Selective Epoxidation of Monoterpenes with Methyltrioxorhenium and H₂O₂

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Abstract: In the presence of pyridine as a co-catalyst, CH_3ReO_3 catalyses the epoxidation of terpenes such as α-pinene with H_2O_2 with minimal rearrangement of the epoxide. Pyridine is also critical to suppress isomerisation of the olefin substrate (in case of nerol, geraniol). The reaction can be directed towards selective single or double epoxidation, or in one step towards the rearranged product (e.g. from linalool to the ring-closure product linalool oxide).
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Terpenes are widely distributed in nature, and their epoxides often serve as starting materials for the synthesis of fragances, flavors and therapeutically active substances.[1] Organic peroxyacids, particularly m-chloroperbenzoic acid (MCPBA), are still the most widely used epoxidation reagents, whether preformed or generated in situ from O_2 and an aldehyde.[2] However, they are economically unattractive and produce the corresponding acid in stoichiometric amounts. Hydrogen peroxide is an efficient oxidant if it is appropriately activated, and if solvolytic reactions due to Brönsted acidity can be controlled. While this seemed till now only possible with W,[3] it has recently been established that the acidity of the CH_3ReO_3 (MTO) epoxidation catalyst [4,5] can be tempered by using a urea/H_2O_2 adduct,[6] or by addition of pyridine.[7-8] Moreover, pyridines seem to increase epoxidation rates with MTO via ligand-accelerated catalysis.[7] We report here on the applicability of MTO to the epoxidation of a series of natural alkenes, alcohols and esters with H_2O_2 as the oxidant. Depending on an appropriate choice of solvent, temperature and co-catalyst, the reaction may be directed towards single or double epoxidation, or directly towards a rearranged product. Even the highly sensitive terpenic epoxides can be obtained in excellent yields, for instance:

CH_3ReO_3 (0.5 mol%), pyridine (40 mol%)

1.7 eq. 35 % H_2O_2, 273 K, CH_2Cl_2

90 % yield
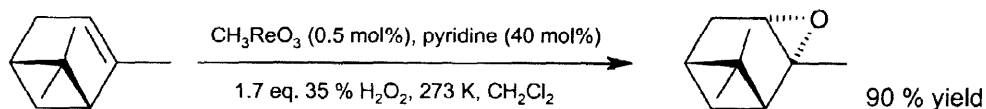
The importance of reaction parameters such as co-catalyst and solvent is illustrated in Table 1 for α-pinene. In the results, all GC product peaks amounting to at least 0.2 % of the total products were taken into account, making the analysis much more precise than even a routine NMR determination. In the absence of a base co-catalyst, the reaction is moderately selective for the epoxide at very low

conversions; however, solvolysis and rearrangement reactions quickly consume most of the formed epoxide (entries 1-2). Note that α-pinene oxide is easily isomerised over Lewis and Brönsted acid catalysts;[9] an MTO/H_2O_2 mixture contains both types of acidity.[5,10] Far better results are obtained in the presence of pyridine. While monophasic systems, e.g. with tetrahydrofuran give acceptable yields, superior results are obtained in a two-phase CH_2Cl_2/H_2O mixture (90 % yield, entry 6). As in the Ishii-Venturello approach,[3] the organic phase seems to shield the product from the acid aqueous phase. Optimum pyridine : Re ratios are between 20 and 100. The precise value depends on the solvent and the phase characteristics in the reaction. With 3-cyanopyridine, the activity is considerable, but the major product is not the epoxide but α-campholenic aldehyde (2,2,3-trimethyl-3-cyclopenteneacetaldehyde). The latter is an important fragrance compound, and thus can be prepared from α-pinene with a single catalyst for epoxidation and rearrangement. Only reactions with pyridine seem to effectively protect α-pinene oxide (compare entries 8-9).

Table 1. Epoxide yields in the reaction of 1 mmol of α-pinene with H_2O_2, catalyzed by MTO (5 μmol) and a co-catalyst at room temperature.

Entry	Co-catalyst (μmol)	Solvent (ml)	H_2O_2, eq.	Yield (%) (t, h)	Product Selectivity (%)
1	--	THF (0.6)	1.1	2 (0.1)	epoxide (67)
2	--	THF (0.6)	1.1	5 (6)	epoxide (9)
3	pyridine (500)	THF (0.25)	2.3	63 (1.4)	epoxide (69)
4	pyridine (70)	CH_3NO_2 (0.6)	1.5	41 (2.8)	epoxide (59)
5	pyridine (500)	CH_3NO_2 (0.6)	2.1	80 (2.8)	epoxide (80)
6	pyridine (120)	CH_2Cl_2 (0.6)	1.7	90 (2.5)	epoxide (90)
7	pyridine (500)	CH_2Cl_2 (0.6)	1.7	40 (1.7)	epoxide (78)
8	3-cyanopyridine (120)	CH_3NO_2 (0.6)	1.6	0 (1.7)	rearrangement product [a] (27)
9	pyridine (120) 3-cyanopyridine (130)	CH_3NO_2 (0.6)	1.7	40 (0.7)	epoxide (78), rearrangement product [a] (3)

[a] α-campholenic aldehyde

Table 2 reports on MTO-catalysed oxidations of a series of terpenic olefins, alcohols and esters in optimum conditions. In order to study the competitive intramolecular oxidation of a double bond and an alcohol, 2-cyclohexen-1-ol was used as a test substrate (entry 4). Even for this secondary alcohol, selectivity for ketone formation is only 5 %, proving the large preference for epoxidation.[11] The 40 : 60 syn : anti ratio for the dominant epoxycyclohexenol shows that for MTO/H_2O_2/pyridine, the allylic alcohol group does not coordinate on the metal center as with V catalysts,[12] in agreement with earlier observations by Adam et al. for MTO in the presence of urea/H_2O_2.[6] Consequently, the primary product from geraniol (entry 1) and nerol (entry 2) is the 6,7-epoxide, with negligible aldehyde production. In order to better monitor the progress of the reaction, it is advisable to work at 0°C. The high k_1/k_2 ratio (11) for the two consecutive epoxidations reflects the strongly electrophilic nature of the MTO/H_2O_2 adducts, and results in high monoepoxide selectivities (76-78 %). However, k_2 is still sufficiently large to allow full double epoxidation at longer reaction times and with slight excess peroxide (entries 1' and 2'). Apart from reaction acceleration, another crucial role of pyridine is the suppression of the Lewis acidity of MTO. Thus MTO as such efficiently catalyses rearrangement of geraniol (or nerol) into linalool.[13] These side reactions are suppressed by pyridine addition, and by first mixing peroxide and

MTO and subsequently adding the olefin. With the geranyl and neryl acetates (entries 5 and 6, respectively) , the k_1/k_2 ratio is even higher than for the alcohols (27 for both substrates), and 6,7-monoepoxide selectivity is over 85 %.

For linalool (entry 3), an appropriate addition order of the reactants and a pyridine co-catalyst largely suppress intramolecular cyclisation, and a 6,7-epoxide yield of 82 % is obtained, which is much better than with the peracid process. With only 3-cyanopyridine as the co-catalyst, linalool oxide is the main product, with a 76 % selectivity at 96 % conversion (entry 3'). Linalool oxide is the 50-50 mixture

Table 2. MTO-catalyzed epoxidations with hydrogen peroxide in the presence of pyridine. [a]

	Alkene	H_2O_2 (mmol)	Conversion (%) (t,h)	Monoepoxide Yield (%)	Product Selectivity (%)
1	(structure) CH₂OH	1.1	92 (1)	72	diepoxide (12), mono (78) [i]
1' [b]		1.4	100 (2)	11	diepoxide (61), mono (11)
2	(structure) CH₂OH	1	89 (0.8)	68	diepoxide (15), mono (76) [i]
2' [b]		1.4	100 (2.4)	7	diepoxide (87), mono (7)
3 [b,c]	(structure) OH	1.7	93 (1.7)	82 [j]	linalool oxide (6)
3' [d]		1.1	96 (12)	0	linalool oxide (76)
4 [e]	(structure) OH	2.2	75 (4)	66	epoxy-ol (88) [k], enone (3), epoxy-one (2)
5 [f]	(structure) CH₂OAc	2.3	93 (2.4)	79	diepoxide (9), mono (85) [l]
5' [b]		1.2	100 (24)	53	diepoxide (43), mono (53)
6 [g]	(structure) CH₂OAc	1.1	81 (4)	72	diepoxide (8), mono (89) [l]
6' [b]		1.3	100 (28)	24	diepoxide (65), mono (24)
7 [b]	(structure) OAc	1.3	100 (1.5)	96 [j]	
8 [g]	(structure)	1.1	96 (2.3)	79	diepoxide (14), mono (82) [m]
8' [b]		1.7	100 (40)	4	diepoxide (90), mono (4)
8'' [b,c]		1.3	100 (6)	0	diepoxide (90), mono (0)
9 [b]	(structure)	2.3	100 (2.3)	80	rearrangement products (8), trans diol (3), α-campholenic aldehyde (3)
10	(structure)	1.5	98 (1.2)	82	rearrangement products (11)

[a] Procedure: alkene (1 mmol) and pyridine (0.42 mmol) are mixed in CH_2Cl_2 (1 ml), and the solution is added to 5 μmol MTO, dissolved in 35 % H_2O_2; 273 K. [b] 0.5 mmol substrate. [c] 0.2 mmol pyridine, 0.2 mmol 3-cyanopyridine. [d] Procedure: the alkene (1 mmol) and 3-cyanopyridine (0.12 mmol) are mixed in tetrahydrofuran (0.7 ml), and this mixture is added to 5 μmol MTO, dissolved in H_2O_2 35%; 293 K. [e] as in d, but with 0.85 mmol pyridine as co-catalyst. [f] as in d, but with 0.42 mmol pyridine co-catalyst. [g] as in d, but with 0.12 mmol pyridine. [h] as in d, but in CH_3NO_2 solvent, and 0.42 mmol pyridine. [i] (6,7) : (2,3) epoxide = 11 : 1. [j] (6,7) : (1,2) > 100. [k] syn : anti = 1 : 1.5. [l] (6,7) : (2,3) epoxide = 28 : 1. [m] (1,2) : (8,9) epoxide = 98 : 2, cis(1,2) : trans(1,2) epoxide= 1.3 : 1.

of the diastereomers of (2-(5-methyl-5-vinyltetrahydro-1-furyl)-2-propanol). The main side product is the corresponding 6-ring 2,2,6-trimethyl-6-vinyl-tetrahydro-2*H*-pyran-3-ol. Even with a co-catalytic pyridine/cyanopyridine mixture, the activity is too low for epoxidation of the monosubstituted 1,2 double bond.

Limonene is first converted into the 1,2-epoxide (entry 8). The almost equal amounts of *cis* and *trans* isomers demonstrate that there is little steric effect on the epoxidation.[14] With more H_2O_2 and a 3-cyanopyridine/pyridine mixture, double epoxidation is fast and selective. With pyridine alone, this reaction takes up to 40 h and extra pyridine is needed, as competitive formation of pyridine N-oxide is observed. Finally, high epoxide yields are obtained from α- and β-pinene (entries 9 and 10).

The present results prove that base-modified MTO is a flexible catalyst for the epoxidation of various terpenic substrates with H_2O_2. For those substrates and products that are not too easily isomerized under acid conditions, it is possible to work in a non-chlorinated solvent. Yields are usually excellent, both on substrate and on H_2O_2 basis. Only in specific cases, *e.g.* epoxidation of a moderately deactivated double bond (8,9 in limonene), it seems appropriate to replace part of the pyridine with 3-cyanopyridine. Finally, gradual pyridine consumption is observed with poorly reactive double bonds. On the whole, this chemistry is far superior to peracid chemistry, particularly with respect to product stability.

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