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PRECLUSION OF THE "SECOND CYCLE" IN THE OSMIUM-CATALYZED ASYMMETRIC DIHYDROXYLATION OF OLEFINS LEADS TO A SUPERIOR PROCESS

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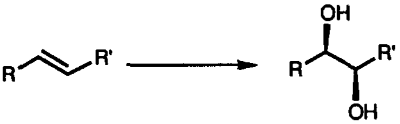
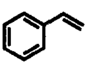
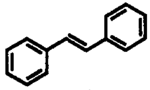
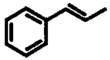
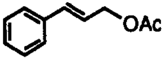
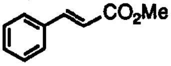
Summary: The highest enantioselectivities yet obtained in catalytic asymmetric dihydroxylations are realized using potassium hexacyanoferrate(III) [potassium ferricyanide, $K_3Fe(CN)_6$] as the reoxidant.

The use of potassium ferricyanide as the stoichiometric oxidant for osmium—catalyzed dihydroxylation of olefins was recently reported by Minato, Yamamoto and Tsuji.[1] With this one-electron oxidant they observed substantial improvement in the ability of the catalytic system to turnover, even in the presence of quinuclidine, a ligand which strongly inhibits catalysis when other oxidants are used [e.g. *N*-methylmorpholine-*N*-oxide (NMO)].[2,3] We tried their oxidant in our cinchona alkaloid—based asymmetric dihydroxylation process (ADH) and the outcome was unexpected (i.e. not just another way to reoxidize the osmium and/or achieve better turnover with difficult substrates). *As revealed in the Table, the use of ferricyanide in place of NMO leads to across-the-board increases in the level of asymmetric induction for all of the olefins examined so far* .

The first two columns of data of the following table are for the old results employing NMO with and without "slow addition" of olefin, respectively.[2,3,4,5] The third column reveals the new results using ferricyanide with the same substrates and *without* "slow addition" of the olefin. The obvious improvements of enantioselectivity are even greater than they appear since all the old results were obtained at 0° C while the new ferricyanide experiments were performed at room temperature.

Table. Percentage enantiomeric excesses of diols obtained in the asymmetric dihydroxylation of olefins under different catalytic conditions using dihydroquinidine *p*-chlorobenzoate as the chiral ligand.



entry	olefins	NMO[a] ee(%) (slow addition)	NMO[a] ee(%) (no slow addition)	$K_3Fe(CN)_6$[b] ee(%) (no slow addition)
1		60	56	73
2		95	78	99
3		86	65	91
4	 OAc	79	76	91
5	 CO_2Me	86	60	95
6		69	20	74

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[a] Reactions were carried out in acetone—water, 10:1 v/v, at 0° C as described in references 2, 4, and 5. [b] Reactions were carried out in *tert*-butyl alcohol—water 1:1 v/v, at ambient temperature. In all cases the isolated yield was 85%-95%. Enantiomeric excesses were determined as described earlier in reference 5.

Work is in progress to determine the mechanistic basis of these enhancements of enantioselectivity, but preliminary results point to two effects. *The most important effect is the apparent complete suppression of the "second cycle",*[4,5] which means that there is no need for the slow addition of olefin (a modification which is usually essential in the NMO-based process). The second effect is an increase in enantioselectivity which we have traced to the *tert*-butyl alcohol/water solvent introduced by Minato, *et. al.*.[1] They use a 1:1 ratio of these solvents, and we found the ee with styrene to be only 58% employing stoichiometric osmium tetroxide and alkaloid ligand at room temperature in that solvent system (the reaction was homogeneous). However, this same stoichiometric control experiment gave 74% ee when carried out in the presence of either potassium ferricyanide or potassium carbonate. Since the addition of these salts was observed to "salt-out" an aqueous layer, the ee for styrene in a stoichiometric control was measured in pure *tert*-butyl alcohol and found to be 74%, establishing this as the best solvent to date for the ADH when optimum enantioselectivity is the prime concern.[6] These controls provide strong evidence that the crucial asymmetric dihydroxylation transition state complex is the same in this new system as it was in the earlier ones.[2,3,4,5,7]

The general procedure for asymmetric dihydroxylation of olefins using potassium ferricyanide:

To a well-stirred mixture of 0.465 g (1 mmol, 0.5 equiv = 0.033 M in ligand) dihydroquinidine *p*-chlorobenzoate (Aldrich, 98%), 1.980 g (6 mmol, 3.0 equiv) potassium ferricyanide, 0.830g (6 mmol, 3.0 equiv) potassium carbonate, and 0.5 mL of a 0.05 M *tert*-butyl alcohol solution of osmium tetroxide (0.025 mmol , 0.0125 equiv) in 30 mL of a *tert*-butyl alcohol—water mixture (1:1, v/v) at room temperature, olefin (2 mmol) was added all at once. The reaction mixture was stirred for 24 h at room temperature. Solid sodium sulfite (Na_2SO_3, 1.5 g) was added, and the mixture was stirred for an additional hour. The solution obtained was concentrated to dryness under reduced pressure, and the residue was extracted with three portions of ether. The combined extracts were dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (silica gel, dichloromethane—ether).

The above procedure is very effective, but not ideal for large scale applications. The olefin concentration is very dilute and the recipe calls for 1.25% osmium tetroxide and 0.5 equiv of alkaloid. Preliminary optimization studies using styrene have shown that the process can be run under the more convenient conditions of the NMO—based process,[4,5] (i.e. one molar in olefin, 0.4% Os catalyst, and 0.25 equiv of chiral ligand) with no deleterious effects, and, of course, without the need for "slow addition". It was also found that the two—phase system of toluene/water works well for some olefins with the ferricyanide—oxidant (e.g. styrene gives 67%ee at 25° C and 73%ee at 0° C).

The observation that the "second cycle" is not operative in this two-phase, *tert*-butyl alcohol—aqueous ferricyanide/carbonate system was totally unexpected and promises to be a discovery of some practical significance for the further development of osmium—catalyzed asymmetric dihydroxylations of olefins. While seeking to understand where the present catalytic cycle differs from NMO—based ones, we are also searching for other oxidant-schemes which display the same valuable properties.

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