Transition Metal Free α-*C*-Alkylation of Ketones Using Secondary Alcohols

Mubarak B. Dambatta, Joseph Santos, Robert R. A. Bolt, and Louis C. Morrill*

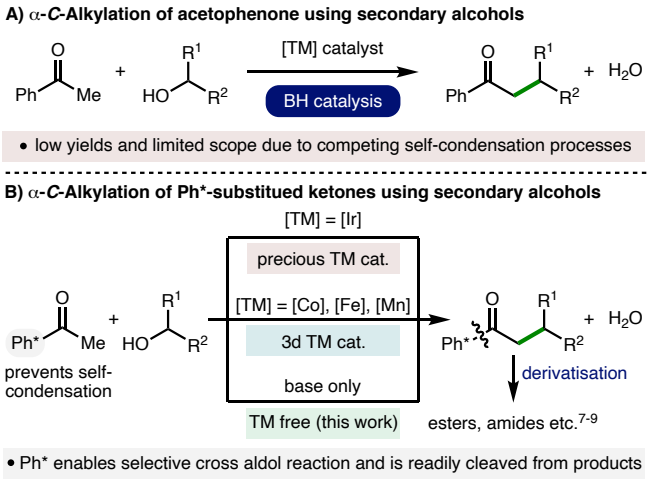
Cardiff Catalysis Institute, School of Chemistry, Cardiff University, Main Building, Park Place, Cardiff, CF10 3AT, U.K.

ABSTRACT: A base-mediated α-*C*-alkylation of ketones with secondary alcohols has been developed. This transition metal free approach employs KO*t*-Bu as the base and exhibits a broad scope, allowing a range of commodity aliphatic secondary alcohols and 1-arylethanols to be employed as alkylating agents. Aryl methyl ketones undergo selective mono-α-*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.[1] 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.[2] 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 alkylating agents, with water generated as the sole by-product.[3] In comparison to primary alcohols, the use of secondary alcohols as alkylating agents in BH processes is considerably less developed, which may partly be attributed towards competing self-aldol processes (of the corresponding ketone).[4] In this domain, several groups have reported catalytic systems for the efficient *N*-alkylation of amines using secondary alcohols.[5] However, only sporadic examples of the α-*C*-alkylation of ketones with secondary alcohols have been reported, presumably due to competing ketone self-condensation processes (Scheme 1A).[6] A significant advance in this regard was disclosed by Donohoe and co-workers, who developed a general iridium-catalyzed approach employing Ph* (C_6Me_5)-substituted ketones (Scheme 1B).[7] 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.[8] Sundararaju, Renaud and Maji subsequently reported related approaches employing earth-abundant transition metal catalysts based cobalt, iron, and manganese, respectively.[9]

Scheme 1. α-*C*-Alkylation of ketones with secondary alcohols.

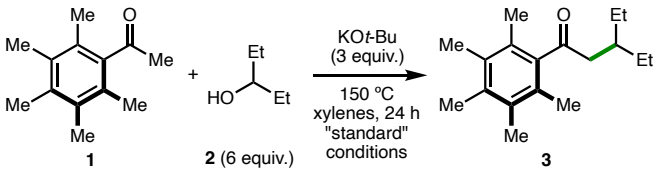


Whilst investigating the use of alternative catalysts for this interesting and challenging transformation, control reactions revealed the presence of a significant base-mediated background reaction in the absence of any transition metal catalyst.[10,11] To this end, herein we report the first base-mediated transition metal free α-*C*-alkylation of ketones using commodity secondary alcohols as alkylating agents.

To commence our studies, we selected the α-*C*-alkylation of commercially available ketone **1** with pentan-3-ol **2** (6 equiv.) as a model system (Table 1).[12] It was found that treatment with KO*t*-Bu (3 equiv.) in xylenes ([**1**] = 1 M) at 150 °C for 24 h, enabled the efficient and selective mono- α-*C*-alkylation of ketone **1**, providing alkylated product **3** in > 98% NMR yield (entry 1). Alternative alkoxide bases (NaO*t*-Bu or NaO*t*-Am) proved equally as effective whereas substitution of KO*t*-Bu for KOH or K_2CO_3 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 KO*t*-Bu could be decreased to one equivalent without significant detriment to conversion (entries 10 and 11). Using one equivalent of KO*t*-Bu, the alkylated product **3** was formed in 91% NMR yield and isolated in 84% yield.

To obtain insight into the reaction mechanism, the α-*C*-

Table 1. Optimization of the base-mediated α-*C*-alkylation of ketones.[a]



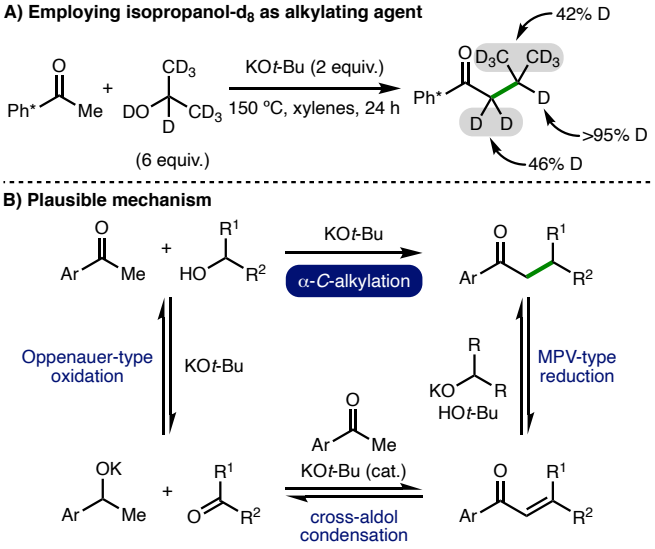
entry	variation from "standard" conditions	yield[b] (%)
1	none	> 98
2	NaO*t*-Bu (3 equiv.) instead of KO*t*-Bu	> 98
3	NaO*t*-Am (3 equiv.) instead of KO*t*-Bu	> 98
4	KOH (3 equiv.) instead of KO*t*-Bu	< 2
5	K_2CO_3 (3 equiv.) instead of KO*t*-Bu	< 2
6	**2** (4 equiv.)	77
7	**2** (2 equiv.)	17
8	130 °C	47
9	reaction time = 8 h	42
10	**KO*t*-Bu (1 equiv.)**	**91 (84)**
11	KO*t*-Bu (0.1 equiv.)	13

[a] Reactions performed using 0.5 mmol of ketone **1** and bench-grade xylenes. [**1**] = 1 M. [b] Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses.

alkylation of ketone **1** was performed using isopropanol-d_8 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 H_2O 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 alkylated 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 addition to the incorporation of

Scheme 2. Mechanistic considerations.



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 alkylated 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 hinderance. 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 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

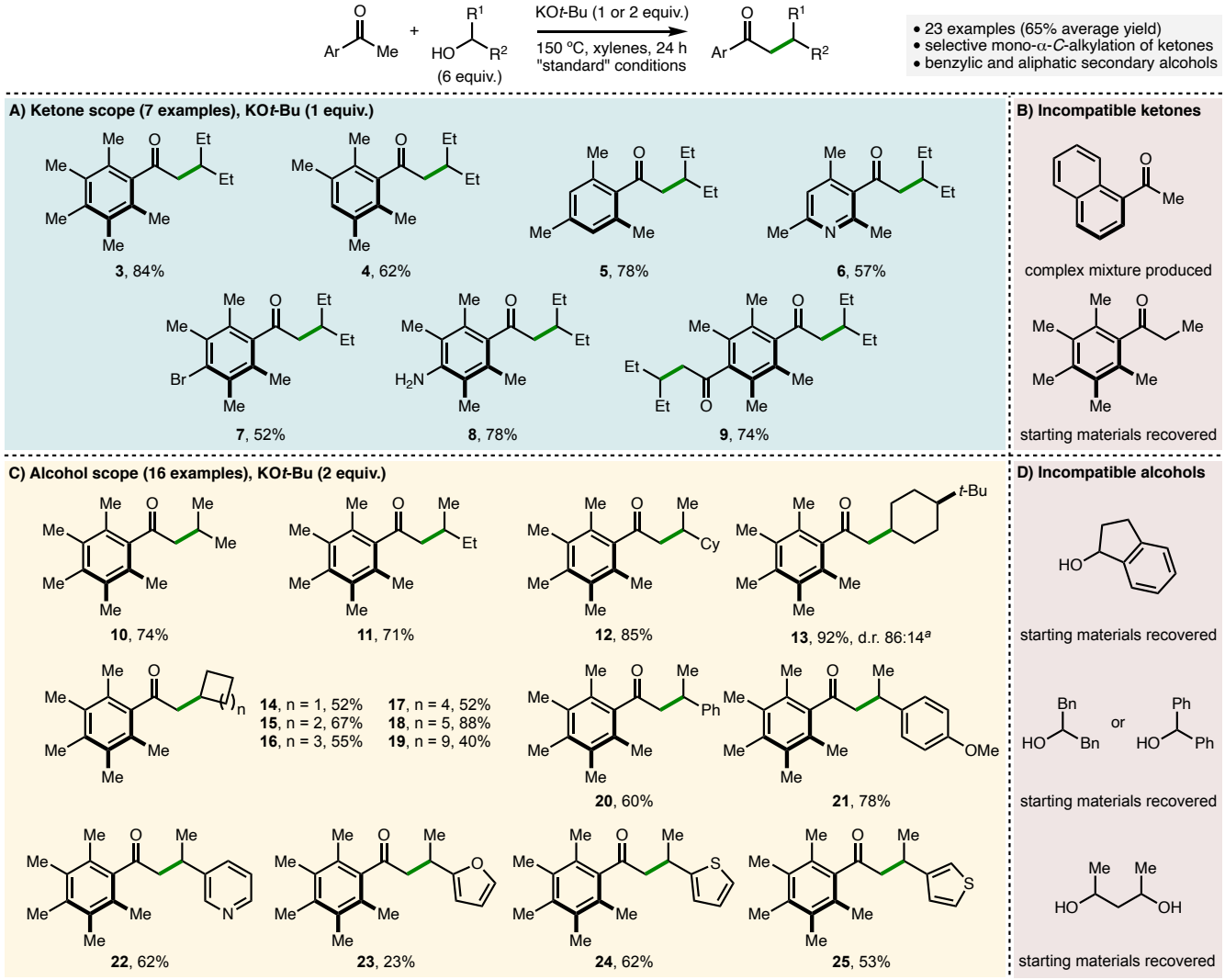
The Supporting Information is available free of charge. Optimization data, experimental procedures, characterization of new compounds and spectral data (PDF)

AUTHOR INFORMATION

Corresponding Authors

*E-mail: MorrillLC@cardiff.ac.uk

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



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

ORCID

Louis C. Morrill: 0000-0002-6453-7531

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 XXXX).

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12 See the Supporting Information for full experimental details.

13 In addition to the ketone **1**, adventitious H_2O, KOH and *t*-BuOH