

Iron-Catalyzed Borrowing Hydrogen β -C(sp³)-Methylation of Alcohols

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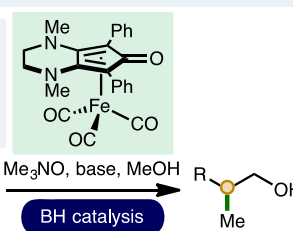
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S Supporting Information

ABSTRACT: Herein we report the iron-catalyzed β -C(sp³)-methylation of primary alcohols using methanol as a C1 building block. This borrowing hydrogen approach employs a well-defined bench-stable (cyclopentadienone)iron(0) carbonyl complex as precatalyst (5 mol %) and enables a diverse selection of substituted 2-arylethanol to undergo β -C(sp³)-methylation in good isolated yields (24 examples, 65% average yield).

- well-defined bench stable Fe(0) carbonyl complex
- most abundant transition metal in the Earth's crust
- β -C(sp³)-methylation
- operationally simple



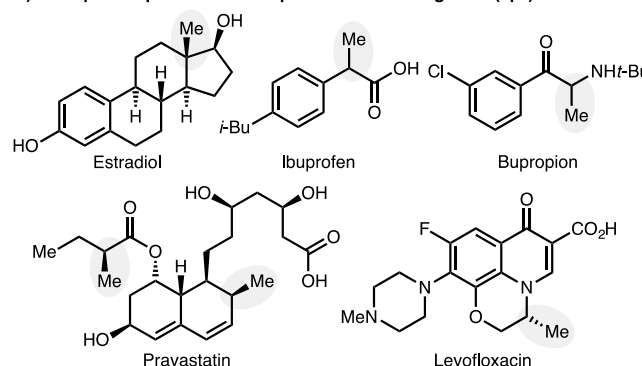
KEYWORDS: borrowing hydrogen, iron catalysis, methylation, methanol, homogeneous catalysis

The incorporation of methyl groups can have a significant impact upon the pharmacological properties of a molecule.¹ Inspection of Njardarson's poster entitled "Top 200 Brand Name Drugs by Prescription in 2016" reveals that a significant proportion contain the C(sp³)-Me motif (Scheme 1A).² As such, the development of new synthetic methods for the direct methylation of C(sp³)-H bonds is an important area of scientific endeavor.³ Methanol is an attractive reagent for methylation processes.⁴ It is an abundant, biodegradable liquid that is less hazardous relative to commonly employed methylation reagents such as diazomethane, dimethyl sulfate, and iodomethane.⁵

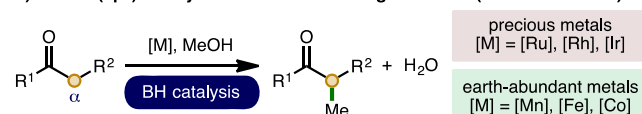
The borrowing hydrogen (BH) approach combines a transfer hydrogenation process with a concurrent reaction on the in situ generated reactive intermediate.⁶ Employing methanol in BH alkylation represents a challenging process, which is partly due to the increased energy of dehydrogenation of methanol to form the required transient reactive formaldehyde intermediate in relation to benzyl and longer chain *n*-alkyl alcohols (ΔH (MeOH) = +84 kJ mol⁻¹, cf. ΔH (EtOH) = +68 kJ mol⁻¹).⁷ Nevertheless, the BH approach has been utilized for the α -C(sp³)-methylation of ketones using methanol as the alkylating agent, employing both precious and earth-abundant metal catalysts (Scheme 1B).⁸ The use of methanol in the catalytic upgrading of ethanol and propanol to *iso*-butanol has been reported at very high temperatures (typically ≥ 180 °C).⁹ However, the general β -C(sp³)-methylation of functionalized alcohols using methanol remains underdeveloped.¹⁰ In 2014, Beller and co-workers reported a homogeneous catalytic system for this challenging process, which required a combination of two distinct ruthenium complexes, namely, Ru-MACHO and Shvo's complex, in addition to pressure release from the reaction vessel to obtain satisfactory conversion across a modest range of 2-arylethanol.^{10a,b} Subsequently, others have described the use

Scheme 1. C(sp³)-Me Motif and BH C(sp³)-Methylation

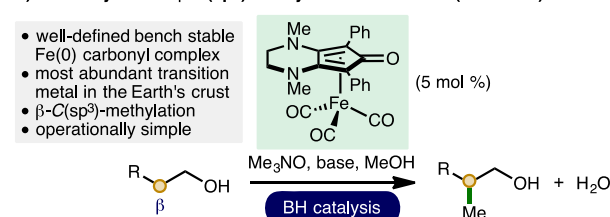
A) Examples of pharmaceutical products containing the C(sp³)-Me motif



B) BH α -C(sp³)-methylation of ketones using methanol (well established)



C) Fe-catalyzed BH β -C(sp³)-methylation of alcohols (this work)



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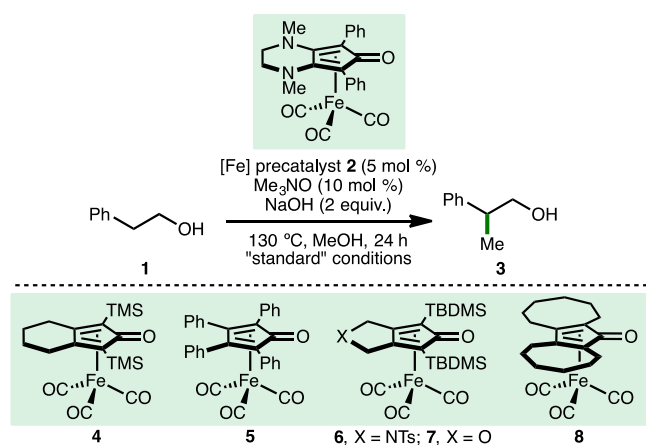
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of iridium nanoclusters^{10c,d} and Pt/C^{10e} as heterogeneous catalysts. Importantly, there are no reports to date that employ a homogeneous or heterogeneous catalyst system based on an earth-abundant first-row transition metal for this process. As part of our ongoing interest in the development of homogeneous hydrogen transfer methods,¹¹ herein we report the use of a well-defined bench-stable (cyclopentadienone)iron(0) carbonyl complex (5 mol %)¹² for the operationally simple and efficient catalytic β -C(sp³)-methylation of various primary alcohols using methanol as the alkylating agent (Scheme 1C).

To commence our studies, we selected the β -C(sp³)-methylation of 2-phenylethanol **1** as a model system (Table 1). After extensive optimization,¹³ it was found that a BH

Table 1. Optimization of Iron-Catalyzed β -C(sp³)-Methylation^a



entry	variation from "standard" conditions	yield ^b (%)
1	none	85 (75)
2	no [Fe] precatalyst	<2
3	no NaOH	<2
4	no Me ₃ NO	81
5	[Fe] precatalysts 4–8 (5 mol %) instead of 2	<2
6	K ₂ CO ₃ (2 equiv.) instead of NaOH	75
7	NaOH (20 mol %)	54
8	[1] = 0.25 M	57
9	[1] = 1 M	69
10	120 °C	64
11	140 °C	79
12	6 h	70
13 ^c	[Fe] precatalyst 2 (2 mol %)	62

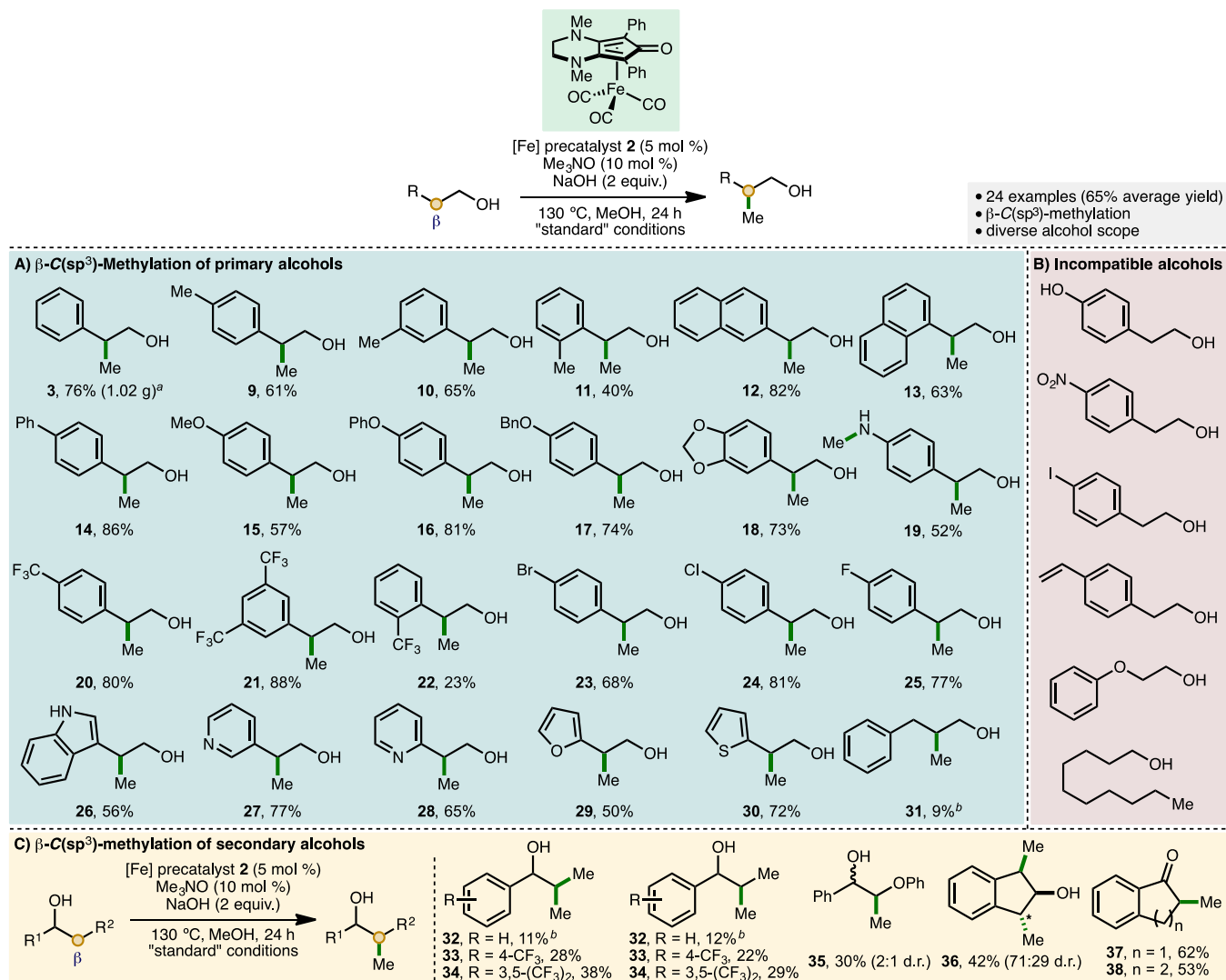
^aReactions performed using **1** (0.5 mmol) and reagent grade MeOH. [1] = 0.5 M. ^bAs determined by ¹H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses. ^cMe₃NO (4 mol %).

system composed of (cyclopentadienone)iron(0) carbonyl complex **2** (5 mol %),¹⁴ Me₃NO (10 mol %), and NaOH (2 equiv.) in MeOH ([1] = 0.5 M) at 130 °C for 24 h, enabled the efficient β -C(sp³)-methylation of **1**, giving **3** in 85% NMR yield and 75% isolated yield (entry 1). No alkylation occurred in the absence of iron precatalyst **2** or NaOH (entries 2 and 3). A small decrease in conversion is observed in the absence of Me₃NO (entry 4),¹⁵ which indicated that NaOH can also activate the precatalyst (Hieber's method).¹⁶ Interestingly, from the iron complexes employed in this study, it was found that (cyclopentadienone)iron carbonyl precatalyst **2**, which

contains a more electron-rich cyclopentadienone framework, was uniquely effective for the desired transformation, with the use of alternative iron precatalysts **4–8** resulting in no observable formation of methylated alcohol **3** (entry 5).¹⁷ Employing K₂CO₃ as base or reducing the quantity of NaOH to 20 mol % resulted in lower conversion to **3** (entries 6 and 7). Furthermore, altering the reaction concentration (entries 8 and 9), reaction temperature (entries 10 and 11), reducing reaction time (entry 12), or reducing the catalyst loading (entry 13), all lowered the efficiency of the β -C(sp³)-methylation of **1**. Employing ethanol as solvent using otherwise standard reaction conditions resulted in 80% recovered **1** with no conversion to any identifiable products. However, when benzyl alcohol was employed as solvent, 38% conversion to the β -C(sp³)-benzylated product was observed.

With optimized reaction conditions in hand (Table 1, entry 1), the full scope of the iron-catalyzed BH β -C(sp³)-methylation of alcohols was explored (Scheme 2).¹⁸ Gratifyingly, a diverse selection of substituted 2-arylethanol underwent efficient β -C(sp³)-methylation, giving the corresponding methylated products in good to excellent isolated yields (products **3** and **9–30**). Within the aryl unit, 4-Me, 3-Me, and 2-Me substitution was tolerated in addition to extended aromatic systems (2-Np and 1-Np). However, the attenuated yields obtained for products **11** and **22** (40% and 23%, respectively) indicated that the increased steric encumbrance provided by aryl substitution at the 2-position hindered β -C(sp³)-methylation. Electron-donating aryl substituents (4-OMe, 4-OPh and 4-OBn) were tolerated in addition to an acetal-protected catechol motif (products **15–18**). Interestingly, when 2-(4-aminophenyl)ethan-1-ol was subjected to the optimized reaction conditions, both β -C(sp³)-methylation and *N*-methylation occurred,¹⁹ providing **19** in 52% isolated yield. Substrates containing electron-withdrawing (4-CF₃ and 3,5-(CF₃)₂) aromatic substituents performed particularly well, giving products **20** and **21** in 80% and 88% isolated yields, respectively. The high yields obtained using these substrates may be attributed toward the increased acidity of the in situ generated aldehyde intermediates. Halogen incorporation within the substrate was accommodated, with 2-(4-bromophenyl)ethan-1-ol successfully employed to provide an additional functional handle within product **23** for subsequent elaboration via established cross-coupling methods. Furthermore, a variety of 2-heteroarylethanol underwent β -C(sp³)-methylation, including alcohols containing pyridyl, furan, thiophene, and unprotected indole motifs (products **26–30**). The β -C(sp³)-methylation procedure performs well upon scale-up, with the formation of **3** successfully carried out on a 10 mmol scale in 76% isolated yield (1.02 g of product). Lengthening the carbon chain proved challenging, with 3-phenylpropan-1-ol being converted to product **31** in only 9% NMR yield. The requirement of a β -aryl group for high conversion was attributed toward the increased acidity of the corresponding in situ-generated aldehyde intermediate. Despite examining a range of alternative reaction conditions 4-OH, 4-NO₂, 4-I, and 4-vinyl aryl substitution were not tolerated, producing a complex mixture of unidentified products in each case (Scheme 2B). 2-Phenoxyethan-1-ol and decan-1-ol were unreactive, with starting materials returned.

Next, we explored the β -C(sp³)-methylation of secondary alcohols. Guided by our success with 2-arylethanol substrates, the previously optimized reaction conditions (Table 1, entry 1)

Scheme 2. Scope of Iron-Catalyzed β -C(sp³)-Methylation^S

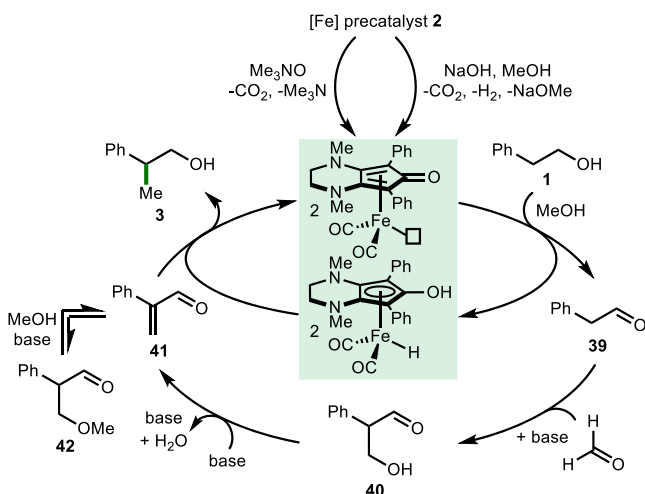
^SReactions performed using 0.5 mmol of alcohol starting material and synthesis grade MeOH. All yields are isolated yields after chromatographic purification. ^aTen mmol of alcohol starting material. ^bAs determined by ¹H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard.

were employed using 1-phenylethan-1-ol as substrate, giving an encouraging 11% conversion to dimethylated product **32**.

Unfortunately, despite reoptimization efforts, this figure could not be increased, although isolated yields of 28% and 38% were obtained for products **33** and **34**, respectively, which contain electron-withdrawing aryl substitution. The same trend was observed for β -C(sp³)-monomethylation using 1-arylpropan-1-ol substrates. Pleasingly, 30% isolated yield was obtained for product **35**, whereas double β -C(sp³)-methylation of 2,3-dihydro-1*H*-inden-2-ol produced **36** in 42% isolated yield as a 71:29 mixture of separable diastereoisomers. For the majority of secondary alcohols examined, ¹H NMR analysis of the crude reaction mixtures revealed the presence of α -C(sp³)-methylated ketones. This observation was particularly evident in the formation of α -C(sp³)-methylated cyclic ketones **37** and **38** in 62% and 53% isolated yields, respectively. As such, the lower conversions observed for secondary alcohols is likely due to the inability of the iron–hydrogen complex species to efficiently reduce the ketone functionality.

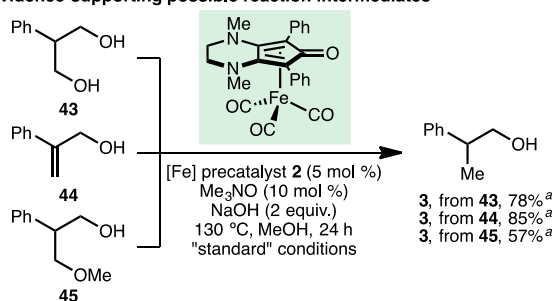
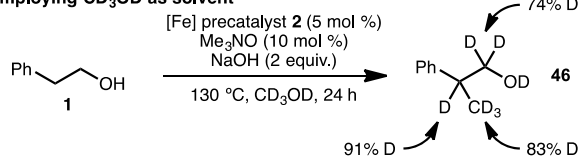
The proposed mechanism begins with CO decooordination of [Fe] precatalyst **2** by Me₃NO to form the active iron complex (**Scheme 3**).¹⁵ However, based upon our observation that catalysis can proceed in the absence of Me₃NO (**Table 1**, entry 4), precatalyst activation may also proceed via addition of hydroxide to a CO ligand followed by loss of CO₂ (Hieber's method) and subsequent loss of H₂ upon reaction with methanol.¹⁶ The active iron complex can then abstract hydrogen from 2-phenylethanol **1** and methanol to form the required transient 2-phenylacetaldehyde **39** and formaldehyde intermediates. A subsequent Aldol reaction generates β -hydroxy aldehyde **40** that undergoes base-catalyzed dehydration to form enal **41**, which may exist in equilibrium with methyl ether **42**. Finally, global reduction of enal **41** by the iron–hydrogen complex gives β -C(sp³)-methylated product **3** with regeneration of the active iron complex. To obtain supporting evidence for the proposed reaction mechanism, the validity of several plausible reaction intermediates was probed (**Scheme 4A**). Diol **43**, allylic alcohol **44**, and methyl ether **45** could be formed via hydrogenation of **40**, **41**, and **42**,

Scheme 3. Proposed Reaction Mechanism



Scheme 4. Mechanistic Experiments

A) Evidence supporting possible reaction intermediates

B) Employing CD₃OD as solvent

^aAs determined by ¹H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard.

respectively. Subjecting these compounds to the “standard” reaction conditions resulted in formation of β -C(sp³)-methylated product **3** in all cases, which indicated that compounds **40–45** are all plausible reaction intermediates. The conversion profile over time was studied for the β -C(sp³)-methylation of alcohol **1**.¹³ It was found that product **3** initially formed quickly, with 44% and 72% conversion to **3** observed after 1 and 2 h, respectively. Beyond 2 h, the conversion to **3** slowed down and steadily increased to 80% after 24 h. No aldehyde intermediates were observed, which indicated that they are short-lived and undergo rapid hydrogenation to the corresponding alcohols. To gain further mechanistic insight, CD₃OD was employed as the solvent under otherwise standard reaction conditions (Scheme 4B). This introduced a β -CD₃ group within alcohol product **46** in addition to significant deuterium incorporation at the α - and β -positions, which confirmed methanol as the methylating agent and provided support for the proposed iron hydride species and the borrowing hydrogen mechanism (cf. Scheme 3).

In conclusion, we have developed an operationally simple and efficient iron-catalyzed β -C(sp³)-methylation of primary

alcohols using methanol as a C1 building block via the borrowing hydrogen approach. This is the first report that employs a catalyst system based on an earth-abundant first-row transition metal for this process. A diverse selection of substituted 2-arylethanol underwent β -C(sp³)-methylation in good to excellent isolated yields (24 examples, 65% average yield). Some encouraging preliminary results were also obtained for the β -C(sp³)-methylation of secondary alcohols, which will be the subject of further investigation from our laboratory.

■ ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.9b02461.

Optimization data, experimental procedures, characterization of new compounds, and spectral data (PDF)

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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/10.17035/d.2019.0082983146>.

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