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Sharpless Asymmetric Dihydroxylation on an Industrial Scale

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Abstract:

It is shown in this study that the inexpensive *N*-methylmorpholine *N*-oxide can be successfully employed as a reoxidant in the Sharpless asymmetric dihydroxylation reaction on a large scale. The reaction of *o*-isopropoxy-*m*-methoxystyrene on a 2 kg scale gave the corresponding diol in high yield and high enantiomeric excess. The extension of this synthetic method to other olefins is also presented.

Introduction

Chiral alcohols are key intermediates in the synthesis of many biologically active compounds. The Sharpless asymmetric dihydroxylation (AD) reaction, shown in Figure 1 for terminal olefins, is one of the most reliable and general reactions to date for obtaining such intermediates with high stereoselectivity.[1] The reaction can be run conveniently on a small scale by use of the commercially available AD mix, which contains potassium ferricyanide as a reoxidant and potassium carbonate as a co-salt. However, handling of a large amount of these salts, subsequent workup, and effluent disposal make it difficult to apply this system on an industrial scale. This problem was first encountered by us during scale-up of one of our candidate drugs for stress incontinence, LS 4416F.[2] In the synthetic scheme, the AD reaction is employed to convert *o*-isopropoxy-*m*-methoxystyrene (**1**) to the corresponding diol. As the potassium ferricyanide/potassium carbonate system was not feasible practically or economically on a large scale, it was necessary to find another oxidant which would satisfy the requirements of large-scale synthesis of this diol.

Prior to the introduction by Sharpless of the potassium ferricyanide/potassium carbonate system in the AD reaction,[3] the reoxidant of choice was *N*-methylmorpholine *N*-oxide (NMO). This later became supplanted by potassium ferricyanide since it led to "across-the-board increases in the level of asymmetric induction for all of the olefins examined so far." The lower ee's obtained from the NMO-based reactions could, in part, have been due to the use of the less favourable *p*-chlorobenzoate chiral ligands and solvent system acetone/water rather than the now preferred phthalazine (PHAL) ligands and *t*-BuOH/water.[3,4] Since the use of the "more effective" phthalazine ligands was first published[5] two years after the discovery of the use of potassium ferricyanide as reoxidant, very little has been published employing both NMO and the "new" chiral ligand. Stilbene[6] and methyl cinnamate[7] seem to be the only examples reported so far which react to give the respective diols with high stereoselectivity when NMO and the phthalazine ligand are employed. This preference for potassium ferricyanide was also found to hold even with the improved procedure of "slow addition" of olefin in the NMO-based reactions.[8] Sharpless suggests that two catalytic cycles, their proposed osmium complexes shown in Figure 2, are operative in the AD reaction, a primary cycle which is stereoselective and a secondary cycle in which the chiral ligand is absent. Slow addition of olefin is thought to have the effect of suppressing the secondary catalytic cycle by having as little olefin in solution as possible. This is also thought to be the reason why high selectivity is obtained for the potassium ferricyanide system, which has the effect of "salting-out" the aqueous layer, thereby creating a two-phase system. In this way, the

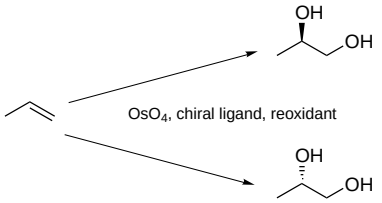

Figure 1. **Sharpless asymmetric dihydroxylation.**

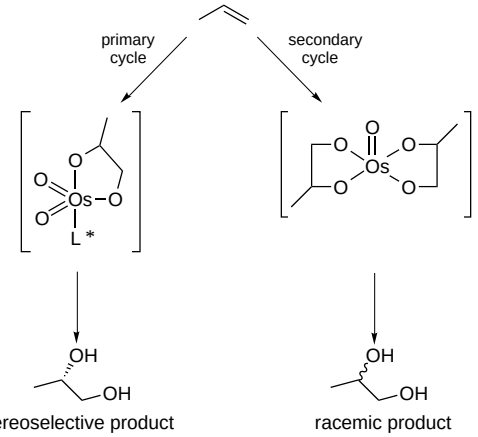

Figure 2. **The proposed osmium complexes and their respective products in the two catalytic cycles of the AD reaction.**

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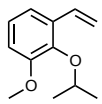
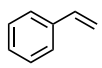
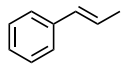
Table 1. **Enantiomeric excesses of diols obtained in the asymmetric dihydroxylation of olefins**

	ee (%)		
		NMO	
olefin	$K_3Fe(CN)_6$[a]	dihydroquinine *p*-chlorobenzoate[b]	$(DHQ)_2PHAL$[c]
 1	94		90
 2	97	54[d]	97 78[e]
 3	97	55	98
 4	66		46

[a] $(DHQ)_2PHAL$ as ligand, *t*-BuOH/H_2O, and 0 °C. The results for olefins 2−4 are taken from ref 1 (reaction times 6−24 h). [b] Acetone/H_2O and 0 °C with *no slow addition*; ref 10 (reaction times of 7 and 12 h for **2** and **3**, respectively). [c] *t*-BuOH/H_2O, ambient temperature, and slow addition of olefin (addition and reaction time of 6 h), unless otherwise stated. The ee's were determined by chiral HPLC (from olefins **1**−**3**) or by ^1H NMR of the bis-MTPA ester (from olefin 4). [d] The *R*-(−) enantiomer was obtained in 60% ee *with slow addition* of olefin.[3] [e] Acetone/H_2O.

concentration of the olefin in the aqueous phase is, at any one time, low, thereby suppressing the secondary cycle.

In the large-scale use of the AD reaction, however, there are definite advantages to the use of NMO. Firstly, there are no large amounts of salts required in the reaction (3 molar equiv of each salt is used in the AD mix) and needing handling in the subsequent workup. Unlike the iron byproducts formed from the usual reaction, the byproduct from NMO, *N*-methylmorpholine, is easily removed and recycled if necessary. Secondly, NMO is economical, by a factor of 5 when compared to the amount of ferricyanide/carbonate salts required per mole of olefin. Thirdly, the NMO-based reactions can be run in high concentration, the concentration of the ferricyanide-based reactions being limited by the solubility of the salts. Finally, as the results from the large-scale reaction of *o*-isopropoxy-*m*-methoxystyrene (**1**) show (Table 1), it is possible to obtain a *high enantiomeric excess (ee)* in the AD reaction using NMO as reoxidant. As a general procedure for the large-scale use of this reaction, we subsequently investigated the applicability of this method to other olefins.

Results and Discussion

The AD reaction employing NMO is run at ambient temperature in the solvent system *t*-BuOH/H_2O. The olefin is added slowly and continuously throughout the time of the reaction to a solution of the osmium salt, the chiral ligand, and NMO. The results of both the large-scale synthesis of olefin **1** and small-scale syntheses of related olefins are shown in Table 1, the latter with reference to earlier results from the literature using both the AD mix and NMO. The most striking observation is with the styrene derivatives **1**−**3**, where the stereoselectivity of the formed *S*-(+) diols is just as high as that obtained with the ferricyanide-based reactions. In fact, these are the only examples reported, apart from stilbene[6] and methyl cinnamate,[7] which show such high ee's when NMO is employed in the AD reaction. This high stereoselectivity seems to be relatively independent of the substituents on the ring, as can be seen by comparison of compounds **1** and **2**; a small effect is noticed, a result of the large isopropoxy group being ortho to the reacting center. In addition, the methyl substituent on the olefin (**3**) seems to have absolutely no effect on the stereoselectivity. The table also shows the large effect of solvent, for example, 78% ee with acetone vs 97% ee with *t*-BuOH/H_2O for **2**.

Since the changes made from the earlier NMO reactions shown in Table 1 include both slow addition of olefin and choice of chiral ligand, it is difficult to ascertain which is the deciding factor. The rate of addition of olefin has previously been shown to be important for the stereoselectivity in NMO-based reactions.[8] However, results from reaction of the parent styrene with NMO and *dihydroquinidine p-chlorobenzoate* to give the *R*-(−) diol with (60% ee) and without (56% ee) slow addition suggest that, at least for olefin **2** and the *p*-chlorobenzoate ligand, the rate of addition of olefin plays a minor role.[3] On the other hand, the rate of addition seems to be important when employing the much more effective "phthalazine" ligands, as demonstrated by preliminary studies on olefins **1**−**3**, which show that excess olefin in solution considerably reduces the ee of the product. This reasoning further supports the presence of the two catalytic cycles discussed in the Introduction, of prime importance when employing effective ligands such as the phthalazines, in which one catalytic cycle is highly stereoselective, but of less importance when employing the less effective ligands, since neither cycle is so selective. In summary, it seems that the choice of chiral ligand is crucial to the high stereoselectivity observed in this study, but as Sharpless has previously shown in the NMO-based reactions,[8] slow addition of olefin does play a role.

The low selectivity in the reaction of the alkyl-substituted olefin, **4**, is not improved on going from the ferricyanide system to NMO. Although this is only one such example, it is reasonable to assume that one cannot obtain a substantially higher ee on going from ferricyanide to NMO, since both reactions are thought to have the same effect of suppressing the second (nonselective) catalytic cycle.

The AD reaction has proven to be an ideal reaction for running on an industrial scale. This has been shown by reaction of *o*-isopropoxy-*m*-methoxystyrene (**1**), which was performed on a 2.5 kg scale using NMO as reoxidant to give both high yield and good stereoselectivity (see Experimental Section).[2] The reaction is run in water, employing ambient temperature and pressure. The chiral ligand, which is the most expensive reagent, is used catalytically and can be recovered by simple acid/base extraction. The osmium, also used catalytically, can be purchased in a reduced form which is less toxic, and upon workup, being water soluble, it is easily separated from the organic product. It can also be recovered in the fully oxidized form for reuse. When using NMO as the reoxidant, it is important that the olefin *not* be

in excess at any time during the reaction, for reasons noted above. This can be accomplished easily on a large scale by addition of the olefin slowly and continuously by the use of a pump, and the reaction can then be followed by GC or HPLC to check for any accumulation of olefin. Addition of a reducing agent limits further oxidation of the product once the reaction is complete. Workup of the reaction is simple: the byproducts either are soluble in water or are removed upon evaporation, leaving a mixture of only the product and the chiral ligand, the latter of which can be removed as described.

It therefore appears that the use of NMO is at least as effective as the use of the potassium ferricyanide/potassium carbonate system with respect to stereoselectivity and avoids some of the problems of the latter.

Conclusion

The results presented above show that it is possible to use NMO as a reoxidant in the AD reaction and obtain good stereoselectivity. Although this study was limited to a few olefins, it suggests that this could be a general method to obtaining chiral alcohols on a large scale. This is especially important in industry where the use of this reaction has been somewhat limited to date.

Experimental Section

Potassium osmate(VI) dihydrate, hydroquinine 1,4-phthalazinediyl diether, *N*-methylmorpholine *N*-oxide, AD-mix-α, (*R*)-(−)-MTPA, styrene, *trans*-β-methylstyrene, and 3,3-dimethylbutene were commercially available. *o*-Isopropoxy-*m*-methoxystyrene was prepared from the aldehyde employing a Grignard reaction to give the alcohol followed by elimination.[2] ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX 500 spectrometer; tetramethylsilane was used as the internal standard. The ee's were calculated by HPLC (weighing of the two peaks obtained) using a Chiralcel OD column with 8% *i*-PrOH/hexane as eluent or by ^{1}H NMR of the bis-MTPA ester. The ester was prepared according to the literature procedure.[9]

General Procedure for the Asymmetric Dihydroxylation of Olefins Using NMO. To a clear yellow solution of $K_2OsO_2(OH)_4$ (74 mg, 0.20 mmol, 0.8 mol %), hydroquinine 1,4-phthalazinediyl diether (175 mg, 0.22 mmol, 0.9 mol %), *N*-methylmorpholine *N*-oxide (60 wt % in water, 6.5 mL, 38 mmol), *t*-BuOH (30 mL), and H_2O (22 mL) was added at 25 °C the neat olefin (25 mmol) via a syringe pump over a period of 6 h. (The syringe was connected to tubing, whose tip was immersed in the solution throughout the reaction time). At this rate, the amount of olefin present at any time was less than 1%, according to GC. The resulting clear orange solution was then stirred for another 30 min, after which time toluene (50 mL) and a solution of Na_2SO_3 (4.8g, 38 mmol) in H_2O (50 mL) were added, and the resulting mixture was stirred for 2 h. The phases were separated, and the chiral ligand was extracted from the organic phase with a solution of 0.3 M H_2SO_4 in saturated Na_2SO_4 (2 × 25 mL). The resulting aqueous phase was made alkaline with 2 M NaOH (2 × 25 mL) and extracted with toluene, and the organic phase was dried with K_2CO_3 and evaporated to give the pure ligand as a white solid (131 mg, 0.17 mmol). The organic phase remaining after extraction with acid was washed with saturated Na_2SO_4 (1 × 25 mL) and dried with K_2CO_3. Evaporation of the solvent gave pure diol as a light yellow oil or white solid in yields of 85−96%.

Large-Scale Synthesis of 2-(*o*-Isopropoxy-*m*-methoxyphenyl)-2-hydroxyethanol. To a 50 L three-neck flask were added $K_2OsO_2(OH)_4$ (34.5 g, 0.09 mol), hydroquinine 1,4-phthalazinediyl diether (81.6 g, 0.10 mol), *N*-methylmorpholine *N*-oxide (60 wt % in water, 3.0 L, 17.4 mol), *t*-BuOH (14 L), and H_2O (10 L). The flask was fitted with a mechanical stirrer, and the reaction mixture was stirred until the solution cleared. *o*-Isopropoxy-*m*-methoxystyrene (**1**) (2.5 kg, 2.2 L, 13.0 mol) was then added at a rate of 5.6 mL/min using a peristaltic pump, such that the tip of the tubing was immersed in the solution. The temperature of the solution was kept at 20 ± 5 °C by an external temperature control. Samples were taken at 1 h intervals and checked to make sure that the olefin content did not exceed 3% and the enantiomeric purity did not fall below 92% by GC and HPLC (chiral column), respectively. At this rate of addition, the olefin content never exceeded 0.7% and the enantiomeric purity was never below 95%. After addition of the olefin, the resulting orange solution was stirred until the olefin content was less than 0.5%, after which time were added toluene (12 L) and a solution of Na_2SO_3 (1.9 kg) in H_2O (4.7 L). After stirring overnight, the phases were separated and the organic phase was washed with an aqueous solution of Na_2SO_4 (0.8 kg/5 L of H_2O). The chiral ligand was extracted from the organic phase using H_2SO_4 (0.38 L) in aqueous Na_2SO_4 (1.6 kg/10 L of H_2O), and the resulting acidic solution was made basic with NaOH and then extracted with toluene (0.70 L). The ligand (61 g) was recovered pure (98% according to HPLC) as a white powder after drying of the solution and evaporation of the solvent. The organic phase remaining after acid extraction was dried with K_2CO_3 (1.0 kg) and the solvent evaporated under vacuum at 60 °C to yield 2.5 kg of a light brown oil (94% pure according to GC and an enantiomeric purity of 95%), which crystallized upon standing. ^{1}H NMR (500 MHz, $CDCl_3$): 7.05−6.8 (m, 3H), 5.15 (m, 1H), 4.65 (heptet, 1 H), 3.85 (s, 3H), 3.75 (m, 1H), 3.65 (m 1H), 3.10 (br s, 1H), 2.50 (br s, 1H), 1.30 (dd, 6H). ^{13}C NMR (500 MHz, $CDCl_3$): 152.3, 143.7, 134.5, 123.6, 118.6, 111.7, 74.6, 70.1, 66.8, 55.7, 22.8, 22.3. Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.7; H, 8.0. Found: C, 63.9; H, 8.0.

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