



An improved version of the Sharpless asymmetric dihydroxylation

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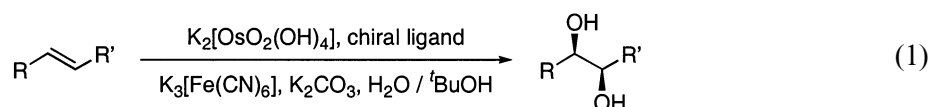
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Abstract

The osmium catalyzed asymmetric dihydroxylation of olefins (Sharpless AD) was studied under controlled pH conditions. It was found that providing a constant pH value of 12.0 leads to improved reaction rates for internal olefins. Hydrolysis aids such as methanesulfonamide can be omitted. For terminal olefins, working at a constant pH of 10.0 at room temperature leads to higher enantioselectivities compared to AD reactions without pH control. © 2000 Elsevier Science Ltd. All rights reserved.

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The osmium catalyzed asymmetric dihydroxylation (Sharpless AD)¹ has developed into one of the most important tools for the enantioselective functionalization of olefins (Eq. (1)).



AD reactions are usually performed with commercially available AD-mixes, consisting of 0.4 mol% $\text{K}_2[\text{OsO}_2(\text{OH})_4]$, 1 mol% $(\text{DHQD})_2\text{PHAL}$ (AD-mix β) or $(\text{DHQ})_2\text{PHAL}$ (AD-mix α), 3 equiv. of $\text{K}_3[\text{Fe}(\text{CN})_6]$ and 3 equiv. of K_2CO_3 . In the case of internal olefins the addition of at least a stoichiometric amount of a hydrolysis aid such as Et_4NOAc ² or MeSO_2NH_2 ³ is required to obtain reasonable reaction rates, due to hydrolysis problems of sterically hindered intermediate osmate esters.

During our work on the osmium catalyzed dihydroxylation of olefins with molecular oxygen as the terminal oxidant,⁴ we recognized that internal olefins react best at pH values between 11.2 and 12.0, due to an enhanced hydrolysis of the intermediate osmate esters under strong basic conditions. Surprisingly, no detailed investigations on the exact influence of the pH value on the

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rate and the selectivity of AD reactions with other reoxidants exist.⁵ In this paper we report our studies on the influence of pH on the rate and selectivity for dihydroxylations of different olefins using $K_3[Fe(CN)_6]$ as the reoxidant.

Initially, we examined the asymmetric dihydroxylation of *trans*-5-decene. Applying original AD conditions (5 mmol *trans*-5-decene, 50 ml H_2O /*t*-BuOH (1:1), 3 equiv. $K_3[Fe(CN)_6]$, 3 equiv. K_2CO_3 , 0.4 mol% $K_2[OsO_2(OH)_4]$, and 1 mol% $(DHQD)_2PHAL$), a pH value of 12.2 is measured in the biphasic mixture at the start of the reaction.⁶ Consistent with the overall stoichiometry (Eq. (2)), the pH of the mixture decreases continuously during the reaction to a final value of 9.9, since two hydroxide ions are consumed for the dihydroxylation of each molecule of *trans*-5-decene. As shown in Fig. 1a, product formation correlates well with the decrease in pH. At room temperature full conversion of the olefin (94% isolated yield of 5,6-decanediol, 93% *ee*) is not achieved before 34 hours reaction time. The dihydroxylation proceeds rapidly at the start, but becomes significantly slower after the pH has reached a value of ca. 11. This may be explained by the fact that the hydrolysis of the intermediate glycolate ester is slower when the reaction mixture becomes less basic. We presumed therefore that an increase in the overall rate would occur if the pH is maintained at a constant value above 11 during the entire reaction period.

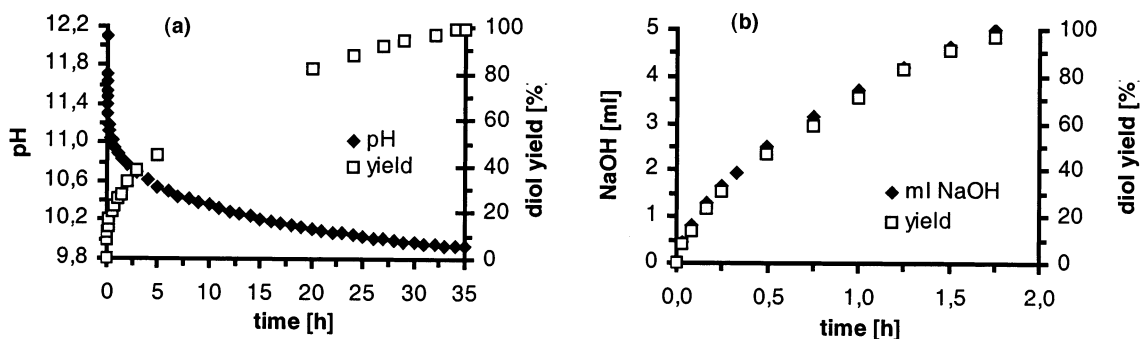


Figure 1. Dihydroxylation of *trans*-5-decene with AD-mix without pH control (a) and with automatic titration (b)

In fact, when the dihydroxylation of *trans*-5-decene is performed at a constant pH value of 12.0 by using an automatic titration unit (2N NaOH), full conversion is obtained after less than 2 hours (95% isolated yield, 90% *ee*, see Table 1).⁷ Thus, the dihydroxylation of *trans*-5-decene is significantly faster when run under a constant pH value of 12.0 rather than without pH control. Even if 1 equiv. of $MeSO_2NH_2$ is added as advised in the original protocol^{1a} (Table 1, entry 2), the reaction is slower than the pH-controlled variant without $MeSO_2NH_2$. In addition, the procedure presented here allows the reaction to be conveniently followed by simply observing the titration curve (see Fig. 1b). Total conversion is indicated by titration of 5 ml of the NaOH solution (10 mmol of OH^- per 5 mmol of olefin).⁸ The obtained *ee* of 90% is somewhat lower compared to 93% *ee* without titration, which is probably due to competition of hydroxide ions with the chiral ligand under the strong basic conditions. Consistent with this assumption, the decrease in *ee* can be overcome by applying a higher ligand concentration (Table 1, entry 4).

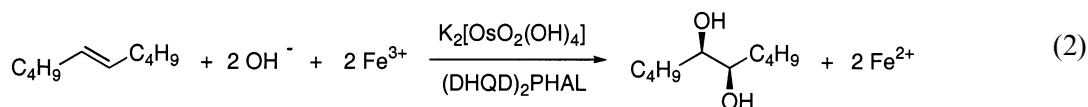


Table 1
 Sharpless AD under controlled pH conditions^a

Olefin	Titration ^b	T [°C]	Ligand	t [h]	yield ^c	ee ^d
1	-	25	PHAL	34	94	93
2 ^e	-	25	PHAL	3	95	93
3	12.0	25	PHAL	1.8	95	90
4	12.0	25	PHAL ^f	1.7	96	93
5	-	25	PHAL	21	82 ^g	99
6	12.0	25	PHAL	1.5	62 ^g	99
7	-	25	quinuclidine	20	50 ^h	-
8	12.0	25	quinuclidine	5	98	-
9	-	25	PHAL	24	28 ^h	33
10	12.0	25	PHAL	24	95	23
11 ⁱ	12.0	0	PHAL	24	71 ^h	52
12 ⁱ	12.0	0	PYR	24	73 ^h	61
13	-	25	PHAL	0.6	95	89
14	12.0	25	PHAL	0.6	96	89
15	10.0 ^k	25	PHAL	1.6	95	93
16	-	25	PHAL	1.5	95	82
17	10.0 ^k	25	PHAL	2	94	84

^a General conditions: 5 mmol olefin, 3 equiv. $K_3[Fe(CN)_6]$, 3 equiv. K_2CO_3 , 0.4 mol% $K_2[OsO_2(OH)_4]$, 1 mol% ligand, 50 ml $H_2O/BuOH$ (1:1). ^b The given value is the pH value to which the automatic titration unit was set. Titration with 2N NaOH. ^c Isolated yields. ^d The *ee* of 5,6-decanediol was determined by HPLC analysis of the bisbenzoate derivative, all others by HPLC analysis of the purified diols (see Ref. 5b for details). ^e 1 equiv. $MeSO_2NH_2$ is added. ^f 4 mol% ligand. ^g No remaining olefin was detected after the given reaction time. Benzaldehyde and acetophenone are formed as the only byproducts. ^h Incomplete reaction. The only other product detected was recovered starting material. ⁱ 1 mol% $K_2[OsO_2(OH)_4]$, 5 mol% ligand. ^k Instead of K_2CO_3 , a buffer solution (0.5 M $KH_2PO_4/2N$ NaOH, pH 10.0) was used.⁹

Next we applied the presented method to tri- and tetrasubstituted olefins. With α -methylstilbene as the substrate, total turnover of the olefin is observed within 1.5 hours at a constant pH of 12.0, compared to 21 hours without pH control (entries 5 and 6). However, the chemoselectivity of the reaction is lower in the case of a constantly high pH throughout the reaction.

The enhancement in rate is most striking for tetrasubstituted olefins. Without titration, dihydroxylation of 2,3-dimethyl-2-butene yields 50% of pinacol after 20 hours, whereas under a constant pH of 12.0 full conversion (98% isolated yield) of the substrate is obtained within only 5 hours (entries 7 and 8). In the case of 2-methyl-3-phenyl-2-butene, with 0.4 mol% catalyst, 95% diol yield is obtained after 24 hours at constant pH compared to only 28% without titration (entries 9 and 10).

This considerable increase in the reaction rate opens the possibility to run the dihydroxylation of 2-methyl-3-phenyl-2-butene even at 0°C (entry 11). This leads to a remarkable gain in enantioselectivity of 52% *ee* compared to 38% *ee* reported by Sharpless et al. for the same substrate at 25°C.¹⁰ Using (DQHD)₂PYR as the chiral ligand, an *ee* of even 61% is obtained under these conditions (entry 12), compared to 44% at 25°C without pH control.¹⁰ Additionally, no MeSO₂NH₂ is required under the presented conditions, whereas 3 equiv. of this additive are advised in the original protocol for tetrasubstituted olefins.

In agreement with the faster hydrolysis of osmium glycolates of *terminal olefins* α -methylstyrene shows no rate enhancement when the AD is performed at a constant pH of 12.0 (entries 13 and 14). However, when the AD of α -methylstyrene and of allyl phenyl ether is run at a constant pH of 10.0 at room temperature, a slight increase in *ee* is observed compared to the reactions without pH control due to the less basic conditions during the whole reaction period (entries 15 and 17).

In conclusion, we have shown that the pH value of the reaction medium in AD reactions is a critical reaction parameter which effects rate, chemo- and enantioselectivity. By applying a constant pH value of 12.0 during the reaction, significant improvements in rate and space-time yield have been realized for 1,2-di-, tri- and tetrasubstituted olefins. In addition, the enantioselectivity in AD reactions of terminal olefins at room temperature is slightly enhanced by applying a constant pH of 10.0. It is likely that the presented methodology is also applicable to dihydroxylation with other reoxidants like NMO, H₂O₂ etc.

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5. The use of buffered reaction conditions (3 equiv. NaHCO_3 , pH 10.3, aqueous layer) was reported to have beneficial effects on the yield in AD reactions when base sensitive substrates are used or base sensitive products are formed: (a) Kolb, H. C.; Bennani, Y. L.; Sharpless, K. B. *Tetrahedron: Asymmetry* **1993**, *4*, 133–141. (b) Vanhessche, K. P. M.; Wang, Z.-M.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 3469–3472.
6. The pH was measured in the vigorously stirred biphasic mixture with a pH sensitive electrode (Mettler Toledo InPro 4200). The values were stable and only slightly different compared to the pH of the pure aqueous phase.
7. Typical procedure: in a 250 ml two necked flask, equipped with a pH sensitive electrode and an automatic titration unit (Schott TitroLine *alpha*), 4.95 g (3 equiv.) $\text{K}_3[\text{Fe}(\text{CN})_6]$, 2.1 g (3 equiv.) K_2CO_3 , 7.4 mg (0.4 mol%) $\text{K}_2[\text{OsO}_2(\text{OH})_4]$ and 39.0 mg (1 mol%) $(\text{DHQD})_2\text{PHAL}$ are dissolved in 50 ml of a 1:1 mixture of H_2O and $t\text{-BuOH}$. After addition of 980 μl (5 mmol) of *trans*-5-decene, the biphasic mixture is stirred at room temperature and kept at a constant pH of 12.0 by automatic titration with a 2N NaOH solution. After titration of 5 ml of NaOH (1.8 h), the reaction is quenched by addition of 7.5 g Na_2SO_3 . The mixture is stirred for another hour, then 100 ml of ethyl acetate are added. After separation, the organic layer is dried over MgSO_4 and concentrated. Purification of the residue by column chromatography (hexane/EtOAc 2:1) gives 826 mg (95%) of 5,6-decanediol as a colorless solid.
8. Titration continues at a lower rate after full conversion due to overoxidation of the 5,6-decanediol product. This is also the case for α -methylstilbene, allyl phenyl ether, but not for α -methylstyrene and the tetrasubstituted olefins.
9. It is advisable to buffer the reaction solutions to avoid strong fluctuations in the pH during titration.
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