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Synthesis of ω-Hydroxy Carboxylic Acids and α,ω-Dimethyl Ketones Using α,ω-Diols As Alkylating Agents

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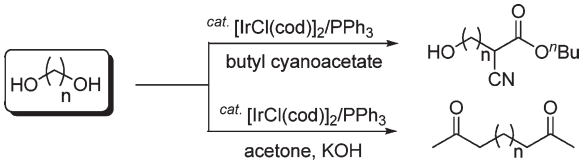

Synthesis of ω-hydroxy carboxylic acids and α,ω-dimethyl diketones was successfully achieved by using α,ω-diols as alkylating agents under the influence of an iridium catalyst. For example, the alkylation of butyl cyanoacetate with 1,13-tridecanediol in the presence of $[IrCl(cod)]_2$ or $[IrCl(coe)_2]_2$ gave rise to butyl 2-cyano-15-hydroxypentadecanoate in good yield which is easily converted to cyclopentadecanolide (CPDL). In addition, the alkylation of acetone with 1,10-decanediol in the presence of $[IrCl(cod)]_2$ and KOH resulted in an important muscone precursor, 2,15-hexadecanedione (HDDO), in good yield.

ω-Hydroxy carboxylic acids and α,ω-dimethyl diketones are very important class of compounds in organic synthesis, particularly in the perfumery industry.[1−3] For instance, ω-hydroxy carboxylic acids like 15-hydroxypentadecanoic acid (CPDA) and α,ω-dimethyl diketones like 2,15-hexadecanedione (HDDO) are useful starting materials to musk and its related compounds. In particular, CPDA is an important precursor of most widely produced macrocyclic synthetic musk lactone, cyclopentadecanolide (CPDL),[2] and several synthetic methods for the synthesis of CPDL from CPDA through intramolecular cyclization have been reported recently.[4−6] Shiina et al. reported that CPDL was prepared by the lactonization by the treatment of CPDA with 2-methyl-6-nitrobenzoic anhydride (MNBA) in 4-(dimethylamino)pyridine (DMAP).[4] Mukaiyama et al reported that the CPDL was obtained by the cyclization of CPDA with an equimolar amount of di-2-thienyl carbonate (2-DTC) combined with a catalytic amount of DMAP followed by treatment with 1−4 equiv of iodine.[5] Furthermore, Otera et al reported the synthesis of CPDL from CPDA by distannoxane-catalyzed macrolactonization.[6]

Although CPDA is an important compound for the synthesis of CPDL, it is conventionally prepared via a multistep synthesis. Typically, CPDA was prepared by condensation of 1,12-dodecanedioate with γ-butyrolactone in the presence of Na, followed by treatment with NaOH and reduction by hydrazine.[7] Therefore, the development of a novel synthetic route to ω-hydroxy carboxylic acids is highly desired.

On the other hand, α,ω-dimethyl diketones like 2,15-hexadecanedione (HDDO) are also attractive precursors for macrocyclic musks.[2] Tsuji et al. reported the preparation of HDDO through six steps from the butadiene telomer.[8] In addition, HDDO is derived from alkyl methyl ketone dimethylhydrazones[9] or from imidazolium salt and Grignard reagent.[10] A well-known method to obtain HDDO is the reaction of 1,10-dibromodecane with 2 equiv of ethyl acetoacetate followed by decarboxylation.[11] By the use of this method, HDDO is prepared in 46% overall yield.[12] However, these methods also need multistage reactions, and some of these are difficult to carry out on a large scale. Therefore, it is important to explore a more convenient synthetic route to HDDO.

During the course of our investigation to develop an efficient and facile synthetic method for preparation CPDA and HDDO, we have demonstrated a novel Ir-catalyzed selective alkylation of cyanoacetates[13] and methyl ketones[14] using alcohols as alkylating agents, leading to the corresponding α-alkylated compounds in good yields. If the alkylation of cyanoacetate and acetone with α,ω-diols is achieved, this strategy would provide a very attractive selective route to ω-hydroxy carboxylic acids like CPDA and α,ω-dimethyl diketones like HDDO, respectively, among the methods reported so far.[7−12] In this paper, we

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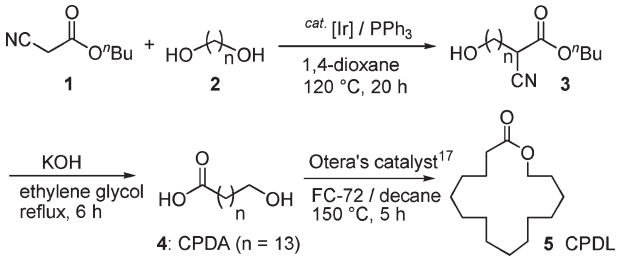
SCHEME 1. Synthesis of CPDA and CPDL



SCHEME 2. Synthesis of HDDO

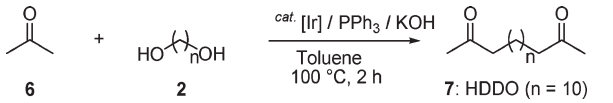
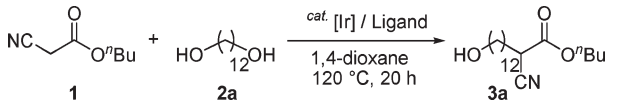


TABLE 1. Reaction of Butyl Cyanoacetate (1) with 1,12-Dodecanediol (2a) by Ir Catalyst under Various Conditions[a]



entry	catalyst	ligand	yield of **3a**[b] (%)
1	$[IrCl(cod)]_2$	PPh_3	82
2	$[IrCl(coe)_2]_2$	PPh_3	85 (70)
3	$[Ir(OH)(cod)]_2$	PPh_3	35
4	$[Ir(OMe)(cod)]_2$	PPh_3	31
5	$[Ir(OAc)(cod)]_2$	PPh_3	7
6	$[Cp^*IrCl_2]_2$	PPh_3	3
7	$IrCl_3 \cdot 3H_2O$	PPh_3	trace
8	$[IrCl(cod)]_2$	PCy_3	trace
9	$[IrCl(cod)]_2$	$P(OPh)_3$	4
10[c]	$[IrCl(cod)]_2$	dppe	66
11	$[IrCl(cod)]_2$	none	n.d.[d]
12[e]	$[IrCl(cod)]_2$	PPh_3	53
13[f]	$[IrCl(cod)]_2$	PPh_3	n.d.[d]
14[g]	$[IrCl(cod)]_2$	PPh_3	23

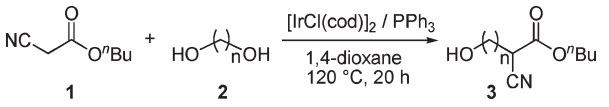
[a]Butyl cyanoacetate (**1**) (1.0 mmol) was allowed to react with 1,12-dodecanediol (**2a**) (3.0 mmol) in the presence of Ir catalyst (0.05 mmol) and PPh_3 (0.2 mmol) in 1,4-dioxane (1 mL) at 120 °C for 20 h. [b]GC yield based on **1a**. The number in the parentheses shows isolated yield. [c]dppe (1,2-bis(diphenylphosphino)ethane) (10 mol %) was used. [d]Not detected by GC. [e]Reaction was performed at 100 °C. [f]Reaction was performed at 80 °C. [g]Reaction was performed at 150 °C.

report the Ir-catalyzed selective synthesis of ω-hydroxy carboxylic acids and α,ω-dimethyl diketones by the reaction of cyanoacetate and acetone with α,ω-diols (Schemes 1 and 2).

We first chose the reaction of butyl cyanoacetate (**1**) with 1,12-dodecanediol (**2a**) as a model reaction and the catalytic performance of various iridium complexes was examined (Table 1).

The reaction of **1** (1.0 mmol) with **2a** (3.0 mmol) using $[IrCl(cod)]_2$ complex (5 mol %) in the presence of PPh_3 ligand (20 mol %) in 1,4-dioxane at 120 °C for 20 h resulted in butyl 2-cyano-14-hydroxytetradecanoate (**3a**) (82%) in good yield (entry 1). When $[IrCl(coe)_2]_2$ was employed as a catalyst, **3a** was obtained in 85% yield (entry 2). However, the catalytic activity of $[Ir(OH)(cod)]_2$, and $[Ir(OMe)(cod)]_2$ was moderate, and $[Ir(OAc)(cod)]_2$ complex was poor

TABLE 2. Reaction of Butyl Cyanoacetate (1) with α,ω-Diols (2) by $[IrCl(cod)]_2$ Catalyst[a]



Entry	Diol (**2**)	Product (**3**)	Yield/%[b]
1	HO$_5$OH (**2b**)	HO$_5$(CN)O^{n}Bu (**3b**)	70[c](53)
2	HO$_6$OH (**2c**)	HO$_6$(CN)O^{n}Bu (**3c**)	83[c](61)
3	HO$_8$OH (**2d**)	HO$_8$(CN)O^{n}Bu (**3d**)	78,75[c](58)
4	HO$_9$OH (**2e**)	HO$_9$(CN)O^{n}Bu (**3e**)	87,80[c](59)
5	HO$_{10}$OH (**2f**)	HO$_{10}$(CN)O^{n}Bu (**3f**)	83(67)
6	HO$_{13}$OH (**2g**)	HO$_{13}$(CN)O^{n}Bu (**3g**)	85[c](72)

[a]Butyl cyanoacetate (**1**) (1.0 mmol) was allowed to react with α,ω-diols (**2**) (3.0 mmol) in the presence of $[IrCl(cod)]_2$ (0.05 mmol) and PPh_3 (0.2 mmol) in dioxane (1 mL) at 120 °C for 20 h. [b]GC yield based on **1** unless otherwise noted. The numbers in the parentheses show isolated yields. [c]NMR yields based on **1** using triphenylmethane as internal standard.

catalyst in this reaction (entries 3−5). $[Cp^*IrCl_2]_2$, which shows high catalytic performance in the Guerbet reaction of primary alcohols,[15] was almost inert the present reaction (entry 6). In this reaction, the highest catalytic activity was attained by combination of $[IrCl(coe)_2]_2$ with triphenylphosphine (PPh_3) as a ligand. Other selected phosphine ligands such as tricyclohexylphosphine (Cy_3P) and triphenyl phosphate ($P(OPh)_3$) were found to be almost inert (entries 8 and 9), but bidentate phosphine ligands like diphenylphosphinoethane (dppe) showed moderate catalytic activity (entry 10). No reaction took place in the absence of phosphine ligand (entry 11). The optimized reaction temperature was 120 °C, the reaction at 100 °C resulted in a considerable decrease of the yield of **3a** (53%) (entry 12), and no alkylation product was observed at 80 °C (entry 13). At 150 °C, the yield of **3a** was low (entry 14).

Under the conditions identified in Table 1, entry 1, **3a** was obtained in substantial yields in various solvents as follows: diglyme (76%), triglyme (75%), THF (75%), toluene (71%), and decane (73%). In addition, the reaction took place without solvent to give **3a** in considerable yield (73%).

Table 2 shows the results for the reaction of **1** with several α,ω-diols under the same conditions as Table 1, entry 1.

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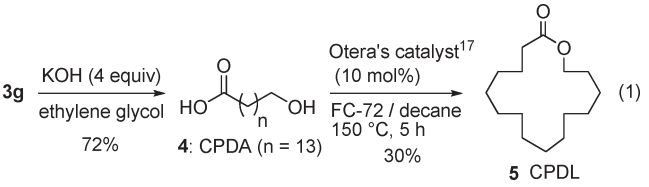
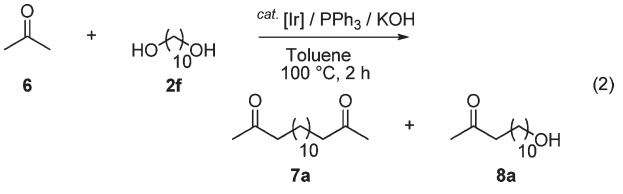
The alkylation of **1** with 1,5-pentanediol (**2b**) afforded butyl 2-cyano-7-hydroxyheptanoate (entry 1). In the same manner, long-chain diols such as 1,6-hexanediol (**2c**), 1,8-octanediol (**2d**), 1,9-nonanediol (**2e**), 1,10-decanediol (**2f**), and 1,13-tridecanediol (**2g**) gave rise to the corresponding alkylated products, butyl 2-cyano-8-hydroxyoctanoate (**3c**), butyl 2-cyano-10-hydroxydecanoate (**3d**), butyl 2-cyano-11-hydroxyundecanoate (**3e**), butyl 2-cyano-12-hydroxydodecanoate (**3f**), and 2-cyano-15-hydroxypentadecanoate (**3g**), respectively, in good yields (entries 2−6).

The synthesis of macrolactones from **3g** was examined (eq 1). Thus, refluxing of **3f** with KOH (4 equiv) in ethylene glycol for 6 h gave 15-hydroxypentadecanoic acid (**4**) in 75% yield.[16] Subsequently, treatment of **4** with the fluoroalkyldistannoxane catalyst (Otera's catalyst)[17] [{$Cl(C_6F_{13}CH_2CH_2)SnOSn(CH_2CH_2C_6F_{13})_2Cl$}$_2$]$_2$ in a mixed solvent of FC-72 and decane, by employing Otera's method for the synthesis of lactones,[6] led to cyclopentadecanolide (**5**).



(1)

In a previous paper, we reported the Ir-catalyzed alkylation of methyl ketones with α,ω-diols.[14b] Thus, this strategy was extended to the general method for synthesizing of α,ω-dimethyl diketones like 2,15-hexadecanedione (HDDO) which is an important precursor of muscone by the use of acetone (**6**) to 1,10-decanediol (**2f**) (eq 2). This method provides the direct route to HDDO (**7a**) by one-step reaction from readily available starting material like acetone and diol.



(2)

Table 3 shows the representative results for the reaction of acetone (**6**) with 1,10-decanediol (**2f**) by several iridium complexes under various conditions.

A stoichiometric reaction for double alkylation of **6** (2.0 mmol) with **2f** (1.0 mmol) using $[IrCl(cod)]_2$ complex (5 mol %) in the presence of PPh_3 ligand (15 mol %) and KOH (40 mol %) in toluene at 100 °C for 2 h resulted in 2,15-hexadecanedione (**7a**) (HDDO) (28%) and 13-hydroxytridecan-2-one (**8a**) (4%) in low yields because of the formation of polymeric products of **2f** (entry 1). When 5 equiv (5.0 mmol) of **6** toward **2f** was used under these conditions, **7a** was obtained in 75% yield along with monoalkylated product, 13-hydroxytridecan-2-one (**8a**) (13%) (entry 2). However, when excess **6** (10 equiv) to **2f** was used, the reaction gave rise to **7a** in 90% yield (77% isolated yield) without formation of **8a** (entry 3). In the present double alkylation of **6** with **2f**, the *amount* of KOH was considerably affected to the yield of **7a** (entries 3−6). The yield of **7a** was decreased to 82% in the reaction of 30 mol % of KOH (entry 4). When KOH was reduced to 20 mol %, diketone **7a** (26%) was formed along with ω-hydroxy ketone **8a** (23%) (entry 5). Almost no alkylation was induced when KOH was reduced to 10 mol % (entry 6). In order to reduce the quantity of base, a strong base like *t*-BuOK was employed instead of KOH, but the result was almost the same as that of KOH (entry 7). The use of $[IrOH(cod)]_2$ in place of $[IrCl(cod)]_2$ led to **7a** in 76% yield even by the use of 20 mol % of KOH (entry 8). As expected, the reaction using $IrCl(PPh_3)_3$ proceeded without phosphine ligand to give **7a** in satisfactory yield (83%) (entry 9). The catalytic activity of [Ir(acac)(cod)] was similar to that of $[IrOH(cod)]_2$ (entry 10). Trivalent iridium complexes like $[Cp^*IrCl_2]_2$ and $IrCl_3 \cdot 3H_2O$ were found to be inactive for the present reaction (entries 11 and 12). Although the formation of an aldol condensation product of **6** under the present conditions is apprehensive, aldol products of **6** were slight (< 5% based on **6**) in all runs in Table 3.

TABLE 3. Reaction of Acetone (6) with 1,10-Decanediol (2f) by Ir Catalyst under Various Conditions[a]

				yield[c] (%)	
entry	catalyst	**6** (mmol)	base[b] (mol %)	**7a**	**8a**
1	$[IrCl(cod)]_2$	2	KOH (40)	28	4
2	$[IrCl(cod)]_2$	5	KOH (40)	75	13
3	$[IrCl(cod)]_2$	10	KOH (40)	90 (77)	n.d.
4	$[IrCl(cod)]_2$	10	KOH (30)	82	3
5	$[IrCl(cod)]_2$	10	KOH (20)	26	23
6	$[IrCl(cod)]_2$	10	KOH (10)	n.d.	1
7	$[IrCl(cod)]_2$	10	*tert*-BuOK (20)	43	13
8	$[Ir(OH)(cod)]_2$	10	KOH (20)	76	3
9[d]	$IrCl(PPh_3)_3$	10	KOH (40)	83	n.d.
10[d]	Ir(acac)(cod)	10	KOH (40)	74	n.d.
11	$[Cp^*IrCl_2]_2$	10	KOH (40)	n.d.	n.d.
12[d]	$IrCl_3 \cdot 3H_2O$	10	KOH (40)	n.d.	n.d.

[a]Acetone (**6**) was allowed to react with 1,10-decanediol (**2e**) (1.0 mmol) in the presence of Ir catalyst (0.05 mmol), PPh_3 (0.15 mmol), and KOH in toluene (0.5 mL) at 100 °C for 2 h. [b]Based on **2f** used. [c]GC yield based on **2e**. The number in the parentheses shows isolated yield. [d]Ir catalyst (10 mol %) was used.

Table 4 shows the preparation of several α,ω-dimethyl diketones from **6** and α,ω-diols (**2**). The reaction of **6** with various α,ω-diols (**2**) was carried out under the same conditions as Table 3, entry 3. The reactions except for 1,4-butanediol (**2h**) and 1,5-pentanediol (**2g**) proceeded satisfactorily to give the corresponding α,ω-dimethyl diketones in good yields (entries 1−5). In the case of the reaction with **2g** and **2h**, monohydroxyketones were formed in low yields, but diketones were not formed at all (entries 6 and 7). For instance, the reaction of **6** with **2g** produced 7-hydroxy-2-heptanone (**8g**) (23%) and polymeric products, but diketone **7g** was not detected by GC analysis. Since the conversion of **2h** was 98%, it is thought that most of the **2h** polymerized to form a complex mixture of polymers by the Guerbet-type reaction.[15]

Compound **7a** has been utilized as a precursor for muscone synthesis. Tanabe et al. reported that cyclization of **3a** with $TiCl_4/Bu_3N$ gave 3-hydroxy-3-methylcyclopentadecanone in 52% yield.[12] (±)-Muscone was prepared by dehydration of 3-hydroxy-3-methylcyclopentadecanone followed by hydrogenation.[12]

ω-Hydroxy methylketones (**8**) are also attractive compounds, but these compounds are difficult to be synthesized

(16) Zimmerman, H. E.; Suryanarayan, V. *Eur. J. Org. Chem.* **2007**, 4091.
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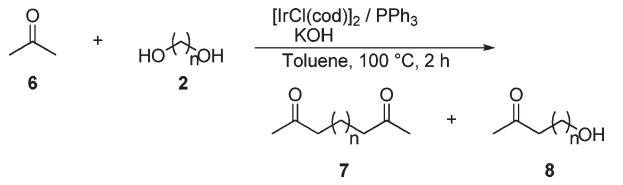
TABLE 4. Reaction of Acetone (6) with α,ω-Diols (2) by Ir Catalyst[a]

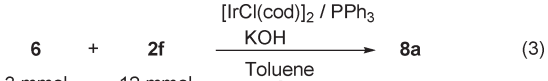


Entry	Diol (2)	Product (7)	Yield/%[b]
1	HO(CH2)6OH (2c)	(7b)	72(57)
2	HO(CH2)7OH (2i)	(7c)	86(68)
3	HO(CH2)8OH (2d)	(7d)	87(69)
4	HO(CH2)9OH (2e)	(7e)	84(70)
5	HO(CH2)12OH (2a)	(7f)	87(75)
6	HO(CH2)4OH (2h)	(7g)	n.d.[c]
7	HO(CH2)5OH (2b)	(7h)	n.d.[d]

[a]Acetone (**6**) (10 mmol) was allowed to react with α,ω-diols (**2**) (1.0 mmol) in the presence of Ir catalyst (0.05 mmol), PPh_3 (0.15 mmol), and KOH (0.40 mmol) in toluene (0.5 mL) at 100 °C for 2 h. [b]GC yield based on **2**. The numbers in the parentheses show isolated yields. [c]7-Hydroxy-2-heptanone (**8g**) was obtained in 23%. [d]8-Hydroxy-2-octanone (**8h**) was obtained in 22%.

by a simple reaction. Our method is expected to apply the synthesis of ω-hydroxy methylketones by allowing **6** to react with α,ω-diols (**2**). Thus, we next try the synthesis of ω-hydroxy ketones from **6** and **2**.

For instance, the reaction of **6** (3.0 mmol) and **2f** (12 mmol) in the presence of $[IrCl(cod)]_2$ (5 mol %), KOH (40 mol %), and PPh_3 (15 mol %) at 80 °C for 0.5 h gave **8a** in 48% isolated yield and a trace amount of **7a** (eq 3), although conventional synthetic methods of the compound **8a** call for multistep reactions.[18]



(3)

It is thought that the reaction proceeds through a similar reaction pathway as described in previously reported relevant works.[13,14] Thus, the iridium-catalyzed dehydrogenation of diols **2** take place to form aldehyde and Ir hydride, followed by cross-aldol condensation with **1** or **6** and hydrogenation with the Ir hydride, giving the desired products (**3**, **7**, and **8**) (Figures S1 and S2, Supporting Information).

In conclusion, ω-hydroxycarboxylic acids and α,ω-dimethyl diketones were successfully prepared by one-step reaction of cyanoacetate and acetone with α,ω-diols, respectively, under the influence of Ir complex and base. This method provides a novel methodology using α,ω-diols as alkylating agents, which is difficult to carry out so far, and a short route to ω-hydroxy carboxylic acids and α,ω-dimethyldiketones, which are important precursors in organic synthesis.

Experimental Section

Typical Reaction Procedure for the Preparation of 3a (Table 1, Entry 2). To a mixture of $[IrCl(coe)_2]_2$ (45 mg, 0.05 mmol) and PPh_3 (53 mg, 0.20 mmol) were added **1a** (141 mg, 1.0 mmol), **2a** (607 mg, 3.0 mmol), and 1,4-dioxane (1.0 mL) under Ar in a 15 mL pressure tube. The reaction mixture was stirred at 120 °C for 20 h. The conversions and yields of products were estimated from the peak areas based on the internal standard techniques using GC which showed that **3a** was obtained in 85% yield. The product (**3a**) was isolated by column chromatography (230−400 mesh silica gel, *n*-hexane/ethyl acetate = 2/1) in 70% yield (238 mg): white solid (mp 48−50 °C); ^{1}H NMR δ 4.17 (t, J = 6.6 Hz, 2H), 3.61 (t, J = 6.6 Hz, 2H), 3.46 (t, J = 6.9 Hz, 1H), 1.91 (q, J = 7.6 Hz, 2H), 1.67−1.60 (m, 2H), 1.57−1.24 (m, 22 H), 0.92 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 166.3 (C), 116.6 (C), 66.5 (CH_2), 63.0 (CH_2), 37.6 (CH), 32.7 (CH_2), 30.3 (CH_2), 29.8 (CH_2), 29.52 (CH_2), 29.45 (CH_2, 2C), 29.36 (CH_2, 2C), 29.1 (CH_2), 28.7 (CH_2), 26.7 (CH_2), 25.7 (CH_2), 18.9 (CH_2), 13.6 (CH_3); IR (neat, cm^{-1}) 3416, 2921, 2851, 2247, 1731, 1470, 1291, 1277, 1057, 1025, 721; GC-MS (EI) *m*/*z* (relative intensity) 325 (0.1) $[M]^+$, 308 (0.6), 252 (7), 224 (10), 196 (19), 140 (12), 57 (85), 41 (100). Anal. Calcd for $C_{19}H_{35}NO_3$: C, 70.11; H, 10.84; N, 4.30. Found: C, 70.24; H, 10.75; N, 4.13.

Typical Reaction Procedure for the Preparation of 7a (Table 3, Entry 3)[12]. To a mixture of $[IrCl(cod)]_2$ (34 mg, 0.05 mmol), PPh_3 (39 mg, 0.15 mmol), and KOH (23 mg, 0.4 mmol) were added **6** (581 mg, 10 mmol), **2f** (174 mg, 1.0 mmol), and toluene (0.5 mL) under Ar in a 15 mL pressure tube. The reaction mixture was stirred at 100 °C for 2 h. The conversions and yields of products were estimated by GC, and the product **7a** was obtained in 90% yield. The product (**7a**) was isolated by column chromatography (230−400 mesh silica gel, *n*-hexane/ethyl acetate = 10/1) in 77% yield (196 mg).

Procedure for the Preparation of 8a (eq 3)[19]. To a mixture of [IrCl(cod)]2 (101 mg, 0.15 mmol), PPh_3 (118 mg, 0.45 mmol), and KOH (68 mg, 1.2 mmol) were added **6** (174 mg, 3.0 mmol), **2f** (2.09 g, 12.0 mmol), and toluene (1.5 mL) under Ar in a 15 mL pressure tube. The reaction mixture was stirred at 80 °C for 0.5 h. The product (**8a**) was isolated by column chromatography (230−400 mesh silica gel, *n*-hexane/ethyl acetate = 3/1) in 48% yield (309 mg).

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Supporting Information Available: Figures S1 and S2, experimental procedure, spectra data, and copies of ^{1}H and ^{13}C NMR of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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