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Catalytic Formal Benzylic C−H Bond Functionalization of 2,5-Dialkylfuran Derivatives with Ferrocenyl Alcohols as Alkylation Reagents

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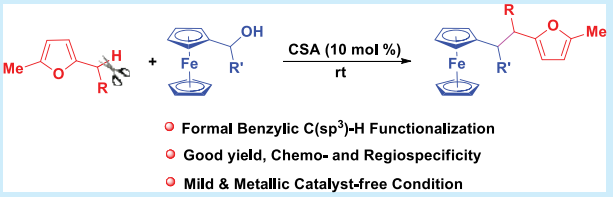
Supporting Information

ABSTRACT: The inert benzylic C−H bond of π-electron-rich heteroaromatic 2,5-dialkylfuran derivatives was conveniently functionalized with ferrocenyl alcohols as alkylation reagents under catalytic acidic conditions at room temperature, which features chemo- and regiospecificity, mild and metallic catalyst-free conditions, and environmental benignity.

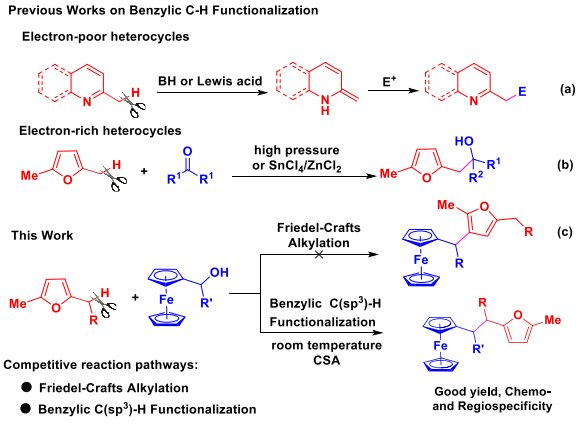


Biomass-derived furans are significant platform molecules and strategically important to improve the sustainability of the chemical industry.[1] Among various biomass-derived furans, 2,5-dimethylfuran (2,5-DMF) is particularly attractive due to its superior energy density, high octane value, and low oxygen content as well as ideal boiling point, which can serve as a second-generation biofuel and valuable chemical feedstock.[2] Remarkably, the elaboration approaches of 2,5-DMF are considerably limited,[3] although 2,5-dialkylfuans are privileged scaffolds, which widely exist in a variety of medicinal molecules.[4] In sharp contrast to 2,5-DMF, a plethora of elegant transformations of common furans are available, e.g., Friedel−Crafts reactions[5] and cycloadditions like [4 + 2],[6] [4 + 3],[7] and [4 + 4],[8] as well as the Achmatowicz reaction,[9] etc.

Ferrocenes have proven to be one of the most versatile scaffolds in organic synthesis,[10] materials science,[11] medicinal chemistry,[12] and especially asymmetric catalysis[13] due to their unique properties. Nowadays, the introduction of a ferrocenyl moiety has been recognized as an attractive approach for the development of more effective therapeutic agents, the bioactivity of which could be significantly enhanced with a ferrocenyl moiety introduced.[14] Presumably, the combination of these two significant pharmaphores, i.e., ferrocenyl moiety and 2,5-DMF, may produce a privileged structure which might possess novel and promising bioactivity or create unexpected medicinal property. Due to the nucleophilicity of 2,5-dimethylfuran, electrophilic ferrocenylmethyl cation is required, and ferrocenylmethanol,[15] which has the attractive advantages, e.g., easy preparation and generation of H_2O as the only side product, was selected as the alkylation reagent, aiming to access a large family of potentially useful hybrids of ferrocene and 2,5-DMF in synthetically useful yields.

Over the past decades, the direct functionalization of C(sp^3)−H bonds has emerged as a powerful method for construction of C−C and C−X bonds.[16] A particularly appealing aspect of this area is the direct benzylic C−H bond functionalization of π-electron-poor 2-alkylazaarenes, e.g., pyridines and quinolines, etc.[17] Due to the inherent acidity of the benzylic C−H bond, 2-alkylazaarene can be converted to its enamine or enamide counterpart under harsh basic[18] or acidic conditions,[19] which is then intercepted by an electrophile (Scheme 1, a). Radical strategy can also be exploited as well for this purpose.[20] In contrast, furan is an inherent π-electron-rich heterocyclic compounds, and the acidity of benzylic C−H bond in 2,5-DMF is much less acidic as compared with 2-alkylazaarenes. To the best of our knowledge, the direct benzylic C−H bond functionalization of 2,5-dialkylfuran under mild conditions still remains elusive to date despite the high significance of 2,5-substituted furan scaffolds in pharmaceutical fields. Very harsh conditions, e.g., high pressure (20 kbar) or strong Lewis acids, were indispensable for effective direct benzylic C−H functionaliza-

Scheme 1. C(sp^3)−H Bond Functionalization of 2-Alkylquinoline and 2,5-Dialkylfuran Derivatives



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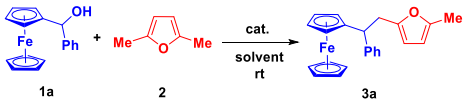
tion, and the electrophiles were considerably limited, which were mainly focused on the highly reactive carbonyl compounds (Scheme 1, b).[21] With increasing concerns on environmental protection, identification of the methods without transition-metal catalysts are of considerable significance. Thereafter, it is highly desirable to develop a mild strategy for direct benzylic C−H bond functionalization of 2,5-dialkylfuran for construction of the more diverse 2,5-disubstituted furan derivatives.

As a continuation of our research on non-transition-metal-catalyzed C−H bond functionalization,[22] herein we present the first formal benzylic C−H bond alkylation of 2,5-dialkylfurans for efficient construction of the pharmaceutically promising hybrids of ferrocene and 2,5-DMF, which addressed the formidable challenges of 2,5-DMF derivatizations with the following features such as (1) mild and metallic catalyst-free conditions, (2) ready access to the hybrids, and (3) wide substrate scope.

At the outset, the feasibility of benzylic C−H bond alkylation was investigated using ferrocenylmethyl alcohol **1a** and the commercially available 2,5-DMF **2** as the starting materials. Initially, phosphoric acid (1,1′-binaphthyl-2,2′-diyl hydrogenphosphate) was employed as the catalyst in 1,2-dichloroethane (DCE) at room temperature, and gratifyingly, the benzylic C(sp^3)−H bond alkylation product **3a** was furnished in 79% yield (Table 1, entry 1). Encouraged by this result, other reaction parameters were then extensively investigated to optimize the reaction. It was found that the option of the acidic catalysts had a dramatic impact on the transformation via evaluation of other Brønsted acidic catalysts, and camphorsufonic acid (CSA) was identified as the optimal catalyst, which furnished **3a** in the highest yield (entries 2−8).

Table 1. Optimization of Reaction Conditions[a]



1a 2 3a

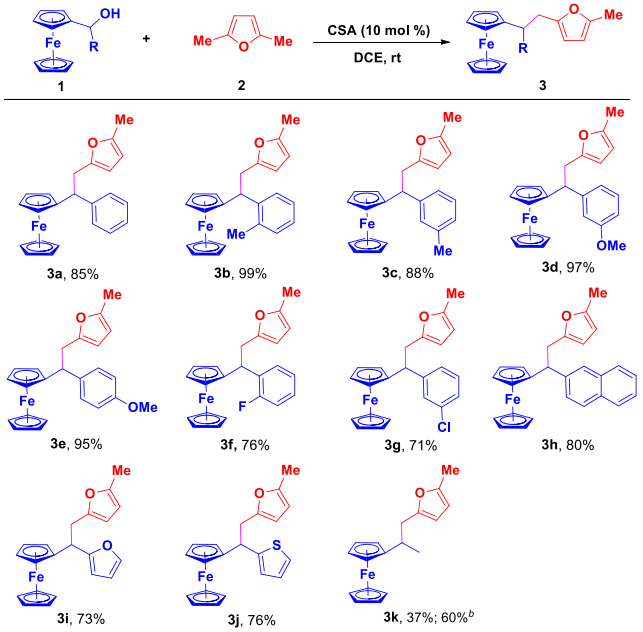
entry	catalyst	solvent	yield[b] (%)
1	phosphoric acid	DCE	79
2	TfOH	DCE	64
3	CSA	DCE	85
4	CCl_3CO_2H	DCE	75
5	TFA	DCE	82
6	AcOH	DCE	NR
7	$4\text{-}NO_2PhCO_2H$	DCE	NR
8	CBr_3CO_2H	DCE	79
9	$Cu(OTf)_2$	DCE	72
10	$Sc(OTf)_3$	DCE	76
11	$InCl_3$	DCE	84
12	CSA	DCM	83
13	CSA	CCl_4	81
14	CSA	CH_3CN	74
15	CSA	THF	34
16	CSA	toluene	77
17	CSA	DMSO	71
18	CSA	1,4-dioxane	27
19	CSA	DMF	60
20	CSA	EtOH	NR
21	CSA	$CHCl_3$	77

[a]Reaction conditions: **1a** (0.1 mmol), **2** (0.3 mmol), and catalyst (10 mol %) in 1 mL of solvent at room temperature. [b]Isolated yield.

Notably, no product could be afforded with less acidic catalysts exploited like AcOH and 4-nitrobenzoic acid (entries 6 and 7). Additionally, Lewis acids, e.g., $Cu(OTf)_2$ and $Sc(OTf)_3$, were also evaluated as catalysts, delivering **3a** in comparatively lower yields (entries 9−11). In addition to DCE, a number of other reaction media were surveyed as well, the employment of which only resulted in inferior results (entries 12−21). Remarkably, no conversion could be achieved at all with EtOH employed as solvent (entry 20).

Subsequently, the generality and limitation of this protocol was investigated with a variety of electronically and sterically diverse ferrocenyl alcohols **1** subjected to the optimal conditions using **2** as nucleophile (Scheme 2). Gratifyingly,

Scheme 2. Substrate Scope Investigation of Ferrocenylmethyl Alcohols[a]



[a]Reaction conditions: **1** (0.1 mmol), **2** (0.3 mmol), and CSA (10 mol %) in 1 mL of DCE at room temperature, isolated yield. [b]$InCl_3$ (10 mol %) as catalyst.

all of the ferrocenylmethyl alcohols **1** showed good substrate tolerance toward the reaction, yielding the corresponding products **3b−k** in good yields. Remarkably, a significant substituent effect could be observed, and electron-donating groups had positive impacts on the yields (**3a−h**). The substrates incorporating electron-donating groups, e.g., methyl and methoxyl, at *ortho*-, *meta*-, and *para*-positions, respectively, furnished the corresponding products **3b−e** in higher yields than the substrates bearing electron-withdrawing groups (**3f** and **g**). The higher yields might be rationalized by the fact that the ferrocenylmethyl carbocation generated in situ could be significantly stabilized by the electron-rich aryl groups, rendering the carbocationic intermediate more readily generated from ferrocenylmethanol **1** under acidic conditions (see Scheme 5). Additionally, other aromatic groups, e.g., 2-naphthyl-, 2-furyl-, and 2-thiophene-yl-substituted ferrocenylmethyl alcohols, were examined as alkylation reagents, and satisfyingly, the corresponding products **3h−j** could be furnished in good yields. Subsequently, other ferrocenyl alcohols **1** carrying aliphatic groups were also examined as

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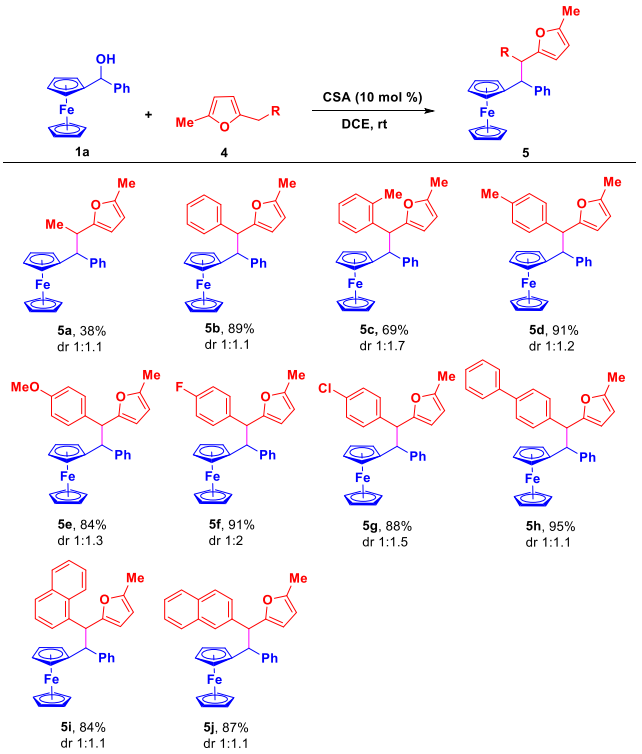
well besides the aryl-substituted ferrocenylmethyl alcohols. The desired product **3k** could be still furnished smoothly albeit in moderate yield when aryl was replaced with methyl, which might be attributed to the low stability of the carbocationic intermediate. Fortunately, the chemical yield of **3k** could be significantly increased to 60% when $InCl_3$ (10 mol %) was employed as catalyst.

Aiming to further demonstrate the robustness of this protocol, other 2,5-dialkylfuran derivatives **4** carrying methyl and various nonmethyl aliphatic groups were evaluated as nucleophiles (Scheme 3). Gratifyingly, almost all of the furan

Scheme 3. Substrate Scope Investigation of 2,5-Dialkylfuran Derivatives[a]

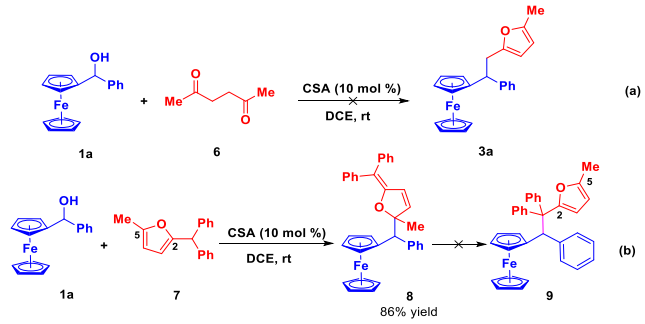


[a]Reaction conditions: **1a** (0.1 mmol), **4** (0.3 mmol), and CSA (10 mol %) in 1 mL of DCE at room temperature, isolated yield.

substrates **4** were well tolerated to furnish the desired products **5a–j** in moderate to good yields, albeit with low diastereoselectivities. Remarkably, all of the alkylations were regiospecific, which only occurred at the more sterically demanding methylene, although the methyl was more readily approached. Notably, a significant substituent effect could be observed. When 2-ethyl-5-methylfuran was exploited as nucleophile, the corresponding product **5a** was furnished only in 38% yield. In contrast, the yield could be significantly increased to 89% when ethyl in **4a** was replaced with benzyl group (**5b**). As to the 2-arylmethyl-5-methylfuran derivatives, the aryl groups had no obvious influence on the transformation, and all the alkylation products were furnished in good yields (**5b**, **5d–j**). The comparatively lower yield of **5c** might be ascribed to the steric hindrance introduced by the *o*-methylphenyl group. In addition to ferrocenylmethyl alcohols, other arylmethyl alcohols, such as 3-indolylmethanols and arylmethanols, e.g., diphenylcarbinol and triphenylcarbinol, which could readily furnish carbocationic intermediates under acidic conditions, were also examined as alkylation reagents; however, no desired product could be afforded.

In order to rationalize the reaction mechanism, two control reactions were conducted (Scheme 4). As it is well-known that

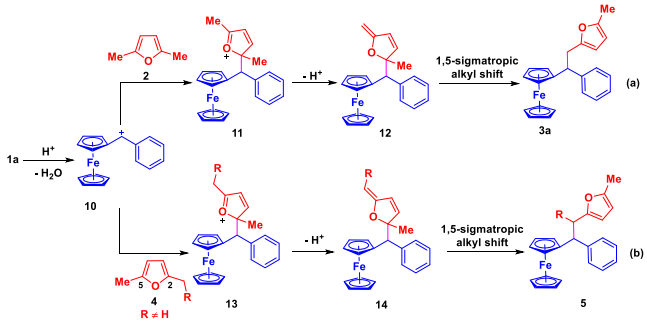
Scheme 4. Control Reactions for Investigation of Reaction Mechanism



2,5-dimethylfuran can be converted to hexane-2,5-dione **6** under acidic conditions via Paal–Knorr furan synthesis,[23] **1a** and **6** were subjected to the optimal conditions to investigate the possibility of the reaction pathway via the intermediate of hexane-2,5-dione **6** (Scheme 4, a). However, no desired product **3a** was furnished; thus, the pathway via **6** could be precluded. In addition, 2-benzhydryl-5-methylfuran **7** was employed as a nucleophile as well (Scheme 4, b), and surprisingly, no benzylic C–H alkylation product **9** could be delivered. However, the dearomatization product **8** was furnished instead.

On the basis of our results and the previous reports,[21c] a plausible mechanism was proposed (Scheme 5, a). Initially,

Scheme 5. Mechanistic Rationalization for the Direct Alkylation of the Formal Benzylic C–H Bond in 2,5-Dialkylfuran



ferrocenylmethyl alcohol **1a** undergoes sequential protonation and dehydration under acidic conditions to furnish the ferrocenylmethyl carbocationic intermediate **10**, which is then attacked by the most nucleophilic C2 of **2**, delivering the cationic intermediate **11**. After deprotonation of **11**, the dearomatized intermediate **12** is afforded, which subsequently undergoes a sigmatropic superafacial shift of ferrocenylmethyl to yield **3a**. The tendency toward rearomatization of furan serves as the driving force for superafacial shift.[24] As far as **4** is concerned (Scheme 5, b), due to the higher steric hindrance of nonmethyl aliphatic groups, e.g., benzyl, **10** would be more readily attacked by the less steric demanding C5 of **4**, followed by consecutive deprotonation and 1,5-sigmatropic alkyl shift to furnish **5**, which can elegantly rationalize the regiospecificity of

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benzylic C−H bond alkylation. As to **7**, the diphenylmethyl is a considerably bulky group, which results in the regiospecific nucleophilic attack of C5 in **7**. Although the dearomatization intermediate **8** can be delivered smoothly, the following 1,5-sigmatropic alkyl shift cannot proceed further due to the significant steric hindrance of diphenymethyl group of **8**.

In conclusion, we have developed an efficient protocol for the formal benzylic C−H bond functionalization of 2,5-dialkylfuran derivatives with ferrocenyl alcohols as alkylation reagents, which features chemo- and regiospecificity, mild conditions, and environmental benignity. For the first time, the inert benzylic C−H bond of π-electron-rich heteroaromatic 2,5-dialkylfuran was conveniently alkylated to afford the potentially useful hybrids of ferrocene and 2,5-DMF under metallic catalyst-free conditions at room temperature.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03701.

Experimental procedures and characterization data for all of the products (PDF)

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Notes

The authors declare no competing financial interest.

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