

NHAc

R

20 examples

yield up to 94%

# Cascade Synthesis of 3-Alkylidene Dihydrobenzofuran Derivatives via Rhodium(III)-Catalyzed Redox-Neutral C–H Functionalization/ Cyclization

Zhi Zhou, Guixia Liu,\* Yan Chen, and Xiyan Lu\*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

ONHAC

+ P

**Supporting Information** 

**ABSTRACT:** An efficient rhodium(III)-catalyzed coupling reaction of *N*-phenoxyacetamides with propargyl carbonates to yield 3-alkylidene dihydrobenzofuran derivatives via C–H functionalization/cascade cyclization has been developed. This transformation represents a redox-neutral process and features the formation of three new bonds under mild conditions.

ver the past decades, transition-metal-catalyzed C-H functionalization has been developed as an efficient and versatile approach for the formation of carbon-carbon or carbon-heteroatom bonds.<sup>1</sup> Among the most investigated metals, [Cp\*Rh<sup>III</sup>] complexes have proven to be competent catalysts for the oxidative couplings of C–H bonds with alkynes, alkenes, allenes, diazo compounds, and other coupling partners. To obviate the use of a stoichiometric amount of external oxidants, a redox-neutral strategy using an oxidizing directing group has been employed in this field, which simplifies the reaction conditions and increases the reactivity as well as the selectivity.<sup>3</sup> However, the cascade reaction has drawn continuous interest in the field of synthetic chemistry due to its convenience in constructing multiple new bonds via a simple one-pot operation, thus providing a step-economical route for the synthesis of complex molecules.<sup>4</sup> We believe that the combination of redox-neutral C-H functionalization and the cascade strategy could provide a powerful method for the rapid buildup of heterocycles.<sup>5</sup>

We recently designed a novel oxidizing directing group for mild C-H functionalizations of N-phenoxyacetamide with alkynes (Scheme 1a).<sup>3f,1</sup> In considering the development of the cascade reaction triggered by C-H activation under redoxneutral conditions, we became interested in the use of propargyl carbonates as the coupling partner. Propargyl carbonates, having a leaving group in propargylic position, are easily accessible and valuable synthetic intermediates in organic synthesis. Although they have been used in diverse reactions, especially cascade reactions, propargyl carbonates are rarely exploited in C-H functionalization. During the preparation of this Letter, Ma and co-workers reported a C-H bond activation of arenes with sterically congested tertiary propargyl carbonates affording fully substituted allenes via regiospecific carborhodation/stereospecific  $\beta$ -oxygen elimination (Scheme 1b).<sup>6</sup> We would like to disclose herein the synthesis of 3-alkyl-idene dihydrobenzofuran derivatives from propargyl carbonates by employing the oxidizing directing group developed by our group (Scheme



 $R^2$ 

OBoc

mild conditions

Redox-neutral cascade reaction

[Cp\*RhCl2]2 (2.5 mol %)

CsOAc/K<sub>2</sub>CO<sub>3</sub>

MeOH. rt

good functional group tolerance

pratical scalable reaction



1c). This synthetic protocol features both redox-neutral C-H functionalization and cascade reaction, in which three new bonds are formed in one step.

We commenced our investigation by examining reactions of *N*-phenoxyamides with 3-phenyl propargylic carbonates using rhodium(III) catalyzed conditions (Table 1). In the presence of  $[Cp*RhCl_2]_2$  (2.5 mol %) and CsOAc (0.5 equiv), the reaction of *N*-phenoxyacetamide (1a) and methyl (3-phenylprop-2-yn-1-yl)carbonate (2aa) took place in DCM at room temperature, affording 3-alkylidene dihydrobenzofuran derivative 3aa in 46% yield (Table 1, entry 1). The structure of 3aa was confirmed by NMR, IR, HRMS, and X-ray crystallography.<sup>7a</sup> Further screening

Received: October 21, 2015

# Table 1. Reaction Conditions Screening<sup>a</sup>

0N 1 R <sup>1</sup> = Ac: 1a Piv: 1 Ts: 1a	$HR^{1} + Ph - HA - H$	[Cp*RhCl CSOAc 2 OR <sup>2</sup> solvent O <sub>2</sub> Me: 2aa Ts: 2ac c: 2ab Boc: 2a	2]2 (2.5 mol %) : (0.5 equiv) : (0.2 M), rt	O NHR <sup>1</sup> Ph
entry	$\mathbb{R}^1$	R <sup>2</sup>	solvent	yield <sup>b</sup> (%)
1	Ac	CO <sub>2</sub> Me	DCM	46
2	Ac	CO <sub>2</sub> Me	MeOH	68
3	Ac	CO <sub>2</sub> Me	dioxane	22
4	Piv	CO <sub>2</sub> Me	MeOH	19
5	Ts	CO <sub>2</sub> Me	MeOH	40
6	Ac	Ac	MeOH	25
7	Ac	Ts	MeOH	18
8	Ac	Boc	MeOH	86
9 <sup>c</sup>	Ac	Boc	MeOH	48
10 <sup>d</sup>	Ac	Boc	MeOH	90

<sup>*a*</sup>Reaction conditions: **1** (0.1 mmol), **2** (0.12 mmol),  $[Cp*RhCl_2]_2$  (2.5 mol %), and CsOAc (0.5 equiv) in solvent (0.2 M) at rt for 24 h under air. <sup>*b*1</sup>H NMR yield. <sup>*c*</sup>I equiv of HOAc was added. <sup>*d*</sup>0.5 equiv of K<sub>2</sub>CO<sub>3</sub> was added.

indicated methanol appeared to be an ideal solvent (Table 1, entries 1–3). Other *N*-phenoxyamides with different substituents on the nitrogen atom were less effective and gave the corresponding products in lower yields (Table 1, entries 4 and 5). A variety of propargylic substrates with different leaving groups were also tested, and *tert*-butyl carbonate **2a** seemed to be the best choice (Table 1, entries 6–8). The addition of acetic acid (1 equiv) gave an inferior result, while  $K_2CO_3$  (0.5 equiv) was helpful to increase the yield of **3aa** (Table 1, entries 9 and 10). Control experiments showed that no reaction occurred in the absence of either the rhodium catalyst or the base additives.<sup>7b</sup>

Utilizing the optimized conditions, a range of substituted *N*-phenoxyacetamides were employed, and the corresponding 2,3-dihydrobenzofuran derivatives were constructed effectively (Scheme 2). With *para* alkyl-, phenyl-, and halogen-substituted





<sup>*a*</sup>Reaction conditions: **1** (0.2 mmol), **2a** (0.24 mmol),  $[Cp*RhCl_2]_2$  (2.5 mol %), CsOAc (0.5 equiv), and K<sub>2</sub>CO<sub>3</sub> (0.5 equiv) in MeOH (0.2 M) at rt for 24 h under air; isolated yield was reported. <sup>*b*</sup>Yield of the product obtained at 60 °C was shown in the parentheses.

*N*-phenoxyacetamides, the reaction proceeded smoothly to afford the desired products in moderate to good yields (**3ca**-**3fa**). In addition, the reaction efficiency was not affected by the position of substituent. Substrates with methyl group at the *para-, meta-,* or *ortho*-position were well tolerated affording the desired products in good yields (**3ba, 3ha, and 3ia**). Of note, when *meta*-substituted *N*-phenoxyacetamides were employed, the C-H functionalization occurred at the less hindered site selectively (**3ia, 3ja**). Moreover, the electron-deficient *N*-phenoxyacetamides seemed to be less effective giving the desired products in moderate yields even at higher temperature (**3ga, 3ka**).

The effect of the substituents on *tert*-butyl propargyl carbonates was next examined under the standard reaction conditions (Scheme 3). The reaction is compatible with various

## Scheme 3. Scope of Alkyne Substrates<sup>a</sup>



"Reaction conditions: 1a (0.2 mmol), 2 (0.24 mmol),  $[Cp*RhCl_2]_2$  (2.5 mol %), CsOAc (0.5 equiv), and  $K_2CO_3$  (0.5 equiv) in MeOH (0.2 M) at rt for 24 h under air; isolated yield was reported.

*tert*-butyl 3-phenylpropargyl carbonates regardless of the electronic properties of the substitution on the phenyl ring (**3ab**-**3af**). Moreover, thienyl substituted propargyl carbonate was also a good reactant for this transformation (**3ag**, 85%). 3-Methylpropargyl carbonate readily participated in this cyclization giving the desired product **3ah** in 42% yield. It is noteworthy that the specifically *E*-selective 3-alkylidene dihydrobenzofuran derivatives were accessible using 1-substituted *tert*-butyl propargyl carbonates as the substrates (**3ai**, **3aj**). Nevertheless, *tert*-butyl (2-methyl-4-phenylbut-3-yn-2-yl) carbonate was unreactive under reaction conditions (**3ak**, 0%) indicating that tertiary 2-alkynylic carbonate are not compatible for this transformation.

Experiments were then carried out to gain more insight into the reaction mechanism. With 3-phenylpropargyl acetate (2ab) as the coupling partner, the desired 2,3-dihydrobenzofuran derivative 3aa was obtained in a low yield under the standard conditions. Further examination implied that *ortho*-hydroxyphenyl substituted enamide 4 was furnished as the major product, which could be smoothly converted to 3aa via intramolecular cyclization in a high yield at 60 °C (eq 1). On the basis of these results, we believed that the 2,3dihydrobenzofuran derivative was derived from the enamide, and different leaving groups on the propargylic position affected the cyclization. Deuterium-labeling experiment was next conducted in deuterated methanol. No deuterium incorporation was observed in the recovered starting material 1a and the

## **Organic Letters**



product **3aa**, indicating that the C–H activation might be irreversible under the reaction conditions (eq 2).<sup>8</sup> Furthermore, a primary KIE value of 1.8 implies the C–H bond cleavage process is not involved in the rate-determining step (eq 3),<sup>9</sup> which is consistent with our previous work.<sup>3f</sup>

Based on the above experiments and the mechanism studies in the precedent literature,<sup>10</sup> a plausible mechanism involving redox-neutral C–H functionalization and cyclization is shown in Scheme 4. With the aid of cesium acetate, an active catalyst was

## Scheme 4. Proposed Reaction Mechanism



generated via anion exchange, followed by the N-H/C-H cleavage to yield a five-membered rhodacycle intermediate A. Regioselective insertion of alkyne generated intermediate B, which underwent reductive elimination to give intermediate C and Rh<sup>I</sup> species. Subsequently, O-N bond cleavage and protonolysis regenerated the active Rh<sup>III</sup> species together with the enamide E. With -OBoc as the leaving group, an intramolecular substitution proceeded to form the C-O bond and the exocyclic double bond simultaneously. The regioselectivity observed in our work is consistent with the reported rhodium catalyzed C-H functionalization with alkynes, in which the insertion of an alkyl-aryl alkyne usually occurred regioselectively with the alkyl-substituted carbon center being installed with the arene substrate.<sup>2,3,8,11</sup> In Ma's allene synthesis using sterically congested tertiary propargy carbonates, the carbonyl group in carbonates are supposed to provide the

Letter

directing coordination to Rh leading to the reversed regioselectivity.<sup>6</sup>

Finally, we were pleased to find that this cascade cyclization could be conducted on gram-scale with a lower catalyst loading, and the desired 2,3-dihydrobenzofuran product **3aa** was afforded facilely without obvious decrease in yield (Scheme 5a). The

## Scheme 5. Derivatization of the Product 3aa



presence of the exocyclic double bond and the dihydrobenzofuran unit in **3aa** made it a useful synthetic intermediate (Scheme 5b). For example, in the presence of Lewis acids and nucleophilic reagents, **3aa** could be converted to different substituted benzofuran derivatives in moderate to high yields.<sup>12</sup> Intriguingly, treatment of **3aa** with Grignard reagent led to ring opening product **8** in moderate yield. Moreover, exposure of **3aa** to either *m*-CPBA or ozonolysis could cleave the exocyclic double bond furnishing benzofuran-3-one derivative **9**.<sup>13</sup>

In summary, by using propargyl carbonates as the coupling partners, an efficient Rh<sup>III</sup>-catalyzed cascade C–H functionalization/cyclization was developed to furnish 3-alkylidene dihydrobenzofuran derivatives. The reaction was demonstrated to be practical and scalable with remarkable features including mild conditions, high yields, and good functional group tolerance. Similar strategies for combining transition-metal-catalyzed C–H activations and cascade cyclizations can be expected in constructing complex compounds with bi- or polycyclic structures.

## ASSOCIATED CONTENT

#### **S** Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03060.

Crystallographic data for compound **3aa** (CIF) Experimental procedures, compounds characterization data, and copies of NMR spectra (PDF)

#### AUTHOR INFORMATION

#### **Corresponding Authors**

- \*E-mail: guixia@sioc.ac.cn.
- \*E-mail: xylu@mail.sioc.ac.cn.

#### Notes

The authors declare no competing financial interest.

# ACKNOWLEDGMENTS

We thank the National Basic Research Program of China (2015CB856600), the National Natural Science Foundation of China (21202184, 21232006, 21572255), and the Chinese Academy of Sciences for financial support.

# REFERENCES

(1) For selected recent reviews, see: (a) Girard, S. A.; Knauber, T.; Li,
 C.-J. Angew. Chem., Int. Ed. 2014, 53, 74. (b) Zhang, X.-S.; Chen, K.; Shi,
 Z.-J. Chem. Sci. 2014, 5, 2146. (c) Gao, K.; Yoshikai, N. Acc. Chem. Res.
 2014, 47, 1208. (d) Noisier, A. F. M.; Brimble, M. A. Chem. Rev. 2014,
 114, 8775. (e) Daugulis, O.; Roane, J.; Tran, L. Acc. Chem. Res. 2015, 48,
 1053. (f) Shin, K.; Kim, H.; Chang, S. Acc. Chem. Res. 2015, 48, 1040.
 (g) Yang, L.; Huang, H. Chem. Rev. 2015, 115, 3468.

(2) For selected recent reviews on Rh<sup>III</sup>-catalyzed C-H functionalization, see: (a) Wencel-Delord, J.; Droge, T.; Liu, F.; Glorius, F. Chem. Soc. Rev. 2011, 40, 4740. (b) Song, G.; Wang, F.; Li, X. Chem. Soc. Rev. 2012, 41, 3651. (c) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. Acc. Chem. Res. 2012, 45, 814. (d) Song, G.; Li, X. Acc. Chem. Res. 2015, 48, 1007.

(3) For selected recent reviews, see: (a) Patureau, F. W.; Glorius, F. Angew. Chem., Int. Ed. 2011, 50, 1977. (b) Mo, J.; Wang, L.; Liu, Y.; Cui, X. Synthesis 2015, 47, 439. (c) Hu, Z.; Tong, X.; Liu, G. Youji Huaxue 2015, 35, 539. (d) Huang, H.; Ji, X.; Wu, W.; Jiang, H. Chem. Soc. Rev. 2015, 44, 1155. For some recent examples on redox-neutral C-H functionalization using oxidizing directing groups, see: (e) Huang, X.; Huang, J.; Du, C.; Zhang, X.; Song, F.; You, J. Angew. Chem., Int. Ed. 2013, 52, 12970. (f) Liu, G.; Shen, Y.; Zhou, Z.; Lu, X. Angew. Chem., Int. Ed. 2013, 52, 6033. (g) Shen, Y.; Liu, G.; Zhou, Z.; Lu, X. Org. Lett. 2013, 15, 3366. (h) Zhao, D.; Shi, Z.; Glorius, F. Angew. Chem., Int. Ed. 2013, 52, 12426. (i) Liu, B.; Song, C.; Sun, C.; Zhou, S.; Zhu, J. J. Am. Chem. Soc. 2013, 135, 16625. (j) Zhao, D.; Lied, F.; Glorius, F. Chem. Sci. 2014, 5, 2869. (k) Hu, F.; Xia, Y.; Ye, F.; Liu, Z.; Ma, C.; Zhang, Y.; Wang, J. Angew. Chem., Int. Ed. 2014, 53, 1364. (1) Zhou, Z.; Liu, G.; Shen, Y.; Lu, X. Org. Chem. Front. 2014, 1, 1161. (m) Piou, T.; Rovis, T. J. Am. Chem. Soc. 2014, 136, 11292. (n) Zhang, H.; Wang, K.; Wang, B.; Yi, H.; Hu, F.; Li, C.; Zhang, Y.; Wang, J. Angew. Chem., Int. Ed. 2014, 53, 13234. (o) Zheng, L.; Hua, R. Chem. - Eur. J. 2014, 20, 2352. (p) Zhang, Z.; Jiang, H.; Huang, Y. Org. Lett. 2014, 16, 5976. (q) Zhang, X.; Qi, Z.; Li, X. Angew. Chem., Int. Ed. 2014, 53, 10794. (r) Chen, Y.; Wang, D.; Duan, P.; Ben, R.; Dai, L.; Shao, X.; Hong, M.; Zhao, J.; Huang, Y. Nat. Commun. 2014, 5, 4610. (s) Fan, Z.; Song, S.; Li, W.; Geng, K.; Xu, Y.; Miao, Z.-H.; Zhang, A. Org. Lett. 2015, 17, 310. (t) Zhou, B.; Chen, Z.; Yang, Y.; Ai, W.; Tang, H.; Wu, Y.; Zhu, W.; Li, Y. Angew. Chem., Int. Ed. 2015, 54, 12121. (u) Dateer, R. B.; Chang, S. J. Am. Chem. Soc. 2015, 137, 4908. (v) Zhou, Z.; Liu, G.; Chen, Y.; Lu, X. Adv. Synth. Catal. 2015, 357, 2944. (w) Yu, S.; Liu, S.; Lan, Y.; Wan, B.; Li, X. J. Am. Chem. Soc. 2015, 137, 1623. (x) Su, B.; Wei, J.-B.; Wu, W.-L.; Shi, Z.-J. ChemCatChem 2015, 7, 2986. (y) Mo, J.; Wang, L.; Cui, X. Org. Lett. 2015, 17, 4960. (z) Zhou, J.; Shi, J.; Qi, Z.; Li, X.; Xu, H. E.; Yi, W. ACS Catal. 2015, 5, 6999.

(4) For selected reviews, see: (a) Nicolaou, K. C.; Chen, J. S. Chem. Soc. Rev. 2009, 38, 2993. (b) Ruiz, M.; López-Alvarado, P.; Giorgi, G.; Menéndez, J. C. Chem. Soc. Rev. 2011, 40, 3445. (c) Patil, N. T.; Shinde, V. S.; Gajula, B. Org. Biomol. Chem. 2012, 10, 211. (d) Lu, L.-Q.; Chen, J.-R.; Xiao, W.-J. Acc. Chem. Res. 2012, 45, 1278.

(5) For selected reviews on transition-metal-mediated cascade reactions, see: (a) Platon, M.; Amardeil, R.; Djakovitch, L.; Hierso, J.-C. Chem. Soc. Rev. 2012, 41, 3929. (b) Ohno, H. Asian J. Org. Chem. 2013, 2, 18. (c) Wang, L.; Xiao, J. Adv. Synth. Catal. 2014, 356, 1137.

(6) Wu, S.; Huang, X.; Wu, W.; Li, P.; Fu, C.; Ma, S. Nat. Commun. 2015, 6, 7946.

(7) (a) See the Supporting Information. (b) For detailed optimization studies, see Table S1 in the Supporting Information.

(8) Hyster, T. K.; Rovis, T. J. Am. Chem. Soc. 2010, 132, 10565.

(9) A similar KIE value ( $k_{H/D} = 1.3$ ) was also obtained from two independent, side-by-side experiments using an equimolar amount of 1a and 1a- $d_5$ . For the details, see the Supporting Information.

(10) (a) Guimond, N.; Gorelsky, S. I.; Fagnou, K. J. Am. Chem. Soc.

Letter

- **2011**, *133*, 6449. (b) Neufeldt, S. R.; Jiménez-Osés, G.; Huckins, J. R.; Thiel, O. R.; Houk, K. N. J. Am. Chem. Soc. **2015**, *137*, 9843. (11) (a) Ueura, K.; Satoh, T.; Miura, M. Org. Lett. **2007**, *9*, 1407.
- (b) Guimond, N.; Gouliaras, C.; Fagnou, K. J. J. Am. Chem. Soc. 2010, 132, 6908.

(12) (a) Zhu, J.-B.; Wang, P.; Liao, S.; Tang, Y. Org. Lett. **2013**, *15*, 3054. (b) Ma, X.; Wu, F.; Yi, X.; Wang, H.; Chen, W. Chem. Commun. **2015**, *51*, 6862.

(13) (a) Woydowski, K.; Liebscher, J. Synthesis 2000, 10, 1444.
(b) Shan, G.; Yang, X.; Ma, L.; Rao, Y. Angew. Chem., Int. Ed. 2012, 51, 13070.
(c) Yu, H.; Huang, W.; Zhang, F. Eur. J. Org. Chem. 2014, 15, 3156.