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C–C Coupling Reactions

C–C Coupling of Ketones with Methanol Catalyzed by a N-Heterocyclic Carbene–Phosphine Iridium Complex

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Abstract: An N-heterocyclic carbene–phosphine iridium complex system was found to be a very efficient catalyst for the methylation of ketone via a hydrogen transfer reaction. Mild conditions together with low catalyst loading (1 mol%) were used for a tandem process which involves the dehydrogenation of methanol, C=C bond formation with a ketone, and hydrogenation of the new generated double bond by iridium hydride to give the alkylated product. Using this iridium catalyst system, a number of branched ketones were synthesized with good to excellent conversions and yields.

The preparation and reactivity of transition-metal complexes of N-heterocyclic carbenes is a field in rapid development within organometallic chemistry. Compared with their phosphine analogues, N-heterocyclic carbenes offer stronger metal–ligand bond formation and better stability properties, and the study of their synthesis[1] and catalytic activities continues to attract considerable attention.[2] Recently, we found a highly efficient N-heterocyclic carbene iridium complex that can catalyze hydrogen transfer alkylation of amines with alcohols.[3] The transition-metal catalysts normally require either high temperature or large catalyst loadings for the hydrogen transfer alkylation of amine with alcohol.[4] For example, using $[RuCl_2(PPh_3)_3]$, which was one of the most widely studied catalysts for alkylation of amines, the reaction was carried out at above 100 °C. In the case of iridium catalytic systems, Fujita and co-workers introduced the use of $[\{Cp^*IrCl_2\}_2]$,[5] which gave full conversion at 110 °C in 17 h. Further study demonstrated that this chemical transformation is a highly efficient method to synthesize a wide range of amines and N-heterocyclic compounds from alcohols. The N-heterocyclic carbene iridium complex was found to be the first catalyst that worked at room temperature with low catalyst loading (1.0 mol%). In these transition-metal catalyzed hydrogen transfer reactions, the catalyst removes the hydrogen atoms from an alcohol to generate an aldehyde, which undergoes bond formation with another nucleophile in a condensation reaction, after which the metal hydride formed from the oxidation of the alcohol reduces this newly generated intermediate to give the final product. The hydrogen transfer reactions of alcohols have more recently also been applied to C–C bond formation.[6] This method allows the α-alkylation of ketones using alcohols as the electrophiles. Advances in this field have been made by a number of groups,[7] but the scope of the reaction has mostly been focused on the alkylation of methyl ketones, using mainly long-chain primary alcohols or benzylic alcohol as the electrophile. The simplest alcohol, methanol, is playing an increasingly important role in the chemical industry, and its transition-metal catalyzed dehydrogenation has been described by Beller,[8] Grützmacher[9] and Milstein[10] who have reported on the potential application of methanol in C–C bond formation via hydrogen transfer reactions. However, only a few successful examples have been published so far. Krische and co-workers[11] developed an elegant method for C–C bond formation using methanol and allenes, Jun and colleagues[12] described dialkyl ketone formation with methanol. Glorius[13] and Li[14] and their co-workers used methanol in metal-catalyzed N-formylation and methylation of amines. Very recently, the groups of Donohoe[15] and Obora[16] reported independently on the success in hydrogen transfer methylation of ketones with methanol. In their catalyst systems, $[\{Cp^*RhCl_2\}_2]$ and $[\{Cp^*IrCl_2\}_2]$ were used as pre-catalysts, 5 mol% of iridium or rhodium dimers, which means that in effect there was 10 mol% of monomer catalysts in the reaction solution, and additionally high temperatures were required when using $[\{Cp^*RhCl_2\}_2]$. With the aim of developing new catalysts for hydrogen transfer reactions, our N-heterocyclic carbene iridium homogeneous system stands out as being one of the most efficient catalysts for the hydrogen transfer alkylation of amines. Herein we report on the high catalytic activity of the hydrogen transfer methylation of ketones using methanol as the electrophile.

The phenyl ketone **1** was used as a benchmark substrate for this reaction and the results are shown in Table 1. Both the reactivity and selectivity of the reaction was found to be highly dependent on the base and the amount of base being used.

In the presence of tetrabutylammonium chloride and pyridine (Table 1, entries 1 and 2), the reactions were inhibited. The reduced alcohol **1b** was the only product when using sodium carbonate, sodium *tert*-butoxide, or potassium *tert*-butoxide (entries 3, 5, and 6). The use of potassium or cesium carbonate led to the formation of desired **1a** in 7% and 11% respectively (Table 1, entries 4 and 7). Use of cesium hydroxide (Table 1, entry 8) did not improve the methylation reaction. Increasing the amount of base, using 5 equiv of cesium

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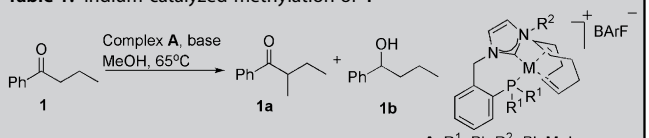
Table 1. Iridium-catalyzed methylation of **1**[a]



Entry	Catalyst	Base (equiv)	**1a** [%]	**1b** [%]
1	**A**	Bu_4NCl (2)	n.d.	n.d.
2	**A**	pyridine (2)	n.d.	n.d.
3	**A**	Na_2CO_3 (2)	n.d.	61
4	**A**	K_2CO_3 (2)	7	37
5	**A**	*t*BuONa (2)	n.d.	65
6	**A**	*t*BuOK (2)	n.d.	57
7	**A**	Cs_2CO_3 (2)	11	18
8	**A**	CsOH H_2O (2)	8	54
9	**A**	Cs_2CO_3 (5)	63	n.d.
10	**B**	Cs_2CO_3 (5)	53	n.d.
11	**C**	Cs_2CO_3 (5)	33	n.d.
12	**D**	Cs_2CO_3 (5)	complex mixture	
13[b]	**A**	Cs_2CO_3 (5)	99 (97)[c]	<1

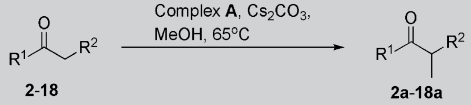
[a] Reaction conditions: ketone **1** (0.1 mmol), base (2 equiv), **A** (1.0 mol%) in MeOH (2.0 mL) at 65 °C for 24 h. [b] Reaction conditions: ketone **1** (0.1 mmol), base (5 equiv), **A** (1.0 mol%) in MeOH (0.5 mL) at 65 °C for 24 h. [c] Isolated yield.

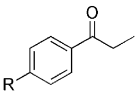
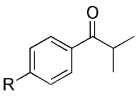
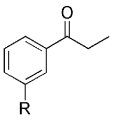
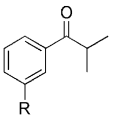
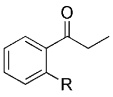
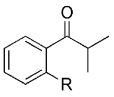
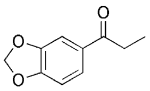
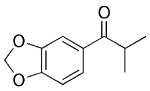
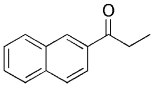
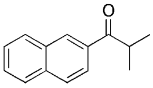
carbonate gave 63% of the desired product **1a** with a trace amount of **1b**. Changing the substituents at the imidazole and phosphine did not result in any improvements (entries 10 and 11). Running the reaction at higher concentration, (Table 1, entry 13) was found to suppress the formation of the reduced product **1b**, and led to full conversion with 97% isolated yield. The corresponding rhodium complex was not an efficient catalyst for the methylation reaction (entry 12).

With the optimized reaction conditions in hand, the scope of the catalyst was tested using a range of different ketones. As shown in Table 2, the catalyst system maintained high activity for the halogenated derivatives; high conversions were obtained for different halogen substituents on all three *ortho*, *meta*, and *para* positions on the phenyl ring. Ketones **3**, **10**, and **14** were converted to the methylation products completely in 24 h, whereas the ketone **4** with the methoxy group gave 96% conversion with 91% isolated yield. Full conversion was obtained with trifluoromethylated ketones **8**, **12**, and **16**. Using standard conditions (0.5 mL of methanol), 83% of the substrate **18** was converted to desired product in 80% isolated yield. Further reduction occurred to generate the corresponding alcohol, which means that after the methylation was complete, the iridium catalyst continued to transfer hydrogen from methanol to the carbonyl group.

When a longer aliphatic chain was introduced on the ketone, slower reaction rates were observed (Table 3). Compared with ethyl ketone **2**, which gave full conversion in 24 h, 5 equivalents of cesium carbonate were required to achieve high conversions for butyl and hexyl phenyl ketones (**19** and **20** with 98% and 94% yields, respectively). Using these conditions the ketone **21** was fully converted in 24 h as well. In the

Table 2. Iridium-catalyzed methylation of propiophenone derivatives.[a]

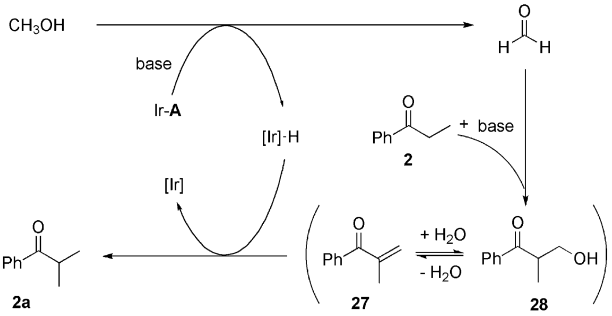


Substrate		Product	Isolated yield [%]
	R = H **2**		95
	R = Me **3**		93
	R = OMe **4**		91
	R = Cl **5**		95
	R = F **6**		92
	R = Br **7**		96
	R = CF_3 **8**		93
	R = Cl **9**		92
	R = Me **10**		95
	R = Br **11**		93
	R = CF_3 **12**		90
	R = Cl **13**		89
	R = Me **14**		90
	R = F **15**		88
	R = CF_3 **16**		85
	**17**		91
	**18**		80

[a] Reaction conditions: ketone (0.1 mmol), base (4 equiv), **A** (1.0 mol%) in MeOH (0.5 mL) at 65 °C for 24 h.

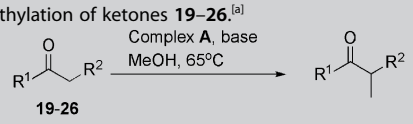
case of ethyl benzyl ketone **22**, the conversion was 83% and 80% of **22a** was isolated. Only trace amounts of dimethylated product **23a** implies a strong dependency of the chemoselectivity on the pK_a value of the α-carbon.[16,17] Other benzylic ketones **24** and **25** gave full conversions and high isolated yields.

Several experiments were carried out to shed some light on the mechanism, which is proposed to start from dehydrogenation of the methanol to form formaldehyde, followed by aldol condensation with the ketone to obtain the conjugated ketone and then, final reduction of the unsaturated ketone intermediate (Scheme 1).

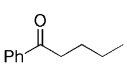
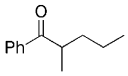
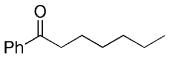
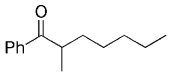
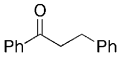
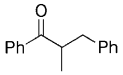
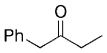
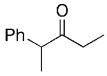
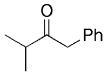
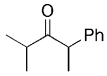
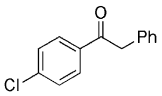
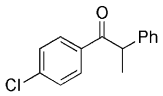
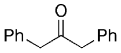
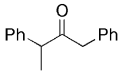


Scheme 1. Proposed mechanism of methylation with iridium catalyst.

Table 3. Methylation of ketones **19–26**.[a]



19-26

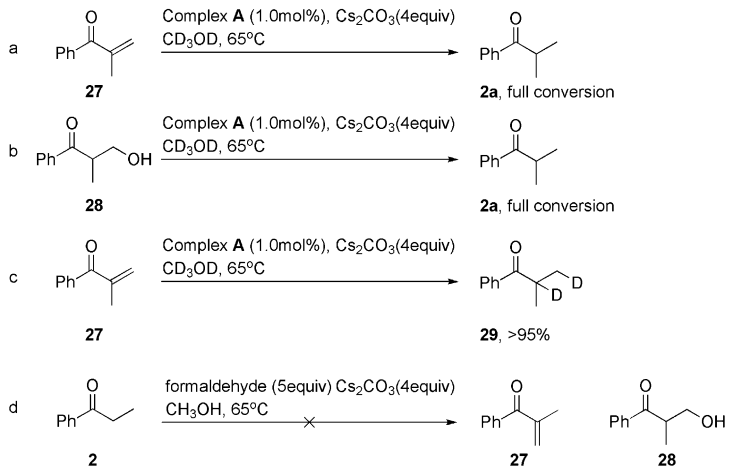
Substrate		Product		Isolated Yield [%]
	**19**		**19a**	98
	**20**		**20a**	94
	**21**		**21a**	97
	**22**		**22a**	80
	**23**		**23a**	96
	**24**		**24a**	96
	**25**		**25a**	95
	**26**		**2a**	96[b]

[a] Reaction conditions: ketone (0.1 mmol), base (5 equiv), **A** (1.0 mol%) in MeOH (0.5 mL) at 65 °C for 24 h. [b] Reaction conditions: ketone (0.1 mmol), base (5 equiv), **A** (3.0 mol%) in MeOH (0.5 mL) at 65 °C for 24 h.

The two proposed intermediates **27** and **28** were prepared separately and both converted smoothly to product **2a** when subjected to the standard reaction conditions (Scheme 2a and b). The use of [D_4]methanol as solvent resulted in the clean formation of the deuterated compound **29**, which was obtained in more than 95% selectivity (Scheme 2c). These results are both in agreement with the fact that a) the reaction appears to follow an aldol condensation pathway, and b) it involves hydrogenation of a C=C bond by iridium hydride. Since also the formaldehyde and ketone **2** were unable to generate either **27** or **28** (Scheme 2d) under standard reaction conditions without the iridium catalyst, the iridium catalyst seems also be involved in the aldol step (Scheme 1, from **2** to **27** and **28**) perhaps by binding with formaldehyde to increase its electrophilicity.[6e]

The mercury poisoning test was carried out in the presence of 5 equiv of mercury with substrate **2**, which gave 97% conversion in 24 h, whereas 99% conversion occurred without mercury. In the time-dependent experiment of the reaction of **2**, 1% of the conversion was detected in the first 24 min, which revealed that there was a pre-activation process of the iridium complex **A** (see Figure S1 in the Supporting Information). Furthermore, when complex **A** was replaced by the cationic iridium complex $[Ir(cod)_2]^+BAr_F^-$, it led to a dramatic loss of both reactivity and selectivity of the reaction. Alongside the desired product, alcohols stemming from the reduction of the starting material together with various methylated products were formed, which clearly shows that the N-heterocyclic carbene phosphine ligand remains bound to the iridium center during the catalytic cycle.

In summary, we have reported the use of methanol in the alkylation of ketones via a hydrogen transfer reaction catalyzed by an N-heterocyclic carbene phosphine iridium complex with high reactivity and good selectivity. Compared with the commercially available $[\{Cp^*IrCl_2\}_2]$ catalyst system, the catalyst loading could be decreased from 10 mol% to 1 mol% when iridium complex **A** was used, and full conversions were obtained in most cases. This catalyst system was found to be applicable to a wide variety of ketones. Experiments suggest that the new bond formation passes through an aldol-type pathway, in which all steps probably are mediated by the iridium catalyst; however, the exact reaction mechanism still remains to be uncovered.



Scheme 2. Methylation of possible intermediates **27** and **28**

Experimental Section

To an oven-dried pressure vessel with a magnetic stir bar, base and iridium complex were added. The vessel was sealed, degassed by vacuum pump and refilled three times with nitrogen. The ketone substrates in degassed methanol were added under a nitrogen atmosphere, and the reaction mixture was heated to 65 °C for 24 h. The reaction mixture was cooled to ambient temperature and aqueous hydrochloride solution (1 M, 1 mL) and diethyl ether (2 mL) were added. The aqueous phase was separated and extracted with diethyl ether (2×2 mL), and all the combined organic phases were washed with brine, dried over sodium sulfate, and the organic solvent was removed under vacuum. The conversion was determined by ^1H NMR spectroscopy, and further purification was carried out by column chromatography.

Acknowledgements

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Keywords: C–C coupling reactions · hydrogen transfer · iridium · ketones · methylation

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