Highly Diastereoselective and Enantioselective Addition of Organometallic Reagents to a Chiral C_2-Symmetrical Bisimine

Xiaoxia Sun,[a,b] Shuangjun Wang,[a] Shangjin Sun,[a] Jin Zhu,[a] Jingen Deng*[a,b]

[a] Key Laboratory of Asymmetric Synthesis & Chirotechnology of Sichuan Province and Union Laboratory of Asymmetric Synthesis, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 610041, P. R. of China
Fax +86(28)85223978; E-mail: jgdeng@cioc.ac.cn

[b] Graduate School of Chinese Academy of Sciences, Beijing, P. R. of China

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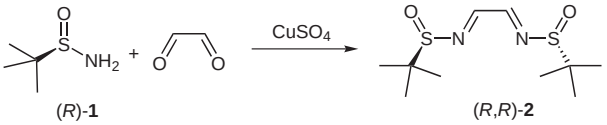
Abstract: An efficient and straightforward method has been developed for the preparation of enantiomerically enriched C_2-symmetrical vicinal diamines via the addition of organometallic reagents to a chiral bisimine, which gives access to a variety of optically pure aromatic and aliphatic C_2-symmetrical vicinal diamines in high yields. The 'Cram–Davis' open transition state model is proposed to rationalize the observed stereoselectivities for the addition of organolithium reagents to the bisimine.

Key words: chiral 1,2-diamine, chiral bisimine, asymmetric addition, organometallic reagents, asymmetric allylation

In recent years, enantiopure vicinal diamines have played an increasingly important role in organic chemistry, particularly due to their use as chiral auxiliaries or precursors for the synthesis of a broad family of bidentate ligands.[1] Many efforts have been made toward the development of methods for the preparation of the vicinal diamines. Among them, the addition of organometallic reagents to the carbon–nitrogen double bonds of the chiral bisimine derived from glyoxal and (*S*)- or (*R*)-methylbenzylamine, followed by removal of the phenylethyl group has been shown to be an attractive method for generating vicinal diamines.[2] Recently, highly selective methods have been developed for the synthesis of diamines.[3] Particularly, the chiral diamines containing unsaturated functionalities have been transformed to some interesting chiral 1,2-diamines,[4] but the unsaturated groups are not tolerant to hydrogenation during the removal of the phenylethyl groups.[2a,3c,d] Highly efficient asymmetric synthesis of enantiopure vicinal diamines remains a significant challenge.[5]

Recently, we have developed a new method for preparing both enantiomers of *tert*-butyl *tert*-butanethiosulfinate suitable for large-scale production in high optical purity and good yield,[6] which are then readily transformed to both (*R*)- and (*S*)-*tert*-butanesulfinamide (**1**). The most straightforward method for the preparation of aldimines is the condensation of aldehydes and **1** with sulfate as a Lewis acid catalyst and a water scavenger.[7] Here we synthesized a novel chiral bisimine **2**[8] derived from glyoxal and (*R*)-**1** (Scheme 1) and found that organometallic reagents added to this bisimine can give vicinal diamines with excellent diastereoselectivity and high enantioselectivity.



Scheme 1 The synthesis of bisimine **2** derived from glyoxal and (*R*)-*tert*-butanesulfinamide (**1**)

Ellman has shown that various organometallic reagents added to *tert*-butanesulfinyl imines have been prepared from enantiopure **1** in good yields and high diastereoselectivities.[9] However, initial results for the addition of PhMgBr to the bisimine (*R*,*R*)-**2** were disappointing. The diastereoselectivity (dl:meso) and enantioselectivity of product **3a** were highly dependent on the reaction conditions (Table 1). In non-coordinating solvents, such as toluene, high dl:meso ratio was obtained for the product **3a** (entry 1), but much lower diastereoselectivity was afforded in THF (entry 2). Fortunately, while PhLi was slowly added to the bisimine **2** in THF at –78 °C, the target compound **3a** was obtained in 78% yield with a 91:9 diastereomeric ratio (dr) and an enantiomeric excess (ee) of 91.1% (entry 3). In the presence of non-coordinating solvents, such as toluene, and at a higher temperature, both the dr and ee decreased (entries 4 and 5). To improve the selectivities, the effects of Lewis acid additives were investigated (Table 1).[10] In the presence of $AlMe_3$, both dr and ee in THF were higher than those in toluene (entry 6 vs. 7). Up to 98% ee was obtained in THF using $BF_3{\cdot}OEt_2$ as an additive (entry 10), albeit in slightly lower dr (95:5).[11] Removal of the *N*-*tert*-butanesulfinyl groups was readily accomplished using HCl in diethyl ether to give quantitatively the known (*R*,*R*)-1,2-diphenylethylenediamine (**4a**)[5e] and allowed assignment of the absolute stereochemistry.

Encouraged by these preliminary results, we next evaluated the addition of other organolithium reagents to bisimine **2** mediated by $BF_3{\cdot}OEt_2$ in THF. High dr (86:14 to >99:1) and ee (86.0–100%) were obtained (Table 2). It was also evident that dr of the product **3** were highly dependent on the different electronic properties of the substituents of the aryl ring and decreased in the following order: *p*-CH_2=CH (>99:1), *p*-CH_3 (96:4), *p*-CH_3O (90:10)

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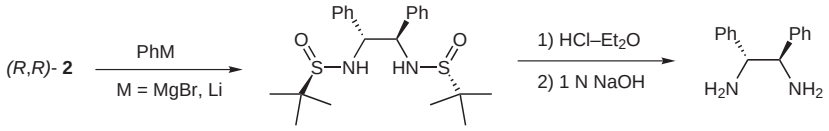
Table 1 Addition of Organometallic Reagents to Bisimine **2** in the Presence of Different Additives[a]



(R,R,R,R)- **3a**
"*anti*-Ellman"

(R,R)- **4a**

Entry	Reagent	Additive	Solvent	Yield (%)[b]	dl:meso[c]	ee (%)[c,d]
1	PhMgBr	None	Toluene	79	93:7	12.9
2	PhMgBr	None	THF	85	43:57	36.0
3	PhLi	None	THF	78	91:9	91.1
4	PhLi	None	Toluene	79	82:18	84.7
5[e]	PhLi	None	THF	81	80:20	46.7
6	PhLi	$AlMe_3$	THF	80	97:3	94.0
7	PhLi	$AlMe_3$	Toluene	77	93:7	89.0
8	PhLi	$ZnBr_2$	THF	82	95:5	94.0
9	PhLi	$MgBr_2$	THF	87	84:16	94.8
10	PhLi	$BF_3{\cdot}OEt_2$	THF	88	95:5	98.0
11	PhLi	$Ti(OEt)_4$	THF	69	96:4	91.6
12	PhLi	TMEDA	THF	77	85:15	96.0

[a] Reactions performed by slow addition of PhMgBr or PhLi (4 equiv) to a 0.1 M solution of **2** at –78 °C and stirred for 3–5 h.
[b] Yield of compound **3a** after flash chromatography.
[c] The dr and ee of the corresponding bis(trifluoroacetamide) prepared from crude **4a** and $(CF_3CO)_2O$ as determined by GC analysis on a chiral column (CP-Chirasil-L-Val).
[d] Absolute configuration of **4a** determined to be *R,R* by comparison of the retention time of its bis(trifluoroacetamide) derivative to that of the known bis(trifluoroacetamide) of (*R,R*)-**4a** reported in the literature (see ref. 5c) based on GC analysis on a chiral column (CP-Chirasil-L-Val).
[e] Reaction conducted at 30 °C for 3 h.

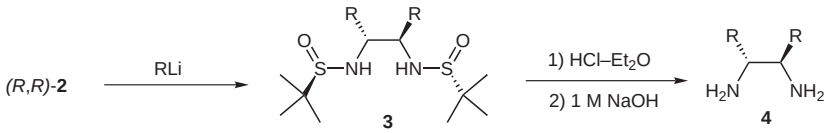
and *p*-F (86:14; entries 8, 5, 3, and 7, respectively). Although the addition of *o*-$MeOC_6H_4Li$ gave high ee (98.3%), lower ee (< 90%) was obtained in the addition of *m*- and *p*-$MeOC_6H_4Li$ (entry 1 vs. entries 2 and 3). Alkyllithium also gave addition products with high dr and ee (entries 9 and 10). The minor *meso*-isomer of **3j** could be removed by chromatographic purification and optically pure *dl*-**3j** could be obtained in 52% yield with dr >99:1. Moreover, the bissulfinamides **3c**–**e** could be further purified by recrystallization in optically pure forms with dr >99:1 and ee >99% (entries 2, 3, and 4).

Among the most frequently employed methods for accessing chiral allylic amines is the Barbier allylation of chiral imines.[12] As expected, this Zn-mediated allylation using THF as the solvent of choice gave the desired allylic diamine **3l** with both high dr (*dl*:*meso* = 88:12) and ee (91.5%). Optically pure diamine **3l** could be obtained in modest yield (64%) by chromatography and subsequently transformed quantitatively to allylic vicinal diamine **4l** by removing the sulfinyl groups with HCl in Et_2O at room temperature. In this case the C=C bonds are tolerant to the deprotection conditions (Scheme 2). The absolute configuration of (*R,R*)-**4l** was determined by correlation with the specific rotation of the HCl salt of the known (*R,R*)-4,5-diaminooctane,[3c] which was obtained via hydrogenation of **4l**.

Optically pure **3e** was obtained in 75% yield by recrystallization from Et_2O (Table 2, entry 4) and the crystals were subjected to X-ray structural analysis,[13] in which an intramolecular hydrogen bond was formed between O1 and N2 of the two sulfonamide moieties. The stereochemistry of the two newly created stereocenters was revealed to possess *R,R*-configuration (Figure 1). It is interesting to note that the stereochemistry of these addition products is contrary to that of the reductive homocoupling products previously obtained by Xu and Lin[5d] and Ellman's addition products ('*anti*-Ellman' addition)[9,14] from the same (*R*)-*tert*-butanesulfinamide (**1**).

The reversal of stereoselectivity for addition to bisimine has ample precedent.[14] The rationale for the reversal and high stereoselectivity of organolithium addition to the bisimine **2** mediated by $BF_3{\cdot}OEt_2$ is that both bisimine **2** and the mono-addition intermediate – monoimine, adopt a 'Cram–Davis' open transition state model[11,15] where the

Table 2 Addition of Various Organolithium Reagents to Bisimine **2**[a]



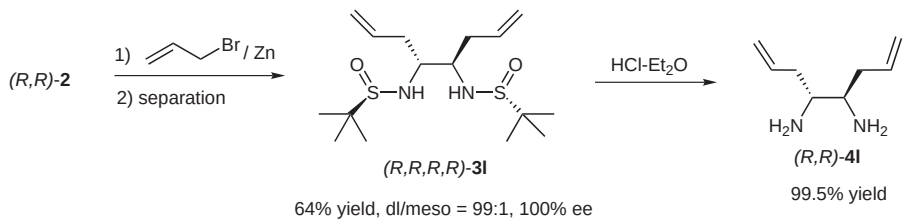
R = *o*-$MeOC_6H_4$, *m*-$MeOC_6H_4$, *p*-$MeOC_6H_4$, *o*-MeC_6H_4, *p*-MeC_6H_4
m-FC_6H_4, *p*-FC_6H_4, *p*-CH_2=CHC_6H_4, *t*-Bu, *n*-Bu

Entry	Reagent	Product	Yield (%)[b]	dl:meso[c]	ee (%)[c]
1	*o*-$MeOC_6H_4Li$	**3b**	88	88:12	98.3
2	*m*-$MeOC_6H_4Li$	**3c**	79 (57)[d]	92:8	90.0
3	*p*-$MeOC_6H_4Li$	**3d**	84 (66)[d]	90:10	86.0[e]
4	*o*-MeC_6H_4Li	**3e**	80 (75)[d]	97:3	98.7[f]
5	*p*-MeC_6H_4Li	**3f**	83	96:4	95.8
6	*m*-FC_6H_4Li	**3g**	81	86:14	95.0
7	*p*-FC_6H_4Li	**3h**	83	86:14	96.8
8	*p*-CH_2=CHC_6H_4Li	**3i**	84	>99:1	100
9	*t*-BuLi	**3j**	58	97:3[g]	100
10	*n*-BuLi	**3k**	86	96:4	96.8

[a] Reactions performed by slow addition of a 0.1 M solution of **2** to a mixture of BF_3·OEt_2 and RLi at –78 °C and stirred for 3–5 h.
[b] Yield of compound **3** after flash chromatography.
[c] The dr and ee of the bis(trifluoroacetamide) derivatives prepared from crude **4** and $(CF_3CO)_2O$ as determined by GC analysis on a chiral column (CP-Chirasil-L-Val).
[d] Values in brackets are yields of compound **3** obtained after recrystallization.
[e] Absolute configuration of compound **4d** determined to be *R*,*R* by comparison of retention time of its bis(trifluoroacetamide) derivative to that of the bis(trifluoroacetamide) of (*R*,*R*)-**4d** (see ref. 5c) based on GC analysis on a chiral column (CP-Chirasil-L-Val).
[f] Absolute configuration of product **3e** determined to be *R*,*R*,*R*,*R* on the basis of X-ray analysis.
[g] The dr was determined by ^{1}H NMR analysis of the crude **3j**.

sulfinyl oxygen coordinates to BF_3 and sterically shields the *Si* face of the imines to give the Cram addition products – monoimine and **3**, respectively, via addition from the *Re* face (Figure 2, A and B). In transition state B, the R group generated via the first addition also favored the second addition from the *Re* face. Excess BF_3 may act to further activate the imine bond.[16]

In summary, we have shown that the addition of different organolithium reagents to the bisimine **2** proceeds with high dr (dl:meso) and ee to give chiral disulfinamides **3** in good yields. The separability of the diastereomers and easy removal of the *N*-sufinyl groups make this highly stereoselective reaction a convenient and practical approach for the synthesis of optically pure C_2-symmetrical vicinal diamines, especially those containing unsaturated bonds, which are not otherwise readily accessible.[2a,3–5] The 'Cram–Davis' open transition state model is proposed to rationalize the observed stereoselectivity for the addition of organolithium to the bisimine **2**. Further studies aimed at exploring the applicability of this methodology toward the preparation of C_2-symmetrical vicinal diamines as polymer-supported chiral ligands for asymmetric catalysis are underway.[17] The addition of other organometallic reagents, especially organozinc reagents,[12] to the bisimine **2** is in progress.



Scheme 2 Zn-Mediated allylation of bisimine **2**

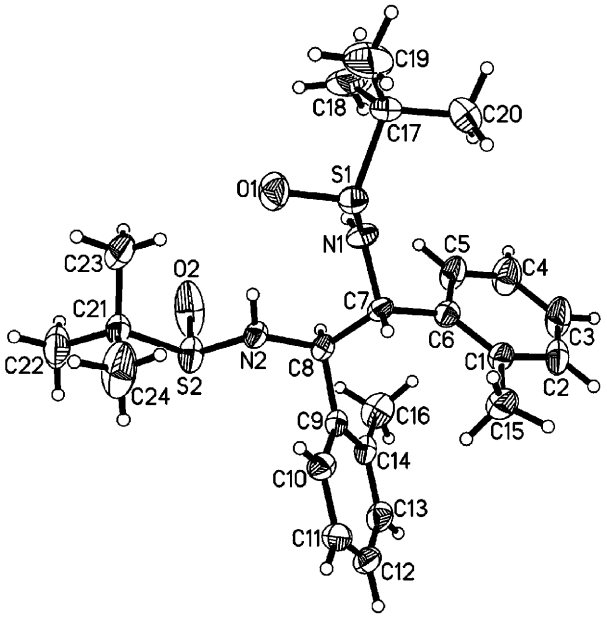


Figure 1 X-ray crystal structure of (*R*,*R*)-**3e**

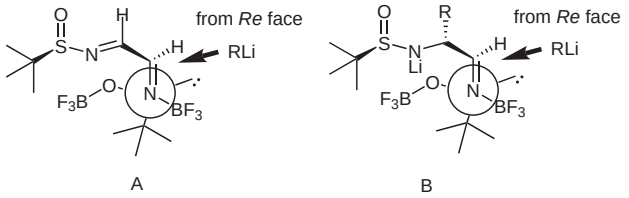


Figure 2 The mechanism for organolithium addition to bisimine **2**

To a flask was added the bisimine (*R*,*R*)-**2** in the specified solvent and the solution was then cooled to –78 °C under Ar. The organometallic reagent (4 equiv) was then added slowly to the solution and then stirred for 3–5 h. The reaction mixture was allowed to warm to r.t. over a period of 5 h and then stirred for a further 2 h. The mixture was cooled to 0 °C and quenched by the addition of a sat. aq solution of Na_2SO_4. The organic phase was separated and the aqueous phase was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified via flash chromatography to afford the disulfinamide **3**.

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References

(1) Vicinal amines are important chiral auxiliaries. For excellent reviews, see: (a) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem. Int. Ed.* **1998**, *37*, 2580. (b) Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161.

(2) (a) Neumann, W. L.; Rogic, M. M.; Dunn, T. J. *Tetrahedron Lett.* **1991**, *32*, 5865. (b) Alvaro, G.; Savoia, D. *Synlett* **2002**, 651.

(3) (a) Roland, S.; Mangeney, P.; Alexakis, A. *Synthesis* **1999**, 228. (b) Roland, S.; Mangeney, P. *Eur. J. Org. Chem.* **2000**, 611. (c) Alvaro, G.; Grepioni, F.; Savoia, D. *J. Org. Chem.* **1997**, *62*, 4180. (d) Alvaro, G.; Grepioni, F.; Grilli, S.; Maini, L.; Martelli, G.; Savoia, D. *Synthesis* **2000**, 581.

(4) (a) Alexakis, A.; Tomassini, A.; Chouillet, C.; Roland, S.; Mangeney, P.; Bernardinelli, G. *Angew. Chem. Int. Ed.* **2000**, *39*, 4093. (b) Grilli, S.; Martelli, G.; Savoia, D.; Zazzetta, C. *Synthesis* **2003**, 1083.

(5) For recent leading references, see: (a) Enders, D.; Meiers, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2261. (b) Prakash, G. K. S.; Mandal, M. *J. Am. Chem. Soc.* **2002**, *124*, 6538. (c) Zhong, Y. W.; Xu, M. H.; Lin, G. Q. *Org. Lett.* **2004**, *6*, 3953. (d) Zhong, Y. W.; Izumi, K.; Xu, M. H.; Lin, G. Q. *Org. Lett.* **2004**, *6*, 4747. (e) Xue, D.; Chen, Y.; Cui, X.; Wang, Q.; Zhu, J.; Deng, J. *J. Org. Chem.* **2005**, *70*, 3584.

(6) Liao, J.; Sun, X.; Cui, X.; Yu, K.; Zhu, J.; Deng, J. *Chem. Eur. J.* **2003**, *9*, 2611.

(7) (a) Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913. (b) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278.

(8) **Procedure for the Synthesis of Bisimine 2.**
To a 0.25 M solution of (*R*)-*tert*-butanesulfinamide (**1**, 1.21 g, 10 mmol) in CH_2Cl_2 (40 mL) was added 6.4 g (40 mmol) of anhyd $CuSO_4$ followed by 40% aq glyoxal (0.72 mL, 5 mmol). The mixture was stirred at r.t. for 2 d. The reaction mixture was filtered through a pad of Celite, and the filter cake was washed well with CH_2Cl_2. The residue obtained after condensation was purified by chromatography twice. Pure **2** was obtained (0.94 g, 71%) as a pale yellow crystalline solid after recrystallized twice from hexane.

(9) For addition reactions to sulfinimines, see: (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984; and references therein. (b) Evans, J. W.; Ellman, J. A. *J. Org. Chem.* **2003**, *68*, 9948. (c) McMahon, J. P.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 1645. (d) Schenkel, L. B.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 3621.

(10) Cogan, D. A.; Liu, G.; Ellman, J. A. *Tetrahedron* **1999**, *55*, 8883; and references therein.

(11) Davis, F. A.; McCoull, W. *J. Org. Chem.* **1999**, *64*, 3396.

(12) For Barbier allylation of chiral imines, see: (a) Legros, J.; Meyer, F.; Coliboeuf, M.; Crousse, B.; Bonnet-Delpon, D.; Bégué, J.-P. *J. Org. Chem.* **2003**, *68*, 6444. (b) Lee, C.-L. K.; Ling, H. Y.; Loh, T.-P. *J. Org. Chem.* **2004**, *69*, 7787.

(13) **X-ray Investigation and Crystal Data.**
Colorless crystals of (*R*,*R*)-**3e** were grown from Et_2O at r.t. The X-ray diffraction data were collected on a Siemens P4 automatic four-circle diffractometer using graphite monochromated Mo-K_α radiation (λ = 0.71073 Å) at r.t. The structure was solved by direct methods using SHELXS-97 and refined by full-matrix least-square calculation on F^2 with SHELXL-97. Crystal data for (*R*,*R*)-**3e** ($C_{24}H_{38}N_2O_3S_2$): *M*w = 466.68, crystal size 0.48 × 0.44 × 0.42 mm, orthorhombic, space group P2 (1)2 (1)2 (1), a = 7.100 (1) Å, b = 19.026 (2) Å, c = 20.197 (2) Å, α = 90°, β = 90°, γ = 90°, V = 2728.36 (56) Å^3, Z = 4, D_{calcd} = 1.136 Mg/m^{-3}, F(000) = 1008, T = 286 (2) K. All non-hydrogen atoms were refined anisotropically, whereas the hydrogen atoms were generated geometrically. Final R indices [I>2σ(I)]: R1 = 0.0415, wR2 = 0.0788. Crystallographic data has been deposited with the Cambridge Crystallographic Data Center supplementary publication no. CCDC-275776. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (1223)762910; e-mail: deposit@ccdc.cam.ac.uk].

(14) (a) Barrow, J. C.; Ngo, P. L.; Pellicore, J. M.; Selnick, H. G.; Nantermet, P. G. *Tetrahedron Lett.* **2001**, *42*, 2051. (b) Tang, T. P.; Volkman, S. K.; Ellman, J. A. *J. Org. Chem.* **2001**, *66*, 8772.

(15) (a) Plobeck, N.; Powell, D. *Tetrahedron: Asymmetry* **2002**, *13*, 303. (b) Jung, P. M. J.; Beaudegnies, R.; De Mesmaeker, A.; Wendeborn, S. *Tetrahedron Lett.* **2003**, *44*, 293.

(16) X-ray crystal structure of BF_3–imine complexes, see: Ma, Y.; Lobkovasky, E.; Collum, D. B. *J. Org. Chem.* **2005**, *70*, 2335.

(17) For polymer-supported chiral C_2-symmetrical vicinal diamine ligands, see: (a) Itsuno, S.; Tsuji, A.; Takahashi, M. *Tetrahedron Lett.* **2003**, *44*, 3825. (b) Li, X.; Chen, W.; Hems, W.; King, F.; Xiao, J. *Org. Lett.* **2003**, *5*, 4559. (c) Liu, W.; Cui, X.; Cun, L.; Wu, J.; Zhu, J.; Deng, J.; Fan, Q. *Synlett* **2005**, 1591.