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Kinetic Resolution of Racemic β-Hydroxy Amines by Enantioselective N-Oxide Formation

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Kinetic resolution of racemic β-hydroxy amines with a t-butyl substituent was attained in high optical yield by asymmetric oxidation.

The chiral β-hydroxy tertiary amines possessing a bulky t-butyl substituent on the carbon atom bonded to the hydroxy group serve as effective catalysts for highly enantioselective addition of dialkylzinc to aldehydes,[1,2] and for kinetic resolution of racemic aldehydes by enantioselective alkylation.[3] Furthermore, we recently disclosed "Asymmetric Amplifying Phenomena", that is the asymmetric reaction giving high ee of the product using low ee of the auxiliary in the reaction of aldehydes with dialkylzinc,[1] and this was also observed remarkably when the β-hydroxy amines with a t-butyl group were used as catalysts. Here we want to describe the convenient preparation of a variety of 1-dialkylamino-3,3-dimethyl-2-butanols that were efficient chiral auxiliary for above asymmetric reactions.

β-Hydroxy amines with a high ee purity could be prepared by kinetic resolution of racemic β-hydroxy amines using t-butyl hydroperoxide (TBHP) catalyzed by chiral titanium/tartrate system.[4] Successively we examined several substrates having a variety of substituents on the nitrogen, such as **1a**—**1c**.[5] The ratio of Ti/DIPT (DIPT: Diisopropyl tartrate) is very important to attain efficient kinetic resolution. When 0.6 equiv. of TBHP was used (Ti/DIPT ratio; 2/1.2 or 2/1.4), unreacted β-hydroxy amines with 92—96% ee were recovered in k_f/k_s = 13—17. The advantage of this method is high predictivity of the stereochemistry. When we use the L-(+)-DIPT faster reacting enantiomer was always R (i.e. recovered β-hydroxy amines possessed S configuration).

Typical procedure is as follows; In a flame-dried Schlenk tube were placed racemic

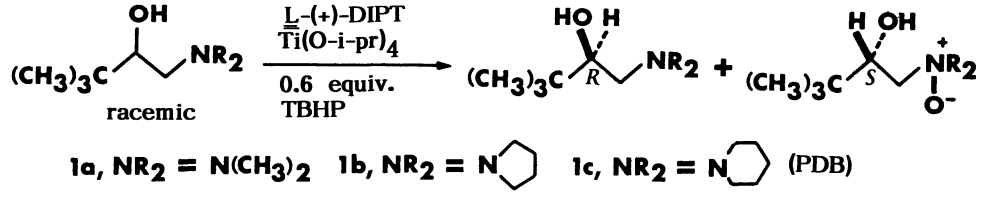

Table 1. Kinetic Resolution of Racemic β-Hydroxy Amines by Enantioselective *N*-Oxide Formation[a]

Substrate	Equiv. of Ti/*L*-DIPT	Unreacted substrate % yield[b]	Unreacted substrate $[\alpha]^{25}_{D}$/°[c]	Unreacted substrate % ee[d,e]	Product % yield[b]	Product $[\alpha]^{25}_{D}$/°[f]	Product % ee[g,h]	k_f/k_s[i]
1a	2/1.2	29.2	-65.2	92.5	56.6	+17.0	56.4	13.4
1b	2/1.4	39.5	-62.3	92.9	46.1	+36.7	59.0	13.7
1c	2/1.1	35.5	-53.3	82.1	55.4	+10.9	36.2	8.3
1c	2/1.2	37.5	-57.8	88.0	55.4	+11.1	37.2	10.7
1c	2/1.3	38.5	-56.5	86.2	60.0	+11.1	37.8	9.8
1c	2/1.4	38.3	-66.5	96.3	60.0	+13.0	46.4	17.4
1c	2/1.5	38.3	-57.5	88.0	55.4	+14.7	47.3	10.7

a) All reactions were carried out using 0.6 equiv. of TBHP in dichlorometane at -15 °C for 4 h. b) Isolated yield. c) Measured in $CHCl_3$ (*c* 1.0). d) HPLC analysis (Sumipax OA 4000) of the 3,5-dinitrophenylurethane derivative. e) Absolute configuration was *R*. f) In H_2O (*c* 1.0). g) HPLC analysis after reduction. h) *S* configuration. i) Calculated as 60% conversion by Kagan's equation. G. Balavoine, A. Moradpour, and H. B. Kagan, J. Am. Chem. Soc., 96, 5152 (1974).

PDB (600 mg, 3.24 mmol), *L*-(+)-DIPT (1.06 g, 4.52 mmol, 1.4 equiv.) and CH_2Cl_2 (25 mL). After addition of Ti(O-*i*-pr)$_4$ (1.84 g, 6.47 mmol, 2.0 equiv.) to this solution, the mixture was stirred for 30 min at room temperature. The 0.6 equiv. of TBHP (0.57 mL, 1.94 mmol, 3.4 M solution in toluene) was added to above solution at -15 °C. The mixture was stirred for 4 h at this temperature, then quenched by adding diethyl ether (32 mL), H_2O (1.3 mL) and 40% NaOH aqueous solution (1.3 mL). This mixture was vigorously stirred for 14 h at room temperature, yielding precipitates which were filtered off through a pad of Celite. The filtrates were evaporated up to give colorless solid. The solid was triturated in hexane (20 mL) followed by filtration, which gave optically active *N*-oxide of PDB (390 mg, 60 %). $[\alpha]_D^{25}$ +13° (*c* 1.0, H_2O). The hexane extracts were concentrated and chromatographed on silica-gel using acetone as an eluent to give (*R*)-(-)-PDB (230 mg, 38.3%). $[\alpha]_D^{25}$ -66.5° (*c* 1.1, $CHCl_3$). The ee of the unreacted substrate was determined by HPLC analysis (Sumipax OA 4000) of 3,5-dinitrophenylurethane derivatives. t_R of (*R*)-(-)-PDB: 9 min, t_R of (*S*)-(+)-PDB: 11 min (hexane—ethanol 99:1, 1.0 mL/min). The ee of *N*-oxide was determined as β-hydroxy amines after reduction by $LiAlH_4$ in THF.

References

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5) Racemic β-hydroxy amines were prepared by the following procedure: 1-Bromo-3,3-dimethyl-2-butanone was reduced by $LiAlH_4$ in ether to give bromohydrine, followed by treatment with 90% KOH aqueous solution afforded *t*-butylethylene oxide. This epoxide was reacted with secondary amines to give corresponding β-hydroxy amines. **1a**, bp 65—67 °C/23 mmHg; **1b**, bp 36—38 °C/1 mmHg; **1c**, bp 59—61 °C/1 mmHg.

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