A simple and efficient method for epoxidation of terminal alkenes

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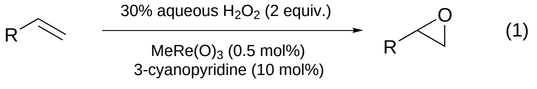
The use of a catalytic amount of 3-cyanopyridine in the methyltrioxorhenium catalysed epoxidation of terminal alkenes with aqueous hydrogen peroxide speeds turnover, which results in the formation of many functionalized epoxides in high yields.

Despite numerous literature precedents, the epoxidation of terminal alkenes remains a challenge in organic synthesis.[1] While screening for other examples of ligand accelerated catalysis (LAC),[2] our group has recently discovered that pyridine enhances the rate of the methyltrioxorhenium (MTO)-catalysed epoxidation of alkenes, while also tempering the Lewis acidity of the metal centre and thereby protecting the epoxide from destruction.[3] This method gives high yields of epoxides for di-, tri- and tetra-substituted alkenes; however, the epoxidation of terminal alkenes requires prolonged reaction times (3–5 days) and the conversion rarely exceeds 60–80%. Therefore, we decided to investigate the epoxidation of styrene, which is both a terminal alkene and the progenitor of a sensitive epoxide. The intention was to probe the relationship between the basicity of various pyridine ligands and their effectiveness.† We found that while basic pyridines (pyridine, 4-*tert*-butyl- and 4-methoxy-pyridine) protected the epoxide from ring opening, they also diminished the catalyst lifetime. On the other hand, less basic pyridines, and especially the ones bearing electron-withdrawing substituents in the meta position, *e.g.* 3-cyano-pyridine, 3-fluoropyridine, methyl nicotinate and even nicotinic acid, allowed high conversions (90–100%), but provided little or no protection for the epoxide. As a result mixtures of benzaldehyde, benzoic acid, styrene diol and only trace amounts of styrene oxide were obtained.

With these two facts in hand, epoxidation with a mixture of the two types of pyridines was attempted. Thus, treatment of a mixture of styrene (20 mmol), pyridine (2 mmol), 3-cyanopyridine (2 mmol) and MTO (0.1 mmol) in CH_2Cl_2 (14 ml) with 30% aqueous H_2O_2 (4 ml, 40 mmol) at room temperature gave, after 17 h, a 76% yield of styrene oxide along with 10% recovered styrene according to GC analysis. Using 2.5 ml instead of 14 ml of CH_2Cl_2—increasing the concentration from 1.2 to 5.0 M—allowed a better conversion (97–99%) in a shorter time (6 h) and gave an 89–92% yield of styrene oxide.‡ Other combinations of pyridines were less effective and presence of the parent pyridine was essential for the protection of the epoxide. In fact, even under the best conditions, benzaldehyde (0–0.5%), benzoic acid (0–1%) and styrene diol (2–3%) were always detected.

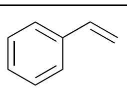
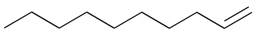
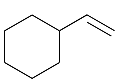
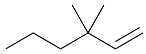
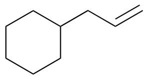
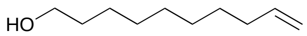
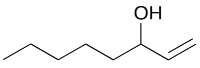
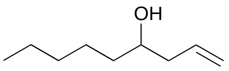
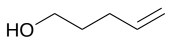
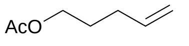
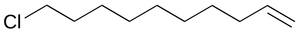
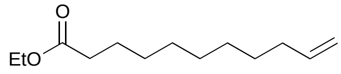
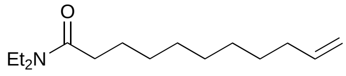
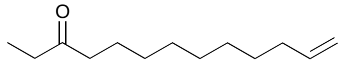
The other terminal alkenes in Table 1 give epoxides which are much less acid sensitive and their epoxidation did not require the use of a mixture of pyridines [eqn. (1)].§



(1)

3-Cyanopyridine proved to be the optimal ligand in these cases.¶ A representative procedure for the epoxidation of such terminal alkenes is as follows: a mixture of dec-1-ene (28.0 g, 200 mmol), 3-cyanopyridine (2.08 g, 20 mmol) and MTO (249 mg, 1 mmol) in CH_2Cl_2 (120 ml) was treated with 40 ml of 30% aqueous H_2O_2 (400 mmol) and stirred for 17 h at 24 °C.‖ The biphasic reaction mixture was then treated with crushed ice (20 g) and a catalytic amount of MnO_2 (25 mg) and stirred until

Table 1 MTO-catalysed epoxidations of terminal alkenes with hydrogen peroxide in the presence of 3-cyanopyridine[a]

Entry	Alkene	Yield (%)[b,c]	*t*/h
1[d]		85	6
2		94	17
3		86	30
4		78	30
5		89	20
6		89	19
7[e]		94	27
8[e]		88	17
9		97[f]	18
10		94	20
11		86	30
12		89	20
13		90	19
14		96	24

[a] Reaction conditions: Alkene (1 equiv.), MTO (0.5 mol%), 3-cyanopyridine (10 mol%), 30% H_2O_2 (aq.) (2 equiv.) in CH_2Cl_2. Alkene concentration: 1.3 M. See footnote §. [b] Conversions are > 99%. [c] Isolated yield. [d] A mixture of 3-cyanopyridine and pyridine (10 mol% of each) was employed. Alkene concentration: 4 M. [e] The epoxides were formed as a 1 : 1 mixture of diastereomers. [f] The initially formed epoxy alcohol cyclized completely to the tetrahydrofurfuryl alcohol **1**, which was isolated in 97% yield.

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oxygen evolution ceased (1 h). Following phase separation, the water layer was extracted with CH_2Cl_2, the combined organic layers were dried over Na_2SO_4 and concentrated to an oil. Hexane was added to this crude product, and the resulting white precipitate was removed by filtration.** The filtrate was concentrated, and the crude colourless oil was distilled to yield 31.4 g of decene oxide (94% yield, 96.5% purity).††

This method is general and quite independent of the steric bulk at the α-position of the alkene (entries 3 and 4). Moreover, the presence of alcohol functionalities did not significantly affect the yield of epoxidation (entries 6–8) or its diastereoselectivity (entries 7 and 8).‡‡ However, the bis(homoallylic) alcohol (entry 9) gave only the furan **1** in high yields, but the epoxide is isolated in excellent yield if the hydroxy group is protected (entry 10). Other remote functionalities (amides, chlorides, esters and ketones) are also compatible with this epoxidation method (entries 11–14), and it is noteworthy that in the epoxidation of the ω-alkenone (entry 14) the possible Baeyer–Villiger products were not detected (*i.e.* $< 1\%$) based on NMR spectroscopy of the crude reaction mixture.[4]

In summary, a remarkable, albeit poorly understood, beneficial effect of 3-cyanopyridine on MTO-catalysed epoxidations of terminal alkenes has been established. For this challenging class of substrates, this method of epoxidation could prove to be one of the most convenient because (i) it shows good functional group compatibility (wide scope), (ii) it is mild (*i.e.* neutral conditions, room temperature), (iii) it uses a readily available, safe and environmentally friendly oxidizing agent (30% aqueous H_2O_2), and (iv) it is easy to perform on the scales common (1 to 200 mmol) in the laboratory (no tedious work-up, no by-products). We are currently investigating ways to increase turnover numbers as well as trying to understand the special nature of the 3-cyanopyridine ligand.

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Footnotes and References

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† Studies on the effect of various pyridine ligands (substituent effect) for the MTO–pyridine derivatives system are still underway.

‡ Longer reaction time did not increase conversion, and favoured formation of the by-products.

§ All compounds were isolated and characterized by standard techniques. All reactions proceeded to $>99\%$ conversion unless otherwise noted.

¶ In the absence of 3-cyanopyridine, the reaction was slower and showed evidence of catalyst deactivation (*i.e.* only 93% conversion after 40 h). Anhydrous H_2O_2—reaction in *tert*-butyl alcohol— resulted in lower yields and prolonged reaction times, see ref. 1(*b*) and especially W. A. Herrmann, R. W. Fischer, M. U. Rauch and W. Scherer *J. Mol. Catal.*, 1994, **86**, 243.

‖ The reaction is slightly exothermic, and should be kept around 24 °C with a water bath.

** It is worth pointing out that 90–100% of the 3-cyanopyridine is consumed by the end of the reaction, and the white precipitate formed was identified as 3-cyanopyridine *N*-oxide. Monitoring the reaction with NMR spectroscopy showed that its formation became significant only late in the reaction, when the amount of alkene remaining was close to the amount of 3-cyanopyridine. For oxidations of amines using MTO, see Z. Zhu and J. H. Espenson, *J. Org. Chem.*, 1995, **60**, 1326; R. W. Murray; K. Iyanar, J. Chen and J. T. Wearing, *Tetrahedron Lett.*, 1996, **37**, 805; A. Goti and L. Nannelli, *Tetrahedron Lett.*, 1996, **37**, 6025; S. Yamazaki, *Bull. Soc. Chem. Jpn.*, 1997, **70**, 877.

†† This yield does not take into account the purity of the starting material; Aldrich dec-1-ene is 94% pure.

‡‡ No or little diastereoselectivity is usually observed in the MTO-catalysed epoxidation of allylic and homoallylic alcohols (W. Adam and C. M. Mitchell, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 533; T. R. Boehlow and C. D. Spilling, *Tetrahedron Lett.*, 1996, **37**, 2717). This is in sharp contrast to some other transition metal-catalysed epoxidation reactions, see K. B. Sharpless and T. R. Verhoeven, *Aldrichim. Acta*, 1979, **12**, 63.

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