCl₃). M.p. 190–191 °C. ¹H NMR (CDCl₃/TMS, 300 MHz): $\delta = 0.93$ (t, J = 7.1 Hz, 3 H, CH₃), 1.30 (s, 9 H, H-*t*Bu), 2.24 (s, 3 H, CH₃-Ts), 2.81–2.86 (m, 2 H, CH₂), 3.06 (d, J = 14.2 Hz, 1 H, H-CH₂), 3.40 (d, J = 14.2 Hz, 1 H, H-CH₂), 3.86–3.94 (m, 2 H, O–CH₂), 4.95–5.03 (m, 1 H, CH), 5.18 (s, 1 H, NH), 6.87 (d, J = 8.0 Hz, 2 H, H_{arom}), 7.01–7.05 (m, 5 H, NH + H_{arom}), 7.24–7.33 (m, 6 H, H_{arom}), 7.39–7.42 (m, 2 H, H_{arom}) ppm. ¹³C

NMR (CDCl₃/TMS, 100 MHz): δ = 13.3, 208, 22.3, 41.9, 44.1, 55.1, 56.6, 59.9, 61.0, 125.9, 126.3, 126.4, 126.6, 127.3, 127.6, 127.7, 128.3, 137.1, 140.5, 141.6, 141.8, 168.7 ppm. IR: \tilde{v} = 3259, 3163, 3063, 2980, 1720, 1599, 1494, 1454, 1330, 1159 cm⁻¹. HRMS (FAB): calcd. for C₃₀H₃₉N₂O₅S₂ [M + H⁺] 571.2294, found 571.2292.

General Procedure for Addition of Benzylmagnesium Bromide to β -Amino Imines 3: In a flame-dried flask was placed the β -amino imine 3 (1.0 equiv., 0.1 mmol) in THF (2 mL) and the solution was cooled to -78 °C. The Grignard reagent (3.0 equiv., 0.3 mmol in 2 mL THF) was added dropwise to the solution and the conversion was monitored by TLC. Then to the reaction mixture was added a saturated aqueous NH₄Cl solution and the mixture was warmed to room temperature. The resulting suspension was diluted with saturated aqueous NaCl and extracted with CH₂Cl₂. The organic layers were combined, dried, and concentrated. The residue was purified by flash column chromatography to give the desired products 9.

N-[1-(4-Methoxyphenyl)-3-(2-methylpropylsulfinylamino)-3,4-diphenylbutyl]-4-methyl-benzenesulfonamide (9e): 43 mg, 71% yield. $[a]_{D}^{20} = +51.3 (c = 1.0, CHCl_{3})$. M.p. 185–186 °C. ¹H NMR (CDCl₃/ TMS, 300 MHz): $\delta = 1.36$ (s, 9 H, H-*t*Bu), 2.24 (s, 3 H, CH₃-Ts), 2.37 (d, J = 15.6 Hz, 1 H, H-CH₂), 2.80 (t, J = 15.6 Hz, 1 H, H-CH₂), 3.24 (d, J = 13.7 Hz, 2 H, CH₂), 3.70 (s, 3 H, O-CH₃), 4.38-4.44 (m, 1 H, CH), 5.01 (s, 1 H, NH), 6.44–6.52 (m, 4 H, H_{arom}), 6.81-6.85 (m, 4 H, H_{arom.}), 6.95-7.06 (m, 3 H, NH, H_{arom.}), 7.12-7.18(m, 4 H, H_{arom}), 7.38–7.41(m, 4 H, H_{arom}) ppm. ¹³C NMR $(CDCl_3/TMS, 75 \text{ MHz}): \delta = 21.3, 23.1, 47.0, 48.5, 54.7, 55.2, 57.3,$ 64.5, 113.5, 126.2, 126.5, 126.7, 127.3, 127.5, 127.7, 128.6, 130.9, 133.6, 135.4, 138.4, 141.2, 141.7, 158.5. IR 3297, 3088. 2925, 1611, 1512, 1454, 1331, 1159 cm⁻¹. HRMS (FAB): calcd. for $C_{34}H_{41}N_2O_4S_2$ [M + H⁺] 605.2502, found 605.2488. The crystal used for the X-ray study had the dimensions $0.50 \times 0.40 \times 0.25$ mm. Crystal data: $C_{34}H_{40}N_2O_4S_2$, M = 604.80, orthorhombic, space group $P2_1$, a = 12.088(2), b = 12.327(3), c = 22.612(5) Å, V =3313.4(11) Å³, Z = 4, $D_{calcd.} = 1.212$ g/cm³, $F_o = 1288$, reflections collected 21574, $\lambda = 0.71073$ Å.

CCDC-601459 (**3e**), -601460 (**9e**) and -601461 (*syn*-**5i**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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- [2] a) N. Risch, M. Arend, Angew. Chem. Int. Ed. Engl. 1994, 33, 2422; b) M. Arend, B. Westermann, N. Risch, Angew. Chem. Int. Ed. 1998, 37, 1044–1070; c) N. Risch, S. Piper, A. Winter, A. Lefarth-Risse, Eur. J. Org. Chem. 2005, 2, 387–394.
- [3] Synthesis of 1,3-diamines via β-amino imines: a) B. Merla, M. Arend, N. Risch, *Synlett* **1997**, 177–178; b) X.-L. Hou, Y.-M. Luo, L.-X. Dai, *J. Chem. Soc., Perkin Trans.* 1 **2002**, 1487–1490; c) B. Merla, N. Risch, *Synthesis* **2002**, 10, 1365–1372; d) the catalytic enantioselective addition of enamides to imino esters was achieved by using Cu(OTf)₂ and chiral diamines to

a) M. Tramontini, L. Angiolini, *Tetrahedron* 1990, 46, 1791– 1837; b) E. F. Kleinmann, in: *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming), Pergamon Press, Oxford, 1991, vol. 2, chapter 4.1; c) S. Kobayashi, H. Ishitani, *Chem. Rev.* 1999, 99, 1069; d) A. Coärdova, *Acc. Chem. Res.* 2004, 37, 102– 112.

give optically active β -amino imines in 94% *ee*, as well as chiral 1,3-diamines: R. Matsubara, Y. Nakamura, S. Kobayashi, *Angew. Chem. Int. Ed.* **2004**, *43*, 1679–1681.

- [4] L. B. Schenkel, J. A. Ellman, Org. Lett. 2004, 6, 3621-3624.
- [5] a) A. S. Franklin, S. K. Ly, G. H. Mackin, L. E. Overman, A. J. Shaka, J. Org. Chem. 1999, 64, 1512–1519; b) F. Cohen, L. E. Overman, J. Am. Chem. Soc. 2001, 123, 10782–10783.
- [6] a) H. F. Kung, Y.-Z. Guo, C.-C. Yu, J. Billings, V. Subramanyam, J. C. Calabresef, *J. Med. Chem.* **1989**, *32*, 433–437; b) K. Vickey, A. M. Bonin, R. R. Fenton, S. O'Mara, P. J. Russel, L. K. Webster, T. W. Hambley, *J. Med. Chem.* **1993**, *36*, 3663–3668; c) R. J. Bergeron, Y. Feng, W. R. Weimar, J. S. Mcmanis, H. Dimova, C. Porter, B. Raisler, O. Phanstiel, *J. Med. Chem.* **1997**, *40*, 1475–1494.
- [7] a) D. Pini, A. Mastantuono, G. Uccello-Barretta, A. Iuliano, P. Salvadori, *Tetrahedron* 1993, 49, 9613–9624; b) K. Ogino, H. Tamiya, Y. Kimura, H. Azuma, W. Tagaki, *J. Chem. Soc.*, *Perkin Trans.* 2 1996, 5, 979–984.
- [8] J. M. Concello'n, E. Riego, J. R. Sua'rez, J. Org. Chem. 2003, 68, 9242–9246.
- [9] J. M. Concello'n, H. Cuervo, R. Fernández-Fano, *Tetrahedron* 2001, 57, 8983–8987.
- [10] A. Chauveau, T. Martens, M. Bonin, L. Micouin, H.-P. Husson, *Synthesis* 2002, 13, 1885–1890.
- [11] G. H. P. Roos, A. R. Donovan, *Tetrahedron: Asymmetry* 1999, 10, 991–1000.
- [12] M. Reetz, F. Kayser, K. Harms, *Tetrahedron Lett.* 1994, 35, 8769–8772.
- [13] A. Kaiser, M. Balbi, *Tetrahedron: Asymmetry* **1999**, 10, 1001– 1014.

- [14] a) F. Davis, P. Zhou, B. Chen, *Chem. Soc. Rev.* 1998, 27, 13–18; b) J. A. Ellman, T. D. Owens, T. P. Tang, *Acc. Chem. Res.* 2002, 35, 984–995; c) P. Zhou, B. Chen, F. Davis, *Tetrahedron* 2004, 60, 8003–8030.
- [15] a) B. Z. Lu, C. Senanayake, N. Li, Z. Han, R. P. Bakale, S. A. Wald, Org. Lett. 2005, 7, 2599–2602; b) J. P. McMahon, J. A. Ellman, Org. Lett. 2004, 6, 1645–1647; c) T. Mukade, D. R. Dragoli, J. A. Ellman, J. Comb. Chem. 2003, 5, 590–596; d) N. Plobeck, D. Powell, Tetrahedron: Asymmetry 2002, 13, 303–310; e) D. A. Cogan, G. Liu, J. A. Ellman, Tetrahedron 1999, 55, 8883–8904.
- [16] a) T. P. Tang, J. A. Ellman, J. Org. Chem. 2002, 67, 7819–7832;
 b) T. P. Tang, J. A. Ellman, J. Org. Chem. 1999, 64, 12–13.
- [17] T. Kochi, J. A. Ellman, J. Am. Chem. Soc. 2004, 126, 15652– 15653.
- [18] H. M. Peltier, J. A. Ellman, J. Org. Chem. 2005, 70, 7342-7345.
- [19] a) T. Kochi, T. P. Tang, J. A. Ellman, J. Am. Chem. Soc. 2002, 124, 6518–6519; b) T. Kochi, T. P. Tang, J. A. Ellman, J. Am. Chem. Soc. 2003, 125, 11276–11282.
- [20] More recently, similar results were reported: J. C. Lanter, H. Chen, X. Zhang, Z. Sui, Org. Lett. 2005, 7, 5905–5907.
- [21] H. E. Zimmerman, M. D. Traxler, J. Am. Chem. Soc. 1957, 79, 1920–1923.
- [22] The racemic compounds **4** for HPLC analysis were synthesized by addition of the corresponding enolates to imines without a chiral auxiliary.

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