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One-Pot Conversion of Allylic Alcohols to α-Methyl Ketones via Iron-Catalyzed Isomerization–Methylation

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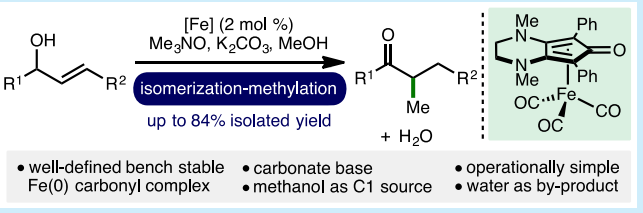
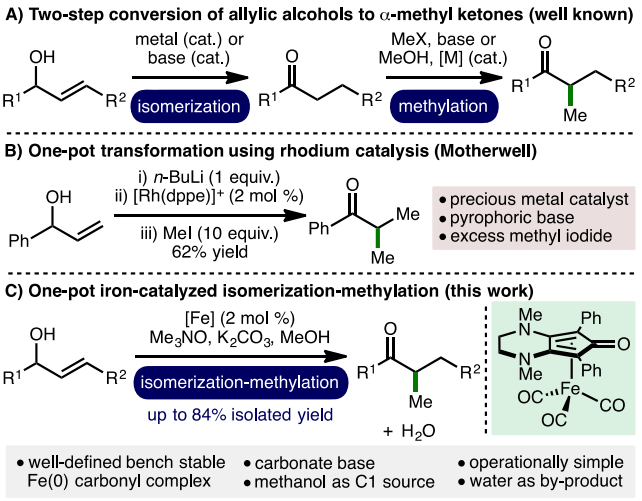
Supporting Information

ABSTRACT: A one-pot iron-catalyzed conversion of allylic alcohols to α-methyl ketones has been developed. This isomerization–methylation strategy utilized a (cyclopentadienone)iron(0) carbonyl complex as precatalyst and methanol as the C1 source. A diverse range of allylic alcohols undergoes isomerization–methylation to form α-methyl ketones in good isolated yields (up to 84% isolated yield).



Allylic alcohols are privileged motifs in synthetic chemistry due to their widespread availability and diverse reactivity profile.[1] An important transformation of allylic alcohols is the redox isomerization to form synthetically useful enolizable carbonyl compounds,[2] which can be performed using metal catalysts[3] or Brønsted base catalysts (Scheme 1A).[4] The

Scheme 1. Context and Outline of Iron-Catalyzed Strategy



subsequent incorporation of methyl groups via α-C(sp^3)-methylation can significantly impact the pharmacological properties of a molecule.[5] Many commonly employed methylation protocols utilize hazardous reagents such as methyl iodide, diazomethane, or dimethyl sulfate.[6] However, recent advances in borrowing hydrogen catalysis[7] have enabled methanol to be employed as an attractive alternative for ketone α-C(sp^3)-methylation,[8] using catalysts based on both precious metals and more abundant 3d transition metals.[9]

Motherwell and co-workers have reported the only direct one-pot conversion of secondary allylic alcohols to α-methyl ketones to date (Scheme 1B).[10] This interesting process involves alkoxide generation using *n*-BuLi followed by rhodium-promoted allylic alkoxide isomerization and subsequent alkylation using excess methyl iodide (10 equiv). Despite the benefits of a one-pot procedure, the disadvantages of this method include the use of a precious metal catalyst, a pyrophoric base, and superstoichiometric quantities of a toxic methylating agent. In an effort to address these drawbacks, we have utilized a (cyclopentadienone)iron(0) carbonyl complex (2 mol %)[11] for the one-pot isomerization–methylation of allylic alcohols to α-methyl ketones (Scheme 1C). This process employs a catalyst based on an earth-abundant transition metal, a carbonate base, and methanol as a C1 building block.

The isomerization–methylation of 1-phenylprop-2-en-1-ol **1** was selected as the model system for optimization studies (Table 1).[12] It was determined that (cyclopentadienone)-iron(0) carbonyl complex **2** (2 mol %),[13] Me_3NO (4 mol %),[14] and K_2CO_3 (2 equiv) in MeOH ([**1**] = 0.5 M) at 130 °C for 24 h, facilitated the isomerization–methylation of **1**, which gave product **3** in 88% NMR yield and 76% isolated yield (entry 1). Control experiments confirmed that no product was formed in the absence of iron precatalyst **2** or K_2CO_3 (entries 2 and 3). A selection of structurally related (cyclopentadienone)iron carbonyl precatalysts **4**–**8** did not enable the formation of α-methyl ketone **3** (entry 4).[15] Substituting K_2CO_3 for NaOH or KO*t*-Bu as base lowered the observed NMR yield of **3** (entries 5 and 6). Altering the concentration (entries 7 and 8), temperature (entries 9 and 10), reaction time (entry 11), or catalyst loading (entry 12), all reduced the efficiency of the isomerization–methylation of **1**. Gratifyingly, the quantity of K_2CO_3 could be lowered to 10 mol % without significant reduction in conversion (entry 13), which increased atom economy.[16]

With optimized reaction conditions in hand (Table 1, entry 1), the scope of the iron-catalyzed isomerization–methylation protocol

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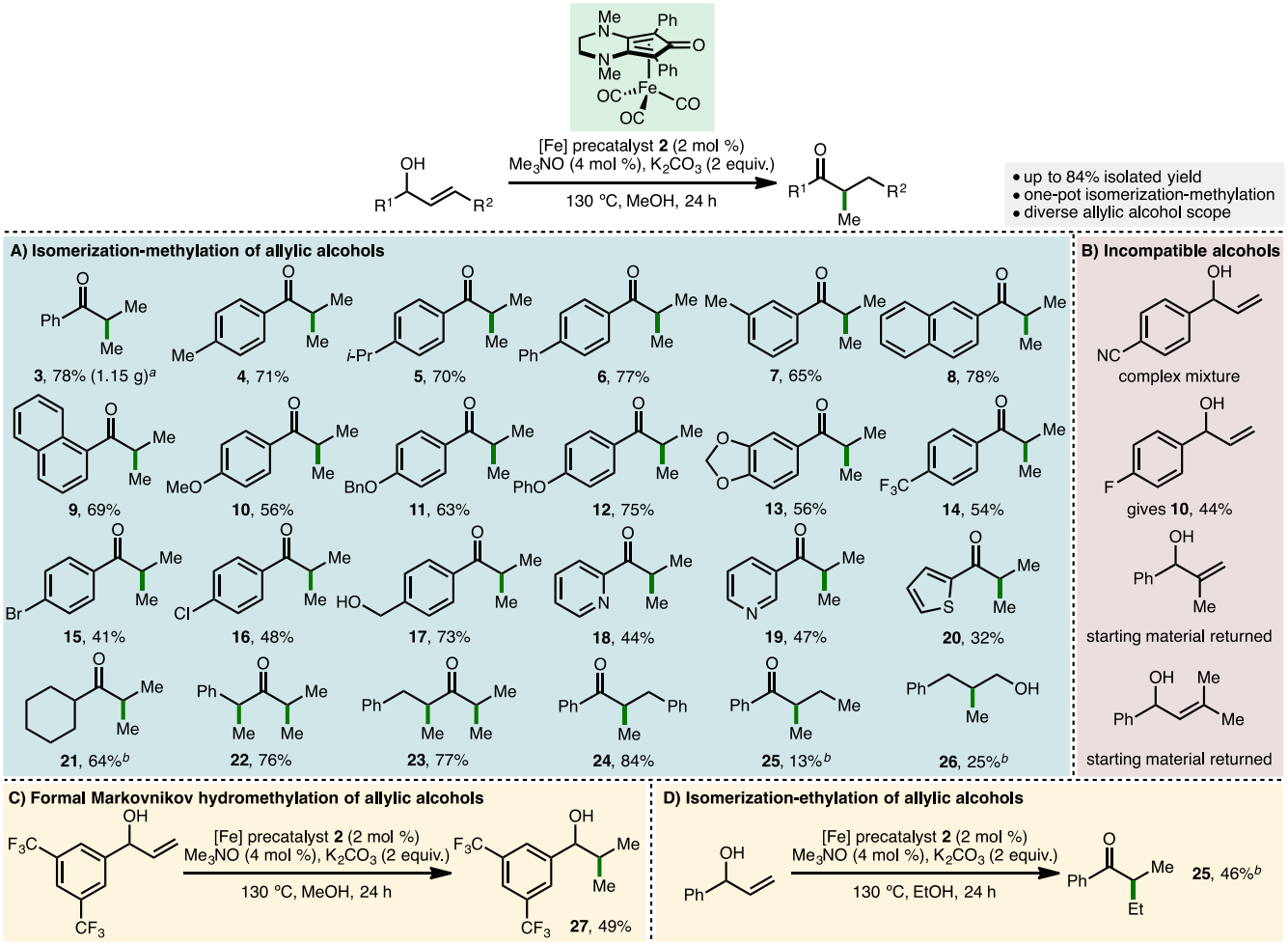
Scheme 2. Scope of the Fe-Catalyzed Isomerization-Methylation Protocol*



*Reactions were performed using allylic alcohol (0.5 mmol) and reagent grade MeOH. Isolated yields after chromatographic purification are reported unless stated otherwise. [a]Ten mmol of allylic 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.

was explored (Scheme 2A/B).[17] A variety of secondary allylic alcohols were tolerated, which provided access to α-methyl ketones in good yields (products **3**–**25**). The isomerization–methylation procedure was performed on a 10 mmol scale to access 1.15 g of product **3** (78% isolated yield). Within the aryl motif, various alkyl or aryl substitution was accommodated at the 3- and 4-positions in addition to the sterically encumbered 1-naphthyl motif. Electron-releasing (4-OMe, 4-OBn, and 4-OPh) and electron-withdrawing (4-CF_3) aryl substituents were accommodated. However, the presence of a nitrile functionality within the allylic alcohol produced a complex mixture of products, presumably due to competing CN reduction. Halide substitution was tolerated within the allylic alcohol, introducing an additional functional handle into ketones **15** and **16**. When 4-F aryl substitution was explored, α-methyl ketone **10** was obtained in 44% isolated yield, which was presumably formed via nucleophilic aromatic substitution of the corresponding 4-F substituted aryl ketone intermediate. Selective isomerization–methylation occurs in the presence of a benzyl alcohol functionality, with product **17** formed in 73% isolated yield. Pyridyl and thiophene motifs were tolerated within the secondary allylic alcohols (products **18**–**20**). The aryl motif could be replaced by cyclohexyl, benzyl, and homobenzyl groups to access dialkyl ketones **21**–**23** in good yields. Additional alkene substitution within the allylic alcohols was also examined. 1,2-Disubstitution within the alkene was tolerated, which gave ketones **24** and **25**. However, allylic alcohols containing 1,1-disubstituted or trisubstituted alkenes were unreactive, which was attributed toward increased steric congestion preventing alcohol dehydrogenation. Finally, 25% conversion to β-C(sp^3)-methylated alcohol **26** was observed when cinnamyl alcohol was utilized as the substrate.

Upon evaluating the effect of electron-withdrawing aryl substituents on the isomerization–methylation process, it was found that 3,5-$(CF_3)_2$ aryl substitution resulted in the formation of secondary alcohol **27** in 49% isolated yield (Scheme 2C). The accumulative inductive effect of the two trifluoromethyl groups increased the electrophilicity of the carbonyl such that the intermediate α-methyl ketone underwent subsequent transfer hydrogenation. This one-pot transformation represented a formal Markovnikov hydromethylation of the allylic alcohol starting material.[18] Furthermore, the model reaction was also performed using ethanol as solvent, which gave 46% conversion to α-ethylated ketone **25** (Scheme 3D).

To gain mechanistic insight, the plausibility of various possible intermediates was investigated (Scheme 3A). Enone **28** and propiophenone **29** would be formed via redox isomerization of allylic alcohol **1**, whereas secondary alcohol **30** would be generated upon transfer hydrogenation of **29**.

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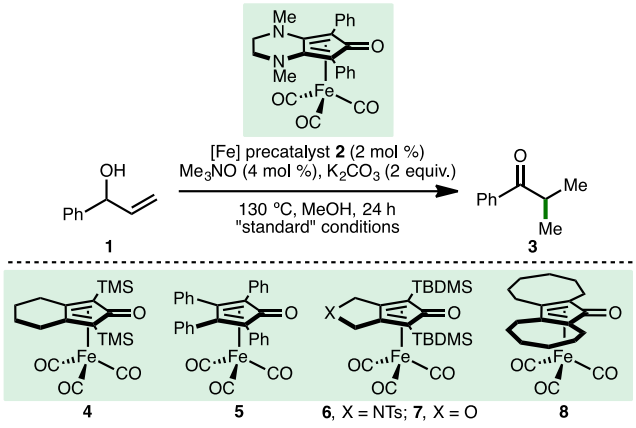
Table 1. Optimization of Model Reaction*

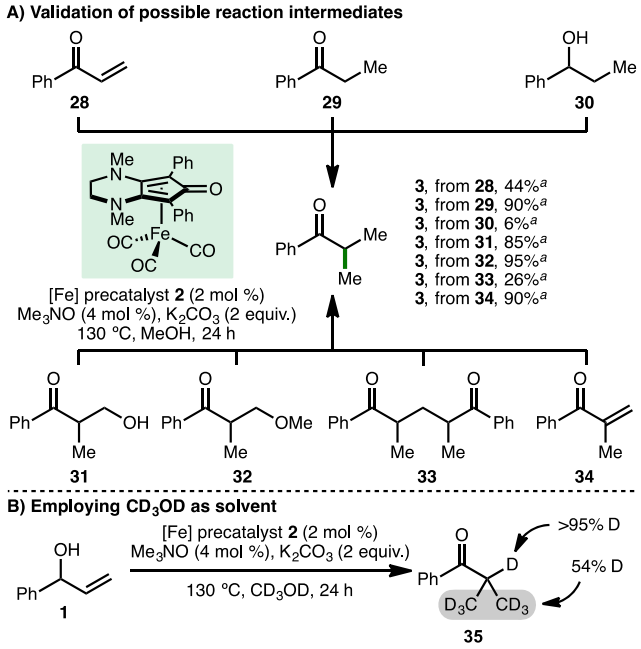


entry	variation from "standard" conditions	yield[a] (%)
1	**none**	**88 (76)**
2	no [Fe] precatalyst	<2
3	no K_2CO_3	<2
4	[Fe] precatalysts **4**-**8** (2 mol %) instead of **2**	<5
5	NaOH (2 equiv) instead of K_2CO_3	47
6	KO*t*-Bu (2 equiv) instead of K_2CO_3	57
7	[**1**] = 0.25 M	73
8	[**1**] = 1 M	80
9	120 °C	32
10	140 °C	85
11	4 h	61
12[b]	[Fe] precatalyst **2** (1 mol %)	37
13	K_2CO_3 (0.1 equiv)	78

*Performed using 0.5 mmol of **1** and reagent grade MeOH. [**1**] = 0.5 M. [a]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. [b]Me_3NO (2 mol %).

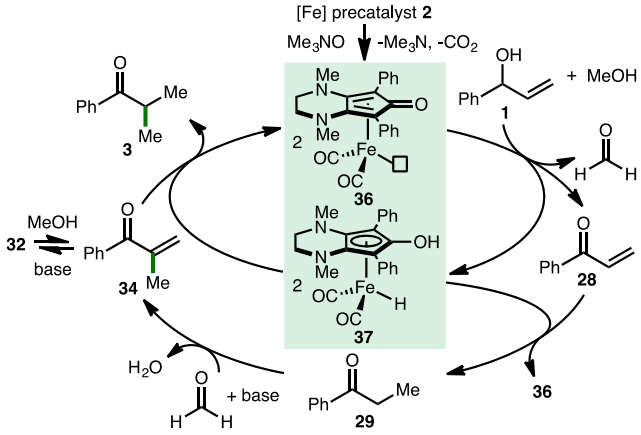
Furthermore, *β*-hydroxy ketone **31**, methyl ether **32**, diketone **33**, and enone **34** were also possible intermediates. As such, compounds **28**−**34** were individually subjected to the optimized reaction conditions, and each gave conversion to *α*-methyl ketone **3**, which indicated that all compounds are plausible reaction intermediates. Alcohol **30** and diketone **33** only gave 6% and 26% conversion to **3** after 24 h, respectively, which indicated that these species would retard product formation if they are indeed formed during the course of the reaction. The reaction progress with time was monitored for the isomerization−methylation of allylic alcohol **1**.[12] Product **3** was initially formed slowly, with only 10% conversion to **3** observed after 2 h. Beyond 2 h, the rate of formation of **3** increased, with 60% conversion observed after 4 h in addition to 5% of ketone **29**. Conversion to **3** reached a maximum of 93% after 16 h after which time small quantities of the corresponding alcohol was observed. The initial slow formation of product **3** in addition to the observation of ketone **29** over the first 2 h of reaction suggested an initial isomerization of allylic alcohol **1** to ketone **3**, followed by *α*-methylation. Further mechanistic information was provided by employing CD_3OD as solvent (Scheme 3B). Significant deuterium incorporation was observed at the *α*- and *β*-positions within product **35**. The 54% D incorporation at the *β*-position indicated the involvement of an iron hydride species in the reaction mechanism, which would be formed upon dehydrogenation of allylic alcohol **1** or methanol. As such, the proposed mechanism proceeds via initial Me_3NO-promoted CO decoordination of precatalyst **2** to form **36** (Scheme 4), which promotes

Scheme 3. Mechanistic Experiments



[a]Determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard.

Scheme 4. Plausible Mechanism



dehydrogenation of allylic alcohol **1** and methanol to form enone **28** and formaldehyde, respectively. Hydrogenation of **28** by iron−hydrogen complex **37** gives ketone **29**, which can undergo a subsequent aldol condensation reaction to produce enone **34**. Reduction of enone **34** by **37** gives *α*-methyl ketone **3** with regeneration of **36**.

To conclude, an operationally simple and efficient one-pot conversion of allylic alcohols to *α*-methyl ketones has been developed using an iron-catalyzed isomerization−methylation approach. A variety of secondary allylic alcohols was converted to *α*-methyl ketones in good isolated yields (up to 84% isolated yield). The process employs a catalyst based on an earth-abundant transition metal, a carbonate base, and methanol as a C1 building block, which improves upon the existing synthetic method.[10]

■ ASSOCIATED CONTENT

Supporting Information

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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 10.17035/d.2019.0084111418 (accessed September 14, 2019).

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