Contrasting Pathways for the Directed Homogeneous Hydrogenation of Vinyl Sulfoxides and Vinyl Sulfones

David Ando,[b] Christopher Bevan,[c] John M. Brown[a] and David W. Price[a]

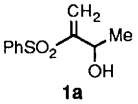
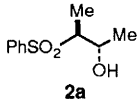
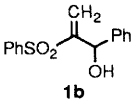
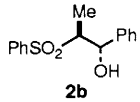
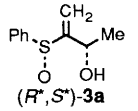
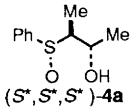
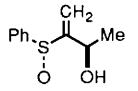
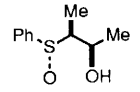
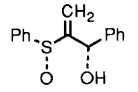
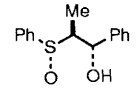
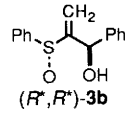
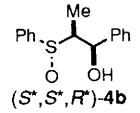
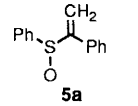
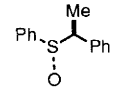
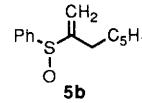
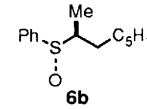
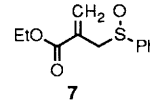
[a] *Dyson Perrins Laboratory, South Parks Rd, Oxford OX1 3QY, UK*
[b] *SERC Crystallography Service, Queen Mary College, Mile End Rd, London, UK*
[c] *Glaxo Group Research, Greenford UB6 0HE, UK*

Rh-complex catalysed directed hydrogenation of (α-hydroxyalkyl)vinyl sulfones follows the same stereochemical course as the corresponding acrylates, *via* HO-coordination; hydrogenation of the related (α-hydroxyalkyl)vinyl sulfoxides is directed by S–O coordination, which overrides HO-participation and is shown to be general.

Despite the substantial effort devoted to stereochemical control in homogeneous hydrogenation, and the many recent successes in this area, there has been a dearth of studies on reactants carrying third-row or heavier atom substituents.[1] Given the importance of heteroatoms, especially sulfur and phosphorus, in asymmetric synthesis, we have examined the HO-direct hydrogenation of simple vinyl sulfoxides and sulfones.

The reaction of MeCHO with phenyl vinyl sulfone in the presence of a catalytic quantity of 1,4-diazabicyclo[2.2.2]octane DABCO gives the Baylis–Hillman analogous product **1a** previously described.[2] The reaction is fast and high-yielding under high-pressure conditions, despite a recent cautionary comment.[3] A number of aliphatic and aromatic analogues have been synthesised in this way. Homogeneous hydrogenation of the α-(hydroxyalkyl)vinyl sulfones with Rh catalyst (**A**)

Table 1 Hydrogenation of unsaturated sulfones and sulfoxides. Catalyst is complex **A** (0.5–2 mol%) at 25 °C, initial pressure H_2 1–1.5 × 10^3 mbar, 0.1–0.2 mol dm^{-3} reactant. All reactants and products are racemates.

Reactant	Product	Initial rate[a] mol l^{-1} s^{-1} × 10^6	Diastereoisomer excess[b] (d.e., %)
 **1a**	 **2a**	75[c]	99[c] 99.7[d]
 **1b**	 **2b**	65[c]	99.5[c] 99.7[d]
 (*R**,*S**)-**3a**	 (*S**,*S**,*S**)-**4a**	1[c]	95[c] 99[e]
 (*R**,*R**)-**3a**	 (*S**,*S**,*R**)-**4a**	10[c]	60[c] 98[e]
 (*R**,*S**)-**3b**	 (*S**,*S**,*S**)-**4b**	2[c]	85[c] 99[d,f]
 (*R**,*R**)-**3b**	 (*S**,*S**,*R**)-**4b**	15[c] 13[e]	81[c] 97[d]
 **5a**	 **6a**	50[c] 90[e]	96[c] 99.5[e]
 **5b**	 **6b**	Fast	86[c] 93[e]
 **7**	No reaction		

[a] Initial rates are normalised to 1 atm, 1 mol% catalyst, 0.1 mol dm^{-3} reactant. [b] Diastereoisomer excesses measured from ^{1}H NMR, 500 MHz, integrating the minor isomer (Me) *vs.* ^{13}C satellite peak of the major isomer for cases of high d.e. [c] MeOH. [d] CH_2Cl_2. [e] $ClCH_2CH_2Cl$. [f] Corrected for the presence of 10% of its diastereoisomer.

proceeded rapidly and quantitatively according to the conditions of Table 1, and it was shown that the *threo*-(*R**,*R**) isomer of phenyl 3-hydroxy-2-butyl sulfone **2a** accounted for 99.5% of the reduced product by NMR comparison.[4] The related vinyl sulfone **1b** as similarly hydrogenated with high *anti*-diastereoselectivity under ambient conditions in MeOH, even greater stereoselection being achieved in the non-coordinating solvents CH_2Cl_2 or $ClCH_2CH_2Cl$. Support for this preference is derived from MMX molecular mechanics calculations, as shown in Fig. 1(*a*), analogous to the directed hydrogenation of α-chiral acrylates.[5] The preferred conformation about the vinyl sulfone moiety is derived from X-ray data. In crystal structures of vinyl sulfones lacking a (*Z*)-β-substituent, one S–O bond is *syn*-coplanar with the alkene.[6] The close relationship observed between the directed hydrogenation of acrylates and vinyl sulfones further encouraged us to attempt kinetic resolution of the racemic reactant **1b** using (*S*,*S*)-dipampRh$^+$ (**B**) {dipamp = (1,2-bis[(2-methoxyphenyl)phenylphosphino]ethane} in the manner previously described.[5] This proved successful, and *S*-**1b** was recovered in 76% enantiometric excess (e.e.) at 50% reaction and 89% e.e. at 57% reaction, corresponding to a selectivity factor *S* of *ca.* 17 in favour of reduction of the (*R*)-enantiomer. The enantiomeric purity was established both by ^{31}P NMR using the Pt(diop)ethene {diop = *trans*-3,4-bis[(diphenylphosphino)methyl]-2,2-dimethyl-1,3-dioxolane} method[7] and by ^{1}H NMR chiral shift experiments [Eu(hfc)$_3$], where hfc = tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedione.

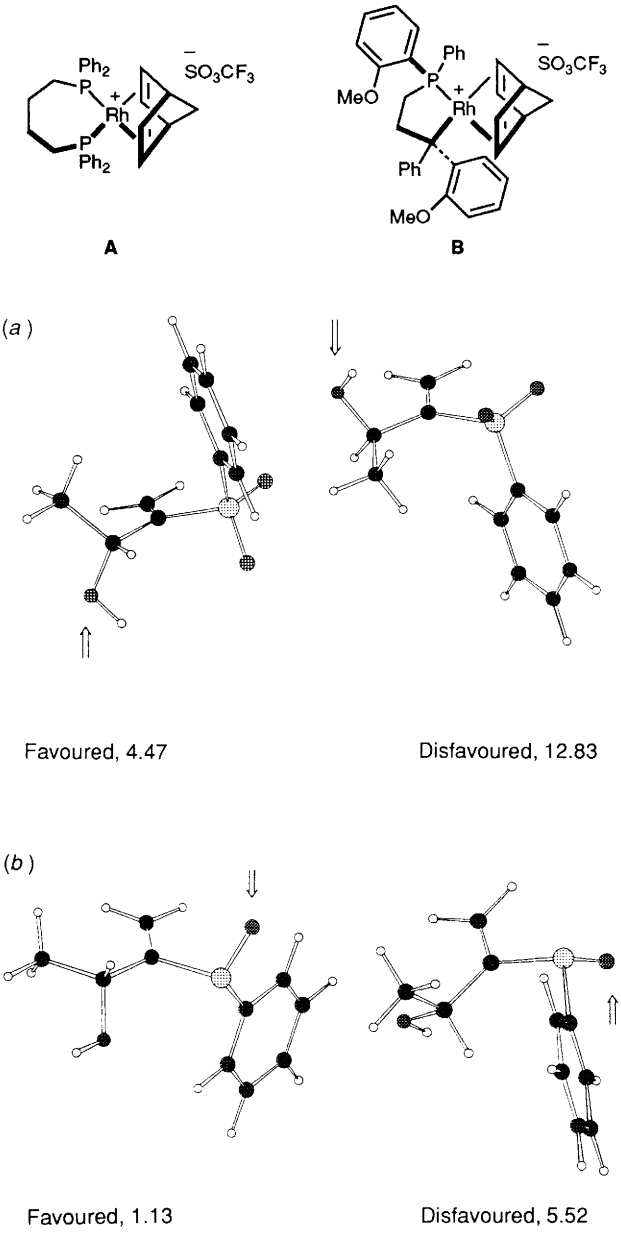


Fig. 1 Lowest energy conformations for directed hydrogenation of sulfone **1a** (*a*) and sulfoxide **3a** (*b*), derived from MMX calculations. The direction of coordination is indicated by arrows. In the first case, the torsion angle C=C···C–O(H) is fixed at +60 or −60° and C=C···S=O fixed at 0° before minimisation and in the second case the torsion angle C=C···S=O is fixed at +60 or −60° before minimisation. Values of energy in kJ mol^{-1} relative to the global minimum energy conformer (ignoring H-bonding) are recorded.

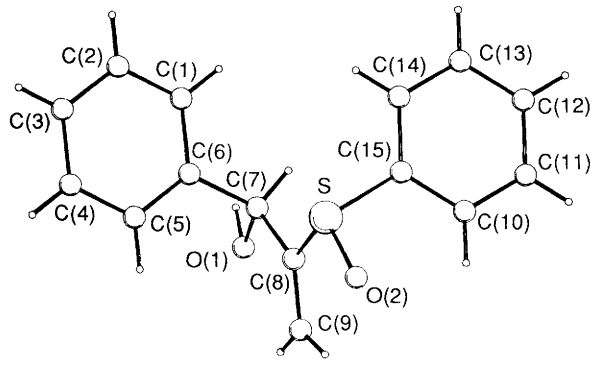


Fig. 2 X-Ray crystal structure of compound (*R**,*R**) **2b** Recrystallised from Et_2O, −20 °C. $C_{15}H_{14}O_2S$, M = 258.34, orthorhombic, *Pcab*, a = 7.266(1), b = 12.200(1), c = 29.593(6) Å, V = 2623.33 Å^3, Z = 8, D_c = 1.31 g cm^3, Mo-Kα radiation, λ = 0.71069 Å, μ(Mo-Kα) = 2.26 cm^{-1}, T = 293 K, R = 0.055 for 2029 unique observed reflections $F_o > 4\sigma F_o$. Selected bond lengths (Å) and torsion angles (°): C(8)–S 1.793(4), C(15)–S 1.767(3), S–O2 1.490(3); C(9)–C(8)–S–O(2) 1.23, O(1)–C(7)–C(8)–C(9) −11.12.

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

The configuration of **1b** follows from the precedent of all other dipampRh$^+$ reductions of electrophilic alkenes.

Since vinyl sulfoxides are poorer Michael acceptors than vinyl sulfones, the formation of **3b** by Baylis–Hillman reaction as above required more forcing conditions [PhS(O)CH=CH_2, PhCHO, 5 mol% DABCO, 19 kbar, 48 h] but satisfactory yields were obtained, as a 50 : 50 mixture of diastereoisomers. Alternatively, **3a** was synthesised as a 60 : 40 mixture by lithiation of phenyl vinyl sulfide[8] and subsequent reaction with MeCHO at −78 to −35 °C. Whilst the diastereoisomeric mixture could be separated by fractional crystallisation, it proved more effective to prepare pure samples of (*R**,*R**) **3a** and (*R**,*S**) **3a**, or the corresponding diastereoisomers from **3b**, by preparative HPLC (Lichrosorb Diol, 90 : 10 heptane–EtOH). The relative configuration was established in the former case by X-ray analysis of the (*R**,*R**) isomer (Fig. 2). As previously observed for vinyl sulfoxides lacking steric constraints,[9] the C=C and S–O are *syn*-coplanar; in the present case the C–O bond of the alcohol also approximates to coplanarity with the double bond. The configurations of the diastereoisomers of **3a** then followed by NMR comparison with the diastereoisomers of **3b**.

Diastereoisomerically pure (*R**,*S**) **3a** hydrogenated more slowly than did the sulfones in MeOH but reacted to completion and 95% of a single diastereoisomer of the reduced product **4a** was isolated. This was oxidised (aq. perborate, AcOH[10]) to the *threo*-sulfone **2a** so that the stereochemistry of hydrogenation was that expected if OH-direction had predominated. When the (*R**,*R**) isomer of **3a** was subjected to the same conditions, reaction was faster and again a single diastereoisomer predominated (80%; 96% overall yield). Oxidation as before produced the *erythro*-isomer of sulfone **2a**, indicating that the *opposite* stereochemistry prevailed in this case. Similar results were obtained in $ClCH_2CH_2Cl$ or CH_2Cl_2 as solvent but in each case the stereoselectivity was higher (Table 1). Consistent results were obtained with the (*R**,*R**)- and (*R**,*S**)-sulfoxides **3b**, but greater stereoselectivity was observed. These results indicate that the reaction course is controlled by the configuration at sulfur rather than at the hydroxy carbon; the results can be explained by the MMX-derived model shown in Fig. 1(*b*) in which S–O functions as the directing group. This implies that the sulfoxide must rotate away from its preferred configuration in order to permit lone-pair coordination to rhodium. The observed predominance of one diastereoisomer is as expected if non-bonded interactions are minimised in the chelate-coordinated reactant.

Further experiments were carried out to determine the generality of sulfoxide-directed hydrogenation. Compound **5a** [$CH_2C(Ph)MgBr$, PhS(O)OMe, Et_2O, −78 °C][11] hydrogenated rapidly and cleanly in $ClCH_2CH_2Cl$ or MeOH to give 97 and 99.5%, respectively of the (*R**,*R**) *anti*-isomer **6a** assigned by literature comparison of its NMR spectrum.[12] The alkyl sulfoxide **5b**[13] likewise gave 96% of the related known compound **6b**.[14] The directing power of sulfoxides may be limited to vinylic examples, for compound **7** in which the S–O and double bond are in an allylic relationship failed to reduce under our standard conditions.

In summary, both the vinyl sulfoxides and vinyl sulfones exemplified here are suitable reactants for directed hydrogenation. In the former case, the S–O group exerts strong stereochemical control by binding to rhodium in preference to an allylic-OH, and provides a synthetically useful general addition to existing directing groups.[15] A full treatment of the kinetics and mechanism will be presented in a separate full paper.

We thank the SERC and Glaxo Group Research for a CASE award (to D. W. P.) and Dr Roger Newton for his help and support. Johnson-Matthey kindly provided a loan of precious metal salts.

Received, 30th December 1991; Com 1/06483E

References

1 *E.g.*, U. Schollkopf, I. Hoppe and A. Thiele, *Liebigs Ann. Chem.*, 1985, 555; M. Lautens, C. M. Crudden and C. H. Zhang, *Abstr.* B28, *IUPAC Organometallics in Organic Synthesis 6*, Utrecht, 1991.
2 P. Auvray, P. Knochel and J. F. Normant, *Tetrahedron Lett.*, 1986, **27**, 5095; P. Auvray, P. Knochel and J. F. Normant, *Tetrahedron*, 1988, **44**, 6095.
3 A. Weichert and H. M. R. Hoffmann, *J. Org. Chem.*, 1991, **56**, 4098.
4 M. Julia, M. Launay, J.-P. Stacino and J.-N. Verpeaux, *Tetrahedron Lett.*, 1982, **23**, 2465.
5 J. M. Brown and I. Cutting, *J. Chem. Soc., Chem. Commun.*, 1975, 578; J. M. Brown, I. Cutting and A. P. James, *Bull. Soc. Chim. Fr.*, 1988, 211; J. M. Brown and A. P. James, *J. Chem. Soc., Chem. Commun.*, 1987, 181.
6 A. Kusa, T. N. Polynova, M. A. Porai-Koshits, Y. A. Kovach and D. Vegkh, *Zh. Strukt. Khim.*, 1979, **20**, 561; K. Inomata, T. Hirata, Y. Sasada, T. Asada, A. Senda and H. Kinoshita, *Chem. Lett.*, 1990, 2153.
7 D. Parker, *Chem. Rev.*, 1991, **91**, 1441; R. J. Taylor and D. Parker, *J. Chem. Soc., Chem. Commun.*, 1987, 1781.
8 *C.f.*, J. P. Marino, A. Viso, R. F. de la Pradilla and P. Fernandez, *J. Org. Chem.*, 1991, **56**, 1349; T. Takeda, H. Funikawa, M. Fujimori, K. Suzuki and T. Fujiwara, *Bull Chem. Soc. Jpn.*, 1984, **57**, 1863.
9 N. Tsuji, K. Nagashima, M. Kobayashi, J. Shoji, T. Kato, Y. Terui, H. Nakai and M. Shiro, *J. Antibiot.*, 1982, **35**, 24; T. Koizumi, Y. Arai, H. Takayama, K. Kuriyama and M. Shiro, *Tetrahedron Lett.*, 1987, **26**, 3689; M. R. Binns, R. K. Haynes, A. G. Katsifis, A. H. White and L. M. Englehardt, *Aust. J. Chem.*, 1987, **40**, 291.
10 A. McKillop and J. A. Tarbin, *Tetrahedron Lett.*, 1983, **24**, 1505.
11 *C.f.*, G. Solladié, *Synthesis*, 1981, 185 and references cited therein.
12 G. Modena, U. Quintily and G. Scorrano, *J. Am. Chem. Soc.*, 1972, **94**, 202.
13 R. Bell, P. D. Cottam, J. Davies and D. N. Jones, *J. Chem. Soc. Perkin Trans. 1*, 1981, 2106.
14 D. J. Cram and S. H. Pine, *J. Am. Chem. Soc.*, 1963, **85**, 1096.
15 S. D. Kahn, K. D. Dobbs and W. J. Hehre, *J. Am. Chem. Soc.*, 1988, **110**, 4602; K. Takaki, T. Maeda and M. Ishikawa, *J. Org. Chem.*, 1989, **54**, 58; S. G. Pyne, P. Bloem, S. L. Chapman, C. E. Dixon and R. Griffith, *J. Org. Chem.*, 1990, **55**, 1086; G. Solladié, F. Colobert, P. Ruiz, C. Hamdouchi, M. C. Carreno and J. L. Garcia-Ruano, *Tetrahedron Lett.*, 1991, **32**, 3635.