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Benzofuran Derivatives from Alkynyl-Substituted Benzynes and Aryl Halides

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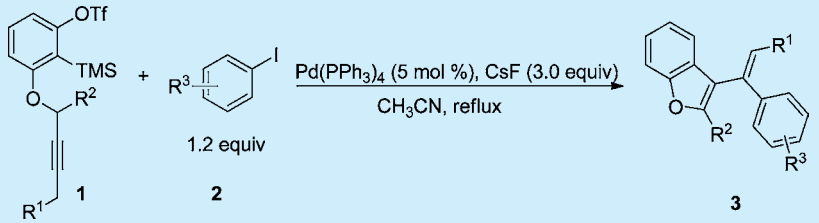
Supporting Information

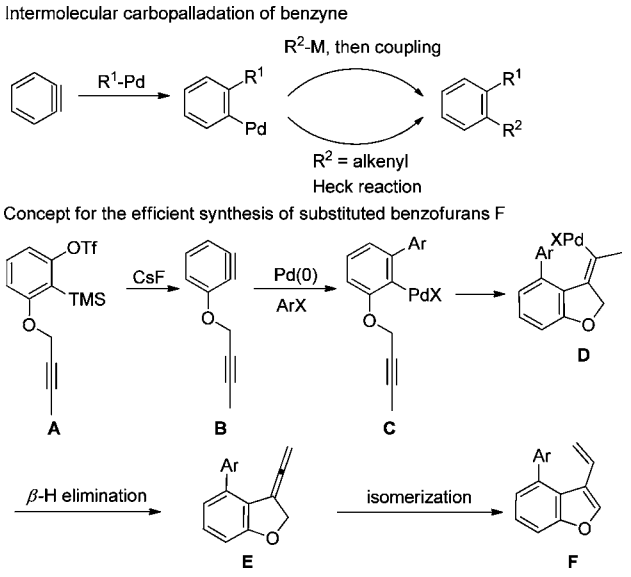


ABSTRACT: A palladium(0)-catalyzed cascade reaction for the efficient synthesis of 2,3-disubstituted benzofuran derivatives **3** containing a 3-trisubstituted alkene functional group in moderate yields from alkynyl-substituted benzynes **1** and aryl halides **2** has been developed. This method provides an efficient and alternative approach to benzofurans which are very useful heterocyclic compounds with biological and pharmacological potentials. A plausible mechanism involving intramolecular ene reaction, intermolecular insertion, and β-H elimination is proposed.

Benzofurans are a class of very important heterocyclic compounds existing widely in natural products and unnatural compounds with biological and pharmacological potentials;[1] thus, much attention has been paid to the development of the synthetic methods.[2−7] Although numerous synthetic approaches to this family of compounds have been developed in the past decades, general protocols for the synthesis of these compounds are still of high interest. On the other hand, arynes have proven to be one of the most important building blocks in organic synthesis.[8] As a highly active species, they have been widely used in various carbon−carbon and carbon−heteroatom bond-forming reactions, such as cycloaddition reactions,[9] nucleophilic addition reactions,[10] and transition-metal-catalyzed cyclization and carbometalation reactions.[11] Intermolecular carbopalladation, in particular, shows a powerful potential for *ortho*-difunctionalization of arynes through multicomponent coupling reactions (Scheme 1).[12−15] Herein, we hypothesize that if a benzyne precursor and an alkyne are preinstalled in the same molecule **A**, subsequent intermolecular carbopalladation of ArPdX with **B** followed by an intramolecular insertion reaction would form intermediate **D**, if the regioselectivity allows. Subsequent β-H elimination would produce allene **E**, which may easily isomerize to benzofuran derivatives **F** (Scheme 1). Such an approach would provide an efficient and alternative approach for the construction of the benzocyclic compounds.

To test our hypothesis, we initially synthesized substrate **1a** as the benzyne precursor to explore this reaction: when we treated **1a** with 5 mol % of $Pd(PPh_3)_4$, 3.0 equiv of CsF, 2.0 equiv of K_3PO_4, and 2.0 equiv of PhI in CH_3CN at 50 °C for 3 h, to our surprise, the desired product 4-aryl-substituted benzofuran-type **F** (Ar = Ph) was not formed. Instead, a new

Scheme 1. Concept for the Efficient Synthesis of Substituted Benzofurans F



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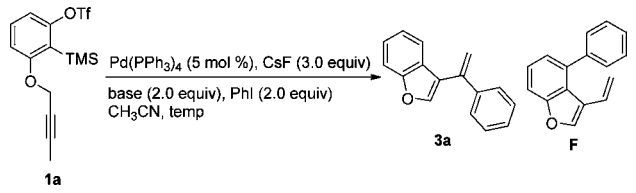
product, which was identified as **3a** with the phenyl group from phenyl iodide located in a different place, was detected in 39% NMR yield (Table 1, entry 1).

Table 1. Optimization of the Reaction Conditions[a]

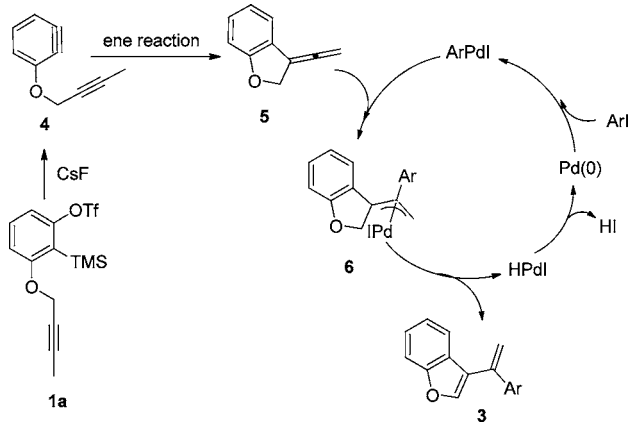


entry	base	temp (°C)	time (h)	yield of **3a**[b] (%)
1	K_3PO_4	50	3	39
2[c]	K_3PO_4	50	3	34
3	Ag_2CO_3	50	3	34
4	K_3PO_4	25	5	23
5	–	50	3	49
6	–	70	45 min	57
7	–	reflux	40 min	60
8[d]	–	reflux	40 min	60

[a]The reaction was conducted with 0.1 mmol of **1a** in 2 mL of solvent. [b]The yield was determined by ^{1}H NMR analysis of the crude product using 1,3,5-trimethylbenzene as the internal standard. [c]THF was used as the solvent. [d]PhI 1.2 equiv was used.

A rationale for the formation of **3** is shown in Scheme 2: first, the benzyne intermediate **4** was formed in situ upon the treatment of **1a** with CsF; an instant intramolecular ene reaction produces readily allene intermediate **5** obviously due to the aromaticity of the benzene ring; insertion reaction with ArPdI forms a π-allylic palladium intermediate **6** and subsequent β-H elimination would afford the unexpected isomeric benzofuran derivative **3**.[16]

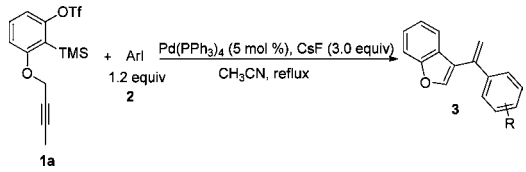
Scheme 2. Proposed Mechanism



Inspired by this result, some reaction parameters such as solvent, base, and temperature effects were investigated for the purpose of improving the yield. First, changing the solvent to THF led to a slightly lower yield of 34% (entry 2); Ag_2CO_3 failed to provide better results (entry 3); the reaction at room temperature afforded **3a** in only 23% yield with a longer time (entry 4); in fact, this reaction could also proceed smoothly in absence of any base (entry 5); raising temperature afforded the product **3a** in better yields within 1 h (entries 6 and 7); 1.2 equiv of PhI were enough to complete this reaction (entry 8).

Thus, we defined 5 mol % of $Pd(PPh_3)_4$, 3.0 equiv of CsF, 1.2 equiv of ArI in CH_3CN under reflux as the standard conditions to explore the feasibility. The scope of the reaction using differently substituted iodobenzene with **1a** is showed in Table 2:

Table 2. Reaction of Different Substituted Iodobenzenes with Benzyne Precursor 1a[a]



entry	Ar	time (min)	isolated yield of **3** (%)
1	Ph (**2a**)	50	55 (**3a**)
2	*p*-MeC_6H_4 (**2b**)	45	46 (**3b**)
3	*m*-MeC_6H_4 (**2c**)	60	53 (**3c**)
4	*p*-*i*-Pr-C_6H_4 (**2d**)	60	46 (**3d**)
5	*p*-AcC_6H_4 (**2e**)	65	47 (**3e**)
6	*p*-$EtO_2CC_6H_4$ (**2f**)	50	53 (**3f**)
7	*p*-F-C_6H_4 (**2g**)	70	46 (**3g**)
8	*p*-ClC_6H_4 (**2h**)	70	43 (**3h**)
9	*p*-BrC_6H_4 (**2i**)	60	47 (**3i**)
10	3,5-$Cl_2C_6H_3$ (**2j**)	80	43 (**3j**)
11	1-naphthyl (**2k**)	60	45 (**3k**)
12	2-thienyl (**2l**)	70	46 (**3l**)

[a]The reaction conditions: 0.3 mmol of **1a**, 0.015 mmol of $Pd(PPh_3)_4$, 0.9 mmol of CsF, and 0.36 mmol of PhI in 5 mL of CH_3CN under reflux.

not only the electron-donating substituted aryl iodides but also electron-withdrawing ones may react smoothly to afford the corresponding products in moderate yields within 1 h (entries 2–6), showing this reaction is not sensitive to the electronic effect; substrates containing a synthetically versatile F-, Cl-, or Br- substituent to the Ar moiety may also be applied (entries 7–10); 1-naphthyl or heteroaryl substituent, such as 2-thienyl were also tolerated (entries 11 and 12); the structure of **3j** was further confirmed by the X-ray single-crystal diffraction studies[17] (Figure 1).

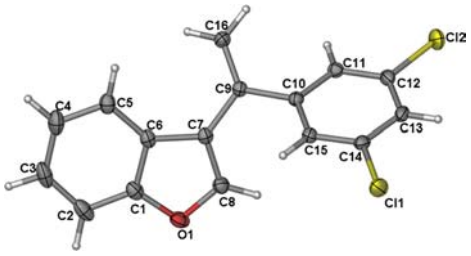


Figure 1. ORTEP representation of **3j**.

Furthermore, substrates **1b** and **1c** containing a methyl or *n*-C_5H_{11} substituent may also work with the introduction of new alkyl substituent to the 2-position of benzofuran to produce 2,3-disubstituted benzofurans with practicable yields (eq 1).

Finally, substrates **1d** and **1e** with longer carbon-chain substituents were also applied to afford the products *E*-**3o** and *E*-**3p** highly stereoselectively in the yields of 41% and 34%, respectively, and the geometry of the double bond of **3o** was determined to be *E*, based on NOESY experiment (eq 2).

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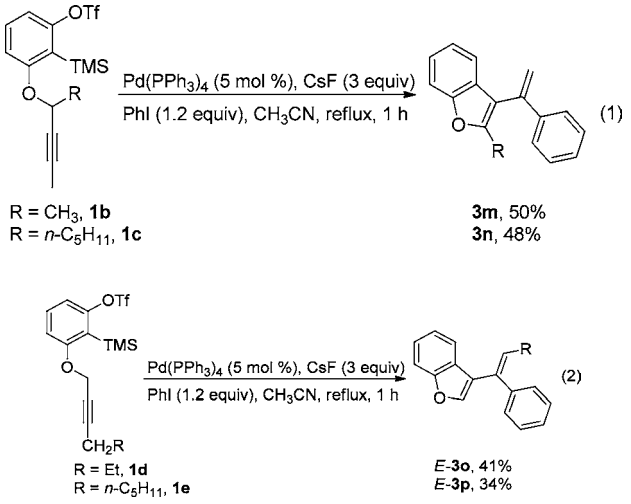

In conclusion, we have developed an efficient approach to synthesize benzofuran derivatives from alkynyl-substituted benzynes and aryl halides via the intermediacy of allene. Further studies including synthetic application are underway in this laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization data. 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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(17) Crystal data for compound **3j**: $C_{16}H_{10}Cl_2O$; MW = 289.14, monoclinic space group $P2(1)/c$, final R indices $[I > 2\sigma(I)]$, R_1 = 0.0396, wR_2 = 0.1022, R indices (all data) R_1 = 0.0436, wR_2 = 0.1062, a = 7.8959(11) Å, b = 13.1930(18) Å, c = 25.493(4) Å, α = 90°, β = 90°, γ = 90°, V = 2655.6(6) Å^3, T = 173(2) K, Z = 8, reflections collected/unique 27306/2345 (R_{int} = 0.0602), number of observations $[>2\sigma(I)]$ 2345, parameters: 180. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center. CCDC 966889.