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LETTERS

N,N-Dialkylalloxans — a new class of catalyst for dioxirane epoxidations

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Abstract

N,N-Dimethyl- and *N,N*-dibenzylalloxans **1a** and **1b** have been prepared and used as novel dioxirane catalysts for the epoxidation of a range of di- and tri-substituted alkenes in good to excellent yield. The dibenzylalloxan **1b** can be recovered in high yield with no evidence of catalyst decomposition.

There has been a great deal of interest in the epoxidation of alkenes using dioxiranes which can be generated in situ from a catalytic amount of a ketone and Oxone® (potassium peroxymonosulphate triple salt).[1–3] Recently, the emphasis has been on the development of chiral ketone catalysts for asymmetric epoxidation,[4–12] most notably the sugar derived ketones used by Shi have been remarkably successful for the production of chiral epoxides from *trans* alkenes. The efficiency of the reaction and stability of the dioxirane catalysts has shown a strong pH dependence in many cases and reactions are generally run at pH 7.5–8.0.[2,7,8] At high pH (>10) Oxone® undergoes autodecomposition at an appreciable rate and can compete with productive catalysis. The importance of catalyst stability in these reactions cannot be underestimated. Baeyer–Villiger type rearrangement of the Criegee intermediate formed by attack of peroxysulphate on the ketone is known to occur at low pH and can lead to catalyst decomposition. In most cases, the recovery of the ketone catalysts has not been demonstrated. It has been recognized that careful design of the catalyst is imperative in order to attain the optimum balance of reactivity and stability. Electron withdrawing groups adjacent to the ketone carbonyl serve to make it more electrophilic and less prone to the Baeyer–Villiger reaction. Recent studies on conformationally locked α-fluorinated cyclohexanones by Denmark[13] have shown the importance of stereoelectronic effects and also led to the suggestion that formation of very stable hydrates from some ketones may impede the rate of dioxirane formation.

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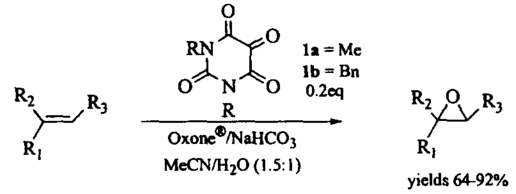
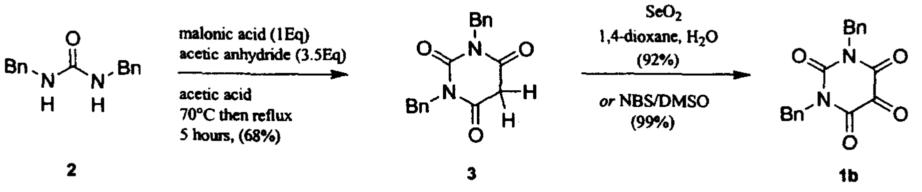
We have investigated the use of alloxans such as **1a** and **1b** as novel catalytic dioxirane precursors and found them to be remarkably efficient and stable for alkene epoxidation (Scheme 1).



Scheme 1.

The catalysts **1a** and **1b** were readily prepared in high yield (Scheme 2). Alloxan **1a** was made by selenium dioxide oxidation[14] of commercially available *N,N*-dimethylbarbituric acid. *N,N*-Dibenzylalloxan **1b** was made starting from benzylamine[15] by reaction with triphosgene to give dibenzylurea **2**. Condensation with malonic acid[16] gave the corresponding dibenzylbarbituric acid **3** which was oxidized with selenium dioxide in high yield. Alternatively, treatment of compound **3** with *N*-bromosuccinimide in dimethylsulfoxide gave **1b** in 99% yield.[17] The epoxidation reactions were routinely carried out over 8 h in an acetonitrile/water mixture by adding solid Oxone® (4 equiv.) and sodium bicarbonate (12 equiv.) portion-wise. The reactions did not appear to be sensitive to short periods of pH fluctuation and addition of these reagents as solutions with closer pH control (7.5–8.0) offered no particular advantage, showing that this class of catalyst is particularly robust. There was virtually no reaction (<5% conversion) under control conditions in which the catalyst was omitted.



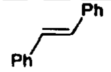
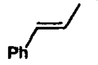
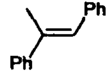
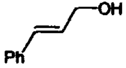
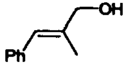
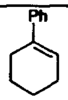
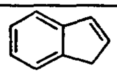
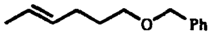
Scheme 2.

Table 1 shows the results for a selection of alkene substrates using *N,N*-dimethylalloxan **1a** as the ketone catalyst.[18] In some cases, it was necessary to use 30 mol% of catalyst **1a** in order to achieve complete conversion of the alkene substrate. As can be seen from the Table, *trans*-disubstituted (entries 1, 2, 4 and 8), *cis*-disubstituted (entry 7) and trisubstituted alkenes (entries 3, 5 and 6) gave good to excellent yields of the corresponding epoxides in 8 h. The reactions were clean and unreacted alkene was recovered from the reactions after column chromatography.

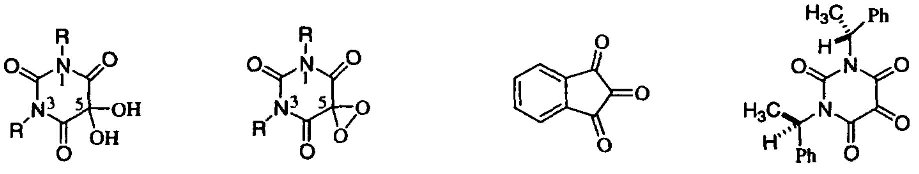
Recovery of the ketone catalyst is an important consideration with respect to potential scale-up of these reactions. Epoxidations using the dibenzylalloxan **1b** gave identical results to those for **1a** for epoxidation of stilbene and β-methylstyrene. It was not possible to isolate the ketone **1a** from the reactions but 70% (unoptimized) of the more organic soluble catalyst **1b** could be recovered from epoxidation of *trans* β-methyl styrene and stilbene after chromatography (entries 1 and 2). There appears to be only two other examples of recovery of a dioxirane catalyst.[11,19] Given the electronic environment of the central ketone in alloxan, Baeyer Villiger oxidation and hence loss of catalyst activity by this mechanism would seem to be extremely unlikely and no by-products of such a reaction were isolated.

Alloxans contain a unique tricarbonyl system with a central electrophilic ketone adjacent to two imide type carbonyls. The ^{13}C NMR spectrum of **1a** and **1b** show them to be symmetrical and to exist exclusively in the hydrated form **4** with the central ketone hydrated δ_C ($CHCl_3$) C-5 85 ppm (Fig. 1). It has not been possible to isolate the actual dioxirane by extraction of the buffered reaction mixture

Table 1
Epoxidation[a] via in situ formation of dioxirane with Oxone® and catalyst **1a** or **1b**

Entry	Substrate	Catalyst (mol/%)	Yields[b] (%) of epoxides
1		1a 30 1b 30	70 70
2		1a 30 1b 30	92 92
3		1a 30	64
4		1a 20	90
5		1a 20	84
6		1a 20	88
7		1a 20	92
8		1a 20	70

[a] All reactions were carried out with alkene (1.1 mmol), ketone **1a** or **b**, Oxone® (4.4 mmol) and $NaHCO_3$(13.2 mmol) in CH_3CN/H_2O (1.5/1) at 0°C for 8 hours. Oxone and $NaHCO_3$ were divided in 8 portions and slowly added at the beginning of each hour. [b] All yields are isolated yields after flash chromatography.



4 **5** **6** **7**

Figure 1.

in the absence of an alkene substrate and it is assumed that the active oxygen transfer species is the C-5 dioxirane **5**. In order to test whether the alloxan system provides any advantages over a triketone the commercially available ninhydrin **6** was utilized. No reaction was observed when substituting the alloxans with ninhydrin for the epoxidation of *trans* β-methyl styrene, indicating that the alloxan system does indeed possess a structure particularly suited to catalytic dioxirane reactions.

The chiral compound **7** has been synthesized as an asymmetric variant of **1b** by using an identical route to that shown in Scheme 1 but starting from (*R*)-α-methylbenzylamine. Unfortunately, no asymmetric induction was achieved on epoxidation of *trans* stilbene, reflecting the requirement for directing groups to be closer to the reaction centre in this system. Since we have shown that they can be recovered in reasonable yield and do not suffer appreciable decomposition, the alloxan catalysts are excellent candidates for use on a solid support. Work in these two areas is ongoing in our group and will be reported elsewhere.

Acknowledgements

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18. Typical catalytic epoxidation procedure: *trans*-β-Methyl styrene (0.13 g, 1.1 mmol), aqueous Na_2EDTA (4×10^{-4} M, 10 cm^3) and a catalytic amount of tetrabutylammonium hydrogen sulfate was dissolved in acetonitrile (15 cm^3) and vigorously stirred at 0°C. Oxone® (2.7 g, 4.4 mmol) and sodium bicarbonate (0.74 g, 8.8 mmol) were mixed and divided into eight equal portions, then a small quantity of the first portion was added to the reaction mixture to adjust the pH to 7.5. *N,N*-Dimethylalloxan (0.056 g, 0.33 mmol) was added to the reaction followed by the first portion of Oxone® and sodium bicarbonate over 10 min. The seven other portions were each added at the beginning of each hour. After 8 h, the reaction was diluted with water (40 cm^3) and extracted with *n*-pentane (4×50 cm^3), the combined extracts were washed with brine, dried (Na_2SO_4), filtered, concentrated and purified by flash chromatography (the silica gel was buffered with 1% triethyl amine solution in *n*-hexane) eluting with diethyl ether (2.5%)/hexane to afford 0.136 g (92%) *trans*-β-methyl styrene oxide as a colourless oil. ν_{max} (NaCl)/cm^{-1} 1249 (C-O-C), 914, 818; δ_H (300 MHz, $CDCl_3$) 1.45 (3H, d, J=5.0, CH_3), 3.0 (1H, dd, $J_{1,2}$=5.0, $J_{2,3}$ 2.0, H-2), 3.5 (1H, d, $J_{2,3}$=2.0, H-3), 7.3–7.2 (5H, m, $H_{aromatic}$); δ_C (100 MHz, $CDCl_3$) 17.7 (CH_3), 58.8 (C2), 59.4 (C3), 125.6 (C5, C9), 128.0 (C7), 128.4 (C6, C8), 137.8 (C4); *m/z* (EI) 134 (25%, $[M]^+$), 119 (5, $C_8H_7O^+$), 105 (46, $C_7H_5O^+$), 90 (100, $C_7H_6^+$), 77 (30, $C_6H_5^+$).
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