ORGANIC LETTERS

2001
Vol. 3, No. 22
3463−3466

Osmium-Catalyzed Asymmetric Dihydroxylation of Olefins by H_2O_2; Dual Role of the Cinchona Alkaloid Ligand

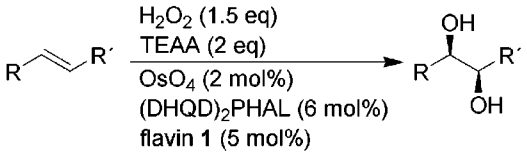
Sandra Y. Jonsson, Hans Adolfsson,* and Jan-E. Bäckvall*

Department of Organic Chemistry, Stockholm University, SE-106 91 Stockholm, Sweden

jeb@organ.su.se

Received July 18, 2001 *(Revised Manuscript Received September 25, 2001)*

ABSTRACT



A novel application of the cinchona alkaloid derivative $(DHQD)_2PHAL$ in the osmium-catalyzed asymmetric dihydroxylation of olefins is presented. In a triple catalytic system using H_2O_2 as the terminal oxidant, the alkaloid ligand has a dual function in providing stereocontrol in the addition step and, via its *N*-oxidized form, acting as reoxidant for the in situ generated osmium(VI). The formation of the *N*-oxide is catalyzed by a biomimetic flavin.

Herein we report on the first example of an enantioselective catalytic redox process where the chiral ligand has two fundamentally different modes of operation: (1) to provide stereocontrol in the addition to the substrate, and (2) through an oxidized form, to be responsible for the reoxidation of the metal. The use of environmentally benign oxidants, like molecular oxygen, air, or aqueous hydrogen peroxide, has become increasingly important in the field of synthetic organic chemistry.[1] The direct oxidation of organic material by these oxidants is, however, often slow and also very unselective. Nature efficiently circumvents this problem in biological redox processes, by introducing one or several relaying *electron-transfer mediators* (ETMs) to reduce the energy barrier between the terminal oxidant and the substrate in question, leading to selectivity in the oxidation step.[2] The same principle is also applied in several synthetically useful transition metal catalyzed oxidation reactions, where the substrate-selective catalyst gets reoxidized by a suitable ETM, which in turn is recycled by molecular oxygen or hydrogen peroxide as the terminal oxidant.[3,4]

The osmium-catalyzed asymmetric dihydroxylation of olefins undoubtedly qualifies as one of the most recognized asymmetric processes known by the scientific community.[5] Osmium tetroxide is an example of a highly substrate-selective oxidant, reacting only with olefins to form the parent *syn*-diols. With the introduction of the cinchona alkaloid-based ligands a highly enantioselective process was developed.[6] In the reaction with an olefin, the catalytically active Os(VIII) is reduced to Os(VI), and in order to run the process with a catalytic amount of osmium tetroxide, a number of different systems have been introduced for the

(1) (a) Simándi, L. I. *Catalytic Activation of Dioxygen by Metal Complexes*; Kluwer: Dordrecht, The Netherlands, 1992. (b) Strukul, G. *Catalytic Oxidations with Hydrogen Peroxide as Oxidant*; Kluwer: Dordrecht, The Netherlands, 1992.

(2) (a) Moser, C. C.; Keske, J. M.; Warncke, K.; Faird, R. S.; Dutton, P. L. *Nature* **1992**, *355*, 796. (b) Nugent, J. H. A. *Eur. J. Biochem.* **1996**, *237*, 519. (c) Hughes, M. N. *The Inorganic Chemistry of Biological Processes*; Wiley: Chichester, U.K., 1981.

(3) (a) Tsuji, J. *Palladium Reagents and Catalysts. Innovations in Organic Synthesis*; Wiley: Chichester, U.K., 1995. (b) Bäckvall, J. E.; Hopkins, R. B.; Grennberg, H.; Mader, M.; Awasthi, A. K. *J. Am. Chem. Soc.* **1990**, *112*, 5160. (c) Wöltinger, J.; Bäckvall, J. E.; Zsigmond, A. *Chem. Eur. J.* **1999**, *5*, 1460.

(4) (a) Bergstad, K.; Jonsson, S. Y.; Bäckvall, J. E. *J. Am. Chem. Soc.* **1999**, *121*, 10424. (b) Jonsson, S. Y.; Färnegårdh, K.; Bäckvall, J. E. *J. Am. Chem. Soc.* **2001**, *123*, 1365. (c) Ell, A. H.; Jonsson, S. Y.; Börje, A.; Adolfsson, H.; Bäckvall, J. E. *Tetrahedron Lett.* **2001**, *42*, 2569.

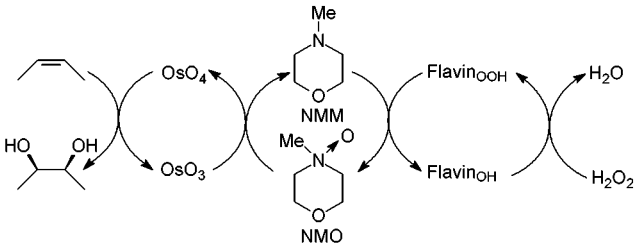
(5) (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (b) Kolb, H. C.; Sharpless, K. B. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; VCH Wiley: Weinheim, 1998.

10.1021/ol016450t CCC: $20.00
Published on Web 10/09/2001

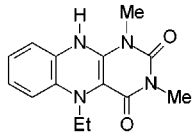
reoxidation of the metal into its active form. The most common oxidants are potassium ferricyanide (present in the AD-mixes)[7] or *N*-methylmorpholine *N*-oxide (NMO, the Upjohn process).[8] Recently, molecular oxygen or air were introduced as oxidants for the direct reoxidation of Os(VI) in the catalytic reaction, thus providing a more environmentally friendly system.[9]

We have previously reported on the use of aqueous hydrogen peroxide as the terminal oxidant in the dihydroxylation of olefins (Scheme 1).[4]

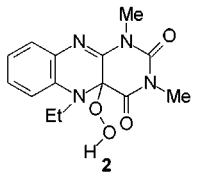
Scheme 1. Triple Catalytic System for Osmium-Catalyzed Dihydroxylation of Olefins Using H_2O_2 as the Terminal Oxidant



In this triple-catalytic system the introduction of a catalytic amount of a biomimetic flavin (**1**) as an electron-transfer



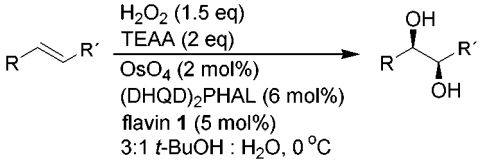
1



2

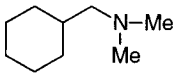
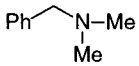
mediator allowed for the selective oxidation of *N*-methylmorpholine (NMM) to NMO,[10] which in turn oxidizes the reduced form of the osmium catalyst. The flavin reacts rapidly with hydrogen peroxide, forming a flavin hydroperoxide (**2**), the active catalyst for the oxidation of the tertiary amine. Here we report on a highly enantioselective dihydroxylation of olefins using a chiral, amine-containing, ligand as the source of chirality and as reoxidant for the in situ-formed osmium(VI) intermediate (Scheme 2).

Scheme 2



Because the flavin/H_2O_2 system works very well for oxidation of various tertiary amines to their corresponding *N*-oxides,[10] it was of interest to investigate if NMM could be replaced by other tertiary amines in the triple catalytic system. Dihydroxylation of *trans*-5-decene was carried out with various tertiary mono- and diamines in the presence of TEAA (tetraethylammonium acetate) (Table 1).

Table 1. *cis*-Selective Dihydroxylation of *trans*-5-Decene Using Different Tertiary Amines in the Triple Catalytic System[a]

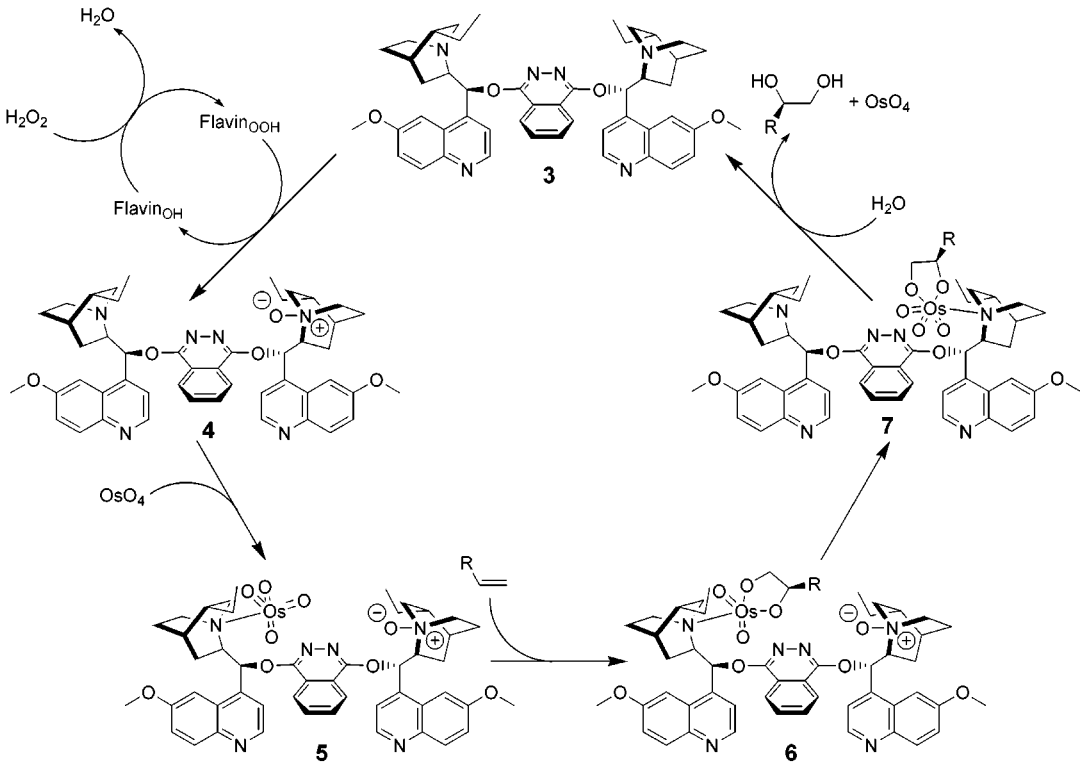
entry	amine	yield (%)[b]
1[c]	NMM	96
2[c]	NEt_3	91
3[c]		90
4[c]		89
5[c]	NMe_3	81
6	quinuclidine	96
7	TMEDA	43
8	$(DHQD)_2PHAL$	93

[a] *trans*-5-Decene (0.5 mmol), tertiary amine (27 mol %), TEAA (2 equiv), flavin **1** (5 mol %), and OsO_4 (2 mol %) were dissolved in acetone (1.88 mL) and H_2O (0.62 mL). H_2O_2 (1.5 equiv, 30% aqueous) was added to this mixture over 9 h. After complete addition of the oxidant, the mixture was stirred for an additional 5−10 h. [b] Isolated yield of the diol. [c] Reference 4b.

Thus, it was found that it is possible to use different tertiary monoamines with essentially the same outcome (entries 1−6). We further investigated if our system was compatible with the use of tertiary diamines (Table 1, entries 7 and 8). When using TMEDA as the amine source a yield of 43% of the corresponding diol was obtained (entry 7). The use of catalytic OsO_4 with chelating diamines is currently unknown, since the bidentate ligands form very stable chelated osmate esters, which are difficult to hydrolyze and/or reoxidize.[5a,11−13] Next, we examined the use of Sharpless' cinchona-based ligand hydroquinidine 1,4-phthalazinediyl diether ($(DHQD)_2$-PHAL, **3**)[6b] as a tertiary amine source in the catalytic system. When employing $(DHQD)_2PHAL$ as the tertiary amine in the dihydroxylation of *trans*-5-decene (entry 8) a yield of 93% of the diol was obtained in 63% ee.

(6) (a) Wai, J. S. M.; Markó, I.; Svendsen, J. S.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 1123. (b) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768. (c) Wang, Z. M.; Sharpless, K. B. *J. Org. Chem.* **1994**, *59*, 8302.
(7) Minato, M.; Yamamoto, K.; Tsuji, J. *J. Org. Chem.* **1990**, *55*, 766.
(8) VanRheenen, V.; Kelly, R. C.; Cha, D. F. *Tetrahedron Lett.* **1976**, 1973.
(9) Döbler, C.; Mehltretter, G.; Sundermeier, U.; Beller, M. *J. Am. Chem. Soc.* **2000**, *122*, 10289.
(10) Bergstad, K.; Bäckvall, J. E. *J. Org. Chem.* **1998**, *63*, 6650.
(11) Blades, K.; Donohoe, T. J.; Winter, J. J. G.; Stemp, G. *Tetrahedron Lett.* **2000**, *41*, 4701.
(12) (a) Donohoe, T. J.; Moore, P. R.; Waring, M. J.; Newcombe, N. J. *Tetrahedron Lett.* **1997**, *38*, 5027. (b) Blades, K.; Donohoe, T. J.; Winter, J. J. G.; Stemp, G. *Tetrahedron Lett.* **2000**, *41*, 4701.
(13) Donohoe, T. J.; Blades, K.; Moore, P. R.; Winter, J. J. G.; Helliwell, M.; Stemp, G. *J. Org. Chem.* **1999**, *64*, 2980.

Scheme 3. Proposed Catalytic Cycle for the Enantioselective Dihydroxylation of Olefins Using $(DHQD)_2PHAL$ for Oxygen Transfer to Os(VI) and as Source of Chirality



Encouraged by the promising results obtained with the triple catalytic system using $(DHQD)_2PHAL$ as the tertiary amine source (cf. Scheme 1) we turned to the asymmetric version of the reaction and set out to investigate the possibility of using the ligand both as reoxidant and source of chirality. For the asymmetric dihydroxylations, the solvent was changed to *t*-BuOH because performing the oxidation in acetone gave substantially lower enantioselectivity.[14] The most important factor for obtaining high enantioselectivity, however, is the use of slow addition of the olefin to the reaction mixture. As discovered in the original studies of the catalytic asymmetric dihydroxylation, a low olefin concentration efficiently prevents the reaction from entering the enantio-detrimental second catalytic cycle.[6a] We have further found that an improvement of the ee was obtained when one-fifth of the hydrogen peroxide was added to the reaction mixture 20 min prior to the introduction of the olefin.[4b] Presumably, this builds up a low buffer concentration of amine oxide by oxidizing some of the tertiary amine. After this initial preactivation, the remaining H_2O_2 as well as the olefin were added over 9 h via separate syringe pumps.

When performing the asymmetric dihydroxylation on styrene using $(DHQD)_2PHAL$ (6 mol %) both as ETM and chiral source, an ee of 95%, was obtained (Scheme 2, Table 2, entry 1). Dihydroxylation of *trans*-stilbene (entry 2) and α-methylstyrene (entry 3) gave the corresponding diols in 90% ee, respectively. Interestingly, with *trans*-*β*-methylstyrene (entry 4) an ee of 99% was obtained, which is higher than with the method based on NMM. However, the trisubstituted olefin 1-phenyl-1-cyclohexene (entry 5) gave a substantially lower ee, even though the addition time of both olefin and hydrogen peroxide was increased from 9 to 20 h.[4b,6a]

The results obtained with $(DHQD)_2PHAL$ both as the ETM and chiral ligand are comparable to those obtained employing NMM together with $(DHQD)_2PHAL$. In two cases, for α-methylstyrene and 1-phenyl-1-cyclohexene, ee's lower than those of the NMM-based procedure were obtained.

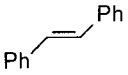
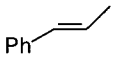
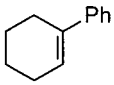
The proposed catalytic cycle for the reaction is depicted in Scheme 3. We envisage a rapid flavin-catalyzed formation of the mono-*N*-oxide **4** of the ligand, which via its non-oxidized tertiary amine coordinates to osmium tetroxide to give **5**. Previously, we have demonstrated that it is possible to oxidize the tertiary amine functionality on DHQD by employing the flavin/H_2O_2 system.[15] Control experiments show that oxidation of $(DHQD)_2PHAL$ using the flavin/H_2O_2 system selectively gives the mono-*N*-oxide **4**.[16] The olefin enters the binding pocket, resulting in the enantioselective formation of an osmium-glycolate (**6**). Reoxidation of Os(VI) can now occur, having the active oxidant within the ligand. The observed efficiency using only 6 mol % of **3** as compared to 50 mol % of NMM indicates a fast intra-

(14) Argren, L.; Sutin, L. *Org. Process Res. Dev.* **1997**, *1*, 425.

(15) Utas, J. E.; Adolfsson, H. Unpublished results.

(16) Only the mono-*N*-oxide was observed according to spectral data (*m*/*z* 794.9474). Performing the oxidation using MCPBA resulted in the formation of a mixture of the mono-*N*-oxide and the di-*N*-oxide (*m*/*z* 810.9302).

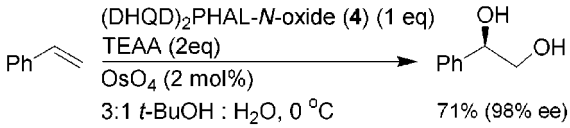
Table 2. Asymmetric Dihydroxylation of Different Olefins Using H_2O_2 as the Terminal Oxidant[a,b]

entry	olefin	method[a,b]	yield (%)[c]	ee (%)[d]
1		$(DHQD)_2PHAL$, NMM[a]	80	95
		$(DHQD)_2PHAL$[b]	**75**	**95**
2[e,f]		$(DHQD)_2PHAL$, NMM[a]	94	90
		$(DHQD)_2PHAL$[b]	**89**	**90**
3		$(DHQD)_2PHAL$, NMM[a]	88	99
		$(DHQD)_2PHAL$[b]	**81**	**90**
4		$(DHQD)_2PHAL$, NMM[a]	67	96
		$(DHQD)_2PHAL$[b]	**61**	**99**
5[g]		$(DHQD)_2PHAL$, NMM[a]	50	92
		$(DHQD)_2PHAL$[b]	**58**	**70**

[a] Reference 4b. [b] TEAA (2 equiv), $(DHQD)_2PHAL$ (0.06 equiv), and flavin **1** (0.05 equiv) were dissolved in *t*-BuOH (1.88 mL) and H_2O (0.62 mL). The mixture was cooled to 0 °C, and OsO_4 (0.02 equiv) was added followed by one-fifth of the H_2O_2 (0.3 equiv, 30% aqueous). The mixture was stirred for 20 min, and then the olefin (0.5 mmol, 1 equiv) and the remaining H_2O_2 (1.2 equiv) were added over 9 h. After complete addition of the oxidant and olefin, the mixture was stirred for an additional 2−7 h. [c] Isolated yields. [d] Enantiomeric excesses were determined by HPLC. The absolute configuration of the diols were determined by comparison of optical rotations with literature values. [e] Acetone/H_2O (4.4:1) was employed. [f] The enantiomeric excess was determined from optical rotational data (see ref 6c). [g] The olefin and H_2O_2 were introduced over 20 h.

molecular oxygen transfer process (**6** → **7**). Although direct oxidation of Os(VI) by flavin hydroperoxide cannot be excluded, this potential background process seems unlikely as a major pathway. When the tertiary amine was omitted in the triple catalytic racemic version of the dihydroxylation, the yield dropped dramatically.[4b] Furthermore, employing the isolated $(DHQD)_2PHAL$-mono-*N*-oxide (**4**) as the stoichiometric reoxidant and chirality transfer agent in the dihydroxylation of styrene afforded the corresponding diol in 71% isolated yield and 98% ee (Scheme 4). Thus, it is likely that the major pathway involves *N*-oxide **4**.

Scheme 4



Hydrolysis of the osmium-glycolate liberates the diol, osmium tetroxide, and the free ligand, which can re-enter the catalytic cycle. Thus, the ligand has a dual role in the reaction, participating in both enantiodifferentiation and in oxygen transfer.

In conclusion, we have developed an osmium-catalyzed asymmetric dihydroxylation protocol using H_2O_2 as the terminal oxidant and the alkaloid ligand $(DHQD)_2PHAL$ as both electron transfer mediator and source of chirality. A number of olefins were efficiently converted to the corresponding *syn*-diols with excellent enantioselectivity via the biomimetic triple catalytic system.

Acknowledgment. Financial support from the Swedish Natural Science Research Council, the Swedish Research Council for Engineering Sciences, and the Swedish Foundation for Strategic Research is gratefully acknowledged.

Supporting Information Available: Experimental procedures, characterizations, and chiral-phase HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016450T