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Iron-Catalyzed Hydroalkylation Reaction of *α*,*β*-Unsaturated Ketones with Ethers

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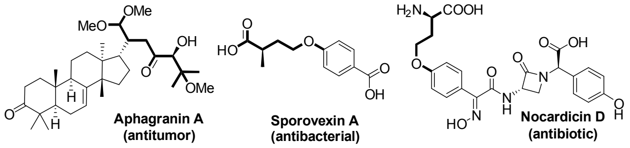
A general strategy for the hydroalkylation of vinylketones using ethers catalyzed by iron catalyst was described. This catalytic method permits direct transformation of easily accessible and abundant precursors into highly substituted, structurally diverse and functionally concentrated products.

Highly substituted and functionally concentrated *α*-substituted ether fragments have been extensively observed in many biologically active compounds and industrial materials (Scheme 1).[1] Therefore, the development of efficient and practical methods to synthesize diverse *α*-substituted ethers is important to discover biologically active molecules. Traditionally, the reliable approaches to access the *α*-substituted ethers include the Williamson ether synthesis, Lewis acid mediated nucleophilic substitution of acetals and hydroalkoxylation of alkenes, the Buchwald-Hartwig reaction and the Ullmann reaction etc.[2] In spite of these conventional methods are still widely used in organic synthesis, the environmental and economic requirements have driven organic chemists to discover new reactions such as enabling the direct derivation of the ubiquitous C-H bond. Therefore, the use of commercial available simple ethers as starting materials to construct complex and functionally concentrated ethers *via* direct C-H bond functionalization will be highly desirable. Early in 1982, Citterio and co-workers reported $TiCl_3$ mediated hemolytic reductive alkylation of methylvinyl ketone with ethers.[3] After that, an approach of metal carbene insertion into a C-H bond adjacent to an oxygen atom was developed for the synthesis of ether derivatives.[4] In addition, the direct C-C bond formation via C-H bond activation/cleavage adjacent to an oxygen atom was proved to be another useful method in organic synthesis.[5,6] Li and colleagues elegantly applied the cross-dehydrogenative coupling (CDC) reaction to prepare complex ethers using simple terminal alkynes, active methylene compounds, alcohols and ketones[7]. On the other hand, J. Li and co-workers has shown the possibilities of coupling of simple ethers with various compounds such as alkenes, 1,*n*-enynes and alkynylphenol by C-H activation[8]. Furthermore, Liu and co-workers have demonstrated the coupling of ethers with aldehydes, ketones and trifluoroborate[9]. In addition, Pan and co-workers developed the relevant chemistry to synthesize cyclic ethers from alkenylcarboxylic acids and benzothiazoles[10]. Moreover, Lei and co-workers have demonstrated the direct coupling of ethers with different compounds, such as arylboronic acids and *N*-alkoxyamides[11]. In contrast to this, Z. Li[12] and Macmillan[13] reported the direct coupling of ethers with 1,3-dione and heteroarene respectively. Recently, the transition-metal-catalyzed etherification of unactivated C-H bonds has also been developed as powerful method to synthesize functional ethers.[14] Despite the explosive advances achieved in the past decades, the direct coupling of sp^3 carbon of ethers with simple alkenes for the preparation of structurally diverse ethers has been difficult. Moreover, most of such demonstrated coupling reactions were limited to cyclic ethers, which will significantly restrict the usage in practice. To the best of our knowledge, there are quite a few reports on the direct coupling of *α*,*β*-unsaturated ketones with various ethers to assemble the highly substituted, structurally diverse ethers with concomitant retention of the synthetically useful carbonyl group in the final products.[3,15] Known approaches lack broad generality, and the scope is narrow. More importantly, the reported approaches were normally limited to use methyl or aryl ketone as their substrate,



Scheme 1. Selective Biological Molecules Containing *δ*-Ether Group Tethered Carbonyl Fragment.

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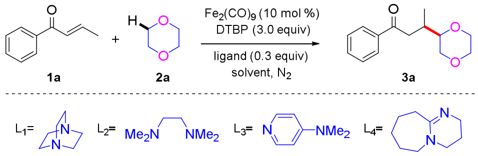
confining their structural diversity. Strategy trying to address this drawback appears to be indispensable and urgent. Herein, we would like to communicate our discovery of direct coupling between ethers and *α*,*β*-unsaturated ketones catalyzed by ferrous system.

Our study was initiated by investigating the coupling reaction of (*E*)-1-phenylbut-2-en-1-one (**1a**), 3 equivalents of *di-tert*-butyl peroxide and 1,4-dioxane using 10 mol % $Fe_2(CO)_9$ as the catalyst at 120 °C. And the anticipated coupling product was obtained in 46% yield. After investigating the solvent effect for the model reaction, it was realized that 0.25 M of **1a** in 1,4-dioxane could afford the product in better yield (entries 2-4). Inspired by previous reports,[7a,8a] different ligands were screened to improve the catalytic efficiency. Pleasing, it was found that the yield of the desired product could be increased significantly up to 60% when the ligand N^1,N^1,N^2,N^2-tetramethylethane-1,2-diamine (TMEDA, $\mathbf{L_2}$) was used (entry 6).[8a] Further studies showed that the use of co-solvents of 1,4-dioxane with 2,2,2-trifluoroethanol (TFE) would give a higher yield of the product (entry 9). However, when the temperature was decreased to 105 °C or 110 °C, the desired product was only obtained in trace amount even though prolonging the reaction time. Finally, adjusting the reaction temperature to 115 °C could benefit the formation of the product in a 70% yield (entry 12).

With the optimized reaction conditions in hand, various ethers as coupling partners were tested to react with (*E*)-1-phenylbut-2-en-1-one (**1a**).

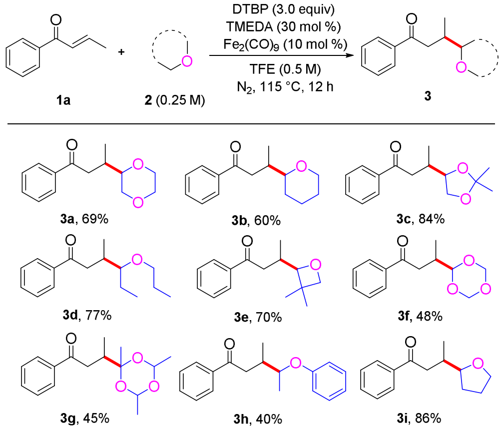
Table 1. Optimization of Reaction Conditions of Iron-Catalyzed Hydroalkylation of (*E*)-1-Phenylbut-2-en-1-one **1a** with Dioxane.[a,b]



entry	ligand	time (h)	solvent (mL)	temp (°C)	yield (%)
1	-	6	dioxane (2.0)	120	46
2	-	6	dioxane (1.0)	120	31
3	-	6	dioxane (1.5)	120	39
4	-	6	dioxane (2.5)	120	45
5	L_1	6	dioxane (2.0)	120	54
6	L_2	6	dioxane (2.0)	120	60
7	L_3	6	dioxane (2.0)	120	52
8	L_4	6	dioxane (2.0)	120	trace
9[c]	L_2	6	dioxane (2.0) /TFE (1.0)	120	65
10[c]	L_2	24	dioxane (2.0) /TFE (1.0)	105	Trace
11[c]	L_2	24	dioxane (2.0) /TFE (1.0)	110	Trace
12[c]	$\mathbf{L_2}$	**12**	**dioxane (2.0) /TFE (1.0)**	**115**	**70**

[a] Unless otherwise noted, typical reaction conditions: **1a** (0.5 mmol), $Fe_2(CO)_9$ (0.05 mmol, 10 mol%), DTBP (1.5 mmol, 3.0 equiv), 1,4-dioxane (1.0-2.5 mL), 120 °C, 6 h, N_2. [b] Isolated yields. [c] Reaction conditions: **1a** (0.5 mmol), $Fe_2(CO)_9$ (0.05 mmol, 10 mol%), DTBP (1.5 mmol, 3.0 equiv), ligand (0.15 mmol, 30 mol%), 1,4-dioxane (2.0 mL), TFE (1.0 mL), 105-120 °C, 6-24 h, N_2.

Table 2. Iron-Catalyzed hydroalkylation of (*E*)-1-phenylbut-2-en-1-one **1a** with Different Ethers.[a,b,c]



[a] Isolated yields of inseparable diastereomers. [b] dr was approximated as 1:1, determined by ^{1}H NMR. [c] Reaction condition: **1** (0.5 mmol), **2** (2.0 mL), TFE (1.0 mL), $Fe_2(CO)_9$ (18 mg, 0.05 mmol, 10 mol%), TMEDA (18 mg, 0.15 mmol, 30 mol%), DTBP (219 mg, 1.5 mmol, 3.0 equiv), 115 °C, N_2, 12 h.

It was observed that the cyclic ether compounds such as tetrahydro-2*H*-pyran, 2,2-dimethyl-1,3-dioxolane and tetrahydrofuran all worked well with **1a** to furnish the corresponding products in good to high yields and with about 1:1 diastereoselectivities. When the 1,3,5-trioxane or 2,4,6-trimethyl-1,3,5-trioxane was used to react with **1a**, only moderate yields of the desired products could be obtained respectively. In addition, when the aliphatic ether such as propyl ether was subjected to this reaction, the product **3d** could be isolated in 77% yield and with about 1:1 diastereoselectivity. While only 40% yield of the product **3h** was obtained when the ethyl phenyl ether was applied in this reaction.

Following, with respect to functional group tolerance and scope of vinylketones were thus addressed, and the results were summarized in Table 2. Firstly, various *α*,*β*-unsaturated ketones bearing substituents at *β*-position were tested to react with tetrahydrofuran. Generally, regarding (hetero)aryl substituted *α*,*β*-unsaturated ketones, both electron-donating (**3i-3r**, and **3t-3v** Table 3) and election-withdrawing (**3da**; **3ab-3cb**) groups on the phenyl ring were all well tolerated, providing the ideal products in moderate to good yields. Gratifyingly, aryl vinylketones bearing synthetically useful functional groups such as -OBn, $-NMe_2$, -Ph, -F, -OMe, -Br, -CN, $-CF_3$, -Cl (**3da**; **3ab-3cb**) were also well accommodated to yield the corresponding products which permitted to be further transformed in next step (**3aa-3ea**; **3ab-3eb**). Moreover, the aliphatic-substituted *α*,*β*-unsaturated ketone such as **1s** also could react well with tetrahydrofuran to give the desired product in 61% yield. Simultaneously, similar reactivity was also observed from *α*,*β*-unsaturated ketone with a substituent such as methyl, benzyl, or long carbon chain. Furthermore, other ethers were also proved to be efficient coupling partners with diverse *α*,*β*-unsaturated ketones. However, *α*,*β*-positions both substituted unsaturated ketone showed poor reactivity, almost no desired product was formed under the optimized reaction conditions.

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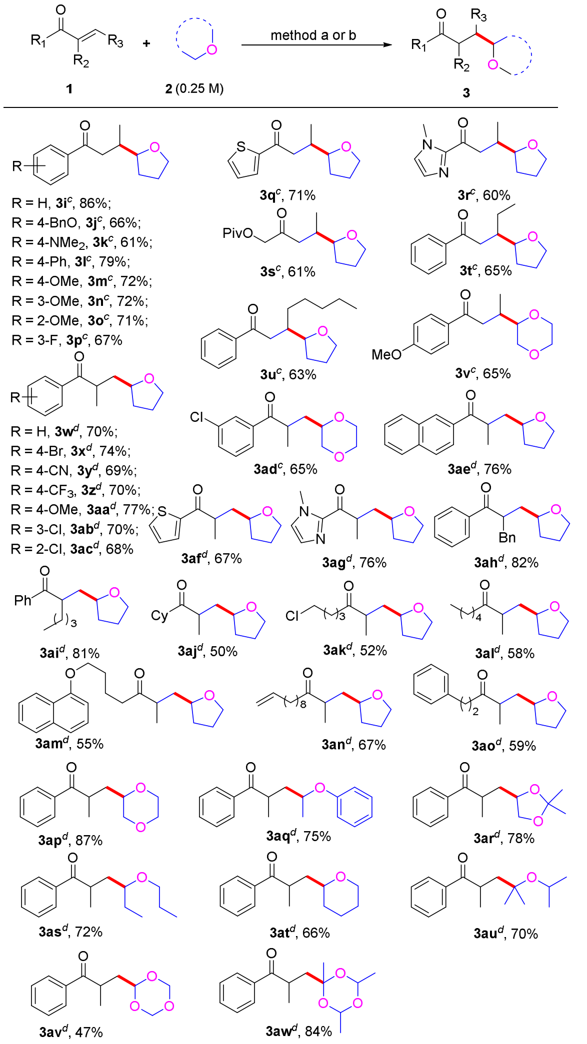
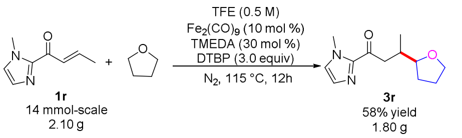
Table 3. Iron-Catalyzed Hydroalkylation of Different α,β-Unsaturated ketones **1** with Different Ethers. [a,b]

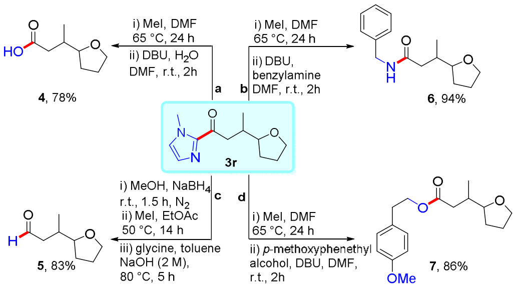


[a] Isolated yields of inseparable diastereomers. [b] dr was approximated as 1:1, determined by ^{1}H NMR. [c] Reaction condition (method a): **1** (0.5 mmol), **2** (2.0 mL), TFE (1.0 mL), $Fe_2(CO)_9$ (18 mg, 0.05 mmol, 10 mol%), TMEDA (18 mg, 0.15 mmol, 30 mol%), DTBP (219 mg, 1.5 mmol, 3.0 equiv), 115 °C, N_2, 12 h. [d] Reaction condition (method b): **1** (0.5 mmol), **2** (2.0 mL), HOAc (60 mg, 1.0 mmol, 2.0 equiv), $Fe_2(CO)_9$ (18 mg, 0.05 mmol, 10 mol%), TMEDA (18 mg, 0.15 mmol, 30 mol%), DTBP (293 mg, 2.0 mmol, 4.0 equiv), 115 °C, N_2, 24 h.

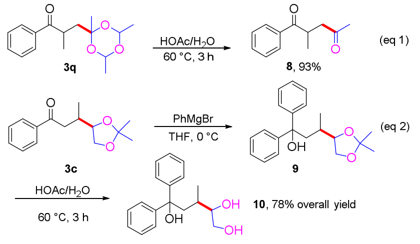
To test the potential application of current method in organic synthesis, a gram-scale reaction of imidazolyl substituted vinylketone **1r** with tetrahydrofuran was performed. And the desired product **3r** was isolated in 58% yield (Scheme 2). Next, the derivative reactions of the coupling products were carried out (Scheme 3). The acyl-imidazole moiety allows the product **3r** to be easily converted into other functional and useful carbonyl and carboxyl derivatives such as acid **4**, aldehyde **5**, amide **6**, and ester **7** in good to excellent yields respectively.[16] Furthermore, the useful 1,4-diketone compound **8** could also be obtained in high yield with treatment of **3q** in acetic acid/water solution (Scheme 4, eq.1). The 1,2,5-triol product **10** could be obtained in 78% overall yield after nucleophilic addition and deprotection steps from the compound **3c** (Scheme 4, eq.2).



Scheme 2. Gram-scale Reaction of **1r** with Tetrahydrofuran.

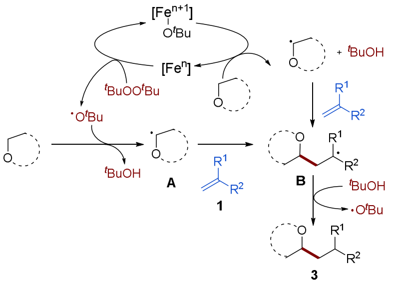


Scheme 3. Derivative Reactions of **3r** to Form Other Functional Carbonyl and Carboxyl Compounds.



Scheme 4. Derivative Reactions of **3q** and **3c** to Form 1,4-Diketone and 1,2,5-Triol Products.

To disclose the possible mechanistic pathway of this iron-catalyzed C-C bond formation reaction between vinylketone and ether, the reaction of 2-methyl-1-phenylprop-2-en-1-one (**1w**) with mixture of tetrahydrofuran (THF) and its deuterated analogue (THF-d_8) (1:1 mole ratio) was carried out under the optimized reaction conditions. A kinetic isotopic effect value (KIE) of 5.7 was observed (Please see the details in Supporting Information), which suggested the sp^3 C-H activation to be the possible rate-determining step in this reaction.



Scheme 8. Proposed Plausible Mechanism for the Iron-Catalyzed Hydroalkylation Reaction of Vinylketone.

On the basis of our experimental results and combined with previous reports[7-13], a proposed mechanistic pathway was demonstrated as in Scheme 6. The iron catalyst was believed to facilitate the generation of a *tert*-butoxy radical.[17,18] Subsequent hydrogen abstraction by the *tert*-butoxy radical would generate an oxygen-adjacent carbon radical which could react with the double bond of α,β-unsaturated ketone. Following, the radical intermediate **B** would react with *tert*-butanol and afford the ether

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product along with regenerating the *tert*-butyloxy radical. The observed selectivity of the product in this hydroalkylation reaction could be attributed to the persistent radical effect.[19] The hydrogen bonding between the oxygen of the carbonyl group and the hydrogen of the 2,2,2-trifluoroethanol (TFE) or acetic acid possibly could lower the activation energy of the radical reaction and then improve the coupling efficiency.[20]

In conclusion, an iron-catalyzed hydroalkylation of vinylketones using simple ethers was developed. In this work, both cyclic and linear simple ethers could couple well with different *α*- and *β*-substituted vinylketones to form multifunctional and complex ether products in moderate to high yields. Moreover, the availability of gram-scale synthesis and the ease of transformation of the coupling products obtained via this protocol to be synthetically useful 1,4-dicarbonyl and 1,2,5-triol compounds has greatly highlighted current method in organic synthesis.

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Conflicts of interest

There are no conflicts to declare.

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