Iron-Catalyzed Borrowing Hydrogen C-Alkylation of Oxindoles with Alcohols


A general and efficient iron-catalyzed C-alkylation of oxindoles has been developed. This borrowing hydrogen approach employing a (cyclopentadienone)iron carbonyl complex (2 mol %) exhibited a broad reaction scope, allowing benzylic and simple primary and secondary aliphatic alcohols to be employed as alkylating agents. A variety of oxindoles underwent selective mono-C3-alkylation in good-to-excellent isolated yields (28 examples, 50–92% yield, 79% average yield).

The oxindole framework is present in a diverse array of naturally occurring compounds.[1] Furthermore, oxindoles that are mono- or disubstituted at the C3 position are commonly employed in drug discovery programs,[2] with examples including the development of HIV-1 non-nucleoside reverse transcriptase inhibitors, spirocyclic compounds with anti-cancer and anti-inflammatory properties, and antagonists of progesterone and 5-hydroxytryptamine, (5-HT, ) receptors (Scheme 1A). The traditional method for alkylation of unprotected oxindoles employs toxic alkyl halides and exhibits poor selectivity (mono- vs. dialkylation, C- vs. N-alkylation) alongside the generation of stoichiometric quantities of undesired byproducts.[3] An alternative approach employs the borrowing hydrogen (BH) principle, also known as hydrogen autotransfer, which allows bench-stable and inexpensive alcohols to be used as alkylating agents, generating water as the sole byproduct.[4] Recent progress in this area has provided alternatives to commonly employed precious-metal catalysts through the development of catalysts based on earth-abundant first-row transition metals.[5]

However, with respect to earth-abundant first-row transition-metal catalysis, only sporadic examples appear in the literature, in each case forming only a minor component of a broader study.[6] As such, the development of a general catalytic BH C-alkylation of oxindoles with well-defined complexes based on earth-abundant first-row transition metals is required and would represent a valuable addition to the synthetic toolbox. To this end, herein we report the use of a bench-stable (cyclopentadieneone)iron(0) carbonyl complex (2 mol %) for the selective mono-C3-alkylation of various oxindoles with both benzylic and aliphatic alcohols (Scheme 1B).

To commence our studies, we selected the C3-benzylation of oxindole 2 with benzyl alcohol 1 (1.2 equiv) as a model system (Table 1). After extensive optimization,[7] it was found that a BH system composed of the bench-stable (cyclopentadieneone)iron(0) carbonyl complex 3 (2 mol %),[8] triphenylphosphine

Scheme 1. Oxindole importance and project overview.
(4 mol %) to form the active catalyst, and K$_2$CO$_3$ (0.5 equiv.) as base in xylenes (2) = 0.5 m) at 150 °C for 24 h enabled the efficient C-benzylation of 2, giving 4 in 97% yield based on $^1$H NMR spectroscopy and 90% isolated yield (entry 1). Importantly, only 1.2 equiv. of the alkylating agent and substituents at 150 °C for 24 h resulted in lower conversion to 4. Lowering the quantity of K$_2$CO$_3$ (entry 13) highlighted that catalytic quantities of base (10 mol %) can be employed, accessing 4 in 88% yield based on $^1$H NMR spectroscopy. Employing toluene as solvent (entry 14), increasing the reaction concentration (entry 15), lowering the reaction temperature (entry 16), reducing the reaction time (entry 17), or reducing the catalyst loading (entry 18) all lowered the efficiency of the iron-catalyzed mono-C3-benzylation of 2.

The full scope of the Fe-catalyzed BH C3-alkylation of oxindoles was explored, starting with the C-alkylation of oxindole 2 (Scheme 2 A, B). Under the optimized reaction conditions (Table 1, entry 1) a variety of substituted benzyl alcohol could be employed as alkylating agents, giving the corresponding mono-C3-alkylated oxindoles in excellent isolated yields (products 4 and 11–24, 52–91% yield). With regard to the alcohol, sterically encumbered aryl units such as o-tolyl and 1-naphthyl were tolerated in addition to electron-donating (4-OMe, 4-Obn) and electron-withdrawing (4-CF$_3$, 4-CN) substituents. The catalytic system exhibited chemoselectivity, tolerating the reducible nitrile and alkene moieties present within products 19 and 20. 4-Iodobenzyl alcohol was employed as the alkylating agent, incorporating an additional functional handle into oxindole 21 for subsequent elaboration through established cross-coupling methods. Furan-2-ylmethanol and thiophene-2-ylmethanol were both compatible with this methodology, incorporating an additional heterocycle into products 23 and 24, which were isolated in 77 and 84% yield, respectively. We were pleased to discover that less activated simple aliphatic alcohols could also be employed as alkylating agents in this process (products 25–31, 53–84% yield). In each case, the alcohol was used as solvent to obtain high isolated yields of the mono-C3-alkylated oxindoles. Under otherwise identical reaction conditions, decan-1-ol, butan-1-ol, ethanol, and methanol were all successfully utilized as alkylating agents. 1,4-Butanediol was also employed as the alkylating agent, accessing the mono-C3-alkylated oxindole 29 in 53% isolated yield, with no dialkylation products observed. Remarkably, it was found that the unactivated secondary alcohols propan-2-ol and butan-2-ol were also tolerated, giving alkylated oxindoles 30 and 31 in excellent isolated yields. This is a rare example of secondary alcohol compatibility as alkylating agents in BH catalysis employing earth-abundant first-row transition-metal catalysts. Unfortunately, despite examining a range of alternative reaction conditions, benzyl alcohols containing nitro or ketone functional groups, allylic alcohols, propargylic alcohols, and bulkier secondary alcohols (e.g., 1-phenylethanol-1-ol) were found to be incompatible with this C-alkylation procedure.

Next, we explored the scope of the reaction with respect to variation within the oxindole component (Scheme 2 C, 4). By employing the optimized reaction conditions (Table 1, entry 1) a variety of substituted oxindoles underwent efficient and selective mono-C3-alkylation with benzyl alcohol (products 32–37,
50–92% yield). Oxindoles containing halogen substitution at the 5-position (5-Br, 5-Cl, and 5-F) in addition to N-methyl, N-benzyl, and N-phenyl substitution were all well tolerated. Barbituric acids are a class of activated amides that have been shown to participate as competent nucleophiles in homogeneous BH alkylation processes employing precious-metal catalysts.\textsuperscript{19} By using the [Fe] precatalyst 3 (4 mol%), it was found that as election of N-alkyl barbituric acid derivatives underwent efficient C5-monoalkylation, giving products 38–42 in 50–75% isolated yield (Scheme 2D).

This iron-catalyzed process is the first example of a BH alkylation of barbituric acid derivatives employing an earth-abundant transition-metal catalyst. Unfortunately, piperdin-2-one and 1-tosylpiperdin-2-one were found to be incompatible with this protocol, with complex reaction mixtures obtained across a range of reaction conditions explored.

To obtain insights into the reaction mechanism, the \(\alpha,\beta\)-unsaturated amide 43 was synthesized and subjected to the “standard” C-alkylation reaction conditions, which produced 4 in 71% yield based on \(^1\)H NMR spectroscopy, indicating that 43 is a plausible reaction intermediate (Scheme 3A). In line with this observation and previous related investigations,\textsuperscript{11} a plausible reaction mechanism begins with CO decoordination of the [Fe] precatalyst 3 by PPh\(_3\) to form the active iron complex, which abstracts hydrogen from benzyl alcohol in the presence of base to form the required transient reactive benzaldehyde intermediate (Scheme 3B). Subsequent nucleophilic attack of oxindole 2 generates the \(\beta\)-hydroxy amide 44, which undergoes rapid base-catalyzed E1cB dehydration to form the \(\alpha,\beta\)-unsaturated amide 43. Finally, reduction of 43 by the iron-hydrogen complex gives the C3-alkylated product 4 with regeneration of the active iron complex.

In conclusion, we have developed a general and efficient Fe-catalyzed C-alkylation of oxindoles with benzylic and simple primary and secondary aliphatic alcohols as alkylating agents through the borrowing hydrogen approach. A variety of oxindoles underwent selective mono-C3-alkylation in excellent isolated yields (28 examples, 50–92% yield, 79% average yield). Ongoing studies are focused on further applications of earth-abundant first-row transition metals in catalysis, and these results will be reported in due course.\textsuperscript{20}
Scheme 3. Mechanistic considerations. [a] Yield after 24 h as determined by 1H NMR spectroscopy of the crude reaction mixture with 1,3,5-trimethylybenzene as the internal standard.

Acknowledgements

We gratefully acknowledge the School of Chemistry, Cardiff University for generous support, TETFund for a Ph.D. studentship (M.B.D.), the EPSRC-funded Bath/Bristol/Cardiff Catalysis Centre for Doctoral Training (K.P., EP/L016443/1), and the EPSRC UK National Mass Spectrometry Facility at Swansea University.

Conflict of interest

The authors declare no conflict of interest.

Keywords: alcohols · alkylation · borrowing hydrogen · iron catalysis · oxindoles
See the Supporting Information for full experimental details.

For an overview of the synthesis and reactivity of (cyclopentadienone)iron carbonyl complexes, see:


c) T. C. Johnson, G. J. Clarkson, M. Wills, Organometallics 2011, 30, 1859–1868;


No observable background reaction occurs in the absence of [Fe] pre-catalyst 3 under any of the reaction conditions employed in this study.

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 under: http://doi.org/10.17035/d.2019.0072633299 (accessed May 1, 2019).