ACS Catalysis

Letter

Cite This: ACS Catal. 2019, 9, 8575–8580

pubs.acs.org/acscatalysis

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

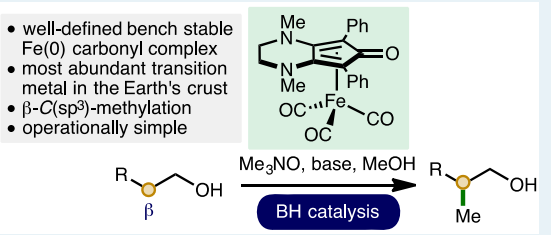
Kurt Polidano,[†] Jonathan M. J. Williams,[‡] and Louis C. Morrill*[,†]

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

[‡]Department of Chemistry, University of Bath, Claverton Down, Bath, BA2 7AY, U.K.

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-arylethanols to undergo β-C(sp³)-methylation in good isolated yields (24 examples, 65% average yield).

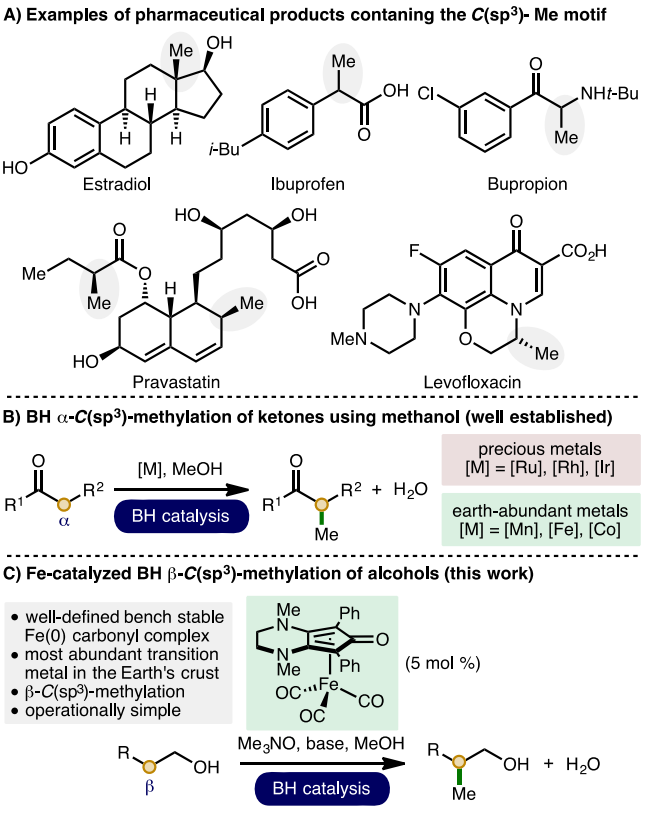


KEYWORDS: *borrowing hydrogen, iron catalysis, methylation, methanol, homogeneous catalysis*

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 (Δ*H* (MeOH) = +84 kJ mol^{-1}, cf. Δ*H* (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-arylethanols.[10a,b] Subsequently, others have described the use

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



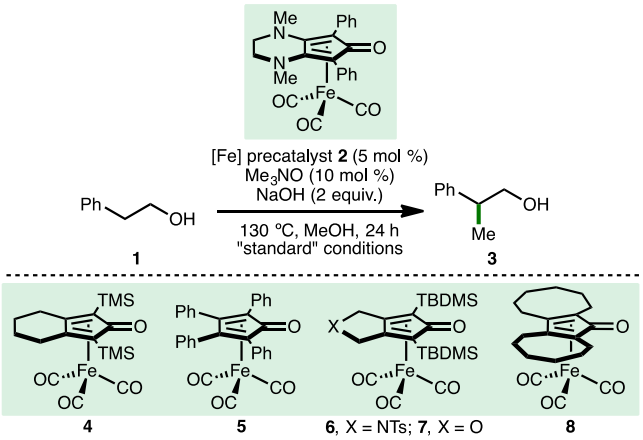
Received: June 12, 2019
Revised: July 30, 2019

DOI: 10.1021/acscatal.9b02461
ACS Catal. 2019, 9, 8575−8580

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-$C(sp^3)$-methylation of various primary alcohols using methanol as the alkylating agent (Scheme 1C).

To commence our studies, we selected the β-$C(sp^3)$-methylation of 2-phenylethanol **1** as a model system (Table 1). After extensive optimization,[13] it was found that a BH system composed of (cyclopentadienone)iron(0) carbonyl complex **2** (5 mol %),[14] Me_3NO (10 mol %), and NaOH (2 equiv.) in MeOH ([**1**] = 0.5 M) at 130 °C for 24 h, enabled the efficient β-$C(sp^3)$-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 Me_3NO (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 K_2CO_3 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-$C(sp^3)$-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-$C(sp^3)$-benzylated product was observed.

Table 1. Optimization of Iron-Catalyzed β-$C(sp^3)$-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_3NO	81
5	[Fe] precatalysts **4**–**8** (5 mol %) instead of **2**	<2
6	K_2CO_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

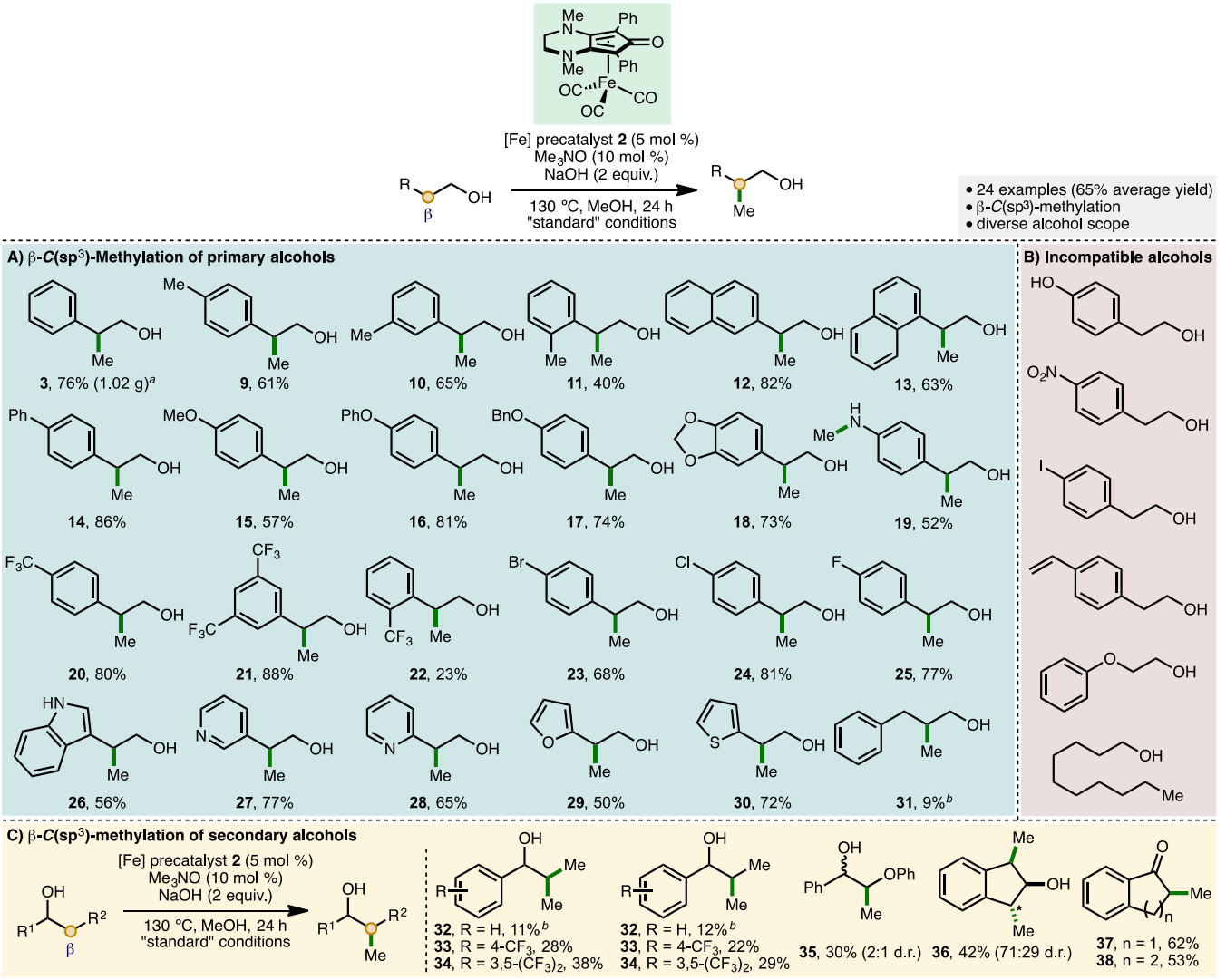
[a]Reactions performed using **1** (0.5 mmol) and reagent grade MeOH. [**1**] = 0.5 M. [b]As determined by ^1H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses. [c]Me_3NO (4 mol %).

With optimized reaction conditions in hand (Table 1, entry 1), the full scope of the iron-catalyzed BH β-$C(sp^3)$-methylation of alcohols was explored (Scheme 2).[18] Gratifyingly, a diverse selection of substituted 2-arylethanols underwent efficient β-$C(sp^3)$-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-$C(sp^3)$-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-$C(sp^3)$-methylation and *N*-methylation occurred,[19] providing **19** in 52% isolated yield. Substrates containing electron-withdrawing (4-CF_3 and 3,5-$(CF_3)_2$) 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-heteroarylethanols underwent β-$C(sp^3)$-methylation, including alcohols containing pyridyl, furan, thiophene, and unprotected indole motifs (products **26**-**30**). The β-$C(sp^3)$-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-NO_2, 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-$C(sp^3)$-methylation of secondary alcohols. Guided by our success with 2-arylethanol substrates, the previously optimized reaction conditions (Table 1, entry 1)

DOI: 10.1021/acscatal.9b02461
ACS Catal. 2019, 9, 8575–8580

Scheme 2. Scope of Iron-Catalyzed β-$C(sp^3)$-Methylation[§]



[§]Reactions performed using 0.5 mmol of alcohol starting material and synthesis grade MeOH. All yields are isolated yields after chromatographic purification. [a]Ten mmol of alcohol starting material. [b]As determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard.

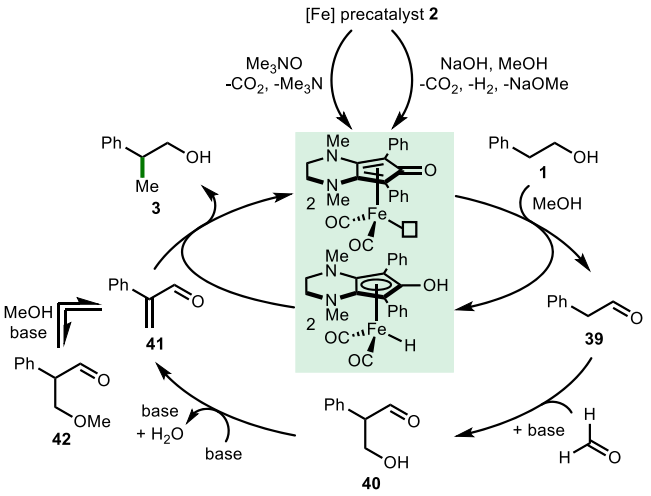
were employed using 1-phenylethan-1-ol as substrate, giving an encouraging 11% conversion to dimethylated product **32**.

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-$C(sp^3)$-monomethylation using 1-arylpropan-1-ol substrates. Pleasingly, 30% isolated yield was obtained for product **35**, whereas double β-$C(sp^3)$-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, ^{1}H NMR analysis of the crude reaction mixtures revealed the presence of α-$C(sp^3)$-methylated ketones. This observation was particularly evident in the formation of α-$C(sp^3)$-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.

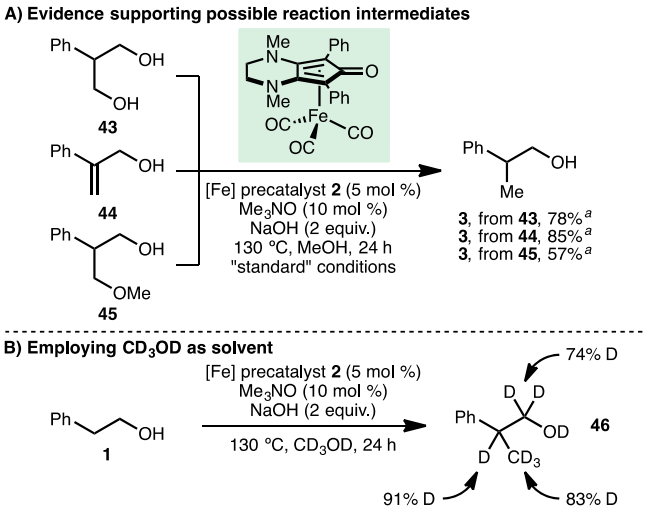
The proposed mechanism begins with CO decoordination of [Fe] precatalyst **2** by Me_3NO to form the active iron complex (Scheme 3).[15] However, based upon our observation that catalysis can proceed in the absence of Me_3NO (Table 1, entry 4), precatalyst activation may also proceed via addition of hydroxide to a CO ligand followed by loss of CO_2 (Hieber's method) and subsequent loss of H_2 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-$C(sp^3)$-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**,

DOI: 10.1021/acscatal.9b02461
ACS Catal. 2019, 9, 8575−8580

Scheme 3. Proposed Reaction Mechanism



Scheme 4. Mechanistic Experiments



[a]As determined by ^{1}H 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-$C(sp^3)$-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-$C(sp^3)$-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, CD_3OD was employed as the solvent under otherwise standard reaction conditions (Scheme 4B). This introduced a β-CD_3 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-$C(sp^3)$-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-arylethanols underwent β-$C(sp^3)$-methylation in good to excellent isolated yields (24 examples, 65% average yield). Some encouraging preliminary results were also obtained for the β-$C(sp^3)$-methylation of secondary alcohols, which will be the subject of further investigation from our laboratory.

■ ASSOCIATED CONTENT

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)

■ AUTHOR INFORMATION

Corresponding Author

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

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/10.17035/d.2019.0082983146.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the School of Chemistry, Cardiff University for generous support, 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.

■ REFERENCES

(1) (a) Bazzini, P.; Wermuth, C. G. *The Practice of Medicinal Chemistry*; John Wiley & Sons, Inc.: New York, 1980; pp 393–418. (b) Barreiro, E. J.; Kümmerle, A. E.; Fraga, C. A. M. The Methylation Effect in Medicinal Chemistry. *Chem. Rev.* **2011**, *111*, 5215–5246.

(2) McGrath, N. A.; Brichacek, M.; Njardarson, J. T. A Graphical Journey of Innovative Organic Architectures That Have Improved Our Lives. *J. Chem. Educ.* **2010**, *87*, 1348–1349.

(3) Schönherr, H.; Cernak, T. Profound Methyl Effects in Drug Discovery and a Call for New C–H Methylation Reactions. *Angew. Chem., Int. Ed.* **2013**, *52*, 12256–12267.

(4) (a) Olah, G. A. Towards Oil Independence Through Renewable Methanol Chemistry. *Angew. Chem., Int. Ed.* **2013**, *52*, 104–107. (b) Sam, B.; Breit, B.; Krische, M. J. Paraformaldehyde and Methanol as C1 Feedstocks in Metal-Catalyzed C-C Couplings of πUnsaturated Reactants: Beyond Hydroformylation. *Angew. Chem., Int. Ed.* **2015**, *54*, 3267–3274. (c) Natte, K.; Neumann, H.; Beller, M.; Jagadeesh, R. V. Transition-Metal-Catalyzed Utilization of Methanol as a C1 Source in Organic Synthesis. *Angew. Chem., Int. Ed.* **2017**, *56*, 6384–6394. (d) Chen, Y. Recent Advances in Methylation: A Guide for Selecting Methylation Reagents. *Chem. - Eur. J.* **2019**, *25*, 3405–3439.

(5) (a) Lamoureaux, G.; Agüero, C. A comparison of several modern alkylating agents. *ARKIVOC* **2009**, 251–264. (b) Szekely, G.; Amores de Sousa, M. C.; Gil, M.; Castelo Ferreira, F.; Heggie, W. Genotoxic Impurities in Pharmaceutical Manufacturing: Sources, Regulations, and Mitigation. *Chem. Rev.* **2015**, *115*, 8182–8229.

DOI: 10.1021/acscatal.9b02461
ACS Catal. 2019, 9, 8575–8580

(6) For selected recent reviews, see: (a) Corma, A.; Navas, J.; Sabater, M. J. Advances in One-Pot Synthesis through Borrowing Hydrogen Catalysis. *Chem. Rev.* **2018**, *118*, 1410−1459. (b) Reed-Berendt, B. G.; Polidano, K.; Morrill, L. C. Recent Advances in Homogeneous Borrowing Hydrogen Catalysis using Earth-Abundant First Row Transition Metals. *Org. Biomol. Chem.* **2019**, *17*, 1595−1607. (c) Irrgang, T.; Kempe, R. 3d-Metal Catalyzed N- and C-Alkylation Reactions via Hydrogen or Hydrogen Autotransfer. *Chem. Rev.* **2019**, *119*, 2524−2549.

(7) (a) Qian, M.; Liauw, M. A.; Emig, G. Formaldehyde synthesis from methanol over silver catalysts. *Appl. Catal., A* **2003**, *238*, 211−222. (b) Lin, W.-H.; Chang, H.-F. A study of ethanol dehydrogenation reaction in a palladium membrane reactor. *Catal. Today* **2004**, *97*, 181−188.

(8) (a) Chan, L. K. M.; Poole, D. L.; Shen, D.; Healy, M. P.; Donohoe, T. J. Rhodium-Catalyzed Ketone Methylation Using Methanol Under Mild Conditions: Formation of α-Branched Products. *Angew. Chem., Int. Ed.* **2014**, *53*, 761−765. (b) Ogawa, S.; Obora, Y. Iridium-catalyzed selective α-methylation of ketones with methanol. *Chem. Commun.* **2014**, *50*, 2491−2493. (c) Shen, D.; Poole, D. L.; Shotton, C. C.; Kornahrens, A. F.; Healy, M. P.; Donohoe, T. J. Hydrogen-Borrowing and Interrupted-Hydrogen-Borrowing Reactions of Ketones and Methanol Catalyzed by Iridium. *Angew. Chem., Int. Ed.* **2015**, *54*, 1642−1645. (d) Quan, X.; Kerdphon, S.; Andersson, P. G. C-C Coupling of Ketones with Methanol Catalyzed by a N-Heterocyclic Carbene-Phosphine Iridium Complex. *Chem. - Eur. J.* **2015**, *21*, 3576−3579. (e) Dang, T. T.; Seayad, A. M. A Convenient Ruthenium-Catalysed α-Methylation of Carbonyl Compounds using Methanol. *Adv. Synth. Catal.* **2016**, *358*, 3373−3380. (f) Chakrabarti, K.; Maji, M.; Panja, D.; Paul, B.; Shee, S.; Kanti Das, G.; Kundu, S. Utilization of MeOH as a C1 Building Block in Tandem Three-Component Coupling Reaction. *Org. Lett.* **2017**, *19*, 4750−4753. (g) Liu, Z.; Yang, Z.; Yu, X.; Zhang, H.; Yu, B.; Zhao, Y.; Liu, Z. Methylation of C(sp3)-H/C(sp2)-H Bonds with Methanol Catalyzed by Cobalt System. *Org. Lett.* **2017**, *19*, 5228−5231. (h) Polidano, K.; Allen, B. D. W.; Williams, J. M. J; Morrill, L. C. Iron-Catalyzed Methylation Using the Borrowing Hydrogen Approach. *ACS Catal.* **2018**, *8*, 6440−6445. (i) Deng, D.; Hu, B.; Yang, M.; Chen, D. Methylation of Amines and Ketones with Methanol Catalyzed by an Iridium Complex Bearing a 2-Hydroxypyridylmethylene Fragment. *Organometallics* **2018**, *37*, 3353−3359. (j) Sklyaruk, J.; Borghs, J. C.; El-Sepelgy, O.; Rueping, M. Catalytic C_1 Alkylation with Methanol and Isotope-Labeled Methanol. *Angew. Chem., Int. Ed.* **2019**, *58*, 775. (k) Bruneau-Voisine, A.; Pallova, L.; Bastin, S.; César, V.; Sortais, J.-B. Manganese catalysed α-methylation of ketones with methanol as a C1 source. *Chem. Commun.* **2019**, *55*, 314−317. (l) Bettoni, L.; Seck, C.; Mbaye, M. D.; Gaillard, S.; Renaud, J.-L. Iron-Catalyzed Tandem Three-Component Alkylation: Access to a-Methylated Substituted Ketones. *Org. Lett.* **2019**, *21*, 3057−3061.

(9) (a) Ueda, W.; Kuwabara, T.; Ohshida, T.; Morikawa, Y. A Low-pressure Guerbet Reaction over Magnesium Oxide Catalyst. *J. Chem. Soc., Chem. Commun.* **1990**, 1558−1559. (b) Carlini, C.; Di Girolamo, M.; Macinai, A.; Marchionna, M.; Noviello, M.; Galletti, A. M. R.; Sbrana, G. Selective synthesis of isobutanol by means of the Guerbet reaction Part 2. Reaction of methanol/ethanol and methanol/ethanol/*n*-propanol mixtures over copper based/MeONa catalytic systems. *J. Mol. Catal. A: Chem.* **2003**, *204−205*, 721−728. (c) Liu, Q.; Xu, G.; Wang, X.; Mu, X. Selective upgrading of ethanol with methanol in water for the production of improved biofuel-isobutanol. *Green Chem.* **2016**, *18*, 2811−2818. (d) Wingad, R. L.; Bergström; Everett, M.; Pellow, K. J.; Wass, D. W. Catalytic conversion of methanol/ethanol to isobutanol − a highly selective route to an advanced biofuel. *Chem. Commun.* **2016**, *52*, 5202−5204. (e) Pellow, K. J.; Wingad, R. L.; Wass, D. F. Towards the upgrading of fermentation broths to advanced biofuels: a water tolerant catalyst for the conversion of ethanol to isobutanol. *Catal. Sci. Technol.* **2017**, *7*, 5128−5134. (f) Newland, R. J.; Wyatt, M. F.; Wingad, R. L.; Mansell, S. M. A ruthenium(ii) bis(phosphinophosphinine) complex as a precatalyst for transfer-hydrogenation and hydrogen-borrowing reactions. *Dalton Trans.* **2017**, *46*, 6172−6176. (g) Newland, R. J.; Delve, M. P.; Wingad, R. L.; Mansell, S. M. Two isomers of a bis(diphenylphosphino)-phosphinine, and the synthesis and reactivity of Ru arene/Cp* phosphinophosphinine complexes. *New J. Chem.* **2018**, *42*, 19625−19636. (h) Liu, Y.; Shao, Z.; Wang, Y.; Xu, L.; Yu, Z.; Liu, Q. Manganese-Catalyzed Selective Upgrading of Ethanol with Methanol into Isobutanol. *ChemSusChem* **2019**, *12*, 3069−3072.

(10) (a) Li, Y.; Li, H.; Junge, H.; Beller, M. Selective ruthenium-catalyzed methylation of 2-arylethanols using methanol as C1 feedstock. *Chem. Commun.* **2014**, *50*, 14991−14994. During the submission of this manuscript, a related homogeneous ruthenium-catalyzed process was reported: (b) Kaithal, A.; Schmitz, M.; Hölscher, M.; Leitner, W. Ruthenium(II)-Catalyzed β-Methylation of Alcohols Using Methanol as C1 Source. *ChemCatChem* **2019**, DOI: 10.1002/cctc.201900788. (c) Oikawa, K.; Itoh, S.; Yano, H.; Kawasaki, H.; Obora, Y. Preparation and use of DMF-stabilized iridium nanoclusters as methylation catalysts using methanol as the C1 source. *Chem. Commun.* **2017**, *53*, 1080−1083. (d) Liu, Q.; Xu, G.; Wang, Z.; Liu, X.; Wang, X.; Dong, L.; Mu, X.; Liu, H. Iridium Clusters Encapsulated in Carbon Nanospeheres as Nanocatalysts for Methylation of (Bio)Alcohols. *ChemSusChem* **2017**, *10*, 4748−4755. (e) Siddiki, S. M. A. H.; Touchy, A. S.; Jamil, Md. A. R.; Toyao, T.; Shimizu, K.-i. *C*-Methylation of Alcohols, Ketones, and Indoles with Methanol Using Heterogenous Platinum Catalysis. *ACS Catal.* **2018**, *8*, 3091−3103.

(11) (a) Polidano, K.; Reed-Berendt, B. G.; Basset, A.; Watson, A. J. A.; Williams, J. M. J.; Morrill, L. C. Exploring Tandem Ruthenium-Catalyzed Hydrogen Transfer and S_NAr Chemistry. *Org. Lett.* **2017**, *19*, 6716−6719. (b) Khan, I.; Reed-Berendt, B. G.; Melen, R. L.; Morrill, L. C. FLP-Catalyzed Transfer Hydrogenation of Silyl Enol Ethers. *Angew. Chem., Int. Ed.* **2018**, *57*, 12356−12359. (c) Reed-Berendt, B. G.; Morrill, L. C. Manganese-Catalyzed N-Alkylation of Sulfonamides Using Alcohols. *J. Org. Chem.* **2019**, *84*, 3715−3724. (d) Dambatta, M. B.; Polidano, K.; Northey, A. D.; Williams, J. M. J.; Morrill, L. C. Iron-Catalyzed Borrowing Hydrogen C-Alkylation of Oxindoles Using Alcohols. *ChemSusChem* **2019**, *12*, 2345−2349.

(12) For selected examples of iron-catalyzed borrowing hydrogen processes, see: (a) Cui, X.; Shi, F.; Zhang, Y.; Deng, Y. Fe(II)-catalyzed *N*-alkylation of sulphonamides with benzlic alcohols. *Tetrahedron Lett.* **2010**, *51*, 2048−2051. (b) Bala, M.; Verma, P. K.; Sharma, U.; Kumar, N.; Singh, B. Iron phthalocanine as an efficient and versatile catalyst for *N*-alkylation of heterocyclic amines with alcohols: one-pot synthesis of 2-substituted benzimidazoles, benzothiazoles and benzoxazoles. *Green Chem.* **2013**, *15*, 1687−1693. (c) Quintard, A.; Constantieux, T.; Rodriguez, J. An Iron/Amine-Catalyzed Cascade Process for the Enantioselective Functionalization of Allylic Alcohols. *Angew. Chem., Int. Ed.* **2013**, *52*, 12883−12887. (d) Yan, T.; Feringa, B. L.; Barta, K. Iron catalysed direct alkylation of amines with alcohols. *Nat. Commun.* **2014**, *5*, 5602. (e) Rawlings, A. J.; Diorazio, L. J.; Wills, M. C-N Bond Formation between Alcohols and Amines Using an Iron Cyclopentadienone Catalyst. *Org. Lett.* **2015**, *17*, 1086−1089. (f) Pan, H.-J.; Wei Ng, T.; Zhao, Y. Iron-catalyzed amination of alcohols assisted by Lewis acid. *Chem. Commun.* **2015**, *51*, 11907−11910. (g) Elangovan, S.; Sortais, J. B.; Beller, M.; Darcel, C. Iron-Catalyzed α-Alkylation of Ketones with Alcohols. *Angew. Chem., Int. Ed.* **2015**, *54*, 14483−14486. (h) Emayavaramban, B.; Sen, M.; Sundararaju, B. Iron-Catalyzed Sustainable Synthesis of Pyrrole. *Org. Lett.* **2017**, *19*, 6−9. (i) Yan, T.; Barta, K. Sustainable Pathways to Pyrroles through Iron-Catalyzed *N*-Heterocyclization from Unsaturated Diols and Primary Amines. *ChemSusChem* **2016**, *9*, 2321−2325. (j) Mastalir, M.; Glatz, M.; Gorgas, N.; Stöger, B.; Pittenauer, E.; Allmaier, G.; Veiros, L. F.; Kirchner, K. Divergent Coupling of Alcohols and Amines Catalyzed by Isoelectronic Hydride Mn^{I} and Fe^{II} PNP Pincer Complexes. *Chem. - Eur. J.* **2016**, *22*, 12316−12320. (k) Di Gregorio, G.; Mari, M.; Bartoccini, F.; Piersanti, G. Iron-Catalyzed Direct C3-Benzylation of Indoles with Benzyl Alcohols through Borrowing Hydrogen. *J. Org. Chem.* **2017**, *82*, 8769−8775. (l) Vayer, M.; Morcillo, S. P.; Dupont,

DOI: 10.1021/acscatal.9b02461
ACS Catal. 2019, 9, 8575−8580

J.; Gandon, V.; Bour, C. Iron-Catalyzed Reductive Ethylation of Imines with Ethanol. *Angew. Chem., Int. Ed.* **2018**, *57*, 3228−3232. (m) Ma, W.; Cui, S.; Sun, H.; Tang, W.; Xue, D.; Li, C.; Fan, J.; Xiao, J.; Wang, C. Iron-Catalyzed Alkylation of Nitriles with Alcohols. *Chem.—Eur. J.* **2018**, *24*, 1311813123. (n) Lichosyt, D.; Zhang, Y.; Hurej, K.; Dydio, P. Dual-Catalytic transition metal systems for functionalization of unreactive sites of molecules. *Nat. Catal.* **2019**, *2*, 114−122.

(13) See the Supporting Information for full experimental details.

(14) (a) Thai, T.-T.; Mérel, D. S.; Poater, A.; Gaillard, S.; Renaud, J.-L. Highly Active Phosphine-Free Bifunctional Iron Complex for Hydrogenation of Bicarbonate and Reductive Amination. *Chem. - Eur. J.* **2015**, *21*, 7066−7070. (b) Seck, C.; Diagne Mbaye, M.; Coufourier, S.; Lator, A.; Lohier, J.-F.; Poater, A.; Ward, T. R.; Gaillard, S.; Renaud, J.-L. Alkylation of Ketones Catalyzed by Bifunctional Iron Complexes: From Mechanistic Understanding to Application. *ChemCatChem* **2017**, *9*, 4410−4416. (c) Lator, A.; Gaillard, S.; Poater, A.; Renaud, J.-L. Well-Defined Phosphine-Free Iron-Catalyzed *N*-Ethylation and *N*-Methylation of Amines with Ethanol and Methanol. *Org. Lett.* **2018**, *20*, 5985−5990. (d) Seck, C.; Diagne Mbaye, M.; Gaillard, S.; Renaud, J.-L. Bifunctional Iron Complexes Catalyzed Alkylation of Indoles. *Adv. Synth. Catal.* **2018**, *360*, 4640−4645.

(15) (a) Luh, T.-Y. Trimethylamine N-oxide−a versatile reagent for organometallic chemistry. *Coord. Chem. Rev.* **1984**, *60*, 255−276. (b) Moyer, S. A.; Funk, T. Air-stable iron catalyse for the Oppenauertype oxidation of alcohols. *Tetrahedron Lett.* **2010**, *51*, 5430−5433. (c) Johnson, T. C.; Clarkson, G. J.; Wills, M. (Cyclopentadienone) iron Shvo Complexes: Synthesis and Applications to Hydrogen Transfer Reactions. *Organometallics* **2011**, *30*, 1859−1868. (d) Plank, T. N.; Drake, J. L.; Kim, D. K.; Funk, T. W. Air-Stable, Nitrile-Ligated (Cyclopentadienone)iron Dicarbonyl Compounds as Transfer Reduction and Oxidation Catalysts. *Adv. Synth. Catal.* **2012**, *354*, 597−601.

(16) Knölker, H.-J.; Baum, E.; Goesmann, H.; Klauss, R. Demetalation of Tricarbonyl-(cyclopentadienone)iron Complexes Initiated by a Ligand Exchange Reaction with NaOH-X-Ray Analysis of a Complex with Nearly Square-Planar Coordinated Sodium. *Angew. Chem., Int. Ed.* **1999**, *38*, 2064−2066.

(17) For an overview of the synthesis and reactivity of (cyclopentadienone)iron carbonyl complexes, see: (a) Quintard, A.; Rodriguez, J. Iron Cyclopentadienone Complexes: Discovery, Properties, and Catalytic Reactivity. *Angew. Chem., Int. Ed.* **2014**, *53*, 4044−4055. For early applications in catalysis, see: (b) Casey, C. P.; Guan, H. An Efficient and Chemoselective Iron Catalyst for the Hydrogenation of Ketones. *J. Am. Chem. Soc.* **2007**, *129*, 5816−5817. (c) Casey, C. P.; Guan, H. Cyclopentadienone Iron Alcohol Complexes: Synthesis, Reactivity, and Implications for the Mechanism of Iron-Catalyzed Hydrogenation of Aldehydes. *J. Am. Chem. Soc.* **2009**, *131*, 2499−2507. (d) Casey, C. P.; Guan, H. Trimethylsilyl-Substituted Hydroxycyclopentadienyl Ruthenium Hydrides as Benchmarks To Probe Ligand and Metal Effects on the Reactivity of Shvo Type Complexes. *Organometallics* **2012**, *31*, 2631−2638. For (cyclopentadienone)iron carbonyl complexes **4**−**8**, see: (e) Schrauzer, G. N. Diphenylacetylene Derivaties of Iron Carbonyl. *J. Am. Chem. Soc.* **1959**, *81*, 5307−5310. (f) Knölker, H.-J.; Heber, J.; Mahler, C. H. Transition Metal-Diene Complexes in Organic Synthesis, Part 14.[1] Regioselective Iron-Mediated [2 + 2+1] Cycloadditions of Alkynes and Carbon Monoxide: Synthesis of Substituted Cyclopentadienones. *Synlett* **1992**, *1992*, 1002−1004. (g) Moulin, S.; Dentel, H.; Pagnoux-Ozherelyeva, A.; Gaillard, S.; Poater, A.; Cavallo, L.; Lohier, J.-F.; Renaud, J.-L. Bifunctional (Cyclopentadienone)Iron-Tricarbonyl Complexes: Synthesis, Computational Studies and Application in Reductive Amination. *Chem. - Eur. J.* **2013**, *19*, 17881−17890. (h) Facchini, S. V.; Neudörfl, J.-M.; Pignataro, L.; Cettolin, M.; Gennari, C.; Berkessel, A.; Piarulli, U. Synthesis of [Bis-(hexamethylene)cyclopentadienone]iron Tricarbonyl and its Application to the Catalytic Reduction of C = O Bonds. *ChemCatChem* **2017**, *9*, 1461−1468.

(18) No observable background reaction occurs in the absence of [Fe] precatalyst **2** under any of the reaction conditions employed in this study.

(19) For a selection of base metal-catalyzed BH *N*-methylation processes, see: (a) Elangovan, S.; Neumann, J.; Sortais, J.-B.; Junge, K.; Darcel, C.; Beller, M. Efficient and selective N-alkylation of amines with alcohols catalyzed by manganese pincer complexes. *Nat. Commun.* **2016**, *7*, 12641. (b) Neumann, J.; Elangovan, S.; Spannenberg, A.; Junge, K.; Beller, M. Improved and General Manganese-Catalyzed N-Methylation of Aromatic Amines Using Methanol. *Chem. - Eur. J.* **2017**, *23*, 5410−5413. (c) Bruneau-Voisine, A.; Wang, D.; Dorcet, V.; Roisnel, T.; Darcel, C.; Sortais, J.-B. Mono-N-methylation of anilines with methanol catalyzed by a manganese pincer-complex. *J. Catal.* **2017**, *347*, 57−62. (d) Liu, Z.; Yang, Z.; Yu, X.; Zhang, H.; Yu, B.; Zhao, Y.; Liu, Z. Efficient CobaltCatalyzed Methylation of Amines Using Methanol. *Adv. Synth. Catal.* **2017**, *359*, 4278−4283.

DOI: 10.1021/acscatal.9b02461
ACS Catal. 2019, 9, 8575−8580