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Stereoselective Rhodium-Catalyzed Imination of Sulfides

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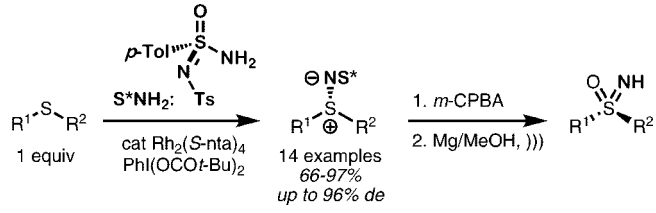
ABSTRACT



The preparation of optically active sulfilimines 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 compounds[9] 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

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(3) The molecular formula of Gleevec $C_{29}H_{31}N_7O$ is a perfect example that illustrates the high number of nitrogen atoms in drugs.

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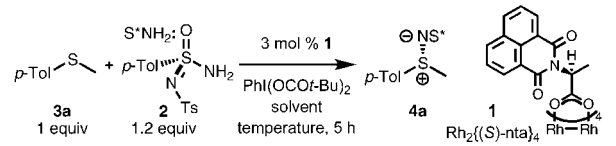
applications in synthesis,[13] catalysis,[14] and medicinal chemistry.[15]

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 sources[16] 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 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.

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



entry	temp (°C)	solvent	yield (%)	de[a]
1	−35	$(CH_2Cl)_2$/MeOH 3:1	93	70
2	−78	$(CH_2Cl)_2$/MeOH 3:1	92	62
3	−50	$(CH_2Cl)_2$/MeOH 3:1	92	66
4	25	$(CH_2Cl)_2$/MeOH 3:1	94	50
5	−35	$(CH_2Cl)_2$	75	40
6	−35	$(CH_2Cl)_2$/MeOH 1:1	88	48
7	−35	$(CH_2Cl)_2$/MeOH 3:1	88	*b*
8	−35	$(CH_2Cl)_2$/MeOH 3:1	93	80[c]

[a] Determined by ^{1}H 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.

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 $Rh_2\{(S)\text{-nta}\}_4$ **1** with 1.2 equiv of (*S*)-*N*-(*p*-toluenesulfonyl)-*p*-toluenesulfonimidamide **2** in the presence of 1.4 equiv of $PhI(OCOt\text{-}Bu)_2$ 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

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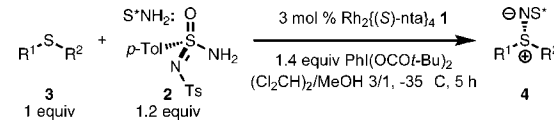
order to improve the selectivity.[21] However, decreasing the temperature down to −78 °C induced a slight drop in selectivity (entries 2 and 3 vs entry 1) while the yield remained unchanged. Changing the solvent ratios also did not improve results (entries 5 and 6). While testing the reaction in the 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 °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).

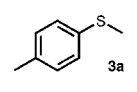
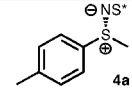
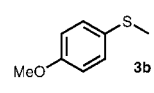
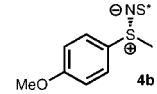
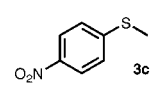
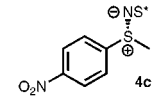
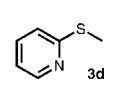
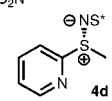
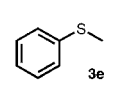
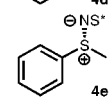
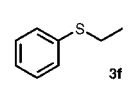
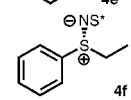
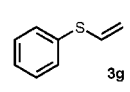
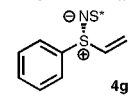
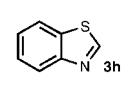
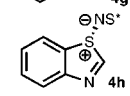
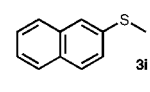
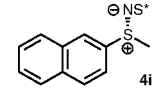
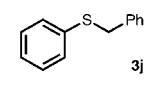
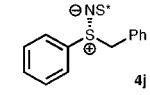
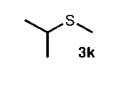
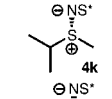
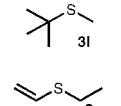
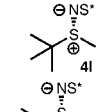
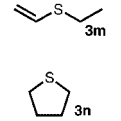
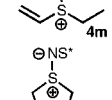
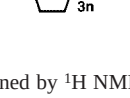
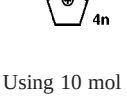
Various sulfides were then screened using the conditions described for compound **3a** in entry 1 of table 1 (Table 2). Aryl alkyl sulfides **3a**−**j** were transformed under stoichiometric conditions into the corresponding sulfilimines **4a**−**j** in very good yields, generally above 80% and up to 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 Rh_2\{(*S*)-nta\}$_4$. Then, use of $Rh_2(OAc)_4$ 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 Rh_2\{(*R*)-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 Malacria[19] that use of a chiral nitrene is likely to induce efficient diastereoselective imination of sulfides.

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	-

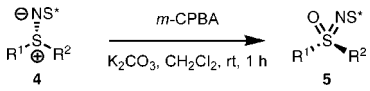
[a] Determined by ^{1}H NMR. [b] Using 10 mol % of catalyst **1** and adding hypervalent iodine reagent via syringe pump over 1 hour.

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-

(21) Further experiments confirmed the optimization of the reaction parameters. Use of the more crowded catalyst [Rh_2\{(*S*)-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 PhI=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 3. Oxidation of Sulfilimines **4**[a]



entry	substrate	R^1	R^2	product	yield (%)	de[b]
1	**4a**	*p*-MeC_6H_4	Me	**5a**	91	72
2	**4b**	*p*-$MeOC_6H_4$	Me	**5b**	94	70
3	**4c**	*p*-$NO_2C_6H_4$	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), K_2CO_3 (3 equiv) in CH_2Cl_2 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.

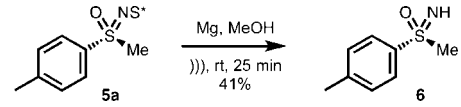
The preparation of sulfoximines **5** allowed determination of the sense of the stereoinduction for the imination of sulfides **3**. Thus, stereospecific imination of optically pure (*S*)-methyl *p*-tolylsulfoxide by application of the same conditions used for sulfides **3** affords the sulfoximine (*S*)-**5a** 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 $Rh_2\{(S)\text{-nta}\}_4$ **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 ^{13}C 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**.