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Iron-Catalyzed Tandem Three-Component Alkylation: Access to α-Methylated Substituted Ketones

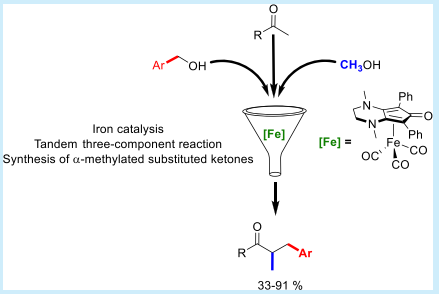
Léo Bettoni,[†] Charlotte Seck,[†,‡] Mbaye Diagne Mbaye,[†,‡] Sylvain Gaillard,[†] and Jean-Luc Renaud*[,†]

[†]Normandie Université, LCMT, ENSICAEN, UNICAEN, CNRS, 6 boulevard du Maréchal Juin, Caen 14000, France

[‡]Université Assane Seck de Ziguinchor, Ziguinchor BP 523, Sénégal

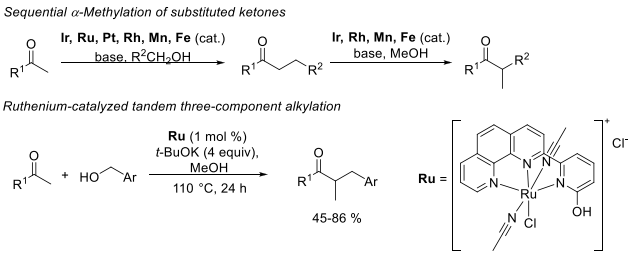
Supporting Information

ABSTRACT: The borrowing hydrogen strategy has been applied in the synthesis of α-branched methylated ketones via a tandem three-component reaction catalyzed by a diaminocyclopentadienone iron tricarbonyl complex. Various alkyl and aromatic methyl ketones underwent dialkylation with various primary alcohols and methanol as alkylating agents in mild reaction conditions and good yields. Deuterium labeling experiments suggested that the benzylic alcohol was the hydrogen source in this tandem process.



Among the substituted ketones, α-branched methylated ketones occupy a singular place. This motive is often encountered in pharmaceutical compounds.[1,2] The methyl substituent can modify both physical and biological properties if incorporated in biologically active compounds.[2] Methylation, and more generally alkylation, of ketones is ubiquitous in organic synthesis. Such a reaction usually involves, on industrial and laboratory scale, the preparation of an enolate, by deprotonation of the ketone with a strong base, followed by trapping with an electrophile (alkyl halide or triflate derivatives).[3] edure is well studied and developed, such an approach generates amounts of wastes and requires the handling of hazardous and toxic chemicals.[4] In recent years, in order to develop more eco-friendly methodologies, new strategies have been proposed for the construction of C−C bonds.[5,6] Among these approaches, the borrowing hydrogen strategy or hydrogen autotransfer possesses several advantages such as the use of easy-to-handle alcohols as alkylating agents and the formation of water as a sole side product. Since the pioneer work of Grigg et al.,[7] several complexes, including Earth-abundant ones, have been described (Scheme 1).[8,9]

Scheme 1. Previous Work in Hydrogen Autotransfer Methylation of Substituted Ketones



However, all these methodologies are based either on the α-methylation of substituted ketones[10−16] or on a sequential double alkylation of methyl ketones, as demonstrated by Donohoe and co-workers[10c] and Dang and Seayad.[13] Another approach to these α-methylated ketones could be a one-pot multicomponent alkylation between a methyl ketone, methanol, and a second alcohol. The challenge in such an approach relies on the possible synthesis of three alkylated products: the dimethylated ketone, the dialkylated ketone, and the target α-methylated α-alkylated ketone. The success of such methodology relies on the difference in reactivity between methanol and the second alcohol. The more energetic demanding dehydrogenation step of methanol, compared to other alcohols (ΔH = +84 kJmol^{-1} for methanol vs ΔH = +68 kJmol^{-1} for ethanol), might be one of the key steps for a successful sequential double alkylation. However, a catalytic one pot multicomponent reaction using two different alcohols and a ketone remains underdeveloped and is still not explored with Earth-abundant metals. To date, only one report by Kundu and co-workers on such a three component alkylation has been disclosed in the literature.[17] This coupling reaction between methanol, benzyl alcohols, and aromatic ketones delivered the α-branched methylated ketones in moderate to good yields in the presence of a ruthenium complex at 110 °C (Scheme 1).

While economic pressure and development of sustainable methodologies urged the replacement of platinum complexes by Earth-abundant ones, there is no report to date of such a one-pot process with an earth abundant catalyst. Following our ongoing interest on the borrowing hydrogen strategy,[18] we report the first three-component alkylation catalyzed by an iron complex, allowing the synthesis of α-branched methylated

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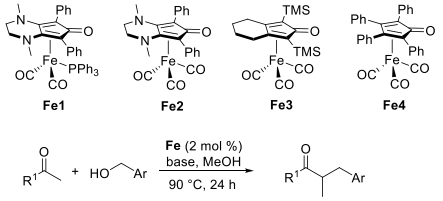
ketones from methanol, as C1 source, benzyl alcohols, and aliphatic and aromatic ketones in mild reaction conditions (Scheme 2).

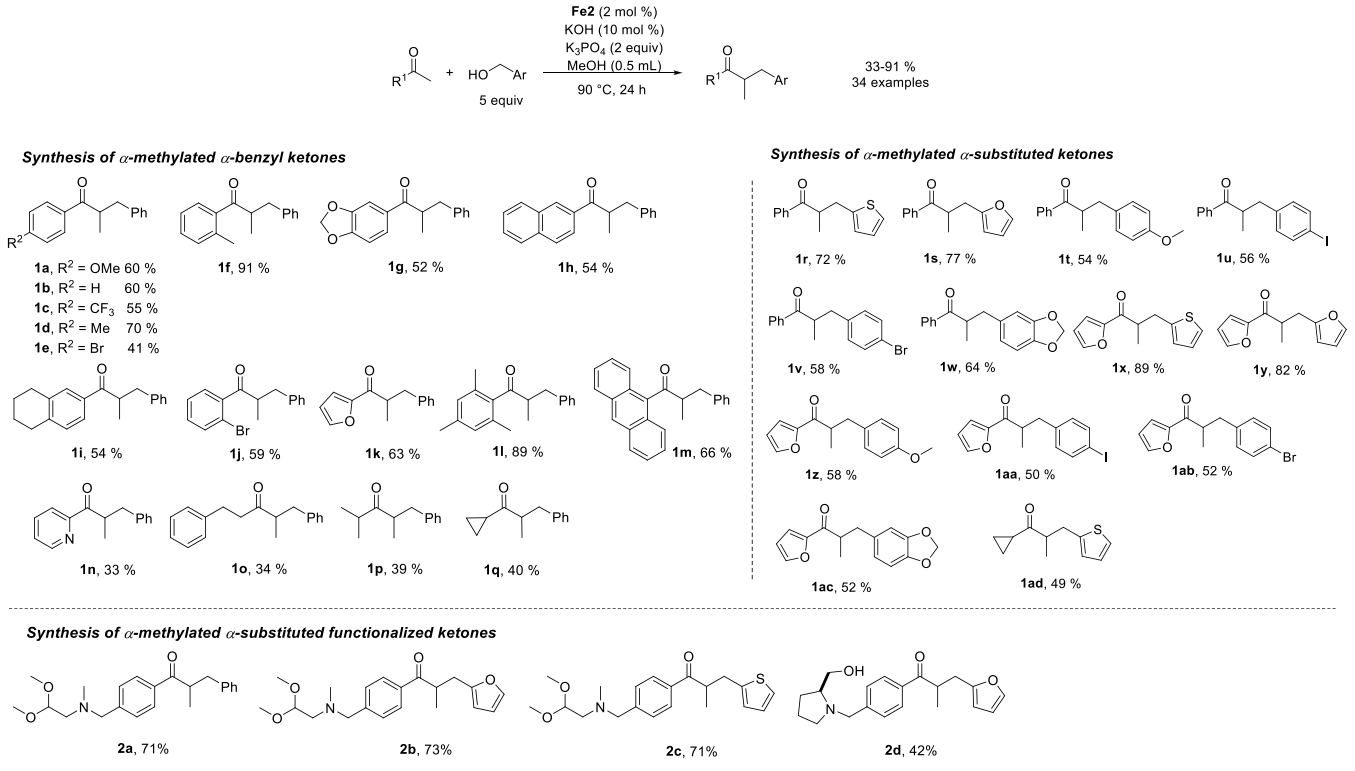
Scheme 2. Outline of the Fe-Catalyzed Tandem Three-Component Alkylation



As a starting point for this multicomponent reaction, we chose the alkylation of 4-methoxyacetophenone (1 equiv) with benzyl alcohol and methanol as a model reaction for the optimization of the reaction conditions (Table S1). Several activation protocols can be used with cyclopentadienone iron carbonyl complexes: photolytic activation,[19a] Me_3NO,[20] or hydroxide base (Hieber's method)[19b] for **Fe2−4** and thermal activation for **Fe1** (Temp. > 70 °C).[18a] A rapid screening of the temperature, using complex **Fe1**, in a mixture of methanol (0.5 mL, 25 equiv) and benzyl alcohol (0.5 mL, 9.3 equiv), revealed that a temperature of 90 °C furnished gratifyingly the α-methylated ketone as a major compound with a good selectivity (entries 1−3, Table S1). Decreasing the amount of benzyl alcohol (0.265 mL, 5 equiv) did not impede the selectivity in favor of the branched dialkyl ketone **1a**, despite a longer reaction time (entry 9, Table S1). An increase of the amount of methanol (50 equiv) led to a mixture of the desired compound **1a** accompanied by the dimethylated derivative (entry 14, Table S1). A significant decrease of the conversion in **1a** was observed when a stoichiometric or substoichiometric amount of base was used (entries 10−11, Table S1), and the benzylated ketone was then the major compound. Gratifyingly, when complex **Fe2** was introduced,[20] the conversion was improved to 91% in **1a**, whatever the activation (entries 22−23, Table S1). Any other alterations of the reaction conditions hampered the yields (Table S1). Finally, other cyclopentadienone iron carbonyl complexes (**Fe3**[21] and **Fe4**[22]) led either to lower selectivity or to only monoalkylation product (entries 25−26, Table S1).

The scope of this unprecedented iron-catalyzed multicomponent alkylation via the borrowing strategy was explored first starting with various aromatic and aliphatic ketones, methanol, and benzyl alcohol (Scheme 3). Various substituents, such as electron-withdrawing group (CF_3), electron-donating group (MeO), acetal, and halide, within the aromatic fragment were tolerated and the corresponding alkylated ketones were isolated in moderate to good yields (compounds **1a−j**, Scheme 3). Heteroaryl methyl ketones (2-furanyl, 2-pyridyl) also underwent the dialkylation, and compounds **1k** and **1n** were isolated in 63% and 33% yield, respectively (Scheme 3). The lower yield with 2-acetylpyridine might be due to some coordination of the pyridine moiety to the 16-electron deficient iron center, which consequently decreased the reaction rate. Sterically hindered and hindered extended aromatic systems did not hamper the reactivity. Compounds **1l** and **1m** have been isolated in 89% and 66% yield, respectively (Scheme 3). Finally, to extend the scope in this tandem sequence, some aliphatic ketones were scrutinized. Yields were

Scheme 3. Tandem Three-Component Alkylation of Ketones[a]



[a]General Conditions: ketone (0.5 mmol), **Fe2** (2 mol %), KOH (10 mol %), K_3PO_4 (2 equiv), benzyl type alcohol (2.5 mmol), MeOH (0.5 mL) at 90 °C for 24 h. Yield was based on isolated product.

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usually lower (**1o−q** and **1ad**, 34−49%, Scheme 3) due to the lower reactivity of these ketones. The deprotonation is less efficient (pK_a values are higher), and the monobenzylated products were the major compounds in this cascade reaction.

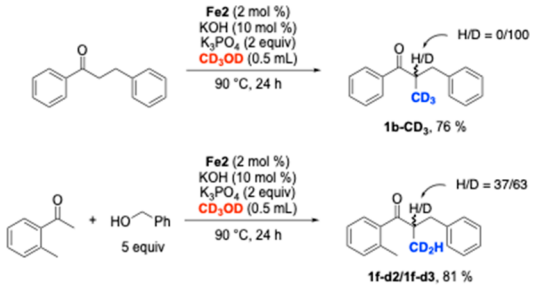
To highlight the robustness of our protocol, the three component alkylation between (2′-methyl)acetophenone, methanol, and benzyl alcohol was carried out on a gram-scale (5 mmol), and the corresponding α-methylated ketone **1f** was isolated in 90% yield (1.08 g).

Having explored the scope on the ketone fragment, we delineated the limitation on the benzylic alcohols (Scheme 3). In this work, acetophenone and 2-acetyl furan were used as models for aromatic and heteroaromatic ketones. Again, a variety of substituted benzylic alcohols were tolerated (**1t−w** and **1z−ad**) and the corresponding isolated yields were reasonably good (50−64%). Higher yields were reached with heteroaromatic alcohols. Compounds **1r−s** and **1x−y** were obtained in 72−89% yield (Scheme 3).

Finally, to increase the versatility of this protocol and increase its potential in synthesis, two more functionalized methyl ketones were engaged in the tandem three-component reaction. These ketones were prepared by an iron-catalyzed chemoselective reductive alkylation of *N*-methylaminoacetaldehyde dimethyl acetal and (*S*)-prolinol with 4-acetylbenzaldehyde in 79% and 99% yield, respectively.[24] The ketones **2a−d** were isolated in good yields (42−73%, Scheme 3). Gratifyingly, the catalytic system tolerated aliphatic acyclic acetal (neither hydrolysis nor hydrogenolysis has been observed), free alcohol, and benzylic amine.

To provide a mechanistic framework consistent with our experiments, deuterium-labeling experiments and stoichiometric complementary experiments were undertaken (Scheme 4 and Schemes S1−S2).

Scheme 4. Mechanistic Studies, Deuterium-Labeling Experiment



When the dihydrochalcone was submitted to the methylation conditions in deuterated methanol, the CD_3-labeled ketone **1b** was isolated in 76% yield (Scheme 4). This result is comparable to that of the nondeuterated version (Scheme 3). Full incorporation of deuterium on the methyl group was obtained, and deuterium was also introduced in the α-carbonyl position. The multicomponent reaction in the optimized conditions with (2′-methyl)acetophenone and benzyl alcohol (5 equiv) in fully deuterated methanol (25 equiv) furnished the CD_2-labeled ketone **1f-d2**/**1f-d3** in 81% yield (Scheme 4). Compared to the previous experiment, first the α-carbonyl position was not fully deuterated (H/D = 37/63) and, second, no CD_3 fragment was observed by NMR spectroscopy (Figures S16 and S17). In sharp contrast with the recent report by Rueping and co-workers on the manganese-catalyzed methylation of ketones,[14b] higher chemoselectivity was observed with **Fe2** in this catalytic experiment as no deuteration of the benzylic position was noticed. These experiments provided some insight into the mechanism: (i) The benzyl alcohol is the source of hydride in the overall process, explaining why an excess of it is required. This result differs from the conclusion reported in Kundu and co-workers' work.[17] (ii) There is no hydrogen/deuterium exchange between deuterated methanol and benzyl alcohol or deuterium scrambling.

To elucidate the possible reversibility of some steps and gain more insights on this reaction, some complementary stoichiometric experiments were conducted with acetophenone, benzaldehyde, and formaldehyde (Schemes S1 and S2). By reacting both aldehydes with acetophenone in basic conditions in methanol at 90 °C, chalcone was observed quantitatively within 4 h while 40% of starting acetophenone remained in the presence of formaldehyde (Scheme S2(i),(ii)). On the basis of the more facile dehydrogenation of benzyl alcohol and the faster condensation of benzaldehyde, the first major intermediate is then the chalcone and not the phenylpropenone (Scheme S1, $k_2 > k_1$ and $k_4 > k_3$). The second key step for a selective three-component reaction is the second condensation. Two unsaturated ketones can be expected, the first one by reaction between the dihydrochalcone and formaldehyde (k_9, Scheme S1) and the second one by reaction with benzaldehyde (k_{10}, Scheme S1). Both unsaturated ketones were fully obtained within 4 h as analyzed by ^{1}H NMR spectroscopy analysis (Scheme S2(iii),(iv)). By adding two drops of water in the reaction medium, reversibility of the aldol condensation was noticed with benzyledene adduct, unlike with the methylene adduct (Scheme S2(v),(vi)). Thus, this reversible aldol reaction drove the overall equilibrium toward the methylene adduct. Surprisingly, when the same sequence was realized with propiophenone, no reversibility of the aldol adducts was noticed (Scheme S2(vi),(viii)). However, a competitive alkylation of the propiophenone with methanol and benzyl alcohol provided the dimethylated ketone as a major compound over the α-methylated α-benzylated ketone in a 96/4 ratio (Scheme S2(ix)).

On the basis of all these results and on our previous works on the borrowing hydrogen methodology and chemoselective reduction of unsaturated enones,[18,23] we proposed the following mechanism (Figure 1). On the basis of the seminal work of Knölker on ligand exchange with sodium hydroxide and our previous DFT calculations,[18c,19b] the intermediate **III** could be generated from **Fe2** through first an initial Hieber's type activation (addition of the hydroxide on one CO ligand followed by the hydride formation and release of CO_2) leading to intermediate **II** and then the release of hydrogen after reaction with methanol (Figure 1). After coordination of the alcohol (intermediate **IV**), the first dehydrogenation step furnished again the intermediate **II** and liberated the aromatic aldehyde. The α,β-unsaturated ketone, resulting from the condensation of the aldehyde and the enolate, could then be reduced via intermediate **V**, and could furnish the monoalkylated ketone and the unsaturated iron species **III** (Figure 1). A similar sequence with methanol could lead to the *exo*-methylene α-benzyl ketone, and its subsequent reduction via intermediate **VII** would deliver the α-branched methylated ketones (Figure 1).

In conclusion, we have developed the first iron-catalyzed three-component alkylation procedure with various aliphatic

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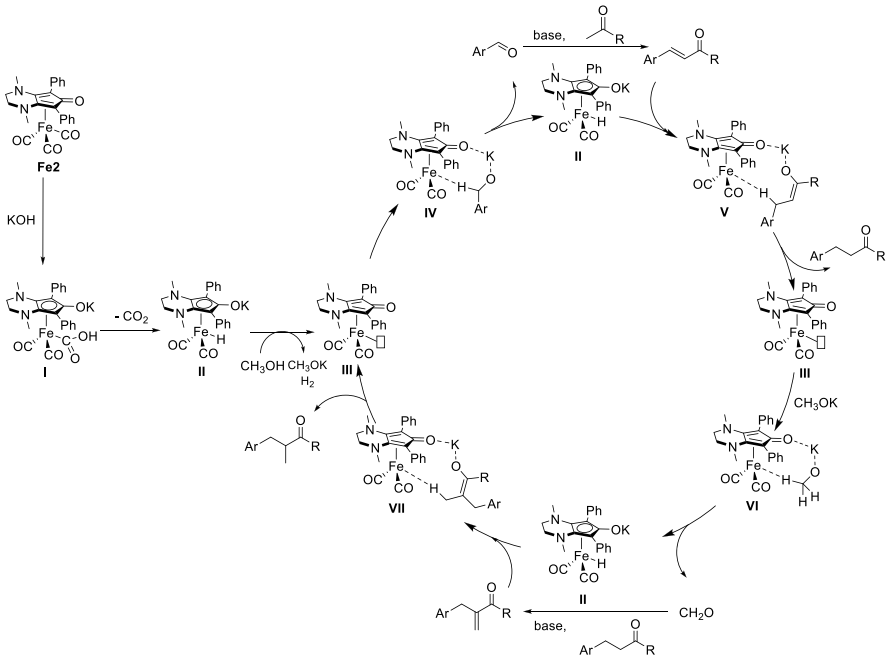

Figure 1. Simplified mechanistic proposal.

and aromatic ketones using benzylic alcohols and methanol as alkylating reagents in the presence of a well-defined bifunctional iron complex. This alkylation process provided α-methylated α-alkylated ketones in moderate to high yields in the presence of other reducible functionalities. These results open the route to an environmentally acceptable atom-efficient procedure to functionalized ketones.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00630.

Preparation details, optimization conditions, and NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jean-luc.renaud@ensicaen.fr.

ORCID

Sylvain Gaillard: 0000-0003-3402-2518
Jean-Luc Renaud: 0000-0001-8757-9622

Notes

The authors declare no competing financial interest.

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■ REFERENCES

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

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

(3) For reviews on α-alkylation of ketones with alkylhalides, see: (a) Caine, D. In *Comprehensive Organic Chemistry*; Trost, B. M., Fleming, I., Pattenden, G., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp 1−63. (b) Otera, J., Ed.; *Modern Carbonyl Chemistry*; Wiley-VCH: Weinheim, 2000.

(4) (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.

(5) For reviews on the C−H functionalization, see: (a) Yeung, C. S.; Dong, V. M. Catalytic Dehydrogenative Cross-Coupling: Forming Carbon-Carbon Bonds by Oxidizing Two Carbon-Hydrogen Bonds. *Chem. Rev.* **2011**, *111*, 1215−1292. (b) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. Direct C-H Transformation via Iron Catalysis. *Chem. Rev.* **2011**, *111*, 1293−1314.

(6) Yan, G. B.; Borah, A. J.; Wang, L. G.; Yang, M. H. Recent Advances in Transition Metal-Catalyzed Methylation Reactions. *Adv. Synth. Catal.* **2015**, *357*, 1333−1350.

(7) (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.

(8) For 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) Dobereiner, G. E.; Crabtree, R. H. Dehydrogenation as a Substrate-Activating Strategy in Homogeneous Transition-Metal Catalysis. *Chem. Rev.* **2010**, *110*, 681−703. (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.

DOI: 10.1021/acs.orglett.9b00630
Org. Lett. XXXX, XXX, XXX−XXX

(d) Chelucci, G. Ruthenium and Osmium Complexes in C-C Bond-Forming Reactions by Borrowing Hydrogen Catalysis. *Coord. Chem. Rev.* **2017**, *331*, 1−36. (e) Corma, A.; Navas, J.; Sabater, M. J. Advances in One-Pot Synthesis through Borrowing Hydrogen Catalysis. *Chem. Rev.* **2018**, *118*, 1410−1459.

(9) For recent reviews, see: (a) Irrgang, T.; Kempe, R. 3d-Metal Catalyzed *N*- and *C*-Alkylation Reactions via Borrowing Hydrogen or Hydrogen Autotransfer. *Chem. Rev.* **2019**, *119*, 2524−2549. (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) Renaud, J.-L.; Gaillard, S. Recent Advances in Iron and Cobalt Complexes-Catalyzed Tandem/Consecutive Processes Involving Hydrogenation. *Synthesis* **2016**, *48*, 3659−3683. (d) Quintard, A.; Rodriguez, J. A Step into an Eco-Compatible Future: Iron- and Cobalt-Catalyzed Borrowing Hydrogen Transformation. *ChemSusChem* **2016**, *9*, 28−30. (e) Maji, B.; Barman, M. K. Recent Developments of Manganese Complexes for Catalytic Hydrogenation and Dehydrogenation Reactions. *Synthesis* **2017**, *49*, 3377−3393.

(10) (a) 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. (b) 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. (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) Ogawa, S.; Obora, Y. Iridium-Catalyzed Selective α-Methylation of Ketones with Methanol. *Chem. Commun.* **2014**, *50*, 2491−2493.

(11) Chan, L. K.; 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.

(12) Siddiki, S. M. A. H.; Touchy, A. S.; Jamil, Md. A. R.; Toyao, T.; Shimizu, K.-i. α-Methylation of Alcohols, Ketones, and Indoles with Methanol Using Heterogeneous Platinum Catalysts. *ACS Catal.* **2018**, *8*, 3091−3103.

(13) Dang, T. T.; Seayad, A. M. A Convenient Ruthenium-Catalysed α-Methylation of Carbonyl Compounds using Methanol. *Adv. Synth. Catal.* **2016**, *358*, 3373−3380.

(14) (a) Bruneau-Voisine, A.; Pallova, L.; Bastin, S.; César, V.; Sortais, J.-B. Manganese Catalyzed a-Methylation of Ketones with Methanol as a C1 Source. *Chem. Commun.* **2019**, *55*, 314−317. (b) Sklyaruk, J.; Borghs, J. C.; El-Sepelgy, O.; Rueping, M. Catalytic C1 Alkylation with Methanol and Isotope-Labeled Methanol. *Angew. Chem., Int. Ed.* **2019**, *58*, 775−779.

(15) 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.

(16) 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.

(17) Chakrabarti, K.; Maji, M.; Panja, D.; Paul, B.; Shee, S.; Das, G. K.; Kundu, S. Utilization of MeOH as a C1 Building Block in Tandem Three-Component Coupling Reaction. *Org. Lett.* **2017**, *19*, 4750−4753.

(18) (a) Seck, C.; Mbaye, M. D.; 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. (b) Seck, C.; Mbaye, M. D.; Gaillard, S.; Renaud, J.-L. Bifunctional Iron Complexes Catalyzed Alkylation of Indoles. *Adv. Synth. Catal.* **2018**, *360*, 4640−4645. (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.

(19) (a) Knölker, H.-J.; Goesmann, H.; Klauss, R. A Novel Method for the Demetalation of Tricarbonyliron-Diene Complexes by a Photolytically Induced Ligand Exchange Reaction with Acetonitrile. *Angew. Chem., Int. Ed.* **1999**, *38*, 702−705. (b) 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.

(20) 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.

(21) (a) Knölker, H.-J.; Heber, J.; Mahler, C. H. Transition Metal-Diene Complexes in Organic Synthesis, Part 14. Regioselective Iron-Mediated [2 + 2+1] Cycloadditions of Alkynes and Carbon Monoxide: Synthesis of Substituted Cyclopentadienones. *Synlett* **1992**, *1992*, 1002−1004. (b) Knölker, H.-J.; Heber, J. Transition Metal-Diene Complexes in Organic Synthesis, Part 18. Iron-Mediated [2 + 2+1] Cycloadditions of Diynes and carbon Monoxide: Selective Demetalation Reactions. *Synlett* **1993**, *1993*, 924−926.

(22) Schrauzer, G. N. Diphenylacetylene Derivatives of Iron Carbonyl. *J. Am. Chem. Soc.* **1959**, *81*, 5307−5310.

(23) Lator, A.; Gaillard, S.; Poater, A.; Renaud, J.-L. Iron-Catalyzed Chemoselective Reduction of α,β-Unsaturated Ketones. *Chem. - Eur. J.* **2018**, *24*, 5770−5774.

(24) Lator, A.; Gaignard Gaillard, Q.; Mérel, D. S.; Lohier, J.-F.; Gaillard, S.; Poater, A.; Renaud, J.-L. Room Temperature Chemoselective Reductive Alkylation of Amines Catalyzed by a Well-Defined Iron(II) Complex using Hydrogen. *J. Org. Chem.* **2019**, accepted.

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