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Generation of (α-Aminoalkyl)samarium(III) by a New Method of Metalation and its Carbon–Carbon Bond-forming Reactions

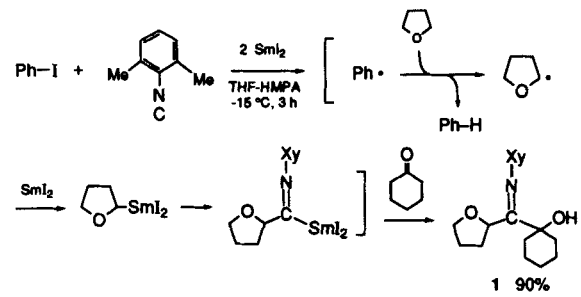
Masahiro Murakami,* Minoru Hayashi and Yoshihiko Ito*
Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Yoshida, Kyoto 606-01, Japan

(α-Aminoalkyl)samarium(III) is generated on treatment of a tertiary amine having a pendant *o*-iodobenzyl group on the nitrogen atom with samarium(II) iodide (SmI_2) in tetrahydropyran containing hexamethylphosphoramide. Deuterium incorporation experiments demonstrate that the reaction proceeds via a delivery of a radical center from the pendant benzyl group to the α-position of nitrogen and the following one-electron transfer from SmI_2 to the delivered radical. Subsequent nucleophilic addition of (α-aminoalkyl)samarium (III) to various electrophiles, such as enolizable ketones, isocyanate and isocyanide, furnishes the C–C bond formation products in good yields. The pendant benzyl group of the product can be readily removed by hydrogenolysis to give the corresponding secondary amine. Therefore, the present reaction provides a useful synthetic process for a variety of nitrogen-containing compounds including β-amino alcohols and α-amino acid derivatives, disclosing a new method for metalation and C–C bond formation.

Keywords: (α-aminoalkyl)samarium(III); metalation; samarium(II) iodide; 1,5-hydrogen shift; tetrahydropyran

INTRODUCTION

The formation of C–C bonds at the α-position of a nitrogen atom is of great importance for the elaboration of amines and, in particular, the synthesis of nitrogen-containing natural products and biologically active compounds. The α-position of an amine can gain an electrophilic reactivity via iminium ions. Unlike sulfur, however, the ability of nitrogen for the generation of an α-carbanion is poor, probably due to the electronic donor character of nitrogen. Whereas amines having a stabilizing or an electron-withdrawing group on nitrogen can be lithiated with strong bases such as lithium diisopropylamide and alkyllithium,[1] carbanions of simple tertiary amines are difficult to access, and deprotonation of those amines requires even more basic conditions.[2,3] Therefore, the generation of a nucleophilic equivalent to an α-amino carbanion remains an active area of research.



Scheme 1 Xy = 2,6-xylyl.

We have been studying metalation of the isocyano carbon by the reaction of an isocyanide with organometallic compounds,[4] and recently developed the samarium(II) iodide (SmI_2)-mediated[5] three-component coupling reaction of an organic halide, 2,6-xylyl isocyanide, and a carbonyl compound.[6] It was found, during the course of the investigation, that the use of iodobenzene as the organic halide in tetrahydrofuran (THF) solvent resulted in the formation of THF-containing adduct **1** (Scheme 1).[6b] It has been reported that the phenyl radical involved in the SmI_2-mediated reaction, in THF solvent, abstracts hydrogen from THF more rapidly than if it is further reduced by SmI_2.[7] In regard to the mechanism of the SmI_2-mediated three-component coupling reaction, the alkyl halide is primarily transformed to alkylsamarium(III) to couple with isocyanide.[6b] Therefore, the formation of **1** is accounted for by assuming that (i) the

† Authors to whom correspondence should be addressed.

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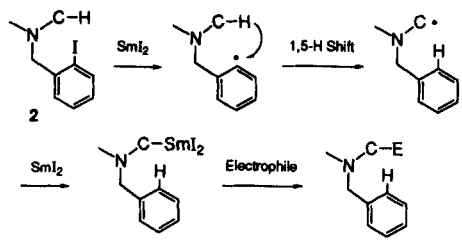
phenyl radical initially formed abstracts hydrogen from THF to give the tetrahydrofuryl radical, and (ii) further reduction of the tetrahydrofuryl radical by SmI_2 generates (tetrahydrofuryl)samarium(III), which undergoes α-addition to isocyanide. Thus, the hydrogen atom at the 2-position of tetrahydrofuran is replaced by samarium through intermolecular radical delivery and subsequent reduction of the delivered radical with SmI_2.

This interesting sequence of metalation involving a radical–solvent reaction led us to explore its synthetic application with a view to forming an α-amino carbanion equivalent. The present paper describes the details of our study on the generation of (α-aminoalkyl)samarium(III) by a new method of methalation and its C–C bond-forming reactions.[8]

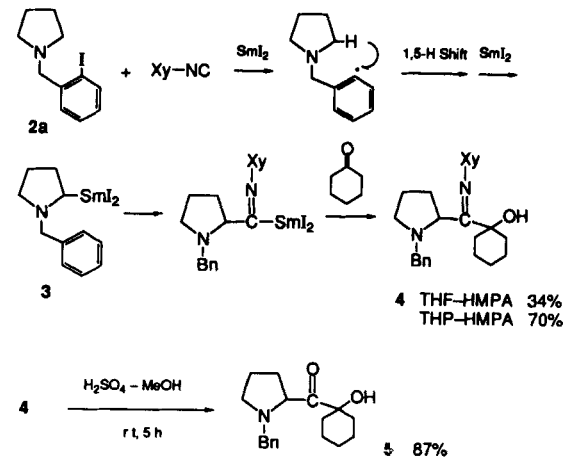
RESULTS AND DISCUSSION

1,5-Hydrogen shift is an efficient process, and has met a number of interesting applications to radical reactions in organic synthesis.[9] It is also known that an amino substituent causes a large rate enhancement of intermolecular hydrogen abstraction from the α-carbon atom by phenyl radicals.[10] Based on these facts, we designed the substrate amine **2** in order to set up an intramolecular variant of the sequence mentioned above, hoping to metalate the α-position of the amine with samarium in a regiospecific manner (Scheme 2).

A tertiary amine **2a** having a pendant *o*-iodobenzyl group on the nitrogen was easily prepared in high yield by treatment of pyrrolidine with *o*-iodobenzyl bromide at room temperature in THF–aqueous K_2CO_3. A mixture of **2a** and 2,6-xylyl isocyanide was treated with SmI_2 in THF containing hexamethylphosphoramide (HMPA)[7a] at -10 °C. The deep purple color disappeared in 3 h, to suggest consumption of SmI_2. Subsequent treatment of the reaction mixture with cyclohexanone afforded α-amino α'-hydroxy imine **4** in



Scheme 2



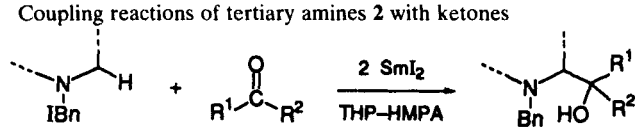
Scheme 3 Bn, benzyl; rt, room temperature.

34% yield. The pyrrolidine skeleton coupled with the isocyanide regioselectively at the 2-position, which supported the mechanism involving (pyrrolidin-2-yl)samarium(III) **3** as depicted in Scheme 3 (*vide infra* for the details). Since a considerable amount of **1** was also formed together with **4**, the desired intramolecular hydrogen abstraction by the initial aryl radical competed with intermolecular hydrogen abstraction from THF. The use of tetrahydropyran (THP) as solvent[11] suppressed intermolcular hydrogen abstraction to improve the yield of **4** to 70%. The imino group of **4** was next hydrolyzed by treatment with aqueous acid to give rise to the corresponding α-amino α'-hydroxy ketone **5**.

A series of tertiary amines **2**, prepared by benzylation of the parent secondary amines, was subjected to the coupling reaction with ketones; a mixture of **2** and a ketone was treated with SmI_2 in THP–HMPA at -10 °C (Table 1). Cyclic amines **2a–2e**, from five- to eight-membered ones, were successfully coupled with ketones at the α-position to furnish 2-aminoalcohols **6a–6i**. Moderate stereoselection was observed in the reaction of **2** with 3-methyl-2-butanone (runs 3, 5). It was noteworthy that a single diastereomer was produced when 3,3-dimethyl-2-butanone was used as the ketone (runs 4, 6). Acyclic amines **2f–2h**, **2k** also underwent efficient C–C bond formation with ketones. Notably, the presence of the N–H bond of the secondary amine **2k** is tolerated, which suggests the less basic character of the (α-aminoalkyl)samarium-(III) (run 15).

Results of runs 10–14 concern the effect of the pendant group. (2-Iodo-6-methylphenyl)methyl

Table 1 Coupling reactions of tertiary amines **2** with ketones



2 IBn : *o*-iodobenzyl

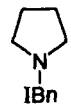
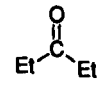
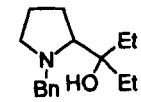
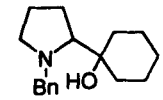
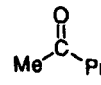
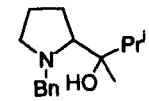
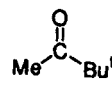
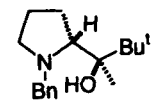
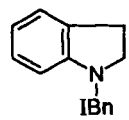
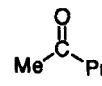
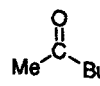
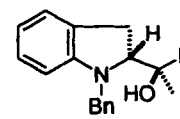
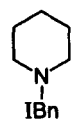
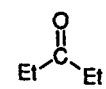
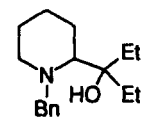
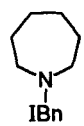
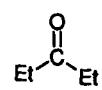
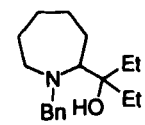
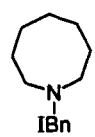
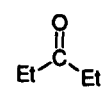
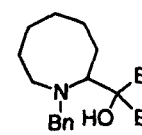
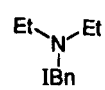
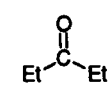
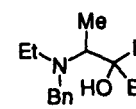
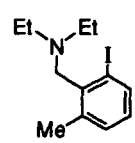
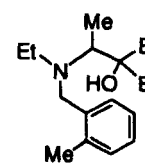
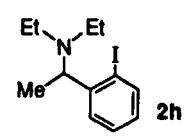
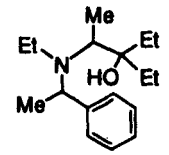
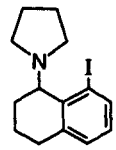
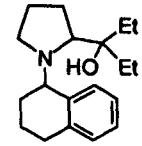
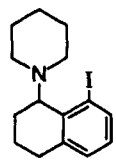
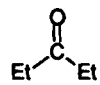
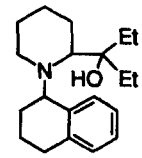
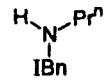
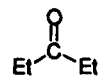
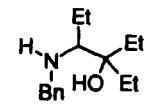
Run	2	Ketone	Product		Yield (%)[a]
1	 **2a**			**6a**	83
2	**2a**			**6b**	63
3	**2a**			**6c**	77 (82 : 18)[b]
4	**2a**			**6d**	87 (>95 : 5)
5	 **2b**			**6e**	83 (76 : 24)[b]
6	**2b**			**6f**	68 (>95 : 5)
7	 **2c**			**6g**	60
8	 **2d**			**6h**	88
9	 **2e**			**6i**	79
10	 **2f**			**6j**	74
11	 **2g**			**6k**	87

Table 1 *Continued*

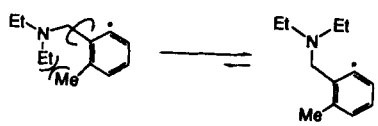
Run	2	Ketone	Product	Yield (%)[a]
12	 **2h**		 **6l**	92 (63 : 37)[b]
13	 **2l**		 **6m**	98 (56 : 44)[b]
14	 **2j**		 **6n**	99 (81 : 19)[b]
15	 **2k**		 **6o**	62

Abbreviation: Bn, Benzyl.

[a] Ratios in parentheses refer to the diasteromeric ratios of **6**.

[b] The stereochemistry is not assigned.

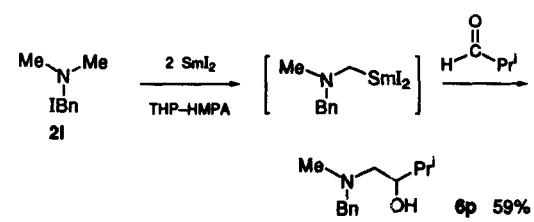
derivative (**2g**) and α-methyl-*o*-iodobenzyl derivative (**2h**) afforded better yields of **6** than simple *o*-iodobenzyl derivative (**2f**) (runs 10–12). Steric repulsion caused by the additional *o*-methyl group of **2g** may force the amino group into the proximity of the aryl radical site (Scheme 4). In particular, considerable improvement of the yield of **6** was observed with 8-iodo-1,2,3,4-tetrahydronaphth-1-yl derivatives **2i** and **2j** (runs 1, 7, 13, 14). The conformation of the pendant group of **2i** and **2j** is fixed in the cyclic structure, where the aryl radical site and the α-position of nitrogen are disposed most favorably for the intramolecular radical transfer. The starting tertiary amines such as **2h–2j** have an asymmetric center in the pendant. However, chiral induction onto the α-position where a C–C bond was formed was poor except the case of **2j** (runs 12–14).



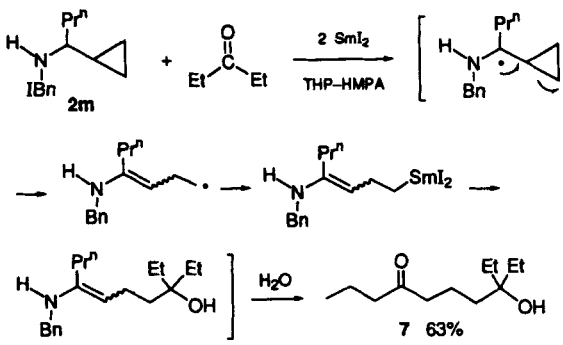
Scheme 4

The generation of (α-aminoalkyl)samarium(III) was usually carried out in the presence of a ketone because of its instability. When an aldehyde was used instead of a ketone, the reaction was complicated by competing pinacol coupling.[12] The cross-coupling of **2l** with an aldehyde was achieved by adding an aldehyde to the reaction mixture after the generation of (α-aminoalkyl)-samarium(III), although the yield of **6p** was moderate enough to suggest intermediate instability (Scheme 5).

The reaction of (1-cyclopropylbutyl)amine **2m** with 3-pentanone afforded δ-hydroxyketone **7** after aqueous workup (Scheme 6). The reaction site was translocated from the α-position of the



Scheme 5 IBn, *o*-iodobenzyl; HMPA, hexamethylphosphoramide.



Scheme 6

nitrogen atom to the δ-position via a ring-opening rearrangement of the α-radical.

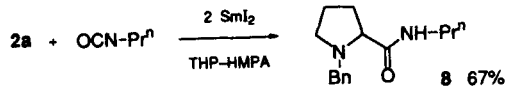
When propyl isocyanate was reacted with **2a**, an amino acid derivative **8** was produced in 67% yield (Scheme 7).

The original pendant on the nitrogen atom, i.e. the *o*-iodobenzylic group, has been reduced during the course of reaction. It should be noted that the resultant pendant of the product **6** can be easily removed by hydrogenolysis to give the deprotected secondary amine. Therefore, the present reactions provide a useful and general method for the synthesis of a variety of nitrogen-cotaining compounds including β-amino alcohols and α-amino acid derivatives.

The stereochemistry of **6d** was determined by the nuclear Overhauser effect (nOe) experiment (^{1}H NMR) of the bicyclic compound **10** derived from the deprotected amine **9** (Scheme 8).

DISCUSSION OF THE POSSIBLE MECHANISM

It has been mentioned in our previous paper[6b] that, in the SmI_2-mediated coupling of alkyl halide with 2,6-xylyl isocyanide, it is not an alkyl



Scheme 7

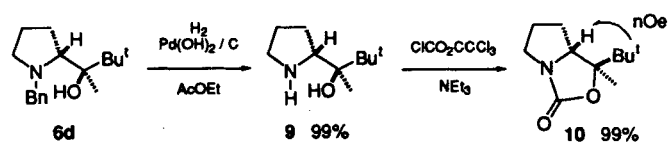
radical but alkylsamarium(III) which adds to the isocyano carbon. Since the amine **2a** also efficiently couples with isocyanide at the α-position (Scheme 3), it is likely that (α-aminoalkyl)-samarium **3** is involved in the present reaction.[13,14]

The *inter*molecular version of the reaction was attempted for comparison; a mixture of 1-benzylpyrrolidine, iodobenzene and 3-pentanone was treated with SmI_2 in THP–HMPA, and no C–C bond formation product **6a** was obtained (Scheme 9). Accordingly, the reactive site is translocated not intermolecularly but *intra*molecularly from the pendant aryl group to the α-position of nitrogen.

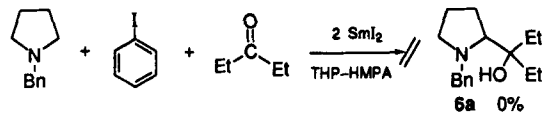
Then, two routes are conceivable for the translocation (Scheme 10). The first, **A**, is the translocation of the radical site; 1,5-*hydrogen* transfer is followed by a futher one-electron transfer from SmI_2 to the resultant alkyl radical. The second (**B**) is the formation of arylsamarium(III) followed by 1,5-*proton* transfer.

Although route **B**, involving the formation of arylsamarium(III), is unlikely on the basis of the precedent reports,[7] the experiments illustrated in Scheme 11 were carried out in order to obtain further support for route **A**. When the cyclic amine **2b** was treated with SmI_2 in the presence of MeOD, deuterium was incorporated not at the *o*-position of the benzyl group but at the α-position of nitrogen in the indoline ring (D-**11**: H-**11** = 92:8). This result eliminates the generation of arylsamarium(III), which would have been deuterated at the *o*-position. In contrast, quenching of aryllithium, formed via *ortho*-lithiation[15] of 1-benzylpyrrolidine, with D_2O furnished not α-deuterated amine but *o*-deuterated derivative **12**, demonstrating that even aryllithium failed to undergo 1,5-proton transfer. Accordingly, 1,5-proton transfer with arylsamarium(III), which should be much less basic than aryllithium, is improbable.

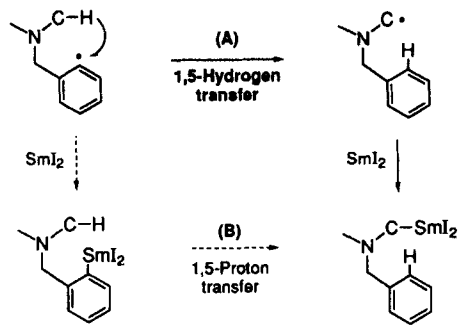
Based on these observations, the mechanism depicted in Scheme 2 seems most likely for the generation of (α-aminoalkyl)samarium(III): (i) de-iodination of the *o*-iodobenzyl group by SmI_2 giving the corresponding aryl radical; (ii) intramolecular 1,5-hydrogen atom transfer producing



Scheme 8



Scheme 9

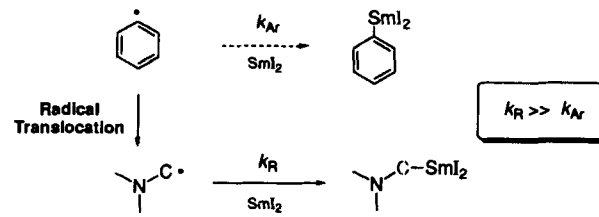


Scheme 10

the α-amino alkyl radical; (iii) one-electron transfer from SmI_2 to the α-amino alkyl radical giving (α-aminoalkyl)samarium(III).

CONCLUSIONS

Metalation by hydrogen–metal exchange has been mostly carried out by abstraction of a proton under strongly basic conditions using alkyllithium or lithium amide. The generation of (α-aminoalkyl)samarium(III) described herein, which constitutes delivery of a radical center from the pendant benzyl group to the α-position of nitrogen and a subsequent one-electron transfer, presents a new method for metalation and C–C bond formation under far less basic conditions. The underlying basis for the success of this novel sequence for metalation are (i) the thermodynamic stability of an α-amino alkyl radical over an aryl radical and (ii) the kinetic lability of an α-amino alkyl radical over an aryl radical toward one-electron transfer from SmI_2 (Scheme 12).

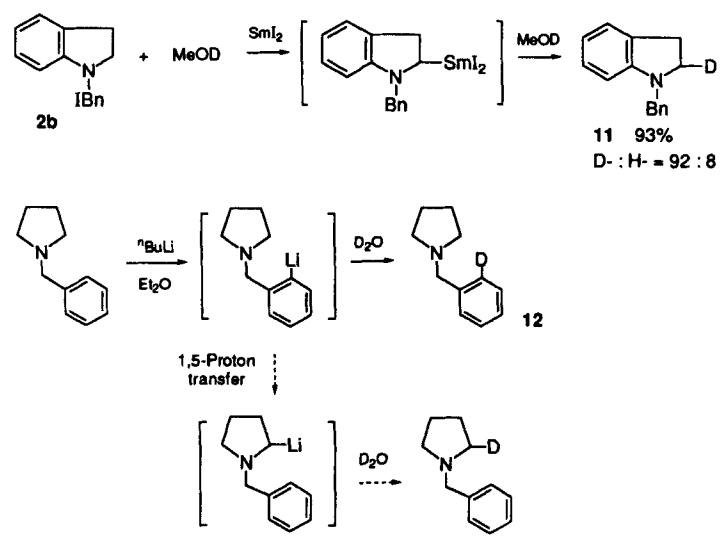


Scheme 12

EXPERIMENTAL

General

Column chromatography was performed with Wakogel C-200 (Wako Pure Chemical Co.), 200-mesh. Preparative thin-layer chromatography was performed with silica gel 60 PF_{245} (E. Merck, Darmstadt, Germany). ^1H and ^{13}C NMR spectra were acquired with a Varian VXR-200 spectrometer at 200 and 50 MHz, respectively, in chloroform-*d* unless otherwise noted. Carbon



Scheme 11

chemical shifts were recorded relative to chloroform-*d* (δ 77.0). Infrared spectra were recorded with a Hitachi 270-30 spectrometer. Mass spectra were recorded with a JEOL JMS-D300 spectrometer. Sodium sulfate (Na_2SO_4) was used to dry organic layers after extraction. Unless otherwise noted, materials were obtained from commercial sources and used after distillation under nitrogen. Tetrahydrofuran and tetrahydropyran were distilled from lithium aluminum hydride ($LiAlH_4$) and ethyl acetate was distilled from calcium hydride (CaH_2). 2,6-Xylyl isocyanide was prepared according to the procedure in the literature.[16] *o*-Iodobenzyl bromide, (2-iodo-6-methylphenyl)methyl bromide and α-methyl-*o*-iodobenzyl bromide were prepared by bromination of *o*-iodobenzyl alcohol, (2-iodo-6-methylphenyl)methanol and α-methyl-*o*-iodobenzyl alcohol, respectively, with CBr_4–PPh_3. 1-Chloro-8-iodo-1,2,3,4-tetrahydronaphthalene was prepared by chlorination of 8-iodo-1,2,3,4-tetrahydronaphthalen-1-ol with CCl_4–PPh_3.

Preparation of *o*-iodobenzylic amines 2

1-(*o*-Iodobenzyl)pyrrolidine (2a)

To a mixture of pyrrolidine (0.80 ml, 9.7 mmol) and *o*-iodobenzyl bromide (890 mg, 3.0 mmol) in THF (3 ml) was added a saturated aqueous solution of potassium carbonate (K_2CO_3) (3 ml), and the reaction mixture was stirred for 1 h. The organic layer was separated and the aqueous layer was extracted twice with ether. The combined extracts were dried, evaporated and the residue was distilled by Kugelrohr (130 °C/0.2 mmHg) to afford **2a** (804 mg, 93%).

o-Iodobenzylic amines **2b**–**2j** and **2l** were prepared from the corresponding secondary amines according to the preceding procedure for **2a**.

(*o*-Iodobenzyl)propylamine (2k)

To a suspension of sodium hydride (NaH) (72 mg, 3.0 mmol) in THF (3 ml) were successively added propylamine (177 mg, 3.0 mmol) and *o*-iodobenzyl bromide (594 mg, 2.0 mmol), and the reaction mixture was stirred for 20 h. Water was added and the mixture was extracted with ether. The combined extracts were dried, evaporated and the residue was distilled by Kugelrohr (140 °C/0.2 mmHg) to afford **2k** (391 mg, 71%).

o-Iodobenzyl amine **2m** was prepared from (1-cyclopropylbutyl)amine according to the preceding procedure for **2k**.

Coupling reactions of 2

1-Benzyl-2-[(1-hydroxycyclohexyl) (2,6-xylylimino)methyl]pyrrolidine (4)

To a mixture of samarium powder (225 mg, 1.5 m-atom) and 1,2-diiodoethane (211 mg, 0.75 mmol) under nitrogen at room temperature was added tetrahydropyran (THP, 7 ml) with vigorous stirring. An exothermic reaction took place and the color changed to deep blue. After stirring for 3 h, the suspension of SmI_2 in THP so formed was cooled (−10 °C), then 2,6-xylyl isocyanide (27 mg, 0.21 mmol), 1-(*o*-iodobenzyl)-pyrrolidine (72 mg, 0.25 mmol) and HMPA (0.37 ml, 2.1 mmol) were added successively. After stirring for 3 h, cyclohexanone (60 mg, 0.61 mmol) was added and the mixture was stirred at −10 °C for 1 h and at 0 °C for 16 h. The cooling bath was removed and saturated aqueous Na_2CO_3 was added. The mixture was extracted with ethyl acetate (AcOEt), and the organic extracts were dried and concentrated. The residue was passed through a short column of silica gel (Et_2O eluent) to remove HMPA. Isolation by preparative thin layer chromatography (Et_2O : hexane = 1:2) afforded **4** (pale yellow oil, 56 mg, 70%).

^{1}H NMR: δ 1.20–2.55 (m, 15H), 2.04 (s, 3H), 2.10 (s, 3H), 2.80–2.90 (m, 1H), 2.96 (d, J = 12.5 Hz, 1H), 3.18 (t, J = 8.9 Hz, 1H), 4.26 (d, J = 12.5 Hz, 1H), 6.85–7.10 (m, 3H), 7.20–7.40 (m, 5H), 7.83 (br s, 1H).

^{13}C NMR: δ 18.2, 18.3, 21.4, 21.8, 22.8, 25.5, 28.8, 39.4, 39.5, 53.2, 60.4, 67.3, 79.3, 122.7, 124.0, 125.5, 127.6, 127.9, 128.0, 128.4, 128.7, 137.9, 147.5, 178.8.

IR (neat): 3196, 2936, 2860, 1714, 1650, 1452, 1202, 990, 768 cm^{-1}. HRMS: calcd for $C_{26}H_{34}N_2O$, m/z 390.2671; found, m/z 390.2662.

(1-Benzylpyrrolidin-2-yl) (1-hydroxycyclohexyl) ketone (5)

A solution of **4** (84 mg, 0.21 mmol) in methanol (MeOH) (5 ml) containing sulfuric acid (H_2SO_4) (0.5 ml) was stirred at 50 °C for 18 h. The mixture was neutralized wit Na_2CO_3, and MeOH was removed under reduced pressure. The residue was extracted with ether, and the organic extracts were subjected to preparative thin-layer chromatograpy (Et_2O : hexane = 1:1) to afford **5** (53 mg, 87%).

^{1}H NMR: δ 1.10–2.36 (m, 15H), 3.03 (ddd, J = 9.8, 7.2, 3.3 Hz, 1H), 3.34 (d, J = 13.1 Hz, 1H), 3.48 (t, J = 8.4 Hz, 1H), 3.99 (d, J = 13.1 Hz, 1H), 6.10–6.80 (br, 1H), 7.18–7.42 (m, 5H).

^{13}C NMR: δ 20.7, 21.0, 23.4, 25.2, 28.3, 35.5, 35.8, 53.4, 59.8, 73.3, 80.6, 127.6, 128.6, 128.7, 137.4, 215.6.

3-(1-Benzylpyrrolidin-2-yl)-3-pentanol (6a)
To a cooled suspension of SmI_2 (0.75 mmol) in THP, prepared as described for **4**, were successively added 1-(*o*-iodobenzyl)pyrrolidine (70 mg, 0.24 mmol), 3-pentanone (18 mg, 0.21 mmol) and HMPA (0.37 ml, 2.1 mmol). After the mixture had been stirred for 4 h, the cooling bath was removed and saturated aqueous Na_2CO_3 was added. The mixture was extracted with AcOEt, and organic extracts were dried and concentrated. The residue was passed through a short column of silica gel (Et_2O eluent) to remove HMPA. Isolation by preparative thin-layer chromatography (Et_2O : hexane = 3 : 2) afforded **6a** (oil, 42 mg, 83%).

^{1}H NMR: δ 0.89 (t, J = 7.4 Hz, 3H), 0.90 (t, J = 7.5 Hz, 3H), 1.25–1.96 (m, 8H), 2.40–2.55 (m, 1H), 2.60–3.00 (m, 3H), 3.61 (d, J = 13.9 Hz, 1H), 4.03 (d, J = 13.9 Hz, 1H), 7.20–7.45 (m, 5H).

^{13}C NMR: δ 7.8, 8.1, 25.0, 26.0, 27.2, 29.3, 55.0, 63.1, 69.8, 76.0, 126.8, 128.0, 128.3, 140.6.

IR (neat): 3488, 2976, 1456, 1374, 736, 700 cm^{-1}.

Analysis calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.38; H, 10.49; N, 5.50%.

1-(1-Benzylpyrrolidin-2-yl)cyclohexanol (6b)
By a procedure similar to that for **6a**, the title compound was obtained from **2a** (70 mg, 0.24 mmol) and cyclohexanone (41 mg, 0.42 mmol) in 63% yield.

^{1}H NMR: 1.00–2.00 (m, 14H), 2.44 (dt, J = 10.3, 6.6 Hz, 1H), 2.53–2.75 (br, 1H), 2.75–3.00 (m, 2H), 3.61 (d, J = 13.9 Hz, 1H), 4.08 (d, J = 13.9 Hz, 1H), 7.19–7.47 (m, 5H).

^{13}C NMR: δ 22.0, 22.1, 25.2, 26.0, 26.9, 33.5, 37.0, 55.2, 63.3, 72.2, 72.9, 126.8, 128.0, 128.3, 140.5.

HRMS: calcd for $C_{11}H_{14}N$ ($M - C_6H_{11}OH$), m/z 160.1126; found m/z 160.1111.

2-(1-Benzylpyrrolidin-2-yl)-3-methyl-2-butanol (6c)
By a procedure similar to that for **6a**, the title compound was obtained as a mixture of diastereomers (82 : 18) from **2a** (73 mg, 0.26 mmol) and 3-methyl-2-butanone (17 mg, 0.20 mmol) in 77% yield.

^{1}H NMR: δ 0.86 and 0.92 (d, J = 6.9 Hz, 3H), 1.00 and 1.02 (d, J = 6.8 Hz, 3H), 1.01 and 1.16 (s, 3H), 1.60–2.00 (m, 5H), 2.40–3.12 (m, 4H), 3.59 and 3.65 (d, J = 13.8 Hz, 1H), 4.07 (d, J = 13.8 Hz, 1H), 7.15–7.45 (m, 5H).

^{13}C NMR δ 17.0, 17.2, 17.4, 17.6, 18.2, 20.3, 25.0, 26.7, 28.2, 33.5, 35.2, 54.9, 55.1, 62.8, 63.5, 69.2, 71.4, 75.9, 76.0, 126.8, 128.0, 128.1, 128.3, 140.5.

IR (neat): 3416, 2976, 1456, 1388, 1100, 924, 734, 700 cm^{-1}. HRMS: calcd for $C_{16}H_{25}NO$, m/z 247.1936; found, m/z 247.1941.

2-(1-Benzylpyrrolidin-2-yl)-3,3-dimethyl-2-butanol (6d)
By a procedure similar to that for **6a**, the title compound was obtained as a single diastereomer from **2a** (73 mg, 0.26 mmol) and 3,3-dimethyl-2-butanone (20 mg, 0.20 mmol) in 87% yield.

^{1} NMR: δ 0.98 (s, 9H), 1.10 (s, 3H), 1.60–2.00 (m, 4H), 2.32–2.50 (m, 1H), 2.80–2.95 (m, 1H), 3.15 (dd, J = 8.8, 3.6 Hz, 1H), 3.51 (d, J = 13.2 Hz, 1H), 3.80–4.20 (br, 1H), 4.09 (d, J = 13.2 Hz, 1H), 7.20–7.40 (m, 5H).

^{13}C NMR: δ 15.2, 25.9, 26.0, 29.7, 36.8, 53.6, 63.1, 67.9, 77.0, 126.9, 128.35, 128.42, 139.9.

IR (neat): 3470, 2968, 1456, 1368, 1126, 1092, 698 cm^{-1}. HRMS: calcd for $C_{17}H_{26}NO$ ($M - H$), m/z 260.2014, found m/z 260.2014.

2-(1-Benzylindolin-2-yl)-3-methyl-2-butanol (6e)
By a procedure similar to that for **6a**, the title compound was obtained as a mixture of diastereomers (73 : 27) from **2b** (82 mg, 0.24 mmol) and 3-methyl-2-butanone (18 mg, 0.21 mmol) in 83% yield.

^{1}H NMR for major isomer: δ 0.96 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H) 1.14 (s, 3H), 1.63

(br, 1H), 1.79 (septet, $J = 6.8$ Hz, 1H), 2.86 (dd, $J = 16.4$, 8.1 Hz, 1H), 3.20 (dd, $J = 16.3$, 10.3 Hz, 1H), 3.94 (dd, $J = 10.3$, 8.1 Hz, 1H), 4.43 (d, $J = 16.4$ Hz, 1H), 4.68 (d, $J = 16.4$ Hz, 1H), 6.45–6.54 (m, 1H), 6.67–6.78 (m, 1H), 7.00–7.10 (m, 2H), 7.20–7.45 (m, 5H).

^{13}C NMR δ 16.5, 17.3, 19.1, 31.9, 34.2, 57.2, 70.5, 77.6, 108.7, 118.4, 123.9, 126.8, 127.1, 127.5, 128.6, 128.9, 139.9, 154.2.

2-(1-Benzylindolin-2-yl)-3,3-dimethyl-2-butanol (6f)

By a procedure similar to that for **6a**, the title compound was obtained as a single diastereomer from **2b** (79 mg, 0.24 mmol) and 3,3-dimethyl-2-butanone (20 mg, 0.20 mmol) in 68% yield. The stereochemistry was assigned by analogy to that of **6d**.

^{1}H NMR: δ 1.02 (s, 9H), 1.15 (s, 3H), 2.11 (br, 1H), 2.83 (dd, $J = 16.8$, 6.2 Hz, 1H), 3.19 (dd, $J = 16.8$, 10.6 Hz, 1H), 3.97 (dd, $J = 10.6$, 6.2 Hz, 1H), 4.35 (d, $J = 16.1$ Hz, 1H), 4.70 (d, $J = 16.1$ Hz, 1H), 6.58 (d, $J = 7.7$ Hz, 1H), 6.76 (dt, $J = 8.2$, 1.0 Hz, 1H), 7.07 (t, $J = 7.3$ Hz, 2H), 7.20–7.40 (m, 5H).

^{13}C NMR: δ 18.0, 26.1, 34.2, 37.1, 59.1, 68.3, 79.2, 110.1, 119.1, 123.9, 126.9, 127.1, 127.4, 128.6, 130.5, 139.7, 153.7.

3-(1-Benzylpiperidin-2-yl)-3-pentanol (6g)

By a procedure similar to that for **6a**, the title compound was obtained from **2c** (76 mg, 0.25 mmol) and 3-pentanone (18 mg, 0.21 mmol) in 60% yield.

^{1}H NMR: δ 0.83 (t, $J = 7.5$ Hz, 3H), 0.90 (t, $J = 7.5$ Hz, 3H), 1.35–1.95 (m, 10H), 2.50–2.90 (m, 3H), 3.00 (br, 1H), 3.83 (d, $J = 13.6$ Hz, 1H), 4.00 (d, $J = 13.6$ Hz, 1H), 7.20–7.40 (m, 5H).

^{13}C NMR: δ 7.8, 8.0, 18.1, 20.1, 21.4, 28.1, 45.7, 57.8, 64.6, 76.4, 126.9, 128.3, 128.5, 140.2.

IR (neat): 3484, 2944, 1456, 1122, 968, 732, 698 cm^{-1}.

Analysis: calcd for $C_{17}H_{27}NO$: C, 78.11; H, 10.41; N, 5.36. Found: C, 78.31; H, 10.69; N, 5.48%.

3-(1-Benzylazepan-2-yl)-3-pentanol (6h)

By a procedure similar to that for **6a**, the title compound was obtained from **2d** (80 mg, 0.25 mmol) and 3-pentanone (18 mg, 0.2 mmol) in 88% yield.

^{1}H NMR: δ 0.89 (t, $J = 7.5$ Hz, 3H), 0.91 (t, $J = 7.4$ Hz, 3H), 1.15–2.00 (m, 12H), 2.70–2.90 (m, 3H), 3.40 (s, 1H), 3.84 (d, $J = 13.6$ Hz, 1H), 4.22 (d, $J = 13.6$ Hz, 1H), 7.20–7.40 (m, 5H).

^{13}C NMR: δ 7.8, 23.6, 26.9, 27.76, 27.81, 29.0, 29.4, 47.5, 59.2, 69.5, 76.0, 121.0, 128.4, 128.5, 139.6.

IR (neat): 3488, 2936, 1464, 954, 732, 698 cm^{-1}.

Analysis: calcd for $C_{18}H_{29}NO$: C, 78.49; H, 10.61; N, 5.08. Found: C, 78.48; H, 10.87; N, 5.05%.

3-(1-Benzylazocan-2-yl)-3-pentanol (6i)

By a procedure similar to that for **6a**, the title compound was obtained from **2e** (79 mg, 0.24 mmol) and 3-pentanone (18 mg, 0.21 mmol) in 79% yield.

^{1}H NMR: δ 0.90 (t, $J = 7.4$ Hz, 6H), 1.20–1.90 (m, 14H), 2.65–2.80 (m, 1H), 2.90–3.10 (m, 2H), 3.65 (br s, 1H), 3.89 (d, $J = 14.7$ Hz, 1H), 4.11 (d, $J = 14.7$ Hz, 1H), 7.20–7.40 (m, 5H).

^{13}C NMR: δ 7.8, 23.4, 25.5, 26.6, 27.08, 27.12, 27.4, 28.1, 53.5, 66.8, 76.1, 126.8, 128.0, 128.5, 140.4.

IR (neat): 3452, 2932, 1454, 1128, 954, 732, 698 cm^{-1}.

Analysis: calcd for $C_{19}H_{31}NO$: C, 78.84, H, 10.79; N, 4.84. Found: C, 78.81; H, 10.83; N, 5.00%.

2-(Benzylethylamino)-3-ethyl-3-pentanol (6j)

By a procedure similar to that for **6a**, the title compound was obtained from **2f** (71 mg, 0.25 mmol) and 3-pentanone (18 mg, 0.21 mmol) in 74% yield.

^{1}H NMR: δ 0.76 (t, $J = 7.4$ Hz, 3H), 0.90 (t, $J = 7.5$ Hz, 3H), 1.05 (d, $J = 7.2$ Hz, 3H), 1.06 (t, $J = 7.2$ Hz, 3H), 1.20–1.80 (m, 4H), 2.30–2.70 (m, 2H), 2.85 (q, $J = 7.2$ Hz, 1H), 3.39 (d, $J = 14.0$ Hz, 1H), 3.66 (br s, 1H), 3.93 (d, $J = 14.0$ Hz, 1H), 7.20–7.40 (m, 5H).

^{13}C NMR: δ 7.4, 7.8, 8.3, 13.6, 27.4, 28.4, 46.6, 55.7, 59.1, 74.5, 126.9, 128.3, 128.5, 140.2.

IR (neat): 3480, 2976, 1458, 1388, 956, 736, 700 cm^{-1}.

Analysis calcd for $C_{16}H_{27}NO$: C, 77.05; H, 10.91; N, 5.62. Found: C, 77.04; H, 10.92; N, 5.62%.

2-[(*o*-Tolylmethyl)ethylamino]-3-ethyl-3-pentanol (6k)

By a procedure similar to that for **6a**, the title compound was obtained from **2g** (78 mg, 0.26 mmol) and 3-pentanone (16 mg, 0.19 mmol) in 87% yield.

^1H NMR: δ 0.65 (t, $J=7.4$ Hz, 3H), 0.85 (t, $J=7.5$ Hz, 3H), 1.09 (t, $J=7.2$ Hz, 3H), 1.12 (t, $J=7.0$ Hz, 3H), 1.19–1.72 (m, 4H), 2.34 (s, 3H), 2.35–2.50 (m, 1H), 2.58–2.77 (m, 1H), 2.84 (q, $J=7.2$ Hz, 1H), 3.35–3.55 (br, 1H), 3.42 (d, $J=14.2$ Hz, 1H), 3.84 (d, $J=14.2$ Hz, 1H), 7.10–7.23 (m, 3H), 7.32–7.42 (m, 1H).

^{13}C NMR: δ 7.2, 7.5, 7.7, 13.7, 19.3, 27.3, 28.3, 46.7, 53.2, 58.0, 74.5, 125.8, 126.8, 129.1, 130.2, 136.5, 137.5.

HRMS: calcd for $C_{12}H_{18}N$ ($M-Et_2COCH$), m/z 176, 1439; found, m/z 176.1436.

2-[(α-Methylbenzyl)ethylamino]-3-ethyl-3-pentanol (6l)

By a procedure similar to that for **6a**, the title compound was obtained as a mixture of diastereomers (63:37) from **2h** (75 mg, 0.25 mmol) and 3-pentanone (18 mg, 0.21 mmol) in 92% yield.

^1H NMR for the mixture of diastereomers: δ 0.42–0.55 (m, 3H), 0.75–0.95 (m, 5H), 0.97–1.82 (m, 11H), 2.58 and 2.67 (q, $J=7.1$ and 7.0 Hz, 2H), 2.89 and 3.09 (q, $J=6.9$ and 7.2 Hz, 1H), 3.20–3.90 (br, 1H), 3.98 and 4.10 (q, $J=7.1$ and 6.9 Hz, 1H), 7.17–7.38 (m, 5H).

^{13}C NMR for the major isomer: δ 7.5, 7.8, 9.9, 14.9, 20.1, 27.2, 28.5, 41.3, 55.8, 58.6, 73.3, 127.1, 128.0, 128.1, 141.8. For the minor isomer: δ 7.1, 7.5, 11.7, 15.3, 20.1, 26.9, 28.1, 41.5, 54.5, 57.7, 73.6, 127.0, 128.0, 128.3, 143.8.

HRMS: calcd for $C_{12}H_{18}N$ ($M-Et_2COH$), m/z 176.1439; found, m/z 176.1440.

3-[1-(1,2,3,4-Tetrahydronaphth-1-yl)pyrrolidin-2-yl]-3-pentanol (6m)

By a procedure similar to that for **6a**, the title compound was obtained as a pair of diastereomers (56:44) from **2i** (88 mg, 0.27 mmol) and 3-pentanone (18 mg, 0.21 mmol) in 98% total yield.

^1H NMR for the major isomer: δ 0.90 (t, $J=7.4$ Hz, 3H), 0.92 (t, $J=7.3$ Hz, 3H), 1.19–2.17 (m, 12H), 2.30–2.90 (m, 5H), 3.65 (dd, $J=7.3$, 6.1 Hz, 1H), 4.15 (t, $J=7.0$ Hz, 1H), 7.05–7.20 (m, 3H), 7.22–7.34 (m, 1H). For the minor isomer: δ 0.88 (t, $J=7.5$ Hz, 3H), 0.91 (t, $J=7.3$ Hz, 3H), 1.15–2.15 (m, 13H), 2.55–2.95 (m, 4H), 3.21 (t, $J=7.7$ Hz, 1H), 4.00 (dd, $J=9.8$, 3.3 Hz, 1H), 7.03–7.27 (m, 3H), 7.81 (d, $J=7.0$ Hz, 1H).

^{13}C NMR for the major isomer: δ 7.8, 8.2, 21.6, 26.1, 27.1, 29.3, 30.0, 32.5, 49.1, 61.2, 70.2, 75.9, 125.3, 126.5, 128.1, 129.2, 138.1, 139.3. For the minor isomer: δ 7.8, 8.2, 22.4, 22.7, 25.9, 27.1, 27.7, 29.5, 29.9, 49.0, 62.9, 65.3, 76.4, 125.9, 126.2, 127.4, 128.8, 137.6, 139.6.

HRMS calcd for $C_{14}H_{18}N$ ($M-Et_2COCH$), m/z 200.1439; found, m/z, 200.1444.

3-[1-(1,2,3,4-Tetrahydronaphth-1-yl)piperidin-2-yl]-3-pentanol (6n)

By a procedure similar to that for **6a**, the title compound was obtained as a pair of diastereomers (81:19) from **2j** (85 mg, 0.25 mmol) and 3-pentanone (18 mg, 0.21 mmol) in 99% total yield.

^1H NMR for the major isomer: δ 0.84 (t, $J=7.4$ Hz, 3H), 0.93 (t, $J=7.3$ Hz, 3H), 1.20–2.14 (m, 15H), 2.46–2.92 (m, 4H), 3.11 (t, $J=4.0$ Hz, 1H), 4.18 (t, $J=5.9$ Hz, 1H), 7.00–7.22 (m, 3H), 7.37–7.48 (m, 1H).

^{13}C NMR for the major isomer: δ 8.0, 20.4, 21.1, 22.0, 22.5, 28.9, 29.2, 29.5, 29.7, 45.1, 61.1, 62.8, 75.8, 125.4, 126.6, 128.7, 128.8, 138.95, 139.04.

HRMS: calcd for $C_{15}H_{20}N$ ($M-Et_2COH$), m/z 214.1596; found m/z 214.1605.

3-(Benzylamino)-4-ethyl-4-hexanol (6o)

By a procedure similar to that for **6a**, the title compound was obtained from **2k** (70 mg, 0.26 mmol) and 3-pentanone (18 mg, 0.21 mmol) in 95% yield.

^1H NMR: δ 0.89 (t, $J=7.3$ Hz, 3H), 0.90 (t, $J=7.4$ Hz, 3H), 1.09 (t, $J=7.4$ Hz, 3H), 1.20–

1.56 (m, 5H), 1.57–1.81 (m, 2H), 1.85–2.40 (br, 1H), 2.50 (dd, J = 9.4, 3.4 Hz, 1H), 3.79 (d, J = 12.5 Hz, 1H), 4.04 (d, J = 12.5 Hz, 1H), 7.22–7.47 (m, 5H).

^{13}C NMR: δ 7.7, 12.4, 24.5, 27.4, 28.3, 55.5, 64.9, 74.7, 127.1, 128.1, 128.4, 140.5.

IR (neat): 3468, 3072, 1462 cm^{-1}. HRMS: calcd for $C_9H_{12}N$ (M – PrCHOH) m/z 134.0970; found, m/z 134.0973.

1-(Benzylmethylamino)-3-methyl-2-butanol (6p)
To a suspension of SmI_2 (0.75 mmol) in THP, prepared as described for **4**, were successively added (*o*-iodobenzyl)dimethylamine (64 mg, 0.24 mmol) and HMPA (0.37 ml, 2.1 mmol) at room temperature. After the reaction mixture had been stirred for 5 min, isobutyraldehyde (50 mg, 0.69 mmol) was added and stirring was continued for 6 h. The reaction mixture was quenched by addition of water (0.1 ml) and hexane (10 ml), and then the mixture was passed through a short column of silica gel (Et_2O eluent) to remove HMPA. Isolation by preparative thin-layer chromatography (Et_2O : hexane = 3 : 1) afforded **6p** (oil, 30 mg, 59%).

^{1}H NMR: δ 0.89 (d, J = 6.6 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H), 1.68 (octet, J = 6.6 Hz, 1H), 2.23 (s, 3H), 2.35–2.50 (m, 2H), 3.05–3.35 (br, 1H), 3.37–3.45 (m, 1H), 3.45 (d, J = 13.1 Hz, 1H), 3.71 (d, J = 13.1 Hz, 1H), 7.20–7.40 (m, 5H).

^{13}C NMR: δ 18.2, 18.5, 32.3, 41.9, 61.0, 62.4, 71.4, 127.2, 128.3, 129.0, 138.3.

8-Ethyl-8-hydroxy-4-decanone (7)
To a cooled suspension of SmI_2 (0.75 mmol) in THP, prepared as described for **4**, were successively added **2m** (80 mg, 0.24 mmol), 3-pentanone (17 mg, 0.20 mmol) and HMPA (0.37 ml, 2.1 mmol). After the reaction mixture had been stirred for 4 h, the cooling bath was removed and water (0.1 ml) and hexane (10 ml) were added. The mixture was passed through a short column of silica gel (Et_2O eluent) to remove HMPA. Isolation by preparative thin-layer chromatography (Et_2O : hexane = 1 : 1) afforded **7** (oil, 25 mg, 63%).

^{1}H NMR: δ 0.85 (t, J = 7.4 Hz, 6H), 0.90 (t, J = 7.3 Hz, 3H), 1.25–1.75 (m, 11H), 2.39 (q, J = 7.3 Hz, 4H).

^{13}C NMR: δ 7.7, 13.7, 17.3, 17.7, 30.9, 37.6, 43.0, 44.7, 74.5, 211.3.

HRMS: calcd for $C_{10}H_{19}O_2$ (M – Et), m/z 171.1385; found, m/z 171.1387.

***N*-Propyl(1-benzylpyrrolidin-2-yl)carboxamide (8)**
By a procedure similar to that for **6a**, the title compound was obtained from **2a** (71 mg, 0.25 mmol) and propyl isocyanate (21 mg, 0.25 mmol) in 67% yield.

^{1}H NMR: δ 0.90 (t, J = 7.5 Hz, 3H), 1.49 (sextet, J = 7.3 Hz, 2H), 1.60–2.00 (m, 3H), 2.10–2.45 (m, 2H), 2.95–3.10 (m, 1H), 3.10–3.30 (m, 3H), 3.48 (d, J = 12.9 Hz, 1H), 3.87 (d, J = 12.9 Hz, 1H), 7.20–7.50 (m, 6H).

^{13}C NMR: δ 11.3, 22.9, 24.1, 30.7, 40.5, 53.9, 59.9, 67.4, 127.2, 128.4, 128.6, 138.6, 174.5.

IR (neat): 3352, 2976, 1662, 1532, 1458, 1124, 732 cm^{-1}. HRMS: calcd for $C_{15}H_{22}N_2O$, m/z 246.1732; found, m/z 246.1717.

2-(1-Hydroxy-1,2,2-trimethylpropyl)pyrrolidine (9)
The tertiary amine **6d** (48 mg, 0.18 mmol) was treated with $Pd(OH)_2$ on charcoal (5%, 20 mg) in AcOEt (3 ml) under H_2 (1 atm) for 22 h at room temperature. Removal of the catalyst followed by evaporation afforded the title compound (31 mg, 99%).

^{1}H NMR: δ 0.91 (s, 9H), 1.07 (s, 3H), 1.50–1.90 (m, 4H), 2.75–2.90 (m, 1H), 2.97–3.10 (m, 1H), 3.43 (dd, J = 8.7, 6.7 Hz, 1H), 3.83 (br s, 2H).

^{13}C NMR: δ 19.3, 26.2, 27.1, 29.1, 38.2, 46.3, 62.0, 74.8.

IR (neat): 3352, 2968, 1486, 1398, 1374, 1120, 1078, 904 cm^{-1}. HRMS: calcd for $C_{10}H_{21}NO$, m/z 171.1623; found, m/z 171.1640.

7-Aza-3-*tert*-butyl-3-methyl-2-oxabicyclo-[3.3.0]octan-1-one (10)
To a solution of **9** (113 mg, 0.66 mmol) and ethyldiisopropylamine (148 mg, 1.14 mmol) in THF (8 ml) was added trichloromethyl chloroformate (114 mg, 0.58 mmol) at 0 °C under nitrogen. After the reaction mixture had been stirred for 4 h, 25% aqueous ammonium hydroxide (4 ml)

was added. The mixture was stirred for 12 h at room temperature and then extracted with dichloromethane (CH_2Cl_2). The organic extracts were dried and evaporated to give the title compound (113 mg, 87%).

^{1}H NMR: δ 0.96 (s, 9H), 1.24 (s, 3H), 1.45–2.15 (m, 4H), 3.13 (ddd, J = 11.0, 8.4, 3.8 Hz, 1H), 3.51 (dt, J = 11.0, 7.8 Hz, 1H), 3.81 (dd, J = 9.3, 6.2 Hz, 1H).

^{13}C NMR: δ 17.8, 24.4, 26.4, 27.6, 37.4, 44.9, 63.4, 87.4, 159.9.

IR (neat): 2976, 1756, 1368, 1064, 774 cm^{-1}. HRMS: calcd for $C_{11}H_{19}NO_2$, m/z 197.1416; found, m/z 197.1441.

1-Benzyl(2-^{2}H)indoline (11)
By a procedure similar to that for **6a**, the title compound was obtained, with 92% deuterium incorporation from **2b** (94 mg, 0.28 mmol) and methanol-*d* (0.2 ml, 4.93 mmol) in 93% yield.

^{1}H NMR: δ 2.98–3.12 (d, J = 8.3 Hz, 2H), 3.30–3.45 (m, 1H) 4.32 (s, 2H), 6.59 (d, J = 7.6 Hz, 1H), 6.75 (t, J = 8.0 Hz, 1H), 7.09–7.25 (m, 2H), 7.28–7.58 (m, 5H).

^{13}C NMR: δ 28.4, 53.2 (t, J = 21.4 Hz), 107.0, 117.6, 124.4, 127.0, 127.3, 127.9, 128.4, 129.9, 138.5, 152.5.

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