Ketone Alkylation | Hot Paper

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Rhodium-Catalyzed Ketone Methylation Using Methanol Under Mild Conditions: Formation of α-Branched Products**

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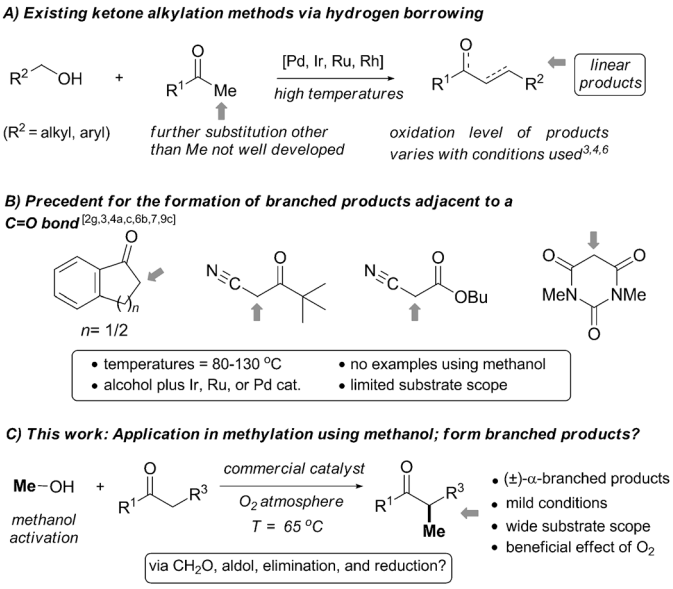
Abstract: *The rhodium-catalyzed methylation of ketones has been accomplished using methanol as the methylating agent and the hydrogen-borrowing method. The sequence is notable for the relatively low temperatures that are required and for the ability of the reaction system to form α-branched products with ease. Doubly alkylated ketones can be prepared from methyl ketones and two different alcohols by using a sequential one-pot iridium- and rhodium-catalyzed process.*

Hydrogen borrowing is a powerful method for functional-group interconversion, which involves reversible changes in the oxidation state of the reacting partners. In essence, a catalyst alters the reactivity of a compound by removing two hydrogen atoms in a formal oxidation of the substrate. This temporarily generates a highly reactive intermediate and permits bond formation to take place. Finally, the intermediate is reduced with the redelivery of two hydrogen atoms, giving a product without a net change in the overall oxidation state.[1]

Since a discovery by Grigg et al., who used alcohols as alkylating reagents,[2] the transition-metal-catalyzed α-alkylation of carbonyl compounds using hydrogen borrowing has emerged as a productive area of research. Contributions from the groups of Cho/Shim,[3] Ishii,[4] Nishibayashi,[5] Ramón/Yus,[6] Park,[7] Uozumi,[8] Williams,[9] and others[10] have demonstrated variations of such alkylation reactions using different metal catalyst systems (Scheme 1 A).[11] These methods have allowed ketone alkylation with benzyl and long-chain *n*-alkyl alcohols (but with surprisingly few, if any, examples using short-chain alcohols such as methanol). Moreover, the scope of the ketone substrates is predominantly limited to methyl ketones with linear products being obtained after monoalkylation, whereafter the reaction stops.



Scheme 1. Different alkylation methods.

The formation of α-branched products from a more-substituted carbonyl starting material is much more challenging and restricted to a handful of examples (Scheme 1 B).[2g,3,4a,c,6b,7,9c]

Our research program seeks to overcome these problems, and we chose to investigate the possibility of performing a methylation at the α-position to a ketone using methanol as the alkylating reagent. We also wanted to address the formation of branched products (i.e., cause the formation of a stereogenic center) because a general procedure would represent an important and useful advance.

The use of methanol in catalytic alcohol dehydrogenation reactions is a worthwhile and challenging goal, with fundamental developments made by the groups of Beller[12] and Milstein[13] and demonstrated further with methanol by the groups of Tincado/Grützmacher[14] and Glorius.[15] However, methods that utilize methanol as an alkylating reagent with C–C bond formation (reported on $PhCH_2CN$[2e,16]) or as a substrate for formal C–H functionalization (such as the work by Krische et al.[17]) are extremely rare and represent an important area in need of development.

Herein, we report our findings on the synthesis of α-branched ketone products (Scheme 1 C). They are significant because 1) they provide a general solution to the problem of ketone methylation using methanol; 2) the conditions are mild and the catalyst commercially available; 3) the formation of α-branched products is now possible.

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Our initial reactions employed valerophenone in methanol, with various transition metal catalysts and Cs_2CO_3 as a base; early on we discovered the beneficial effect of performing reactions under an atmosphere of oxygen, which is unusual in the context of hydrogen-borrowing chemistry. Interestingly, we also found that the alkylation of valerophenone by methanol was observed at temperatures as low as 65 °C,[18] implying that methanol dehydrogenation was taking place under these relatively mild conditions.

Early experiments using catalytic amounts of $[\{Cp^*IrCl_2\}_2]$ or $[\{Cp^*RuCl_2\}_n]$ gave a mixture of the desired α-methylated ketone **2a**, dimer **3a**, enone **4a**, and β-methoxyketone **5a** (Table 1, entries 1,2). The product distribution shows that, along with consumption of the starting material **1a**, the conjugate reduction process was interrupted by the addition of nucleophiles to the enone **4a**. Thus, in an attempt to improve the yield of **2a**, we turned to using Rh, a well-known catalyst for 1,4-reduction.[19] When using 5 mol% of $[\{Cp^*RhCl_2\}_2]$, α-methylation could be accomplished in 98% yield (entry 3); the use of a stronger base such as KOH resulted in a higher amount of dimer **3a** formed (entry 4); $RhCl_3$ gave a mixture of unreduced intermediates (entry 5), whereas a respectable 74% yield of **2a** was achieved by using a mixture of $RhCl_3$ and added Cp* ligand (entry 6).[20] We were pleased to find that the reaction does not require the use of anhydrous methanol or extra precautions such as the exclusion of moisture, making this a highly practical method when compared to the traditional lithium–enolate alkylation methods.

When testing other Rh complexes, we found that Rh^I, Rh^{II}, and Rh^{III} complexes such as $RhCl_3/PPh_3$, $[RhCl(PPh_3)_3]$, and $[Rh_2(OAc)_4]$ gave small amounts of the desired product (entries 7–9). As a control experiment, the reaction was performed in the absence of the Rh catalyst and no product (**2a**) or intermediates were observed (entry 10). In reactions that were run under argon (entry 11), the yield of **2a** was acceptable but inferior to that shown earlier (entry 3). A further reaction with Cp*H as an additive, in the absence of $RhCl_3$, did not promote a reaction (entry 12).

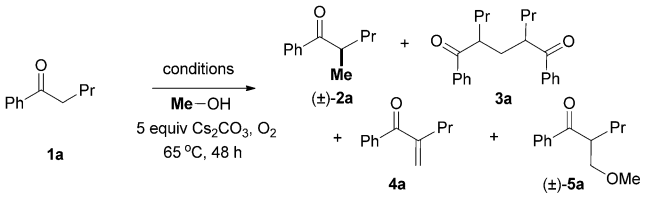
We turned our attention to explore the substrate scope of the methylation reaction (Table 2) and found that a ketone with a shorter ethyl sidechain gave the product (**2b**) in 73% yield. When varying the electronic properties of the aromatic ring, good to high yields were obtained with electron-rich (**2d**, **2h**, **2k**) and electron-poor (**2c**, **2e**, **2g**, **2i**, **2j**) rings and with heteroaromatic alkyl ketones (**2l**). We found that electron-poor substrates required a lower catalyst loading as well as shorter reaction times to achieve optimal yields. For example, **2i** was obtained in 73% yield with 2.5 mol% of $[\{Cp^*RhCl_2\}_2]$ after 2 h versus in only 41% yield with 5 mol% of $[\{Cp^*RhCl_2\}_2]$ after 4 h.[21] We think that this variation derives from 1,2-reduction of the carbonyl group in both starting ketone and product and leads to an undesired consumption of material. On the other hand, an electron-rich aniline substrate (**2h**) required portionwise catalyst addition and a longer reaction time to reach full conversion. Notably, halogen-substituted substrates (**2c**, **2e**, **2g**, **2j**) are tolerated under the reaction conditions.

Many products **2** were formed in good to excellent yields, significantly extending the scope of the reaction and showing that other primary alkyl chains were compatible with the methylation. Furthermore, the reaction was found to work well with β-substitution on the alkyl chains: high to excellent yields of the α-methylation products **2m**,**n** were obtained with KOH as a base. Unfortunately, a stereogenic center at the β-position did not induce diastereoselectivity under these reaction conditions.

We also investigated the methylation of alkyl/alkyl ketone substrates. As alkylation does not occur on secondary centers, site-selective alkylation was accomplished on α-*n*-alkyl-α′-dialkyl ketones in 81% and 49% yields for **2s** and **2u**, respectively. The lower yield obtained for **2u** may be due to the higher pK_a value of the dialkylketone versus the aryl–alkyl ketones. In this case, the slower reaction led to decomposition of both substrate and product under the reaction conditions. With double (α,α′) dimethylation reactions we obtained **2t** in 55% yield (74% yield per methylation), although no 1,3-diastereoselectivity was observed.

During our investigation, we noted that several of the starting ketones required multi-step synthesis, usually via the corresponding Weinreb amides. The wide commercial accessibility of many methyl ketones encouraged us to examine the double alkylation of these substrates (Scheme 2 A). Ketone **2k** was synthesized directly from the corresponding methyl ketone in 56% yield (i.e., 75% yield per methylation). Direct access to isopropyl ketones **2v** and **2w** from commercially

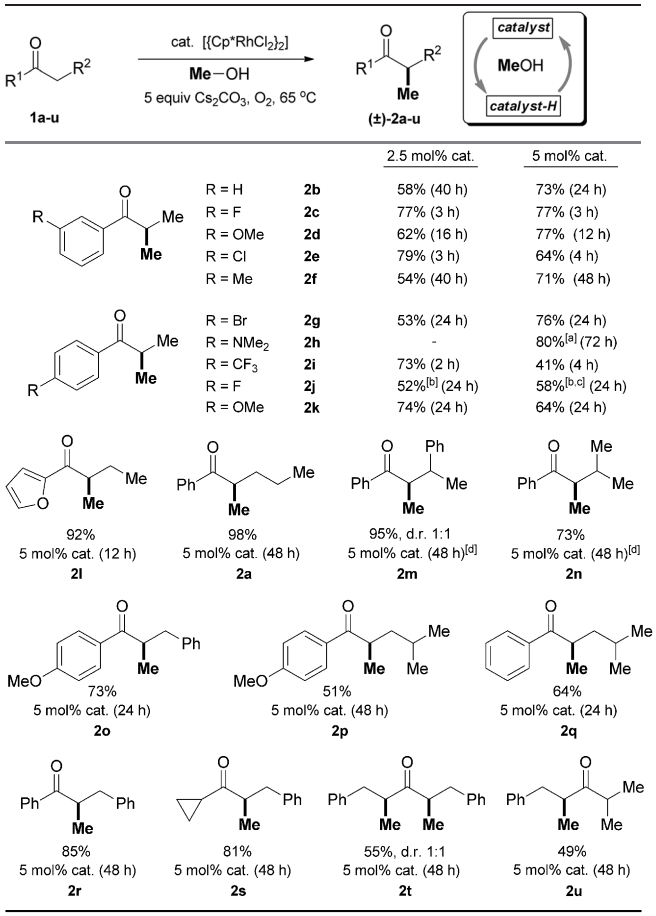
Table 1: Optimization of the α-methylation of ketone **1a** (0.2 M).[a]



Entry	Conditions	Yield [%] (±)-**2a**	**3a**	**4a**	(±)-**5a**
1	5 mol% $[\{Cp^*IrCl_2\}_2]$	42	12	14	27
2	10 mol% $[Cp^*RuCl_2]$	<2	19	23	39
3	**5 mol% $[\{Cp^*RhCl_2\}_2]$**	**98**	n/o	n/o	n/o
4[b]	5 mol% $[\{Cp^*RhCl_2\}_2]$	53	33	n/o	n/o
5	10 mol% $RhCl_3 \cdot H_2O$	14	10	18	30
6	10 mol% $RhCl_3 \cdot H_2O$, 10 mol% Cp*H	74	8	n/o	n/o
7	10 mol% $RhCl_3 \cdot H_2O$, 10 mol% PPh_3	15	12	27	44
8	10 mol% $[RhCl(PPh_3)_3]$	23	n/o	n/o	n/o
9	5 mol% $[Rh_2(OAc)_4]$	10	21	5	23
10	**no catalyst**	n/o (98)[c]	<5	n/o	n/o
11	5 mol% $[\{Cp^*RhCl_2\}_2]$, **argon**	57	9	n/o	n/o
12	10 mol% Cp*H	n/o (86)[c]	trace	n/o	n/o

[a] n/o = not observed. All yields given are of isolated material. Compound **3a** was isolated as a 1:1 mixture of diastereomers. [b] 5 equiv of KOH instead of Cs_2CO_3. [c] Yield of recovered starting material.

Table 2: Scope of the α-methylation of ketones; structures of the products formed. All yields are of isolated material and d.r. was determined from ^{1}H NMR spectroscopy of the crude reaction mixture.

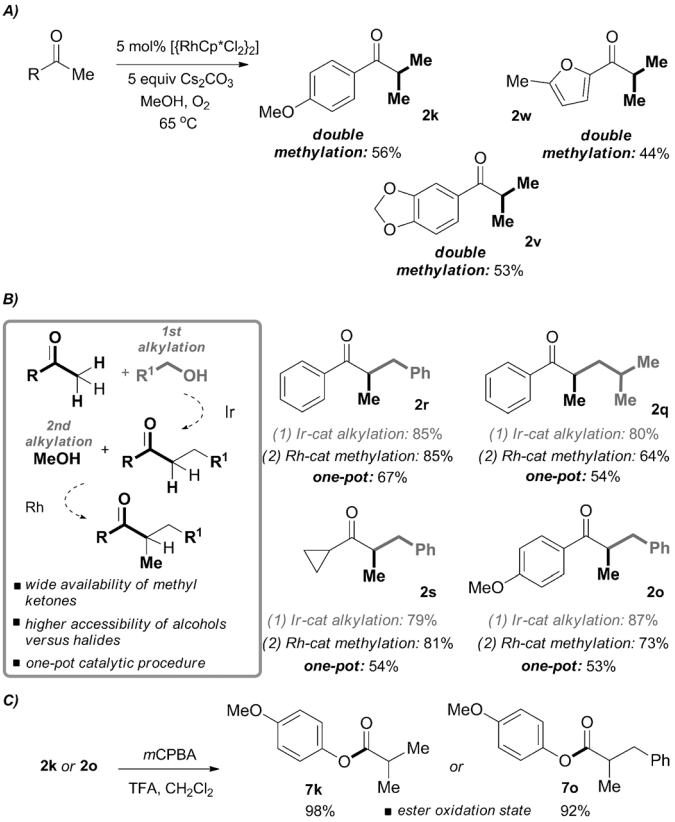


[a] [{Cp*RhCl$_2$}$_2$] (7.5 mol%) was added over 72 h in 3 portions. [b] 2 equiv of Cs_2CO_3 was used. [c] S_NAr product (**2k**) was also isolated in 21% yield. [d] 5 equiv of KOH was used as a base instead of Cs_2CO_3.

available material was achieved in 53% and 44% yields, respectively.

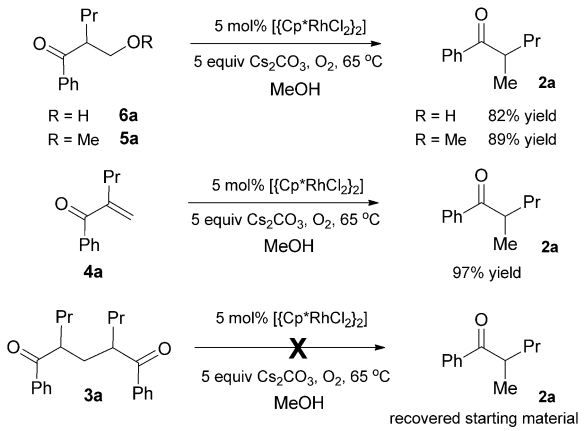
To extend this concept further, we examined the conditions for ketone alkylation reported by Ishii et al.[4a] and combined them with our methylation reaction in a one-pot procedure (Scheme 2B). This sequence further demonstrates the orthogonal reactivity between the new system and the existing alkylation methods which use hydrogen-borrowing chemistry (and which do not form branched products). We were able to perform the one-pot consecutive alkylation of methyl ketones using tandem alcohol alkylation reactions, firstly with a benzyl (**2r**, **2s**, **2o**) or primary alkyl alcohol (**2q**) and secondly with methanol. Once the first alkylation was complete (Ir catalysis; no over-alkylation observed), methanol, oxygen, Cs_2CO_3, and Rh catalyst were added directly to the reaction mixture without any solvent removal or purification.[5] Moderate to good yields of doubly alkylated products **2o,q,r,s** were obtained in this one-pot process (note that the overall yields are comparable to the multiples of the individual steps). We suggest that this double alkylation method holds considerable promise for the generation of complex carbonyl compounds from simple methyl ketone precursors.

It is important to expand the synthetic utility of the methylation reaction so that other alkylated carbonyl derivatives can be prepared. At this point we have only investigated the methylation of ketones, however, we were able to transform the products formed through this reaction into ester-derived products in a single, high-yielding step. Regioselective Baeyer–Villiger oxidation of **2k** and **2o** with *m*CPBA was accomplished in 98% and 92% yield, respectively (Scheme 2C), thus providing access to α-branched alkylated (and activated) esters (**7k**, **7o**).[4d]



Scheme 2. A) Rh-catalyzed double methylation. B) One-pot sequential Ir/Rh-catalyzed dialkylation; typical conditions: 1 mol% of [{IrCl(cod)}$_2$], KOH, Ph_3P, 1.2–5 equiv of alcohol, 100°C, 4 h; then 5 mol% of [{Cp*RhCl$_2$}$_2$], 5 equiv of Cs_2CO_3, MeOH, 65°C, O_2. In addition to the overall yields, those of the individual steps are given. C) Baeyer–Villiger oxidation.—See the Supporting Information for experimental details; structures of the products shown.

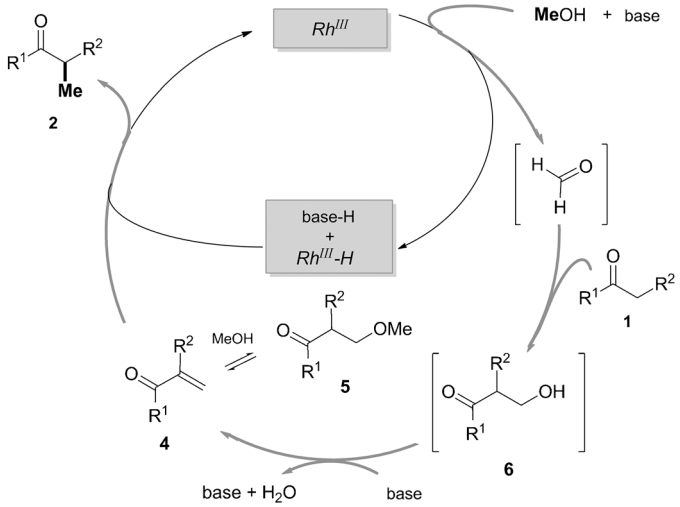
To provide insight into the reaction mechanism, we carried out a series of reactions whereby the proposed (and in some cases observed) intermediates were resubjected to the reaction conditions (Scheme 3). In every case but one, we found that these compounds were converted into the methylation product **2a**, providing evidence for their participation in a reaction sequence involving an aldol reaction with formaldehyde, elimination, and alkene reduction. However, when we used the reaction conditions on **3a** (which might derive from the conjugate addition of an enolate to enone



Scheme 3. Mechanistic experiments.

4a), we recovered only starting material, which suggests that **3a** is a dead-end that does not contribute to the formation of methylated product **2a**.

At this point, we interpret our results as shown below (Scheme 4). The key steps are methanol oxidation to formaldehyde, followed by an aldol reaction and elimination to form enone **4**. Reduction of the enone by hydride appears to be competitive with the addition of methanol, although we cannot rule out the formation of **5** directly from **1** and methanol through oxidation.



Scheme 4. A preliminary mechanistic interpretation of the results. The exact nature of the ligands on the active Rh catalyst is not currently known.[24]

Further investigation is required to elucidate the exact role of oxygen in this process, although we would draw attention to a report from Gabrielsson et al. who showed that methanol oxidation can be achieved under aerobic and mild conditions with an Ir catalyst.[22] One working hypothesis at this point is that the oxygen may reoxidize any Rh^{I} species formed by deprotonation (and elimination of a leaving group) of Rh^{III}–H, thus regenerating the active catalyst in situ, although other possibilities exist.[23]

Finally, it should be noted that the reactive and unhindered nature of formaldehyde as an electrophile may explain why this system is uniquely effective for making branched alkyl products, as only this particular electrophile is able to couple effectively with a substituted enolate under these conditions.

In conclusion, we have reported a method for the use of methanol as an alkylating reagent in a rhodium-catalyzed reaction. We found that an atmosphere of oxygen is beneficial to the yields of methylation and have shown that methanol oxidation could be achieved under remarkably mild conditions. The scope of this reaction includes aromatic and aliphatic ketones and consecutive one-pot double alkylation reactions provide a convenient route to branched ketones from simple methyl ketones. A brief study into the mechanism of the reaction has given evidence for an aldol-based reaction pathway.

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