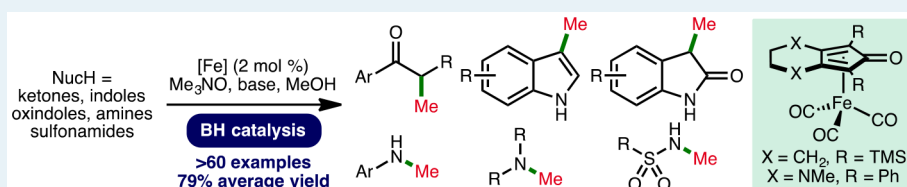# Iron-Catalyzed Methylation Using the Borrowing Hydrogen Approach

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S *Supporting Information*

ABSTRACT: A general iron-catalyzed methylation has been developed using methanol as a C1 building block. This borrowing hydrogen approach employs a Knölker-type (cyclopentadienone)iron carbonyl complex as catalyst (2 mol %) and exhibits a broad reaction scope. A variety of ketones, indoles, oxindoles, amines, and sulfonamides undergo mono- or dimethylation in excellent isolated yields (>60 examples, 79% average yield).

KEYWORDS: borrowing hydrogen, iron catalysis, methylation, methanol, mechanistic studies

Methylation is a fundamental transformation in synthetic chemistry that is widely used for the synthesis and functionalization of fine chemicals.[1] Traditional methylation procedures often employ toxic and/or potentially explosive reagents including iodomethane, dimethyl sulfate, or diazomethane, among many others.[2] In recent years, methanol, an abundant and biodegradable liquid, has emerged as an attractive alternative reagent for methylation.[3] Borrowing hydrogen (BH), or hydrogen autotransfer, combines a transfer hydrogenation process with a concurrent reaction on the in situ-generated reactive intermediate.[4] This one-pot oxidation-reaction−reduction sequence has received much attention due to its inherent high atom economy and minimal waste generation,[5] allowing bench stable and inexpensive alcohols to be used as alkylating agents.[6] In comparison with benzyl and long-chain *n*-alkyl alcohols, it is challenging to use methanol as the alkylating agent in BH processes, due partly to the increased energy of dehydrogenation (ΔH (MeOH) = +84 kJ mol^{-1}, cf. ΔH (EtOH) = +68 kJ mol^{-1})[7] to form the required transient reactive formaldehyde intermediate.

Following the pioneering work of Grigg on the ruthenium- and rhodium-catalyzed methylation of arylacetonitriles and aromatic amines,[8] respectively, there have been a number of subsequent reports describing precious metal-catalyzed BH methylation (Scheme 1A).[9] Despite these advances, a key challenge in hydrogen transfer chemistry is the development and use of catalysts based on earth-abundant, inexpensive metals for more sustainable processes.[10] Considerable progress has been made in this regard, with well-defined iron, manganese, and cobalt catalysts being employed for a variety of homogeneous BH alkylation processes.[11] With the vast majority of reports primarily focusing on the use of benzyl

Scheme 1. Previous Work and Outline of the Fe-Catalyzed BH Methylation Strategy

A) Borrowing hydrogen methylation using methanol (previous work)
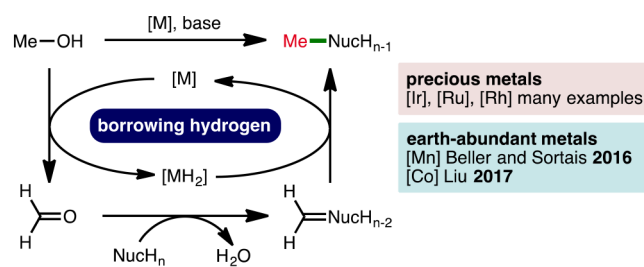
B) Fe-catalyzed BH methylation of diverse pronucleophiles (this work)
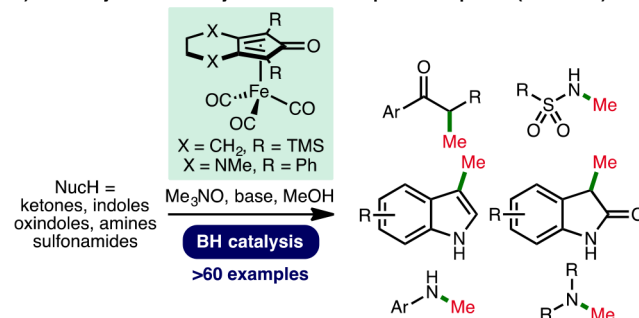
alcohols as alkylating agents, Beller and Sortais have reported the methylation of aromatic amines using manganese pincer

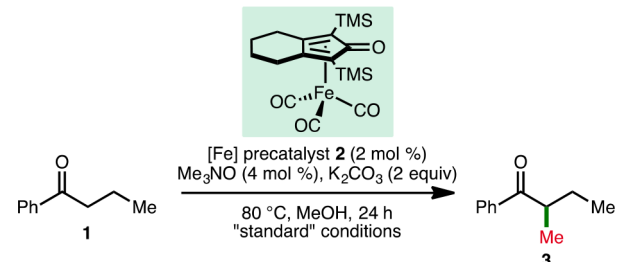complexes.[12] Furthermore, Liu has recently disclosed a cobalt-based catalytic system for methylation.[13] However, the catalytic BH methylation using iron,[14] the most abundant transition metal in the Earth's crust, remains an unsolved problem. Herein, we report an efficient and general iron-catalyzed methylation of ketones, indoles, oxindoles, amines, and sulfonamides using methanol as a sustainable C1 building block (Scheme 1B).

To commence our studies, we selected butyrophenone **1** as a model substrate (Table 1). After extensive optimization,[15] it

Table 1. Optimization of Fe-Catalyzed BH Methylation[a]

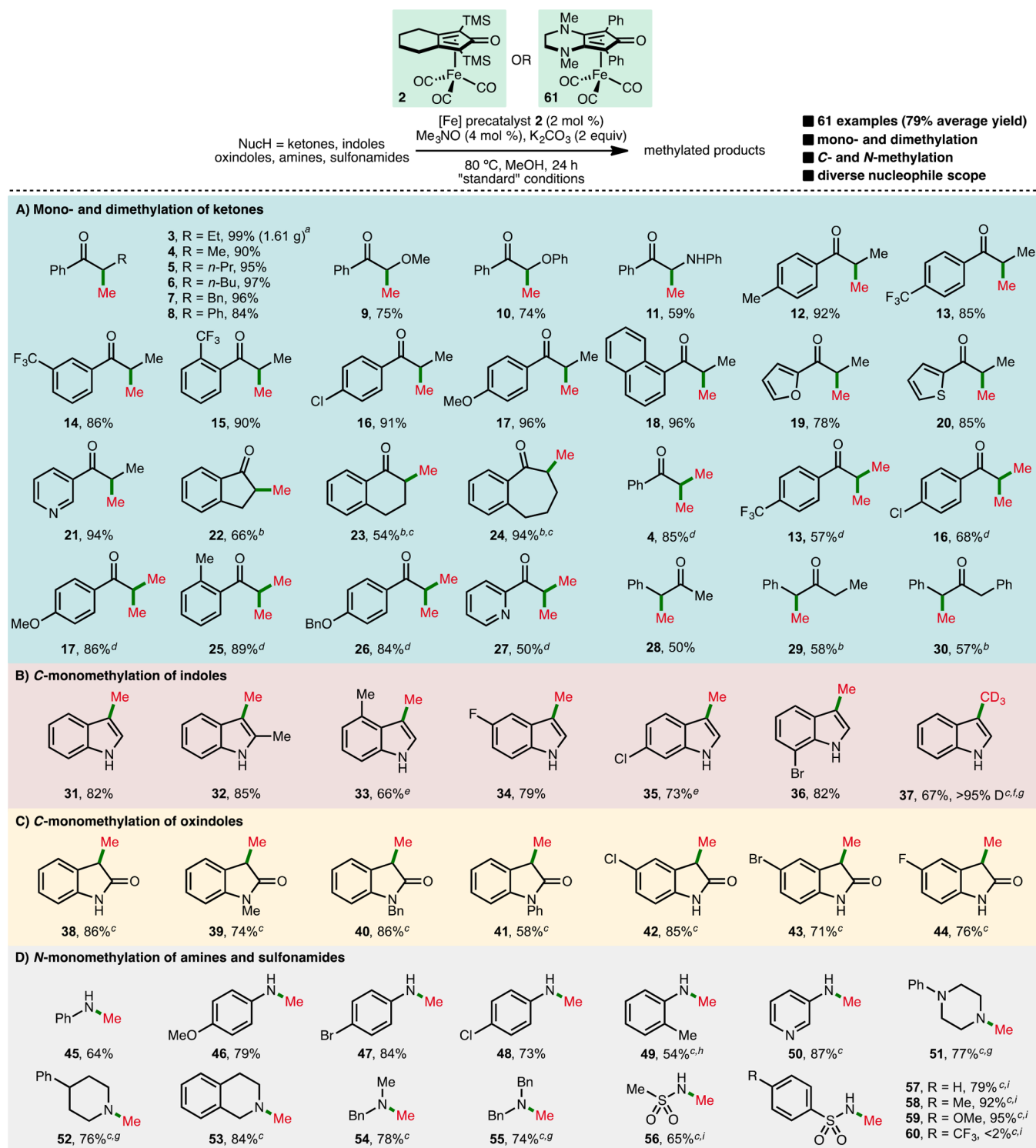| entry	variation from "standard" conditions	yield[b] (%)
1	none	>98 (88)
2	no [Fe] precatalyst	<2
3	no Me₃NO activator	55
4	PPh₃ (4 mol %) instead of Me₃NO	37
5	2 mol % of Me₃NO	92
6	KOH (2 equiv) instead of K₂CO₃	93
7	KOt-Bu (2 equiv) instead of K₂CO₃	91
8	K₂CO₃ (0.5 equiv)	85
9	MeOH:toluene (1:1)	40
10	[**1**] = 0.2 M	94
11	[**1**] = 1 M	93
12	100 °C	94
13	60 °C	88
14[c]	[Fe] precatalyst **2** (1 mol %)	81

[a]Reactions performed using 1 mmol of ketone **1** and bench-grade MeOH. [**1**] = 0.5 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. [c]2 mol % of Me₃NO.

was found that a BH system composed of Knölker-type (cyclopentadienone)iron carbonyl precatalyst **2** (2 mol %),[16] trimethylamine N-oxide (4 mol %) to activate the catalyst,[17] K₂CO₃ (2 equiv) as base in MeOH ([**1**] = 0.5 M) at 80 °C for 24 h, enabled the methylation of **1**, giving **3** in 98% NMR yield and 88% isolated yield (entry 1). No methylation occurs in the absence of the iron precatalyst **2** (entry 2), with a significant reduction in conversion observed in the absence of trimethylamine N-oxide (entry 3). Substituting Me₃NO for PPh₃ as activator or lowering the loading of Me₃NO to 2 mol %, both result in decreased NMR yield of **3** (entries 4 and 5). Employing KOH or KOt-Bu as base, or using substoichiometric quantities of K₂CO₃ (0.5 equiv) all result in lower conversions to **3** (entries 6–8). Using methanol as solvent is crucial, with a mixed solvent system (MeOH:toluene (1:1)) resulting in only 40% NMR yield (entry 9). Altering the reaction concentration (entries 10 and 11), reaction temperature (entries 12 and 13), or reducing the catalyst loading to 1 mol % (entry 14), lowers the efficiency of the methylation of **1** to **3**.

The full scope of the Fe-catalyzed BH methylation process was explored, starting with the mono- and dimethylation of ketones (Scheme 2A).[18] Using the optimized reaction conditions (Table 1, entry 1) a variety of aryl alkyl substituted ketones were converted to the corresponding methylated products in excellent isolated yields (products **3–21**, 87% average yield). Acetophenone derivatives bearing α-alkyl (Me, Et, n-Pr, n-Bu, Bn), α-phenyl and α-heteroatom (OMe, OPh, NHPh) substitution undergo efficient methylation without cleavage of the carbon-heteroatom bonds within products **9–11**.[19] Within the aryl unit, 4-CF₃, 3-CF₃, and 2-CF₃ substitution is tolerated in addition to halide (4-Cl) and electron-donating (4-OMe) substituents. Hindered extended aromatic systems (1-Np) and heteroaryls (2-furanyl, 2-thiophenyl and 3-pyridyl) can also be present within the ketone. The monomethylation procedure performs well upon scale-up, with the formation of **3** successfully carried out on a 10 mmol scale in 99% (1.61 g) isolated yield. 5-, 6-, and 7-membered cyclic ketones also undergo methylation, using KOt-Bu (10 mol %) as base, giving products **22–24**. A representative selection of acetophenone derivatives, which are unsubstituted at the α-position, undergo dimethylation using 2 equiv of KOt-Bu at 110 °C in high isolated yields (products **4, 13, 16, 17**, and **25–27**, 74% average yield). The catalytic system tolerated the reducible benzyl ether moiety within **26**. Selectivity considerations exist when employing ketones that are enolizable at both α-positions. Phenyl acetone, 1-phenylbutan-2-one, and dibenzyl ketone undergo selective monomethylation at 80 °C, giving **28, 29,** and **30** in 50%, 58%, and 57% isolated yields, respectively. For phenyl acetone and 1-phenylbutan-2-one, monomethylation occurs preferentially at the more acidic benzylic position.

Next, we explored the use of indoles and oxindoles as substrates for the Fe-catalyzed BH methylation process (Scheme 2B/C). Using 2 equiv of K₂CO₃ as base, a variety of indoles undergo C(3)-methylation in high isolated yields (products **31–36**, 78% average yield).[20] In addition to unsubstituted indole, methyl and halide substituents are tolerated at the 2-, 4-, 5-, 6-, and 7-positions. Furthermore, by employing CD₃OD as solvent, d_3-skatole **37**, which has utility in studying metabolism kinetics,[21] was accessed in 67% yield. Oxindoles, a class of activated amide, also undergo facile C(3)-methylation at 110 °C (products **38–44**, 77% average yield). N-Methyl, N-benzyl, and N-phenyl substitution is tolerated in addition to various halide substitutions at the 5-position. This is the first example of borrowing hydrogen C-methylation of an amide using a homogeneous catalytic system.[22]

We also investigated the Fe-catalyzed BH N-methylation of amines using methanol (Scheme 2D). Using the optimized reaction conditions (Table 1, entry 1), a variety of arylamines undergo monomethylation in high isolated yields (products **45–50**, 74% average yield). Within the aryl unit, electron-donating (4-OMe) substituents are tolerated in addition to halides (4-Br, 4-Cl), hindered aromatic systems (2-Me), and heteroaryls (3-pyridyl).[23] A selection of cyclic and acyclic secondary amines also undergo efficient N-monomethylation, accessing the corresponding tertiary amines in high yields (products **51–55**, 78% average yield). Finally, employing Renaud's (cyclopentadienone)iron carbonyl precatalyst **61** (4 mol %),[24] which contains a more electron-rich cyclopentadienone framework, the N-monomethylation of sulfonamides was also demonstrated (products **56–59**, 83% average

Scheme 2. Scope of the Fe-Catalyzed BH Methylation Process[§]

■ 61 examples (79% average yield)
■ mono- and dimethylation
■ C- and N-methylation
■ diverse nucleophile scope

A) Mono- and dimethylation of ketones

3, R = Et, 99% (1.61 g)[a]
4, R = Me, 90%
5, R = n-Pr, 95%
6, R = n-Bu, 97%
7, R = Bn, 96%
8, R = Ph, 84%

9, 75%   10, 74%   11, 59%   12, 92%   13, 85%

14, 86%   15, 90%   16, 91%   17, 96%   18, 96%   19, 78%   20, 85%

21, 94%   22, 66%[b]   23, 54%[b,c]   24, 94%[b,c]   4, 85%[d]   13, 57%[d]   16, 68%[d]

17, 86%[d]   25, 89%[d]   26, 84%[d]   27, 50%[d]   28, 50%   29, 58%[b]   30, 57%[b]

B) C-monomethylation of indoles

31, 82%   32, 85%   33, 66%[e]   34, 79%   35, 73%[e]   36, 82%   37, 67%, >95% D[c,f,g]

C) C-monomethylation of oxindoles

38, 86%[c]   39, 74%[c]   40, 86%[c]   41, 58%[c]   42, 85%[c]   43, 71%[c]   44, 76%[c]

D) N-monomethylation of amines and sulfonamides

45, 64%   46, 79%   47, 84%   48, 73%   49, 54%[c,h]   50, 87%[c]   51, 77%[c,g]

52, 76%[c,g]   53, 84%[c]   54, 78%[c]   55, 74%[c,g]   56, 65%[c,i]

57, R = H, 79%[c,i]
58, R = Me, 92%[c,i]
59, R = OMe, 95%[c,i]
60, R = CF3, <2%[c,i]

[§]Reactions performed using 1 mmol of ketone, indole, oxindole, amine or sulfonamide starting material. All yields are isolated yields after chromatographic purification Reagents and conditions: [a]10 mmol of ketone starting material; [b]KOt-Bu (10 mol %); [c]110 °C; [d]KOt-Bu (2 equiv); [e]48 h; [f]CD3OD as solvent; [g][Fe] precatalyst **2** (4 mol %), Me3NO (8 mol %); [h]96 h; [i][Fe] precatalyst **61** (4 mol %), Me3NO (8 mol %).

yield). Methanesulfonamide and sulfonamides containing electron-rich aromatic rings all undergo efficient N-methyl-ation, whereas 4-CF3C6H4 substituted sulfonamide **60** was unreactive.

Selecting the monomethylation of propiophenone as a representative reaction, a number of experiments were performed in order to obtain mechanistic insight (Scheme 3). First, the validity of several proposed intermediates (β-hydroxy ketone **62**, methyl ether **63**, diketone **64**, and enone **65**) was probed by subjecting them to the "standard" methylation reaction conditions (Scheme 3A). Conjugate addition of methanol or the enolate of propiophenone to
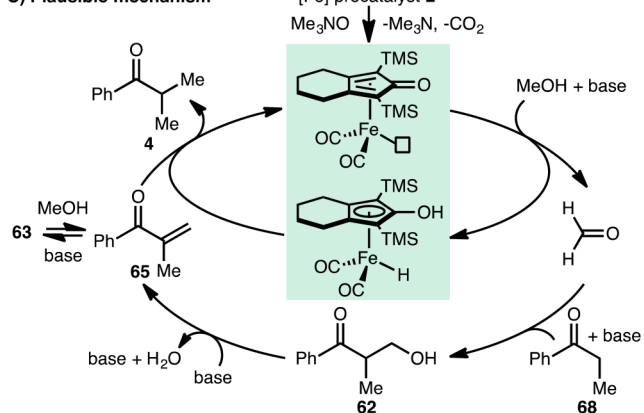
Scheme 3. Mechanistic Considerations

A) Validation of possible reaction intermediates
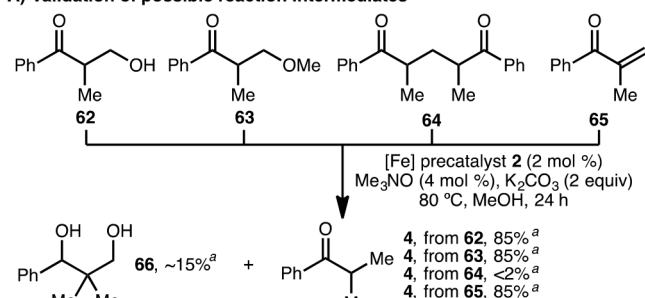
B) Evidence for iron hydride species and methanol as methylating agent
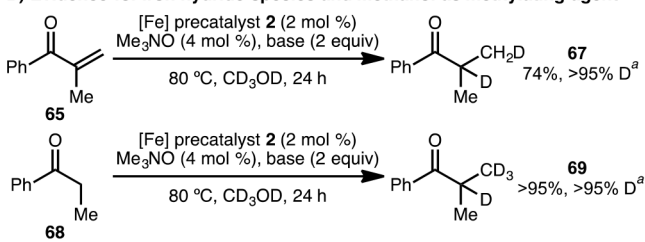
C) Plausible mechanism

[a]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.

enone **65**, would result in the formation of **63** and **64**, respectively. Compounds **62**, **63**, and **65** were all converted to **4** in 85% NMR yield, indicating that they are all plausible reaction intermediates. The remaining mass balance in these reactions (~15%) was diol **66**, which likely forms via conjugate addition of the iron hydride species to **65**, followed by trapping of the resulting enolate with formaldehyde and subsequent hydrogenation.[25] Diketone **64** was returned after 24 h, indicating that this is a nonproductive reaction pathway and that **64** does not lead to the formation of **4**. To gain further mechanistic insight, employing CD_3OD as solvent under the otherwise standard reaction conditions, enone **65** was converted to **67** (74%, > 95% D) providing evidence for the proposed iron hydride species (Scheme 3B). Furthermore, propiophenone **68** was converted to **69** (>95%, > 95% D), confirming that methanol is the source of the methyl group. As such, the proposed mechanism begins with CO decoordination by Me_3NO to form the active iron complex, which abstracts hydrogen from methanol in the presence of base to form the required transient reactive formaldehyde intermediate (Scheme 3C). A subsequent aldol reaction with propiophenone generates β-hydroxy ketone **62** that undergoes base-catalyzed dehydration to form enone **65**, which may exist in

equilibrium with **63**. Finally, reduction of enone **65** by the iron−hydrogen complex gives methylated product **4** with regeneration of the active iron complex.

In conclusion, we have developed a general and efficient Fe-catalyzed methylation using methanol as a sustainable C1 building block via the borrowing hydrogen approach. A diverse array of ketones, indoles, oxindoles, amines, and sulfonamides undergo mono- or dimethylation in excellent isolated yields (61 examples, 79% average yield). Mechanistic experiments provided evidence for plausible reaction intermediates, an iron-hydride species, and methanol as the methylating agent in this catalytic process. Ongoing studies are focused on further applications of earth-abundant transition metals in catalysis, and these results will be reported in due course.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.8b02158.

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

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Notes

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■ REFERENCES

(1) (a) Barreiro, E. J.; Kümmerle, A. E.; Fraga, C. A. M. The Methylation Effect in Medicinal Chemistry. *Chem. Rev.* **2011**, *111*, 5215−5246. (b) 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.

(2) (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.

(3) (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 π-Unsaturated 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.

(4) For selected reviews, see: (a) Hamid, M. H. S. A.; Slatford, P. A.; Williams, J. M. J. Borrowing Hydrogen in the Activation of Alcohols. *Adv. Synth. Catal.* **2007**, *349*, 1555–1575. (b) Guillena, G.; Ramón, D. J.; Yus, M. Hydrogen Autotransfer in the N-Alkylation of Amines and Related Compounds using Alcohols and Amines as Electrophiles. *Chem. Rev.* **2010**, *110*, 1611–1641. (c) Huang, F.; Liu, Z.; Yu, Z. C-Alkylation of Ketones and Related Compounds by Alcohols: Transition-Metal-Catalyzed Dehydrogenation. *Angew. Chem., Int. Ed.* **2016**, *55*, 862–875. (d) Corma, A.; Navas, J.; Sabater, M. J. Advances in One-Pot Synthesis through Borrowing Hydrogen Catalysis. *Chem. Rev.* **2018**, *118*, 1410–1459.

(5) (a) Trost, B. M. Atom Economy-A Challenge for Organic Synthesis: Homogeneous Catalysis Leads the Way. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259–281. (b) Trost, B. M. On Inventing Reactions for Atom Economy. *Acc. Chem. Res.* **2002**, *35*, 695–705.

(6) Watson, A. J. A.; Williams, J. M. J. The Give and Take of Alcohol Activation. *Science* **2010**, *329*, 635–636.

(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) Grigg, R.; Mitchell, T. R. B.; Sutthivaiyakit, S.; Tongpenyai, N. Oxidation of alcohols by transition metal complexes part V. Selective catalytic monoalkylation of arylacetonitriles by alcohols. *Tetrahedron Lett.* **1981**, *22*, 4107–4111. (b) Grigg, R.; Mitchell, T. R. B.; Sutthivaiyakit, S.; Tongpenyai, N. Transition metal-catalysed N-alkylation of amines by alcohols. *J. Chem. Soc., Chem. Commun.* **1981**, 611–612.

(9) For selected Ru-catalyzed processes, see: (a) Arcelli, A.; Bui-The-Khai; Porzi, G. Selective conversion of primary amines into N,N-dimethylalkyl- or N,N-dialkylmethyl-amines with methanol and RuCl₂(Ph₃)₃. *J. Organomet. Chem.* **1982**, *235*, 93–96. (b) 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. (c) Dang, T. T.; Seayad, A. M. A Convenient Ruthenium-Catalysed α-Methylation of Carbonyl Compounds using Methanol. *Adv. Synth. Catal.* **2016**, *358*, 3373–3380. For selected Ir-catalyzed processes, see: (d) Ogawa, S.; Obora, Y. Iridium-catalyzed selective α-methylation of ketones with methanol. *Chem. Commun.* **2014**, *50*, 2491–2493. (e) 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. (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. For a Rh-catalyzed process, see: (g) 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. For C–H functionalization of MeOH, see: (h) Moran, J.; Preetz, A.; Mesch, R. A.; Krische, M. J. Iridium-catalysed direct C-C coupling of methanol and allenes. *Nat. Chem.* **2011**, *3*, 287–290. (i) Nguyen, K. D.; Herkommer, D.; Krische, M. J. Enantioselective Formation of All-Carbon Quaternary Centers via C-H Functionalization of Methanol: Iridium-Catalyzed Diene Hydro-hydroxymethylation. *J. Am. Chem. Soc.* **2016**, *138*, 14210–14213. (j) Holmes, M.; Nguyen, K. D.; Schwartz, L. A.; Luong, T.; Krische, M. J. Enantioselective Formation of CF₃-Bearing All-Carbon Quaternary Stereocenters via C-H Functionalization of Methanol: Iridium Catalyzed Allene Hydrohydroxymethylation. *J. Am. Chem. Soc.* **2017**, *139*, 8114–8117.

(10) For selected reviews, see: (a) Quintard, A.; Rodriguez, J. A Step into an eco-Compatible Future: Iron- and Cobalt-catalyzed Borrowing Hydrogen Transformation. *ChemSusChem* **2016**, *9*, 28–30. (b) Zell, T.; Langer, R. From Ruthenium to Iron and Manganese-A Mechanistic View on Challenges and Design Principles of Base-Metal Hydrogenaton Catalysts. *ChemCatChem* **2018**, *10*, 1930–1940.

(c) Filonenko, G. A.; van Putten, R.; Hensen, E. J. M.; Pidko, E. A. Catalytic (de)hydrogenation promoted by non-precious metals − Co, Fe and Mn: recent advances in an emerging field. *Chem. Soc. Rev.* **2018**, *47*, 1459–1483. (d) Kallmeier, F.; Kempe, R. Manganese Complexes for (De)Hydrogenation Catalysis: A Compatison to Cobalt and Iron Catalysts. *Angew. Chem., Int. Ed.* **2018**, *57*, 46–60.

(11) For selected Fe-catalyzed processes, see: (a) 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. (b) Yan, T.; Feringa, B. L.; Barta, K. Iron catalysed direct alkylation of amines with alcohols. *Nat. Commun.* **2014**, *5*, 5602. (c) 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. (d) 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. (e) Mastalir, M.; Pittenauer, E.; Allmaier, G.; Kirchner, K. Manganese-Catalyzed Aminomethylation of Aromatic Compounds with Methanols as a Sustainable C1 Building Block. *J. Am. Chem. Soc.* **2017**, *139*, 8812–8815. (f) Vayer, M.; Morcillo, S. P.; Dupont, J.; Gandon, V.; Bour, C. Iron-Catalyzed Reductive Ethylation of Imines with Ethanol. *Angew. Chem., Int. Ed.* **2018**, *57*, 3228–3232. For selected Mn-catalyzed processes, see: (g) 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. (h) Peña-López, M.; Piehl, P.; Elangovan, S.; Neumann, H.; Beller, M. Manganese-Catalyzed Hydrogen-Authotransfer C-C Bond Formation: α-Alkylation of Ketones with Primary Alcohols. *Angew. Chem., Int. Ed.* **2016**, *55*, 14967–14971. For selected Co-catalyzed processes, see: (i) Rösler, S.; Ertl, M.; Irrgang, T.; Kempe, R. Cobalt-Catalyzed Alkylation of Aromatic Amines by Alcohols. *Angew. Chem., Int. Ed.* **2015**, *54*, 15046–15050. (j) Deibl, N.; Kempe, R. General and Mild Cobalt-Catalyzed C-Alkylation of Unactivated Amides and Esters with Alcohols. *J. Am. Chem. Soc.* **2016**, *138*, 10786–10789. (k) Yin, Z.; Zeng, H.; Wu, J.; Zheng, S.; Zhang, G. Cobalt-Catalyzed Synthesis of Aromatic, Aliphatic, and Cyclic Secondary Amines via a "Hydrogen-Borrowing" Strategy. *ACS Catal.* **2016**, *6*, 6546–6550.

(12) (a) ref 11g. (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.

(13) (a) 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. (b) Liu, Z.; Yang, Z.; Yu, X.; Zhang, H.; Yu, B.; Zhao, Y.; Liu, Z. Efficient Cobalt-Catalyzed Methylation of Amines Using Methanol. *Adv. Synth. Catal.* **2017**, *359*, 4278–4283.

(14) For selected general reviews on iron catalysis, see: (a) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. Iron-Catalyzed Reactions in Organic Synthesis. *Chem. Rev.* **2004**, *104*, 6217–6254. (b) Junge, K.; Schröder, K.; Beller, M. Homogeneous catalysis using iron complexes: recent developments in selective reductions. *Chem. Commun.* **2011**, *47*, 4849–4859. (c) Bauer, I.; Knölker, H.-J. Iron Catalysis in Organic Synthesis. *Chem. Rev.* **2015**, *115*, 3170–3387.

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

(16) For an overview of the synthesis and reactivity of Knölker-type 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.

DOI: 10.1021/acscatal.8b02158
ACS Catal. 2018, 8, 6440–6445

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.

(17) (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 Oppenauer-type 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.

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

(19) (a) Nichols, J. M.; Bishop, L. M.; Bergman, R. G.; Ellman, J. A. Catalytic C-O Bond Cleavage of 2-Aryloxy-1-arylethanols and Its Application to the Depolymerization of Lignin-Related Polymers. *J. Am. Chem. Soc.* **2010**, *132*, 12554−12555. (b) 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.

(20) For selected examples of the alkylation of indoles via borrowing hydrogen catalysis, see: (a) Whitney, S.; Grigg, R.; Derrick, A.; Keep, A. [Cp*IrCl$_2$]$_2$-Catalyzed Indirect Functionalization of Alcohols: Novel Strategies for the Synthesis of Substituted Indoles. *Org. Lett.* **2007**, *9*, 3299−3302. (b) Imm, S.; Bähn, S.; Tillack, A.; Mevius, K.; Neubert, L.; Beller, M. Selective ruthenium-catalyzed alkylation of indoles by using amines. *Chem. - Eur. J.* **2010**, *16*, 2705−2709.

(21) Skiles, G. L.; Yost, G. S. Mechanistic Studies on the Cytochrome P450-Catalyzed Dehydrogenation of 3-Methylindole. *Chem. Res. Toxicol.* **1996**, *9*, 291−297.

(22) For the methylation of oxindoles using Raney Nickel as a heterogeneous catalyst, see: (a) Wenkert, E.; Bringi, N. V. A New Procedure for Forming Carbon-Carbon Bonds. *J. Am. Chem. Soc.* **1958**, *80*, 5575−5576. (b) Wenkert, E.; Bringi, N. V.; Choulett, H. E. Raney Nickel-induced Alkylation Reactions. *Acta Chem. Scand.* **1982**, *36b*, 348−350. (c) Volk, B.; Mezei, T.; Simig, G. Raney Nickel-Induced 3-Alkylation of Oxindole with Alcohols and Diols. *Synthesis* **2002**, 595−597.

(23) No conversion to the *N*-methylanilines is observed in the absence of K$_2$CO$_3$.

(24) (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 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.

(25) Diols such as **66** were not observed as byproducts in any of our ketone mono- or dimethylation experiments, presumably due to formaldehyde reacting preferentially with the conjugate base of the ketone starting material, as illustrated in Scheme 3C.