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Iridium-Catalyzed α-Methylation of α-Aryl Esters Using Methanol as the C1 Source

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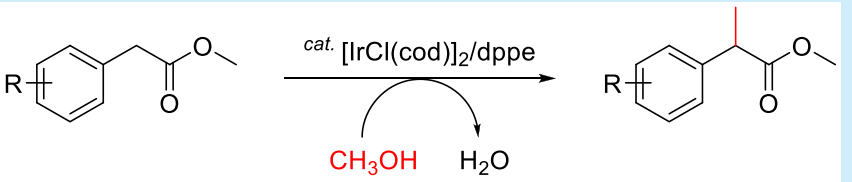
Supporting Information



ABSTRACT: $IrCl(cod)_2]$/dppe-catalyzed α-methylation of aryl esters using methanol as the C1 source was developed. This methylation process is useful in several fields including organic chemistry, biochemistry, and medicinal chemistry. Readily available methanol as methylation reagent was successfully adapted. The reaction processed high atom economy and efficient. By applying the reaction system, the synthesis method of naproxen was provided.

Carbon−carbon bond formation reactions via alkylation can transform simple substrates into valuable materials.[1] Methylation reactions are important alkylation reactions that are used in several fields such as organic chemistry,[2] biochemistry,[3] and medicinal chemistry.[4] In particular, regarding development of drugs,[5] it is known that installation of methyl groups can dramatically improve IC_{50} values.[6] For example, methylation increased the potency of inhibitors of P38 mitogen-activated protein kinase by 208 times compared with that before methylation.[7] In addition, methylation was useful to increase selectivity and improve half-life.[8] Thus, methylation is important to change the physical properties of drugs; indeed, methyl groups in pharmaceuticals are known to induce the "magic methyl effect".[9]

Recently, methylation reactions using readily available and renewable methanol with a transition-metal catalyst have been extensively investigated for various substrates.[10] Donohoe and co-workers, Andersson and co-workers, and our group have reported the α-methylation of ketones in the presence of a rhodium- or iridium-based catalyst.[11] Beller and colleagues investigated the β-methylation of aryl alcohol in the presence of a ruthenium catalyst,[12] and Cai et al.[13] reported iridium-catalyzed methylation of indoles and pyrroles. The catalyst used for methylation needs to display high activity, so typically heterogeneous,[14] supported,[15] or nanoparticle catalysts[16] are used in methylation reactions. These reactions involve C−C bond formation via hydrogen transfer in one pot. Nevertheless, the methylation of esters has rarely been reported because of their low reactivity and the presence of side reactions such as transesterification. The only example is the α-methylation of esters with methanol under microwave irradiation in the presence of $[RuCp^*Cl_2]_2$ catalyst.[17] There have also been few reports of alkylation of esters using a highly reactive alcohol[18] rather than methanol.[19] Therefore, the α-methylation of esters using methanol is challenging to overcome the drawbacks of the existing methylation process especially in the field of bio- and medicinal chemistry.

In this paper, we report ester methylation catalyzed by a $[IrCl(cod)]_2$/dppe system using methanol as the methylating reagent. The conventional method uses indomethane as the methylation reagent.[20] However, indomethane is a toxic reagent and produces halogen-based waste. The reaction developed in this work is atom-economical and environmentally friendly.

We selected methyl phenylacetate (**1a**) as a model substrate and examined its reaction with methanol under various reaction conditions (Table 1). Substrate **1a** (1 mmol) and methanol (**2**, 3 mL) were reacted in the presence of $[IrCl(cod)]_2$ (0.05 mmol) as a catalyst, dppe (0.07 mmol) as a ligand, and *t*-BuOK (0.35 mmol) as a base at 150 °C for 48 h, giving the desired product **3a** in 88% gas-chromatography (GC) yield and 79% isolated yield (entry 1). Ring methylation was not observed under these conditions.

Other Ir complex catalysts gave moderate to high yields (entries 2−4). In addition, although the yield decreased slightly, using a Rh complex as a catalyst instead of an Ir complex was also feasible (entry 5). In this reaction, the phosphine ligand plays an important role to raise catalytic activity (entry 6). Monophosphine or biphosphine allowed α-methylation of aryl esters (entries 7−10). Furthermore, aggregation was observed after the reaction in which dppe was not added. Next, the base was investigated. A strong base such as *t*-BuOK or KOH was suitable for the reaction (entries 1 and 11, respectively), whereas a weak base such as K_2CO_3 or

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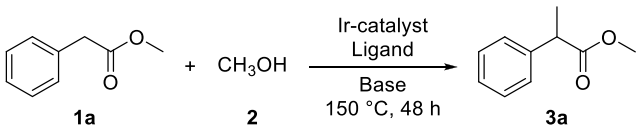
Table 1. Reaction of Methyl Phenylacetate (1a) with Methanol[a]



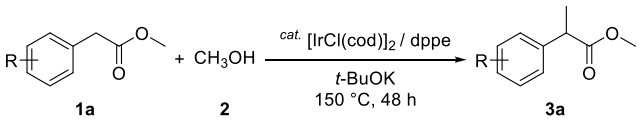
entry	catalyst	ligand	base	yield[b] (%)
1	$[IrCl(cod)]_2$	dppe	*t*-BuOK	88 [79[c]]
2	$[Ir(OMe)(cod)]_2$	dppe	*t*-BuOK	82
3	$[Cp^*IrCl_2]_2$	none	*t*-BuOK	53
4	$[Cp^*IrCl_2]_2$	dppe	*t*-BuOK	36
5	$[RhCl(cod)]_2$	dppe	*t*-BuOK	71
6	$[IrCl(cod)]_2$	none	*t*-BuOK	4
7[d]	$[IrCl(cod)]_2$	PPh_3	*t*-BuOK	60
8	$[IrCl(cod)]_2$	dppm	*t*-BuOK	69
9	$[IrCl(cod)]_2$	dppb	*t*-BuOK	62
10	$[IrCl(cod)]_2$	Xantphos	*t*-BuOK	28
11	$[IrCl(cod)]_2$	dppe	KOH	64
12	$[IrCl(cod)]_2$	dppe	K_2CO_3	56
13	$[IrCl(cod)]_2$	dppe	Cs_2CO_3	58
14[e]	$[IrCl(cod)]_2$	dppe	*t*-BuOK	36
15[f]	$[IrCl(cod)]_2$	dppe	*t*-BuOK	49
16[g]	$[IrCl(cod)]_2$	dppe	*t*-BuOK	32

[a]Reaction conditions: **1a** (1 mmol), **2a** (3.0 mL), Ir catalyst (0.05 mmol), ligand (0.07 mmol), and base (0.35 mmol) were stirred at 150 °C for 48 h under Ar. [b]GC yields based on **1a**. [c]Isolated yield. [d]PPh_3 (0.14 mmol) was used. [e]*t*-BuOK (1.0 mmol) was used. [f]*t*-BuOK (0.2 mmol) was used. [g]At 120 °C.

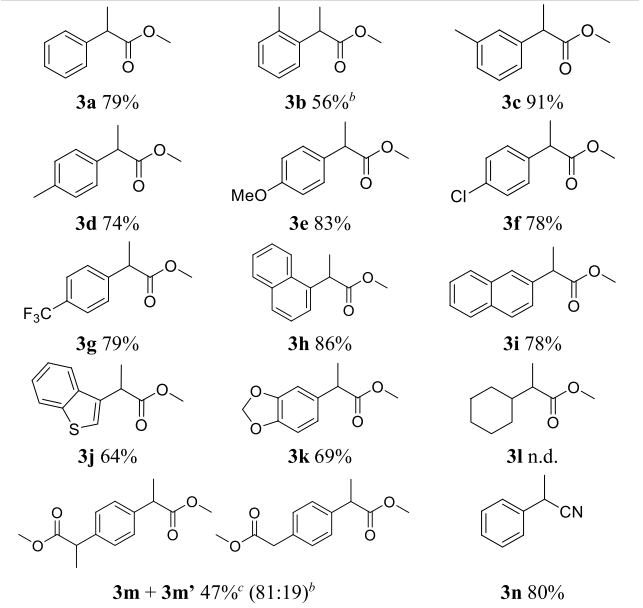
Cs_2CO_3 gave moderate yields (entries 12 and 13, respectively). Increasing and decreasing the amount of base resulted in lower yield (entries 14−15). The control of the amount of base was crucial to achieve the high yield of the product. Therefore, the basicity and amount of base present are important for promoting the reaction. Our investigation indicated that a high reaction temperature was also necessary (entry 16). The reaction required high reaction temperature, long reaction, and the use of excess methanol.

Subsequently, α-methylation of various aryl esters (**1**) with methanol under the optimized conditions was attempted (Table 2). In this reaction, aryl esters with a phenyl ring bearing electron-donating methyl (**1b−1d**) and methoxy groups (**1e**) and electron-withdrawing chloro (**1f**) and trifluoromethyl (**1g**) groups smoothly gave the corresponding methylated products in good yield (**3b−3g**). In addition, a methyl group was introduced at *ortho*-, *meta*-, and *para*-positions on the phenyl ring (**3b−3d**). Naphthalene compounds (**1h** and **1i**) and heterocyclic compounds (**1j** and **1k**) gave corresponding products (**3h−3k**); however, an alicyclic compound aryl ester did not give the corresponding product (**3l**). It is generally reported that aliphatic compounds possess lower CH acidity and stability than aromatic compounds. We assumed that the low acidity and stability of the alicyclic compound aryl ester were the reasons for its lack of reaction. Next, diaryl esters were used as substrates in the methylation reaction. An excess amount of base selectively gave the dimethylated product (**3m**). Using this catalytic system, α-methylation of phenylacetonitrile was realized in high yield (**3n**). Reaction of methyl 3-phenylpropanoate with methanol was carried out and gave a trace amount of the methylation product under these conditions.

Table 2. Iridium-Catalyzed α-Methylation of Various α-Aryl Esters with Methanol[a]



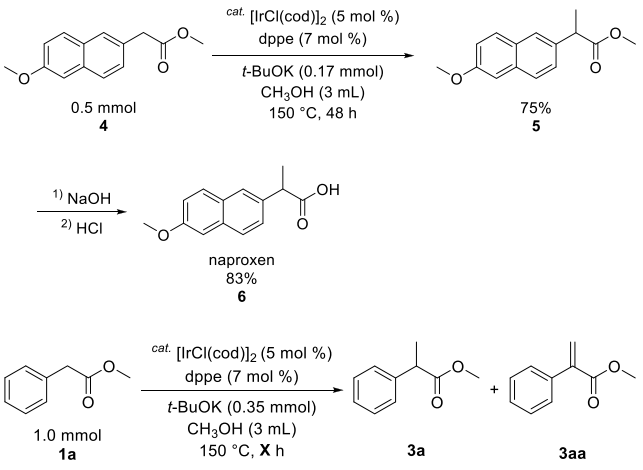
Yield



[a]Reaction conditions: **1** (1.0 mmol), **2** (3 mL), $[IrCl(cod)]_2$ (0.05 mmol), dppe (0.07 mmol), and *t*-BuOK (0.35 mmol) were stirred at 150 °C for 48 h under Ar. [b]*t*-BuOK (0.70 mmol) was used. [c]Total yield (**3m** + **3m'**)

Based on the development of Ir-catalyzed α-methylation using methanol, we also attempted to synthesize naproxen, which is a nonsteroidal anti-inflammatory drug (Scheme 1). Conventionally, naproxen is synthesized via methyl 6-methoxynaphthalene-2-acetate (**4**) using iodomethane as a methylating agent.[21] Here, we reacted substrate **4** with methanol using the $[IrCl(cod)]_2$/dppe catalytic system. The desired methyl ester (**5**) was obtained in 75% yield. Compound **5** was then hydrolyzed to give naproxen.

Scheme 1. Synthesis of Naproxen



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The time course of the reaction was then investigated (Figure 1). As the reaction time was extended, the yield of

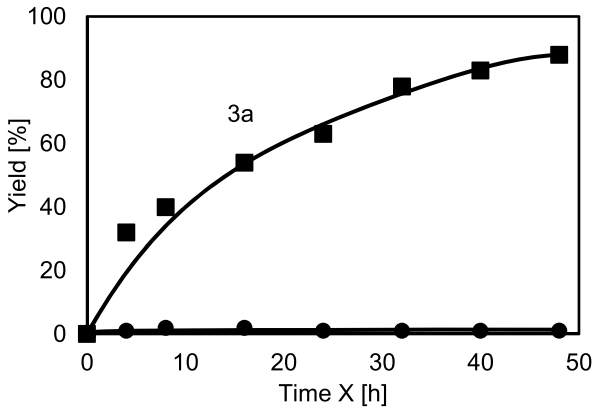
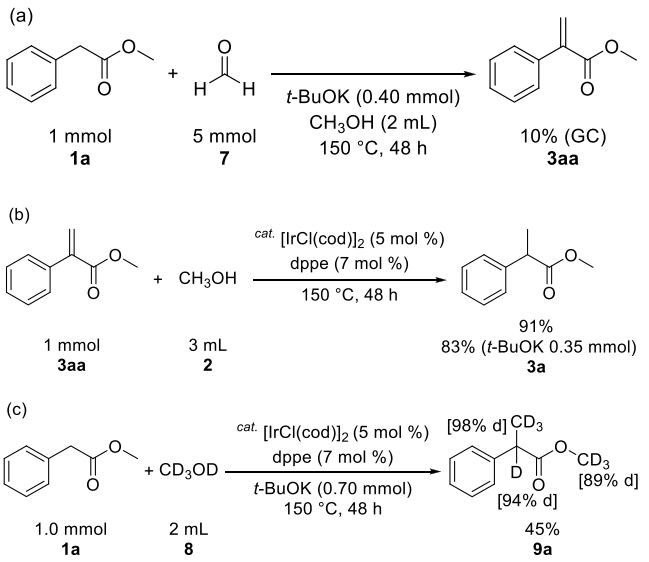


Figure 1. Time course of iridium-catalyzed α-methylation of aryl esters using methanol

methylated product **3a** increased and the conversion of methyl phenylacetate gently rose (see the Supporting Information for details). In addition, the formation of unsaturated ester **3aa** was also confirmed, although its yield remained low regardless of the reaction time. These results suggested that the formation of **3aa** was low during the course of the reaction.

In addition, we investigated potential reaction intermediates (Scheme 2). First, we confirmed that unsaturated aryl ester **3aa**

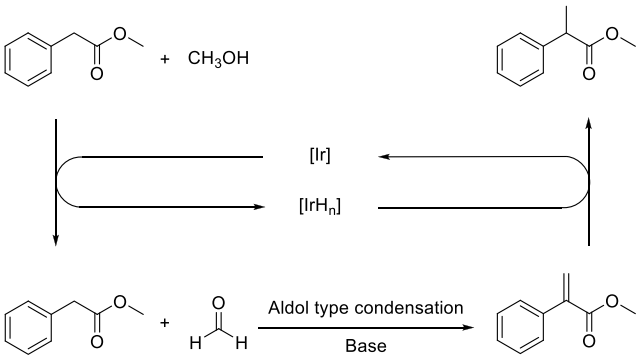
Scheme 2. Intermediates Considered in Iridium-Catalyzed α-Methylation of Aryl Esters



was produced using paraformaldehyde instead of methanol with no catalyst (Scheme 2a). Next, the unsaturated aryl ester **3aa** that was observed in the time-course experiment was reacted in the presence of the Ir catalyst to give α-methyl aryl ester **3a** in 91% (83% in the presence of *t*-BuOK) (Scheme 2b). Moreover, a deuterium labeling reaction using methanol-d_4 was attempted. This reaction gave the deuterated product **9a** in 45% yield (Scheme 2c). These results indicated that formaldehyde and unsaturated ester **3aa** were produced as reaction intermediates and methanol acted as a hydrogen source through oxidation and reduction reactions. In this reaction, we used an excess amount of methanol (>70 equiv), and the hydrogenation from methanol prevailed to the reaction with water. However, the possibility of the hydrolysis by water can not be ruled out.

Based on these experiments, a plausible reaction mechanism was proposed, as shown in Scheme 3. First, the Ir catalyst

Scheme 3. Proposed Reaction Mechanism for Iridium-Catalyzed α-Methylation of Aryl Esters



abstracts a hydrogen from methanol, which simultaneously generates Ir−H and the formaldehyde intermediate. Subsequently, the α-hydrogen of the carbonyl group is abstracted by the base, and an unsaturated ester is produced via an aldol-type condensation. Finally, the unsaturated bond allows hydrogenation by Ir−H to proceed, giving the α-methyl product.

In conclusion, we developed an iridium-catalyzed α-methylation of aryl esters using methanol as the methylating agent. Several aryl esters were successfully obtained by this approach. This system was applied to the fragment synthesis of naproxen.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01025.

Experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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