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Alkene epoxidation catalyzed by bicyclo[3.2.1]octan-3-ones: effects of structural modifications on catalyst efficiency and epoxidation enantioselectivity

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Abstract

Several 2-substituted bicyclo[3.2.1]octan-3-ones are prepared and have been tested as catalysts for alkene epoxidation by Oxone®.

1. Introduction

The use of chiral dioxiranes, generated in situ from ketones and Oxone®, is an extremely promising approach for the asymmetric epoxidation of 'unfunctionalised' alkenes.[1–4] Amongst several notable contributions, the fructose derived ketone **1** reported by Shi and co-workers[2] affords very high enantioselectivities for epoxidation of a range of alkenes. However, it suffers from decomposition by Baeyer–Villiger reaction under the reaction conditions, necessitating the use of relatively high quantities, although loadings can be lowered if the reaction is performed at higher pH.[2] We recently described the novel ketone **2**, obtained by electrophilic fluorination of the trimethylsilyl enol ether of commercially available *N*-carbethoxytropinone.[4] This ketone was found to be stable to the Baeyer–Villiger reaction, allowing its use in relatively low loadings (< 10 mol%), even at near neutral pH (7.5). Non-racemic **2** was prepared by chiral base desymmetrisation of *N*-carbethoxytropinone **3**, which proceeded in ca. 70% ee; fortunately, it was possible to increase the enantiomeric purity of **2** by recrystallisation. Enantiomerically pure **2** prepared in this way provided encouraging epoxidation enantioselectivities: for example, room temperature epoxidation of *E*-stilbene proceeded in 76% ee, whilst phenylstilbene afforded the corresponding epoxide in 83% ee.[4] While these results are promising, clearly it would be desirable to increase epoxidation

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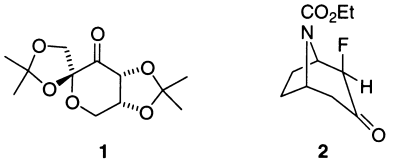
enantioselectivity still further. An attractive feature of the tropinone template is the possibility of preparing a range of modified derivatives by structural alteration at several sites in the catalyst. Here we describe initial investigations into some of these modifications, and show that highly promising catalysts can indeed be prepared.



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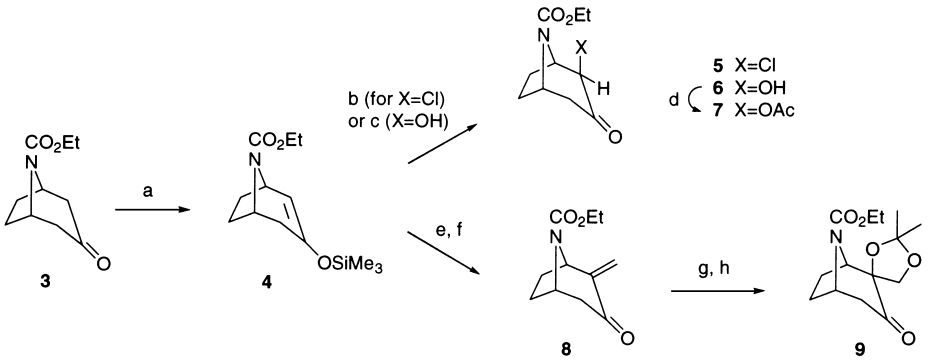
2. Results and discussion

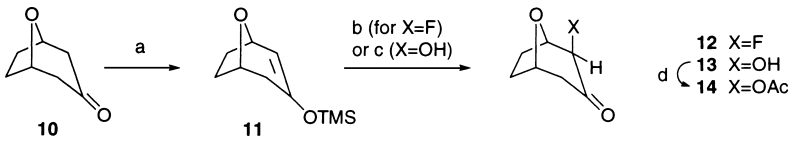
The most obvious alteration of **2** is to replace the α-fluorine substituent. Several such derivatives were prepared, initially in racemic form, from the common silyl enol ether **4**.[5] Reaction with *N*-chlorosuccinimide (NCS) afforded the chloride **5**, while oxidation with dimethyldioxirane (DMDO) provided the α-hydroxy ketone **6**, acetylation of which led to **7**.[6] We were intrigued by the idea of incorporating the α-acetonide motif believed to be responsible for the high enantioselectivities afforded by the Shi ketone **1**. The target **9** was accessed from **4** by a sequence of cyclopropanation and regioselective ring opening to give the enone **8**,[7] followed by dihydroxylation and acetonide protection (Scheme 1).



Scheme 1. (a) LDA, TMSCl, THF, –78°C; (b) NCS, NaOAc, acetone/H_2O, 18 h, 73% from **3**; (c) dimethyldioxirane, acetone, CH_2Cl_2, 60% from **3**; (d) Ac_2O, $Sc(OTf)_3$, 74%; (e) Et_2Zn/CH_2I_2, Et_2O, rt, 18 h, 42% from **3**; (f) $SnCl_4$, DMSO, CH_2Cl_2, rt, 24 h, 80%; (g) $K_2OsO_4{\cdot}2H_2O$, NMO, quinuclidine, acetone/H_2O, rt, 16.5 h, 82%; (h) 2,2-dimethoxypropane, $HClO_4$, acetone, 0°C, 3 h, 70%

In order to evaluate the effect of varying the bridgehead heteroatom, we also prepared the corresponding oxabicycles **12**–**14** from the parent ketone **10**[8] (Scheme 2).

These new racemic ketones were then subjected to preliminary screening for catalytic activity under the Yang[9] Oxone®/CH_3CN/H_2O system (pH ca. 7.5). For comparison, results using **2**[4] are also included in Table 1. Chloride **5** (entry 2) was markedly less effective than **2**, while, disappointingly, use of **9** led to low conversion (entry 3), with the catalyst appearing to undergo Baeyer–Villiger decomposition. This result underscores the dramatic structural dependency of



Scheme 2. (a) (i) LDA, THF, –78°C; (ii) TMSCl, Et_3N, THF; (b) Selectfluor^{TM}, CH_3CN, rt, 1 h, 33% from **10**; (c) dimethyldioxirane, acetone, CH_2Cl_2, 40% from **10**; (d) Ac_2O, $Sc(OTf)_3$, 77%

catalyst stability.[2c,10] The alcohol **6** was also a poor promoter (entry 4), presumably due to susceptibility to oxidation to an unstable diketone. However, the corresponding acetate **7** afforded better results: although less active than **2**, it appeared to be stable (entries 5–7). The oxygen heterocycles **12** and **14** were also effective catalysts (entries 8–12), although again slightly less active than **2**.

Table 1
Epoxidation of *E*-stilbene catalysed by racemic ketones **2**, **5**, **6**, **7**, **9**, **12** and **14**[a]

Entry	Ketone	Mol % ketone	Time (h)	Conversion[b]
1	**2**	10	2	100
2	**5**	100	24	21
3	**9**	100	24	13
4	**6**	100	24	8
5	**7**	100	< 1	100
6	**7**	50	< 1	100
7	**7**	10	24	44
8	**12**	100	< 1	100
9	**12**	20	< 1	100
10	**12**	10	24	73
11	**14**	100	1	98
12	**14**	20	24	85

[a]Alkene (0.1 mmol), Oxone® (1.0 mmol $KHSO_5$), $NaHCO_3$ (1.55 mmol), CH_3CN (1.5 ml), aq. Na_2EDTA (1 ml of 0.4 mmol dm^{-3} solution).

[b]Estimated by integration of the crude ^1H NMR spectrum.

Having evaluated the racemic catalysts, we now attempted their preparation in non-racemic form using chiral base desymmetrisation.[11] Unlike ketone **2**, we were not able to improve catalyst enantiomeric excess of **5**, **7**, **12** or **14** by recrystallisation, so the ketones tested for the epoxidation of *E*-stilbene were not enantiomerically pure. Table 2 therefore includes an 'ee_{max}' value, the

expected product ee with enantiomerically pure catalyst based on the assumption that there is an approximately linear relationship between catalyst ee and product ee. We have established that this is indeed the case for fluoroketone **2**.[12] Again, results using **2** are included in Table 2 for comparison. As well as being a less active catalyst, the chloride **5** affords lower enantioselectivity than **2** (compare entries 1 and 2). However, acetate **7** showed higher ee_{max} than **2** (entry 3). Altering the bridgehead heteroatom to oxygen, with **12**, also improved the ee_{max} relative to **2** (entry 4). Pleasingly, the effects of the two beneficial features appeared to be additive: the α-acetoxy-oxabicycle **14** afforded ee_{max} of up to 95% (entries 5 and 6). These are highly encouraging results given that they were obtained at room temperature and without optimisation of solvent or reaction pH. Moreover, the potential exists for replacement of the acetate unit with a range of alternative ester substituents.

Table 2
Epoxidation of *E*-stilbene catalysed by non-racemic ketones **2**, **5**, **7**, **12** and **14**[a]

Entry	Ketone	Mol% ketone	Time (h)	Conversion[b]	Ketone ee[c]	Product ee[d]	ee_{max}[e]
1	**2**	10		100	100	76	76
2	**5**	100	24	21	76	41	54
3	**7**	20	3	100	76	66	86
4	**12**	20	< 1	100	76	63	83
5	**14**	100	< 1	90	75	71	95
6	**14**	20	24	85	80	74	93

[a]Alkene (0.1 mmol), Oxone® (1.0 mmol $KHSO_5$), $NaHCO_3$ (1.55 mmol), CH_3CN (1.5 ml), aq. Na_2EDTA (1 ml of 0.4 mmol dm^{-3} solution). [b]Estimated by integration of the crude ^1H NMR spectrum. [c]Determined by chiral HPLC analysis. [d]Measured by chiral HPLC (Chiralcel OD column using 10% isopropylalcohol / hexane as eluent). (*R*,*R*)-product obtained in each case. [e]100 x product ee/ketone ee.

In summary, we have prepared and tested several novel bicyclo[3.2.1]octan-3-ones as catalysts of Oxone® epoxidation of alkenes. The highest ee_{max} is obtained using the α-acetoxy-oxabicycle **14**. Ongoing work must address the efficient preparation of **14** in enantiomerically pure form, and its testing in the asymmetric epoxidation of a wider range of alkenes.

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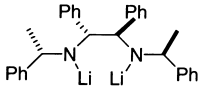

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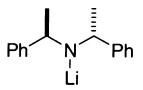

16

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