Diastereo- and enantioselective synthesis of α,β-epoxyketones using aqueous NaOCl in conjunction with dihydrocinchonidine derived phase-transfer catalysis at room temperature. Scope and limitations

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Received 30th April 2007, Accepted 18th May 2007
First published as an Advance Article on the web 13th June 2007
DOI: 10.1039/b706546a

In this paper we present studies into the scope and limitations of asymmetric PTC epoxidation of enones and the oxidation–epoxidation of allylic alcohols using aqueous NaOCl in conjunction with a dihydrocinchonidine derived quaternary ammonium salt catalyst.

Introduction

Asymmetric phase-transfer catalysis (PTC) using chiral quaternary ammonium salts has now been established as a powerful method for the generation of high value enantio-enriched synthetic intermediates.[1] This technology has proved particularly effective for the asymmetric alkylation of active methylene and methine compounds, leading to highly practical methods for the production of a wide variety of chiral intermediates including indanones,[2] α-amino acids,[3] and β-ketoesters.[4] The application of asymmetric quaternary ammonium PTC in the epoxidation of α,β-unsaturated ketones has also attracted considerable interest in recent years.[5–10] This is in part because of the simplicity of the procedures involved,[11–13] and in part because of the synthetic utility of the resulting α,β-epoxyketones.[14,15]

The utility of chiral quaternary ammonium PTCs as catalysts for the asymmetric epoxidation of α,β-unsaturated ketones was pioneered by Wynberg *et al.*,[5] who demonstrated that quinine derivative **3** was capable of promoting enantioselective Weitz–Scheffer epoxidation of chalcones **1** under liquid–liquid phase-transfer conditions (Fig. 1).

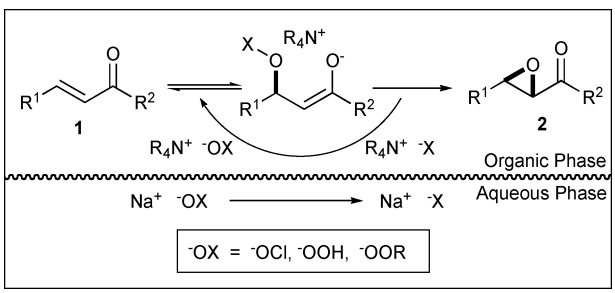

Fig. 1 Weitz–Scheffer PTC epoxidation.

This process had a number of attractive features: the procedure is extremely simple to carry out; the catalyst **3** is easily prepared (1 step) from an inexpensive, renewable, chiral starting material (quinine) and is effective at reasonably low catalyst loadings (2.5 mol%); the oxidants (NaOCl, $NaOH/H_2O_2$ or NaOH/*t*-BuOOH) are readily available and produce relatively innocuous by-products (NaCl, H_2O, or *t*-BuOH); and the two-phase reaction system allows for simple separation of products and reagents.

There were however some aspects of this procedure that limited its usefulness, most notably the modest levels of enantioselectivity obtained with simple acyclic α,β-unsaturated ketones (typically 20–50% ee).

Our own investigations in this area led to improved reaction conditions and established that substantially increased levels of enantioselectivity could be obtained by using dihydrocinchonidine and cinchonine derived quaternary ammonium salts **4** and **5** (Fig. 2).[6] These latter two catalysts are enantio-complimentary, the dihydrocinchonidine-derived salt **4** giving high selectivity for (2*S*,3*R*)-epoxide **2** and the cinchonine-derived salt **5** giving similar levels of selectivity for the (2*R*,3*S*)-isomer. In this paper we focus on reactions involving these catalysts and describe detailed studies aimed at defining their scope and limitations in the preparation of enantiomerically-enriched α,β-epoxyketones.

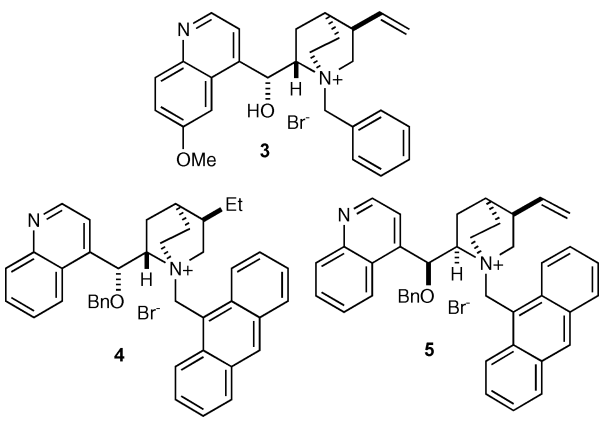

Fig. 2 Quaternary ammonium salts used as catalysts in Weitz–Scheffer PTC epoxidation.

Results and discussion

In our earlier studies we identified aqueous sodium hypochlorite as an effective oxidant for Weitz–Scheffer epoxidations involving catalyst **4**.[6c] Subsequent to this potassium hypochlorite was also shown to be highly effective when used in conjunction with lower temperatures.[7] More recently the *in situ* generation of this unstable

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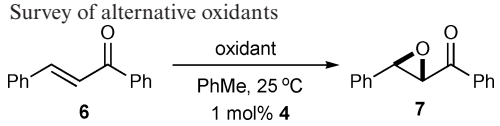
Table 1 Survey of alternative oxidants



Entry	Oxidant	Time/h	Conv. (%)	Ee (%)
1	30% aq. H_2O_2, 50% aq. KOH	48	≥95	11
2	70% aq. *t*-BuOOH, 50% aq. KOH	16	≥95	20
3	$Na_2CO_3 \cdot 1.5H_2O_2$	48	≤10	—
4	44% aq. $Na_2CO_3 \cdot 1.5H_2O_2$	48	≤10	—
5	$NaBO_3 \cdot H_2O$	48	≤10	—
6	$Ca(OCl)_2$	48	≤10	—
7	TCCA, 50% aq. KOH	15[a]	≥95	89
8	NaDCCA, 50% aq. KOH	24[a]	≥95	88
9	NDDH, 50% aq. KOH	24[a]	80	86
10	NCS, 50% aq. KOH	48[a]	20	90
11	15% aq. NaOCl	12	≥95	86
12		24[a]	≥95	89

TCCA = trichloroisocyanuric acid, NaDCCA = dichloroisocyanuric acid, NDDH = 1,3-dichloro-5,5-dimethylhydantoin; NCS = *N*-chlorosuccinimide.[a] Reaction performed at 0 °C.

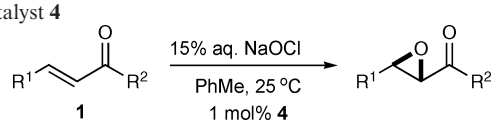
oxidant *via* reaction of trichlororisocyanuric acid (TCCA) with potassium hydroxide has also been successfully applied in this chemistry.[8]

In principle a variety of other nucleophilic oxidants could also be used. Thus, in an effort to compare the effectiveness of aqueous sodium hypochlorite with alternatives, we screened a range of commercially available reagents in the epoxidation of chalcone **6** (Table 1). Reactions involving TCCA–aq. KOH, NaDCCA–aq. KOH, NDDH–aq. KOH, NCS–aq. KOH, were all expected to generate potassium hypochlorite *in situ*[16] and so these reactions were performed at 0 °C in order to minimize decomposition of this intermediate. They all proved successful, generating epoxide **7** in high enantiomeric excess, although the reaction employing NCS gave poor levels of conversion. Interestingly, the reaction involving TCCA–KOH in conjunction with catalyst **4** (Table 1, entry 7) has previously been reported to require 5 mol% catalyst,[8] however in our hands this procedure worked equally well using 1 mol%. Reactions involving aqueous sodium hypochlorite (Table 1, entries 11–12) were similarly successful, suggesting that the metal counterion has little effect on enantioselectivity. All other oxidants investigated gave either low enantioselectivity (Table 1, entries 1, 2) or poor conversion (Table 1, entries 3–6) in this reaction.[17]

The results in Table 1 also seem to indicate that the enantioselectivity increases slightly as the reaction temperature decreases (compare entry 11 with entries 7–10, 12),[18] however, given the convenience of operating at ambient temperatures, we have focused on exploring the utility of this chemistry at room temperature. For this purpose we opted to employ the more stable oxidant, sodium hypochlorite, for all subsequent investigations.

To test the generality of these conditions we examined the epoxidation of a range of α,β-unsaturated ketones (Table 2). Almost all of the substrates examined were converted into the corresponding epoxides in high yield. The only exceptions were 4-methyl-1-phenylpent-1-en-3-one and 4-phenylbut-3-en-2-one (entries 7 and 8). Both of these enones gave low conversions under the standard reaction conditions, and the starting materials were recovered in high yield. Given that all the other substrates had non-enolizable R^2-substituents, it would seem that competing enolization is the most likely explanation for this observation. Apart from this limitation, this epoxidation appears to tolerate a wide variety of different substituents in positions R^1 and R^2. Enantioselectivities

Table 2 Enantioselective epoxidation using catalyst **4**



Entry	R^1	R^2	Product	Yield (%)[a]	Ee (%)
1	Ph	Ph	**7**	98	86(98)[b]
2		3,4-$(OCH_2O)C_6H_3$	**8**	95	92(≥99)[b]
3		4-NO_2-C_6H_4	**9**	85	86
4		4-Br-C_6H_4	**10**	93	88
5		4-F-C_6H_4	**11**	94	87(98)[b]
6		*t*-Bu	**12**	83	87
7		i-Pr	**13**	≤10	—
8		Me	**14**	≤10	—
9		2-Thienyl	**15**	97	84
10	3,4-$(OCH_2O)C_6H_3$	Ph	**16**	94	92(≥99)[b]
11	4-Br-C_6H_4	3,4-$(OCH_2O)C_6H_3$	**17**	89	91(≥99)[b]
12	*n*-$C_{13}H_{27}$	Ph	**18**	98	81(≥99)[b]
13		2-Thienyl	**19**	96	78(≥99)[b]
14		2-Furyl	**20**	96	80(≥99)[b]
15	*n*-C_6H_{13}	Ph	**21**	90	81
16		4-Br-C_6H_4	**22**	91	84
17		4-NO_2-C_6H_4	**23**	84	90
18		3,4-$(OCH_2O)C_6H_3$	**24**	77	86
19	PhCO	Ph	**25**	93	68
20	BnO_2C		**26**	76	67
21	EtO_2C	4-NO_2-C_6H_4	**27**	74	86(93)[b]
22		4-MeO-C_6H_4	**28**	97	65

[a] After purification by chromatography. [b] Ee of crude reaction product. Ee given in parentheses is that obtained after one recrystallization.

of the crude products were generally high, typically in the range 80–90% ee, although some substrates, most notably those with R^1 = carbonyl, generally gave lower enantioselectivities. In all cases the diastereoselectivity was high (≥95% de).

As the majority of these products were crystalline solids, for selected examples we investigated whether the initial enantiomeric excess could be improved by recrystallization. In all cases investigated a single recrystallization led to a significant improvement in enantiomeric excess (see Table 2, entries 1, 2, 5, 10–14, and 21), and in most cases this provided the product with ≥98% ee. Isolated yields after recrystallization were 50–80% (see Experimental for examples), suggesting that this is a highly effective means of preparing highly enantiomerically-enriched α,β-epoxyketones.

To further probe the scope of this chemistry we briefly examined other substitution patterns in the starting enone. The tri-substituted chalcones **29** and **30** (Fig. 3) did not undergo epoxidation under the standard reaction conditions, suggesting that further substitution around the alkene is not tolerated. *cis*-Chalcone **31** reacted slowly, requiring 10 mol% catalyst to go to completion, but interestingly delivered the corresponding *cis*-epoxide **32** albeit with moderate enantioselectivity (Scheme 1). High selectivity for the *cis*-epoxide diastereoisomer with enones such as *cis*-chalcone **31** is unusual for Weitz–Scheffer epoxidations as the two-step mechanism (Fig. 1) allows for bond rotation prior to ring closure. This generally results in loss of stereochemical information and results in formation of the *trans*-epoxide product.[19] It seems unlikely that this reaction is proceeding *via* an alternative (concerted) mechanism, so the diastereoselectivity observed here is probably an indication that electrostatic interactions in the intermediate ion-pair slow the rate of bond rotation relative to ring closure.

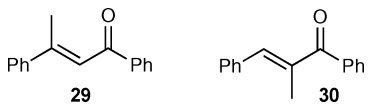
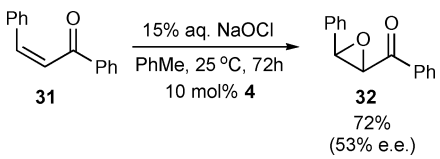


Fig. 3 Tri-substituted chalcones that did not undergo epoxidation under standard conditions.

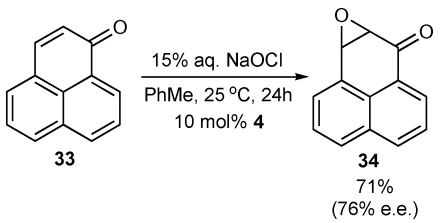


Scheme 1

To probe the effect of enone conformation in *cis*-alkenes we also briefly investigated epoxidation of perinaphthenone **33** (Scheme 2). In this case the reaction was complete within 24 h and epoxide **34** was obtained with significantly higher enantiomeric excess.

Unfortunately we have been unable to determine the absolute stereochemistry of epoxides **32** and **34**, so at this point in time it is not possible to draw any further conclusions from these experiments.

The modest enantioselectivity obtained in the epoxidation of *cis*-chalcone **31** is of limited synthetic utility, but the capacity to generate *cis*-epoxyketones with high diastereoselectivity is a potentially useful feature of this chemistry. To probe this further we investigated the PTC epoxidation of enones **35** and **38**. These particular enones are of interest as the corresponding epoxides have been shown to be useful precursors to novel carbohydrate derivatives.[20] In addition, both of these enones have previously been investigated using the Julia–Colonna–Roberts epoxidation, which employs polyleucine in conjunction with urea–hydrogen peroxide complex,[20] hence this study would allow an interesting comparison of the quaternary ammonium PTC epoxidation with this complimentary procedure.



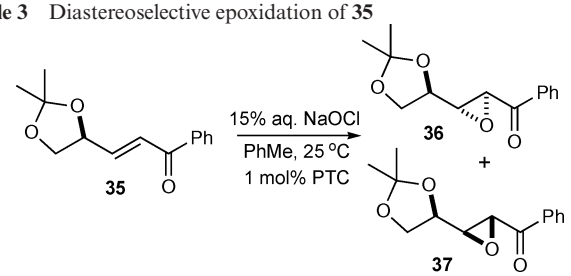
Scheme 2

It was found that when (*E*)-enone **35** was employed as the substrate, *trans*-epoxides **36** and **37** were produced in high yield (Table 3). With a simple achiral PTC (Bu_4NBr), the *anti*-isomer **36** was favoured, and this selectivity was significantly enhanced when PTC **4** was employed. With PTC **5** the diastereoselectivity was reversed, giving the *syn*-isomer **37** as the major product. In all cases we could detect no sign of the corresponding *cis*-epoxides by ^{1}H NMR.

With (*Z*)-enone **38**, the PTC conditions produced the corresponding *cis*-epoxides (**39** and **40**) in high yield. In this case Bu_4NBr also favoured the *anti*-isomer **39** and again this selectivity was significantly enhanced when PTC **4** was employed (Table 4). This time the mismatched PTC **5** also produced the *anti*-isomer **39** albeit with lower levels of diastereoselectivity. Again we could detect no sign of the corresponding *trans*-epoxides by ^{1}H NMR.

These results echo those found with (*E*)- and (*Z*)-chalcone, and confirm that the PTC conditions employed are capable of generating *cis*-epoxyketones with high diastereoselectivity. This contrasts with the Julia–Colonna–Roberts procedure which is reported to produce only *trans*-epoxides **36** and **37** from *cis*-enone **38**.

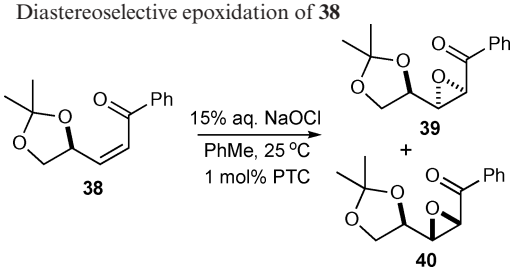
Table 3 Diastereoselective epoxidation of **35**



Catalyst	Yield (%)[a]	Ratio **36** : **37**[b]
n-Bu_4NBr	96	2 : 1
4	96	11 : 1[c]
5	97	1 : 3[c]

[a] After purification by chromatography. [b] By ^{1}H NMR spectroscopy. [c] Ratio of major diastereoisomer could be improved to ≥20 : 1 by recrystallization.

Table 4 Diastereoselective epoxidation of **38**



Catalyst	Yield (%)[a]	Ratio **39** : **40**[b]
n-Bu_4NBr	98	4 : 1
4	96	13 : 1[c]
5	97	2.5 : 1

[a] After purification by chromatography. [b] By ^1H NMR spectroscopy. [c] Ratio could be improved to ≥20 : 1 by recrystallization.

In an effort to further expand the synthetic utility of the asymmetric PTC epoxidation reaction we have also investigated the one-pot conversion of allylic alcohols into α,β-epoxyketones.[21] At the outset of this study it was known that secondary alcohols could be oxidized to the corresponding ketones using NaOCl under PTC conditions. Ethyl acetate appeared to be the optimal organic solvent for this process,[22] but we have previously observed that this solvent leads to significantly reduced enantiomeric excess when employed as the organic phase in the asymmetric PTC epoxidation of chalcone **6** using a cinchonidine-derived PTC.[6a] In order to confirm that the dihydrocinchonidine-derived PTC **4** behaves in the same way, we investigated the asymmetric PTC epoxidation of chalcone **6** in ethyl acetate. The desired epoxide **7** was obtained in high yield, but as anticipated, it had a significantly reduced enantiomeric excess (45% ee) compared to when the reaction was performed in toluene.

To probe this further, we investigated the asymmetric epoxidation of chalcone **6** with PTC **4** using a selection of other water-immiscible organic solvents of varying dielectric constant (ε) and also using two water-immiscible solvent mixtures. The results obtained clearly show that enantioselectivity decreases with increasing solvent polarity (Fig. 4 and 5).

Taken together, these results suggest that polar solvents (or polar additives) should be avoided wherever possible.

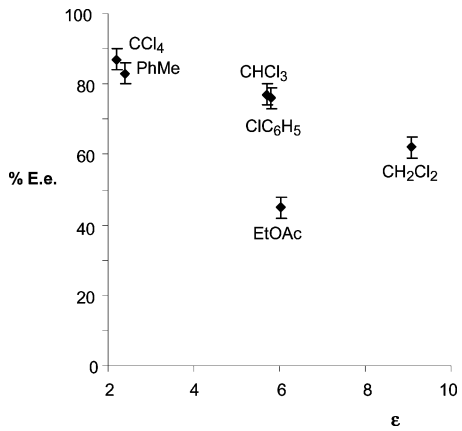


Fig. 4 Ee *vs.* dielectric constant (ε) for the epoxidation of chalcone **6** using catalyst **4**.

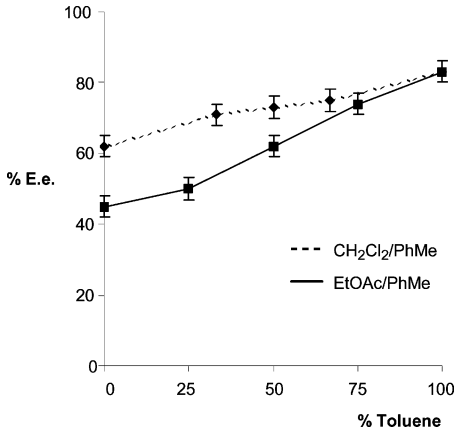
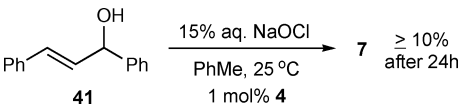


Fig. 5 Ee *vs.* solvent composition for the epoxidation of chalcone **6** using catalyst **4**.

Thus, in order to develop a one-pot conversion of allylic alcohols to enantioenriched α,β-epoxyketones it was necessary to develop conditions that employed as non-polar an organic medium as possible. To this end, we elected to investigate the use of toluene as this was expected to be a good solvent for the substrates and has already been shown to be compatible with the asymmetric epoxidation step. Initially we attempted the reaction of allylic alcohol **41** under the same conditions that had proved successful for the epoxidation of chalcone **6** (Scheme 3).



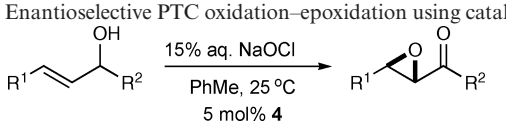
Scheme 3

Disappointingly, although we could detect formation of both chalcone **6** and epoxide **7**, overall conversions were low. By increasing the catalyst loading to 10 mol% we were able to obtain complete conversion of **41** into the desired epoxide **7**, but during the course of this study we noted that the enantiomeric excess of the product **7** changed as the reaction progressed. At low conversions (<10%), the enantiomeric excess was low; this then increased rapidly once the starting alcohol **41** had been consumed. In the direct epoxidation of chalcone **6**, the enantiomeric excess of the product **7** remains constant throughout the course of the reaction, so this suggested that high starting concentrations of the alcohol **41** might be detrimental to enantioselectivity. To probe this further we investigated varying the catalyst loading and rate of addition of the starting alcohol (Fig. 6).

This study established that simply by combining increased catalyst loading (5 mol%) with slow addition of the substrate, oxidation and epoxidation could be combined to deliver the α,β-epoxyketone **7** in enantioselectivities approaching those obtained by epoxidation of the preformed enone **6**.

This approach was then tested on a series of allylic alcohols (Table 5). The reactions all proceeded to completion, and delivered the desired α,β-epoxyketones in good overall yield. In all cases the products were produced with enantioselectivities similar to, but slightly lower than, those obtained by direct epoxidation of the corresponding enone.

Table 5 Enantioselective PTC oxidation–epoxidation using catalyst **4**



R^1	R^2	Product	Yield (%)[a]	Ee (%)[b]
Ph	Ph	**7**	66	79
	3,4-$(OCH_2O)C_6H_3$	**8**	63	87(≥99)[b]
	4-Br-C_6H_4	**9**	73	86
	4-F-C_6H_4	**11**	95	84(98)[b]
	2-Thienyl	**15**	84	82
4-Br-C_6H_4	3,4-$(OCH_2O)C_6H_3$	**17**	78	86(≥99)[b]
n-C_6H_{13}	Ph	**21**	77	80
	4-Br-C_6H_4	**22**	76	80

[a] After purification by chromatography. [b] Ee of crude reaction product. Ee given in parentheses is that obtained after one recrystallization.

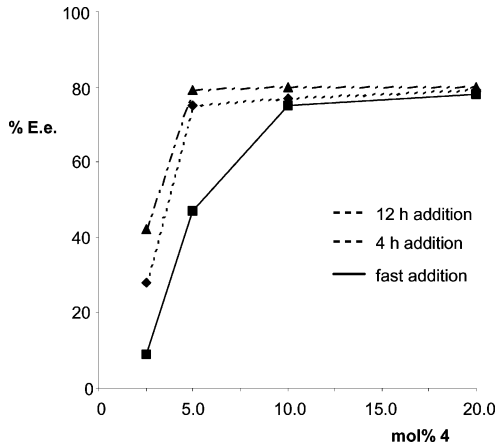


Fig. 6 Effect of catalyst loading and rate of substrate addition on enantioselectivity in the conversion of **41** to **7**.

For three examples we also examined purification of the final products by recrystallization, and as before this led to significant enhancement of the enantiomeric excess. This demonstrates that the direct oxidation of allylic alcohols to α,β-epoxyketones can serve as an effective means of obtaining highly enantiomerically-enriched products.

Conclusion

This study has demonstrated that the readily prepared dihydrocinchonidine derived PTC **4** is an effective catalyst for the asymmetric epoxidation of a range of simple *trans*-α,β-unsaturated ketones of type **1**. The epoxidations can be performed at room temperature under operationally simple conditions and in many instances the enantiomeric excess of the product can be further enhanced by simple recrystallization. Simple *cis*-α,β-unsaturated ketones can also be converted into *cis*-α,β-epoxyketones, using the same conditions, although the reactions are slower and stereoselectivity is lower. Further alkene substitution in the substrate does not appear to be tolerated. The reaction conditions employed for epoxidation can also be used to effect oxidation of allylic alcohols, allowing for direct formation of enantioenriched α,β-epoxyketones from these substrates.

Experimental

General details

All solvents and chemicals were used as provided by the supplier. Reactions were monitored by thin layer chromatography using Merck silica gel 60 F_{254} precoated glass TLC plates, visualised using UV light and then basic potassium permanganate solution. Flash chromatography was performed using Merck silica gel (230–400 mesh) as the stationary phase. Melting points were determined using a Kopfler hot-stage apparatus and are uncorrected.

Infrared spectra were recorded using either a Perkin-Elmer FT 1600 or a Nicolet Avatar 360 FT-IR infrared spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV400 or DRX500 spectrometer at ambient temperature. Chemical shifts are quoted relative to residual solvent and *J* values are given in Hz. Multiplicities are designated by the following abbreviations: s, singlet, d, doublet, t, triplet, q, quartet, br, broad, m, multiplet. Mass spectra were obtained on a Micromass Autospec or Micromass LCT instrument using electron impact (EI), fast atom bombardment (FAB) or electrospray (ES). Specific rotations were measured using a Jasco DIP370 digital polarimeter at ambient conditions and are given in units of deg cm^2 g^{-1}; *c* is in g per 100 ml of solvent. HPLC analysis was performed on a Hewlett Packard 1100LC machine fitted with a diode array detector. ee was determined *via* HPLC comparison with racemates using Chiralcel OD-H, Chiralpak AD, or Chiralpak AS columns. Epoxides **7–10**, **12**, **15**, **16**, **21–24**,[6] **11**,[7] **25**,[10g] **37** and **38**[20] were characterised by comparison of ^{1}H NMR and HPLC retention times with previously reported data.

General procedure for the epoxidation of enones (Method A)

A solution of the enone (3.40 mmol) and PTC catalyst **4** (0.03 mmol) in toluene (10 ml) in a 25 ml round-bottom flask was treated with 15% aqueous sodium hypochlorite (6.80 mmol) and the resulting mixture was stirred vigorously (magnetic stirrer at *ca.* 1000 rpm) at room temperature for 4–24 h. After this time water (20 ml) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 30 ml) and the combined organics were dried over sodium sulfate then concentrated under reduced pressure. The residue was purified either by chromatography on silica gel or by recrystallization (from either ethyl acetate–petroleum ether or *t*-butylmethyl ether–petroleum ether).

General procedure for the oxidation–epoxidation of allylic alcohols (Method B)

A mixture of PTC catalyst **4** (0.13 mmol) in toluene (5 ml) and 15% aqueous sodium hypochlorite (10.0 mmol) was placed in a 25 ml round-bottom flask. The mixture was stirred vigorously (magnetic stirrer at *ca.* 1000 rpm) at room temperature and a solution of the allylic alcohol (2.5 mmol) in toluene (10 ml) added dropwise over 5 h. The reaction mixture was then stirred for a further 18 h, then water (10 ml) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 30 ml) and the combined organics were dried over sodium sulfate then concentrated under reduced pressure. The residue was purified either by chromatography on silica gel or by recrystallization

(from either ethyl acetate–petroleum ether or *t*-butylmethyl ether–petroleum ether).

(2*S*,3*R*)-3-(4-Bromophenyl)-2,3-epoxy-1-[3,4-(methylenedioxy)phenyl]propan-1-one, 17

Method A: 89% yield, 91% ee after chromatography or 68% yield, ≥99% ee after recrystallization. Method B: 78% yield, 86% ee after chromatography or 61% yield, ≥99% ee after recrystallization. R_f (silica gel): 0.3 (80 : 20 petroleum ether : ethyl acetate); mp 142–143 °C (from *tert*-butylmethylether–petroleum ether); $[\alpha]_D$ 203.0 (*c* 1.4 in $CHCl_3$, >99% ee); found: C, 55.4; H, 3.2; Br, 22.8. Calc. for $C_{16}H_{11}O_4Br$: C, 55.4; H, 3.2; Br, 23.0%; ν_{max} (solid)/cm^{-1} 1678; δ_H (400 MHz, $CDCl_3$): 7.62 (1H, dd, *J* 8.0, 1.0, 6′-H), 7.53 (2H, d, *J* 7.0, Ar-H), 7.48 (1H, d, *J* 1.0, 2′-H), 7.24 (2H, d, *J* 7.0, Ar-H), 6.87 (1H, d, *J* 8.0, 5′-H), 6.07 (2H, s, CH_2), 4.15 (1H, d, *J* 2.0, 2-H), 4.03 (1H, d, *J* 2.0, 3-H); δ_C (125 MHz, $CDCl_3$): 190.6 (C), 152.8, 148.6, 134.8 (C), 132.0 (CH), 130.3 (C), 127.5, 125.2 (CH), 123.1 (C), 108.3, 108.0 (CH), 102.2 (CH_2), 60.8, 58.7 (CH); HRMS (EI): found M$^+$ 345.9828, $C_{16}H_{11}O_4{}^{79}Br$ requires 345.9841; R_t HPLC (Chiralpak AD column, 60 : 40 hexane : ethanol, 1.0 ml min^{-1}, 254 nm) 15.5 min (major), 21.4 min (minor).

(2*S*,3*R*)-2,3-Epoxy-1-phenylhexadecan-1-one, 18

Method A: 97% yield, 81% ee after chromatography on silica, 42% yield, 99% ee after recrystallization. R_f (silica gel): 0.5 (80 : 20 petroleum ether : ethyl acetate); mp 59–60 °C (from ethyl acetate–petroleum ether); $[\alpha]_D$ −13.3 (*c* 1.1 in $CHCl_3$, 99% ee); found: C, 79.8; H, 10.4. Calc. for $C_{22}H_{34}O_2$: C, 80.0; H 10.4%; ν_{max} (solid)/cm^{-1} 1691; δ_H (400 MHz, $CDCl_3$): 8.06–8.03 (2H, m, Ar-H), 7.66–7.62 (1H, m, Ar-H), 7.54–7.50 (2H, m, Ar-H), 4.04 (1H, d, *J* 2, 2-H), 3.16 (1H, dt, *J* 2.0, 5.5, 3-H), 1.84–1.70 (2H, m, 4-CH_2), 1.59–1.48 (2H, m, 5-CH_2), 1.40–1.21 (20H, m, 10 × CH_2), 0.88 (3H, t, *J* 7.5, CH_3); δ_C (100 MHz, $CDCl_3$): 194.8 (CO), 135.6 (C), 133.8, 128.8, 128.3, 60.1, 57.5 (CH), 32.0–22.7 (12 × CH_2), 14.1 (CH_3); HRMS (EI): found M$^+$ 330.2552, $C_{22}H_{34}O_2$ requires 330.2559; R_t HPLC (Chiralcel OD-H column, 98.5 : 1.5 hexane : IPA, 0.5 ml min^{-1}, 254 nm) 24.4 min (major), 22.7 min (minor).

(2*S*,3*R*)-2,3-Epoxy-1-(thien-2-yl)hexadecan-1-one, 19

Method A: 96% yield 79% ee after chromatography on silica gel, 56% yield, 99% ee after recrystallization. R_f (silica gel): 0.5 (80 : 20 petroleum ether : ethyl acetate); mp 61–62 °C (from ethyl acetate–petroleum ether); $[\alpha]_D$ −16.1 (*c* 0.3 in $CHCl_3$, 99% ee); found: C, 71.2; H, 9.5. Calc. for $C_{20}H_{32}O_2S$: C, 71.4; H, 9.6%; ν_{max} (solid)/cm^{-1} 1668; δ_H (400 MHz, $CDCl_3$): 8.00–7.99 (1H, m, Ar-H), 7.71–7.70 (1H, m, Ar-H), 7.17–7.15 (1H, m, Ar-H), 3.77 (1H, d, *J* 2.0, 2-H), 3.22 (1H, dt, *J* 2.0, 5.5, 3-H), 1.73–1.68 (2H, m, 4-CH_2), 1.52–1.48 (2H, m, 5-CH_2), 1.38–1.20 (20H, m, 10 × CH_2), 0.88 (3H, t, *J* 7.5, CH_3); δ_C (100 MHz, $CDCl_3$): 188.6 (C), 141.1 (C), 135.2, 133.8, 128.7 (CH), 60.5, 59.1 (CH), 32.3–23.1 (12 × CH_2), 14.5 (CH_3); HRMS (EI): found M$^+$ 336.2136, $C_{20}H_{32}O_2S$ requires 336.2123; R_t HPLC (Chiralcel OD-H column, 90 : 10 hexane : IPA, 0.5 ml min^{-1}, 254 nm) 13.3 min (major), 15.0 min (minor).

(2*S*,3*R*)-2,3-Epoxy-1-(furan-2-yl)hexadecan-1-one, 20

Method A: 96% yield, 80% ee after chromatography on silica gel, 54% yield, 99% ee after recrystallization. R_f (silica gel): 0.5 (80 : 20 petroleum ether : ethyl acetate); mp 74–76 °C (from ethyl acetate–petroleum ether); $[\alpha]_D$ −1.9 (*c* 5.1 in $CHCl_3$, 99% ee); found: C, 75.0; H, 10.1. Calc. for $C_{20}H_{32}O_3$: C, 74.9; H, 9.9%; ν_{max} (solid)/cm^{-1} 1669; δ_H (400 MHz, $CDCl_3$): 7.68–7.67 (1H, m, Ar-H), 7.44–7.43 (1H, m, Ar-H), 6.59–6.58 (1H, m, Ar-H), 3.83 (1H, d, *J* 2, 2-H), 3.20 (1H, dt, *J* 2.0, 5.5, 3-H), 1.74–1.66 (2H, m, 4-CH_2), 1.54–1.47 (2H, m, 5-CH_2), 1.45–1.24 (20H, m, 10 × CH_2), 0.89 (3H, t, *J* 7.5, CH_3); δ_C (100 MHz, $CDCl_3$): 184.2 (CO), 151.4 (C), 147.8, 119.7, 112.9, 60.7, 57.7 (CH), 32.3–23.1 (12 × CH_2), 14.5 (CH_3); HRMS (EI): found M$^+$ 320.2348, $C_{20}H_{32}O_3$ requires 320.2351; R_t HPLC (Chiralcel OD-H column, 95 : 5 hexane : IPA, 0.5 ml min^{-1}, 254 nm) 15.5 min (major), 13.5 min (minor).

Benzyl (2*S*,3*S*)-2,3-epoxy-4-phenyl-4-oxobutanoate, 26

Method A: 76% yield, 67% ee after chromatography. R_f (silica gel): 0.3 (80 : 20 petroleum ether : ethyl acetate); $[\alpha]_D$ 62.1 (*c* 0.3 in $CHCl_3$, 67% ee); ν_{max} (film)/cm^{-1} 1756, 1687; δ_H (400 MHz, $CDCl_3$): 8.01–7.98 (2H, m, Ar-H), 7.67–7.36 (8H, m, Ar-H), 5.28 (2H, apparent d, *J* 4.5, CH_2), 4.46 (1H, d, *J* 2.0, 3-H), 3.75 (1H, d, *J* 2.0, 2-H); δ_C (100 MHz, $CDCl_3$): 191.8, 167.2 (CO), 135.1, 134.7 (C), 134.5, 129.1, 128.9, 128.8, 128.7 (CH), 68.0 (CH_2), 55.4, 53.1 (CH); HRMS (ES): found $[M + Na]^+ + CH_3CN$ 346.1073, $C_{19}H_{17}NNa$ requires 346.1055. R_t HPLC (Chiralcel OD-H column, 90 : 10 hexane : IPA, 0.8 ml min^{-1}, 254 nm) 22.4 min (major), 35.4 min (minor).

Ethyl (2*S*,3*S*)-2,3-epoxy-4-(4-nitrophenyl)-4-oxobutanoate, 27

Method A: 74% yield, 86% ee after chromatography or 52% yield, 93% ee after recrystallization. R_f (silica gel): 0.3 (80 : 20 petroleum ether : ethyl acetate); mp 89–91 °C (from *tert*-butylmethylether–petroleum ether); $[\alpha]_D$ 126.9 (*c* 0.25 in $CHCl_3$, 93% ee); found: C, 54.2; H, 4.1; N, 5.3. Calc. for $C_{12}H_{11}O_6N$: C, 54.3; H, 4.2; N, 5.3%; ν_{max} (solid)/cm^{-1}: 1742, 1730; δ_H (400 MHz, $CDCl_3$): 8.38–8.35 (2H, m, Ar-H), 8.21–8.16 (2H, m, Ar-H), 4.41 (1H, d, *J* 2.0, 3-H), 4.34–4.31 (2H, m, CH_2), 3.71 (1H, d, *J* 2.0, 2-H), 1.36 (3H, t, *J* 7.0, CH_3); δ_C (100 MHz, $CDCl_3$): 191.2, 166.7, 151.0, 139.2 (C), 129.9, 124.2 (CH), 62.7, 55.8 (CH), 53.2 (CH_2), 14.2 (CH_3); HRMS (EI): found M$^+$ 265.0590, $C_{12}H_{11}O_6N$ requires 265.0586. R_t HPLC (Chiralcel OD-H column, 70 : 30 hexane : IPA, 0.65 ml min^{-1}, 254 nm) 57.4 min (minor), 68.4 min (major).

Ethyl (2*S*,3*S*)-2,3-epoxy-4-(4-methoxyphenyl)-4-oxobutanoate, 28

Method A: 97% yield, 65% ee after chromatography. R_f (silica gel): 0.3 (80 : 20 petroleum ether : ethyl acetate); $[\alpha]_D$ 69.2 (*c* 0.75 in $CHCl_3$, 65% ee); mp 32–33 °C; ν_{max} (solid)/cm^{-1} 1745, 1683; δ_H (400 MHz, $CDCl_3$): 8.05–8.01 (2H, m, Ar-H), 7.00–6.97 (2H, m, Ar-H), 4.41 (1H, d, *J* 2.0, 3-H), 4.35–4.27 (2H, m, CH_2), 3.90 (3H, s, OCH_3), 3.70 (1H, d, *J* 2.0, 2-H), 1.35 (3H, t, *J* 7.0, CH_3); δ_C (100 MHz, $CDCl_3$): 190.0, 167.5, 164.7 (C), 131.1 (CH), 128.3 (C), 114.3 (CH), 62.3 (CH_2), 55.7 (CH_3), 55.2, 53.0 (CH), 14.2 (CH_3); HRMS (EI): found M$^+$ 250.0838, $C_{13}H_{14}O_5$ requires 250.0841. R_t HPLC (Chiralpak AD column, 90 : 10 hexane : IPA, 1.5 ml min^{-1}, 254 nm), 10.8 min (minor), 23.4 min (major).

cis-2,3-Epoxy-1,3-diphenylpropan-1-one, 32

Method A: 72% yield, 56% ee after chromatography on silica. R_f (silica gel): 0.1 (90 : 10 petroleum ether : ethyl acetate); mp 86–87 °C; ν_{max} (solid)/cm^{-1} 1694; δ_H (400 MHz, $CDCl_3$): 7.92–7.85 (2H, m, Ar-H), 7.56–7.18 (8H, m, Ar-H), 4.51 (1H, d, *J* 4.5, 2-H), 4.49 (1H, d, *J* 4.5, 3-H); δ_C (100 MHz, $CDCl_3$): 193.3 (C), 136.9 (C), 135.1 (CH), 134.3 (C), 130.1, 129.8, 129.5, 129.5, 127.8, 62.3, 60.1 (CH); HRMS (EI): found M$^+$ 224.0834, $C_{15}H_{12}O_2$ requires 224.0837; R_t HPLC (Chiralpak AD column, 90 : 10 hexane : ethanol, 1 ml min^{-1}, 254 nm) 12.9 min (major), 13.8 min (minor).

(−)-2,3-Dihydro-2,3-epoxyphenalen-1-one, 34

Method A: 71% yield, 76% ee after chromatography. R_f (silica gel): 0.6 (80 : 20 petroleum ether : ethyl acetate); mp 139–141 °C; $[\alpha]_D$ −427.8 (*c* 0.1 in $CHCl_3$, 76% ee); ν_{max} (solid)/cm^{-1} 1682; δ_H (400 MHz, $CDCl_3$): 8.38 (1H, dd, *J* 7.5, 1.0, Ar-H), 8.15 (1H, dd, *J* 8.0, 1.0, Ar-H), 7.96 (1H, dd, *J* 8.5, 1.0, Ar-H), 7.86 (1H, dd, *J* 7.0, 1.0, Ar-H), 7.67 (1H, dd, *J* 8.0, 7.5, Ar-H), 7.57 (1H, dd, *J* 8.5, 7.0, Ar-H), 4.59 (1H, d, *J* 3.5, 2-H), 4.14 (1H, d, *J* 3.5, 3-H); δ_C (100 MHz, $CDCl_3$): 192.5 (C), 135.0 (CH), 133.2 (C), 129.9, 129.8 (CH), 129.1 (C), 128.5 (CH), 127.7, 127.0 (C), 126.6, 126.0, 57.2, 56.8 (CH); HRMS (FAB): found M$^+$ 197.0598, $C_{13}H_8O_2$ requires 197.0603; R_t HPLC (Chiralpak AS column, 90 : 10 hexane : ethanol, 0.2 ml min^{-1}, 254 nm) 7.2 min (minor), 9.2 min (major).

(2*R*,3*R*,4*R*)-2,3-Epoxy-4,5-isopropylidenedioxy-1-phenylpentan-1-one, 39

Method A: 96% yield, 86% de after chromatography or 81% yield, ≥95% de after recrystallization. R_f (silica gel): 0.3 (80 : 20 petroleum ether : ethyl acetate); mp 65–68 °C (from ethyl acetate–petroleum ether); $[\alpha]_D$ −22.9 (*c* 0.6 in $CHCl_3$, ≥95% de); found: C, 67.8; H, 6.5. Calc. for $C_{14}H_{16}O_4$: C, 67.7; H, 6.5%; ν_{max} (solid)/cm^{-1} 1692; δ_H (400 MHz, $CDCl_3$): 8.08–7.50 (5H, m, Ar-H), 4.21 (1H, d, *J* 4.5, 2-H), 3.88–3.84 (2H, m, 5_a-H, 5_b-H), 3.79–3.73 (1H, m, 4-H), 3.45 (1H, dd, *J* 6.5, 4.5, 3-H), 1.38 (3H, s, CH_3), 1.27 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$): 193.4 (C), 135.4 (C), 134.3, 129.0, 128.6 (CH), 110.5 (C), 74.5 (CH), 66.0 (CH_2), 58.7, 56.0 (CH), 26.4, 25.3 (CH_3); HRMS (FAB): found [M + H]$^+$ 249.1127, $C_{14}H_{17}O_4$ requires 249.1127.

Acknowledgements

We thank Dr John Crosby for helpful discussions. Financial support for this work was provided by EPRSC, GSK, and the University of Nottingham.

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