DOI: 10.1002/ejoc.200600147

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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Keywords: Asymmetric Mannich reaction / *N*-(*tert*-Butylsulfinyl) ketimine / Chiral β-amino imine / Chiral β-amino ketone / Chiral 1,3-diamine

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 diastereomeric 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.

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 1,3-diamines 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 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 β-amino 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 1,3-diamines.

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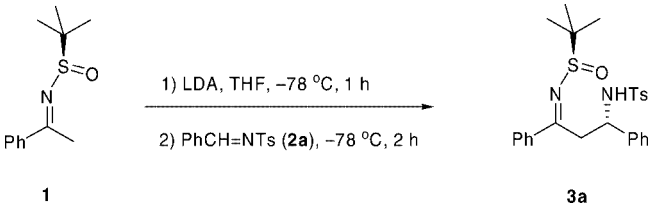
Results and Discussion

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 *n*BuLi 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 Et_2O 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. $MgBr_2$) 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 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)].



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	*n*BuLi	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.

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; **2j**) 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/H_2O 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 $NaBH_4$, DIBALH, or $NaCNBH_3$ to provide racemic 1,3-diamines. In Kobayashi's work, chiral β-amino imines could be reduced by LiAlH($OtBu$)$_3$ in the presence of LiI to generate the optically active 1,3-diamine in good diastereoselectivity (*syn*/*anti* = 14:86).[3d] On the other hand, Ellman[19] reported the highly

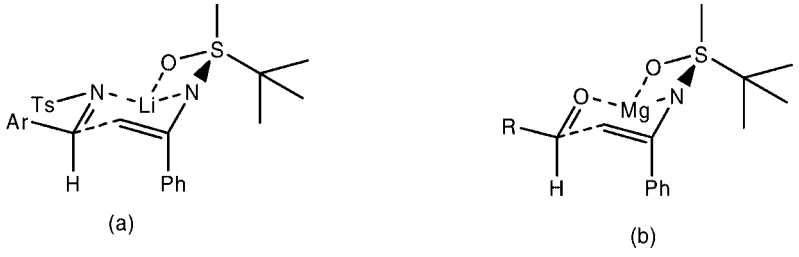
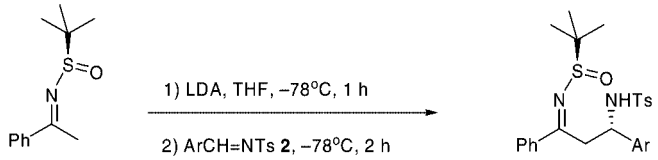
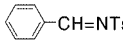
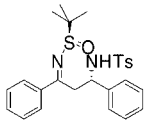
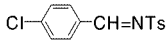
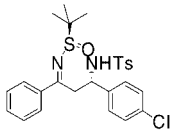
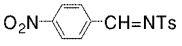
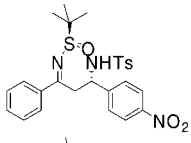
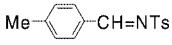
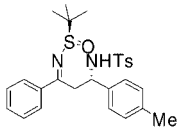
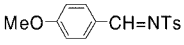
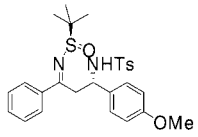
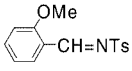
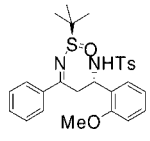
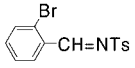
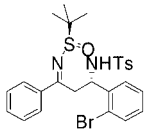
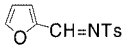
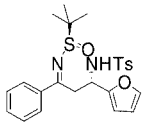
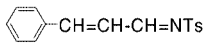
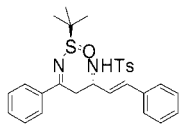
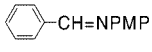
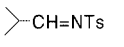


Figure 1. (a) Addition of a metalloenamine to an imine; (b) addition of a metalloenamine to an aldehyde.

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



1 **3**

Entry		Imine		Product	Yield [%][a]	dr[b]
1	**2a**		**3a**		89	>99:1
2	**2b**		**3b**		83	>99:1
3	**2c**		**3c**		59	>99:1
4	**2d**		**3d**		69	>99:1
5	**2e**		**3e**		94	>99:1
6	**2f**		**3f**		72	>99:1
7	**2g**		**3g**		53	>99:1
8	**2h**		**3h**		91	>99:1
9	**2i**		**3i**		73	>99:1
10	**2j**		—		—	—
11	**2k**		—		—	—

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

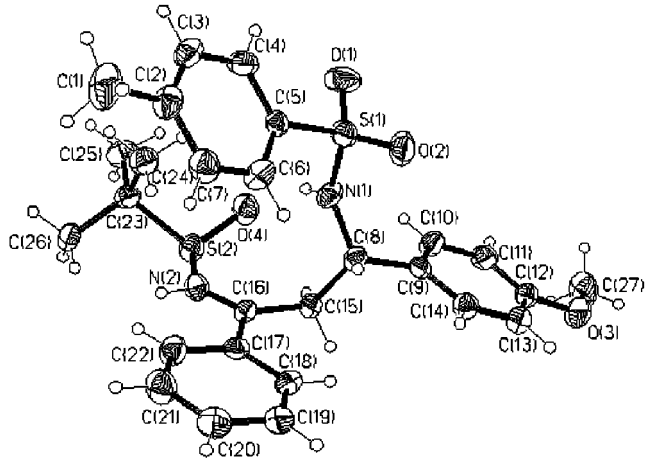
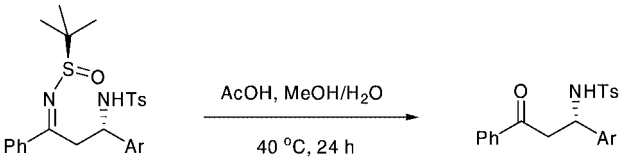


Figure 2. ORTEP drawing of (*Rs*,*S*)-**3e**.

diastereoselective reduction of β-hydroxy-sulfinyl imine with catecholborane or $LiBHEt_3$, offering *syn*- and *anti*-1,3-amino alcohols in >99:1 *dr*, respectively. Similarly β-amino-sulfinyl 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 $LiBHEt_3$, 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 $LiBHEt_3$ 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).

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

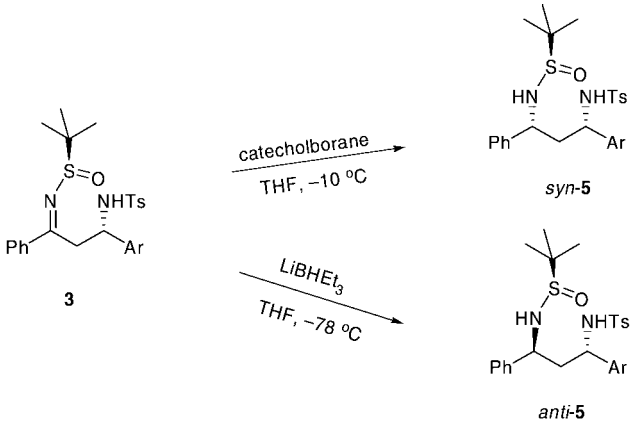


3 **4**

Entry	β-Amino imine	Product	Yield [%][a]	ee [%][b]
1	**3a**	**4a**	90	>99
2	**3b**	**4b**	85	>99
3	**3c**	**4c**	88	n.d.[c]
4	**3d**	**4d**	87	>99
5	**3e**	**4e**	80	>99
6	**3f**	**4f**	89	98
7	**3g**	**4g**	91	>99
8	**3h**	**4h**	84	>99
9	**3i**	**4i**	86	98

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

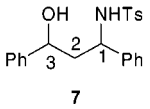
Table 4. Selective reduction of β-amino imines **3** with different reducing agents.



Entry	β-Amino imine	Reducing agent	Product	Yield [%][a]	dr[b]
1	**3a**	catecholborane	*syn*-**5a**	65	>99:1
2	**3a**	$LiBHEt_3$	*anti*-**5a**	81	>99:1
3	**3b**	catecholborane	*syn*-**5b**	70	>99:1
4	**3b**	$LiBHEt_3$	*anti*-**5b**	86	>99:1
5	**3h**	catecholborane	*syn*-**5h**	62	>99:1
6	**3h**	$LiBHEt_3$	*anti*-**5h**	90	>99:1
7	**3i**	catecholborane	*syn*-**5i**	71	>99:1
8	**3i**	$LiBHEt_3$	*anti*-**5i**	83	>99:1

[a] Isolated yield. [b] Determined by ^{1}H 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.



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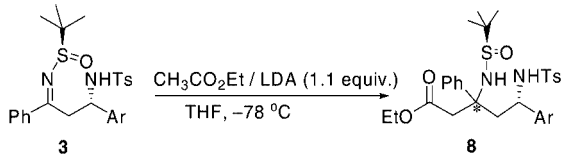
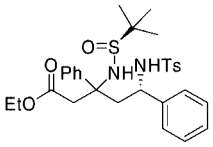
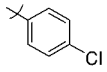
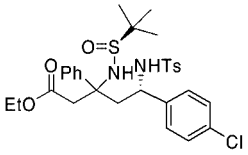
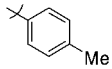
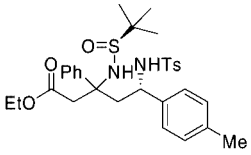
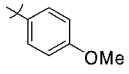
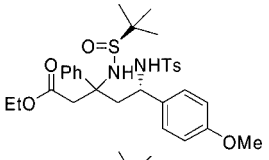
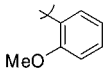
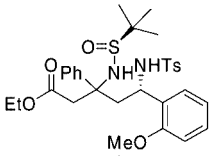
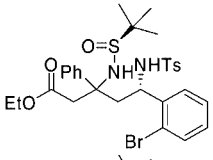
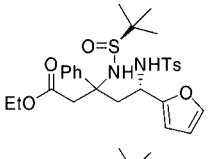
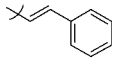
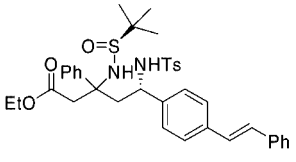
To further demonstrate the utility of the chiral β-amino imines **3** as versatile intermediates in organic synthesis, we investigated the nucleophilic addition reaction of organometallic reagents with β-amino imines **3**. It was found from screening several organometallic reagents that lithium enolates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

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 $ClTi(OiPr)_3$.[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

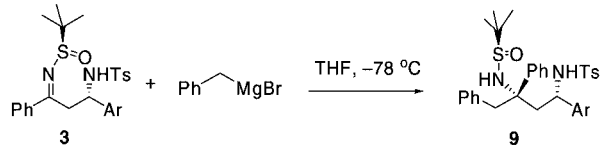
Table 5. Addition of the enolate derived from ethyl acetate/LDA to **3**.



Entry	β-Amino imine (Ar)		Product		Yield [%][b]	dr[a]
1	**3a**		**8a**		80	99:1
2	**3b**		**8b**		72	90:10
3	**3d**		**8d**		70	99:1
4	**3e**		**8e**		85	99:1
5	**3f**		**8f**		75	99:1
6	**3g**		**8g**		91	99:1
7	**3h**		**8h**		75	75:25
8	**3i**		**8i**		75	99:1

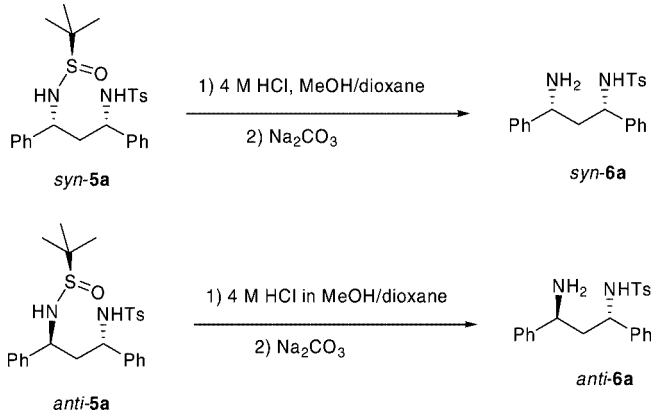
[a] Determined by ^1H NMR. [b] Isolated yield.

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



Entry	β-Amino imine	Product	Yield [%][a]	dr[b]
1	**3a**	**9a**	83	99:1
2	**3d**	**9d**	90	99:1
3	**3e**	**9e**	71	99:1
4	**3i**	**9i**	65	99:1

[a] Isolated yield. [b] Determined by ^{1}H 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]

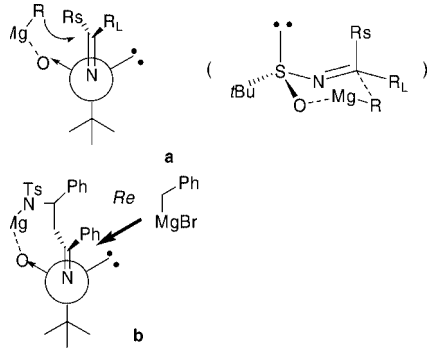


Figure 3. Transition state in the addition of Grignard reagents to sulfinyl imines.

Conclusions

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

(*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. ^{1}H NMR and ^{13}C NMR spectra were obtained in $CDCl_3$ 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 NH_4Cl (5 mL) was then added to the mixture with stirring. The mixture was warmed to room temperature, followed by extraction with CH_2Cl_2. The combined organic phases were dried with Na_2SO_4 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, $CHCl_3$). M.p. 134–135 °C. ^{1}H NMR ($CDCl_3$/TMS, 300 MHz): δ = 1.45 (s, 9 H, *t*Bu), 2.25 (s, 3 H, CH_3-Ts), 3.24 (dd, *J* = 4.1, 13.4 Hz, 1 H, H-CH_2), 3.26–3.74 (m, 4 H, OCH_3, 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 Hz, 2 H, $H_{arom.}$), 7.10 (d, *J* = 8.3 Hz, 2 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. ^{13}C NMR ($CDCl_3$/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: $\tilde{\nu}$ = 3121, 1329, 1155 cm^{-1}. $C_{27}H_{32}N_2O_4S_2$ (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 × 0.42 × 0.18 mm. Crystal data: $C_{27}H_{32}N_2O_4S_2$, *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) Å^3, *Z* = 4, $D_{calcd.}$ = 1.308 g/cm^3, F_o = 1092, reflections collected: 3354, λ = 0.71073 Å.

Typical Experimental Procedure for the Hydrolysis of β-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 CH_2Cl_2, dried with Na_2SO_4, 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. $[a]_D^{20}$ –22.0 (*c* = 1.0, $CHCl_3$). M.p. 106–107 °C. ^{1}H NMR ($CDCl_3$/TMS, 300 MHz): δ = 2.49 (s, 3 H, CH_3-Ts), 3.48 (dd, *J* = 6.1, 17.4 Hz, 1 H, H-CH_2), 3.62 (dd, *J* = 5.1, 17.4 Hz, 1 H, H-CH_2), 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. ^{13}C 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}. $C_{22}H_{21}NO_3S$ (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 CH_2Cl_2. The combined organic phases were dried with Na_2SO_4, concentrated and purified by flash chromatography to provide the *syn*-1,3-diamines *syn*-**5**.

(*Rs*,1*R*,3*S*)-*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, $CHCl_3$). M.p. 81–82 °C. ^{1}H NMR ($CDCl_3$/TMS, 300 MHz): δ = 1.21 (s, 9 H, *t*Bu), 1.95–1.99 (m, 1 H, H-CH_2), 2.24 (s, 3 H, CH_3-Ts), 2.44–2.50 (m, 1 H, H-CH_2), 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. ^{13}C NMR ($CDCl_3$/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: $\tilde{\nu}$ = 3258, 3062, 1326, 1157 cm^{-1}. HRMS (FAB): calcd. for $C_{28}H_{34}N_2O_3S_2Na$ [M + Na] 533.1923; found 533.1899. The crystal used for the X-ray study had the dimensions 0.66 × 0.53 × 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, β = 105.9490(19)°, *V* = 2853.8(3) Å^3, *Z* = 4, $D_{calcd.}$ = 1.189 g/cm^3, F_o = 1088, reflections collected: 3385, λ = 0.71073 Å.

Typical Experimental Procedure for the Reducion of β-Amino Imines 3 with $LiBHEt_3$: To a solution of β-amino-sulfinyl imines **3** (0.1 mmol) in THF (2 mL) at –78 °C was added $LiBHEt_3$ (0.25 mmol, 1.0 M in THF) and the solution was stirred at –78 °C for 3 h. A saturated aqueous solution of NH_4Cl was added to the solution. Then the solution was warmed to room temperature followed by extraction with CH_2Cl_2. The combined organic phases were dried with Na_2SO_4, 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,

$CHCl_3$). M.p. 144–145 °C. ^{1}HNMR ($CDCl_3$/TMS, 400 MHz): δ = 1.20 (s, 9 H, *t*Bu), 2.30 (s, 3 H, CH_3-Ts), 2.35–2.42 (m, 1 H, H-CH_2), 2.50–2.57 (m, 1 H, H-CH_2), 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. ^{13}C NMR ($CDCl_3$/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: $\tilde{\nu}$ = 3267, 3064, 1324, 1156 cm^{-1}. HRMS (FAB): calcd. for $C_{26}H_{33}N_2O_3S_2$ [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 M HCl in dioxane (2 mL) at room temperature for 1 h. To the mixture was added a saturated aqueous Na_2CO_3 solution and the mixture was extracted with CH_2Cl_2. The combined organic portions were dried with Na_2SO_4, concentrated under reduced pressure and recrystallized from CH_2Cl_2/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. $[a]_D^{20}$ = –26.0 (c = 1.0, $CHCl_3$). M.p. 150–151 °C. ^{1}HNMR ($CDCl_3$/TMS, 300 MHz): δ = 1.88–2.01 (m, 2 H, CH_2), 2.36 (s, 3 H, CH_3-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. ^{13}C NMR ($CDCl_3$/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: $\tilde{\nu}$ = 3357, 3302, 3061, 3030 cm^{-1}. HRMS (FAB): calcd. for $C_{22}H_{25}N_2O_2S$ [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, $CHCl_3$). M.p. 129–130 °C. ^{1}HNMR ($CDCl_3$/TMS, 300 MHz): δ = 1.98–2.02 (m, 2 H, CH_2), 2.36 (s, 3 H, CH_3-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. ^{13}C NMR ($CDCl_3$/TMS, 100 MHz): δ = 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: $\tilde{\nu}$ = 3278, 3061, 3030 cm^{-1}. $C_{22}H_{24}N_2O_2S$ (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 NH_4Cl (5 mL) was then added to the mixture with stirring. The mixture was warmed up to room temperature, followed by extraction with CH_2Cl_2. The combined organic phases were dried with Na_2SO_4 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, $CHCl_3$). M.p. 190–191 °C. ^{1}H NMR ($CDCl_3$/TMS, 300 MHz): δ = 0.93 (t, J = 7.1 Hz, 3 H, CH_3), 1.30 (s, 9 H, H-*t*Bu), 2.24 (s, 3 H, CH_3-Ts), 2.81–2.86 (m, 2 H, CH_2), 3.06 (d, J = 14.2 Hz, 1 H, H-CH_2), 3.40 (d, J = 14.2 Hz, 1 H, H-CH_2), 3.86–3.94 (m, 2 H, O–CH_2), 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. ^{13}C NMR ($CDCl_3$/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: $\tilde{\nu}$ = 3259, 3163, 3063, 2980, 1720, 1599, 1494, 1454, 1330, 1159 cm^{-1}. HRMS (FAB): calcd. for $C_{30}H_{39}N_2O_5S_2$ [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 NH_4Cl solution and the mixture was warmed to room temperature. The resulting suspension was diluted with saturated aqueous NaCl and extracted with CH_2Cl_2. 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. ^{1}H NMR ($CDCl_3$/TMS, 300 MHz): δ = 1.36 (s, 9 H, H-*t*Bu), 2.24 (s, 3 H,CH_3-Ts), 2.37 (d, J = 15.6 Hz, 1 H, H-CH_2), 2.80 (t, J = 15.6 Hz, 1 H, H-CH_2), 3.24 (d, J = 13.7 Hz, 2 H, CH_2), 3.70 (s, 3 H, O–CH_3), 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. ^{13}C NMR ($CDCl_3$/TMS, 75 MHz): δ = 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 × 0.40 × 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) Å^3, Z = 4, $D_{calcd.}$ = 1.212 g/cm^3, F_o = 1288, reflections collected 21574, λ = 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.

Acknowledgments

We are grateful to the National Natural Science Foundation of China, and the Chinese Academy of Sciences for financial support.

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Received: February 21, 2006
Published Online: May 9, 2006

