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Domino reaction of 2-isocyanophenyloxyacrylate and aryne to synthesize arenes with vicinal olefin and benzoxazole

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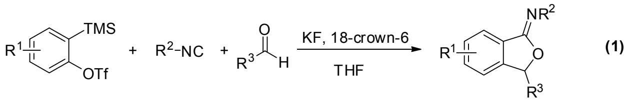
An unusual domino reaction of 2-isocyanophenyloxyacrylate and aryne has been disclosed. The present strategy experiences nucleophilic addition, Michael addition, carbon-oxygen cleavage, and cyclization, thus enables the quick aryne vicinal difunctionalization by the installation of a benzoxazole and an olefin.

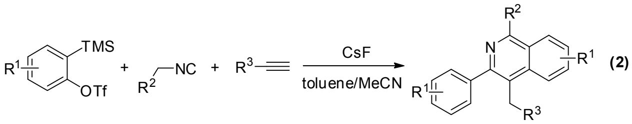
Arynes represent one of the most reactive intermediates, which have been broadly used in various carbon-carbon and carbon-heteroatom bond-forming reactions.[1,2] As such, reactions involving the insertion of aryne into C-C,[3] C-N,[4] C-O,[5] and other bonds have been well documented.[6] Furthermore, the aryne-based Diels-Alder reaction, [2+5], [2+8] and many other pericyclic reactions have been intensively investigated for the construction of various benzo-fused frameworks.[7] Usually, aryne can serve as efficient building block for the synthesis of diverse difunctionalized arenes. Of late, Li and co-workers discovered a new aryne precursor,[8] thus providing a quick access to assemble three consecutive functional groups on a benzene ring in an efficient manner. In particular, the generation of aryne from *ortho*-(trimethylsilyl)aryl triflate developed by Kobayashi under mild conditions appears to be the key to the success of these reactions.[9] Regardless of the transition-metal-catalyzed reactions, many efforts have also been devoted to the exploration of new transition-metal-free reactions.[10]

Owing to their versatile reactivity, isocyanides have received considerable attention from organic community.[11] For instance, the classical carbine-like reactivity made them particularly reaction partners in various multicomponent reactions (IMCRs) ever since Passerini and Ugi reaction.[12] Additionally, these reactive species were also widely used in synthesis of many carbocycles and heterocycles.[13] Remarkably, many achievements have been made on the multicomponent reactions involving isocyanide and aryne.[14] The initial successful example on three component reaction containing both isocyanide and aryne was reported by Yoshida et. al. (Scheme 1a).[14a] Following these works, Huang and co-workers described another interesting multicomponent reaction of aryne, isocyanide, and terminal alkyne, thus providing a straightforward route to polysubstituted pyridines and isoquinolines (Scheme 1b).[14b] In addition, Stoltz and co-workers discovered the aryne-intercepted version of the Passerini reaction to furnish phenoxyiminoisobenzofuran motifs.[14c] In contrast to multicomponent reactions, there are few study on the direct two-component reaction of functionalized isocyanides and arynes.[15] In view of the diverse reactivity of isocyanide, more concise methods combining functionalized isocyanide and aryne remain highly in demand to expand the realm of aryne chemistry. Recently, the exploration of new reactivity of isocyanides has been a new research focus and much important progress has been made with the outstanding contributions of Zhu and Xu.[16] As a

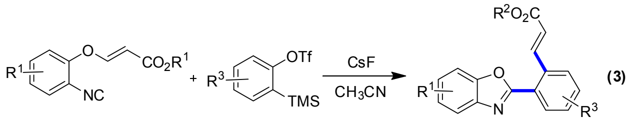
a) Multicomponent reaction of aryne, isocyanide, and aldehyde



b) Multicomponent reaction of aryne, isocyanide, and alkyne



c) This work



Scheme 1. Representative examples involving isocyanide and aryne

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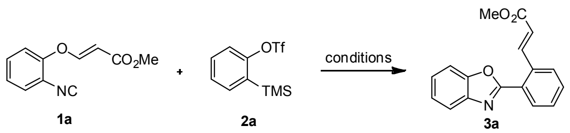
continuation of our previous works on isocyandie chemistry and heterocycle synthesis,[17] herein we wish to report the newly designed functionalized isocyanide containing phenyloxyacrylate and its first transition-metal-free reaction with aryne.

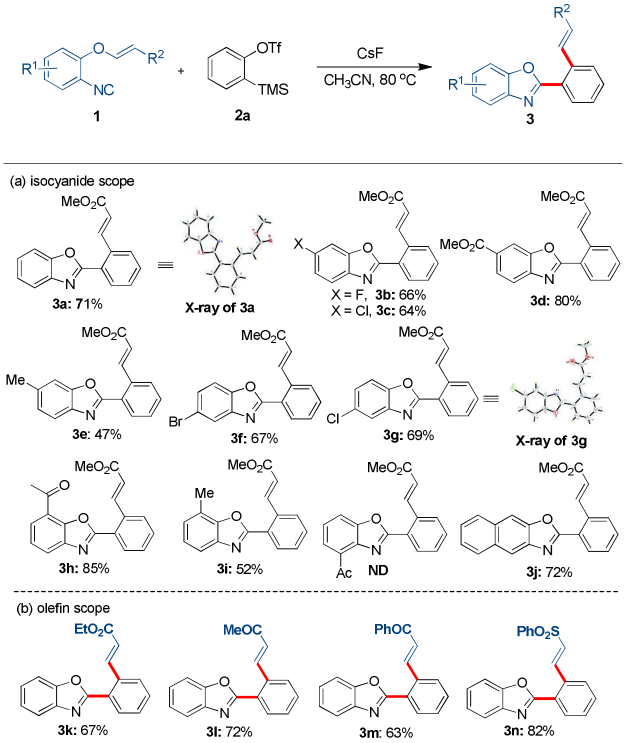
Table 1. Reaction optimization[a]



Entry	F source (equiv)	Temp (°C)	Solvent	Yield (%)[b]
1	CsF (2.0)	60	THF	18
2	KF/18-C-6 (2.0)	60	THF	<5
3	TBAF (2.0)	60	THF	0
4	CsF (3.0)	60	THF	26
5	CsF (4.0)	60	THF	31
6	CsF (4.0)	60	Toluene	NR
7	CsF (4.0)	60	CH_3CN	46
8	CsF (4.0)	60	DME	18
9	CsF (4.0)	60	1,4-dioxane	<5
10	CsF (4.0)	40	CH_3CN	25
11	CsF (4.0)	80	CH_3CN	53
12[c]	CsF (4.0)	80	CH_3CN	61
13[c,d]	CsF (4.0)	80	CH_3CN	68
14[c,e]	CsF (4.0)	80	CH_3CN	71

[a] Unless otherwise noted, all reactions were carried out with 0.5 mmol 2-isocyanophenyloxyacrylate **1a**, 0.5 mmol benzyne precursor **2a**, fluorine source, in 5 mL solvent, 24 hours. [b] Yields of product after silica gel chromatography. [c] Reaction time is 36 h. [d] The ratio of **2a**:**1a** was 1.2:1. [e] The ratio of **2a**:**1a** was 1.5:1.

We initially examined the model reaction of ethyl 3-(2-isocyanophenoxy)acrylate (**1a**) and benzyne precursor (**2a**) to exploit the possible domino conversion. As shown in Table 1, upon treatment with the mixture in THF essentially afforded a new product **3a** in 18% yield (Table 1, entry 1). Next, investigation on the effect of parameters including fluorine source, catalyst loading, temperature, and solvent was conducted to enhance the yield of **3a**. Of the fluorine sources tested, KF/18-C-6 led to very poor performance while TBAF showed no reactivity (Table 1, entries 2-3). The experimental results also revealed that the fluorine source loading had a significant impact on present transformation. The yield of **3a** was elevated to 31% when 4.0 equivalents CsF was added (Table 1, entry 5). Reactions with other solvents including Toluene, CH_3CN, DME, and 1,4-dioxane were also screened to make some improvement. Gratifyingly, the employment of CH_3CN as solvent increased the yield of **3a** significantly (Table 1, entry 7). Encouraged by these results, we then turned our attention to the other influence factors. The experimental outcome demonstrated that higher temperature favored the formation of **3a**, whereas lower yields were observed when reactions were performed at 40 °C (Table 1, entries 10-11). Finally, the yield of **3a** was improved to 71% when the ratio of substrate **2a**:**1a** was adjusted to 1.5:1.



Scheme 2 Scope of the reaction with respect to the functionalized isocyanide **1**. [a] Reaction condition **A**: 0.5 mmol isocyanide **1**, 0.75 mmol benzyne precursor **2a**, CsF (4.0 equiv), CH_3CN (5 mL), 80 °C, 36 hours. [b] Yields of product after silica gel chromatography.

To establish the scope and limitation of present approach, the compatibility of substrates **1** with substituents at the aromatic ring bearing the isocyano group was firstly evaluated. As shown in Scheme 2, a series of substituents including methyl, acetyl, halide, ester groups at position 6, 5, 4 of the aromatic ring in substrate **1** were found to be compatible to produce the desired compounds **3a**-**3j**. Furthermore, the structures of compounds **3a** and **3g** were unambiguously confirmed by single crystal X-ray analysis.[18] Unfortunately, no reaction occurred when substituent was present at position 3 of the aromatic ring in **1**. Next, the experimental results showed that an array of substituted olefins with electron-withdrawing groups including ethyl acetate, acetyl, benzoyl, and sulphonyl groups were well tolerated to furnish the desired products **3k**-**3n**.

After showing a broad scope of different ethyl 3-(2-isocyanophenoxy)acrylate **1**, we then focused our attention to the feasibility of substituted aryne precursors. First, symmetric

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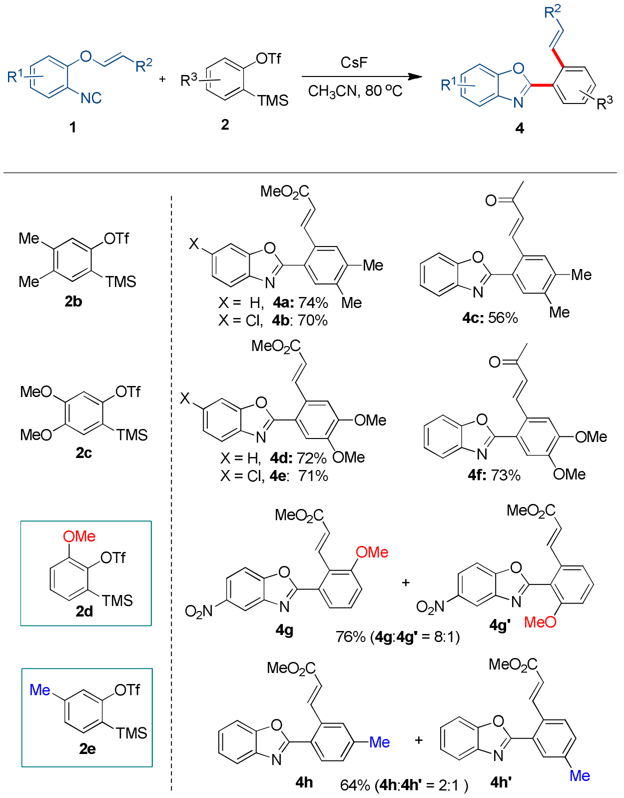
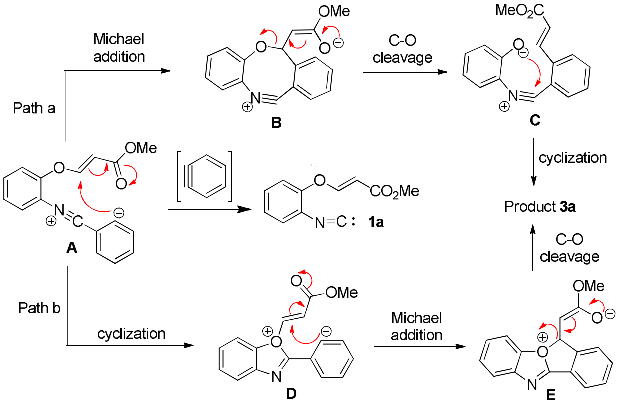


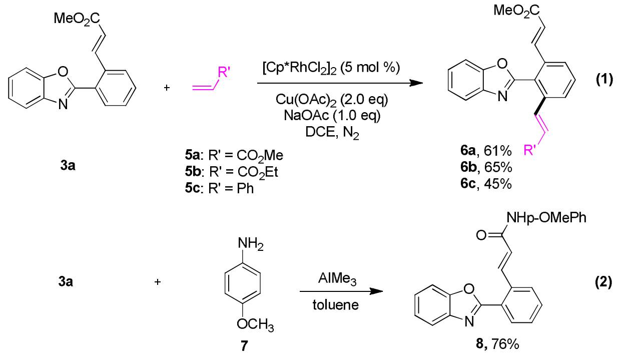
Scheme 3 Scope of the reaction with respect to the aryne presursor **2**. [a] Reaction condition **A**. [b] Yields of product after silica gel chromatography.

aryne precursors were used to react with several substituted substrate **1** containing the acrylate and alkenone unit to form the desired products **4a**-**4f**. Then, the reactions with unsymmetrical aryne precursors were conducted under standard conditons. To our delight, reaction with aryne precursor **2d** containing *ortho*-methoxy substitution afforded the corresponding products **4g** and **4g'** in good regioselectivity. Moreover, aryne precursor **2e** having *meta*-substituent was found to be compatible substrate to yield **4h** and **4h'**.



Scheme 4. Proposed mechanism

Based on the aforementioned results and previous reports, a plausible reaction mechanism is described in Scheme 4 to explain the formation of product. The beginning of present reaction involves the generation of a reactive zwitterionic intermediate **A** from **1a** and **2a**. After that, two following reaction pathways seem to be possible. In path a, intramolecular Michael addition on the carbon-carbon double bond take place to generate the enolate **B**. Next, carbon-oxygen rupture occurs to yield intermediate **C**. On the other hand, direct benzoxazole formation on intermediate **A** generates an oxonium intermediate **D**, which then undergo olefin migration *via* a five-membered ring transition state to give product **3a**.



Scheme 5. Synthetic application of the product

To further illustrate the utility of present protocol, more detailed investigation regarding the application of the products was carried out (Scheme 5). From the standpoint of structural characters, substrate **3a** contains a benzoxazole which might function as a directing group.[19] In this light, the reactions of **3a** and acrylates **5a**, **5b** were performed in the presence of catalytic amount of rhodium catalyst, respectively. Then, the *ortho*-olfination reaction with styrene **6c** also proceeded well to furnish **6c** albeit somewhat lower yield (Scheme 5, eq 1). Finally, the amidation reaction with aromatic amine **7** worked well to yield the corresponding products **8** (Scheme 5, eq 2).

In conclusion, we have described an unusual reaction with a newly designed 2-isocyanophenyloxyacrylate and aryne. This domino reaction introduces a benzoxazole ring and an olefin into the aromatic ring of aryne spontaneously, thus providing a new reactivity mode for both isocyanide and aryne chemistry. Furthermore, the unique structure of the products also enables further olefination *via* the Rhodium-catalyzed C-H activation. Other distinguished features include the absence of any catalyst and a wide substrate scope. Further study of present reaction is still underway in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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18 CCDC 1854485, 1854502 for compounds **3a**, **3g** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

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