Alkylation of active methylene compounds with alcohols catalyzed by an iridium complex†

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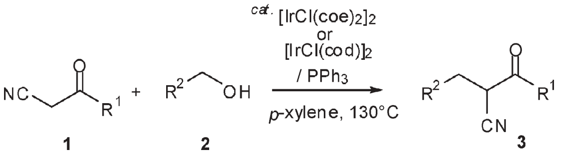
Base-free catalytic α-alkylation of active methylene compounds with primary alcohols was successfully achieved using an $[IrCl(cod)]_2$ complex in the presence of PPh_3 to afford the corresponding saturated α-alkylated products in good yields.

The transition metal-catalyzed aldol reaction of active methylene compounds with carbonyl compounds provides a useful tool for construction of new carbon–carbon bonds.[1] For example, Murahashi and co-workers reported that Ru complexes like $RuH_2(PPh_3)_4$ promote efficiently the aldol condensation of nitriles with aldehydes.[1a–c] However, there has been little study so far on the direct catalytic α-alkylation of nitriles with alcohols, but not aldehydes, which provides a promising synthetic tool. Recently, we have reported that the $[IrCl(cod)]_2$ catalyst combined with KOH promotes the α-alkylation of methyl ketones with primary alcohols leading to α-alkylated ketones.[2] During the course of this study, we found that this catalytic system promotes the alkylation of arylacetonitriles with primary alcohols to give α-alkylated nitriles in good yields.[3] Recently, Grigg and co-workers have also reported the alkylation of arylacetonitriles with alcohols by $[Cp^*IrCl_2]_2$ in the presence of KOH.[4] The same reaction was achieved by a heterogeneous catalyst consisting of Ru-grafted hydrotalcite.[5] We wish to report here that active methylene compounds like alkyl cyanoacetates undergo alkylation with primary alcohols under the influence of Ir complexes like $[IrCl(cod)]_2$ and $[IrCl(coe)_2]_2$ without any base to give the corresponding saturated α-alkylated products in good yields (eqn 1).‡

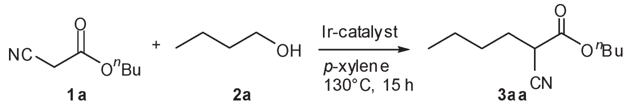


(1)

Table 1 shows the reaction of butyl cyanoacetate (**1a**) with 1-butanol (**2a**) in the presence of Ir complexes under several reaction conditions. **1a** (1 mmol) reacted with **2a** (1 mmol) in the presence of $[IrCl(cod)]_2$ (0.05 mmol) and PPh_3 (0.2 mmol) in *p*-xylene (1 cm^3) at 130 °C for 15 h, giving butyl 2-cyanohexanoate (**3aa**) in 81% yield (entry 1). When two equiv. of **2a** (2 mmol) with respect to **1a** was employed, the yield of **3aa** increased to 96% (entry 2). The present reaction afforded only saturated alkyl cyanoacetate **3aa** in contrast to the Ru-catalyzed reaction of alkyl cyanoacetates with aldehydes by Murahashi *et al.* where (*E*)-α,β-unsaturated nitriles were formed.[1a,b] Although the reaction of methyl ketones with alcohols using $[IrCl(cod)]_2$ calls for the coexistence of a strong base like KOH,[4] the present alkylation could be efficiently achieved without any base. This may be attributed to the stronger acidity of the α-hydrogen of **1a** than that of methyl ketones. When $[IrCl(coe)_2]_2$ was used instead of $[IrCl(cod)]_2$ under these conditions, **3aa** was obtained in quantitative yield (entry 3). The reaction was found to be considerably affected by the phosphine ligands used. No alkylation was induced by aliphatic phosphine ligands like PCy_3 or $^tBu_3P$, or without a ligand (entries 4–6). The bidentate phosphine ligand dppe was also inefficient (entry 7). Several Ir complexes other than $[IrCl(coe)_2]_2$ were examined. Trivalent iridium complexes like $IrCl_3$ and $[Cp^*IrCl_2]_2$, which shows high catalytic activity for the alkylation of arylacetonitriles with alcohols in the presence of KOH,[4] were found to be inert in the present reaction (entries 8 and 9).

On the basis of these results, the α-alkylation of **1a** with various alcohols was examined under optimized reaction conditions (Table 2). The alkylation of **1a** with a higher alcohol like 1-heptanol (**2c**) proceeded more smoothly than that with a lower alcohol like ethanol (**2b**) to give butyl 2-cyanononanoate (**3ac**) (95%) and butyl 2-cyanobutyrate (**3ab**) (43%), respectively (entries 1 and 2). 3-Methyl-1-butanol (**2d**), which has a methyl side chain, and 2-phenylethanol (**2e**) reacted with **1a** to form the

Table 1 Reaction of **1a** with **2a** in the presence of an Ir complex under several reaction conditions[a]



Entry	Ir complex	Ligand	Conversion (%)	Yield[b] (%)
1[c]	$[IrCl(cod)]_2$	PPh_3	84	81
2	$[IrCl(cod)]_2$	PPh_3	>99	96
3	$[IrCl(coe)_2]_2$	PPh_3	>99	99 (96)
4	$[IrCl(coe)_2]_2$	None	19	n.d.[d]
5	$[IrCl(coe)_2]_2$	PCy_3	47	n.d.[d]
6	$[IrCl(coe)_2]_2$	P^tBu_3	29	2
7[e]	$[IrCl(coe)_2]_2$	dppe	74	32
8	$[Cp^*IrCl_2]_2$	PPh_3	No reaction	
9	$IrCl_3$	PPh_3	No reaction	

[a] **1a** (1 mmol) was allowed to react with **2a** (2 mmol) in the presence of an Ir complex (0.05 mmol) and phosphine ligand (0.2 mmol) in *p*-xylene (1 cm^3) at 130 °C for 15 h unless otherwise noted. [b] GLC yields. The number in parenthesis shows isolated yield. [c] **2a** (1 mmol) was used. [d] Not detected by GC. [e] Ligand (0.1 mmol) was used.

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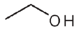
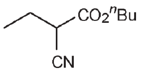
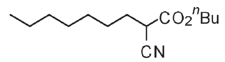
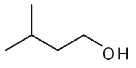
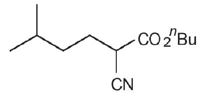
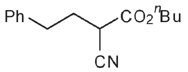
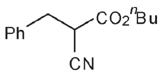
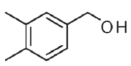
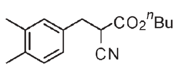
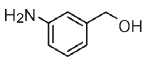
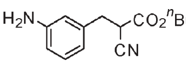
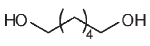
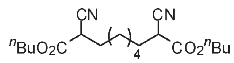
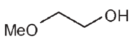
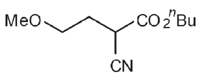
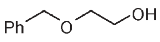
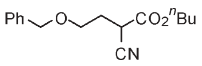
† Electronic supplementary information (ESI) available: Compound characterization data (^1H, ^{13}C NMR, IR and MS) for **3**. See DOI: 10.1039/b702293j

Table 2 Alkylation of **1a** with various alcohols catalyzed by an Ir complex[a]

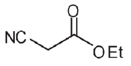
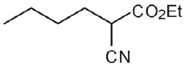
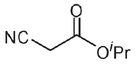
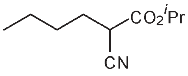
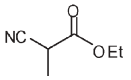
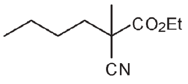
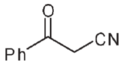
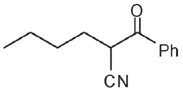
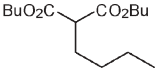
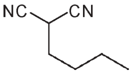
Entry	Alcohol (2)		Product (3)		Yield (%)[b]
1[c]		**2b**		**3ab**	43
2		**2c**		**3ac**	95 (94)
3		**2d**		**3ad**	83
4		**2e**		**3ae**	>99 (91)
5		**2f**		**3af**	93
6		**2g**		**3ag**	78
7[d,e]		**2h**		**3ah**	76
8[f]		**2i**		**3ai**	72 (71)
9		**2j**		**3aj**	94 (91)
10[d]		**2k**		**3ak**	>99 (93)

[a] **1a** (1 mmol) was allowed to react with alcohol **2** (2 mmol) in the presence of $[IrCl(cod)]_2$ (0.05 mmol) and PPh_3 (0.2 mmol) in *p*-xylene (1.0 cm^3) at 130 °C for 15 h. [b] GLC yields. The numbers in parentheses show isolated yields. [c] **2b** (4 mmol) was used. [d] $[IrCl(coe)_2]_2$ (0.05 mmol) was used instead of $[IrCl(cod)]_2$. [e] Solvent (1.5 cm^3) was used. [f] **1a** (2 mmol) was allowed to react with **2i** (1 mmol) in the presence of $[IrCl(cod)]_2$ (0.05 mmol) and PPh_3 (0.2 mmol) in *p*-xylene (1 cm^3) at 130 °C for 20 h.

corresponding alkylated products, **3ad** (83%) and **3ae** (>99%) (entries 3 and 4). Benzyl and substituted benzyl alcohols, **2f**, **2g**, and **2h**, gave **3af** (93%), **3ag** (78%) and **3ah** (76%), respectively (entries 5–7). It is interesting that 1,6-hexanediol (**2i**) reacted with two equiv. of **1a**, giving 1,8-dibutyl-2,6-dicyanosuberic acid (**3ai**) in 72% yield (entry 8). 2-Methoxyethanol (**2j**) and 2-(benzyloxy)-ethanol (**2k**) afforded **3aj** (94%) and **3ak** (>99%), respectively (entries 9 and 10).

Furthermore, we tried the reaction of several active methylene compounds with **2a** (Table 3). Ethyl cyanoacetate (**1b**) and isopropyl cyanoacetate (**1c**) reacted with **2a** to give **3ba** (75%), and **3ca** (76%), respectively (entries 1 and 2). However, for ethyl 2-cyanopropionate (**1d**), the methyl substituent on the α-carbon hampered the alkylation with **2a**, and a transesterification reaction took place to afford butyl 2-cyanopropionate as the product (entry 3).[6] Benzoylacetonitrile (**1e**) produced α-cyanohexanophenone (**3ea**) in 66% yield (entry 4). Dibutyl malonate (**1f**) led to dibutyl 2-butylmalonate (**3fa**) (80%) (entry 5). Unfortunately, the reaction of malononitrile (**1g**) with **2a** resulted in a mixture of unidentified polymerized products (entry 6).

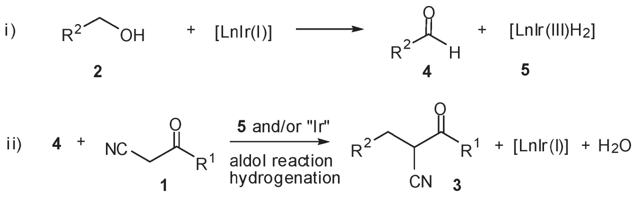
Table 3 Alkylation of various active methylene compounds with **2a** catalyzed by $[IrCl(cod)]_2$ catalyst[a]

Entry	Active methylene compound (1)		Product (3)		Yield (%)[b]
1		**1b**		**3ba**	75
2[c]		**1c**		**3ca**	76
3[d]		**1d**		**3da**	n.d.[e,f]
4[g]		**1e**		**3ea**	66
5[h]		**1f**		**3fa**	80
6		**1g**		**3ga**	n.d.

[a] The active methylene compound (1 mmol) was allowed to react with **2a** (2 mmol) in the presence of $[IrCl(cod)]_2$ (0.05 mmol) and PPh_3 (0.2 mmol) in *p*-xylene (1.0 cm^3) at 130 °C for 15 h. [b] GLC yields. [c] **1a** (4 mmol) was used. [d] **1d** (1 mmol) was reacted with **2a** (3 mmol) in the presence of $[IrCl(cod)]_2$ (0.05 mmol), dppe (0.1 mmol) in mesitylene (1.0 cm^3) at 150 °C for 15 h. [e] Not detected by GLC. [f] Transesterification product, butyl 2-cyanopropionate, was obtained in 52% yield. [g] *p*-Xylene (1.5 cm^3) was used. [h] **1f** (4 mmol) was allowed to react with **2a** (1 mmol) in the presence of $[IrCl(cod)]_2$ (0.05 mmol), dppe (0.1 mmol) and Cs_2CO_3 (0.2 mmol) in *p*-xylene (1.0 cm^3) at 130 °C for 15 h.

Although a detailed reaction mechanism is not confirmed at this stage, the Ir catalyst serves as a hydrogen acceptor from the alcohol to give the corresponding aldehyde and an Ir-dihydride species[2,7,8] as a key intermediate of this reaction. Subsequently, the aldehyde is subjected to reaction with the active methylene compound *via* an Ir-catalyzed aldol-type reaction followed by hydrogenation that affords the saturated α-alkylated product (Scheme 1). Similar to the Ru-catalyzed aldol reaction with nitriles and aldehydes,[1b] coordination of the nitrile to the Ir complex may assist in the facile activation of the α-C–H bond of **1**. Further study on the detailed mechanism of the present reaction is currently in progress.

In conclusion, we have developed the Ir-catalyzed alkylation of active methylene compounds with alcohols or a diol to give the corresponding α-alkylated compounds in good yields. This method provides a clean route to α-alkylated methylene compounds which generates only water as a by-product.



Scheme 1 A plausible reaction course.

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Notes and references

‡ Typical reaction procedure for the alkylation (entry 3 in Table 1): a mixture of **1a** (1 mmol, 141 mg), **2a** (2 mmol, 148 mg), $[IrCl(coe)_2]_2$ (0.05 mmol, 45 mg) and PPh_3 (0.2 mmol, 52 mg) in *p*-xylene (1 cm^3) was placed in a 10 cm^3 Schlenk flask under an Ar atmosphere and the resulting solution was stirred at 130 °C for 15 h. The conversion and the yield of product were estimated from the peak areas based on the internal standardtechnique using GC and showed that **3aa** was obtained in >99% yield. The product (**3aa**) was isolated in 96% yield (190 mg) using column chromatography (230–400 mesh silica gel, *n*-hexane–ethyl acetate = 15–30 : 1); δ_H (270 MHz; $CDCl_3$; Me_4Si) 0.91–0.98 (m, 6H), 1.32–1.73 (m, 8H), 1.91–1.99 (m, 2H), 3.50 (t, J = 7 Hz, 1H) and 4.21 (t, J = 7 Hz, 2H); δ_C (67.5 MHz; $CDCl_3$; Me_4Si) 13.51 (CH_3), 13.58 (CH_3), 18.88 (CH_3), 21.85 (CH_2), 28.77 (CH_2), 29.52 (CH_2), 30.30 (CH_2), 37.52 (CH), 66.43 (CH_2), 116.52 (C) and 166.25 (C). ν_{max}/cm^{-1} 2965, 2874, 2249, 1751, 1466, 1382, 1252, 1121, 1060, 1020 and 961; *m/z* (EI) 197.1414 (M^+; $C_{11}H_{19}NO_2$ requires 197.1416), 142 (15%), 82 (22), 69 (36), 57 (100) and 41 (61).

1 (*a*) T. Naota, H. Taki, M. Mizuno and S.-I. Murahashi, *J. Am. Chem. Soc.*, 1989, **111**, 5954; (*b*) S.-I. Murahashi, T. Naota, H. Taki, M. Mizuno, H. Takaya, S. Komiya, Y. Mizuho, N. Oyasato, M. Hiraoka, M. Hirano and A. Fukuoka, *J. Am. Chem. Soc.*, 1995, **117**, 12436; (*c*) S.-I. Murahashi and H. Takaya, *Acc. Chem. Res.*, 2000, **33**, 225; (*d*) R. Grigg, T. R. B. Mitchell, S. Sutthivaiyakit and N. Tongpenyai, *Tetrahedron Lett.*, 1981, **22**, 4107; (*e*) R. Kuwano, H. Miyazaki and Y. Ito, *Chem. Commun.*, 1998, 71; (*f*) Y. Ito, M. Sawamura and T. Hayashi, *J. Am. Chem. Soc.*, 1986, **108**, 6405.

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6 Even though a reaction was carried out in the presence of a base (Cs_2CO_3, 0.2 mmol, 20 mol% based on **1d**) under the same reaction conditions as entry 3 in Table 3, no alkylation product was obtained, but the transesterfication product, butyl 2-cyanopropionate, was obtained in 46% yield.

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