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Iron(II) Triflate as an Efficient Catalyst for the Imination of Sulfoxides

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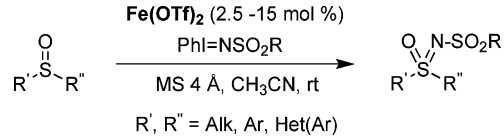
ABSTRACT



The challenging imination of benzyl-, sterically demanding alkyl-, and heteroaryl-substituted sulfoxides has been studied. Iron(II) triflate was identified as a highly efficient and robust catalyst for sulfur imination reactions. A variety of sulfoxides and sulfides were efficiently iminated with sulfonyliminoiodinanes (PhI=NSO$_2$R) at room temperature to give the corresponding sulfoximines and sulfilimines in good yields and with short reaction times.

Sulfoximines can be bioactive,[1] and they have been used as building blocks for the preparation of chiral ligands[2] and pseudopeptides.[3] A number of approaches for their synthesis have been developed, the most straightforward being direct nitrogen transfer onto the corresponding sulfoxide.[4−6] Various metal-based catalysts including copper,[7] rhodium,[8] and silver[9] complexes have been described for this reaction.[10] The use of cheap and environmentally friendly iron salts presents an attractive alternative.[11] Bach and Körber reported the first iron-catalyzed sulfur imination, which employed

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(1) For recent examples of the patent literature related to agrochemicals, see: (a) Jeanguenat, A.; O'Sullivan, A. C. WO 032462 A1, 2006 (Syngenta). (b) Jeanguenat, A.; O'Sullivan, A. C. WO 061200 A1, 2006 (Syngenta). (c) Plant, A.; Boehmer, J. E.; Peace, A. L. WO 037945 A1, 2006 (Syngenta). (d) Huang, J. X.; Rogers, R. B.; Orr, N.; Sparks, T. C.; Gifford, J. M.; Loso, M. R.; Zhu, Y.; Meade, T. WO 2007149134 A1, 2007 (Dow Agrosciences). (e) Loso, M. R.; Nugent, B. M.; Huang, J. X. WO 2008027073 A1, 2008 (Dow Agrosciences). (f) Loso, M. R.; Nugent, B. M.; Zhu, Y.; Siddall, T. L.; Tisdell, F. E.; Huang, J. X.; Benko, Z. L. WO 2008027539 A1 (Dow Agrosciences). (g) Zhu, Y.; Loso, M. R.; Nugent, B. M.; Huang, J. X.; Rogers, R. B. WO 2008057129 A1 (Dow Agrosciences).

(2) Reviews: (a) Harmata, M. *Chemtracts* **2003**, *16*, 660. (b) Okamura, H.; Bolm, C. *Chem. Lett.* **2004**, *33*, 482. (c) Bolm, C. In *Asymmetric Synthesis with Chemical and Biological Methods*; Enders, D., Jaeger, K.-E., Eds.; Wiley-VCH: Weinheim, 2007; p 149. (d) Worch, C.; Mayer, A. C.; Bolm, C. In *Organosulfur Chemistry in Asymmetric Synthesis*; Toru, T., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2008; p 209. For recent examples, see: (e) Lu, S.-M.; Bolm, C. *Adv. Synth. Catal.* **2008**, *350*, 1101. (f) Lu, S.-M.; Bolm, C. *Chem.—Eur. J.* **2008**, *14*, 7513. (g) Lu, S.-M.; Bolm, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 8920. (h) Frings, M.; Atodiresei, I.; Runsink, J.; Raabe, G.; Bolm, C. *Chem.—Eur. J.* **2009**, *15*, 1566.

(3) (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.

(4) For classical methods, see the following. NaN_3/H_2SO_4: (a) Fusco, R.; Tenconi, F. *Chim. Ind. (Milan)* **1965**, *47*, 61. (b) Johnson, C. R.; Schroeck, C. W. *J. Am. Chem. Soc.* **1973**, *95*, 7418. (c) Brandt, J.; Gais, H.-J. *Tetrahedron: Asymmetry* **1997**, *6*, 909. *O*-Mesitylenesulfonyl hydroxylamine (MSH): (d) Tamura, Y.; Minamikawa, J.; Sumoto, K.; Fujii, S.; Ikeda, M. *J. Org. Chem.* **1973**, *38*, 1239. (e) Johnson, C. R.; Kirchhoff, R. A.; Corkins, H. G. *J. Org. Chem.* **1974**, *39*, 2458. (f) Tamura, Y.; Matushima, H.; Minamikawa, J.; Ikeda, M.; Sumoto, K. *Tetrahedron* **1975**, *31*, 3035. (g) Fieser, M.; Fieser, L. F. *Reagents for Organic Synthesis*; John Wiley & Sons: New York, 1975; Vol. 5, p 430. See also: (h) Allenmark, S.; Claeson, S.; Lowendahl, C. *Tetrahedron: Asymmetry* **1996**, *7*, 361.

(5) For reviews on synthetic approaches to sulfoximines, see: (a) Johnson, C. R. *Acc. Chem. Res.* **1973**, *6*, 341. (b) *Methoden Org. Chem. (Houben−Weyl)*; Klamann, D., Ed.; VCH Thieme: Stuttgart, 1985; Vol. E11, Parts 1 and 2. (c) Pyne, S. *Sulfur Rep.* **1992**, *12*, 57. (d) Mikolajczk, M.; Drabowicz, J.; Kielbasinski, P. In *Chiral Sulfur Reagents*; CRC Press: Boca Raton, 1997. (e) Taylor, P. C. *Sulfur Rep.* **1999**, *21*, 241. (f) Reggelin, M.; Zur, C. *Synthesis* **2000**, 1. (g) Bentley, R. *Chem. Soc. Rev.* **2005**, *34*, 609.

(6) For an excellent review on metal-catalyzed nitrogen transfer reactions, see: Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905.

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$FeCl_2$ as the catalyst.[12] However, high catalyst loadings, the need for large excesses of the sulfoxide, and the use of potentially explosive $BocN_3$ as a nitrogen source have limited the applicability of this method.

Subsequently, we discovered that $Fe(acac)_3$ conveniently catalyzes the imination of various sulfides and sulfoxides using sulfonyl amides in combination with iodosylbenzene (PhI=O).[13] However, iminations of heteroaromatic substrates or sulfoxides bearing bulky substituents remained unsatisfactory.[14] To overcome this limitation, the development of more efficient iron catalysts was envisaged. In the course of this search,[15] we found that iron(II) triflate, which is easily prepared from iron powder or iron(II) chloride and trifluoromethanesulfonic acid,[16] catalyzed the imination of thioanisole and methyl phenyl sulfoxide (**1a**). Using only 2.5 mol % of $Fe(OTf)_2$, both substrates (used in 2-fold excess) reacted well with iminoiodinane (PhI=NNs) affording the corresponding sulfilimine and sulfoximine in 91% and 98% yield, respectively.[17] Compared to the previously reported $Fe(acac)_3$-based system, which required 5−10 mol % of the iron salt, this new catalyst appeared favorable.[18] In order to assess the real value of these findings, an in depth investigation into the $Fe(OTf)_2$-catalyzed sulfur imination was initiated, and the current status of this research is described here.

The imination of methyl phenyl sulfoxide (**1a**) with PhI=NNs in the presence of 2.5 mol % of $Fe(OTf)_2$ in acetonitrile was chosen as a model reaction (Table 1). A short optimization study of the reaction conditions showed that

Table 1. Optimization of the $Fe(OTf)_2$-Catalyzed Imination of Methyl Phenyl Sulfoxide (**1a**)[a]

entry	sulfoxide (equiv)	PhI=X (equiv)	time (min)	yield[b] (%)
1	2	PhI=NNs (1.0)	60	98
2[c]	1	PhI=NNs (1.1)	30	51
3	1	PhI=NNs (1.1)	30	66
4	1	PhI=NNs (1.3)	30	92
5	1	$NsNH_2$ (1.2), PhI=O (1.3)	20	85

[a] Reaction conditions: Sulfoxide **1a**, 2.5 mol % of $Fe(OTf)_2$, PhI=X, and MS 4 Å in acetonitrile (0.1 M) at rt. [b] After column chromatography. [c] Performed without MS 4 Å.

the sulfoxide-to-iminoiodinane ratio could be reduced (entries 2−4). However, the use of a slight excess of iminoiodinane (1.3 equiv) was required to achieve complete conversion of the sulfoxide **1a** and high yields of sulfoximine **2a** (entry 4). The use of molecular sieves (4 Å) also proved to be beneficial to the reaction yields (entries 2 and 3). The reactions were efficient, allowing for short reaction times (30 min). Moreover, the combination of *p*-nosylamide ($NsNH_2$) and iodosylbenzene (PhI=O) to generate the corresponding iminoiodinane in situ was also effective, providing sulfoximine **2a** in 85% yield after 20 min (entry 5).

The use of alternative nitrogen sources to PhI=NNs was explored under the optimized conditions (Table 1, entries 4 and 5). Whereas simple amides such as $BnCONH_2$ or CF_3CONH_2 with PhI=O were unreactive, a variety of iminoiodinanes (PhI=NPy and PhI=NTs) or sulfonamides ($ThiophSO_2NH_2$, $BusNH_2$, and $SESNH_2$) in combination with PhI=O could be efficiently employed. Thus, the corresponding *N*-substituted 5-methyl-2-pyridinyl- (Py), *p*-tolyl- (Ts), *tert*-butyl- (Bus), 2-thiophenyl- (Thioph), and 2-trimethylsilylethylsulfonyl (SES) sulfoximines **2b**−**f** (Figure 1) were obtained in moderate to good yields (65−95%), offering a

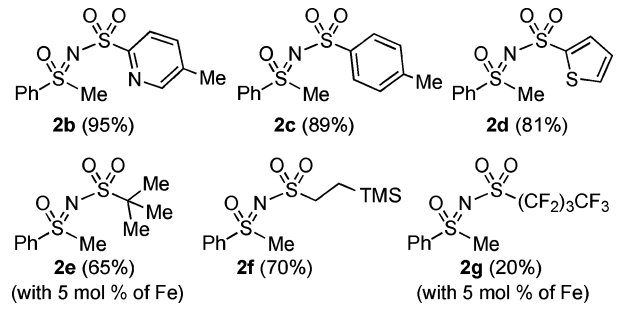


Figure 1. Various products obtained in iminations of **1a**.

(7) (a) Kwart, H.; Kahn, A. A. *J. Am. Chem. Soc.* **1967**, *89*, 1950. (b) Müller, J. F. K.; Vogt, P. *Tetrahedron Lett.* **1998**, *39*, 4805. (c) Bolm, C.; Muñiz, K.; Aguilar, N.; Kesselgruber, M.; Raabe, R. *Synthesis* **1999**, 1251. (d) Takada, H.; Ohe, K.; Uemura, S. *Angew. Chem., Int. Ed.* **1999**, *38*, 1288. (e) Nakayama, J.; Otani, T.; Sugihara, Y.; Sano, Y.; Ishii, A.; Sakamoto, A. *Heteroatom Chem.* **2001**, *12*, 333. (f) Cren, S.; Kinahan, T. C.; Skinner, C. L.; Tye, H. *Tetrahedron Lett.* **2002**, *43*, 2749. (g) Lacôte, E.; Amatore, M.; Fensterbank, L.; Malacria, M. *Synlett* **2002**, 116.

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

(9) Cho, G. Y.; Bolm, C. *Org. Lett.* **2005**, *7*, 4983.

(10) For alternative metal-free sulfur iminations, see: (a) Cho, G. Y.; Bolm, C. *Tetrahedron Lett.* **2005**, *46*, 8007. (b) Siu, T.; Picard, C. J.; Yudin, A. K. *J. Org. Chem.* **2005**, *70*, 932. (c) Karabuga, S.; Kazaz, C.; Kilic, H.; Ulukanli, S.; Celik, A. *Tetrahedron Lett.* **2005**, *46*, 5225. (d) Krasnova, L. B.; Hili, R. M.; Chernoloz, O. V.; Yudin, A. K. *Arkivoc* **2005**, *iv*, 268. (e) García Mancheño, O.; Bistri, O.; Bolm, C. *Org. Lett.* **2007**, *9*, 3809.

(11) For reviews on iron catalysis, see: (a) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217. (b) Fürstner, A.; Martin, R. *Chem. Lett.* **2005**, 624. (c) Diaz, D. D.; Miranda, P. O.; Padrón, J. I.; Martin, V. S. *Curr. Org. Chem.* **2006**, *10*, 457. (d) Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3317. (e) Sherry, B. D.; Fürstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500. (f) Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3317. (g) Bauer, E. B. *Curr. Org. Chem.* **2008**, *12*, 1341. (h) Gaillard, S.; Renaud, J.-L. *ChemSusChem* **2008**, *1*, 505. (i) Correa, A.; García Mancheño, O.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108. (j) Fürstner, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 1364.

(12) (a) Bach, T.; Körber, C. *Tetrahedron Lett.* **1998**, *39*, 5015. (b) Bach, T.; Körber, C. *Eur. J. Org. Chem.* **1999**, *64*, 1033.

(13) García Mancheño, O.; Bolm, C. *Org. Lett.* **2006**, *8*, 2349.

(14) García Mancheño, O.; Bolm, C. *Chem.—Eur. J.* **2007**, *13*, 6674.

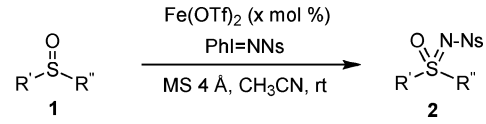
(15) Iron(II)/(III) perchlorates and iron(III) diketonates such as 1-acetyl-2-oxo-1-cyclopentanide and 2-methyl acetylacetonate catalyzed sulfoxide iminations, but they were less efficient than $Fe(acac)_3$.

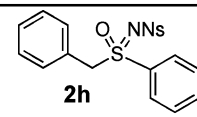
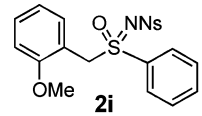
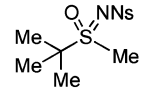
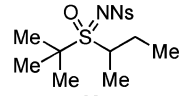
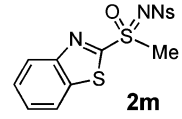
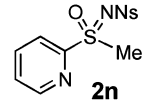
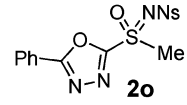
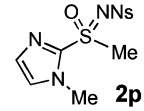
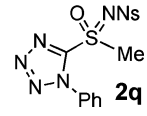
(16) (a) Haynes, J. S.; Sams, J. R.; Thomson, R. C. *Can. J. Chem.* **1981**, *59*, 669. (b) Hagen, K. S. *Inorg. Chem.* **2000**, *39*, 5867.

(17) For preliminary results, see: Nakanishi, M., Dissertation, RWTH Aachen University, 2007.

(18) For the application of $Fe(OTf)_2$-based catalytic systems in nitrene transfer reactions onto enol silyl ethers and olefins, see: (a) Nakanishi, M.; Salit, A.-F.; Bolm, C. *Adv. Synth. Catal.* **2008**, *350*, 1835. (b) Mayer, A.; Salit, A.-F.; Bolm, C. *Chem. Commun.* **2008**, 5975. For the use of related iron triflate catalysts, see: (c) Klotz, K. L.; Slominski, L. M.; Hull, A. V.; Gottsacker, V. M.; Mas-Ballesté, R.; Que, L; Halfen, J. A. *Chem. Commun.* **2007**, 2063.

Table 2. $Fe(OTf)_2$-Catalyzed Sulfoxide Imination Scope[a]



Entry	Fe (mol %)	R'	R''	Sulfoximine **2**	Yield (%)[b]
1	5	Bn	Ph	 **2h**	96 (46)[c]
2	5	*o*-MeO(C_6H_4)	Ph	 **2i**	96 (44)[c]
3	5	*i*-Pr	*i*-Pr	 **2j**	60
4	5	*t*-Bu	Me	 **2k**	86 (80)[d]
5	5	*t*-Bu	*s*-Bu	 **2l**	55
6	5	2-benzothizolyl	Me	 **2m**	83 (86)[c,e]
7	5	2-pyridinyl	Me	 **2n**	80 (92)[c,e]
8	5	2-(5-Ph-1,2,3-oxadiazolyl)	Me	 **2o**	45 (21)[c,e]
9	15				62
10	15	2-(*N*-Me-imidazolyl)	Me	 **2p**	50 (47)[c,f]
11	15	2-(*N*-Ph-tetrazolyl)	Me	 **2q**	57

[a] Reaction conditions: sulfoxide (1 equiv), $Fe(OTf)_2$, PhI=NNs (1.3 equiv), and MS 4 Å in acetonitrile (0.1 M) at rt. [b] After column chromatography. [c] Yield obtained by using 10 mol % of $Fe(acac)_3$ as catalyst. [d] See ref 13. [e] See ref 14.

variety of possibilities for the deprotection of the sulfoximine nitrogen.[19] The enhanced reactivity of this catalyst compared to previously reported iron systems[12−14] was demonstrated by the sulfoxide imination of **1a** with the bulky $BusNH_2$, which could be performed with only 5 mol % of $Fe(OTf)_2$ to afford the sulfoximine in 65% yield. Additionally, the use of perfluorinated alkylic sulfonamide $CF_3(CF_2)_3SO_2NH_2$ as a nitrogen source was also possible, albeit in poor yield (20% for **2g**).

The unexpectedly high catalytic activity of the $Fe(OTf)_2$-based system prompted further investigation into its applicability to the imination of more challenging substrates

(19) For example, nosylamides can be easily cleaved using thiolates, SES-amides react upon treatment with fluorides to give amines, *tert*-butyl sulfonylamides are deprotected under acidic conditions, and deprotection of the pyridinyl and thiophenyl derivatives could be achieved by reaction with Mg. For general methods for the deprotection of sulfonylamides, see: (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999; p 603.

such as sulfoxides bearing benzylic, bulky alkyl or heteroaryl substituents (Table 2). Initially, the imination of benzyl sulfoxides **1h** and **1i** with PhI═NNs was explored (entries 1 and 2). Whereas the use of 10 mol % of $Fe(acac)_3$ had led to only moderate yields (46 and 44%, respectively), 5 mol % of $Fe(OTf)_2$ was sufficiently active to drive both reactions to completion. Interestingly, and in contrast to the previously observed limitations of iron-catalyzed sulfur iminations, the presence of a coordinating substituent such as an alkoxy group (as present in **1i**) did not inhibit the reaction, and both sulfoximines **2h** and **2i** were obtained in excellent yield (96%). The use of 5 mol % of $Fe(OTf)_2$ was also effective in the imination of dialkyl sulfoxides with bulky isopropyl, *tert*-butyl, or *sec*-butyl substituents leading to good yields of the corresponding sulfoximines **2j**−**l** (55−86%, entries 3−5).

Iminations of sulfoxides with heteroaryl substituents were subsequently studied (entries 6−11). Benzothiazolyl- and pyridinyl-substituted sulfoxides (**1m** and **1n**) were successfully iminated with only 5 mol % of $Fe(OTf)_2$, while the equivalent reactions with $Fe(acac)_3$[14] required 10 mol % to achieve comparable yields (83 and 80% vs 86 and 92%, respectively; entries 6 and 7).

Pleasingly, the more challenging imination of oxadiazolyl sulfoxide **1o** was clearly improved by use of $Fe(OTf)_2$. When 5 mol % of this iron salt was employed, a 45% yield of sulfoximine **2o** was obtained (entry 8), signifying a 2-fold improvement in yield compared to $Fe(acac)_3$ (10 mol %).[14] Increasing the catalytic loading to 15 mol % to circumvent potential deactivation of the iron catalyst by coordination to the heteroatom-containing substrate or product, afforded a 62% yield of **2o** (entry 9).

Even in iminations of challenging substrates bearing imidazolyl and tetrazolyl substituents (entries 10−11) remarkable yields of the corresponding heteroaromatic sulfoximines were achieved (up to 57%).

Finally, the reactions of a representative array of heterocyclic sulfides, such as imidazolyl and tetrazolyl substituted substrates, were examined (Figure 2). Under the same reaction conditions as described for the iminations of heteroaromatic sulfoxides (15 mol % of $Fe(OTf)_2$ and PhI═NNs as nitrene source), the more nucleophilic sulfides

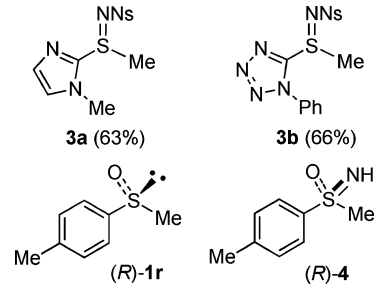


Figure 2. Heteroaryl-substituted sulfilimines **3a** and **3b** prepared under iron catalysis and optically active sulfoximine (*R*)-**4** obtained from sulfoxide (*R*)-**1r**.

provided the corresponding sulfilimines **3a** and **3b** in good yields (63 and 66%, respectively).

Lastly, the stereospecificity of the imination reaction was investigated by using optically pure (*R*)-methyl *p*-tolylsulfoxide (**1r**). Iron-catalyzed imination and subsequent standard nitrogen deprotection of the resulting *N*-nosylsulfoximine afforded enantiopure NH-sulfoximine (*R*)-**4** in good yield (77% over two steps).[20] Both the ee analysis of **4** by chiral HPLC (>99% ee) and the optical rotation revealed that the imination reaction had occurred without epimerization and retention of configuration at the stereogenic sulfur.

In summary, we have demonstrated the use of $Fe(OTf)_2$ in the preparation of challenging sulfoximines and sulfilimines with benzylic, bulky alkyl, or heteroaryl substituents.

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Supporting Information Available: Experimental procedures, full characterization of new products, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) For experimental details, see the Supporting Information.