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Highly Diastereoselective and Enantioselective Synthesis of Enantiopure C_2-Symmetrical Vicinal Diamines by Reductive Homocoupling of Chiral *N-tert*-Butanesulfinyl Imines

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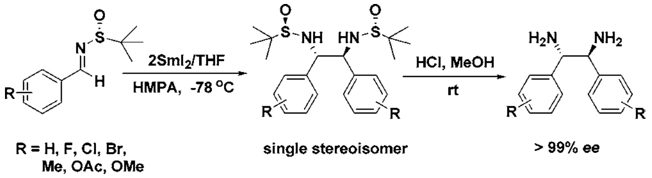
ABSTRACT



An efficient and straightforward method for the preparation of highly enantiomerically enriched C_2-symmetrical vicinal diamines by the reductive homocoupling of aromatic *N-tert*-butanesulfinyl imines in the presence of SmI_2 and HMPA was developed. It gives access to a variety of enantiopure C_2-symmetrical 1,2-diamines in a very mild and practical way.

Enantiopure vicinal diamines are of great importance in organic chemistry because of their presence in many biologically active compounds and their use as versatile chiral ligands or auxiliaries in asymmetric synthesis.[1] Many efforts have been devoted to the development of methods for their preparation.[1−3] Among them, a method based on the reductive coupling of imine species promoted by a reducing agent is one of the most straightforward and promising approaches for generating vicinal diamines.[3] In recent decades a number of reaction systems have been developed for this transformation, but very often with low stereoselectivity.[4] Highly efficient asymmetric synthesis of enantiopure vicinal diamines remains a significant synthetic challenge.

Recently, we reported the first use of samarium diiodide-induced cross-coupling of nitrones with chiral *N-tert*-butanesulfinyl imines for the asymmetric synthesis of

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[1] (a) Michalson, E. T.; Szmuskovicz, J. *Prog. Drug. Res.* **1989**, *33*, 135. (b) Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161. (c) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580.

[2] For recent leading references, see: (a) Muñiz, K.; Nieger, M.; Mansikkamäki, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 5958. (b) Muñiz, K.; Iaseto, A.; Nieger, M. *Chem. Eur. J.* **2003**, *9*, 5581. (c) Westermann, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 151 and references therein. (d) Alexakis, A.; Tomassini, A.; Chouillet, C.; Roland, S.; Mangeney, P.; Bernardinelli, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 4093. (e) Prakash, G. K. S.; Mandal, M. *J. Am. Chem. Soc.* **2002**, *124*, 6538. (f) Viso, A.; de la Pradilla, R. F.; García, A.; Guerrero-Strachan, C.; Alonso, M.; Tortosa, M.; Flores, A.; Martínez-Ripoll, M.; Fonseca, I.; André, I.; Rodríguez, A. *Chem. Eur. J.* **2003**, *9*, 2867. (g) Ooi, T.; Sakai, D.; Takeuchi, M.; Tayama, E.; Maruoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 5868. (h) Corey, E. J.; Lee, D.-H.; Sarshar, S. *Tetrahedron: Asymmetry* **1995**, *6*, 3.

[3] For examples of intramolecular coupling, see: (a) Mercer, G. J.; Sigman, M. S. *Org. Lett.* **2003**, *5*, 1591. (b) Shono, T.; Kise, N.; Oike, H.; Yoshimoto, M.; Okazaki, E. *Tetrahedron Lett.* **1992**, *33*, 5559. (c) Kise, N.; Oike, H.; Okazaki, E.; Yoshimoto, M.; Shono, T. *J. Org. Chem.* **1995**, *60*, 3980. (d) Periasamy, M.; Srinivas, G.; Suresh, S. *Tetrahedron Lett.* **2001**, *42*, 7123. (e) Annunziata, R.; Benaglia, M.; Caporale, M.; Raimondi, L. *Tetrahedron: Asymmetry* **2002**, *13*, 2727. (f) Shimizu, M.; Iida, T.; Fujisawa, T. *Chem. Lett.* **1995**, 609. (g) Imamoto, T.; Nishimura, S. *Chem. Lett.* **1990**, 1141. (h) Enholm, E. J.; Forbes, D. C.; Holub, D. P. *Synth. Commun.* **1990**, *20*, 981. For examples of intermolecular coupling, see: (i) Yanada, R.; Negoro, N.; Okaniwa, M.; Miwa, Y.; Taga, T.; Yanada, K. Fujita, T. *Synlett* **1999**, 537. (j) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron Lett.* **1998**, *39*, 3333. (k) Taniguchi, N.; Uemura, M. *Synlett* **1997**, 51. (l) Taniguchi, N.; Hata, T.; Uemura, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1232.

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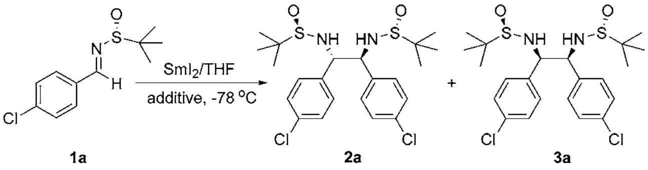
unsymmetrical vicinal diamines.[5] Excellent enantioselectivities, as well as high diastereoselectivities, were observed in this reaction. The reaction gives access to a variety of highly enantiomerically enriched unsymmetrical vicinal diamines after further transformation of the obtained products. Our continuous efforts[6] in the investigations of samarium diiodide-mediated reductive coupling have led us to the discovery that enantiomerically enriched C_2-symmetrical vicinal diamines can also be effectively prepared under the proper reaction conditions.

During the course of our studies on the above-mentioned cross-coupling reactions, we observed the minor formation of the homocoupling product of *N-tert*-butanesulfinyl imine **1a** upon treatment with 2 equiv of SmI_2 in the presence of nitrone. Thus, we felt the potential of the reductive homocoupling to synthesize chiral C_2-symmetrical diamines. To our knowledge, no radical reactions of *N-tert*-butanesulfinyl imines[7] have been documented before. Our initial investigations were carried out by using (*R*)-sulfinyl aldimine **1a** as a substrate under various conditions (Scheme 1).

Scheme 1



As anticipated, the homocoupling of sulfinyl aldimine **1a** successfully proceeded in the presence of 2 equiv of SmI_2 in THF at −78 °C to produce both *d*/*l*- and *pseudo-meso*-adduct in totally 81% of yield.[8] The *d*/*l*-adduct **2a** is slightly superior to the *pseudo-meso*-adduct **3a** with a ratio of 1.4:1 (Table 1, entry 1). No significant improvement was found when *tert*-butyl alcohol or NiI_2[9] was added to the reaction system (entries 2 and 3). Very gratifyingly, when 2 equiv of HMPA[10] was used as an additive, the coupling reaction proceeded smoothly to give only *d*/*l*-product **2a** as a single diastereomer in an almost quantitative yield of 99% (entry 4). The structure of the obtained diamine product **2a** was unambiguously established by X-ray analysis, and the stereochemistry of the two newly formed carbon centers was revealed to possess (*S*,*S*)-configuration[11] (Figure 1). Further experiments showed that the stereoselectivity of the reaction was largely affected by the reaction condition. A decrease in the amount of both SmI_2 and HMPA from 2 to 1.2 equiv led to the formation of the *pseudo-meso*-product **3a**. As a result, a 6:1 mixture of diastereomeric diamine **2a** and **3a** was observed, although a high yield was still obtained (entry 5). These results suggest that the presence of a suitable amount of donor ligand HMPA in conjunction with SmI_2 is the critical combination required for achieving excellent stereoselectivity.

Table 1. Initial Examination of the Reductive Homocoupling Conditions

entry	additive	yield (%)[a]	**2a**:**3a**[b]
1		81	1.4:1
2	^{t}BuOH (2.0 equiv)	77	1.7:1
3	NiI_2 (2%)	72	1.7:1
4	**HMPA (2.0 equiv)**	**99**	**only 2a**
5[c]	HMPA (1.2 equiv)	96	6:1

[a] Total isolated yield of *d*/*l*- and *pseudo-meso*-products. [b] Determined by the individual isolated yield of **2a** and **3a** after flash column chromatography. [c] Performed with 1.2 equiv of SmI_2.

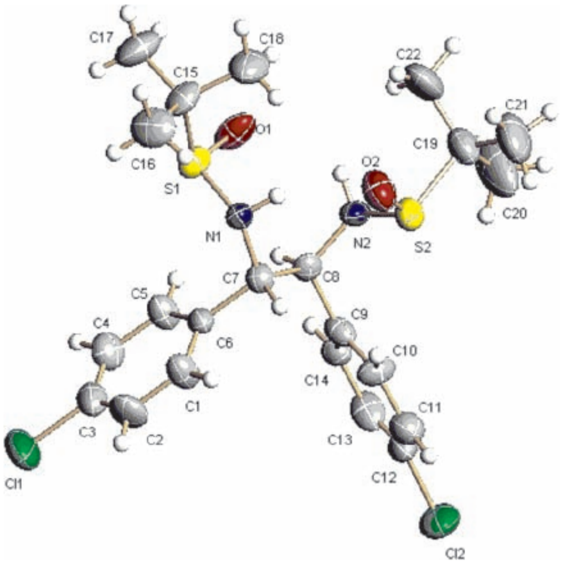


Figure 1. X-ray crystal structure of homocoupling product **2a**.

On the basis of the established optimum reaction conditions used in entry 4 of Table 1, a variety of other enantiomerically pure aromatic *N-tert*-butanesulfinyl imines

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[4] For selected recent examples, see: (a) Hatano, B.; Ojawa, A.; Hirao, T. *J. Org. Chem.* **1998**, *63*, 9421. (b) Alexakis, A.; Aujard, I.; Mangeney, P. *Synlett* **1998**, 873. (c) Liu, X.; Liu, Y.-K.; Zhong, Y.-M. *Tetrahedron Lett.* **2002**, *43*, 6787. (d) Kise, N.; Ueda, N. *Tetrahedron Lett.* **2001**, *42*, 2365. (e) Ortega, M.; Rodríguez, M. A.; Campos, P. J. *Tetrahedron* **2004**, *60*, 6475.

[5] Zhong, Y.-W.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2004**, *6*, 3953.

[6] (a) Xu, M.-H.; Wang, W.; Lin, G.-Q. *Org. Lett.* **2000**, *2*, 2229. (b) Wang, W.; Xu, M.-H.; Lei, X.-S.; Lin, G.-Q. *Org. Lett.* **2000**, *2*, 3773. (c) Xu, M.-H.; Wang, W.; Xia, L.-J.; Lin, G.-Q. *J. Org. Chem.* **2001**, *66*, 3953. (d) Wang, W.; Zhong, Y.-W.; Lin, G.-Q. *Tetrahedron Lett.* **2003**, *44*, 4613.

[7] Ellman, J. A.; Wens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984.

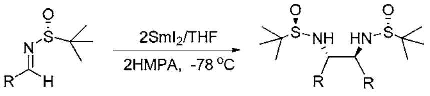
[8] The *d*/*l*- and *pseudo-meso*-adducts were readily separable by column chromatography.

[9] Machrouhi, F.; Namy, J.-L. *Tetrahedron Lett.* **1999**, *40*, 1315.

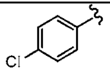
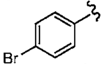
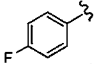
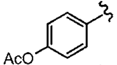
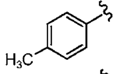
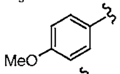
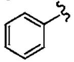
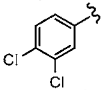
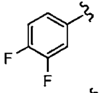
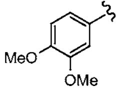
[10] HMPA was found to be a good additive in many SmI_2 involved reactions; for examples, see: (a) Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 5763. (b) Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Chem. Lett.* **1987**, 1485. (c) Molander, G. A.; Mckie, J. A. *J. Org. Chem.* **1992**, *57*, 3132. (d) Enemaerke, R. J.; Kertz, T.; Skrydstrup, T.; Daasbjerg, K. *Chem. Eur. J.* **2000**, *6*, 3747. (e) Prasad, E.; Knettle, B. W.; Flowers, R. A., II. *J. Am. Chem. Soc.* **2004**, *126*, 6891.

[11] For X-ray structure-related data, see Supporting Information.

Table 2. SmI_2-Mediated Reductive Homocoupling of Chiral *N-tert*-Butanesulfinyl Imines[a]



1 **2**

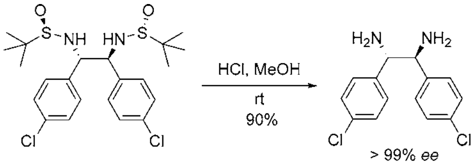
entry	R	substrate	product	yield (%)[b]
1		**1a**	**2a**	99
2[c]		**1b**	**2b**	93
3		**1c**	**2c**	83
4		**1d**	**2d**	61
5		**1e**	**2e**	71 (72)[d]
6		**1f**	**2f**	58 (80)[d]
7		**1g**	**2g**	25 (30)[d]
8[e]		**1h**	**2h**	81
9		**1i**	**2i**	69
10		**1j**	**2j**	52 (85)[d]

[a] All reactions were performed using 2.0 equiv of SmI_2 and 2.0 equiv of HMPA in THF at −78 °C unless otherwise noted. [b] Isolated yield. [c] Another 7% of *pseudo-meso*-product was isolated. [d] Performed with 6 equiv of HMPA. [e] Another 19% of *pseudo-meso*-product was isolated.

were employed as substrates to probe the generality of this reductive homocoupling reaction. As summarized in Table 2, imines containing either electron-withdrawing or electron-donating substituents were all successfully coupled to afford the corresponding sulfinyl 1,2-diamines. In most cases, the reactions proceeded to completion in 2−3 h, giving *d*/*l*-adducts **2a** as the only products in moderate to excellent yields.[12] In accordance with our earlier studies of cross-coupling,[5] electron-donating substituted imines were relatively less reactive and gave a lower yield of homocoupling products (entries 5, 6, and 10). Interestingly, a significant HMPA effect was found in the cases of methoxy-substituted imines **1f** and **1j**; when the amount of HMPA added was increased from 2 to 6 equiv, a dramatic improvement of the coupling yield from 58 to 80% and 52 to 85% was observed, respectively (entries 6 and 10).[13] We presume that this may be due to the increase of the reduction potential of SmI_2 by HMPA; however, no obvious increase of the yields in the cases of **1e** and **1g** was observed (entries 5 and 7). Nonsubstituted imine **1g** appears to be the least reactive under the current reaction conditions (entry 7).[14] Notably, for those diamines obtained in entries 1, 2, 4, and 6, the *para*-halogen, acetoxy, or methoxy substituent on the benzene ring would be a useful functionality for further attachment onto solid support materials such as via O-alkylation or Suzuki coupling reactions.[15] Moreover, the obtained diamine products with different electronic properties would also be very useful chiral ligands in asymmetric reactions.

Conversion of the homocoupling products to the corresponding free diamines has also been examined. As exemplified by **2a**, the chiral free diamine can be readily obtained by removal of the *N-tert*-butanesulfinyl group under acidic conditions (Scheme 2). To determine the ee, both enantiomers were prepared separately and the enantiomeric purities were then ascertained by chiral HPLC analysis of the corresponding diacetate.[16] For example, the diacetates of diamines **4a**, ***ent*-4a**, **4b**, ***ent*-4b**, and **4f**, ***ent*-4f** each show an extremely high ee of >99%.

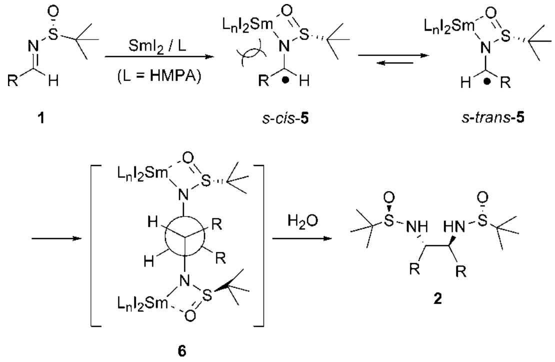
Scheme 2



2a **4a**

On the basis of the known samarium diiodide chemistry[17] and the observed stereoselectivity, a plausible reaction mechanism is shown in Scheme 3. Upon treatment of SmI_2 in THF and HMPA, sulfinyl imine substrate **1** undergoes one-electron reduction to give a radical intermediate *s-cis-*

Scheme 3. Proposed Reaction Mechanism



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(12) See footnotes of Table 2 for details.

(13) When 8 equiv of HMPA was employed, no further improvement of the yield was observed.

(14) Fortunately, its corresponding chiral 1,2-diphenylethylenediamine is already commercially available from many chemical companies.

(15) For recent examples, see: (a) Ferrand, A.; Bruno, M.; Tommasino, M. L.; Lemaire, M. *Tetrahedron: Asymmetry* **2002**, *13*, 1379. (b) Itsuno, S.; Tsuji, A.; Takahashi, M. *Tetrahedron Lett.* **2003**, *44*, 3825.

5. Due to the bulkiness of samarium complex with HMPA, *s-cis*-**5** is rapidly transformed into a structurally more stable intermediate *s-trans*-**5**. During the homocoupling, the *tert*-butanesulfinyl group serves as a powerful chiral directing group, both the *Re*-face approach of the formed radical intermediate *s-trans*-**5** occurs predominantly because of steric repulsion between the two bulky *tert*-butanesulfinyl groups on the nitrogen atom. The excellent diastereoselectivity and enantioselectivity of the reaction can thus be explained by assuming the transition state **6**. Enantiomerically enriched C_2-symmetrical vicinal diamine **2** is then provided after quenching by water.

In summary, we have discovered and developed a new reaction system that allows efficient reductive homocoupling of aromatic *N-tert*-butanesulfinyl imines in the presence of SmI_2 and HMPA generation of C_2-symmetrical l,2-diamines in a very mild and stereoselective way. The simple experimental procedure and the mild reaction conditions make this highly diastereoselective and enantioselective homocoupling reaction a convenient, practical, and straightforward approach for the synthesis of enantiomerically enriched C_2-symmetrical vicinal diamines. Further studies aimed at exploring the applicability of these new C_2-symmetrical vicinal diamines in asymmetric reactions are in progress.

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Supporting Information Available: Experimental procedure and characterization data, including X-ray crystallographic data of **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0479803

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(16) See Supporting Information for details.

(17) For a recent review on samarium diiodide chemistry, see: Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351.