DOI: 10.1002/adsc.200900020

Hydrogen-Bonding Catalysis: Mild and Highly Chemoselective Oxidation of Sulfides

Alessio Russo[a] and Alessandra Lattanzi[a,*]

[a] Dipartimento di Chimica, Università di Salerno, Via Ponte don Melilllo, 84084 Fisciano, Italy
Fax: (+39)-089-969-603; e-mail: lattanzi@unisa.it

Received: January 13, 2009; Published online: March 5, 2009

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900020.

Abstract: *N*,*N*′-Bis[3,5-bis(trifluoromethyl)phenyl]thiourea, employed at only 1 mol% loading, was found to be a very effective catalyst for the oxidation of sulfides with *tert*-butyl hydroperoxide (TBHP), affording the sulfoxides in high yield, excellent chemoselectivity, fairly good diastereoselectivity.

Keywords: chemoselectivity; hydrogen bonds; oxidation; sulfoxides; thioureas

Sulfoxides are both useful elements of stereocontrol in asymmetric synthesis and important targets of pharmaceutical interest.[1] The oxidation of sulfides is undoubtly the most direct and easy approach for the preparation of sulfoxides and several transition metal-based methodologies have been reported to date employing different sources of oxygen donors.[2] More recently, particular attention has been paid to the development of efficient and highly selective methodologies of sulfoxidation with favourable environmetal impact. Thus, the most important issues to be addressed are i) the use of as low as possible catalyst loading, cheap and environmentally friendly oxidants, ii) high control of the chemoselectivity, iii) mild reaction conditions amenable to tolerate other oxidable functional groups present in the molecule. Some examples of Brønsted acid-catalysed oxidation of sulfides have been reported.[3] Interestingly, alcohols[4] and phenol,[5] used as solvents, in the presence of hydrogen peroxide, proved to be suitable systems for the sulfoxidation. These neutral hydrogen-bonding donors were suggested to provide electrophilic activation of hydrogen peroxide through hydrogen-bonding interactions.

Given our interest in the development of metal-based[6] and organocalysed[7] methodologies of oxidation, we envisaged the possibility to employ an organic compound having good hydrogen-bonding donating ability as a *catalytic* activator of the oxygen donor in sulfoxidation. Recently, ureas and thioureas have been shown to behave as excellent organocatalysts, operating through double hydrogen-bonding activation of different electrophiles.[8] The readily accessible, electron-poor diaryl thiourea **3** displayed high catalytic efficiency in carbon-carbon bond forming reactions,[9] acetalisation,[10] epoxide opening[11] and reduction of imines[12] (Figure 1). Herein, we report the first example of a thiourea employed as promoter in an oxidative process. An efficient, chemoselective and diastereoselective sulfoxidation protocol was established using *N*,*N*′-bis[3,5-bis(trifluoromethyl)phenyl] thiourea **3** at low loadings and TBHP as the oxidant.

Electron-poor diarylureas **1**[9] and **2**[11b] (Figure 1) were firstly employed at 10 mol% loading in the oxidation of model compound methyl *p*-tolyl sulfide **5a** in CH_2Cl_2 at room temperature with TBHP (Table 1).

Compound **1** and more acidic urea **2** afforded sulfoxide **6a** in low yields after 22 h, but with complete chemoselectivity, since traces of sulfone were not detected by ^{1}H NMR analysis of the crude reaction mixture (entries 1 and 2). The experiment carried out under otherwise identical conditions, but in the absence of the catalyst (entry 3), proved that the uncatalysed oxidation was a negligible process and confirmed that ureas could moderately catalyse the sulfoxidation.

When using thiourea **3**, we were very pleased to observe complete conversion to sulfoxide (entry 4) and the chemoselectivity was mantained high with a 99/1 sulfoxide/sulfone ratio.[13] A different double hydrogen-bonding donor, (*R*)-BINOL, was then checked (entry 5). Compound **4** proved to be as active as ureas **1** and **2**. In apolar toluene and chloroform, thiourea **3** could be equally employed although displaying lower activity than in CH_2Cl_2 as solvent (entries 6–8). As expected, in hydrogen-bonding acceptor THF, catalyst

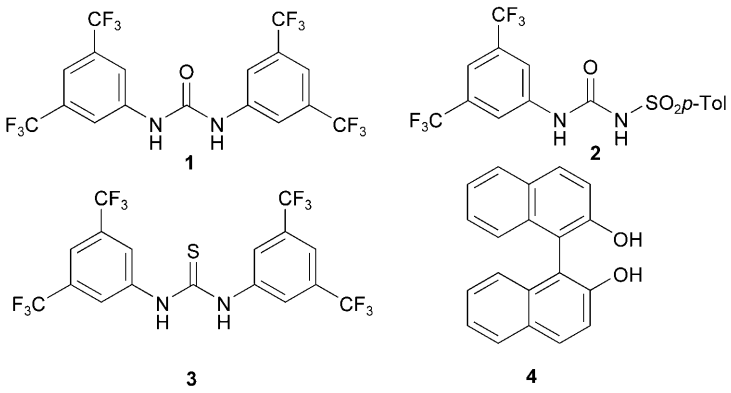
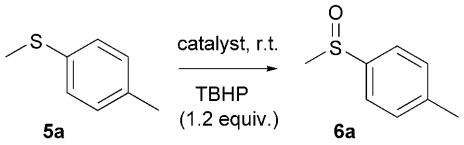


Figure 1. Catalysts checked in the sulfoxidation.

Table 1. Oxidation of sulfide **5a** with TBHP promoted by catalysts **1–4**.



Entry	Cat. [mol%]	Solvent	Conc. [M]	Time [h]	Yield **6a** [%][a]
1	**1** [10]	CH_2Cl_2	0.25	22	29
2	**2** [10]	CH_2Cl_2	0.25	22	31
3	–	CH_2Cl_2	0.25	22	5
4	**3** [10]	CH_2Cl_2	0.25	15	99
5	**4** [10]	CH_2Cl_2	0.25	30	26
6	**3** [10]	toluene	0.25	22	84
7	–	toluene	0.25	22	7
8	**3** [10]	$CHCl_3$	0.25	22	56
9	**3** [10]	THF	0.25	23	29
10	**3** [5]	CH_2Cl_2	0.25	20	99
11	**3** [1]	CH_2Cl_2	0.25	20	99
12	**3** [0.1]	CH_2Cl_2	0.25	47	99
13	**3** [1]	CH_2Cl_2	0.5	16	99
14	–	CH_2Cl_2	0.5	22	20

[a] Isolated yields after flash chromatography.

activity was almost suppressed (entry 9). Loadings of **3** as low as 1 mol% led to completion of the reaction within the same reaction time (entries 10 and 11) and although a longer reaction time was required, only 0.1 mol% loading can be successfully employed (entry 12). Working at 1 mol% loading under more concentrated conditions (0.5 M), enabled us to speed up the reaction, whereas a poor contribution of the uncatalysed oxidative pathway was demonstrated (entries 13 and 14).

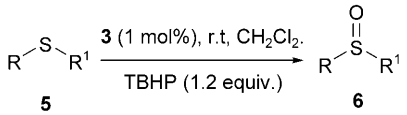
In order to check the stability of the catalyst under oxidative degradation, compound **3** was reacted with TBHP (12 equiv.) in the absence of the sulfide at room temperature. After a prolonged reaction time of 72 h, compound **3** was recovered in 89% yield. This is a clear indication that thiourea **3** is not prone to decomposition and catalyst preservation is assured throughout the oxidation of the sulfide. With the optimised conditions in hand, a variety of sulfides were reacted with TBHP and catalyst **3** at room temperature to study the scope of the oxidation (Table 2).

Different types of phenyl substitution in the methyl aryl sulfides are well-tolerated although sulfides bearing *para*-electron-withdrawing groups or *ortho*-Lewis basic substituents required longer reaction times in order to be converted to sulfoxides in high yields (entries 2–4). The ethyl substitution at sulfur significantly slowed down the reaction rate (entry 5). This result showed that steric effects seem to play an important role in the sulfoxidation. The less reactive diphenyl sulfide was oxidised in good yield (entry 6).

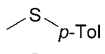
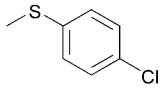
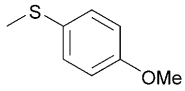
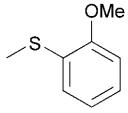
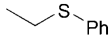
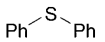
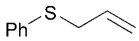
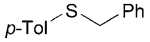
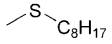
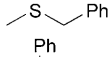
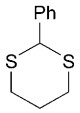
Sulfides having functional groups susceptible to oxidation were selectively sulfoxidated (entries 7 and 8). Aryl benzyl and dialkyl sulfides afforded the sulfoxides in high yields and general excellent chemoselectivity (entries 9–11). Finally, the issue of diastereoselectivity was briefly investigated. Interestingly, 2-phenyl-1,3-dithiane and dithiolane gave the *trans*-monosulfoxides in high yield and diastereoselectivity (entries 12 and 13). The stereocontrol achieved with thiourea **3**/TBHP system is comparable to that observed in metal-catalysed[14] sulfoxidation processes and better than the diastereoselectivity afforded by classical and strong oxidants such as *m*-chloroperbenzoic acid[15] or $NaIO_4$.[14a]

It is interesting to note that the catalytic performance of thiourea **3** in terms of turnover numbers (TON up to 990) competes well with transition metal complexes generally used in the oxidation of sulfides with alkyl hydroperoxides. The effectiveness in the activation of TBHP could be rationalised according to a double hydrogen-bonding interaction of **3** with the proximal oxygen of TBHP, which should significantly enhance the electrophilic character of the distal oxygen attacked by the sulfide (Figure 2).

Table 2. Chemoselective oxidation of sulfides with thiourea **3**/TBHP system.[a]



5 **6**

Entry	**5**	Time [h]	Yield **6** [%][b]
1		16	99
2		48	95 (99/1)
3		36	99
4		69	85
5		40	87
6		72	69
7		21	79
8[c]		41	98
9		17	84
10		46	91 (98/2)
11		22	99
12		40	92 *t*/*c*: 96/4[d]
13		47	92 *t*/*c*: 81/19[d]

[a] *Molar ratios*: **5**/**3**/TBHP 1/0.01/1.2. The sulfoxide/sulfone ratio is reported in parenthesis whenever detected by ^{1}H NMR analysis.
[b] Isolated yields after flash chromatography.
[c] 5 mol% of **3** was used.
[d] The *trans*/*cis* ratio determined by ^{1}H NMR analysis.

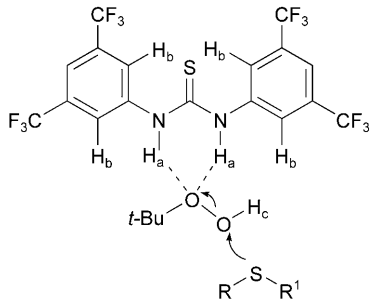


Figure 2. Proposed mode of activation of TBHP by thiourea **3**.

^{1}H NMR analysis of the **3**/TBHP 1/1 mixture, under diluted conditions (0.02 M) in $CDCl_3$ (400 MHz), supported the formation of the TBHP-catalyst **3** complex. Indeed, the chemical shift of H_a was downfield shifted from 7.96 to 8.12 ppm after the addition of TBHP. The aromatic protons H_b were downfield shifted from 7.88 to 7.91 ppm. Finally, the H_c proton of TBHP was downfield shifted from 7.14 to 7.42 ppm.[16]

In conclusion, we have disclosed that simple and readily accessible *N*,*N*′-bis[3,5-bis(trifluoromethyl)-phenyl] thiourea **3** can efficiently activate an oxygen donor such as *tert*-butyl hydroperoxide at remarkable low loadings of up to 0.1 mol%. A mild, metal-free methodology of sulfoxidation has thus been developed. A variety of sulfoxides were obtained in high yields, excellent chemoselectivity, fairly good diastereoselectivity. This study opens new possibilities for the employment of thioureas in the area of organocatalysed oxidations.

Experimental Section

General Procedure

Sulfide **5** (0.2 mmol) and **3** (0.002 mmol, 1 mg) were dissolved in anhydrous CH_2Cl_2 (400 μL) at room temperature. TBHP (0.24 mmol, 44 μL of 5–6 M decane solution) was then added. After the completion of the reaction, as monitored by TLC, the solvent was removed under reduced pressure and the crude mixture was analysed by ^{1}H NMR to determine the sulfoxide/sulfone ratio. The sulfoxide was then isolated by flash chromatography eluting with PE/ethyl acetate mixtures (8/2 to pure ethyl acetate). All sulfoxides are known compounds, their analytical data were identical to those reported in the literature.[2,3,6b]

Acknowledgements

MIUR is acknowledged for financial support.

References

[1] For reviews, see: a) M. C. Carreño, *Chem. Rev.* **1995**, *95*, 1717; b) I. Fernández, N. Khiar, *Chem. Rev.* **2003**, *103*, 3651; c) J. Legros, J. R. Dehli, C. Bolm, *Adv. Synth. Catal.* **2005**, *347*, 19.
[2] For selected examples, see: a) F. Di Furia, G. Modena, R. Seraglia, *Synthesis* **1984**, 325; b) P. Pitchen, E. Duñach, M. N. Desmukh, H. B. Kagan, *J. Am. Chem. Soc.* **1984**, *106*, 8188; c) N. Komatsu, M. Hashizume, T. Sugita, S. Uemura, *J. Org. Chem.* **1993**, *58*, 4529; d) C. Bolm, F. Bienewald, *Angew. Chem.* **1995**, *107*, 2883; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2640; e) M. Palucki, P. Hanson, E. N. Jacobsen, *Tetrahedron Lett.* **1992**, *33*, 7111; f) C. Kokubo, T. Katsuki, *Tetrahedron* **1996**, *52*, 13895; g) H. Q. N. Gunaratne, M. A. McKervey, S.

Feutren, J. Finlay, J. Boyd, *Tetrahedron Lett.* **1998**, *39*, 5655; h) J. Legros, C. Bolm, *Angew. Chem.* **2004**, *116*, 4321; *Angew. Chem. Int. Ed.* **2004**, *43*, 4225; i) M. Mba, L. J. Prins, G. Licini, *Org. Lett.* **2007**, *9*, 21. For a metal-free procedure of sulfoxidation, see: F. Shi, M. K. Tse, H. M. Kaiser, M. Beller, *Adv. Synth. Catal.* **2007**, *349*, 2425.

[3] a) F. Bonadies, F. De Angelis, L. Locati, A. Scettri, *Tetrahedron Lett.* **1996**, *37*, 7129; b) S. Vayssié, H. Elias, *Angew. Chem.* **1998**, *110*, 2246; *Angew. Chem. Int. Ed.* **1998**, *37*, 2088; c) V. G. Shukla, P. D. Salgaonkar, K. G. Akamanchi, *J. Org. Chem.* **2003**, *68*, 5422; d) G. P. Romanelli, P. G. Vázquez, P. Tundo, *Synlett* **2005**, 75; e) H. Firouzabadi, N. Iranpoor, A. A. Jafari, E. Riazymontazer, *Adv. Synth. Catal.* **2006**, *348*, 434.

[4] a) M. A. P. Dunkleff, R. Curci, J. O. Edwards, H.-Y. Pyun, *J. Am. Chem. Soc.* **1968**, *90*, 3209; b) K. S. Ravikumar, J.-P. Bégué, D. Bonnet-Delpon, *Tetrahedron Lett.* **1998**, *39*, 3141.

[5] W. L. Xu, Y. Z. Li, Q. S. Zhang, H. S. Zhu, *Synthesis* **2004**, *2*, 227.

[6] a) A. Lattanzi, P. Iannece, A. Vicinanza, A. Scettri, *Chem. Commun.* **2003**, 1440; b) A. Lattanzi, S. Piccirillo, A. Scettri, *Adv. Synth. Catal.* **2007**, *349*, 357.

[7] a) A. Lattanzi, *Org. Lett.* **2005**, *7*, 2579; b) A. Russo, A. Lattanzi, *Adv. Synth. Catal.* **2008**, *350*, 1991.

[8] a) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289; b) Y. Takemoto, *Org. Biomol. Chem.* **2005**, *3*, 4299; c) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; d) S. J. Connon, *Chem. Eur. J.* **2006**, *12*, 5418.

[9] a) D. P. Curran, L. H. Kuo, *J. Org. Chem.* **1994**, *59*, 3259; b) P. R. Schreiner, A. Wittkopp, *Org. Lett.* **2002**, *4*, 217; c) P. R. Schreiner, A. Wittkopp, *Chem. Eur. J.* **2003**, *9*, 407; d) G. Dessole, R. P. Herrera, A. Ricci, *Synlett* **2004**, *13*, 2374; e) D. J. Maher, S. J. Connon, *Tetrahedron Lett.* **2004**, *45*, 1301; f) M. Kirsten, J. Rehben, M. Hiersemann, T. Strassner, *J. Org. Chem.* **2007**, *72*, 4001.

[10] M. Kotke, P. R. Schreiner, *Tetrahedron* **2006**, *62*, 434.

[11] a) C. M. Kleiner, P. R. Schreiner, *Chem. Commun.* **2006**, 4315; b) E. M. Fleming, C. Quigley, I. Rozas, S. J. Connon, *J. Org. Chem.* **2008**, *73*, 948.

[12] a) Z. Zhang, P. R. Schreiner, *Synlett* **2007**, 1455; b) Z. Zhang, P. R. Schreiner, *Synthesis* **2007**, 2559.

[13] The oxidation of **6a** carried out with **3** (20 mol%) and TBHP (1.2 equiv.) in CH_2Cl_2 at room temperature afforded after 63 h the sulfone in 5% yield.

[14] a) F. Di Furia, G. Licini, G. Modena, *Gazz. Chim. Ital.* **1990**, *120*, 165; b) G. Della Sala, S. Labano, A. Lattanzi, C. Tedesco, A. Scettri, *Synthesis* **2002**, 505.

[15] F. A. Carey, O. D. Dailey, O. Hernandez, J. R. Tucker, *J. Org. Chem.* **1976**, *41*, 3975.

[16] ^{1}H NMR spectra are reported in the Supporting Information.

