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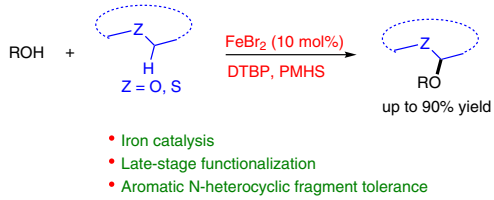
Iron-Catalyzed Direct Cross-Coupling of Ethers and Thioether with Alcohols for the Synthesis of Mixed Acetals

Wei Han *[a,b]
Lu Cheng[a] §
Hongyuan Zhao[a] §

[a] Jiangsu Key Laboratory of Biofunctional Materials, Key Laboratory of Applied Photochemistry, School of Chemistry and Materials Science, Nanjing Normal University, Wenyuan Road NO.1, Nanjing 210023, P. R. of China
hanwei@njnu.edu.cn
[b] Jiangsu Collaborative Innovation Center of Biomedical Functional Materials, Nanjing 210023, P. R. of China

§ These authors contributed equally to this work.



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Abstract An iron-catalyzed direct O-alkylation of alcohols via α-C(sp^3)–H activation of ethers and a thioether has been established that tolerates cyclic and acyclic ethers and alcohols containing aromatic N-heterocyclic moieties, providing an efficient and green method for the synthesis of mixed acetals with good to excellent yields. The robustness of this protocol is demonstrated by the late-stage oxidation of a structurally complex natural product.

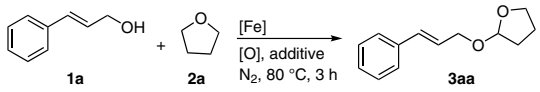
Key words iron catalysis, oxidation, alcohols, ethers, mixed acetals, synthetic methods

The mixed acetal unit constitutes an important structural feature that is widely found in pharmaceuticals and fragrances and is also a common synthetic intermediate.[1] Among the methods developed to prepare mixed acetals,[2] the direct sp^3 α-C–H bond activation and alkoxylation of ethers is the most straightforward and efficient.[3] Typically, cross-dehydrogenative coupling of alcohols with α-C(sp^3)–H of ethers gives access to mixed acetals. Although a number of methods have been reported for the transformation (using, for example, THF in combination with SO_2Cl_2,[4] CAN,[5] TsCl/NaH,[6] $CrCl_2/CCl_4$,[7] peroxy-λ^3-iodane/CCl_4,[8] VCl_3/CCl_4,[9] Mn(0)/CCl_4,[10] or $BrCCl_3$/2,4,6-collidine[11]), the use of stoichiometric amounts of reagents makes these processes environmentally unfriendly.

In contrast, more modern and greener methodologies based on catalysis are much less well developed. Recently, two examples of catalytic systems based on $CuBr_2$[12] and Cp_2TiCl/Mn(0)[13] for direct tetrahydrofuranylation of alcohols have been reported. However, they all display limited scope, and are only applicable to symmetrical cyclic ethers such as tetrahydrofuran and/or tetrahydropyran.

Here, we report an efficient and selective iron-catalyzed direct coupling of alcohols with a variety of ethers and a thioether. The practicality of the protocol is further illustrated by late-stage functionalization of a structurally complex molecule.

Table 1 Optimization of Reaction Conditions[a]



1a **2a** **3aa**

Entry	[Fe] (%)	Oxidant	Additive	Yield of **3aa** (%)[b]
1	$FeCl_2$	DTBP	PMHS	78
2	$FeCl_2$	DTBP	–	30
3	–	DTBP	PMHS	0
4	$FeCl_3$	DTBP	PMHS	77
5	**$FeBr_2$**	**DTBP**	**PMHS**	**85**
6	$Fe(acac)_2$	DTBP	PMHS	25
7	$Fe(acac)_3$	DTBP	PMHS	25
8	$Fe(OAc)_2$	DTBP	PMHS	trace
9	$Fe^{II}Pc$	DTBP	PMHS	trace
10	$FeBr_2$	TBHP	PMHS	70
11	$FeBr_2$	$K_2S_2O_8$	PMHS	20
12	$FeBr_2$	BPO	PMHS	54
13	$FeBr_2$	O_2 (1 atm)	PMHS	20
14	$FeBr_2$	DTBP	$(EtO)_3SiH$	25
15	$FeBr_2$	DTBP	Et_3SiH	79
16	$FeBr_2$	DTBP	$PhSiH_3$	80

[a] Reaction conditions (unless otherwise stated): **1a** (0.25 mmol), [Fe] (10 mol%), [Si] (3 equiv), oxidant (2 equiv), THF (2 mL), 80 °C, and 3 h. $Fe^{II}Pc$: Iron(II) phthalocyanine; BPO: Dibenzoyl peroxide.
[b] Isolated yield.

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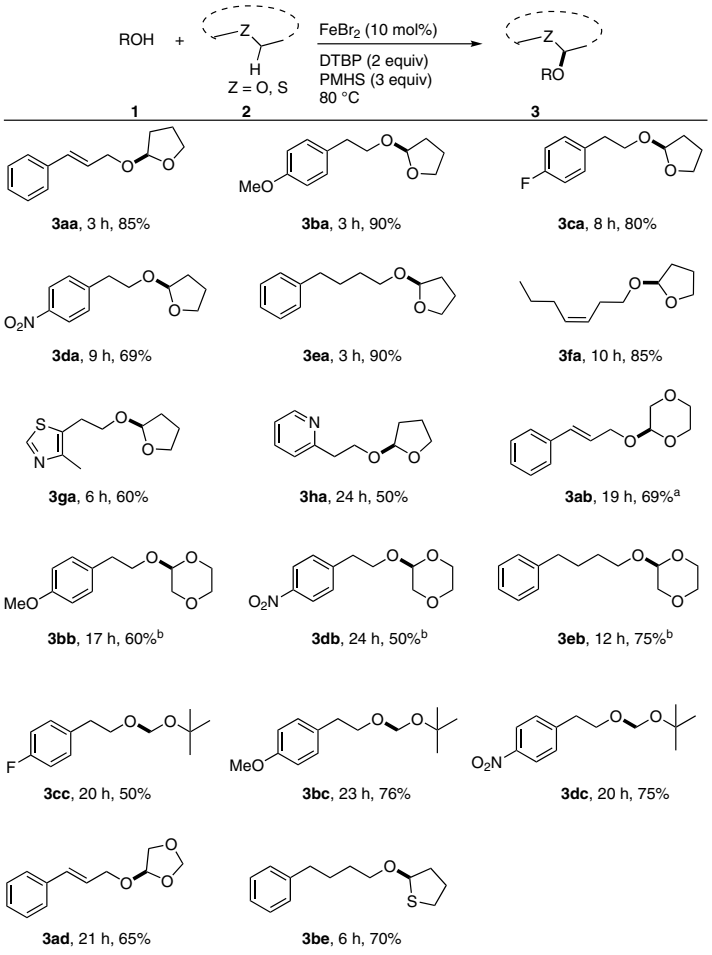
Encouraged by our recent studies on iron-catalyzed oxidations[14,15] for which the performance of the catalytic systems based on PMHS (polymethylhydrosiloxane) additive was highly desirable, we initiated our investigation by examining $FeCl_2$-catalyzed direct cross-coupling of cinnamyl alcohol (**1a**) and THF with DTBP as an oxidant and polymethylhydrosiloxane (PMHS)[16] as an additive (Table 1).

To our delight, the desired product **3aa** could be obtained in 78% yield (Table 1, entry 1), whereas poor results were observed in the absence of PMHS or $FeCl_2$ (entries 2–3). Further optimization showed that the inclusion of $FeBr_2$ resulted in a higher yield (85%) and $FeCl_3$ led to a slightly lower yield (77%), while other tested iron compounds, such as $Fe(acac)_2$ (25%), $Fe(acac)_3$ (25%), $Fe(OAc)_2$ (0), and $Fe^{II}Pc$ (0) had a remarkable negative influence on the reaction (entries 4–9). Reactions with other oxidants did not give any improvement (entries 10–13). Finally, replacing PMHS with $(EtO)_3SiH$, Et_3SiH, or $PhSiH_3$ as the additive gave **3aa** in 25, 79, and 80% yields, respectively (entries 14–16).

Using the optimized reaction conditions (Table 1, entry 5), we then explored the substrate scope of this cross-dehydrogenative coupling reaction. As shown in Scheme 1, a variety of alcohols reacted smoothly with various ethers under the reaction conditions to provide the desired mixed acetals in moderate to excellent yields. Notably, (*Z*)-hept-3-en-1-ol (**1f**) did not isomerize into the corresponding thermodynamically more stable *E*-olefin and afforded the desired product with *Z*-configuration in 85% yield (**3fa**). Other functional groups such as methoxy, fluoro, and nitro were also well tolerated. Remarkably, catalytic oxidative couplings of alcohols containing N-heteroaryl moieties with THF to give mixed acetals worked well under iron-based catalysis; this is a transformation that remains a challenge owing to the oxidative lability of the fragments and their ligating ability leading to catalyst deactivation and has not been achieved by previous studies. Specifically, 2-(4-methylthiazol-5-yl)ethan-1-ol (**3g**) and 2-(pyridin-2-yl)ethan-1-ol (**3h**) were reactive in the reaction, thus delivering the expected products in 60 and 50% yields, respectively. Further-



Scheme 1 Iron-catalyzed direct cross-coupling of ethers with alcohols. Reaction conditions (unless otherwise stated): **1** (0.25 mmol), $FeBr_2$ (10 mmol%), PMHS (3 equiv), DTBP (2 equiv), solvent (2 mL), 80 °C; [a] 120 °C; [b] 100 °C. Isolated yields are given.

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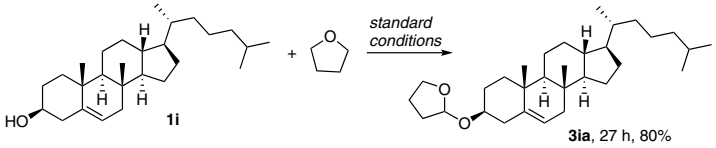


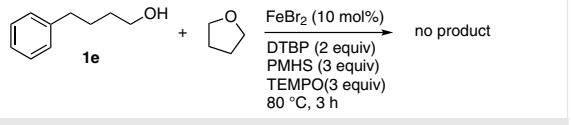
Equation 1

more, comparable outcomes could be achieved with use of 1,4-dioxane as the substrate by increasing the reaction temperature to 100–120 °C. After testing the transformation with symmetric ethers, THF and 1,4-dioxane, we then tried to extend the substrate scope of the reaction to asymmetric ethers as substrates, to investigate the reactivity and regioselectivity of this system.

Acyclic methyl *tert*-butyl ether (MTBE), a typical unactivated substrate, which has rarely been demonstrated under CDC reactions, proceeded well via primary sp^3 C–H activation under the optimized reaction conditions (**3cc**–**dc**). 1,3-Dioxolane was then used in this transformation and underwent coupling with cinnamyl alcohol (**1a**) to give **3ad** in 65% yield with high regioselectivity even in the presence of a more acidic sp^3 C–H. The abnormal regioselectivity of the reaction on the substrate 1,3-dioxolane could be ascribed to a bridgehead radical being extremely difficult to form.[17] Notably, the methodology was also suitable for tetrahydrothiophene (**3be**; 70%).

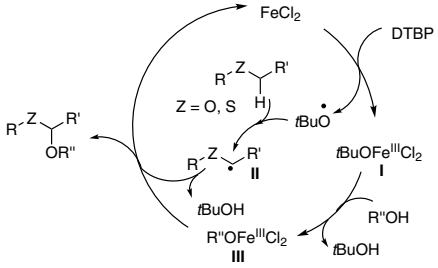
To demonstrate the synthetic utility of the methodology, the structurally complex natural product cholesterol was subjected to the reaction under the optimized conditions. As shown in Equation 1, the reaction proceeded smoothly, giving the desired product **3ia** in 80% yield.

To get an insight into the mechanism, control experiments were carried out. A radical trapping experiment was conducted by using TEMPO as a radical scavenger (Equation 2). No desired product was observed in the reaction of **1e** with THF. This result suggests that the reaction probably includes a radical process. In addition, an intermolecular competing kinetic isotope effect (KIE) experiment was performed (Equation 3). As a result, a significant KIE was observed with k_H/k_D = 5.26 (the KIE was determined by ^{1}H NMR spectroscopy by analyzing the ratio of **3ea** and **3ea**-D), indicating that C(sp^3)–H bond cleavage may be one of the rate-determining steps of this transformation.



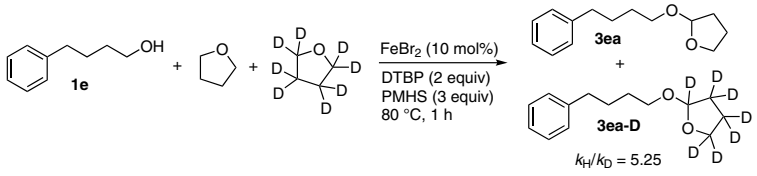
Equation 2

On the basis of the above results and previous studies,[17b,18–21] a plausible catalytic mechanism is presented in Scheme 2. Initially, the iron catalyst ($FeCl_2$) reacts with the oxidant DTBP to form the *tert*-butoxyl radical and *t*BuOFe^{III}-Cl_2 (**I**).[18] Then, the *tert*-butoxyl radical abstracts a hydrogen atom from the ether to produce carbon radical intermediate **II**,[17b,18–20] while the *t*BuOFe$^{III}Cl_2$ is attacked by the alcohol R″OH to give R″OFe$^{III}Cl_2$ species **III**.[18–20] Finally, the carbon radical intermediate **II** is trapped by the R″OFe$^{III}Cl_2$ species **III** to afford the product and regenerate the iron catalyst for the next catalytic cycle.



Scheme 2 Proposed mechanism for the transformation

In summary, we have developed a mild, efficient, $FeCl_2$-catalyzed direct O-alkylation of alcohols via α-C(sp^3)–H activation of ethers and a thioether for the synthesis of mixed acetals.[22] This transformation is outstanding for its inherent advantages, including nontoxic iron catalysis, high atom economy, cheap and widely available substrates without pre-established functional groups, and a broad substrate scope with excellent aromatic N-heterocyclic fragment compatibility. The synthetic utility of this transformation was demonstrated by the late-stage O-alkylation of a natural complex molecule.



Equation 3

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707162.

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(22) **Typical procedure for the synthesis of 3ba**: A 25 mL flask equipped with a magnetic stir bar was charged with $FeBr_2$ (5.5 mg, 0.025 mmol), 2-(4-methoxyphenyl)ethanol **1b** (39.2 mg, 0.25 mmol), PMHS (170 μL, 0.75 mmol), DTBP (94 μL, 0.5 mmol) and THF (2 mL) before standard cycles evacuation and backfilling with dry N_2. The mixture was then stirred at 80 °C for 3 h. After cooling to room temperature, the reaction mixture was diluted with water (15 mL) and extracted with diethyl ether (3 × 15 mL). The organic phases were combined, and the volatile components were evaporated in a rotary evaporator. The residue was purified by column chromatography on silica gel (petroleum ether/diethyl ether = 50:1) to afford **3ba** (49.0 mg, 90%) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 (dt, J_1 = 8.73 Hz, J_2 = 2.54 Hz, 2 H), 6.87 (dt, J_1 = 8.73 Hz, J_2 = 2.54 Hz, 2 H), 5.15 (q, J = 2.07 Hz, 1 H), 3.90–3.82 (m, 3 H), 3.80 (s, 3 H), 3.62 (dt, J_1 = 9.72 Hz, J_2 = 4.84 Hz, 1 H), 2.86 (t, J = 7.23 Hz, 2 H), 2.03–1.79 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.9, 131.0, 129.7, 113.6, 103.7, 68.1, 66.7, 55.1, 35.3, 32.2, 23.4.

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