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A Convenient Ruthenium-Catalysed α-Methylation of Carbonyl Compounds using Methanol

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Abstract: An efficient ruthenium catalyst is reported, for the first time, to catalyse the α-methylation of ketones and esters using methanol as a green methylating agent. The *in situ* generated catalyst from the complexes $[RuCp^*Cl_2]_2$ or $[RuCp^*Cl_2]_n$ with dpePhos provided up to quantitative yields in the presence of only 20 mol% of lithium *tert*-butoxide (LiO-*t*-Bu) as a base. Regioselective mono- or multi-methylation could be effectively controlled by temperature. This catalyst system was also effective for the one-pot sequential α-alkylation–α-methylation of methyl ketones and conjugate reduction–α-methylation of α,β-unsaturated ketones to synthesise α-branched ketones. An application of the α-methylation of esters using the ruthenium catalyst was demonstrated for an alternative catalytic synthesis of Ketoprofen.

Keywords: borrowing hydrogen strategy; esters; ketones; ketoprofen synthesis; methanol activation; α-methylation; ruthenium catalyst

Methylation is one of the fundamental organic transformations having a pivotal role in the synthesis and functionalisation of bioactive molecules.[1] The methyl fragment is present in many top selling pharmaceutical compounds and is, in part, responsible for adjusting both physical and biological properties of the compound.[2] Accordingly, efficient methods to introduce the methyl group into organic molecules have been a topic of active research both in academia and industry.[3]

α-Methyl ketones appear in many important natural products and pharmaceutically active compounds (Figure 1).[4] For instance, Eperisone and Tolperisone are antispasmodic agents,[5] Eprazinone (trade name Eftapan) is a mucolytic agent and relieves bronchospasms.[6] In addition, the α-methylcarboxylic acid group is present in the "profen family" (e.g., Suprofen, Ibuprofen, Naproxene, Ketoprofen, Flurbiprofen and Fenoprofen) of drugs that are used as non-steroidal anti-inflammatory agents.[7]

The conventional methods for methylation of ketones and other active methylene compounds are based on the use of reactive and genotoxic methyl halides or diazomethane or other electrophilic compounds as methylating agents.[8] In addition, the use of an excess amount of base and the generation of toxic halogenated waste makes such processes environmentally unfriendly.[9] Hence, developing sustainable[10] methylation protocols by exploiting readily available and greener methylating agents is highly desirable. Methanol[11] is one such promising methylating agent and could be potentially activated through the formation of a transient reactive formaldehyde in-

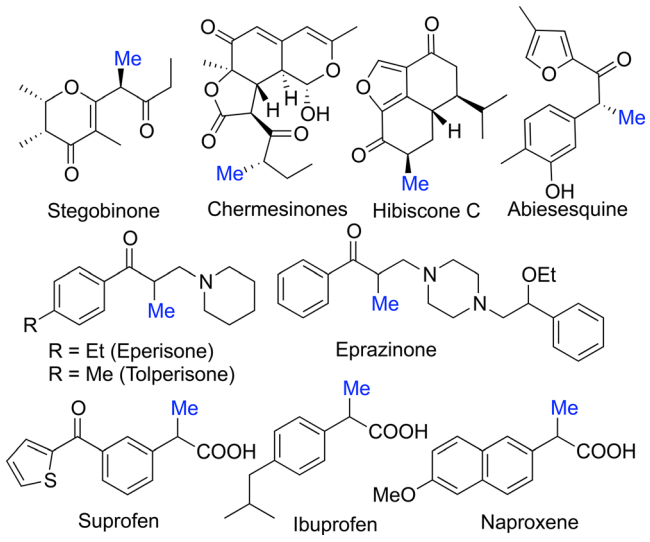


Figure 1. Example of natural products and drugs containing α-methyl groups.

termediate following the catalytic borrowing hydrogen (BH) strategy or hydrogen auto-transfer (HA).[12] Due to the difficulty in the dehydrogenation of methanol that needs a higher activation energy in comparison to other higher alcohols, for example, ethanol ($\Delta H = +84$ *vs.* $+68$ kJ mol^{-1}),[13] only a few reports on the transition metal-catalysed methylation of ketones using methanol have been published so far.

Although several transition metal catalysts were reported to be efficient for the α-alkylation of ketones using higher alcohols,[14] only iridium[15] and rhodium[16] based catalysts were reported for the α-methylation of ketones using methanol. However, ruthenium-based catalysts were recently reported for the activation of methanol towards hydrogen production[17] and *N*-methylation reactions.[18] The only C-methylation reported so far using ruthenium catalysts following the borrowing hydrogen strategy was by Beller and co-workers for the methylation of 2-arylethanols as a substrate in the presence of a mixture of two ruthenium precatalysts such as Ru-MACHO and the Shvo catalysts.[19]

One of the first reports on the α-methylation of ketones using methanol following the borrowing hydrogen strategy was from Feng Li and co-workers using an iridium-Cp* complex coordinated with a non-innocent bipyridonate ligand.[15a] Up to 85% yield was reported under reflux conditions for 12–18 h in the presence of 2 mol% of catalyst and 30 mol% of $CsCO_3$ as a base. Later, Ogawa and Obora reported an Ir-phosphine catalyst in the presence of 0.5 equivalents of KOH at 120 °C for 15 h, achieving up to 91% yield.[15b] Recently, Donohoe and co-workers demonstrated an Ir-phosphine-catalysed methylation and methylation–conjugate addition reaction of ketones at 65 °C in presence of three equiv. of KOH under an atmosphere of oxygen for 48 h.[15c] An N-heterocyclic carbene-phosphine-Ir complex was reported by Andersson and co-workers in the presence of five equivalents of $CsCO_3$ at 65 °C for 24 h.[15d] A Rh-phosphine complex was also reported by Donohoe and co-workers in the presence of oxygen gas at 60 °C for 48–72 h.[16] In this case, five equivalents of KOH or Cs_2CO_3 as a base were required to achieve the products in up to 98% yield.

Until now, only expensive metal catalysts such as Rh, Ir complexes could be used for the α-methylation of ketones using methanol. In this context, developing a more general and less expensive catalyst such as ruthenium[20] (a well-known metal catalyst for alcohol activation for alkylation) could be advantageous for developing future sustainable manufacturing technologies. Herein we report, for the first time, an efficient ruthenium-catalysed α-methylation of ketones (Figure 2) and esters in the presence of sub-stoichiometric amount of base. To the best of our knowledge, no efficient metal catalysts were reported so far for

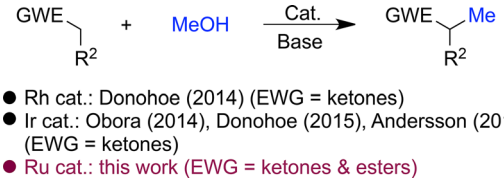


Figure 2. Reports on transition metal-catalysed α-methylation of ketones following the BH strategy.

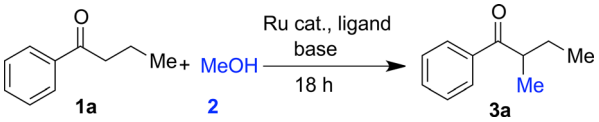
the α-methylation of esters using methanol following the BH strategy.

Encouraged by our recent findings[18d] that activation of methanol is possible using a ruthenium catalyst system [RuCp*(dpePhos)Cl] and is efficient for the hydrogenation of an *in situ* formed imine towards *N*-methylation, we believe that α-methylation of an active methylene compound could also be possible if the ruthenium catalyst is effective in the hydrogenation of the *in situ* formed C=C double bond following a BH mechanism. We were delighted to observe an initial yield of up to 36% and 52% for the α-methylated ketone **3a** (2-methyl-1-phenylbutan-1-one) from butyrophenone (**1a**) and methanol (**2**) with the *in situ* generated catalyst from $[RuCp^*Cl_2]_2$ and dpePhos when 0.2 equivalents of KO-*t*-Bu and LiO-*t*-Bu were used as bases, respectively at 90 °C for 18 h (Table 1, entries 1 and 2).

LiO-*t*-Bu is found to the more suitable base compared to others (entries 3–5). This may be due to the ready formation of LiOMe as well as the effective stabilisation of various intermediates by the smaller Li^+ cation towards the *in situ* formation of the active Ru(II)-OMe species (see the Supporting Information). $[Ru(cod)Cl_2]_2$ gave a lower yield of 29% with 30% conversion (entry 6), while other ruthenium precursors such as $Ru(acac)_3$ and $RuCl_3 \cdot x H_2O$ (entries 7 and 8) gave inferior results. Phosphine ligands such as xantphos, dppe, dppb, dppf (entries 9 to 12) were found to be less effective compared to dpePhos. The flexibility of the dpePhos backbone could be an important factor for this enhanced catalytic performance under the present set of conditions. Increasing the temperature to 100 °C resulted in up to 95% conversion with the formation α-methylated product (**3a**) in up to 92% yield using $[RuCp^*Cl_2]_2$ or $[RuCp^*Cl_2]_n$ as the catalyst precursor and dpePhos as the ligand (entry 13). No appreciable amounts of side products were observed in this reaction. In the absence of $[RuCp^*Cl_2]_2$ or $[RuCp^*Cl_2]_n$, no product was observed indicating the necessity of the ruthenium catalyst in this reaction.

With the optimised conditions in hand, we evaluated the substrate scope of this *in situ* formed Ru-Cp*(dpePhos)Cl-catalysed α-methylation reaction. For this purpose, the reaction conditions were slightly changed to 110 °C for 24 h compared to the

Table 1. Optimisation of the Ru-catalysed α-methylation of butyrophenone.[a]



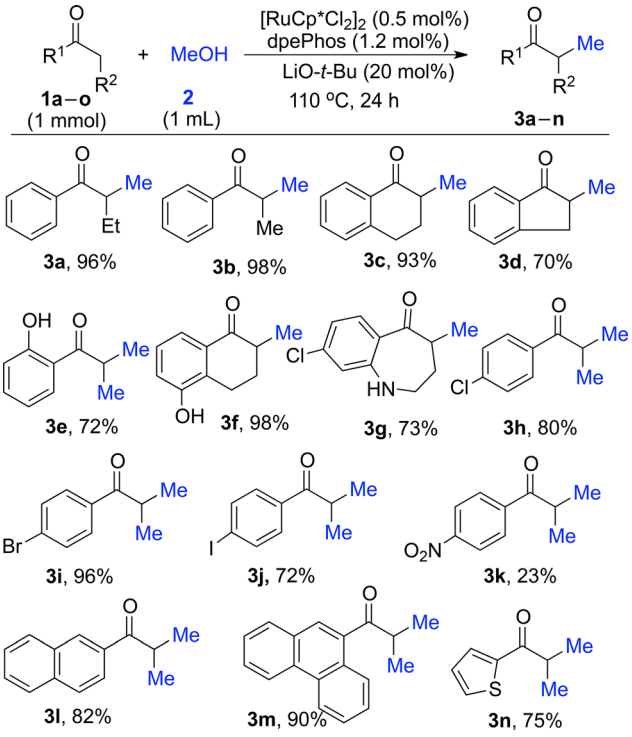
No.	Ru cat.	Ligand	Base	Temp. [°C]	Conv. [%]	Yield [%][b]
1	$[RuCp^*Cl_2]_2$	dpePhos	KO-*t*-Bu	90	38	36
2	$[RuCp^*Cl_2]_2$	dpePhos	LiO-*t*-Bu	90	53	52
3	$[RuCp^*Cl_2]_2$	dpePhos	LiOH	90	32	32
4	$[RuCp^*Cl_2]_2$	dpePhos	NaOH	90	25	24
5	$[RuCp^*Cl_2]_2$	dpePhos	K_2CO_3	90	21	21
6	$[Ru(cod)Cl_2]_2$	dpePhos	LiO-*t*-Bu	90	30	29
7	$Ru(acac)_3$[c]	dpePhos	LiO-*t*-Bu	90	n.d	–
8	$RuCl_2 \cdot x\,H_2O$[c]	dpePhos	LiO-*t*-Bu	90	n.d	–
9	$[RuCp^*Cl_2]_2$	xantphos	LiO-*t*-Bu	90	n.d.	4
10	$[RuCp^*Cl_2]_2$	dppe	LiO-*t*-Bu	90	19	17
11	$[RuCp^*Cl_2]_2$	dppp	LiO-*t*-Bu	90	21	20
12	$[RuCp^*Cl_2]_2$	dppf	LiO-*t*-Bu	90	25	25
13	$[RuCp^*Cl_2]_2$[d]	dpePhos	LiO-*t*-Bu	100	95	92
14	–	dpePhos	LiO-*t*-Bu	100	n.d.	–

[a] Ketone **1a** (1 mmol), methanol (1 mL), Ru cat. (0.5 mol%), ligand (1.2 mol%), base (20 mol%).
[b] Yields were determined by ^{1}H NMR using mesitylene as the internal standard.
[c] 1 mol% of Ru cat. is used.
[d] A similar result was achieved with the polymeric $[RuCp^*Cl_2]_n$.

optimised conditions (Table 1, entry 13) to ensure complete conversion even when less reactive substrates were used. A preformed RuCp*(dpePhos)Cl[18d] complex could also be used as a pre-catalyst that gives similar results as that of the *in situ* formed catalyst (see the Supporting Information).

Excellent isolated yields were achieved for the α-methylated ketone products **3a** (96%) and **3b** (98%) from the corresponding ketones, butyrophenone (**1a**) and propinophenone (**1b**), as shown in Scheme 1. Cyclic phenyl ketones were also promising substrates and up to 93% (**3c**) yield was achieved in the case of six-membered tetralone (**1c**), while the five-membered indanone (**1d**) gave up to 70% (**3d**) isolated yield under the present reaction conditions.

Aryl methyl ketones generally provided the double methylated products (**3e**, **3h**–**3n**) in up to 96% yield. The presence of hydroxy (**3e**, **3f**), chloro (**3g**, **3h**), bromo (**3i**) and iodo (**3j**) functionalities was well tolerated. The reducible nitro (**3k**) functionality was tolerated, however **3k** was isolated in a lower yield of 23% at a conversion of about 75%. In this case, side products such as condensation products and transfer hydrogenation of the ketone were observed. Increasing the temperature did not improve the yield and partial reduction of the NO_2 group was observed. Interestingly, the cyclic amino group was also tolerated and preferential α-methylation of the ketone occurred and the product **3g** was isolated in 73% yield. In this case, no appreciable *N*-methylation was observed. Methyl ketones with fused aromatic rings (**1l**, **1m**) and heterocycles (**1n**) were also found to be promising substrates providing the corresponding α-methylated products in up to 90% isolated yield.



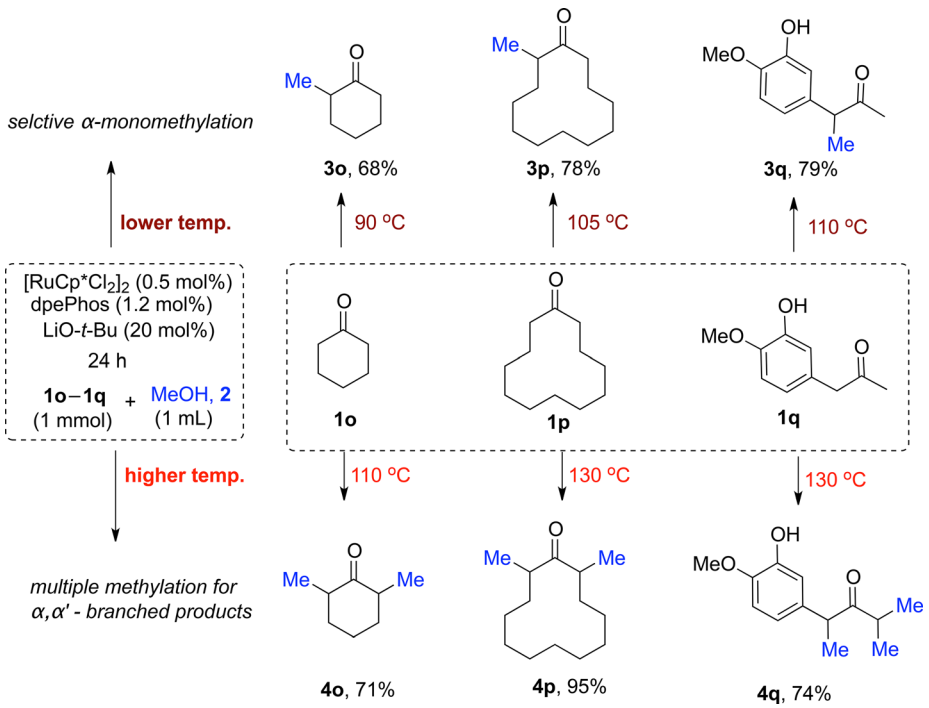
Scheme 1. Substrate scope for the Ru-catalysed α-methylation of ketones using methanol.

The scale-up potential of this promising Ru-catalysed α-methylation procedure was investigated by performing a gram-scale reaction. Considering the higher pressure generated (vapour pressure and the potential generation of hydrogen) at 110 °C with the higher amount of methanol, the reaction was performed in a 25-mL high-pressure Parr stirred reactor. The standard reaction of α-methylation of butyrophenone (**1a**) was scaled up to 10-mmol scale (1.34 g) in 8 mL of methanol using only 0.1 mol% Ru catalyst at 120 °C for 72 h, achieving up to 71% yield with a TON of 710.

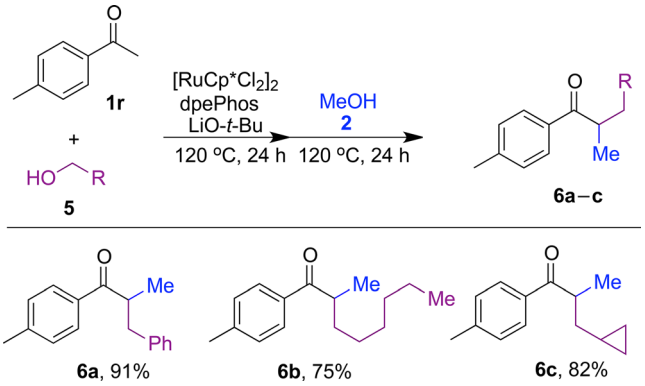
Substrates having two α-carbons that are prone to potential methylation, generally pose selectivity issues. Interestingly, we found that the present catalyst system offers a temperature-controlled selective mono-, di-, or tri-methylation depending upon the substrate used (Scheme 2). For example, the selective monomethylation of cyclohexanone was achieved when the reaction was performed at a lower temperature of 90 °C achieving **3o** in up to 68% isolated yield. With an increase in temperature to 110 °C, the second methylation also occurred to give the α,α′-double methylated product **4o** in 71% isolated yield. However, the five-membered cyclopentanone gave a mixture of products (methylated and condensation products, see the Supporting Information) even at a lower temperature of 50 °C. With higher membered aliphatic cyclic ketones such as cyclododecanone (**1p**), the selective mono-methylation was achieved at 105 °C, providing up to 78% isolated yield of **3p**. At a temperature of 130 °C, the second methylation also occurred to give the α,α′-double methylated product **4p** in up to 95% isolated yield. In the case of benzyl methyl ketone (**1q**), preferential mono-methylation occurred at the benzylic position at a temperature of 110 °C and the mono-methylated product **3q** was isolated in up to 79% yield. Prolonged reaction (72 h) at this temperature did not produce any further methylated products. However increasing the temperature to 130 °C provided the triple methylated product **4q** in up to 74% isolated yield.

We have shown in Scheme 1 and Scheme 2 that the *in situ* formed Ru-Cp*(dpePhos)Cl catalyst is effective in producing α-branched ketones from the corresponding aryl alkyl or cyclic ketones through mono-methylation or from aryl methyl ketones through double-methylation. Accordingly, we envisaged that this "single *in situ* formed Ru-Cp*(dpePhos)Cl catalyst" could be used for the preparation of various α-branched ketones in a one-pot sequential α-alkylation followed by α-methylation of aryl methyl ketones under the current optimised reaction conditions. Such a protocol was demonstrated by Donohoe and co-workers[16] using a "dual catalyst" system involving an initial iridium-catalysed alkylation followed by rhodium-catalysed methylation as well as by Ogawa and Obora by using an iridium catalyst at 140 °C.[15b]

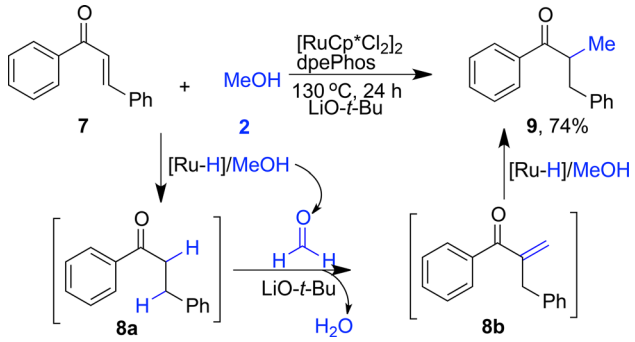
We were delighted to see that the present Ru catalyst system is effective for this sequential reaction and notably, only 0.5 mol% of catalyst and 20 mol% of LiO-*t*-Bu were required under moderate conditions of



Scheme 2. Temperature-dependent selective α-methylation of ketones.



Scheme 3. Ru-catalysed sequential α-alkylation–α-methylation of ketones.

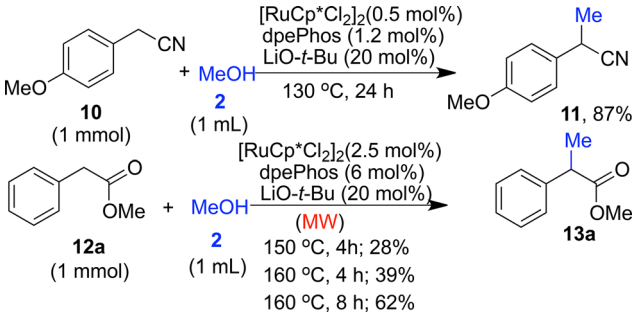


Scheme 4. Ru-catalysed sequential conjugate reduction–α-methylation of chalcone.

120 °C. As shown in Scheme 3 (other reaction conditions are the same as entry 13, Table 1), up to 91% isolated yield was achieved for **6a**, when 4-methylacetophenone was used as the substrate together with benzyl alcohol and methanol. Long chain aliphatic alcohols could also be used and the product **6b** was obtained in 75% yield when 1-hexanol was used as the alcohol. Short chain alcohols such as ethanol and *n*-propanol could be potentially used, however the selectivity during the first alkylation was slightly lower due to side reactions such as transfer hydrogenation (see the Supporting Information). A methylated ketone with a cyclopropylethyl α-branching (**6c**) was also readily obtained in 82% yield when cyclopropylethanol and methanol were used in this sequential α-alkylation–α-methylation protocol. A one-pot, one-step procedure as reported by Ogawa and Obora for this sequential reaction was not successful and the only product isolated was the double methylated ketone showing the preferential activation of methanol in the presence of other alcohols with the present *in situ* formed Ru-Cp*(dpePhos)Cl catalyst system. Another interesting fact is that no appreciable di-alkylation was observed when using alcohols other than methanol. Hence a one-pot, two-step procedure is preferred for this Ru-catalysed sequential α-alkylation-methylation protocol.

The promising results from this sequential reaction encouraged us to investigate the reduction of a conjugate double bond followed by α-methylation using methanol. Interestingly, reaction of methanol with the α,β-unsaturated ketone **7** in the presence of the present Ru catalyst system provided the saturated α-methylated ketone **9** in up to 74% isolated yield, possibly *via* sequential reactions involving an initial conjugate reduction of **7** to form **8** (see the Supporting Information) followed by α-methylation (Scheme 4, other reaction conditions are the same as entry 13, Table 1). In order to understand the reaction pathway, an intermediate sample was analysed by GC-MS to observe the reaction intermediates. Identification of the intermediates **8a** and **8b** along with the product **9** suggests a possible pathway involving initial Ru-catalysed reduction followed by α-methylation in the presence of methanol (see the Supporting Information).

After successful α-methylation of ketones, we turned our attention to the α-methylation of potential substrates such as nitriles[21] **10** and esters[22] **12a**, **b**. As shown in Scheme 5, 2-(4-methoxyphenyl)acetonitrile

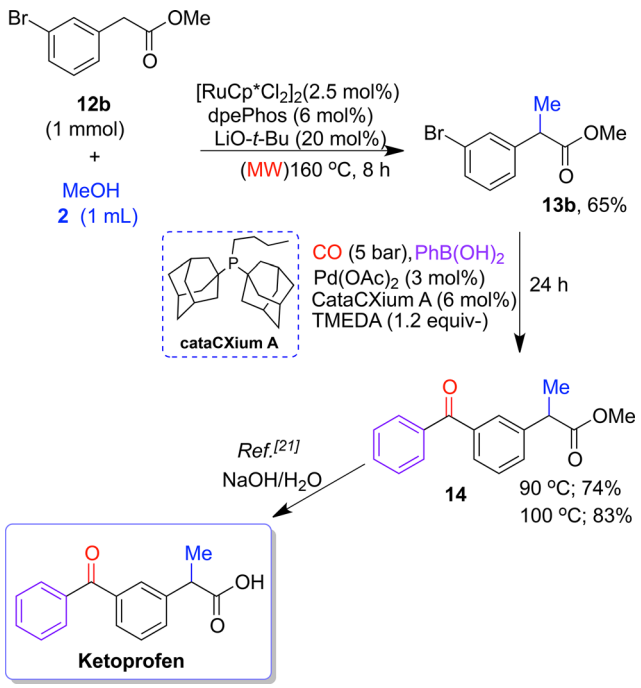


Scheme 5. Ru-catalyzed α-methylation of representative nitrile and ester.

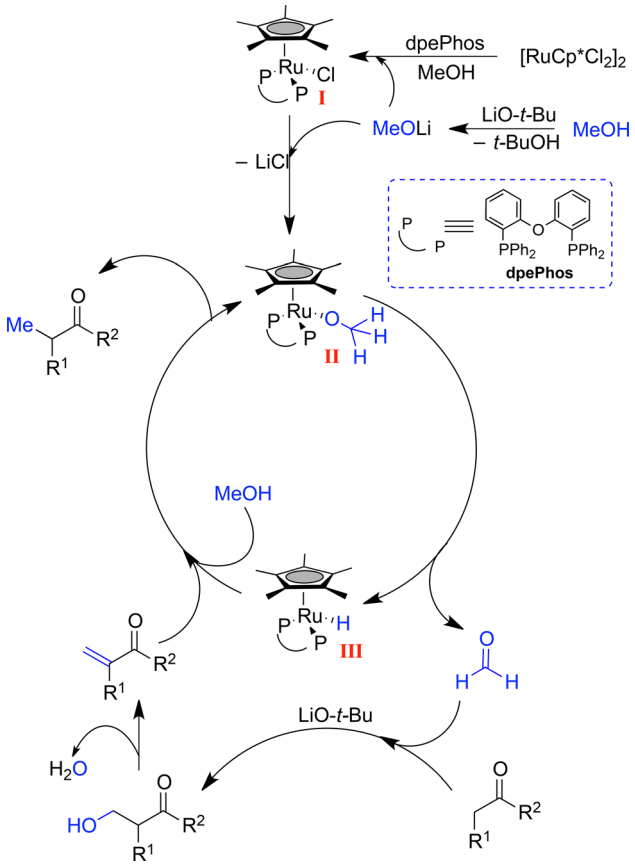
(**10**) provided a promising yield of 87% at 130 °C for 24 h of the corresponding α-methylated nitrile product **11**. However, under these conditions, the ester **12a** provided low conversion. Esters are particularly challenging substrates for α-alkylation using alcohols (following the BH strategy) with only a few reports available so far.[22] Only iridium-based catalysts were reported with higher alcohols as alkylating agents either with activated esters as substrates or in the presence of over-stoichiometric amounts of base. A quick optimisation using the present Ru catalyst system resulted in up to 62% isolated yield under microwave conditions after 8 h of reaction at 160 °C in the presence of 20 mol% of base (Scheme 5). To the best of our knowledge, this is the first report of a ruthenium-catalysed α-alkylation, particularly, α-methylation of esters following the BH strategy.

An application of this ruthenium-catalysed α-methylation of esters was demonstrated for a concise alter-

native synthesis of Ketoprofen,[23] a representative non-steroidal anti-inflammatory agent from the "profen" family. Although improvements are required, this two-step catalytic pathway (Scheme 6)



Scheme 6. Ru-catalysed α-methylation in an alternative synthesis of Ketoprofen.



Scheme 7. Proposed mechanism for Ru-catalysed α-methylation of ketones (or esters) using methanol.

leading to the ketoprofen methyl ester could potentially circumvent the direct use of genotoxic methyl iodide. Methylation of bromide-functionalized ester **12b** using the optimised *in situ* formed Ru-Cp*(dpePhos)Cl catalyst system afforded the methylated product **13b** in up to 65% yield. The methyl ester of Ketoprofen (**14**) was successfully prepared in 83% isolated yield through a palladium-catalysed carbonylative coupling with phenylboronic acid.[24] The methyl ester could be readily hydrolysed to the racemic Ketoprofen.[24]

Both the α-methylation of ketones and esters could follow a borrowing hydrogen strategy and a possible catalytic cycle starting from the preformed complex **I** is proposed in Scheme 7. Complex **I** could readily form under the reaction conditions from $[RuCp^*Cl_2]_2$ or $[RuCp^*Cl_2]_n$ in the presence of dpePhos, LiO-*t*-Bu and methanol (see the Supporting Information).[18d,25] Complex **I** could activate methanol in the presence of LiO-*t*-Bu/LiOMe through the intermediate ruthenium methoxide complex **II** to form formaldehyde and the ruthenium hydride complex **III** as shown in Scheme 7.[16d] Formaldehyde condenses with ketone (or ester) through an aldol condensation pathway and the resultant unsaturated ketone gets reduced by the ruthenium hydride complex **III** in the presence of methanol to generate the product and the complex **II** for the next catalytic cycle.

In conclusion, we have demonstrated, for the first time, an efficient and economically attractive ruthenium-catalysed α-methylation of ketones and esters using methanol as a greener and more sustainable methylating agent, following the catalytic borrowing hydrogen (BH) strategy. Key to the success is the use of an *in situ* generated Ru-Cp*(dpePhos)Cl catalyst together with sub-stoichiometric amount of LiO-*t*-Bu as a base. Scale-up possibility was demonstrated using a gram-scale reaction of α-methylation of ketone using 0.1 mol% of catalyst, achieving up to a TON of 710. This catalyst system is also effective for the synthesis of α-branched ketones from methyl ketones through a one-pot sequential alkylation–methylation as well as conjugate reduction–methylation strategies. Nitriles and esters having α-benzylic carbons were found to be promising substrates. An application of this Ru-catalysed methylation of esters was demonstrated for an alternative two-step catalytic synthesis of the methyl ester of Ketoprofen from readily available starting materials.

Experimental Section

General Procedure 1 for the α-Methylation of Ketones using Methanol

The Ru precursor $[RuCp^*Cl_2]_2$ (3.1 mg, 0.5 mol%), dpePhos (6.4 mg, 1.2 mol%), LiO-*t*-Bu (16.0 mg, 20 mol%), and ketone (1.0 mmol) were charged under an argon atmosphere in a 5-mL glass pressure reaction tube. 1 mL of dry methanol was added into the mixture, the reaction tube was closed with the cap and was heated in an oil bath to the desired temperature under magnetic stirring. After the desired reaction time, the reaction mixture was allowed to cool to room temperature and diluted with methanol (5 mL). SiO_2 (400 mg) was added into the crude mixture. The organic solvent was removed under vacuum and the product was purified by column chromatography. The product was analysed by NMR spectroscopy.

General Procedure 2 for Sequential α-Alkylation–α-Methylation of Ketones

The Ru precursor $[RuCp^*Cl_2]_2$ (3.1 mg, 0.5 mol%), dpePhos (6.4 mg, 1.2 mol%), LiO-*t*-Bu (16.0 mg, 20 mol%), and ketone (1.0 mmol) were charged under an argon atmosphere in a glass pressure reaction tube. 1 mL of dry alcohol was added into the mixture, the reaction tube was closed with the cap and was heated to 120 °C in an oil bath under magnetic stirring. After the 24 h reaction time, the reaction mixture was allowed to cool to room temperature and 1 mL methanol was added. Reaction mixture was heated to 120 °C for another 24 h. After the reaction, the reaction mixture was cooled to room temperature. Methanol (5 mL) and SiO_2 (400 mg) were added into the crude mixture. The organic solvent was removed under vacuum, purified by column chromatography and the product was analysed by NMR spectroscopy.

General Procedure 3 for the α-Methylation of Esters using Methanol

The Ru precursor $[RuCp^*Cl_2]_2$ (15.5 mg, 2.5 mol%), dpePhos (32 mg, 6 mol%), LiO-*t*-Bu (16.0 mg, 20 mol%), and ester (1.0 mmol) were charged under an argon atmosphere in a microwave tube. 1 mL of dry methanol was added into the mixture. The reaction tube was closed with the microwave cap and was heated to 160 °C under microwave irradiation in an Anton Paar microwave instrument (Monowave 300). After 8 h, the reaction mixture was allowed to cool to room temperature and diluted with methanol (5 mL). SiO_2 (400 mg) was added into the crude mixture. The organic solvent was removed under vacuum, the product was purified by column chromatography and analysed by NMR spectroscopy.

Scale-Up Procedure for α-Methylation of Butyrophenone

The Ru precursor $[RuCp^*Cl_2]_2$ (3.1 mg, 0.05 mol%), dpePhos (6.4 mg, 0.12 mol%), LiO-*t*-Bu (16.0 mg, 2 mol%), butyrophenone (10.0 mmol, 1.34 g) and 8.0 mL of dry methanol were charged under an inert atmosphere in to a 25-mL Parr high pressure stirred reactor (5550 series with controller 4848). The reactor was closed, purged with nitrogen and was heated to 120 °C under stirring. After 72 h, the reaction mixture was allowed to cool to room temperature, depressurised and the sample collected for analysis. The yield of product (71%) was determined by GC using mesitylene as an internal standard.

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