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Iridium-Catalyzed Oxidative Methyl Esterification of Primary Alcohols and Diols with Methanol

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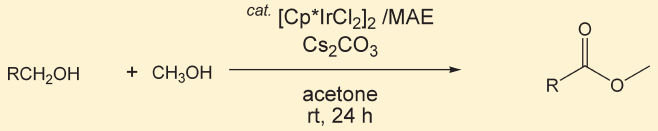
Supporting Information

ABSTRACT: Oxidative methyl esterification of primary alcohols and diols with methanol was successfully achieved, using acetone as a hydrogen acceptor, under the influence of an iridium complex combined with 2-(methylamino)ethanol (MAE) as catalyst.



Methyl esterification is a ubiquitous methodology in organic synthesis,[1] especially in the transformation of pectins,[2] amino acids,[3] prostaglandins,[4] and peptides.[5] Methyl esterification has also been successfully applied to the production of biodiesel fuel (BDF) from waste vegetable oils/fats.[6] Various methods for achieving this reaction have therefore been developed.[7−9] Methyl esters have been prepared by the reaction of carboxylic acids with methanol under acidic or basic conditions.[7] Another conventional procedure for the synthesis of methyl esters is reaction of carboxylic acids with trimethylsilyldiazomethane (TMS-CHN_2) in methanol solution.[8] In addition, there have been recent reports of the catalytic methyl esterification of carboxylic acids with methanol.[9]

Alternatively, oxidative methyl esterification of aldehydes and alcohols has also attracted considerable interest. However, this method generally requires stoichiometric amounts of toxic and hazardous reagents like manganese dioxide or sodium dichromate and/or peroxides.[10] The development of a single-step catalytic direct oxidative methyl esterification of alcohols under mild conditions is therefore highly desirable from both economic and environmental points of view. Although several catalytic oxidative esterifications of primary alcohols to esters have been reported so far,[11] less attention has been paid to the oxidative methyl esterification of alcohols with methanol.[12]

It is known that Ir and Ru complexes serve as efficient catalysts for hydrogen transfer from alcohols to aldehydes,[13] and we have recently developed Ir-catalyzed α-alkylations and β-alkylations using alcohols as the alkylating agents.[14] These results prompted us to design a reaction system for Ir-catalyzed oxidative dimerization of primary alcohols to esters in the presence of dioxygen (air) or acetone as a hydrogen acceptor.[15] Furthermore, Suzuki and co-workers have reported that Cp*Ir−aminoalkoxide complexes promote the oxidative dimerization of primary alcohols to esters in the presence of 2-butanone as the hydrogen acceptor and K_2CO_3. However, they did not report the preparation of methyl esters using cross-esterification of primary alcohols and methanol.[16] Quite recently, Williams and co-workers reported the esterification of primary alcohols in methanol by $Ru(PPh_3)_3(CO)H_2$ combined with xantphos in the presence of crotononitrile as the hydrogen acceptor.[17]

In this paper, we disclose a facile, divergent, and atom-economical methodology for oxidative methyl esterification by the Ir-catalyzed reaction of primary alcohols and diols with methanol using acetone as the hydrogen acceptor.

1-Hexanol (**1a**) with methanol (**2**) was chosen as the model substrate, and the reaction was carried out under various conditions (Table 1).

For instance, the reaction of **1a** with **2** in the presence of $[Cp^*IrCl_2]_2$ (2 mol %) with 2-(methylamino)ethanol (MAE) (6 mol %) and Cs_2CO_3 (10 mol %) in acetone at room temperature for 24 h produced methyl hexanoate (**3a**) in 84% yield (entry 1). $[Cp^*IrCl_2]_2$ showed the best catalytic activity as a catalyst precursor (entry 1). When $[IrCl(cod)]_2$ and $[IrCl(coe)_2]_2$ were selected as the catalyst precursor, **3a** was obtained in lower yields (entries 2 and 3). $IrCl_3 \cdot 3H_2O$ was totally ineffective, and no **3a** was formed (entry 4). This reaction was markedly influenced by the base employed. Among bases examined, Cs_2CO_3 was found to be a suitable base (entry 1), but K_2CO_3 only had moderate activity, giving **3a** in 61% yield (entry 5). Other selected bases such as Na_2CO_3, K_3PO_4, and KOH were less effective, affording **3a** in 12%, 61% and 58% yields, respectively (entries 6−8).[18] The addition of a base and MAE was essential for achieving the reaction, and the reaction in the absence of either a base or MAE did not produce **3a** at all (entries 9 and 10). The yield of **3a** was decreased at elevated temperature because of the instability of the catalyst (entry 11). In this reaction, acetone functioned as the best hydrogen acceptor; the reaction using 2-butanone gave a lower yield of **3a** (entry 12). Alkenes like 1-octene were not efficient hydrogen acceptors (entry 13). The reaction under air was also found to be sluggish (entry 14).

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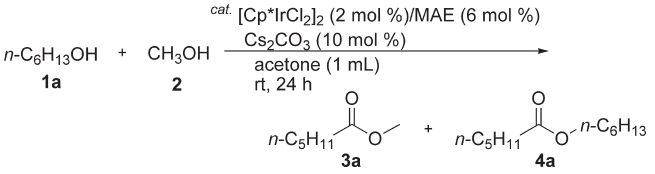
Table 1. Ir-Catalyzed Oxidative Methyl Esterification of 1a with 2[a]



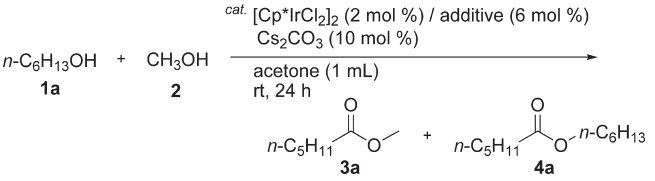
entry	Ir complex	base	conv 1a[b] (%)	yield[b] (%) 3a	yield[b] (%) 4a
1	$[Cp^*IrCl_2]_2$	Cs_2CO_3	90	84 (80)	4
2	$[IrCl(cod)]_2$	Cs_2CO_3	3	1	n.d.[c]
3	$[IrCl(coe)_2]_2$	Cs_2CO_3	2	1	n.d.[c]
4	$IrCl_3.3H_2O$	Cs_2CO_3	<1	n.d.[c]	n.d.[c]
5	$[Cp^*IrCl_2]_2$	K_2CO_3	73	61	3
6	$[Cp^*IrCl_2]_2$	Na_2CO_3	26	12	1
7	$[Cp^*IrCl_2]_2$	K_3PO_4	70	61	6
8	$[Cp^*IrCl_2]_2$	KOH	71	58	3
9	$[Cp^*IrCl_2]_2$	none	2	n.d.[c]	n.d.[c]
10[d]	$[Cp^*IrCl_2]_2$	Cs_2CO_3	11	n.d.[c]	n.d.[c]
11[e]	$[Cp^*IrCl_2]_2$	Cs_2CO_3	71	56	3
12[f]	$[Cp^*IrCl_2]_2$	Cs_2CO_3	75	65	2
13[g]	$[Cp^*IrCl_2]_2$	Cs_2CO_3	<1	n.d.[c]	n.d.[c]
14[h]	$[Cp^*IrCl_2]_2$	Cs_2CO_3	<1	n.d.[c]	n.d.[c]

[a] Conditions: **1a** (2 mmol) was allowed to react with **2** (8 mmol) in the presence of Ir complex (0.04 mmol), MAE (0.12 mmol), and base (0.1 mmol) in acetone (1 mL) at rt (ca. 25 °C) for 24 h. [b] GC yields except the values in the parentheses. [c] Not detected by GC. [d] Reaction was performed in the absence of MAE. [e] Reaction was performed at 40 °C. [f] 2-Butanone was used in place of acetone. [g] 1-Octene was used in place of acetone. [h] Reaction was performed in toluene (1 mL) instead of acetone under air (1 atm).

As mentioned above, the addition of MAE was indispensable, and this effect was investigated using various additives under the conditions for Table 1, entry 1 (Table 2). Like MAE, 2-(ethylamino)ethanol and 2-(propylamino)ethanol efficiently promoted the oxidative methyl esterification of **1a** with **2** in 75% and 66% yields, respectively (entries 1 and 2). The yield of **3a** decreased with increasing carbon number of the alkyl group on the amino group. Addition of 2-anilinoethanol and 2-aminoethanol only afforded trace amounts of **3a** (entries 3 and 4). Other additives such as diethylaminoethanol, 3-methylaminopropan-1-ol, and ethylendiamine did not afford **3a** at all (entries 5–7).

In the reaction, the equimolar reaction of **1a** to **2** significantly affected the yields of **3a** and **4a** because of the formation of oxidative dimerization of **1a**.[15] Figure 1 shows the effect on the yields of **3a** and **4a** by changing the amount of methanol (**2**) (2 mmol–10 mmol) to **1a** (2 mmol) under the same conditions as in entry 1 in Table 1. The reaction of **1a** in the absence of methanol gave **4a** in 72% yield, as we previously reported.[15] When 2 mmol of **2** were used, i.e., a 1:1 ratio of **1a** and **2a**, **3a** and **4a** were obtained in an approximately 3:1 mixture. The use of excess methanol increased the selectivity of **3a**. Thus, the optimum ratio of **1a** to **2** for obtaining **3a** in the highest yield, and with the highest selectivity, was found to be 1:4.

Table 2. Effects of Additives in the Ir-Catalyzed Oxidative Methyl Esterification of 1a with 2[a]



entry	additive	conv 1a[b] (%)	yield[b] (%) 3a	yield[b] (%) 4a
1	$EtNH(CH_2)_2OH$	81	75	2
2	$n\text{-}PrNH(CH_2)_2OH$	73	66	2
3	$PhNH(CH_2)_2OH$	5	2	n.d.[c]
4	$H_2NC_2H_4OH$	9	3	n.d.[c]
5	$Et_2N(CH_2)_2OH$	<1	n.d.[c]	n.d.[c]
6	$MeNH(CH_2)_3OH$	<1	n.d.[c]	n.d.[c]
7	$H_2NC_2H_4NH_2$	<1	n.d.[c]	n.d.[c]

[a] Conditions: same as for Table 1, entry 1. [b] GC yields based on **1a** used. [c] Not detected by GC.

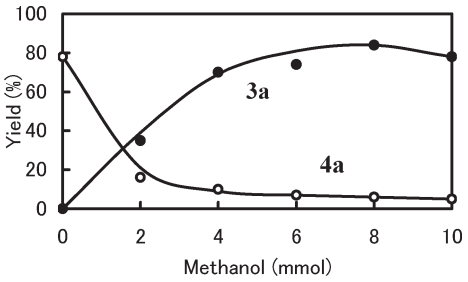


Figure 1. Effect of the amounts of **1a** (2 mmol) and methanol (**2**) (2–10 mmol) on yields of **3a** and **4a** under the conditions for Table 1, entry 1.

The scope of the methyl esterification of various primary alcohols was examined (Table 3). The reaction of **2** with aliphatic alcohols 1-octanol (**1b**), 1-decanol (**1c**), and 1-dodecanol (**1d**) afforded the corresponding methyl esters, i.e., methyl octanoate (**3b**), methyl decanoate (**3c**), and methyl dodecanoate (**3d**), in 83%, 82%, and 92% yields, respectively (entries 1–3). 5-Methyl-1-hexanol (**1e**) and 2-ethyl-1-hexanol (**1f**) afforded the corresponding methyl esters, i.e., methyl 5-methylhexanoate (**3e**) and methyl 2-ethylhexanoate (**3f**), in 82% and 42% yields, respectively (entries 4 and 5). An alcohol (**1g**) bearing a carbon–carbon double bond provided methyl 7-octenoate (**3g**), exclusively, without hydrogenation of the double bond (entry 6). An alcohol (**1h**) bearing a terminal halogen group was also tolerated under the reaction conditions and produced methyl 6-chlorohexanoate (**3h**) in good yield (entry 7). Furthermore, various benzyl alcohols (**1i–l**) afforded the corresponding methyl esters, i.e., methyl benzoate (**3i**), methyl *p*-toluate (**3j**), and methyl 4-chlorobenzoate (**3l**), in good yields (entries 8–11). Phenethyl alcohols (**1m–n**) also reacted with **2** to produce methyl phenylacetate (**3m**) and methyl (4-chlorophenyl)acetate (**3n**) in substantial yields, respectively (entries 12 and 13).

Table 4 shows representative results for the reaction of methanol **2** with 1,10-decanediol (**5a**) under the conditions for

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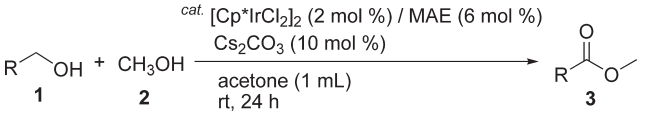
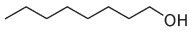
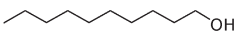
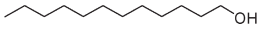
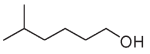
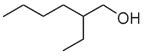
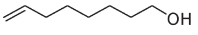
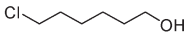
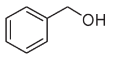
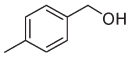
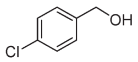
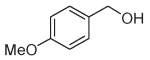
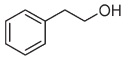
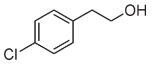
Table 3. Oxidative Methyl Esterification of Primary Alcohols (1) with 2[a]



entry	alcohol		conv. 1/%	product	yield / %
1		**1b**	88	**3b**	83
2		**1c**	88	**3c**	82
3		**1d**	95	**3d**	92
4		**1e**	85	**3e**	82
5		**1f**	44	**3f**	42
6		**1g**	56	**3g**	52
7		**1h**	82	**3h**	81
8		**1i**	77	**3i**	75
9		**1j**	85	**3j**	83
10		**1k**	80	**3k**	69
11		**1l**	30	**3l**	23
12		**1m**	89	**3m**	75
13		**1n**	90	**3n**	86

[a] Conditions: same as for Table 1, entry 1. Trace amounts (<2%) of self-condensation products (**4**) were detected by GC.

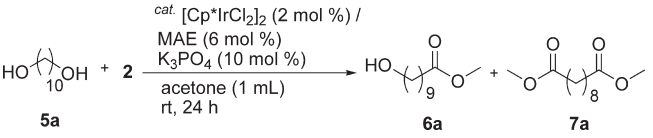
entry 1, Table 1, using various bases. When the reaction was performed using Cs_2CO_3 as the base, the corresponding monomethyl ester (**6a**) and dimethyl ester (**7a**) were obtained in 38% and 31% yields, respectively (69% total yield of **6a** and **7a**; entry 1). The use of K_2CO_3 and Na_2CO_3 led to lower yields (entries 2 and 3). K_3PO_4 was found to be the best effective base, giving the highest total yield of **6a** and **7a** (92%) (entry 5). In addition, when the amount of K_3PO_4 was decreased from 10 mol % to 5 mol % of **5a** used, selective monomethyl esterification was promoted to give **6a** as the major product (entry 6).

Scheme 1 shows the results for the reactions of several α,ω-diols with **2** under the same conditions as for Table 4, entry 5.

The reactions of 1,8-octanediol (**5b**), 1,9-nonanediol (**5c**), and 1,12-dodecanediol (**5d**) with methanol (**2**) proceeded satisfactorily to give mixtures of the corresponding monomethyl (**6b**–**d**) and dimethyl (**7b**–**d**) esters, in excellent total yields.

To gain insight into the reaction mechanism, some control experiments were carried out. The reaction might proceed via ester-exchange between hexyl hexanoate (**4a**) and

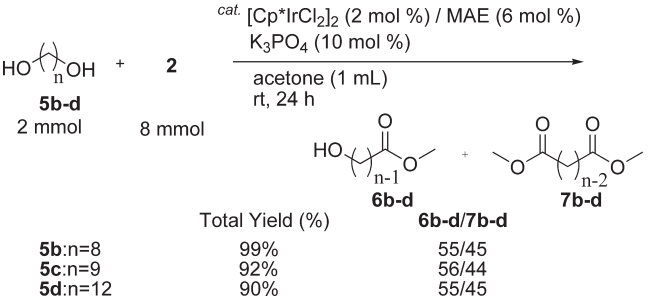
Table 4. Ir-Catalyzed Oxidative Methyl Esterification of α,ω-Diols 5a with 2[a]



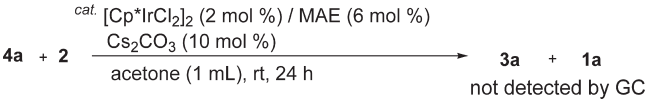
				yield[b] (%)	
entry	base	conv **5a**[b] (%)	total yield (%)	**6a**	**7a**
1	Cs_2CO_3	92	69	38	31
2	K_2CO_3	48	30	20	10
3	Na_2CO_3	15	10	10	n.d.[c]
4	KOH	90	82	44	38
5	K_3PO_4	>99	92	51 (48)	41 (39)
6[d]	K_3PO_4	64	62	55	7

[a] Conditions: **5a** (2 mmol) was allowed to react with **2** (8 mmol) in the presence of $[Cp^*IrCl_2]_2$ (0.04 mmol), MAE (0.12 mmol), and a base (0.1 mmol, 10 mol %) in acetone (1 mL) at rt (ca. 25 °C) for 24 h. [b] GC yields except the values in the parentheses. [c] Not detected by GC. [d] K_3PO_4 (0.05 mmol, 5 mol %) was used.

Scheme 1. Methyl Esterification of α,ω-Diols (5b–d) with 2



Scheme 2. Ester Exchange of 4a with 2



methanol (**2**), but no ester-exchange product, **3a**, was detected (Scheme 2).

Furthermore, we carried out the ester-exchange reaction of 1-hexanol (**1a**) and isopropyl alcohol derived from acetone under these conditions, but no corresponding isopropyl ester was detected at all.

Next, we performed a competitive experiment using methanol with alcohol and aldehyde (Scheme 3). If the oxidation of the alcohols to aldehydes is the rate-determining step, methyl esterification from aldehyde should be predominant over that from alcohol. Thus, treatment of an equimolar mixture of **1a** and *n*-octanal (**8**) with **2** was carried out under the same conditions as for entry 1, Table 1. The time–yield curves for the formation of **3a** and **3b** are shown in Figure 2. In the early stage of the reaction

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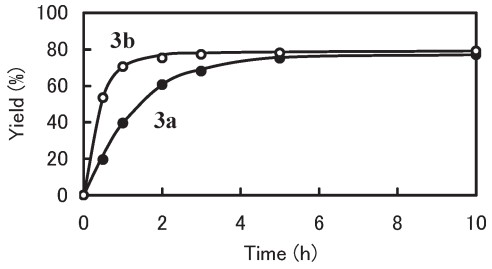
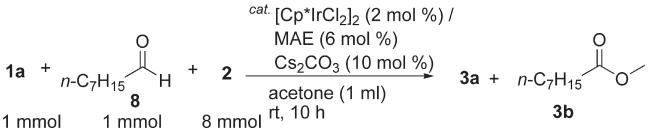


Figure 2. Time−yield curves for the formation of **3a** and **3b** in the oxidative methyl esterification of **1a**, **8**, and **2** under the same conditions as for Table 1, entry 1.

Scheme 3. Competitive Reaction of Methanol (2) with *n*-Hexanol (1a) and *n*-Octanal (8)



(ca. 30 min), methyl esterification from aldehyde (**8**) took place predominantly, and the resulting methyl esters, **3a** and **3b**, were obtained in 18% and 53% yields, respectively (Figure 2). This result suggests that this reaction involves the oxidation of alcohols to aldehydes as the key rate-determining step in the course of the reaction.

It is thought that the reaction proceeds through a hydrogen transfer pathway similar to that of the reaction reported previously.[13−17] The reaction is initiated by iridium-catalyzed dehydrogenation of alcohols (**1**) or α,ω-diols (**5**) to form the corresponding aldehydes, which readily undergo acetalization with methanol (**2**) to give the hemiacetals. Subsequent dehydrogenation of the hemiacetals by the action of the Ir complex affords the corresponding methyl esters.

Here, an Ir−aminoalkoxylate complex derived from $[Cp^*IrCl_2]_2$ and MAE seems to be a real active catalyst species as that reported in the previous literature.[15b,16] In addition, we performed the reaction of hexanal with paraformaldehyde under the same conditions as for entry 1, Table 1, which resulted no **3a** formation. This result indicates the reaction did not proceed via Tischenko reaction pathway.[19]

EXPERIMENTAL SECTION

General Methods. GC analysis was performed with a flame ionization detector using a 0.22 mm × 25 m capillary column (BP-5). ^{1}H and ^{13}C NMR were measured at 400 and 100 MHz, respectively, in $CDCl_3$ with Me_4Si as the internal standard.

Compounds **3a**,[20a] **3b**,[17a] **3c**,[20b] **3d**,[20a] **3e**,[20c] **3f**,[20d] **3g**,[20e] **3h**,[20f] **3i**,[20g] **3j**,[20d] **3k**,[20g] **3l**,[20g] **3m**,[17a] **3n**,[20h] **4a**,[15a] **6a**,[20i] **7a**,[20j] **6b**,[20k] **7b**,[20b] **6c**,[20l] **7c**,[20j] **6d**,[20m] and **7d**[20a] were known compounds reported previously.

Typical Reaction Procedure for the Preparation of 3a (Table 1, Entry 1). To a mixture of $[Cp^*IrCl_2]_2$ (32 mg, 0.04 mmol), Cs_2CO_3 (65 mg, 0.20 mmol), and MAE (9.6 mg, 0.12 mmol) were added **1a** (204 mg, 2.0 mmol), **2** (256 mg, 8.0 mmol), and acetone (1.0 mL) under Ar. The reaction mixture was stirred at 25 °C for 24 h. The conversions and yields of products were estimated from the peak areas based on the internal standard technique using GC showed that **3a** was obtained in 84% yield. The product (**3a**) was isolated by column chromatography (230−400 mesh silica gel, *n*-hexane/ethyl acetate = 10/1) in 80% yield (208 mg).

Typical Reaction Procedure for the Preparation of 6a and 7a (Table 4, Entry 5). To a mixture of $[Cp^*IrCl_2]_2$ (32 mg, 0.04 mmol), K_3PO_4 (42 mg, 0.2 mmol), and MAE (9.6 mg, 0.12 mmol) were added **5a** (349 mg, 2 mmol), **2** (256 mg, 8.0 mmol), and acetone (1.0 mL) under Ar. The reaction mixture was stirred at 25 °C for 24 h. The conversions and yields of products were estimated by GC, and the products **6a** and **7a** were obtained in 92% total yield. The products (**6a** and **7a**) were isolated by column chromatography (230−400 mesh silica gel, *n*-hexane/ethyl acetate = 10/1) in 48 and 39% yield, respectively (194 and 180 mg).

3a:[20a] ^{1}H NMR δ 0.82 (t, *J* = 6.9 Hz, 3H), 1.21−1.26 (m, 4H), 1.52−1.59 (m, 2H), 2.23 (t, *J* = 7.6 Hz, 2H), 3.6 (s, 3H); ^{13}C NMR δ 174.3 (C), 51.4 (CH_3), 34.0 (CH_2), 31.3 (CH_2), 24.6 (CH_2), 22.3 (CH_2), 13.9 (CH_3).

3b:[17a] ^{1}H NMR δ 0.88 (t, *J* = 6.6 Hz, 3H), 1.25−1.32 (m, 8H), 1.59−1.65 (m, 2H), 2.30 (t, *J* = 7.6 Hz, 2H), 3.67 (s, 3H); ^{13}C NMR δ 174.4 (C), 51.5 (CH_3), 34.1 (CH_2), 31.7 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 25.0 (CH_2), 22.6 (CH_2), 14.1 (CH_3).

3c:[20b] ^{1}H NMR δ 0.81 (t, *J* = 6.9 Hz, 3H), 1.19−1.23 (m, 12H), 1.51−1.57 (m, 2H), 2.23 (t, *J* = 7.6 Hz, 2H), 3.59 (s, 3H); ^{13}C NMR δ 174.3 (C), 51.4 (CH_3), 34.1 (CH_2), 31.8 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 24.9 (CH_2), 22.6 (CH_2), 14.0 (CH_3).

3d:[20a] ^{1}H NMR δ 0.87 (t, *J* = 6.6 Hz, 3H), 1.25−1.32 (m, 16H), 1.58−1.66 (m, 2H), 2.30 (t, *J* = 7.6 Hz, 2H), 3.66 (s, 3H); ^{13}C NMR δ 174.4 (C), 51.4 (CH_3), 34.1 (CH_2), 32.0 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 25.0 (CH_2), 22.7 (CH_2), 14.1 (CH_3).

3e:[20c] ^{1}H NMR δ 0.88 (d, *J* = 6.9 Hz, 6H), 1.17−1.30 (m, 2H), 1.52−1.66 (m 2H), 2.04 (s, 1H), 2.29 (t, *J* = 7.6 Hz, 2H), 3.67 (s, 3H); ^{13}C NMR δ 174.3 (C), 51.4 (CH_3), 38.4 (CH_2), 34.4 (CH_2), 27.8 (CH_2), 22.9 (CH_2), 22.5 (CH_3).

3f:[20d] ^{1}H NMR δ 0.81 (t, *J* = 7.3 Hz, 6H), 1.13−1.31 (m, 4H), 1.34−1.60 (m 4H), 2.20 (m, 1H), 3.60 (s, 3H); ^{13}C NMR δ 176.9 (C), 51.2 (CH_3), 47.2 (CH), 31.8 (CH_2), 29.6 (CH_2), 25.5 (CH_2), 22.6 (CH_2), 13.9 (CH_3), 11.8 (CH_3).

3g:[20e] ^{1}H NMR δ 1.23−1.35 (m, 4H), 1.52−1.60 (m, 2H), 1.95−2.01 (m 2H), 2.24 (t, *J* = 7.6 Hz, 2H), 3.60 (s, 3H) 4.85−4.95 (m, 2H), 5.67−5.77 (m, 1H); ^{13}C NMR δ 174.2 (C), 138.7 (CH), 114.4 (CH_2), 51.4 (CH_3), 34.0 (CH_2), 33.5 (CH_2), 28.5 (CH_2), 28.4 (CH_2), 24.7 (CH_2).

3h:[20f] ^{1}H NMR δ 1.45−1.50 (m, 2H), 1.65−1.68 (m, 2H), 1.80−1.83 (m 2H), 2.33 (t, *J* = 3.9 Hz, 2H), 3.52−3.56 (m, 2H) 3.67 (s, 3H); ^{13}C NMR δ 173.8 (C), 51.4 (CH_3), 44.7 (CH_2), 33.7 (CH_2), 32.1 (CH_2), 26.3 (CH_2), 24.1 (CH_2).

3i:[20g] ^{1}H NMR δ 3.92 (s, 3H), 7.41−7.57 (m, 3H), 8.01−8.04 (m, 2H); ^{13}C NMR δ 167.1 (C), 132.9 (C), 128.6 (CH), 128.4 (CH), 128.2 (CH), 52.1 (CH_3).

3j:[20d] ^{1}H NMR δ 2.31 (s, 3H), 3.81 (s, 2H), 7.13−7.15 (m, 2H) 7.83−7.85 (m, 2H); ^{13}C NMR δ 167.1 (C), 143.5 (C), 129.5 (CH), 129.0 (CH), 127.4 (C), 51.9 (CH_3), 21.6 (CH_3).

3k:[20g] ^{1}H NMR δ 3.85 (s, 3H), 7.33−7.36 (m, 2H) 7.90−7.93 (m, 2H); ^{13}C NMR δ 166.2 (C), 139.4 (C), 131.0 (CH), 128.7 (CH), 128.5 (C), 52.2 (CH_3).

3l:[20g] ^{1}H NMR δ 3.79 (s, 3H), 3.82 (s, 3H), 7.84−7.86 (m, 2H) 7.92−7.94 (m, 2H); ^{13}C NMR δ 166.9 (C), 163.3 (C), 131.6 (CH), 122.6 (C), 113.6 (CH), 55.4 (CH_3), 51.9 (CH_3).

3m:[17a] ^{1}H NMR δ 3.55 (s, 2H), 3.61 (s, 3H), 7.17−7.27 (m, 5H); ^{13}C NMR δ 172.0 (C), 133.9 (C), 129.2 (CH), 128.5 (CH), 127.1 (CH), 52.0 (CH_3), 41.1 (CH_2).

3n:[20h] ^{1}H NMR δ 3.55 (s, 2H), 3.65 (s, 3H), 7.16−7.18 (m, 2H) 7.23−7.26 (m, 2H); ^{13}C NMR δ 171.6 (C), 133.0 (C), 132.3 (C), 130.6 (CH), 128.7 (CH), 52.1 (CH_3), 40.4 (CH_2).

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4a:[15a] ^{1}H NMR δ 0.79−0.84 (m, 6H), 1.15−1.25 (m, 8H), 1.51−1.59 (m, 4H) 2.22 (t, J = 7.6 Hz, 2H) 3.99 (t, J = 6.6 Hz, 3H); ^{13}C NMR δ 174.0 (C), 64.4 (CH_2), 34.4 (CH_2), 31.4 (CH_2), 31.3 (CH_2), 28.6 (CH_2), 25.6 (CH_2), 24.7 (CH_2), 22.5 (CH_2), 22.3 (CH_2), 14.0 (CH_3), 13.9 (CH_3).

6a:[20i] ^{1}H NMR δ 1.21−1.25 (m, 12H), 1.45−1.56 (m, 4H), 2.23 (t, J = 7.6 Hz, 2H), 3.56 (t, J = 6.6 Hz, 2H), 3.56 (s, 3H); ^{13}C NMR δ 174.3 (C), 62.9 (CH_2), 51.4 (CH_3), 34.0 (CH_2), 32.7 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 25.6 (CH_2), 24.9 (CH_2).

6b:[20k] ^{1}H NMR δ 1.30−1.33 (m, 6H), 1.54−1.64 (m, 4H), 2.30 (t, J = 6.9 Hz, 2H), 3.62 (t, J = 6.6 Hz, 2H), 3.66 (s, 3H); ^{13}C NMR δ 174.4 (C), 62.9 (CH_2), 51.5 (CH_3), 34.1 (CH_2), 32.7 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 25.6 (CH_2), 24.9 (CH_2).

6c:[20l] ^{1}H NMR δ 1.30−1.33 (m, 8H), 1.54−1.62 (m, 4H), 1.90 (s, 1H) 2.31 (t, J = 7.6 Hz, 2H), 3.62 (t, J = 6.6 Hz, 2H), 3.67 (s, 3H); ^{13}C NMR δ 174.4 (C), 62.9 (CH_2), 51.5 (CH_3), 34.1 (CH_2), 32.7 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 25.7 (CH_2), 24.9 (CH_2).

6d:[20m] ^{1}H NMR δ 1.27−1.32 (m, 12H), 1.55−1.63 (m, 4H), 2.30 (t, J = 7.6 Hz, 2H), 3.64 (t, J = 6.6 Hz, 4H), 3.67 (s, 3H); ^{13}C NMR δ 174.4 (C), 63.1 (CH_2), 51.5 (CH_3), 34.1 (CH_2), 32.8 (CH_2), 29.59 (CH_2), 29.56 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.24 (CH_2), 29.15 (CH_2), 25.7 (CH_2), 25.0 (CH_2).

7a:[20j] ^{1}H NMR δ 1.21−1.26 (m, 8H), 1.52−1.56 (m, 4H), 2.23 (t, J = 7.3 Hz, 4H), 3.56 (s, 6H); ^{13}C NMR δ 174.2 (C), 51.4 (CH_3), 34.0 (CH_2), 29.0(CH_2), 28.9 (CH_2), 24.8 (CH_2).

7b:[20b] ^{1}H NMR δ 1.32−1.34 (m, 4H), 1.61−1.63 (m, 4H), 2.30 (t, J = 7.3 Hz, 4H), 3.67 (s, 6H); ^{13}C NMR δ 174.2 (C), 51.5 (CH_3), 34.0 (CH_2), 28.8 (CH_2), 24.8 (CH_2).

7c:[20j] ^{1}H NMR δ 1.30−1.35 (m, 6H), 1.60−1.63 (m, 4H), 2.30 (t, J = 7.3 Hz, 4H), 3.67 (s, 6H); ^{13}C NMR δ 174.2 (C), 51.5 (CH_3), 34.1 (CH_2), 28.9 (CH_2), 28.9 (CH_2), 24.9 (CH_2).

7d:[20a] ^{1}H NMR δ 1.27−1.33 (m, 12H), 1.58−1.62 (m, 4H), 2.30 (t, J = 7.6 Hz, 4H), 3.67 (s, 6H); ^{13}C NMR δ 174.3 (C), 51.5 (CH_3), 34.1 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 25.0 (CH_2).

■ ASSOCIATED CONTENT

Supporting Information. 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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■ REFERENCES

(1) Otera, J. *Esterification*; Wiley-VCH: Weinheim, 2003, and references cited therein.

(2) Grabber, J. H.; Hatfield, R. D. *J. Agric. Food Chem.* **2005**, *53*, 1546 and references cited therein.

(3) Pozgan, F.; Lukman, K.; Kocevar, M. *Heterocycles* **2010**, *82*, 543 and references cited therein.

(4) Miyano, M. *J. Org. Chem.* **1970**, *35*, 2314 and references cited therein.

(5) Simon, E. S.; Young, M.; Chan, A.; Bao, Z.-Q.; Andrews, P. C. *Anal. Biochem.* **2008**, *377*, 234 and references cited therein.

(6) Kusdiana, D.; Saka, S. *Appl. Biochem. Biotechnol.* **2004**, *113−116*, 781.

(7) (a) Danishefsky, S.; Hirama, M.; Gombatz, K.; Harayama, T.; Berman, E.; Schuda, P *J. Am. Chem. Soc.* **1978**, *100*, 6536. (b) Otera, J. *Chem. Rev.* **1993**, *93*, 1449 and references cited therein.

(8) (a) Seyferth, D.; Dow, A. W.; Menzel, H.; Flood, T. C. *J. Am. Chem. Soc.* **1968**, *90*, 1080. (b) Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475. (c) Hirai, Y.; Aida, T.; Inoue, S. *J. Am. Chem. Soc.* **1989**, *111*, 3062.

(9) (a) Ishihara, K.; Ohara, S.; Yamamoto, H. *Science* **2000**, *290*, 1140. (b) Mineno, T.; Kansui, H. *Chem. Pharm. Bull.* **2006**, *54*, 918. (c) Shinada, T.; Hamada, M.; Miyoshi, K.; Higashino, M.; Umezawa, T.; Ohfune, Y. *Synlett* **2010**, 2141.

(10) (a) Reddy, K. R.; Venkateshwar, M.; Maheswari, C. U.; Prashanthi, S. *Synth. Commun.* **2010**, *40*, 186. (b) Foot, J. S.; Kanno, H.; Giblin, G. M. P.; Taylor, R. J. K. *Synthesis* **2003**, 1055 and references cited therein.

(11) (a) Tamaru, Y.; Yamada, Y.; Inoue, K.; Yamamoto, Y.; Yoshida, Z. *J. Org. Chem.* **1983**, *48*, 1286. (b) Murahashi, S. −i.; Naota, T.; Ito, K.; Maeda, Y.; Taki, H. *J. Org. Chem.* **1987**, *52*, 4319 and references cited therein.

(12) Recently, heterogeneous Au/TiO_2 and Au/β-Ga_2O_3-catalyzed methyl esterifications of alcohols and methanol have been reported; see: (a) Nielsen, I. S.; Taarning, E.; Egeblad, K.; Madsen, R.; Christensen, C. H. *Catal. Lett.* **2007**, *116*, 35. (b) Su, F.-Z.; Ni, J.; Sun, H.; Cao, Y.; He, H.-Y.; Fan, K.-N. *Chem.—Eur. J.* **2008**, *14*, 7131.

(13) For selected reviews, see: (a) Hanasaka, F.; Fujita, K.; Yamaguchi, R. *Organometallics* **2004**, *23*, 1490. (b) Guillena, G.; Ramon, D. J.; Yus, M. *Angew. Chem.,Int. Ed.* **2007**, *46*, 2358. (c) Nixon, T. D.; Whittlesey, M. K.; Williams, J. M. J. *Dalton Trans.* **2009**, 753. (d) Bower, J. F.; Kim, I. S.; Patman, R. L.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 34. (e) Guillena, G.; Ramon, D. J.; Yus, M. *Chem. Rev.* **2010**, *110*, 1611. (f) Debereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681.

(14) For a review, see: Obora, Y.; Ishii, Y. *Synlett* **2011**, 30 and references cited therein.

(15) (a) Izumi, A.; Obora, Y.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2006**, *47*, 9199. (b) Yamamoto, N.; Obora, Y.; Ishii, Y. *Chem. Lett.* **2009**, *38*, 1106.

(16) (a) Suzuki, T.; Matsuo, T.; Watanabe, K.; Katoh, T. *Synlett* **2005**, 1453. (b) Suzuki, T.; Yamada, T.; Matsuo, T.; Watanabe, K.; Katoh, T. *Synlett* **2005**, 1450. (c) Zhang, J.; Leitus, G.; Ben-David, Y.; Milstein, D. *J. Am. Chem. Soc.* **2005**, *127*, 10840.

(17) (a) Owston, N. A.; Nixon, T. D.; Parker, A. J.; Whittlesey, M. J.; Williams, J. M. J. *Synthesis* **2009**, 1578. (b) Owston, N. A.; Parker, A. J.; Williams, J. M. J. *Chem. Commun.* **2008**, 624.

(18) When Cs_2CO_3, K_3PO_4, and KOH were used as base, we could perform the reaction in homogeneous solution. Therefore, we concluded the differences between the bases is not a result of different solubilities.

(19) Morita, K.; Nishiyama, Y.; Ishii, Y. *Organometallics* **1993**, *12*, 3748.

(20) (a) Hiegel, G. A.; Gilley, C. B. *Synth. Commun.* **2003**, *33*, 2003. (b) Kawabata, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Tetrahedron Lett.* **2003**, *44*, 9205. (c) Rodriguez, J. C.; Foster, D. F.; Eastham, G. R.; Cole-Hamilton, D. J. *Chem. Commun.* **2004**, 1720. (d) Rekha, V. V.; Ramani, M. V.; Ratnamala, A.; Rupakalpana, V.; Subbaraju, G. V.; Satyanarayana, C.; Rao, C. S. *Org. Process Res. Dev.* **2009**, *13*, 769. (e) Chavan, S. P.; Ethiraj, K. S. *Tetrahedron Lett.* **1995**, *36*, 2281. (f) Hamed, O.; El-Qisairi, A.; Henry, P. M. *J. Org. Chem.* **2001**, *66*, 180. (g) Yu, M.; Wen, W.; Wang, Z. *Synth. Commun.* **2006**, *36*, 2851. (h) Vieira, T. O.; Green, M. J.; Alper, H. *Org. Lett.* **2006**, *8*, 6143. (i) He, D.-H.; Wakasa, N.; Fuchikami, T. *Tetrahedron Lett.* **1995**, *36*, 1059. (j) Zimmermann, F.; Meux, E.; Mieloszynski, J.-L.; Lecuire, J.-M.; Oget, N. *Tetrahedron Lett.* **2005**, *46*, 3201. (k) Terent'ev, A. O.; Chodykin, S. V. *Cent. Eur. J. Chem.* **2005**, *3*, 417. (l) Lin, D.; Zhang, J.; Sayre, L. M. *J. Org. Chem.* **2007**, *72*, 9471. (m) Khan, A. T.; Mondal, E.; Borah, B. M.; Ghosh, S. *Eur. J. Org. Chem.* **2003**, *21*, 4113.