

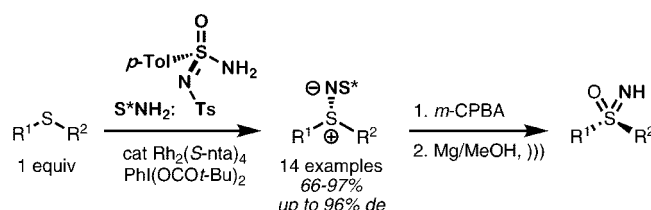
Stereoselective Rhodium-Catalyzed
Imination of Sulfides

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ABSTRACT



The preparation of optically active sulfoximines via the catalytic diastereoselective imination of sulfides using a chiral nitrene is described. Excellent yields up to 97% and good diastereoselectivities up to 96% have been obtained. Oxidation of the sulfilimines then stereospecifically affords the corresponding sulfoximines with very good yields in the 88–96% range.

Nitrogen is ubiquitous in Nature as evidenced by the prevalence of alkaloids and amino acids in the world of natural products.¹ Importantly, nitrogen is even more present in the structure of biologically active agents.^{2,3} The search for its efficient and selective incorporation into various molecules is therefore an area of intensive investigation and a source of inspiration for synthetic chemists, who have designed a still growing number of methodologies for this purpose.^{1a,4}

In this highly proliferating field, the emergence of catalytic nitrene transfers, particularly those developed using hypervalent iodine reagents,⁵ has offered unique opportunities culminating with the discovery of new transformations for the direct introduction of nitrogen into various substrates.

Nitrene insertion into C–H and C=C bonds now allows an easy and efficient access to *N*-protected amines and aziridines, respectively.⁶ In parallel, their catalytic addition to sulfides or sulfoxides affords useful sulfilimines or sulfoximines, respectively.

Since the discovery of methionine sulfoximine,⁷ these sulfur(VI) derivatives have been extensively studied.⁸ The sulfoximine moiety has been incorporated into a wide range of biologically active compounds⁹ or has served as a functional building block in materials science.¹⁰ It has also been used as an efficient chiral auxiliary in total synthesis,^{8,11} while the central chirality has been often applied to the design of chiral ligands in the field of asymmetric synthesis.¹² Similarly, but to a lesser extent, sulfilimines have found

(1) (a) Kibayashi, C. *Chem. Pharm. Bull.* **2005**, *53*, 1375–1386. (b) Hili, R.; Yudin, A. K. *Nat. Chem. Biol.* **2006**, *2*, 284–287.

(2) (a) Clardy, J.; Walsh, C. *Nature* **2004**, *432*, 829–837. (b) Henkel, T.; Brunne, R. M.; Müller, H.; Reichel, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 643–647.

(3) The molecular formula of Gleevec C₂₉H₃₁N₇O is a perfect example that illustrates the high number of nitrogen atoms in drugs.

(4) For recent overviews, see: (a) *Amino Group Chemistry, from Synthesis to the Life Sciences*; Ricci, A., Ed.; Wiley-VCH: Weinheim, 2007. (b) Takemoto, Y.; Miyabe, H. In *Comprehensive Organometallic III*; Crabtree, R. H.; Mingos, D. M. P., Eds.; Elsevier: Oxford, 2007; Vol. 10, pp 695–724. (c) Kienle, M.; Dubbaka, S. R.; Brade, K.; Knochel, P. *Eur. J. Org. Chem.* **2007**, 4166–4176.

(5) Dauban, P.; Dodd, R. H. *Synlett* **2003**, 1571–1586.

(6) (a) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905–2919. (b) Espino, C. G.; Du Bois, J. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005, 379–416. (c) Halfen, J. A. *Curr. Org. Chem.* **2005**, *9*, 657–669. (d) Dauban, P.; Dodd, R. H. In *Amino Group Chemistry, from Synthesis to the Life Sciences*; Ricci, A., Ed.; Wiley-VCH: Weinheim, 2007; pp 55–92. (e) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417–424.

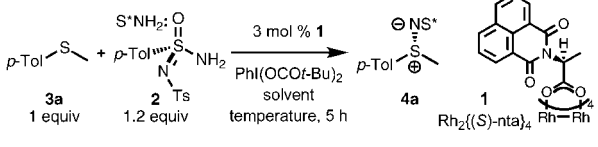
(7) Bentley, H. R.; McDermott, E. E.; Pace, J.; Whitehead, J. K.; Moran, T. *Nature* **1949**, *163*, 675–676.

(8) For reviews, see: (a) Johnson, C. R. *Acc. Chem. Res.* **1973**, *6*, 341–347. (b) Pyne, S. *Sulfur Rep.* **1992**, *12*, 57–89. (c) Reggelin, M.; Zur, C. *Synthesis* **2000**, 1–64. (d) Okamura, H.; Bolm, C. *Chem. Lett.* **2004**, *33*, 482–487. (e) Gais, H. J. *Heteroat. Chem.* **2007**, *18*, 472–481.

applications in synthesis,¹³ catalysis,¹⁴ and medicinal chemistry.¹⁵

Several synthetic strategies have been developed for the preparation of these chiral sulfur derivatives, and among these, direct oxidative imination is by far the most studied methodology.^{8d} Various nitrogen sources¹⁶ such as chloramines^{16a–c} and azides^{16d–f} can be used for these transformation, but the most significant achievements have been realized starting from iminoiodanes in combination with a transition metal catalyst.¹⁷ Copper salts have been found to be optimal in this context,^{17a–d} but manganese,^{17e} rhodium,^{17f,i} silver,^{17g,i} or iron^{17h,i} complexes are also efficient catalysts. Surprisingly, a limited number of studies have been dedicated to the stereoselective imination of sulfides and sulfoxides using hypervalent iodine

Table 1. Catalytic Imination of Methyl *p*-Tolyl Sulfide **3a**



entry	temp (°C)	solvent	yield (%)	de ^a
1	–35	(CH ₂ Cl) ₂ /MeOH 3:1	93	70
2	–78	(CH ₂ Cl) ₂ /MeOH 3:1	92	62
3	–50	(CH ₂ Cl) ₂ /MeOH 3:1	92	66
4	25	(CH ₂ Cl) ₂ /MeOH 3:1	94	50
5	–35	(CH ₂ Cl) ₂	75	40
6	–35	(CH ₂ Cl) ₂ /MeOH 1:1	88	48
7	–35	(CH ₂ Cl) ₂ /MeOH 3:1	88	^b
8	–35	(CH ₂ Cl) ₂ /MeOH 3:1	93	80 ^c

^a Determined by ¹H NMR. ^b Three days at –35 °C without the rhodium(II) catalyst **1**. ^c Using 10 mol % of catalyst **1** and adding hypervalent iodine reagent via syringe pump over 1 h.

(9) (a) Mock, W. L.; Tsay, J.-T. *J. Am. Chem. Soc.* **1989**, *111*, 4467–4472. (b) Koizumi, M.; Hiratake, J.; Nakatsu, T.; Kato, H.; Oda, J. *J. Am. Chem. Soc.* **1999**, *121*, 5799–5800. (c) Bolm, C.; Moll, G.; Kahmann, J. D. *Chem. Eur. J.* **2001**, *7*, 1118–1128. (d) Kahraman, M.; Sinishtaj, S.; Dolan, P. M.; Kensler, T. W.; Peleg, S.; Saha, U.; Chuang, S. S.; Bernstein, G.; Karcz, B.; Posner, G. H. *J. Med. Chem.* **2004**, *47*, 6854–6863. (e) For a recent review, see: Worch, C.; Mayer, A. C.; Bolm, C. In *Organosulfur Chemistry in Asymmetric Synthesis*; Toru, T., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2008; pp 209–229.

(10) Kirsch, P.; Lenges, M.; Kühne, D.; Wanczek, K.-P. *Eur. J. Org. Chem.* **2005**, 797–802.

(11) (a) Trost, B. M.; Matsuoka, R. T. *Synlett* **1992**, 27–30. (b) Reggelin, M.; Weinberger, H.; Gerlach, M.; Welcker, R. *J. Am. Chem. Soc.* **1996**, *118*, 4765–4777. (c) Reggelin, M.; Junker, B.; Heinrich, T.; Slavik, S.; Böhle, P. *J. Am. Chem. Soc.* **2006**, *128*, 4023–4034. (d) Schleusner, M.; Gais, H.-J.; Koep, S.; Raabe, G. *J. Am. Chem. Soc.* **2002**, *124*, 7789–7800. (e) Köhler, F.; Gais, H.-J.; Raabe, G. *Org. Lett.* **2007**, *9*, 1231–1234. (f) Harmata, M.; Hong, X. *J. Am. Chem. Soc.* **2003**, *125*, 5754–5756. (g) Harmata, M.; Hong, X. *Org. Lett.* **2005**, *7*, 3581–3583. (h) Craig, D.; Grellepois, F.; White, A. J. P. *J. Org. Chem.* **2005**, *70*, 6827–6832.

(12) (a) Johnson, C. R.; Stark, C. J. *Tetrahedron Lett.* **1979**, *20*, 4713–4716. (b) Bolm, C.; Simic, O. *J. Am. Chem. Soc.* **2001**, *123*, 3830–3831. (c) Harmata, M.; Ghosh, S. K. *Org. Lett.* **2001**, *3*, 3321–3323. (d) Moessner, C.; Bolm, C. *Angew. Chem. Int. Ed.* **2005**, *44*, 7564–7567. (e) For a recent review, see: Bolm, C. In *Asymmetric Synthesis with Chemical and Biological Methods*; Enders, D., Jaeger, K.-E., Eds.; Wiley-VCH: Weinheim, 2007; pp 149–176.

(13) (a) Ruano, J. L. G.; Alemparte, C.; Clemente, F. R.; Gutiérrez, L. G.; Gordillo, R.; Martín Castro, A. M.; Rodríguez Ramos, J. H. *J. Org. Chem.* **2002**, *67*, 2919–2925. (b) Padwa, A.; Nara, S.; Wang, Q. *J. Org. Chem.* **2005**, *70*, 8538–8549. (c) Marino, J. P.; Zou, N. *Org. Lett.* **2005**, *7*, 1915–1917. (d) Raghavan, S.; Mustafa, S. *Tetrahedron Lett.* **2008**, *49*, 3216–3220.

(14) Thakur, V. V.; Ramesh Kumar, N. S. C.; Sudalai, A. *Tetrahedron Lett.* **2004**, *45*, 2915–2918.

(15) (a) Andersen, K. K.; Bhattacharyya, J.; Mukhopadhyay, S. K. *J. Med. Chem.* **1970**, *13*, 759–760. (b) Strekowski, L.; Henary, M.; Kim, N.; Michniak, B. B. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1033–1034.

(16) (a) Aujla, P. S.; Baird, C. P.; Taylor, P. C.; Mauger, H.; Vallée, Y. *Tetrahedron Lett.* **1997**, *38*, 7453–7456. (b) Takada, H.; Ohe, K.; Uemura, S. *Angew. Chem., Int. Ed.* **1999**, *38*, 1288–1289. (c) Marzinzik, A. L.; Sharpless, K. B. *J. Org. Chem.* **2001**, *66*, 594–596. (d) Bach, T.; Körber, C. *Eur. J. Org. Chem.* **1999**, *103*, 3–1039. (e) Murakami, M.; Uchida, T.; Katsuki, T. *Tetrahedron Lett.* **2001**, *42*, 7071–7074. (f) Tamura, Y.; Uchida, T.; Katsuki, T. *Tetrahedron Lett.* **2003**, *44*, 3301–3303. (g) Tomooka, C. S.; Carreira, E. M. *Helv. Chim. Acta* **2002**, *85*, 3773–3784. (h) Siu, T.; Yudin, A. K. *Org. Lett.* **2002**, *4*, 1839–1842. (i) Garcia Mancheno, O.; Bistri, O.; Bolm, C. *Org. Lett.* **2007**, *9*, 3809–3811.

(17) (a) Müller, J. F. K.; Vogt, P. *Tetrahedron Lett.* **1998**, *39*, 4805–4806. (b) Lacôte, E.; Amatore, M.; Fensterbank, L.; Malacria, M. *Synlett* **2002**, 116–118. (c) Cren, S.; Kinahan, T. C.; Skinner, C. L.; Tye, H. *Tetrahedron Lett.* **2002**, *43*, 2749–2751. (d) Lakshmi Kantam, M.; Kavita, B.; Neeraja, V.; Haritha, Y.; Chaudhuri, M. K.; Dehury, S. K. *Adv. Synth. Catal.* **2005**, *347*, 641–645. (e) Nishikori, H.; Ohta, C.; Oberlin, E.; Irie, R.; Katsuki, T. *Tetrahedron* **1999**, *55*, 13937–13946. (f) Okamura, H.; Bolm, C. *Org. Lett.* **2004**, *6*, 1305–1307. (g) Cho, G. Y.; Bolm, C. *Org. Lett.* **2005**, *7*, 4983–4985. (h) Garcia Mancheno, O.; Bolm, C. *Org. Lett.* **2006**, *8*, 2349–2352. (i) Garcia Mancheno, O.; Bolm, C. *Chem. Eur. J.* **2007**, *13*, 6674–6681.

reagents,^{17d,e,18,19} and in all cases the combined yields and selectivities range from low to moderate with substrates sometimes used in excess.

We have recently reported the use of sulfonimidamides for the generation of chiral nitrenes and their subsequent metal-catalyzed insertion into C=C^{20a} and C–H bonds.^{20b,c} In all cases, high yields were obtained starting from stoichiometric amounts of alkenes and alkanes as a consequence of the high reactivity of the nitrene species. More importantly, the matched combination of the sulfonimidamide and a chiral rhodium catalyst proved optimal to induce selective benzylic and allylic C–H aminations with stereoselectivities generally above 90%.^{20b,c} Thus, these results combined with previous observations convinced us to explore the stereoselective imination of sulfides using chiral nitrenes derived from sulfonimidamides.

Application of the previously determined optimal conditions for C–H amination to methyl *p*-tolyl sulfide **3a**, i.e., combining 3 mol % of Rh₂{(S)-nta}₄ **1** with 1.2 equiv of (S)-N-(*p*-toluenesulfonyl)-*p*-toluenesulfonimidamide **2** in the presence of 1.4 equiv of PhI(OCOt-Bu)₂ in a 3:1 mixture of 1,1,2,2-tetrachloroethane/methanol at –35 °C for 3 days,^{20c} allowed us to isolate the corresponding sulfilimine **4a** with a very good yield of 93% and a diastereoselectivity of 70% (Table 1, entry 1).

NMR studies indicated that consumption of starting material was in fact complete after only 5 h, **4a** being isolated with the same yield and de as before. This shorter reaction time encouraged us to screen the reaction temperature in

(18) Takada, H.; Nishibayashi, Y.; Ohe, K.; Uemura, S.; Baird, C. P.; Sparey, T. J.; Taylor, P. C. *J. Org. Chem.* **1997**, *62*, 6512–6518.

(19) Leca, D.; Toussaint, A.; Mareau, C.; Fensterbank, L.; Lacôte, E.; Malacria, M. *Org. Lett.* **2004**, *6*, 3573–3575.

(20) (a) Di Chenna, P.; Robert-Peillard, F.; Dauban, P.; Dodd, R. H. *Org. Lett.* **2004**, *6*, 4503–4505. (b) Liang, C.; Robert-Peillard, F.; Fruit, C.; Müller, P.; Dodd, R. H.; Dauban, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 4641–4644. (c) Liang, C.; Collet, F.; Robert-Peillard, F.; Müller, P.; Dodd, R. H.; Dauban, P. *J. Am. Chem. Soc.* **2008**, *130*, 343–350.

order to improve the selectivity.²¹ However, decreasing the temperature down to $-78\text{ }^{\circ}\text{C}$ induced a slight drop in selectivity (entries 2 and 3 vs entry 1) while the yield remained unchanged. Changing the solvent ratios also did not improve results (entries 5 and 6). While testing the reaction in the absence of the rhodium catalyst, we observed, as did Bolm in a recently reported study,²² that the racemic sulfilimine **4a** is indeed isolated in 88% yield after 3 days at $-35\text{ }^{\circ}\text{C}$ (entry 7). Such non-catalyzed imination clearly operates in parallel to the stereoselective rhodium-mediated process and is probably the main reason for the lower diastereoselectivities observed when compared to those obtained in our previously described C–H amination. In order to circumvent this side reaction, we increased the amount of catalyst while adding the hypervalent iodine reagent very slowly, but this led to only a modest 10% increase of the diastereoselectivity (entry 8 vs entry 1).

Various sulfides were then screened using the conditions described for compound **3a** in entry 1 of table 1 (Table 2). Aryl alkyl sulfides **3a–j** were transformed under stoichiometric conditions into the corresponding sulfilimines **4a–j** in very good yields, generally above 80% and up to 97% (entries 1–10). High yields in the 91–95% range were also observed with dialkyl sulfides **3k–n** (entries 11–14), thereby confirming the superior reactivity of sulfonimidamide-derived nitrenes when compared to that of nitrenes generated from sulfonamides.²⁰ The reaction is also chemoselective since neither aziridines nor a benzylic C–H amination product were isolated in the case of, respectively, vinylic sulfides **3g,m** and benzylic sulfide **3j**. Another noteworthy feature of this reaction is the total absence of the sulfoxide often formed as a byproduct in sulfide imination.^{16c,19}

As far as diastereoselectivity is concerned, despite the occurrence of the undesirable non-catalyzed imination, aryl alkyl sulfilimines **4a–j** were isolated with moderate to excellent diastereoisomeric excesses of up to 96% while imination of dialkyl sulfides **3k–m** proved to be poorly diastereoselective. Once more, these selectivities have been found to be the consequence of a matched effect between the sulfonimidamide (*S*)-**2** and the catalyst $\text{Rh}_2\{(\text{S})\text{-nta}\}_4$. Then, use of $\text{Rh}_2(\text{OAc})_4$ with (*S*)-**2** in the presence of sulfide **3a** affords the corresponding sulfilimine **4a** in 89% yield but with a low de of 10%, while the mismatched combination of (*S*)-**2** and $\text{Rh}_2\{(\text{R})\text{-nta}\}_4$ leads to **4a** in 88% yield and a de of only 32%.

All of these results indicate that this methodology is as efficient^{17e} or even better^{17d,18} than known published stereoselective preparations of sulfilimines using iminoiodanes. Moreover, our results demonstrate more convincingly than the previous report by Fensterbank, Lacote, and Malacria¹⁹ that use of a chiral nitrene is likely to induce efficient diastereoselective imination of sulfides.

(21) Further experiments confirmed the optimization of the reaction parameters. Use of the more crowded catalyst $[\text{Rh}_2\{(\text{S})\text{-nttl}\}_4]$ afforded compound **4a** in 90% yield but with a lower de of 62%. The *p*-nitro analog of **4a** was isolated in 76% yield and 70% de starting from *N*-(*p*-toluenesulfonyl)-*p*-nitrobenzenesulfonimidamide. Finally, use of the less soluble $\text{PhI}=\text{O}$ led to a decrease of the reactivity and the selectivity (69% yield and 60% de).

(22) Cho, G. Y.; Bolm, C. *Tetrahedron Lett.* **2005**, 46, 8007–8008.

Table 2. Catalytic Oxidative Imination of Sulfides **3**

entry	substrate	product	yield (%)	de ^a
1			93	80 ^b
2			93	70
3			89	24
4			87	56
5			97	64
6			93	80
7			93	90
8			66	96
9			76	56
10			80	40
11			92	14
12			93	12
13			91	12
14			95	-

^a Determined by ¹H NMR. ^b Using 10 mol % of catalyst **1** and adding hypervalent iodine reagent via syringe pump over 1 hour.

Sulfilimines **4** were then transformed into their corresponding sulfoximines **5** by oxidation under standard conditions using *m*-CPBA (Table 3). The expected sulfur(VI) products **5a–f** and **5i** were isolated in very good yields in the 88–96% range and with diastereoisomeric excesses similar to those obtained for sulfilimines **4**, thereby indicating that the oxidation proceeds stereospecifically. The diastere-

Table 3. Oxidation of Sulfilimines **4**^a

$ \begin{array}{c} \ominus \text{NS}^+ \\ \\ \text{R}^1 - \text{S}^+ - \text{R}^2 \\ \mathbf{4} \end{array} \xrightarrow[\text{K}_2\text{CO}_3, \text{CH}_2\text{Cl}_2, \text{rt, 1 h}]{m\text{-CPBA}} \begin{array}{c} \text{O} \quad \text{NS}^+ \\ \diagup \quad \diagdown \\ \text{R}^1 - \text{S} - \text{R}^2 \\ \mathbf{5} \end{array} $						
entry	substrate	R ¹	R ²	product	yield (%)	de ^b
1	4a	<i>p</i> -MeC ₆ H ₄	Me	5a	91	72
2	4b	<i>p</i> -MeOC ₆ H ₄	Me	5b	94	70
3	4c	<i>p</i> -NO ₂ C ₆ H ₄	Me	5c	90	20
4	4d	2-Py	Me	5d	94	44
5	4e	Ph	Me	5e	96	64
6	4f	Ph	Et	5f	92	72
7	4i	2-Naph	Me	5i	88	52

^a Reaction conditions: sulfilimine **4** (1 equiv), *m*-CPBA (1.5 equiv), K₂CO₃ (3 equiv) in CH₂Cl₂ at room temperature for 1 h. ^b Determined by ¹H NMR.

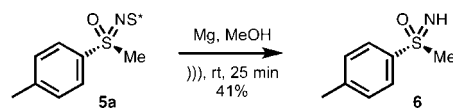
oisomeric sulfoximines **5** can be easily separated by simple flash chromatography on silica gel.

The preparation of sulfoximines **5** allowed determination of the sense of the stereoinduction for the imination of sulfides **3**. Thus, stereospecific imination of optically pure (*S*)-methyl *p*-tolylsulfoxide by application of the same conditions used for sulfides **3** affords the sulfoximine (*S*)-**5a** in 85% yield and 99% ee. Comparison of the optical rotation of this enantiomerically pure compound with that of the product obtained from sulfilimine **4a** then allowed us to determine that the latter has the same absolute configuration. Therefore, the combination of (*S*)-**2** and the rhodium catalyst Rh₂{(*S*)-nta}₄ **1** induces the formation of the (*R*)-sulfilimines **4**.²³

Finally, it was found that free NH sulfoximines could be obtained by removal of the sulfonimidoyl group under reductive conditions. Thus, treatment of **5a** with 10 equiv of magnesium under sonication in methanol^{20c,24} afforded the deprotected product **6** with a non-optimized yield of 41% (Scheme 1).²⁵

(23) On the basis of this result, sulfides **4** have always been drawn with this (*R*)-configuration in each previous scheme.

(24) Xu, Y. M.; Shi, M. *J. Org. Chem.* **2004**, 69, 417–425.

Scheme 1. Deprotection of Sulfoximine **5a**

In conclusion, rhodium(II)-catalyzed transfer of a chiral nitrene generated from (*S*)-*N*-(*p*-toluenesulfonyl)-*p*-toluenesulfonimidamide **2** in the presence of a hypervalent iodine reagent allows the mild chemo- and diastereoselective imination of sulfides used in stoichiometric amounts. Optically active sulfilimines were isolated with excellent yields up to 97% and good diastereoselectivities up to 96%. They can in turn be stereospecifically transformed into the corresponding sulfoximines with excellent yields. This study demonstrates that use of a sulfonimidamide-derived chiral nitrene for sulfide imination is more efficient, albeit of comparable selectivity, than that involving the combination of a sulfonamide and a chiral transition metal catalyst. Work is now in progress to optimize the design of the chiral nitrene precursor.

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Supporting Information Available: Experimental details, characterization data, and spectra (¹H and ¹³C NMR) for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(25) It should be mentioned that this procedure cannot be applied to sulfilimines of type **4** because use of magnesium in methanol under sonication leads to the starting sulfide **3**.