Catalytic enantioselective epoxidation of alkenes with a tropinone-derived chiral ketone

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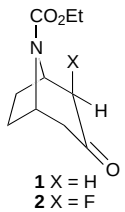
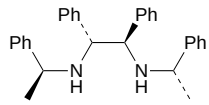
α-Fluoro-*N*-ethoxycarbonyltropinone is an efficient catalyst for the epoxidation of alkenes by Oxone® with good enantioselectivity.

The development of catalytic methods for the asymmetric epoxidation of unfunctionalised alkenes continues to be an important goal in organic chemistry.[1] The chiral manganese salen complexes developed by Jacobsen and Katsuki provide a solution to this problem for certain alkene substitution patterns, but these catalysts generally give poor enantioselectivity for epoxidation of, for example, *trans*-disubstituted alkenes.[1] Recently, attention has focused on the catalysis of Oxone® epoxidation of alkenes[2] by chiral ketones[3–6] (*via* a dioxirane[7]‡) and by chiral iminium salts[8] (*via* an oxaziridinium species) as a possible solution to this problem, and some impressive advances have been recorded. Yang and co-workers described a catalytic binaphthyl-based ketone which, with appropriate substitution, can give high selectivity [up to 84% ee for the epoxidation of (*E*)-stilbene].[3] Shi has reported a D-fructose-derived chiral ketone which gives extremely high enantioselectivities, but is destroyed under the Oxone® epoxidation conditions, presumably by Baeyer–Villiger reaction.[4] It must therefore be used in relatively large quantities, although modified pH conditions have improved the catalytic efficiency of the process.[4b] The enantiomeric catalyst derived from L-fructose is less readily available, however. Here we describe some of our own results in the development of new ketone catalysts which have led to the discovery of a new class of chiral ketone which can be used catalytically and recycled if required, as well as affording high enantioselectivities for alkene epoxidation.

Recognising the need for an efficient ketone catalyst to be activated electronically towards attack,[3,9] we initially examined several classes of α-functionalised ketone. Of these, α-amido ketones were attractive with regard to the easy introduction of asymmetry, but were prone to decomposition by Baeyer–Villiger reaction.[9] We therefore turned our attention to β-amido ketones and in particular, in view of the need eventually to prepare conformationally well-defined chiral catalysts, tropinone derivatives. Commercially available *N*-ethoxycarbonyltropinone **1** provided promising initial results: using **1** (10 equiv.) and Oxone® (10 equiv.) under the Yang MeCN–H_2O conditions,[10] (*E*)-stilbene was epoxidised completely within 3 h. Importantly, there was no evidence for decomposition of **1** under these conditions. Reasoning that electron-withdrawing substituents should further increase the activity of the catalyst,[11] we prepared the α-fluoro derivative **2** from **1** by treatment of the derived trimethylsilyl enol ether with a Selectfluor reagent.[12]§ Racemic **2** proved to be an excellent catalyst for the epoxidation of (*E*)-stilbene (Table 1): using 10 mol% **2**, reaction was complete in less than 2 h (entry 4), while reasonable conversions were possible at the 1 mol% level over longer time periods (entry 6).¶ There was no evidence for Baeyer–Villiger reaction by ^{1}H NMR spectroscopy, and the catalyst could be recovered (*ca*. 70% yield) by column chromatography.



1 X = H
2 X = F



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In view of the extremely promising catalytic activity of **2**, we then attempted its synthesis in enantiomerically pure form. Following the work of the Simpkins group on desymmetrisation of tropinones using chiral lithium amide bases,[13] treatment of **1** with the lithium amide base derived from **3**[14] (1 equiv.) and Bu^nLi (2 equiv.) in the presence of Me_3SiCl (5 equiv.) and LiCl (1 equiv.) gave the crude silyl enol ether which was reacted without purification with the Selectfluor reagent. The resulting sample of **2** (36% yield, unoptimised), *ca*. 60% ee, was recrystallised once from Et_2O–light petroleum and then once from CH_2Cl_2–light petroleum to provide ketone **2** in > 98% ee according to chiral HPLC.‖ The relative stereochemistry of **2** was proven by X-ray crystallography;** the absolute stereochemistry is assigned based on the precedent of Simpkins, who converted the same intermediate silyl enol ether into (−)-anatoxin-a.[13] It should be noted that the antipodal form of the chiral amine **3** is also readily available,[14] and so it should be possible to access the other enantiomer of **2** by this route. We are also currently exploring resolution methods.

Enantiomerically enriched **2** was used as catalyst for the Oxone® epoxidation of a range of alkenes (Table 2) and the results are extremely promising. Enantioselectivities of up to 83% have been obtained. Interestingly, all our results to date fit a simple transition state model (Fig. 1), which assumes attack on the sterically less hindered *exo*-oxygen of the dioxirane intermediate and a spiro transition state (in accord with Yang[3] and Shi[4]). The hydrogen substituent on the alkene occupies the region of the fluorine substituent of the catalyst. In accord with this model, the epoxidation of styrene, where there are two possible hydrogens on the terminal carbon of the alkene that can occupy the catalyst fluorine region, proceeds with lower enantioselectivity (entry 5). Amongst the other substrates examined so far, it is noteworthy that α,β-unsaturated esters can be epoxidised under these conditions with moderate (but

Table 1 Oxone® epoxidation of (*E*)-stilbene catalysed by ketone **2**[a]

Entry	(±)-**1** (mol%)[b]	Conversion (%)[c]	*t*/h
1	100	100	< 0.25
2	50	100	< 0.25
3	25	100	< 0.5
4	10	100	2
5	5	100	⩽20
6	1	62[d]	24

[a] Alkene (0.1 mmol), Oxone® (1.0 mmol $KHSO_5$), $NaHCO_3$ (1.55 mmol), MeCN (1.5 ml), aq. Na_2EDTA (1 ml of 0.4 mmol dm^{-3} solution). [b] Relative to alkene. [c] By TLC analysis. [d] Measured by ^{1}H NMR spectroscopy.

Table 2 Asymmetric epoxidation of alkenes catalysed by ketone (+)-**2**[a]

Entry	Alkene	(+)-**2** (mol%)[b]	Conversion (%)[c]	*t*/h	Yield (%)[d]	Ee (%)[e] configuration[f]
1	(*E*)-Stilbene	10	100	< 3	88	76[g] *R,R*
2	(*E*)-α-Methylstilbene	10	100	< 4	100	73 *R,R*
3	Phenylstilbene	10	100	< 4	100	83 *R*
4	1-Phenylcyclohexene	10	100	< 6	97	69 *R*
5	Styrene	10	100	< 2	33	29 *R*
6	(*E*)-Methylcinnamate	25	64[h]	24	33	64[i]

[a] Alkene (0.1 mmol), Oxone® (1.0 mmol $KHSO_5$), $NaHCO_3$ (1.55 mmol), MeCN (1.5 ml), aq. Na_2EDTA (1 ml of 0.4 mmol dm^{-3} solution), (+)-**2**. [b] Relative to alkene. [c] Estimated by TLC. [d] Isolated yield of epoxide product. [e] Enantiomeric excesses were measured by ^1H NMR spectroscopy in the presence of $Eu(hfc)_3$ as chiral shift reagent. [f] Absolute configurations were determined by comparison to literature data (refs. 3 and 4). [g] Determined by HPLC (Chiracel OD). [h] Measured by ^1H NMR spectroscopy. [i] Absolute configuration not assigned.

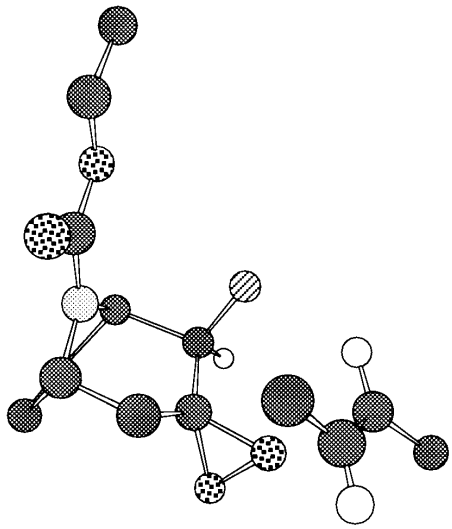

Fig. 1 Model for the approach of a *trans*-disubstituted alkene to the dioxirane derived from ketone (+)-**2**

promising) enantioselectivity (entry 6), albeit requiring longer reaction times and higher catalyst loadings.

In conclusion, we have found that α-fluoro-*N*-ethoxycarbonyltropinone is an efficient catalyst for the epoxidation of alkenes by Oxone®; it can be used in low loadings and recovered and recycled. Moreover, when prepared in enantiomerically pure form, it affords high enantioselectivity for alkene epoxidation. Attempts to prepare related bicyclo[3.2.1]octanone derivatives with alternative α-substitution, in order to improve enantioselectivity further and to clarify the factors responsible for asymmetric induction, are underway.

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Notes and References

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‡ A dioxirane is almost certainly the active species in the monophasic MeCN–H_2O solvent system: A. Armstrong, B. R. Hayter and P. A. Clarke, unpublished results. See also ref. 5 for ^{18}O labelling experiments in support of this. Earlier ^{18}O labelling experiments (A. Armstrong, P. A. Clarke and A. Wood, *Chem. Commun.*, 1996, 849) were performed in a two phase, CH_2Cl_2–H_2O solvent system.

§ 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate).

¶ It is probable that the lower conversions at the 1 mol% level are due to decomposition of the Oxone® over the extended reaction times rather than decomposition of the catalyst.

‖ The ketone had mp 57.5 °C, $[\alpha]_D^{27}$ +7.3 (*c* 1.16, CH_2Cl_2). Chiral HPLC was performed using a Chiracel OD column with 100 : 1 hexane–Pr^iOH + 0.1% TFA as eluent; detection at 224 nm; flow rate 1 cm^3 min^{-1} retention time 27 min (minor enantiomer), 29.3 min (major enantiomer).

** Details will appear in a full account of this work. We thank Dr A. J. Blake and Dr Wan-Sheung Li of this Department for this structure determination.

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