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Silver-Catalyzed Imination of Sulfoxides and Sulfides

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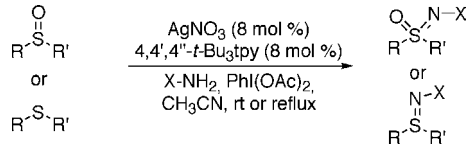
ABSTRACT



Silver salts in the presence of a chelating ligand efficiently catalyze the stereospecific imination of sulfoxides and sulfides with sulfonylamides and PhI(OAc)$_2$ to afford sulfoximines and sulfilimines, respectively, in good yields.

Sulfoximines and sulfilimines have been used as building blocks for chiral ligands[1] and pseudopeptides,[2] and various approaches have been developed for their synthesis.[3] Most of them start from a sulfide, which is oxidized and iminated sequentially. For the latter step, initiations by metal catalysts have recently attracted much attention, since they allow one to avoid the use of toxic and potentially explosive reagents such as hydrazoic acid and *O*-mesitylenesulfonylhydroxylamine (MSH).[4−6] For example, copper and iron salts[7] or manganese and ruthenium complexes[8] have been shown to be capable of catalyzing the conversion of sulfoxides into sulfoximines. However, common disadvantages of those methods are that they either lead to products with protecting groups at the sulfoximine nitrogen (such as tosyl), that are difficult to cleave to give synthetically valuable *NH*-sulfoximines, or that they still use potentially dangerous reagents such as Boc-azide as nitrogen source. In 2004, we

(1) For recent examples, see: (a) Bolm, C.; Simic, O. *J. Am. Chem. Soc.* **2001**, *123*, 3830. (b) Harmata, M.; Ghosh, S. K. *Org. Lett.* **2001**, *3*, 3321. (c) Bolm, C.; Martin, M.; Simic, O.; Verrucci, M. *Org. Lett.* **2003**, *5*, 427. (d) Bolm, C.; Verrucci, M.; Simic, O.; Cozzi, P. G.; Raabe, G.; Okamura, H. *Chem. Commun.* **2003**, 2816. (e) Bolm, C.; Martin, M.; Gescheidt, G.; Palivan, C.; Neshchadin, D.; Bertagnolli, H.; Feth, M. P.; Schweiger, A.; Mitrikas, G.; Harmer, J. *J. Am. Chem. Soc.* **2003**, *125*, 6222. (g) Langner, M.; Bolm, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 5984. Reviews: (h) Harmata, M. *Chemtracts* **2003**, *16*, 660. (i) Reetz, M. T.; Bondarev, O. G.; Gais, H.-J.; Bolm, C. *Tetrahedron Lett.* **2005**, *46*, 5643. (j) Okamura, H.; Bolm, C. *Chem. Lett.* **2004**, *33*, 482 and references therein.

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(3) Reviews on sulfoximines and sulfilimines: (a) Johnson, C. R. *Acc. Chem. Res.* **1973**, *6*, 341. (b) Pyne, S. G. *Sulfur Rep.* **1999**, *21*, 281. (c) Taylor, P. C. *Sulfur Rep.* **1999**, *21*, 241. (d) Reggelin, M.; Zur, C. *Synthesis* **2000**, 1.

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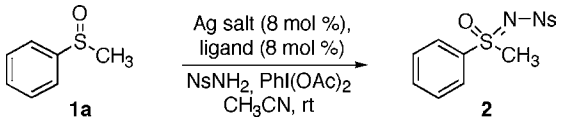
introduced an improved procedure for the imination of sulfur compounds, which utilizes a rhodium catalyst and readily available trifluoroacetamide or sulfonylamides as nitrogen source.[9] Following this method, sulfoximines and sulfilimines can easily be prepared from the corresponding sulfoxides and sulfides, respectively, under very mild reaction conditions at room temperature. Furthermore, the imination is stereospecific, making this approach particularly attractive for the synthesis of optically active products. A drawback of this protocol, however, is the high cost of the rhodium catalyst {[$Rh_2(OAc)_4$]}.

Silver reagents have long been believed to have low catalytic efficiency. Most commonly, they are silver(I) complexes, which rely on the high Lewis acidity of the involved metal species. Only recently have synthetically attractive silver catalysts (including chiral ones) for oxidations as well as other group-transfer reactions been developed.[10] Here, we report on a novel application of silver catalysts, which allows efficient imination of sulfides and sulfoxides.

For the initial screening and optimization we chose methyl phenyl sulfoxide (**1a**) as substrate and a nitrogen source generated in situ from $NsNH_2$ and $PhI(OAc)_2$. The effect of various combinations of silver salts and ligands (8 mol % each) on the formation of sulfoximine **2** was first examined, and the most relevant results are summarized in Table 1.

Table 1. Optimization of the Silver-Catalyzed Imination with Ns-NH_2[a]

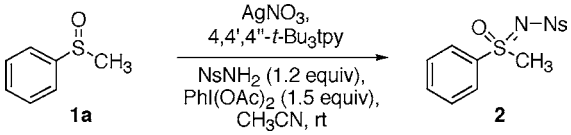


entry	silver salt	ligand	yield (%)
1	$AgNO_3$	terpyridine	52
2	$AgNO_3$	4,4′,4″-*t*-Bu_3tpy	83
3	$AgNO_3$	4,4′,4″-*t*-Bu_3tpy	66[b]
4	AgOTf	4,4′,4″-*t*-Bu_3tpy	85
5	AgOAc	4,4′,4″-*t*-Bu_3tpy	74
6	$AgNO_3$	4,4′,4″-*t*-Bu_3tpy	86[c]

[a] Reaction conditions: sulfoxide **1a** (1 equiv), $AgNO_3$ (8 mol %), ligand (8 mol %), $NsNH_2$ (1.2 equiv), $PhI(OAc)_2$ (1.5 equiv) in CH_3CN (0.1 M) at room temperature. [b] Use of CH_2Cl_2 as solvent instead of CH_3CN. [c] Use of 4 mol % of the catalyst under reflux instead of 8 mol % at room temperature.

The screening showed that $AgNO_3$ and AgOTf (Table 1, entries 2 and 4) were superior to other silver salts such as AgOAc (entry 5) or Ag_2CO_3 (incomplete conversion; not included in Table 1). Next, a broad range of ligands was tested, and as previously observed in silver-catalyzed aziridinations and intramolecular amidations,[10a,b] the imination reaction of **1a** required a very carefully selected reagent combination. All attempts to use phosphines, diamines, or pyridines remained unsuccessful, and finally, terpyridine and 4,4′,4″-tri-*tert*-butyl-2,2′:6′,2″-terpyridine (4,4′,4″-*t*-Bu_3tpy) proved to be the most suitable ligands giving silver catalysts (from $AgNO_3$ as silver source), which afforded sulfoximine **2** in 52 and 83% yield, respectively (Table 1, entries 1 and 2). As expected from those results,[11] the presence of a ligand was essential for substrate conversion, and $AgNO_3$ alone did not catalyze the imination. Furthermore, at room temperature no reaction occurred in the absence of the catalyst. The presence of a base such as MgO did not affect the yield, and acetonitirile was superior to other solvents such as dichloromethane, DMF, and THF (which gave **2** in 66, 60, and 52% yield, respectively). In less polar solvents such as toluene and diethyl ether the imination did not proceed at all. Generally, under reflux full conversion was achieved within 1 h, and slightly improved yields were observed (entry 6).[12] The catalyst loading could be as low as 2 mol %, although under those conditions an extended reaction time and a lower yield compared to iminations with more catalyst had to be accepted (Table 2). Combinations of 4 or 8 mol

Table 2. Optimization of the Catalyst Loading



entry	catalyst loading (mol %)	reaction time (h)	yield (%)
1	2	48	62
2	4	16	83
3	8	16	83

% of both silver salt and ligand led to the best results in the imination of **1a**, giving sulfoximine **2** in 83% yield after 16 h (Table 2, entries 2 and 3).

To investigate the substrate scope of the novel silver catalysis, sulfoxides **1a**−**d** were iminated with various sulfonylamides (Table 3). Gratifyingly, most iminating agents such as *p*-nosylamide ($NsNH_2$), *p*-tosylamide ($TsNH_2$), and *p*-methyl-2-pyridinylsulfonylamide proved applicable, and even at room temperature the corresponding sulfoximines **3**−**8** were obtained in moderate to excellent yield (up to 98%). The imination of **1a** with 2-trimethylsilylethylsulfonylamide ($SesNH_2$) to give **7** was more difficult, and the

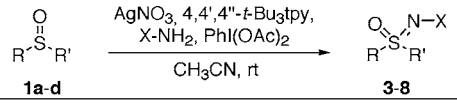
(9) Okamura, H.; Bolm, C. *Org. Lett.* **2004**, *6*, 1305.

(10) For selected examples, see: (a) Cui, Y.; He, C. *J. Am. Chem. Soc.* **2003**, *125*, 16202. (b) Cui, Y.; He, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 4210. (c) Cirakovic, J.; Driver, T. G.; Woerpel, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 9370. (d) Driver, T. G.; Woerpel, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 9993. (e) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4018. (f) Ji, J.-X.; Au−Yeung, T. T.-L.; Wu, J.; Yip, C. W.; Chan, A. S. C. *Adv. Synth. Catal.* **2004**, *346*, 42. (g) Yanagisawa, A.; Kageyama, H.; Nakatsuka, Y.; Asakawa, K.; Matsumoto, Y.; Yamamoto, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 3701. (h) Yanagisawa, A.; Touge, T.; Arai, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 1546.

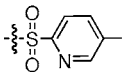
(11) A combination of $AgNO_3$ and 4,4′,4″-*t*-Bu_3tpy also proved useful in silver-catalyzed aziridinations and nitrene insertions as reported by Cui and He (compare ref 10b,c).

(12) The microwave-assisted (200 W) silver-catalyzed imination of methyl phenyl sulfoxide (**1a**) led to sulfoximine **2** in 85% yield (unoptimized) after 20 min, and it occurred in a sterospecific manner.

Table 3. Silver-Catalyzed Imination of Sulfoxides[a]



1a-d 3-8

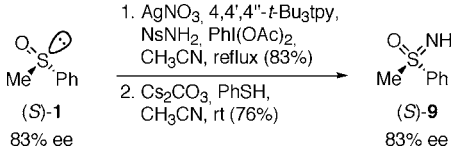
entry	sulfoxide	R	R'	X	sulfoximine	yield (%)
1	**1b**	Ph	Ph	Ns	**3**	98
2	**1c**	-[CH$_2$CH$_2$]$_2$-		Ns	**4**	84
3	**1d**	Ph	-CH=CH$_2$	Ns	**5**	92
4	**1a**	Ph	Me	Ts	**6**	79
5	**1a**	Ph	Me	SES	**7**	83[b] (66[c])
6	**1a**	Ph	Me		**8**	73 (94[b])

[a] Reaction conditions: sulfoxide (1.0 equiv), X-NH$_2$ (1.2 equiv), PhI(OAc)$_2$ (1.5 equiv), AgNO$_3$ (8 mol %), 4,4′,4″-*t*-Bu$_3$tpy (8 mol %) in CH$_3$CN (0.1 M) at rt, ca. 16 h. [b] Reaction time of 7 days. [c] Use of 4 mol % of the catalyst under reflux instead of 8 mol % at room temperature.

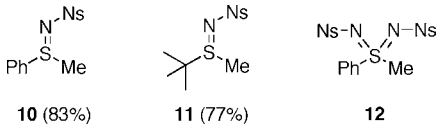
reaction required a higher temperature to afford the product in satisfying yield (Table 3, entry 5). Unfortunately, all attempts to utilize trifluoroacetamide as the nitrogen source, which affords a product with an *N*-protecting group that can easily be cleaved by mild hydrolysis to provide synthetically valuable *NH*-sulfoximines, remained unsuccessful under silver catalysis.

With the objective to investigate the stereochemical path of the silver-catalyzed imination and the hope that optically active *NH*-sulfoximines could be accessed by subsequent cleavage of the protecting group of the sulfoximine nitrogen, sulfoxide (*S*)-**1a** with 83% ee[13] was iminated in acetonitrile under reflux using the catalyst prepared from AgNO$_3$ and 4,4′,4″-*t*-Bu$_3$tpy (8 mol % each), and the resulting nosylated sulfoximine **2** (83% yield) was then deprotected by treatment with a mixture of Cs$_2$CO$_3$ and thiophenol in acteonitrile at room temperature to give *NH*-sulfoximine (*S*)-**9** (76% yield). The absolute configuration of this product and its ee (83%) revealed that the overall process proceeded with net retention of configuration and without epimerization at the stereogenic center (Scheme 1).[14]

Scheme 1



Application of the silver-catalyzed imination reaction to methyl phenyl sulfide and *tert*-butyl methyl sulfide under identical reaction conditions afforded the corresponding sulfilimines **10** and **11** in 83 and 77% yield, respectively. Interestingly, in contrast to the rhodium-catalyzed imination, almost identical reactivities were observed in conversions of sulfides and sulfoxides. Unfortunately, all attempts to prepare sulfodiimine **12**[15] by imination of sulfilimine **10** with NsNH$_2$ and PhI(OAc)$_2$ in the presence of the silver catalyst failed, and no formation of **12** was observed (Figure 1).



10 (83%) **11** (77%) **12**

Figure 1.

In conclusion, we developed a novel silver-catalyzed sulfur imination, which allows the preparation of various sulfoximines and sulfilimines from sulfoxides and sulfides, respectively. The combination of AgNO$_3$ and 4,4′,4″-*t*-Bu$_3$tpy forms a catalyst, which iminates the substrates under mild reaction conditions at either ambient or elevated temperature (reflux of acetonitrile). Since the nitrogen transfer proceeds with retention of configuration at the stereogenic sulfur atom, enantiopure sulfoximines are accessible from enantiomerically pure sulfoxides by this method. The use of readily available sulfonylamides and iodobenzene diacetate results in the formation of *N*-protected products, which can readily be converted into their synthetically valuable *NH*-counterparts without epimerization. As a net result, the new catalytic system circumvents the disadvantages of existing methodologies by introducing easy-to-cleave protective groups and the use of both unproblematic iminating agents as well as less cost-intensive metal catalysts.[16] Further applications of the silver-catalyzed imination process are currently under investigation.

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Supporting Information Available: Experimental procedures and full characterization (^{1}H and ^{13}C NMR data and spectra, MS, IR, and CHN analyses) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) The enantiomer ratio was determined by HPLC using a chiral column (Chiralcel OJ, 20 °C, heptane/*i*-PrOH = 85:15, 0.5 mL/min); t_R(*R*): 36.8 min, t_R(*S*): 42.6 min.

(14) Cleavage of the SES-group by treatment with TBAF is also well-established (compare ref 7c), and there is no indication that this protocol leads to racemization.

(15) For a recent contribution on sulfodiimines, see: Dehli, J. R.; Bolm, C. *Synthesis* **2005**, 1058.

(16) Noteworthy is the fact that [Rh$_2$(OAc)$_4$] is about 100 times more expensive than AgNO$_3$ (Aldrich prices per gram in 2005).