Simple Preparation of β-Amino Alcohols Possessing a *tert*-Butyl Group at the α-Carbon

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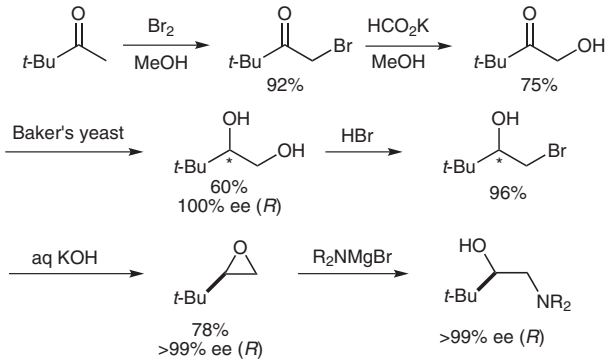
Abstract: Simple preparation of β-amino alcohols possessing a *tert*-butyl group at the α-carbon was achieved. These β-amino alcohols proved to work effectively as catalysts in the enantioselective alkylation of aldehydes.

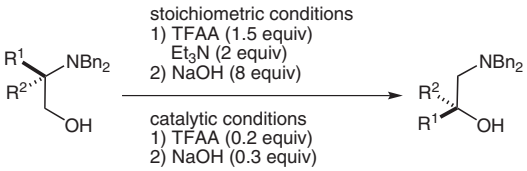
Key words: amino alcohols, alkylation, organocatalysis, enantioselectivity, rearrangements

Enantioselective alkylation of aldehydes with dialkylzincs catalyzed by β-amino alcohol is one of the most established methods of obtaining optically active secondary alcohols. There have thus been many reports on the development of β-amino alcohol type catalysts to be used in such reactions.[1,2] However, many of the β-amino alcohols used in these reactions are not easy to prepare. Actually, a highly enantioselective reaction of aldehydes with dialkylzincs using β-amino alcohols possessing a *tert*-butyl group at the α-carbon (i.e., the hydroxy carbon) has previously been reported.[3] At that time, the desired β-amino alcohols were prepared according to the procedure depicted in Scheme 1, which involved a Baker's yeast mediated reduction.



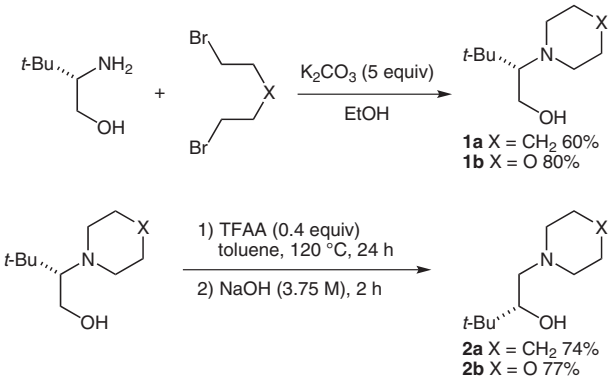
Scheme 1 Previous method used for the synthesis of β-amino alcohols possessing a *tert*-butyl group at the α-carbon

In 2006, Cossy and co-workers reported the rearrangement of *N*,*N*-dibenzylamino alcohols using a trifluoroacetic anhydride, triethylamine and sodium hydroxide (TFAA/Et_3N/NaOH) system to give 1,2-amino alcohols (Scheme 2).[4] They reported both stoichiometric and catalytic systems, however, most of the substrates they employed were dibenzylamines and rearranged amino alcohols were obtained in 88–99% enantiomeric excess.



Scheme 2 Rearrangement of *N*,*N*-dibenzylamino alcohols using TFAA/Et_3N/NaOH system reported by Cossy and co-workers[4]

We planned the synthesis of β-amino alcohols possessing a *tert*-butyl group at the α-carbon based on Cossy's rearrangement method. Although Cossy and co-workers did not provide examples of β-amino alcohols having a cyclic protected amino groups, we wanted to synthesized β-amino alcohols having piperidino and morphorino groups (**2a** and **2b**), because they have been shown to work efficiently as catalysts in enantioselective alkylation.[2]



Scheme 3 Three-step synthesis of β-amino alcohols possessing an α-*tert*-butyl group

Gratifyingly, the desired products (**2a** and **2b**) were obtained very easily in three steps (Scheme 3). Thus, starting from the α-amino acid, reduction of the carboxylic acid and protection of the amino group, followed by rearrangement, gave the desired products **2a** and **2b** in good yield. After confirming the optical purity of the β-amino alcohol to be more than 99% ee (HPLC analysis), these compounds were then employed in the reaction of diethylzinc with benzaldehyde; the results are summarized in Table 1.

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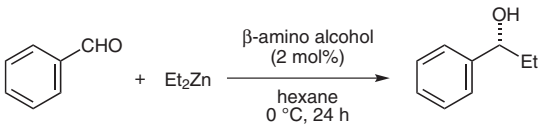
Table 1 Enantioselective Ethylation of Benzaldehyde[a]



Entry	β-Amino alcohol	Yield (%)	ee (%)
1	**1a**	20	56 (*R*)
2	**1b**	17	36 (*R*)
3	**2a**	94	98 (*R*)
4	**2b**	70	98 (*R*)

[a] Reaction conditions: diethylzinc (1.2 equiv), β-amino alcohol (2 mol%) in hexane (0.5 M), 0 °C, 24 h.

From the results presented in Table 1, it is clear that β-amino alcohols possessing a *tert*-butyl group at the α-carbon group (**2a** and **2b**) worked more efficiently than β-amino alcohols possessing the *tert*-butyl group at the carbon linked to the amino group (**1a** and **1b**) with respect to both catalytic activity and enantioselectivity (Figure 1).

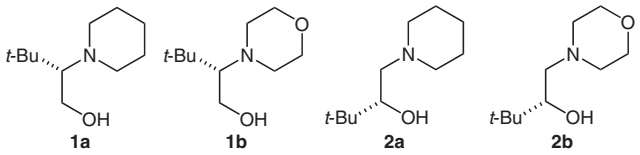


Figure 1

Thus, we have disclosed a simple preparation of α-*tert*-butyl β-amino alcohols.

All reactions were carried out in thoroughly cleaned and oven-dried glassware with magnetic stirring. Operations were performed under an atmosphere of anhydrous argon using Schlenk and vacuum techniques. All starting materials were obtained from commercial sources and used without further purification. ^{1}H and ^{13}C NMR spectra (400 and 100.6 MHz, respectively) were recorded with a JEOL JNM-LA 400 instrument with Me_4Si as an internal standard (δ = 0 ppm). FTIR spectra were recorded with a Thermo Scientific, NICOLET iS5, iD5 ATR instrument. Mass spectra were measured with a Thermo Quest LCQ DECA plus. HPLC analyses were carried out with a HITACHI L-2000 series instrument equipped with diode array detector using chiral columns CHIRALCEL OD-H (DAICEL, 0.46 × 25 cm). Optical rotations were measured with a HORIBA SEPA-300 polarimeter for a solution in a 1 dm cuvette. Preparative column chromatography was carried out using Fuji Silysia BW-4:10MH silica gel or YMC_GEL Silica (6 nm I-40–63 um). Thin-layer chromatography (TLC) was carried out on Merk 25 TLC aluminum sheets coated with silica gel 60 F_{254}.

2-Piperidino-3,3-dimethyl-1-butanol (1a)
K_2CO_3 (6.9 g, 49.9 mmol) was placed in a dry three-necked flask under an argon atmosphere. (*S*)-*tert*-Leucinol (1.2 g, 1.0 mmol) dissolved in anhydrous EtOH (15 mL) was added into the flask followed by 1,5-dibromopentane (2.8 mL, 20 mmol). The reaction mixture was stirred at 60 °C for 48 h, then cooled to r.t., filtered to remove undissolved K_2CO_3. The solution was concentrated to a residue, which was purified by silica gel column chromatography (hexane–EtOAc, 10:1) and the final product was recrystallized (hexane–EtOAc) to give (*S*)-**1a**.

Yield: 1.1 g (5.9 mmol, 60%); colorless solid; mp 73–75 °C; $[\alpha]_D^{26}$ +22.3 (*c* 1.0, $CHCl_3$); R_f = 0.15 (hexane–EtOAc, 3:1).

IR (KBr): 3265, 2932, 1440, 1354, 1269, 1167, 1122, 1044, 1014, 993, 753 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (s, 9 H), 1.5–1.6 (m, 7 H), 2.40 (dd, *J* = 10.8, 4.8 Hz, 1 H), 2.7–2.8 (m, 2 H), 2.9–3.0 (m, 2 H), 3.4–3.5 (m, 1 H), 3.5–3.6 (m, 1 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 24.9, 27.8, 29.1, 36.8, 51.6, 57.3, 74.8.

MS: *m*/*z* = 186 $[M + H]^+$.

Determination of Enantiopurity of β-Amino Alcohol 1a
A mixture of THF (4 mL), β-amino alcohol **1a** (37.2 mg, 0.2 mmol), and anhydrous $NaHCO_3$ (42.0 mg, 0.5 mmol) was stirred at 0 °C. To the mixture, a solution of benzoyl chloride (58 μL, 0.5 mmol) in THF (1 mL) was added. The reaction mixture was stirred at 20 °C for 1 h, heated at reflux (70 °C) for 10 h, and then quenched by adding H_2O (5 mL). After extraction with EtOAc (3 × 10 mL) and purification by silica gel column chromatography (hexane–EtOAc, 3:1), the O-protected product was obtained (53.1 mg, 92%). The enantiomeric excess of **1a** was determined to be more than 99.8% (*S*) by HPLC analysis using chiral column (CHIRALCEL OD-H; DAICEL, 0.46 × 25 cm; hexane–*i*-PrOH, 99.9:0.1; 0.5 mL/min; detection 220 nm): t_R = 11.7 (*S*-isomer), 13.0 (*R*-isomer) min.

2- Morpholino-3,3-dimethyl-1-butanol (1b)
K_2CO_3 (294.8 mg, 2.1 mmol) was placed in a dry three-necked flask under an argon atmosphere. (*S*)-*tert*-Leucinol (50 mg, 0.42 mmol) dissolved in anhydrous EtOH (15 mL) was added into the flask, followed by 2,2′-dibromodiethyl ether (197.1 mg, 0.85 mmol, 2 equiv). The reaction mixture was stirred at 60 °C for 48 h, then cooled to r.t., filtered to remove undissolved K_2CO_3. The solution was concentrated to a residue, which was purified by silica gel column chromatography (hexane–EtOAc, 10:1) and the final product was recrystallized (hexane–EtOAc).

Yield: 63.0 mg (80%); R_f = 0.09 (hexane–EtOAc, 3:1); mp 56–58 °C; $[\alpha]_D^{26}$ +17.2 (*c* 1.0, $CHCl_3$).

IR (KBr): 3260, 2955, 1735, 1653, 1483, 1356, 1270, 1118, 1040, 1018, 944, 853, 762 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.0 (s, 9 H), 2.37 (dd, *J* = 10.8, 4.4 Hz, 1 H), 2.8–2.9 (m, 3 H), 3.0–3.1 (m, 2 H), 3.5–3.7 (m, 6 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 28.9, 36.6, 51.2, 57.9, 68.4, 74.7.

MS: *m*/*z* = 188 $[M + H]^+$.

1-Piperidino-3,3-dimethyl-2-butanol (2a)
2-Piperidino-3,3-dimethyl-1-butanol (370.6 mg, 2 mmol) dissolved in anhydrous toluene (5 mL) was added to a pre-dried three-necked flask equipped with a magnetic stirrer and a condenser under an argon atmosphere. TFAA (168.0 mg, 0.8 mmol, 0.4 equiv) was added dropwise while stirring, then the mixture was heated at reflux (120 °C) for 24 h. The reaction mixture was cooled to r.t. and then quenched by adding aq NaOH (3.75 M, 5 mL) followed by H_2O (3 mL). The mixture was extracted with EtOAc (3 × 20 mL) and the combined organic phase was dried with anhydrous Na_2SO_4, filtered, and concentrated to a residue, which was purified by silica gel column chromatography (hexane–EtOAc, 3:1).

Yield: 274.3 mg (74%); R_f = 0.11 (hexane–EtOAc, 3:1); $[\alpha]_D^{31}$ –70.3 (*c* 1.0, $CHCl_3$).

IR (KBr): 3440, 2937, 1479, 1385, 1304, 1155, 1092, 1015 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (s, 9 H), 1.4–1.5 (m, 2 H), 1.5–1.6 (m, 4 H), 2.2–2.3 (m, 4 H), 2.6 (br, 2 H), 3.31 (dd, *J* = 10.0, 4.4 Hz, 1 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 24.3, 25.6, 26.2, 33.2, 54.6, 59.7, 72.9.

MS: *m*/*z* = 186 $[M + H]^+$.

Determination of Enantiopurity for β-Amino Alcohol 2a
A mixture of THF (4 mL), β-amino alcohol **2a** (37.5 mg, 0.2 mmol), and anhydrous $NaHCO_3$ (42.0 mg, 0.5 mmol) was stirred at 0 °C. To the mixture, a solution of benzoyl chloride (58 μL, 0.5 mmol) in THF (1 mL) was added. The reaction mixture was stirred at 20 °C for 1 h, heated at reflux (70 °C) for 10 h, and then quenched by adding H_2O (5 mL). After extraction with EtOAc (3 × 10 mL) and silica gel column chromatography (hexane–EtOAc, 3:1), the O-protected product was obtained.

Yield: 51.0 mg (87%).

The enantiomeric excess of O-protected β-amino alcohol **2a** was determined to be more than 99.8% (*R*) by HPLC analysis using a chiral column (CHIRALCEL OD-H, DAICEL, 0.46 × 25 cm; hexane–*i*-PrOH, 99.9:0.1; 1.0 mL/min; detection 220 nm): t_R = 18.0 (*S*-isomer), 19.5 (*R*-isomer) min.

1-Morpholino-3,3-dimethyl-2-butanol (2b)
2-Morpholino-3,3-dimethyl-1-butanol (374.56 mg, 2 mmol) dissolved in anhydrous toluene (5 mL) was added to a pre-dried three-necked flask equipped with a magnetic stirrer and a condenser under an argon atmosphere. TFAA (168.02 mg, 0.8 mmol, 0.4 equiv) was added dropwise while stirring. The mixture was heated at reflux (120 °C) for 24 h, then cooled to r.t. and quenched by adding aq NaOH (3.75 M, 5 mL) followed by H_2O (3 mL). The mixture was extracted with EtOAc (3× 20 mL) and the combined organic phase was dried with anhydrous Na_2SO_4, filtered, and concentrated to a residue. The residue was purified by silica gel column chromatography (hexane–EtOAc, 3:1).

Yield: 288.4 mg (77%); R_f = 0.10 (hexane–EtOAc, 3:1); $[\alpha]_D^{25}$ –69.2 (*c* 0.99, $CHCl_3$).

IR (KBr): 3464, 2954, 2855, 1645, 1456, 1295, 1119, 1014, 870 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.9 (s, 9 H), 2.3–2.4 (m, 4 H), 2.6–2.7 (m, 2 H), 3.33 (dd, *J* = 10.8, 3.2 Hz, 1 H), 3.7–3.8 (m, 4 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 25.6, 33.1, 53.6, 59.7, 67.1, 72.7.

MS: *m*/*z* = 188 $[M + H]^+$.

Asymmetric Ethylation of Benzaldehyde (Table 1)
To a solution of chiral β-amino alcohol (0.036 mmol) in hexane (2.6 mL) at –40 °C, was added diethylzinc (0.22 mL, 2.2 mmol). The solution was warmed to 0 °C, stirred for 30 min, and then cooled to –40 °C again, after which benzaldehyde (191 mg, 1.8 mmol) was added. The reaction mixture was stirred for 24 h at 0 °C and then quenched by adding aq HCl (1 M, 20 mL). After extraction with Et_2O (3 × 20 mL), silica gel column chromatography (hexane–EtOAc, 10:1), and Kugelrohr distillation, the product was obtained. Enantiomeric excess was determined by HPLC analysis using a CHIRALCEL OD-H (DAICEL) column.

(*R*)-1-Phenyl-1-propanol
Yield: 210.0 mg (94%); 98% ee; $[\alpha]_D^{29}$ +41.9 (*c* 1.00, $CHCl_3$) {Lit.[2] $[\alpha]_D^{20}$ +42.9 [*c* 3.58, $CHCl_3$, 87.5% *ee* (*R*)]}; HPLC [CHIRALCEL OD-H (DAICEL); hexane–*i*-PrOH, 97.5:2.5; 1.0 mL/min]: t_R = 10.2 (*R*-isomer), 11.9 (*S*-isomer) min.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included is an explanation for the origin of reactivity and enantioselectivity,

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