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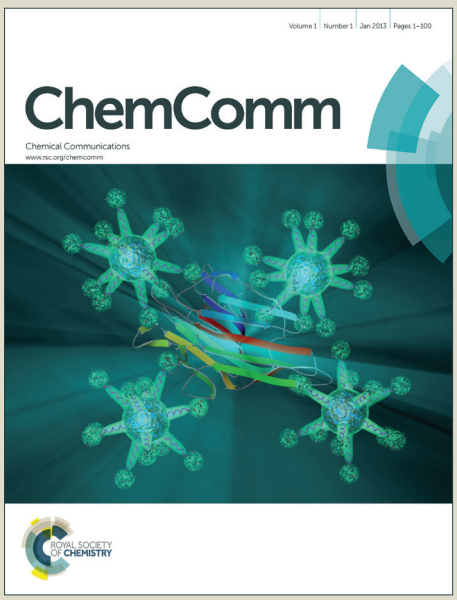

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ARTICLE TYPE

Iridium-catalyzed selective α-methylation of ketones with methanol†

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Iridium-catalyzed selective α-dimethylation and α-methylation of ketones or phenylacetonitriles, using methanol as the methylating agent, were achieved. In addition, three-component cross α-methyl-alkylation was successfully performed using methyl ketones with methanol and primary alcohols with long-chain alkyl groups. This method provides a very convenient direct route to α-methylated ketones, using methanol.

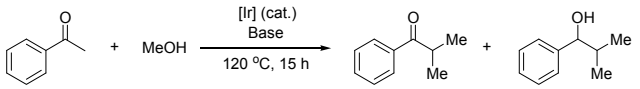
The development of transition-metal-catalyzed C−C bond formation using sustainable feedstocks is vital for bulk and fine chemical manufacture.[1] In particular, methylation is an essential function of biologically active molecules. The development of methyl functionalization is therefore a topic of current interest.[2] Ketone methylation using iodomethane or diazomethane as the methylating agent is a typical example.[3] However, such methods use toxic or extremely sensitive explosive reagents. It is well known that Ir and Ru complexes are efficient catalysts for transfer hydrogenation (also known as hydrogen borrowing) from alcohols to aldehydes and ketones.[4] This important strategy has been applied to C−C bond formation in α- and β-alkylation reactions, using alcohols as alkylating agents.[5] Our group has reported Ir-catalyzed α-alkylations of ketones,[6a] methyl esters,[6b] active methylene compounds,[6c] acetonitrile,[6d] and methylquinolines,[6e] and dimerizations of alcohols.[6f–g] In addition, we achieved Ir-catalyzed reactions of alcohols with alkynes or enones led to homoallylic alcohols,[7a] β-enones,[7b] and 1,3-diketones.[7c] These reactions were restricted to benzyl alcohols or aliphatic alcohols with long-chain alkyl groups; only a few reactions using methanol have been reported,[8] although methanol is an abundant and renewable resource.[9] In our previous study, we showed that methyl esterification was selectively achieved by the Ir-catalyzed reactions of methanol and alcohols with long-chain alkyl groups,[10] because methanol oxidation is relatively difficult; the reaction energy for methanol dehydrogenation (ΔH = 84 kJ mol^{-1}) is higher than those for the dehydrogenation of higher alcohols such as ethanol (ΔH = 68 kJ mol^{-1}).[11]

In pioneering work on transfer hydrogenation using methanol, Krische reported Ir-catalyzed direct C–C coupling of methanol and allenes.[12] Li described Ir-catalyzed *N*-monomethylation of aromatic primary amines with methanol, and reported the reaction of indoles with methanol to give 3,3'-bisindolylmethanes.[13] Beller and Grützmacher reported Ru-catalyzed dehydrogenation of methanol to hydrogen and carbon dioxide.[14] Recently, Donohoe reported Rh-catalyzed O_2-assisted ketone methylation.[15]

In this communication, we report a simple and versatile method for selective α-methylation of ketones or phenylacetonitriles, with methanol as the methylating agent, in the presence of an Ir catalyst and a base. In addition, we report the three-component one-step or one-pot α-methyl-alkylation of methyl ketones using methanol and primary alcohols with long-chain alkyl groups.

Initially, acetophenone (**1a**) and methanol (**2**) were used as model substrates for optimization of the α-methylation conditions; the results are shown in Table 1.

Table 1. Ir-Catalyzed Reactions of Acetophenone (**1a**) with Methanol (**2**) under Various Conditions[a]



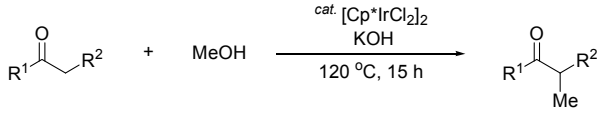
1a **2** **3a** **4a**

Entry	Ir catalyst	Base	Yield (/%)[b]	
			3a	**4a**
1	$[Cp^*IrCl_2]_2$	KOH	87 (83)	<1
2[c]	$[IrCl(cod)]_2/PPh_3$	KOH	39	9
3[c]	$[Ir(OH)(cod)]_2/PPh_3$	KOH	55	12
4	$[Cp^*RhCl_2]_2$	KOH	18	4
5	$RuHCl(CO)(PPh_3)_3$	KOH	12	12
6	$[Cp^*IrCl_2]_2$	Cs_2CO_3	76	<1
7	$[Cp^*IrCl_2]_2$	*t*-BuOK	51	11
8	$[Cp^*IrCl_2]_2$	Na_2CO_3	n.d.[d]	n.d.
9[e]	$[Cp^*IrCl_2]_2$	KOH	79	<1

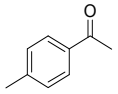
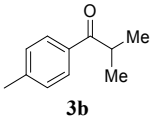
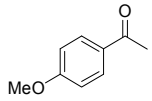
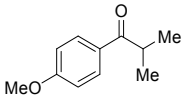
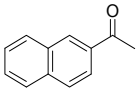
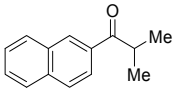
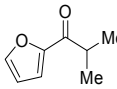
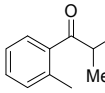
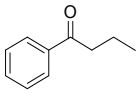
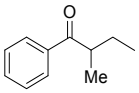
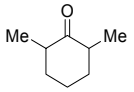
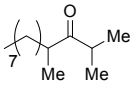
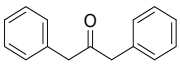
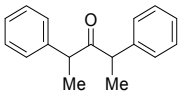
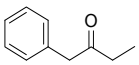
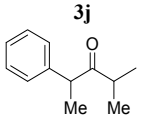
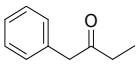
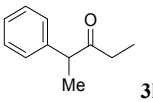
[a]Conditions: **1a** (1 mmol), **2** (1.5 mL), Ir catalyst (0.05 mmol), and base (0.50 mmol) at 120 °C for 15 h under Ar. [b]GC yields based on **1a** used. The number in parentheses shows isolated yield. [c]PPh_3 (0.20 mmol) was used. [d]Not detected by GC. [e]$[Cp^*IrCl_2]_2$ (0.005 mmol) was used.

For example, the reaction of **1a** (1 mmol) with **2** (1.5 mL) was performed in the presence of $[Cp^*IrCl_2]_2$ (0.05 mmol, 5 mol%) and KOH (0.5 mmol, 50 mol%) at 120 °C for 15 h, giving the α-dimethylated product **3a** in 87% yield. This reaction was highly chemoselective (Table 1, entry 1). With regard to the Ir complex, $[Cp^*IrCl_2]_2$ gave **3a** in high yield with high selectivity. The use of $[IrCl(cod)]_2/PPh_3$ and $[Ir(OH)(cod)]_2/PPh_3$ gave **3a** in moderate yields, along with the formation of **4a** (9–12%; entries 2 and 3). When $[Cp^*RhCl_2]_2$ and $RuHCl(CO)(PPh_3)_3$ were used as catalysts, the yields of ketone methylation products were low (entries 4 and 5). The methylation was influenced by the base used. KOH and Cs_2CO_3 were found to be suitable bases (entries 1 and 6). When *t*-BuOK, was used, **4a** was also detected (entry 7). However, weak bases such as Na_2CO_3 resulted in total inactivity under these conditions (entry 8).

Table 2. Ir-Catalyzed Reactions of Ketones **1** with Methanol (**2**)[a]



1 **2** **3**

Entry	Ketone (**1**)	Product (**3**)	Yield (%)
1	 **1b**	 **3b**	82
2	 **1c**	 **3c**	85
3	 **1d**	 **3d**	80
4	 **1e**	 **3e**	80
5	 **1f**	 **3f**	84
6	 **1g**	 **3g**	89
7[b]	 **1h**	 **3h**	78[c]
8[d,e]	 **1i**	 **3i**	85[c]
9	 **1j**	 **3j**	91[c]
10[e]	 **1k**	 **3k**	78[c]
11[b,f,g]	 **1k**	 **3k'**	74[c]

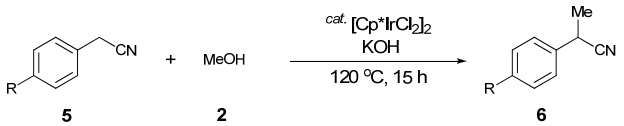
[a]Reaction conditions: **1** (1.0 mmol), **2** (1.5 mL), Ir catalyst (0.05 mmol), and KOH (0.50 mmol) at 120 °C for 15 h under Ar. All yields are isolated yields. [b]Reaction temperature was 130 °C. [c]The stereochemistry is not determined. [d]Reaction temperature was 150 °C. [e]KOH (1.0 mmol) was used. [f]**2** (0.75 mL) was used. [g]Na_2CO_3 (0.50 mmol) was used instead of KOH.

Furthermore, a reduced catalyst loading was found to give **3a** in 79% yield (entry 9). No reaction took place in the absence of an Ir complex. The reaction proceeded with an excess of **2**, and the use of 1 equiv of **2** for **1a** was found to be sluggish under these conditions.

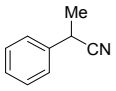
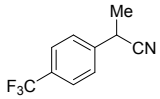
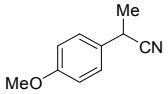
After obtaining these optimized conditions, we investigated the reactions of various ketones **1** with methanol (**2**) (Table 2). Various aryl methyl ketones (**1b**–**1f**) were allowed to react with **2** under the optimized conditions (entries 1–5). 4-Methylacetophenone (**1b**), 4-methoxyacetophenone (**1c**), 4-naphthylacetophenone (**1d**), 2-acetylfuran (**1e**), and 2-methylacetophenone (**1f**) participated in the reaction and the corresponding α-dimethylated products **3b**–**3f** were obtained in 80–85% isolated yields, with high chemoselectivity. When butyrophenone (**1g**) was used, the monomethylated product **3g** was obtained in 89% yield (entry 6). Aliphatic and benzyl ketones (**1h**–**1k**) were also used in this reaction and the products were isolated in 78–91% yields (entries 7–10). If Na_2CO_3 was used instead of KOH in the reaction of benzyl ethyl ketone (**1k**), monomethylation proceeded at the benzyl position with high chemoselectivity (entry 11). Time-course monitoring of the reaction of **1k** with **2** showed initial formation of **3k'**, followed by formation of **3k** (See Fig. S1, ESI†); this is probably the result of the different pK_a values at the benzyl and ethyl positions.[16]

We anticipated that this catalytic system would be compatible with other compounds. A series of phenylacetonitriles bearing electron-donating or electron-withdrawing groups gave the α-methylated products **6a**–**6c** in good to excellent yields; the results are shown in Table 3.

Table 3. Ir-Catalyzed Reactions of Phenylacetonitriles **5** with Methanol (**2**)[a]



5 **2** **6**

76%[b] (**6a**)	87% (**6b**)	75%[b,c] (**6c**)
		

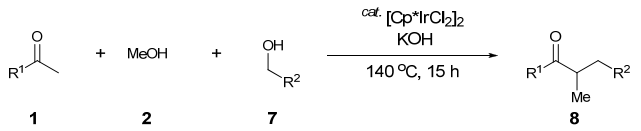
[a]Reaction conditions: **3** (1.0 mmol), **2** (1.5 mL), Ir catalyst (0.05 mmol), and KOH (0.50 mmol) at 120 °C for 15 h under Ar. All yields are isolated yields. [b]Corresponding amide (<10%) was also obtained. [c]Reaction temperature was 130 °C.

With the results in hand for the selective α-dimethylation of methyl ketones using methanol, the catalytic system was successfully extended to three-component one-step or one-pot cross α-methyl-alkylations of methyl ketones using methanol and primary alcohols; the results are shown in Table 4.

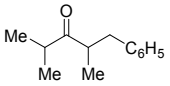
For example, the reaction of **1a** (2 mmol) with **2** (1.0 mL) and benzyl alcohol (**7a**) (1 mmol) was performed in the presence of $[Cp^*IrCl_2]_2$ (0.05 mmol, 5 mol%) and KOH (0.5 mmol, 50 mol%) at 140 °C for 15 h, giving the α-methyl-alkylated product **8aa** in 81% yield, with high chemoselectivity (Table 4, entry 1). Ketones **1b** and **1c** participated in the reaction, and the corresponding products **8ba** and **8ca** were obtained in 83–84% yields (entries 2 and 3). Furthermore, acetone (**1l**), one of the simplest ketones, was accommodated in this reaction and **8al** was isolated in good yield (entry 4). 4-Methylbenzyl alcohol (**7b**) and 4-methoxybenzyl alcohol (**7c**) participated in the reaction and the corresponding products **8ab** and **8ac** were obtained in good yields (entries 5 and 6). We performed one-pot-type methyl-alkylations

of **1a**, first using aliphatic alcohols **7d** and **7e** and then with **2**. Methyl-alkylated products were obtained in high yields (entries 7 and 8). These methods generate various multisubstituted ketones from simple methyl ketones.

Table 4. Ir-Catalyzed Cross Methyl-Alkylations of Ketones **1** with Methanol (**2**) and Primary Alcohols **7**[a]



1 **2** **7** **8**

Entry	**1** (R^1)	**7** (R^2)	Product (**8**)	Yield (%)
1	**1a**	C_6H_5 **7a**	**8aa**	81
2	**1b**	**7a**	**8ba**	84
3	**1c**	**7a**	**8ca**	83
4	CH_3 **1l**	**7a**	 **8al**	61
5	**1a**	*p*-$CH_3C_6H_4$ **7b**	**8ab**	79
6	**1a**	*p*-$CH_3OC_6H_4$ **7c**	**8ac**	72
7[b]	**1a**	*n*-C_5H_{11} **7d**	**8ad**	88
8[b]	**1a**	*n*-C_7H_{15} **7e**	**8ae**	90

[a]Reaction conditions: **1** (2.0 mmol), **2** (1.0 mL), **7** (1 mmol), Ir catalyst (0.05 mmol), and KOH (0.50 mmol) at 140 °C for 15 h under Ar. All yields are isolated yields. [b]Reaction conditions: **1** (1.2 mmol), **7** (1 mmol), Ir catalyst (0.05 mmol), and KOH (0.50 mmol) at 80 °C for 2 h, and, after adding **2** (1.5 mL), 140 °C for 15 h under Ar.

Ketone methylation is believed to proceed according to a previously reported reaction pathway (Fig. S2, ESI†).[6] Dehydrogenation of methanol by an Ir complex leads to formaldehyde and an Ir–hydride species.[17] Base-catalyzed aldol condensation of formaldehyde with the ketone then leads to formation of an α,β-unsaturated ketone, which reacts with the Ir–hydride complex to give the α-methylated product.

In conclusion, an efficient α-methylation of ketones or phenylacetonitriles, using methanol, an Ir complex, and a base, was successfully developed. Furthermore, the catalytic system was successfully extended to three-component cross α-methyl-alkylations of methyl ketones using methanol and primary alcohols. This reaction provides a simple and atom-economical direct route to various multisubstituted ketones in good yields.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Fig. S1-2, Experimental procedures and compound characterization data (^{1}H NMR, ^{13}C NMR) of the compounds. See DOI:10.1039/b000000x/

1 (a) C. S. Yeung and V. M. Dong, *Chem. Rev.,* 2011, **111**, 1215. (b) *Green Catalysis*, ed P. T. Anastas, Wiley-VCH, Weinheim, 2009.

2 (a) E. J. Barreiro, A. E. Kümmerle and C. A. M. Fraga, *Chem. Rev.* 2011, **111**, 5215. (b) H. Schönherr and T. Cernak, *Angew. Chem. Int. Ed.,* 2013, **52**, 2.

3 (a) E. Langhals and H. Langhals, *Tetrahedron Lett.,* 1990, **31**, 859. (b) K. Maruoka, A. B. Concepcion and H. Yamamoto, *Synthesis* 1994, 1283

4 For selected reviews, see: (a) S. Ourida and J. M. J. Williams, *Top. Organomet. Chem.,* 2011, **34**, 77. (b) J. Zhang, G. Leitus, Y. Ben-David and D. Milstein, *J. Am. Chem. Soc.,* 2005, **127**, 10840. (c) F. Hanasaka, K. Fujita and R. Yamaguchi, *Organometallics* 2004, **23**, 1490. (d) M. H. S. A. Hamid, P. A. Slatford and J. M. J. Williams, *Adv. Synth. Catal.,* 2007. 349. 1555. (e) J. F. Bower, I. S. Kim, R. L. Patman and M. J. Krische, *Angew. Chem. Int. Ed.,* 2009, **48**, 34. (f) G. Guillena, D. J. Ramón and M. Yus, *Chem. Rev.,* 2010, **110**, 1611. (g) G. E. Dobereiner and R. H. Crabtree, *Chem. Rev.,* 2010, **110**, 681. (h) T. Suzuki, *Chem. Rev.,* 2011, **111**, 1825. (i) R. Takeuchi and S. Kezuka, *Synthesis* 2006. 3349 and references therein.

5 For selected reviews, see: (a) C. S. Cho, B. T. Kim, T.-J. Kim and S. C. Shim, *J. Org. Chem.,* 2001, **66**, 9020. (b) A. S. Ndou, N. Plint and N. J. Coville, *Appl. Catal. A: Gen.,* 2003, **251**, 337. (c) C. S. Cho, B. T. Kim, H.-S. Kim, T.-J. Kim and S. C. Shim, *Organometallics* 2003, **22**, 3608. (d) R. Martínez, D. J. Ramón and M. Yus, *Tetrahedron* 2006, **62**, 8982. (e) K. Fujita, C. Asai, T. Yamaguchi, F. Hanasaka and R. Yamaguchi, *Org. Lett*., 2005, **7**, 4017. (f) G. Onodera, Y. Nishibayashi and S. Uemura, *Angew. Chem. Int, Ed.,* 2006, **45**, 3819. (g) G. Guillena, D. J. Ramón and M. Yus, *Angew. Chem. Int, Ed.,* 2007, **46**, 2358. (h) T. D. Nixon, M. K. Whittlesey and J. M. J. Williams, *Dalton Trans.,* 2009, 753. (i) T. Kuwahara, T. Fukuyama and I. Ryu, *Org. Lett.,* 2012, **14**, 4703 and references therein

6 (a) K. Taguchi, H. Nakagawa, T. Hirabayashi, S. Sakaguchi and Y. Ishii, *J. Am. Chem. Soc.* 2004, **126**, 72. (b) Y. Iuchi, Y. Obora and Y. Ishii, *J. Am. Chem. Soc.,* 2010, **132**, 2536. (c) M. Morita, Y. Obora and Y. Ishii, *Chem. Commun.,* 2007, 2850. (d) T. Sawaguchi and Y. Obora, *Chem. Lett.,* 2011, **40**, 1055. (e) Y. Obora, S. Ogawa and N. Yamamoto, *J. Org. Chem.,* 2012, **77**, 9429. (f) Y. Obora, Y, Anno, R. Okamoto, T. Matsu-ura and Y. Ishii, *Angew. Chem. Int, Ed.,* 2011, **50**, 8618. (g) T. Matsu-ura, S. Sakaguchi, Y. Obora and Y. Ishii, *J. Org. Chem.,* 2006, **71**. 8306. (h) Y. Obora and Y. Ishii, *Synlett*., 2011, 30.

7 (a) Y. Obora, S. Hatanaka and Y. Ishii, *Org. Lett*., 2009, **11**, 3510. (b) S. Hatanaka, Y. Obora and Y. Ishii, *Chem. Eur. J.,* 2010, **16**, 1883. (c) Y. Obora, K. Nakamura and S. Hatanaka, *Chem. Commun.,* 2012, **48**, 6720.

8 (a) K. Motokura, N. Fujita, K. Mori, T. Mizugaki, K. Ebitani, K. Jitsukawa and K. Kaneda, *Chem. Eur. J.,* 2006, **12**, 8228. (b) N. Ortega, C. Richter and F. Glorius, *Org. Lett*., **2013**, *15*, 1776.

9 N. Yamamoto, Y. Obora and Y. Ishii, *J. Org. Chem.,* 2011, **76**, 2937.

10 The Methanol Institute: http://www.methanol.org.

11 (a) M. Qian, M. A. Liauw and G. Emig, *Appl. Catal. A: Gen.,* 2003. **238**. 211. (b) W.-H. Lin and H.-F. Chang, *Catal. Today* 2004, **97**, 181. (c) T. Yamagata, A. Iseki and K. Tani, *Chem. Lett.,* 1997, 1215. (d) K. Tani, A. Iseki and T. Yamagata, *Chem. Commun.,* 1999, 1821.

12 J. Moran, A. Preetz, R. A. Mesch and M. J. Krische, *Nat.. Chem.,* 2011, **3**. 287.

13 (a) F. Li, J. Xie, H.Shan, C. Sun and L. Chen, *Rsc Adv*., 2012, **2**, 8645. (b) C. Sun, X. Zou and F. Li, *Chem. Eur. J.,* 2013, **19**, 14030.

14 (a) M. Nielsen, E. Alberico, W. Baumann, H.-J. Drexler, H. Junge, S. Gladiali and M. Beller, *Nature* 2013, **495**, 85. (b) R. E. Rodríguez-Lugo, M. Trincado, M. Vogt, F. Tewes, G. Santiso-Quinones and H. Grützmacher, *Nat. Chem*., 2013, **5**, 342.

15 L. K. M. Chan, D. L. Poole, D. Shen, M. P. Healy and T. J. Donohoe, *Angew. Chem. Int. ed.,* 2013, **53**, 761.

16 F. G. Bordwell and J. A. Harrelson Jr., *Can. J. Chem.,* 1990, **68**, 1714.

17 (a) M. J. Burk, R. H. Crabtree and D. V. McGrath, *J. Chem. Soc., Chem. Commun.,* 1985, 1829. (b) M. Gupta, C. Hagen, W. C. Kaska, R. E. Cramer and C. M. Jensen, *J. Am. Chem. Soc.*, 1997, **119**, 840. (c) F. Liu and A. S. Goldman, *Chem. Commun*., 1999, 655.