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Asymmetric Dihydroxylation (AD) of *N,N*-Dialkyl and *N*-Methoxy-*N*-methyl α,β- and β,γ-Unsaturated Amides

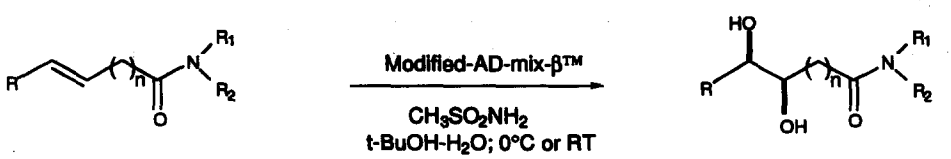
Youssef L. Bennani and K. Barry Sharpless*

Department of Chemistry, The Scripps Research Institute, 10666 N. Torrey Pines Road, La Jolla, CA 92037, U.S.A.

Abstract: *The asymmetric dihydroxylation of α,β- and β,γ-unsaturated amides affords the corresponding diols in good yields and excellent enantiomeric excesses. However, both N,N-dialkyl and N-methoxy-N-methyl α,β- and β,γ-unsaturated amides require a Modified-AD-mix™ formulation to achieve good catalytic turnover rates*

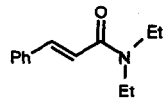
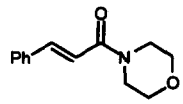
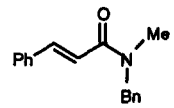
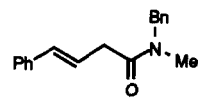
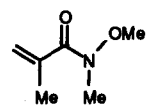
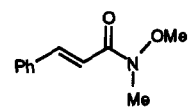
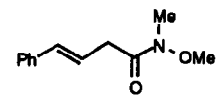
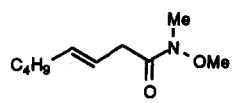
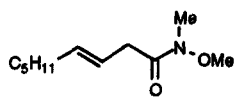
We have recently reported a new cinchona alkaloid-phthalazine based class of ligands, $(DHQD)_2$-PHAL and $(DHQ)_2$-PHAL, and an improved process for the osmium-catalyzed asymmetric dihydroxylation (AD) of olefins.[1] As part of general studies on the scope and limitations of this reaction, the reactivity and compatibility of allylic and homoallylic nitrogen containing olefins such as amines,[2] azides[3] and amides towards the new AD conditions were examined. Reported here are the results for the catalytic asymmetric dihydroxylation of unsaturated amides. Both *N,N*-dialkyl and *N*-methoxy-*N*-methyl[4] α,β- and β,γ-unsaturated amides of type **1** react sluggishly[5] using the originally reported AD-mix™ formulation.[1] However, by increasing the ligand, $(DHQD)_2$-PHAL, and the potassium osmate content in the AD-mix-β™ five-fold (5 mol% and 1 mol% respectively)[6] from the original formulation, such amides do turnover rapidly in the presence of methane sulfonamide[1] to give the corresponding diols **2** in excellent yields and ee's, Scheme, Table.[7]

Scheme



1 **2**

Table

Entry	Olefin[a]	Diol[b]			
		Yield, %[c]	Temp.	%ee[d]	Config.[e]
1.		96	r.t.	96	*(2S, 3R)*
2.		97	r.t.	97	*(2S, 3R)*
3.		95	r.t.	98	*(2S, 3R)*
4.		97	r.t.	98	*(3R, 4R)*
5.		81	0°C	93	*(2S)*
6.		92	r.t.	96	*(2S, 3R)*
7.		81	r.t.	98[f]	*(3R, 4R)*
8.		84	0°C	96[f]	*(3R, 4R)*
9.		83	0°C	96[f] (94, α)[g]	*(3R, 4R)*

a. All amides were prepared in 87-95% yields from the corresponding acid chlorides and dialkyl amines or *N*-methoxy-*N*-methyl amine hydrochloride.[4] b. All diols gave satisfactory IR, ^{1}H NMR and HRMS spectroscopic data. c. Yields of isolated diols. d. The ee was determined by ^{1}H NMR (entry 2, 5, 6) and HPLC (Chiralcell-OD™) of diols or their *bis*-MTPA esters. e. Configuration tentatively assigned based on our mnemonic[1] and on the transformation of the diol obtained from the AD of the amide in entry 9 to natutral (+)-Coriolic acid (see following paper). f. The ee was determined on the MTPA ester of corresponding γ-hydroxy α,β-unsaturated amide. g. ee obtained using Modified-AD-mix-α™ containing $(DHQ)_2$-PHAL.

The catalytic asymmetric dihydroxylation of *N*-methyl *N*-cinnamyl aniline was reported[8] to proceed with 99% conversion and 30% ee using chiral isooxazolidine ligands. However, we found that under the Modified-AD-mix™/$CH_3SO_2NH_2$ conditions, cinnamyl *N,N*-dimethylamine does not turnover rapidly (only trace amount, <5%, of the corresponding diol could be detected after 36 h. at r.t.), while 4-*N*-phenyl *N*-allyl piperazine was 70% converted to the corresponding diol in 55% ee after 7 days at r.t. It appears that in contrast to the allylic amide functionality, substrates having a more basic nitrogen lone pair in the allylic position can result in dramatically slowed catalytic turnover. Therefore, if 2,3– or 3,4–dihydroxy aliphatic amines of high enantiomeric purity are required, the better route would be via the reduction of the corresponding amides of type 2 from entries 1-4.

We have also found that unlike their corresponding esters,[9] β,γ–unsaturated amides[10] (entries 4 and 7-9) react under the above conditions to give predominantly (81-97% yield) the corresponding diols, with only a small amount of γ-lactone (8-12%) being isolated.[11] Excellent ee's were also recorded for this class of substrates.

Since unsaturated aldehydes and ketones have thus far proven to be poor substrates for the AD process,[12] 2,3 and 3,4- dihydroxy *N*-methoxy-*N*-methylamides (entries 5-9) should serve as masked equivalents for these important functionalities.[4, 7, 13]

Acknowledgments

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2. Suitably protected allylic amines undergo catalytic AD in good yields and ee's: Bennani, Y.L.; Walsh, P.J.; Sharpless, K.B. (unpublished results).

3. For example cinnamyl azide undergoes catalytic AD in 91% yield and >95% ee using AD-mix-β™ at 0°C; Bennani, Y.L.; Sharpless, K.B. (unpublished results), see also ref. (8).

4. Nahm , S.; Weinreb, S.M. *Tetrahedron Letters*, **1981**, *22*, 3815.

5. Reaction of cinnamyl *N*-methoxy-*N*-methylamide (Entry 6, Table) with AD-mix-β™ (Containing 1 mol% of $(DHQD)_2$-PHAL and 0.2 mol% of $K_2OsO_2(OH)_4$) gave ~15% yield of diol after 36 h at room temperature.

6. Modified-AD-mix-β™ contains 5 mol% of $(DHQD)_2$-PHAL and 1 mol% of $K_2OsO_2(OH)_4$ (i.e. a five-fold increase as compared to the original AD-mix-β™, see ref. 1(a) for AD-mix™ formulation). It was found recently that the AD of cinnamyl *N,N*-diethtylamide (Entry 1) proceeds in 94% yield and 94% ee at 0°C and 88 %ee at r.t. (compared to 96% ee using the Modified-AD-mix™ at r.t.), using a 1 mol% $(DHQD)_2$-PHAL : 1 mol% OsO_4 ratio; (Wang, Z.-M.; Sharpless K. B., unpublished results)

7. A recent communication describes the dihydroxylation of an α,β-unsaturated *N*-methoxy-*N*-methylamide, having a chiral center in the γ position, using with OsO_4 using NMO as cooxidant in acetone-H_2O; Hale, M.R. Hoveyda A. H. *J. Org. Chem.* **1992**, *57*, 1643.

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11. Under buffered AD-mix-β™ conditions (using an additional 3 mmol of $NaHCO_3$ per mmol of olefin) at 0°C, 3-octene-*N*-methoxy-*N*-methylamide (Entry 8, Table) gave 78% of diol, 8% γ-lactone in the presence of 1 equiv. of $CH_3SO_2NH_2$ after 22 h. For the use of buffered-AD conditions, see Kolb, H.C.; Bennani, Y.L.; Sharpless, K.B.; (*Tetrahedron: Asymmetry*; in press).

12. Walsh, P.J.; Sharpless, K.B. (unpublished results).

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