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The Ruthenium-Catalyzed Reduction and Reductive N-Alkylation of Secondary Amides with Hydrosilanes: Practical Synthesis of Secondary and Tertiary Amines by Judicious Choice of Hydrosilanes

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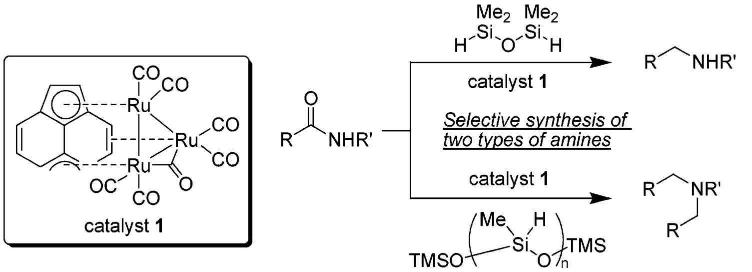

A triruthenium cluster, (μ_3,η^2,η^3,η^5-acenaphthylene)$Ru_3(CO)_7$ (**1**) catalyzes the reaction of secondary amides with hydrosilanes, yielding a mixture of secondary amines, tertiary amines, and silyl enamines. Production of secondary amines with complete selectivity is achieved by the use of higher concentration of the catalyst (3 mol %) and the use of bifunctional hydrosilanes such as 1,1,3,3-tetramethyldisiloxane. Acidic workup of the reaction mixture affords the corresponding ammonium salts, which can be treated with a base, providing a facile method for isolation of secondary amines with high purity. In contrast, tertiary amines are formed with high selectivity by using lower concentration of the catalyst (1 mol %) and polymeric hydrosiloxanes (PMHS) as reducing agent. Reduction with PMHS encapsulates the ruthenium catalyst and organic byproducts to the insoluble silicone resin. The two reaction manifolds are applicable to various secondary amides and are practical in that the procedures provide the desired secondary or tertiary amine as a single product. The product contaminated with only minimal amounts of ruthenium and silicon residues. On the basis of the products and observed side products as well as NMR studies a mechanistic scenario for the reaction is also described.

Introduction

It is well-known that the hydride reductions by alumino- or borohydrides are useful for chemical transformation of carbonyl compounds.[1,2] Lithium aluminum hydride (LAH) and its derivatives are one of the most powerful hydrides, which reduces a wide variety of compounds having carbon−oxygen double bonds unselectively. Despite their utility, sensitivity of aluminohydrides to air and moisture is a drawback for their manipulation in the laboratory. From this point of view, hydrosilanes are attractive reducing reagents, which themselves do not react with air and moisture but promote the reduction of carbonyl compounds in the presence of the activator of a silicon−hydrogen bond such as fluorides, Lewis acids, and transition metals. In particular, it is well-known that certain transition-metal catalysts effectively activate the Si−H bonds,[3] leading to hydrosilylative reduction of aldehydes and ketones.[4] In contrast to the hydrosilylation of ketones and aldehydes, catalytic silane-reduction of carboxylic acids and its derivatives have not been fully investigated. In particular, reductions of carboxamides with hydrosilanes were not accomplished until recently. Ito and co-workers reported that the conversion of carboxamides to the corresponding amines could be achieved by Ph_2SiH_2 with the aid of rhodium catalysts.[5] In a brief communication by

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(1) (a) *Reductions in Organic Chemistry*; Hudlicky, M., Ed.; John Wiley & Sons: New York, 1984. (b) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I. Eds.; Pergamon: Oxford, U.K., 1991; Vol. 8.

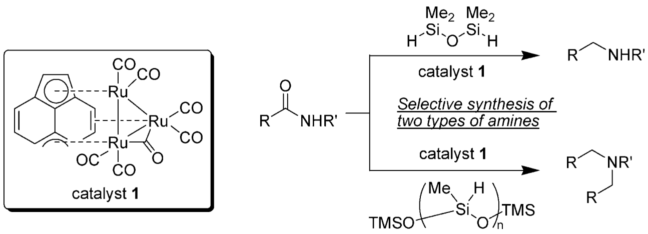
(2) *Reductions by the Alumino- and Borohydrides in Organic Synthesis*; Seyden-Penne, J., Ed.; Wiley-VCH: New York, 1997.

10.1021/jo070591c CCC: $37.00

Fuchikami and Igarashi, carboxamides were reported to be reduced with trialkylsilanes by the catalysis of several transition metal complexes and salts around 100 °C.[6] Buchwald and coworkers published hydrosilylative reduction of tertiary amides mediated by stoichiometric amounts of titanium compounds; however, the products were not the corresponding amines but the aldehydes.[7] In these previously reported reactions, tertiary amides are reduced to the tertiary amines in good yields; however, the reduction of secondary amides remains a problem to be solved. Ohta reported that Ito's protocol for the $RhH(CO)(PPh_3)_3$-catalyzed reduction of tertiary amides with Ph_2SiH_2 was not effective for the reduction of secondary amides, and change of the catalyst structure and the catalyst concentration are necessary to improve this.[8] Fuchikami and Igarashi mentioned without experimental details that application of temperatures higher than 100 °C was required for the reduction of secondary amides with their ruthenium catalyst system.[6] The reduction of secondary amides is also problematic with aluminohydrides in that the reaction is much slower than the reaction of tertiary amide. To improve the reaction rate, reduction of secondary amides requires a large excess of the reagent and long reaction time; however, such harsh conditions sometimes cause formation of a complex mixture of the product.[1]

We have recently reported a ruthenium cluster complex, $(\mu_3,\eta^2,\eta^3,\eta^5$-acenaphthylene$)Ru_3(CO)_7$ (**1**),[9] which enables activation of a silicon-hydrogen bond of various trialkylsilanes effectively, promoting catalytic reduction of tertiary amides to tertiary amines under mild conditions.[10] Despite great success as the reduction protocol for tertiary amides, there remains a problem for the reduction of secondary amides as described in our previous paper. Under the typical reaction conditions used for the reduction of tertiary amides, only hydrogen gas evolution was observed, and the starting amides were recovered quantitatively from the reaction mixture. In this paper, we wish to report a clear solution of this problem which can be achieved by combination of a judicious choice of hydrosilanes, higher catalyst loadings, and application to the elevated reaction temperatures (40∼60 °C). The improved procedure results in efficient production and facile isolation of the desired secondary amines from secondary amides. Furthermore, we discovered in the course of the study that the reaction afforded two byproducts other than the desired amines: one is the silylated enamine, whereas the other is the tertiary amine formed according to the equation, $2RCONHR' + 6Si{-}H \rightarrow (RCH_2)_2NR' + 2Si{-}O{-}Si + R'NSi_2$. Production of the tertiary amine formed by this process involving reductive N-alkylation was reported as a side reaction of borohydride reduction of secondary amides in the presence of a phospholic activator;[11] however, there is no report on the practical procedure to synthesize the tertiary amines by this reaction. We have just found that use of PMHS as the hydride source for the ruthenium cluster-catalyzed reaction of secondary amides accomplished both synthesis of tertiary amines with moderate to good selectivity and facile separation of only the desired tertiary amine from other products. This actually provides the first practical method for synthesizing tertiary amines by reductive N-alkylation of secondary amides (Scheme 1).

SCHEME 1. Selective Reduction of Secondary Amides to Two Types of Amines



Results and Discussion

Screening of the Reduction Conditions. As described above, the reduction of secondary amides does not proceed under the usual conditions of the ruthenium cluster-catalyzed reduction of tertiary amides. In a typical example, gas evolution was observed in the reaction of *N*-methyl-3-phenylpropionamide **2a** with $EtMe_2SiH$ in the presence of 1.0 mol % of **1** at 20 °C. The starting material was recovered quantitatively after the work-up process. As described later in detail, dehydrogenative silylation is likely to take place to form silyl imidoyl ester, which is hardly reducible under the conditions. We found that further hydride reduction actually occurred at elevated temperatures.

When the reaction of **2a** with $EtMe_2SiH$ in the presence of 1.0 mol % of **1** was carried out at 40 °C, **2a** was slowly consumed, and the conversion reached 70% by ^1H NMR analysis after 8 h. The reaction is much slower than that of the corresponding tertiary amide, which is completely reduced within 30 min under the same conditions. Three products were isolated from the reaction mixture; one was the desired secondary amine **3a**, the other two were unexpected products, *N*,*N*-di(3-phenylpropyl)methylamine (**4a**) and a silylated enamine **5a** (Scheme 2).[12] The tertiary amine **4a** was reported to be a byproduct of the reduction of **2a** with the phosphoryl chloride/sodium borohydride system (10% yield);[11] selective reduction of **2a** was not accomplished. Under these particular conditions, the yields of **3a**, **4a**, and **5a** determined by ^1H NMR in the presence of dibenzyl ether as the internal standard were 27, 30, and 13%, respectively, with the recovery of **2a** (the ratio of **3a**/**4a**/**5a** = 39:42:19; Table 1, entry 2).

The ratio of these three products can be controlled by appropriate choice of the hydrosilane, the reaction temperature, and the catalyst concentration. The results are summarized in

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(3) (a) Ojima, I. In *The Chemistry of Organic Silicon Compounds*; Patai, S., Rappoport, Z., Eds; John Wiley & Sons: New York, 1989; Part 2, Chapter 25, pp 1479−1526. (b) *Comprehensive Handbook on Hydrosilylation*; Marciniec, B. Ed.; Pargamon: Oxford, U.K., 1992. (c) Marciniec, B. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann, W. A., Eds.; Wiley-VCH: Weinheim, Germany, 1996; Vol. 1, Chapter 2.

(4) For asymmetric reduction of ketones, see: Nishiyama, H.; Itoh, K. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 111−143.

(5) Kuwano, R.; Takahashi, M.; Ito, Y. *Tetrahedron Lett.* **1998**, *39*, 1017.

(6) Igarashi, M.; Fuchikami, T. *Tetrtahedron Lett.* **2001**, *42*, 1945.

(7) Bower, S.; Kreutzer, K. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1515.

(8) Ohta, T.; Kamiya, M.; Nobumoto, M.; Kusui, K.; Furukawa, I. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 1856.

(9) Synthesis of the catalyst **1** was first reported in the paper, Nagashima, H.; Fukahori, T.; Aoki, K.; Itoh, K. *J. Am. Chem. Soc*. **1993**, *115*, 10430. For details, see the ref 10c.

(10) (a) Nagashima, H.; Suzuki, A.; Iura, T.; Ryu, K.; Matsubara, K. *Organometallics*, **2000**, *19*, 3579. (b) Matsubara, K.; Iura, T.; Maki, T.; Nagashima, H. *J. Org. Chem.* **2002**, *67*, 4985. (c) Motoyama, Y.; Itonaga, C.; Ishida, T.; Takasaki, M.; Nagashima, H. *Org. Synth.* **2005**, *82*, 188.

(11) Kuehne, M. E.; Shannon, P. J. *J. Org. Chem.* **1977**, *42*, 2082.

(12) The silylated enamine **5a** showed two characteristic vinyl signals at δ 6.35 ppm (d, J = 13.7 Hz) and 4.49 ppm (dt, J = 13.7, 6.6 Hz), respectively, in ^1H NMR, giving 3-phenylpropanal in contact with silica gel.

SCHEME 2. Three Reaction Products in the 1-Catalyzed Reduction of 2a with $EtMe_2SiH$

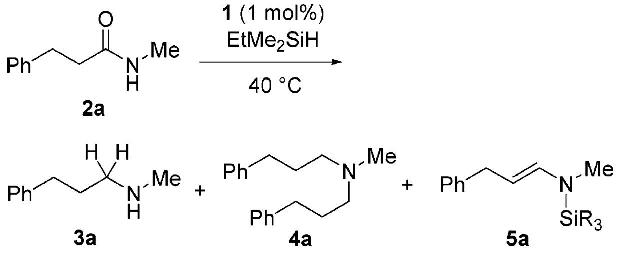


TABLE 1. Reaction of 2a with Various Hydrosilanes

$$\mathbf{2a} \xrightarrow[\text{cat. }\mathbf{1}\text{, silane 3.2 equiv}]{\text{DME, 40 °C}} \mathbf{3a} + \mathbf{4a} + \mathbf{5a}$$

entry	silane	cat. (mol %)	time (h)	conversion (%)[a] of **2a**	ratio of **3a**/**4a**/**5a**
1	$EtMe_2SiH$	0.5	24	70	0:68:32
2	$EtMe_2SiH$	1.0	8	70	39:42:19
3	$EtMe_2SiH$	3.0	8	>90	>99:0:0
4	$(EtO)Me_2SiH$	1.0	8	64	48:0:52
5	$Me_3SiOSiMe_2H$	1.0	8	66	71:0:29
6	$[H(Me)_2SiCH_2]_2$	1.0	8	>99	90:0:10
7	$[H(Me)_2Si]_2O$	1.0	8	>99	64:7:29
8	$[H(Me)_2Si]_2O$	3.0	6	>99	>99:0:0

[a] The conversion and product ratios were determined by ^1H NMR.

Table 1. In the experiments with $EtMe_2SiH$ as the hydrosilane, slow reaction occurred to give a mixture of products, in which **4a** and **5a** formed in relatively higher ratios at lower catalyst concentration (entries 1 and 2). By increasing the catalyst concentration, selectivity of the desired secondary amine **3a** was improved, and exclusive formation of **3a** without contamination of **4a** and **5a** was accomplished by using 3 mol % of **1** (entry 3). The higher catalyst loading also solved the problem of the reaction rate; in the presence of 3 mol % of **1**, conversion of **2a** reached over 90% after 8 h (entry 3). Selectivity of the formation of **3a** was alternatively improved by changing the hydrosilane. With the use of $(EtO)Me_2SiH$ or $(Me_3SiO)Me_2SiH$, the selectivity to give **3a** was somewhat improved, but a concomitant formation of **4a** and **5a** was also observed (entries 4 and 5). Interestingly, the hydrosilanes having two Si−H groups in the molecule improved the conversion and the selectivity. In the reduction with $[H(Me)_2SiCH_2]_2$, the selectivity of **3a** reached 90% with complete conversion of the amide **2a** (entry 6). Use of $[H(Me)_2Si]_2O$ attained the high conversion but did not improve the selectivity of **2a** significantly. However, the selectivity problem can be solved by using 3 mol % of **1** as the catalyst [>99% selectivity in quantitative yield (entries 7 vs 8)].[13]

It should be noted that higher selectivity of **3a** tended to be achieved under the conditions that **2a** was quickly consumed. Reaction profiles for the reduction of **2a** with four hydrosilanes are shown in Figure 1.

The initial reaction rate with $[H(Me)_2SiCH_2]_2$ was surprisingly high, reaching three hundred times faster than that with $EtMe_2SiH$ ($t_{1/4}$ was 1.7×10^{-2} h for $[H(Me)_2SiCH_2]_2$ versus 5.7 h for $EtMe_2SiH$). Similarly, reduction with $[H(Me)_2Si]_2O$ was about five times faster than the corresponding reaction with $(Me_3SiO)Me_2SiH$ containing only one Si−H group ($t_{1/4}$ was 0.33 h for $[H(Me)_2Si]_2O$ versus 1.6 h for $(Me_3SiO)Me_2SiH$). These bifunctional hydrosilanes are apparently more effective than the monofunctional trialkylsilanes. In particular, the most suitable silane is $[H(Me)_2SiCH_2]_2$ in view of the reaction rate, whereas combined use of $[H(Me)_2Si]_2O$ and 3.0 mol % catalyst loading is beneficial because of the availability of the former as a low cost commercial hydride source. In the experiments described below, we usually used $[H(Me)_2Si]_2O$ as the reducing reagent.

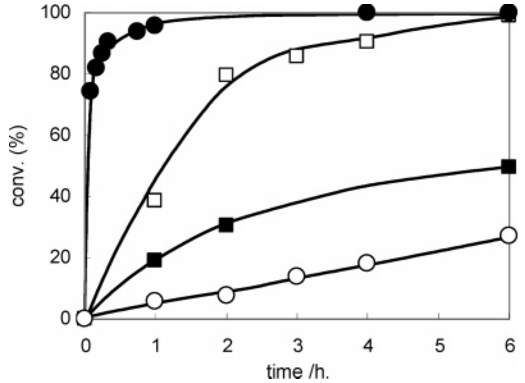
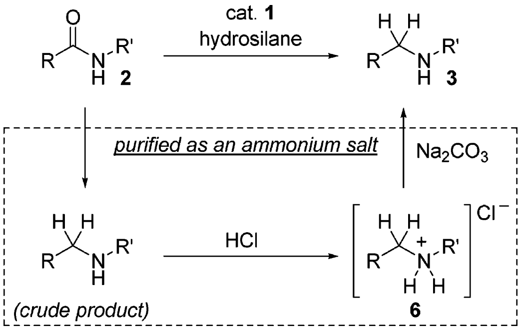


FIGURE 1. Reaction profiles of **1** (1.0 mol %) catalyzed reduction of **2a** (0.5 mmol) with various hydrosilanes (3.2 equiv Si−H) at 40 °C (●, with $[H(Me)_2SiCH_2]_2$; □, with $[H(Me)_2Si]_2O$; ■, with $(Me_3SiO)Me_2SiH$; ○, with $EtMe_2SiH$). The conversion was determined by ^1H NMR analysis with dibenzylether as an internal standard.

SCHEME 3. Simple and Facile Process for Isolation of Secondary Amines 3



Application of the Optimum Conditions to Reduction of Various Secondary Amides. We next investigated application of the above reduction with optimum conditions to the preparation of various secondary amines. In a typical example, reaction of **2a** (0.5 mmol) with $[H(Me)_2Si]_2O$ (0.8 mmol) was carried out with 3 mol % of catalyst **1** (0.015 mmol) in dimethoxyethane (DME) (0.5 mL) at 40 °C.[14] Since the isolation of secondary amines **3** is generally problematic due to their high polarity, we converted to the corresponding ammonium salts **6** by treatment of the reaction product **3** with an ethereal solution of HCl (Scheme 3).

The resulting ammonium chloride **6** was precipitated as solids insoluble in ethereal solvents; silicon compounds produced by the reduction and the catalyst residues were easily removed by

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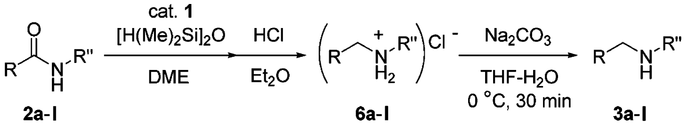
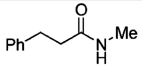
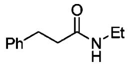
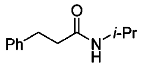
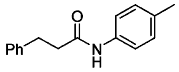
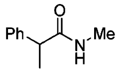
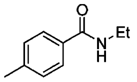
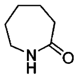
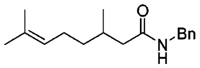
[13] As described in the mechanistic aspects, reduction of secondary amides contains three elementary reactions. The selectivity of **3a**/**4a**/**5a** is dependent on the rate of the elementary reactions, in particular, the hydride reduction rate from *sec*-**B** to *sec*-**3** through *sec*-**C**. The low rate of this step is favorable for the side reactions giving **4a** and/or **5a**. The higher catalyst loading and the use of bifunctional silanes are likely to help for raising the rate of this step.

[14] For the catalytic reductions using **1**, good solvents for dissolution of **1** are favorable. The original optimal solvent was dioxane, but we changed it to tetrahydropyran to consider the toxity of dioxane. DME is a better solvent for dissolving higher amounts of **1** (e.g., 3 mol %).

TABLE 2. Reduction of Various Amides 2a−l to the Corresponding Amines 3a−l[a]



entry	substrate		conditions				ammonium		amine	
			Si-H (eq.)	time (h)	temp. (°C)	conv.[b] (%)		Yield from **2** (%)		Yield from **2** (%)
1		**2a**	3.2	6	40	>99	**6a**	69	**3a**	68
2		**2b**	3.2	8	40	>99	**6b**	86	**3b**	82
3		**2c**	4.5	12	60	>99	**6c**	62	**3c**	60
4		**2d**	4.5	12	60	>99	**6d**	98	**3d**	98
5		(±)-**2e**	4.5	12	60	>99	**6e**	82	**3e**	60
6[c]		(*R*)-**2e**				90		64		34[d]
7		**2f**	4.5	12	60	>99	**6f**	87	**3f**	82
8[e]			4.0	12	60	>99		92		83
9		**2g**	3.2	8	40	>99	**6g**	72	**3g**	46
10		**2l**	4.5	12	60	>99	**6l**	-	**3l**[f]	61

[a] Reaction conditions: substrate **2** (0.5 mmol), silane, catalyst **1** (0.015 mmol, 3 mol %) in DME (0.5 mL). [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] (*R*)-**2e** (>99.9% ee) was used. [d] (*R*)-**3e** was obtained at >99.9% ee. [e] Reaction run using 10 mmol (1.63 g) of **2f**. [f] This compound was directly obtained by column chromatography.

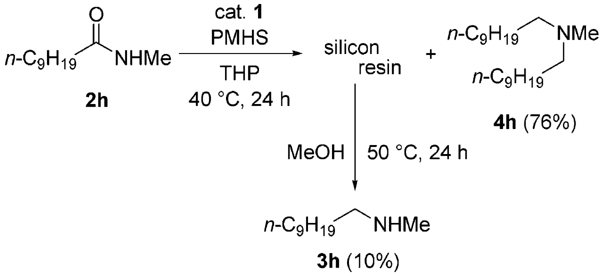
washing the ammonium chloride with diethyl ether. ICP−MS analysis of **6** revealed that the 10∼20% of the charged ruthenium was removed in this stage. Recrystallization of **6** from hot cyclopentyl methyl ether resulted in successful removal of the ruthenium residue (>99% of the charged amount). The isolated ammonium chloride **6** was converted to the desired amine **3** by treatment with Na$_2$CO$_3$ in THF containing a small amount of water. This workup process without using chromatography or distillation actually offers a practical method for preparation of various secondary amines as summarized in Table 2.

In the reduction of three derivatives of 3-phenylpropionamides, the rate was decreased with the steric bulkiness on the nitrogen substituent (entries 1−3). Reaction of *N*-*p*-tolyl derivative **2d** also proceeded more slowly than that of **2a** (entry 4). Decrease in the reaction rate was also seen in the reduction of two amides **2e** and **2f**, in which the former has a α-methyl group as a steric factor, whereas the latter conjugates to the aromatic ring. However, these problems of the slow reactions can be solved at higher reaction temperatures (60 °C) to give the desired amine in reasonable yields (entries 5 and 7). The reduction of ϵ-caprolactam **2g** successfully proceeded at 40 °C (entry 9). Possible racemization of optically pure amides is a problem to be studied. As shown in entry 6, optically pure (*R*)-**2e** was subjected to the reduction. When the reaction was quenched at the conversion of (*R*)-**2e** of 90%, the amine **3e** was obtained with over 99.9% ee and the recovered (*R*)-**2e** was optically pure. Transition metal-catalyzed hydrosilylation of carbon double bonds (C═C bonds) is also a possible side reaction. The amide **2l** with a C═C bond in the same molecule was quantitatively converted to the desired alkenylamine **3l**; no hydrosilylation at the alkenyl moiety was observed (entry 10). The present procedure was adaptable to a gram-quantity production of amines: in a typical example, from 1.63 g (10 mmol) of **2f**, **6f** (1.70 g) and **3f** (1.23 g) were obtained in 92% and 83% yields, respectively (entry 8). It should be noted that NMR observation revealed that the conversion of the starting amide reached 100% in each experiment, and no byproduct was observed. Loss of the product during the isolation process, which is mainly attributed to the solubility of their ammonium hydrochloride in ether, caused the moderate isolated yields seen in entries 1, 3, and 9. These results clearly demonstrate that the procedure presented in this paper offers a practical method for the synthesis of various secondary amines with high purity in moderate to good isolated yields.

Reduction of Secondary Amides Involving N-Alkylation: A Practical Synthetic Method for Tertiary Amines. As described in Scheme 1 and Table 1, the ruthenium-catalyzed silane reduction of secondary amides produces tertiary amines as a byproduct. Although this type of reduction is interesting as a synthetic method for tertiary amines,[15] our search revealed only one paper that briefly referred to this type of reduction; in that report several secondary amides underwent the reduction with phosphoryl chloride and sodium borohydride to give the tertiary amines in low yield.[11] In this context, refinement of the above-described silane reduction of **2** as a synthetic method for **4** is the next interesting target for us. We first attempted selective preparation of **4** from **2** without formation of secondary amines **3** by optimization of the reaction conditions. As shown in Table 1, entry 1, reduction with $EtMe_2SiH$ afforded **4a** in relatively higher ratios, particularly, in the experiment with the lower catalyst loading (0.5 mol %). Our further efforts to suppress the formation of secondary amines **3** or enamines **5** were not successful, and 100% selective production of the desired amine **4** has not yet been achieved.

We next turned our attention to facile and selective *isolation* of the desired amines **4** without contamination of **3** and **5** as the product. In our previous papers, we reported an unique property of polymethylhydrosiloxane (PMHS) as a reducing reagent of tertiary amides.[16] PMHS is known as an easily available and inexpensive hydrosilane in organic synthesis.[17] Moreover, we have reported that the **1**-catalyzed reduction of tertiary amides with PMHS is accompanied by self-encapsulation of the resulting ruthenium species into the insoluble silicon resin.[16a] Since the produced tertiary amines are not encapsulated to the silicon resin, simple extraction of the reaction mixture leads to selective isolation of the ruthenium-free tertiary amines in good yields. We discovered that the ruthenium catalyzed reduction of *N*-methyldecanamide **2h** with PMHS followed by extraction of the reaction mixture including insoluble silicon resins formed gave *N*,*N*-didecylmethylamine **4h** in 76% yield.[18] The initial homogeneous solution began to gel in the progress of the reaction. After the reaction was complete, removal of the volatiles in vacuo afforded dry gel. Extraction of the dry gel by ether gave colorless extracts including **4h** as a single product and the insoluble resinous product. Although the secondary amine **3h** should be formed as a byproduct, it was not detectable in the extract. Since decomposition of the formed silicon resin by methanol at 50 °C for 24 h gave **3h** in 10% yield, **3h** was encapsulated into the silicon resins and there was no contamination of **3h** to **4h** in the above procedure (Scheme 4). The extracts were contaminated by only a tiny amount of ruthenium species.[19] Thus, both the ruthenium species and **3h** are encapsulated into the silicon resin insoluble in ether. As reported previously, PMHS mediated reduction of tertiary amide results in oxidation of the PMHS chain, which produces the cross-linked resinous siloxane insoluble in ether and common organic solvents. In these insoluble siloxane resin matrices, ruthenium species were *encapsulated* and not extracted by organic solvent, while the produced tertiary amines had no interaction with this insoluble resin, and were extracted with ether easily. Facile separation of **4h** from the silicon resin formed suggests that the concomitantly formed secondary amine **3h** would be encapsulated through a Si−N bond. In fact, solid state ^{13}C and ^{29}Si NMR spectrum of the silicon resin revealed the existence of the signals due to $-NMe(C_{10}H_{21})$ species and Si−N species, respectively. The Si−N bond in low molecular weight aminosilanes is usually unstable to moisture and undergoes hydrolysis rapidly. In fact, reduction of **2h** with $EtMe_2SiH$ gave $EtMe_2SiNMe(C_{10}H_{21})$, which was converted to *N*-methyldecylamine during the workup process under aerobic conditions. The lack of contamination of **3h** in **4h** isolated in the ruthenium-catalyzed reduction of **2h** with PMHS indicates that the aminosilane derived from **3h** must be stabilized by the produced polysiloxane matrix, and be protected from the hydrolysis by contact with moisture during the workup.[20] As a result, only N-alkylated tertiary amines which have no interaction with siloxane matrices can be extracted from the produced siloxane resin as a sole product.

SCHEME 4. Reduction of Secondary Amide 2h with PMHS



Other examples of the ruthenium-catalyzed reduction of secondary amides with PMHS are summarized in Table 3. Didecylethylamine **4i** was formed from the corresponding secondary amide **2i** selectively (entry 2). The reduction of 3-phenylpropionamide derivatives, **2a** and **2j**, α-substituted amide **2k**, and benzamide **2m** resulted in isolation of the corresponding tertiary amines, **4a**, **4j**, **4k**, and **4m**, in moderate yields by simple washing of the formed insoluble silicon resin with ether; their secondary amine derivatives were encapsulated in the siloxane resin and were hardly extractable (entries 3−6). In all cases, secondary amines **3** were recovered from the silicon resin by careful decomposition of the insoluble silicon matrix with methanol. The reduction from **2** to **4** is accompanied by the formation of $R'NH_2$, which is encapsulated in the silicone matrix formed. In a typical example, CPMAS spectrum of the silicone resin formed in the reaction shown in entry 4 in Table 3 gave the signals assignable to a $PhCH_2N$ moiety.

An interesting outcome was obtained by changing the N-substituent of the secondary amides. The reduction of secondary amides with bulky substituent of nitrogen (*tert*-butyl or isopropyl) proceeded more slowly than those with sterically smaller N-substituents, and the product isolated by ether extraction was the secondary amine **3c** and **3n** as a single product (Scheme 5). It is of interest that tertiary amines **4c** and

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(15) (a) Hutchins, R. O.; Hutchins, M. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 6, p 724. (b) Baxter, E. W.; Reitz, A. B. *Org. React.* **2002**, *59*, 1.

(16) (a) Motoyama, Y.; Mitsui, K.; Ishida, T.; Nagashima, H. *J. Am. Chem. Soc.* **2005**, *38*, 13150. (b) Hanada, S.; Motoyama, Y.; Nagashima, H. *Tetrahedron Lett.* **2006**, *47*, 6173.

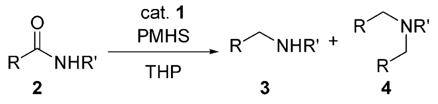
(17) (a) Lipowitz, J.; Bowman, S. A. *Aldrichimica Acta* **1973**, *6*, 1. (b) Lawewnce, N. J.; Drew, M. D.; Bushell, S. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3381.

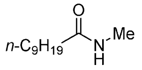
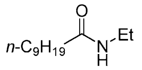
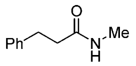
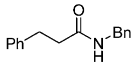
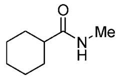
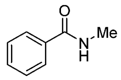
(18) The reaction concentration is important for the yield of the product. The higher reaction concentration prevented dissolution of the catalyst to give the desired amine in low yields. The lower reaction concentration did not give gel, which is useful for separation of the tertiary amine from other products without leaching of the ruthenium and silicone residues.

(19) In ICP−MS analysis of produced amine **4h**, only 117 ppm of ruthenium residue was detected: >99.4% of Ru can be removed.

(20) The matrices made by PMHS are known to be effective for stabilization of active species. See: Chauhan, B. P. S.; Rathore, J. S.; Bandoo, T. *J. Am. Chem. Soc.* **2004**, *126*, 8493.

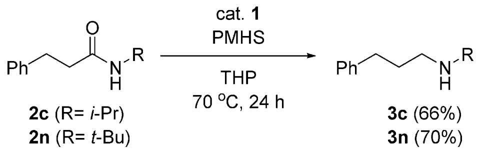
TABLE 3. Reaction of Secondary Amides with PMHS[a]



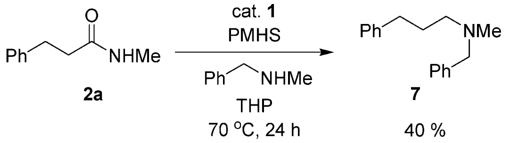
entry	substrate		temp. (°C)	Yield of **4** (%)	Yield of **3** (%)[b]
1		**2h**	40	76	10
2		**2i**	50	63	18
3		**2a**	40	54	10
4		**2j**	60	60	15
5		**2k**	60	51	21
6		**2m**	70	47	20

[a] Reaction conditions: substrate **2** (1 mmol), PMHS (5.5 equiv Si−H), catalyst **1** (0.01 mmol, 1 mol %) in THP, 24 h. [b] The yield of secondary amines **3** which recovered from the siloxane resin.

SCHEME 5. Reduction of Bulky Amides with PMHS



SCHEME 6. Reductive Benzlyation of 2a



4n were not detected in the reaction mixture, and the secondary amines **3c** and **3h** were not encapsulated into the silicon resin. Thus, the ruthenium-catalyzed reduction of secondary amides with PMHS is effective for the formation of tertiary amines when the N-substituent of the starting amide is sterically small, whereas it is good for a simple synthetic method for ruthenium-free secondary amines when the N-substituent of the starting amide is bulky.

Another interesting observation is the possible formation of tertiary amines with three different alkyl groups on the nitrogen, which was achieved by the ruthenium-catalyzed reduction of **2a** in the presence of 1.5 equiv of *N*-methylbenzylamine (Scheme 6). The byproducts are secondary amines, **3a** formed by the silane reduction and *N*-methylbenzylamine unreacted, which are recovered by decomposition of the silicon resin formed by methanol. Although the yield of the product is not high, this reaction provides an interesting access to tertiary amines having three different substituents. The results also provide interesting suggestions on the mechanisms. In the reaction of **2a** to **4a**, one of the 3-phenylpropyl groups in **4a** is derived from the secondary amine **3a** formed by the reduction of **2a**. In contrast, the *N*-benzyl group of **7** is derived from *N*-benzylmethylamine which was added to the reaction medium. As the mechanisms discussed in the final part of this paper, the formation of tertiary amines, **4a** and **7**, should involve the reaction of an intermediate with a derivative of **3a**.

Mechanistic Aspects. As described above, we have achieved successful reduction of secondary amides to secondary amines by judicious choice of hydrosilanes and increase of the catalyst concentration. It was also accomplished that the ruthenium-catalyzed reduction of secondary amides with PMHS results in formation of the tertiary amines described above, which are facilely isolated as a single product by extraction from the resinous silicon products with ether. The following questions remain on the reaction mechanisms: The first is why the reduction of secondary amides is slower than that of tertiary amides. The second is why the hydrosilanes bearing two Si−H groups in the molecule accelerate the reaction. The third is what the reaction pathways are where the byproducts **4** and **5** are produced. The fourth is what the mechanism of the encapsulation of ruthenium species and secondary amines is to the silicon resin formed in the ruthenium-catalyzed reduction of secondary amides with PMHS. Possible reaction pathways are illustrated below (Scheme 7).

The reduction mechanism of secondary amides is compared with that of tertiary amides as follows: Tertiary amides react with two equivalents of Si−H groups to give the corresponding tertiary amines via three intermediates, **A**, *tert*-**B**, and *tert*-**C**. As described in our previous paper, the result that THF is polymerized by the species produced by a Si−H group with the ruthenium catalyst **1** implicates the formation of a polar species closes to R_3Si^+ in the reaction medium.[10a] The activation of amide **2** (R″ = alkyl) or the *tert*-**B** by R_3Si^+ followed by reaction with $Ru-H^-$ counterion results in reduction of **2** to *tert*-**3**. The first step in the reduction of secondary amides **2** (R″ = H) is different from that of tertiary amides. The reduction of secondary amides initiated from the formation of the intermediate **D** which involves dehydrogenative silylation of **2**. The N-silylated species **D′** may alternatively be formed in this step; however, the following results strongly suggest the exclusive formation of **D**. Treatment of secondary amides with R_3SiCl in the presence of base such as Et_3N reportedly forms two types of products, *O*-silyl imidoyl esters and *N*-silylamides (Scheme 8),[21] which are differentiated by the chemical shift of ^{29}Si NMR.[22] Treatment of acetanilide with 1 equiv of *tert*-butyldimethylsilane in the presence of a catalytic amount of **1** indeed resulted in gas evolution; ^{29}Si NMR spectrum of the reaction product showed the signal due to O-silylated acetanilide derivative (δ 22.6 ppm), which was independently synthesized by the reaction of a sodium salt of acetanilide with *tert*-butyldimethylchlorosilane.[23] From this result, we consider **D** to be an intermediate of the silane reduction of secondary amide **2** in general. We have already found that the reduction of carbon−nitrogen double bonds is slower than that of carbon−

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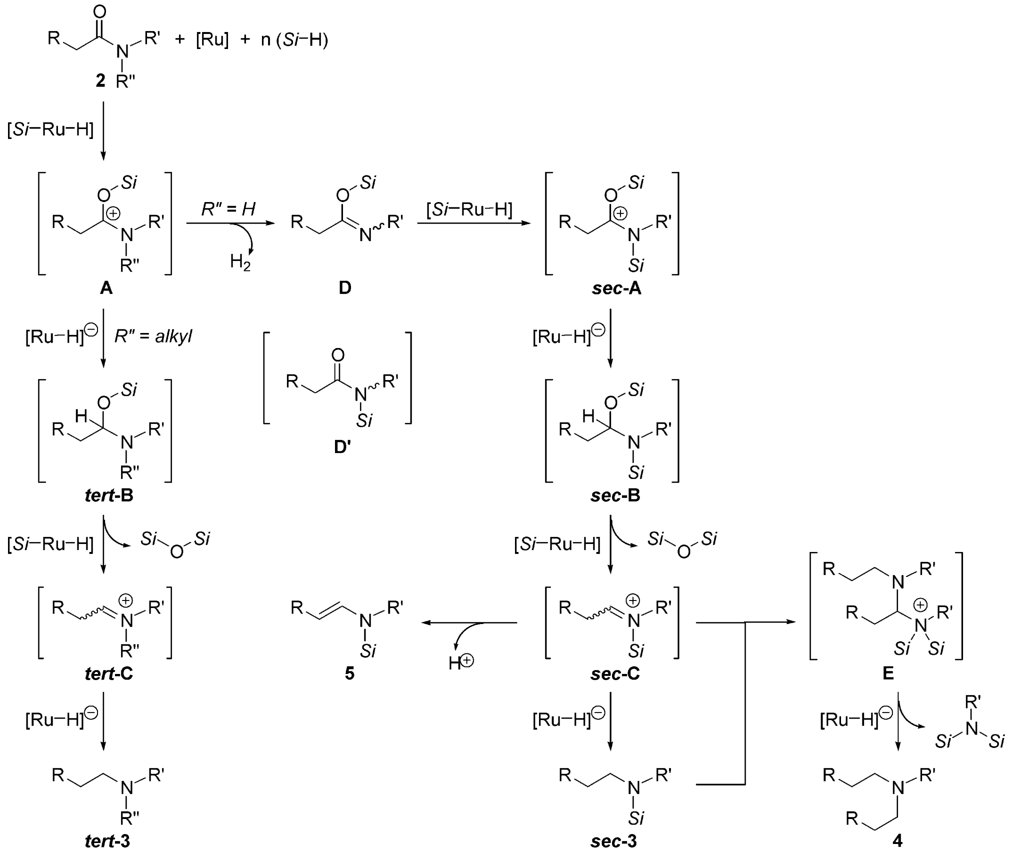
[21] (a) Yoder, C. H.; Belber, A. D. *J. Organomet. Chem.* **1976**, *114*, 251. (b) Hausman, C. L.; Yoder, C. H. *J. Organomet. Chem.* **1978**, *161*, 313. Also see: (c) Klebe, J. F. *Acc. Chem. Res.* **1970**, *3*, 299.

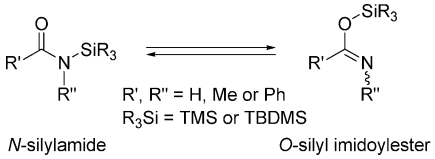
[22] Bassindale, A. R.; Posner, T. B. *J. Organomet. Chem.* **1979**, *175*, 275.

[23] See Supporting Information.

SCHEME 7. Possible Reaction Mechanism



SCHEME 8. The Equilibrium between O- and N-Silylated Secondary Amides



oxygen double bonds by trialkylsilane in the presence of **1**.[24] The reason for slower reduction of secondary amides than that of tertiary amides is due to the functionality of **D** including a carbon−nitrogen double bond.

The second step of the reduction is reaction of **D** with Si−H groups, giving the corresponding aminoacetal *sec*-**B**. If the hydrosilane is bifunctional and their two Si−H groups are located near each other, addition of Si−H to C═N of **D** occurs intramolecularly, and produces *sec*-**B** smoothly. This may be the reason for the acceleration by $[H(Me)_2Si]_2O$ and $[H(Me)_2SiCH_2]_2$ described above. Such a bifunctional effect was also observed in rhodium-catalyzed hydrosilylative reduction of ketones.[25]

The third step of the reduction is extrusion of a siloxane from *sec*-**B**, providing an imine activated by a cationic silyl group, *sec*-**C**. Since the C═N bond is activated by the R_3Si^+, two side reactions take place; one is the deprotonation at the α-position of an iminium intermediate *sec*-**C** to form silylenamine **5**, whereas the reduction of the C═N bond of *sec*-**C** forms silylamine *sec*-**3**. Formation of **E** from *sec*-**C** can be explained by attack of *sec*-**3** on the silylated iminium ion *sec*-**C**. In further reduction of the resulting intermediate, an aminal **E** gives the tertiary amine **4**. The supporting evidence of the latter process is the reaction described in Scheme 6, in which reduction of *N*-methyl-3-phenylpropionamide **2a** in the presence of *N*-benzlymethylamine gave benzylated tertiary amine, *N*-benzyl-*N*-methyl-3-phenylpropylamine **7**. In fact, treatment of PMHS with secondary amine in the presence of **1** resulted in fixation of the amine in the PMHS chain. In the presence of *N*-benzylmethylamine, the intermediate *sec*-**C** is formed from *N*-methyl-3-phenylpropionamide **2a**, whereas *sec*-**3** is produced from *N*-benzylmethylamine because the ruthenium complex **1** is also an active catalyst for dehydrogenative silylation of alcohols and primary or secondary amines. Coupling of these two species, *sec*-**C** from **2a** and *sec*-**3** from *N*-benzylmethylamine gives the tertiary amine **7**. These explain the third question described above.

The explanation for the fourth question requires an understanding of the self-encapsulation phenomenon. Treatment of tertiary amides with PMHS in the presence of catalyst **1** results in conversion of two Si−H groups in PMHS chains to a Si−O−Si moiety. As reported previously,[16a] this causes bridging of the siloxane chains derived from PMHS, leading to formation of siloxane gel. The ruthenium species is encapsulated into the siloxane gel, presumably through Si−Ru bonds, which are formed by the oxidative addition of the Si−H bonds in PMHS to the catalytically active ruthenium species. Since tertiary amine produced under these conditions has no interaction with the formed siloxane gel, it was facilely separated from the silicon

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[24] Nagashima, H.; Sakai, S.; Motoyama, Y. Unpublished results.

[25] Nagashima, H.; Tatebe, K.; Ishibashi, T.; Nakaoka, A.; Sakakibara, J.; Itoh, K. *Organometallics* **1995**, *14*, 2868.

resin by simple extraction with ether. In sharp contrast, reduction of secondary amides with PMHS affords silylated secondary amines; this means that the amine product is attached to the siloxane chain through a Si−N bond. Thus, isolation of secondary amine from the produced silicon resin requires the fission of the Si−N bond by hydrolysis, which cannot be accomplished by simple extraction with ether. This explains the reason why the selective isolation of tertiary amine **4** is possible in the reduction of **2** with PMHS. Interesting exceptions are described in Scheme 5, where the reduction of secondary amides having a bulky N-substituent was accomplished with PMHS; the corresponding secondary amines are facilely isolated from the reaction mixture by simple extraction with ether. The bulky N-substituent would prevent the reaction of *sec*-**C** with *sec*-**3**; this blocks production of tertiary amine **4**. The secondary-amine product should be attached to the PMHS chain; however, the bulkiness of the N-substituent would instabilize the Si−N bonds, which can be facilely hydrolyzed by contact with trace amounts of moisture.

Conclusion

In this paper, we have described selective synthetic methods for secondary amines and tertiary amines in the hydrosilane reduction of secondary amides catalyzed by a triruthenium complex **1**. As described above, the reaction essentially produces a mixture of three products, and we have succeeded in the development of practical synthesis of two of them, secondary amines and tertiary amines, which are synthesized according to the equation: $2RC(=O)NHR' + 6R''_3Si-H \rightarrow (RCH_2)_2NR' + 2R''_3Si-O-SiR''_3 + R'N(Si\ R''_3)_2 + H_2$. In the preparation of the secondary amines, key discoveries are application of higher catalyst concentration than usual and use of bifunctional hydrosilanes. In contrast, use of polymeric hydrosiloxanes as a hydride source helps for raising the selectivity and separating the desired tertiary amines from other reaction products. It should be noted that both of the ruthenium-free reaction products are isolated without further purification using chromatography and distillation. Possible mechanisms for the reduction can be drawn as Scheme 7. These new results provide unique and practical reduction protocols of secondary amides in organic synthesis. Further studies on the ruthenium-catalyzed reactions of organic molecules with hydrosilanes are now underway.

Experimental Section

General Procedure for the Reduction of Secondary Amides 2 to Secondary Amines 3. To a solution of **1** (9.8 mg, 0.015 mmol, 3 mol % based on the amide) in 0.5 mL of dimethoxyethane was added 1,1,3,3-tetramethyldisiloxane (3.2−4.5 equiv Si−H to **2**), and the resulting solution was stirred at room temperature for 10 min. After 10 min, amide **2** (0.5 mmol) was added, and gas evolution was observed. The solution was heated at 40−60 °C with stirring for 6−12 h. After complete consumption of **2** was confirmed by TLC analysis, the reaction mixture was filtered through a pad of Florisil, and the filtrate was poured into an ethereal solution of hydrogen chloride [0.1 M, 10 mL; prepared from commercially available 1 M HCl/ether (1 mL) and ether (9 mL)]. The ammonium salt **6** was precipitated as a white powder. Separation of the supernatant by decantation or centrifugation followed by washing of the residue with ether afforded **6** without contamination of silicone or ruthenium residues. **6** was treated with excess amounts of sodium carbonate in wet THF at 0 °C for 0.5−1 h. The solid materials were filtered off, and the desired amine **3** was obtained by concentration of the filtrate. This procedure can be applicable to a large scale synthesis of secondary amines. In a typical example, **2f** (1.63 g, 10 mmol) was allowed to react with 1,1,3,3-tetramethyldisiloxane (3.5 mL, 4.0 equiv Si−H to **2f**) in DME (10 mL) in the presence of **1** (195 mg, 0.3 mmol) at 60 °C for 12 h. The workup in the same manner as above was followed by treatment of the crude product with an ethereal solution of hydrogen chloride (0.17 M, 48 mL). The ammonium salt **6f** was obtained in 92% yield (1.70 g). The reaction of **6f** with Na_2CO_3 (4 g) in THF (60 mL) at 0 °C to room temperature for 3 h afforded the amine product **3f** in 83% yield (1.23 g).

***N*-Methyl-3-phenylpropylamine (3a):** 51 mg (68% yield). ^1H NMR (270 MHz, $CDCl_3$): δ 1.22 (bs, 1H), 1.83 (tt, $J = 7.3$, 7.9 Hz, 2H), 2.44 (s, 3H), 2.62 (t, $J = 7.3$ Hz, 2H), 2.67 (t, $J = 7.9$ Hz, 2H), 7.16−7.32 (m, 5H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ 31.7, 33.8, 36.6, 51.8, 125.7, 128.28, 128.32, 142.1. HRMS (EI): calcd for $C_{10}H_{15}N$ (M^+), 149.1204; found, 149.1208.

General Procedure for Secondary Amides 2 to Tertiary Amines 4. To a solution of **1** (6.3 mg, 0.01 mmol) in tetrahydropyran (0.2 mL) was added PMHS (370 μL, Si−H = 5.5 mmol), and the mixture was stirred at ambient temperature for 30 min. The initial dark-orange color of the solution gradually turned to light orange. Then, a solution of amide (1.0 mmol) in THP (0.7 mL) was added, and the solution was stirred at 40−70 °C. The homogeneous solution turned to gel after several hours. After it was allowed to stand for 24 h, tetrahydropyran was removed in vacuo (6 Torr) to form a silicone resin insoluble in common organic solvents. The resultant resin was extracted 10 times with ether (totally 20 mL), and the combined extracts were concentrated in vacuo. Purification of the residue by alumina column chromatography (ether) gave the desired tertiary amine. Decomposition of the silicone resin by hot methanol (50 °C, 24 h) was followed by concentration of the resulting methanol solution. The residue was purified by alumina chromatography (ether) to give the secondary amine formed by simple reduction of the secondary amide. Reduction of **2c** and **2n** in the same manner as above gave the corresponding secondary amine **3c** and **3n**. No reductive N-alkylation product was observed.

Di(3-phenylpropyl)methylamine (4a):[11] 72 mg (54% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 1.85 (tt, $J = 7.6$, 7.9 Hz, 4H), 2.28 (s, 3H), 2.43 (t, $J = 7.6$ Hz, 4H), 2.69 (t, $J = 7.9$ Hz, 4H), 7.21−7.37 (m, 10H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 29.2, 33.8, 42.3, 57.3, 125.8, 128.4, 128.5, 142.5. HRMS (EI): calcd for $C_{19}H_{25}N$ (M^+), 267.1987; found, 267.1982.

Reduction of 2a in the Presence of *N*-Methylbenzylamine: Formation of *N*-Methyl-*N*-(3-phenylpropyl)benzylamine (7).[26] To a solution of **1** (6.3 mg, 0.01 mmol) in tetrahydropyran (0.2 mL) was added PMHS (450 μL, Si−H = 6.6 mmol), and the mixture was stirred at ambient temperature for 30 min. The initial dark-orange color of the solution gradually turned to light orange. Then, *N*-methylbenzylamine (193 μL, 1.5 mmol) was added, and the mixture was stirred for 30 min at 50 °C. After cooling the solution to ambient temperature, a solution of *N*-methyl-3-phenylpropionamide **2a** (163 mg, 1.0 mmol) in THP (0.7 mL) was added, and the resultant solution was stirred at 70 °C. The homogeneous solution turned to gel after several hours. After it was allowed to stand for 24 h, tetrahydropyran was removed in vacuo (6 Torr) to form a silicone resin insoluble in common organic solvents. The resin was extracted 10 times with ether (totally 20 mL), then the combined organic extracts were evaporated under a reduced pressure. Purification of the residue by alumina column chromatography gave the tertiary amine **7**, 95 mg (40% yield). ^1H NMR (396 MHz, $CDCl_3$): δ 1.86 (tt, $J = 7.9$, 7.3 Hz, 2H), 2.21 (s, 3H), 2.44 (t, $J = 7.3$ Hz, 2H), 2.67 (t, $J = 7.9$ Hz, 2H), 3.50 (s, 2H), 7.16−7.34 (m, 10H). ^{13}C NMR (99.5 MHz, $CDCl_3$): δ 29.3, 33.6, 42.2, 57.0, 62.4, 125.7, 126.9, 128.25, 128.34, 128.5, 129.1, 139.3, 142.5. Treatment of the silicon resins formed with methanol at 50

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[26] Hon, Y.-S.; Chang, F.-J.; Lu, L.; Lin, W.-C. *Tetrahedron* **1998**, *54*, 5233.

°C for 24 h led to recovery of secondary amine **3a** and unreacted *N*-methylbenzylamine.

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Supporting Information Available: Detailed experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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