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Samarium Diiodide-Induced Asymmetric Synthesis of Optically Pure Unsymmetrical Vicinal Diamines by Reductive Cross-Coupling of Nitrones with *N-tert*-Butanesulfinyl Imines

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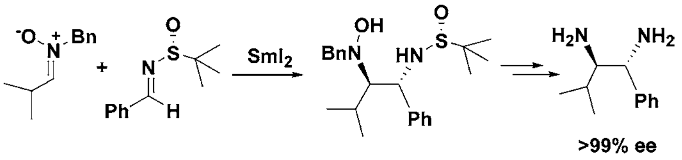
ABSTRACT



An efficient method for the preparation of optically pure unsymmetrical vicinal diamines by the SmI_2-induced reductive cross-coupling of nitrones with chiral *N-tert*-butanesulfinyl imines was developed. This is the first successful example of the highly diastereoselective and enantioselective cross-coupling between two different imine species. It provides a straightforward access to enantiopure unsymmetrical vicinal diamines that are widely applicable in asymmetric synthesis.

Optically pure vicinal diamines have played significant roles in organic chemistry due to their broad utility, serving both as useful units for many biologically active compounds and as important chiral ligands or chiral auxiliaries for asymmetric synthesis.[1] In the past several years, although much attention has been paid to the development of methods for their preparation, the highly efficient asymmetric synthesis of enantiopure vicinal diamines remains a challenging topic. Among the approaches developed such as resolution,[2] asymmetric diamination,[3] aza-Henry reaction,[4] nucleophilic addition to imine derivatives,[5] and alkylation of glycine amide derivatives,[6] those that involve stereoselective C−C bond formation in a single transformation are of particular interest.

The simplest and most direct method for the preparation of vicinal diamines is the reductive coupling between two imine species. Generally, it is applied to the synthesis of symmetrical 1,2-diamines via homocoupling.[7,8] Efficient cross-coupling of two different imines is apparently rather difficult, mainly due to the competition of the homocoupling

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[1] For a review on the chemistry of vicinal diamines, see: Lucet, D.; Gall, T. L.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580.

[2] Selected examples: (a) Jacobsen, E. N.; Gao, Y.; Hong, Y.-P., Nie, X.; Zepp, C. M. *J. Org. Chem.* **1994**, *59*, 1939. (b) Corey, E. J.; Lee, D.-H.; Sarshar, S. *Tetrahedron: Asymmetry* **1995**, *6*, 3.

[3] (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.

[4] For a recent highlight article, see: Westermann, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 151 and references therein.

[5] (a) Reetz, M. T.; Jaeger, R.; Drewlies, R.; Hübel, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 103. (b) Alexakis, A.; Tomassini, A.; Chouillet, C.; Roland, S.; Mangeney, P.; Bernardinelli, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 4093. (c) Prakash, G. K. S.; Mandal, M. *J. Am. Chem. Soc.* **2002**, *124*, 6538. (d) Viso, A.; Pradilla, R. F. de la; 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.

[6] Ooi, T.; Sakai, D.; Takeuchi, M.; Tayama, E.; Maruoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 5868.

[7] For selected homocoupling examples: (a) Kim, M.; Knettle, B. W.; Dahlén, A.; Hilmersson, G.; Flowers, R. A. *Tetrahedron* **2003**, *59*, 10397. (b) Annunziata, R.; Benaglia, M.; Caporale, M.; Raimondi, L. *Tetrahedron: Asymmetry* **2002**, *13*, 2727. (c) Selvakumar, K.; Harrod, J. F. *Angew. Chem., Int. Ed.* **2001**, *40*, 2129. (d) Okaniwa, M.; Yanada, R.; Ibuka, T. *Tetrahedron Lett.* **2000**, *41*, 1047. (e) Tanigushi, N.; Uemura, M. *Synlett* **1997**, 51.

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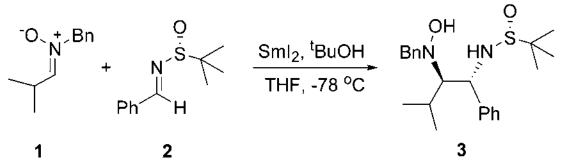
of each imine substrate. To the best of our knowledge, only one example of direct intermolecular cross-coupling of two different imine species to give racemic 1,2-diamines was reported;[9] a new strategy is still in high demand. Recently, Uemura[10] and Py[11] showed their success in the reductive cross-coupling of carbonyl compounds with imine derivatives mediated by $\mathrm{SmI_2}$.[12,13] Given our interest in $\mathrm{SmI_2}$-mediated asymmetric reactions,[14] we decided to explore the possibility of the $\mathrm{SmI_2}$-induced reductive cross-coupling between two different imine species. Herein, we report our preliminary results for the asymmetric synthesis of unsymmetrical chiral vicinal diamines by $\mathrm{SmI_2}$-induced reductive cross-coupling of nitrones with *N*-*tert*-butanesulfinyl imines.

It has been reported that nitrones (iminium ion equivalents) could be added to the carbonyl compounds[11] or the α,*β*-unsaturated esters[15] in the presence of $\mathrm{SmI_2}$. The mechanism may involve an α-aza-nucleophilic species from $\mathrm{SmI_2}$ to the nitrone group. As we know, Ellman's *N*-*tert*-butanesulfinyl imines[16] have shown versatile application in the asymmetric synthesis of amines. However, they have never been employed in the $\mathrm{SmI_2}$-mediated reactions. To check the potential of the cross-coupling between these two species, we began our investigation by examining the reaction of nitrone compound **1** with (*R*)-*N*-*tert*-butanesulfinyl imine **2** (see scheme in Table 1).

Table 1. Initial Examination of the Cross-Coupling Reaction Conditions



entry[a]	**1** (mmol)	**2** (mmol)	$\mathrm{SmI_2}$ (mmol)	yield (%)[b]
1	0.5	0.5	1.0	54
2	0.5	0.5	1.5	63
3	0.5	0.6	1.5	76
4	0.7	0.5	1.5	75
5[c]	0.5	0.6	1.5	46

[a] All reactions were reacted for 3−4 h. [b] Isolated yield of the single diastereomer. [c] Reaction was conducted in the absence of *t*-BuOH.

To our delight, when a solution of nitrone **1** and *N*-*tert*-butanesulfinyl imine **2** in THF at −78 °C was treated with 2 equiv of $\mathrm{SmI_2}$ in the presence of 2 equiv of *tert*-butyl alcohol, the reaction proceeded as we expected, and the 1,2-diamine derivative **3** resulting from this reductive cross-coupling was isolated as a single diastereomer[17] in an acceptable yield of 54% (Table 1, entry 1). The stereochemistry of the two newly formed carbon centers of diamine **3** was determined to be (*R*,*R*)- by X-ray crystallography (Figure 1).[18] In our attempt to optimize the reaction conditions, we found that the yield of product **3** could be increased to 63% when more $\mathrm{SmI_2}$ (3 equiv) was used (entry 2). A further improvement of the yield (∼ 75%) was achieved by employing a slight excess of either substrate (entries 3 and 4). The effect of *tert*-butyl alcohol in the reaction was examined, and a relatively lower yield (46%) was obtained in its absence (entry 5).

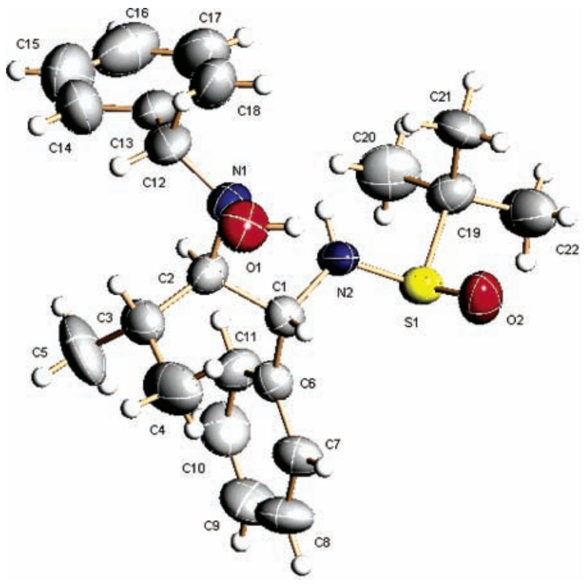


Figure 1. X-ray crystal structure of the cross-coupling product **3**

Encouraged by these results, the cross-coupling of various nitrones with *N*-*tert*-butanesulfinyl imines using the reaction conditions of entry 4 in Table 1 was then studied. The experimental results are summarized in Table 2. In entries 1−6, a range of nitrones with diverse steric and electronic properties were tested to react with sulfinyl aldimine **2**. It was found that the coupling yield and diastereoselectivity were largely influenced by steric hindrance.[19] A less hindered

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(8) For intramolecular coupling: (a) Taniguchi, N.; Hata, T.; Uemura, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1232. (b) Kise, N.; Oike, H.; Okazaki, E.; Yoshimoto, M.; Shono, T. *J. Org. Chem.* **1995**, *60*, 3980. (c) Pansare, S. V.; Malusare, M. G. *Tetrahedron Lett.* **1996**, *37*, 2859.

(9) Shimizu, M.; Suzuki, I.; Makino, H. *Synlett* **2003**, 1635.

(10) (a) Tanaka, Y.; Taniguchi, N.; Uemura, M. *Org. Lett.* **2002**, *4*, 835. (b) Taniguchi, N.; Uemura, M. *J. Am. Chem. Soc.* **2000**, *122*, 8301.

(11) Masson, G.; Py, S.; Vallée, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 1772.

(12) Related reductive cross-coupling of imines with aldehydes has been carried out using samarium diiodide in the presence of $\mathrm{NiI_2}$, see: Machrouhi, F.; Namy, J.-L. *Tetrahedron Lett.* **1999**, *40*, 1315.

(13) For recent reviews on $\mathrm{SmI_2}$ in organic synthesis, see: (a) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307. (b) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321. (c) Krief, A.; Laval, A. M. *Chem. Rev.* **1999**, *99*, 9, 745. (d) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351.

(14) (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.

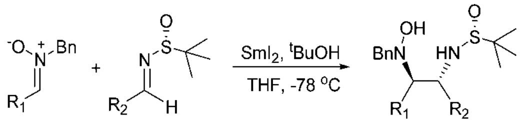
(15) (a) Masson, G.; Cividino, P.; Py, S.; Vallée, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 2265. (b) Riber, D.; Skrydstrup, T. *Org. Lett.* **2003**, *5*, 229.

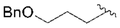
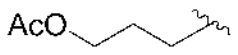
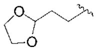
(16) (a) Ellman, J. A.; Evans, J. W. *J. Org. Chem.* **2003**, *68*, 9948. (b) Ellman, J. A.; wens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984.

(17) No other stereoisomer was observed according to ^{1}H NMR analysis of the crude material.

(18) For X-ray structure-related data, see Supporting Information.

Table 2. SmI_2-Induced Reductive Cross-Coupling of Nitrones with *N*-*tert*-Butanesulfinyl Imines



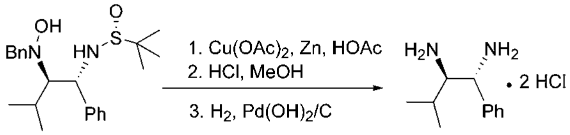
entry	R_1	R_2	T (h)	yield (%)[a] (*d.r.*)[b]
1	^iPr	Ph	3	75
2	C_6H_{11}	Ph	3	65
3	$CH_3(CH_2)_5$	Ph	4	85 (15:1)
4	$^iPrCH_2$	Ph	2.5	67 (10:1)
5	$PhCH_2CH_2$	Ph	2.5	54 (>10:1)
6	^tBu	Ph	5	22
7	^iPr	p-$CH_3C_6H_4$	7	71
8	^iPr	p-$CH_3OC_6H_4$	8	65
9	^iPr	p-ClC_6H_4	1.5	52
10	^iPr	p-BrC_6H_4	1	51
11	^iPr	p-$AcOC_6H_4$	4	69
12		Ph	4	55 (10:1)
13		Ph	4	68 (7:1)
14		Ph	4	71 (>10:1)

[a] Isolated yield. [b] According to ^1H NMR of the crude materials.

nitrone (R_1 = *n*-hexyl) gave the best yield of 85% (entry 3). However, when the R_1 substituent became bulky, the yield of the coupling product decreased, and in the case of entry 6 (R_1 = *tert*-butyl), only 22% of the product was produced. In most cases, excellent diastereoselectivities were achieved, and extremely high diastereoselectivities were observed when isopropyl-, cyclohexyl-, and *tert*-butyl-substituted nitrones were employed (entries 1, 2, and 6). Surprisingly, no reaction occurred if both substrates were aromatic ($R_1 = R_2$ = Ph) or aliphatic ($R_1 = R_2 = {}^iPr$), probably due to the electronic effect. We also investigated the reactions of nitrone **1** with a variety of aromatic *N*-*tert*-butanesulfinyl imines containing electron-donating or electron-withdrawing substituents at the para position, and the cross-coupling products could be formed in reasonable yields (entries 7–11). Reactions with imines having electron-withdrawing substituents were much faster (entries 9 and 10). For the diamines obtained in entries 9–11, it is noteworthy that the *para*-halogen or acetoxyl substituent on the benzene ring would largely facilitate their subsequent synthetic applications. For example, in entry 11, the readily available phenol group would be a very useful functionality to attach the chiral 1,2-diamine moiety onto solid support materials.[20] Different substituted long-chain aliphatic nitrones were also found to be effective substrates for the cross-coupling reactions (entries 12–14). Notably, these obtained cross-coupling products that bear hydroxylamino and sulfinylamino functions may be useful ligands in asymmetric synthesis.

Conversion of the cross-coupling product to the corresponding free diamine could be easily accomplished in a three-step reaction sequence. For example, as shown in Scheme 1, deoxygenation of the hydroxylamino function of the coupling product **3** by Zn/Cu$(OAc)_2$,[21] followed by the removal of the sulfinyl and benzyl group, afforded the optically pure (*R*,*R*)-3-methyl-1-phenyl-butane-1,2-diamine (**4**) in 87% overall yield.[22]

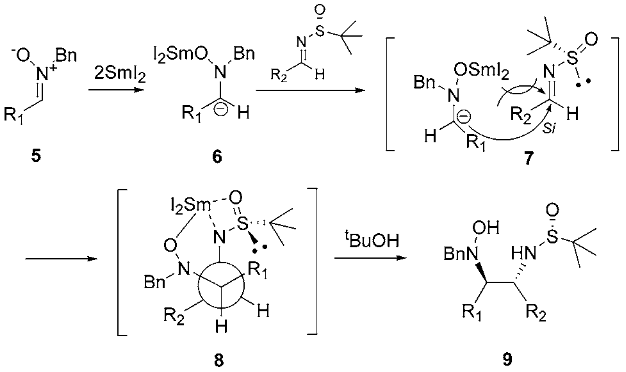
Scheme 1



3 **4**

A plausible reaction mechanism for the observed stereoselective cross-coupling process is presented in Scheme 2.

Scheme 2. Proposed Reaction Mechanism



Upon treatment with SmI_2, the nitrone **5** is first reduced to generate probably an α-aza-nucleophilic anion (**6**) by two-electron reduction, which then adds intermolecularly to the C=N bond of the *N*-*tert*-butanesulfinyl imine. Two independent experimental studies seem to be able to support this hypothesis.[23] First, mainly the reduced product of nitrone **1**

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(19) In most cases in Table 2, the yields of most of the cross-coupling reactions are modest mainly due to the remaining starting material *N*-*tert*-butanesulfinyl imines.

(20) For a recent example: Itsuno, S.; Tsuji, A.; Takahashi, M. *Tetrahedron Lett.* **2003**, *44*, 3825.

(21) Dhavale, D. D.; Gentilucci, L.; Piazza, M. G.; Trombini, C. *Liebigs Ann. Chem.* **1992**, 1289.

(22) Chiral HPLC showed 99.6% ee of its diacetate derivative. For comparison, (*S*,*S*)-**4** was also prepared by the reaction of nitrone **1** with (*S*)-*N*-*tert*-butanesulfinyl imine **2**; see Supporting Information for details.

(23) Other experimental results that may be supportive are as follows: When nitrone **5** (R_1 = Ph) was treated with SmI_2, the corresponding homocoupling product was obtained in 75% yield, indicating a radical mechanism and the formation of the nitrone radical. However, nitrone **5** (R_1 = Ph) did not react with *N*-*tert*-butanesulfinyl imine **2** in the presence of SmI_2 under similar conditions. Thus, this suggests that a radical-based addition of the nitrone radical to the imine followed by further reduction of the nitrogen-based radical may not be preferred.

by SmI_2 was formed in the absence of *N*-*tert*-butanesulfinyl imine **2**. Second, no reaction occurred when only *N*-*tert*-butanesulfinyl imine **2** was treated with SmI_2. The *tert*-butanesulfinyl group serves as a nice chiral directing group in the reaction. Due to its steric bulkiness, the nitrone anion approaches preferably from the *Si*-face of the C═N bond (see **7**), and formation of transition state **8** could be explained by chelation control and steric repulsion between R_1 and R_2. Therefore, the addition reaction takes place with very high stereospecificity. Optically pure unsymmetrical vicinal diamine **9** is then afforded after protonation by *tert*-butyl alcohol.

In conclusion, we have developed an efficient method for the preparation of optically pure unsymmetrical vicinal diamines by the SmI_2-induced reductive cross-coupling of nitrones with chiral *N*-*tert*-butanesulfinyl imines. This is the first successful example of highly diastereoselective and enantioselective cross-coupling between two different imine species. It provides straightforward access to enantiopure vicinal diamines that are widely useful in asymmetric synthesis. Further efforts are being directed toward exploring the applicability of those cross-coupling products and their corresponding diamines, both as chiral ligands in asymmetric catalysis and as precursors in natural products synthesis.

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Supporting Information Available: Experimental procedure and characterization data, including X-ray crystallographic data of **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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