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Synthesis of 2-Vinylbenzofurans via the Copper-Catalyzed Multicomponent Reactions Involving an Oxa-Michael/Arylation/Vinylation Cascade

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Supporting Information

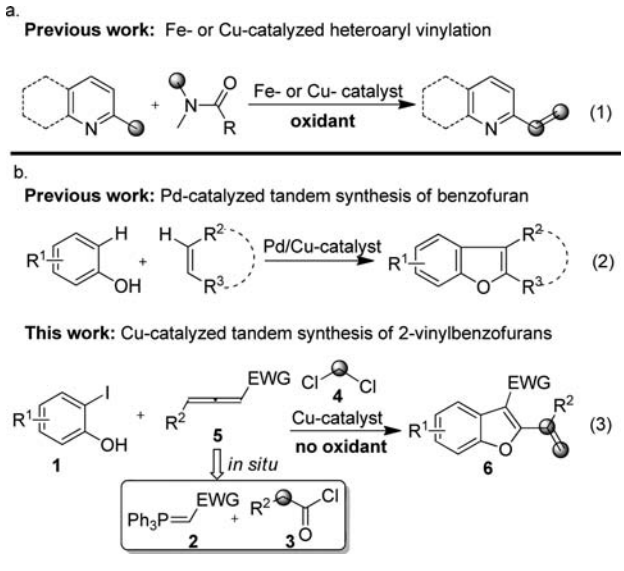
ABSTRACT: 2-Vinylbenzofurans have been synthesized via the copper-catalyzed one-pot, three-component reactions of *o*-iodophenols, in situ generated allenes, and dichloromethane. Cascade transformation of oxa-Michael addition, C-arylation, and sp^3C-H/sp^3C-Cl conversion-based vinylation has been involved in realizing the construction of this 2-vinylbenzofuran framework.

Developing novel organic transformations, especially those that functionalize inert chemical bonds such as the C−H bond, constitutes a research topic of extensive significance. Because of the tremendous endeavors of chemists, the chemistry of C−H activation and functionalization has made substantial progress during the past decade.[1] While the powerful C−H activation strategy has contributed enormously to the progress of organic synthesis, the frequent reliance of such chemistry on the presence of directing groups (DG), noble metal catalysis, and/or the assistance of oxidants has drastically hindered its broad application.

As one of the fundamental and most broadly utilized functional groups, the C═C double bond occupies a central and irreplaceable position in organic synthesis. While classical olefination methods such as elimination, Wittig olefination, Henry condensation, and Knoevenagel reaction are currently the dominant strategies for producing C═C bonds, searching for new approaches that do not rely on the prior prepared functional groups is presently a central aim in this area. Very recently, interesting methods of Cu- and Fe-catalyzed and metal-free oxidative C−H functionalization have been found useful for generating the C═C bond of vinylated aromatics (Scheme 1).[2] Despite these important advances, C−H bond conversion-based methods for C═C bond construction remain rather rare. The exploration of additional routes is thus an issue of urgency.

As a component of numerous natural products and biologically relevant organic compounds,[3] the benzofuran ring has received tremendous interest as a synthetic target. Among the large number of known synthetic methods, transition-metal-catalyzed tandem reactions provide powerful tools for accessing this and other related heterocycle compounds.[4,5] While a variety of different chemical transformations have been involved in the tandem reactions, transition-metal-catalyzed C−C bond formation is among the most prevalently employed. For example, Maiti and co-workers have developed a practical synthesis of

Scheme 1. (a) Vinylation of Pyridine Derivatives. (b) Benzofuran Synthesis



benzofurans through the Pd/Cu-catalyzed C−H oxygenation/C−H olefination of phenols and alkenes, wherein three sp^2C-H bonds were functionalized to enable the annulation (eq 2, Scheme 1).[6] In addition, the Pd-catalyzed intramolecular tandem C−H arylation/isomerization of *o*-bromophenyl allyl esters,[7] Ru-catalyzed tandem dehydration/C−H oxygenation,[8] and Cu-catalyzed tandem C−C/C−O coupling[9] represent other practical protocols.[10] Interestingly, despite the extensive research efforts being directed at benzofuran synthesis, the synthetic

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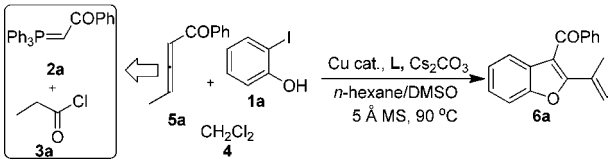
methods for obtaining benzofurans with a vinyl fragment at C2-position are not known. Herein, we report the first copper-catalyzed one-pot synthesis of 2-vinylbenzofurans from *o*-iodophenols **1**, Wittig reagents **2**, acyl chlorides **3**, and dichloromethane **4**,[11] wherein the vinyl fragment is generated via the direct conversion of sp^3C-H and sp^3C-Cl bonds, following a C-arylation-based cascade for benzofuran ring formation (eq 3, Scheme 1).

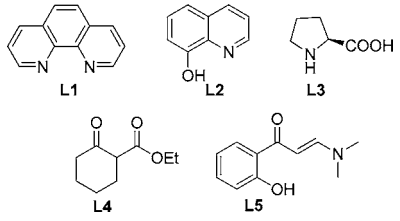
Initially, *o*-iodophenol **1a**, Wittig reagent **2a**,[12] propionyl chloride **3a**, and dichloromethane (DCM) **4** were employed in a model reaction. To obtain the product **6a**, the prior treatment of **2a** and **3a** with Et_3N in DCM was first conducted for the in situ preparation of allene **5a**.[13] Subsequent employment of **1a** and **4** with copper catalysis was able to provide the vinylbenzofuran **6a**. Extensive optimization experiments were then conducted. The temperature, solvent, catalyst species/loading, ligand, base additive, as well as reaction medium were all screened in order to obtain a satisfactory yield. Our typical results at optimizing the catalyst species and ligands were outlined in Table 1 (see the Supporting Information for additional data on optimization). At first, by employing 1,10-phenanthroline (1,10-phen. **L1**) as ligand, the entries in the presence of different copper catalysts demonstrated that CuBr possessed the best catalytic activity (entries 1–5, Table 1), and no expected transformation was observed in the entry employing $FeCl_3$ (entry 6, Table 1). Examination on the effect of different ligands, including 8-hydroxyquinoline (**L2**), L-proline (**L3**), cyclic *β*-ketoester **L4**, and enaminone **L5**, showed that the ligand also impacted the result, and **L1** was among the best candidates (entries 1 and 7–10, Table 1). Finally, the optimal amount of Cs_2CO_3 was 4 equiv based on the results (entries 11 and 12, Table 1). Additionally, a control experiment using *o*-bromophenol provided **6a** with 29% yield.

Table 1. Typical Experiments in Optimizing the Metal Catalyst and Ligand[a]



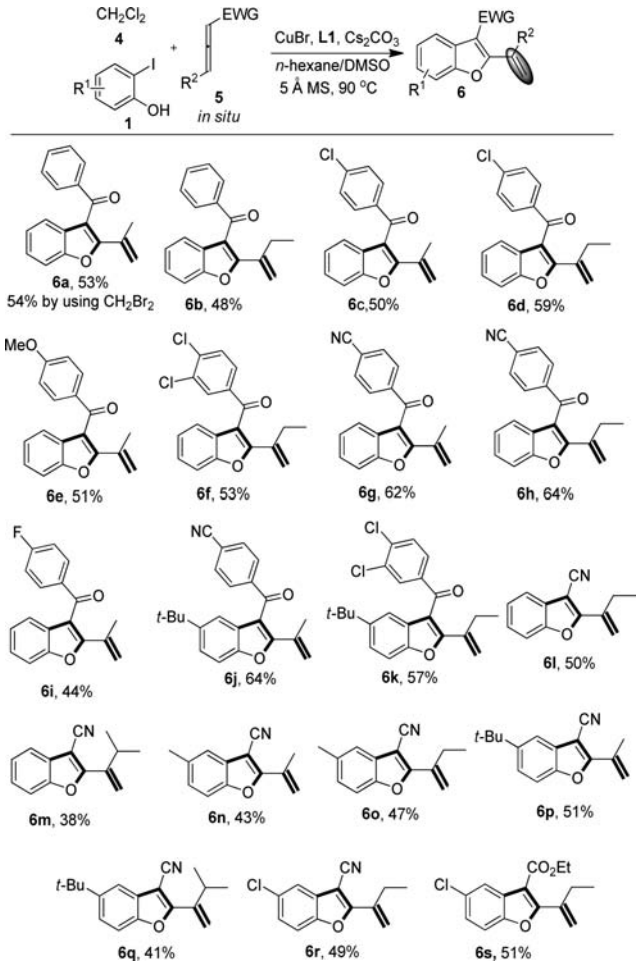
entry	Cu cat.	ligand	yield[b] (%)
1	CuI	**L1**	39
2	CuBr	**L1**	53
3	$CuBr_2$	**L1**	29
4	Cu_2O	**L1**	19
5	$Cu(OAC)_2{\cdot}H_2O$	**L1**	24
6	$FeCl_3$	**L1**	trace
7	CuBr	**L2**	11
8	CuBr	**L3**	16
9	CuBr	**L4**	32
10	CuBr	**L5**	28
11[c]	CuBr	**L1**	32
12[d]	CuBr	**L1**	39

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), **3a** (0.75 mmol), copper cat. (0.1 mmol), ligand (0.3 mmol), and Cs_2CO_3 (2.0 mmol) in DMSO/*n*-hexane (2 mL/3 mL) in the presence of 5 Å MS (150 mg) at 90 °C for 12 h in a sealed tube. [b]Yields of isolated products based on **1a**. [c]1.5 mmol Cs_2CO_3 is used. [d]3.0 mmol Cs_2CO_3 is used.



In light of these optimization experiments, the scope of this protocol was subsequently investigated. As shown in Scheme 2, a range of Wittig reagents, acyl chlorides, and *o*-iodophenols all engaged in the protocol, as expected, and many different vinyl benzofurans were acquired in generally moderate-to-good yields. According to the results, the entries employing electron-deficient aryl ketone-based Wittig reagents usually provided the corresponding products with slightly higher yields than other entries (**6g**, **6h**, **6j**, and **6k**). On the other hand, most entries using cyano-based Wittig reagents gave relatively lower yields of the corresponding 3-cyanobenzofurans probably because of the lower efficiency of these Wittig reagents (**6m**, **6n**, **6o**, and **6q**). The functional groups on *o*-iodophenol and acyl chloride, however, did not noticeably influence the reaction results. Although alkyl chlorides with both linear and branched groups were found to be applicable, attempts at employing aryl containing acyl chlorides such as 2-phenylacetyl chloride were not successful. As an issue of higher importance, we also made

Scheme 2. Tandem Synthesis of Various 2-Vinylbenzofurans[a]



[a]Isolated yields.

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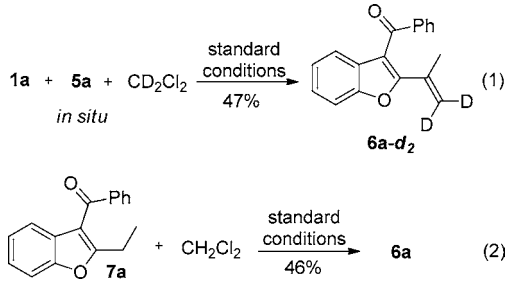
extensive efforts to investigate the reactivity of other alkyl dichlorides. Related substrates, including 1,1-dichloroethane, 1,1-dichloropropane, 2,2-dichloropropane, and 2,2-dichloroacetonitrile were employed, respectively. Unfortunately, none of the experiments gave the desired benzofuran products either with standard operation or modified operation probably because of their lower reactivity caused by the steric hindrance from the alkyl/aryl substitution. In addition, an entry using CH_2Br_2 as the alternative of CH_2Cl_2 in the model reaction provided **6a** with similar yield, implying that dichloro- and dibromoalkanes possess similar reactivity in the reaction. Furthermore, employing *o*-iodoaniline did not yield a potential synthesis of indoles by a similar transformation.

Subsequently, in order to confirm participation of dichloromethane in the formation of the C=C bond, the control isotope-labeling experiment was conducted. When CD_2Cl_2 was utilized as the alternative substrate in the model reaction, as hypothesized, the deuterium-labeled product **6a**-d_2 was isolated in 47% yield (eq 1, Scheme 3), which unambiguously confirmed

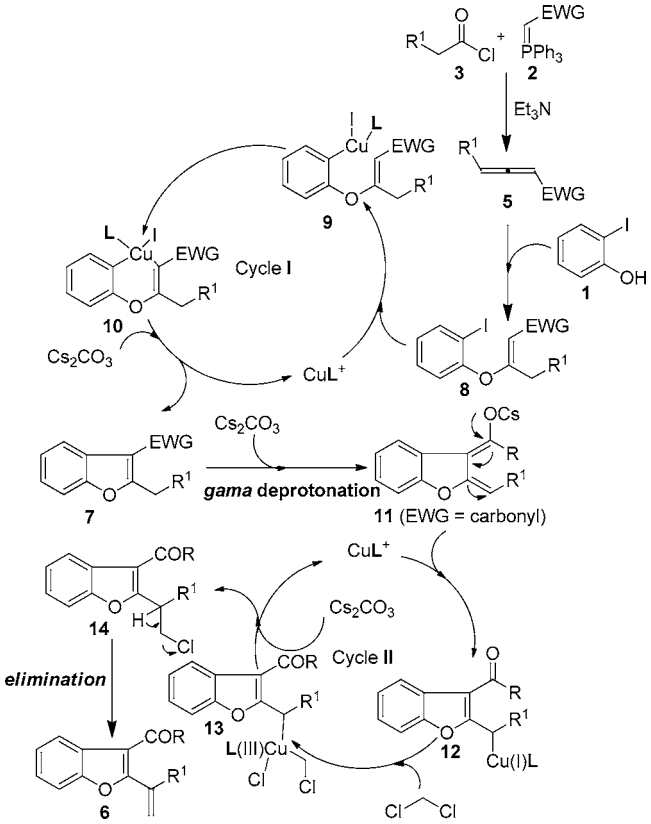
Scheme 3. Control Experiments



that dichloromethane served as the source of the terminal methylene of the C=C bond. In addition, another control experiment employing directly the benzofuran **7a** and dichloromethane under standard conditions gave vinylbenzofuran **6a** in 46% yield (eq 2, Scheme 3), which supported the fact that the C=C double bond was generated via direct sp^3C−H bond conversion.

With these results in hand, we tentatively summarized the general reaction mechanism. As outlined in Scheme 4, product **6** is formed through two main catalytic cycles, the cycle **I** for copper-catalyzed tandem benzofuran annulation and the cycle **II** for sp^3C−H and sp^3C−Cl conversion-based vinylation. Initially, the in situ prepared allenes **5** underwent oxa-Michael addition in the presence of *o*-iodophenol to afford intermediates **8**,[14] under the catalysis of Cu(I). The active methylene-based intramolecular C-arylation reaction proceeds via the intermediates **9** and **10** to give benzofurans **7**. According to the structure of **7** and related literature on the Cu-catalyzed sp^3C−Cl bond conversion,[11a] the second catalytic cycle is assumed to be initiated by the γ-deprotonation of **7** in the presence of a base. This deprotonation process activated the methylene adjacent to C2 of the benzofuran via another intermediate **11** which could incorporate Cu(I) catalyst and proceed to **12**. Subsequently, the active sites containing Cu(I) in **12** insert into the C−Cl bond in CH_2Cl_2 via the oxidative addition transformation and proceed to intermediate **13**. The following reductive elimination on **13** then leads to the formation of intermediates **14** while releasing the Cu(I) catalyst for recycling. Finally, in the presence of a base, the products **6** were generated via a conventional β-elimination on the alkyl chloride fragment in **14**.

Scheme 4. Plausible Mechanism



In conclusion, we have developed a new copper-catalyzed cascade reaction for the synthesis of vinylbenzofuran scaffolds. With the cascade benzofuran construction and the subsequent CH_2Cl_2-based C=C bond formation, together with the multiple transformations including the conversions of the sp^3C−H bond and sp^3C−Cl bonds involved, the significance of the present work lies not only in providing a facile synthetic method toward unprecedented 2-vinylbenzofurans, but more importantly in disclosing the new reactivity of the inert dichloromethane as a reaction partner in the construction of terminal C=C bonds.

■ ASSOCIATED CONTENT

Supporting Information

Additional data on condition optimization, general experimental information, synthetic procedure, and characterization data as well as $^1H/^{13}C$ NMR spectra of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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