

nearly quantitative yield after about one week. The crystals were found to be stable in air. M.p. 148–150 °C (decomp); IR(KBr): $\tilde{\nu}$ = 3435 (s, br), 3315 (ms, sh), 3261 (ms, sh), 3091 (w, sh), 2961 (m, sharp), 2874 (w), 1699 (s, sharp), 1678 (m, sh), 1604 (s, sharp), 1547 (vs, sharp), 1522 (vs, sh), 1494 (s, sh), 1353 (m, sh), 1327 (m, br), 1178 (m, sharp), 1158 (m, sharp), 875 (m, sharp), 778 (m, sharp), 699 (w) cm^{-1} ; C, H, N analysis calcd for $[(n\text{-C}_4\text{H}_9)_4\text{N}^+]_2\text{C}_6\text{O}_6^{2-} \cdot 2m\text{-OHC}_6\text{H}_4\text{NHCONH}_2 \cdot 2\text{H}_2\text{O}$ (M_r = 993.32): C 62.88, H 9.33, N 8.46; found: C 62.48, H 9.37, N 8.41.

Bis(tetra-*n*-butylammonium) rhodizonate–1,1'-ethylenediurea–water (1/2/3) (**2**): The above procedures were employed using tetrahydroxy-1,4-quinone (0.051 g), tetra-*n*-butylammonium hydroxide (1.00 mL), and 1,1'-ethylenediurea (0.107 g). Air-stable rose red prisms were obtained in nearly quantitative yield after about ten days. M.p. 187.9–191.5 °C, IR(KBr): $\tilde{\nu}$ = 3426 (vs, br), 3295 (s, sh), 3100 (w, sh), 2958 (m, sharp), 2873 (w), 1666 (s, sharp), 1550 (vs, sharp), 1521 (vs, sh), 1360 (w, sharp), 1158 (w, sharp), 790 (w, sh), 702 (m, sh), 543 (ms, br) cm^{-1} ; C, H, N analysis calcd for $[(n\text{-C}_4\text{H}_9)_4\text{N}^+]_2\text{C}_6\text{O}_6^{2-} \cdot 2\text{NH}_2\text{CONHCH}_2\text{CH}_2\text{NHCONH}_2 \cdot 3\text{H}_2\text{O}$ (M_r = 999.34): C 55.29, H 9.88, N 14.01; found: C 54.18, H 10.04, N 13.81. The results of elemental analysis are in better agreement with the presence of an extra water molecule in the structural formula of **2**, which might be due to absorption of atmospheric moisture by the mailed sample.

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$2\text{NH}_2\text{CONHCH}_2\text{CH}_2\text{NHCONH}_2 \cdot 3\text{H}_2\text{O}$ (**2**), M_r = 999.34, monoclinic, space group $P2_1/c$ (no. 14), a = 13.933(2), b = 15.576(2), c = 26.713(3) Å, β = 91.042(2)°, V = 5797(1) Å³, Z = 4, ρ_{calcd} = 1.145 Mg m^{-3} , $F(000)$ = 2192, $\mu(\text{Mo K}\alpha)$ = 0.080 mm^{-1} , 25 578 reflections measured, 7585 unique (R_{int} = 0.0685), final R_1 = 0.0494, wR_2 = 0.1165 for 3310 observed reflections [$I > 2\sigma(I)$]. Data collection was performed at 293 K on a Bruker SMART 1000 CCD diffractometer using frames of oscillation range 0.3°, with 3° < θ < 28°. The structures were solved by direct methods, and all non-hydrogen atoms were refined anisotropically by full-matrix least-squares on F^2 using the SHELXTL program.^[18] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-163556 (**1**) and CCDC-163557 (**2**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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A Practical and Highly Efficient Aminohydroxylation of Unsaturated Carboxylic Acids**

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Dedicated to Professor Harry H. Wasserman on the occasion of his 80th birthday

Osmium-catalyzed aminohydroxylation is a powerful synthetic transformation that allows conversion of olefins to commonly occurring β -amino alcohols. Products obtained by this route are important intermediates in the synthesis of natural products, pharmaceutically important compounds,

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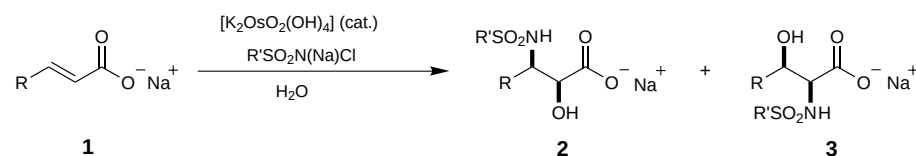
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new materials, and catalysts. Both racemic^[1] ("A") and asymmetric^[2] ("AA") variants of this reaction have been reported, and various classes of olefins have been studied as substrates. In efforts to develop this process further, α,β -unsaturated carboxylic acids were examined as potential substrates. The ready availability of these olefins from natural sources, outstanding synthetic methods for their preparation, and importance of α,β -hydroxyamino acid derivatives obtained make them one of the most attractive classes of olefins for aminohydroxylation.

The present asymmetric versions of both the osmium-catalyzed dihydroxylation and aminohydroxylation reactions depend crucially on the ligand-acceleration effect.^[3] Additionally, the cinchona alkaloid ligands enhance chemoselectivity in the aminohydroxylation by suppressing diol formation. Herein, we report that with α,β -unsaturated carboxylates as substrates the aminohydroxylation proceeds rapidly *in the absence* of cinchona alkaloid ligands (Scheme 1). A consequence of this remarkable ligand-independent reactivity is that the process is not enantioselective, even in the presence of a large excess of the chiral ligand.

However, this new ligand-independent aminohydroxylation process is otherwise superior to the AA with alkaloid ligands in the following ways: 1) it requires much lower loading of the osmium catalyst (0.1–1.0 mol % as opposed to 4–5 mol %); 2) it needs only a stoichiometric amount of the nitrogen source (cf. the >3 equivalents needed in the AA); 3) diol



Scheme 1. Aminohydroxylation of α,β -unsaturated carboxylates.

formation, an inevitable side reaction under standard A and AA conditions, and which, in worst cases, accounts for as much as 40% of the product, has not been observed; 4) a range of solvents can be employed for the reaction (e.g. water/*tert*-butyl alcohol and water/acetonitrile), but very importantly, *it often proceeds just as well in water without any organic cosolvent*; 5) scale-up is greatly facilitated by the ability to run the reaction at high concentrations (0.3–0.8 M in olefin being typical), whereas the AA requires concentrations <0.1 M for optimal results; and finally, 6) since the only coproduct is sodium chloride, product isolation is very easy for, upon acidification, most of the α,β -hydroxyamino acid derivatives precipitate and are collected by simple filtration as pure materials. It should be noted that carboxylic acids must be converted to the corresponding salts before addition of the chloramine. Given that aminohydroxylation is markedly impeded in a highly alkaline medium (pH > ca. 10), sodium bicarbonate appears to be among the best neutralizing agents. It can be used in slight excess without raising the pH significantly, thus further simplifying the experimental procedure.

A wide range of unsaturated acids was examined in this study. Simple alkenoic acids, such as acrylic, methacrylic, and

fumaric, participate readily in the reaction providing easy access to α,β -hydroxyamino acids. When unsymmetrically substituted alkenes are used, only one product results, always bearing nitrogen on the less substituted carbon. Selected results are presented in Table 1. For example, *N*-(*p*-toluene-

Table 1. Aminohydroxylation of simple alkenoic acids.

Entry	Substrate	Os [mol %]	Time [h]	Yield [%]
1		0.5	8	94
2		0.5	6	98
3		0.2	6	98
4		0.5	6	98
5		1.0	12	88

sulfonyl)-protected isoserine and hydroxyaspartic acids were easily prepared in one step in excellent yields. When necessary, the tosyl protecting group can be reductively removed, liberating the free amino acid.^[4]

When variously substituted aryl-acrylic acids (Table 2) were subjected to aminohydroxylation, mixtures of both regioisomers were obtained, favoring nitrogen in the benzylic position (**2**) in all cases. Most of the time, separation of these regioisomers did not present a problem as their solubility in water and/or water/alcohol mixtures differs significantly.^[5]

Although at present this process yields racemic mixtures of products, their resolution with chiral bases is a well-established methodology that can be easily carried out on a large scale.^[6]

The scope of the reaction regarding viable sulfonamide precursors of the electrophilic nitrogen was also examined and found to be excellent, including, for example, 4-nitrobenzene- and methanesulfonamide.^[7] The former one, devised by Fukuyama et al. to allow removal under very mild conditions,^[8] enables liberation of parent hydroxyamino acids in high yields.

In conclusion, we have developed a new method for converting α,β -unsaturated carboxylic acids to α,β -hydroxyamino acid derivatives in one step. The reaction exhibits wide scope and excellent chemoselectivity. It is the latest, and most impressive, example to date in the ligand-independent family of aminohydroxylations. Hence, unsaturated acids now join α,β -unsaturated amides^[9] and Baylis–Hillman olefins^[10] as privileged substrates for this transformation. These ligand-

Table 2. Aminohydroxylation of arylacrylic acids.^[a]

Entry	Substrate	Time [h]	Ratio 2:3	Yield [%]
1		10	1.6:1	96
2		10	1.6:1	91
3		10	1.8:1	88
4		5	3.0:1	92
5		8	1.6:1	90
6		12	3.0:1	88

[a] All reactions were performed with 1.0 mol % of Os catalyst.

independent catalytic processes are several orders of magnitude more efficient than the other versions of the osmium-catalyzed aminohydroxylations which have been reported since its discovery in 1976. The mechanistic foundation for this exceptional catalytic behavior, as well as additional practical applications it has enabled, will be reported elsewhere.^[11]

Experimental Section

General experimental procedure as described for fumaric acid: Fumaric acid (116 g, 1.0 mol) and sodium bicarbonate (186 g, 2.2 mol) were dissolved in tap water (1.5 L) in a 3 L Erlenmeyer flask. After gas evolution ceased, Chloramine-T trihydrate (281 g, 1.0 mol) was added, followed by potassium osmate (0.74 g, 0.2 mol %). The dark brown color of the reaction mixture is characteristic at this point. The reaction mixture was stirred for 8 h, after which time it cleared and turned green. No oxidant could be detected at this point (starch/iodide paper). HCl (5 M, 500 mL) was then added, and the reaction mixture was left in the refrigerator overnight. Crystals formed were filtered, washed with a small amount of cold water, and dried to yield 280 g (92 %) of pure product. M.p. 201–203 °C (decomp, H₂O); ¹H NMR (500 MHz, [D₆]DMSO): δ = 7.65 (d, *J* = 7.8 Hz, 2H), 7.29 (d, *J* = 7.8 Hz, 2H), 4.05 (d, *J* = 3.4 Hz, 1H), 3.88 (d, *J* = 3.4 Hz, 1H), 2.33 (s, 3H); ¹³C NMR (125 MHz, [D₆]DMSO): δ = 173.93, 171.29, 142.26, 138.33, 129.27, 126.78, 71.63, 58.84, 21.03.

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