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DMF as Carbon Source: Rh-Catalyzed α-Methylation of Ketones

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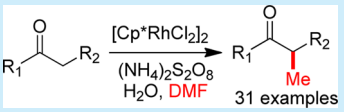
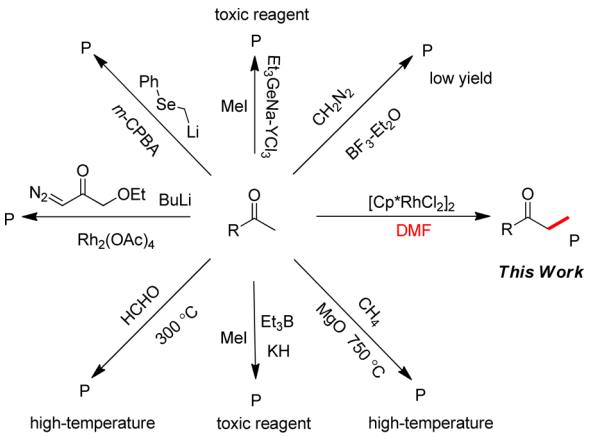
Supporting Information

ABSTRACT: An unprecedented Rh-catalyzed direct methylation of ketones with *N*,*N*-dimethylformamide (DMF) is disclosed. The reaction shows a broad substrate scope, tolerating both aryl and alkyl ketones with various substituents. Mechanistic studies suggest that DMF delivers a methylene fragment followed by a hydride in the methylation process.



Alkylation of ketones is a fundamental C−C bond formation reaction in organic synthesis. Traditionally, the coupling between nucleophilic enolates or enolate equivalents and electrophilic alkylating agents, such as alkyl halides, is the method of choice.[1] Methylation of ketones catalyzed by metals or under metal-free conditions has been investigated,[2] but these reactions suffer from such drawbacks as harsh reaction conditions or the use of toxic reagents (Scheme 1). In recent years, α-alkylation of ketones using alcohols[3] or amines[4] as electrophilic alkylating agents has been accomplished. However, no reports on methylation with these new methods have appeared thus far.

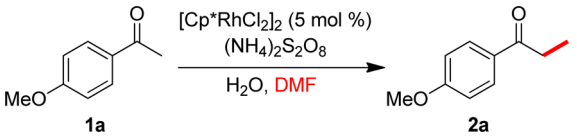
Scheme 1. Examples of α-Methylation of Ketones



DMF is generally used as a polar solvent in various reactions. Recently, the chemical transformation of DMF to multipurpose building blocks has drawn a great deal of attention.[5] Serving as reaction precursor, DMF has been used in a range of reactions,[6−11] such as formylation,[6] amination,[8] and cyanation.[10] To the best of our knowledge, however, the use of DMF as a methylating reagent in organic synthesis has not been reported until now. In continuing our research on the development of catalytic synthesis of ketones,[12] herein we report a highly effective method that allows the direct methylation of ketones with DMF under rhodium catalysis.

In an effort to functionalize ketones, we serendipitously found that *p*-methoxyacetophenone **1a** was converted into *p*-methoxypropiophenone **2a** in the presence of $(NH_4)_2S_2O_8$ and a catalytic quantity of $[Cp^*RhCl_2]_2$ at 110 °C in wet DMF (containing ∼0.5 equiv of water) (Table 1, entry 1). Subsequent optimization revealed that the amount of water present in the system affected the isolated yield, with the best yield obtained on addition of 4 equiv of water (Table 1, entries

Table 1. Optimization of Conditions for the Methylation of 1a[a]



1a 2a

entry	catalyst	oxidant	water (equiv)	yield[b] (%)
1	$[Cp^*RhCl_2]_2$	$(NH_4)_2S_2O_8$	0.5	22
2	$[Cp^*RhCl_2]_2$	$(NH_4)_2S_2O_8$	1	46
3	$[Cp^*RhCl_2]_2$	$(NH_4)_2S_2O_8$	2	49
4	$[Cp^*RhCl_2]_2$	$(NH_4)_2S_2O_8$	4	56
5	$[Cp^*RhCl_2]_2$	$(NH_4)_2S_2O_8$	5	37
6	$[Cp^*RhCl_2]_2$	$(NH_4)_2S_2O_8$	15	13
7	$[Cp^*RhCl_2]_2$	$(NH_4)_2S_2O_8$	28	0
8	$[Cp^*RhCl_2]_2$	$K_2S_2O_8$	4	20
9	$[Cp^*RhCl_2]_2$	$Na_2S_2O_8$	4	34
10	$[Cp^*RhCl_2]_2$	O_2 (balloon)	4	0
11	$[(p\text{-cymene})RuCl_2]_2$	$(NH_4)_2S_2O_8$	4	49
12	$[Cp^*IrCl_2]_2$	$(NH_4)_2S_2O_8$	4	46
13	$[Cp^*RhCl_2]_2$	$(NH_4)_2S_2O_8$	4	84[c]

[a]Reaction conditions: ketone (0.5 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), $(NH_4)_2S_2O_8$ (1.0 mmol), H_2O (0.25−14 mmol), DMF (2 mL), 110 °C, 3 h. [b]Isolated yield. [c]3 equiv of oxidant was used.

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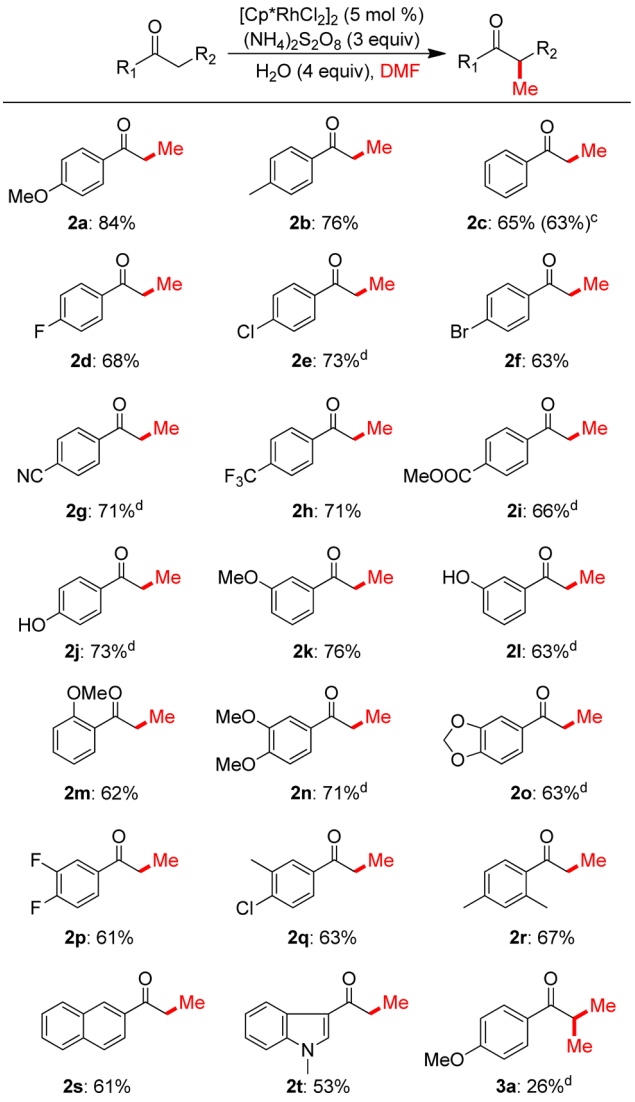
2−7). Control reactions showed that without $[Cp^*RhCl_2]_2$, $(NH_4)_2S_2O_8$, or water, no methylation took place. With other catalysts or oxidants, lower yields or no reaction resulted (Table 1, entries 9−12). By increasing the amount of $(NH_4)_2S_2O_8$ to 3 equiv, a satisfactory yield of 84% was achieved (Table 1, entry 13).

With the optimized conditions in hand, the α-methylation of a variety of aryl ketones with DMF was explored (Scheme 2).

Scheme 2. Rh-Catalyzed Methylation of Ketones[a,b]

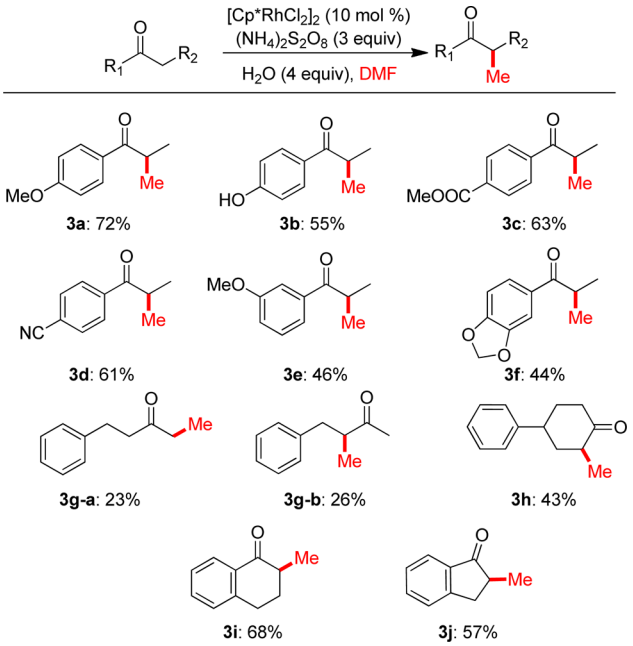


[a]Reaction conditions: ketone (0.5 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), $(NH_4)_2S_2O_8$ (1.5 mmol), H_2O (2 mmol), DMF (2 mL), 110 °C, 3 h. [b]Isolated yield is given below the product. [c]The number in parentheses refers to yield starting from *para*-iodide acetophenone. [d]10 mol % of catalyst.

Good yields were obtained for *para*-substituted aromatic ketones with both electron-rich and -deficient substituents (Scheme 2, **2a**−**2j**). In particular, aryl ketones bearing *p*-CN, *p*-COOMe, or *p*-OH groups are all viable substrates for the reaction, albeit requiring a higher catalyst loading in some cases (Scheme 2, **2g**, **2i**, **2j**). Halogen substituents are tolerated, except for the iodide (Scheme 2, **2c**−**2f**). In this case, dehalogenation took place, affording the same product as acetophenone (Scheme 2, **2c**). Substrates having *m*- or *o*-substituents also reacted with acceptable yields (Scheme 2, **2k**−**2m**). Disubstituted aromatic ketones were also tested, giving good yields (Scheme 2, **2n**−**2r**). The substrate scope could be extended to ketones with a naphthyl ring or indole heterocycle (Scheme 2, **2s**, **2t**). We even found that this method could afford dimethylation when we used *p*-methoxyacetophenone as substrate (Scheme 2, **3a**).

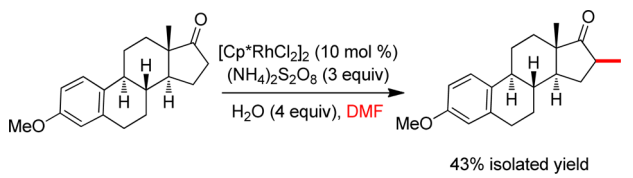
Sterically more hindered, α-substituted ketones are also suitable substrates, albeit necessitating a longer reaction time (Scheme 3). Thus, aryl propiophenones with both electron-rich and -deficient substituents on *p*- or *m*-positions all underwent the methylation, affording the α-branched ketones in moderate to good yields (Scheme 3, **3a**−**3f**). For a substrate with α-hydrogen on both sides of the carbonyl group, a mixture of methylation products was observed (Scheme 3, **3g**). Moderate to good yields were obtained for both aliphatic and aromatic cyclic ketones, such as tetralone and 1-indanone (Scheme 3, **3h**−**3j**). To test the viability of the method with more complex substrates, we applied the methylation to estrone 3-methyl ether, an estrogenic hormone. Under the standard reaction conditions, the C16-methylated product was isolated in 43% yield, showing the potential of the method in modifying natural products (Scheme 4).

Scheme 3. Rh-Catalyzed Methylation of α-Substituted Aryl Ketones[a]



[a]Reaction conditions: ketone (0.5 mmol), $[Cp^*RhCl_2]_2$ (10 mol %), $(NH_4)_2S_2O_8$ (1.5 mmol), H_2O (2 mmol), DMF (2 mL), 110 °C, 12 h. Isolated yield is given below the product.

Scheme 4. Methylation of Estrone 3-Methyl Ether with DMF



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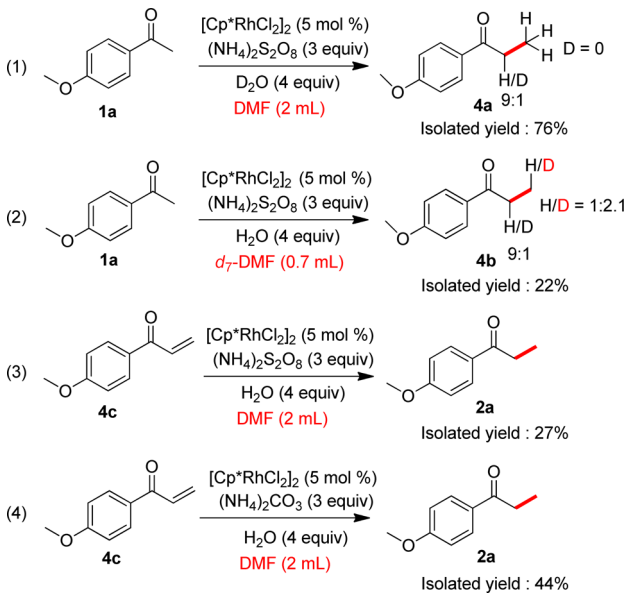
To gain insight into the mechanism of the reaction, deuterium labeling experiments were carried out. Replacing water with deuterium oxide did not affect significantly the product yield (Scheme 5, eq 1). H/D exchange was observed at

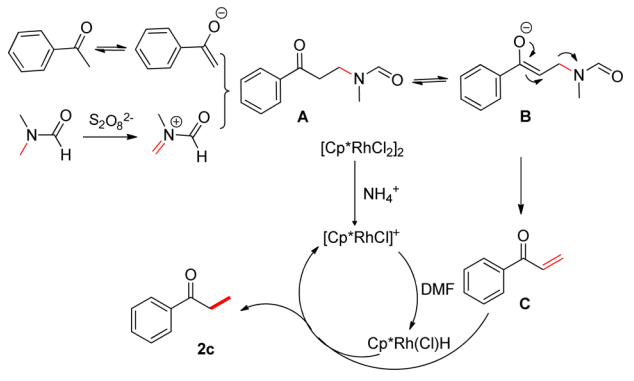
Scheme 5. Mechanistic Investigations



the α position of the carbonyl group, most likely due to a keto−enol tautomerism process.[13] No deuterium labeling was observed on the newly installed methyl group. However, when DMF was switched to DMF-d_7, the reaction became considerably slower (Scheme 5, eq 2). Most notably, on the newly formed methyl group, a H/D ratio of 1:2.1 was observed, suggesting that the new methyl group comes from DMF.

On the basis of these observations, a plausible reaction mechanism is suggested in Scheme 6. DMF is oxidized by the

Scheme 6. Plausible Mechanism



persulfate to form an iminium intermediate,[14] which is attacked by an enolate generated from the ketone to form an intermediate **A**. **A** could undergo a C−N bond cleavage through an intermediate **B**, leading to an unsaturated ketone intermediate **C**, a process which is known in the literature.[15] **C** is then reduced by a Rh−H complex, possibly generated from dehydrogenation of DMF by $[Cp^*RhCl_2]_2$, affording the methylated product **2c**, with the overall process transferring a methyl group from DMF to the ketone.[16]

To lend further support to this proposed mechanism, the α,β-unsaturated ketone **4c** was subjected to the standard reaction conditions. Reduction of the C=C double bond was indeed observed, albeit in a lower yield than using **1a** (eq 3). The reduction can also be effected by replacing $(NH_4)_2S_2O_8$ with $(NH_4)_2CO_3$ or Na_2CO_3 (Scheme 5, eq 4), showing that DMF is the reducing agent and the persulfate anion is not directly involved in the reduction. The role of $(NH_4)_2S_2O_8$ during the reduction step could be to help the dissociation of the chloride from Rh(III) via hydrogen bonding with its NH_4^+ ion.[17] However, $(NH_4)_2CO_3$ is not effective for the overall methylation reaction.

An interesting question is why $(NH_4)_2S_2O_8$ is indispensible for the reaction, given that the iminium intermediate required for the initial steps could also be generated from the Rh-catalyzed dehydrogenation step (Scheme 6). One possible explanation could be that the dehydrogenation of DMF and reduction of the iminiuim intermediate by the resulting Rh−H is reversible. Without an external oxidant, the iminium intermediate would be expected to be readily reduced by the Rh−H complex, thus competing with the olefin reduction. This also explains why a low yield was obtained for the reduction of **4c** (Scheme 5, eqs 3 and 4). Water may play multiple roles in the reaction, including promotion of the formation of the various ionic species and the dissolution of persulfate in DMF.

In conclusion, a novel method for the α-methylation of ketones with DMF as carbon source has been developed, providing a general, convenient way to access α-methylated ketones. Mechanistic studies indicate that both the oxidant and DMF play dual roles, with $(NH_4)_2S_2O_8$ oxidizing DMF and helping the dissociation of chloride from rhodium, while DMF acts as the carbon source for methylation and hydrogen source for the Rh-catalyzed reduction of the methylene into methyl.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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