

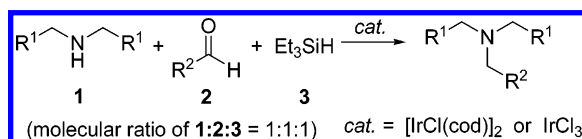
Catalytic Reductive Alkylation of Secondary Amine with Aldehyde and Silane by an Iridium Compound

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An efficient methodology for the reductive alkylation of secondary amine with aldehyde and Et_3SiH using an iridium complex as a catalyst has been developed. For example, treatment of dibutylamine with butyraldehyde and Et_3SiH (a 1:1:1 molar amount of amine, aldehyde, and silane) in 1,4-dioxane at 75 °C under the influence of a catalytic amount of $[\text{IrCl}(\text{cod})]_2$ gave tributylamine in quantitative yield. In this reaction, no reduction of aldehyde took place. It was found that IrCl_3 , which is a starting material for preparation of iridium complexes such as $[\text{IrCl}(\text{cod})]_2$, acts as an efficient catalyst for the present reductive alkylation of amine. In addition, a cheaper, easy-to-handle, and environmentally friendly reducing reagent such as polymethylhydrosiloxane (PMHS) in place of Et_3SiH was also useful. Thus, a variety of secondary amines could be alkylated by allowing them to react with aldehydes and PMHS in the presence of an iridium catalyst to afford the corresponding tertiary amines in good to excellent yields. From the deuterium label experiments, it was revealed that silane and water, generated during the formation of enamine by the reaction of amine and aldehyde, seem to behave as a hydrogen source. The catalytic cycle was discussed.

Introduction

The synthesis of tertiary amines by the reductive alkylation of amines with carbonyl compounds has been often used as a synthetic tool in organic chemistry.¹ Because the reduction of imines (or enamines), generated in situ by the reaction of amines with aldehydes (or ketones), can compete with the reduction of the starting carbonyl compounds, the reducing agents must serve on the reduction of imine (or enamine) with high selectivity for the reductive alkylation amines. Although a number of reducing agents have been developed so far for this purpose,^{1,2} sodium cyanoborohydride (NaBH_3CN)³ and sodium triacetoxyborohydride ($\text{NaBH}(\text{OAc})_3$)⁴ are the most commonly used agents.

Silanes are also employed for the reductive alkylation of amines (the reductive amination of carbonyl compounds),⁵ and several reduction systems such as $\text{Cl}_3\text{SiH}/\text{DMF}$,^{5a} $\text{Et}_3\text{SiH}/\text{CF}_3\text{COOH}$,^{5b,c} and polymethylhydrosiloxane (PMHS)/ $\text{Ti}(\text{O}^i\text{Pr})_4$ ^{5d} have been proposed. To the best of our knowledge, however, there are only two reports on the catalytic reductive alkylation of amines using organosilane as a reducing reagent. Apodaca and co-workers showed that the reductive alkylation of amines with carbonyl compounds and phenylsilane (PhSiH_3) was achieved in the presence of a catalytic amount of dibutyltin dichloride.⁶ Ti-catalyzed reduction of imines, prepared independently from the reaction of amines with aldehydes, with PhSiH_3 was also reported by Buchwald

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TABLE 1. Reductive Alkylation of 1a with 2a and 3 to 4aa in the Presence of an Ir or Rh Catalyst (mol ratio of 1a:2a:3 = 1:1:1)^a

run	catalyst ^b	yield (%)
1	[IrCl(cod)] ₂	98
2	[IrCl(coe)] ₂	83
3	[Ir(cod)] ₂ BF ₄	79
4	[Cp*IrCl] ₂	27
5	IrCl(CO)(PPh ₃) ₂	29
6	[RhCl(cod)] ₂	19
7	IrCl ₃	44
8 ^c	IrCl ₃	99

^a **1a** (1 mmol) was allowed to react with **2a** (1 mmol) and **3** (1 mmol) in the presence of catalyst (0.01 mmol – Ir or Rh) in 1,4-dioxane (2 mL) at 75 °C for 8 h. ^b cod, 1,5-cyclooctadienyl; coe, cyclooctenyl; Cp*, 1,2,3,4-tetramethylcyclopentadienyl. ^c Reaction was run in toluene (1 mL) at 110 °C for 15 h.

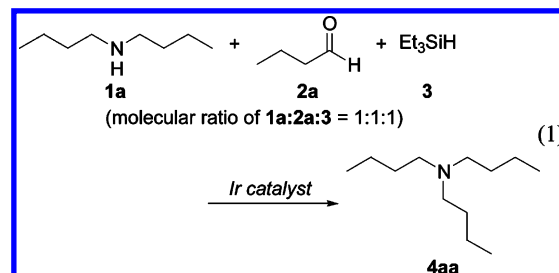
et al.⁷ Quite recently, Fujita and Yamaguchi established the N-alkylation of primary and secondary amines with alcohols catalyzed by [Cp*IrCl]₂ in the presence of a base such as K₂CO₃.⁸

During the course of our studies on the iridium-catalyzed organic syntheses,⁹ we have disclosed the chemoselective transfer hydrogenation of α,β -unsaturated ketones to saturated ketones using 2-propanol as a hydrogen donor catalyzed by the [IrCl(cod)]₂/dppp/Cs₂CO₃ system (dppp: diphenylphosphinopropane).^{9c} In addition, the α -alkylation of ketones with alcohols without employment of any solvents has been successfully achieved by the use of a similar catalytic system.^{9b} These reactions are thought to proceed through an iridium–hydride [Ir–H] (or iridium–dihydride [H–Ir–H]) generated in situ from [IrCl(cod)]₂, alcohol, and a base as a key catalytic species. Now, we have considered that the [Ir–H] species could be generated by allowing [IrCl(cod)]₂ to react with organosilanes. Here, we would like to report the reductive alkylation of secondary amine with aldehyde and triethylsilane in the presence of a catalytic amount of an iridium compound by using a 1:1:1 mixture of amine, aldehyde, and Et₃SiH.

Results

The reductive alkylation of dibutylamine (**1a**) with butyraldehyde (**2a**) and triethylsilane (**3**) was selected as a model reaction and was examined under the influence of several Ir and Rh catalysts (eq 1, Table 1). The reaction of **1a** with **2a** and **3** in 1,4-dioxane at 75 °C for 8 h catalyzed by [IrCl(cod)]₂ afforded tributylamine (**4aa**) in almost quantitative yield (run 1). Notably, the reaction took place by the use of a 1:1:1 molar ratio of **1a**:**2a**:**3**. The conventional method for the reductive alkylation of amine with aldehyde and silane required the use of excess silane as a hydrogen source.^{5–7} However, the present reaction could be performed by using only one-half of the stoichiometric amount of Et₃SiH, although 2 equiv of Et₃SiH with respect to amine and aldehyde

seems to be necessary to reduce the resulting enamine. In this reaction, water, generated in the enamine formation from amine and aldehyde, would play an important role as a hydrogen source as discussed later. Additionally, it is worth noting that no reduction of aldehyde **2a** occurred during the reaction. The enamine formed in situ from secondary amine and aldehyde could be reduced with complete selectivity.



Among the iridium complexes examined, [IrCl(cod)]₂ was found to be the best catalyst, followed by [IrCl(coe)]₂ and a cationic complex such as [Ir(cod)]₂BF₄, but [Cp*IrCl]₂ and the Vaska complex were inert (runs 1–5). A rhodium complex such as [RhCl(cod)]₂ had difficulty catalyzing the reductive alkylation of **1a** with **2a** and **3** (run 6). Surprisingly, it was found that IrCl₃, which is a starting material for the preparation of [IrCl(cod)]₂ complex, was also an efficient catalyst for the present reaction. When **1a** was allowed to react with **2a** and **3** in the presence of a catalytic amount of IrCl₃ (mol. ratio of **1a**:**2a**:**3**:IrCl₃ = 1:1:1:0.01) at 110 °C for 15 h, **4** was obtained in excellent yield (run 8). This is the first example of the Ir-catalyzed reductive alkylation of secondary amine with aldehyde and Et₃SiH.

Table 2 summarizes the reductive alkylation of various secondary amines with aldehydes and **3** under the influence of [IrCl(cod)]₂. These reactions were performed by the use of a 1:1:1 molar ratio of amine:aldehyde:**3** to furnish the corresponding tertiary amines in good yields. Unfortunately, the reductive alkylation of primary amine was difficult to carry out with selectivity, because a part of the secondary amines formed was further reacted under these reaction conditions. Almost no reaction occurred by using ketone in place of aldehyde in the present reaction.

Next, we examined the reductive alkylation with polymethylhydrosiloxane (PMHS, **5**) as a reducing reagent. It is known that use of PMHS is advantageous as a cheap, easy-to-handle, and environmentally friendly reagent for reduction of organic functional groups, because it could be removed with ease.^{5d,10} Treatment of **1a** (1 mmol) with **2a** (1 mmol) and **5** (0.05 mmol, about 1.4 equiv of hydride) in the presence of [IrCl(cod)]₂ (0.005 mmol) in THF at 50 °C gave **4aa** in 99% yield (Scheme 1). It is interesting that the reaction was also promoted by IrCl₃, forming **4aa** in 91% yield. On the basis of these results, several amines were alkylated with aldehydes and **5** (Table 3). Except for the reaction of **1f** with **2a**, tertiary amines were obtained in excellent yields. Because a polymer derived from PMHS was dissolved in

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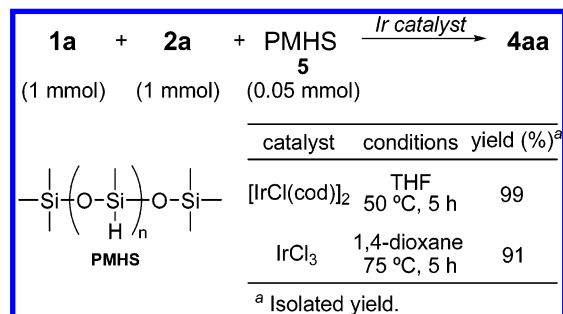
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TABLE 2. Ir-Catalyzed Reductive Alkylation of Various Secondary Amines with Aldehydes and **3** (mol ratio of amine:aldehyde:**3** = 1:1:1)^a

run	substrate		product (yield / %)
	amine	aldehyde	
1	1a	2b	4ab (83)
2	1b	2a	4ba (88)
3	1c	2a	4ca (82)
4 ^b	1a	2c	4ac (81)
5 ^{b,c}	1d	2a	4da (90)
6 ^{b,d}	1e	2a	4ea (71)
7 ^{b,c}	1f	2a	4fa (84)

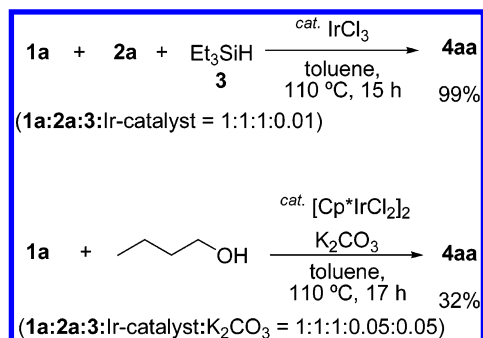
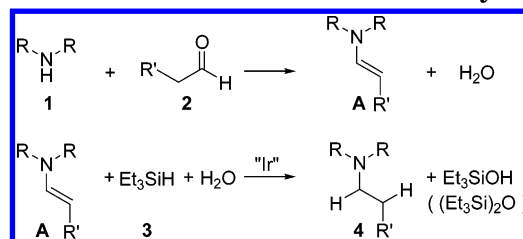
^a Amine (**1a–f**) (1 mmol) was allowed to react with **2a–c** (1 mmol) and **3** (1 mmol) in the presence of [IrCl(cod)]₂ (0.005 mmol) in 1,4-dioxane (2 mL) at 75 °C for 8 h. ^b [IrCl(cod)]₂ (0.02 mmol) was used. ^c Reaction was run in octane (1 mL) at 120 °C. ^d Reaction was run in toluene (1 mL) at 110 °C.

SCHEME 1. Ir-Catalyzed Reductive Alkylation of **1a** with **2a** and PMHS**TABLE 3.** Ir-Catalyzed Reductive Alkylation of Secondary Amines with Aldehydes and **5**^a

run	amine	aldehyde	product	yield (%) ^b
1	1a	2a	4aa	99
2	1a	2b	4ab	93
3	1b	2a	4ba	98
4	1c	2a	4ca	99
5	1e	2a	4ea	92
6	1f	2a	4fa	71

^a Amine (**1a–f**) (1 mmol) was allowed to react with **2a** or **b** (1 mmol) and **5** (0.05 mmol) in the presence of [IrCl(cod)]₂ (0.005 mmol) in THF (2 mL) at 50 °C for 5 h. ^b Isolated yield.

water, an extraction of the resulting reaction mixture with Et₂O/H₂O, followed by removal of the solvent by evaporation, gave an almost pure product.

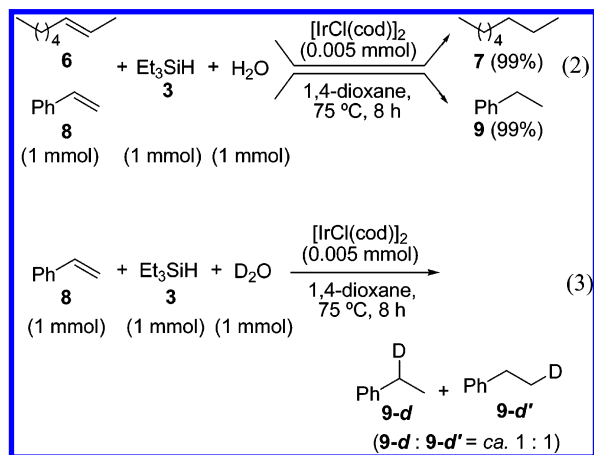
SCHEME 2. Ir-Catalyzed Alkylation of **1a** with **2a** and **3** or Butanol**SCHEME 3.** A Plausible Reaction Pathway

Discussion

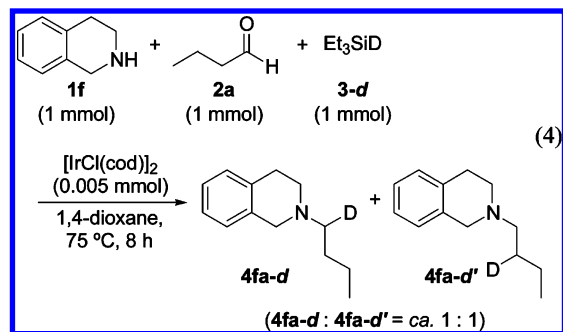
Quite recently, Fujita and Yamaguchi reported the N-alkylation of primary and secondary amines with alcohols catalyzed by [Cp*IrCl₂]₂ in the presence of a base such as K₂CO₃.⁸ Although their work seems to provide an efficient method for N-alkylation of amines catalyzed by an Ir-complex, the substrates used were limited to amines having a phenyl group. In fact, the reaction of simple amines such as **1a** with simple alcohols such as butanol under the influence of [Cp*IrCl₂]₂ and K₂CO₃ had difficulty occurring, leading to the desired product **4aa** in 32% yield (Scheme 2). In contrast, the present reductive alkylation of **1a** with **2a** and **3** proceeded smoothly even by the use of IrCl₃, which is a synthetic precursor of [Cp*IrCl₂]₂ or [IrCl(cod)]₂, and the yield of **4aa** was quite high. Additionally, PMHS, which is easy-to-handle, can be employed as a hydrogen source. Therefore, we thought that the present Ir-catalyzed reaction provides an alternative route for the reductive alkylation of secondary amines.

It is interesting to note that the present Ir-catalyzed reductive alkylation took place by the use of a 1:1:1 molar ratio of amine, aldehyde, and **3**, because the stoichiometry of the reduction calls for the use of 2 equiv of **3** with respect to amine and aldehyde. Scheme 3 showed a plausible reaction pathway. The reaction of amine **1** with aldehyde **2** produces enamine **A** and water. Although the enamine **A** is considered to be reduced with 2 equiv of **3**, it seems likely that **3** and water serve as the hydrogen source under the influence of an iridium complex to lead to tertiary amine and Et₃SiOH (and/or (Et₃Si)₂O). In fact, most of **3** was found to be converted into Et₃SiOH and (Et₃Si)₂O after the reaction. According to the suggested reaction pathway as shown in Scheme 3, the carbon–carbon double bonds would be hydrogenated by the Et₃SiH/H₂O system in the presence of an Ir catalyst. Therefore, we next examined the Ir-catalyzed hydrogenation of alkenes with silane and H₂O. Treatment of

2-octene (**6**) with **3** and H₂O catalyzed by [IrCl(cod)]₂ (molar ratio of **6**:**3**:H₂O:Ir-catalyst = 1:1:1:0.005) in 1,4-dioxane at 75 °C for 8 h resulted in *n*-octane (**7**) in quantitative yield (eq 2). Similarly, styrene (**8**) was reduced under these reaction conditions to furnish ethylbenzene (**9**) in 99% yield. Moreover, when **8** was reacted with a 1:1 mixture of **3** and D₂O under the influence of [IrCl(cod)]₂, **9-d** and **9-d'**, in which a deuterium atom is incorporated into the C1 or C2 position of **8**, were produced (eq 3). These results strongly indicated that water behaves as a hydrogen source in the Ir-catalyzed reduction with silane and water and that one hydrogen of the hydrogenated products comes from water. Similar phenomena are observed in the Pd-catalyzed hydrogenation of alkenes and alkynes with the (EtO)₃SiH/H₂O system^{11a,c} and the Et₃SiH/EtOH system.^{11b}

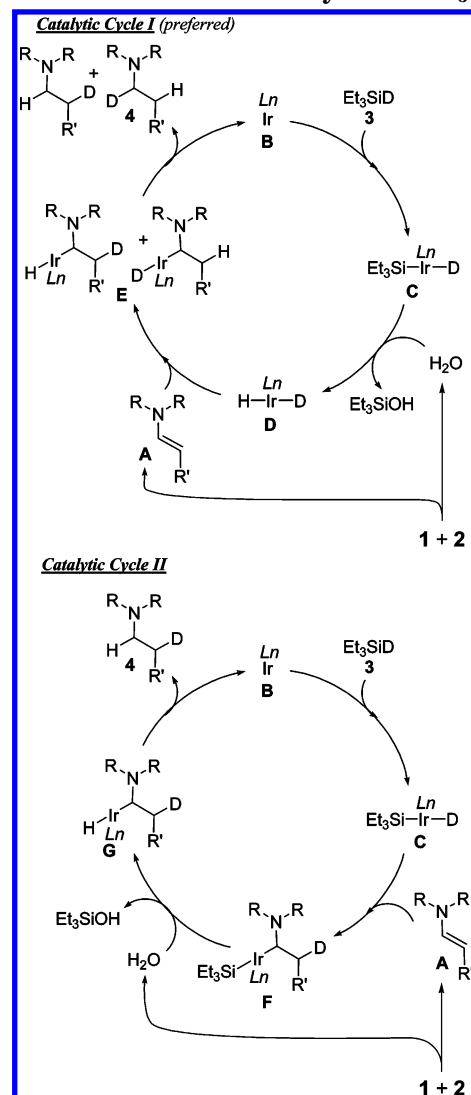


To obtain further insight on the reaction pathway, alkylation of 1,2,3,4-tetrahydroisoquinoline (**1f**) with **2a** and Et₃SiD (**3-d**) was examined. A 1:1:1 mixture of **1f**, **2a**, and **3-d** was treated with a catalytic amount of [IrCl(cod)]₂ in 1,4-dioxane at 75 °C for 8 h to form *N*-(1-deuteriobutyl)-1,2,3,4-tetrahydroisoquinoline (**4fa-d**) and *N*-(2-deuteriobutyl)-1,2,3,4-tetrahydroisoquinoline (**4fa-d'**) in almost 1:1 ratio (eq 4).



On the basis of these results, the catalytic cycles **I** and **II** may be proposed for the present reductive alkylation (Scheme 4). In cycle **I**, the oxidative addition of a low-

SCHEME 4. Catalytic Cycles for the Reductive Alkylation of Amine with Aldehyde and Et₃SiH



valence Ir complex **B** to **3-d** gives Et₃Si-Ir-D (**C**), which subsequently reacts with water, generated during the formation of enamine **A** from **1** and **2**, to produce an iridium-dihydride complex **D** and Et₃SiOH. The **D** thus formed reduces enamine **A** via the formation of **E** to afford tertiary amine **4**, and the regeneration of the Ir complex **B** completes the catalytic cycle. On the other hand, in cycle **II**, the complex **C** first reacts with enamine **A** affording the adduct **F**. The resulting **F** reacts with water to furnish a complex **G**, followed by reductive elimination giving **4** and **B**. It is assumed that the addition of **D** (in cycle **I**) or **C** (in cycle **II**) to enamine **A** takes place with regioselectivity to form **E** or **F**, respectively, where an Ir species adds to the carbon adjacent to the nitrogen atom in enamine **A**. Because a 1:1 regioisomeric mixture of **4fa-d** and **4fa-d'** was obtained in the reaction of **1f** with **2a** and Et₃SiD, it seems likely that the reaction proceeds via the catalytic cycle **I**, which includes the Ir-dihydride species **D** as a key intermediate. If the reaction occurs through the catalytic cycle **II**, **4fa-d'** would be formed as the sole product. Therefore, we considered that the formation of Ir-dihydride species **D** seems to be essential in the present reaction.

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In conclusion, the reductive alkylation of secondary amines with aldehydes and silane has been established by the use of $[\text{IrCl}(\text{cod})]_2$ as a catalyst. IrCl_3 was found to also work well. Only 1 mole of silane with respect to amines and aldehydes was required as a hydrogen source. In this reaction, polymethylhydrosiloxane (PMHS) can be employed, and, as a result, this process can be conducted very easily. The present reaction provides an alternative efficient method for the reductive alkylation of secondary amines with aldehydes. The deuterium experiments suggested that water, generated in situ, as well as silane behaved as hydrogen sources. The reaction seems to proceed via the in situ formation of the Ir–dihydride (and/or the Ir–hydride) from an iridium complex, silane, and water.

Experimental Section

All starting materials were commercially available and used without any purification. GLC analysis was performed with a flame ionization detector using a 0.2 mm \times 25 m capillary column (OV-1). ^1H and ^{13}C NMR spectra were measured at 270 or 400 and 67.5 MHz, respectively, in CDCl_3 with Me_4Si as the internal standard.

A typical reaction procedure of the reaction of **1a** with **2a** and **3** is as follows: To a 1,4-dioxane solution (2.0 mL) of dichlorobis(1,5-cyclooctadiene)diiridium $[\text{IrCl}(\text{cod})]_2$ (0.005 mmol) were added **1a** (1 mmol), **2a** (1 mmol), and **3** (1 mmol). The reaction mixture was then stirred at 75 °C for 8 h. The reaction was quenched with wet ether, and the GC and GC-MS analyses were performed. The yields of products were estimated from the peak areas based on the internal standard technique using GC.

In the reaction using PMHS (**5**) in place of **3**, the isolation procedure of the products is as follows: After the reaction, the

reaction mixture was extracted four times with Et_2O and water. The organic layer was dried over anhydrous MgSO_4 . After evaporation of the extract under reduced pressure, an almost pure product was obtained. The products **4ab**,¹² **4ba**,¹³ **4ca**,¹³ **4ac**,¹⁴ **4da**,¹⁵ **4ea**,¹⁵ and **4fa**¹⁶ were known compounds and have been reported previously.

Spectral data for a mixture of **4fa**: ^1H NMR (CDCl_3/TMS) δ 7.09–6.97 (m, 4H), 3.59 (s, 2H), 2.88 (t, $J = 5.7$ Hz, 2H), 2.69 (t, $J = 5.7$ Hz, 2H), 2.47 (t, $J = 7.3$ Hz, 2H), 1.62–1.51 (m, 2H), 1.43–1.29 (m, 2H), 0.94 (t, $J = 7.3$ Hz, 3H). ^{13}C NMR (CDCl_3/TMS) δ 134.6, 134.1, 128.3, 126.3, 125.7, 125.2, 58.2, 56.1, 50.9, 29.3, 29.1, 20.7, 14.1.

Spectral data for a mixture of **4fa-d** and **4fa-d'**: ^1H NMR (CDCl_3/TMS) δ 7.09–6.97 (m, 4H), 3.59 (s, 2H), 2.88 (t, $J = 6.0$ Hz, 2H), 2.69 (t, $J = 6.0$ Hz, 2H), 2.48 (t, $J = 7.2$ Hz, 1.5H), 1.61–1.53 (m, 1.5H), 1.40–1.32 (m, 2H), 0.94 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (CDCl_3/TMS) δ 134.6, 134.1, 128.3, 126.3, 125.7, 125.2, 58.2, 56.1, 50.9, 29.2, 29.1, 20.6, 14.0.

Acknowledgment. This work was partially supported by MEXT.KAKENHI (No. 15750095).

Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra of **4ab**, **4ba**, **4ca**, **4ac**, **4da**, **4ea**, **4fa**, and **4fa-d**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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