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LETTERS

A *syn* selective dihydroxylation of cyclic allylic trichloroacetamides using catalytic osmium tetroxide

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Abstract

A range of cyclic allylic trichloroacetamides has been synthesised. Dihydroxylation utilising catalytic osmium tetroxide and quinuclidine-*N*-oxide monohydrate as the re-oxidant in dichloromethane yields diols with good levels of *syn* selectivity. © 2000 Elsevier Science Ltd. All rights reserved.

We have recently shown that the addition of TMEDA to a stoichiometric amount of OsO₄ generates a reagent which dihydroxylates allylic alcohols¹ and allylic amides² with excellent *syn* selectivity. This phenomenon is due to efficient hydrogen bonding between the oxidant and the substrate, thus promoting a contrastreric oxidation with stereochemistry opposite to that obtained under more standard (e.g. Upjohn) conditions.³ However, utilisation of this protocol has one drawback, namely the use of a stoichiometric amount of osmium tetroxide: the use of catalytic OsO₄ with chelating diamines is currently unknown, probably because the (chelated) osmate esters so produced are difficult to reoxidise *in situ*.

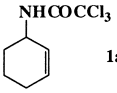
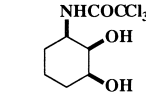
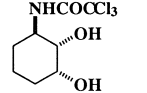
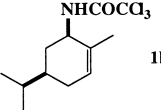
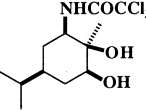
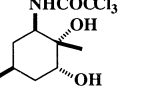
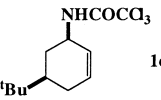
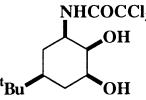
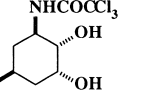
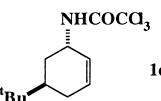
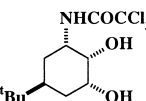
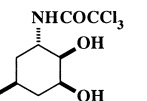
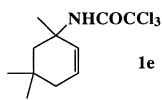
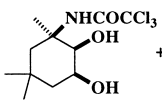
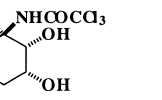
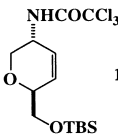
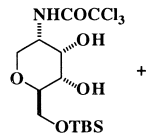
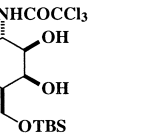
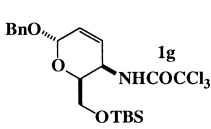
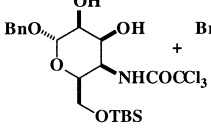
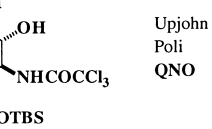
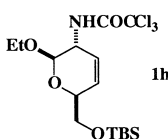
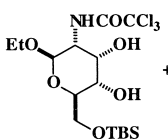
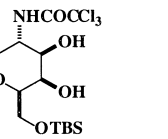
In preliminary studies we found that the addition of quinuclidine (1 equiv.) to OsO₄ (1 equiv.) went some way to producing a *syn* selective dihydroxylation of allylic alcohols. However, the complex formed between osmium tetroxide and quinuclidine displays reduced hydrogen-bonding ability compared to the bidentate OsO₄·TMEDA complex,⁴ probably because there is less electron density pushed onto the transition metal by the monodentate donor. From such observations it was postulated that this, weakly directing, oxidation could be made catalytic in OsO₄ by introducing quinuclidine as its corresponding *N*-oxide (QNO)⁵ and with sufficient water to allow the catalytic cycle to turn over. One way of utilising this weak directing effect is to oxidise a strongly directing substrate, such as an allylic trichloroacetamide.²

In order to fully examine the scope of this reaction, a range of six-membered allylic trichloroacetamides was synthesised. These substrates were then oxidised under Upjohn (1.5 equiv. NMO,

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cat. OsO₄, acetone/H₂O, rt),⁶ Poli (1.5 equiv. Me₃NO·2H₂O, cat. OsO₄, CH₂Cl₂, rt)⁷ and quinuclidine-*N*-oxide (1.3 equiv. QNO·H₂O, 5% OsO₄, CH₂Cl₂, rt)⁸ conditions, see Table 1. The results show that under Upjohn conditions these substrates give low stereoselectivity, mostly for the *anti* diol. While dihydroxylation using Poli's conditions gave improved levels of *syn* stereoselectivity, oxidation with QNO and catalytic osmium tetroxide (5 mol%) generated the diol in excellent yields with the highest levels of *syn* stereoselectivity yet observed for a catalytic system.

Table 1

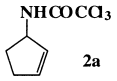
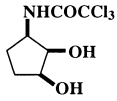
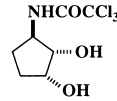
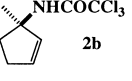
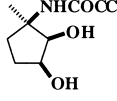
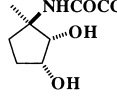
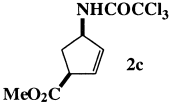
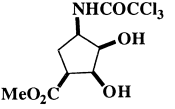
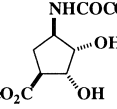
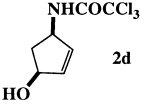
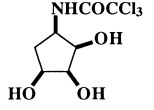
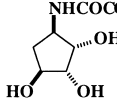
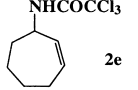
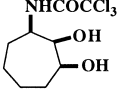
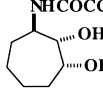
Substrate	(<i>syn</i>)	Adducts	(<i>anti</i>)	Syn : Anti	Yield
 1a		+		Upjohn 1.0 : 3.2 Poli 3.0 : 1.0 QNO 4.3 : 1.0	98% 93% 86%
 1b		+		Upjohn 1.3 : 1.0 Poli 13 : 1.0 QNO 20 : 1.0	86% 84% 95%
 1c		+		Upjohn 1.0 : 1.6 Poli 6.0 : 1.0 QNO 13 : 1.0	96% 81% 77%
 1d		+		Upjohn 1.0 : 2.8 Poli 1.6 : 1.0 QNO 2.1 : 1.0	82% 91% 88%
 1e		+		Upjohn no reaction Poli 11 : 1.0 QNO 20 : 1.0	– 81% 79%
 1f		+		Upjohn 1.5 : 1.0 Poli 25 : 1.0 QNO 25 : 1.0	80% 85% 89%
 1g		+		Upjohn no reaction Poli 2.0 : 1.0 QNO 2.4 : 1.0	– 90% 94%
 1h		+		Upjohn no reaction Poli 20 : 1.0 QNO 20 : 1.0	– 80% 91%

The stereoselectivity of both the Poli and QNO reactions was checked by ^1H NMR of the crude reaction mixture and in comparison with the compounds produced from the corresponding Upjohn reaction.

We then prepared and oxidised four five-membered and one seven-membered allylic trichloroacetamide to examine the generality of the process, see Table 2. The seven-membered (**2e**) and two sterically undemanding five-membered (**2a,b**) substrates displayed enhanced levels of *syn* stereoselectivity under QNO dihydroxylation conditions. However, **2c** and **2d** failed to give a significant increase in *syn* selectivity over the Upjohn and Poli reactions. Again the diastereoselectivity of the reaction was measured by ^1H NMR spectroscopy on the crude reaction mixture.

The reasons behind the difference in selectivity between Poli's conditions and the QNO reaction could derive from a number of factors including the relative amounts of water present in the reaction, the relative contributions from first and second cycle¹⁰ oxidants and also the effectiveness of quinuclidine versus trimethylamine as an electron donating ligand for osmium. Further work is in progress to investigate these issues.

Table 2
The products from oxidation of **2d** and **2e** were peracetylated in situ prior to isolation

Substrate	(<i>syn</i>) Adducts	(<i>anti</i>) Adducts		<i>Syn</i> : <i>Anti</i>	Yield
 2a			Upjohn Poli QNO	1.1 : 1.0 7.8 : 1.0 13 : 1.0	78% 84% 69%
 2b			Upjohn Poli QNO	7.0 : 1.0 9.0 : 1.0 13 : 1.0	88% 81% 69%
 2c			Upjohn Poli QNO	1.3 : 1.0 1.5 : 1.0 1.6 : 1.0	78% 81% 69%
 2d			Upjohn QNO [(TMEDA, OsO4 1 eq.)	1.0 : 2.0 1.0 : 1.0 18 : 1.0	63% 72% 83%
 2e			Upjohn Poli QNO	1.3 : 1.0 10 : 1.0 17 : 1.0	85% 87% 82%

To conclude, we have introduced a method for the *syn* selective dihydroxylation of allylic amides that uses only 5 mol% of osmium tetroxide and quinuclidine-*N*-oxide as a reoxidant. While the levels of *syn* selectivity that are obtained with this system are not quite as high as those achieved with stoichiometric OsO₄ and TMEDA, the use of catalytic transition metal makes the procedure more useful for work on a large scale.

Representative experimental procedure: quinuclidine (1.00 g, 9.01 mmol) was dissolved in dichloromethane (20 mL) under nitrogen and cooled to -78°C . Recrystallised *m*-chloroperbenzoic acid (1.94 g) was added in one portion. The mixture was stirred for 30 min and then allowed to warm to room temperature. The crude reaction mixture was flushed through a column of silica gel with dichloromethane as eluent until all of the benzoic acid by-product was removed, then the solvent gradient was increased to 30% methanol–dichloromethane to strip quinuclidine-*N*-oxide from the column. Concentration in vacuo produced a brown oil, which crystallised under high vacuum conditions to produce QNO as an off-white solid, 1.25 g (95%) and this was stored under reduced pressure. KF analysis showed this hygroscopic material contained 11% water by weight ($\sim\text{QNO}\cdot\text{1H}_2\text{O}$),¹¹ and on standing open to air this increased to 40% water by weight ($\sim\text{QNO}\cdot\text{5H}_2\text{O}$).

Quinuclidine-*N*-oxide monohydrate (0.36 g, 2.18 mmol) was added in one portion to a stirred solution of allylic amide (**1b**) (0.50 g, 1.68 mmol) in dichloromethane at room temperature under nitrogen. Osmium tetroxide (0.02 g, 0.08 mmol) was added and the reaction was stirred until complete consumption of the starting amide was observed via TLC. Methanol (10 mL) and concentrated HCl (4 drops) were added and stirred for 2 h, then the mixture was concentrated in vacuo to afford a dark yellow viscous oil. Column chromatography ($R_f=0.41$, 80% ether in 40–60 petroleum ether) yielded the diol (0.53 g, 95%) as a colourless crystalline solid.

Acknowledgements

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