Articles

Reaction of Diisopropoxytitanium(III) Tetrahydroborate with Selected Organic Compounds Containing Representative Functional Groups

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Diisopropoxytitanium(III) tetrahydroborate, $(^{i}PrO)_2TiBH_4$), generated *in situ* in dichloromethane from diisopropoxytitanium dichloride and benzyltriethylammonium borohydride in a 1:2 ratio selectively reduces aldehydes, ketones, acid chlorides, carboxylic acids, and *N*-Boc-protected amino acids to the corresponding alcohols in excellent yield under very mild reaction conditions (−78 to 25 °C).

The interaction of $TiCl_4$ and excess $LiBH_4$ has long been known to yield the unstable titanium(III) tetrahydroborate complex $Ti(BH_4)_3$,[1] and this species has been reported in the patent literature to be an active olefin polymerization catalyst (or catalyst precursor).[2] However, it was only a few years ago the crystal structure of $Ti(BH_4)_3{\cdot}(PMe_3)_2$ was reported by Girolami et al.[3] which showed the presence of a highly unusual tetrahydroborate bonding mode in which one B−H bond of a BH_4^- unit is coordinated in a "side on" fashion to the titanium center. This bonding mode closely resembles the one proposed as the transition state for the activation of alkanes.[4]

Recently, we reported an unusual anti-Markovnikov hydration of alkenes with titanium(III) tetrahydroborate, $Ti(BH_4)_3$, **1**.[5] In order to explore the scope and utility of this reagent, we studied the reduction of α,β-unsaturated carbonyl compounds with this reagent system and found that this transition metal borohydride produces the corresponding allylic alcohols in 90% selectivity. The chemoselectivity was increased to >99% with the modified reagent, $(^{i}PrO)_2TiBH_4$, **2**.[6]

Results and Discussion

Reduction of Selected Organic Compounds. In order to establish the synthetic utility of the reagent **2**, we studied the reductions of a series of selected organic compounds containing various functional groups.

Reduction of Cyclic and Bicyclic Ketones. The development of methods for the stereoselective reduction of the carbonyl group continues to be of interest in organic chemistry.[7] Anh[8] has suggested that the more flattened the ring, the more axial attack, i.e., axial attack may approach antiperiplanarity to the C_2-H_{ax} and C_6-H_{ax} bonds (Figure 1). With this background information we studied the stereochemical course of reduction of a number of cyclic ketones with **2**, and the results are summarized in Table 1.

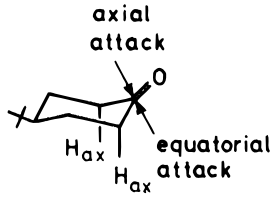

Figure 1.

Treatment of the moderately hindered ketone 2-methylcyclohexanone with **2** (−78 to −20 °C) led to the formation of *trans*-2-methylcyclohexanol (97% selectivity) as the major product (Table 1). The unhindered ketone 3-methylcyclohexanone afforded *cis* alcohol in 92% stereoselectivity. Even better discrimination was observed in the reduction of 4-alkylcyclohexanone, the least hindered of the alkylcyclohexanones. In the case of 4-alkyl isomers, due to the remote position of the alkyl substituent, approach of the reducing species from either side of the carbonyl group is equally favored.[9] Accordingly, 4-*tert*-butylcyclohexanone was reduced to the corresponding *trans* alcohol in 97% selectivity (−78 to −20 °C). Since the reduction of ketones by tetrabutylammonium tetrahydroborate is slower[10] than that by **2**, the titanium(III) ion must be participating in the reaction in some manner. In the transition state, the ring may be flattened,[8] as indicated in Figure 2. In axial attack, antiperiplanarity is clearly achievable and can be improved

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(3) Jensen, J. A.; Wilson, S. R.; Girolami, G. S. *J. Am. Chem. Soc.* **1988**, *110*, 4977.
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(10) (a) Raber, D. J.; Guida, W. C. *J. Org. Chem.* **1976**, *41*(4), 690. (b) Sullivan, E. A.; Hinckley, A. A. *J. Org. Chem.* **1962**, *27*, 3731.

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Table 1. Reduction of Cyclic Ketones with Tetrahydroborate 2 and Comparison of Stereoselectivity with Other Hydride Reagents

entry	ketone	time (min)	major isomer	$(^iPrO)_2TiBH_4$[a] (−78 to −20 °C)	yield (%)	BH_3·THF[b] (0 °C)	$NaBH_4$[c] (0 °C)	Li-*n*-$BuBH_3$[c] (−78 °C)	LAH[d] (0 °C)
1.	2-methylcyclohexanone	30	trans	97	98	74	73	69	76
2.	3-methylcyclohexanone	15	cis	92	97	77	75	90	85
3.	4-*tert*-butylcyclohexanone	15	trans	97	100	72	86	98	90
4.	3-cholestanone	20	*β*-isomer	98	96		87[e]		88[e]
5.	3,3,5-trimethylcyclohexanone	30	trans	87	96		55	66	80
6.	2-methylcyclopentanone	60	trans	93	94	75			84
7.	2,4,4-trimethylcyclopentanone	60	trans	85	96				91[f]
8.	camphor	60	exo	98	90	52	89	85	91

[a] Analysis by 1H NMR or GC. [b] Reference 37. [c] Reference 38. [d] Reference 39. [e] Reference 40. [f] Reference 35.

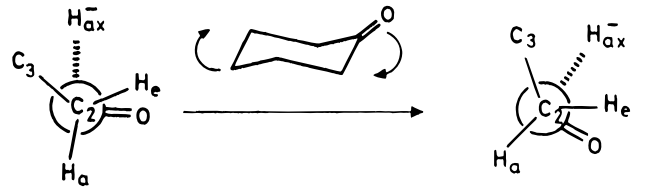

Figure 2.

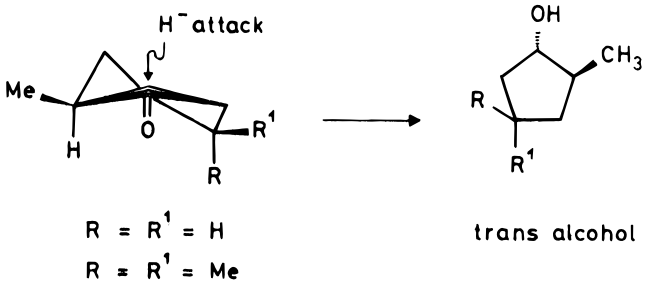

Figure 3.

by flattening the ring, whereas in equatorial attack this is not possible. The highly selective axial attack of 2-methyl-, 3-methyl-, and 4-*tert*-butylcyclohexanones and cholestan-3-one induced by **2** supports Anh's hypothesis.[8,11]

3,3,5-Trimethylcyclohexanone introduces a methyl group in the 3-axial position which reduces the flattening factor,[12] thereby equatorial attack of **2** predominates to give 87% of *axial* alcohol.

The preferred conformation of cyclopentanone is the half-chair model (Figure 3), which allows attack of the reagent from either side; however, ring substituents change the picture in the case of 2-methylcyclopentanone where the methyl group is in a quasi-equatorial position. Hence the attack of the hydride takes place from the side antiperiplanar to the quasi-axial hydrogen at C_2.

In the case of 2,4,4-trimethylcyclopentanone, the C_2 methyl group is in a quasi-equatorial position to avoid steric interaction with the quasi-axial methyl group at C_4. The stereochemistry of the reduction is controlled by the quasi-axial methyl group at C_4, and the hydride attack appears to be from the side antiperiplanar to the quasi-axial hydrogen at C_2. The reduction of camphor with **2** leads to a higher proportion (98%) of *endo* attack to give the *exo* alcohol as the major product. An explanation for this stereoselectivity can be offered on the basis of less flattening effect due to the severe interaction between the C_1 methyl group and the C_7 methyl group.

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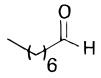
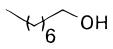
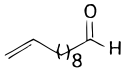
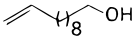
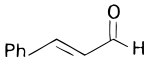
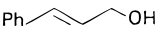
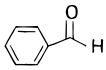
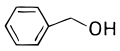
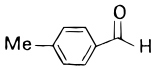
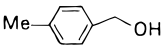
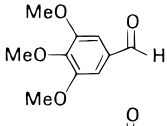
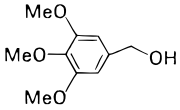
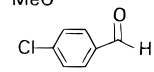
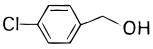
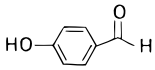
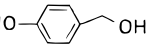
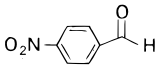
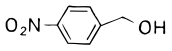
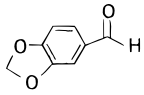
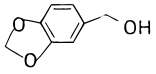
(12) Arnaud, C.; Accary, A.; Huet, J. *C.R. Acad. Sci.* **1977**, *285*, 325.

Table 2. Reduction of Aldehydes with Tetrahydroborate 2

Entry	Substrate	Product[a,b]	Yield[c] (%)
1			94
2			94
3			90
4			100
5			100
6			98
7			100
8			94
9			98
10			100

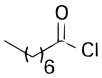
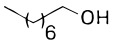
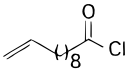
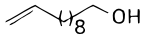
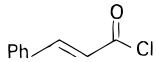
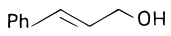
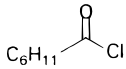
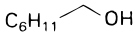
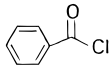
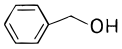
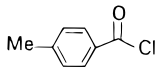
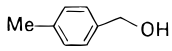
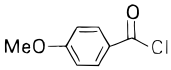
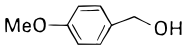
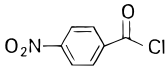
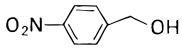
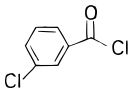
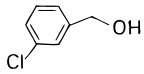
a. All the products were identified by direct comparison of physical data with those of authentic samples. b. Reaction time 5-10 min. c. Yield refers to pure isolated products.

When the reduction of cyclic ketones discussed above was carried out at −20 °C, though the yields were good the stereoselectivity in most of the cases was only around 90%. For example, reduction of 2-methylcyclopentanone with **2** at −20 °C (20 min) afforded the *trans*-2-methylcyclopentanol with 83% stereoselectivity.

Reduction of Aldehydes. Treatment of a variety of aldehydes with **2** at −20 °C led to the formation of the corresponding alcohols in quantitative yield. In general, aryl aldehydes underwent reduction almost instantaneously. Reduction of aliphatic aldehydes was equally facile, but the reaction was slower when compared to that with the aromatic aldehydes. The results of reduction of several aldehydes are given in Table 2.

Reduction of Acid Chlorides. Many reagents[13] have been developed for the reduction of acid chlorides to the corresponding alcohols. Reduction of acid chlorides with

Table 3. Reduction of Acid Chlorides with Tetrahydroborate 2

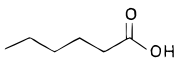
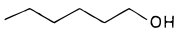
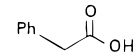
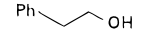
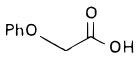
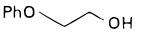
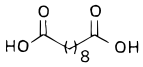
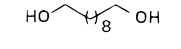
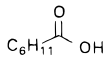
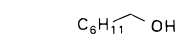
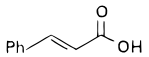
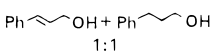
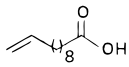
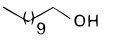
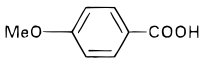
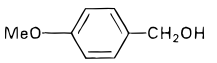
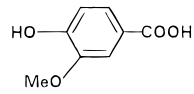
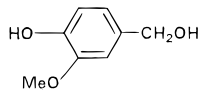
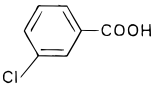
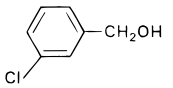
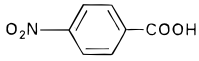
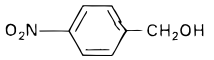
Entry	Substrate	Product[a,b]	Yield[c] (%)
1			86
2			95
3			96
4			88
5			100
6			98
7			98
8			97
9			99

a. All the products were identified by direct comparison of physical data with those of authentic samples. b. Reaction time 5-10 min. c. Yield refers to pure isolated products.

$Zn(BH_4)_3$·TMEDA[14] (0−40 °C, 0.5−6 h) or $NaBH_4$−Alox[15] (rt, 2−4 h) required higher temperatures and longer reaction times. $NaBH_4$ reduces acid chlorides to the corresponding alcohols in very low yield.[16] LAH required a very long reaction time for the reduction of acid chlorides.[17] In our work, we treated a number of acid chlorides with **2**. It turns out that **2** reduces aromatic and aliphatic acid chlorides with high selectivity to the corresponding alcohols in excellent yield (-20 °C) in a very short time (5−10 min). The results are summarized in Table 3. From these results it is apparent that the double bond conjugated to the acid chloride group enhances the rate of reduction. Also, it is of interest to note that the selective reduction of acid chlorides can be achieved in the presence of other functional groups such as hydroxy, alkoxy, chloro, and nitro and carbon−carbon double bonds. When the reduction of octanoyl chloride with **2** was performed at −78 °C (0.5 h), the intermediate aldehyde could not be detected and only octanol was isolated in low yield (22%).

Reduction of Carboxylic Acids. Reduction of carboxylic acids to the corresponding alcohols has been examined with a variety of hydride reagents.[10] $NaBH_4$ and related reagents do not reduce carboxylic acids. Sodium borohydride in combination with Lewis acids shows reactivity comparable to that of diborane. Thus

Table 4. Reduction of Carboxylic Acids with Tetrahydroborate 2

Entry	Substrate	Product[a,b]	Yield[c] (%)
1			93
2			93
3			92
4			88
5			90
6		 1:1	78
7			86
8	PhCOOH	$PhCH_2OH$	94
9			89
10			73
11			94
12			82

a. All the products were identified by direct comparison of physical data with those of authentic samples. b. Reaction time 4h (25°C). c. Yield refers to pure isolated products.

carboxylic acids have been reduced using $NaBH_4$ in the presence of $AlCl_3$, BF_3·OEt_2, $ZnCl_2$, $TiCl_4$, or $MeSO_3H$.[10] In exploring further the synthetic utility of this reagent system, **2**, we find that carboxylic acids are reduced selectively in CH_2Cl_2 under very mild reaction conditions (−20 to 25 °C) to the corresponding alcohols in high yields. When benzoic acid (1 equiv) was added into the solution of **2** (1 equiv) in CH_2Cl_2 at −20 °C, the blue color of the solution changed instantaneously to dark brownish black. However, after aqueous workup benzyl alcohol was obtained only in 47% yield with a substantial amount of unreacted acid. Accordingly, when benzoic acid was treated with **2** in 1:1 and 1:2 ratios (25 °C, 4 h), benzyl alcohol was obtained in 70% and 94% yields respectively. The results of this facile reduction of a wide variety of aliphatic and aromatic carboxylic acids are summarized in Table 4. The presence of acidic functional groups such as the phenolic group does not interfere in the reduction of the carboxylic acid group. Interestingly when undecylenic acid was reduced with **2**, 1-undecanol was obtained in 86% yield, involving reduction of the carbon−carbon double bond.[18] In the case of cinnamic acid, the

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(18) In the reduction of aldehydes or acid chlorides (1 equiv) with **2** (1 equiv), the reaction at the carbonyl site was much faster than at the alkene at −20 °C (5−10 min) and hence reduction of the C−C double bond was not observed.

corresponding saturated and unsaturated alcohols were obtained in a 1:1 ratio (78% yield). Although cinnamyl alcohol (1 equiv) when treated with **2** (1 equiv) at −20 °C for 0.5 h gave back the starting material, the same reaction carried out at room temperature (25 °C, 1 h) gave 3-phenylpropanol in 15% yield involving reduction of the carbon−carbon double bond. When 10-undecen-1-ol (1 equiv) was treated with **2** (1 equiv) at −20 °C for 10 min, it was recovered unchanged. However, when the reaction was allowed to proceed at −20 °C for 1 h, 1-undecanol was obtained in 55% yield. Hence it is apparent that longer reaction time affects the C−C double bond during the reduction of undecylenic acid.

Reduction of α-amino acids[19] with **2** afforded *β*-amino alcohols in poor yields (≈10%). This may be due to the poor solubility of amino acids in CH_2Cl_2.

N-Protected amino alcohols and N-protected peptide alcohols have received considerable attention in recent years. N-Protected amino alcohols have been utilized as intermediates in the preparation of amino aldehydes,[20] which are inhibitors of proteolytic enzymes[21] and are important synthetic intermediates.[22]

Several procedures for the reduction of N-protected α-amino acids and esters have been reported.[23] Lithium aluminum hydride and diisobutylaluminum hydride, which are generally used for the reduction of the carboxyl group, were found unsuitable for reduction of N-protected α-amino acids and esters because of their reactivity with many protecting groups. Reduction of *N*-Boc-protected amino acids by a borane−THF complex is reported as smooth,[17] but the optical rotations of *N*-Boc-protected amino alcohols[24] obtained revealed that the enantiomeric homogeneity was lost. In exploring further the utility of our reagent, a number of *N*-Boc-protected α-amino acids were treated with **2** (−20 to 25 °C, 4 h) and it was found that it led to the formation of the corresponding *N*-Boc-protected amino alcohols in moderate to good yields (61−89%) without any racemization. The results are summarized in Table 5.

Reduction of Miscellaneous Functional Groups. The reaction of diisopropoxytitanium tetrahydroborate, **2** was studied with a number of other substrates. For example, benzyl azide, ethyl benzoate, benzaldoxime, benzyl cyanide, and octanamide on treatment with **2** (1−2 equiv, −20 to 25 °C, 1−4 h) were recovered unchanged.

Table 5. Reduction of N-Protected Amino Acids with Tetrahydroborate 2

entry	substrate	product[a,b]	yield[c] (%)	[α_D] (*c*, solvent)
1.	Boc-L-Gly-OH	Boc-L-Gly-ol	88	
2.	Boc-L-Ala-OH	Boc-L-Ala-ol	70	−11.2 (0.6, $CHCl_3$)
3.	Boc-L-Val-OH	Boc-L-Val-ol	64[d]	−16.0 (1.0, MeOH)
4.	Boc-L-Leu-OH	Boc-L-Leu-ol	83	−28.0 (1.0, MeOH)
5.	Boc-L-Ile-OH	Boc-L-Ile-ol	59	−18.7 (0.2, $CHCl_3$)
6.	Boc-L-Pro-OH	Boc-L-Pro-ol	61	−47.0 (1.0, $CHCl_3$)
7.	Boc-L-Phe-OH	Boc-L-Phe-ol	75	−27.8 (1.0, MeOH)

[a] All the products were identified by direct comparison of physical data with those of authentic samples. [b] Reaction time 4 h (25 °C). [c] Yield refers to pure isolated products. [d] Yield based on recovered starting material.

Conclusion

The present study confirms the versatility of the reagent system. The reagent has unique and unusual reducing properties and is shown to be exceptionally powerful but highly selective. The advantages of this reagent system are (i) the reagent can be prepared very easily in CH_2Cl_2, (ii) the reactions are carried out under mild conditions, (iii) the reaction period is very short and (iv) generally the yields are very high.

Experimental Section

General Remarks. ^{1}H NMR spectra were recorded at 60, 90, or 300 MHz in $CDCl_3$. ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$. TLC were performed on 0.25-mm precoated silica plates (60F-254). Gas chromatographic (GLC) analyses of product mixtures and purified samples were performed on 5% OV-17 on a Chromosorb W-HP 80/100 (3 mm × 6 m) column. All glasswares were dried in a drying oven and cooled under nitrogen. All reduction experiments were carried out under nitrogen. 2-Methylcyclohexanone,[25] 3-methylcyclohexanone,[26] 4-*tert*-butylcyclohexanone,[27] cholestan-3-one,[28] 3,3,5-trimethylcyclohexanone,[29] 2-methylcyclopentanone,[30] 2,4,4-trimethylcyclopentanone,[31] and *N*-Boc-protected amino acids[32] were prepared according to the literature procedures. The aldehydes, carboxylic acids, and camphor were commercially available and were used without further purification. All the acid chlorides were prepared according to the literature procedure and freshly distilled before use.[33] A stock solution of diisopropoxytitanium dichloride in dry CH_2Cl_2 (11.8% w/v) was used.[6]

Preparation of Benzyltriethylammonium Tetrahydroborate.[34] To a stirred solution of benzyl triethylammonium chloride (22.7 g, 0.1 mol) in 5 M aqueous sodium hydroxide solution (20 mL) was added a solution of $NaBH_4$ (4.5 g, 0.12 mol) in 5 M aqueous sodium hydroxide (10 mL) at room temperature (25 °C). The resulting mixture was stirred at rt for 0.5 h and then extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried (K_2CO_3), and the solvent was evaporated under vacuum to afford a crystalline

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white solid (20 g, 97%): mp 145−147 °C; IR (KBr)ν 2990, 2290, 2210, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.08(q, $J_{B\text{-}H}$ = 81 Hz, 4H), 1.45 (t, 9H), 3.34 (q, 6H), 4.60 (s, 2H), 7.46 (m, 5H).

General Procedure for the Preparation of the Reagent Diisopropoxytitanium(III) Tetrahydroborate (2). To a stirred solution of diisopropoxytitanium dichloride (4 mL, 2 mmol) was slowly added benzyltriethylammonmium tetrahydroborate (0.828 g, 4 mmol) in dry CH_2Cl_2 (8mL) under N_2 at −20 °C, and the reaction mixture was stirred for 30 min.

General Procedure for the Reduction of Ketones. The solution of tetrahydroborate **2** obtained as above was cooled to −78 °C and the ketone 2,4,4-trimethylcyclopentanone (0.252 g, 2 mmol) in dry CH_2Cl_2 (2 mL) was added. The reaction mixture was brought to −20 °C and stirred for 60 min. A solution of saturated K_2CO_3 (10 mL) was added and stirred for an additional 15 min (25 °C). The reaction mixture was extracted with ether (3 × 20 mL), and it was washed with brine and dried (Na_2SO_4). Removal of solvent afforded 2,4,4-trimethylcyclopentanol as an oil[35] (0.245 g, 96%). ^1H NMR analysis of the crude product indicated the presence of *cis*/*trans* alcohols in a ratio of 15:85. ^1H NMR ($CDCl_3$): δ *cis* 4.0−4.2 (m), *trans* 3.6−3.9 (q, J = 6.4 Hz).

General Procedure for the Reduction of Aldehydes and Acid Chlorides. 4-Nitrobenzoyl chloride (0.371 g, 2 mmol) in dry CH_2Cl_2 (2 mL) was added into the solution of **2** (2 mmol), as mentioned above, and the reaction mixture was stirred (5−10 min) at −20 °C. A solution of saturated K_2CO_3 (10 mL) was added and stirred for an additional 15 min (25 °C). The reaction mixture was extracted with ether (3 × 20 mL), and it was washed with brine and dried (Na_2SO_4). Removal of solvent afforded 4-nitrobenzyl alcohol (0.297 g, 97%) as a solid:[36] mp 90−92 °C (lit.[30] mp 90−91 °C); IR (thin film) ν 3500, 1610, 1515, 1345, 1060, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.1 (s, 1H), 4.8 (s, 2H), 7.4−8.4 (dd, J = 9, 63 Hz, 4H).

General Procedure for the Reduction of Carboxylic Acids and *N*-Boc-Protected Amino Acids. The *N*-Boc-protected amino acid Boc-L-Ala-OH (0.19 g, 1.0 mmol) in dry CH_2Cl_2 (2 mL) was added to a solution of tetrahydroborate **2** (2 mmol), as mentioned above, and the reaction mixture was brought to room temperature (25 °C) and stirred for 4 h. A solution of saturated K_2CO_3 (5 mL) was added and stirred for an additional 15 min (25 °C). The reaction mixture was extracted with ether (3 × 20 mL), and it was washed with brine and dried (Na_2SO_4). Removal of solvent afforded Boc-L-Ala-ol as a white solid[18a] (0.124g, 70%): mp 51−53 °C (from diethyl ether−hexane; lit.[18a] mp 53−54.5 °C); $[\alpha]_D$ −11.2 [*c* 0.6, $CHCl_3$; lit.[18a] −11.6 (*c* 0.6, $CHCl_3$)]; IR (thin film) ν 3300, 1670, 1520, 1450, 1360, 1160, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.11 (d, J = 9Hz, 3H), 1.45 (s, 9H), 3.4−3.5 (dd, J = 8.3, 12.5 Hz, 1H), 3.55−3.65 (dd, J = 4.1, 12.5 Hz, 2H), 3.65−3.81 (m, 1H), 4.62−4.72 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 17.14, 28.20, 48.32, 66.81, 79.45, 156.16.

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Supporting Information Available: Spectral data of all *N*-Boc-protected β-amino alcohols (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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