Transition Metal Free $\alpha$-C-Alkylation of Ketones Using Secondary Alcohols

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ABSTRACT: A base-mediated $\alpha$-C-alkylation of ketones with secondary alcohols has been developed. This transition metal free approach employs KOt-Bu as the base and exhibits a broad scope, allowing a range of commodity aliphatic secondary alcohols and 1-arylethanols to be employed as alkylation agents. Aryl methyl ketones undergo selective mono-$\alpha$-C-alkylation in high isolated yields (23 examples, 65% average yield).

Alkylation is a fundamental transformation in synthetic chemistry that is routinely performed across the entire spectrum of chemical industries. Traditionally, hazardous alkyl (pseudo)halides are commonly employed for alkylation processes, which can result in non-selective transformations due to multiple alkylation, whilst generating stoichiometric waste products that must be separated from the target compound. As such, the development of selective alkylation methodologies that employ less toxic reagents, whilst generating benign by-products, is an important goal for improving sustainability within the synthetic community.

The borrowing hydrogen (BH) approach, which combines a transfer hydrogenation with a concurrent reaction on the in situ-generated reactive intermediate, enables commodity alcohols to be employed as alkylation agents, with water generated as the sole by-product. In comparison to primary alcohols, the use of secondary alcohols as alkylation agents in BH processes is considerably less developed, which may partly be attributed towards competing self-aldol processes (of the corresponding ketone). In this domain, several groups have reported catalytic systems for the efficient $N$-alkylation of amines using secondary alcohols. However, only sporadic examples of the $\alpha$-C-alkylation of ketones with secondary alcohols have been reported, presumably due to competing ketone self-condensation processes (Scheme 1A). A significant advance in this regard was disclosed by Donohoe and co-workers, who developed a general iridium-catalyzed approach employing Ph* (C8Mes)-substituted ketones (Scheme 1B). The Ph* group prevents ketone self-aldol processes and can be easily cleaved, via a retro-Friedel-Crafts acylation, to access a range of alternative carbonyl derivatives including esters and amides. Sundararaju, Renaud and Maji subsequently reported related approaches employing earth-abundant transition metal catalysts based cobalt, iron, and manganese, respectively.

Scheme 1. $\alpha$-C-Alkylation of ketones with secondary alcohols.

<table>
<thead>
<tr>
<th>A) $\alpha$-C-Alkylation of acetophenone using secondary alcohols</th>
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<tbody>
<tr>
<td>$\text{OCH}_3 + \text{H}_2\text{O} \rightarrow \text{H}_2\text{O} + \text{R}^2$</td>
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<tr>
<td>[TM] catalyst</td>
</tr>
<tr>
<td>NH</td>
</tr>
<tr>
<td>$\text{Ph}^* - \text{Me} + \text{R}^1$</td>
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<td>BH catalysis</td>
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- low yields and limited scope due to competing self-condensation processes

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<tr>
<th>B) $\alpha$-C-Alkylation of Ph*-substituted ketones using secondary alcohols</th>
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<tbody>
<tr>
<td>$\text{OCH}_3 + \text{H}_2\text{O} \rightarrow \text{H}_2\text{O} + \text{R}^2$</td>
</tr>
<tr>
<td>[TM] = [Ir]</td>
</tr>
<tr>
<td>3d TM cat.</td>
</tr>
<tr>
<td>base only</td>
</tr>
<tr>
<td>TM free (this work)</td>
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<tr>
<td>esters, amides etc.</td>
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Whilst investigating the use of alternative catalysts for this interesting and challenging transformation, control reactions revealed the presence of a significant base-mediated background reaction in the absence of any transition metal catalyst. To this end, herein we report the first base-mediated transition metal free $\alpha$-C-alkylation of ketones using commodity secondary alcohols as alkylation agents.

To commence our studies, we selected the $\alpha$-C-alkylation of commercially available ketone 1 with pentan-3-ol 2 (6 equiv.) as a model system (Table 1). It was found that treatment with KOt-Bu (3 equiv.) in xylene ([1] = 1 M) at 150 °C for 24 h, enabled the efficient and selective mono-$\alpha$-C-alkylation of ketone 1, providing alkylated product 3 in > 98% NMR yield (entry 1). Alternative alkoxide bases (NaOt-Bu or NaOt-Am) proved equally as effective whereas substitution of KOt-Bu for KOH or K2CO3 resulted in no observable formation of 3 (entries 2-5). Reducing the equivalents of alcohol (entries 6 and 7), lowering the reaction temperature (entry 8), or shortening the reaction time (entry 9), all resulted in decreased conversion to alkylated product 3. Pleasingly, it was found that the loading of KOt-Bu could be decreased to one equivalent without significant detriment to conversion (entries 10 and 11). Using one equivalent of KOt-Bu, the alkylated product 3 was formed in 91% NMR yield and isolated in 84% yield.

To obtain insight into the reaction mechanism, the $\alpha$-C-
alkylation of ketone 1 was performed using isopropanol-d₈ as the alkylating agent (Scheme 2A). Analysis of the alkylation product revealed 46% D, >95% D and 42% D incorporation at the α-, β-, and γ-positions, respectively. The H/D scrambling at both the α- and γ-positions result from carbonyl acid-base equilibria. Adventitious HzO and/or t-BuOH may account for the high % H incorporation at the α- and γ-positions. The >95% D recovery at the β-position provided supporting evidence for the MPV-type reduction of an enone intermediate. Furthermore, during reaction optimization studies, trace quantities of the secondary alcohol that would be generated via a MPV-type reduction of ketone 1 was observed, which supported the initial Oppenauer-type oxidation of secondary alcohol 2.12 In line with these observations, and previous related investigations,10,11 a plausible reaction mechanism would initiate with an Oppenauer-type alcohol oxidation followed by a selective cross-aldol condensation to form an enone intermediate (Scheme 2B). A subsequent Meerwein-Ponndorf-Verley (MPV)-type enone reduction would form the observed alkylation product.

With optimized reaction conditions in hand (Table 1, entry 10), the full scope of the base-mediated α-C-alkylation of ketones with secondary alcohols was explored (Scheme 3). Fixing pentan-3-ol 2 as the alkylating agent, a selection of aryl methyl ketones could be employed as the nucleophilic component to access the corresponding alkylation products in high isolated yields (Scheme 3A, products 3–9, 69% average yield). Within the aryl methyl ketone, sterically encumbered aryl units containing 2,6-substitution were required to prevent undesired ketone self-condensation processes. This requirement was illustrated by the complex mixture of unidentified products formed when the Ph* group was substituted with a 1-Np moiety (Scheme 3B). Within the aryl unit, other alkyl substitution to the incorporation of pyridyl, aryl bromide, and aniline moieties. Furthermore, a symmetrical diketone underwent bisalkylation to give product 9 in 74% isolated yield. Employing an aryl ethyl ketone as the nucleophile resulted in complete recovery of starting materials. Fixing ketone 1 as the nucleophile, a variety of secondary alcohols could be employed as the alkylating agent (Scheme 3C), accessing the corresponding alkylation products in high isolated yields (products 10–25, 63% average yield). A selection of both acyclic and cyclic aliphatic secondary alcohols were employed, including 4-(t-butyl)cyclohexan-1-ol, which gave product 13 with 86:14 d.r. and in 92% combined isolated yield. A selection of 1-arylethanols could also be employed as the alkylating agent, with a variety of heteroaryls incorporated into products 22-25 including pyridyl, furanyl and thiophenyl moieties. Starting materials were recovered when 1-indanol, 1,3-diphenylpropan-2-ol and diphenylmethanol were employed, which may be attributed towards increased steric hindrance. An attempted alkylation using pentane-2,4-diol also resulted in complete recovery of starting materials.

In conclusion, we have developed the first base-mediated transition metal free α-C-alkylation of ketones using secondary alcohols as the alkylating agent. Ketones undergo selective mono-α-C-alkylation with a variety of aliphatic secondary alcohols and 1-arylethanols in high isolated yields (23 examples, 65% average yield). It was proposed that the reaction proceeds via an Oppenauer-type alcohol oxidation followed by a selective cross-aldol condensation and Meerwein-Ponndorf-Verley (MPV)-type enone reduction. This base-mediated process offers an attractive and green alternative to existing transition metal-catalyzed borrowing hydrogen processes.

ASSOCIATED CONTENT
The Supporting Information is available free of charge. Optimization data, experimental procedures, characterization of new compounds and spectral data (PDF)

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Scheme 3. Scope of the base-mediated α-C-alkylation of ketones.

A) Ketone scope (7 examples), KOtBu (1 equiv.)

1. 84%
2. 62%
3. 52%
4. 78%
5. 78%
6. 57%
7. 52%

B) Incompatible ketones

complex mixture produced

starting materials recovered

C) Alcohol scope (16 examples), KOtBu (2 equiv.)

10. 74%
11. 71%
12. 85%
13. 92%, d.r. 86:14
14. n = 1, 52%
15. n = 2, 67%
16. n = 3, 55%
17. n = 4, 52%
18. n = 5, 88%
19. n = 9, 40%
20. 60%
21. 78%
22. 62%
23. 23%
24. 62%
25. 53%

D) Incompatible alcohols

starting materials recovered

starting materials recovered

Reactions performed using 0.5 mmol of ketone starting material and bench-grade xylenes. All yields are isolated yields after chromatographic purification. *As determined by 1H NMR analysis of the crude reaction mixture, major isomer shown.

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NOTES
The authors declare no competing financial interest.
Information about the data that underpins the results presented in this article, including how to access them, can be found in the Cardiff University data catalogue at http://doi.org/XXXX (accessed XXX).

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REFERENCES


13 In addition to the ketone 1, adventitious H$_2$O, KOH and t-BuOH.

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