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Rhodium-Catalyzed Imination of Sulfoxides and Sulfides: Efficient Preparation of N-Unsubstituted Sulfoximines and Sulfilimines

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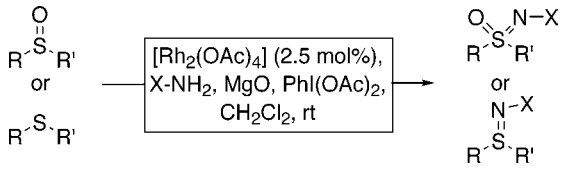
ABSTRACT



The Rh(II)-catalyzed imination of sulfoxides and sulfides using $[Rh_2(OAc)_4]$ as a catalyst and trifluoroacetamide or sulfonylamides in combination with iodobenzene diacetate and magnesium oxide affords sulfoximines and sulfilimines, respectively, in a stereospecific manner.

Recently, sulfoximines and sulfilimines have attracted significant attention due to their use as building blocks for chiral ligands[1] and pseudopeptides.[2] A number of synthetic approaches have been developed that allow the preparation of various derivatives in a relatively straightforward manner.[3] Most of them, however, rely on the use of toxic and potentially explosive reagents such as combinations of NaN_3 and H_2SO_4 or *O*-mesitylenesulfonylhydroxylamine (MSH).[4,5] More recently, metal-catalyzed iminations of sulfoxides and sulfides giving sulfoximines and sulfilimines, respectively, have been described, which utilize copper or iron salts[6] and manganese or ruthenium complexes as catalysts.[7] Furthermore, an electrochemical iminaton of sulfoxides has been reported.[8] The limitations of most of those methods stem from the fact that often N-substituted products such as tosylated imine derivatives are obtained, which are difficult

(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. (f) Review: Harmata, M. *Chemtracts* **2003**, *16*, 660 and references therein.

(2) (a) Bolm, C.; Kahmann, J. D.; Moll, G. *Tetrahedron Lett.* **1997**, *38*, 1169. (b) Bolm, C.; Moll, G.; Kahmann, J. D. *Chem. Eur. J.* **2001**, *7*, 1118. (c) Tye, H.; Skinner, C. L. *Helv. Chim. Acta* **2002**, *85*, 3272. (d) Bolm, C.; Müller, D.; Hackenberger, C. P. R. *Org. Lett.* **2002**, *4*, 893. (e) Bolm, C.; Müller, D.; Dalhoff, C.; Hackenberger, C. P. R.; Weinhold, E. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3207.

(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) Reggelin, M.; Zur, C. *Synthesis* **2000**, 1. (d) Taylor, P. C. *Sulfur Rep.* **1999**, *21*, 241.

(4) NaN_3/H^+: (a) Fusco, R.; Tericoni, F. *Chim. Ind. (Milan)* **1965**, *47*, 61. (b) Johnson, C. R.; Schroeck, C. W. *J. Am. Chem. Soc.* **1973**, *95*, 7418. (c) For an improved protocol, see: Brandt, J.; Gais, H.-J. *Tetrahedron: Asymmetry* **1997**, *6*, 909. (d) For the toxicity of NaN_3: *Merck Index*, 12th ed.; Budavari, S., Ed.; Merck & Co., Inc.: Rahway, NJ, 1996; p 451.

(5) MSH: (a) Tamura, Y.; Minamikawa, J.; Sumoto, K.; Fujii, S.; Ikeda, M. *J. Org. Chem.* **1973**, *38*, 1239. (b) Johnson, C. R.; Kirchhoff, R. A.; Corkins, H. G. *J. Org. Chem.* **1974**, *39*, 2458. (c) Tamura, Y.; Matushima, H.; Minamikawa, J.; Ikeda, M.; Sumoto, K. *Tetrahedron* **1975**, *31*, 3035. (d) Fieser, M.; Fieser, L. F. *Reagents for Organic Synthesis*; John Wiley & Sons: New York, 1975; Vol. 5, p 430.

(6) Cu salts: (a) Müller, J. F. K.; Vogt, P. *Tetrahedron Lett.* **1998**, *39*, 4805. (b) Lacôte, E.; Amatore, M.; Fensterbank, L.; Malacria, M. *Synlett* **2002**, 116. (c) Cren, S.; Kinahan, T. C.; Skinner, C. L.; Tye, H. *Tetrahedron Lett.* **2002**, *43*, 2749. (d) Tomooka, C. S.; Carreira, E. M. *Helv. Chim. Acta* **2003**, *85*, 3773. (e) Takada, H.; Ohe, K.; Uemura, S. *Angew. Chem., Int. Ed.* **1999**, *38*, 1288. Fe salts: (f) Bach, T.; Körber, C. *Tetrahedron Lett.* **1998**, *39*, 5015. (g) Bach, T.; Körber, C. *Eur. J. Org. Chem.* **1999**, 1033.

(7) Mn complexes: (a) Nishikori, H.; Ohta, C.; Oberlin, E.; Irie, R.; Katsuki, T. *Tetrahedron* **1999**, *55*, 13937. (b) Ohta, C.; Katsuki, T. *Tetrahedron Lett.* **2001**, *42*, 3885. Ru complexes: (c) Murakami, M.; Uchida, T.; Katsuki, T. *Tetrahedron, Lett.* **2001**, *42*, 7071. (d) Tamura, Y.; Uchida, T.; Katsuki, T. *Tetrahedron Lett.* **2003**, *44*, 3301. (e) Murakami, M.; Uchida, T.; Saito, B.; Katsuki, T. *Chirality* **2003**, *15*, 116. (f) Uchida, T.; Tamura, Y.; Ohba, M.; Katsuki, T. *Tetrahedron Lett.* **2003**, *44*, 7965.

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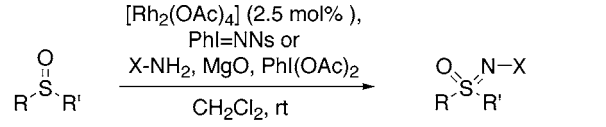
Scheme 1



1: R = Ph, R' = Me
3: R = R' = Ph
5: R = R' = Me
7: R = *t*-Bu, R' = Me

2a: R = Ph, R' = Me, X = Ns
2b: R = Ph, R' = Me, X = Ms
2c: R = Ph, R' = Me, X = $COCF_3$
4a: R = R' = Ph, X = Ns
6a: R = R' = Me, X = Ns
8a: R = *t*-Bu, R' = Me, X = Ns

to convert into the synthetically more valuable ("free") NH compounds. Accordingly, it appeared attractive to search for a novel alternative protocol, which allowed the reaction to be performed with readily available and safe iminating agents and which finally would lead to products with "free" *NH*-imino groups.

Focusing the attention on catalytic transformations we found that $[Rh_2(OAc)_4]$, which is known to be a catalyst for nitrene insertion reactions into C−H bond and nitrene additions to C−C double bonds,[9] is an efficient catalyst for the imination of sulfoxides and sulfides (Scheme 1).

The results of imination reactions of sulfoxides are listed in Table 1. Accordingly, the conversion of methylphenyl-

Table 1. Metal-Catalyzed Iminations of Sulfoxides[a]

entry	substrate		time (h)	product	yield (%)
1	**1**	PhI=NNs	1	**2a**	93
2	**1**	$NsNH_2$, $PhI(OAc)_2$, MgO	6	**2a**	86
3	**1**	$MsNH_2$, $PhI(OAc)_2$, MgO	6	**2b**	79
4	**1**	CF_3CONH_2, $PhI(OAc)_2$, MgO	12	**2c**	84
5[b]	**1**	CF_3CONH_2, $PhI(OAc)_2$, MgO	24		0[c]
6	**1**	$AcNH_2$, $PhI(OAc)_2$, MgO	24		0[d]
7	**1**	$BzNH_2$, $PhI(OAc)_2$, MgO	24		0[c]
8	**3**	$NsNH_2$, $PhI(OAc)_2$, MgO	6	**4a**	68
9	**5**	$NsNH_2$, $PhI(OAc)_2$, MgO	6	**6a**	50
10	**7**	$NsNH_2$, $PhI(OAc)_2$, MgO	6	**8a**	49

[a] Reaction conditions: sulfoximine (1.0 mmol), PhI=NNs (1.5 mmol) and $[Rh_2(OAc)_4]$ (2.5 mol %) in CH_2Cl_2 (10 mL) at room temperature (for entry 1) or sulfoximine (1.0 mmol), $X\text{-}NH_2$ (2.0 mmol), $PhI(OAc)_2$ (1.5 mmol), MgO (4.0 mmol), and $[Rh_2(OAc)_4]$ (2.5 mol %) in CH_2Cl_2 (10 mL) at room temperature (for entries 2−10). [b] $Cu(OTf)_2$ (2.5 mol %) was used as a catalyst. [c] Sulfoximine was almost quantitatively recovered. [d] Complex mixture was formed, and small amounts of the sulfoximine were recovered.

sulfoxide (**1**) with NsN=IPh[10] as an iminating agent and $[Rh_2(OAc)_4]$ as a catalyst proceeded very rapidly, and after 1 h, *N*-nosyl sulfoximine **2a** was obtained in high yield (entry 1). To simplify the process and to avoid the use of a preformed iminating agent, mixtures of $NsNH_2$, MgO, and $PhI(OAc)_2$ instead of NsN=IPh were applied next.[11] Again, **2a** was obtained from **1** in good yield (entry 2), albeit under those conditions the reaction time was longer. Iminations of **1** with $MsNH_2$ (entry 3) and CF_3CONH_2 (entry 4) also proceeded well, affording sulfoximines **2b** and **2c** bearing *N*-mesyl and *N*-trifluoroacetyl groups, respectively. With regard to the synthesis of *NH*-sulfoximines, the latter result was particularly important (vide infra).

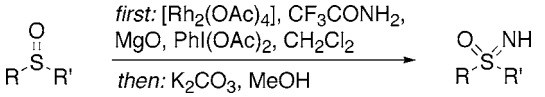
$Cu(OTf)_2$, which is a known catalyst for the imination of sulfoxides,[6b] showed a much lower catalytic activity than $[Rh_2(OAc)_4]$ under these conditions (entry 5). Attempts to use acetamide or benzamide as nitrogen sources in the Rh-catalyzed conversions of **1** failed (entries 6 and 7), indicating that the intermediate iminoiodanes should be stabilized by strong electron-withdrawing substituents.

To investigate the scope of the reaction, several sulfoxides were used as substrates. All of them were readily converted into sulfoximines, albeit in the reactions with sulfoxides **5** and **7** (entries 9 and 10) the yields of the corresponding sulfoximines **6a** and **8a** were only moderate (50 and 49%, respectively). Presumably, the steric hindrance of the bulky *tert*-butyl group of **7** hampered its smooth conversion.

The novel rhodium-catalyzed protocol for the imination of sulfoxides to give sulfoximines described here has several advantages over the existing methodology. Since the reagents and the catalyst are stable toward atmospheric moisture and oxygen, the imination requires neither dried solvents nor an inert atmosphere. Furthermore, iodobenzene diacetate is known as a mild and nonexplosive compound, which renders this process safer than the known ones, which rely on the use of potentially dangerous iminating agents such as azido derivatives or MSH.[4, 5]

For synthetic purposes, the resulting *N*-trifluoroacetyl sulfoximines are highly valuable since they can easily be hydrolyzed to give synthetically useful *NH*-sulfoximines. Consequently, a simple two-step process, which does not even require the isolation of intermediates, allows the preparation of those N-unprotected products in high yields (Table 2). Their subsequent conversions have been described and lead to ligands for asymmetric catalysis and building blocks of pseudopeptides.[1,2]

Table 2. Rhodium-Catalyzed Iminations of Sulfoxides to Give *NH*-sulfoximines[a]



entry	substrate	R	R′	product	yield (%)
1	**1**	Ph	Me	**9**	71
2	**3**	Ph	Ph	**10**	66
3	**11**	$-[CH_2CH_2]_2-$		**12**	88
4	(*R*)-**13**	*p*-Tol	Me	(*R*)-**14**	76

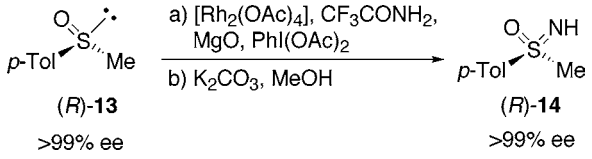
[a] Reaction conditions: Sulfoximine (1.0 mmol), CF_3CONH_2 (2.0 mmol), $PhI(OAc)_2$ (1.5 mmol), MgO (4.0 mmol), and $[Rh_2(OAc)_4]$ (2.5 mol %) in CH_2Cl_2 (10 mL) at room temperature; then K_2CO_3 (5 equiv) in MeOH (10 mL).

(8) Siu, T.; Yudin, A. K. *Org. Lett.* **2002**, *4*, 1839. The authors also report the preparation of "free" sulfoximines by electrolysis of the corresponding *N*-phthalimido derivatives.

(9) For recent reviews including Rh-catalyzed nitrene transfer reactions, see: (a) Dauban, P.; Dodd, R. H. *Synlett* **2003**, 1571. (b) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905.

(10) For the use of NsN=IPh in copper-catalyzed sulfoxide iminations, see: (a) Bolm, C.; Muñiz, K.; Aguilar, N.; Kesselgruber, M.; Raabe, G. *Synthesis* **1999**, 1251. (b) ref 6c.

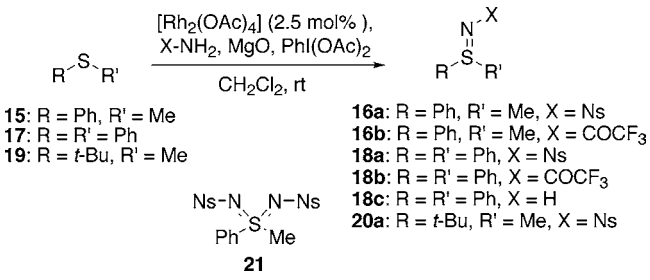
Scheme 2



The stereospecificity of this reaction was examined by using optically pure sulfoxide (*R*)-**13** (Scheme 2). Rhodium-catalyzed imination and subsequent methanolysis afforded enantiopure sulfoximine (*R*)-**14** in good yield (76%). The sign of the optical rotation of the product[5b] revealed that the reaction had occurred with retention of configuration.

Next, the rhodium-catalyzed imination of sulfides leading to sulfilimines was examined (Scheme 3). Under the same

Scheme 3



reaction conditions, sulfides were more reactive than sulfoxides, and all the reactions listed in Table 3 were finished within 6 h giving sulfilimines in high yields.

To demonstrate the applicability of the process in the preparation of NH derivatives, *N*-trifluoroacetyl-protected sulfilimine **18b** was subjected to methanolysis using MeOH−KOH, which led to the corresponding "free" sulfilimine **18c** in 88% yield.[12]

The attempted synthesis of sulfodiimine **21** by double imination of sulfide **15** remained unsuccessful.[13] Thus, treatment of **15** with 3 equiv of $NsNH_2$ and 2 equiv of PhI-

(11) Recently, several nitrogen transfer reactions using in-situ-formed iminoiodanes have been reported. For examples, see ref 9.

(12) Acid hydrolysis of N-sulfonylated sulfilimines is known. (a) Furukawa, N.; Omata, T.; Yoshimura, T.; Aida, T.; Oae, S. *Tetrahedron Lett.* **1972**, 1619. (b) Yoshimura, T.; Omata, T.; Furukawa, N.; Oae, S. *J. Org. Chem.* **1976**, *41*, 1728.

Table 3. $[Rh_2(OAc)_4]$-Catalyzed Imination of Sulfides[a]

entry	substrate	X-NH_2 reagents	product	time (h)	yield (%)
1	**15**	$NsNH_2$	**16a**	6	90
2	**15**	CF_3CONH_2	**16b**	6	87
3	**17**	$NsNH_2$	**18a**	6	98
4	**17**	CF_3CONH_2	**18b**	6	98
5	**19**	$NsNH_2$	**20a**	6	61

[a] Reaction conditions: sulfide (1.0 mmol), X-NH_2 (2.0 mmol), $PhI(OAc)_2$ (1.5 mmol), MgO (4.0 mmol), and $[Rh_2(OAc)_4]$ (2.5 mol %) in CH_2Cl_2 (10 mL) at room temperature.

$(OAc)_2$ in the presence of 2.5 mol % of $[Rh_2(OAc)_4]$ only afforded sulfilimine **16a** (90% yield). This result suggested that the second imination reaction was hampered by the strongly electron-withdrawing *N*-nosyl group of **16a**. Consequently, the electron density at the sulfur atom was too low to allow a second nitrene transfer.

In summary, various sulfoxides and sulfides have been converted into their corresponding sulfoximines and sulfilimines, respectively, using $[Rh_2(OAc)_4]$ as a catalyst and trifluoroacetamide or sulfonylamides in combination with iodobenzene diacetate and magnesium oxide. Synthetically valuable *NH*-sulfoximines and sulfilimines can easily be obtained by cleavage of the *N*-acyl bond of the resulting *N*-trifluoroacetyl-protected derivatives. The imination reaction is stereospecific and proceeds with retention of configuration at the stereogenic center. Consequently, enantiomerically pure sulfoximines are accessible by starting from enantiopure sulfoxides. Asymmetric iminations using chiral rhodium catalysts are currently under investigation.

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Supporting Information Available: Experimental procedures and full characterization (^1H 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) For a review on sulfodiimines, see: (a) Haake, M. In *Topics in Sulfur Chemistry*; Senning, A., Ed; Thieme: Stuttgart, 1976; Vol. 1, p 185. For recent reports on the use of sulfodiimines, see: (b) Diederich, W. E.; Haake, M. *J. Org. Chem.* **2003**, *68*, 3817. (c) Stoller, A.; Kreuz, K.; Haake, M.; Wenger, J. *Chimia* **2003**, *57*, 725.