

# Asymmetric epoxidation *via* phase-transfer catalysis: direct conversion of allylic alcohols into $\alpha,\beta$ -epoxyketones

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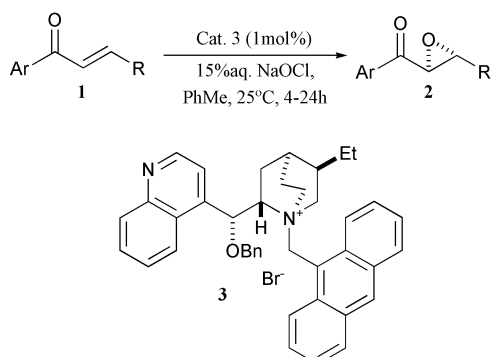
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Studies into the use of a chiral phase-transfer catalyst in conjunction with sodium hypochlorite to effect the enantioselective formation of  $\alpha,\beta$ -epoxyketones from allylic alcohols are described.

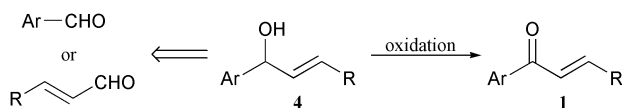
Chiral  $\alpha,\beta$ -epoxyketones of type **2** are versatile synthetic intermediates<sup>1</sup> and consequently there is considerable interest in the development of asymmetric processes that provide clean and efficient access to these materials.<sup>2–4</sup> We have examined the utility of asymmetric phase-transfer catalysts in this context<sup>3</sup> and have recently demonstrated that the Cinchona alkaloid derived catalyst **3** is a highly effective additive in the NaOCl epoxidation of enones **1** (Scheme 1). The resulting chemistry is straightforward to perform, has minimal environmental impact (the solvent and catalyst are readily recycled), and provides the target  $\alpha,\beta$ -epoxyketones **2** with high levels of enantiomeric excess. In order to further enhance the utility of this chemistry, we have been investigating whether it is possible to effect additional transformations under the same reaction conditions.



Scheme 1

During the course of our earlier studies the enone substrates **1** were prepared either *via* aldol condensation, Wittig reaction, or by carbanion addition to an appropriate aldehyde. This latter approach is often utilised as a means of accessing enones that are not readily prepared *via* aldol condensation,<sup>5,6</sup> but suffers from the requirement for an additional oxidation step to convert intermediate **4** into the target enone **1** (Scheme 2). Clearly this approach would be substantially improved if the two sequential oxidation processes could be effected under the same reaction conditions.

With this in mind we have been investigating whether it is possible to convert the allylic alcohol intermediate **4** directly to the  $\alpha,\beta$ -epoxyketone **2** utilising asymmetric phase-transfer catalysis. We considered that this ought to be possible, as it is known that secondary alcohols can be oxidised to ketones using sodium hypochlorite in conjunction with a phase-transfer



Scheme 2

catalyst.<sup>8</sup> Unfortunately the optimal conditions reported for this transformation require the use of ethyl acetate as solvent and we have previously established that the presence of this solvent severely degrades selectivity in the asymmetric epoxidation.<sup>3</sup> Hence for this approach to be successful it was necessary to establish alternative conditions that would allow both transformations to proceed smoothly.

Fortunately preliminary experiments indicated that it was possible to convert allylic alcohols of type **4** directly to  $\alpha,\beta$ -epoxyketones **2** utilising our normal epoxidation conditions (0.17 M substrate in PhMe,  $R_4NBr$ , 15% aq. NaOCl, RT).<sup>3</sup> Consequently we selected allylic alcohol **4a** as a test substrate and using chiral phase-transfer catalyst **3**, examined the effect of varying the catalyst loading (Fig. 1).

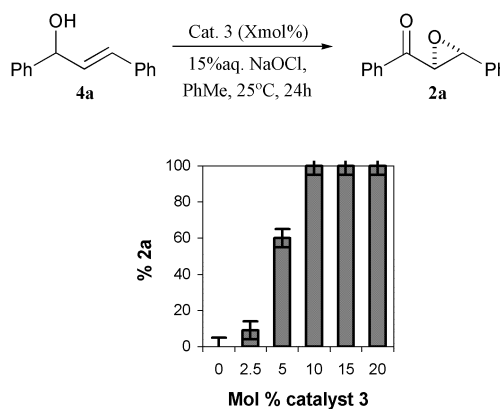
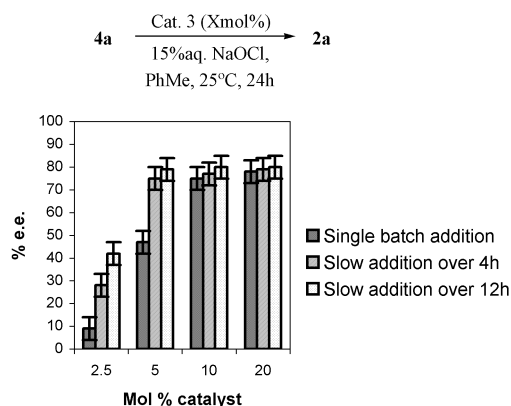


Fig. 1 Effect of catalyst loading on reaction progress.

This study indicated that, under the conditions investigated, at least 10 mol% catalyst was required in order to obtain complete conversion of the substrate **4a** to chalcone oxide **2a** within 24 h. With 2.5–5 mol% catalyst, the substrate **4a** had been completely consumed, but significant amounts of the intermediate chalcone **1a** remained. No reaction was observed in the absence of catalyst.

The enantiomeric excess of the product **2a** was also found to vary (Fig. 2), with high enantiomeric excesses only being obtained with  $\geq 10$  mol% catalyst. By monitoring the level of enantioselectivity over time we were able to establish that the reaction initially proceeded with poor enantioselectivity ( $< 60\%$  ee) and that this increased significantly once all the initial allylic alcohol **4a** had been consumed. We had previously observed that polar additives reduced the enantioselectivity of the asymmetric epoxidation,<sup>3c</sup> so it appeared likely that the high concentration of the starting alcohol during the early stages of the process may be responsible for this effect. In order to test this we limited the concentration of alcohol *via* slow addition of the substrate **4a** to the reaction system (Fig. 2). This led to a substantial improvement in enantioselectivity at lower catalyst loadings. Intriguingly it also resulted in an increased rate of reaction with 100% conversion was now possible within 24 h using 5 mol% catalyst.

To test the generality of these observations we examined a range of allylic alcohol substrates (Table 1). It was found that all



**Fig. 2** Effect of catalyst loading and rate of substrate addition on enantioselectivity.

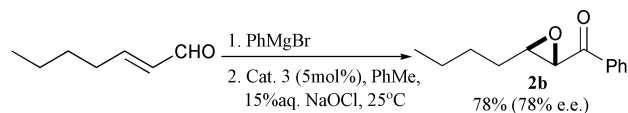
**Table 1** Enantioselective oxidation of a range of allylic alcohols **4<sup>a</sup>**

Ar	R	Time <sup>b</sup> /h	Ee of <b>2<sup>c</sup></b> (%)
		20	84
		15	86
		12	87
		15	86
		18	78
		18	82
		20	80

<sup>a</sup> Substrate **4** (0.25 mmol) in toluene (1 ml) was added dropwise over 4 h to a rapidly stirred mixture of quaternary ammonium salt **3** (0.013 mmol), toluene (0.5 ml), and 15% aqueous sodium hypochlorite (1.0 mmol) at room temperature. The resulting mixture was then stirred for the time specified.  
<sup>b</sup> Time to 100% conversion to epoxide **2**, in all cases the yield of epoxide was > 90% (by <sup>1</sup>H NMR). <sup>c</sup> ee's determined to ±3% by HPLC (Chiralpak AD).

reactions proceeded to completion within 24 h, and in all cases high levels of enantioselectivity were obtained.

In order to demonstrate the utility of this chemistry we examined its application in the synthesis of  $\alpha,\beta$ -epoxyketone **2b** (Scheme 3). The enantioselective synthesis of this material utilising Sharpless asymmetric epoxidation methodology has recently been reported<sup>5</sup> and so this provided an opportunity to compare the effectiveness of these two approaches towards targets of this type. We found that reaction of *E*-hept-2-enal with phenylmagnesium bromide,<sup>9</sup> followed by asymmetric PTC



**Scheme 3**

oxidation of the resulting crude allylic alcohol gave the enone **2b** in good overall yield.

The enantioselectivity observed was comparable with that obtained in the previous synthesis,<sup>5</sup> suggesting that, at least for substrates of this type, asymmetric PTC oxidation is competitive with Sharpless epoxidation chemistry.

In conclusion, we have demonstrated that it is possible to obtain  $\alpha,\beta$ -epoxyketones in high enantiomeric excess *via* direct oxidation of allylic alcohols using asymmetric phase-transfer catalysis. The operational simplicity of this chemistry should make it a valuable alternative to existing methodology.

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## Notes and references

- See, for example: W. P. Chen and S. M. Roberts, *Chem. Commun.*, 1999, 103; N. W. Cappi, W-P. Chen, R. W. Flood, Y-W. Liao, S. M. Roberts, J. Skidmore, J. A. Smith and N. M. Williamson, *Chem. Commun.*, 1998, 1159; B. M. Adger, J. V. Barkley, S. Bergeron, M. W. Cappi, B. E. Flowerdew, M. P. Jackson, R. McCague, T. C. Nugent and S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1997, 3501.
- For a review on the asymmetric epoxidation of electron-deficient alkenes, see: M. J. Porter and J. Skidmore, *Chem. Commun.*, 2000, 1215.
- For selected recent publications relating to the use of quaternary ammonium PTC in the asymmetric epoxidation of enones, see: W. Adam, P. B. Rao, H. G. Degen, A. Levai, T. Patonay and C. R. Saha-Moller, *J. Org. Chem.*, 2002, **67**, 259; S. Arai, H. Tsuge, M. Oku, M. Miura and T. Shioiri, *Tetrahedron*, 2002, **58**, 1623; B. Lygo and D. C. M. To, *Tetrahedron Lett.*, 2001, **42**, 1343; E. J. Corey and F-Y. Zhang, *Org. Lett.*, 1999, **1**, 1287; B. Lygo and P. G. Wainwright, *Tetrahedron*, 1999, **55**, 6289; S. Arai, H. Tsuge and T. Shioiri, *Tetrahedron Lett.*, 1998, **39**, 7563; G. Macdonald, L. Alcaraz, N. J. Lewis and R. K. Taylor, *Tetrahedron Lett.*, 1998, **39**, 5433; B. Lygo and P. G. Wainwright, *Tetrahedron Lett.*, 1998, **39**, 1599.
- For examples of other recent publications relating to the asymmetric epoxidation of enones, see: W. Adam, P. B. Rao, H. G. Degen and C. R. Saha-Moller, *Eur. J. Org. Chem.*, 2002, 630; O. Jacques, S. J. Richards and R. W. F. Jackson, *Chem. Commun.*, 2001, 2712; P. E. Coffey, K. H. Drauz, S. M. Roberts, J. Skidmore and J. A. Smith, *Chem. Commun.*, 2001, 2330; P. A. Bentley, R. W. Flood, S. M. Roberts, J. Skidmore, C. B. Smith and J. A. Smith, *Chem. Commun.*, 2001, 1616; T. Nemoto, T. Ohshima, K. Yamaguchi and M. Shibasaki, *J. Am. Chem. Soc.*, 2001, **123**, 2725; R. F. Chen, C. T. Qian and J. G. de Vries, *Tetrahedron*, 2001, **57**, 9837; C. L. Dwyer, C. D. Gill, O. Ichihara and R. J. K. Taylor, *Synlett*, 2000, 704.
- C. Hardouin, F. Chevallier, B. Rousseau and E. Doris, *J. Org. Chem.*, 2001, **66**, 1046.
- For reports that illustrate variations of this approach, see: C. D. Brown, J. M. Chong and L. Shen, *Tetrahedron*, 1999, **55**, 14233; D. Soulez, G. Ple, L. Duhamel and P. Duhamel, *J. Chem. Soc., Chem. Commun.*, 1995, 563; S. M. Graham and G. D. Prestwich, *J. Org. Chem.*, 1994, **59**, 2956; M. Miyashita, M. Hoshino and A. Yoshikoshi, *Chem. Lett.*, 1990, 791; R. G. Harvey, J. T. Hahn, M. Bukowska and H. Jackson, *J. Org. Chem.*, 1990, **55**, 6161.
- For an alternative method for the direct oxidation of allylic alcohols to racemic  $\alpha,\beta$ -epoxyketones, see: K. Takai, K. Oshima and H. Nozaki, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 3791.
- G. A. Mirafzal and A. M. Lozeva, *Tetrahedron Lett.*, 1998, **39**, 7263; J-S. Do and T-C. Chou, *Ind. Eng. Chem.*, 1990, **29**, 1095; G. A. Lee and H. H. Freedman, *Isr. J. Chem.*, 1985, **26**, 229.
- J. Furukawa, S. Iwasaki and S. Okuda, *Tetrahedron Lett.*, 1983, **24**, 52.