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Rh^{III}-catalyzed dual directing group assisted sterically hindered C-H bond activation: a unique route to *meta* and *ortho* substituted benzofurans

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Chien-Hung Yeh,[§] Wei-Chen Chen,[§] Parthasarathy Gandeepan, Ya-Chun Hong, Cheng-Hung Shih and Chien-Hong Cheng*

A new strategy for the synthesis of highly benzofurans from *meta*-substituted hydroxybenzenes and alkynes via a rhodium(III)-catalyzed activation of a sterically hindered C-H bond is demonstrated. A possible mechanism involving dual directing group assisted *ortho* C-H bond activation is proposed.

Benzofuran derivatives are an important class of heterocycles found in many natural[1] and biologically active molecules[2] and are often used as a building block in organic materials (Fig. 1).[3] Due to the many applications of benzofurans in medicinal and materials chemistry, continuous interests have been shown in the development of new synthetic methods. Classical methods that involve acid or base mediated cyclocondensations of phenols and its derivatives are less interesting due to the requirement of harsh reaction conditions and the starting materials are difficult to obtain.[4] Later on, transition metal catalyzed cyclization of *ortho*-alkynyl phenols and annulation reaction of ortho-halo phenols with alkynes to form benzofurans were reported.[5] Recently, a transition metal catalyzed C-H bond activation route for the synthesis of benzofurans from phenols and alkynes also has been reported.[6] In general, transition metal catalyzed C-H bond functionalization reactions of *meta* substituted arenes proceed at less hindered *ortho* C-H bonds.[7] Only in a few cases that both *ipso* and *meta* carbons have a directing group, the C-H bond activation occurs at the *ortho* carbon between the two directing groups.[8] In these reactions, the coordinating ability of *meta* substituent overpasses the steric hindrance. Our continuous interests in the transition metal catalyzed C-H bond activation reactions prompt us to find a suitable reaction system for the activation of sterically hindered C-H bonds. Herein, we report a new Rh(III)-catalyzed sterically hindered C-H bond activation for the synthesis of highly substituted benzofurans from *meta*-substituted hydroxybenzenes and alkynes (Scheme 1).

Our investigations started with a 3-hydroxybenzaldehyde *O*-methyl oxime derivative **1a** and diphenylacetylene (**2a**) as the substrates. After examining a wide range of reaction conditions (see Table S1 for the detailed optimization studies), we found

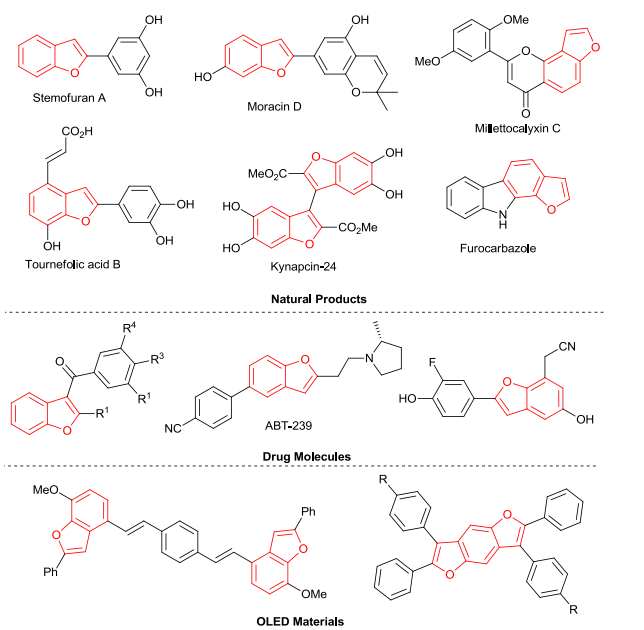
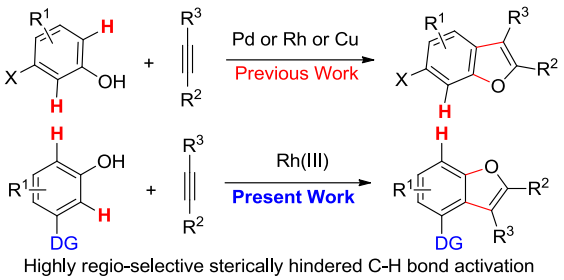


Fig. 1 Benzofuran cored natural and useful compounds.

that the reaction of **1a** (0.10 mmol) with **2a** (0.150 mmol) in the presence of $[RhCp^*Cl_2]_2$ (0.0020 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (0.35 mmol) in MeOH at 60 °C for 30 h gave substituted benzofuran **3aa** in 83% isolated yield (Table 1). Of the two possible C-H activation sites C2 and C6 of 3-hydroxy-4-methoxybenzaldehyde *O*-methyl oxime **1a**, the reaction proceeds regio specifically at the more congested C-H bond at C2 position. Moreover, the reaction undergoes annulation specifically with the *meta* phenolic OH instead of the oxime nitrogen. The reaction sites do not occur at the directing group

instead it happens at the *meta* and *ortho* positions. The presence of the oxime ether group is important for the benzofuran formation, although the oxime ether group is not involved in the product formation. No formation of benzofuran product was observed if phenol or resorcinol was used as the substrate to replace oxime ether **1a** indicating that hydroxyl group itself is not enough to promote the benzofuran formation reaction. In addition, when 3-hydroxybenzaldehyde O-methyl oxime **1b**, which does not have a substituent at the para position of the aryl ring, is employed as the substrate (Table 1, product **3ba**), the reaction does not occur at the *meta* and *para* positions, but only at the metal and ortho positions. It is noteworthy that the present site selective benzofuran formation is controlled by the reaction temperature. While the reaction temperature depends on the individual substrates used (see Table 1), a lower reaction temperature favours the formation of benzofuran product; the formation of isoquinoline derivative, a product from the reaction of oxime ether **1** with alkyne **2**, takes place only at a higher reaction temperature (see Scheme 2).



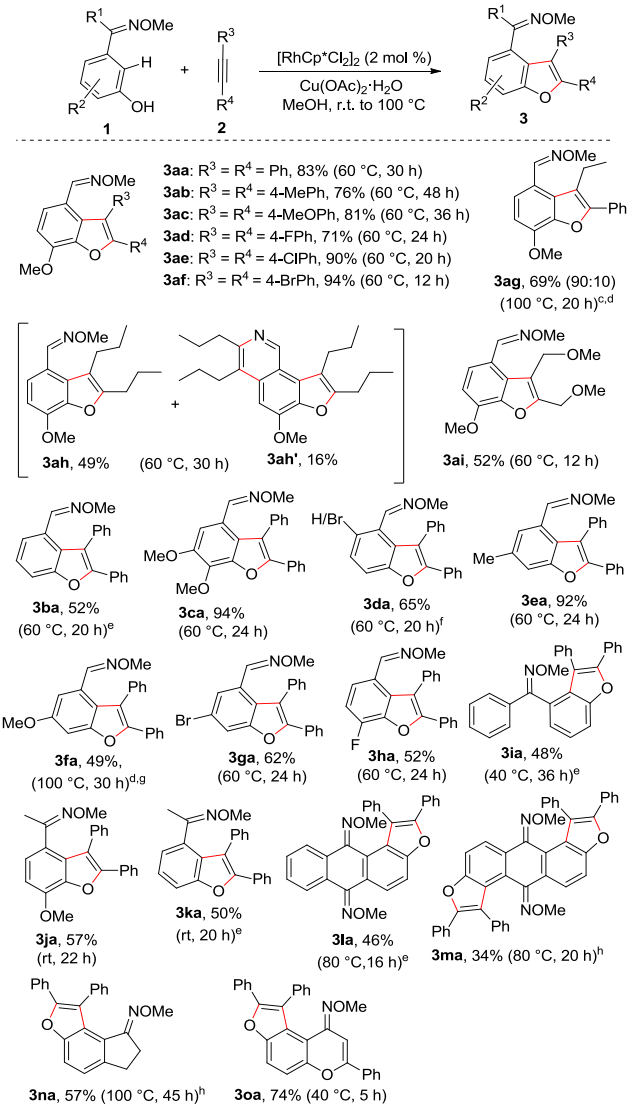
Scheme 1 New strategy for sterically hindered C-H bond activation

Having the optimized reaction conditions in hand, we tested the scope of the present benzofuran formation reaction with a diverse substituents on the arene ring and the results are shown in Table 1. Thus the reaction of **1a** with various substituted aryl acetylenes **2b-f** gave the respective benzofuran products **3ab-af** in excellent yields. The reaction of unsymmetrical alkyne 1-phenyl-1-butyne (**2g)** with **1a** gave benzofuran **3ag** in 69% with a 9:1 regio-isomeric ratio. Similarly, dialkylalkynes such as oct-4-yne (**2h**) and 1,4-dimethoxybut-2-yne (**2i**) reacted with **1a** to produce the corresponding benzofuran products **3ah** and **3ai** in 49% and 52% yields respectively. Under similar reaction conditions, substrates **1b-h** having H, OMe, Me, Br, or F substituent at different position of the aromatic ring reacted with **2a** to form benzofuran products **3ba**-**3ha** *via* the hindered C-H bond activation (Table 1).

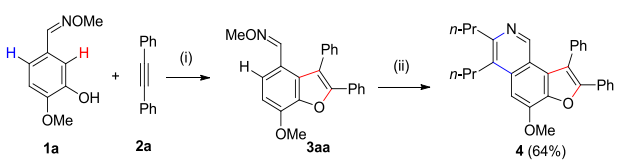
In addition to aldehyde oxime ether, we also tested ketoxime ether as a directing group for sterically hindered C-H bond activation reaction. Thus, phenol substrates having acetophenone and benzophenone oxime ethers at the *meta* position also drive the catalytic reaction to form benzofurans (Table 1, products **3ia-ka**). Likewise, anthraquinone (**1l-m**), indenone (**1n**) and chromone (**1o**) substrates also undergo sterically congested C-H bond activation with **2a** to form benzofuran products **3la-oa**. Compounds **3aa**, **3ga** and **3ma** were also confirmed by single crystal X-ray structure analysis.[9]

We also demonstrated an extended application of secondary directing group for further C-H bond activation reaction. Thus, a sequential C-H bond activation reaction of **1a** with **2a** and **2h** allowed the synthesis of furo[2,3-*h*]isoquinoline **4** in one-pot (Scheme 2).

Table 1 Scope of the reaction[a,b]



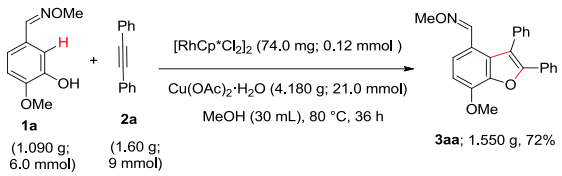
[a] General reaction conditions: **1** (0.20 mmol), alkyne **2** (0.30 mmol) $Cu(OAc)_2·H_2O$ (0.70 mmol) and $[RhCp^*Cl_2]_2$ (0.004 mmol) in MeOH (0.2 M) under N_2. [b] Isolated yields. [c] Major isomer is shown and the ratio of isomers was determined by ^1H NMR of crude reaction mixture. [d] Toluene was used as solvent. [e] 2.0 equiv of oxime was used and the yield was determined based on alkyne as limiting reagent. [f] 60% of debromination product was obtained. [g] 2.0 equiv of **2a** was used. [h] 3.0 equiv of **2a** and 5.0 equiv of $Cu(OAc)_2·H_2O$ were used.



Reaction conditions: (i) **1a** (0.2 mmol), **2a** (0.24 mmol), $[RhCp^*Cl_2]_2$ (0.004 mmol), $Cu(OAc)_2·H_2O$ (0.7 mmol), MeOH (0.2 M) at 60 ºC for 30 h; (ii): **2h** (0.60 mmol), $[RhCp^*Cl_2]_2$ (0.004 mmol), $Cu(OAc)_2·H_2O$ (0.7 mmol), MeOH (0.2 M) at 100 ºC for 16 h.

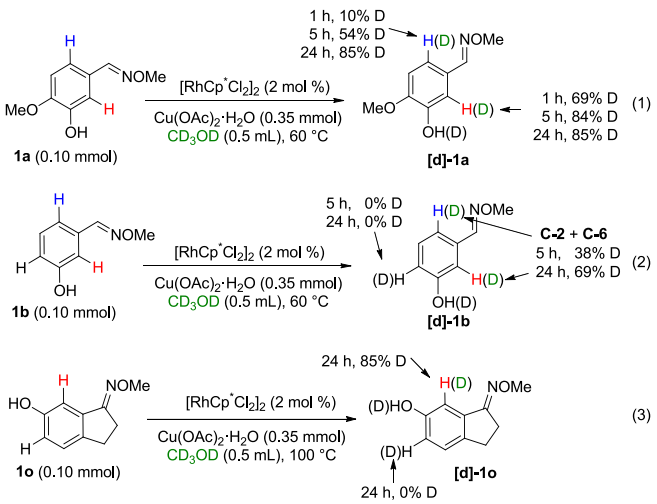
Scheme 2 Sequential C-H bond activation for the one-pot synthesis of furo[2,3-*h*]isoquinoline

To demonstrate a practical utility of the present rhodium-catalyzed C-H activation methodology, we performed a gram-scale synthesis of **3aa** and a satisfactory yield of 72% was observed (Scheme 3).



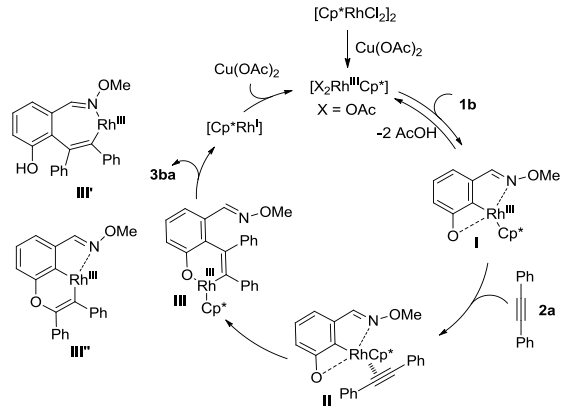
Scheme 3 Gram-scale synthesis.

To understand the mechanism of present catalytic reaction, we carried out three deuterium exchange studies (eqs 1-3). The results indicate that hydrogen/deuterium exchange occurs preferentially at the congested C–H bond between the oxime ether and the hydroxyl groups. Moreover, the results also suggest that the oxime ether group is the primary directing group and the coordination of oxime ether group to the rhodium center readily leads to hydrogen/deuterium exchange at all the *ortho* carbons. On the other hand, the hydroxy group is likely not strongly bound to the rhodium and the coordination did not result in H/D exchange at all the *ortho* carbons. However, despite the weak coordination of the hydroxyl group, the final annulation of alkyne occurs only with it.



Based on our experimental results and the known literatures,[6-8] a plausible mechanism for the present catalytic reaction is outlined in Scheme 4 by using **1b** and **2a** as the substrates. First, the coordination of both oxime nitrogen and phenolic oxygen to the rhodium center occurs assisting the ortho C-H bond activation of **1b** to give intermediate **I**. Coordination of diphenylacetylene **2a** to **I**, followed by the insertion into Rh–C bond to form intermediate **III** in which the Rh–N bond in **II** no longer exists. Subsequent C–O bond forming reductive elimination affords product **3ba** and Rh^{I} which was oxidized to Rh^{III} by Cu^{II} to regenerate the active species.

Alternatively, insertion of **2a** into the Rh-C bond might lead to the formation of a 7-membered ring intermediate **III'**. Reductive elimination leads to the formation of the corresponding *N*-methoxyisoquinolinium salt.[10] However, the relative high energy of this product that requires higher temperature for the reductive step greatly inhibits this pathway. Another pathway involving the insertion of **2a** into Rh-O bond might also lead to the formation of product **3ba** via intermediate III'. The pathway cannot be ruled out totally, but is less likely.



Scheme 4 Proposed mechanism for Rh^{III}-catalyzed benzofuran formation.

In summary, we have developed a new efficient regioselective method for the synthesis of substituted benzofurans by dual directing assisted sterically hindered *ortho* C-H bond activation of phenols using Rh^{III}-catalyst. The detailed mechanistic study of this new strategy employing dual directing groups for sterically hindered C-H bond activation reaction and further application of this method to the synthesis of useful compounds are in progress.

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Notes and references

[a] **Department of Chemistry, National Tsing Hua University, Hsinchu 30013, Taiwan Fax: 886-3-5724698; Tel: 886-3-5721454; E-mail: chcheng@mx.nthu.edu.tw*

[§] *These two authors contributed equally.*

† Electronic Supplementary Information (ESI) available: General experimental procedures, characterization details and ^{1}H and ^{13}C NMR spectra of new compounds. See DOI: 10.1039/c000000x/

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