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ASYMMETRIC EPOXIDATION OF HYDROCARBON OLEFINS BY TERT-BUTYL HYDROPEROXIDE WITH MOLYBDENUM(VI) CATALYSTS IN THE PRESENCE OF OPTICALLY ACTIVE DIOLS. APPLICATION TO THE ASYMMETRIC SYNTHESIS OF (3S)-2,3-OXIDOSQUALENE

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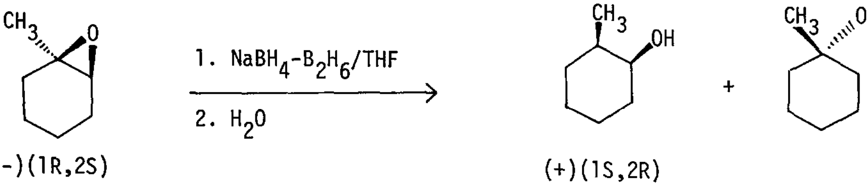
Summary: Catalytic enantioselective epoxidation of prochiral olefins without functional groups was achieved by _tert_-BuOOH using $Mo(O)_2(acac)_2$—optically active diols as catalysts.

In spite of dramatic developements in asymmetric hydrogenations using optically active transition metal catalysts during recent years[1], little has been achieved in the field of asymmetric oxidations with chiral transition metal catalysts. One of the reasons resides in the difficulties in developing appropriate chiral ligands which are stable to oxidation. Only recently catalytic asymmetric epoxidation of allylic alcohols has been reported by two research groups.[2,3]

Catalytic asymmetric epoxidation of simple hydrocarbon olefins without functional groups can, however, only be enzymatically achieved.[4,5] Here we report the results of a catalytic asymmetric epoxidation of such hydrocarbon olefins by _tert_-butyl hydroperoxide with Mo(VI) catalysts in the presence of optically active diols. A typical run was performed as follows. $Mo(O)_2(acac)_2$ (0.33 g, 1.0 mmole) was treated for 2 hrs with an excess of diisopropyl (+)-tartrate (4.7 g, 20 mmole) at 40°C under nitrogen. After removing the liberated acetylacetone from the almost colorless reaction mixture _in vacuo_, 1-methylcyclohexene (4.8 g, 50 mmole) and a solvent (60 ml) were added. _Tert_-BuOOH (70 %, 50 mmole) was added dropwise at 20-25°C and the reaction mixture was stirred at that temperature for another 15 hrs. 1-Methylcyclohexene oxide was separated by vacuum distillation (25°C, 1 Torr) from the catalyst system and purified further by fractional distillation and preparative GLC. (+)(1R, 2S)-1-Methylcyclohexene oxide[6] was isolated in 7.0 % optical yield. When the reaction was conducted at lower temperature, 5-10°C, the optical yield of 1-methylcyclohexene oxide improved to 10.2 %. The table shows the result of the asymmetric epoxidation with Mo(VI)-chiral diol systems. As the optically active diols were employed several

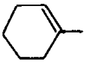
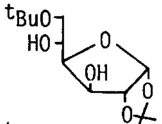
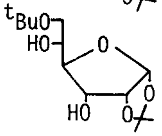
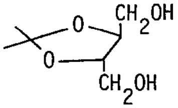
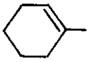
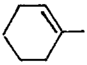
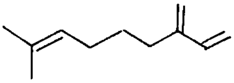
1,2-, 1,3-, and 1,4-diols (see Table) which can be easily derived from natural products. In general 1,2-diols, which can coordinate more firmly to Mo metal, were the most effective for asymmetric induction. In a separate experiment, reaction of $Mo(O)_2(acac)_2$ and diethyl (+)-tartrate gave a bis-tartrate complex, $Mo(O)_2(C_8H_{13}O_6)_2$, as colorless crystals.[7]

The optical purity and the absolute configuration of 1-methylcyclohexene oxide were determined by converting stereospecifically[8] to cis-2-methylcyclohexanol whose maximum rotation and the stereochemistry[9,10] are known. Treatment of 1-methylcyclohexene oxide, having $[\alpha]_D^{25}$ -0.84°(neat), with $NaBH_4$-B_2H_6 in tetrahydrofuran gave a mixture of (+)(1S, 2R)-cis-2-methylcyclohexanol ($[\alpha]_D^{25}$ +0.61°(neat)) and 1-methylcyclohexanol in 64 % and 36 % yield respectively. Based on the reported maximum rotation of (+)(1S, 2R)-cis-2-methylcyclohexanol ($[\alpha]_D^{20}$ + 13.6°(neat))[9], the optical purity of (+)(1S, 2R)-cis-2-methylcyclohexanol ($[\alpha]_D^{25}$ + 0.61°(neat)) and therefore the starting 1-methylcyclohexene oxide ($[\alpha]_D^{25}$ + 0.84°(neat)) can be estimated to be 4.5 %. It is further concluded that (-)-1-methylcyclohexene oxide has the (1R, 2S)-configuration. From these results the maximum rotation of (-)(1R, 2S)-1-methylcyclohexene oxide can be calculated to be $[\alpha]_D^{25}$ - 18.65°(neat).

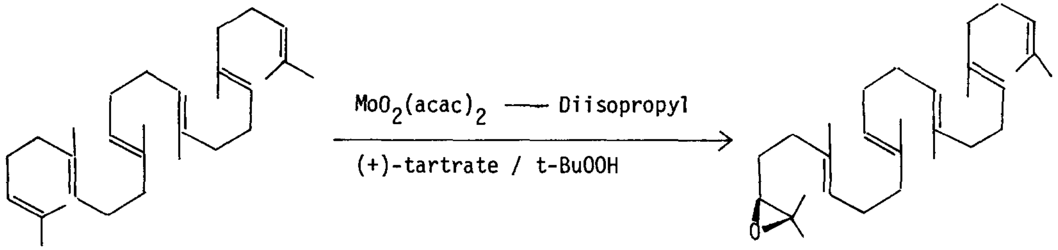


This catalytic asymmetric epoxidation can be applied to the preparation of optically active 2,3-oxidosqualene. The intermediacy of (3S)-2,3-oxidosqualene in the biogenesis of 3β-hydroxy triterpenes from squalene has been proposed.[11] Preparation of optically active 2,3-oxidosqualene has been recently reported[12] but very tedious steps are employed. Squalene was oxidized with <u>tert</u>-BuOOH in the presence of $Mo(O)_2(acac)_2$ and diisopropyl (+)-tartrate in CH_2Cl_2 at 20°C. After 40 hrs, the reaction products were separated from the catalyst and the diol by column chromatography on silica gel using n-hexane and further purified by preparative HPLC. The 2,3-epoxide[13] was isolated in 31 % yield in addition to 47 % of a mixture of the 6,7- and 10,11-epoxide and 23 % of a mixture of the diepoxides. The 2,3-oxidosqualene showed a rotation of $[\alpha]_D^{25}$ -0.28°(c 7.17, MeOH) which corresponds to 14 % optical purity based on a reported maximum rotation ((3S)-2,3-oxidosqualene; $[\alpha]_D^{25}$ -2.0°(c 1.01, MeOH))[12a] and therefore has the (3S)-configuration.

Asymmetric Epoxidation of Olefins$^{a)}$

Substrate	Diol	Epoxide$^{b)}$			
		Conv.(%)	$[\alpha]_D^{25\,c)}$	O.Y.(%)	Absolute Config.
 Me	Dimethyl (+)-tartrate	65	-0.12	0.7	(1R, 2S)
"	Diethyl (+)-tartrate	75	-1.2	6.5	(1R, 2S)
"	Diisopropyl (+)-tartrate	66	-1.3	7.0	(1R, 2S)
"	" $^{d)}$	50	-1.9	10.2	(1R, 2S)
"		76	+0.92	4.9	(1S, 2R)
"		80	+0.69	3.7	(1S, 2R)
"		48	-0.08	0.4	(1S, 2R)
 Et	Diisopropyl (+)-tartrate	59	+0.33	n.d.	n.d.$^{g)}$
 ^{i}Pr	"	25	+0.18	n.d.	n.d.$^{g)}$
	"	77$^{e)}$	-0.59	10.4$^{f)}$	n.d.

a) Mo(O)$_2$(acac)$_2$/Diol/Olefin/<u>tert</u>-BuOOH = 1/20/50/50, in CH$_2$Cl$_2$, 20°, 15 hr unless otherwise noted; b) Yield ≅ 100 %; c) Optical rotations of a neat sample were recorded in a 0.5 dm cell; d) Reaction conditions: 5~10°C, 80 hrs; e) The 7, 8-epoxide is the only product; f) The optical yield is calculated from ^{1}H-nmr; g) CD shows no conspicuous peak which prevents reliable determination of the absolute configuration.



Squalene (3S)-2, 3-Oxidosqualene

References and Notes

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6) Satisfactory a) spectral and b) analytical data were obtained for this substance.

7) The crystals involve one molecule of the tartrate as a solvent of crystallization. m. p. 117∿119°C; $[\alpha]_D^{25}$ + 41.6°(c3.28, EtOH); Anal., Found: C, 38.10; H, 5.39. Calcd. for $C_{24}H_{40}MoO_{20}$: C, 38.71; H, 5.41 %. Ir ν_{max}^{Nujol} cm^{-1}: 3390 (OH), 1735, 1650 (C=O), 940, 915, (Mo=O). NMR (d_6-DMSO): δ 1.17 (18H, t, J=7.5Hz, $CH_2\underline{CH_3}$), 4.06 (12H, q, J=7.5Hz, $\underline{CH_2}CH_3$), 4.32 (6H, s, CH), 4.58 (4H, br s, OH).

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13) Satisfactory a) spectral and b) analytical data were obtained for this substance.

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