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N-Chloro-*N*-Sodio-2-Trimethylsilyl Ethyl Carbamate: A New Nitrogen Source for the Catalytic *Asymmetric* Aminohydroxylation

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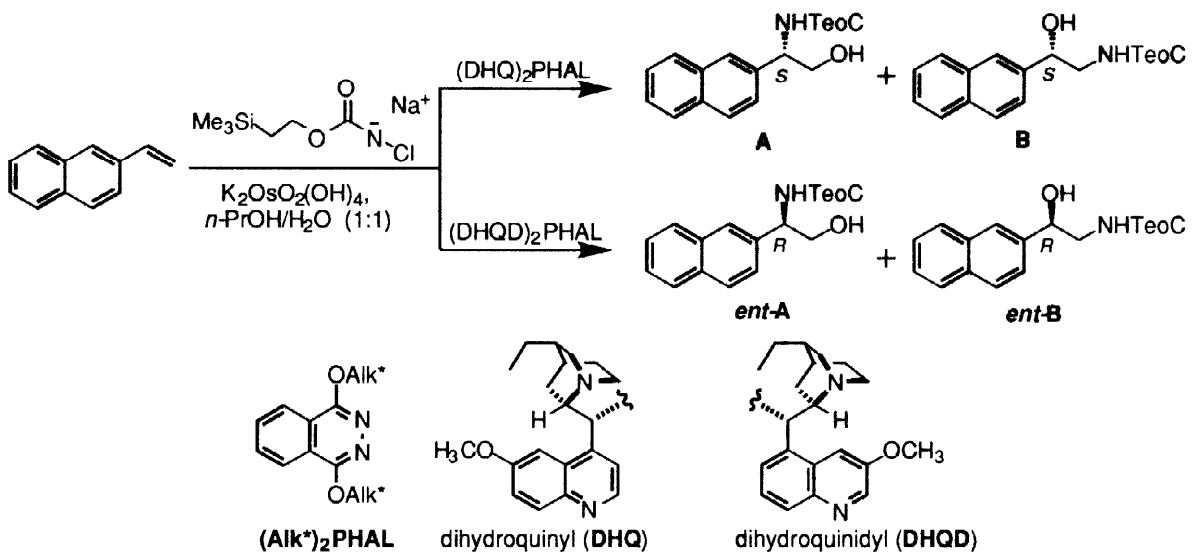
Abstract: The use of *N*-chloro-*N*-sodio-2-trimethylsilyl ethyl carbamate in the osmium-catalyzed *asymmetric* aminohydroxylation of alkenes leads to enantiomerically enriched *N*-trimethylsilyleth-oxycarbonyl (TeoC) protected aminoalcohols in yields up to 80% and ee's up to 99%.

The vicinal aminoalcohol moiety appears as a key component in many biologically active compounds. This important functionality is obtained directly from olefins with excellent enantioselectivities and in very good yields by the recently discovered osmium-catalyzed *asymmetric* aminohydroxylation (AA) reaction.[1] This reaction first emerged as a process in which TsNClNa (chloramine-T) was used as the nitrogen source/oxidant. Subsequently, with the development of procedures which utilize carbamates[2] and amide-derived oxidants[3] the substrate scope and selectivity was greatly improved. Among these three classes of nitrogen sources, carbamate-based nitrogen sources are especially useful because the resulting products are easily converted to the free amino alcohols.



Scheme 1: AA-Reaction with TeocNClNa DHQ-H = dihydroquinine, DHQD-H = dihydroquinidine, PHAL = 1, 3-phthalazinediyl, TeoC = trimethylsilylethoxycarbonyl.

Endeavoring to further develop the AA and to expand its scope, new carbamates were examined as potential nitrogen sources. In earlier studies[1-3], we had observed that, other things being equal, sterically less demanding

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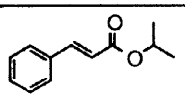
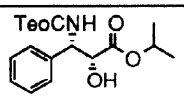
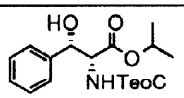
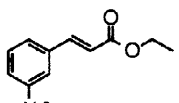
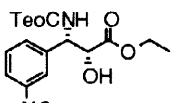
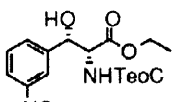
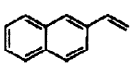
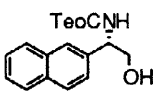
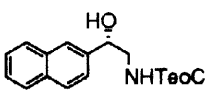
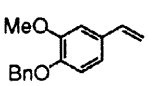
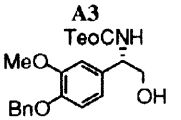
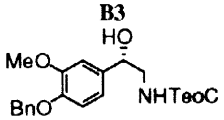
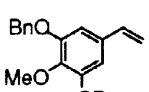
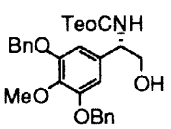
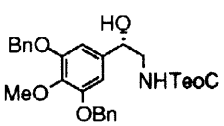
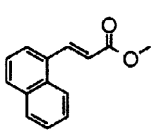
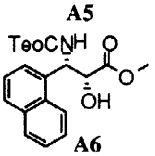
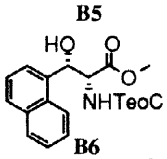
nitrogen sources exhibited superior reactivity and gave higher enantioselectivities. The sterically more demanding nitrogen sources most likely inhibit the hydrolysis of the osmium(VI)-azaglycolate intermediate (see scheme **2** in ref. 1b), thereby favoring the non-selective second cycle which can explain the poorer results.

Therefore, it seemed advisable to study *N*-chloro-*N*-sodio carbamates which combined little steric demand, good solubility, as well as mild conditions for their deprotection. These concerns led us to try the use of *N*-chloro-*N*-sodio-2-trimethylsilyl ethyl carbamate (TeoCNClNa) and the results are described here.

2-Trimethylsilyl ethyl carbamate was made by adding successively carbonyldiimidazole and ammonia to 2-trimethylsilylethanol in benzene. 2-Trimethylsilyl ethyl carbamate was then converted to its *N*-chloro-*N*-sodio salt by reaction with NaOH and *t*-BuOCl. The standard experimental conditions[5] for the AA reaction employed 2 mmol of the alkene, 4 mol% $K_2OsO_2(OH)_4$, 5 mol% of the alkaloid ligand $(DHQ)_2PHAL$ or $(DHQD)_2PHAL$, 6.2 mmol TeoCNClNa, in 30 mL *n*-PrOH/H_2O (1:1) at room temperature. The results are summarized in **Table 1**.

Table 1. AA Reaction using TeoCNNaCl as the Nitrogen Source

Entry	Substrate[a]	Product A[b]	Product B[b]	Yield A [%][c]	Regioselectivity A:B[d]	ee values [%][e,f] $(DHQ)_2PHAL$ A	$(DHQD)_2PHAL$ ent-A
1		 A1	 B1	70	>98:2	99	-99
2		 A2	 B2	74	>98:2	99	-98
3		 A3	 B3	76	86:14	97	-96
4		 A4	 B4	70	78:22	99	-99
5		 A5	 B5	81	91:9	98	-97
6		 A6	 B6	86	>98:2	95	-91

a) Conditions: 2 mmol alkene, 4 mol% $K_2OsO_4(OH)_2$, 5 mol% ligand, and *n*-PrOH/H_2O (1:1) at 25 °C. b) Products shown are the major enantiomers from the reaction using $(DHQ)_2PHAL$. c) Isolated yield of regioisomer **A** using $(DHQ)_2PHAL$. d) Regioselectivity **A:B** determined by ^{1}H-NMR. e) ee determined by HPLC. The ee's of the minor regioisomers **B** were poor (0% to 32%). f) The negative ee values emphasize that $(DHQD)_2PHAL$ as ligand gives the mirror image isomer to $(DHQ)_2PHAL$ (**A** -> ***ent*-A**).

A 25 mmol reaction was performed with 2-vinylnaphalene (entry **3**). The yield, the regioselectivity and the enantioselectivity of the product **A3** remained unchanged, hence this procedure is also reliable on a multigram scale. All the reactions with $Me_3SiCH_2CH_2OC(O)NNaCl$ were completed within 30 min and are therefore faster than reactions using BnOC(O)NNaCl or *t*-BuOC(O)NNaCl. Because of the high reactivity of

$Me_3SiCH_2CH_2OC(O)NNaCl$, we lowered the catalyst loading to 2 mol% $K_2OsO_4(OH)_2$ and the ligand loading to 2.5 mol% in the case of substrate **3** and obtained **A3** in the same yield, enantioselectivity, and regioselctivity as with 4 mol% osmium and 5 mol% ligand. However, if the amount of the chloramine salt was reduced below three equivalents the reaction rate and yield were diminished.

The trimethylsilylethoxycarbonyl group of **A3** was then cleaved with TBAF in acetonitrile a under standard conditions[5] to give the free aminoalcohol in 85% yield. These mild conditions are compatible with most of the functional groups found in organic compounds.

In conclusion, the scope of the osmium-catalysed *asymmetric* aminohydroxylation of alkenes is substantially extended by using *N*-chloro-*N*-sodio-trimethylsilylethylcarbamate. The high reactivity of this new nitrogen-source/oxidant enables the AA reaction to proceed well with half of the osmium catalyst and ligand normally used in the previously reported BoC- and Z-carbamate-based AA procedures. In addition, the TeoC-protected aminoalcohols are generally obtained in better regioselectivities, better enantioselectivities, and yields than are possible with the best AA-process based on BoC- or Z-protection. The TeoC group is cleaved by fluoride under very mild conditions yielding the free aminoalcohols.

EXPERIMENTAL

2-Trimethylsilylethyl carbamate: Carbonyl diimidazole (Aldrich, 99 g, 610 mmol, 1.2 eq) was added to a solution of 2-trimethylsilylethanol (Aldrich, 60 g, 508 mmol) in 500 mL of benzene. The resulting suspension was stirred for 6 h at 25 °C and then saturated aq ammonia (Fischer, 52 g, 915 mmol, 1.8 eq) was added. The mixture was stirred for additional 5-6 h and transferred to a separatory funnel. The phases were separated and the water layer extracted with ethyl acetate (20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated in vacuo to obtain the product as a colorless solid 68 g, 83 % yield. M.p. 50 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.05 (br s, 2H), 4.09 (t, J = 8.5 Hz, 2H), 0.95 (t, J = 8.5 Hz, 2H), -0.01 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.6, 63.2, 17.5, -1.6. HRMS (FAB, NBA/NaI): [C6H15NO2Si Na+] calc: 184.0770, found: 184.0778.

General Procedure for the *N*-Chloro-*N*-Sodio-2-Trimethylsilylethyl Carbamate Based AA described for 2-Vinyl Naphthalene: 2-Trimethylsilylethyl carbamate (12.5 g, 77.7 mmol) was dissolved in *n*-PrOH (50 mL) in a 1-L round bottom flask. The solution was stirred and a freshly prepared aqueous solution of NaOH [180.0 mL, prepared by dissolving NaOH (3.05 g, 76.3 mmol) in water (187.5 mL); the remainder of this NaOH solution (7.5 mL) was set aside for later use] was added, followed by *t*-butylhypochlorite (8.75 mL, 8.27 g, 76.3 mmol). After 5 min a solution of $(DHQ)_2PHAL$ (1.0 g, 1.25 mmol, 5 mol%) in *n*-PrOH (75 mL) was added. The mixture should be homogeneous at this point.[6] 2-Vinylnaphthalene (entry 3, **Tab. 1**; Aldrich, recryst. from EtOH, 3.87 g, 25.0 mmol, dissolved in 63.0 mL *n*-PrOH) was added, followed by a solution of $K_2OsO_2(OH)_4$ (0.375 g, 1.02 mmol, 4 mol%) freshly prepared in the aforementioned 7.5 mL of NaOH solution[7] saved. The reaction mixture turned green, immediately, and then became light yellow after 25 min at RT. The reaction mixture stirred for an additional 20 min. It was then cooled in an ice-bath, quenched by the addition of a saturated aqueous sodium sulfite solution (200 mL), and stirred for 15 min. The two phases were separated and the aqueous phase was extracted with ethyl acetate (3x 100 mL). The combined organic phases were washed with water (120 mL), brine (150 mL), dried ($MgSO_4$), and concentrated to afford the crude mixture of regioisomers (**A**:**B** = 86:14) and 2-trimethylsilylethyl carbamate. Flash chromatography (SiO_2, 5 x 25

cm, 15–35% EtOAc/hexane gradient elution) provided regioisomers **A3** (6.3 g, 76%) as a colorless solid and **B3** (0.9 g, 11%). **A3**: R_f = 0.43 (EtOAc/hexane = 4:6); mp 105 °C; $[\alpha]_D^{25}$ = 124.2° (c = 1.67, DCM); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.84 (d, *J* = 7.8 Hz, 1H), 7.82-7.80 (m, 2H), 7.76 (s, 1H), 7.49-7.45 (m, 2H), 7.41 (d, *J* = 8.2 Hz, 1H), 6.47 (d, *J* = 6.6 Hz, 1H), 4.99 (br. s, 1H), 4.17 (t, *J* = 8.2 Hz, 2H), 3.95 (d, 3.2 Hz, 2H), 1.82 (br, 1H), 0.99 (br, 2H), 0.03 (s. 9H).; ^{13}C NMR (150 MHz, $CDCl_3$): δ 156.9, 136.7, 133.3, 132.9, 128.6, 127.9, 127.6, 126.3, 126.0, 125.4, 124.6, 66.3, 63.5, 61.9, 57.1, 17.7, -1.5.; HRMS (FAB, NBA/NaI) [$C_{18}H_{25}NO_3$ Na+] calc.: 354.1501, found: 354.1513; ee = 97% (HPLC, Chiralcel AD, 5% *i*-PrOH/hexane, 1 mL min^{-1}, 254 nm, 13.53 min (*S*), 19.50 min (*R*)). **B3**: R_f = 0.33 (EtOAc/hexane = 4:6); mp 116 °C; $[\alpha]_D^{25}$ = 18.5° (c = 2.5, DCM); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.83-7.81 (m, 4H), 7.49-7.44 (m, 3H), 5.05 (s, 1H), 5.00 (s, 1H), 4.16 (t, *J* = 8.4 Hz, 2H), 3.61 (br., 1H), 3.39-3.35 (m, 1H), 3.10 (br., 1H), 0.96 (t, *J* = 8.4 Hz, 2H), 0.03 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 157.8, 139.0, 133.2, 133.0, 128.3, 128.0, 127.7, 126.2, 126.0, 124.8, 123.8, 74.0, 63.5, 48.5, 17.7, -1.5.; HRMS (FAB, NBA/NaI) [$C_{18}H_{25}NO_3$ Na+] calc.: 354.1501, found: 354.1511; ee = 31% (HPLC: Chiralcel AS, 5% *i*-PrOH/hexane, 1 mL min^{-1}, 254 nm, 15.80 min (*S*), 13.73 min (*R*)).

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3. Bruncko, M.; Schlingloff, G.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1483.
4. For the most recent experimental details for the carbamate-based AA process see Reddy, K. L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 1207.
5. TBAF in acetonitrile at 60 °C, 7 h. See also Carpino, L. A.; Tsao, J.-H.; Ringsdorf, H.; Fell, E.; Hettrich, G. J. *J. Chem. Soc., Chem. Commun.* **1978**, 358, and Carpino, L. A.; Sau, A. C. *J. Chem. Soc., Chem. Commun.* **1979**, 514.
6. The reaction will give a lower yield if the mixture is not homogeneous at this point. Sonication for ca. 5 min at RT may be required.
7. This solution of $K_2OsO_2(OH)_4$ in dilute NaOH should be used within 15 min after its preparation.