ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 7814–7816

www.rsc.org/chemcomm

COMMUNICATION

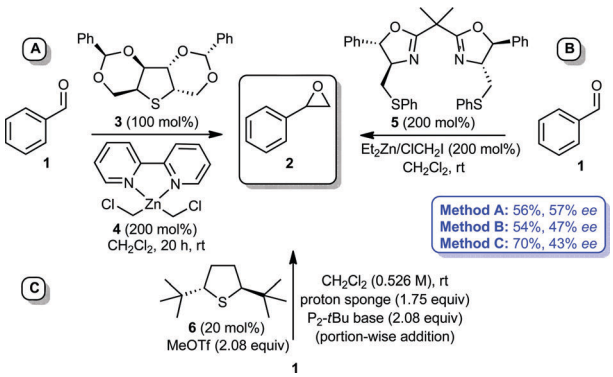
Highly enantioselective ylide-mediated synthesis of terminal epoxides†

Alessandro Piccinini, Sarah A. Kavanagh and Stephen J. Connon*

Received 22nd March 2012, Accepted 25th May 2012
DOI: 10.1039/c2cc32101g

The highly efficient asymmetric epoxidation of aldehydes by methylene transfer is now possible using new sulfonium salts.

The importance of chiral epoxides as synthetic building blocks in asymmetric synthesis is extremely difficult to overstate. While the highly enantioselective Sharpless,[1,2] and Jacobsen-Katsuki,[3–5] protocols for the epoxidation of internal alkenes are now mature technologies of inestimable value, the conversion of terminal alkenes to enantioenriched 1-oxiranes has proven a considerably more difficult process to control.[5,6] Arguably the current method of choice (in terms of product *ee*) for the catalytic synthesis of these molecules is the Co-salen complex-catalysed kinetic resolution of racemic epoxides.[6a,7,8] While progress towards the efficient asymmetric oxidation of terminal alkenes has been made – *e.g.* Fe/Mn-porphyrin complexes,[9] chiral Ti[10] and Pt-complexes[11] and chiral dioxiranes (styrene substrates only),[12] the difficulties in preparing terminal epoxides in >90% *ee via* alkene oxidation has fostered interest in alternative protocols.[13] One methodology which holds promise is catalytic methylene transfer to aldehydes mediated by sulfonium ylides.[14] Since it is often from the aldehyde that the alkene substrate for oxidation processes is prepared, a methylene transfer reaction would represent a more direct synthesis of the product, which could potentially be performed in an operationally simple manner, in a transition metal-ion free environment. The stabilised- and semi-stabilised sulfonium ylide-mediated asymmetric epoxidation of aldehydes catalysed by chiral sulfides has proven a highly useful process for the formation of 1,2-disubstituted epoxides with excellent product diastereo- and enantioselectivity.[15,16] In an unfortunate parallel to the alkene oxidation methodologies, the corresponding sulfonium ylide-mediated aldehyde oxidation to form terminal epoxides (nearly 40 years after the first disclosed asymmetric attempt)[17] is characterised by moderate yields and low-moderate levels of product enantiomeric excess.[18–22] For instance, both benchmark methodologies (**A** and **B**, developed by Goodman[19] and Aggarwal[20] respectively, Scheme 1) for the conversion of the archetypal substrate benzaldehyde (**1**) to styrene oxide (**2**) involve the employment of (super)stoichiometric loadings of



Scheme 1 Benchmark methodologies for the asymmetric synthesis of styrene oxide (**2**) from benzaldehyde (**1**) by methylene transfer.

a chiral sulfide and a Simmons–Smith type Zn-carbenoid, and furnish the product in <60% yield and *ee*. In an attempt to develop a more atom-economic process, we have shown that the ylide can be generated *via* an alkylation and subsequent deprotonation route (**C**, Scheme 1).[23,24b] Sulfide **6** could be utilised at 20 mol% loading if the alkylating agent and base were added portion-wise, however no progress was made towards improving upon the mediocre enantioselectivity which bedevils this (otherwise) potentially very useful reaction.

With the goal of solving this problem, we reflected upon the likely causes of the low enantioselectivity. The first major difficulty - as Aggarwal[14b] has pointed out - associated with epoxidation using unstabilised ylides is irreversible betaine formation. Thus the enantioselectivity is derived from the face-selective addition of the ylide to the aldehyde alone. Our thinking behind the identification of the second problem, *i.e.* the root-cause of the poor facial selectivity which results from the use of the C_2-symmetric catalyst **6**, is outlined in Fig. 1. It is assumed that the aldehyde is likely to approach the ylide in such a way that: (a) it avoids the large catalyst substituent in the β-orientation (as drawn, Fig. 1A and B), (b) charge separation/*gauche* interactions are minimised in the transition state, and c) that the large aryl aldehydic substituent is directed into the solvent. In this scenario one can see that attack at the aldehyde *si*-face (leading to the observed (*R*)-product enantiomer, Fig. 1B) appears favourable to attack at the *re*-face (Fig. 1A) due to an unavoidable steric clash between the carbonyl group (which increases as the tetrahedral betaine geometry is approached) and the large α-catalyst substituent. This may explain why enantioselectivity is unsatisfactory: one is attempting to act upon a relatively small steric discrepancy between the aldehydic

School of Chemistry, Centre for Synthesis and Chemical Biology, Trinity Biomedical Sciences Institute, University of Dublin, Trinity College, Dublin 2, Ireland. E-mail: connons@tcd.ie; Fax: +35316712826

† Electronic supplementary information (ESI) available: Experimental procedures and characterisation data. See DOI: 10.1039/c2cc32101g

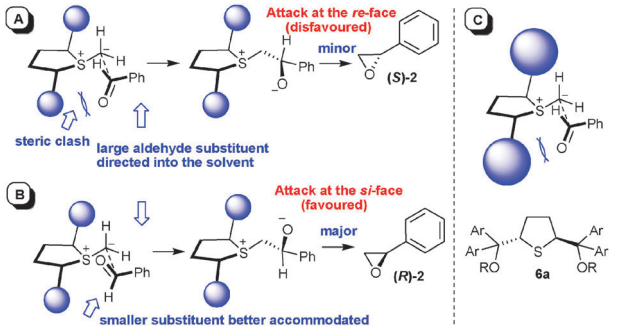
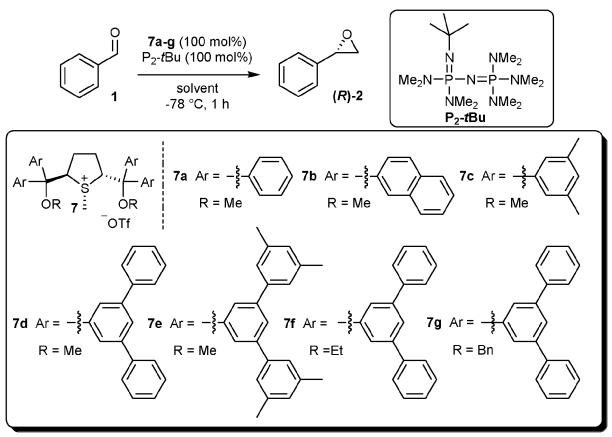


Fig. 1 Proposed stereochemical rationale and catalyst design.

C═O (Fig. 1A) and C–H bonds. The catalyst's *t*-butyl group is seemingly not of sufficient steric bulk to allow efficient discrimination between the two possible Bürgi-Dunitz trajectories. If our hypothesis is correct, the circumvention of the problem would involve the relatively straightforward matter of designing a catalyst with considerably larger substituents at C–2 and C–5, so that the steric interaction with the aldehyde carbonyl group is of sufficient magnitude to preclude attack at the *re*-face (Fig. 1C). We envisaged that sulfonium salts derived from sulfides of augmented steric bulk (*e.g.* **6a** - the size of the aryl and alkoxide substituents of which is tunable, Fig. 1) could represent a solution to the problem. Accordingly, novel sulfonium salts were prepared and evaluated in the epoxidation of **1** (Table 1). Even the salt equipped with the smallest of aryl and alkoxide substituents (*i.e.* **7a**) represented a step forwards – leading to the formation of **(S)-2** in excellent yield and 50% *ee* (entry 1). The 2-naphthyl analogue **7b** proved only marginally superior to **7a** (entry 2), with a further increase in product *ee* possible through the modification of **7a** *via* the introduction of *m*-methyl substituents (*i.e.* **7c**, entry 3). Interestingly, we also noted the mild influence of reaction concentration on enantioselectivity (entry 4). Replacement of the methyl substituents with larger phenyl moieties resulted in a significant improvement in performance (*i.e.* **7d**, 79–83% *ee*, entries 4–5), however further aggrandisement of the aryl substituents led to decreased product yields and optical purity (*i.e.* **7e**, entries 7–8).

Table 1 Preliminary catalyst evaluation



Entry	Salt	Solvent	Conc. (M)	Yield[a] (%)	*ee*[b] (%)
1	**7a**	CH_2Cl_2	0.066	89	50
2	**7b**	CH_2Cl_2	0.066	83	56
3	**7c**	CH_2Cl_2	0.066	93	57
4	**7c**	CH_2Cl_2	0.02	82	61
5	**7d**	CH_2Cl_2	0.066	92	79
6	**7d**	CH_2Cl_2	0.02	89	83
7	**7e**	CH_2Cl_2	0.066	70	62
8	**7e**	CH_2Cl_2	0.02	60	64
9	**7f**	CH_2Cl_2	0.066	93	78
10	**7f**	THF	0.02	95	95
11	**7g**	CH_2Cl_2	0.066	94	92
12	**7g**	CH_2Cl_2	0.02	92	92
13	**7g**	THF	0.02	92	92

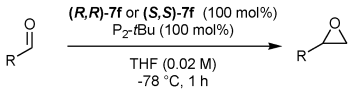
[a] Determined by ^{1}H NMR spectroscopy using styrene as an internal standard. [b] Determined by CSP-HPLC.

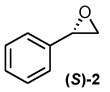
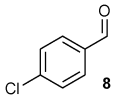
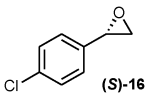
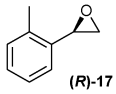
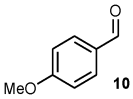
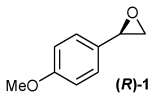
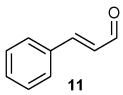
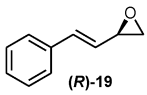
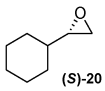
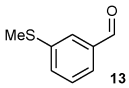
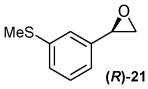
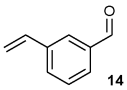
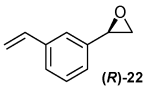
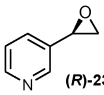
Our attention now turned to the alkoxide substituent. We had posited that in lower energy conformations the alkoxy substituent would be likely to be orientated towards the ylide carbon (and thus be capable of influencing enantioselectivity) in order to allow the larger aryl moieties to be directed into the solvent. It was found that **7f** – an ethoxy analogue of **7d** – could promote the epoxidation of **1** with good enantioselectivity in CH_2Cl_2 (entry 9), however, in THF solvent the product *ee* increased to 95% (entry 10). The corresponding benzyloxy salt **7g** mediated the formation of **(S)-2** in >90% *ee* in either the halogenated or ethereal solvent (entries 11–13), albeit with slightly lower product *ee* than was possible using **7f**. While it is possible to utilise the salt in catalytic amounts if the base and alkylating agent are added portion-wise, the S_N2 alkylation of **7f** is too slow under the relatively dilute conditions conducive to enantioselective epoxidation for this to be practicable. However, after methylene transfer the sulfide can be efficiently recovered by chromatography and re-alkylated to give **7f**. Our study now concentrated on the question of substrate scope (Table 2).

We were pleased to find that benzaldehyde (**1**), along with both activated and hindered analogues (**8** and **9** respectively) underwent methylene transfer in excellent isolated yield and enantioselectivity (entries 1–3). The relatively electron-rich *p*-anisaldehyde (**10**), enal **11** and the aliphatic aldehyde **12** were produced in good yields but with lower optical purity (72, 82 and 81% *ee* respectively, entries 4–6). It is noteworthy, that these general levels of product *ee* remain considerably higher than those hitherto obtainable using ylide-based procedures. The high potential utility of this metal-free epoxidation (and its complementarity to existing methods) is illustrated by formation of epoxides **21–23** in >90% yield and ≥90% *ee* (entries 7–9). These products bear readily oxidisable sulfide, olefin and *N*-heterocyclic functionality likely to be incompatible with epoxidation methodologies involving the use of strong oxidants.

In summary, new chiral sulfonium salts have been designed. The optimal material (**7f**) is capable of mediating highly enantioselective aldehyde epoxidation reactions involving methylene transfer – a process hitherto characterised by prohibitively low enantioselectivity. While the current process still requires 100 mol% of the salt, the sulfide generated after methylene transfer can be readily recycled in 70–75% yield after chromatography. The protocol generates terminal epoxides in good-excellent yield inside one hour *via* an operationally simple protocol. This aldehyde-based methodology has the potential to serve as a complementary technology for the enantioselective synthesis of epoxides bearing readily oxidisable sulfide-, *N*-heterocycle- and olefin-based functionality likely to be

Table 2 Evaluation of the substrate scope



Entry	Substrate	Product	Yield[a] (%)	*ee*[b] (%)
1[c]			95	95
2[c]			92	95
3[d]			89	93
4[d]			80	72
5[d]			88	82
6[c]			75	81
7[d]			94	90
8[d]			91	92
9[d,e]			92	90

[a] Isolated yields. [b] Determined by CSP-HPLC. [c] Using **(R,R)–7f**. [d] Using **(S,S)–7f**. [e] 0.015 M reaction concentration.

problematic in reactions which rely on olefin oxidation chemistry.

Financial support from Science Foundation Ireland is gratefully acknowledged. We thank Dr J. Goodman for helpful discussions.

Notes and references

1 R. M. Hanson and K. B. Sharpless, *J. Org. Chem.*, 1986, **51**, 1922.
2 R. A. Johnson and K. B. Sharpless, in *Catalytic Asymmetric Synthesis*, ed. I. Ojima, VCH, New York, 1993, p. 101.
3 W. Zhang, J. L. Loebach, S. R. Wilson and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1990, **112**, 2801.
4 R. Irie, K. Noda, Y. Ito, N. Matsumoto and T. Katsuki, *Tetrahedron Lett.*, 1990, **31**, 7345.
5 E. M. McGarrigle and D. G. Gilheany, *Chem. Rev.*, 2005, **105**, 1563.
6 (*a*) M. Palucki, P. J. Pospisil, W. Zhang and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1994, **116**, 9333; (*b*) E. N. Jacobsen and M. H. Wu, in *Comprehensive Asymmetric Catalysis*, ed. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer, New York, 1999, p. 621; (*c*) T. Katsuki, in *Comprehensive Asymmetric Catalysis*, ed. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer, New York, 1999, p. 649; (*d*) E. N. Jacobsen, *Acc. Chem. Res.*, 2000, **33**, 421.
7 (*a*) M. Tokunaga, J. F. Larrow, F. Kakiuchi and E. N. Jacobsen, *Science*, 1997, **277**, 936; (*b*) S. E. Schaus, B. D. Brandes, J. F. Larrow, M. Tokunaga, K. B. Hansen, A. E. Gould, M. E. Furrow and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2002, **124**, 1307.
8 For related methodologies see: W. Hirahata, R. M. Thomas, E. B. Lobkovsky and G. W. Coates, *J. Am. Chem. Soc.*, 2008, **130**, 17658.
9 (*a*) J. P. Collman, Z. Wang, A. Straumanis, M. Quelquejeu and E. Rose, *J. Am. Chem. Soc.*, 1999, **121**, 460; (*b*) E. Rose, B. Andrioletti, S. Zrig and M. Quelquejeu-Ethève, *Chem. Soc. Rev.*, 2005, **34**, 573.
10 (*a*) K. Matsumoto, Y. Sawada, B. Saito, K. Sakai and T. Katsuki, *Angew. Chem., Int. Ed.*, 2005, **44**, 4935; (*b*) Y. Sawada, K. Matsumoto and T. Katsuki, *Angew. Chem., Int. Ed.*, 2007, **46**, 4559.
11 M. Colladon, A. Scarso, P. Sgarbossa, R. A. Michelin and G. Strukui, *J. Am. Chem. Soc.*, 2006, **128**, 14006.
12 (*a*) M. Hickey, D. Goeddel, Z. Crane and Y. Shi, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5794; For biocatalytic methods see: (*b*) K. Furuhashi, *Biological Routes to Optically Active Epoxides*, Wiley, New York, 1992, p. 167.
13 Representative examples: (*a*) M. Amatore, T. D. Beeson, S. P. Brown and D. W. MacMillan, *Angew. Chem., Int. Ed.*, 2009, **48**, 5121; (*b*) M. Marigo, T. B. Poulsen, W. Zhang and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2004, **126**, 4790.
14 Reviews: (*a*) V. K. Aggarwal and C. L. Winn, *Acc. Chem. Res.*, 2004, **37**, 611; (*b*) E. M. McGarrigle, E. L. Myers, O. Illa, M. A. Shaw, S. L. Riches and V. K. Aggarwal, *Chem. Rev.*, 2007, **107**, 5841.
15 Representative examples: (*a*) N. Furukawa, Y. Sugihara and H. Fujihara, *J. Org. Chem.*, 1989, **54**, 4222; (*b*) V. K. Aggarwal, H. Abdel-Rahman, R. V. H. Jones, H. Y. Lee and B. D. Reid, *J. Am. Chem. Soc.*, 1994, **116**, 5973; (*c*) V. K. Aggarwal, J. G. Ford, A. Thompson, R. V. H. Jones and M. C. H. Standen, *J. Am. Chem. Soc.*, 1996, **118**, 7004; (*d*) J. Zanardi, C. Leriverend, D. Aubert, K. Julienne and P. Metzner, *J. Org. Chem.*, 2001, **66**, 5620; (*e*) C. L. Winn, B. R. Bellenie and J. M. Goodman, *Tetrahedron Lett.*, 2002, **43**, 5427; (*f*) V. K. Aggarwal, E. Alonso, I. Bae, G. Hynd, K. M. Lydon, M. J. Palmer, M. Patel, M. Porcelloni, J. Richardson, R. A. Stenson, J. R. Studley, J. L. Vasse and C. L. Winn, *J. Am. Chem. Soc.*, 2003, **125**, 10926; (*g*) M. Davoust, J. F. Brière, P. A. Jaffrès and P. Metzner, *J. Org. Chem.*, 2005, **70**, 4166; (*h*) X. –M. Deng, P. Cai, S. Ye, X. –L. Sun, W. –W. Liao, K. Li, Y. Tang, Y. –D. Wu and L.-X. Dai, *J. Am. Chem. Soc.*, 2006, **128**, 9730; (*i*) J. Bi and V. K. Aggarwal, *Chem. Commun.*, 2008, 120.
16 Shibasaki *et al.* found that chiral La-complexes can catalyse the enantioselective epoxidation of ketones with superstoichiometric sulfoxonium methylide: T. Sone, A. Yamaguchi, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, 2008, **130**, 10078.
17 B. M. Trost and R. F. Hammen, *J. Am. Chem. Soc.*, 1973, **95**, 962.
18 L. Breau and T. Durst, *Tetrahedron: Asymmetry*, 1991, **2**, 367.
19 B. R. Bellenie and J. M. Goodman, *Chem. Commun.*, 2004, 1076.
20 (*a*) V. K. Aggarwal, A. Ali and M. P. Coogan, *J. Org. Chem.*, 1997, **62**, 8628; (*b*) V. K. Aggarwal, M. P. Coogan, R. A. Stenson, R. V. H. Jones, R. Fieldhouse and J. Blacker, *Eur. J. Org. Chem.*, 2002, 319.
21 Early claims involving the use of chiral phase-transfer catalysts (ref. 21a,b) were later shown (ref. 21c) to be in error: (*a*) T. Hiyama, T. Mishima, H. Sawada and H. Nozaki, *J. Am. Chem. Soc.*, 1975, **97**, 1626; (*b*) Y. Zhang and W. Wu, *Tetrahedron: Asymmetry*, 1997, **8**, 2723; (*c*) S. A. Kavanagh and S. J. Connon, *Tetrahedron: Asymmetry*, 2008, **19**, 1414.
22 Aminosulfoxonium and sulfimide ylide precursors: (*a*) S. S. Taj, A. C. Shah, D. Lee, G. Newton and R. Soman, *Tetrahedron: Asymmetry*, 1995, **6**, 1731; (*b*) C. P. Baird and P. C. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3399.
23 A. Piccinini, S. A. Kavanagh, P. B. Connon and S. J. Connon, *Org. Lett.*, 2010, **12**, 608.
24 Related work: (*a*) S. A. Kavanagh, A. Piccinini, E. M. Fleming and S. J. Connon, *Org. Biomol. Chem.*, 2008, **6**, 1339; (*b*) S. A. Kavanagh, A. Piccinini and S. J. Connon, *Adv. Synth. Catal.*, 2010, **352**, 2089.

