Asymmetric Catalysis

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Vanadium-Catalyzed Sulfur Oxidation/Kinetic Resolution in the Synthesis of Enantiomerically Pure Alkyl Aryl Sulfoxides**

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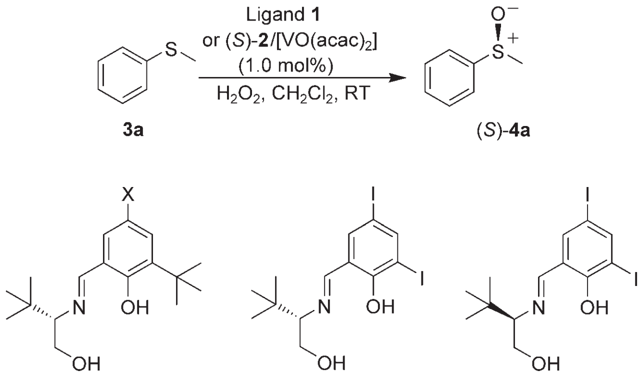
Chiral sulfoxides are an important class of compounds that find increasing use as chiral auxiliaries in asymmetric synthesis.[1,2] Current interest also reflects the existence of products with biological properties containing a sulfinyl group with a defined configuration.[3]

Several methods for the asymmetric oxidation of prochiral sulfides have been reported, including the use of chiral oxidants, such as chiral oxaziridines,[4] chiral hydroperoxides,[5] and enzymes.[6,7] The majority of investigations have concentrated on the use of chiral metal complexes[1,3,8–11] following the initial reports by Kagan and co-workers[12,13] and Modena and co-workers[14] on the use of variously modified Sharpless reagents for this reaction.

One of the most widely studied metal-based systems has been that discovered by Bolm and Bienewald,[15,16] who employed a combination of Schiff bases **1** derived from chiral amino alcohols and $[VO(acac)_2]$ (1.0 mol%; acac = acetylacetanoate), with aqueous hydrogen peroxide as the oxidant, in a two-phase system using dichloromethane as the solvent at 20 °C (Scheme 1). The advantages of the system developed by Bolm et al. include high activity, the very simple reaction conditions, and the use of hydrogen peroxide as the oxidant. The only drawback associated with the initial ligands tested was that the levels of enantiomeric excess were good, rather than excellent. Other research groups sought to optimize the system, by variation of the aromatic aldehyde,[17–19] the amino alcohol,[20] and the manner of addition of hydrogen peroxide,[21] and in many cases it is striking that the best outcome was usually obtained when the reaction was conducted in dichloromethane at 0 °C. A very nice application of the system developed by Bolm et al. was the asymmetric oxidation of di-*tert*-butyl disulfide, reported by Ellman and co-workers,[22] who have since reported the results of spectroscopic studies with a view to understanding the nature of the active catalytic species better.[23] The nature of the active species is still not completely established, but while spectroscopic studies indicate the presence of a vanadium(v)oxomonoperoxo species,[24] recent calculations suggest that the active species may be a vanadium(v)oxohydroperoxide.[25] Recently, the use of analogous salan ligands has been reported to give high levels of enantioselectivity (95% *ee*) in the oxidation of methyl phenyl sulfide, but lower levels of enantioselectivity were observed with other substrates.[26]



3a (*S*)-**4a**

1a: X = NO_2
1b: X = *t*Bu

(*S*)-**2** (*R*)-**2**

Scheme 1. Vanadium-catalyzed asymmetric oxidation of alkyl aryl sulfides.

Anson and co-workers screened a variety of chiral Schiff base ligands, and found that the 3,5-diiodo ligand (*S*)-**2**, in combination with $[VO(acac)_2]$ gave excellent results in the catalytic asymmetric sulfoxidation of alkyl aryl sulfides with hydrogen peroxide, again in dichloromethane at 0 °C.[27] For example, methyl phenyl sulfide was oxidized to (*S*)-methyl phenyl sulfoxide (81%, 90% *ee*). Recently, Bolm and co-workers reported that a combination of this ligand with iron is also very effective for the asymmetric oxidation of prochiral sulfides,[28,29] especially in the presence of substituted benzoic acids and with the corresponding lithium salts as additives.[30,31]

In all asymmetric oxidations of prochiral sulfides to sulfoxides, the possibility of subsequent kinetic resolution of the product sulfoxide by oxidation to the corresponding sulfone exists. Uemura and co-workers had demonstrated the viability of this process as long ago as 1993; they observed stereoselectivity factors of 7.4–8.5 for kinetic resolutions[32] using a catalyst prepared from $Ti(OiPr)_4$, 2,2′-dihydroxy-1,1′-binaphthyl (binol), and H_2O.[33] A more recent example makes use of a catalyst derived from WO_3 and cinchona alkaloids for the kinetic resolution of alkyl aryl sulfoxides using hydrogen peroxide.[34] The process developed by Uemura and co-workers[33,35] has been exploited by Scettri and co-workers (using furyl hydroperoxides as the oxidant)[36] and more recently by Chan and co-workers (using *tert*-butylhydroperoxide as the oxidant).[37] Specifically, Chan and co-workers described a process in which an initial oxidation at 0 °C (at which temperature the enantioselectivity is optimum) and then at 25 °C (where the kinetic resolution is most efficient) allowed the isolation of sulfoxides in reasonable

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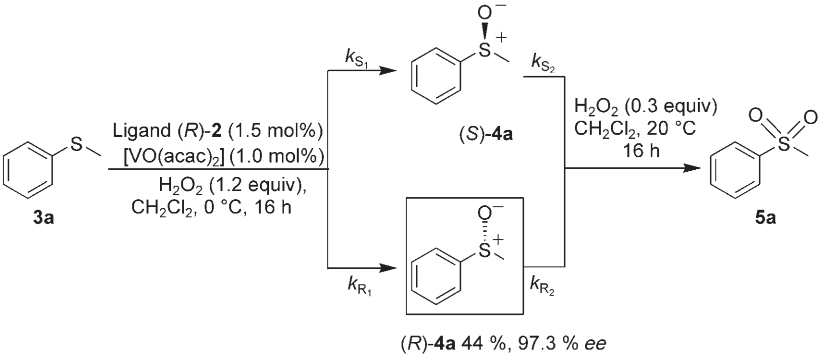
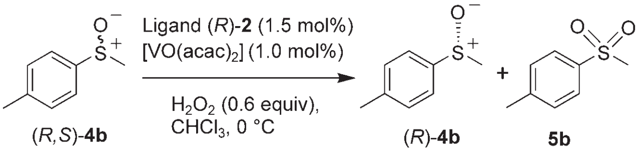
yields and excellent *ee* values (65 % and 99.9 % *ee* in the case of methyl *para*-tolyl sulfoxide, the best so far published).[37] However, it appears that no significant kinetic resolution in the oxidation of sulfoxides has so far been reported in studies in which chiral vanadium(IV)–Schiff base complexes were used. Nevertheless, such an effect has been reported in the case of vanadium–salan systems (selectivity factor $S = 7.3$ for the resolution of methyl phenyl sulfoxide) when larger amounts of catalyst (5 mol %) were used.[26]

In an initial experiment it was confirmed that there was no significant kinetic resolution in the oxidation of racemic methyl phenyl sulfoxide using 3,5-diiodo ligand (*R*)-**2** (prepared from (*R*)-*tert*-leucinol, which has recently become commercially available) in combination with [VO(acac)$_2$] and hydrogen peroxide in dichloromethane at 0 °C ($S = 1.1$). However, a significant effect was observed ($S = 5.8$) when the kinetic resolution was carried out at 20 °C. A tandem catalytic approach to the asymmetric oxidation of methyl phenyl sulfoxide using a combination of (*R*)-**2** with [VO(acac)$_2$] in dichloromethane was developed: an initial oxidation step at 0 °C followed by the addition of further oxidant to the same reaction vessel and warming to 20 °C allowed the isolation of (*R*)-methyl phenyl sulfoxide (44 %, 97.3 % *ee*; Scheme 2). While this was an interesting result, the modest yield meant that it was not ideal from a preparative perspective.

Given the striking effect of temperature on the efficiency of the kinetic resolution, it seemed appropriate to explore the influence of the solvent. After substantial solvent screening in the oxidation of racemic methyl phenyl sulfoxide (**4a**) using (*R*)-**2** and [VO(acac)$_2$] as the catalyst, and hydrogen peroxide as oxidant (0.5 equiv), it was found that the use of chloroform as the solvent[38] resulted in an improved kinetic resolution effect at 20 °C ($S = 7.7$). No other solvent that was screened gave comparable results. The kinetic resolution in chloroform was more efficient at 0 °C ($S = 11.6$). The highest value so far reported ($S = 28$) was obtained when the kinetic resolution of racemic methyl *para*-tolyl sulfoxide (**4b**) at 0 °C was investigated (Scettri and co-workers reported $S = 23$ by using a stoichiometric process).[36] This kinetic resolution could be adapted for preparative use (with 0.6 equiv of hydrogen peroxide), which allowed the isolation of (*R*)-methyl *para*-tolyl sulfoxide (**4b**, 41 % of a maximum of 50 %, 98.0 % *ee*), as well as sulfone **5b** (Scheme 3).



Scheme 2. Oxidation/kinetic resolution process for the preparation of (*R*)-methyl phenyl sulfoxide (**4a**).



Scheme 3. Kinetic resolution of methyl *para*-tolyl sulfoxide.

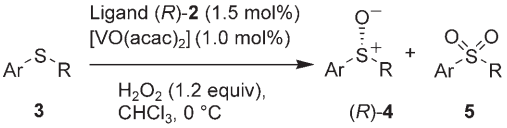
The observation that the optimum temperature for the kinetic resolution of racemic sulfoxides with the catalyst derived from (*R*)-**2** and [VO(acac)$_2$] in chloroform was 0 °C (the optimum temperature for most previous asymmetric oxidations of prochiral sulfides using chiral vanadium(IV)–Schiff base complexes) suggested that these conditions might also be extremely effective for the enantioselective preparation of alkyl aryl sulfoxides. This indeed proved to be the case, and Table 1 shows results from the oxidation of a range of alkyl aryl sulfides to give the (*R*)-alkyl aryl sulfoxides (Scheme 4). In each case, the corresponding sulfone **5** was also observed, thus indicating that, as expected, some kinetic resolution had taken place. The only unsatisfactory result was the oxidation of methyl *para*-nitrophenyl sulfide (**3d**), which gave the product **4d** in only 86.9 % *ee*.

Table 1: Asymmetric oxidation of alkyl aryl sulfides **3** in chloroform using ligand (*R*)-**2** with [VO(acac)$_2$] and H_2O_2 (1.2 equiv).

Ar	R	Product	Yield [%][a]	*ee* [%][b]
Ph	Me	(*R*)-**4a**	70	96.7
4-MeC$_6$H$_4$	Me	(*R*)-**4b**	70	>99.5
2-naphthyl	Me	(*R*)-**4c**	73	>99.5
4-NO$_2$C$_6$H$_4$	Me	(*R*)-**4d**	88	86.9
4-ClC$_6$H$_4$	Me	(*R*)-**4e**	72	96.9
4-MeOC$_6$H$_4$	Me	(*R*)-**4f**	71	99.5
4-BrC$_6$H$_4$	Me	(*R*)-**4g**	79	95.5
Ph	Pr	(*R*)-**4h**	86	98.3
Ph	Et	(*R*)-**4i**	76	97.4

[a] Yield of isolated product. Reactions were conducted on a 1.5 mmol scale. [b] Determined by HPLC of the purified products on a chiral stationary phase using a DAICEL Chiralpak AS column.

These encouraging results on a small scale prompted an investigation into scaling the reaction up. Oxidation of methyl phenyl sulfide (**3a**) with 60.0 mmol of substrate under the same reaction conditions (albeit with an increase in the reaction time from 16 h to 48 h) allowed the isolation of (*R*)-



Scheme 4. Optimized asymmetric oxidation of alkyl aryl sulfides.

methyl phenyl sulfoxide (**4a**; 87 %, 93 % *ee*). The oxidation was also performed on the same scale using methyl *para*-tolyl sulfide (**3b**), to give (*R*)-methyl *para*-tolyl sulfoxide (**4b**; 82 %, > 99.5 % *ee* after one recrystallization from Et_2O/hexane), and methyl *para*-bromophenyl sulfide (**3g**), to give (*R*)-methyl *para*-bromophenyl sulfoxide (**4g**; 77 %, > 99.5 % *ee* after one recrystallization from Et_2O/hexane). In these latter two cases, the efficiency of the process was even higher than that observed on a small scale.

The combination of very high *ee* values with high yield, the consequence of an efficient initial asymmetric oxidation followed by an efficient kinetic resolution process, makes this system very practical for the catalytic asymmetric oxidation of simple alkyl aryl sulfides. Both enantiomers of ligand **2** are easily prepared on a multigram scale from commercially available precursors, and the ligands may be stored at room temperature on the open bench without any special precautions.

Experimental Section

Typical large-scale asymmetric oxidation procedure for the preparation of (*R*)-**4b**: A solution of [VO(acac)$_2$] (159.0 mg, 0.60 mmol) in chloroform (15 mL) was added to a solution of (*R*)-**2** (425.8 mg, 0.90 mmol) in chloroform (15 mL) and the reaction mixture was stirred for 2 h. A solution of **3b** (8.29 g, 60.0 mmol) in chloroform (30 mL) was added and the reaction mixture stirred for 30 min at room temperature before cooling it to 0 °C. After 30 min, 30 % H_2O_2 (7.36 mL, 72.0 mmol) was added to the reaction mixture, which was stirred vigorously at 0 °C for 48 h. Samples (1–2 μL) were then removed at different times and diluted with 20 % isopropanol/heptane for analysis by HPLC. The reaction was quenched with 10 % $Na_2S_2O_3$ solution (200 mL) and the mixture extracted with chloroform (3 × 100 mL). The extracts were combined, washed with brine (3 × 100 mL), and dried ($MgSO_4$). Finally, the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether 50:50). The purified product was dissolved in the minimum amount of hot diethyl ether, and hexane was added until the solution became turbid. The solution was then gently warmed to give a clear solution, which was allowed to cool to room temperature and then kept at −15 °C overnight to give the product sulfoxide as needles. The crystalline solid was then filtered and washed with cooled (−15 °C) hexane to (*R*)-**4b** (7.60 g, 82 %), *ee* > 99.5 % (determined by HPLC on a Daicel Chiralpak AS column, with 15 % isopropanol in heptane, and a flow rate of 1.0 mL min^{-1}), $[\alpha]^{20}_{D} = 151$ ($c = 1.0$, acetone); [(Lit.[39] (*R*)-**4b**; *ee* 95 %); $[\alpha]^{20}_{D} = 142$ ($c = 1.5$, acetone)].

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[1] I. Fernández, N. Khiar, *Chem. Rev.* **2003**, *103*, 3651–3705.
[2] M. C. Carreño, *Chem. Rev.* **1995**, *95*, 1717–1760.
[3] J. Legros, J. R. Dehli, C. Bolm, *Adv. Synth. Catal.* **2005**, *347*, 19–31.
[4] F. A. Davis, R. T. Reddy, W. Han, P. J. Carroll, *J. Am. Chem. Soc.* **1992**, *114*, 1428–1437.
[5] W. Adam, M. N. Korb, K. J. Roschmann, C. R. Saha-Möller, *J. Org. Chem.* **1998**, *63*, 3423–3428.
[6] E. G. Mata, *Phosphorus Sulfur Relat. Elem.* **1996**, *117*, 231–286.
[7] D. R. Boyd, N. D. Sharma, S. A. Haughey, M. A. Kennedy, B. T. McMurray, G. N. Sheldrake, C. C. R. Allen, H. Dalton, K. Sproule, *J. Chem. Soc. Perkin Trans. 1* **1998**, 1929–1933.
[8] K. Kaczorowska, Z. Kolarska, K. Mitka, P. Kowalski, *Tetrahedron* **2005**, *61*, 8315–8327.
[9] H. B. Kagan, T. O. Luukas, in *Transition Metals for Organic Synthesis, Vol. 2*, 2nd ed. (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **2004**, pp. 479–495.
[10] K. P. Volcho, N. F. Salakhutdinov, A. G. Tolstikov, *Russ. J. Org. Chem.* **2003**, *39*, 1537–1552.
[11] C. Bolm, *Coord. Chem. Rev.* **2003**, *237*, 245–256.
[12] P. Pitchen, E. Duñach, M. N. Deshmukh, H. B. Kagan, *J. Am. Chem. Soc.* **1984**, *106*, 8188–8193.
[13] P. Pitchen, H. B. Kagan, *Tetrahedron Lett.* **1984**, *25*, 1049–1052.
[14] F. DiFuria, G. Modena, R. Seraglia, *Synthesis* **1984**, 325–326.
[15] C. Bolm, F. Bienewald, *Angew. Chem.* **1995**, *107*, 2883–2885; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2640–2642.
[16] C. Bolm, G. Schlingloff, F. Bienewald, *J. Mol. Catal. A* **1997**, *117*, 347–350.
[17] A. H. Vetter, A. Berkessel, *Tetrahedron Lett.* **1998**, *39*, 1741–1744.
[18] J. Skarzewski, E. Ostrycharz, R. Siedlecka, *Tetrahedron: Asymmetry* **1999**, *10*, 3457–3461.
[19] Y. C. Jeong, S. Choi, Y. D. Hwang, K. H. Ahn, *Tetrahedron Lett.* **2004**, *45*, 9249–9252.
[20] C. Ohta, T. Katsuki, *Tetrahedron Lett.* **2001**, *42*, 3885–3888.
[21] N. N. Karpyshev, O. D. Yakovleva, E. P. Talsi, K. P. Bryliakov, O. V. Tolstikova, A. G. Tolstikov, *J. Mol. Catal. A* **2000**, *157*, 91–95.
[22] D. A. Cogan, G. C. Liu, K. J. Kim, B. J. Backes, J. A. Ellman, *J. Am. Chem. Soc.* **1998**, *120*, 8011–8019.
[23] S. A. Blum, R. G. Bergman, J. A. Ellman, *J. Org. Chem.* **2003**, *68*, 150–155.
[24] K. P. Bryliakov, N. N. Karpyshev, S. A. Fominsky, A. G. Tolstikov, E. P. Talsi, *J. Mol. Catal. A* **2001**, *171*, 73–80.
[25] D. Balcells, F. Maseras, G. Ujaque, *J. Am. Chem. Soc.* **2005**, *127*, 3624–3634.
[26] J. T. Sun, C. J. Zhu, Z. Y. Dai, M. H. Yang, Y. Pan, H. W. Hu, *J. Org. Chem.* **2004**, *69*, 8500–8503.
[27] B. Pelotier, M. S. Anson, I. B. Campbell, S. J. F. Macdonald, G. Priem, R. F. W. Jackson, *Synlett* **2002**, 1055–1060.
[28] J. Legros, C. Bolm, *Angew. Chem.* **2003**, *115*, 5645–5647; *Angew. Chem. Int. Ed.* **2003**, *42*, 5487–5489.
[29] A. Korte, J. Legros, C. Bolm, *Synlett* **2004**, 2397–2399.
[30] J. Legros, C. Bolm, *Angew. Chem.* **2004**, *116*, 4321–4324; *Angew. Chem. Int. Ed.* **2004**, *43*, 4225–4228.
[31] J. Legros, C. Bolm, *Chem. Eur. J.* **2005**, *11*, 1086–1092.
[32] All stereoselectivity factors were calculated using the equation developed by Kagan and Fiaud.[40]
[33] N. Komatsu, M. Hashizume, T. Sugita, S. Uemura, *J. Org. Chem.* **1993**, *58*, 7624–7626.
[34] V. V. Thakur, A. Sudalai, *Tetrahedron: Asymmetry* **2003**, *14*, 407–410.
[35] N. Komatsu, M. Hashizume, T. Sugita, S. Uemura, *J. Org. Chem.* **1993**, *58*, 4529–4533.
[36] A. Massa, F. R. Siniscalchi, V. Bugatti, A. Lattanzi, A. Scettri, *Tetrahedron: Asymmetry* **2002**, *13*, 1277–1283.
[37] X. Jia, X. Li, L. Xu, Y. Li, Q. Shi, T. Au-Yeung, C. Yip, X. Yao, A. Chan, *Adv. Synth. Catal.* **2004**, *346*, 723–726.
[38] Chloroform had been used by Ellman and co-workers in the oxidation of di-*tert*-butyl disulfide,[22] and by Zhu and co-workers[26] in oxidations of alkyl aryl sulfides catalyzed by vanadium–salan complexes.
[39] A. Lattanzi, F. Bonadies, A. Senatore, A. Soriente, A. Scettri, *Tetrahedron: Asymmetry* **1997**, *8*, 2473–2478.
[40] H. B. Kagan, J. C. Fiaud, *Top. Stereochem.* **1988**, *18*, 249.