N,2-Dilithioalkylamines from Aziridines by Naphthalene-Catalyzed Reductive Opening. Synthetic Applications†

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The reductive opening of aziridines **1a–c** with lithium in the presence of a catalytic amount of naphthalene at −78 °C led to the corresponding dianionic intermediates **2a–c**, which are stable species under these reaction conditions and react with electrophilic reagents [H_2O, D_2O, Me_2S_2, Bu^{t}CHO, PhCHO, Me_2CO, $(CH_2)_5CO$, $(EtO)_2CO$, $CH_2{=}CHCO_2Me$, $PhCON(CH_2)_4$, PhCH=NPh, MeI, and $CH_2{=}CHCH_2Br$] to give, after hydrolysis with water, the corresponding difunctionalized compounds **3–5**. When the reductive opening and the reaction with electrophiles [H_2O, D_2O, $CH_2{=}CHCH_2Br$, Me_2CO, $(c\text{-}C_3H_5)_2CO$] were carried out on chiral aziridines **8** and **9**, enantiomerically pure difunctionalized compounds **12** were obtained with the same stereochemistry, independently of the stereochemistry of diastereomeric starting aziridines **8** and **9**.

Introduction

Functionalized organolithium compounds[1] are interesting intermediates in preparative organic chemistry because their reactions with electrophilic reagents lead directly to polyfunctionalized molecules. The stability of these organolithium reagents depends strongly on three factors: (a) the hybridization of the carbon atom that bears the lithium atom; (b) the compatibility of the functionality and the carbon–lithium bond, and (c) the relative positions of the functional group and the carbanionic center. Considering the corresponding less stable sp^3-hybridized intermediates (in comparison to the corresponding sp^2 or sp ones) and the second factor, species of the type **I** with X = Hal, OR, NR_2, which should be considered d^n-reagents,[2] are generally stable and have been used in organic synthesis.[3] Because of the relative positions of the lithium atom and the heteroatom X, intermediates of type **I** with $n = 0$, the so-called carbenoids, are unstable species, which decompose by an α-elimination process giving carbenes.[4] Even more unstable are the corresponding d^2-reagents[2] of type **I** with $n = 1$, which at very low temperatures undergo β-elimination yielding olefins.[5] In the last decade we have studied the preparation and synthetic applications of species of type **II** with Y = O, RN and $n = 1$, in which the existence of a negative charge on the heteroatom inhibits the β-elimination process at low temperatures.[1] The preparation of primary d^2-reagents of type **III** was carried out by (a) mercury–lithium transmetalation of β-aminated organomercurials **IV** with lithium powder[6,7] or (b) chloro–lithium exchange from the corresponding β-chloro amides **V** with lithium naphthalenide.[8] In both cases, the reactions were carried out at −78 °C after the starting material had been *N*-deprotonated with an alkyllithium reagent (Scheme 1). This second procedure could not be applied to β-chloro amines **VI** because, after the necessary first *N*-deprotonation, an intramolecular S_N-type reaction took place yielding aziridines **VII**, even at very low temperatures (−78 °C). *Aziridines **VII** do not undergo reductive opening by lithioarenes at low temperature* under the reaction conditions necessary to prevent decomposition of intermediate **III**.[9] These aziridines contrast with oxiranes, which undergo the reductive opening with a lithio arene at low temperature, which allows the preparation of intermediates of type **II** when Y = O and $n = 1$.[10]

I **II**

Recently we have discovered[11] that the use of an arene, usually naphthalene, as a catalyst in the lithiation process with lithium powder represents a very powerful procedure for lithiating not only a carbon–chlorine bond[12] but also other types of substrates[13] such as tetrahydrofuran,[13a] sulfonates,[13b] sulfates,[13c] phenones,[13d] phenone imines,[13e] and dioxolanes.[13f]

The application of this methodology[11–13] permits the preparation under very mild reaction conditions of very

† Dedicated to Professor E. J. Corey on his 65th birthday.

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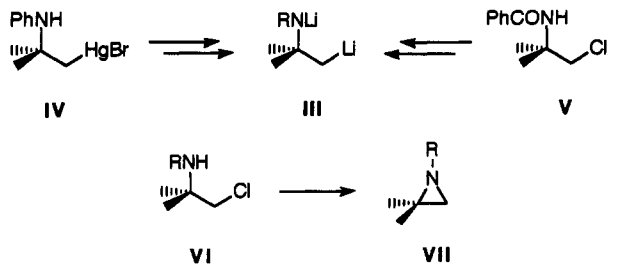
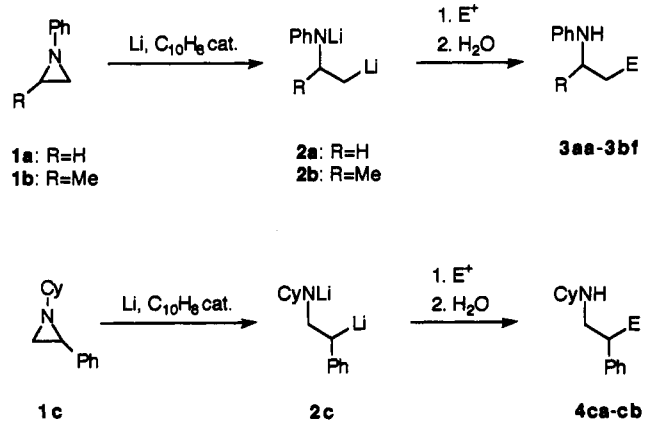
Scheme 1



Scheme 2[a]



[a] Key: Cy = cyclohexyl.

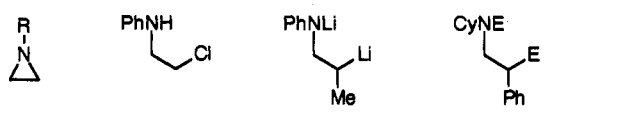
reactive intermediates that are difficult to access by other synthetic approaches. In this paper we report for the first time the low temperature naphthalene-catalyzed reductive opening of aziridines with lithium powder, this method being a new route to β-amide organolithium compounds of type **III**. We also explore the application of these intermediates to preparative organic chemistry.[14]

Results and Discussion

The reaction of *N*-phenylaziridine (**1a**) with an excess of lithium powder (1:5 molar ratio) and a catalytic amount of naphthalene (1:0.05 molar ratio, 5 mol %) in THF at −78 °C gave a solution of dianionic intermediate **2a**, which upon treatment with electrophiles at temperatures ranging between −78 and 20 °C afforded, after hydrolysis, the corresponding functionalized anilines **3aa–3ak** (Scheme 2 and Table 1, entries 1–11). An alternative to this procedure uses *N*-(2-chloroethyl)aniline **1'a** as a starting material; in this case it is necessary to carry out the *N*-deprotonation with butyllithium at −78 °C prior to the lithiation step. When this reaction was followed by GLC, after 10 min the transformation **1'a** → **1a** was quantitative (see Scheme 1), so the *real lithiation* takes place on aziridine **1a** (Table 1, entries 3, 5–7, and 10). From products **3aa–3ak** obtained through intermediate **2a**, we find especially interesting 1,3-amino alcohols **3ad–3ag**, 1,3-diamine **3ak**, as well as amino esters **3ah** and **3ai**; the last compound was obtained by a Michael-type addition of intermediate **2a** to methyl acrylate (Table 1, entry 9). The reaction with benzylideneaniline was carried out under Barbier-type conditions (in the presence of the imine during the lithiation step) at room temperature with 4,4'-di-*tert*-butylbiphenyl as a catalyst; the success of the reaction under these conditions means that intermediate **2a** is a stable species under these reaction conditions and undergoes a rapid reaction with the imine before decomposition, in at least a 50% isolated yield (Table 1, entry 11).

A behavior similar to that of **1a** was observed for methylaziridine **1b**; in this case the opening of the ring under the same reaction conditions yielded more-stable primary carbanionic intermediate **2b**, which as above reacted with electrophiles to give expected products **3ba–3bf** (Scheme 2 and Table 1, entries 12–17). Only when we used H_2O or D_2O as an electrophile did we isolate *ca.* 15% of *N*-propylamine, from the unexpected reductive opening of the aziridine ring to give less-stable secondary carbanion **2'b**. Since the same result was observed both for hydrolysis and deuterolysis, we think that intermediate **2'b** is very unstable and, once formed, abstracts a proton from the reaction media yielding a lithium/hydrogen exchange before the final hydrolysis with H_2O or D_2O (Table 1, entries 12 and 13).

A different result was obtained when the substituent at the aziridine ring was a phenyl group. Then, the lithiation of aziridine **1c** under the above-described reaction conditions yielded exclusively benzylic intermediate **2c**, which upon treatment with H_2O or D_2O afforded expected product **4ca** or **4cb**, respectively (Scheme 2 and Table 1, entries 18 and 19). We tried, in this case, the alkylation of intermediates **2c** with methyl iodide and allyl bromide; in both cases we had to work with an excess of the alkylating agent (1:2.2 molar ratio) in order to get a clean reaction yielding compounds **5ca** and **5cb**, respectively, which resulted from a double *C*- and *N*-alkylation (Table 1, entries 20 and 21).



1d: R=Cy
1e: R=PhCH$_2$
1f: R=PhCO

1'a **2'b**

5ca: E=Me
5cb: E=CH$_2$=CHCH$_2$

The naphthalene-catalyzed reductive opening of aziridines failed when no phenyl group was present in the heterocyclic ring, either on the nitrogen or the carbon atom. Thus the process did not work when applied to aziridines **1d–f**. *N*-Cyclohexylaziridine **1d** did not react even at room temperature; the starting material was the only compound isolated. Under the standard reaction conditions, benzylic derivative **1e** suffered benzylic cleavage yielding toluene and aziridine after hydrolysis. In the case of benzoylaziridine (**1f**) we observed destruction of the starting material but the expected reaction products were not found.

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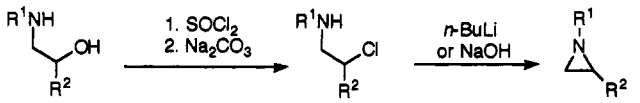
Table 1. Preparation of Functionalized Amines 3–5

entry	starting material	intermediate dianion	electrophile E^+	product[a] no.	product[a] E	yield (%)[b]
1	**1a**	**2a**	H_2O	**3aa**	H	93
2	**1a**	**2a**	D_2O	**3ab**	D	89[c]
3	**1'a**	**2a**	Me_2S_2	**3ac**	MeS	75
4	**1a**	**2a**	Bu^tCHO	**3ad**	Bu^tCHOH	71
5	**1'a**	**2a**	PhCHO	**3ae**	PhCHOH	68
6	**1'a**	**2a**	Me_2CO	**3af**	Me_2COH	79
7	**1'a**	**2a**	$(CH_2)_5CO$	**3ag**	$(CH_2)_5COH$	66
8	**1a**	**2a**	$(EtO)_2CO$	**3ah**	CO_2Et	75
9	**1a**	**2a**	$CH_2{=}CHCO_2Me$	**3ai**	$(CH_2)_2CO_2Me$	71
10	**1'a**	**2a**	$PhCON(CH_2)_4$	**3aj**	PhCO	79
11[d]	**1a**	**2a**	PhCH=NPh	**3ak**	PhCHNHPh	50
12	**1b**	**2b**	H_2O	**3ba**	H	68[e]
13	**1b**	**2b**	D_2O	**3bb**	D	69[c,e]
14	**1b**	**2b**	Me_2S_2	**3bc**	MeS	73
15	**1b**	**2b**	Bu^tCHO	**3bd**	Bu^tCHOH	65
16	**1b**	**2b**	Me_2CO	**3be**	Me_2COH	60
17	**1b**	**2b**	$(EtO)_2CO$	**3bf**	CO_2Et	68
18	**1c**	**2c**	H_2O	**4ca**	H	95
19	**1c**	**2c**	D_2O	**4cb**	D	93[c]
20	**1c**	**2c**	MeI	**5ca**	Me	75
21	**1c**	**2c**	$CH_2{=}CHCH_2Br$	**5cb**	$CH_2{=}CHCH_2$	71

[a] All isolated products **3–5** were >95% pure by GLC and 300-MHz ^1H NMR. [b] Isolated yield after flash chromatography (silica gel, hexane/ethyl acetate) based on the starting aziridine **1**. [c] >90% Deuterium incorporation from mass spectrum. [d] The reaction was carried out at 20 °C under Barbier-type conditions and using 4,4'-di-*tert*-butylbiphenyl as catalyst (see text). [e] A 15% isolated yield of *N*-propylaniline was obtained (see text).

Scheme 3[a]

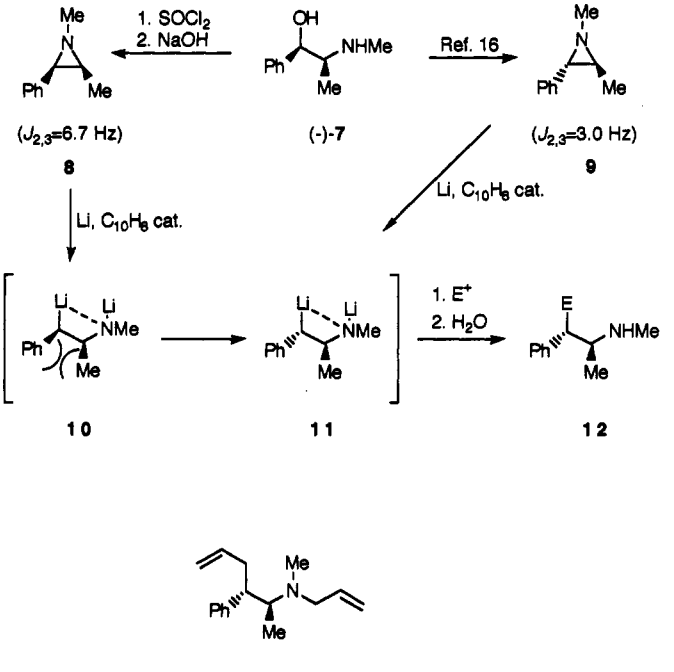


6a: R^1=Ph, R^2=H
6b: R^1=Ph, R^2=Me
6c: R^1=Cy, R^2=Ph

1'a-c **1a-c**

[a] Key: Cy = cyclohexyl.

Scheme 4



12'c

Starting aziridines **1a–c** were prepared by treatment of the corresponding amino alcohols **6a–c** with thionyl chloride[15] to give chloro amines **1'a–c**, which were cyclized under basic reaction conditions (Scheme 3).

In the final part of this study we considered using chiral aziridines as starting materials for the preparation of enantiomerically or diastereomerically pure compounds. Starting from commercially available (−)-ephedrine [(−)-**7**], we prepared chiral aziridines **8** and **9** by the procedure used for compound **1c** and an intramolecular Mitsunobu-type process,[16] respectively. Surprisingly, when we submitted both of these enantiomerically pure starting materials **8** and **9** to the naphthalene-catalyzed lithiation and the reaction with electrophiles, as described above for racemic compounds **3** or **4** (Scheme 2) *only one product of type 12 was isolated, and it was the same in both cases* (Scheme 4 and Table 2). An excess of allyl bromide (1:2.2 molar ratio) was used in order to get the product of both *N*- and *C*-allylation (**12'c**). As was the case for compound **1c** (see *supra*), a stoichiometric amount of allyl bromide (1:1 molar ratio) yielded a mixture of *C*-allylated and *C*/*N*-diallylated products.

The stereochemistry of products **12d,e** was determined by considering the coupling constants in 1,3-amino alcohols **12d** ($J_{3,4}$ = 11.3 Hz) and **12e** ($J_{2,3}$ = 11.3 Hz) and was confirmed by the transformation of compound **12d** into cyclic tetrahydro-1,3-oxazine **13** ($J_{4,5}$ = 11.2 Hz) by treatment with formaldehyde[17] (88% yield; Scheme 5). By correlation, we assumed that the same stereochemistry is present in compounds **11b** and **11c**.

As a possible explanation for the results indicated in Scheme 4, we believe that in the case of *cis*-aziridine **8**, the first dianionic species **10**[6] undergoes inversion at the carbanionic benzylic center[18] giving less-hindered intermediate **11**, the same one that results from the direct

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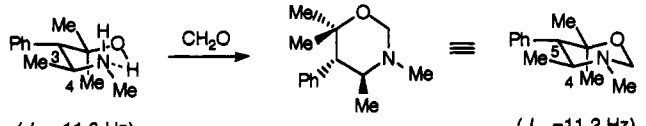
Table 2. Preparation of Enantiomerically Pure Compounds 12

entry	starting aziridine	electrophile E^+	product[a] no.	product[a] E	yield (%)[b]
1	8	H_2O	12a	H	85
2	9	H_2O	12a	H	84
3	8	D_2O	12b	D	85
4	9	D_2O	12b	D	87
5	8	CH_2=$CHCH_2Br$[c]	12'c	-	74
6	9	CH_2=$CHCH_2Br$[c]	12'c	-	71
7	8	Me_2CO	12d	Me_2COH	62
8	9	Me_2CO	12d	Me_2COH	61
9	8	$(c\text{-}C_3H_5)_2CO$	12e	$(c\text{-}C_3H_5)_2COH$	52
10	9	$(c\text{-}C_3H_5)_2CO$	12e	$(c\text{-}C_3H_5)_2COH$	52

[a] All isolated products 12 were >95% pure by GLC and 300-MHz ^1H NMR. [b] Isolated yield after flash chromatography (silica gel, hexane/ethyl acetate) and recrystallization (dichloromethane/pentane). [c] An excess of the electrophile (1:2.2) was used.

Scheme 5



($J_{3,4}$=11.3 Hz) 12d 13 ($J_{4,5}$=11.2 Hz)

opening of the other *trans*-aziridine **9**. In the reaction of dianion **11** with the electrophiles, retention of configuration is observed, this behavior being the normal one in S_E-type reactions.[19]

Conclusions

From the results described in this paper we conclude that phenyl (*N*- or *C*-) substituted aziridines **1** are suitable precursors for the preparation of highly reactive β-amido organolithium reagents **2** (d^2-reagents), which by reaction with electrophiles afford difunctionalized molecules **3–5**. The methodology used, naphthalene-catalyzed lithiation of aziridines at low temperatures, was also applied to the reductive opening of chiral aziridines **8** and **9**. The reaction is stereoselective, giving only one enantiomerically pure compound, independent of the configuration of the benzylic carbon atom in the starting aziridine.

Experimental Section

General Methods. Melting points are uncorrected. IR spectra were recorded using NaCl plates for neat liquids or KBr pellets for solid samples. Only the strongest and structurally most important peaks (IR, cm^{-1}) are listed. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, using $CDCl_3$ as solvent and TMS (0.00 ppm, ^1H) and $CDCl_3$ (77.00 ppm, ^{13}C) as internal standards; chemical shifts are given in δ (ppm) and coupling constants (*J*) are measured in hertz. The purity of volatile distilled products and the chromatographic analysis (GLC) were determined with a flame ionization detector and a 12-m HP-1 capillary column (0.2 mm diam, 0.33 mm film thickness) with nitrogen (2 mL/min) as the carrier gas, $T_{injector}$ = 270 °C, T_{column} = 60 °C (3 min), and 60–270 °C (15 °C/min). TLC was carried out on Schleicher & Schuell F1500/LS 254 plates coated with a 0.2-mm layer of silica gel. A mixture of hexane/ethyl acetate was used as eluant; R_f values are given under these conditions. Microanalyses were performed by the Microanalyses Service of the University of Alicante. All reagents were commercially available (Aldrich) and of the best grade. Reaction solvents were dried and distilled under nitrogen using standard procedures. Merck silica gel 60 (70–270 mesh) was employed for flash chromatography. Preparation, yields, and physical, analytical, and spectroscopic data of 1-anilino-2-propanol (**6b**),[20] 2-(cyclohexylamino)-1-phenylethanol (**6c**), *N*-(2-chloroethyl)aniline (**1'a**),[21] and *N*-(2-chloropropyl)aniline (**1'b**), as well as starting aziridines *N*-phenylaziridine (**1a**),[22] *N*-phenyl-2-methylaziridine (**1b**), *N*-cyclohexyl-2-phenylaziridine (**1c**),[16] (2*S*,3*R*)-1,2-dimethyl-3-phenylaziridine (**8**),[23] and (2*S*,3*S*)-1,2-dimethyl-3-phenylaziridine (**9**)[16] are included as supplementary material.

General Procedure for the Reductive Opening of Aziridines and Reaction of the Corresponding Dianions with Electrophiles. To a cooled (−78 °C) green suspension of lithium powder (0.125 g, 18.0 mmol) and naphthalene (0.023 g, 0.18 mmol) in THF (10 mL) was added the corresponding aziridine (1.8 mmol) under argon, and the mixture was stirred for 6 h at the same temperature. The corresponding electrophile (2.0 mmol; 0.5 mL in the case of H_2O and D_2O) was added, and the temperature was allowed to rise to 20 °C over a period of *ca.* 3 h. The resulting mixture was hydrolyzed with water, acidified with 3 M HCl, and extracted with CH_2Cl_2. The aqueous layer was then basified with 2.5 M NaOH and extracted with CH_2Cl_2. The organic layer was dried over anhyd Na_2SO_4 and evaporated (15 mmHg). The resulting residue was purified by column chromatography (silica gel; hexane/ethyl acetate) and/or recrystallized to yield pure products **3–5** and **12**.

When the starting material was 2-chloro amine **1'a** (see Table 1, entries 3, 5–7, and 10), a 1.6 M hexane solution of *n*-BuLi (2.0 mmol) was added to a cooled (−78 °C) solution of **1'a** (0.21 g, 1.8 mmol) under argon. The reaction mixture was stirred at this temperature for 30 min and then transferred *via cannula* to a cooled (−78 °C) green suspension of lithium powder as previous described. The reaction was continued as described above for compounds **3**, **4**, **5**, or **12**.

***N*-Ethylaniline (3aa)**:[24] characterized by comparison with the commercially available product (Aldrich).

***N*-(2-Deuterioethyl)aniline (3ab)**:[25] R_f = 0.30 (hexane/ethyl acetate, 20:1); IR (film) 3390 cm^{-1}; ^1H NMR δ 1.17–1.25 (2H, m), 3.11 (2H, t, *J* = 7.1), 3.61 (1H, s), 6.59 (2H, d, *J* = 7.8), 6.69 (1H, t, *J* = 7.3), 7.15 (2H, m); ^{13}C NMR δ 14.4 (t, J_{CD} = 19.4), 38.4, 112.8, 117.3, 129.1, 148.2; MS 123 (M^+ + 1, 3%), 122 (M^+, 22), 121 (10), 106 (100), 77 (18).

***N*-[2-(Methylthio)ethyl]aniline (3ac)**:[6d] R_f = 0.42 (hexane/ethyl acetate, 10:1); IR (film) 3460 cm^{-1}; ^1H NMR δ 2.07 (3H, s), 2.71 (2H, t, *J* = 6.4), 3.29 (2H, t, *J* = 6.4), 4.02 (1H, s), 6.61 (2H, d, *J* = 7.8), 6.70 (1H, t, *J* = 7.3), 7.16 (2H, m); ^{13}C NMR δ 14.8, 33.4, 41.7, 112.9, 117.5, 129.1, 147.6; MS 169 (M^+ + 2, 1%), 168 (M^+ + 1, 2), 167 (M^+, 11), 106 (100), 77 (12).

1-Anilino-4,4-dimethyl-3-pentanol (3ad):[26] mp 70–71 °C (pentane/CH_2Cl_2) [lit. mp 74 °C (petroleum ether)]; IR (KBr) 3660–3120 cm^{-1}; ^1H NMR δ 0.92 (9H, s), 1.52–1.68 (3H, m), 1.85 (1H, ddd, *J* = 20.3, 6.3, 1.8), 3.31 (2H, t, *J* = 6.3), 3.41 (1H, dd, *J* = 10.5, 1.8), 6.65 (2H, dd, *J* = 8.6, 1.0), 6.71 (1H, td, *J* = 7.3, 1.0), 7.18 (2H, dd, *J* = 8.6, 7.3); ^{13}C NMR δ 25.5, 30.6, 34.8, 42.9, 79.2, 113.2, 117.5, 129.1, 148.3; MS 208 (M^+ + 1, 1%), 207 (M^+, 10), 106 (100), 93 (10), 77 (12).

3-Anilino-1-phenyl-1-propanol (3ae): mp 62–63 °C (pentane/CH_2Cl_2); IR (KBr) 3500–3100 cm^{-1}; ^1H NMR δ 2.01–2.09 (2H, m), 3.20 (2H, s), 3.27 (2H, t, *J* = 6.4), 4.88 (1H, dd, *J* = 7.4, 5.2), 6.61 (2H, dd, *J* = 8.6, 1.0), 6.72 (1H, td, *J* = 7.3, 1.0), 7.17 (2H, dd, *J* = 8.6, 7.3), 7.27–7.36 (5H, m); ^{13}C NMR δ 38.1, 41.5, 73.4, 113.2, 117.7, 125.6, 127.5, 128.5, 129.1, 144.3, 148.2; MS 228

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($M^+ + 1$, 4%), 227 (M^+, 17), 133 (11), 107 (22), 106 (100), 105 (36), 104 (17), 93 (20), 79 (35), 77 (71), 65 (25), 51 (28). Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.27; H, 7.53; N, 6.11.

4-Anilino-2-methyl-2-butanol (3af): mp 58–59 °C (pentane/CH_2Cl_2); IR (KBr) 3500–3100 cm^{-1}; ^1H NMR δ 1.26 (6H, s), 1.77 (2H, t, J = 6.8), 3.25 (2H, t, J = 6.8), 3.30 (2H, s), 6.63 (2H, d, J = 8.0), 6.71 (1H, t, J = 7.3), 7.17 (2H, m); ^{13}C NMR δ 29.5, 40.4, 41.7, 70.8, 113.2, 117.6, 129.1, 148.3; MS 179 (M^+, 10%), 106 (100), 77 (19), 51 (10), 43 (13). Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.40; H, 9.62; N, 7.74.

1-(2-Anilinoethyl)cyclohexanol (3ag): mp 128 °C (pentane/CH_2Cl_2); IR (Nujol) 3400–3100 cm^{-1}; ^1H NMR δ 1.47–1.63 (10H, m), 1.79 (2H, t, J = 6.8), 2.55 (2H, s), 3.28 (2H, t, J = 6.8), 6.64 (2H, dd, J = 8.5, 0.9), 6.71 (1H, td, J = 7.3, 0.9), 7.18 (2H, dd, J = 8.5, 7.3); ^{13}C NMR δ 22.2, 25.8, 37.8, 39.5, 40.4, 71.7, 113.2, 117.6, 129.2, 148.4; MS 220 ($M^+ + 1$, 1%), 219 (M^+, 6), 106 (100), 77 (71). Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.73; H, 9.68; N, 6.42.

Ethyl 3-Anilinopropanoate (3ah):[6b] R_f = 0.30 (hexane/ethyl acetate, 5:1); IR (film) 3330, 1710 cm^{-1}; ^1H NMR δ 1.24 (3H, t, J = 7.1), 2.58 (2H, t, J = 6.4), 3.43 (2H, t, J = 6.4), 4.02 (1H, s), 4.15 (2H, q, J = 7.1), 6.60 (2H, dd, J = 8.6, 1.0), 6.70 (1H, td, J = 7.3, 1.0), 7.16 (2H, dd, J = 8.6, 7.3); ^{13}C NMR δ 14.1, 33.9, 39.3, 60.5, 112.9, 117.6, 129.2, 147.6, 172.3; MS 194 ($M^+ + 1$, 4%), 193 (M^+, 29), 106 (100), 77 (13).

Methyl 5-Anilinopentanoate (3ai): R_f = 0.36 (hexane/ethyl acetate, 3:1); IR (film) 3380, 1720 cm^{-1}; ^1H NMR δ 1.62–1.70 (4H, m), 2.36 (2H, t, J = 7.2), 3.13 (2H, t, J = 6.6), 3.35 (1H, s), 3.67 (3H, s), 6.59 (2H, d, J = 7.6), 6.69 (1H, t, J = 7.3), 7.16 (2H, dd, J = 7.6, 7.3); ^{13}C NMR δ 22.4, 28.9, 33.7, 43.4, 51.5, 112.7, 117.2, 129.2, 148.3, 173.9; MS 208 ($M^+ + 1$, 4%), 207 (M^+, 32), 106 (100), 77 (15); HRMS calcd for $C_{12}H_{17}NO_2$ 207.125929, found 207.125080.

3-Anilinopropiophenone (3aj):[27] mp 113–114 °C (pentane/CH_2Cl_2) (lit. mp 115–116.5 °C); IR (KBr) 3380, 1670 cm^{-1}; ^1H NMR δ 3.28 (2H, t, J = 6.1), 3.62 (2H, t, J = 6.1), 4.10 (1H, s), 6.64 (2H, dd, J = 8.6, 1.0), 6.70 (1H, td, J = 7.3, 1.0), 7.17 (2H, dd, J = 8.6, 7.3), 7.45 (2H, dd, J = 8.2, 6.7), 7.54–7.59 (1H, m), 7.94 (2H, dd, J = 8.2, 1.2); ^{13}C NMR δ 37.6, 38.6, 112.9, 117.4, 127.9, 128.5, 129.2, 133.2, 136.6, 147.6, 199.2; m/z 226 ($M^+ + 1$, 2%), 225 (M^+, 14), 106 (100), 105 (19), 77 (13), 51 (13).

***N*-Isopropylaniline (3ba)**:[28] R_f = 0.41 (hexane/ethyl acetate, 10:1); IR (film) 3380 cm^{-1}; ^1H NMR δ 1.20 (6H, d, J = 6.3), 3.40 (1H, s), 3.62 (1H, heptet, J = 6.3); 6.58 (2H, dd, J = 8.6, 1.0), 6.66 (1H, td, J = 7.3, 1.0), 7.16 (2H, dd, J = 8.6, 7.3); ^{13}C NMR δ 22.8, 44.0, 113.1, 116.8, 129.1, 147.4; MS 136 ($M^+ + 1$, 2%), 135 (M^+, 19), 120 (100), 77 (14), 65 (10).

***N*-(1-Methyl-2-deuterioethyl)aniline (3bb)**: R_f = 0.41 (hexane/ethyl acetate, 10:1); IR (film) 3380 cm^{-1}; ^1H NMR δ 1.13 (5H, d, J = 6.2), 3.30 (1H, s), 3.54 (1H, sextet, J = 6.2); 6.50–6.53 (2H, m), 6.61–6.65 (1H, m), 7.09–7.15 (2H, m); ^{13}C NMR δ 22.5 (t, J_{CD} = 19.4), 22.8, 43.8, 112.1, 116.7, 129.1, 147.4; MS 137 ($M^+ + 1$, 3%), 136 (M^+, 24), 121 (70), 120 (100), 93 (13), 92 (14), 77 (19), 65 (16), 51 (14).

***N*-[2-(Methylthio)isopropyl]aniline (3bc)**:[6d] R_f = 0.29 (hexane/ethyl acetate, 9:1); IR (film) 3360 cm^{-1}; ^1H NMR δ 1.29 (3H, d, J = 6.4), 2.12 (3H, s), 2.59 (1H, dd, J = 13.2, 6.6), 2.76 (1H, dd, J = 13.2, 4.7), 3.66–3.72 (2H, m), 6.61 (2H, dd, J = 8.6, 0.9), 6.73 (1H, td, J = 7.3, 0.9), 7.17 (2H, dd, J = 8.6, 7.3); ^{13}C NMR δ 16.5, 20.3, 40.8, 48.0, 113.4, 117.5, 129.3, 147.0; MS 183 ($M^+ + 2$, 1%), 182 ($M^+ + 1$, 2), 181 (M^+, 14), 121 (15), 120 (100), 118 (11), 77 (13).

5-Anilino-2,2-dimethyl-3-hexanol (3bd): mp 74–75 °C (pentane/CH_2Cl_2); IR (KBr) 3600–3100 cm^{-1}; ^1H NMR δ 0.90 (9H, s), 1.29 (3H, d, J = 6.2), 1.45–1.53 (1H, m), 1.65 (1H, ddd, J = 14.2, 4.7, 1.7), 3.45 (1H, dd, J = 10.3, 1.7), 3.54 (2H, s), 3.62–3.67 (1H, m), 6.70 (2H, dd, J = 8.4, 0.9), 6.76 (1H, td, J = 7.4, 0.9), 7.18 (2H, dd, J = 8.4, 7.4); ^{13}C NMR δ 21.5, 25.6, 34.7, 38.1, 50.3, 79.7, 115.1, 118.7, 129.2, 146.9; MS 222 ($M^+ + 1$, 2%), 221 (M^+, 11), 121 (10), 120 (100). Anal. Calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 76.10; H, 10.54; N, 6.31

4-Anilino-2-methyl-2-pentanol (3be): R_f = 0.31 (hexane/ethyl acetate, 3:1); IR (film) 3600–3100 cm^{-1}; ^1H NMR δ 1.06 (3H, d, J = 6.2), 1.17 (3H, s), 1.23 (3H, s), 1.57–1.60 (2H, m), 3.33 (1H, d, J = 9.9), 3.65–3.85 (1H, m), 3.96 (1H, s), 6.65 (2H, dd, J = 8.4, 1.0), 6.71 (1H, td, J = 7.4, 1.0), 7.12 (2H, dd, J = 8.4, 7.4); ^{13}C NMR δ 21.9, 28.5, 31.2, 47.6, 48.8, 70.7, 115.4, 119.1, 129.3, 146.8; MS 194 ($M^+ + 1$, 2%), 193 (M^+, 11), 106 (100), 105 (17), 77 (11); HRMS calcd for $C_{12}H_{19}NO$ 193.146664, found 193.147121.

Ethyl 3-Anilinobutanoate (3bf):[6b] R_f = 0.28 (hexane/ethyl acetate, 5:1); IR (film) 3360, 1710 cm^{-1}; ^1H NMR δ 1.24 (3H, t, J = 7.2), 1.27 (3H, d, J = 6.2), 2.41 (1H, dd, J = 14.9, 6.8), 2.76 (1H, dd, J = 14.9, 5.2), 3.80 (1H, s), 3.91–3.97 (1H, m), 4.13 (2H, q, J = 7.2), 6.61 (2H, dd, J = 8.4, 1.0), 6.69 (1H, td, J = 7.4, 1.0), 7.17 (2H, dd, J = 8.4, 7.4); ^{13}C NMR δ 14.2, 20.6, 41.0, 46.0, 60.4, 113.5, 117.6, 129.3, 146.8, 171.8; MS 208 ($M^+ + 1$, 3%), 207 (M^+, 23), 121 (10), 120 (100), 118 (12), 104 (11), 77 (10).

***N*-Cyclohexyl-*N*-(2-phenylethyl)amine (4ca)**: R_f = 0.16 (ethyl acetate); IR (film) 3260 cm^{-1}; ^1H NMR δ 0.97–1.31 (6H, m), 1.57–1.87 (5H, m), 2.41 (1H, tt, J = 10.4, 3.7), 2.78 (2H, t, J = 6.6), 2.89 (2H, t, J = 6.6), 7.15–7.30 (5H, m); ^{13}C NMR δ 24.9, 26.0, 33.4, 36.6, 48.1, 56.6, 125.9, 128.3, 128.5, 140.1; MS 204 ($M^+ + 1$, 0.3%), 203 (M^+, 0.6), 112 (100), 91 (16), 56 (10), 55 (13), 41 (11).

***N*-Cyclohexyl-*N*-(2-deuterio-2-phenylethyl)amine (4cb)**: R_f = 0.16 (ethyl acetate); IR (film) 3260 cm^{-1}; ^1H NMR δ 1.02–1.27 (6H, m), 1.58–1.87 (5H, m), 2.41 (1H, tt, J = 10.4, 3.7), 2.77 (1H, t, J = 7.2), 2.88 (2H, d, J = 7.2), 7.16–7.30 (5H, m); ^{13}C NMR δ 24.9, 26.1, 33.5, 36.2 (t, J_{CD} = 19.4), 48.1, 56.6, 125.9, 128.3, 128.5, 140.0; MS 205 ($M^+ + 1$, 0.2%), 204 (M^+, 0.8), 113 (9), 112 (100), 55 (11).

***N*-Cyclohexyl-*N*-(2-methyl-2-phenylethyl)-*N*-methylamine (5ca)**: R_f = 0.20 (ethyl acetate); IR (film) 3040, 1590, 1490 cm^{-1}; ^1H NMR δ 1.05–1.20 (6H, m), 1.25 (3H, d, J = 7.0), 1.57–1.75 (5H, m), 2.25 (3H, s), 2.24–2.42 (1H, m), 2.43–2.57 (2H, m), 2.84 (1H, sextet, J = 7.0), 7.13–7.30 (5H, m); ^{13}C NMR δ 19.8, 26.0, 26.1, 26.4, 28.0, 28.8, 38.5, 38.6, 61.2, 63.3, 125.9, 127.2, 128.2, 146.5; MS 231 (M^+, 0.5%), 126 (100), 44 (35).

***N*-Allyl-*N*-cyclohexyl-*N*-(2-allyl-2-phenylethyl)amine (5cb)**: R_f = 0.39 (hexane/ethyl acetate, 10:1); IR (film) 1630 cm^{-1}; ^1H NMR δ 0.99–1.26 (6H, m), 1.57–1.73 (4H, m), 2.20–2.76 (6H, m), 3.08–3.12 (2H, m), 4.86 (1H, dd, J = 5.1, 2.2), 4.93 (1H, dd, J = 8.6, 2.2), 5.01 (1H, dd, J = 5.1, 2.0), 5.10 (1H, dd, J = 8.6, 2.0), 5.59–5.82 (2H, m), 7.11–7.29 (5H, m); ^{13}C NMR δ 26.2, 26.3, 26.4, 28.2, 29.7, 37.9, 45.5, 54.2, 56.6, 59.9, 115.4, 125.9, 128.0, 137.5, 138.4, 144.4; MS 283 (M^+, 0.1%), 153 (10), 152 (100), 91 (14), 70 (53), 55 (17), 41 (28).

(2*S*)-2-(Methylamino)-1-phenylpropane (12a): bp 37–41 °C/0.1 mmHg; IR (film) 3280 cm^{-1}; ^1H NMR δ 1.05 (3H, d, J = 6.1), 2.05 (1H, s), 2.38 (3H, s), 2.60 (1H, dd, J = 12.9, 6.2), 2.72 (1H, dd, J = 12.9, 6.9), 2.75–2.79 (1H, m), 7.16–7.31 (5H, m); ^{13}C NMR δ 19.5, 33.8, 43.3, 56.2, 126.0, 128.2, 129.1, 139.3; MS 149 (M^+, 0.1%), 91 (24), 65 (14), 58 (100); $[\alpha]^{25}_D$ = +3.2° [c = 1.76 (CH_2Cl_2)].

(1*R*,2*S*)-2-(Methylamino)-1-deuterio-1-phenylpropane (12b): bp 37–41 °C/0.1 mmHg; IR (film) 3300 cm^{-1}; ^1H NMR δ 1.04 (3H, d, J = 6.2), 1.56 (1H, s), 2.37 (3H, s), 2.58 (1H, d, J = 6.2), 2.77 (1H, quintet, J = 6.2), 7.16–7.30 (5H, m); ^{13}C NMR δ 19.4, 33.7, 42.8 (t, J_{CD} = 19.2), 56.1, 125.9, 128.2, 129.1, 139.2; MS 151 ($M^+ + 1$, 0.1%), 150 (M^+, 0.1), 92 (14), 42 (12); $[\alpha]^{25}_D$ = +2.61° [c = 2.07 (CH_2Cl_2)].

(4*R*,5*S*)-5-(*N*-Allyl-*N*-methylamino)-4-phenyl-1-hexene (12'c): R_f = 0.27 (hexane/ethyl acetate, 3:1); IR (film) 1630 cm^{-1}; ^1H NMR δ 1.01 (3H, d, J = 6.5), 2.06 (3H, s), 2.28–2.37 (1H, m), 2.45–2.54 (1H, m), 2.71 (1H, ddd, J = 8.4, 4.2, 4.1), 2.81–3.03 (3H, m), 4.82–5.03 (4H, m), 5.49–5.63 (2H, m), 7.11–7.27 (5H, m); ^{13}C NMR δ 10.8, 36.9, 37.1, 50.0, 57.0, 60.8, 115.5, 115.9, 125.6, 127.7, 128.6, 137.1, 137.2, 143.7; MS 230 ($M^+ + 1$, <0.1%), 228 ($M^+ - 1$, <0.1), 98 (100), 91 (14), 56 (26), 42 (11), 41 (23); $[\alpha]^{25}_D$ = −22.7° [c = 2.06 (CH_2Cl_2)].

(3*S*,4*S*)-2-Methyl-4-(methylamino)-3-phenyl-2-pentanol (12d): mp 94–95 °C (pentane); IR (KBr) 3600–3100 cm^{-1}; ^1H NMR δ 0.87 (3H, d, J = 6.2), 0.89 (3H, s), 1.33 (3H, s), 2.52 (3H, s), 2.57 (1H, d, J = 11.3), 3.20 (1H, qd, J = 11.3, 6.2), 4.40 (2H, s), 7.12–7.29 (5H, m); ^{13}C NMR δ 19.5, 25.0, 30.5, 33.5, 57.2, 62.4, 73.6, 126.4, 128.0, 141.4; MS 208 ($M^+ + 1$, 0.2%), 207 (M^+, 0.2),

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118 (41), 117 (36), 91 (14), 59 (11), 58 (100), 43 (15); $[\alpha]^{25}_D$ = +76.5° [c = 1.15 (CH_2Cl_2)]. Anal. Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found: C, 75.95; H, 10.04; N, 6.41.

(2*S*,3*S*)-1,1-Dicyclopropyl-3-(methylamino)-2-phenyl-1-butanol (12e): mp 121–122 °C (pentane/CH_2Cl_2); IR (KBr) 3300–3000 cm^{-1}; ^1H NMR δ 0.10–0.54 (9H, m), 0.85 (3H, d, J = 6.2), 1.01–1.06 (1H, m), 1.60 (2H, s), 2.46 (3H, s), 2.64 (1H, d, J = 11.3), 3.49–3.55 (1H, m), 7.20–7.32 (5H, m); ^{13}C NMR δ −1.3, −1.0, −0.2, 0.8, 15.5, 19.4, 20.7, 32.9, 56.3, 62.1, 72.3, 126.2, 127.6, 140.9; MS 218 ($M^+ - C_3H_5$, 1%), 133 (13), 118 (100), 117 (49), 115 (15), 91 (22), 69 (29), 58 (62), 41 (30); $[\alpha]^{25}_D$ = +13.4° [c = 1.50 (CH_2Cl_2)]. Anal. Calcd for $C_{13}H_{21}NO$: C, 78.72; H, 9.71; N, 5.40. Found: C, 78.94; H, 9.81; N, 4.67.

Preparation of 1,3-Dianilino-1-phenylpropane (3ak) under Barbier-type Conditions. To a blue suspension of an excess of lithium powder (0.125 g, 18.0 mmol) and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (0.047 g, 0.18 mmol) in THF (5 mL) was added very slowly (*ca.* 2 h) a solution of **1a** (0.160 g, 1.35 mmol) and *N*-benzylideneaniline (0.51 g, 2.85 mmol) in THF (2 mL) at 20 °C. The resulting mixture was hydrolyzed with water and extracted with CH_2Cl_2. The organic layer was dried over anhyd Na_2SO_4 and evaporated (15 mmHg). The resulting residue was purified by column chromatography (silica gel; hexane/ethyl acetate, 20/1) to yield pure **3ak**:[6d] R_f = 0.31 (hexane/ethyl acetate, 4:1); IR (film) 3380 cm^{-1}; ^1H NMR δ 2.08 (2H, q, J = 6.7), 3.21 (2H, t, J = 6.7), 3.90 (2H, s), 4.50 (1H, t, J = 6.7), 6.50–7.33 (15H, m); ^{13}C NMR δ 38.1, 41.3, 56.6, 113.0, 113.4, 117.5, 117.7, 126.3, 127.2, 128.7, 129.1, 129.3, 143.4, 147.1, 147.9; MS 303 (M^+ + 1, 6%), 302 (M^+, 23), 210 (15), 209 (98), 208 (84), 182 (100), 180 (18), 117 (34), 106 (75), 105 (32), 104 (45), 93 (35), 78 (15), 77 (83), 65 (17), 51 (14).

Preparation of (4*S*,5*S*)-3,4,6,6-Tetramethyl-5-phenyltetrahydro-1,3-oxazine (13).[17] To a solution of (3*S*,4*S*)-2-methyl-4-(methylamino)-3-phenyl-2-pentanol (**12d**) (0.338 g, 1.63 mmol) in ether at 20 °C was added 30% aqueous formaldehyde (0.168 g, 1.63 mmol). The reaction was stirred for 20 h at 20 °C. Solvent was removed, and the resulting residue was dried under reduced pressure (15 mmHg) and purified by column chromatography (silica gel; hexane/ethyl acetate, 10/1) to yield pure compound **13**: R_f = 0.22 (hexane/ethyl acetate, 1:1); IR (film) 3020, 3010, 1590, 1570, 730, 700 cm^{-1}; ^1H NMR δ 0.87 (3H, d, J = 6.4), 1.15 (3H, s), 1.21 (3H, s), 2.40 (3H, s), 2.78 (1H, d, J = 11.2), 3.23 (1H, qd, J = 11.2, 6.4), 4.28 (1H, d, J = 9.8), 4.51 (1H, d, J = 9.8), 7.13–7.29 (5H, m); ^{13}C NMR δ 18.1, 18.8, 29.6, 34.4, 54.3, 55.0, 75.2, 80.5, 126.5, 127.8, 139.5; MS 220 (M^+ + 1, 2%), 219 (M^+, 10), 132 (100), 131 (10), 118 (61), 117 (89), 115 (29), 91 (23), 58 (16), 43 (12), 42 (10); $[\alpha]^{25}_D$ = −130.9° [c = 1.32 (CH_2Cl_2)].

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Supplementary Material Available: Preparation, yields, and physical, analytical, and spectroscopic data of compounds **6b**, **6c**, **1′a**, **1′b**, **1a**, **1b**, **1c**, **8**, and **9**, as well as copies of ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra of new compounds lacking microanalyses (**1′b**, **1b**, **3ai**, **3bb**, **3be**, **4ca**, **4cb**, **5ca**, **5cb**, **12a**, **12b**, **12′c**, and **13**) (29 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.