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Iridium-Catalyzed α-Alkylation of Acetates with Primary Alcohols and Diols

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Carboxylic acids and their esters are among the most frequently used compounds in organic chemistry and are widely used as raw materials in the organic and industrial chemistry fields.[1] In general, carboxylates are prepared by coupling of ester enolate anions with alkyl halides and tosylates[2] or the reaction of silyl ketene acetals with alkyl halides in the presence of a Lewis acid.[3] However, the main disadvantages of these methodologies are the formation of lithium salts and undesired side products.

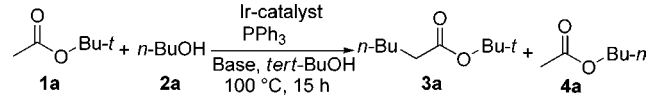
Alternatively, it is known that Ir and Ru complexes serve as efficient catalysts for hydrogen transfer from alcohols to aldehydes,[4] and they have been utilized in α-alkylations of carbonyl and related compounds[5] as well as *β*-alkylation (Guerbet reaction) of alcohols.[6] In this communication, we report the first successful α-alkylation of *tert*-butyl acetate with primary alcohols and α,*ω*-diols catalyzed by an Ir complex. This reaction provides a novel environmentally clean alkylation of acetates using alcohols as alkylating agents.[7,8] In addition, this method was applied to the synthesis of ethylene brassylate, which is currently manufactured in large scale as a synthetic perfume having musk odor.[9]

The reaction of *tert*-butyl acetate (**1a**) with *n*-butanol (**2a**) was chosen as a model reaction and carried out under various conditions (Table 1). For instance, the reaction of **1a** with **2a** in the presence of $[IrCl(cod)]_2$ (5 mol %), PPh_3 (15 mol %), and *tert*-BuOK (2 equiv) in *tert*-BuOH at 100 °C for 15 h produced *tert*-butyl hexanoate (**3a**) in 74% yield (entry 1). When $[IrCl(coe)_2]_2$ was employed as the catalyst, **3a** was obtained in a slightly lower yield (entry 2). It was found that the employment of reluctant acetates for the ester-exchange reaction is important to achieve the alkylation reaction. [Ir(acac)(cod)] was also effective, affording **3a** in 68% yield, while $[Cp^*IrCl_2]_2$ and $IrCl_3$ were inert toward the present alkylation, giving **4a** as the major product rather than **3a** (entries 3−5). The alkylation was extensively influenced by the base employed. *tert*-BuOK and NaH were found to be suitable bases (entries 1 and 6). The use of NaOEt resulted in **4a** in preference to **3a** under these conditions (entry 7). In contrast to the alkylation of ketones with alcohols, where KOH was an efficient base,[5a] no alkylation was induced by KOH (entry 8). A weak base such as Na_2CO_3 was also inert in this alkylation (entry 9). When the amount of *tert*-BuOK was decreased, the ester-exchange reaction between **1a** and **2a** was promoted to give **4a** in high yield (entries 10−12). These results indicate that the basicity and the amount of base used are very important factors in promoting the reaction. The alkylation proceeded to some extent without solvent and in *n*-octane and toluene as solvents (entries 13−15). Polar solvents such as dimethyl sulfoxide (DMSO) promoted the ester-exchange reaction to give **4a** as the major product (entry 16).

The reaction with secondary alcohols does not occur under these conditions, similar to our previous study.[5a] Thus, the reaction of **1a** with 2-butanol gave no α-alkylated product at all.

Table 2 shows the results of alkylation of **1a** with several primary alcohols under the same conditions as for entry 1 in Table 1. The

Table 1. Ir-Catalyzed α-Alkylation of **1a** with **2a**[a]



1a **2a** **3a** **4a**

entry	Ir catalyst	base	yield (%)[b] 3a	4a
1	$[IrCl(cod)]_2$	*tert*-BuOK	74 (62)	n.d.[c]
2	$[IrCl(coe)_2]_2$	*tert*-BuOK	60	2
3[d]	[Ir(acac)(cod)]	*tert*-BuOK	68	n.d.[c]
4	$[Cp^*IrCl_2]_2$	*tert*-BuOK	5	38
5[d]	$IrCl_3 \cdot 3H_2O$	*tert*-BuOK	n.d.[c]	51
6	$[IrCl(cod)]_2$	NaH	55	10
7	$[IrCl(cod)]_2$	NaOEt	9	59
8	$[IrCl(cod)]_2$	KOH	n.d.[c]	8
9	$[IrCl(cod)]_2$	Na_2CO_3	n.d.[c]	n.d.[c]
10[e]	$[IrCl(cod)]_2$	*tert*-BuOK	65	8
11[f]	$[IrCl(cod)]_2$	*tert*-BuOK	32	43
12[g]	$[IrCl(cod)]_2$	*tert*-BuOK	8	79
13[h]	$[IrCl(cod)]_2$	*tert*-BuOK	27	18
14[i]	$[IrCl(cod)]_2$	*tert*-BuOK	36	15
15[j]	$[IrCl(cod)]_2$	*tert*-BuOK	34	12
16[k]	$[IrCl(cod)]_2$	*tert*-BuOK	n.d.[c]	74

[a] Conditions: **1a** (10 mmol) was allowed to react with **2a** (1 mmol) in the presence of Ir catalyst (0.05 mmol), PPh_3 (0.15 mmol), and base (2 mmol) in *tert*-BuOH (1 mL) at 100 °C for 15 h. [b] GC yields based on the amount of **2a** used. Values in parentheses are isolated yields. [c] Not detected by GC. [d] Ir catalyst (0.10 mmol) was used. [e] *tert*-BuOK (1.5 mmol) was used. [f] *tert*-BuOK (1.0 mmol) was used. [g] *tert*-BuOK (0.5 mmol) was used. [h] Reaction was performed without solvent. [i] *n*-Octane (1 mL) was used as the solvent. [j] Toluene (1 mL) was used as the solvent. [k] DMSO (1 mL) was used as the solvent.

reaction of **1a** with the aliphatic alcohols *n*-hexanol (**2b**), *n*-octanol (**2c**), and 3-methyl-1-butanol (**2d**) afforded the corresponding *tert*-butyl carboxylates **3b**, **3c**, and **3d** in 75, 78, and 71% isolated yields, respectively (entries 1−3). Similarly, **1a** was efficiently alkylated with cyclohexylmethanol (**2e**) to give **3e** in good yield (89%) (entry 4). The alkylation of **1a** with various 4-substituted benzyl alcohols **2f**−**j** gave rise to the corresponding *tert*-butyl carboxylates **3f**−**j** in 64−82% isolated yields (entries 5−9). 3-Phenyl-1-propanol (**2k**) and 2-naphthylmethanol (**2l**) also reacted with **1a** to produce carboxylates **3k** and **3l**, respectively, in substantial yields (entries 10 and 11).

To obtain information on the reaction pathway, the time course of the reaction of **1a** with **2a** without solvent was compared with that in *tert*-BuOH (Figure 1). The reaction without solvent reached an equilibrium between **3a** and **4a** in the early stage of the reaction (within 1 h). This observation suggests that the alkylation of **1a** with **2a** and the ester-exchange reaction between **1a** and **2a** proceed competitively. On the other hand, in the reaction using *tert*-BuOH as the solvent, ester exchange to form **4a** was rapidly induced until 0.5 h and then gradually decreased with an increase in **3a**. This observation indicates that the ester exchange proceeds faster than the alkylation, and the resulting **4a** undergoes exchange with *tert*-

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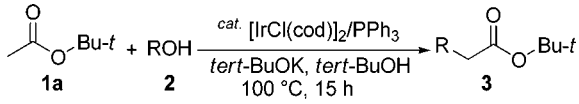
BuOH, which exists in excess as the solvent, to regenerate **1a**, which then reacts with **2a** to form **3a**.

Table 2. Ir-Catalyzed α-Alkylation of **1a** with Various Alcohols **2**[a]



entry	R	2	product	yield (%)[b]
1	n-C_6H_{13}	**2b**	**3b**	78 (75)
2	n-C_8H_{17}	**2c**	**3c**	79 (78)
3	$(CH_3)_2CH(CH_2)_2$	**2d**	**3d**	80 (71)
4	*cyclo*-$C_6H_{11}CH_2$	**2e**	**3e**	95(89)
5	$PhCH_2$	**2f**	**3f**	89 (82)
6	p-$CH_3C_6H_4CH_2$	**2g**	**3g**	75 (64)
7	p-$CH_3OC_6H_4CH_2$	**2h**	**3h**	75 (69)
8	p-$CF_3C_6H_4CH_2$	**2i**	**3i**	71 (67)
9	p-$ClC_6H_4CH_2$	**2j**	**3j**	70 (67)
10	$Ph(CH_2)_3$	**2k**	**3k**	75 (72)
11	2-$NaphCH_2$	**2l**	**3l**	78 (68)

[a] Conditions: Same as Table 1, entry 1. [b] GC yields based on the amount of **2** used. Values in parentheses are isolated yields.

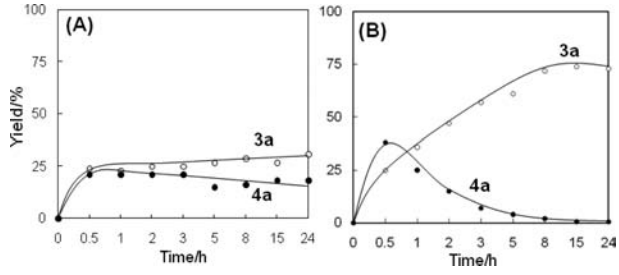


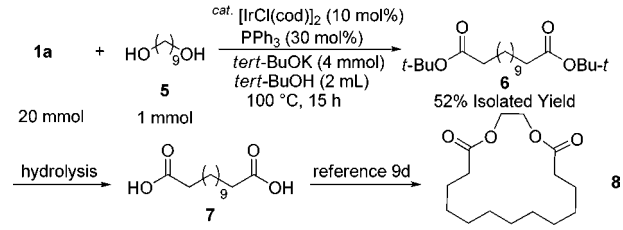
Figure 1. Time−conversion curves for the α-alkylation reaction of **1a** with **2a** (A) without solvent (same conditions as for Table 1, entry 13) and (B) in *tert*-BuOH (same conditions as Table 1, entry 1).

In order to confirm the present phenomena, the reaction of **1a** with **2a** was compared with that of **1a** with *n*-butyl acetate (**4a**) in place of **2a**. The reaction of **1a** with **4a** in *tert*-BuOH under these conditions gave **3a** in 70% yield, which is comparable to the result for **1a** with **2a** (74%; see Table 1, entry 1). This finding shows that **4a** undergoes the exchange reaction in *tert*-BuOH to leave *n*-BuOH (**2a**), which subsequently serves as the alkylating agent of **1a**, leading to **3a**. The result shown in Figure 1 is fairly compatible with this working hypothesis.

The present methodology was applied to the synthesis of a fragrant compound, ethylene brassylate (**8**) (Musk T). The reaction of **1a** with the α,ω-diol, 1,9-nonanediol (**5**), under these conditions gave di-*tert*-butyl tridecanoate (**6**). Subsequently, hydrolysis of **6** to give dicarboxylic acid **7**, followed by the reaction of **7** according to the reported method,[9d] led to the product **8** in 17% yield (lit[9d] 20% yield) (Scheme 1).

The reaction mechanism may be explained by the following pathway (see Figure S1 in the Supporting Information). First, ester exchange between **1a** and **2a** by *tert*-BuOK leading to *n*-butyl acetate (**4a**) occurs in competition with the Ir-catalyzed dehydrogenation of **2a** leading to butanal and Ir−hydride complex.[5] The resulting butanal undergoes base-catalyzed aldol condensation with **1a** to form an α,β-unsaturated ester, which then reacts with the Ir hydride to give **3a** and Ir complex. On the other hand, *n*-butyl acetate (**4a**) generated in situ by ester exchange is converted to **1a** by the base-catalyzed exchange reaction in *tert*-BuOH. Hence, in the reaction without *tert*-BuOH, the alkylation stopped at the stage of the formation of **4a** because of the difficulty of regenerating *n*-BuOH (**2a**) from **4a**.

Scheme 1. Synthesis of Ethylene Brassylate (**8**) (Musk T) from **6**



In conclusion, we have developed a method for alkylation of acetates with primary alcohols and diols using an Ir complex, which provides a very convenient clean route to carboxylates.

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Supporting Information Available: Figure S1 and experimental procedures, characterization data, and spectra of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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