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Asymmetric epoxidation catalyzed by esters of α-hydroxy-8-oxabicyclo[3.2.1]octan-3-one

Alan Armstrong,[a,*] William O. Moss[b] and Jonathan R. Reeves[a]

[a]*Department of Chemistry, Imperial College, London SW7 2AY, UK*
[b]*AstraZeneca R&D Charnwood, Loughborough, Leicestershire, UK*

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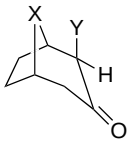
Abstract—Several esters of α-hydroxy-8-oxabicyclo[3.2.1]octan-3-one were prepared and tested as catalysts for alkene epoxidation by Oxone®.

1. Introduction

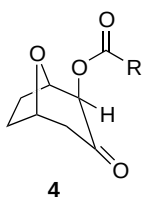
Asymmetric alkene epoxidation with Oxone® catalyzed by chiral ketones, via dioxirane intermediates, is providing extremely promising results.[1] A major challenge is the development of active catalysts that do not suffer decomposition by Baeyer–Villiger reaction.[2] We have identified bicyclo[3.2.1]octan-3-ones as a class of conformationally well defined catalysts with low intrinsic tendency to undergo decomposition.[3] Our initial study indicated that α-fluoro-*N*-carbethoxytropinone **1** afforded high activity, allowing use at low loadings at pH 7.5.[3a] Promising enantioselectivities were also recorded.[3a] This work was followed by a study of the corresponding oxabicyclic compound **2** which provided higher enantioselectivity in the epoxidation of (*E*)-stilbene.[3b] Additionally, we found that replacement of the α-fluoro substituent with an acetoxy group provided further improvement.[3b] Herein, we report further studies on asymmetric epoxidation promoted by these promising oxabicyclic ketones, focusing on the effect of modifying the α-ester substituent.

2. Results and discussion

Since α-acetoxyketone **4a** gave promising enantioselectivity in the epoxidation of (*E*)-stilbene,[3b] we decided to use the parent alcohol **3**[3b] as a starting point for the preparation of several ester derivatives **4**.[5] We were particularly interested in aromatic esters in view of the possibility of π–π interactions with aromatic alkene substrates; accordingly, we prepared both electron-rich and electron-poor esters with the substituents at either the *meta*- or *para*-positions in order to probe their effect on epoxidation enantioselectivities. The results for the epoxidation of (*E*)-stilbene using these racemic ketones (20 mol%) under the Yang[4] Oxone®/CH_3CN/H_2O system (pH ca. 7.5) are shown in Table 1. The trifluoroacetate **4b** showed low conversion (entry 2) due to hydrolysis under the reaction conditions. All of the aromatic esters examined afforded lower conversion than the acetate **4a** (entries 1, 3–7), although they appeared to be stable under the reaction conditions. Perhaps surprisingly, there appeared to be little difference between electron-poor and electron-rich aromatics.



1 X=NCO_2Et, Y=F
2 X=O, Y=F
3 X=O, Y=OH



4

a R=CH_3
b R=CF_3
c R=Ph
d R=*p*-NO_2Ph
e R=*m*-NO_2Ph
f R=*p*-MeOPh
g R=*m*-MeOPh

* Corresponding author. E-mail: a.armstrong@ic.ac.uk

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Table 1. Epoxidation of (*E*)-stilbene catalyzed by racemic ketones **4a**–**g**[a]

Entry	Ketone	R	Time (h)	Conversion[b]
1	**4a**	CH_3	24	85
2	**4b**	CF_3	24	3
3	**4c**	Ph	24	36
4	**4d**	*p*-NO_2Ph	24	39
5	**4e**	*m*-NO_2Ph	24	46
6	**4f**	*p*-MeOPh	24	53
7	**4g**	*m*-MeOPh	24	33

[a] Alkene (0.1 mmol), Oxone® (1.0 mmol $KHSO_5$), ketone (0.02 mmol), $NaHCO_3$ (1.55 mmol), CH_3CN (1.5 ml), aq. Na_2EDTA (1 ml of 0.4 mmol dm^{-3} solution), rt.
[b] Estimated by integration of the crude ^1H NMR spectrum.

Starting from alcohol **3** of 72% e.e. obtained by chiral base chemistry as described earlier,[3b,6] the esters were prepared in enantiomerically enriched form and evaluated for asymmetric epoxidation of alkenes with different substitution patterns: (*E*)-stilbene, styrene and α-methylstyrene (Table 2). The last two compounds represent terminal alkenes, which are still problematic for asymmetric epoxidation.[7] The esters were assumed to have the same enantiomeric excess as the parent alcohol, and none of the solid esters (**4c**, **4d** and **4f**) were recrystallized. Table 2 includes an 'e.e.$_{max}$' value, the expected product e.e. with enantiomerically pure catalyst based on the assumption that there is a linear relationship between catalyst e.e. and product e.e. We have established that this is indeed the case in the epoxidation of (*E*)-stilbene catalyzed by fluoroketone **2**[8a] and by **4a**.[8b] For the epoxidation of (*E*)-stilbene, all of the aromatic esters **4c**–**g** afforded lower e.e. than the acetate **4a** (entries 1, 2–6). Amongst the aromatic esters, the nitroaromatics provided higher e.e. than the methoxy analogues (compare entries 3 and 4 to 5 and 6). A similar trend was noted in the epoxidation of styrene. For α-methylstyrene, selectivities were low in all cases but the methoxyaromatics gave marginally better results than the other catalysts.

Table 2. Epoxidation of aromatic alkenes catalyzed by non-racemic ketones **4a**–**g**[a]

Entry	Ketone	R	(*E*)-Stilbene[b]		Styrene[c]		α-Methylstyrene[d]	
			Conversion[e]	E.e.$_{max}$[f,g]	Conversion[e]	E.e.$_{max}$[f,h]	Conversion[e]	E.e.$_{max}$[f,i]
1	**4a**	CH_3	85	93	100	48	100	10
2	**4c**	Ph	39	75	100	36	100	11
3	**4d**	*p*-NO_2Ph	41	78	100	35	100	15
4	**4e**	*m*-NO_2Ph	46	81	100	40	100	10
5	**4f**	*p*-MeOPh	53	67	100	31	75	19
6	**4g**	*m*-MeOPh	24	46	100	25	65	26

[a] Alkene (0.1 mmol), Oxone® (1.0 mmol $KHSO_5$), ketone (0.02 mmol), $NaHCO_3$ (1.55 mmol), CH_3CN (1.5 ml), aq. Na_2EDTA (1 ml of 0.4 mmol dm^{-3} solution), rt, 24 h.
[b] The major isomer had (*R*,*R*)-configuration in each case.[9]
[c] The major isomer had (*R*)-configuration in each case.[7]
[d] The major isomer had (*S*)-configuration in each case.[7]
[e] Estimated by integration of the crude ^1H NMR spectrum.
[f] E.e.$_{max}$ = 100×product e.e./ketone e.e. All catalysts were derived from alcohol **3** of 72% e.e.
[g] Measured by chiral HPLC (Chiralcel OD column using 10% isopropylalcohol/hexane as eluent).
[h] Measured by chiral GC (Chiraldex GTA column using a thermal ramp 50–180°C).
[i] Measured by chiral HPLC (Chiralcel OD column using 0.8% *iso*-propylalcohol/hexane as eluent).

Table 3. Asymmetric epoxidation of alkenes catalyzed by non-racemic ketone **4a**[a]

Entry	Alkene	Conversion[b]	E.e.$_{max}$[c]	Product configuration
1	Styrene	100	48	(*R*)[d]
2	α-Methylstyrene	100	10	(*S*)[e]
3	(*E*)-Stilbene	85	93	(*R*,*R*)[e]
4	β-Methylstyrene	100	70	(*R*,*R*)[f]
5	Phenylcyclohexene	89	82	(*R*,*R*)[f]
6	Phenylstilbene	71	98	(*R*,*R*)[e]
7	Methyl (*E*)-cinnamate	4	84	n.d.[g]
8	2-Cyclohexenone	51	3	(*R*,*R*)[h]

[a] Alkene (0.1 mmol), Oxone® (1.0 mmol $KHSO_5$), ketone (0.02 mmol), $NaHCO_3$ (1.55 mmol), CH_3CN (1.5 mL), aq. Na_2EDTA (1 ml of 0.4 mmol dm^{-3} solution), rt, 24 h.
[b] Estimated by integration of the crude ^1H NMR spectrum.
[c] E.e.$_{max}$ = 100×product e.e./ketone e.e. Catalyst **4a** used was of 82% e.e. in all cases, except for entries 2, 5 and 6 where **4a** was of 72% e.e.
[d] Product e.e. and configuration were determined by chiral GC.[7]
[e] Product e.e. and configuration determined by chiral HPLC analysis.[7]
[f] Product e.e. and configuration determined by chiral shift reagent ^1H NMR analysis.[9]
[g] Configuration not determined.
[h] Product e.e. determined by GC; configuration determined by comparing the measured optical rotation with the reported one.[10]

Since the α-acetoxyketone **4a** appeared to be the best of the esters examined, we investigated its use in the epoxidation of a wider range of alkenes (Table 3). The results are highly encouraging given that they were obtained at room temperature and without optimization of solvent or reaction pH. Importantly, catalyst **4a** does not appear to undergo Baeyer–Villiger decomposition under the reaction conditions. Very high $e.e._{max}$ was observed for epoxidation of phenylstilbene (98%, entry 6). *Trans*- or trisubstituted aromatic olefins generally afforded products with good $e.e._{max}$ (entries 3–6). Since there are few examples of the asymmetric epoxidation of electron-poor alkenes with chiral dioxiranes, we tested methyl (*E*)-cinnamate. Although good $e.e._{max}$ was observed, the conversion was very low (entry 7). 2-Cyclohexenone proved more reactive but the enantioselectivity was very poor (entry 8).

In summary, we have further investigated the use of esters of α-hydroxy-bicyclo[3.2.1]octan-3-one as catalysts in the Oxone® epoxidation of alkenes. The highest $e.e._{max}$ was obtained using the α-acetoxy-oxabicycle **4a** and the scope of this catalyst was explored. We are continuing to examine further derivatives of this ring system as well as addressing the efficient preparation of **4a** in enantiomerically pure form.

Acknowledgements

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