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OsO_4-catalyzed amination of silyl enol ethers: enantioselective synthesis of α-amino ketones

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Abstract

Osmium tetroxide catalyzed asymmetric aminohydroxylation of silyl enol ethers using cinchona alkaloids as chiral ligands and chloramine-T as the nitrogen source affords enantiomerically pure α-amino ketones.

1. Introduction

The synthesis of enantiomerically enriched α-amino alkyl or aryl ketones is of wide interest in that it provides a direct route to the synthesis of biologically active β-amino alcohols containing the phenylethylamine moiety in their active configurations.[1] Also, more than 75% of drugs and drug candidates incorporate an amine functionality. Nonetheless, the asymmetric synthesis of amines excluding α-amino acids is much less developed than the asymmetric synthesis of other common functional groups such as epoxides[2] or diols.[3] Literature searches reveal that a few direct methods are available for the preparation of *racemic* amino ketones. For instance, the direct amination of silyl enol ethers and silyl ketene acetals affording racemic α-amino ketones has been achieved by (i) thermolysis or photolysis of azidoformates in low yields,[4] (ii) Cu(I)-catalyzed reaction of enol silanes using PhI=NTs as a nitrene precursor[5] and (iii) nitridomanganese(V) complexes with Schiff bases as ligands.[6]

Considerable attention has been devoted to the development of reactions that effect catalytic atom transfer to olefins. In this regard, the OsO_4-catalyzed asymmetric aminohydroxylation of olefins has become the most powerful method for the preparation of a wide variety of enantiomerically enriched amino alcohols.[7]

In this paper, we wish to report for the first time that the direct amination of silyl enol ethers using Sharpless asymmetric aminohydroxylation conditions (OsO_4–cinchona alkaloid derivatives–chloramine-T) has been achieved to provide enantiomerically enriched α-amino ketones (Scheme 1).

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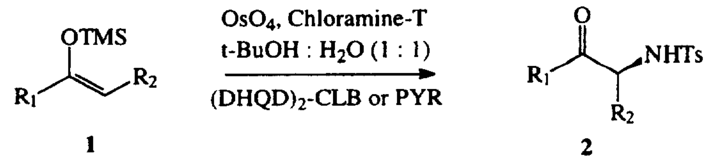


Scheme 1.

2. Results and discussion

The catalytic asymmetric aminohydroxylations were carried out using OsO_4–dihydroqunidine–p-chlorobenzoate [$(DHQD)_2$–CLB] and dihydroquinidine–pyrimidine [$(DHQD)_2$–PYR] as chiral ligands, and chloramine-T as the nitrogen source with a variety of silyl enol ethers. The results are summarized in Table 1. As can be seen from Table 1, the amination of silyl enol ethers took place rapidly (<15 min) in most of the cases studied. When cyclohexanone silyl enol ether was subjected to aminohydroxylation at 25°C with $(DHQD)_2$–CLB using chloramine-T in t-BuOH:H_2O (1:1), the reaction proceeded rapidly to completion as indicated by the distinct colour change from dark green to dark brown. The progress of the reaction was further monitored by TLC. The moderate yield, 28–45%, of the optically active α-amino ketones is due to the difficulty experienced in the work up of the coloured reaction mixtures. However, the crude reaction mixture was purified by column chromatography and crystallized from $CHCl_3$. Both chiral ligands, $(DHQD)_2$–CLB and $(DHQD)_2$–PYR, have performed almost to the same extent in inducing enantioselectivity as has been found in the case of 4-methylcyclohexanone silyl enol ether. It is remarkable that the aminations of silyl enol ethers have proceeded with a good extent of enantioselectivity; the % ee of α-amino ketones ranges from 70–92%. The absolute configurations of the α-amino ketones were assigned based on the reasoning that the DHQD ligands generally direct the addition to the β-face of the olefins in asymmetric aminohydroxylation processes.[7]

In conclusion, we have demonstrated the practical utility of an asymmetric aminohydroxylation process for the synthesis of enantiomerically pure α-amino ketones in a single step from silyl enol ethers.

3. Experimental section

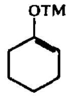
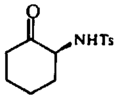
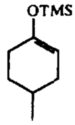
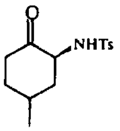
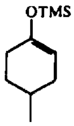
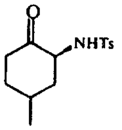
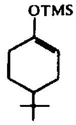
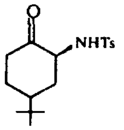
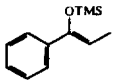
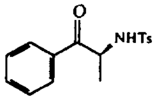
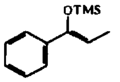
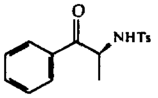
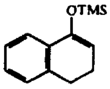
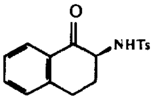
All solvents were distilled before use. Compounds were purified by flash chromatography over silica gel (230–400 mesh). IR spectra were recorded on a Perkin–Elmer 137 E spectrometer. ^1H and ^{13}C NMR spectra were recorded on 200 MHz and 300 MHz instruments using TMS as an internal standard. The mass spectra (MS) were recorded on an automated Finnigan MAT 1020C mass spectrometer using an ionization energy of 70 eV. The optical rotations were carried out on a JASCO-181 digital polarimeter at 25°C using sodium D light. HPLC analyses were performed using a Waters HPLC system consisting of pump model 510, UV detector model 481, model 730 data module and Rheodyne injector. Chiral analyses were performed using Macherey Nagel CEL-AC 40 F (4.0 mm×25 cm) column.

Chiral ligands viz; $(DHQD)_2$–CLB and $(DHQD)_2$–PYR were prepared as per literature procedures.[8] Silyl enol ethers were prepared from corresponding ketones by following procedures reported elsewhere.[9]

3.1. Typical procedure for the asymmetric aminohydroxylation of silyl enol ethers

A mixture consisting of DHQD–CLB (10 mg, 0.02 mmol) in 20 mL of t-butanol:H_2O (1:1) and OsO_4 (20 µL of 0.5 molar solution in toluene, 0.01 mmol) was stirred for 2 min. To this solution, chloramine-T

Table 1
OsO_4-catalyzed asymmetric aminohydroxylation of silyl enol ethers

Expt. No.	Silyl enol ether **1**	Chiral Ligand	α - Amino Ketone **2**	t (min)	Yield[b] (%)	ee[c] (%)	m.p. (°C)
1.		$(DHQD)_2$-CLB		15	35	92	139- 140
2.		$(DHQD)_2$-CLB		15	38	72	99-100
3.		(DHQD)2- PYR		15	40	86	99-100
4		$(DHQD)_2$-CLB		15	34	76	120-121
5.		$(DHQD)_2$-CLB		120	41	70	115-116
6.		$(DHQD)_2$- PYR		120	45	85	115-116
7.		$(DHQD)_2$-CLB		10	28	76	105- 106

a: Molar ratio of silyl enol ether : OsO_4 : chiral ligand = 1 : 0.01 : 0.02 ; temp 25°C ; b : isolated yield after chromatographic purification and crystallization ; c : % ee was determined by chiral HPLC analysis : chiral CEL-AC-40F column.

(570 mg, 2.5 mmol) was added and stirred for 2 min., followed by the addition of the silyl enol ether of cyclohexanone (170 mg, 1 mmol). A pale green colour was formed immediately and turned to dark brown after 10 minutes. The progress of the reaction was monitored by TLC. After an additional 5 min. stirring the reaction was quenched by the addition of sodium metabisulfite. The two layers were separated. The aqueous layer was extracted with ethyl acetate, and the combined organic layer was washed with brine, dried over anhydrous sodium sulphate and the solvent was distilled off under reduced pressure. The crude product was purified by flash chromatography (8–10% ethyl acetate:pet. ether) to give the pure

product. Yield: 92 mg (35%). Chiral analysis was performed using 96% ethanol–water with a flow rate of 0.4 mL/min. The detector wavelength was fixed at 210 nm; retention times: 20.60 (minor) and 23.00 (major).

3.1.1. 2-(N-(p-Tolylsulfonyl)amino)cyclohexanone

Yield: 35%; mp: 139–140°C; IR ($CHCl_3$, cm^{-1}): 3290, 1695, 1585, 1350, 1310, 1265, 1160, 1090, 815, 740, 670; ^1H NMR (300 MHz, $CDCl_3$): δ 1.5 (m, 3H, ring CH), 1.8 (m, 1H, ring CH), 2.0 (m, 1H, ring CH), 2.2 (dt, 1H, ring CH) 2.35 (s, 3H, Ar-CH_3), 2.5 (m, 2H, ring CH), 3.7 (m, 1H, CHN), 5.75 (d, J=6.2 Hz, NH), 7.25 (d, J=9.4 Hz, 2H, Ar-H) 7.7 (d, J=9.4 Hz, 2H, Ar-H); MS: m/z (% rel intensity) 239 (68), 211 (20), 155 (83), 154 (41), 139 (23), 133 (12), 111 (17), 97 (12), 91 (100), 90 (63), 84 (42), 83 (33), 73 (7). $[\alpha]_D=-10$ (c 0.5, $CHCl_3$). Anal.: $C_{13}H_{17}NO_3S$ requires C, 58.43; H, 6.37; N, 5.24; S, 11.985%. Found: C, 58.44; H, 6.3; N, 5.3; S, 11.91%.

3.1.2. 2-(N-(p-Tolylsulfonyl)amino)-4-methylcyclohexanone

Yield: 38%; mp: 99–100°C; IR ($CHCl_3$, cm^{-1}): 3280, 1695, 1590, 1400, 1320, 1220, 1160, 1090, 920, 810, 740, 660; ^1H NMR (200 MHz, $CDCl_3$): δ 1.0 (d, J=8.1 Hz, 3H, ring-CH_3), 1.15–1.35 (m, 2H, ring CH), 1.6–1.7 (bs, 1H, ring CH), 1.9–2.0 (m, 1H, ring CH), 2.25–2.35 (m, 1H, ring CH), 2.4 (s, 3H, Ar-CH_3), 2.4–2.5 (m, 2H, ring CH), 3.75 (m, 1H, CHN), 5.75 (d, J=5.4 Hz, 1H, NH), 7.3 (d, J=9.2 Hz, 2H, Ar-H), 7.7 (d, J=9.2 Hz, 2H, Ar-H); MS: m/z (% rel. intensity) 281 (M^+, 6), 237 (8), 224 (51), 216 (51), 155 (88), 133 (9), 126 (26), 98 (81), 91 (100), 81 (29), 70 (14), 65 (37), 55 (15); $[\alpha]_D=-8.3$ (c 0.5, $CHCl_3$ using $(DHQD)_2$–CLB); −14.8 (c 0.5, $CHCl_3$ using $(DHQD)_2$–PYR). Anal.: $C_{14}H_{19}NO_3S$ requires C, 59.79; H, 6.76; N, 4.98; S, 11.39%. Found: C, 59.77; H, 6.78; N, 4.95; S, 11.36%.

3.1.3. 2-(N-(p-Tolylsulfonyl)amino)-4-tert-butylcyclohexanone

Yield: 34%; mp: 120–121°C; IR ($CHCl_3$, cm^{-1}): 3290, 1700, 1600, 1340, 1290, 1160, 1090, 980, 920, 810, 760, 670; ^1H NMR (200 MHz, $CDCl_3$): δ 0.9 (s, 9H, tBu), 1.25–1.5 (m, 2H, ring-CH), 1.55–1.7 (m, 1H, ring CH), 2.05–2.15 (m, 1H, ring CH) 2.2–2.35 (m, 1H, ring CH), 2.4 (s, 3H, Ar-CH_3), 2.45–2.6 (m, 2H, ring CH), 3.75 (m, 1H, CHN), 5.75 (bd, J=5.4 Hz, 1H, NH), 7.25 (d, J=9.2 Hz, 2H, Ar-H), 7.75 (d, J=9.2 Hz, 2H, Ar-H). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ 21.7, 27.8, 28.6, 32.6, 38.3, 39.9, 46.0, 60.4, 127.3, 129.9, 143.8, 206.4; MS: m/z (% rel. intensity) 323 (M^+, 3), 266 (54), 238 (22), 210 (25), 172 (9), 155 (49), 140 (17), 123 (24), 110 (17), 91 (100), 82 (20), 77 (7), 65 (36), 57 (70), 55 (49). $[\alpha]_D=-11.4$ (c 0.5, $CHCl_3$). Anal.: $C_{17}H_{25}NO_3S$ requires C, 63.16: H, 7.74; N, 4.33; S, 9.91%. Found: C, 63.13; H, 7.74; N, 4.34; S, 6.02%.

3.1.4. 2-(N-(p-Tolylsulfonyl)amino)propiophenone

Yield: 41%; mp: 115–116°C; IR ($CHCl_3$, cm^{-1}): 3280, 1670, 1590, 1400, 1345, 1220, 1160, 1090, 960, 860, 750, 700, 660; ^1H NMR (200 MHz, $CDCl_3$): δ 1.4 (d, J=8.1 Hz, 3H, CH_3) 2.3 (s, 3H, Ar-CH_3), 4.95 (m, 1H, $CHCH_3$), 5.8 (d, J=8.1 Hz, 1H, NH), 7.15 (d, J=8.1 Hz, 2H, ArH), 7.45 (t, J=8.1 Hz, 2H, ArH), 7.55 (t, J=8.1 Hz, 1H, ArH), 7.7 (d, J=8.1 Hz, 2H, ArH), 7.8 (d, J=8.1 Hz, ArH); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 21.0, 21.5, 53.5, 127.2, 128.6. 128.8, 129.0, 129.8, 133.6, 134.2, 137.3, 143.6, 198.4; MS: m/z (% rel. intensity) 303 (M^+, 1) 199 (10), 198 (100), 155 (70), 105 (33), 91 (26), 90 (16), 77 (9); $[\alpha]_D=-17$ (c 1, $CHCl_3$, using $(DHQD)_2$–CLB); −20.7 (c 1, $CHCl_3$, using $(DHQD)_2$–PYR). Anal.: $C_{16}H_{17}NO_3S$ requires C, 63.36; H, 5.61; N, 4.62; S, 10.561%. Found: C, 63.35; H, 5.60; N, 4.64; S, 10.57%.

3.2. 2-(N-(p-Tolylsulfonyl)amino)tetralone

Yield: 28%; mp: 105–106°C; IR ($CHCl_3$ cm^{-1}): 3280, 1690, 1600, 1460, 1400, 1360, 1330, 1295, 1210, 1165, 1095, 1000, 960, 815, 750, 680; ^1H NMR (200 MHz, $CDCl_3$): δ 2.1–2.35 (m, 2H, ring CH), 2.45 (s, 3H, Ar-CH_3), 2.7 (m, 1H), 3.9 (m, 1H, CHN), 6.1 (bs, 1H, NH), 7.2–7.35 (m, 4H, ArH), 7.55 (t, J=6 Hz, 1H, ArH), 7.85 (d, J=8.2 Hz, 2H, ArH), 7.95 (d, J=8.2 Hz, 1H, ArH); MS: m/z (% rel. intensity) 315 (M^+, 4), 266 (11), 160 (72), 155 (15), 144 (26), 130 (47), 124 (13), 117 (40), 115 (29), 110 (11), 112 (22), 91 (100), 84 (26), 81 (13), 77 (32), 69 (16), 65 (46), 60 (8), 57 (47); $[\alpha]_D=-6.5$ (c 0.5, $CHCl_3$). Anal.: $C_{17}H_{17}NO_3S$ requires C, 64.762; H, 5.40; N, 4.44, S, 10.16%. Found: C, 64.70; H, 5.36; N, 4.43; S, 10.2%.

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