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# Iron-Catalyzed Photoredox Alcohol α-C−H Alkylation and Tandem Intramolecular Cyclization: Facile Access to Multisubstituted 2,3-Dihydrofurans and γ-Butyrolactones

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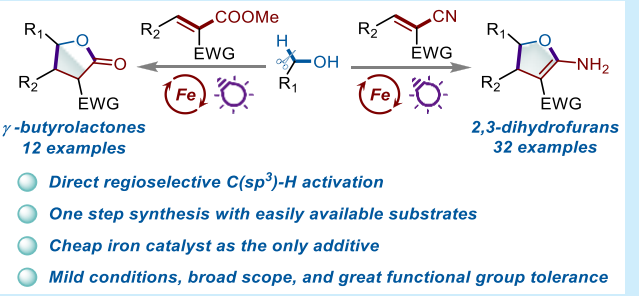
**ABSTRACT:** Multisubstituted furans occupy a pivotal position within the realms of synthetic chemistry and pharmacological science due to their distinctive chemical configurations and inherent properties. We herein introduce a tandem difunctionalization protocol of alcohols for the efficient synthesis of multisubstituted 2,3-dihydrofurans and γ-butyrolactones through the combination of photocatalysis and iron catalysis under mild conditions. Photoredox alcohol α-C(sp$^3$)−H activation and Pinner-type intramolecular cyclization are two key processes. This method features significant convenience, economic benefits, and environmental friendliness.






Multisubstituted furans are extensively integrated as structural motifs within natural products[1] and pharmaceutical compounds,[2] and versatile precursors in organic synthesis.[3] They exhibit profound biological and pharmacological activities that are crucial for the prevention and treatment of cardiovascular diseases, food safety, advancements in the wine industry, antiviral therapies, animal disease management, and antineoplastic interventions.[4] 2,3-Dihydrofurans and γ-butyrolactones, as two distinctive frameworks among this family, are not only integral to a multitude of bioactive natural and pharmaceutical entities[5] but also critical in the synthesis of bioactive tetrahydrofurans with notable stereoselectivity.[6] Many typical examples isolated from various biological sources, including Whisky lacton,[7] Arglabin,[8] Cryptotanshinone,[9] Aflatoxin B1,[10] and Pukalide,[11] are playing significant roles ranging from antibacterial agents to antineoplastic interventions (Scheme 1a). Furthermore, these structures are instrumental in 1,3-dipolar cycloaddition reactions, enabling the synthesis of heterocyclic compounds with varying ring sizes and atomic compositions.[12] Hence great interest from researchers of synthetic chemistry has been attracted in devising novel strategies for the assembly of this highly sought-after molecular architecture.

The past decade has witnessed significant advancement in this field (Scheme 1b). Bobek et al. reported the synthesis of substituted γ-butyrolactone from readily available δ-nitro alcohols via $Boc_2O$-mediated cyclization, successfully affording a series of natural lignans.[13] The Bai group developed a 3-step process to synthesize optically pure γ-butyrolactones through enzyme catalysis.[14] Maiti and co-workers developed a copper-catalyzed strategy using aryl ketones and a wide range of aromatic olefins as reactants to get 2,3-dihydrofuran derivatives.[15] Woo, Park, and co-workers presented a controllable one-pot synthesis for constructing these scaffolds with α-TMS-substituted alcohols as substrates via a photoredox Giese reaction.[16] Further transformations of 2,3-dihydrofurans and α-cyano-γ-butyrolactones were also achieved for applications in drug discovery. Despite these advancements, challenges such as high-temperature requirements, complex reaction processes, and the necessity for prefunctionalized substrates still persist. Consequently, there is a compelling need for the development of an accessible and sustainable synthetic method for these oxygen-containing five-membered heterocycles.

The recent shift toward the direct functionalization of carbon−hydrogen bonds in organic compounds presents a streamlined method for the synthesis of valuable molecular entities.[17] As one of the most popular approaches in this field, the generation of chlorine radicals through photoinduced ligand-to-metal charge transfer (LMCT) developed by many groups[18] and us[19] has been demonstrated as an effective method for hydrogen atom transfer (HAT), which is attributed to the availability of metal-chloride-based photocatalysts and their high reactivity toward inert C(sp$^3$)−H bonds functionalization. Although great success has been achieved in light-

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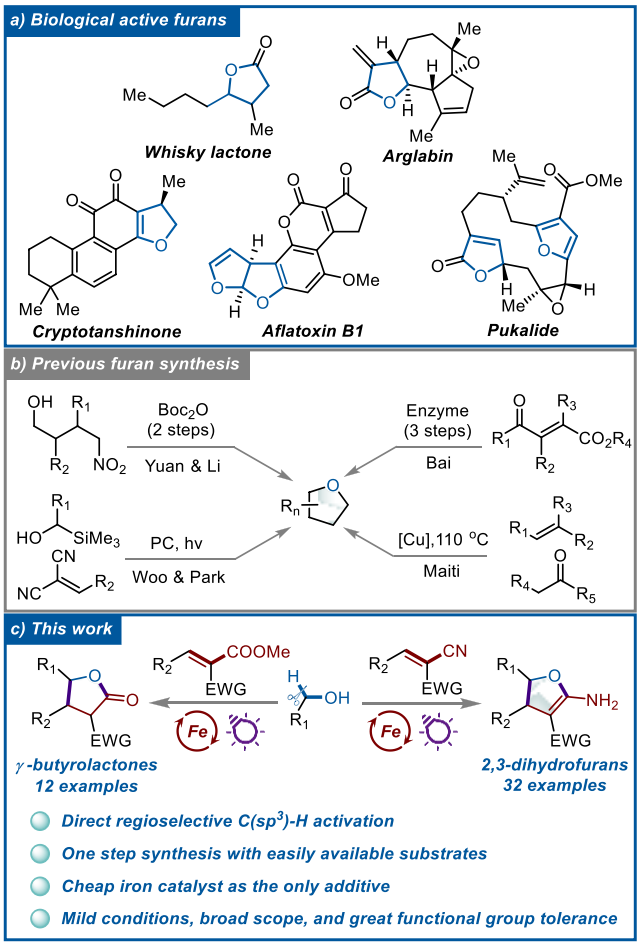
**Scheme 1. Approaches for Construction of Multisubstituted 2,3-Dihydrofurans and γ-Butyrolactones**

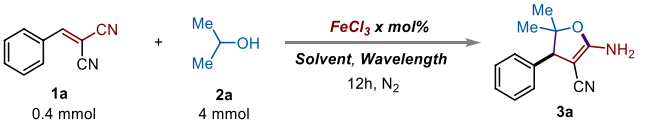



driven alcohol-functionalizing reactions,[20] the prohibitive cost of photocatalysts and stringent reaction conditions have hindered further application to a certain extent. Drawing upon our preceding work and foundational chemical principles,[21] we herein report a highly efficient, convenient, and cost-effective access to multisubstituted 2,3-dihydrofurans and γ-butyrolactones through the combination of photocatalysis and iron catalysis (Scheme 1c). Photoredox alcohol α-C($sp^3$)−H activation and tandem intramolecular cyclization are two key processes in the system.

Initially, we selected benzylidenemalononitrile (**1a**) and isopropanol (**2a**) as the model substrates to refine the reaction conditions (Table 1). After extensive experiments, the reaction achieved a 95% yield using $FeCl_3$ (0.01 equiv) as the catalyst and $CH_3CN$ as the solvent under $N_2$ atmosphere and irradiation of a 30W 405 nm LED for 12 h (entry 3). In the absence of $FeCl_3$ (entry 6) or visible-light irradiation (entry 8), the desired product was nearly not formed. The exploration of solvents demonstrated acetone had inferior reactivity compared to $CH_3CN$ (entry 5). Furthermore, the impact of different wavelengths on the reaction was assessed. It was observed that illumination at 365, 395, and 405 nm (entries 1−3) yielded similar outcomes, whereas irradiation at 455 nm (entry 4) resulted in reduced efficiency. Additionally, the reaction proved ineffective under aerobic conditions.

Based on the optimized reaction conditions, the scope of the substrates for the synthesis of 2,3-dihydrofurans was examined

**Table 1. Optimization of Reaction Conditions**[a]




| Entry | Catalyst loading | Solvent | Wavelength (nm) | Yield (%)[b] |
|---|---|---|---|---|
| 1 | 1 mol % | MeCN | 365 | 91 |
| 2 | 1 mol % | MeCN | 395 | 94 |
| **3** | 1 mol % | **MeCN** | **405** | **95** |
| 4 | 1 mol % | MeCN | 455 | 23 |
| 5 | 1 mol % | Acetone | 405 | 75 |
| 6 | – | MeCN | 405 | 0 |
| 7[c] | 1 mol % | MeCN | 405 | Trace |
| 8[d] | 1 mol % | MeCN | – | 0 |

[a]Reaction conditions: **1a** (0.4 mmol), **2a** (4 mmol), $FeCl_3$ (1 mol %), Solvent (2 mL), 12 h, $N_2$, rt, irradiated with a 30 W LED. [b]Isolated yield. [c]Reaction in air. [d]No light.

(Scheme 2). Various alcohols, including aliphatic, cycloalkyl, and aromatic ones, displayed commendable reactivity. The yield decreased gradually with the increase in the carbon chain length of the alcohols (**3b**-**3e**), which might have resulted from the steric hindrance effect. Trifluoroethanol as a specific strong polar solvent in drug synthesis was tried next, giving the corresponding product in 74% yield (**3g**). Benzyl alcohols that always exist in spices and cosmetics were also applied as candidates. With different types of functional groups assembled on the phenyl ring of benzyl alcohols, the desired multisubstituted 2,3-dihydrofurans were obtained in good yields (**3h**-**3m**), examples of which with electron-donating groups (**3j**, **3k**) exhibited a slightly enhanced reactivity than that with an electron-withdrawing group (**3m**). Among the alcohol scope, secondary alcohols have been found to present an obviously higher reaction efficiency than primary alcohols. Sequently, an array of electronically diverse benzylidenemalononitriles were evaluated, affording the 2,3-dihydrofuran molecules in good to excellent yields. Benzylidenemalononitriles with electron-donating groups presented better outcomes than those with electron-withdrawing groups. For instance, benzylidenemalononitrile adorned with a methoxy group on the benzene ring, when reacted with isopropanol, provided the corresponding products (**3p**-**3r**) in yields of 80−92%. Conversely, the yields, respectively, reduced to 70% (**3x**) and 73% (**3y**) with the introduction of an electron-withdrawing group. Furthermore, the investigation on substituted sites showed that *ortho*-substitution (**3r**) would draw an efficiency loss compared to *meta*- and *para*-substitution (**3p**, **3q**) thanks to the high spatial density around the synthesized furan ring. As vital synthons and coordinative groups, halogen- and hydroxyl-substituted **1** were all suitable substrates to furnish multifunctionalized products (**3s**-**3w**), offering a good chance for further derivatization. Additionally, three typical tetrasubstituted ethylenes were chosen as acceptors, and the corresponding fully substituted 2,3-dihydrofuran skeletons with adjacent quaternary $sp^3$ carbon centers were effectively synthesized in satisfying yields (**3z**-**3ab**). The reaction exhibited excellent functional group tolerance on a myriad of substitutions including alkyl (**3i**, **3j**, **3n**, and **3o**), methoxy (**3k**, **3p**-**3r**), hydroxyl (**3s**), fluoro (**3t**), chloro (**3l**, **3u**), bromo (**3v**), iodine (**3w**), cyano (**3x**), ester (**3y**), and trifluoromethyl (**3g**, **3m**) groups. Moreover, whether a synthetic reaction can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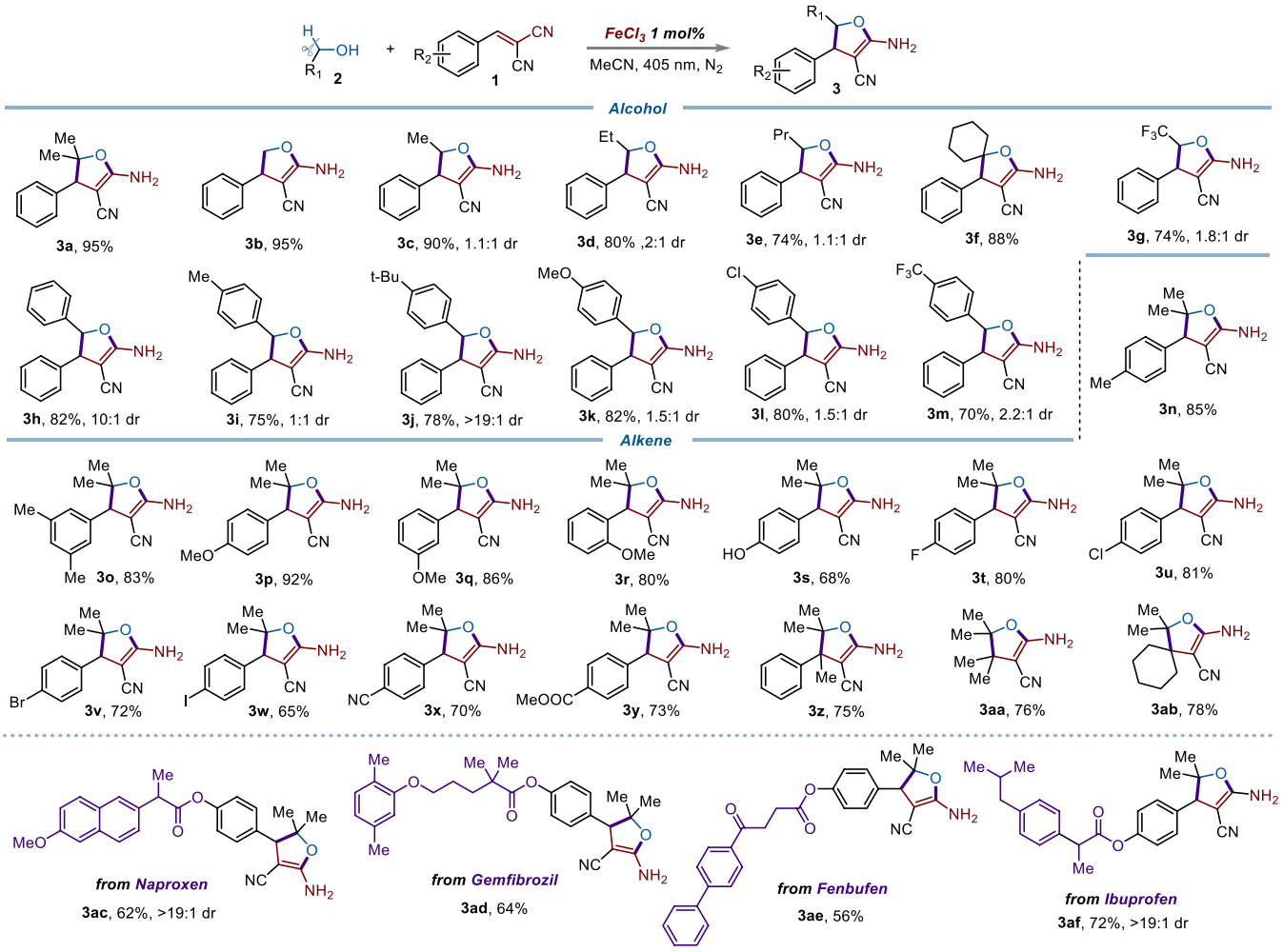
**Scheme 2. Scope for Multisubstituted 2,3-Dihydrofurans**[a,b,c]




[a]Reaction conditions: benzylidenemalononitrile (**1**, 0.4 mmol), alcohol (**2**, 4 mmol), $FeCl_3$ (1 mol %), $CH_3CN$ (2 mL), $N_2$, 30 W 405 nm LED, 12 h. [b]Isolated yield. [c]*dr* value was determined by $^1H$ NMR.

be applied in the late-stage functionalization of drug molecules is a key factor in evaluating synthetic practicability. Depending on this opinion, complex substrates derived from *Naproxen*, *Gemfibrozil*, *Fenbufen*, and *Ibuprofen* were respectively prepared and examined in our protocol, yielding the syncretic products from drug moieties and 2,3-dihydrofuran units (**3ac**-**3af**) with remarkable reactivity. These results rendered this method promising for the further processing of natural products and bioactive pharmaceuticals.

When one or two cyano groups of benzylidene-malononitriles were replaced by ester groups, multisubstituted $\gamma$-butyrolactones were acquired instead of 2,3-dihydrofurans. This phenomenon indicated that the ester exchange process occurred prior to the acid-induced Pinner addition in this system. The substrate scope toward $\gamma$-butyrolactone synthesis was then re-examined under similar conditions (Scheme 3). By increasing the catalyst loading from 0.01 to 0.05 equiv, various $\gamma$-butyrolactones were successfully achieved in good yields (**5a**-**5l**). Similar functional group tolerance was also observed in the scope. In comparison, the reactivity of dimethyl 2-benzylidene-malonate **4** seemed to be inferior to that of benzylidene-malononitrile **1**. For instance, **1a**, when reacted with isopropanol, offered the corresponding product (**3a**) in 95% yield, whereas dimethyl 2-benzylidenemalonate (**4b**) with increased iron loading resulted in a reduced yield (**5b**) at 71%. The reason for this issue was proposed to be attributed to the attenuated radical-trapping ability because of the weaker electron-withdrawing capability of ester groups in comparison to that of cyano groups.

To elucidate the reaction mechanism, several control experiments were conducted. The addition of radical-trapping agents, such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or butylated hydroxytoluene (BHT), to the mixture of the model reaction completely inhibited the formation of desired products, suggesting a radical pathway for the reaction (Scheme S1). A light on−off experiment was performed next, revealing that continuous light irradiation was essential for this transformation (Figure S1). Furthermore, kinetic isotopic effect (KIE) studies with separate kinetic experiments were employed to gain insights into the C($sp^3$)−H cleavage step. The KIE values given by $K_H/K_D$ and $P_H/P_D$ were measured as 1.03 and 1.51 using (a) **2b**/$d_4$-**2b** respectively as substrates or (b) a 1:1 mixture of **2b** and $d_4$-**2b** as substrates to produce **3b** (for more details see Scheme S2). These values indicated the radical-intermediated HAT process to be a "product-determining step", but not a "rate-determining step" in this catalytic system.[22] The competing reaction was then carried out for an in-depth examination of the HAT process



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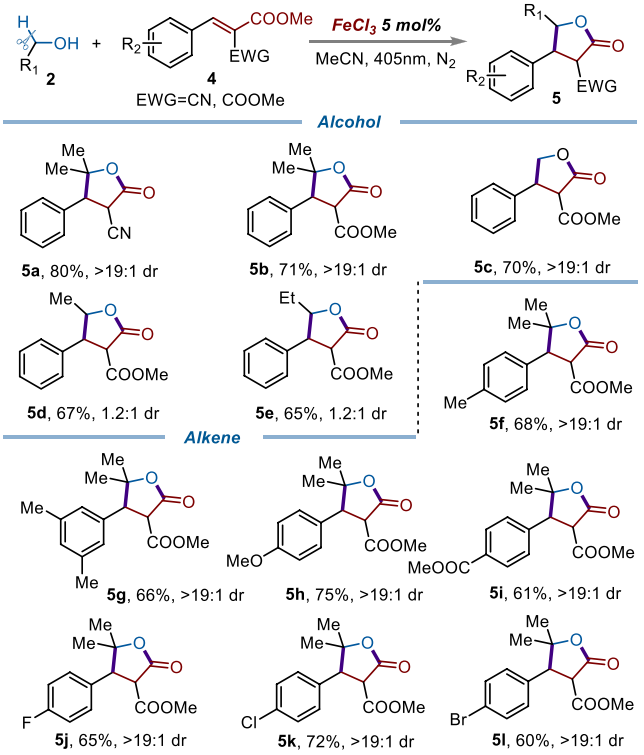
**Scheme 3. Scope for Multisubstituted γ-Butyrolactones**[a,b,c]



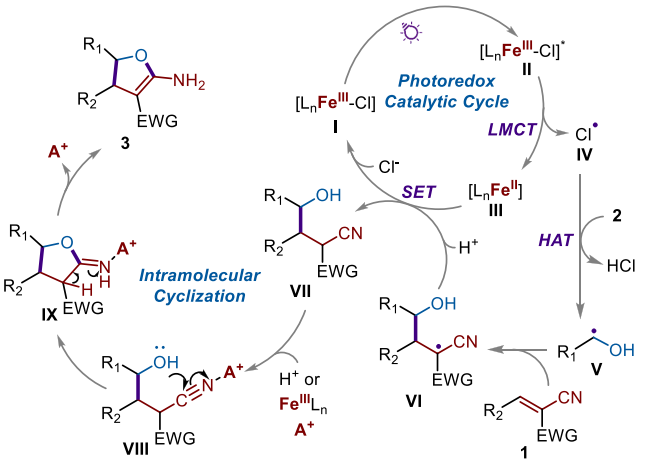

[a]Reaction conditions: dimethyl 2-benzylidenemalonate (**4**, 0.4 mmol), alcohol (**2**, 4 mmol), $FeCl_3$ (5 mol %), $CH_3CN$ (2 mL), $N_2$, 30 W 405 nm LED, 12 h. [b]Isolated yield. [c]*dr* value was determined by $^1H$ NMR.

over a 12 h period, utilizing a mixture of methanol and isopropanol as the substrates (Scheme S3). The assessment of the competing reaction dynamics was facilitated by meticulously analyzing the ratio of products **3a** and **3b** through the application of $^1H$ NMR. Our findings revealed a product ratio of **3a** to **3b** as 1.35:1. Later calculations showed that the HAT regioselectivity (*r.s.*) between one 3° and 1° hydrogen at the α-site of −OH in this catalytic system was 2.2:1 which constitutes robust evidence underscoring the regioselective properties.

Based on these findings and reported literature,[23] a proposed reaction mechanism was shown in Scheme 4. Initially, Fe(III)−Cl complex **I** is excited by visible light, generating excited complex **II**. A subsequent homolysis of the Fe(III)−Cl bond in **II** called the LMCT process gives intermediate Fe(II) complex **III** along with highly active chlorine radical **IV** as a HAT species. A HAT between alcohol substrate **2** and **IV** produces an α-hydroxyl radical **V** and hydrogen chloride. Radical **V** is efficiently trapped by the C=C bond of benzylidenemalononitrile **1**, forming carbon radical **VI**. A single-electron reduction from Fe(II) complex **III** and a following protonation provide the addition product **VII** between **1** and **2**, regenerating the iron catalyst **I** at the same time. Subsequently, the cyano group is activated by $H^+$ or Fe(III) from the system, and an acid-induced Pinner-type intramolecular addition occurs to form the desired oxygen-containing five-membered heterocyclic compound **3**.

In conclusion, we have developed a photoinduced difunctionalization protocol of alcohols for the efficient synthesis of multisubstituted 2,3-dihydrofurans and γ-butyrolactones under mild conditions. This method features significant convenience, economic benefits, and environmental friendliness. We hope that this approach will make some contribution to the field of synthetic chemistry and provide some inspiration for the convenient synthesis of complex molecules.

**Scheme 4. Proposed Mechanism**




## ■ ASSOCIATED CONTENT

### Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.4c01719.

Mechanism investigations, synthetic procedures, characterization data, and $^1H$, $^{13}C$ NMR spectra of these synthesized compounds. (PDF)

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‡J.C. and Z.G. contributed equally.

## Notes

The authors declare no competing financial interest.

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