

Synthesis of Benzo[*b*]furans by Intramolecular C–O Bond Formation Using Iron and Copper Catalysis

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ABSTRACT: One-pot processes for the synthesis of benzo[*b*]furans from 1-aryl- or 1-alkylketones using nonprecious transition metal catalysts have been developed. Regioselective iron(III)-catalyzed halogenation of the aryl ring, followed by iron- or copper-catalyzed *O*-arylation allowed the synthesis of various structural analogues, including the benzo[*b*]furan-derived natural products corsifuran C, moracin F, and caleprunin B.



- one-pot procedures
- earth-abundant metal catalysis
- down to ppm Cu loading
- air tolerant transformations

The benzo[*b*]furan ring system is a privileged structure, found in a wide range of natural products and pharmaceutically active compounds.¹ 2-Substituted analogues, in particular, have been isolated from various plant and marine sources, as well as bacterial and fungal organisms and have been shown to have activity as antimicrobial, antifungal, and anti-inflammatory agents.

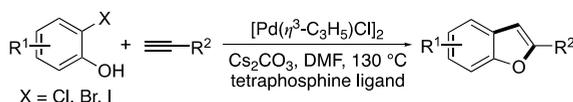
Due to the medical importance of benzo[*b*]furans, there has been significant efforts in developing new synthetic methods for their preparation,² including transition-metal-catalyzed processes.^{3–5} A common approach is the reaction of 2-halophenols with alkynes via a Sonogashira reaction, followed by transition-metal-catalyzed *O*-heterocyclization.^{2a} Li and co-workers have shown that these steps can be combined in a one-pot process using a catalytic system composed of [Pd(η^3 -C₃H₅)Cl]₂ and a tetraphosphine ligand (Scheme 1a).^{4c} Low catalyst loading (<0.1 mol %) could be used with a wide range of 2-chloro-, 2-bromo-, and 2-iodophenol substrates. Although less common,

preparation of benzo[*b*]furans by formation of the C_{7a}–O bond has also been reported via metal-catalyzed cyclization of 1-(2-haloaryl)ketones.⁵ A general process was reported by Willis and co-workers, who showed that enolates of 1-(2-bromoaryl)ketones were effective substrates for palladium-catalyzed *O*-heterocyclization and the preparation of 2,3-disubstituted benzo[*b*]furans (Scheme 1b).^{5a} Similar transformations that use nonprecious transition metal catalysts have also been described.^{5b–f} Whereas high-temperature reactions, under basic conditions involving copper(I) salts, are typically used, Bolm and co-workers reported that this transformation could also be catalyzed by iron(III) chloride.^{5f}

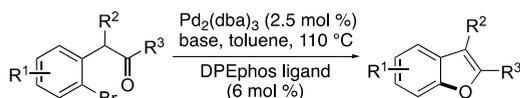
Although several methods for the synthesis of benzo[*b*]furans through C_{7a}–O bond formation have been described, these require prehalogenated 1-arylketone starting materials. We recently reported the use of iron(III) triflimide as a super Lewis acid for the activation of *N*-halosuccinimides and the subsequent regioselective halogenation of arenes.⁶ This process could also be combined with copper-catalyzed inter- and intramolecular C–N and C–O bond forming reactions for the preparation of anilines, aryl amides, and benzannulated heterocycles.⁷ Based on this research program, we envisaged a one-pot approach for the preparation of highly substituted benzo[*b*]furans from simple 1-aryl- or 1-alkylketones, involving regioselective iron(III)-catalyzed halogenation, followed by metal-mediated *O*-arylation. We now report the development of various one-pot processes for the synthesis of benzo[*b*]furans. As well as demonstrating the use of parts per million (ppm) copper loading to perform C–O cyclization (Scheme 1c), we report that both steps can also be catalyzed using a single iron salt.

Scheme 1. Selected Metal-Catalyzed Approaches for the Synthesis of Benzo[*b*]furans

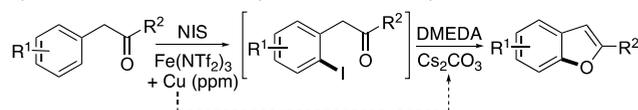
a) Pd-catalyzed Sonogashira and cyclization of 2-halophenols and alkynes.



b) Pd-catalyzed intramolecular *O*-arylation of enolates.



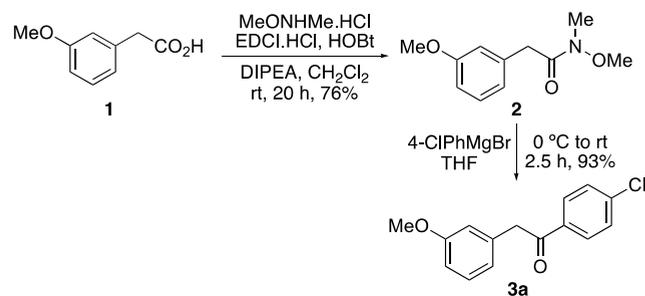
c) **This work:** Fe and Cu catalyzed activation and cyclization.



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The 1-aryl- and 1-alkylketones used in this study were readily accessed from commercially available phenylacetic acids. For example, the synthesis of 1-arylketone **3a**, used to optimize the one-pot processes, was prepared in two steps (Scheme 2). 3-

Scheme 2. Synthesis of 1-Arylketone **3a**^a

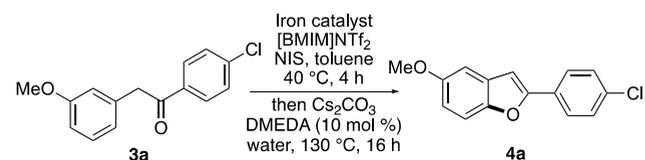


^aIsolated yields.

Methoxyphenylacetic acid (**1**) was converted to Weinreb amide **2** under standard conditions, and subsequent reaction with 4-chlorophenylmagnesium bromide allowed the efficient, scalable synthesis of **3a**.

Initial development of a one-pot synthesis of benzo[*b*]furans focused on iron(III)-catalyzed halogenation and copper(I)-catalyzed cyclization of 1-arylketone **3a** (Table 1). Iron

Table 1. Optimization Studies for the Iron- and Copper-Catalyzed Synthesis of Benzo[*b*]furan **4a^a**



entry	catalyst	catalyst loading (mol %)	catalyst purity (%)	yield (%) ^b
1 ^c	FeCl ₃ + CuI	2.5 + 10	97	59
2	FeCl ₃	2.5	97	48
3	FeCl ₃	2.5	99.9	44
4	FeCl ₃	5	99.9	60
5	FeCl ₃	10	99.9	63
6 ^d	Fe(NO ₃) ₃ ·9H ₂ O	5	99.999	55

^aAll reactions used [BMIM]NTf₂ (3 times the amount of Fe catalyst).

^bIsolated yields. ^cConducted using CuI (10 mol %) and DMEDA (20 mol %). ^dReaction times for each step was 5 and 20 h.

triflimide (2.5 mol %), generated from iron(III) chloride and the ionic liquid, [BMIM]NTf₂, was used for activation of *N*-iodosuccinimide (NIS) and subsequent iodination of **3a** (entry 1). ¹H NMR studies confirmed that despite the *meta*-arylethanone substituent, iron(III)-catalyzed iodination proceeded exclusively at the position *para* to the methoxy activating group. The second stage of the one-pot process was conducted using copper(I) iodide (10 mol %) and DMEDA (20 mol %), which gave benzo[*b*]furan **4a** in 59% yield.

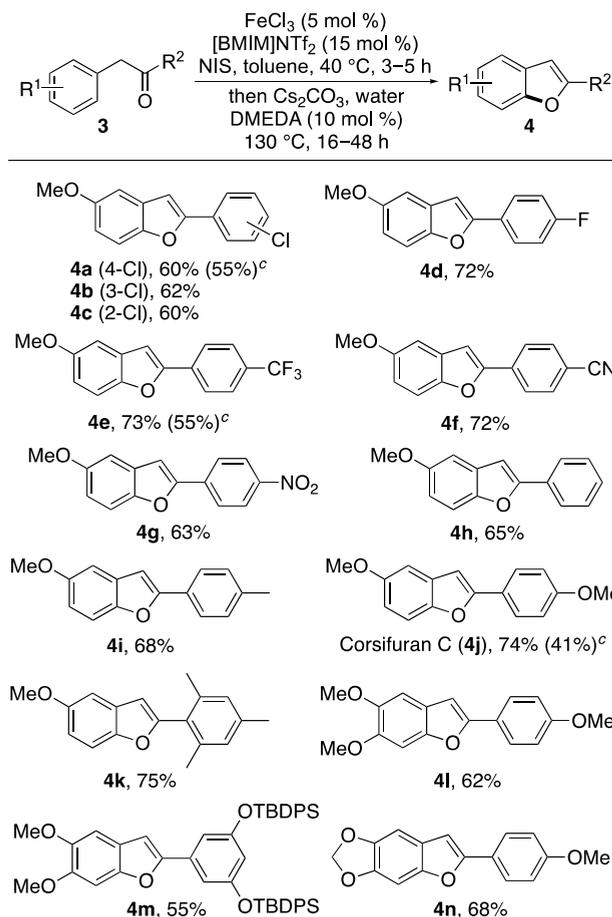
As Bolm and co-workers reported that iron(III) could be used for the *O*-cyclization of 1-(2-bromoaryl)ketones,^{5f} we next investigated whether a single iron salt could be used to perform both iodination and cyclization steps during a one-pot process. This goal became more challenging when we were made aware that most grades of commercial FeCl₃ contain various levels of metal contaminants, including sufficient copper to catalyze the

O-arylation step (e.g., FeCl₃ with 99.9% purity contains 31.1 ppm of Cu).⁸ However, this presented an opportunity to develop a one-pot process using a single iron complex in which the residual ppm levels of copper could be used to catalyze the cyclization step. The one-pot process was repeated using only FeCl₃, with either 97 or 99.9% purity, which gave benzo[*b*]furan **4a** in 48 and 44% yields, respectively (Table 1, entries 2 and 3). To verify that ppm loading of copper could catalyze the heterocyclization of 1-(2-haloaryl)ketones, we performed the single-step cyclization with the iodide of **3a** using CuI (0.001 mol %, 14 ppm).⁹ This gave benzo[*b*]furan **4a** in 55% yield. Thus, in the one-pot process, we believe that whereas iron(III) performs the iodination step, the ppm loading of copper is responsible for the intramolecular *O*-arylation step. To improve the yield of this one-pot process, catalyst loading was next investigated. Using FeCl₃ (99.9% purity) at 5 mol % loading gave **4a** in 60% yield (entry 4). Increasing the catalyst loading further (entry 5) did not lead to substantially higher yields, and so 5 mol % was deemed the optimal amount for subsequent studies.

To determine whether iron(III) could catalyze both halogenation and cyclization steps, the one-pot process was performed using an ultrapure iron(III) salt. As ultrapure iron(III) chloride was not commercially available, iron(III) nitrate nonahydrate (99.999% purity), which contains no copper, was investigated. Initial trials demonstrated that in combination with [BMIM]NTf₂, Fe(NO₃)₃·9H₂O was an effective Lewis acid for regioselective halogenation, with complete conversion to the iodide intermediate after 5 h. Then, using only this complex (5 mol %) for the entire one-pot process gave benzo[*b*]furan **4a** in 55% yield (Table 1, entry 6). To verify that iron(III) was responsible for catalysis of the cyclization step, control reactions were performed. For example, a reaction in which the iodide of **3a** was treated with DMEDA (10 mol %), Cs₂CO₃ in a mixture of toluene and water, under standard cyclization conditions (130 °C) resulted in no conversion to benzo[*b*]furan **4a**. This result confirmed that the C–O bond forming step (entry 6) is catalyzed by iron(III) and not due to the introduction of ppm amounts of copper with the addition of reagents and solvents (e.g., water) during the second step.

Having developed three different one-pot processes involving various copper loadings (zero, ppm, and 10 mol %), the scope of these with a range of 1-arylketones was next studied. Initially, the one-process involving Fe(NO₃)₃·9H₂O that uses iron(III) to catalyze both steps was performed with electron-deficient (*p*-CF₃Ph, **3e**) and electron-rich (*p*-MeOPh, **3j**) 1-arylketone substrates (Scheme 3). This gave benzo[*b*]furan **4e** and the natural product, corsifuran C (**4j**) (from *Corsinia coriandrina*),¹⁰ in 55 and 41% yields, respectively. These results confirm that a single iron complex can be used to catalyze both steps and access various benzo[*b*]furans. However, due to the moderate yields (also, 55% for **4a**), the requirement of an ultrapure metal salt, and the avoidance of copper contaminants, we felt that the other one-pot processes that use standard grades of iron(III) chloride would be more synthetically useful.

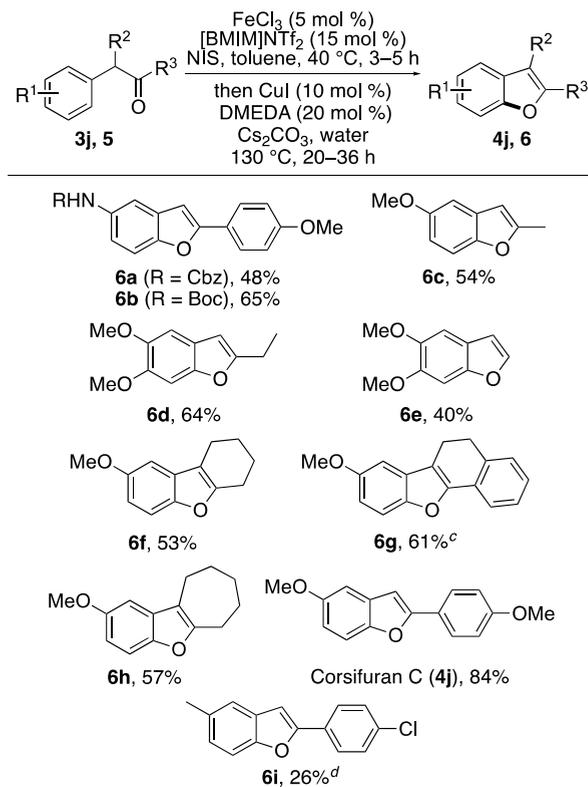
The one-pot process involving FeCl₃ (99.9% purity) to catalyze the iodination step and then residual copper (31.1 ppm) to catalyze the *O*-heterocyclization was next investigated for the preparation of biologically important 2-arylbenzo[*b*]furans (Scheme 3). 1-Arylketone substrates bearing electron-deficient and electron-rich aryl groups, as well as various *o*-, *m*-, and *p*-substituents were found to be effective substrates, allowing the

Scheme 3. Scope of One-Pot Synthesis of Benzo[*b*]furans 4^{a,b}

^aIron(III) chloride with 99.9% purity was used. ^bIsolated yields. ^cIsolated yields using $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (5 mol %).

synthesis of a range of structural analogues 4a–4n in 55–75% yields. This included the efficient preparation of corsifuran C (4j) in 74% yield.

This one-pot process was also used to investigate the synthesis of more challenging benzo[*b*]furan targets. This included less reactive 1-arylketones with amino-substituted aryl rings or bearing alkylketone side chains (Scheme 4). Although some of the benzo[*b*]furans were formed using this one-pot process, the cyclization step with ppm loading of copper required a longer reaction time (>48 h), resulting in low yields (<40%). For this reason, the synthesis of these targets was investigated using the one-pot process involving CuI (10 mol %). Following a brief optimization study of the original one-pot process (Table 1, entry 1), the use of FeCl_3 (97% purity) at 5 mol % loading, followed by CuI (10 mol %), proved most effective for these substrates. Amino-substituted benzo[*b*]furans 6a and 6b with synthetically useful protecting groups were prepared in 48 and 65% yields, respectively. Substrates with alkylketone (5c and 5d) or aldehyde (5e) side chains were also tolerated and gave the corresponding benzo[*b*]furans in moderate to good yields. Cyclic ketones (5f–5h) were also found to be substrates for this one-pot process, allowing the effective preparation of polycyclic benzo[*b*]furans 6f–6h. This one-pot process was also used for the gram-scale synthesis of corsifuran C (4j). Whereas the use of ppm loading of copper for the heterocyclization step on a small scale gave 4j in 74% yield (Scheme 3), for a larger-scale reaction,

Scheme 4. One-Pot Synthesis of Benzo[*b*]furans 4j and 6^{a,b}

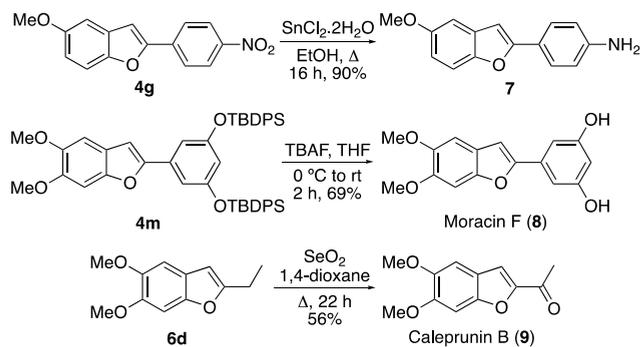
^aIron(III) chloride with 97% purity was used. ^bIsolated yields. ^cIodination step was performed at 50 °C for 6 h. ^dIodination step done separately using $[\text{BMIM}]\text{NTf}_2$ as solvent and at 70 °C for 16 h.

the use of CuI (10 mol %) resulted in a more efficient reaction with the isolation of corsifuran C (4j) in 84% yield. It should be noted that this $\text{C}_{7a}\text{--O}$ bond forming approach does have limitations,¹¹ as shown by the synthesis of benzo[*b*]furan 6i. Our previous studies have shown that electron-rich arenes are required for regioselective and efficient iron(III)-catalyzed halogenations.^{6,7} Iodination of unactivated 3-methylphenyl-substituted 1-arylketone 5i required forcing conditions (70 °C for 16 h), yielding a 4:1 mixture of desired 6-iodo and undesired 4-iodo regioisomers. Copper-catalyzed cyclization of the mixture led to the isolation of 6i in 26% yield, over the two steps.

Although these one-pot processes are most effective for the preparation of electron-rich benzo[*b*]furans, this type of benzannulated system is widely found in pharmaceutically important compounds and natural products (e.g., corsifuran C, 4j). To further demonstrate this, a number of benzo[*b*]furans prepared in this study were converted to target compounds (Scheme 5). For example, the nitro group of analogue 4g was reduced with tin dichloride in 90% yield to give amine 7, a nanomolar affinity agent of amyloid plaque.¹² Removal of the silyl protecting groups of benzo[*b*]furan 4m with TBAF, under standard conditions, gave moracin F (8), an antifungal phytoalexin, isolated from the tissue of mulberry shoots infected with *Fusarium solani*.^{13,14} Finally, allylic oxidation of benzo[*b*]furan 6d with selenium dioxide gave caleprunin B (9), a natural 2-acetylbenzo[*b*]furan, isolated from both *Eupatorium sternbergianum* and *Calea berteriana*.^{15,16}

In summary, we have developed new one-pot processes for the synthesis of benzo[*b*]furans from 1-aryl- or 1-alkylketones, using earth-abundant, nonprecious transition metal catalysts for

Scheme 5. Synthesis of Biologically Active Benzo[*b*]furans and Natural Products^a



^aIsolated yields.

aryl C–H halogenation and then intramolecular *O*-arylation. Although, in principle, iron(III) can be used to perform each step in a tandem catalytic process, the use of copper at either ppm or 10 mol % loading was found to be more effective, leading to the synthesis of a wide range of structural analogues, including a number of pharmaceutically active targets and natural products. Work is currently underway to discover new one-pot, transition-metal-catalyzed processes for the preparation of other benzannulated heterocycles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.0c00754>.

Experimental procedures, characterization data, NMR spectra of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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