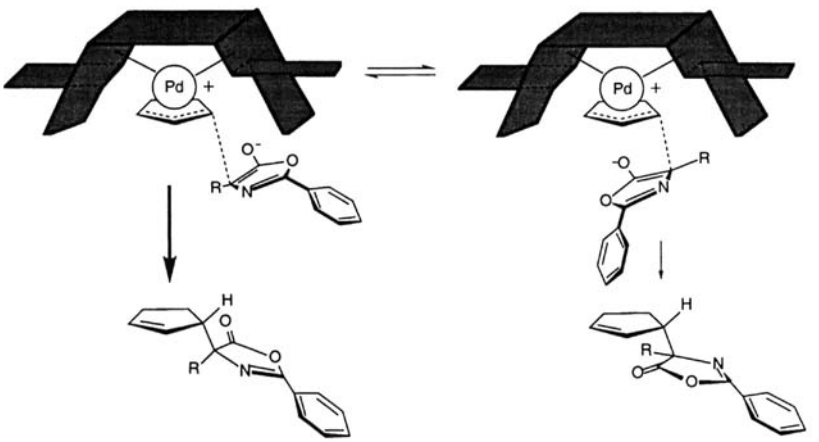

Scheme 4. Cartoon depicting the sense of asymmetric induction at an azlactone-derived nucleophile.

temperature (see Table 2). The reaction mixture was quenched (2–24 h) with aqueous phosphate buffer (pH 7, 40 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (eluent: petroleum ether/EtOAc).

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A Highly Efficient Aminohydroxylation Process**

A. Erik Rubin and K. Barry Sharpless*

Dedicated to Professor Dieter Seebach on the occasion of his 60th birthday

Stereospecific transformations of olefins to 1,2-diols[1,2] and β-amino alcohols[3,4] are very important due to the ready availability of the starting materials and the significance of the products as building blocks in the syntheses of drugs and natural products, ligands for asymmetric catalysis, and chiral auxiliaries.[1–5] The recently discovered catalytic asymmetric aminohydroxylation (AA) of olefins,[4] a close "relative" of the highly reliable catalytic asymmetric dihydroxylation (AD),[1] stereospecifically provides N-protected β-amino alcohols with the added benefit of good to excellent regio- and enantioselectivities. However, in the absence of cinchona alkaloid ligands (i. e., in the achiral mode, which yields racemic products if the olefin is prochiral), the reaction is plagued by the formation of large amounts of diol and suffers from a significant decrease in regioselectivity.[4,6]

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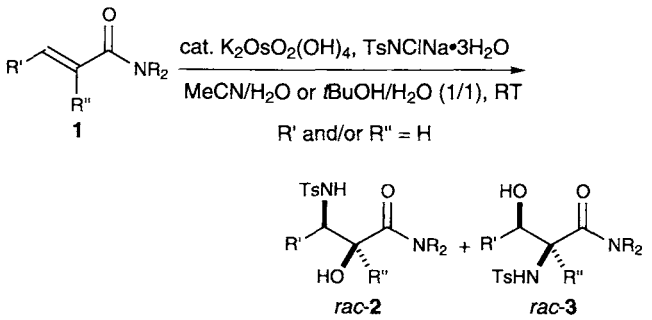
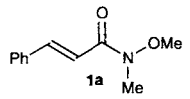
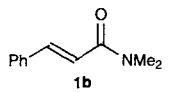
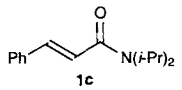
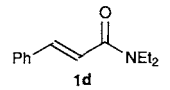
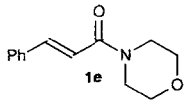
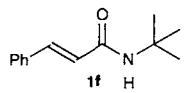
In our continuing effort to develop the AA further and to expand its scope, α,β-unsaturated amides were examined as potential substrates. Remarkably, they gave only racemic products in the AA with chloramine T.[7] On the other hand, they exhibited excellent reactivity and afforded very high yields of the hydroxysulfonamide products, whether or not ligand was added. A more detailed study of the "ligand-independent" aminohydroxylation of α,β-unsaturated amides was then undertaken (Scheme 1).



Scheme 1. Osmium-catalyzed aminohydroxylation of α,β-unsaturated amides with chloramine T; Ts = p-$MeC_6H_4SO_2$.

Aminohydroxylation of the differently N-substituted cinnamamides **1a**–**1f** gave excellent results, even though much lower amounts of the osmate catalyst, chloramine salt, and solvent were employed than are optimal for the standard AA (Table 1).[8] In all cases, the major regioisomer was **2**, in which the newly added nitrogen atom was in the benzylic position (see Scheme 1, R' = Ph).[9] This is the same, albeit weaker, regioselectivity observed for cinnamate *esters* in AA.[4] However, under otherwise identical experimental conditions, the nature of the substituents on the amide nitrogen atom had a significant effect on the extent to which **2** predominanted over **3** as well as on the reaction rates. The Weinreb methoxymethyl cinnamamide (**1a**)[10] proved to be the best substrate; it gave the highest regioselectivity and required the shortest reaction time. However, indicating that rapid turnover and high regioselectivity are not necessarily directly related, *N-tert*-butylcinnamamide (**1f**) was almost as reactive as **1a**, yet gave the poorest regioselectivity of the cinnamamides examined.

Table 1. Effect of N-substituents on the aminohydroxylation of cinnamamides [a].

Entry	Substrate	t[h][b]	**2**:**3**[c]	Yield of *rac*-**2**[%] (M.p.[°C])[d]
1	 **1a**	1	7.3:1	82 (180–181)
2	 **1b**	4	5.0:1	75 (176–177)
3	 **1c**	20	3.3:1	65 (223–225)
4	 **1d**	6	2.8:1	65 (170–171)
5	 **1e**	2	2.6:1	51 (185–186)
6	 **1f**	2	1.6:1	[e]

[a] Reaction conditions: 1.0 mol% $K_2OsO_2(OH)_4$, 1.2 equiv of TsNClNa·$3H_2O$, $MeCN/H_2O$ (1/1), RT, 0.2 M olefin. [b] Approximate reaction time required for the disappearance of the starting olefin, as determined by TLC. [c] Determined by ^1H NMR spectroscopy. [d] Yield and melting point of the pure major regioisomer (**2**) after recrystallization of the crude product (which consisted of **2**, **3**, and excess $TsNH_2$) from *i*PrOH. [e] Recrystallization from *i*PrOH afforded **2f** and **3f** (2:1) in 72% yield.

Further studies with **1b** demonstrated that higher initial concentrations of the olefin as well as much lower loadings of the catalyst could be employed without compromising either the yield or the regioselectivity of the aminohydroxylation.[11] In addition, at olefin concentrations of 0.5 M or greater and with *t*BuOH in place of MeCN as the co-solvent, the hydroxysulfonamide products derived from cinnamamides precipitated directly from the reaction solution in high yield and could be conveniently isolated by filtration. This led to the development of two procedures for aminohydroxylation of α,β-unsaturated amides: method A when the products are insoluble in the reaction mixture, and method B when they are soluble. These procedures differ only in that the former calls for a 25% excess of the chloramine salt and *t*BuOH as the co-solvent, whereas the latter requires one equivalent of the co-oxidant and MeCN as the co-solvent. The excess chloramine T used in procedure A supports better turnover near the end of the reaction. However, elimination of the necessity of removing excess *p*-toluenesulfonamide (produced in the reductive workup) from the product far outweighs the inconvenience of the slightly longer reaction times needed in procedure B because no excess chloramine salt is used. Table 2 lists the results from the aminohydroxylation of different cinnamamides, alkyl-substituted acrylamides, and a parent acrylamide (**1i**) using procedures A and B.

As can be seen in Table 2, excellent yields of the hydroxysulfonamide products were obtained from each of the olefins examined. Most importantly, these high yields and short reaction times were achieved at high substrate concentrations and at room temperature with as little as 0.10 mol% of the catalyst. In the old racemic aminohydroxylation of olefins with on chloramine T,[3a–c] 1 mol% of OsO_4, reaction times in excess of 12 h, and temperatures of 60 °C were required to obtain moderate to good yields of the hydroxysulfonamide products. The poor turnover rates in the old system are now largely attributed to the small amount of water present in the original recipes. However, as mentioned earlier, in the absence of ligands the presence of more water does lead to greater intrusion of the competing dihydroxylation cycle. With olefins other than α,β-unsaturated amides, diol can be expected to constitute up to 70% of the product mixture in some cases.[6] It is the unique ability of α,β-unsaturated amides (e. g. **1a**–**1k**) to benefit from the rapid turnover rates associated with high concentrations of water while somehow avoiding the paths leading to a diol by-product, which accounts for their unprecedented efficiency in the aminohydroxylation.

The hydroxysulfonamide products are in general highly crystalline, and, due to the regioselectivity of the aminohydroxylation, the major regioisomer is usually obtained in pure form following a single recrystallization of the mixture of isomers. However, for cases in which separation is difficult or in order to fully exploit the high combined yields in which the products are obtained, reactions which transform both regioisomers into the same product are of interest. One such

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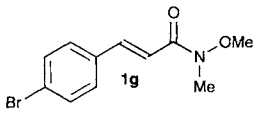
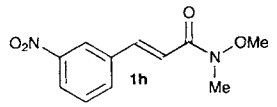
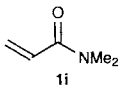
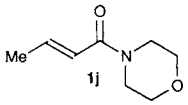
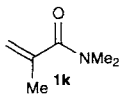
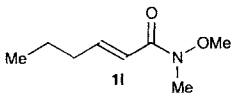
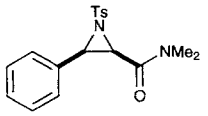
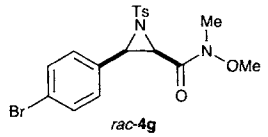
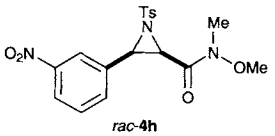
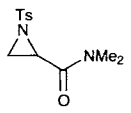
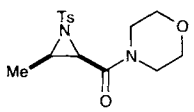
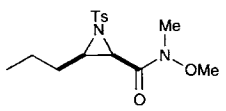
Table 2. Aminohydroxylation of α,β-unsaturated amides.

Entry	Substrate	Procedure [a] (Os [mol %]) [b]	t [h] [c]	2:3 [d]	Yield [%]
1	**1a**	A (0.10)* [e]	4	6.5:1	93
2	**1b**	A (0.25)	12	5.0:1	94
3	**1b**	A (0.20) [e]	12	3.0:1	94
4	 **1g**	A (0.25)*	2.5	3.7:1	95
5	 **1h**	A (0.50)*	4	5.8:1	95
6	 **1i**	B (0.50)	10	10:1	99
7	 **1j**	B (0.50)	10	1:1.4	97
8	 **1k**	B (1.0)	23	>20:1 [f]	90
9	 **1l**	B (0.50)* [g]	24	3.0:1	99

[a] Procedure A (for products that are *insoluble* in the reaction medium): 1. cat. $K_2OsO_2(OH)_4$ or OsO_4, 1.25 equiv of $TsNClNa \cdot 3H_2O$, tBuOH/H_2O (1/1), RT, olefin concentration: 0.5 M; 2. filtration; procedure B (for products that are *soluble* in the reaction medium): 1. cat. $K_2OsO_2(OH)_4$ or OsO_4, 1.0 equiv of $TsNClNa \cdot 3H_2O$, MeCN/H_2O (1/1), RT, olefin concentration: 0.5 M, 2. Na_2SO_3, 1 h. [b] An asterisk indicates that OsO_4 (0.1 M solution in MeCN) was used in place of $K_2OsO_2(OH)_4$. [c] Approximate reaction time required for the disappearance of the starting olefin, as determined by TLC. [d] Determined by ^1H NMR spectroscopy. [e] The concentration of the olefin was 0.8 M. [f] The presence of **3k** was not detected by ^1H NMR spectroscopy. [g] tBuOH was used as the co-solvent.

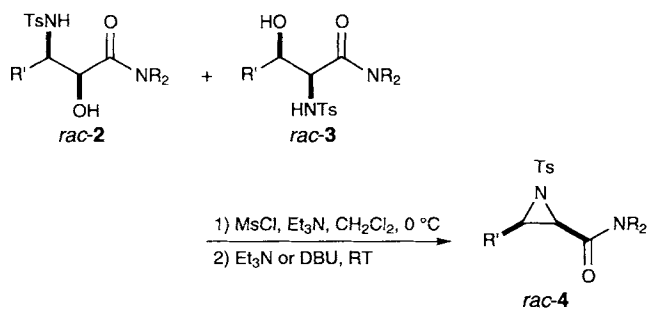
Table 3. Preparation of aziridines from regioisomeric mixtures of hydroxysulfonamides **2** and **3**.

Entry	Substrates (ratio)	Product	M.p. [°C]	Yield [%] [a]
1	**2b/3b** (5.0:1)	 *rac*-**4b**	130–131	95
2	**2g/3g** (3.7:1)	 *rac*-**4g**	50–53	97
3	**2h/3h** (5.8:1)	 *rac*-**4h**	127–128	94
4	**2i/3i** (10:1)	 **4i**	(oil)	81
5	**2j/3j** (1:1.4)	 *rac*-**4j**	151–152	92
6	**2l/3l** (3.0:1)	 *rac*-**4l**	(oil)	87

[a] Yield of the pure aziridine after flash chromatography.

example is cyclodehydration of hydroxysulfonamides to give the corresponding aziridines (Scheme 2).[12] "Activated aziridines" such as **4** are versatile synthetic intermediates and have found wide use in the synthesis of biologically active compounds.[13]

The crude mixtures of hydroxysulfonamides **2** and **3**, obtained directly from the aminohydroxylation of olefins **1**, were cyclized to the aziridines **4** in a one-pot procedure (Scheme 2). The yields of the ring closure for several pairs of regioisomers are listed in Table 3. Thus, a highly efficient two-step synthesis of aziridines **4** from readily available



Scheme 2. Conversion of regioisomeric aminohydroxylation products **2** and **3** into the same aziridine **4**; Ms = $MeSO_2$.

olefins and without the need for purification of the intermediates is now available.

α,β-Unsaturated amides represent one of the few olefin classes for which the osmium-catalyzed aminohydroxylation is highly efficient in the absence of added ligands. The principal advantages of the method are excellent chemical yields, rapid turnover rates (enabling the use of very low loads of catalyst), the ability to use high concentrations of substrate, and the necessity for only one equivalent or a small excess of chloramine salt. The latter consideration along with the favorable "crystallinity factor" greatly simplifies product isolation and makes these processes ideal for large-scale applications. In addition, the rapid emergence of diversity chemistry[14] makes such powerful transformations, especially those yielding racemates,[15] more important than ever.

Experimental Section

Aminohydroxylation procedure A (when the products are insoluble in the reaction mixture), as described for the aminohydroxylation of *N,N*-dimethylcinnamamide (**1b**): To a mechanically stirred solution of **1b** (17.52 g, 100 mmol) and chloramine T trihydrate (35.2 g, 125 mmol) in tBuOH/water (130 mL, 1/1) was added $K_2OsO_2(OH)_4$ (73.7 mg, 0.20 mmol, 0.20 mol %). As the catalyst dissolved (20–30 min) the supernatant became orange and then darkened to deep orange-red once the solution was homogeneous. The reaction was stirred overnight at room temperature, during which time a fine precipitate appeared.

Subsequent thin-layer chromatography (TLC; silica, R_f(**1b**) = 0.20, R_f(products) = 0.15, EtOAc/hexane (1/1), two developments) indicated that the olefin had been completely consumed. The endpoint of the reaction was accompanied by a change in the color of the reaction solution back to yellow-orange. Water (50 mL) was added, and the reaction slurry cooled with stirring in an ice/water bath for 1 h. The solid product was collected by filtration, washed with water (2 × 50 mL), and dried under a stream of air overnight to afford the product (34.0 g, 94%) as a mixture of **2b** and **3b** (3.0:1). Recrystallization of a portion of this mixture from MeOH afforded analytically pure **2b** as colorless blocks: m.p. 176–177 °C (sealed tube); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.56–7.53 (m, 2H), 7.24–7.20 (m, 5H), 7.16–7.13 (m, 2H), 5.52 (d, J = 6.1 Hz, 1H), 4.46 (dd, J = 6.9, 4.4 Hz, 1H), 4.42 (dd, J = 6.1, 4.4 Hz, 1H), 4.02 (d, J = 6.9 Hz, 1H), 2.84 (s, 3H), 2.67 (s, 3H), 2.36 (s, 3H); elemental analysis calcd for $C_{18}H_{22}N_2O_4S$: C 59.65, H 6.12, N 7.73; found: C 59.68, H 5.99, N 7.76.

Aminohydroxylation procedure B (when the products are soluble in the reaction mixture), as described for the aminohydroxylation of *N,N*-dimethylacrylamide (**1i**): To a magnetically stirred solution of **1i** (5.0 mL, 4.81 g, 48.5 mmol) and chloramine T trihydrate (14.0 g, 49.7 mmol) in MeCN (50 mL) and water (50 mL) was added $K_2OsO_2(OH)_4$ (89.3 mg, 0.24 mmol, 0.50 mol%). The color changes described for procedure A were noted, and the reaction mixture was stirred overnight at room temperature. TLC (silica, R_f(**1i**) = 0.27, R_f(products) = 0.40, EtOAc) revealed that the olefin had been completely consumed. Na_2SO_3 (10 g) and ethyl acetate (50 mL) were added and the triphasic mixture was vigorously stirred for a further hour, during which time the solids completely dissolved. After separating the phases and extracting the aqueous phase with ethyl acetate (2 × 50 mL), the combined organic phases were shaken with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield an oil. Trituration of the oil with diethyl ether (ca. 30 mL) followed by filtration afforded the solid product (13.8 g, 99%) as a mixture of **2i** and **3i** (10:1). Recrystallization of a portion of this mixture from MeOH afforded analytically pure **2i** as colorless needles: m.p. 123–124 °C (sealed tube); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.76–7.72 (m, 2H), 7.33–7.30 (m, 2H), 5.24–5.21 (m, 1H), 4.47–4.42 (m, 1H), 3.84 (d, J = 7.4 Hz, 1H), 3.28 (ddd, J = 13.2, 8.2, 3.2 Hz, 1H), 3.00 (s, 3H), 2.97 (s, 3H), 2.89 (ddd, J = 13.2, 7.4, 4.4 Hz, 1H), 2.43 (s, 3H); elemental analysis calcd for $C_{12}H_{18}N_2O_4S$: C 50.34, H 6.34, N 9.78; found: C 50.34, H 6.25, N 9.79.

Preparation of aziridines **4**, as described for *rac*-**4b**: A magnetically stirred solution of a mixture of **2b** and **3b** (5.0:1, 2.10 g, 5.8 mmol) and Et_3N (1.1 mL, 7.9 mmol) in CH_2Cl_2 (30 mL) under N_2 was cooled in an ice/H_2O bath, and methanesulfonyl chloride (0.58 mL, 7.5 mmol) was added dropwise over 30 min. After the addition was complete, stirring was continued at 0 °C for 30 min, before 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 2.6 mL, 17.4 mmol) was added and the ice/water bath removed. After 15 min TLC (silica, R_f(**4b**) = 0.44, EtOAc/hexane 4/1) indicated that aziridine formation was complete. The reaction mixture was extracted with 2 N aqueous HCl (30 mL) followed by saturated aqueous $NaHCO_3$ (30 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography on silica gel with EtOAc/hexane (3/1) as the eluent and subsequent removal of solvent provided **4b** (1.90 g, 95%) as a colorless solid: m.p. 130–131 °C (sealed tube); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.98–7.95 (m, 2H), 7.35–7.33 (m, 2H), 7.30–7.26 (m, 5H), 4.14 (d, J = 7.5 Hz, 1H), 3.79 (d, J = 7.5 Hz, 1H), 2.90 (s, 3H), 2.70 (s, 3H), 2.42 (s, 3H); elemental analysis calcd for $C_{18}H_{20}N_2O_3S$: C 62.77, H 5.85, N 8.13; found: C 62.61, H 5.69, N 8.24.

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[15] Another advantage of racemates, pointed out by a reviewer, is that modern preparative chiral HPLC often enables access to both enantiomers. The pharmaceutical industry now favors this approach for quick "enantiodeconvolutiuon" of biological activity.

Di-, Tri-, and Tetranuclear Alkoxyaluminum Hydrides

Heinrich Nöth,* Andreas Schlegel, Jörg Knizek, and Holger Schwenk

Little is known about the degree of association of alkoxyalanes in the solid state or in solution. Seminal papers published in the 1960s describe reactions of short-chain alcohols with aluminum hydride.[1] Determination of the molecular mass proved that tBuOAlH$_2$ and (tBuO)$_2$AlH are dimeric in benzene. Recent X-ray structure analysis ascertained that the association occurs via an Al_2O_2 four-membered ring.[2] The syntheses of alkoxyalanes are described by Equations (1) and (2).

$$AlH_3 + HOR \longrightarrow H_2Al(OR) + H_2 \quad (1)$$

$$AlH_3 + 2\,HOR \longrightarrow HAl(OR)_2 + 2\,H_2 \quad (2)$$

Although it was demonstrated that the amount of hydrogen liberated during the reaction is equivalent to the molar amount of the alcohol, the composition of the product is dependent on the size and the branching of the alkyl

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