Chemical Science

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EDGE ARTICLE

View Article Online
View Journal

Cite this: DOI: 10.1039/c3sc51489g

Benzofuran synthesis *via* copper-mediated oxidative annulation of phenols and unactivated internal alkynes†

Ruyi Zhu,[a] Jiangbo Wei[a] and Zhangjie Shi*[ab]

Received 27th May 2013
Accepted 3rd June 2013

DOI: 10.1039/c3sc51489g

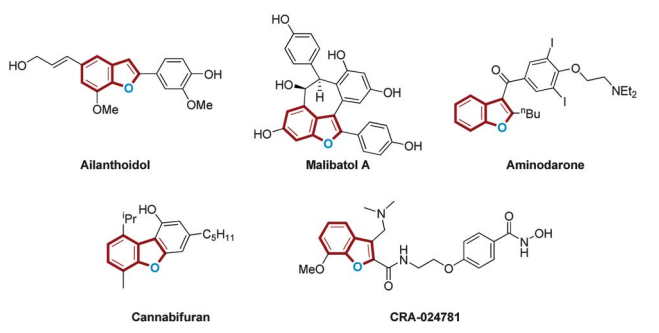
www.rsc.org/chemicalscience

The first example of copper-mediated oxidative annulation of phenols and unactivated internal alkynes to afford benzofuran derivatives was reported. Various phenols and unactivated internal alkynes were successfully employed. Mechanistic studies disclosed a new strategy on annulations of alkynes with phenols through reversible electrophilic carbocupration of phenol followed by alkyne insertion and cyclization.

Introduction

Benzofurans are a class of important structural motifs owing to their wide existence in natural products, pharmaceuticals and biologically active compounds (Scheme 1).[1] The synthesis towards this core backbone always draws chemists' attention, and so far many efficient synthetic methods have been developed.[2] Among these methods, the annulation reaction represents one of the most powerful and straightforward ways to afford the target molecules. Traditional annulations which are accomplished through cross coupling of *ortho*-halo phenol and alkyne or a tandem Sonagashira coupling/5-*endo-dig* cyclization usually require prefunctionalized substrates, such as *ortho*-halo or -alkynyl phenol.[3] To the best of our knowledge, phenols are rarely utilized as substrates to synthesize the benzofuran scaffolds directly.[4,9b,c]

Since the boom of C–H bond activation and functionalization,[5] we planned to take this advantage to develop a straightforward synthetic method to approach benzofuran derivatives through the oxidative annulation of phenols and unactivated internal alkynes. Based on pioneers' contributions to the metal-catalyzed oxidative annulations of alkynes with aryl or alkenyl substrates bearing various heteroatom-containing functional groups, a range of valuable heterocyclic compounds have been synthesized efficiently.[6] Recently, two examples of carbanion directed oxidative annulations of internal alkynes with aryl substrates have been reported.[7] This strategy (**strategy I**) could be named as a heteroatom- or carbanion-directed oxidative annulation reaction of alkynes with aryl or alkenyl substrates. In this strategy, a five- or six-membered metallacycle was formed as the key intermediate,[8] followed by subsequent insertion of the alkyne and reductive elimination to generate the product. However, substrates such as anilines and phenols cannot form such a key intermediate through directed *ortho* C–H activation. In 2009, Jiao and co-workers achieved the direct synthesis of indole derivatives *via* Pd-catalyzed oxidative annulation of anilines with activated internal alkynes. In their work, the authors hypothesized that the reaction was initiated by the nucleophilic attack of the amino group to the electron-deficient alkyne to form an aryl alkenyl amine intermediate. This strategy (**strategy II**) faced the difficulty that unactivated alkynes were inefficient partners due to their low reactivity.[9] Up to date, either directing groups or activated internal alkynes are necessary despite the significant advances shown. Only recently, Sahoo and co-workers reported the palladium-catalyzed oxidative annulation of phenols and unactivated internal alkynes to form benzofurans during the preparation of this manuscript.[10] Simultaneously, we also achieved the direct synthesis of



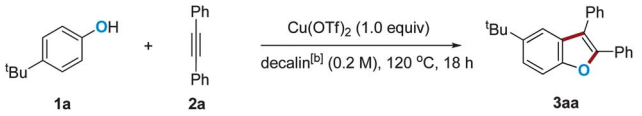
Scheme 1 Selected natural products, pharmaceuticals and biologically active compounds containing benzofuran structural motifs.

[a]*Beijing National Laboratory of Molecular Sciences (BNLMS), Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry and PKU Green Chemistry Center, Peking University, Beijing 100871, China. E-mail: zshi@pku.edu.cn; Fax: +86 10-6276-0890; Tel: +86 10-6276-0890*

[b]*State Key Laboratory of Organometallic Chemistry Chinese Academy of Sciences, Shanghai 200032, China*

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3sc51489g

Table 1 Optimization of reaction conditions[a]

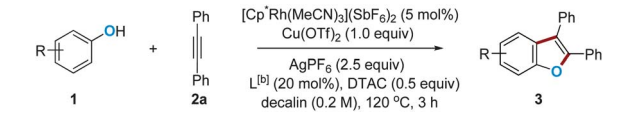


1a 2a 3aa

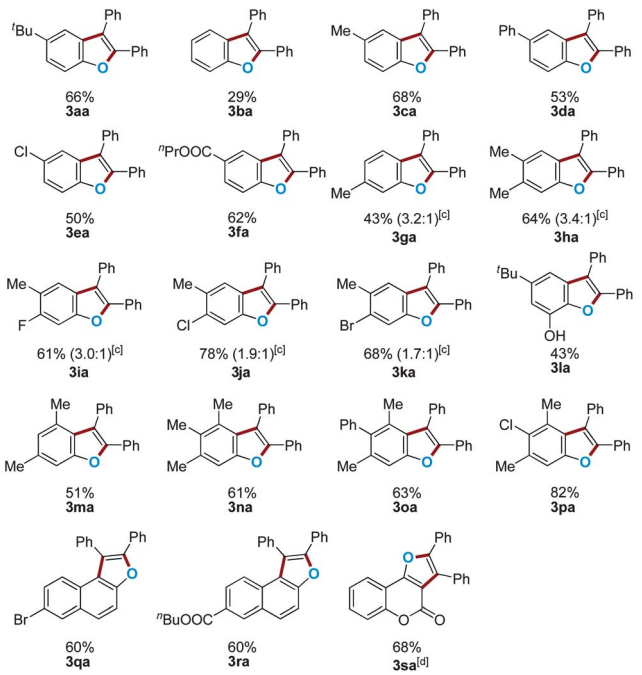
Entry	Additives	Yield[h]
1	Rh[c]	35
2[d]	$AgPF_6$[e] and Rh	45
3	$AgPF_6$	41
4	L[f] and $AgPF_6$	48
5	L, $AgPF_6$ and Rh	57
6	DTAC,[g] L, $AgPF_6$ and Rh	66
7	DTAC, L and $AgPF_6$	45
8	$AgPF_6$ and Rh, but no $Cu(OTf)_2$	n.d.

[a] *Reaction conditions*: 0.30 mmol of **1a**, 0.10 mmol of **2a**, 0.10 mmol of $Cu(OTf)_2$, 0.50 mL of solvent, 120 °C, 18 h. [b] Decalin: decahydronaphthalene. [c] Rh: $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5 mol%, 0.005 mmol). [d] Reaction time is 3 h for entries 2–8. [e] $AgPF_6$: 2.5 equiv., 0.25 mmol. [f] L: acetanilide (20 mol%, 0.02 mmol). [g] DTAC: dodecyl trimethyl ammonium chloride (0.5 equiv, 0.05 mmol). [h] Isolated yield.

Table 2 Substrate scope of phenols[a]



1 2a 3



[a] *Reaction conditions*: 0.30 mmol of **1**, 0.10 mmol of **2a**, 0.005 mmol of $[Cp^*Rh(MeCN)_3](SbF_6)_2$, 0.10 mmol of $Cu(OTf)_2$, 0.25 mmol of $AgPF_6$, 0.02 mmol of L, 0.05 mmol of DTAC, 0.50 mL of solvent, 120 °C, 3 h. [b] L: acetanilide. [c] Major isomer is shown, number in parenthesis is the ratio of two regioisomers which was determined by ^1H NMR. [d] 18 h.

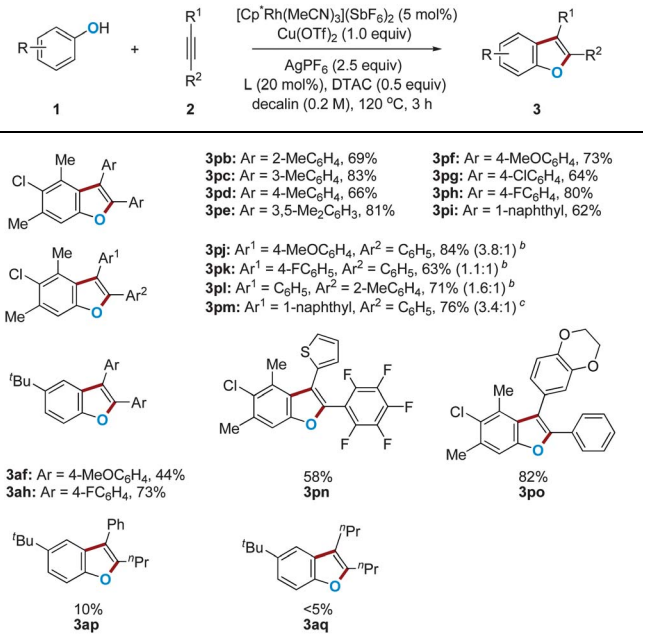
benzofuran *via* copper-mediated oxidative annulation of unactivated internal alkynes with phenols.

Results and discussion

At the beginning of our study, 4-*tert*-butylphenol **1a** and diphenylacetylene **2a** were chosen as model substrates (Table 1). Initially, the classical Rh(III)/Cu(II) system which was widely applied to **strategy I** was tested in our study.[6a–z,7a] Fortunately, a trace amount of desired product was observed. The examination of oxidants disclosed that $Cu(OTf)_2$ was optimal. The combination of cationic rhodium complex and $Cu(OTf)_2$ in decalin gave a 35% yield (entry 1). The ratio of **1a** to **2a** was also important, an excess amount of phenol gave better results (Table S1†). The addition of stoichiometric silver salts generally more or less increased the yield (Table S2†), $AgPF_6$ showed significant acceleration of the reaction and promotion of the yield (entry 2). To our surprise, the transformation could also proceed in the absence of rhodium complex albeit in a slightly lower yield (entry 3). This result implied a completely different pathway and the rhodium complex might play a role as a Lewis acid. Besides the rhodium complex, other metals were also surveyed, while no better results were obtained (Table S4†). Among the trials of *N*-containing ligands, acetanilide was proven beneficial (entry 5, Table S5†). Meanwhile, the rhodium complex was also advantageous under the circumstances (entry 4). Considering the presence of inorganic salts in the nonpolar solvent, phase transfer catalysts (PTCs) were taken into account to speed up the reaction. After screening we found that DTAC was the best one (entry 6, Table S8†). Interestingly, under this condition, the rhodium complex seemed to play a more important role in facilitating the transformation (entry 7). Notably, the product was not detected in the absence of $Cu(OTf)_2$ (entry 8). This result indicated that $Cu(OTf)_2$ was indispensable for this reaction. The type of solvent was also crucial, and generally, non- or low polar solvents, such as decalin, xylene, PhCl *etc.*, were better.

With the optimized reaction conditions in hand, various phenols were employed in the reaction (Table 2). Particularly, the reaction of *para*-alkyl- and aryl-substituted phenols led to the products in moderate to good yields (**3aa**, **3ca**, **3da**). The chloro substituent was compatible albeit in a moderate yield (**3ea**). Unfortunately, some electron-donating groups, such as methoxy and amino groups, were not compatible, which may arise from the preferential oxidation or other side processes.[11] On the other hand, electron-withdrawing groups, like the ester group, were well tolerated (**3fa**). However, a low yield was obtained when simple phenol was utilized (**3ba**). Based on this result, we speculated that the electrophilic carbocupration preferred occurring at the relatively electron-rich *ortho* and *para* positions.[11,12] Since the *para* position of simple phenol was vacant, the subsequent reaction occurring at the *para* position would lead to low yield. A similar result was observed for *meta*-substituted phenol (**3ga**), which might prove the hypothesis. Moreover, these results may also properly rule out the possibility that this transformation is similar to **strategy I** or **strategy II**. Meanwhile, moderate regioselectivity was observed for **3ga**,

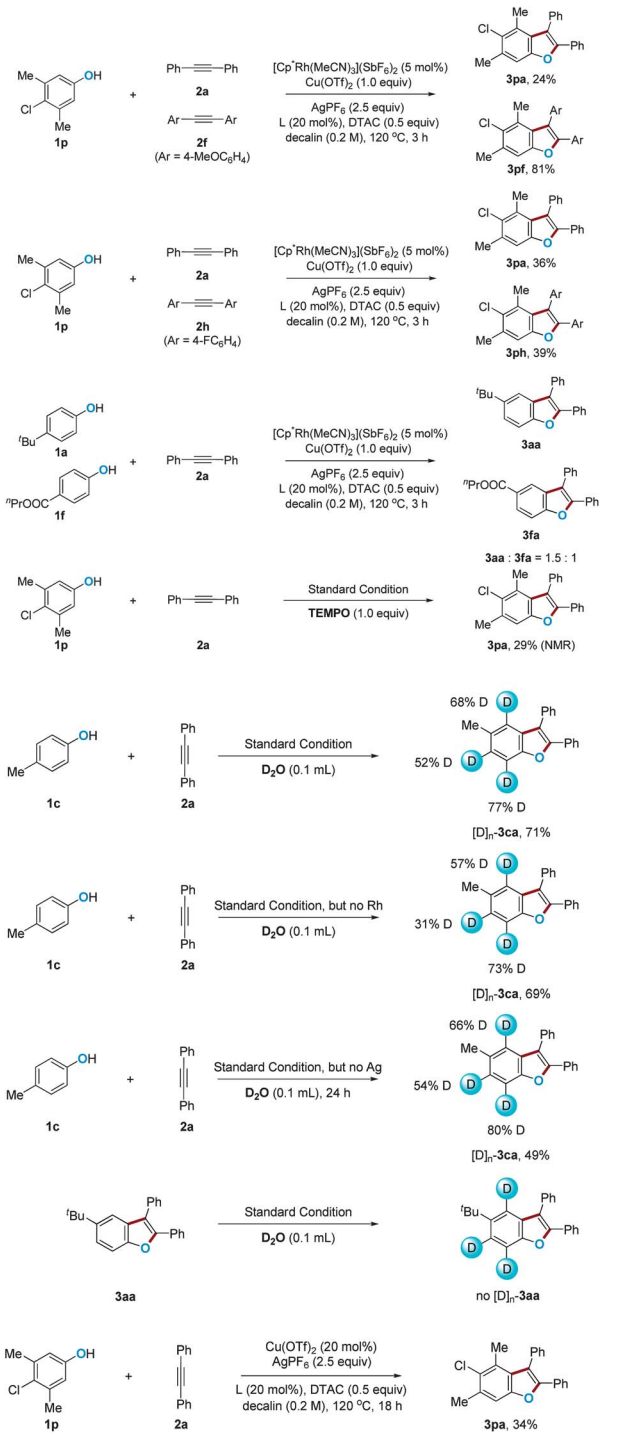
Table 3 Substrate scope of alkynes[a]



[a] *Reaction conditions*: 0.30 mmol of **1**, 0.10 mmol of **2**, 0.005 mmol of $[Cp^*Rh(MeCN)_3](SbF_6)_2$, 0.10 mmol of $Cu(OTf)_2$, 0.25 mmol of $AgPF_6$, 0.02 mmol of L, 0.05 mmol of DTAC, 0.50 mL of solvent, 120 °C, 3 h. [b] Major isomer is shown, number in parenthesis is the ratio of two regioisomers which was determined by ^1H NMR. [c] The ratio was determined by isolated yield.

presumably due to the steric hindrance of the methyl group. In addition, 3,4-disubstituted phenols would give products in moderate to good yields as the *para* positions were blocked (**3ha–ka**), and it was noteworthy that steric hindrance dominated the regioselectivities for **3ha**, **3ja** and **3ka**, while the regioselectivity of **3ia** might be controlled by the electronic effect. A phenolic hydroxyl group was tolerated though in moderate yield (**3la**). For 3,5-disubstitued substrates, moderate yield was obtained though the *para* position was available (**3ma**). Perhaps the steric hindrance of two adjacent methyl groups restrained the side reaction. When 3,4,5-trisubstitued phenols were examined, the yields were good which was in accordance with expectations (**3na–pa**). Not only can the phenyl substrates be used in this reaction, but the naphthyl substrates also could be successfully employed in good yields with single selectivity (**3qa**, **3ra**). In addition, various functional groups were compatible. The reaction of 4-hydroxycoumarin would selectively result in the corresponding benzofuran product which was endowed with many interesting biologically properties in good yield (**3sa**).[13]

Next the substrate scope for a variety of alkynes was investigated (Table 3). Symmetrical diarylalkynes bearing electron-donating or electron-withdrawing groups reacted smoothly to give high yields (**3pb–pi**). Moreover, the reaction was not inhibited by the steric hindrance of *ortho*-substituted diphenylacetylene (**3pb**). Several functional groups such as methoxy and halide groups were intact. Furthermore, an alkyne containing fused ring such as the naphthyl ring could also be utilized (**3pi**). In order to get more information about the electronic and steric effect of alkynes on the regioselectivity of this reaction, some representative unsymmetrical diarylalkynes were tested (**3pj–pm**). Good yields with low to moderate regioselectivities were observed. The elucidation for these regioselectivities is still in progress. Other phenol substrates such as **1a** could also be coupled with different



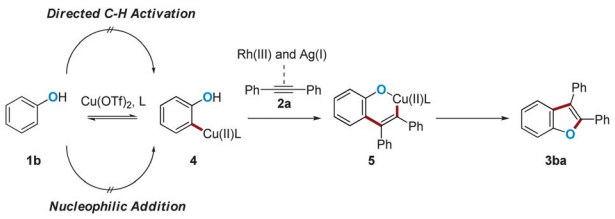
Scheme 2 Mechanistic studies.

alkynes with moderate to good yields (**3af**, **3ah**). To further test the utility of this method, heteroatom-containing alkynes were employed and resulted in corresponding products with good yields and single regioselectivities (**3pn**, **3po**). However, dialkylalkynes or alkylarylalkynes were inefficient partners presumably due to their instability under this oxidative condition (**3ap**, **3aq**). An activated internal alkyne, such as dimethyl acetylenedicarboxylate, was not an ideal coupling partner, which might evidence that the process of this reaction was not analogous to **strategy II**.

To gain more insight into the reaction mechanism, competitive experiments were conducted between electronically different alkynes [Scheme 2 eqn (1) and (2)], showing remarkable preference for electron-rich alkynes. However, there was almost no distinction between electron-neutral and electron-deficient alkynes. The results probably excluded the likelihood that the process was nucleophilic addition of phenol to alkyne through **strategy II** or a Friedel–Crafts-type reaction. The competitive experiments between electronically different phenols were also performed [Scheme 2 eqn (3)], and the results revealed that the reaction favored electron-rich phenols, agreeing with our hypothesis about electrophilic carbocupration.[12] In addition, TEMPO was added to the reaction as a radical scavenger, and the yield decreased significantly to 29% (NMR) [Scheme 2 eqn (4)], which may indicate that a radical process was involved.

Then deuterium-labeling experiments were conducted. The reaction of **1c** and **2a** in the presence of D_2O would result in the corresponding deuterated product [Scheme 2 eqn (5)], which clearly demonstrated the scrambling of H/D under the reaction condition. Without rhodium complex or $AgPF_6$, similar results were obtained [Scheme 2 eqn (6) and (7)]. Besides, **3aa** was introduced to the reaction under standard condition [Scheme 2 eqn (8)], while no detectable deuterium incorporation was observed. These results indicated that H/D exchange only occurred at the phenol substrate in the presence of $Cu(OTf)_2$. The catalytic reaction indicated that $Cu(OTf)_2$ was able to catalyze the reaction albeit with low efficiency [Scheme 2 eqn (9)].

According to our observations, we tentatively propose the reaction pathway (Scheme 3).[12] First, it is unlikely that the reaction was initiated with neither the phenolic hydroxyl group directed *ortho* C–H activation nor the nucleophilic addition of the phenolic hydroxyl group to the unactivated alkyne. We propose that the first step might be the reversible electrophilic carbocupration of phenol to form intermediate **4**. Then the insertion of **2a** to the C–Cu bond of **4** would lead to intermediate **5**. Finally, the product is formed through a reductive elimination or single electron transfer (SET) process.



Scheme 3 Proposed mechanism.

Conclusions

In conclusion, we have developed the first example of copper-mediated oxidative annulation of phenols and unactivated internal alkynes to afford benzofuran derivatives. Starting from commercially available phenols and alkynes, the direct one-step/pot synthesis of benzofuran derivatives has been achieved with high efficiency. The mechanistic study gives us a hint that the process is likely to initiate with the reversible electrophilic carbocupration, followed by alkyne insertion and cyclization to afford the desired product. The study of the detailed mechanism of this reaction is in progress.

Acknowledgements

This work was supported by the "973" Project from the MOST of China (2009CB825300) and NSFC (Nos. 20925207 and 21002001).

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