Use of N,N'-Dimethylpropyleneurea (DMPU) as Solvent in the Efficient Preparation of Enantiomerically Pure Secondary Amines[1]

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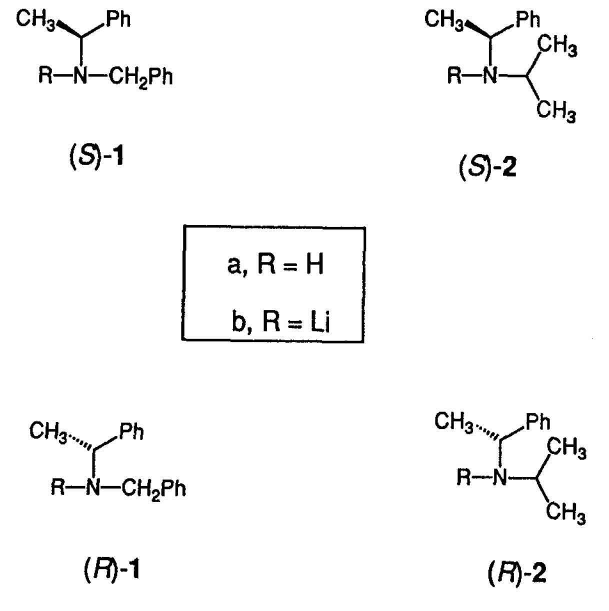
Received 26 April 1993

The monoalkylation of (*R*)- and (*S*)-1-phenylethylamine proceeds readily with DMPU as the solvent. An efficient procedure was then developed for the high-yield preparation of the chiral secondary amines *N*-benzyl-, *N*-isopropyl-, *N*-(2-biphenylyl)methyl-, *N*-(diphenyl)methyl-, and *N*-(2,2-dimethyl)propyl-1-phenylethylamine, in enantiomerically pure form.

The interest of organic chemists in the use of chiral lithium amides for the development of new asymmetric syntheses is growing rapidly.[3] Pertinent examples are the enantioselective deprotonation of symmetric ketones,[4-6] the diastereoselective 1,4-addition to nonchiral α,β-unsaturated esters,[7,8] the kinetic resolution of 2-substituted cyclohexanones,[9] and the enantiocontrolled protonation of enolates.[10] Lithium organo(amido)cuprates, prepared from enantiomerically pure secondary amines, have also been found to undergo enantioselective conjugate addition to 2-cycloalkenones.[11] Furthermore, it has been demonstrated that achiral enolates afford enantioselective aldol additions, Michael additions to nitroolefins, carboxylation, and alkylation *in the presence* of chiral lithium amides or amines.[12]

Among the most useful chiral amines that have been examined in these reactions are the secondary amines **1a** and **2a**, which are readily metalated to **1b** and **2b** by means of butyllithium (Scheme 1).

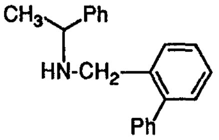


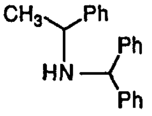
Scheme 1

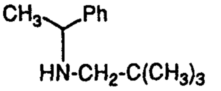
The preparation of amines **1a** and **2a** was described by Simpkins et al.[13] by reaction of (*R*)- or (*S*)-1-phenylethylamine with benzaldehyde or acetone and $NaBH_3CN$. This experimental procedure is fairly laborious, and careful control of the pH is required in order to prevent racemization. In fact, some racemization cannot be avoided in this procedure, so that crystallization of the HCl salts of the product is required. The alkylated products **1a** and **2a** are obtained in 56–64% yield.[13]

The use of hexamethylphosphoramide (HMPA) as solvent has been recommended for the alkylation of unreactive amines,[14] and several interesting applications have been described.[15] On the other hand, DMPU[1] has been shown to be an excellent replacement for the carcinogenic HMPA.[16,17]

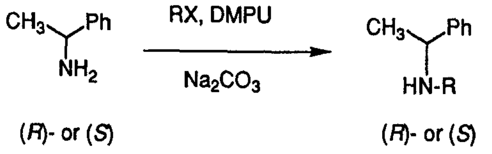
We describe here the convenient and high-yield preparation of **1a** and **2a** by direct monoalkylation of 1-phenylethylamine in DMPU as solvent. In addition, the new chiral secondary amines **3–5** have been prepared according to the same method.


(*R*)- or (*S*)-**3**


(*R*)- or (*S*)-**4**


(*R*)- or (*S*)-**5**

When an equimolar mixture of (*R*)- or (*S*)-1-phenylethylamine and benzyl bromide was dissolved in DMPU and heated to 100 °C for 1.5 h, the desired, enantiomerically pure monoalkylated amine (*R*)- or (*S*)-**1** was obtained in over 95% yield (eq 1; R = CH_2Ph). This reaction is carried out in the presence of two equivalents of Na_2CO_3, in order to neutralize the HX which is initially formed.



(1)

In similar fashion, (*R*)- and (*S*)-**2a** were obtained in 91% yield of purified product from the reaction of the corresponding 1-phenylethylamine and isopropyl iodide (eq 1; R = *i*-Pr). In this case, the reaction temperature employed for this alkylation was slightly lower: 4 h at 80 °C, plus 0.5 h at 90 °C.

Having demonstrated the utility of DMPU in the preparation of the known chiral amines **1a** and **2a**, we explored the generality of the method for the synthesis of other secondary amines, where the steric or electronic requirements would be different. Of course, such structural and inductive properties may lead to substantial differences in

Table 1. Monoalkylation of (*R*)- and (*S*)-1-Phenylethylamine in the Preparation of Enantiomerically Pure Secondary Amines **1**–**5**.

Product	Configuration	Reaction temp. (°C) Reaction time (h)	Yield (%)[a]	$[\alpha]_D^b$ (°)
1a	*R*	100/1.5	>95	+54.4
	S	100/1.5	>95	−52.8
2a	*R*	80/4+90/0.5	91	+60.1
	S	80/4+90/0.5	91	−59.7
3	*R*	100/2.5	92	+41.6
	S	100/2.5	91	−45.7
4	*R*	130/4.5	70	+38.9
	S	130/4.5	75	−39.9
5	*R*	120/65	32	+63.8
	S	120/65	29	−60.7

[a] After flash chromatography.

[b] Solvent and concentration in the experimental section.

the enantioselectivities by the chiral amine (or its chiral lithium amide) in the processes of interest (protonation, deprotonation, addition, kinetic resolution).

In the event, (*R*)- and (*S*)-1-phenylethylamine were monoalkylated with 2-(bromomethyl)biphenyl to afford (*R*)- and (*S*)-**3** in 92 and 91 % yield, respectively (eq 1; R = 2-biphenylylmethyl).

Furthermore, diphenylmethyl bromide as the electrophile allowed the preparation of (*R*)- and (*S*)-**4** in 70 and 75 % yield, respectively, according to the general procedure (eq 1; R = $CHPh_2$).

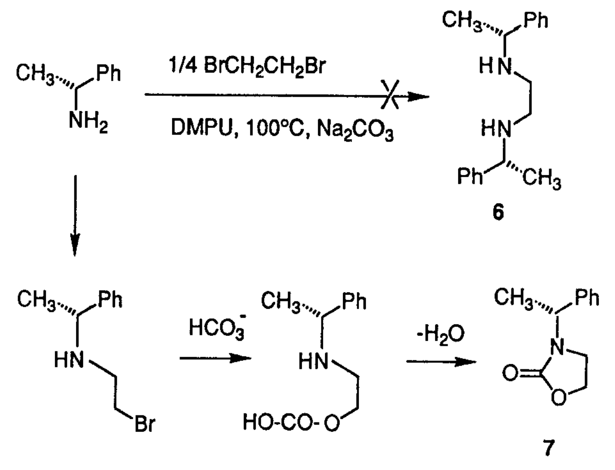
Interestingly, even neopentyl iodide reacted with (*R*)- and (*S*)-1-phenylethylamine under similar conditions (albeit in lower yield) to afford the highly hindered secondary amines (*R*)- and (*S*)-**5** (eq 1; R = neopentyl) in 32 and 29 % yields, respectively.

Table 1 contains pertinent data concerning the preparation of secondary amines (*R*)- and (*S*)-**1**–**5** from (*R*)- and (*S*)-1-phenylethylamine.

Attempted preparation of the C_2-symmetric chiral diamine **6** by treatment of 1,2-dibromoethane with four equivalents of (*R*)-1-phenylethylamine afforded, under the same conditions, the chiral oxazolidin-2-one **7** in 82 % isolated yield. This unexpected product probably arises from the reaction of the initially formed *β*-amino bromide and HCO_3^- (Scheme 2). Indeed, the preparation of **6** can been carried out *in the absence* of Na_2CO_3.[18]

On the other hand, in a related study,[19] the *N*-alkylation of highly hindered diamines was only possible in solvent DMPU.

In summary, the alkylation of highly hindered and other unreactive amines is facilitated by the use of DMPU as solvent. This procedure has been used for the efficient preparation of the previously described chiral secondary amines **1a** and **2a**, as well as the new, enantiomerically pure amines **3**–**5**. The different steric and electronic characteristics present in **1**–**5** render these amines, and their corresponding lithium amides, as attractive chiral reagents for the development of enantioselective reactions,[3,20] and as synthetic equivalents of "chiral NH_3".[8,21]



Scheme 2

DMPU was stirred at 60 °C over CaH_2 for 1 h, and then distilled at reduced pressure (bp 71–72 °C/0.1 mmHg) before use.

TLC: Merck-DC-F_{254} plates; detection by UV light. Flash column chromatography:[22] Fluka silica gel (40–63 μm), and a pressure of 0.2–0.6 bar.

Melting points: Büchi-510; in open capillary tubes. Optical rotations, $[\alpha]_D$: Perkin-Elmer 241, 1 dm cells; concentration *c* in g/100 mL. ^1H NMR spectra: Varian-Gemini-200, in $CDCl_3$; chemical shifts (δ) are given in parts per million downfield from the internal TMS reference. MS: Hitachi-Perkin-Elmer RMU-6M instrument; *m*/*z* values with relative intensity in parenthesis. IR spectra: Perkin-Elmer 983.

Microanalyses were performed by the microanalytical laboratories at ETH-Zürich. All compounds **3**–**5** and **7** gave C, H, N ± 0.3 %, except (*R*)-**7**, C − 0.40, N + 0.41.

Alkylation of 1-Phenylethylamine in DMPU;[23] General Procedure:
(*R*)- or (*S*)-1-Phenylethylamine was dissolved under argon in DMPU, and treated with two equivalents of Na_2CO_3. To the resulting white suspension was then added the alkylating agent (1–1.2 equiv of alkyl halide; dropwise addition), and the reaction mixture was heated until no starting amine was observable by TLC. The white suspension was then cooled down in an ice bath, and treated with water until a solution was formed, which was extracted with three portions of Et_2O. The combined organic phases were washed three times with water, dried over anhydr. $MgSO_4$ and concentrated in a rotary evaporator. Final purification was achieved by flash chromatography or by distillation on a Kugelrohr apparatus.

(*R*)-*N*-Benzyl-1-phenylethylamine [(*R*)-1a]:
(*R*)-1-Phenylethylamine (1.21 g, 10 mmol) in 40 mL of DMPU was treated with 2.12 g (20 mmol) of Na_2CO_3 and 1.2 mL (10 mmol) of benzyl bromide, and heated to 100 °C for 1.5 h, according to the general procedure. Workup (30 mL of H_2O, 3 × 50 mL of Et_2O, 50 mL of H_2O) and flash chromatography (hexane/EtOAc, 1 : 1) afforded 2.0 g (9.5 mmol, 95 % yield) of (*R*)-**1a** as a colorless oil with bp 135 °C/0.15 mmHg (lit.[11] bp 128–130 °C/0.2 mmHg) $[\alpha]_D$ = + 54.5° (*c* = 0.5, EtOH) [lit.[11] $[\alpha]_D$ = + 54.4° (*c* = 3.86, EtOH)].

^1H NMR: δ = 1.37 (d, *J* = 12.5 Hz, CH_3), 1.62 (s, NH), 3.59 and 3.68 (AB, *J* = 12.5 Hz, CH_2), 3.82 [q, *J* = 12.5 Hz, H-C(1)], 7.18–7.45 (m, 5 arom H). (*S*)-**1a**. Quantitative yield; $[\alpha]_D$ = − 52.8° (*c* = 0.60, EtOH) {Lit.[13] $[\alpha]_D$ = − 53.6° (*c* = 3.80, EtOH)}.

(*R*)-*N*-Isopropyl-1-phenylethylamine [(*R*)-2a]:
(*R*)-1-Phenylethylamine (1.21 g, 10 mmol) in 25 mL of DMPU was treated with 2.12 g (20 mmol) of Na_2CO_3 and 1.2 mL (12 mmol) of

isopropyl iodide, and heated to 80 °C for 4 h plus an additional 0.5 h at 90 °C, according to the general procedure. Workup (50 mL of H_2O, 3 × 50 mL of Et_2O, and 3 × 50 mL of H_2O) and Kugelrohr distillation, bp 50–55 °C/0.1 mmHg (lit.[13] bp 60–66 °C/0.5 mmHg) afforded 1.48 g (91 % yield) of (*R*)-**2a** as a colorless oil. $[\alpha]_D = +60.1°$ ($c = 0.71$, $CHCl_3$) {lit.[13] $[\alpha]_D = +61.4°$ ($c = 2.23$, $CHCl_3$)}.

IR (film): ν = 3320 (w), 2960 (s), 1945 (w), 1874 (w), 1806 (w), 1735 (w), 1602 (m), 1492 (s), 1451 (s), 1368 (s), 1169 (s), 749 (s), 687 (s).

^1H NMR: δ = 0.99 [d, J = 6.0 Hz, CH_3–C(1′)], 1.03 [d, J = 6.0 Hz, $CH_3C(1')$], 1.25–1.40 (bs, NH), 1.34 [d, J = 6.0 Hz, $CH_3C(1)$], 2.62 [m, H–C(1′)], 3.89 [q, J = 6.0 Hz, H–C(1)], 7.18–7.40 (m, 5 arom H).

^{13}C NMR: δ = 21.91, 23.80, 24.60, 45.21, 54.77, 126.14, 126.44, 128.11, 145.82.

(*S*)-**2a**: Yield = 91 %; $[\alpha]_D = -59.7°$ ($c = 1.01$, $CHCl_3$) {lit.[13] $[\alpha]_D = +61.4°$ ($c = 2.23$, $CHCl_3$)} for the (*R*)-enantiomer.

(*R*)-*N*-(2-Biphenylyl)methyl-1-phenylethylamine [(*R*)-3]:
According to the general procedure, 1.21 g (10 mmol) of (*R*)-1-phenylethylamine in 20 mL of DMPU was treated with 2.12 g (20 mmol) of Na_2CO_3 and 1.9 mL (10 mmol) of 2-(bromomethyl)biphenyl, and heated to 100 °C for 2.5 h. Workup (50 mL of H_2O, 3 × 50 mL of Et_2O, 3 × 50 mL of H_2O) and flash chromatography (hexane/EtOAc, 4:1) afforded 1.33 g (92 % yield) of (*R*)-**3** as a colorless oil with bp 200–210 °C/0.15 mmHg. $[\alpha]_D = +41.6°$ ($c = 0.76$, $CHCl_3$).

IR (film): ν = 3323 (w), 3023 (w), 1953 (w), 1877 (w), 1811 (w), 1599 (w), 1478 (m), 1450 (m), 1010 (w), 751 (s), 701 (s).

^1H NMR: δ = 1.25 (d, J = 6.0 Hz, CH_3), 1.48 (s, NH), 3.56 and 3.70 (AB, J = 12.5 Hz, CH_2), 3.66 [q, J = 6.0 Hz, H–C(1)], 7.16–7.50 (m, 14 arom H).

^{13}C NMR: δ = 24.13, 49.40, 57.49, 126.37, 126.51, 126.67, 126.76, 127.21, 127.92, 128.09, 128.77, 129.41, 129.88, 137.61, 140.98, 141.57, 145.18.

MS: m/z = 287 (M^+, 5), 272 (100), 210 (3), 182 (18), 167 (99), 152 (18), 136 (4), 128 (2), 120 (5), 105 (24), 77 (10), 51 (4), 39 (2), 28 (22).

(*S*)-**3**: Yield: 91 %; $[\alpha]_D = -45.7°$ ($c = 0.82$, $CHCl_3$).

(*R*)-*N*-Diphenylmethylamine [(*R*)-4]:
According to the general procedure, 0.61 g (5 mmol) of (*R*)-1-phenylethylamine in 15 mL of DMPU was treated with 1.06 g (10 mmol) of Na_2CO_3 and 1.54 g (6 mmol) of diphenylmethyl bromide, and heated to 120–130 °C for 4.5 h. Workup (50 mL of H_2O, 3 × 50 mL of Et_2O, 3 × 50 mL of H_2O) and flash chromatography (hexane/EtOAc, 3:1) afforded 1.0 g (70 % yield) of (*R*)-**4** as a colorless oil with bp 200–210 °C/0.1 mmHg. $R_f = 0.46$ (hexane/EtOAc, 3:1); $[\alpha]_D = +38.5°$ ($c = 0.74$, $CHCl_3$).

IR (film): ν = 3326 (w), 3025 (s), 2961 (m), 2863 (w), 1950 (w), 1881 (w), 1808 (w), 1754 (w), 1599 (m), 1492 (s), 1451 (s), 1028 (m), 763 (s), 745 (s).

^1H NMR: δ = 1.36 (d, J = 6.0 Hz, CH_3), 1.68 (bs, NH), 3.69 [q, J = 6.0 Hz, H–C(1)], 4.63 [s, H–C(1′)], 7.12–7.49 (m, 15 arom H).

^{13}C NMR: δ = 24.25, 54.99, 63.57, 126.49, 126.65, 126.71, 127.17, 127.47, 128.15, 128.27, 143.45, 144.44, 145.38.

MS: m/z = 287 (M^+, 2), 272 (35), 210 (14), 182 (26), 167 (100), 152 (11), 134 (3), 120 (5), 105 (45), 77 (13), 51 (5), 28 (23).

(*S*)-**4**: Yield: 75 %; $[\alpha]_D = 39.9°$ ($c = 0.7$, $CHCl_3$).

(*R*)-*N*-(2,2-Dimethyl)propyl-1-phenylethylamine [(*R*)-5]:
According to the general procedure, 0.61 g (5 mmol) of (*R*)-1-phenylethylamine in 15 mL of DMPU was treated with 1.06 g (10 mmol) of Na_2CO_3 and 1.0 g (7.5 mmol) of (2,2-dimethyl)propyl iodide, and heated to 100 °C for 65 h. Workup (50 mL of H_2O, 3 × 50 mL of Et_2O, and 3 × 50 mL of H_2O), and flash chromatography (hexane/EtOAc, 1:1) afforded 0.31 g (32 % yield) of (*R*)-**5** as a colorless oil with bp 50–60 °C/0.1 mmHg. $R_f = 0.74$ (hexane/EtOAc, 1:1); $[\alpha]_D = +63.8°$ ($c = 0.58$, $CHCl_3$).

IR (film): ν = 3300 (w), 3025 (w), 2952 (s), 1945 (w), 1875 (w), 1807 (w), 1737 (w), 1689 (m), 1603 (m), 1452 (m), 1362 (m), 1126 (m), 761 (s).

^1H NMR: δ = 0.90 (s, *t*-Bu), 1.34 [d, J = 6.0 Hz, $CH_3C(1)$] 2.14 and 2.28 (*AB*, J = 11.0 Hz, CH_2), 3.70 [7, J = 6.0 Hz, H-C(1)], 7.15–7.35 (m, 5 arom H).

^{13}C NMR: δ = 24.64, 27.49, 31.07, 58.63, 59.82, 126.31, 127.97, 145.80.

MS: m/z = 191 (M^+, 2), 176 (5), 134 (44), 118 (3), 105 (100), 91 (5), 77 (17), 72 (7), 56 (3), 51 (6), 41 (11), 30 (34).

(*S*)-**5**: Yield: 29 %; bp 60–70 °C/0.15 mmHg; $[\alpha]_D = -60.7°$ ($c = 0.75$, $CHCl_3$).

3*N*-[(*R*)-1-Phenylethyl]oxazolidin-2-one [(*R*)-7]:
According to the general procedure, 1.45 g (12 mmol) of (*R*)-1-phenylethylamine in 10 mL of DMPU was treated with 2.12 g (20 mmol) of Na_2CO_3 and 0.26 mL (3 mmol) of ethylene bromide, and heated to 100 °C for 36 h. The usual workup procedure and flash chromatography (hexane/EtOAc 1:1) afforded 0.36 g (82 % yield) of (*R*)-**7** as a yellowish oil with bp 200–210 °C/0.1 mmHg. $R_f = 0.29$ (hexane/EtOAc, 1:1); $[\alpha]_D = 95.6°$ ($c = 0.66$, $CHCl_3$).

IR ($CHCl_3$): ν = 3008 (m), 2922 (w), 1742 (s), 1603 (w), 1493 (m). 1483 (s), 1454 (m), 1424 (s), 1120 (w), 1067 (m), 1043 (m), 1020 (m), 639 (w).

^1H NMR: δ = 1.59 [d, J = 6.0 Hz, CH_3–C(1′)], 3.15 (distorted ddd, 2 H), 3.50 (distorted ddd, 2 H), 4.22 (distorted ddd, 2 H), 4.30 (distorted ddd, 2 H), 5.23 [q, J = 6.0 Hz, H–C(1′)], 7.23–7.43 (m, 10 arom H).

^{13}C NMR: δ = 1605, 39.77, 51.18, 61.63, 126.75, 127.59, 128.41, 139.21, 157.9.

MS: m/z = 191 (M^+, 97), 176 (80), 163 (8), 146 (5), 132 (30), 114 (7), 105 (100), 91 (8), 77 (24), 70 (9), 51 (9), 42 (5), 28 (6).

HRMS: m/z (M^+) Found 191.0931. Calc. for $C_{11}H_{13}NO_2$, 191.0946.

We are grateful to W. Amrein, B. Jaun, and M. Hayakawa for useful discussions.

(1) DMPU = *N,N′*-dimethylpropyleneurea = 1,3-dimethyl-2-oxo-hexahydropyrimidine.

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