Iodomethylation of Chiral α-Amino Aldehydes by Means of Samarium/Diiodomethane. Application to the Synthesis of Various Enantiomerically Pure Compounds

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Chiral iodohydrins **2** have been obtained from α-amino aldehydes **1** and Sm/CH_2I_2. Treatment of compound **2** with acetic anhydride, NaH, or $AgBF_4$ affords, with high diastereoselectivity, *O*-protected 3-(dibenzylamino)-1-iodoalkan-2-ol **3**, amino epoxides **4**, or azetidinium salts **5**, respectively. The synthesis of enantiomerically pure allylamines **6** is also described by metallation of **3** with zinc. The reaction of α-amino aldehydes **1** with Sm/CH_2I_2 and further treatment with organocuprates affords chiral amino alcohols **7** in a one-pot process.

Introduction

Chiral α-amino aldehydes are important compounds widely used in organic synthesis owing to their ready availability from α-amino acids[1] and pronounced versatility. In recent years, several basic organic reactions using α-amino aldehydes have been described to prepare enantiomerically pure compounds such as organometallic addition to carbonyl groups,[2] aldol condensations,[3] [4 + 2] cycloadditions with activated 1,3-dienes,[4] and transformations into other functionalities such as aminoalkenes[5] or α-amino aldimines.[6]

On the other hand, the halomethylation of carbonyl compounds is known to be difficult to achieve under ordinary reaction conditions due to the instability of (halomethyl)lithium compounds.[7] As an alternative, this kind of reaction proceeds smoothly at room temperature using samarium metal[8] or samarium(II) iodide[9] and diiodomethane. However, to the best of our knowledge, iodomethylation of chiral carbonyl compounds has not been reported in the literature to date, and consequently, there is no information about the utility of this methodology in the synthesis of optically pure compounds.[10]

The halomethylation of chiral α-amino aldehydes would afford iodohydrins, which could be easily transformed into α-amino epoxides, azetidines, β-amino alcohols, or allylic amines. These compounds are important because of their biological properties and synthetic applications. As examples, chiral α-amino epoxides are highly useful intermediates in the synthesis of protease inhibitors[11] and other pharmaceutically interesting compounds;[12] the azetidine ring is present in an important number of molecules with biological activity;[13] β-amino

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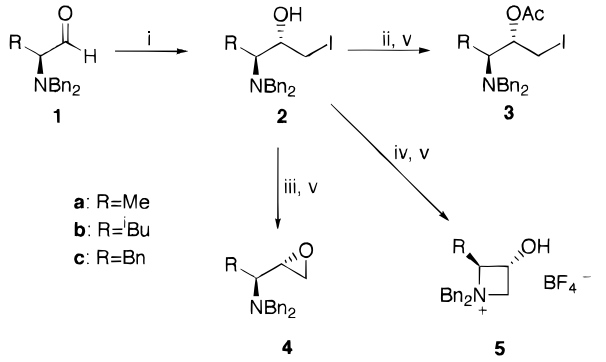
S0022-3263(97)00318-6 CCC: $14.00

Scheme 1[a]



[a] Reagents and conditions: (i) Sm^0/CH_2I_2, THF, 0 °C, 40 min, then H_3O^+; (ii) Ac_2O, pyridine, rt; (iii) NaH, CH_2Cl_2, rt; (iv) $AgBF_4$, Et_2O, rt; (v) H_2O.

alcohols are biologically important,[14] and the allylic amine moiety appears in many natural and bioactive compounds.[15] Moreover, α-amino epoxides,[16] azetidines,[17] and allylamines[18] can be used as chiral building blocks for a wide variety of compounds, and *β*-amino alcohols can be used as chiral auxiliaries.[19]

In this paper, we describe the preparation of enantiomerically pure, protected 3-amino-1-iodo 2-alcohols from chiral α-amino aldehydes and Sm/CH_2I_2, which are appropriate starting compounds for a simple and direct entry to amino epoxides, 3-hydroxy azetidinium salts, allylamines, and *β*-amino alcohols.

Results and Discussion

Treatment of a mixture of diiodomethane and different *N*,*N*-dibenzylated α-amino aldehydes **1** with samarium metal at 0 °C gave, after hydrolysis, the corresponding iodohydrins **2** (Scheme 1). When iodohydrins were taken to dryness they became unstable and decomposed to a mixture of several products. Therefore, these compounds were identified by NMR spectroscopy of the crude reaction mixture before the solvent was completely removed.[20] In order to characterize compounds **2** they were transformed into their *O*-acetyl derivatives **3** by treatment with acetic anhydride at room temperature, and these could be isolated and purified by flash column chromatography (Scheme 1 and Table 1, entries 1−3). Despite their instability, iodohydrins **2** could be converted to different compounds using the crude product (see the Experimental Section). Reaction of iodohydrins **2** with NaH at room temperature led to *erythro* amino epoxides **4** (Scheme 1 and Table 1). The stereochemistry of amino epoxides **4** was established unambiguously by comparison of their NMR spectra with those previously reported.[21] The iodomethylation of amino aldehydes **1** with Sm/CH_2I_2 took place with good diastereoselectivity. The diastereomeric excess (de) of compounds **4a**−**c** was higher than 80%, as determined by 300-MHz ^1H NMR and quantitative ^{13}C NMR spectroscopy. Interestingly, when the reaction was carried out at lower temperature the de of **4b** decreased (entry 5 in Table 1).[22]

Table 1. Synthesis of Compounds 3−6

entry	R	product[a]	yield[b] (%)	de[c] (%)
1	Me	**3a**	72	81
2	iBu	**3b**	65	79
3	Bn	**3c**	70	81
4	Me	**4a**	81	82
5	iBu	**4b**	77 (48[d])	80 (61[d])
6	Bn	**4c**[e]	74	81
7	Me	**5a**	62	81
8	iBu	**5b**	60	80
9	Bn	**5c**	59	82
10	Me	**6a**	87[f]	
11	iBu	**6b**[e]	84[f]	
12	Bn	**6c**	82[f]	

[a] All reactions were carried out at room temperature. [b] Isolated yield after purification based on the starting α-amino aldehyde **1**. [c] Diastereomeric excess determined by ^1H NMR (300 MHz) and/or quantitative ^{13}C NMR analysis of the crude products. [d] Reaction temperature −50 °C. [e] ee > 99% HPLC (Chiracel OD-H; 0.8 mL/min; UV detector; **4c**, 225 nm; 50:1 hexane/2-propanol; t_R = 17.15 min; **6b**, 235 nm; 400:1 hexane/2-propanol; t_R = 6.15 min). [f] Isolated yield after purification based on the starting compound **3**.

Iodomethylation of **1** proceeds with no detectable racemization. The enantiomeric purity of the major diastereomer of compound **4c**[23] was determined by chiral HPLC analysis (Chiracel OD-H) showing an enantiomeric excess (ee) >99%; for comparison, a racemic mixture of **4c** was prepared and HPLC analysis excluded the possibility of coelution of both enantiomers.

The observed stereochemistry of **4** can be explained by assuming a nonchelation control model in the iodomethylation reaction of aldehyde **1**. This diastereofacial preference is the same as that previously reported for the addition of other organometallic compounds to dibenzylated amino aldehydes.[21]

Reaction of compounds **2** with $AgBF_4$ at room temperature afforded the corresponding azetidinium salts **5** with high diastereoselectivity, in agreement with the de of compounds **4** (Scheme 1 and Table 1, entries 7−9). Configurational assignments of products **5** were estab-

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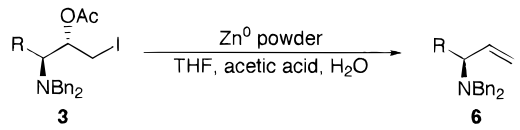
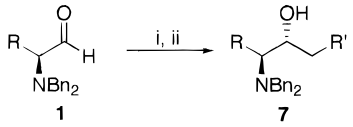
Scheme 2



a: R=Me
b: R=^{i}Bu
c: R=Bn

Scheme 3[a]



a: R, R'= Me
b: R=^{i}Bu, R'= Me
c: R=Bn, R'=Me
d: R= Me, R'=Allyl
e: R= ^{i}Bu, R'= Allyl

[a] Reagents and conditions: (i) Sm/CH_2I_2, THF, 0 °C; (ii) Me_2CuLi, 0 °C or $(CH_2{=}CHCH_2)CuCNMgBr$ or $CH_2{=}CHCH_2MgBr$, −78 °C → rt; then NH_4OH.

Table 2. Synthesis of Amino Alcohols 7a−e

entry	R	R′	product	yield[a] (%)	de[b] (%)
1	Me	Me[c]	**7a**	60	87
2	^{i}Bu	Me[c]	**7b**	58	87
3	Bn	Me[c]	**7c**	56	90
4	Me	allyl[d]	**7d**	56	76
5	Me	allyl[e]	**7d**	46	76
6	^{i}Bu	allyl[d]	**7e**	54	77

[a] Isolated yield after purification based on the starting α-amino aldehyde **1**. [b] Diastereomeric excess determined by ^{1}H NMR (300 MHz) and/or quantitative ^{13}C NMR analysis of the crude products. [c] Lithium dimethylcuprate was used. [d] Magnesium allylcyanocuprate bromide was used. [e] Allylmagnesium bromide was used.

lished by NOESY experiments in the case of compound **5a**, showing the *trans* relative configuration for methyl and hydroxyl groups.

On the other hand, allylamines **6** were obtained by the treatment of **3** with zinc powder in the presence of aqueous acetic acid[24] (Scheme 2 and Table 1, entries 10−12). Compounds **6a**−**c** were synthesized with no detectable racemization; chiral HPLC analysis of **6b** using a racemic mixture as reference indicated an ee of 99%. The formation of these amines can be explained by formation of the corresponding organozinc compounds that undergo a β-elimination process to give the carbon−carbon double bond.[25]

Finally, secondary amino alcohols were prepared in a one-pot synthesis starting from α-amino aldehydes **1**. Succesive treatment of *N*,*N*-dibenzylated α-amino aldehydes **1** with Sm/CH_2I_2 and Grignard or organocuprate reagents led to β-amino alcohols **7a**−**e** (Scheme 3 and Table 2). Diastereoisomeric excesses, between 76 and 87%, were determined using either 300 MHz ^{1}H NMR or quantitative ^{13}C NMR spectroscopy of crude products.[26] This methodology is a better strategy to prepare some amino alcohols than direct reaction of α-amino aldehydes with organolithium compounds or Grignard derivatives, for instance, to obtain **7d**,**e**.[27]

In conclusion, iodomethylation of chiral carbonyl compounds using Sm/CH_2I_2 is an easy, rapid, and mild methodology for the transformation of α-amino aldehydes into optically pure amino epoxides, 3-hydroxy azetidinium salts, allylamines, and β-amino alcohols.

Experimental Section

General Methods. Reactions requiring an inert atmosphere were conducted under dry nitrogen, and the glassware was oven dried (120 °C). THF and ether were distilled from sodium/benzophenone ketyl immediately prior to use. All reagents were purchased from Aldrich or Acros and were used without further purification. Amino aldehydes **1** were prepared according to literature procedures.[2a] Powdered zinc was washed successively with aqueous HCl, H_2O, MeOH, and ether and then dried *in vacuo*. Pyridine was stored over NaOH. Silica gel for flash chromatography was purchased from Scharlau or Merck (200−450 mesh), and compounds were visualized on analytical thin-layer chromatograms (TLC) by UV light (254 nm). ^{1}H NMR spectra were recorded at 200, 300, or 400 MHz. ^{13}C NMR spectra and DEPT experiments were determined at 50 or 75 MHz. Chemical shifts are given in ppm relative to tetramethylsilane (TMS), which is used as an internal standard, and coupling constants (*J*) are reported in Hz. The diastereomeric excesses were obtained using ^{1}H-NMR analysis of crude products or by *inverse gated decoupling* experiments using chromium acetylacetonate (1 mg) as additive (namely quantitative ^{13}C NMR). GC−MS and HRMS were measured at 70 eV or using FAB conditions. When HRMS could not be measured on the molecular ion the HRMS of a significant fragment is given. Only the most important IR absortions (in cm^{-1}) and the molecular ions and/or base peaks in MS are given. The enantiomeric purity was determined by chiral HPLC analysis using a Chiracel OD-H (0.46 × 25 cm, Diacel) column.

General Procedure for the Preparation of Protected Iodohydrins 3. Under a nitrogen atmosphere, samarium powder (300 mg, 2 mmol) was placed in a Schlenk tube at 0 °C. A solution of CH_2I_2 (0.24 mL, 3 mmol) and the corresponding amino aldehyde **1** (1 mmol) in THF (6 mL) were added dropwise with stirring over 20 min. After stirring at the same temperature for 20 min, the mixture was quenched with 1 M HCl (30 mL) and extracted with CH_2Cl_2 (4 × 10 mL). The combined organic layers were dried (Na_2SO_4), and to the resulting solution were added pyridine (10 mL), acetic anhydride (10 mL), and a catalytic amount of DMAP (5 mg). The reaction mixture was then stirred at room temperature overnight. Finally, the solution was carefully quenched with water/ice. The organic layer was separated, and the aqueous layer was extracted with ether (3 × 20 mL). The combined extracts were dried over (Na_2SO_4) and the solvents removed under reduced pressure (bath temperature 40 °C). Flash column chromatography over silica gel (hexane/triethylamine 75/1) provided *erythro*-3-amino-1-iodo-2-acetoxyalkanes **3**.

(2*S*,3*S*)-3-(*N*,*N*-Dibenzylamino)-1-iodobutan-2-yl acetate (3a): R_f = 0.4 (hexane/ethyl acetate 10/1); $[\alpha]^{22}_D$ = +4.74 (*c* 2.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.41−7.23 (10 H, m), 4.89 (1 H, ddd, *J* = 9.2, 6.7, 3.5), 3.81 and 3.43 (4 H, AB syst, *J* = 13.5), 3.68 (1 H, dd, *J* = 6.7, 3.9), 3.29 (1 H, dd, *J* = 3.9, 3.5), 2.96 (1 H, dq, *J* = 9.2, 6.7), 2.11 (3 H, s), 1.11 (3 H, d, *J* = 6.7); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.11 (C), 139.0 (C), 128.7, 128.2 and 127.0 (3 × CH), 73.2 (CH), 55.8 (CH), 54.0 (CH_2), 20.9 (CH_3), 8.3 (CH_3), 7.9 (CH_2); IR (neat) 1742; MS *m*/*z* 437.1 (M^+, <1), 250.1 (22), 224.1 (95), 210.1 (92), 181.1 (60), 91.0 (100), 65.0 (42), 43.0 (38); HRMS calcd for $C_{20}H_{24}INO_2$ 437.0852, found 437.0864.

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(27) For example, allylmagnesium bromide (Table 2, entry 5) and magnesium allylcyanocuprate bromide (Table 2, entries 4,6) are more readily available than but-3-enyl-1-magnesium bromide (direct reaction of α-amino aldehydes with organometallic compounds).

(2*S*,3*S*)-3-(*N*,*N*-Dibenzylamino)-1-iodo-5-methylhexan-2-yl acetate (3b): R_f = 0.4 (hexane/ethyl acetate 10/1); $[\alpha]^{21}_D$ = −24.2 (*c* 2.41, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.55−7.20 (10 H, m), 5.31−5.22 (1 H, m), 3.69 (4 H, AB syst, *J* = 13.5), 3.45 and 3.31 (2 × 1 H, AB portion of ABX), 3.03−2.94 (1 H, m), 2.12 (3 H, s), 1.95−1.83 and 1.75−1.62 (2 × 1 H, m), 1.38−1.17 (1 H, m), 1.04 and 0.82 (2 × 3 H, d, *J* = 6.4); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.2 (C), 139.5 (C), 128.9, 128.2 and 127.0 (3 × CH), 72.5 (CH), 57.4 (CH), 53.9 (CH_2) 35.4 (CH_2), 25.2 (CH), 23.1, 22.5 and 21.2 (3 × CH_3), 7.05 (CH_2); IR (neat) 1742; MS *m*/*z* 479.1 (M^+, <1), 266.3 (100), 210.1 (84), 91.0 (96).

(2*S*,3*S*)-3-(*N*,*N*-Dibenzylamino)-1-iodo-4-phenylbutan-2-yl acetate (3c): R_f = 0.4 (hexane/ethyl acetate 10/1); $[\alpha]^{22}_D$ = +1.54 (*c* 2.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.50−7.15 (15 H, m), 5.30−5.20 (1 H, m), 3.76 (2 H, d, *J* = 13.3), 3.59−3.53 (3 H, m), 3.34−3.27 (1 H, m), 3.20−3.13 (2 H, m), 2.77 (1 H, dd, *J* = 14.6, 6.9), 1.8 (3 H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.1 (C), 140.0, 138.8 (2 × C), 128.7, 128.2, 127.0 and 125.8 (4 × CH), 73.0 (CH), 61.2 (CH), 54.1 (CH_2), 32.1 (CH_2), 20.9 (CH_3), 7.4 (CH_2); IR (neat) 1740; MS *m*/*z* 513.1 (M^+, <1), 422.0 (30), 300.2 (63), 210.1 (10), 91.0 (100); HRMS calcd for $C_{19}H_{21}INO_2$ (M − C_7H_7) 422.0621, found 422.0617.

General Procedure for the Synthesis of Amino Epoxides 4.[21a] A solution of CH_2I_2 (0.24 mL, 3 mmol) and the corresponding amino aldehyde **1** (1 mmol) in THF (6 mL) was added dropwise over 20 min to stirred samarium powder (300 mg, 2 mmol) at 0 °C. After being stirred for 20 min, the mixture was quenched with 1 M HCl (30 mL) and extracted with CH_2Cl_2 (4 × 10 mL), and the combined organic layers were dried (Na_2SO_4). To the stirred resulting solution was added NaH (0.24 g, 10 mmol) at room temperature under nitrogen. After 30 min, the mixture was carefully quenched with H_2O (10 mL) and extracted with ether (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), and the solvents were removed *in vacuo*. Column flash chromatography over silica gel (hexane/triethylamine 75/1) provided *erythro* amino epoxides **4**.

(2*S*)-[1′(*S*)-Dibenzylamino)ethyl]oxirane (4a): R_f = 0.5 (hexane/ethyl acetate 10/1); $[\alpha]^{25}_D$ = +9.3 (*c* 0.68, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.50−7.24 (10 H, m), 3.87 and 3.65 (2 × 2H, AB syst, *J* = 14.0), 3.17−3.11 (1 H, m), 2.91−2.78 (1 H, m), 2.72 (1 H, dd, *J* = 4.8, 4.1), 2.46 (1 H, dd, *J* = 4.8, 2.9), 1.09 (3 H, d, *J* = 6.7); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 140.1 (C), 128.4, 128.1 and 126.8 (3 × CH), 54.2 (CH), 54.2 (CH_2), 53.8 (CH), 44.8 (CH_2), 8.9 (CH_3); IR (neat) 3066; MS *m*/*z* 267.2 (M^+, 2), 224.1 (8), 91.0 (100); HRMS calcd for $C_{18}H_{21}NO$ 267.1623, found 267.1629. Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.71; H, 7.90; N, 5.29.

(2*S*)-[1′(*S*)-(Dibenzylamino)-3′-methylbutyl]oxirane (4b): R_f = 0.6 (hexane/ethyl acetate 10/1); $[\alpha]^{25}_D$ = −14.1 (*c* 0.32, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.45−7.20 (10 H, m), 3.87 and 3.67 (2 × 2 H, AB syst, *J* = 13.7), 3.04−3.11 (1 H, m), 2.84 (1 H, dd, *J* = 5.1, 4.1), 2.53 (1 H, dd, *J* = 5.1, 2.9), 2.53−2.43 (1 H, m), 1.96−1.80 (1 H, m), 1.72−1.53 (1 H, m), 1.39−1.15 (1 H, m), 0.88 and 0.69 (2 × 3 H, d, *J* = 6.5); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 140.0 (C), 128.6, 128.1 and 126.8 (3 × CH), 56.4 (CH), 54.2 (CH_2), 51.9 (CH), 46.0 (CH_2), 36.9 (CH_2), 24.3 (CH), 23.3 and 22.1 (2 × CH_3); IR (neat) 3028; MS *m*/*z* 309.1 (M^+, 2), 266.1 (28), 91.0 (100); HRMS calcd for $C_{21}H_{27}NO$ 309.2093, found 309.2106. Anal. Calcd for $C_{21}H_{27}NO$: C, 81.51; H, 8.79; N, 4.53. Found: C, 81.32; H, 8.70; N, 4.59.

(2*S*)-[1′(*S*)-(Dibenzylamino)-2′-phenylethyl]oxirane (4c): R_f = 0.36 (hexane/ethyl acetate 15/1); $[\alpha]^{25}_D$ = +6.5 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.35−7.13 (15 H, m), 3.91 and 3.81 (2 × 2 H, AB system, *J* = 14.0), 3.25−3.21 (1 H, m), 3.13−3.05 (1 H, m), 2.97−2.72 (3 H, m), 2.59 (1 H, dd, *J* = 5.1, 2.8); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 139.4 (C), 129.4, 128.3, 128.1, 128.0, 126.7 and 125.9 (6 × CH), 60.1 (CH), 54.0 (CH_2), 51.9 (CH), 44.9 (CH_2), 33.7 (CH_2); IR (neat) 3051; MS *m*/*z* 343.1 (M^+, 1), 91.0 (100); HRMS calcd for $C_{24}H_{25}NO$ 343.1936, found 343.1934.

General Procedure for the Preparation of *N*,*N*-Dibenzylamino Azetidinium Salts 5. In this case, the samarium-promoted iodomethylation reaction was quenched with H_2O and then a saturated aqueous solution of $NaHCO_3$ was added. The resulting suspension was filtered through a pad of Celite and extracted with ether (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and filtered in a flask covered with aluminum foil. To the resulting solution was added $AgBF_4$ (2 mmol, 0.40 g) with vigorous stirring under nitrogen. After being stirred for 0.5 h, the mixture was quenched with H_2O (10 mL), and the solution was filtered, extracted with CH_2Cl_2 (5 × 20 mL), dried (Na_2SO_4), and concentrated. The resulting oil was washed with ether (2 × 5 mL), and azetidinium salts **4** were obtained as colored solids.

(2*S*,3*R*)-1,1-Dibenzyl-3-hydroxy-2-methylazetidinium tetrafluoroborate (5a): $[\alpha]^{20}_D$ = +16.0 (*c* 1, acetone); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.93−7.81 (2 H, m), 7.70−7.51 (8 H, m), 6.36 (1 H, d, *J* = 5.71), 4.87, 4.72, 4.61 and 4.18 (4 × 1 H, d, *J* = 13.15), 4.80−4.70 (1 H, m), 4.45 (1 H, dd, *J* = 10.8, 7.04), 4.32−4.28 (1 H, m), 3.71−3.66 (1 H, m), 1.62 (3 H, d, *J* = 7.04); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 133.1, 133.0, 130.5, 130.3, 129.4, and 129.3 (6 × CH), 128.5, 128.4 (2 × C), 76.9 (CH), 63.7 (CH), 62.1, 61.4, 59.2 (3 × CH_2), 11.5 (CH_3); IR (KBr) 3441; MS (FAB) *m*/*z* 268.3 (M^+, 100), 224.3 (12), 210.2 (22). Anal. Calcd for $C_{18}H_{22}NOBF_4$: C, 60.87; H, 6.24; N, 3.94. Found: C, 60.78; H, 6.30; N, 3.90.

(2*S*,3*R*)-1,1-Dibenzyl-3-hydroxy-2-(2-methylpropyl)azetidinium tetrafluoroborate (5b): $[\alpha]^{20}_D$ = +20.8 (*c* 1, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.72−7.41 (2 H, m), 7.40−7.21 (8 H, m), 6.43 (1 H, br s), 4.93−4.76 (3 H, m), 4.64 (1 H, d, *J* = 12.7), 4.52−4.46 (1 H, m), 4.28−4.15 (2 H, m), 3.77−3.70 (1 H + residual DMSO, m), 2.20−2.13 (1 H, m), 1.90−1.65 (2 H, m), 1.04 and 0.95 (2 × 3 H, d, *J* = 6.2); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 133.0, 132.9, 130.6, 130.2, 129.3 and 129.2 (6 × CH), 128.5 (C), 78.7 (CH), 63.6 (CH), 62.4, 61.6, 59.5 (3 × CH_2), 34.4 (CH_2), 24.2 (CH), 23.3 and 21.6 (2 × CH_3); IR (KBr) 3528; MS (FAB) *m*/*z* 310.3 (M^+, 100), 220.2 (10), 133.0 (15). Anal. Calcd for $C_{21}H_{28}NOBF_4$: C, 63.49; H, 7.10; N, 3.53. Found: C, 63.38; H, 7.16; N, 3.57.

(2*S*,3*R*)-1,1,2-Tribenzyl-3-hydroxyazetidinium tetrafluoroborate (5c): $[\alpha]^{20}_D$ = +10.8 (*c* 1, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.02−7.81 (2 H, m), 7.73−7.55 (8 H, m), 7.51−7.32 (5 H, m), 6.20 (1 H, d, *J* = 6.6), 5.13−5.09 (2 H, m), 4.87−4.82 (2 H, m), 4.53 (1 H, dd, *J* = 10.5, 7.0), 4.43−4.22 (2 H, m), 3.78−3.52 (2 H + residual DMSO, m), 3.43−3.40 (1 H, m); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 134.5 (C), 133.2, 133.1, 130.6, 130.3, 129.5, 129.4, 129.3 and 128.9 (8 × CH), 128.4 (C), 127.2 (CH), 79.5 (CH), 63.5 (CH), 62.4, 61.7, 60.0 (3 × CH_2), 32.1 (CH_2); IR (KBr) 3520; MS (FAB) *m*/*z* 344.3 (M^+, 100), 254.3 (26), 241.2 (75), 210.2 (15). Anal. Calcd for $C_{24}H_{26}NOBF_4$: C, 66.84; H, 6.08; N, 3.25. Found: C, 66.69; H, 6.11; N, 3.28.

General Procedure for the Synthesis of Allylamines 6. To a stirred solution of **5** (1 mmol) in a mixture of THF (10 mL), acetic acid (2 mL), and H_2O (2 mL) was added powdered zinc at room temperature and the resulting solution stirred overnight. The solution was decanted and extracted with ether (3 × 20 mL). The organic layer was washed with a saturated aqueous solution of Na_2CO_3, (2 × 10 mL), dried over Na_2SO_4, and concentrated, yielding crude allylamines **6**, which were purified by column flash chromatography using hexane/ethyl acetate (gradient of elution).

(2*S*)-*N*,*N*-Dibenzylbut-3-en-2-amine (6a): R_f = 0.4 (hexane); $[\alpha]^{25}_D$ = −11.6 (*c* 8.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.5−7.2 (10 H, m), 6.0 (1 H, ddd, *J* = 17.5, 10.5, 6.4), 5.2 (1 H, d, *J* = 10.5), 5.1 (1 H, d, *J* = 17.5), 3.71 and 3.59 (4 H, AB syst, *J* = 14.0), 3.32 (1 H, m), 1.22 (3 H, d, *J* = 6.7); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.7 (CH), 140.5 (C), 128.4, 128.1 and 126.6 (3 × CH), 115.6 (CH), 54.9 (CH), 53.4 (CH_2), 14.6 (CH_3); IR (neat) 1603; MS *m*/*z* 251.1 (M^+, 9), 236.1 (96), 224.1 (7), 91.0 (100); HRMS calcd for $C_{18}H_{21}N$ 251.1674, found 251.1664.

(3*S*)-*N*,*N*-Dibenzyl-5-methylhex-1-en-3-amine (6b): R_f = 0.5 (hexane); $[\alpha]^{25}_D$ = −3.0 (*c* 8.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.5−7.2 (10 H, m), 5.8 (1 H, ddd, *J* = 17.2, 10.2, 8.6), 5.3 (1 H, dd, *J* = 10.2, 1.6), 5.1 (1 H, dd, *J* = 17.2, 1.6), 3.81 and 3.39 (2 × 2 H, AB syst, *J* = 13.7), 3.11 (1 H, m), 1.82−1.52 (2 H, m), 1.39−1.25 (1 H, m), 0.82 and 0.69 (2 × 3 H, d, *J* = 6.5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.5 (C), 136.7 (CH), 128.7, 128.0 and 126.6 (3 × CH), 117.3 (CH), 58.4 (CH), 53.5 (CH_2), 41.3 (CH_2), 24.3 (CH), 22.9 and 22.4 (2 × CH_3); IR (neat) 1603; MS *m*/*z* 293.2 (M^+, 1), 237.1 (38), 236.1 (100), 181.1 (7), 91.0 (99), 65.0 (13); HRMS calcd for $C_{21}H_{27}N$ 293.2144, found

293.2142. Anal. Calcd for $C_{21}H_{27}N$: C, 85.95; H, 9.27; N, 4.77. Found: C, 85.98; H, 9.22; N, 4.80.

(2*S*)-*N*,*N*-Dibenzyl-1-phenylbut-3-en-2-amine (6c): R_f = 0.7 (hexane/ethyl acetate 25:1); $[\alpha]^{19}_D = +10.0$ (*c* 0.58, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2−7.1 (15 H, m), 5.9 (1 H, ddd, *J* = 17.2, 10.3, 8.2), 5.2 (1 H, d, *J* = 10.3), 5.02 (1 H, d, *J* = 17.2), 3.85 and 3.42 (2 × 2 H, AB syst, *J* = 14.0), 3.37 (1 H, m), 3.02 and 2.81 (2 × 1 H, dd, *J* = 13.8, 7.3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.7 (CH), 140.0 (C), 129.5, 128.4, 128.0, 127.9, 126.6 and 125.8 (6 × CH), 117.9 (CH), 62.0 (CH), 53.4 (CH_2), 38.1 (CH_2); IR (neat) 1603; MS *m*/*z* 237.1 (20), 236.1 (100), 91.0 (92), 65.0 (7); HRMS calcd for $C_{17}H_{18}N$ (M − C_7H_7) 236.1439, found 236.1440. Anal. Calcd for $C_{24}H_{25}N$: C, 88.03; H, 7.69; N, 4.28. Found: C, 87.89; H, 7.76; N, 4.30.

General Procedure for the Synthesis of Amino Alcohols 7a−c.[26] The procedure described for the preparation of **2** was employed, but instead of H_2O, lithium dimethylcuprate[28] was added at the same temperature. After being stirred for 3 h, the reaction was quenched with a saturated aqueous solution of NH_4Cl (20 mL), the stirring was maintained for 2 h, and then 1 M HCl (20 mL) was added. The mixture was filtered through a pad of Celite, extracted with CH_2Cl_2 (3 × 20 mL), dried over Na_2SO_4, and concentrated to give crude amino alcohols **7a**−**c**. Column flash chromatography over silica gel (10:1 hexane−ethyl acetate) provided the pure amino alcohols **7**.

(2*S*,3*R*)-2-(*N*,*N*-Dibenzylamino)pentan-3-ol (7a): R_f = 0.2 (hexane/ethyl acetate 10/1); $[\alpha]^{18}_D = +44.5$ (*c* 2.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.51−7.23 (10 H, m), 3.79 and 3.50 (4 H, AB syst, *J* = 13.4), 3.52 (1 H, m), 2.75 (1 H, m), 1.93−1.69 (2 H, m), 1.42−1.23 (1 H, m), 1.11 (3 H, d, *J* = 6.9), 0.89 (3 H, d, *J* = 7.3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.0 (C), 128.7, 128.2 and 126.8 (3 × CH), 75.1 (CH), 57.0 (CH), 54.7 (CH_2), 27.1 (CH_2), 10.3 (CH_3), 8.6 (CH_3); IR (neat) 3320; MS *m*/*z* 266.2 (40), 224.1 (98), 181.1 (65), 132.0 (32), 91.0 (100), 65.0 (42); HRMS calcd for $C_{19}H_{24}N$ (M^+ − OH) 266.1897, found 266.1909.

(3*R*,4*S*)-4-(*N*,*N*-Dibenzylamino)-6-methylheptan-3-ol (7b): R_f = 0.2 (hexane/ethyl acetate 10/1); $[\alpha]^{32}_D = +13.8$ (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45−7.22 (10 H, m), 3.68 (5 H, m), 2.74 (1 H, td, *J* = 6.9, 3.9), 1.84−1.73 (1 H, m), 1.66−1.19 (4 H, m), 0.98−0.92 (6 H, m), 0.74 (3 H, d, *J* = 6.4); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.1 (C), 128.9, 128.2 and 126.9 (3 × CH), 72.1 (CH), 58.1 (CH), 55.0 (CH_2), 34.3 (CH_2), 27.5 (CH_2), 24.6 (CH), 23.1, 22.6 and 11.0 (3 × CH_3); IR (neat) 3433; MS *m*/*z* 266.2 (40), 210.1 (12), 181.1 (15), 91.0 (98). Anal. Calcd for $C_{22}H_{31}NO$: C, 81.18; H, 9.60; N, 4.30. Found: C, 81.03; H, 9.68; N, 4.22.

(2*S*,3*R*)-2-(*N*,*N*-Dibenzylamino)-1-phenylpentan-3-ol (7c): R_f = 0.2 (hexane/ethyl acetate 10/1); $[\alpha]^{20}_D = +23.2$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.45−7.12 (15 H, m), 3.65−3.62 (5 H, m), 3.13−3.05 (2 H, m), 2.96−2.85 (1 H, m), 1.82−1.69 (1 H, m), 1.59−1.39 (1 H, m), 1.00 (3 H, t, *J* = 7.3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.4 (C), 139.4 (C), 129.1, 128.4, 127.9, 126.6 and 126.5 (5 × CH), 72.6 (CH), 62.6 (CH), 54.5 (CH_2), 31.6 (CH_2), 27.4 (CH_2), 10.6 (CH_3); IR (neat) 3420; MS *m*/*z* 300.2 (88), 268.1 (32), 181.1 (28), 91.0 (100). 65.0 (19); HRMS calcd for $C_{18}H_{22}NO$ (M − C_7H_7) 268.1701, found 268.1698. Anal. Calcd for $C_{25}H_{29}NO$: C, 83.52; H, 8.13; N, 3.90 Found: C, 83.49; H, 8.11; N, 3.93.

General Procedure for the Synthesis of Homoallylic Amino Alcohols 7d,e. The procedure described for the preparation of **2** was employed, but instead of H_2O, magnesium allylcyanocuprate[29] was added via cannula at −78 °C. The mixture was allowed to warm to room temperature overnight and was quenched with a saturated aqueous solution of NH_4-OH (30 mL). After being stirred for 2 h, the mixture was filtered through a pad of Celite and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried over Na_2SO_4 and concentrated to give crude amino homoallyl alcohols **7d**,**e**, which were purified by column chromatography using hexane/ethyl acetate (10:1).

(2*S*,3*R*)-4-(*N*,*N*-Dibenzylamino)hept-6-en-3-ol (7d): R_f = 0.3 (hexane/ethyl acetate/triethylamine 10/1/1); $[\alpha]^{19}_D = +18.9$ (*c* 2.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.50−7.35 (10 H, m), 5.96−5.82 (1 H, m), 5.12−5.01 (2 H, m), 3.83 and 3.51 (4 H, AB syst, *J* = 13.75), 3.69−3.62 (1 H, m), 2.82−2.73 (1 H, m), 2.28−1.32 (3 H, m), 1.18 (3 H, d, *J* = 6.4); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.8 (C), 138.6 (CH), 128.6, 128.1 and 126.7 (3 × CH), 114.5 (CH_2), 72.8 (CH), 57.0 (CH), 54.7 (CH_2), 33.2 and 30.0 (2 × CH_2), 8.4 (CH_3); IR (neat) 3420, 1639, 1603; MS *m*/*z* 224.1 (71), 181.0 (11), 178.0 (19), 91.0 (100).

(4*S*,5*R*)-4-(*N*,*N*-Dibenzylamino)-2-methylnon-8-en-5-ol (7e): R_f = 0.3 (hexane/ethyl acetate); $[\alpha]^{20}_D = +8.34$ (*c* 2.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.51−7.19 (10 H, m), 5.93−5.80 (1 H, m), 5.11−5.00 (2 H, m), 3.92−3.70 (5 H, m), 2.81−2.74 (1 H, m), 2.38−2.24 (1 H, m), 2.17−2.14 (1 H, m), 1.86−1.72 (1 H, m), 1.68−1.42 (2 H, m), 1.33−1.22 (2 H, m), 0.95 and 0.80 (2 × 3 H, d, *J* = 6.9); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.0 (C), 138.4 (CH), 128.8, 128.2 and 126.9 (3 × CH), 114.8 (CH_2), 69.8 (CH), 58.3 (CH), 55.0 (CH_2), 34.3, 33.5 and 30.7 (3 × CH_2), 24.6 (CH), 22.9 and 22.8 (2 × CH_3); IR (neat) 3433, 1639, 1602; MS *m*/*z* 267.2 (66), 266.2 (100), 210.1 (20), 181.1 (18), 91.0 (93); HRMS calcd for $C_{20}H_{24}NO$ (M − C_4H_9) 294.1858, found 294.1858. Anal. Calcd for $C_{24}H_{33}NO$: C, 82.00; H, 9.46; N, 3.98. Found: C, 81.84; H, 9.57; N, 4.01.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectral data of **3**−**7** (34 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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