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A One-Pot Synthesis of Dibenzofurans from 6-Diazo-2-cyclohexenones

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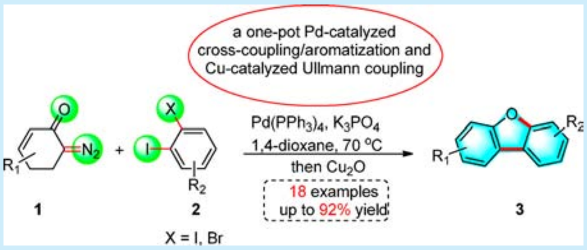
S *Supporting Information*

ABSTRACT: A novel and efficient protocol for the rapid construction of dibenzofuran motifs from 6-diazo-2-cyclohexenone and *ortho*-haloiodobenzene has been developed. The process involves one-pot Pd-catalyzed cross-coupling/aromatization and Cu-catalyzed Ullmann coupling.



Heterocyclic compounds usually demonstrate impressive biological activities, and a variety of new synthetic methods have been developed for the construction of these distinct structures.[1] Among the heterocycles, dibenzofurans have attracted tremendous attention in both biological and material sciences owing to their pharmacological, electronic, and/or optical properties.[2] To date, an array of approaches have emerged for the synthesis of the dibenzofuran motifs, which can be divided into two main categories (Scheme 1). First, cyclization of unsubstituted (X = H)[3] or 2-substituted phenoxybenzenes (X = halogen, CO_2H, BF_3K, OTs, N_2^+)[4−8] was used to assemble the dibenzofuran framework through the formation of a C−C bond in the presence of a Cu, Ag, Pd, or Rh catalyst (eq 1). Second, Pd- or Cu-catalyzed intramolecular O-arylation of 2-arylphenols[9] or 2-(2′-haloaryl)phenols[10] opened up a new path to dibenzofurans (eq 2). Nevertheless, these methods suffer from several drawbacks such as lengthy operation, substrate dependence, tedious purification, or unsatisfactory regioselectivity. Therefore,

Scheme 1. Approaches to Dibenzofurans

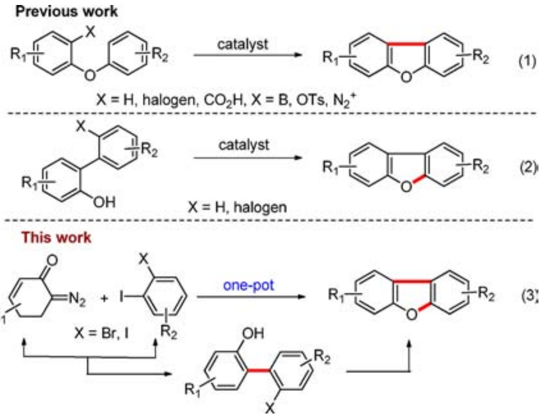
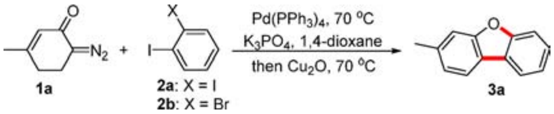
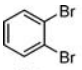


Table 1. Optimization of the Reaction Conditions[a]

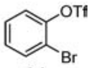


entry	X	1a:2	$Pd(PPh_3)_4$ (mol %)	Cu_2O (mol %)	yield (%)[c]
1[b]	I	1.1:1	10	0	50
2	I	1.1:1	10	10	80
3	I	1.1:1	5	10	60
4	I	1:1.1	10	20	70
5	I	1:1.3	10	10	73
6	Br	1.1:1	10	10	72
7	Br	1.1:1	5	10	80
8	**Br**	**1.1:1**	**5**	**20**	**82**
9	Br	1:1.3	5	20	75

[a]Reaction conditions: **1a** (0.275 mmol), K_3PO_4 (3 equiv), 1,4-dioxane (4 mL), 12 h; then Cu_2O, 24 h. [b]$Pd(PPh_3)_4$, 70 °C, 12 h; then 105 °C, 60 h. [c]Isolated yield.



2c



2d

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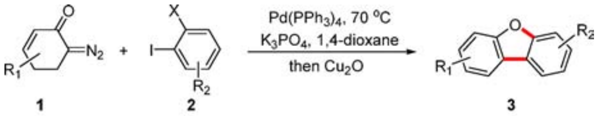
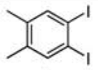
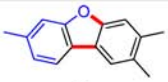
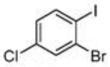
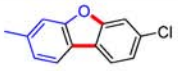
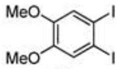
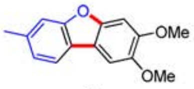
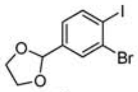
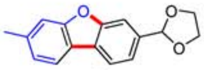
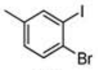
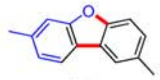
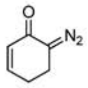
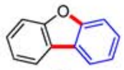
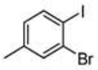
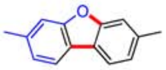
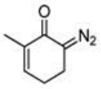
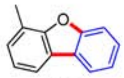
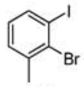
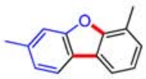
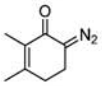
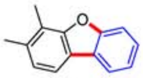
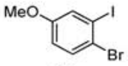
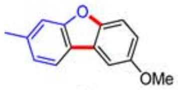
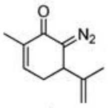
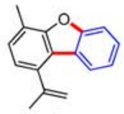
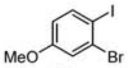
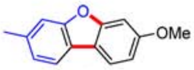
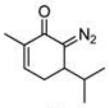
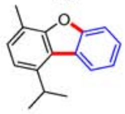
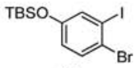
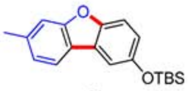
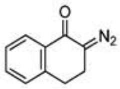
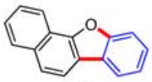
Table 2. Scope of the One-Pot Pd-Catalyzed Cross-Coupling/Aromatization and Cu-Catalyzed Ullmann Coupling

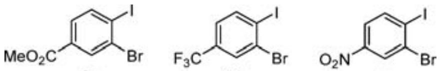


1 + 2 → 3

X = I[c], Br[a]

entry[a]	diazo (1)	haloiodobenzenes (2)	product	yield (%)[b]	entry[a]	diazo (1)	haloiodobenzenes (2)	product	yield (%)[b]
1[c]	1a	 2e	 3b	78	9	1a	 2m	 3j	85
2[c]	1a	 2f	 3c	61	10	1a	 2n	 3k	88
3	1a	 2g	 3d	82	11	 1b	2b	 3l	79
4	1a	 2h	 3e	89	12	 1c	2b	 3m	88
5[d]	1a	 2i	 3f	90	13	 1d	2b	 3n	87
6	1a	 2j	 3g	92	14[d]	 1e	2b	 3o	80
7	1a	 2k	 3h	80	15[d]	 1f	2b	 3p	71
8	1a	 2l	 3i	77	16	 1g	2b	 3q	83

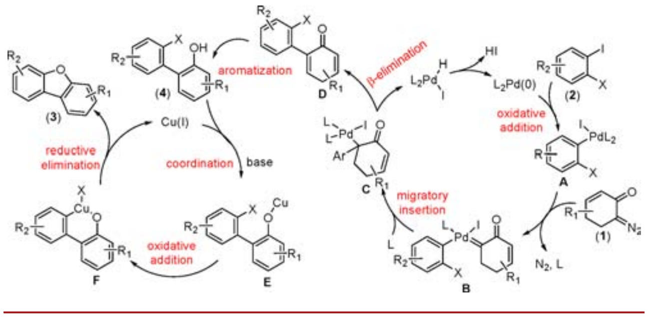
[a]Reaction conditions: **1** (0.275 mmol), **2** (0.25 mmol), K_3PO_4 (0.75 mmol), $Pd(PPh_3)_4$ (5 mol %), 1,4-dioxane (4 mL), 70 °C; then Cu_2O (0.050 mmol), 70 °C. [b]Isolated yield. [c]**1** (0.25 mmol), **2** (0.325 mmol), $Pd(PPh_3)_4$ (10 mol %); then Cu_2O (0.025 mmol), 105 °C. [d]Then Cu_2O (0.050 mmol), 105 °C.



2o 2p 2q

Figure 1. *ortho*-Bromoiodobenzenes bearing electron-withdrawing group.

Scheme 2. Proposed Mechanism



development of more efficient synthetic methods for dibenzofurans remains an attractive objective for synthetic chemists.

Recently, diazo compounds have found increasingly wide applications in synthetic organic chemistry.[11] Pd-catalyzed cross-coupling reactions involving a carbenoid as the key intermediate, in particular, have garnered considerable attention over the past decade.[12] Since the pioneering works from the Vranken group,[13] a number of elegant protocols have been reported, including the innovative synthesis of 1,3-dienes and *α,β*-unsaturated carbonyl compounds accomplished by Wang and co-workers.[12d,g,r,s] In 2013, our group disclosed a novel tandem Pd-catalyzed cross-coupling/aromatization reaction for the synthesis of 2-arylphenols.[14] Herein, we wish to report a novel one-pot synthetic method to rapidly construct dibenzofurans from a 6-diazo-2-cyclohexenone and an *ortho*-haloiodobenzene through

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tandem Pd-catalyzed cross-coupling/aromatization followed by a Cu-catalyzed Ullmann coupling reaction (eq 3).[15]

At the outset of the investigation, we examined the reaction of diazo compound **1a** and aryl iodide **2a** in the presence of $Pd(PPh_3)_4$ (10 mol %) as the catalyst and K_3PO_4 (3 equiv) as the base in 1,4-dioxane heated at 70 °C for 12 h, and then at 105 °C for 60 h. To our delight, the desired dibenzofuran **3a** was furnished in 50% yield (Table 1, entry 1). This promising result encouraged us to screen other related catalysts; however, $Pd_2(dba)_3$ along with various phosphine ligands (for example, $^tBu_3P$ and XPhos) were ineffective for this transformation. It is significant to note that upon adding Cu_2O as a catalyst for the Ullmann coupling step, the yield of **3a** was improved dramatically to 80% (entry 2), indicating the significant role of Cu_2O in this process. Whereas decreasing the Pd catalyst loading to 5 mol % resulted in less efficient formation of the final product (entry 3), increasing the loading of Cu_2O (20 mol %) led to a slight drop in the yield of **3a** (entry 4). The ratio of the substrates was next taken into consideration. With a slight excess of **2a**, the desired product was obtained in a comparable yield (entry 5). When bromoiodobenzene **2b** was used in place of diiodobenzene **2a**, the product could be isolated in 72% yield (entry 6). Interestingly, it was later found that using catalytic $Pd(PPh_3)_4$ (only 5 mol %) for the reaction involving bromoiodobenzene **2b** led to a much improved yield of **3a** (80%, entry 7). It was noteworthy that a slightly better result was obtained (82% yield) when this reaction was performed with a higher loading (20 mol %) of Cu_2O (entry 8), while increased loading of **2b** did not improve the overall process (entry 9). In addition, neither 1,2-dibromobenzene (**2c**) nor TfO-substituted bromobenzene (**2d**) was a suitable substrate for this particular transformation (Table 1).

With the optimized conditions secured, we studied the scope of the new tandem reaction sequence. As described in Table 2, the substitution pattern of the *ortho*-haloiodobenzene was first explored. A wide range of haloiodobenzene derivatives proved to be amenable to the reaction conditions, delivering the desired products in good to excellent yields (entries 1−10). Disubstitution on the *ortho*-diiodobenzenes allowed for the formation of dibenzofuran products in good yields at higher temperature (105 °C, entries 1 and 2). *ortho*-Bromoiodobenzenes were also competent substrates for this process. A methyl group on the *meta*- or *para*-postion of the aromatic ring was well-tolerated, furnishing the desired product in 80−90% yields (entries 3−5). It should be noted that a higher temperature (105 °C) was required to ensure a good yield for the formation of **3f**, presumably due to the steric hindrance caused by the adjacent methyl group in **2i**. Additionally, strongly electron-donating methoxy derivatives showed good tolerance and afforded **3g** and **3h** with high reaction efficiency (entries 6 and 7). This reaction is also compatible with the bulky TBS group, a protecting group commonly used in organic synthesis (entry 8). Gratifyingly, an impressive yield could be exhibited even in the presence of halogen substituents, such as a Cl atom on the *para*-position of aromatic ring (entry 9). Furthermore, substrate bearing synthetically useful functional groups such as an acetal was also compatible with the process to generate the expected product **3k** in a satisfactory yield. In contrast, the *ortho*-bromoiodobenzene substrates bearing electron-withdrawing groups such as *p*-CO_2Me, *p*-CF_3, and *p*-NO_2 (Figure 1) gave no observable product, indicating the significant impact of electronic effect for the process.

Having investigated the influence of substituents on the haloiodobenzenes, the scope of the diazocyclohexenones was next evaluated. A variety of 6-diazo-2-cyclohexenones was found to be able to furnish the corresponding dibenzofurans in good yields (Table 2, entries 11−16). The following observations have been made: (i) Different substituents of cyclohexenones such as a methyl, isopropyl or isopropenyl group showed broad tolerance. Both monosubstitued and disubstituted substrates were compatible for this transformation (entries 12 and 13). (ii) The reaction of 5-substituted 6-diazo-2-cyclohexenones derivatives (**1e** and **1f**) proceeded smoothly, although such substrates bearing an adjacent bulky group required higher reaction temperature to ensure suffcient conversion (entries 14 and 15). (iii) Substrate **1g** with a benzo moiety could also be transformed into the desired product **3q** successfully (entry 16).

A plausible mechanism is proposed for the current protocol (Scheme 2).[12l] Initially oxidative addition of aryl iodide **2** to the Pd(0) catalyst generates Pd (II) complex **A**, which reacts with diazo compound **1** through dediazoniation and forms the palladium-carbenoid complex **B**. Subsequently, migratory insertion of the aryl group would afford intermediate **C**, followed by β-elimination to deliver **D** and to regenerate the Pd(0) catalyst. Next, aromatization of intermediate **D** yields 2-arylphenol **4**, the oxygen of which is coordinated to Cu(I) in the presence of a base to give **E**. Intramolecular oxidative addition of **E** produces Cu(III) complex **F**, which undergoes reductive elimination to deliver the final product **3** and to regenerate the Cu(I) catalyst.

In summary, we have developed a novel approach to rapidly construct dibenzofuran motifs from 6-diazo-2-cyclohexenones and *ortho*-haloiodobenzenes through Pd-catalyzed cross-coupling/aromatization followed by a Cu-catalyzed Ullmann coupling performed in a one-pot fashion. The new method is operationally simple, highly selective, and synthetically useful. A wide range of substrates are compatible for the transformation and the desired products have been obtained in good to excellent yields.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02783.

Experimental details and spectral data for all unknown compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) *Name Reactions in Heterocyclic Chemistry*; Li, J., Corey, E. J., Eds.; Wiley-Interscience: Hoboken, NJ, 2005.

(2) (a) Tsang, K. Y.; Diaz, H.; Graciani, N.; Kelly, J. W. *J. Am. Chem. Soc.* **1994**, *116*, 3988. (b) Asakawa, M.; Ashton, P. R.; Brown, C. L.; Fyfe, M. C. T.; Menzer, S.; Pasini, D.; Scheuer, C.; Spencer, N.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Chem. - Eur. J.* **1997**, *3*, 1136. (c) Kaniwa, K.; Ohtsuki, T.; Yamamoto, Y.; Ishibashi, M. *Tetrahedron Lett.* **2006**, *47*, 1505. (d) Ye, Y. Q.; Koshino, H.; Onose, J.; Yoshikawa, K.; Abe, N.; Takahashi, S. *Org. Lett.* **2009**, *11*, 5074. (e) Teng, H.; Thakur, G. A.; Makriyannis, A. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5999.

(3) Liégault, B.; Lee, D.; Huestis, M. P.; Stuart, D. R.; Fagnou, K. *J. Org. Chem.* **2008**, *73*, 5022.

(4) (a) Ames, D. E.; Opalko, A. *Synthesis* **1983**, *1983*, 234. (b) Liu, Z.; Larock, R. C. *Org. Lett.* **2004**, *6*, 3739. (c) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581. (d) Liu, Z.; Larock, R. C. *Tetrahedron* **2007**, *63*, 347. (e) Xu, H.; Fan, L. *Chem. Pharm. Bull.* **2008**, *56*, 1496.

(5) (a) Wang, C.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 4194. (b) Shen, Z.; Ni, Z.; Mo, S.; Wang, J.; Zhu, Y. *Chem. - Eur. J.* **2012**, *18*, 4859. (c) Maetani, S.; Fukuyama, T.; Ryu, I. *Org. Lett.* **2013**, *15*, 2754.

(6) Lockner, J. W.; Dixon, D. D.; Risgaard, R.; Baran, P. S. *Org. Lett.* **2011**, *13*, 5628.

(7) (a) Nervig, C. S.; Waller, P. J.; Kalyani, D. *Org. Lett.* **2012**, *14*, 4838. (b) Ferguson, D. M.; Rudolph, S. R.; Kalyani, D. *ACS Catal.* **2014**, *4*, 2395.

(8) Du, Z.; Zhou, J.; Si, C.; Ma, W. *Synlett* **2011**, *2011*, 3023.

(9) (a) Xiao, B.; Gong, T.; Liu, Z.; Liu, J.; Luo, D.; Xu, J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 9250. (b) Wei, Y.; Yoshikai, N. *Org. Lett.* **2011**, *13*, 5504. (c) Zhao, J.; Wang, Y.; He, Y.; Liu, Y.; Zhu, Q. *Org. Lett.* **2012**, *14*, 1078. (d) Zhao, J.; Zhang, Q.; Liu, L.; He, Y.; Li, J.; Li, J.; Zhu, Q. *Org. Lett.* **2012**, *14*, 5362.

(10) (a) Kawaguchi, K.; Nakano, K.; Nozaki, K. *J. Org. Chem.* **2007**, *72*, 5119. (b) Liu, J.; Fitzgerald, A. E.; Mani, N. S. *J. Org. Chem.* **2008**, *73*, 2951. (c) Panda, N.; Mattan, I.; Nayak, D. K. *J. Org. Chem.* **2015**, *80*, 6590.

(11) For selected reviews, see: (a) Zhang, Y.; Wang, J. *Eur. J. Org. Chem.* **2011**, *2011*, 1015. (b) Barluenga, J.; Valdes, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 7486. (c) Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2012**, *41*, 560. (d) Xiao, Q.; Zhang, Y.; Wang, J. *Acc. Chem. Res.* **2013**, *46*, 236. (e) Xia, Y.; Zhang, Y.; Wang, J. *ACS Catal.* **2013**, *3*, 2586. (f) Liu, Z.; Wang, J. *J. Org. Chem.* **2013**, *78*, 10024.

(12) (a) Greenman, K. L.; Van Vranken, D. L. *Tetrahedron* **2005**, *61*, 6438. (b) Peng, C.; Cheng, J.; Wang, J. *J. Am. Chem. Soc.* **2007**, *129*, 8708. (c) Van Vranken, D. L.; Devine, S. K. J. *Org. Lett.* **2007**, *9*, 2047. (d) Peng, C.; Wang, Y.; Wang, J. *J. Am. Chem. Soc.* **2008**, *130*, 1566. (e) Devine, S. K. J.; Van Vranken, D. L. *Org. Lett.* **2008**, *10*, 1909. (f) Kudirka, R.; Van Vranken, D. L. *J. Org. Chem.* **2008**, *73*, 3585. (g) Chen, S.; Wang, J. *Chem. Commun.* **2008**, 4198. (h) Yu, W. Y.; Tsoi, Y. T.; Zhou, Z.; Chan, A. S. C. *Org. Lett.* **2009**, *11*, 469. (i) KudirKa, R.; Devine, S. K. J.; Adams, C. S.; Van Vranken, D. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 3677. (j) Zhang, Z.; Liu, Y.; Gong, M.; Zhao, X.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 1139. (k) Tsoi, Y. T.; Zhou, Z.; Chan, A. S. C; Yu, W. Y. *Org. Lett.* **2010**, *12*, 4506. (l) Peng, C.; Yan, G.; Wang, Y.; Jiang, Y.; Wang, J. *Synthesis* **2010**, *2010*, 4154. (m) Shu, Z.; Zhang, J.; Zhang, Y.; Wang, J. *Chem. Lett.* **2011**, *40*, 1009. (n) Zhou, L.; Liu, Y.; Zhang, Y.; Wang, J. *Chem. Commun.* **2011**, *47*, 3622. (o) Zhang, Z.; Liu, Y.; Ling, L.; Li, Y.; Dong, Y.; Gong, M.; Zhao, X.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 4330. (p) Chen, Z.; Duan, X.; Zhou, P.; Ali, S.; Luo, J.; Liang, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 1370. (q) Zhou, P.; Zhou, Z.; Chen, Z.; Ye, Y.; Zhao, L.; Yang, Y.; Xia, X.; Luo, J.; Liang, Y. *Chem. Commun.* **2013**, *49*, 561. (r) Xiao, Q.; Wang, B.; Tian, L.; Yang, Y.; Ma, J.; Zhang, Y.; Chen, S.; Wang, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 9305. (s) Xia, Y.; Liu, Z.; Zhang, Y.; Wang, J. *J. Org. Chem.* **2014**, *79*, 7711.

(13) Greenman, K. L.; Carter, D. S.; Van Vranken, D. L. *Tetrahedron* **2001**, *57*, 5219.

(14) Yang, K.; Zhang, J.; Li, Y.; Cheng, B.; Zhao, L.; Zhai, H. *Org. Lett.* **2013**, *15*, 808.

(15) For reviews on Ullmann coupling, see: (a) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (c) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (d) Dehli, J. R.; Legros, J.; Bolm, C. *Chem. Commun.* **2005**, 973. (e) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450.