Highly Efficient Epoxidation of Olefins Using Aqueous H_2O_2 and Catalytic Methyltrioxorhenium/ Pyridine: Pyridine-Mediated Ligand Acceleration

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We report here the discovery of a ligand-accelerated[1] mode for methyltrioxorhenium (MTO)-catalyzed olefin epoxidations.[2,3] Aqueous H_2O_2 is the oxidant, and the ligands are pyridine derivatives. In addition to its beneficial effect on rate, the pyridine ligand shuts down the acid-catalyzed ring-opening reactions which are the bane of most epoxidation methods in use today.[2,4] The standard procedure is exemplified in Scheme 1 for 1-phenylcyclohexene whose epoxide is sensitive to acid-catalyzed destruction and is difficult to prepare by most existing epoxidation methods.[5]

Use of *aqueous* H_2O_2 as the oxidant in transition metal catalyzed epoxidations was first described by Venturello who employed a tungstate catalyst under phase transfer conditions.[6] A more effective version was recently published by Noyori, but this system also presents epoxide-opening problems caused by the slight acidity of the reaction milieu.[7,8]

Inorganic rhenium compounds such as Re_2O_7 or ReO_3 were long known to exhibit modest catalytic activity for H_2O_2-based oxidations.[9] However, real interest in the potential of rhenium oxidation catalysts began with an extraordinary discovery by the Herrmann group. They found that organometallic oxorhenium(VII) species (especially MTO)[10] are powerful epoxidation catalysts with H_2O_2 as oxidant.[2a−c] Their work focused on the use of anhydrous H_2O_2 (particularly in *t*-BuOH) because water was detrimental, increasing losses via acid-catalyzed epoxide destruction pathways.[4] This epoxide-instability problem has not been overcome by Herrmann or others,[2] although improvements have been made.[2d,e,i] The addition of tertiary nitrogen bases, including pyridine, was found to suppress epoxide ring-opening processes but at the expense of a strong *detrimental effect on catalyst activity*. In any case, amine additives were apparently not regarded as overall beneficial, since they do not appear in any of the recommended "general procedures".[2c,d]

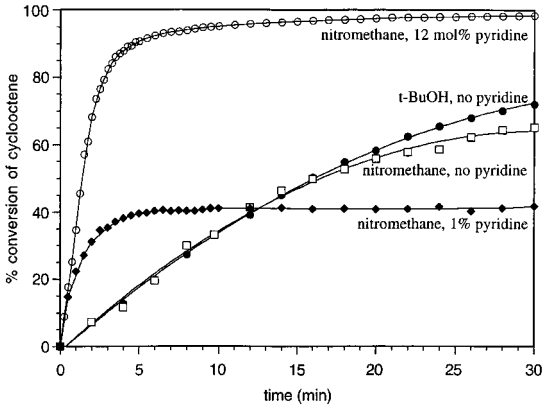
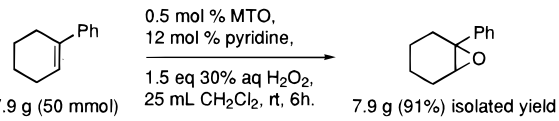


Figure 1. Reaction profile of the MTO-catalyzed epoxidation of cyclooctene in different solvents with different amounts of pyridine added (0.5 mol % MTO, 2 equiv of 30% H_2O_2, $c_{substrate} = 0.8$ mol/L); analysis via GC after quenching the aliquots with MnO_2.

Scheme 1. Epoxidation of 1-Phenylcyclohexene by MTO/Pyridine (50 mM scale)



In accord with observations of Herrmann and Adam, we found that a range of saturated nonaromatic tertiary amines strongly inhibit catalyst activity. This effect is independent of the solvent, the amount of amine, and the presence or absence of water. However, we were surprised to find that pyridine and pyridine derivatives exhibited a remarkable acceleration effect on the epoxidation rate, for pyridine too was found to have a deleterious effect in the earlier work.[2c,11] This acceleration effect of pyridines is most pronounced in aprotic and noncoordinating solvents (e.g., CH_2Cl_2 and CH_3NO_2).

While the reaction profile for the epoxidation of cyclooctene (Figure 1) clearly shows the rate enhancing effect of the pyridine ligand, it also reveals that *catalyst lifetime is critically dependent on the amount of pyridine present*. The initial rates using either 1 mol % or 12 mol % pyridine in CH_3NO_2 (or CH_2Cl_2, not shown) as solvent are nearly the same, but in the former case, the catalyst decomposes completely within about 5 min, resulting in poor conversion. In CH_3NO_2 or CH_2Cl_2 and about 3 mol % (or more) pyridine present, the catalyst is preserved and cyclooctene is more than 95% converted to the epoxide within 15 min.[12] In summary, pyridine plays three crucial roles in enhancing this process: (1) it speeds catalytic turnover, (2) it prevents decomposition of epoxide products, and (3) in sufficient concentration, it increases catalyst lifetime. The fact that pyridine actually accelerates catalyst decomposition until a threshold concentration is reached, probably explains why earlier workers did not see its dramatic beneficial effects. Furthermore, with *t*-BuOH as the solvent, the enhancing effects of pyridine are only evident at much higher pyridine concentrations.[13] Since both CH_3NO_2 and CH_2Cl_2 result in biphasic

(1) Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059.

(2) (a) Hoechst AG; Herrmann, W. A.; Marz, D. W.; Kuchler, J. G.; Weichselbaumer, G.; Fischer, R. W.; DE 3.902.357, 1989. (b) Herrmann, W. A.; Fischer, R. W.; Marz, D. W. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1638−1641. (c) Herrmann, W. A.; Fischer, R. W.; Rauch, M. U.; Scherer, W. *J. Mol. Catal.* **1994**, *86*, 243. (d) Adam, W.; Mitchell, C. M. *Angew. Chem.* **1996**, *108*, 78−581; *Angew. Chem., Int. Ed.* **1996**, *35*, 533. (e) Boelow, T. R.; Spilling, C. S. *Tetrahedron Lett.* **1996**, *37*, 2717. (f) Al-Ajlouni, A. M.; Espenson, J. H. *J. Am. Chem. Soc.* **1995**, *117*, 9243. (g) Pestovsky, O.; van Eldik, R.; Huston, P.; Espenson, J. H. *J. Chem. Soc., Dalton Trans. 2* **1995**, 133. (h) Al-Ajlouni, A. M.; Espenson, J. H. *J. Org. Chem.* **1996**, *61*, 3969. (i) ARCO Chemical Technology; Crocco, G. L.; Shum, W. P.; Zajacek, J. G.; Kesling, H. S., Jr.; US 5.166.372, 1992.

(3) For an excellent review on rhenium and technetium oxo complexes in the study of organic oxidation mechanisms, see: Gable, K. P. *Adv. Organomet. Chem.* **1997**, *41*, 127.

(4) Epoxide ring opening is a serious problem in the *ligand-free* MTO-catalyzed epoxidation process,[2] which is therefore only applicable for olefins which yield very robust epoxides (e.g., cyclooctene).

(5) Berti, G.; Bottari, F.; Macchia, B.; Macchia, F. *Tetrahedron* **1965**, *21*, 3277.

(6) (a) Venturello, C.; Alneri, E.; Ricci, M. *J. Org. Chem.* **1983**, *48*, 3831. (b) Venturello, C.; D'Aloisio, R. *J. Org. Chem.* **1988**, *53*, 1553. (c) See also: Prandi, J.; Kagan, H. B.; Mimoun, H. *Tetrahedron Lett.* **1986**, *27*, 2617.

(7) Sato, K.; Aoki, M.; Ogawa, M.; Hashimoto, T.; Noyori, R. *J. Org. Chem.* **1996**, *61*, 8310.

(8) (a) Romano, U.; Esposito, A.; Maspero, F.; Neri, C.; Clerici, M. G. *Chim. Ind. (Milan)* **1990**, *72*, 610. (b) Clerici, M. G.; Ingallina, P. *J. Catal.* **1993**, *140*, 71.

(9) (a) E. I. DuPont de Nemours & Co.; Parshall, G. W.; US 3,646,130 and 3,657,292, 1972. (b) See references in *Applied Homogeneous Catalysis with Organometallic Compounds Vols. I and II*; Cornils, B., Herrmann, W. A., Eds.; VCH: Weinheim, 1996.

(10) Methyltrioxorhenium (MTO) was first prepared by Beattie and Jones: Beattie, I. R.; Jones, P. J. *Inorg. Chem.* **1979**, *18*, 2318.

(11) It is known that MTO decomposes in basic aqueous solutions, and the process has been studied in detail by Espenson: Abu-Omar, M. M.; Hansen, P. J.; Espenson, J. H. *J. Am. Chem. Soc.* **1996**, *118*, 4966. Investigations aimed at resolving this apparent conflict with our system are currently underway.

(12) Preliminary results show that *the amount of water present* (delivered with H_2O_2 and/or generated in the course of the reaction) has a major influence on catalyst activity, both turnover rate and lifetime.

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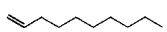
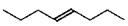
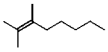
Table 1. MTO/Pyridine-Catalyzed Epoxidation of Olefins[a]

entry	substrate	time (h)	conversion (%)[b] (isolated yield) (%)[c]	selectivity (%)
1		48	82	> 99
2		16	84	> 99
3		6	92 (82)	> 98
4		4	99 (96)	> 99
5		24	97 (91)	> 99
6		6	99 (92)	> 98
7		30	85	> 98
8		6	99 (97)	> 99
9		5	99 (94)	> 98
10		30	99	> 98
11		4	92	> 98
12		6	96	> 99
13		5	99 (96)	> 98
14		7	97 (86)	> 98 (only exo)
15		3	99	> 99
16		2	99 (97)	> 99
17		6	99 (91)	> 98
18		2	99	> 99

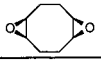
[a] Reaction conditions: $c_{substrate}$ = 2 mol/L (except entry 2 where 3 mol/L was used); 0.5 mol % MTO, 12 mol % pyridine, 1.5 equiv 30% aqueous H_2O_2, CH_2Cl_2, rt, water bath. [b] Determined on a 2 mmol scale by GLC or ^{1}H NMR (400 MHz) using internal standards. [c] Determined on a 50 mmol scale.

conditions, we also determined the reaction profiles shown in Figure 1 in a homogeneous solvent system (i.e., CH_3NO_2/*t*-BuOH 85:15 v/v) and the results were almost identical.[14] In addition, when the more sterically hindered 2-picoline is used in place of pyridine, the acceleration feature is lost regardless of the solvent system employed.[14] These control experiments speak against both phase transfer and/or simple base effects as the origin of the rate enhancement by pyridine.

The wide scope of this process is revealed in Tables 1 and 2.[15] Even epoxides that are very sensitive to ring opening (Table 1, entries 3, 11, and 17) do not undergo hydrolytic ring opening.[16] Epoxidation of selected cyclic dienes resulted in high diastereoselectivities for the cases studied (Table 2).[17,18]

We conclude by enumerating some advantages of this new process over the *m*-chloroperbenzoic acid (*m*-CPBA) method, which is the one in widest use for research-scale epoxidations

Table 2. MTO/Pyridine-Catalyzed Epoxidation of Dienes[a]

entry	substrate	product	time (h)	ratio monoepoxide: diepoxide	selectivity (%)[c]	diastereomeric ratio for diepoxide
1[b]			3	1.2:1	95	99% *anti*
2			6	1:100	99	96:4 (*anti*:*syn*)
3[b]			7	1:1.3	99	99% *anti*
4			5	1:100	97	99% *syn*

[a] Reaction conditions: $c_{substrate}$ = 2 mol/L; 0.5 mol % MTO, 12 mol % pyridine, 2.5 equiv *50%* aqueous H_2O_2, CH_2Cl_2, rt, water bath, 2 mmol scale, selectivities and rates determined by ^{1}H NMR (400 MHz). [b] Reaction performed at 10 °C. [c] Chemoselectivity with respect to the epoxidation reaction. [d] See Supporting Information for details.

at present:[19−21] (1) the MTO/pyridine process is comparable in cost as well as safer than the *m*-CPBA process; (2) both selectivity and scope are much greater, because even acid sensitive epoxides do not suffer ring opening or rearrangement reactions;[21] (3) the new system is more reactive, can be run with significantly less solvent, and workup/product isolation is substantially easier; finally, (4) the only byproduct is water.

This ligand-accelerated, rhenium-catalyzed epoxidation process may be the first example of rate enhancement by a basic ligand of an oxidative transformation involving peroxometal species.[22] The mechanistic basis for this pyridine effect deserves careful study but could take years to work out (cf., OsO_4/ligand/olefin mechanism). *However, the importance of decoupling epoxidation activity from acidity will be immediately apparent to all synthetic chemists.*[23] The search for a simple, catalytic epoxidation process which functions optimally under neutral-to-basic conditions has been a constant, albeit elusive, goal of ours for the past 25 years. Having found such a system,[24] we are of course interested in understanding and exploiting the new reactivity features it offers. For example, experiments aimed at adding the feature of enantioselectivity are now underway.

Acknowledgment. This paper is dedicated to Anthony Rappé and William Goddard whose pioneering calculations on metal oxo species inspired this work. We thank the National Institutes of Health (GM 28384), the National Science Foundation (CHE 9531152), the W. M. Keck Foundation, and the Skaggs Institute for Chemical Biology for financial support. J.R. is grateful for a NATO postdoctoral fellowship granted by the Deutscher Akademischer Austauschdienst (DAAD).

Supporting Information Available: Experimental details (6 pages). See any current masthead page for ordering and Internet access instructions.

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(13) J. Rudolph, K. L. Reddy, J. P. Chiang, K. B. Sharpless, unpublished results, not shown in Figure 1.

(14) See Supporting Information for these results.

(15) (a) Due to practical considerations, we used CH_2Cl_2 as solvent for all examples even though CH_3NO_2 is slightly superior with regard to reaction rate. (b) See Supporting Information for scale-up experimental procedure.

(16) Such substrates yield only products derived from acid-catalyzed epoxide opening under the ligand-free conditions of the original MTO-catalyzed procedure even though anhydrous H_2O_2 is the oxidant: J. Rudolph, K. L. Reddy, J. P. Chiang, K. B. Sharpless, unpublished results.

(17) Diastereoselective MTO-catalyzed epoxidations of allylic alcohols and other chiral olefins using the H_2O_2−urea complex as oxidant have already been reported by Adam[2d] and Boelow.[2e]

(18) Compare to the peracid-mediated bisepoxidation of 1,4-cyclohexadiene and 1,5-cyclooctadiene, respectively: (a) Craig, T. W.; Harvey, G. R.; Berchtold, G. A. *J. Org. Chem.* **1967**, *32*, 3743. (b) Cope, A.; Fisher, B. S.; Funke, W.; McIntosh, J. M.; McKervey, M. A. *J. Org. Chem.* **1969**, *34*, 2231.

(19) The buffered *m*-CPBA procedures partly overcome the "acidity problem" but not as efficiently as this new MTO/pyridine system. See for example: (a) Camps, F.; Coll, J.; Messeguer, A.; Pujol, F. *J. Org. Chem.* **1982**, *47*, 5402. (b) Imuta, M.; Ziffer, H. *J. Org. Chem.* **1979**, *44*, 1351. (c) Anderson, W. K.; Veysoglu, T. *J. Org. Chem.* **1973**, *38*, 2267. Only the Payne epoxidation process[20] and the Murray DMDO reagent[21] are of comparable effectiveness.

(20) Payne, G. B. *Tetrahedron* **1962**, *18*, 763. The Payne epoxidation is often the method of choice for industrial batch-type applications, but on a small scale, the need for continuous pH-control is inconvenient.

(21) Murray, R. W.; Singh, S. *Org. Synth.* **1996**, *74*, 91.

(22) An accelerating effect for tertiary amine ligands in catalytic epoxidations is well documented for systems involving d^2, d^3, and d^4 oxo metal species. For reviews, see: (a) Meunier, B. *Bull. Soc. Chim. Fr.* **1986**, 578. (b) McMurry, T. J.; Groves, J. T. In *Cytochrome P-450: structure, mechanism, and biochemistry*; Ortiz de Montellano, P. R., Ed.; Plenum Press: New York, 1986; p 1.

(23) With few exceptions (e.g., Payne[20] and Murray reagents[21]), the existing catalytic and stoichiometric epoxidation systems are most reactive under acidic conditions, and of course, the latter often cause destruction of the epoxide product.

(24) The complex path by which we arrived at the present system will be described elsewhere. Suffice it to say here that the Rappé−Goddard "spectator oxo" concept has been a key guiding principle ever since it was first published in 1980: (a) Rappé, A. K.; Goddard, W. A., III *Nature* **1980**, *285*, 311. (b) Rappé, A. K.; Goddard, W. A., III *J. Am. Chem. Soc.* **1982**, *104*, 448. (c) Rappé, A. K.; Goddard, W. A., III *J. Am. Chem. Soc.* **1982**, *104*, 3287.