Enantiopure epoxidation of electrophilic alkenes

Otto Meth-Cohn,*[a] David J. Williams[b] and Yi Chen[a]

[a] *Chemistry Department, University of Sunderland, Sunderland, UK SR1 3SD. E-mail: otto.meth-cohn@sunderland.ac.uk*

[b] *Chemistry Department, Imperial College of Science, Technology and Medicine, London, UK SW7 2AY*

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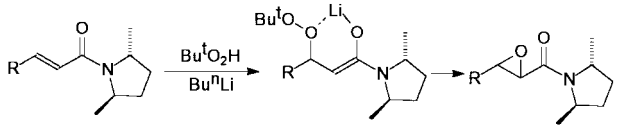
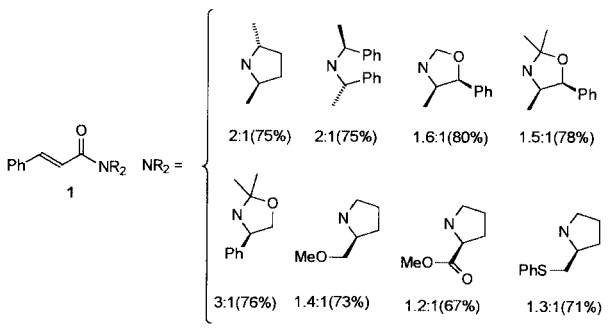
Cinnamamides derived from prolinols (*e.g.* –CH_2OH and –CPh_2OH) and from proline amides (*e.g.* prolineanilide) are epoxidised with total retention of the alkene configuration, to give either epoxides or bicyclic derivatives thereof, essentially enantiopure, using *tert*-butyl hydroperoxide and butyllithium.

Recently we disclosed[1] that our general method for the stereocontrolled epoxidation of electrophilic alkenes using lithium *tert*-butylhydroperoxide[2] was capable of homochiral application using α,β-unsaturated amides derived from homochiral secondary amines (Scheme 1). However, the method produced two diastereomers, albeit easily separable, that could then be further converted into, for example, α,β-unsaturated ketones with organolithium derivatives. It would be much more elegant and extremely useful synthetically, if the epoxidation could be conducted to give solely one or other enantiopure diastereomer in a predictable manner. This would be especially worthwhile if the chiral auxiliary were cheap, easily available as both enantiomers and was recyclable. We herein present our recent endeavours to achieve these goals.

The first requirement in this search was to understand the basis of the diastereomeric selection that operates in this reaction. On the basis of a very large body of work by ourselves and numerous others, the reaction proceeds with total retention of the alkene configuration of the epoxide. We have already proposed[2] that this stereocontrol of the epoxidation derives from the potent 'lithium bonding' which ensures a chelate control of the epoxidation process (Scheme 1). For diastereocontrol of the process, a mechanism whereby a similar fixation of the geometry of the transition state is required. In order to achieve optimum diastereoselection we examined a series of homochiral secondary amines from which were made cinnamamides **1** (Scheme 2). These alkenes proved universally disappointing, giving diastereomeric ratios between 1.2 : 1 and 3 : 1 (Scheme 2). Clearly, the usual steric or geometric factors alone were not sufficient to generate a high diastereomeric excess (de).

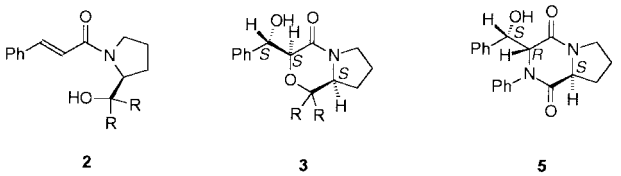


Scheme 1



Scheme 2 Diastereomeric ratios and yields from epoxidation of homochiral cinnamamides.

We next examined the (*S*)-prolinol-derived cinnamamides **2**. These compounds reacted very rapidly and generated essentially enantiopure products in reasonable yield. However, the products were not the expected epoxides but the pyrrolidinooxazinones **3**. The structures were confirmed both by spectroscopy and by X-ray crystallography (Fig. 1)† which showed that the product had the (*S*,*S*,*S*)-configuration.



2 a, R = H; b, R = Ph

3 a; de >99:1, 65%; b, de >99:1, 61%

5

We then made a series of cinnamamides **4** based on (*S*)-proline, with the proline side-chain being varied. Using proline itself or prolinamide, epoxidation of the cinnamamide (**4**, R = H) gave complex mixtures, and thus derivatives were studied. Some remarkable variations in diastereomeric ratio were uncovered, the more surprising in that closely similar systems proved to be either highly effective or of little value (Scheme 3). In general, the de of the epoxidation increased with the steric bulk of the group R on the proline side-chain. However, spectacular ratios were observed using prolineanilide (> 99 : 1), the epoxide always being accompanied by an interesting bicyclic product. Spectroscopy and ultimately X-ray crystallography (Fig. 2)† confirmed that the product was the pyrrolidinopiperazinedione **5** but surprisingly with (*S*,*R*,*S*)-configuration.

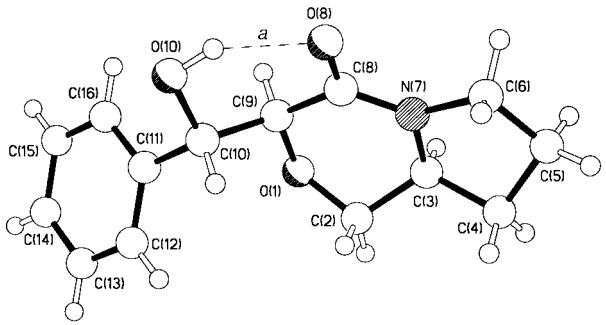
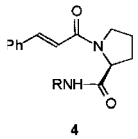


Fig. 1 The molecular structure of **3**. The hydrogen bonding geometry, (*a*) is O···O, H···O 2.66, 1.84 Å; O–H···O 149°.



4

R	Me	Pr^i	$PhCH_2$	Ph	1-adamantyl	mesityl
de	1.5:1	2.5:1	3.5:1	>99:1	5:1	5:1
Yield (%)	48	62	61	48	58	64

Scheme 3 Diastereomeric ratios and yields from epoxidation of proline-derived cinnamamides.

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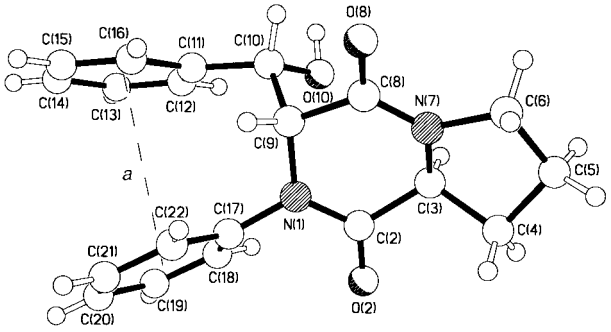
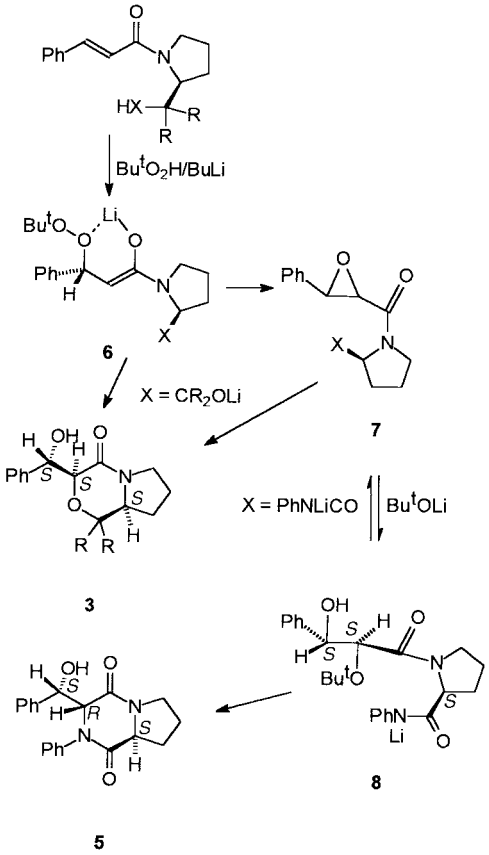


Fig. 2 The molecular structure of **5**. The ring-centroid ring-centroid separation (*a*) is 3.75 Å.



Scheme 4

Short reaction times gave primarily the epoxide (61%) while longer reaction time resulted in the sole formation of the potentially useful pyrrolidinopyrazinedione **5** (45%), both in >99% de. The related *p*-chloro-, *p*-cyano- and *p*-methoxy-anilides gave solely the bicyclic analogue of **5**, again essentially enantiopure (41–45%), while proline-*N*-methylanilide (CONMePh) gave only the corresponding epoxide **7** though with poor diastereo-discrimination (1.4:1, 68%). Both of these cyclic derivatives **3** and **5** are of considerable interest *per se*, being potential sources of novel homochiral amino acids and dihydroxy acids respectively. It should be underlined that while the *oxazine* derivative **3** shows (*S,S,S*)-stereochemistry the *piperazine* **5** is (*S,R,S*)!

A possible explanation for this stereochemical surprise is presented in Scheme 4. The prolinol-derived system **4** could arise either by direct interception of the hydroperoxide intermediate **6** *en route* to the epoxide **7** or by ring-opening of the epoxide **7**, in both cases by the pendant OLi group, both processes being highly enantioselective. The stereochemical inversion involved in the generation of the compound **5** suggests that a double inversion at the central chiral centre occurs. Thus, the *trans*-epoxide **7** is opened rapidly (and probably reversibly; this reversibility is probably a general, though degenerate process in all such epoxidations) firstly by LiOBu^t, the by-product of the epoxidation, followed by a slow attack by the considerably less nucleophilic CONPhLi side-chain. This would explain (a) the comparatively slow formation of this product compared to the oxygen analogue **3** and (b) the fact that brief reaction gives the epoxide while prolonged reaction generates the bicyclic product **5**. Treatment of the isolated epoxide **7** (X = CONHPh) with butyllithium does not yield the piperazine **5**.

As regards the remarkable diastereospecificity observed in the epoxidation of prolinol and prolineanilide derivatives (not in the case of NMePh, and other NHR derivatives of proline) we propose: (a) The preferred conformation of the cinnamamides prior to epoxidation is as shown (*e.g.* Scheme 4) to backside attack by the Bu^{t}O$_2$Li. This backside attack is further favoured by side-chain OLi or NLi 'lithium bonding' to the carbonyl oxygen. (b) As shown in the X-ray crystallographic study (Fig. 2) a π–π interaction between the two benzenoid rings of the prolinamide is favoured; this effect also tends to lock the preferred conformation for backside attack in the epoxidation, enhancing the otherwise weaker 'lithium bonding' between an NLi and the carbonyl oxygen. Presumably, this interaction is weakened by steric factors (*e.g.* as with the 2,4,6-trimethylanilide).

A fuller explanation of the specificities and mechanisms is clearly necessary and the application of these epoxidations and their the interesting downstream derivatives is under active study.

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Notes and references

† *Crystal data*: for **3**: $C_{14}H_{17}NO_3$, M = 247.3, monoclinic, space group $P2_1$ (no. 4), a = 6.269(1), b = 8.642(1), c = 12.173(2) Å, β = 104.16(2)°, V = 639.5(2) Å^3, Z = 2, D_c = 1.289 g cm^{-3}, μ(Mo-Kα) = 0.90 cm^{-1}, T = 293 K, F(000) = 264. For **5**: $C_{20}H_{20}N_2O_3$, M = 336.4, orthorhombic, space group $P2_12_12_1$ (no. 19), a = 6.271(1), b = 10.994(1), c = 24.771(5) Å, V = 1707.7(5) Å^3, Z = 4, D_c = 1.308 g cm^{-3}, μ(Cu-Kα) = 7.19 cm^{-1}, T = 293 K, F(000) = 712. For **3**, 2121 independent reflections, 2θ < 60°, were measured on a Siemens P4 diffractometer with Mo-Kα radiation, and for **5**, 1675 independent reflections, 2θ < 128°, were measured on a Siemens P4 rotating anode diffractometer with Cu-Kα radiation, using ω-scans. The structures were solved by direct methods and the non-hydrogen atoms were refined anisotropically by full-matrix least squares based on F^2 to give, for **3**, R_1 = 0.046, wR_2 = 0.117, and for **5**, R_1 = 0.066, wR_2 = 0.151, for 1674 and 1071 independent observed reflections [$|F_o| > 4\sigma(|F_o|)$], respectively. The absolute chiralities of both structures were determined by internal reference to the known centre at C(3). CCDC 182/1547. See http://www.rsc.org/suppdata/cc/b0/b000520g/ for crystallographic files in .cif format.

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2 O. Meth-Cohn, C. Moore and H. C. Taljaard, *J. Chem. Soc., Perkin Trans. 1*, 1988, 2663. For other diastereoselective epoxidation methods: see, *e.g.* S. Julia, J. Masana and J. C. Vega, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 929; S. Watanabe, T. Arai, H. Sasai, M. Bougauchi and M. Shibasaki, *J. Org. Chem.*, 1998, **63**, 8090; B. Lygo and P. G. Wainwright, *Tetrahedron Lett.*, 1998, **39**, 1599; W. P. Chen and S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1999, 103; C. L. Elston, R. F. W. Jackson, S. F. MacDonald and P. J. Murray, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 410, and references in these papers.

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