The Effect of Reduced Osmium Amounts on the Asymmetric Dihydroxylation of 1-Arylcyclohexenes

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Abstract: The amount of osmium required for satisfactory levels of conversion and asymmetric induction in the AD reaction of 1-arylcyclohexenes has been established.

The advent of reliable and highly enantioselective reactions induced by chiral catalysts has revolutionized synthetic organic chemistry. Among the most useful of these is the Sharpless asymmetric dihydroxylation (AD) reaction.[1,2] For suitable substrates, very high enantioselectivity favoring either enantiomer can be achieved using commercially available ligand/catalyst/oxidant mixtures ("AD-mix"®). This material contains 0.4 mol% of osmium and 1.0 mol% of ligand. In connection with other work we needed a reliable source of a series of optically active *trans* 2-(*p*-substitutedaryl)cyclohexanols. The original method for the preparation involved resolution of the racemic mixture obtained by copper catalyzed ring opening of cyclohexene oxide with phenylmagnesium bromide.[3] A literature report[4] on the preparation of the parent alcohol by Raney Nickel hydrogenolysis of the AD product derived from l-phenylcyclohexene drew our attention to this method. The well known ability of *trans* 2-phenylcyclohexanol to function as an effective chiral auxiliary in many reactions makes the synthesis of this and related molecules of significant importance.[5,6] However, for the quantities we required, large quantities of the ligand/catalyst/oxidant mixture would be needed using the published recipe. As the stoichiometric oxidant (ferricyanide) is inexpensive, we carried out a study of the reaction parameters with a view to minimizing the amount of AD-mix required while maintaining the high enantioselectivity.

Table 1. Percent Conversion of 1-Phenylcyclohexene as a Function of mol% Osmium[a]

Mol% Os	Time (hr)	Temp (°C)	% Conversion[b]
0.40	24	25	100
0.06	24	0	10
0.04	72	25	41
0.10	44	25	100

[a] AD-mix supplemented with required amounts of $K_3Fe(CN)_6$ and K_2CO_3;
[b] based on 300MHz NMR

The reported method[4] required 3 mmol of $K_3Fe(CN)_6$, 3 mmol of K_2CO_3, 0.01 mmol of $(DHQ)_2PHAL$ or $(DHQD)_2PHAL$ and 0.002 mmol (0.2 mol%) of K_2OsO_4 - or 1.40g of the commercial AD-mix mixture -per mmol of l-phenylcyclohexene and the diol was isolated in 98% recrystallized yield with an ee of >99%. The effect on the chemical yield of reducing the amount of osmium is shown in Table 1. The experiments shown in the Table were run either until the reaction rate fell to zero or until all the substrate had been consumed. As can be seen, reducing the osmium to 0.1 mol% and allowing the reaction to proceed for twice the normal time at 25°C gave the same chemical yield of diol. The use of less osmium made the reaction too sluggish to be useful.

Dihydroxylation of six other representative alkenes was performed under these standard conditions to examine the effect of reduced osmium amounts on the reaction enantioselectivity. The results are shown in Table 2. As can be seen, in all cases except that of the 1-naphthyl substituent, the stereoselectivity remained excellent although extended reaction times were required in some cases. There is an unexpected effect on the reaction rate of the aromatic substituent. All substitutents retard the reaction rate, with sterically more demanding (cpd. 3,7) and more electronegative substituents (cpd 6) having the greatest effect.

Table 2. Enantiomeric Excess and Percent Conversion of Various Alkenes. Using 0.10 mol% Osmium

Cpd #	Ar	Time(h)	%ee[a]	% Conversion
1	phenyl	44	96	95
2	4-methylphenyl	72	96	84
3	4-^{t}butylphenyl	96	93	49
4	4-methoxyphenyl	60	95	95
5	4-fluorophenyl	72	94	58
6	4-CF_3-phenyl	96	91	42
7	1-naphthyl	96	NA	~5

[a] determined by 500 MHz ^1H NMR of MTPA esters

These data show that, when large amounts of dihydroxylated products are required which are derived from good substrates for the AD reaction such as 1-arylcyclohexenes and stilbenes[7,8], it may be possible to modify the standard conditions significantly to reduce the use of osmium without affecting the level of asymmetric induction appreciably. In addition, a less obvious benefit occurs. A referee has noted that the cost per mole of osmium ($58/mmol) is not significantly more than that of the ligand ($45/mmol). Therefore, the reduced use of AD-mix also reduces the use of this material. Sharpless[7] has referred to the extremely low ligand concentrations required to obtain very high enantioselectivities when reactive substrates are used.

Example experimental procedure on 10 mmol scale: A mixture of 50 mL of ^{t}BuOH, 50 mL of water, 3.5g AD-mix-β, 3. 1g K_2CO_3 and 7.4g $K_3Fe(CN)_6$ was prepared and stirred at room temperature. After 2 min, 950 mg of $MeSO_2NH_2$ was added followed by 10 mmol of alkene. The reaction was stirred at room temperature while monitoring by TLC (3:1 pet ether:EtOAc). After the indicated time, 5g of Na_2SO_3 was added, the mixture stirred 30 min, 100 mL of EtOAc was added and vigorous stirring was continued for 5 min. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organics were washed with 1M KOH solution, dried, evaporated and chromatographed on silica gel using 3:1 petroleum ether:ether as eluant. Mosher esters were prepared in the usual manner[9] in quantitative yield.

References and Notes

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