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Catalytic Aminohydroxylation Using Adenine-Derivatives as the Nitrogen Source‡

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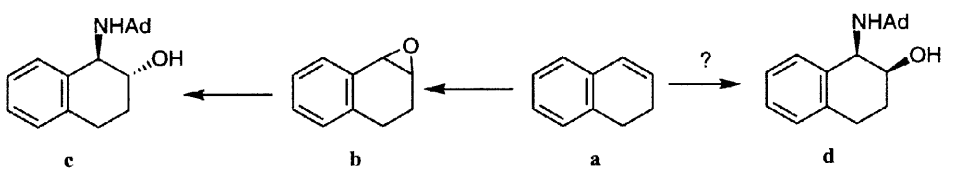
Abstract: The *N*-chloro-*N*-sodio salts of adenine derivatives are suitable nitrogen sources for the osmium catalyzed aminohydroxylation of olefins, achieving suprafacial, vicinal addition of adenine and a hydroxyl group. The scope of this transformation was examined using adenine and adenosine-derivatives in conjunction with three different olefins. © 1998 Elsevier Science Ltd. All rights reserved.

Numerous commercially available drugs, for example nucleotidin, eritadenine, zeatin, puromycin, and bucladesine contain an adenine moiety. These compounds are used as antibiotics, neoplastics, antivirals, anticholesteremics, and cardiotonics,[1] so that new routes to adenine derivatives are constantly sought. Whereas in the case of cyclic olefins (e.g., **a**), *trans*-vicinal N^6-adenine-alcohols (e. g., **c**) can in principle be obtained by *trans*-opening of the corresponding epoxide (**b**),[2] the corresponding *cis*-diastereomers (e. g., **d**) have been difficult to prepare (Scheme 1).[3]



Scheme 1. Synthesis of either 1-(N^6-adenino)-2-ol diastereomers for the same olefin

In many cases, the osmium-catalyzed aminohydroxylation of olefins provides the most direct route to vicinal aminoalcohols.[4] This process first emerged using the nitrenoid Chloramine-T (TsNClNa) as the nitrogen source. With the recent development of procedures based on both carbamate[5] and amide-derived nitrenoids,[6] the scope and the selectivity of this transformation was greatly improved. Ongoing endeavors at Scripps to expand the classes of nitrogen sources to include simple heterocyclic compounds have been frustrated by fickle reactivity and serious side reactions, especially ring chlorination.[7] Then, in the NIH laboratories of one of us (D. M. J.), a window of excellent reactivity was discovered in the conjunction of an adenosine derivative with a unique olefin partner.[3] This direct method for vicinal attachment of a hydroxyl group and a nucleoside moiety to an olefin could prove important, especially if it were demonstrated to have reasonable breadth of application. The present collaboration was founded to address this issue and some promising initial results are reported here.

‡ *Dedicated to Professor Reinhard W. Hoffmann on the occasion of his 65th birthday.*

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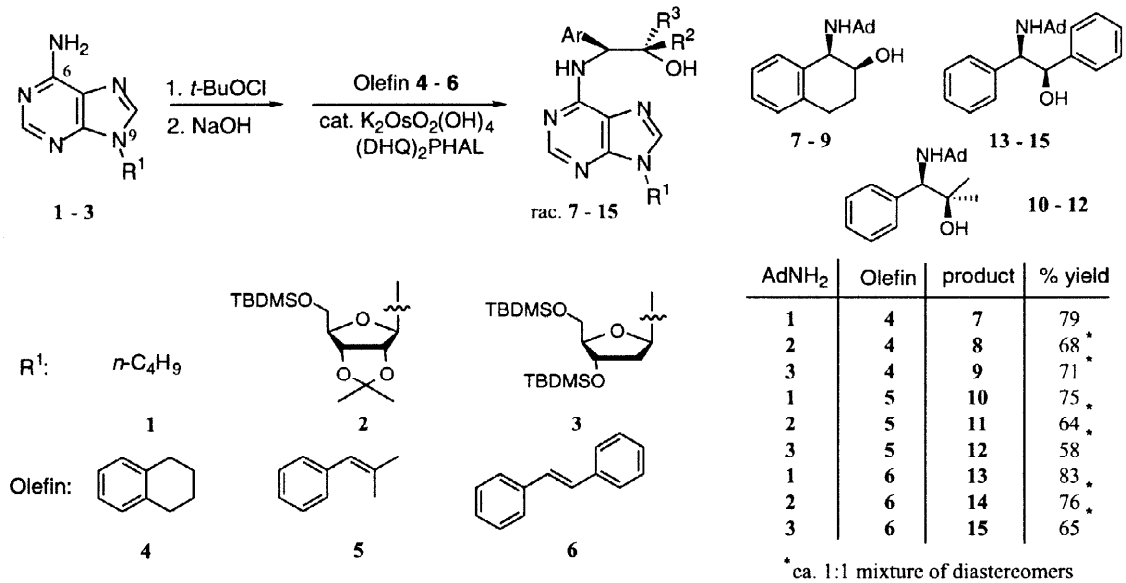
The scope has been substantially improved by optimizing three reaction variables: solvent, temperature, and exclusion of oxygen by inert atmosphere. With these changes, good results were realized for all nine combinations of three different olefin types with three different adenosine derivatives (Scheme 2).

In the first step of the one-pot procedure, the adenine-derivative (three equivalents) is treated with *tert*-butyl hypochlorite and then with aqueous NaOH to form the *N*-chloro-*N*-sodio-salt. Finally, one equivalent of olefin and catalytic amounts of both $(DHQ)_2PHAL$ ligand and $K_2OsO_2(OH)_4$ are added and the aminohydroxylation proceeds.



$AdNH_2$	Olefin	product	% yield
1	4	7	79
2	4	8	68 *
3	4	9	71 *
1	5	10	75 *
2	5	11	64 *
3	5	12	58
1	6	13	83 *
2	6	14	76 *
3	6	15	65

*ca. 1:1 mixture of diastereomers

Scheme 2. Aminohydroxylations with adenine-derivatives

In the case of the 1,2-dihydronaphthalene (**4**) and 2-methyl-1-phenyl-1-propene (**5**) only the regioisomers with the N^6-adenine nitrogen in the benzylic position were observed.[8] The 9-substituent on the adenine-derivative did not affect the regio- or diastereoselectivity. The yields range from 58 to 83 % (Scheme 2).

The addition of a chiral dihydroquinuclidine AA-ligand leads to a significantly higher reaction rate. However, under the conditions described, the reaction was not enantioselective nor, in the case of chiral adenosine-derivatives, diastereoselective. For compounds **8**, **9**, **11** and **14**, the diastereomeric mixtures can be separated by means of column chromatography. After removal of the sugar moiety a pair of enantiomerically pure adenine-alcohols can thus be obtained.[9]

Choice of the reaction solvent proved to be crucial for the success of this transformation. Many solvent systems were tested, especially those which had previously been optimized for aminohydroxylation reactions with other nitrogen sources.[4,5,6] Surprisingly, conversion was only observed using mixtures of small primary alcohols with water. The solvent system for each pair of substrates was chosen such that both the adenine-derivative and the alkene were completely solublized. A high water content was found to be important for achieving good catalytic turnover frequencies, suggesting that hydrolysis of an azaglycolate osmium complex is the rate determining step in the catalytic cycle.[4b]

EXPERIMENTAL

Representative procedure for the aminohydroxylations: Reaction of 5'-*O*-*tert*-butyldimethylsilyl-2',3'-*O*-isopropylideneadenosine (2) with 1,2-dihydronaphthalene (4). All solvents were deoxygenated by three freeze pump / thaw cycles under nitrogen. 5'-*O*-*tert*-butyldimethylsilyl-2',3'-*O*-isopropylideneadenosine (421 gmol^{-1}, 650 mg, 1.55 mmol) was dissolved in dry ethanol (14 mL). The solution was cooled in an ice bath. *tert*-Butylhypochlorite (108.5 gmol^{-1}, 175 µL, 1.55 mmol) was added. The solution was warmed to rt in a water bath and stirred for 15 min. Then it was cooled again to 0 °C and aqueous NaOH (1.0 M, 1.50 mL, 1.50 mmol) was added. The solution was again warmed to rt in a water bath, water (7 mL) was added and the mixture was stirred for 5 min. 1,2-Dihydronaphthalene (130 gmol^{-1}, 65 mg, 0.50 mmol), $(DHQ)_2PHAL$ (778 gmol^{-1}, 23 mg, 30 µmol, 6 mol%), and $K_2OsO_2(OH)_4$ (368 gmol^{-1}, 9.2 mg, 25 µmol, 5 mol%) were added.[10] The mixture was stirred and heated to 50 °C for 12 h. A saturated solution of Na_2SO_3 (4 mL), water (10 mL) was added and the mixture was stirred for additional 30 min at 50 °C. The mixture was then placed in a separatory funnel and EtOAc (80 mL) was added. The organic phase was separated and washed with water (40 mL) and brine (40 mL). After drying over $MgSO_4$, the solvent was evaporated to leave a dark residue. After chromatography, the diastereoisomers 8A and 8B were obtained in a combined yield of 193 mg (68%) as a 1:1 mixture. Both isomers have the amino group attached at the benzylic position (proven by COSY). The separation of the isomers was achieved by gradient column chromatography (SiO_2, EtOAc/Hexane/Et_3N 33:66:1 to 66:33:1). The diastereoisomers of **8** are isolated as foam after removing last traces of solvent *in vacuo* (50 °C, 10^{-2} Torr). Diastereoisomer **8A**: R_f (ether) = 0.37; HRMS [$C_{29}H_{41}N_5O_5SiH^+$] calc. 568.2955 found 568.2969; ^{1}H NMR ($CDCl_3$, 600 MHz, rt) δ 8.34 (br, 1 H), 7.90 (s, 1 H), 7.23 (d, J = 7.6 Hz, 1 H), 7.16 (t, J = 6.9 Hz, 1 H), 7.10 - 7.07 (m, 2 H), 6.45 (br, 1 H), 6.13 (d, J = 2.4 Hz, 1 H), 5.60 (br, 1 H), 5.24 (dd, J = 6.2, 2.4 Hz, 1 H), 4.93 (dd, J = 6.2, 2.5 Hz, 1 H), 4.90 (br, 1 H), 4.38 (dd, J = 6.6, 3.9 Hz, 1 H), 4.31 (dt, J = 3.9, 3.9 Hz, 1 H), 3.85 (dd, J = 11.1, 4.2 Hz, 1 H), 3.75 (dd, J = 11.1, 4.3 Hz, 1 H), 3.00 (dt, J = 17.2, 5.6 Hz, 1 H), 2.83 - 2.78 (m, 1 H), 2.06-1.99 (m, 2 H), 1.58 (s, 3 H), 1.37 (s, 3 H), 0.85 (s, 9 H), 0.03 (s, 3 H), 0.02 (s, 3 H) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz, rt): δ 154.9, 152.9, 138.7, 136.6, 134.7, 129.6, 128.7, 127.7, 126.3, 119.8, 114.1, 91.2, 87.3, 85.0, 81.4, 69.9, 63.4, 53.7, 29.9, 27.1, 26.9, 26.6, 25.9, 18.3, -5.4, -5.5 ppm; $[\alpha]_D^{20}$ = -12.3 ° (c = 0.73, EtOH, α = -9.0 °).

Diastereomer **8B**: R_f (ether) = 0.23; HRMS [$C_{29}H_{41}N_5O_5SiCs^+$] calc. 700.1931 found 700.1933; ^{1}H NMR ($CDCl_3$, 600 MHz, rt) δ 8.35 (br, 1 H), 7.86 (s, 1 H), 7.25 (d, J = 7.6 Hz, 1 H), 7.18 (t, J = 7.4 Hz, 1 H), 7.12 - 7.10 (m, 2 H), 6.41 (br, 1 H), 6.11 (d, J = 2.2 Hz, 1 H), 5.63 (s, 1 H), 5.27 (dd, J = 6.1, 2.2 Hz, 1 H), 4.93 (dd, J = 6.1, 2.5 Hz, 1 H), 4.93 (br, 1 H), 4.40 (dd, J = 6.7, 3.9 Hz, 1 H), 4.32 (dt, J = 3.7, 3.7 Hz, 1 H), 3.84 (dd, J = 11.1, 4.2 Hz, 1 H), 3.75 (dd, J = 11.1, 4.3 Hz, 1 H), 2.95 (dt, J = 17.2, 5.6 Hz, 1 H), 2.83 - 2.78 (m, 1 H), 2.06 - 1.99 (m, 2 H), 1.62 (s, 3 H), 1.40 (s, 3 H), 0.84 (s, 9 H), 0.00 (s, 3 H), -0.02 (s, 3 H) ppm; ^{13}C NMR ($CDCl_3$, 151 MHz, rt): δ 154.9, 152.9, 138.8, 136.6, 134.9, 129.7, 128.8, 127.8, 126.4, 119.9, 114.0, 91.5, 87.4, 84.9, 81.5, 69.7, 63.5, 60.3, 27.2, 26.8, 26.6, 25.8, 25.4, 18.3, -5.4, -5.5 ppm; $[\alpha]_D^{20}$ = +57.7 ° (c = 1.02, EtOH, α = +58.9 °).

Compounds **7** and **9 - 15** were produced similarly. For the generation of the chloramine salt of **1**, methanol proved to be the best solvent, the olefin was added as a solution in propanol. The chloramine salt of **3** was prepared in propanol.

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REFERENCES AND NOTES

1. (a) *The Merck Index*; Chapman & Hall: New York, 1996; 12th Ed. (b) Shaw, G. Bicyclic 5-6 System: Purines. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon: New York, 1996; Vol. 7, pp. 397 - 429.
2. Lakshman, M. K.; Yeh, H. J. C.;Yagi, H.; Jerina, D. M. *Tetrahedron Lett.* **1992**, *33*, 7121 - 7124. Kim, S. J.; Harris, C. M.; Jung, K.-Y.; Koreeda, M.; Harris, T. M. *Tetrahedron Lett.* **1991**, *32*, 6073 - 6076. Kiselyov, A. S.; Steinbrecher, T.; Harvey, R. G. *J. Org. Chem.* **1995**, *60*, 6129 - 6134.
3. Pilcher, A. S.; Yagi, H.; Jerina, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 3520 - 3521.
4. (a) Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 451 - 454. (b) Rudolph, J.; Sennhenn, P. C.; Vlaar, C. P.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2810 - 2813. (c) Schlinghoff, G.; Sharpless, K. B. Asymmetric Aminohydroxylation. In *Asymmetric Oxidation Reactions: A practical Approach*; Katsuki, T., Ed.; Oxford University Press: Oxford, 1998; in press.

   (d) Kolb, H. C.; Sharpless, K. B. Asymmetric Aminohydroxylation. In *Transition Metals for Fine Chemicals and Organic Synthesis*; Beller, M.; Bolm, C., eds.; Wiley-VCH: New York, 1998; in press.
5. (a) Li, G.; Angert, H. H.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2813 - 2815. (b) Reddy, K. L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 1207 - 1217.
6. Bruncko, M.; Schlingloff, G.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1483 - 1486.
7. Sharpless, K. B.; Gooßen, L. G.; Liu, H.; Dress, K. R. publication in preparation.
8. The regiochemistry of the products were confirmed by variable temperature 2D NMR studies.
9. Verenikina, G.; Chauser, E. G.; Yurkevich, A. M. *Zh. Obshch. Khim.* **1971**, *41*, 1630 - 1632.
10. For maximum reliability on small scale, a high osmium catalyst concentration (10 %) is recommended in these reactions. In most cases however, it was possible to reduce the catalyst content to 3 % without significant yield loss. (for compound **14**: 76 % yield with 10 % catalyst, 74 % with 5 %, and 72 % with 3 %). It is also usually possible to reduce the excess of the chloramine salt of the adenine-derivative to two equivalents. At room temperature, for some substrates relatively long reaction times were required so that the reactions are best performed at 40 - 50 °C.