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Samarium(II) Iodide-Mediated Intermolecular Coupling Reactions of *N*,*N*-Dibenzylenamides with Carbonyl Compounds and Transformation of the Product, *N*,*N*-Dibenzyl-γ-hydroxyamide to δ-Aminoalcohol

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Samarium(II) iodide-mediated intermolecular coupling reactions of *N*,*N*-dibenzylenamides (1a—d) with carbonyl compounds (2a—i) produced the corresponding *N*,*N*-dibenzyl-γ-hydroxyamides (3a—i) in moderate to good yields. Attempts to remove the two benzyl groups of 3a using hydrogenolysis and Birch reduction were unsuccessful. On the other hand, the lithium aluminum hydride reduction of 3a produced 10 in 61% yield, and dedibenzylation using 20% $Pd(OH)_2$ on carbon gave the corresponding δ-aminoalcohol (11).

Key words samarium(II) iodide; *N*,*N*-dibenzylenamide; coupling reaction; *N*,*N*-dibenzyl-γ-hydroxyamide; δ-aminoalcohol

Since Kagan *et al.* introduced samarium(II) iodide (SmI_2) in 1980,[1] this powerful one-electron reducing agent has become an essential reagent in organic synthesis.[2] In 1986, Fukuzawa *et al.*[3] and Inanaga *et al.*[4] reported SmI_2-mediated reductive coupling reactions of carbonyl compounds with α,β-unsaturated esters to form γ-lactones. That is, treatment of α,β-unsaturated esters and carbonyl compounds with SmI_2 for 2—10 h gave the corresponding lactones.[3] Inanaga *et al.* reported that the coupling reaction was greatly accelerated by the addition of *N*,*N*,*N*′,*N*′,*N*″,*N*″-hexamethylphosphoric triamide (HMPA).[4] Furthermore, efficient intermolecular carbon–carbon bond formation *via* SmI_2-promoted anion radical alkylation[5] and an instantaneous hydrodimerization of *N*,*N*-dibenzylcrotonamide using SmI_2–THF–HMPA–*tert*-BuOH,[6] were described by Inanaga *et al.* However, little is known about the SmI_2-mediated intermolecular reductive coupling reactions of enamides with carbonyl compounds. Recently, we reported SmI_2-mediated intermolecular aldol-type reactions between phenacyl bromides and carbonyl compounds as a route to β-hydroxyketones[7] and between *N*,*N*-dibenzyl-α-haloamides and carbonyl compounds yielding β-hydroxyamides.[8] In this paper, we report the SmI_2-mediated coupling reactions of *N*,*N*-dibenzylenamides (**1a**—**d**) with carbonyl compounds (**2a**—**i**) and the transformation of *N*,*N*-dibenzyl-γ-hydroxyamide (**3a**), thus obtained, to the corresponding δ-aminoalcohol (**11**).

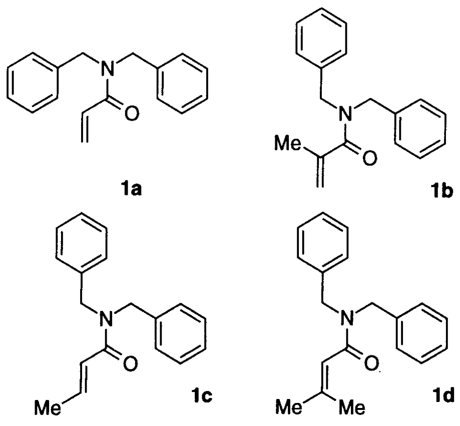
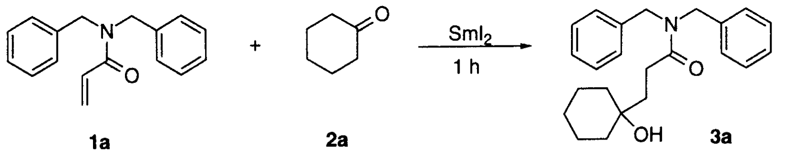


Fig. 1

Table 1. SmI_2-Mediated Coupling Reactions of the Enamide (**1a**) with Cyclohexanone (**2a**) under Several Reaction Conditions



Entry	Reaction temperature (°C)	Additive	Yield (%) of **3a**
1	Room temperature	None	Trace[a)]
2	Room temperature	*tert*-BuOH	57
3	0	*tert*-BuOH	55
4	−78	*tert*-BuOH	Trace
5	Room temperature	*tert*-BuOH/Et_2AlCl[b)]	75
6	Room temperature	*tert*-BuOH/HMPA[c)]	38
7	Room temperature	*tert*-BuOH/TMEDA[c)]	67
8	Room temperature	*tert*-BuOH/DMPU[c)]	27

a) Complex mixture. *b*) Ratio Et_2AlCl : **1a** = 2 : 1. *c*) 10% (v/v) HMPA, TMEDA, and DMPU in THF.

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N,*N*-Dibenzylenamides (**1a**—**c**) were synthesized according to the reported methods.[9] The enamide **1d** was prepared by reaction between 3,3-dimethylacryloyl chloride and dibenzylamine.

Next, to determine the optimum conditions, the reaction of *N*,*N*-dibenzylacrylamide (**1a**) with cyclohexanone (**2a**) was examined under a variety of conditions. Table 1 summarizes the results of all the experiments that we conducted.

In the absence of *tert*-BuOH, the reaction did not give the desired **3a**, but a complex mixture. Namely, it was suggested that the addition of *tert*-BuOH is essential. When the reactions were carried out under the conditions of entries 2, 5, and 7 in Table 1, comparatively good results were obtained.

We then allowed the acrylamide **1a** to react with several kinds of carbonyl compounds (**2a**—**i**) under the conditions of entries 2 (method A) and 5 (method B) in Table 1. These results are shown in Table 2.

With acyclic dialkyl ketones (**2d** and **e**), the yields were low, because of low reactivity (entries 7—10 in Table 2). However, except for these runs, *N*,*N*-dibenzyl-γ-hydroxyamides (**3a**—**c**, and **f**—**i**) were obtained in moderate to good yields and the scope of the reaction seems to be broad. The reactions between *N*,*N*-dibenzylacrylamide (**1a**) and α,β-unsaturated ketone (**2f**) were regioselective and yielded only the 1,2-addition product (**3f**) (entries 11 and 12 in Table 2). This reaction was considered to proceed as follows: first 2-cyclopenten-1-one (**2f**) was reduced to give the corresponding ketyl radical, which was then reacted with **1a** to give only the 1,2-addition product (**3f**). With β-tetralone (**2g**), an enolizable ketone, the corresponding γ-hydroxyamide (**3g**) was produced in good yield, under non-basic reaction conditions (entries 13 and 14 in Table 2). In the coupling reactions of **1a** with carbonyl compounds, except for cyclohexanone (**2a**), the addition of Et_2AlCl was ineffective or only slightly effective. On

Table 2. SmI_2-Mediated Coupling Reactions of the Enamide (**1a**) with Carbonyl Compounds (**2a**—**i**)

Entry	Carbonyl compound	Method[a]	Product (Yield %)
1	Cyclohexanone (**2a**)	A	**3a** (57)
2	**2a**	B	**3a** (75)
3	Acetophenone (**2b**)	A	**3b** (91)
4	**2b**	B	**3b** (88)
5	Benzophenone (**2c**)	A	**3c** (81)
6	**2c**	B	**3c** (64)
7	Ethyl isopropyl ketone (**2d**)	A	**3d** (18)
8	**2d**	B	**3d** (20)
9	2-Octanone (**2e**)	A	**3e** (27)
10	**2e**	B	**3e** (31)
11	2-Cyclopenten-1-one (**2f**)	A	**3f** (87)
12	**2f**	B	**3f** (63)
13	β-Tetralone (**2g**)	A	**3g** (86)
14	**2g**	B	**3g** (70)
15	Benzaldehyde (**2h**)	A	**3h** (69)
16	**2h**	B	**3h** (74)
17	Octanal (**2i**)	A	**3i** (83)
18	**2i**	B	**3i** (83)

a) Method A: A solution of 0.1 M SmI_2 in THF (7.5 mmol) was added dropwise to a dry THF (5 ml) solution of **1** (0.25 mmol), **2** (0.25 mmol), and *tert*-BuOH (0.25 ml) at room temperature. Method B: A solution of 1.0 M Et_2AlCl in hexane (0.5 mmol) was added to a dry THF (5 ml) solution of **1** (0.25 mmol), **2** (0.25 mmol), and *tert*-BuOH (0.25 ml) at room temperature. A 0.1 M solution of SmI_2 in THF (7.5 mmol) was then added dropwise to the reaction mixture.

Table 3. SmI_2-Mediated Coupling Reactions of Enamide (**1b**—**e**) with Carbonyl Compounds

Entry	Enamide	Carbonyl compound	Method[a]	Reaction Temperature (°C)	Product (Yield %)
1	**1b**	Cyclohexanone (**2a**)	B	Room temperature	**3j** (54)
2	**1b**	**2a**	C	Room temperature	**3j** (73)
3	**1b**	**2a**	D	Room temperature	**3j** (97)
4	**1b**	Acetophenone (**2b**)	A	Room temperature	**3k** (70) (49% de)[b,c]
5	**1b**	**2b**	D	Room temperature	**4**[d] (48)
6	**1b**	Benzaldehyde (**2h**)	A	Room temperature	Trace
7	**1b**	**2h**	C	Room temperature	—
8	**1b**	**2h**	D	Room temperature	**4**[d] (38)
9	**1c**	**2a**	A	Room temperature	**3l** (58)
10	**1c**	**2a**	B	Room temperature	**3l** (64)
11	**1c**	**2a**	D	Room temperature	**3l** (65)
12	**1c**	**2b**	A	Room temperature	**3m** (65) (53% de)[e,f]
13	**1c**	**2b**	A	−78	**3m** (59) (55% de)[e,f]
14	**1c**	**2b**	B	Room temperature	**3m** (19) (44% de)[e,f]
15	**1c**	**2b**	B	−78	**3m** (36) (58% de)[e,f]
16	**1c**	**2b**	C	Room temperature	Trace
17	**1c**	**2b**	D	Room temperature	**5**[g] (79)
18	**1d**	**2a**	B	Room temperature	Recovery[h]
19	**1d**	**2a**	D	Room temperature	**3n** (76)
20	**1d**	**2b**	A	Room temperature	Recovery[h]
21	**1d**	**2h**	A	Room temperature	Recovery[h]

a) Method A: A 0.1 M solution of SmI_2 in THF (7.5 mmol) was added dropwise to a dry THF (5 ml) solution of **1** (0.25 mmol), **2** (0.25 mmol), and *tert*-BuOH (0.25 ml) at the temperature indicated in the table. Method B: A 1.0 M solution of Et_2AlCl in hexane (0.5 mmol) was added to a dry THF (5 ml) solution of **1** (0.25 mmol), **2** (0.25 mmol), and *tert*-BuOH (0.25 ml) at the temperature indicated in the table. A 0.1 M solution of SmI_2 in THF (7.5 mmol) was then added dropwise to the reaction mixture. Method C: A 0.1 M solution of SmI_2 in THF (7.5 mmol) was added dropwise to a dry THF (5 ml) solution of **1** (0.25 mmol), **2** (0.25 mmol), *tert*-BuOH (0.25 ml), and TMEDA (0.5 ml) at the temperature indicated in the table. Method D: A 0.1 M solution of SmI_2 in THF (7.5 mmol) was added dropwise to a dry THF (5 ml) solution of **1** (0.25 mmol), **2** (0.25 mmol), *tert*-BuOH (0.25 ml), and HMPA (0.5 ml) at the temperature indicated in the table. *b*) The diastereomers were separated by PTLC. *c*) The relative configurations of the diastereomers of **3k** were determined on the basis of X-ray crystallographic analysis. *d*) See ref. 10. *e*) Since the diastereomers could not be separated, the diastereomeric excess (de) was determined from the ^{1}H-NMR spectral data. *f*) The relative configuration of the diastereomers could not be determined. *g*) See ref. 6. *h*) Recovery of the enamide (**1d**).

the other hand, when **2a** was employed as a carbonyl component, the addition of Et_2AlCl (method B) was found to be effective (entries 1 and 2 in Table 2). Owing to the activation of **2a** with Et_2AlCl, the ketyl radical of **2a** may be produced more easily.

In addition, the SmI_2-mediated couplings of several kinds of substituted enamides (**1b**—**d**) with carbonyl compounds were carried out. These results are shown in Table 3.

The coupling reaction of benzaldehyde (**2h**) with the substituted enamides (**1b** and **d**) did not proceed. Side reactions such as the pinacol-type coupling of **2h** and the

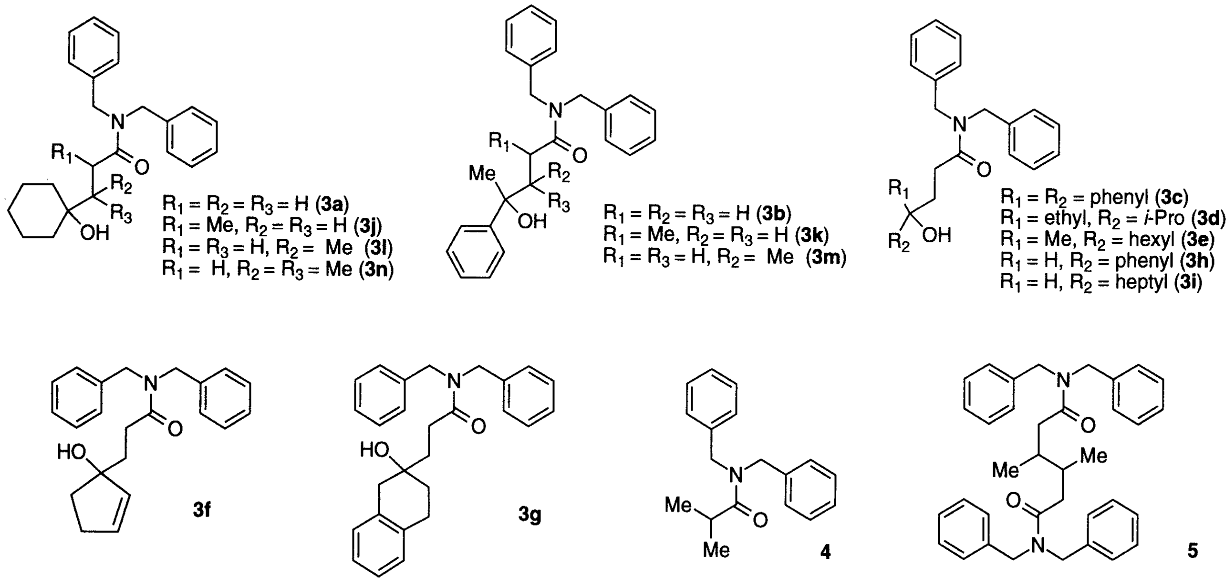
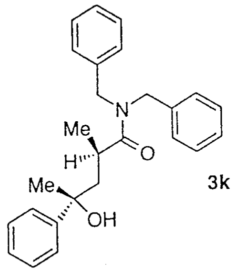


Fig. 2



$3k_1$

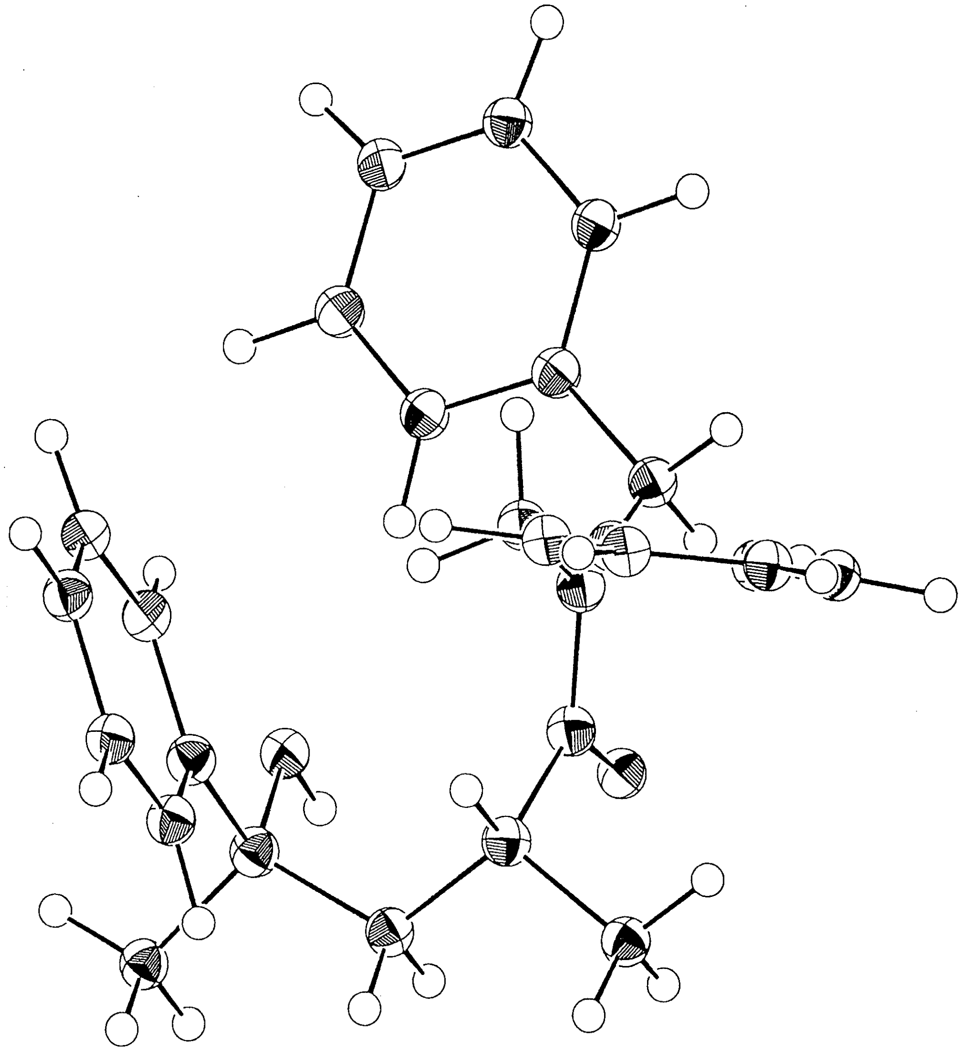
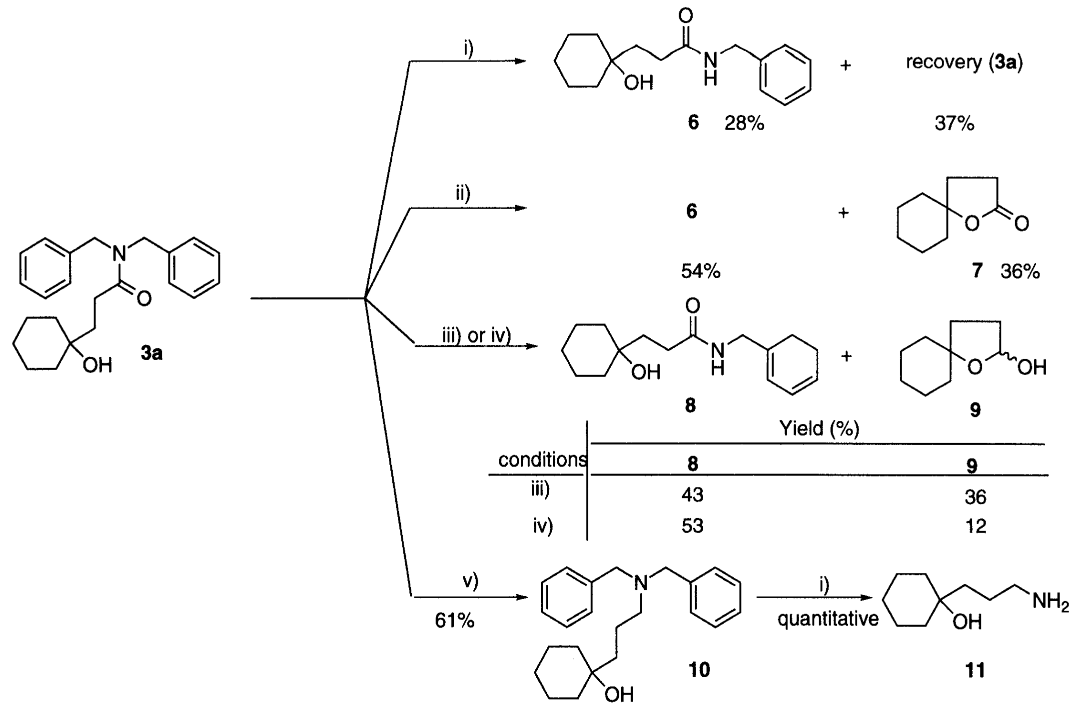


Fig. 3



conditions	Yield (%) 8	Yield (%) 9
iii)	43	36
iv)	53	12

i) H_2 (1 atm) / 20% $Pd(OH)_2$ / MeOH / room temperature ii) H_2 (5 atm) / 20% $Pd(OH)_2$ / MeOH / room temperature
iii) Li / liq. NH_3 /*tert*-BuOH / -78°C iv) Ca / liq. NH_3 /*tert*-BuOH / -78°C v) $LiAlH_4$ / THF / room temperature

Chart 1

reduction of the double bond probably occurred under the reaction conditions used, as shown in entries 6—8 and 21 in Table 3. The coupling reactions of monosubstituted enamides (**1b** and **c**) with ketones (**2a** and **b**) gave **3j** and **k** (entries 1—5 and 9—17 in Table 3). The addition of HMPA (method D) in the reaction of **1b** with acetophenone (**2b**) was ineffective (entry 5 in Table 3, Fig. 2), because the reduction of olefin (**1b**) proceeded faster than the coupling reaction between **1b** and **2b**. Further, the reactions with the β,β-disubstituted enamide (**1d**) were examined (entries 18—21). In the presence of HMPA, the coupling of **1d** with **2a** gave the desired β-hydroxyamide (**3n**). However, with **2b** and **2h**, the corresponding coupling products could not be obtained (entries 18, 20, and 21 in Table 3). Under these conditions, pinacol couplings of **2b** and **2h** probably occurred. When cyclohexanone **2a** was employed as a carbonyl compound in these coupling reactions, the addition of HMPA was generally effective. Presumably the addition of HMPA as a co-solvent raised the reducing potential of SmI_2[2] and produced the ketyl radical more easily than in the absence of HMPA.

The diastereomeric excess in these reactions is 44—58%. The diastereomers, $\mathbf{3k}_1$ (less polar component) and $\mathbf{3k}_2$ (more polar component), were separated by preparative thin layer chromatography (PTLC). The relative configuration of $\mathbf{3k}_1$ was determined by X-ray crystallographic analysis (Fig. 3). The diastereomers obtained in entries 12—15 in Table 3 could not be separated.

Next, in order to remove the two benzyl groups on the amide nitrogen of the product, *N*,*N*-dibenzyl-γ-hydroxyamide (**3a**), and to synthesize *N*-unsubstituted γ-hydroxyamide, hydrogenolysis and Birch reduction of **3a** were examined (Chart 1). When the hydrogenolysis was carried out under atmospheric pressure, the monodebenzylated compound (**6**) was obtained in 28% yield after allowing for recovery of the starting material. On the other hand, hydrogenolysis of **3a** with $Pd(OH)_2$ on carbon under a pressure of 5 atm gave a γ-lactone (**7**) in 36% yield. Next, debenzylation of **3a** by Birch reduction was investigated. Treatment of **3a** under Birch conditions, such as Li/liq. NH_3/*tert*-BuOH and Ca/liq. NH_3/*tert*-BuOH, did not give the unsubstituted γ-hydroxyamide, but compound **8** and a γ-lactol (**9**), an equivalent to γ-hydroxycarboxaldehyde. In either event, removal of the two benzyl groups of **3a** was not achieved.

Finally, transformation of **3a** to the δ-aminoalcohol (**11**) was carried out. Namely, treatment of **3a** with lithium aluminum hydride (LAH) gave the *N*,*N*-dibenzyl-δ-hydroxyamine (**10**) in 61% yield. Removal of the two benzyl groups on the nitrogen of **10** was accomplished by hydrogenolysis using 20% $Pd(OH)_2$ on carbon to give the corresponding δ-aminoalcohol (**11**) in quantitative yield (Chart 1).

In conclusion, the SmI_2-mediated coupling reactions of *N*,*N*-dibenzylacrylamide (**1a**) with carbonyl compounds (**2a**—**i**) proceeded to give the *N*,*N*-dibenzyl-γ-hydroxyamides (**3a**—**i**) in moderate to satisfactory yields. In the reactions of the substituted enamides (**1b**—**d**) with cyclohexanone (**2a**), the addition of HMPA is effective. Although SmI_2-mediated coupling of the enamides (**1b** and **d**) with benzaldehyde (**1h**) was examined under several reaction conditions, the corresponding coupling products could not be obtained. The coupling reactions of β,β-disubstituted enamide with acetophenone and benzaldehyde did not proceed. Removal of the two benzyl groups on the amide nitrogen of **3a** was unsuccessful. On the other hand, the transformation of *N*,*N*-dibenzyl-γ-hydroxyamide (**3a**) to the unsubstituted δ-aminoalcohol

(**11**) was accomplished in 2 steps. Further studies dealing with the stereoselective coupling reactions of chiral enamides with carbonyl compounds are in progress.

Experimental

Melting points were obtained using a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO A-100 spectrometer or a Shimadzu IR-470 spectrometer. ^{1}H-NMR spectra were recorded for solutions in $CDCl_3$ with tetramethylsilane (TMS) as the internal standard on a Varian Gemini 300 spectrometer and Brucker AM 400. Mass spectra were determined on a Fisons VG Auto Spec instrument. Medium-pressure liquid column chromatography (MPLC) was conducted using a UVILOG 5III spectrometer as the UV detector (Oyo Bunko Kiki Co., Ltd. Tokyo) and Kieselgel 60 (Merck AG, Darmstadt) as the packing material. PTLC was conducted using a Merck TLC plate (Art. 1.05744). A 1.0 M solution of Et_2AlCl in hexane and 0.1 M solution of SmI_2 in tetrahydrofuran (THF) were purchased from the Aldrich Chemical Co. THF was distilled from purple sodium benzophenone ketyl under argon immediately prior to use. HMPA (Aldrich Chem. Co., Ltd.) was distilled from CaH_2 under reduced pressure.

***N*,*N*-Dibenzyl-3-methyl-2-butenamide (1d)** 3,3-Dimethylacryloyl chloride (1.18 g, 10 mmol) was added dropwise to a THF (40 ml) solution of dibenzylamine (1.97 g, 10 mmol) and Et_3N (2.8 ml, 20 mmol) at 0 °C under an argon atmosphere. The resulting mixture was stirred at 0 °C for 1 h, then the mixture was poured into ice water (40 ml). The whole was extracted with Et_2O (30 ml × 3). The combined organic layer was washed with 5% HCl (30 ml × 3), 5% $NaHCO_3$ (30 ml × 3), and saturated NaCl (20 ml × 3) successively, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give an oily residue, which was purified by MPLC (hexane : AcOEt = 6 : 1) to give **1d** (2.72 g, 97%) as a colorless oil. After distillation, it solidified to give colorless crystals. bp 180—190 °C/1 torr (bath temperature), mp 52—53 °C. IR (neat): 1650 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.83 (3H, d, J = 1.3 Hz), 2.04 (3H, d, J = 1.1 Hz), 4.46 (2H, s), 4.59 (2H, s), 5.94 (1H, m), 7.15—7.40 (10H, m). MS *m/z*: 279 (M$^+$), 264 (M$^+$ − Me). *Anal.* Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.74; H, 7.59; N, 5.11.

***N*,*N*-Dibenzyl-γ-hydroxyamides (3a—n). General Procedure** Method A: Under an argon atmosphere, a 0.1 M SmI_2 solution in THF (7.5 ml, 0.75 mmol) was added dropwise to a dry THF (5 ml) solution of **1** (0.25 mmol), **2** (0.25 mmol), and *tert*-BuOH (0.25 ml) at the temperature indicated in Tables 2, 3. The reaction mixture was stirred at room temperature for 1 h, then saturated NH_4Cl (30 ml) and Et_2O (20 ml) were added. The resulting deposit was collected by filtration on Celite® and washed with Et_2O (20 ml). The filtrate was washed with saturated NaCl (30 ml), 8% $Na_2S_2O_3$ (30 ml), and saturated NaCl (30 ml) successively, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give an oily residue, which was purified by MPLC or PTLC to give **3**.

Method B: Under an argon atmosphere, a 1.0 M solution of Et_2AlCl in hexane (0.5 ml, 0.5 mmol) was added to a dry THF (5 ml) solution of **1** (0.25 mmol), **2** (0.25 mmol), and *tert*-BuOH (0.25 ml) at the temperature indicated in Tables 2, 3. A 0.1 M SmI_2 solution in THF (7.5 ml, 0.75 mmol) was then added dropwise to the reaction mixture. According to the procedure (method A) described above, compound **3** was obtained.

Method C: Under an argon atmosphere, a 0.1 M SmI_2 solution in THF (7.5 ml, 0.75 mmol) was added dropwise to a dry THF (5 ml) solution of **1** (0.25 mmol), **2** (0.25 mmol), *tert*-BuOH (0.25 ml), and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA, 0.5 ml) at the temperature indicated in Table 3. According to the procedure (method A) described above, compound **3** was obtained.

Method D: Under an argon atmosphere, a 0.1 M SmI_2 solution in THF (7.5 ml, 0.75 mmol) was added dropwise to a dry THF (5 ml) solution of **1** (0.25 mmol), **2** (0.25 mmol), *tert*-BuOH (0.25 ml), and HMPA (0.5 ml) at the temperature indicated in Table 3. According to the procedure (method A) described above, compound **3** was obtained.

***N*,*N*-Dibenzyl-3-(1-hydroxycyclohex-1-yl)propanamide (3a)** Colorless viscous oil. IR (neat): 3425 (OH), 1625 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.24—1.65 (10H, m), 1.68 (1H, br s), 1.89 (2H, t, J = 7.1 Hz), 2.57 (2H, t, J = 7.1 Hz), 4.61 (2H, s), 4.84 (2H, s), 7.15—7.39 (10H, m). MS *m/z*: 352 (M$^+$ + 1). *Anal.* Calcd for $C_{23}H_{29}NO_2$: C, 78.59; H, 8.32; N, 3.99. Found: C, 78.48; H, 8.42; N, 3.99.

***N*,*N*-Dibenzyl-4-hydroxy-4-phenylpentanamide (3b)** Colorless viscous oil. IR (neat): 3410 (OH), 1620 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.57 (3H, s), 2.12—2.23 (1H, m), 2.27—2.46 (3H, m), 4.26 (1H, d, J = 17.2 Hz), 4.34 (1H, d, J = 17.0 Hz), 4.57 (2H, s), 4.61 (1H, s), 6.99 (2H, d, J = 6.5 Hz), 7.18—7.34 (11H, m), 7.44 (2H, d, J = 7.6 Hz). MS *m/z*: 356 (M$^+$ − OH). *Anal.* Calcd for $C_{25}H_{27}NO_2$: C, 80.39; H, 7.29; N, 3.75. Found: C, 80.23; H, 7.29; N, 3.96.

***N*,*N*-Dibenzyl-4-hydroxy-4,4-diphenylbutanamide (3c)** Colorless prisms, mp 119—120 °C (MeCN). IR (KBr): 3280 (OH), 1640 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.49 (2H, t, J = 6.5 Hz), 2.76 (2H, t, J = 6.0 Hz), 4.32 (2H, s), 4.59 (2H, s), 4.70 (1H, s), 7.02 (2H, dd, J = 7.7, 1.7 Hz), 7.17—7.35 (14H, m), 7.44—7.47 (4H, m). MS *m/z*: 417 (M$^+$ − H_2O). *Anal.* Calcd for $C_{30}H_{29}NO_2$: C, 82.72; H, 6.71; N, 3.22. Found: C, 82.63; H, 6.68; N, 3.29.

***N*,*N*-Dibenzyl-4-ethyl-4-hydroxy-5-methylhexanamide (3d)** Colorless viscous oil. IR (neat): 3450 (OH), 1630 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.85 (3H, t, J = 7.4 Hz), 0.89 (3H, d, J = 6.9 Hz), 0.90 (3H, d, J = 6.9 Hz), 1.44 (2H, q, J = 7.7 Hz), 1.71—1.83 (2H, m), 1.94—2.04 (1H, m), 2.54 (2H, m), 2.73 (1H, s), 4.48 (2H, s), 4.59 (1H, d, J = 14.8 Hz), 4.65 (1H, d, J = 14.8 Hz), 7.16—7.40 (10H, m). MS *m/z*: 353 (M$^+$), 335 (M$^+$ − H_2O). HRMS Calcd for $C_{23}H_{31}NO_2$ (M$^+$): 353.235480. Found: 353.235001.

***N*,*N*-Dibenzyl-4-hydroxy-4-methyldecanamide (3e)** Colorless viscous oil. IR (neat): 3420 (OH), 1635 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.87 (3H, t, J = 6.7 Hz), 1.12 (3H, s), 1.17—1.43 (10H, m), 1.77—1.86 (1H, m), 1.90—2.20 (1H, m), 2.55 (2H, dd, J = 6.9, 2.2 Hz), 2.67 (1H, br s), 4.29 (2H, s), 4.59 (1H, d, J = 15.1 Hz), 4.65 (1H, d, J = 16.0 Hz), 7.15—7.40 (10H, m). MS *m/z*: 382 (M$^+$ + 1), 364 (M$^+$ − H_2O). *Anal.* Calcd for $C_{25}H_{35}NO_2$: C, 78.68; H, 9.25; N, 3.67. Found: C, 78.58; H, 9.22; N, 3.81.

***N*,*N*-Dibenzyl-3-(1-hydroxy-2-cyclopent-1-yl)propanamide (3f)** Colorless viscous oil. IR (neat): 3420 (OH), 1640 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.81—1.99 (2H, m), 2.06 (2H, td, J = 7.0, 1.9 Hz), 2.18—2.30 (1H, m), 2.41—2.52 (1H, m), 2.61 (2H, t, J = 7.0 Hz), 3.11 (1H, br s), 4.48 (2H, s), 4.62 (2H, s), 5.69 (1H, m), 5.84 (1H, m), 7.15—7.40 (10H, m). MS *m/z*: 335 (M$^+$), 317 (M$^+$ − H_2O). HRMS Calcd for $C_{22}H_{23}NO$ (M$^+$ − H_2O): 317.177965. Found: 317.178299.

***N*,*N*-Dibenzyl-3-(2-hydroxy-1,2,3,4-tetrahydronaphth-2-yl)propanamide (3g)** Colorless viscous oil. IR (neat): 3400 (OH), 1630 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.70—1.79 (1H, m), 1.87—1.96 (1H, m), 2.01 (2H, t, J = 6.9 Hz), 2.66 (2H, t, J = 6.9 Hz), 2.80 (2H, s), 2.70—2.86 (1H, m), 2.95—3.06 (1H, m), 3.40 (1H, br s), 4.51 (2H, s), 4.64 (2H, s), 7.00—7.41 (14H, m). MS *m/z*: 399 (M$^+$), 381 (M$^+$ − H_2O). *Anal.* Calcd for $C_{27}H_{29}NO_2$: C, 81.17; H, 7.32; N, 3.51. Found: C, 80.90; H, 7.52; N, 3.70.

***N*,*N*-Dibenzyl-4-hydroxy-4-phenylbutanamide (3h)** Colorless viscous oil. IR (neat): 3400 (OH), 1620 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.05—2.27 (2H, m), 2.58 (2H, t, J = 6.5 Hz), 4.01 (1H, d, J = 4.1 Hz), 4.42 (2H, s), 4.59 (1H, d, J = 14.8 Hz), 4.67 (1H, d, J = 14.8 Hz), 4.84 (1H, m), 7.11 (2H, d, J = 6.8 Hz), 7.22—7.36 (13H, m). MS *m/z*: 358 (M$^+$ − H), 341 (M$^+$ − H_2O). *Anal.* Calcd for $C_{24}H_{25}NO_2$: C, 80.19; H, 7.01; N, 3.90. Found: C, 80.01; H, 7.23; N, 4.07.

***N*,*N*-Dibenzyl-4-hydroxyundecanamide (3i)** Colorless viscous oil. IR (neat): 3425 (OH), 1630 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.88 (3H, t, J = 6.8 Hz), 1.25—1.49 (12H, m), 1.80 (1H, m), 1.88 (1H, m), 2.60 (2H, td, J = 6.9, 1.9 Hz), 3.09 (1H, br s), 3.61 (1H, m), 4.47 (2H, s), 4.54 (1H, d, J = 14.8 Hz), 4.66 (1H, d, J = 14.8 Hz), 7.13—7.39 (10H, m) ppm. MS *m/z*: 381 (M$^+$). HRMS Calcd for $C_{25}H_{35}NO_2$ (M$^+$): 381.266780. Found: 381.266721.

***N*,*N*-Dibenzyl-3-(1-hydroxycyclohex-1-yl)-2-methylpropanamide (3j)** Colorless prisms, mp 72—73 °C (pentane–iso-Pr_2O). IR (neat): 3440 (OH), 1615 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.16 (3H, d, J = 6.9 Hz), 1.13—1.63 (10H, m), 1.46 (1H, dd, J = 14.5, 2.8 Hz), 1.97 (1H, s), 2.30 (1H, dd, J = 14.5, 10.0 Hz), 2.97 (1H, m), 4.28 (1H, d, J = 14.6 Hz), 4.44 (1H, d, J = 17.2 Hz), 4.62 (1H, d, J = 16.8 Hz), 4.96 (1H, d, J = 14.6 Hz), 7.20—7.40 (10H, m). MS *m/z*: 365 (M$^+$), 347 (M$^+$ − H_2O). *Anal.* Calcd for $C_{24}H_{31}NO_2$: C, 78.86; H, 8.55; N, 3.84. Found: C, 78.82; H, 8.62; N, 3.92.

(2*R,4*S**)-*N*,*N*-Dibenzyl-4-hydroxy-2-methyl-4-phenylpentanamide (3k$_1$) (Less Polar Component)** Colorless prisms, mp 92—93 °C (iso-Pr_2O). IR (KBr): 3420 (OH), 1635 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.00 (3H, d, J = 6.9 Hz), 1.54 (3H, s), 2.01 (1H, dd, J = 14.3, 2.2 Hz), 2.52—2.60 (1H, m), 2.69 (1H, dd, J = 14.3, 10.5 Hz), 3.46 (1H, s), 3.94 (1H, d, J = 16.5 Hz), 4.21 (1H, d, J = 16.4 Hz), 4.53 (1H, d, J = 14.8 Hz), 4.60 (1H, d, J = 14.7 Hz), 6.92 (2H, dd, J = 6.6, 2.1 Hz), 7.18—7.40 (13H, m). MS *m/z*: 387 (M^+), 369 ($M^+ - H_2O$). HRMS Calcd for $C_{26}H_{29}NO_2$ (M^+): 387.219829. Found: 387.218108.

(2*R,4*R**)-*N*,*N*-Dibenzyl-4-hydroxy-2-methyl-4-phenylpentanamide (3k$_2$) (More Polar Component)** Colorless viscous oil. IR (neat): 3420 (OH), 1625 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.20 (3H, d, J=6.9 Hz), 1.42 (3H, s), 1.86 (1H, dd, J=14.4, 3.6 Hz), 2.61 (1H, dd, J=14.7, 8.9 Hz), 2.90 (1H, s), 2.94—3.01 (1H, m), 4.23 (1H, d, J=14.9 Hz), 4.27 (1H, d, J=16.8 Hz), 4.53 (1H, d, J=17.3 Hz), 4.95 (1H, d, J=14.6 Hz), 7.19—7.40 (13H, m), 7.44 (2H, d, J=8.6 Hz). MS *m/z*: 387 (M^+), 369 ($M^+ - H_2O$). HRMS Calcd for $C_{26}H_{29}NO_2$ (M^+): 387.219829. Found: 387.222572.

***N*,*N*-Dibenzyl-3-(1-hydroxycyclohex-1-yl)butanamide (3l)** Colorless viscous oil. IR (neat): 3440 (OH), 1630 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.99 (3H, d, J=6.8 Hz), 1.12—1.33 (2H, m), 1.45—1.64 (8H, m), 2.19 (1H, m), 2.29 (1H, dd, J=15.3, 6.9 Hz), 2.41 (1H, br s), 2.76 (1H, dd, J=15.3, 4.4 Hz), 4.45 (1H, d, J=17.3 Hz), 4.53 (1H, d, J=17.3 Hz), 4.55 (1H, d, J=14.8 Hz), 4.68 (1H, d, J=14.6 Hz), 7.16—7.40 (10H, m). MS *m/z*: 365 (M^+), 347 ($M^- - H_2O$). *Anal.* Calcd for $C_{24}H_{31}NO_2$: C, 78.86; H, 8.55; N, 3.84. Found: C, 79.06; H, 8.72; N, 3.96.

***N*,*N*-Dibenzyl-4-hydroxy-3-methyl-4-phenylpentanamide (3m) (Diastereomixture)** Colorless viscous oil. IR (neat): 3430 (OH), 1620 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 0.88 (2.31H, d, J=7.0 Hz), 1.12 (0.69H, d, J=6.9 Hz), 1.51 (0.69H, s), 1.58 (2.31H, s), 2.19—2.29 (1H, m), 2.45—2.64 (2H, m), 3.81 (0.77H, s), 4.26 (0.23H, d, J=17.1 Hz), 4.33 (0.23H, d, J=17.1 Hz), 4.38 (1.54H, s), 4.43 (0.23H, s), 4.50 (0.23H, d, J=14.8 Hz), 4.57 (0.77H, d, J=14.7 Hz), 4.59 (0.23H, d, J=14.7 Hz), 4.68 (0.77H, d, J=14.7 Hz), 6.97 (0.46H, d, J=7.2 Hz), 7.09 (1.54H, d, J=7.0 Hz), 7.14—7.46 (13H, m). MS *m/z*: 387 (M^+), 369 ($M^+ - H_2O$). HRMS Calcd for $C_{26}H_{29}NO_2$ (M^+): 387.219829. Found: 387.217186. *Anal.* Calcd for $C_{26}H_{29}NO_2$: C, 80.58; H, 7.54; N, 3.61. Found: C, 80.10; H, 7.61; N, 3.72.

***N*,*N*-Dibenzyl-4-(1-hydroxycyclohex-1-yl)-3-methylbutanamide (3n)** Colorless viscous oil. IR (neat): 3320 (OH), 1625 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.05 (6H, s), 1.24—1.35 (2H, m), 1.52—1.75 (8H, m), 2.56 (2H, s), 4.52 (2H, s), 4.63 (2H, s), 4.81 (1H, s), 7.16 (2H, d, J=7.6 Hz), 7.22—7.41 (8H, m). MS *m/z*: 379 (M^+), 362 ($M^+ - OH$). HRMS Calcd for $C_{25}H_{33}NO_2$ (M^+): 379.251130. Found: 379.250473.

***N*-Benzyl-3-(1-hydroxycyclohexyl)propanamide (6)** 1) Under atmospheric pressure: A mixture of **3a** (0.197 g, 0.56 mmol), 20% $Pd(OH)_2$ on carbon (0.197 g), and MeOH (10 ml) was stirred at room temperature under H_2 gas (1 atm) for 3 d. The catalyst was removed by filtration through a short pad of Celite 545® with MeOH (300 ml), and the solvent was evaporated under reduced pressure to give an oily residue, which was purified by PTLC (AcOEt) to give **6** (0.041 g, 28%) as colorless prisms. mp 94—96 °C (iso-Pr_2O). IR (KBr): 3200 (OH), 1610 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.24—1.60 (10H, m), 1.80 (2H, t, J=7.5 Hz), 2.34 (2H, t, J=7.4 Hz), 2.62 (1H, br s), 4.40 (2H, d, J=5.8 Hz), 6.21 (1H, br s), 7.24—7.34 (5H, m). MS *m/z*: 262 ($M^+ + H$), 244 ($M^+ - OH$). *Anal.* Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.40; H, 8.91; N, 5.46.

2) Under a pressure of 5 atm: A mixture of **3a** (0.120 g, 0.34 mmol), 20% $Pd(OH)_2$ on carbon (0.220 g), and MeOH (5 ml) was stirred at room temperature under H_2 gas (5 atm) for 12 h. The catalyst was removed by filtration through a short pad of Celite 545® with MeOH (300 ml), and the solvent was evaporated under reduced pressure to give an oily residue, which was purified by PTLC (hexane : AcOEt = 1 : 1) to give **6** (0.048 g, 54%) as colorless crystals and the γ-lactone (**7**)$^{3)}$ (0.019 g, 36%) as a colorless oil.

Birch Reduction of 3a 1) Li/Liquid NH_3: Liquid NH_3 (20 ml) was added to a dry THF (5 ml) solution of **3a** (0.090 g, 0.256 mmol) and *tert*-BuOH (1 ml) at −78 °C. To this solution, Li (0.010 g, 1.28 mmol) was added. The reaction mixture was stirred at −78 °C for 1 h, then powdered NH_4Cl (3.0 g) was added. The resulting mixture was warmed to room temperature and stirred until evolution of NH_3 ceased. Saturated aqueous NH_4Cl (20 ml) was added to the residue, and the aqueous layer was extracted with AcOEt (20 ml × 3). The extract was dried over Na_2SO_4 and the solvent was evaporated off under reduced pressure to give an oily residue, which was purified by PTLC (hexane : AcOEt = 1 : 1) to give **8** (0.024 g, 36%) as colorless crystals and **9** (0.017 g, 43%) as a colorless oil.

***N*-(2′,3′-Dihydrobenzyl)-3-(1-hydroxycyclohexyl)propanamide (8)** Colorless scales, mp 108—109 °C (iso-Pr_2O). IR (KBr): 3353 (OH), 3261 (NH), 1645 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.25—1.64 (10H, m), 1.80 (2H, t, J=7.4 Hz), 2.34 (2H, t, J=7.2 Hz), 2.39 (1H, br s), 2.57—2.63 (2H, m), 2.67—2.73 (2H, m), 3.78 (2H, d, J=5.8 Hz), 5.58 (1H, br s), 5.65—5.73 (3H, m). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 23.84, 27.38, 28.11, 28.84, 32.01, 38.53, 39.26, 46.83, 72.12, 122.59, 125.46, 133.49, 142.79, 175.58. MS *m/z*: 262($M^+ - H$), 244 ($M^+ - OH$). HRMS Calcd for $C_{16}H_{25}NO_2$: 263.188529. Found: 263.189842.

3-Hydroxy-2-oxaspiro[4.5]decane (9) Colorless oil. IR (neat): 3400 (OH) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.33—2.04 (14H, m), 2.85 (1H, br s), 5.50 (1H, d, J=4.1 Hz). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 23.89, 25.41, 33.01, 33.60, 37.38, 39.95, 84.85, 97.93, 98.21. MS *m/z*: 156 (M^+), 139 ($M^+ - OH$). HRMS Calcd for $C_9H_{16}O_2$ (M^+): 156.115030. Found: 156.115898.

2) Ca/Liquid NH_3: Liquid NH_3 (20 ml) was added to a dry THF (5 ml) solution of **3a** (0.188 g, 0.53 mmol) and *tert*-BuOH (1 ml) at −78 °C. Then, Ca (0.210 g, 5.3 mmol) was added to the solution. The reaction mixture was stirred at −78 °C for 1 h, then powdered NH_4Cl (3.0 g) was added. The resulting mixture was warmed to room temperature and stirred until evolution of NH_3 ceased. Saturated aqueous NH_4Cl (20 ml) was added to the residue, and the aqueous layer was extracted with AcOEt (20 ml × 3). The extract was dried over Na_2SO_4 and the solvent was evaporated off under reduced pressure to give an oily residue, which was purified by PTLC (hexane : AcOEt = 1 : 1) to give **8** (0.074 g, 53%) as colorless crystals and **9** (0.010 g, 12%) as a colorless oil.

1-(3-*N*,*N*-Dibenzylaminopropyl)cyclohexanol (10) A dry THF (3 ml) solution of **3a** (0.145 g, 0.41 mmol) was added to a suspension of LAH (0.026 g, 0.69 mmol) in THF (5 ml) at 0 °C under an argon atmosphere. The reaction mixture was stirred at room temperature overnight, then cooled in an ice bath, and saturated NH_4Cl (5 ml) was carefully added. The resulting deposit was collected by filtration on Celite®. The deposit was washed with Et_2O (20 ml). The filtrate was dried over Na_2SO_4 and evaporated under reduced pressure to give an oily residue, which was purified by PTLC (hexane : AcOEt = 4 : 1) to give **10** (0.084 g, 61%) as a colorless viscous oil. IR (neat): 3420 (OH) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.24—1.66 (14H, m), 2.45 (1H, br s), 2.45 (2H, t, J=6.6 Hz), 3.58 (4H, s), 7.22—7.39 (10H, m). MS *m/z*: 337 (M^+), 320 ($M^+ - OH$). HRMS Calcd for $C_{23}H_{31}NO$ (M^+): 337.240565. Found: 337.240921.

1-(3-Aminopropyl)cyclohexanol (11) A mixture of **10** (0.078 g, 0.23 mmol), 20% $Pd(OH)_2$ on carbon (0.100 g), and MeOH (5 ml) was stirred at room temperature under H_2 gas (1 atm) for 24 h. The catalyst was removed by filtration through a short pad of Celite 545® with MeOH (300 ml), and the filtrate was evaporated under reduced pressure to give **11** (0.036 g, quantitative yield) as a colorless oil. bp 120—130 °C/1 torr (oil bath temperature). IR (neat): 3350 (NH_2, OH) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.24—1.63 (14H, m), 2.52 (3H, br s), 2.75 (2H, t, J=6.3 Hz). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 23.95, 27.57, 27.74, 39.98, 41.93, 43.97, 71.64. MS *m/z*: 158 (M^+), 140 ($M^+ - H_2O$). HRMS Calcd for $C_9H_{19}NO$ (M^+): 157.146664. Found: 157.148022.

X-Ray Structure Determination of 3k$_1$ Colorless prism crystals of **3k$_1$** were grown from heptane. Diffraction measurements were performed on a Mac Science DIP 2000 using graphite-monochromated MoK_α radiation (λ=0.71073 Å). Crystal data: $C_{26}H_{29}NO_2$, M_r=387.50, triclinic, space group *P*-1, a=9.494(0) Å, b=10.731(0) Å, c=12.362(0) Å, α=73.03 degrees, β=89.93 degrees, γ=76.91 degrees, V=1073.742(0) Å^3, Z=2, D_c=1.10 g/cm^3. The structure was solved by a direct method and refined by a full-matrix least-squares methods using 2739 reflections. The final refinement converged to R=0.0482 and R_w=0.0565.

References and Notes

1) Girard P., Namy J. L., Kagan H. B., *J. Am. Chem. Soc.*, **102**, 2693—2698 (1980); Kagan H. B., Namy J. L., Girard P., *Tetrahedron*, **37** suppl., 175—180 (1981).

2) Soderquist J. A., *Aldrichimica Acta*, **24**, 15—23 (1991); Molander G. A., *Chem. Rev.*, **92**, 29—68 (1992); Molander G. A., *Org. React.*, **46**, 211—367 (1994); Molander G. A., Harris C. R., *Chem. Rev.*, **96**, 307—338 (1996) and references cited therein; Inanaga J., *Yuki Gosei Kagaku Kyokaishi*, **47**, 200—211 (1989).

3) Fukuzawa S., Nakanishi A., Fujinami T., Sakai S., *J. Chem. Soc., Chem. Commun.*, **1986**, 624—625; *idem, J. Chem. Soc., Perkin Trans., 1*, **1988**, 1669—1675.

4) Otsubo K., Inanaga J., Yamaguchi M., *Tetrahedron Lett.*, **27**, 5763—5764 (1986).

5) Ujikawa O., Inanaga J., Yamaguchi M., *Tetrahedron Lett.*, **30**, 2837—2840 (1989).

6) Inanaga J., Handa Y., Tabuchi T., Otsubo K., Yamaguchi M.,

Hanamoto T., *Tetrahedron Lett.*, **32**, 6557—6558 (1991).

7) Aoyagi Y., Yoshimura M., Tsuda M., Tsuchibuchi T., Kawamata S., Tateno H., Asano K., Nakamura H., Obokata M., Ohta A., Kodama Y., *J. Chem. Soc., Perkin Trans., 1*, **1995**, 689—692.

8) Aoyagi Y., Asakura R., Kondoh N., Yamamoto R., Kuromatsu T., Shimura A., Ohta A., *Synthesis*, in press (1996).

9) Hasegawa T., Watabe M., Aoyama H., Omote Y., *Tetrahedron*, **33**, 485—488 (1977).

10) Inanaga J., Sakai S., Hanada Y., Yamaguchi M., Yokoyama Y., *Chem. Lett.*, **1991**, 2117—2118.